2011

De Novo Asymmetric Syntheses of Bioactive Natural Products and Carbohydrate Motifs

Yalan Xing
West Virginia University

Follow this and additional works at: <https://researchrepository.wvu.edu/etd>

Recommended Citation

Xing, Yalan, "De Novo Asymmetric Syntheses of Bioactive Natural Products and Carbohydrate Motifs" (2011). *Graduate Theses, Dissertations, and Problem Reports*. 4819.
<https://researchrepository.wvu.edu/etd/4819>

This Dissertation is protected by copyright and/or related rights. It has been brought to you by the The Research Repository @ WVU with permission from the rights-holder(s). You are free to use this Dissertation in any way that is permitted by the copyright and related rights legislation that applies to your use. For other uses you must obtain permission from the rights-holder(s) directly, unless additional rights are indicated by a Creative Commons license in the record and/ or on the work itself. This Dissertation has been accepted for inclusion in WVU Graduate Theses, Dissertations, and Problem Reports collection by an authorized administrator of The Research Repository @ WVU. For more information, please contact researchrepository@mail.wvu.edu.

De Novo Asymmetric Syntheses of Bioactive Natural Products and Carbohydrate Motifs

Yalan Xing

**Dissertation submitted to the
Eberly College of Arts and Sciences
at West Virginia University
in partial fulfillment of the requirements
for the degree of**

**Doctor of Philosophy
in
Organic Chemistry**

**John H. Penn, Ph.D., Chair
George A. O'Doherty, Ph.D.
Patrick Callery, Ph.D.
Alan Stolzenberg, Ph.D.
Kung K. Wang, Ph.D.**

C. Eugene Bennett Department of Chemistry

**Morgantown, West Virginia
2011**

Keywords: Glycosylation, Daumone, Deoxysugars, Cladosporoides, Aspergillides

Copyright 2011 Yalan Xing

ABSTRACT

De Novo Asymmetric Syntheses of Bioactive Natural Products and Carbohydrate Motifs

Yalan Xing

De novo asymmetric syntheses of daumone **I-1** and the fluorescent analog have been described. This route took advantage of the Noyori asymmetric hydrogenation of acetyl furan and alkynyl ketone, the Pd-catalyzed glycosylation and various post-glycosylation transformations to finish the total synthesis of Daumone **I-1**, which provided materials for mechanism of action studies.

In an effort to mimic nature's use of rare sugars in the synthesis of biologically important natural products (e.g., the carbohydrate portion of Daumone **I-1**), the O'Doherty group has been interested in developing new methods for practical and stereoselective synthesis. As part of these efforts, a concise synthesis of benzyl α -6-deoxy-*altro*-pyranoside and benzyl-ascarylo-pyranoside has been developed. The synthesis relied upon a Pd-catalyzed glycosylation reaction, a highly diastereoselective epoxidation and ring opening.

An enantioselective synthesis of cladospolide B, C and (*ent*)-cladospolide D has been achieved. This synthesis not only provided access to these antimicrobial natural products but also corrected the structural assignment of cladospolide D by means of a de novo synthesis and kinetic/thermodynamic alkene isomerization. The synthesis coupled the Noyori reduction of alkynyl ketone and the alkyl zipper reaction with the conversion to and asymmetric oxidation of dienoates to enable the successful synthesis of cladospolides B-D.

A de novo asymmetric total synthesis of aspergillides has been investigated. The challenge of our route is using a novel palladium-catalyzed addition of a vinyl group to install the key *trans*-pyran ring system. To date, an intermediate which is five steps away from a formal synthesis of aspergillide C has been prepared by Pd-catalyzed C-glycosylation and Julia olefination. Noyori reductions of furyl and propargyl ketone, alkyne zipper reaction and Au-catalyzed alkyne hydration have been utilized.

DEDICATED TO

My husband, Wuming Yan, my daughter, Emma J. Yan

And my parents, Xinhui Zhang, Yifeng Xing

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my research advisor, Dr. George A. O'Doherty, I have been so fortunate to have an advisor who gave me the freedom to explore on my own, and at the same time the guidance to recover when I failed. George taught me how to become a better organic chemist, his patience and support helped me overcome many crisis situations and finish this dissertation.

I am deeply grateful to the chair of my committee Dr. John Penn for the valuable assistance and helpful suggestions. I also would like to give my sincere appreciation to other members of my committee, Dr. Patrick Callery, Dr. Wang and Dr. Alan Stolzenberg.

Though only my name appears on the cover of this dissertation, a great many people have contributed to its production. I would like to express my heart-felt gratitude to my family. My parents, my husband and my daughter have been a constant source of love, concern, support and strength all these years. I have to give a special mention for the support and love given by my parents-in-law. Without their understanding, encouragement and support, I could not have finished this thesis.

I would like to acknowledge the members of the O'Doherty group who I've had the pleasure of working with, Dr. Haibing Guo, Dr. Mingde Shan, Dr. Maoquan Zhou, Dr. Miaosheng Li, Dr. Dong Gao, Dr. Sanjeeva Rao Guppi, Dr. Matt Mortensen, Dr. Sang-Woo Kang, Dr. Qian Chen, Dr. Rajender Vemula, Dr. Hongyan Li, Dr. Mingzong Li, Phillip, Harsh, Xiaomei Yu, Bulan Wu, Leo Wang, Melvin Rajaratnam, Ehesan Sharif,

Qi Zhang, Mike Cuccarese, Sumit Bajaj, Yashan Zhong, Pei Shi, Yangping Wang for all of the assistance they have given me in the last five years. I would also like to thank Dr. Novruz Akhmedov for his kind and friendly help during NMR experiments.

Financial supports from Dissertation fellowship WVU, the C. Eugene Bennett department of chemistry at West Virginia University, the National Institutes of Health and the National Science Foundation are also gratefully acknowledged.

TABLE OF CONTENTS

Title Page.....	i
Abstract.....	ii
Dedications	iii
Acknowledgements.....	iv
Table of Contents.....	vi
List of Figures.....	viii
List of Abbreviations	ix
Chapter 1. De novo asymmetric synthesis of pheromone daumone I-1	1
1.1. Introduction.....	1
1.2. Previous approach to daumone I-2	2
1.3. De novo asymmetric synthesis of daumone I-1	3
1.4. Conclusions.....	9
1.5. References and notes	9
Chapter 2. De novo asymmetric synthesis of α -6-deoxy- <i>altro</i> -pyranoside and α -3, 6-dideoxy- <i>altro</i> -pyranoside	11
2.1. Introduction.....	11
2.2. Previous approaches to deoxysugars	12
2.3. De Novo Synthesis of α -6-deoxy- <i>altro</i> -pyranoside and α -3, 6-dideoxy- <i>altro</i> -pyranoside.....	14
2.4. Conclusions.....	17
2.5. References and notes	18
Chapter 3. Structure investigations of <i>ent</i> -cladospolide D by de novo synthesis and kinetic and thermodynamic isomerization.....	21

3.1. Introduction.....	21
3.2. Previous approaches to cladospolides	23
3.3. De Novo approach to natural product natural products cladospolides	25
3.4. Conclusions.....	37
3.5. References and notes	38
Chapter 4. De novo asymmetric total synthesis of aspergillids.....	41
4.1. Introduction.....	41
4.2. Previous approaches to aspergillides	42
4.3. Retrosynthetic analysis of aspergillides.....	45
4.4. De novo approach to aspergillides.....	46
4.5. Conclusions.....	55
4.6. References and notes	55
Experimental Section.....	58

List of Figures

Figure 1. Daumone	1
Figure 2. α -6-Deoxy-altrose and α -ascarylose	14
Figure 3. The cladospolide A-D	22
Figure 4. (<i>E/Z</i>)-cladospolide D	22
Figure 5. Aspergillides.....	41

List of Abbreviations

Ac	acetyl		hydride
AIBN	Azobisisobutyronitrile	DMAP	4-(dimethylamino)
Bn	benzyl		pyridine
Boc	<i>tert</i> -Butyloxycarbonyl	DMF	dimethylformamide
BuLi	<i>n</i> -Butyllithium	dr	diastereomeric ratio
Bz	benzoyl	ee	enantiomeric excess
calc	calculated	EI	electron impact
δ	chemical shift (ppm)	<i>ent</i>	enantiomer
d	doublet	equiv	equivalent(s)
dba	<i>trans,trans</i> - dibenzylideneacetone	ESI	electrospray ionization
DBU	1,8-Diazabicycloundec- 7-ene	Et	ethyl
		EtOAc	ethyl acetate
DCC	Dicyclohexylcarbo Diimide	Et ₂ O	diethyl ether
		g	gram(s)
DDQ	2,3-Dichloro-5,6- Dicyanobenzoquinone	h	hour(s)
		HBTU	2-(1 <i>H</i> -Benzotriazole-1- yl)-1,1,3,3-tetramethylu- roniumhexafluorophos- phate
DIAD	diisopropyl azodicarboxylate		
Dibal-H	diisobutylaluminium		

Hex	hexanes	Piv	Pivalate
HPLC	high pressure liquid Chromatography	PMB	<i>para</i> -methoxybenzyl
HRMS	High resolution mass Spectrum	ppm	parts per million
Hz	hertz (cycles per second)	py	pyridine
IR	infrared	q	quartet
<i>J</i>	spin-spin coupling Constant	R _f	ratio to front
KAPA	potassium 3- aminopropylamide	rt	room temperature
Me	methyl	t	triplet
MHz	megahertz	TBAF	tetrabutylammonium Fluoride
min	minute(s)	TBDPS	<i>t</i> -Butyldiphenylsilyl
mol	mole(s)	TBS	<i>t</i> -butyldimethylsilyl
mmol	millimole(s)	TEMPO	2,2,6,6-tetramethyl- piperidin-1-oxyl
mp	melting point	THF	tetrahydrofuran
NBS	<i>N</i> -Bromosuccinimide	TLC	thin layer chromatography
NMR	nuclear magnetic resonance	TMS	trimethylsilyl
Ph	phenyl	Tf	trifluoromethanesulfonyl
		<i>p</i> -TsOH	<i>para</i> -toluenesulfonic acid

Chapter 1

De Novo Asymmetric Synthesis of Pheromone Daumone I-1

1.1. Introduction

Daumone, a family of small molecule pheromones, can control multiple behaviors in the nematode in *Caenorhabditis elegans*.¹ Developmental arrest at the dauer stage and male mating behavior are the two basic *C. elegans* traits which are controlled by daumone pheromones. Under harsh growth condition, daumone could signal *C. elegans* to enter the dauer stage, an enduring and non-ageing stage of the nematode life cycle with distinctive adaptive features and extended life.² At low concentrations, a synergistic mixture of daumone produced by hermaphrodites causes male-specific attraction.

Figure 1. Daumone

In 2005, Jeong *et al.* have first isolated, characterized and completed a total synthesis of daumone **I-2**,³ recently, another two daumone pheromones (**I-1** and **I-3**) were isolated and characterized by the Clardy's group.² Because of the fascinating biological activity, we desired to access synthetic samples of daumone.

Herein, I wish to present a de novo route of preparing daumone using our recently developed palladium catalyzed glycosylation reaction.^{4,5} This de novo route starts from

the non-chiral materials and uses asymmetric catalysis such as Noyori reduction to install the stereochemistry of daumone. Our strategies allowed us to not only access the natural products but also synthesize many daumone analogs which could be studied for the biological activities.

1.2. Previous Approach to Daumone I-2

In our group, former student Haibing Guo has developed a de novo asymmetric route⁵ for daumone **I-2** and provided the synthetic sample of **I-2** for the mechanism of action study in the Noel labs at The Salk Institute.⁶ After the biological activity study, daumone **I-2** was not as active as people thought before. Thus, based on Haibing's synthesis, I finished the total synthesis of daumone **I-1** as well as its fluorescent analog. The mechanism of action study showed that daumone **I-1** is the most active daumone component in terms of the dauer activity.

Scheme 1. Retrosynthetic analysis of Daumone **I-1** and **I-2**

As we can see from the retrosynthetic analysis (Scheme 1), both daumone **I-1** and daumone **I-2** could be established from diol **I-4**, which could be stereoselectively derived by a palladium-catalyzed glycosylation of the pyranone **I-5** and alcohol **I-6** and several post-glycosylation transformations. The Noyori reductions of acylfuran **I-7** and propargyl ketone **I-8** respectively could install the absolute stereochemistry of both **I-5** and **I-6**.⁷ For the synthesis of daumone **I-2**, the TBS protecting group of common intermediate **I-4** can be removed by TBAF, the resulting primary alcohol **I-9** was oxidized by TEMPO condition to provide Daumone **I-2**.

Scheme 2. Synthesis of Daumone **I-2**

1.3. De Novo Asymmetric Synthesis of Daumone **I-1**

As a de novo route, we wish to introduce both of the absolute stereochemistry of furan alcohol **I-10** and propargyl alcohol **I-12** by Noyori reduction respectively (Scheme 3).⁸ Furan alcohol **I-10** was obtained from acylfuran **I-7** using Noyori (*S,S*) catalyst in a very high enantiomeric excess (93% yield and > 96% ee). Noyori reduction of propargyl

ketone **I-8** provided propargyl alcohol **I-12** with high yield (81%) and enantiomeric purity (> 96% ee). Propargyl ketone **I-8** was established from 4-pentynol **I-11** by metalation of the TBS ether with *n*-BuLi and then quenching with acetaldehyde followed by oxidation with MnO₂ (98%).

Scheme 3. Noyori reduction to install stereochemistry

With successful installation of the stereochemistry of **I-10** and **I-12**, we next proceeded to couple **I-5** and **I-6** (Scheme 4) using palladium-catalyzed glycosylation reaction. Achmatowicz reaction (NBS in THF/H₂O) of **I-10** gave the ring-expanded pyranone product **I-13** in good yield (91%).⁹ The mechanism of Achmatowicz reaction is shown in scheme 5. The hemiacetal of **I-13** was then protected with (Boc)₂O to obtain Boc-protected pyranone **I-5** in good yield (78%) .

Scheme 4. Palladium-catalyzed glycosylation

Scheme 5. Achmatowicz reaction

Propargyl alcohol **I-12** was reduced (H_2 , 10% Pd/C) to generate the coupling partner alcohol **I-6** (82%). The palladium-catalyzed glycosylation of pyranone **I-5** and alcohol **I-6** by using 5% palladium (0) and 10% triphenylphosphine provided enone **I-14** as a single diastereomer (94%).¹⁰ The mechanism of the glycosylation reaction is shown in scheme 6. First, the Pd- π -allyl species was formed from the opposite face of the Boc group, and then

the alcohol nucleophile comes to attack the anomeric position from the top face to give the glycosylation product with the retention of stereochemistry.

Scheme 6. Palladium-catalyzed glycosylation

As shown in scheme 7, enone **I-14** was diastereoselectively epoxidized to give epoxy-enone **I-15** (81%) using hydrogen peroxide in the presence of a catalytic amount of base (10 mol % NaOH).¹¹ Then we turned our efforts to the diastereoselective opening of the epoxide ring. We decided to use reductive hydration strategy. Epoxy-enone **I-15** was diastereoselectively reduced to provide the equatorial alcohol **I-16** (93%) with NaBH_4 (-78 to -20 °C). The epoxide **I-16** was regioselectively and diastereoselectively opened with LiAlH_4 to generate diol **I-4** (88%) in a *trans*-diaxial way.¹² Diol **I-4** can also be achieved in a one-step reaction by treating **I-15** with LiAlH_4 at -78 °C followed by warming to room temperature (86%).

Scheme 7. Reductive hydration

With diol **I-4** in hand, we next protected it with acetic anhydride to provide the acetate **I-17** (85%), which was treated with aq. HCl to remove TBS group to give alcohol **I-18** (97%). The aldehyde **I-19** was obtained from oxidation of alcohol **I-18** with TEMPO in 88% yield. Wittig reaction of corresponding aldehyde **I-19** installed ethyl ester **I-20** in 97% yield. Treatment of **I-20** with LiOH in MeOH provided the acetyl deprotected methyl ester **I-21** in 99% yield. Finally, hydrolysis of methyl ester **I-21** with LiOH in THF/H₂O generated daumone **I-1** in 99% yield (Scheme 8).

Scheme 8. Synthesis of Daumone **I-1**

As an effort to study the dauer activity of *C. elegans*, we also made the fluorescent daumone analog **I-23**. Simple peptide coupling linked fluorescent probe **I-22** and daumone **I-1** to provide fluorescent daumone analog **I-23** which has been used for the mechanism of action study in The Salk Institute.

Scheme 9. Synthesis of fluorescent Daumone.

1.4. Conclusion:

In conclusion, the de novo enantioselective total syntheses of daumone **I-1** and its fluorescent analog have been accomplished. This approach takes advantage of our highly enantio- and diastereoselective palladium-catalyzed glycosylation reaction and Noyori reduction of two ketones. Daumone **I-1**, **I-2** and the fluorescent analogs we accessed were utilized in the biological study of the dauer stage of *C. elegans* in The Salk Institute along with antihelminthic studies at USDA. These compounds have been used as probes to track the uptake and localization of dauer stage of *C. elegans* and the fluorescent probes have been shown to have activity in dauer formation.⁶

Reference:

¹ Edison, A.S. *Neurobiology*. **2009**, 19, 378-388.

² (a) Butcher, R. A.; Fujita, M.; Schroeder, F. C.; Clardy, J. *Nature Chem. Bio.* **2007**, 3,

420-422. (b) Boucher, Y. & Doolittle, W. F. *Nature*. **2002**, *417*, 27–28. (c) Gordon, J. W.; Riddle *Dev. Biol.* **1984**, *102*, 368-378. (d) Cassada, R. C.; Russell, R. L. *Dev. Biol.* **1975**, *46*, 326-342.

³ Jeong, P.-Y.; Jung, M.; Yim, Y.-H.; Kim, H.; Kim, K.; Paik, Y.-K. *Nature* **2005**, *433*, 541-545.

⁴ (a) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406-12407. (b) Babu, R. S.; M. Zhou; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428-3429. (c) Babu, R. S.; O'Doherty, G. A. *J. Carb. Chem.* **2005**, *24*, 169-177.

⁵ H. Guo; O'Doherty, G.A. *Org. Lett.* **2005**; *7*(18); 3921-3924.

⁶ Baiga, T. J.; Guo, H.; Xing, Y.; O'Doherty, G. A.; Dillin, A.; Austin, M. B.; Noel, J. P.; La Clair, J. J. *ACS Chem. Bio.* **2008**, *3*, 294-304

⁷ (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521-2522. (b) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40-73.

⁸ Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005-1009.

⁹ (a) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165-176. (b) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863-866. (c) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 4033-4036.

¹⁰ Tsuji, J. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*; John Wiley & Sons: New York, 1995; pp 290-422.

¹¹ Jung, M. E.; Pontillo, J. J. *J. Org. Chem.* **2002**, *67*, 6848-6851.

¹² Mastihubova, M; Biely, P. *Tetrahedron Lett.* **2001**, *42*, 9065-9067.

Chapter 2

De Novo Asymmetric Synthesis of α -6-deoxy-*altro*-pyranoside and α -3, 6-dideoxy-*altro*-pyranoside[†]

2.1. Introduction

Deoxysugars are a common structural motif in biologically active natural products.¹ The removal of the hydroxyl groups in sugars along with the use of unusual stereochemistry imparts resistance to most glycosidases and thus conveys improved metabolic stability.¹ Examples of nature's reliance of these structural motifs are seen in the use of α -6-deoxy-*altro* as the main constituent of bacterial lipopolysaccharides,² as well as, the use of α -2,6- and α -3,6-dideoxy-*altro* (i.e., α -digitoxose and α -ascarylose) in biologically active natural products, such as jadomycin B³ and daumone,⁴ respectively.⁵

Scheme 1. De novo approach to carbohydrate

[†] Reproduced with permission from *J. Org. Chem.* **2009**, 74, 5961-5966. Copyright 2009, with permission from American Chemical Society

Over the last 10 years, there has been considerable effort made toward the synthesis of monosaccharides from achiral starting materials.⁶ In this regard, our group has developed a de novo asymmetric synthesis of carbohydrates using achiral acylfurans **II-1** (Scheme 1).⁷ Our approach used a Noyori reduction, an Achmatowicz reaction and a Pd(0)-catalyzed glycosylation (**II-2** to **II-3**) to prepare pyranone intermediate **II-3**,^{7,8,9} which via post-glycosylation transformations were converted into corresponding carbohydrates (e.g., **II-3** to **II-4**, **II-5** and **II-6**).^{7,9} This method has allowed for the stereoselective synthesis of a variety of sugars, including rare sugars, aminosugars and even unnatural sugars.¹⁰

These approaches primarily rely on the osmium catalyzed dihydroxylation reaction for the *syn*-addition of two hydroxyl groups across the C-2/C-3 pyran double bond, which has been used to prepare D- or L-sugars with *manno*-, *gulo*- and *talo*-stereochemistry.^{9,10} A related dihydroxylation on the C-3/C-4 pyran double bond provided the sugars with *galacto*- and *allo*-stereochemistry.^{10, 11} By combining this approach with protection/inversion reactions, this route has also been used to access to the *gluco*-stereoisomers.¹²

2.2. Previous approaches to deoxysugars

In 2009, Lowary and co-workers reported the use of 2, 3-anhydrosugars as glycosylating agents for the preparation of 2-deoxypyranosides.^{5a} Glycosylation of a panel of alcohols with one of two 6-deoxy-2,3-anhydrosugar thioglycosides (**II-7** and **II-8**) afforded 2,6-dideoxy-2-thiotolyl glycoside products **II-9** and **II-11** in excellent yields with an exclusively *syn* relationship between the aglycon and the C-3 hydroxyl group.

Removal of the 2-thiotolyl group can be achieved via reaction with tri-*n*-butyltin hydride and AIBN to give the corresponding 2, 6-dideoxy pyranosides **II-10** and **II-12** (Scheme 2).

Scheme 2. Lowary's approach to 2, 6-dideoxysugars.

The synthesis of glycosyl donors **II-7** and **II-8** is outline in Scheme 3. The preparation of **II-7** started with the known benzylidene acetal protected 6-deoxy-D-mannopyranoside **II-13**. The Hanessian-Huller reaction to **II-13** led to the formation of **II-14** in 75% yield. After five steps transformations, **II-14** was converted to glycosyl donor **II-7**. The preparation of **II-8** proved more challenging than **II-7**. They first synthesized thioglycoside **II-15**, which underwent five steps transformations to provide **II-16**. PMB protection followed by the removal of allyl group and reaction with sodium hydride led the formation of glycosyl donor **II-8**.

Scheme 3. Lowary's synthesis of glycosyl donors **II-7** and **II-8**.

2.3. De Novo Asymmetric Synthesis of α -6-deoxy-*altro*-pyranoside and α -3,6-dideoxy-*altro*-pyranoside

As part of our efforts to expand upon this methodology, we have been investigating epoxidation/nucleophilic ring-opening reactions for the net *anti*-addition of hydroxyl groups across the C-2/C-3 pyran double bond. Herein I would like to introduce our successful application of this new post-glycosylation transformation for the de novo synthesis of two deoxysugar targets (i.e., benzyl pyranosides with α -*altro*-stereochemistry and its 3-deoxy (α -ascarylose) congeners) (Figure 2).

Figure 2. α -6-Deoxy-altrose and α -ascarylose

2.3.1. Retrosynthetic Analysis

Retrosynthetically, we envisioned both α -6-deoxy-*altro*-pyranoside and α -3, 6-dideoxy-*altro*-pyranoside **II-17** as being derived from the *trans*-diaxial opening of epoxide **II-18** with either a formal hydroxy or hydride nucleophile, respectively (Scheme 4). Epoxide **II-18** could be prepared by epoxidation of pyran **II-19**, which in turn could be prepared by a ketone reduction of pyranone **II-20**. Because our route began with the Noyori reduction of acylfuran, it is amenable to the synthesis of either D- or L-enantiomers of these sugars.¹³

Scheme 4. Retrosynthetic analysis

2.3.2. De Novo Synthesis of α -Boc-pyranone

As we have previously reported,^{13b} the Noyori reduction of acylfuran **II-21**, with formic acid/triethylamine as the hydride source, produced either enantiomer of furfuryl alcohol **II-22** in 96% yield with high enantiomeric excess (> 96% ee).¹³ An Achmatowicz rearrangement transformed the furfuryl alcohol to pyranone in 91% yield. The hemiacetal was then protected as *t*-butyl carbonate **II-23** at low temperature in 78% yield with 3:1 ratio of α - and β -diastereomers (Scheme 5).

Scheme 5. De Novo synthesis of α -Boc-pyranone

2.3.3. Synthesis of α -6-deoxy-*altro*-pyranoside

Our proposed synthesis of α -6-deoxy-*altro*-pyranoside started with the attempted

epoxidation of pyran **II-19**. Unfortunately, our efforts to epoxidize allylic alcohol **II-19** were not satisfactory. As a result, we decided to reverse the reduction/oxidation sequence. These efforts began with our Pd(0)-catalyzed glycosylation reaction to diastereoselectively install the anomeric benzyloxy group with complete α -selectivity (Scheme 6). Similarly, treating pyranone **II-20** with hydrogen peroxide in the presence of catalytic amount of base (10 mol % NaOH/H₂O₂) diastereoselectively installed the epoxide **II-24** in 88% yield.^{4b} In an equally diastereoselective fashion, the ketone **II-24** was reduced with NaBH₄ (-78 to -20 °C) to form the equatorial alcohol **II-18** in 85% yield.

Scheme 6. Synthesis of α -6-deoxy-*altro*-pyranoside

With the alcohol **II-18** in hand, we turned our attention to the epoxide ring opening with acetic acid. After investigating the use of a variety of Lewis acids, we found Sc(OTf)₃ gave the best results. In practice, treatment of epoxide **II-18** with Sc(OTf)₃ in HOAc afforded an inseparable mixture of acetates which presumably resulted from acid catalyzed ester migration of the initial epoxide ring opening product. This mixture was directly hydrolyzed with LiOH in aqueous THF producing α -6-deoxy-altrose **II-25** in 69% yield. The stereochemistry of the ring opening was confirmed by analysis of the

corresponding proton/proton coupling constants at *C*-2, *C*-3 and *C*-4 positions of **II-25**.

2.3.4. Synthesis of α -ascarylo-pyranoside

As we previously reported,^{4b} epoxide **II-18** was converted into the α -ascarylose sugar **II-26** in 85% yield using LiAlH_4 (Scheme 7). This same regioselective Lewis acid promoted ring opening reaction can also be used for 3-deoxy-sugars, which provides a less basic alternative to our previously reported LiAlH_4 method.^{4b} Simply switching the Lewis acid to $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ promoted a regioselective opening to form bromide **II-27**. The axial bromide in **II-27** was cleanly removed to give **II-26** in 76% yield, using an AIBN promoted tris(trimethylsilyl)silane (TTMSS) radical reduction.

Scheme 7. Synthesis of α -ascarylo-pyranoside

2.4. Conclusions

In summary, a highly enantio- and diastereoselective procedure for the preparation of *C*-3 and *C*-6 deoxypyranosides has been developed. Our approach to these sugars provides rapid and practical access to these rare and naturally occurring sugars, which should be of use for further natural product synthesis. Critical to the success of this synthesis was the use of the $\text{Pd}(0)$ -catalyzed glycosylation and corresponding post-glycosylation transformations. It is also worth noting that our method is structurally

divergent in that it produces four different sugar congeners from the same advanced intermediate. We believe that this approach will be particularly useful for medicinal chemistry. Finally, by selecting either enantiomeric form of the Noyori catalyst (*R, R*) or (*S, S*), our strategy is also amenable to the synthesis of both D- or L-forms of these sugars.

Reference:

¹ (a) Johnson, D. A.; Liu, H.-w. *Comprehensive Natural Products Chemistry*; Elsevier: Amsterdam, New York, 1999; Vol. 3, pp 311-365. (b) Thibodeaux, C.; Melancuon, C. E., III; Liu, H.-w. *Nature* **2007**, *446*, 1008-1016. (c) Kren, V.; Martinkova, L. *Curr. Med. Chem.* **2001**, *8*, 1303-1328.

² Gorshkova, R. P.; Kalmykova, E. N.; Isakov, V. V.; Ovodov, Y. S. *Eur. J. Biochem.* **1985**, *150*, 527-531.

³ (a) Doull, J. L.; Singh, A. K.; Hoare, M.; Ayer, S. W. *J. Ind. Microbiol.* **1994**, *13*, 120-125. (b) Jakeman, D. L.; Borissow, C. N.; Graham, C. L.; Timmons, S. C.; Reid, T. R.; Syvitski, R. T. *Chem. Commun.* **2006**, 3738-3740.

⁴ (a) Jeong, P.-Y.; Jung, M.; Yim, Y.-H.; Kim, H.; Kim, K.; Paik, Y.-K. *Nature* **2005**, *433*, 541-545. (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921-3924. (c) Baiga, T. J.; Guo, H.; Xing, Y. O'Doherty, G. A.; Parrish, A.; Dillin, A.; Austin, M. B.; Noel, J. P.; La Clair, J. J. *ACS Chem. Biol.* **2008**, *3*, 294-304.

⁵ For a recent approach to 2,6-dideoxy-sugars, see: (a) Hou, D.; Lowary, T. L. *J. Org. Chem.* **2009**, *74*, 2278–2289. For approaches to 3,6-dideoxy-sugars, see: (b) Weigel, T. M.; Liu, H.-w. *Tetrahedron Lett.* **1988**, *29*, 4221-4224 and ref. 4b.

⁶ (a) Zamoiski, A., Banaszek, A.; Gryniewicz, G. *Advances in Carbohydrate Chemistry and Biochemistry* **1982**, *40*, 1. (b) Ernst, B.; Hart, G. W.; Sinay, P., Eds.; *Carbohydrates in Chemistry and Biology*; Wiley-VCH: New York, 2000. (c) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A.; Sharpless, K. B. *Science* **1983**, *220*, 949-951. (d) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752-1755.

⁷ (a) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982-2983. (b) Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17-36. For its use in oligosaccharide synthesis see: (c) Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428-3429. (d) Ahmed, Md. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2005**, *46*, 3015-3019. (e) Ahmed, Md. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745-748. (f) Guo, H.; O'Doherty, G. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 5206-5208. (g) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 2283-2286.

⁸ Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849-1851.

⁹ (a) Babu, R. S.; Guppi, S. R.; O'Doherty, G. A. *Org. Lett.*, **2006**, *8*, 1605–1608. (b) Shan, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 5149-5152. (c) Guppi, S. R.; O'Doherty, G. A. *J. Org. Chem.*, **2007**, *72*, 4966–4969.

¹⁰ (a) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 3899-3992. (b) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771-1774. (c) Ahmed, Md. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2005**, *46*, 4151-4155.

¹¹ (a) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339-4342. (b) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485-2493.

¹² Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 4033-4036.

¹³ (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521-2522. (b) Li, M.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 6407-6411.

Chapter 3

Structure Investigations of *ent*-Cladospolide D by De Novo Synthesis and Kinetic and Thermodynamic Isomerization[†]

3.1. Introduction

In an interesting synergistic relationship between parasite and host, the *Cladosporium* species produce secondary metabolites that can regulate the host plant's growth.¹ This growth regulation is believed to occur via the inhibition of gibberellin biosynthesis.^{1c} Structurally these fugal products/plant pheromones are made up of a group of diastereoisomeric 12-membered macrolactone diols, which differ in stereochemistry at the C-4/C-5 diol and C-2/C-3 double bond stereochemistry (Figure 3).¹ These stereochemical differences affect the biological activity. For instance, cladospolides A-C inhibit the shoot elongation in rice seedlings,^{1c} whereas, cladospolides A and B have the opposite effect on the root growth of lettuce seedlings.^{1b}

[†] Reproduced with permission from *Synthesis*. **2009**, 17, 2847-2854. Copyright 2009, with permission from Thieme Stuttgart. Reproduced with permission from *Org. Lett.* . **2009**, 11, 1107-1110. Copyright 2009, with permission from American Chemical Society.

Figure 3: The cladospolide A-D

Because these three natural products, cladospolides A-C,^{2,3,4} are produced by the same and related organisms, it was initially suggested that they should share the C-11 carbinol stereochemistry, which biosynthetically would be formed earliest in the fatty acid biosynthetic pathway. The relative stereochemistry for the cladospolides A-C have been confirmed by several total syntheses, although it should be noted that questions remain around cladospolide B, where the different signs of rotation were found for the same absolute stereoisomer for synthetic cladospolide B by Banwell and us.^{2,3,4}

Figure 4 : (*E/Z*)-cladospolide D

In contrast to the plant pheromone activity of cladospolide A-C, cladospolide D possesses antimicrobial activity with IC₅₀ values of 0.1 and 29 g/mL against *M. racemosus* and *P. oryzae*, respectively.^{1d} Until our work, the absolute and relative stereochemistry of cladospolide D had not been correctly determined.⁵ At issue was

the stereochemical assignment of the C2/C3 double bond, which was solely based on a 13.5 Hz vicinal coupling constant for the purported *trans*-enoate carbon/carbon double bond.^{1d}

Using asymmetric synthesis of all the possible diastereomers and the comparison of optical rotation data, we assigned the absolute and relative stereochemistry for cladospolide D (Figure 4).^{3c} This work resulted in a correction of the initially assigned C-2/C-3 double bond stereochemistry, which the first synthesis of cladospolide D, by Hou, initially confirmed the structure as *E*-isomer **III-6**.⁵ Unfortunately, this synthetic study missed a facile *E/Z*-double bond isomerization and thus they actually prepared the enantiomer of the *Z*-isomer, (*ent*)-cladospolide D **III-4**. Herein, I describe the full account of our synthetic studies toward the successful synthesis of cladospolide B/C and the (*ent*)-cladospolide D, which includes our study of the *E/Z*-double bond isomerization of cladospolides and their diastereomers.

3.2. Previous Approaches to Cladospolides

In Hou's synthesis of cladospolide D, they started from chiral starting material diol **III-7** which was converted to allylic alcohol **III-8** after four steps (Scheme 1). The cross-metathesis between the allylic alcohol **III-8** and both enantiomerically pure (*R*)- and (*S*)-2-(6-heptenyl) acetates (**III-9a** and **III-9b**, respectively) provided **III-10a** and **III-10b**. The allylic alcohol of **III-10** was protected as its TBDPS ether followed by Michael addition to give **III-11a** and **III-11b** respectively. Acid **III-12** was achieved by five steps transformations from **III-11**.

Scheme 1. Total synthesis of cladospolide D by Hou

With **III-12** in hand, they next preceded the Yamaguchi lactonization to generate lactone **III-13** (Scheme 2). After deprotection of MEM group and oxidation with DMP, **III-15** was prepared in good yield. Diastereomers **III-16a** and **III-16b** were established after removing the *tert*-butyldiphenyl silyl (TBDPS) groups by tetrabutylammonium fluoride (TBAF) or hydrogen fluoride/pyridine. They noticed that the diastereomer **III-16b** was only generated by HF-Py (46%).

After comparing the spectra data with the isolation paper, Hou claimed that the structure **III-16b** was the natural product cladospolide D. However, in their last deprotection of TBDPS step using HF-Py, they missed a facile double bond isomerization. Therefore, they actually prepared the natural product cladospolide D, but they mis-assigned the structure as *E* isomer **III-16b**.

Scheme 2. Lactonization to form cladospolide D by Hou

3.3. De Novo Approach to Natural Products Cladospolides

Our de novo synthesis linked the use of Noyori asymmetric hydrogenation of propargyl ketone, alkyne zipper reaction and Sharpless dihydroxylation together to construct natural products cladospolides B, C and (*ent*)-cladospolide D as well as all the possible isomers of cladospolide D.

3.3.1. Retrosynthetic Analysis

At the outset of this project, we had reservations regarding the assignment of double bond stereochemistry for purported cladospolide D (**III-5**). Thus our retrosynthetic analysis envisioned that *Z*-cladospolide D (**III-4**) could be prepared from cladospolide B (**III-2**) or its *bis*-epimer **III-17**. Similarly, *E*-cladospolide D (**III-6**) could be

prepared from cladospolide C (**III-3**) or its bis-epimer **III-18**. In turn, cladospolides B, C (**III-2**, **III-3**) and their *bis*-epimers **III-17** and **III-18** could come from the lactonization reactions of diols **III-19** and **III-20**. Diols **III-19** and **III-20** could come from the diastereoselective and regioselective dihydroxylation⁶ and diene conjugation of ynone **III-21**,⁷ which could be prepared from commercially available 1-nonyne **III-22** employing the Noyori asymmetric reduction/alkyne zipper isomerization (Scheme 3).

Scheme 3. Retrosynthetic analysis

3.3.2. Synthesis of diols

Lithiation of commercially available 1-nonyne **III-22** and alkylation with acetaldehyde gave racemic propargylic alcohol (*rac*)-**III-23** (69%, two steps) (Scheme 4). Propargylic oxidation of (*rac*)-**III-23** with MnO_2 gave the ynone **III-21**.

Exposure of ynone **III-21** to our modified Noyori conditions provided an excellent yield (85%) of propargyl alcohol **III-23** with high enantiomeric purity (> 96% ee). Exposure of **III-23** to the KAPA reagent readily isomerized it to the terminal undecynol, which was protected as a TBS-ether (TBSCl/imid. in DMF) in good overall yield (82%) and with no loss of enantiomeric purity (> 96% ee).⁸

Scheme 4. Synthesis of diol

The mechanism of alkyne zipper reaction is shown in Scheme 5.⁹ KAPA reagent which refers to potassium 3-aminopropylamide is a readily prepared difunctional superbase. KAPA is prepared by quantitative reaction of KH with excess 3-aminopropylamine. In this KAPA catalyzed alkyne zipper reaction, the triple bond from the middle of the carbon chain migrates to the end of the carbon chain because of the formation of stable acetylide ion.

Scheme 5. Mechanism of alkyne zipper reaction

The terminal alkyne **III-24** was carboxylated (*n*-BuLi/ ClCO_2Et , 83%) to give an ynoate, which by means of the Rychnovsky variant of the Trost ynoate to dienoate isomerization ($\text{Ph}_3\text{P}/\text{PhOH}$) was cleanly converted into *E,E*-dienoate **III-25** in good yields (90%) and stereoselectivity.⁷ Dienoate **III-25** was subjected to Sharpless asymmetric dihydroxylation conditions (2% OsO_4 and 4% $(\text{DHQD})_2\text{PHAL}$) to give diol **III-19** in approximately 80% yield and as a single diastereomer.⁶ Similarly, diennoate **III-25** was dihydroxylated with the pseudo-enantiomeric reagent (2% OsO_4 and 4% $(\text{DHQ})_2\text{PHAL}$) to give diol **III-20** in approximately 80% yield and as a single diastereomer. The mechanism of Rychnovsky variant of the Trost ynoate to dienoate isomerization is outlined in scheme 6.

Scheme 6. Mechanism of ynoate to dienoate isomerization

3.3.3. Synthesis of cladospolide B, C and isomers

With all the sp^3 stereocenters established for the cladospolides, we turned to the assembly of the macrocycle (Scheme 7). To our delight this occurred with a small amount of double bond isomerization. Thus exposing diol **III-19** to acid catalyzed acetonide formation/TBS deprotection conditions gave the desired seco-acid, which when exposed to the Yamaguchi lactonization conditions¹⁰ gave a 6:1 mixture of cladospolide C (**III-3**) (36%) and its double bond isomer **III-17** (6%), after TFA promoted acetonide deprotection. Following a virtually identical macrocyclization protocol, diol **III-20** was converted into a similar mixture of cladospolide B (**III-2**) (6%) and its double bond isomer **III-18** (34%).

Scheme 7. Synthesis of cladospolide B, C and isomers

3.3.4. Synthesis of cladospolide D and diastereomers

With the construction of the required four stereoisomeric macrolactone diols, we turned our attention to the synthesis and structural proof of cladospolide D. This began with the investigation of the selective oxidation of the allylic alcohol in cladospolide C (**III-3**) (Scheme 8). Unfortunately, several oxidants (e.g., MnO_2 and Dess-Martin Periodinane) led to oxidative diol cleavage giving a dialdehyde product. In our grahamimycin A synthesis, we had previously found that the enone functionality could be installed by a stoichiometric TEMPO oxidation of the allylic alcohol in colletodiol, without the need for selective protection.^{6c} Unfortunately, when we applied these same conditions to the cladospolides, only products of double oxidation were obtained. Thus, when we exposed cladospolide C (**III-3**) and its C-4,5-bis-epimer **III-18** to the catalytic TEMPO oxidation conditions (1 mol% 2,2,6,6-tetramethylpiperidinoxy/1 equiv trichloroisocyanuric acid),¹¹ only diketone **III-26** was observed. When only one equiv

of co-oxidant was used (1 mol% 2,2,6,6-tetramethylpiperidinoxy/0.33 equiv trichloroisocyanuric acid), only low yields of **III-26** and starting material were observed. Similarly, cladospolide B (**III-2**) and its *C*-4,5-*bis*-epimer **III-17** reacted under the TEMPO oxidation conditions to give diketone **III-27**. Thus, we turned to a selective protection/oxidation/deprotection sequence.

Scheme 8. Diol per-oxidation

Because the absolute stereochemistry of cladospolide D was not known and we had our doubts about the assigned olefin geometry, we decided to perform the protection/oxidation/deprotection sequence on both cladospolide B (**III-2**) and C (**III-3**) as well as their 4,5-*bis*-epimers **III-17** and **III-18**. Because of the exploratory nature of these studies, no effort was made to maximize the regioselectivity in the protection-step. Rather a regio-unselective TBS-protection was chosen for simplicity's sake (*i.e.*, no bis-protection was observed and the minor regioisomer could be recycled). This in turn helped with the assignment of the regioisomers.

Scheme 9. Synthesis of cladospolide D and diastereomers

Thus exposure of cladospolide C (**III-3**) to the three-step TBS mono-protection/Dess-Martin oxidation/HF deprotection gave a 27% yield of enone **III-28** (Scheme 9). Cladospolide B (**III-2**) and its 4,5-*bis*-epimer **III-17** gave the corresponding enones **III-31** and **III-30**, respectively, with similar yields for this three-step sequence. The low yield for these sequences was due to the poor regioselectivity (1:2 against) in the TBS-protection step. In contrast, when the 4,5-*bis*-epimer **III-18** was exposed to the same three-step sequence a higher yield of enone **III-29** was obtained due to improved regioselectivity in the TBS-protection (2:1). Of the enones produced only **III-31** had spectral data that matched cladospolide D,^{1d} although the rotation was opposite in sign. The spectral data also matched the data

reported by Hou for (*ent*)-cladospolide D, who reported its structure to be the *E*-isomer **III-29**. Therefore, we concluded that a hidden alkene isomerization reaction must have occurred during the Hou synthesis.

3.3.5. Photo Isomerization of Double Bond

Thus, we decided to investigate the isomerization of the olefin **III-29**. When enone **III-29** was irradiated with UV-light (300 nm) with and without iodine, a 1:1 ratio of **III-29** and (*ent*)-cladospolide D (**III-31**) was found along with a significant amount of photo-degradation products. While this isomerization explained the problem with Hou's assignment of cladospolide D, the photochemical isomerization reaction was not clean enough to be consistent with his reported yield. Similarly byproducts were also observed, when we explored the photoisomerization of **III-28** and **III-30**. However, much cleaner isomerization reactions were observed for the TBS-protected enones, **III-32**, **III-33**, **III-34** and **III-35** (Scheme 10).

Thus when we irradiated D₆-benzene solutions of pure **III-32** and **III-33** for 24 h with 300 nm light through a Pyrex filter, a photo-equilibrium (1:1.3, *E/Z*) was established with the *Z*-isomer **III-33** being slightly favored. When we irradiated D₆-benzene solutions of **III-34** and **III-35** under identical conditions a photo-equilibrium (1:2, *E/Z*) was established, which slightly favored the *Z*-isomer **III-35** (Scheme 10).

Scheme 10. Photo equilibration

Because the photo-isomerization give photo-equilibriums and not true K_{eq} , we decided to isomerize the enones under iodine radical conditions. Thus we exposed pure D_6 -benzene solutions of **III-32** and **III-33** to a catalytic amount of I_2 under thermal and photochemical conditions (Scheme 11). Under these conditions, both solutions rapidly (< 1 h) reached equilibrium ($K_{\text{eq}} = 1:4$, E/Z) with the Z -isomer being more stable. When we turned to the E/Z -isomers of the natural cladospolide D diastereomer, we found a much greater difference in stability. When the same isomerization was preformed with pure solutions of **III-34** and **III-35** the equilibrium was reached much more quickly and the equilibrium achieved was in even greater preference for the Z -isomer **III-35** ($K_{\text{eq}} > 20$, Z/E). Thus, we can conclude that the driving force and barrier to isomerization of the cladospolide D diastereomer **III-35** is quite strong.

Scheme 11. Photochemical equilibrium

For comparison, we decided to study the double bond isomerization between cladospolide C (**III-3**) and its 4,5-bis-epimer **III-18** using the same equilibration condition (Scheme 12). This study showed that no strong thermodynamic preference for the *Z*-isomers could be found. For example, when cladospolide C (**III-3**) and its double bond isomer **III-17** were isomerized under radical iodine conditions (24 h irradiation with I_2), we found equal isomers of **III-3** and **III-17** ($K_{\text{eq}} = 1$). In contrast, we were not able to reach to full equilibrium for the isomerization of 4,5-bis-*epi*-cladospolide C (**III-18**) to cladospolide B (**III-2**), but we could bracket the equilibrium constant to be between 0.3 and 6 (Scheme 12). Thus, we can conclude that the C-4 carbonyl in cladospolide D has a strong effect on the *E/Z*-stability.

Scheme 12. Photochemical equilibrium

3.3.6. Improved approaches to cladospolide D

With the knowledge of the structure of the desired target molecule, we next sought an improved synthesis (Scheme 13). These efforts lead to the discovery of the double bond isomerization found in the Hou's synthesis. Thus we returned to the *trans*-diol **III-18**, which could be regioselectively protected to give **III-36** in good yield. Dess-Martin oxidation of **III-36** cleanly gave enone **III-34**. At this stage a photo-chemical isomerization of **III-34** cleanly gave the previous prepared *cis*-isomer **III-35** in near quantitative yield (> 95%). Interestingly, when **III-34** was treated with the conditions used by Hou (HF/Py), instead of our preferred conditions (5 % HF/CH₃CN), a clean double bond isomerization occurred to give **III-35**. As before, TBS-deprotection with 5 % HF/CH₃CN occurred to give γ -keto-enoate **III-31**. Synthetic **III-31** material was spectroscopically (¹H NMR, ¹³C NMR, IR and MS) identical with natural cladospolide D, although the optical rotation was opposite in sign ($[\alpha]_D$ -58 vs + 56 in MeOH). Thus structure **III-31** must be the enantiomer of

cladospolide D and the structure should be revised to structure **III-4** as shown in Figure 1.

Scheme 13. Improved approaches to cladospolide D

3.4. Conclusions

In conclusion, a short and enantioselective synthesis of (*ent*)-cladospolide D has been developed, which clears up any ambiguities with its structural assignment. This structural proof involved the synthesis of all the possible stereoisomers of cladospolide D as well as to other members of this family of natural products, cladospolides B and C. This de novo asymmetric approach used two remote catalytic asymmetric reactions (Noyori reduction and Sharpless asymmetric dihydroxylation) to establish its asymmetry, therefore, this synthesis is also a formal synthesis of the natural stereoisomer of cladospolide D. This de novo route to the cladospolides compares favorably (i.e., less steps and greater overall efficiency) to the previous

routes from chiral starting materials. In addition, this route enabled the study of the C-2/3 alkene isomerization that was of central importance to the structural proof of cladospolide D.

Reference:

¹ (a) Hirota, A.; Isogai, A.; Sakai, H. *Agric. Biol. Chem.* **1981**, *45*, 799. (b) Hirota, A.; Sakai, H.; Isogai, A. *Agric. Biol. Chem.* **1985**, *49*, 731. (c) Fujii, Y.; Fukuda, A.; Hamasaki, T.; Ichimoto I.; Nakajima, H. *Phytochemistry*. **1995**, *40*, 1443. (d) Zhang, H.; Tomoda, H.; Tabata, N.; Miura, H.; Namikoshi, M.; Yamaguchi, Y.; Masuma R.; Omura, S, *J. Antibiot.* **2001**, *54*, 635. (e) Hirota, A.; Sakai, H.; Isogai, A.; Kitano, Y.; Ashida, T.; Hirota H.; Takahashi, T. *Agric. Biol. Chem.* **1985**, *49*, 903. (f) Hirota, H.; Hirota, A.; Sakai, H.; Isogai, A.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2147. (g) Smith, C. J.; Abbanat, D.; Bernan, V. S.; Maiese, W. M.; Greenstein, M.; Jompa, J.; Tahir A.; Ireland, C. M. *J. Nat. Prod.* **2000**, *63*, 142.

² For the synthesis of cladospolide A, see: (a) Banwell, M. G.; Loong, D. T. J. *Org. Biomol. Chem.* **2004**, *2*, 2050. (b) Banwell, M. G.; Jolliffe, K. A.; Loong, D. T. J.; McRae, K. J.; Vounatsos, F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 22. (c) Solladie, G.; Almario, A. *Tetrahedron: Asymmetry* **1995**, *6*, 559. (d) Solladie, G.; Almario, A. *Pure Appl. Chem.* **1994**, *66*, 2159. (e) Ichimoto, I.; Sato, M.; Kirihaata, M.; Ueda, H. *Chem.*

Express. **1987**, 2, 495. (f) Maemoto, S.; Mori, K. *Chem. Lett.* **1987**, 109. (g) Mori, K.; Maemoto, S. *Liebigs Ann. Chem.* **1987**, 863.

³ For the synthesis of cladospolide B, see: (a) Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2005**, 46, 6625. (b) Austin, K. A. B.; Banwell, M. G.; Loong, D. T. J.; Rae, A. D.; Willis, A. C. *Org. Biomol. Chem.* **2005**, 3, 1081. (c) Xing, Y.; O'Doherty, G. A. *Org. Lett.* **2009**, 11, 1107-1110.

⁴ For the synthesis of cladospolide C, see: ref. 3c and (a) Banwell, M. G.; Loong, D. T. J.; Willis, A. C. *Aust. J. Chem.* **2005**, 58, 511. (b) Chou, C.-Y. Hou, D.-R. *J. Org. Chem.* **2006**, 71, 9887. (c) Sharma, G. V. M.; Reddy, K. L.; Reddy, J. J. *Tetrahedron Lett.* **2006**, 47, 6537. (d) Reddy, C. R.; Rao, N. N. *Tetrahedron Lett.* **2009**, 50, 2478-2480.

⁵ For the synthesis of cladospolide D, see: ref. 3c and Lu, K.-J.; Chen, C.-H.; Hou, D.-R. *Tetrahedron* **2009**, 65, 225.

⁶ The regioselectivity of the asymmetric dihydroxylation of dienates has been studied by Sharpless and our group, see: (a) Berker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, 51, 1345. (b) Zhang, Y.; O'Doherty, G. A. *Tetrahedron* **2005**, 61, 6337-6351. For synthetic application of this, see: (c) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, 4, 4447-4450. (d) Guo, H.; Mortensen, M. S.; O'Doherty, G. A. *Org. Lett.* **2008**, 10, 3149-3152. (e) Ahmed, Md., M. Mortensen, M. S.; O'Doherty, G. A. *J. Org. Chem.* **2006**, 71, 7741-7746. (f) Ahmed, Md. M.; O'Doherty, G. A. *Tetrahedron*

Lett. **2005**, *46*, 3015-3019. (g) Ahmed, Md. M.; Berry, B. P. ; Hunter, T. J. ; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745-748.

⁷ (a) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659-2660. (b) Trost, B.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933-7935. For synthetic application of this, see: (c) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 3987-3990.

⁸ Trost, B. M.; Horne, D. B.; Woltering M. *J. Chem. Eur. J.* **2006**, *12*, 6607.

⁹ Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891-892

¹⁰ Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.

¹¹ (a) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041-3043. (b) Md. M. Ahmed, H. Cui and G. A. O'Doherty, *J. Org. Chem.* **2006**, *71*, 6686-6689.

Chapter 4

De Novo Asymmetric Total Synthesis of Aspergillides

4.1. Introduction

In 2007, Kusumi and coworkers had isolated three new 14-membered macrolides, aspergillides A (**IV-1**), B (**IV-2**), and C (**IV-3**) from marine-derived fungus *Aspergillus ostianus* strain 01F313 (Figure 5).¹ The aspergillides contain interesting tri-substituted tetrahydro and dihydropyran rings. These compounds were found to exhibit significant cytotoxicity against mouse lymphocytic leukemia cells (L1210) with LD₅₀ values of 2.1, 71.0, and 2.0 µg/ml for aspergillide A (**IV-1**), B (**IV-2**), and C (**IV-3**), respectively. The structures and absolute configurations of aspergillides were determined by analyses of NMR spectra and modified Mosher's method.

Figure 5. Aspergillides

Based on the unique molecular architectures and important biological features of these natural products, they have attracted interest from synthetic community. To date, five total syntheses of **IV-1**,² seven of **IV-2**,^{3,2e} and two of **IV-3**⁴ have been reported.

provided resulting diol, the secondary alcohol was protected as a TES ether to generate alcohol **IV-10**. Cross-metathesis of **IV-10** with the phosphonoacetate **IV-6** in the presence of the second-generation Grubbs catalyst provided the coupled product as the *E* alkene **IV-11** (>20:1) in 98% yield. Oxidation of **IV-11** with Dess–Martin periodinane and a subsequent intramolecular Horner–Wadsworth–Emmons reaction gave the macrolactone. Selective removal of the TES ether provided intermediate **IV-4**.

Scheme 2. Total synthesis of aspergillide A and B by Shishido

With the precursor **IV-4** in hand, Shishido next investigated the transannular oxy-Michael reaction (Scheme 3). They found that the best result was for the treatment of **IV-4** with DBU and LiCl in acetonitrile at room temperature for 1.5 hours which provided a quantitative amount of the syn-adduct **IV-12** as a single product (entry 1). The best condition for quantitative formation of **IV-13** was achieved by using KH and

[18]crown-6 at 0 °C for 0.5 hours. Removal of the TBS group of **IV-12** and **IV-13** generated aspergillide A (**IV-1**) and aspergillide B (**IV-2**), respectively.

Scheme 3. Transannular oxy-Michael reaction

In 2007, Kuwahara reported the first total synthesis of aspergillide C.^{4a} They envisioned that aspergillide C (**IV-3**) could be established from a macrolactonization of seco acid **IV-14**, which can be synthesized from compound **IV-15**. To construct **IV-15**, they took advantage of a Ferrier-type reaction of acetal **IV-16**, which could be formed by Julia olefination of aldehyde **IV-18** and sulfone **IV-17**. The aldehyde **IV-18** could be prepared via epoxide opening of commercially available epoxide **IV-19** and alkyne **IV-20** (Scheme 4).

Scheme 4. Retrosynthetic analysis of Kuwahara's synthesis

E-isomer **IV-16** was established within 10 steps from starting materials and then converted to desired *trans*-substituted ester **IV-21** by Ferrier-type reaction using silyl ketene acetal (Scheme 5). Treating **IV-21** with aqueous NaOH solution followed by KI₃/NaHCO₃ provided iodolactone which was exposed to DBU in THF to give **IV-22**. With lactone intermediate **IV-22** in hand, they proceeded the final construction of aspergillide C. After a hydrolysis, protection/deprotection and macrolactonization sequence, aspergillide C (**IV-3**) was finally established.

Scheme 5. Total synthesis of aspergillide C by Kuwahara

4.3. Retrosynthetic Analysis of Aspergillides

Our strategy proposed to link the Noyori reductions of furyl ketone and alkynyl ketone, the alkyne zipper reaction and palladium-catalyzed glycosylation together to construct aspergillides. The challenge of our route is using a novel palladium-catalyzed addition of a vinyl group to install the key *trans*-pyran ring system.

Scheme 6. Retrosynthetic analysis

Retrosynthetically, we envisioned that aspergillide C (**IV-3**) could be prepared from the macrolactonization of compound **IV-24**, which could be synthesized from Julie-Kocienski olefination of sulfone precursor **IV-25**.⁵ The key transformation Pd-catalyzed C-glycosylation should allow the coupling of pyranone **IV-26** and sulfone **IV-27**. Pyranone **IV-26** could be established from acetyl-furan by three steps. The other coupling partner sulfone **IV-27** could be prepared from pivalate protected alkynol **IV-29** by Au-catalyzed alkyne hydration⁶ and the following transformations. Alkynol **IV-29** could be derived by Noyori reduction and alkyne zipper reaction from non-chiral starting material pentyne **IV-31** (Scheme 6).

4.4. De Novo Approach to Aspergillides

Scheme 7. Synthesis of Boc-pyranone

Taking advantage of our classic three-step Noyori reduction/Achmatowicz reaction/Boc-protection sequence,⁷ we successfully installed α -Boc pyranone in 48% yield (3 steps) from furan **IV-28**, which was derived from acetyl furan **IV-30** by alkylation with dimethyl carbonate (Scheme 7).⁸

Scheme 8. Synthesis of sulfone precursor

With the pyranone building block **IV-33** in hand, we next proceeded to establish the other coupling partner sulfone intermediate **IV-27** (Scheme 8). Treating commercially

available non-chiral starting material 1-pentyne with *n*-BuLi followed by quenching with acetyl aldehyde generated racemic propargyl alcohol. The corresponding propargyl alcohol was oxidized with manganese dioxide to provide propargyl ketone **IV-35**. Exposure of the propargyl ketone **IV-36** with Noyori (*S,S*) catalyst generated enantioenriched propargyl alcohol **IV-36**. The propargyl alcohol **IV-36** was treated with KAPA reagent to give the terminal alkyne, the secondary alcohol was protected as its pivalate ether **IV-29**. With the alkynol **IV-29** in hand, we next converted the triple bond functional group to a α -bromo-ketone. Au-catalyzed alkyne hydration⁶ of pivalate ether **IV-29** provided ketone **IV-37** in 85% yield. Treatment of ketone **IV-37** with bromine in methanol generated less hindered α -bromo-ketone **IV-38** as the major product (70% yield).⁹ Alternatively, one pot reaction of Au-catalyzed hydration and bromination with NBS gave α -bromo-ketone **IV-38** in 85% yield. The α -bromo-ketone **IV-38** was converted to a sulfide by S_N2 substitution, the resulting sulfide was oxidized by Mo catalyst to provide sulfone intermediate **IV-27**.

Scheme 10. Double addition

In practice, when we treated α -Boc-pyranone **IV-33** and sulfone **IV-27** with $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and PPh_3 , it actually gave us the Michael addition product **IV-42** (Scheme 10). We thought maybe Boc protecting group provided too much basic condition in the glycosylation reaction, therefore the double addition occurred. Thus, we made α -Piv-pyranone **IV-43** to undergo the glycosylation reaction. However, similar result was observed from the coupling of α -Piv-pyranone **IV-43** and sulfone **IV-27**, we still received the double addition product **IV-42**. The mechanism of this double addition is shown in scheme 11. After the coupling of pyranone **IV-26** and sulfone **IV-27**, a further 1, 4 addition took place to generate the double addition product **IV-42**.

Scheme 12. Attempt to correct double addition product

Consequently, we decided to avoid the double addition by diastereoselectively reducing the α , β unsaturated ketone **IV-33** to an equatorial allylic alcohol **IV-48** using NaBH_4 . When we utilized our Pd-catalyzed glycosylation reaction followed by one-pot reduction with NaBH_4 without isolation of the coupling product, we accessed the mixture of trans/cis double bond isomers of **IV-41** and **IV-49**. After careful chromatography separation, *E*-olefine **IV-41** was collected in 26% yield (Scheme 13).

Scheme 13. Glycosylation of equatorial allylic alcohol with sulfone

We were delighted that the *E*-olefine **IV-41** had been established by our glycosylation reaction, but both the yield and selectivity needed to be improved. Thus, we tried many different substitutes for the glycosylation reactions. Firstly, we protected the allylic alcohol **IV-48** as a TBS ether **IV-50**, however, the Pd-catalyzed glycosylation of the TBS ether **IV-50** and the sulfone **IV-27** failed (Scheme 14), and we could only isolate the unknown side products.

Scheme 14. Glycosylation of TBS ether of the equatorial allylic alcohol with sulfone

Scheme 15. Glycosylation of axial allylic alcohol with sulfone

Scheme 16. Glycosylation of TBS ether of the axial allylic alcohol with sulfone

Secondly, because the stereochemistry of the allylic alcohol **IV-48** was opposite with the natural product aspergillides, we reversed the stereochemistry by Mitsunobu reaction to generate axial allylic alcohol **IV-52** (Scheme 15). Unfortunately, no product can be isolated from the glycosylation reaction to couple **IV-52** and **IV-27**. Consequently, we tried the glycosylation reaction on the TBS protected allylic alcohol **IV-54**, however, no coupling reaction occurred (Scheme 16).

Scheme 17. Glycosylation of pivalate equatorial allylic alcohol with sulfone

Scheme 18. Glycosylation of pivalate axial allylic alcohol with sulfone

Finally, we prepared pivalate protected allylic alcohol **IV-56** and **IV-58**, when we treated these two diastereomers with Pd-catalyzed glycosylation condition, **IV-56** gave us the similar result as **IV-48**, however, we still could not **IV-58** with the sulfone under this condition, only starting materials were recovered.

4.5. Conclusions

In summary, a de novo asymmetric total synthesis of aspergilliges has been investigated. To date, intermediate **IV-41** which is five steps away from a formal synthesis^{4a} (compound **IV-23**) of aspergillide C (**IV-3**) has been prepared by Pd-catalyzed C-glycosylation and the following Julia olefination. Noyori reductions of furyl and propargyl ketone, alkyne zipper reaction and Au-catalyzed alkyne hydration have been utilized.

Reference:

¹ K. Kito, R. Ookura, S. Yoshida, M. Namikoshi, T. Ooi, T. Kusumi, *Org. Lett.* **2008**, *10*, 225-228.

² Syntheses of aspergillide A: a) T. Nagasawa, S. Kuwahara, *Tetrahedron Lett.* **2010**, *51*, 875-877; b) S. Diaz-Oltra, C. A. Angulo-Pachon, J. Murga, M. Carda, J. A. Marco, *J. Org. Chem.* **2010**, *75*, 1775-1778; c) H. Fuwa, H. Yamaguchi, M. Sasaki, *Org. Lett.* **2010**, *12*, 1848-1851; H. Fuwa, H. Yamaguchi, M. Sasaki, *Tetrahedron* **2010**, *66*, 7492-7503; d) G. Sabitha, D. V. Reddy, A. S. Rao, J. S. Yadav, *Tetrahedron Lett.* **2010**, *51*, 4195-4198; e) M. Kanematsu, M. Yoshida, K. Shishido, *Angew. Chem. Int. Ed.* **2011**, *50*, 1-4.

³ Syntheses of aspergillide B: a) S. M. Hande, J. Uenishi, *Tetrahedron Lett.* **2009**, *50*, 189-192; b) S. Diaz-Oltra, C. A. Angulo-Pachon, M. N. Kneeteman, J. Murga, M. Carda, J. A. Marco, *Tetrahedron Lett.* **2009**, *50*, 3783-3785; c) T. Nagasawa, S. Kuwahara, *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1893-1894; d) J. Liu, K. Xu, J. He, L. Zhang, X. Pan, X. She, *J. Org. Chem.* **2009**, *74*, 5063-5066; e) A. J. Mueller, M. P. Jennings, *Tetrahedron Lett.* **2010**, *51*, 4260-4262.

⁴ Syntheses of aspergillide C: a) T. Nagasawa, S. Kuwahara, *Org. Lett.* **2009**, *11*, 761-764; b) J. D. Panarese, S. P. Waters, *Org. Lett.* **2009**, *11*, 5086-5088.

⁵ M. Nielsen, C. B. Jacobsen, M.W. Paixao, N. Holub, K. Jorgensen, *J. Am. Chem. Soc.* **2009**, *131*, 10581-10586.

⁶ a) N. Marion, R. S. Ramon, S. P. Nolan, *J. Am. Chem. Soc.* **2009**, *131*, 448-449. b) Fremont, N. M. Scott, E. D. Stevens, S. P. Nolan, *Organometallics*, **2005**, *24*, 2411-2418.

-
- ⁷ a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521-2522. b) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40-73. c) Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005-1009. d) Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165-176. e) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863-866. f) Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 4033-4036.
- ⁸ *Organic Synthesis*, Coll. Vol. 5, p. 198(**1973**)
- ⁹ H. Ha, S. Lee, Y. Ha. J. Park, *Synthetic Communications*, **1994**, *24*, 2557-2562

Experimental Section

Section A: General Information

General Methods and materials: ^1H and ^{13}C spectra were recorded on 270 and 600 spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or CDCl_3 (δ 7.26 ppm) or CD_3OD (δ 4.89 ppm) for ^1H and CDCl_3 (δ 77.1 ppm) or CD_3OD (δ 49.15 ppm) for ^{13}C . Optical rotations were measured with a digital polarimeter in the solvent specified. Infrared (IR) spectra were obtained on a FT-IR spectrometer. Flash column chromatography was performed on ICN reagent 60 (60-200 mesh) silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates (K6F 60Å, F₂₅₄) and visualized by quenching of fluorescence and by charring after treatment with *p*-anisaldehyde or phosphomolybdic acid or potassium permanganate stain. R_f values were obtained by elution in the stated solvent ratios (v/v). Ether, THF, methylene chloride and triethylamine were dried by passing through activated alumina (8 x 14 mesh) column with nitrogen gas pressure. Commercial reagents were used without purification unless otherwise noted. Air and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven/flamed-dried glassware and standard syringe/septa techniques.

Section B: Experimental Procedures

(*S*)-1-(furan-2-yl)ethanol (**I-10**)¹

To a solution of acylfuran **I-7** (15 g, 136.4 mmol) in CH₂Cl₂ (20 mL) was added a prepared solution of formic acid/triethylamine (40 mL, 2:1 (mol/mol)) and Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6 -mesitylene)-(*S,S*)-TsDPEN (0.2 g, 0.25 mol%). The resulting solution was stirred at room temperature for 24 h. Then it was diluted with water (90 mL) and extracted with Et₂O (200 mL x 3). The combined organic layer was washed with saturated aqueous NaHCO₃ (50 mL) saturated brine (50 mL), dried over Na₂SO₄ and then concentrated under reduced pressure to give a residue. Flash chromatography on silica gel eluting with hexane/Et₂O (1:1, v/v) gave furfuryl alcohol **I-10** (14 g, 92%) as colorless oil: *R*_f 0.45 (7:3 (v/v) hexane/EtOAc); [α]_D²⁵ = −20.1 (c 1.0, CH₂Cl₂); ¹H NMR (600 MHz CDCl₃) δ 7.30 (d, *J* = 1.8, 1H), 6.26 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.15 (d, *J* = 3.0, 1H), 4.78 (dq, *J* = 6.6, 6.6 Hz, 1H), 3.11 (s, 1H), 1.46 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 157.7, 141.6, 109.9, 104.9, 63.3, 21.1.

¹ 1 (a) Shan, M., O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 5149-5152. (b) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921-3924. (c) Li, M.; Scott, J. G.; O'Doherty, G. A. *Tetrahedron Lett.* **2004**, *45*, 1005-1009.

(2*S*, 6*R*)-6-hydroxy-2-methyl-2*H*-pyran-3(6*H*)-one (I-13)¹

To a solution of furfuryl alcohol **I-10** (14 g, 125 mmol) in THF/H₂O (416 mL, 3:1 (v/v)) was added NaHCO₃ (21 g, 250 mmol), NaOAc·3H₂O (17 g, 125 mmol), and NBS (22.3 g, 125 mmol) at 0 °C. The reaction mixture was kept stirring at this temperature for 1 hour, then at 0 °C saturated aqueous NaHCO₃ (200 mL) was added to quench the reaction. The reaction mixture was directly extracted with Et₂O (300 mL × 3) and the combined organic layer was washed by saturated brine (100 mL), dried over Na₂SO₄ and then concentrated under reduced pressure to give a residue, which was rapidly subjected to flash chromatography on silica gel. Elution with hexane/EtOAc (1:1, v/v) afforded diastereomeric mixture of pyranone alcohol **I-13** (14.4 g, 90%, α:β=2.8:1): White solid; *R_f* 0.25 (7:3 (v/v) hexane/EtOAc); ¹H NMR (600 MHz, CDCl₃, α isomer) δ 6.82 (dd, *J* = 10.2, 3.0 Hz, 1H), 5.96 (d, *J* = 10.2, 1H), 5.48 (d, *J* = 3.0 Hz, 1H), 3.99 (q, *J* = 7.2 Hz, 1H), 1.23 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃, α isomer) δ 197.6, 145.3, 126.6, 87.2, 74.8, 15.1.

tert-Butyl (2*S*,6*S*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl carbonate (I-5)¹

To a solution of pyranone alcohol **I-13** (7.4 g, 57.8 mmol) in CH₂Cl₂ (80 mL) was added DMAP (528 mg, 4.33 mmol) at -78 °C. A pre-cooled solution of (Boc)₂O (25.2 g, 115.6 mmol) in CH₂Cl₂ (30 mL) was added dropwise to the reaction mixture via a cannula. The reaction mixture was stirred at -78 °C for 12 hours. The reaction was quenched by saturated aqueous NaHCO₃ (100 mL) and then extracted with Et₂O (300 mL × 3). The combined organic layers was washed by saturated brine (70 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give a residue. Flash chromatography on silica gel eluting with hexane/Et₂O (100:7, v/v) gave α-Boc-pyranone **I-5** (7.8 g, 60%). Elution with hexane/Et₂O (10:1, v/v) gave β-Boc-pyranone (2.5g, 19%). α-Boc-pyranone **15(α-L)**: *R*_f = 0.60 (7:3 (v/v) hexane/EtOAc); [*α*]_D²⁵ = +98 (*c* 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) *ν* 2986, 1752, 1703, 1633, 1278, 1258, 1159, 1090, 1058, 1029, 944. ¹H NMR (600 MHz, CDCl₃) δ 6.78 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.22 (d, *J* = 3.6 Hz, 1H), 6.09 (d, *J* = 10.2 Hz, 1H), 4.53 (q, *J* = 6.6 Hz, 1H), 1.40 (s, 9H), 1.28 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150.8 MHz, CDCl₃) δ 195.5, 151.7, 140.9, 128.2, 89.1, 83.3, 72.0, 27.5, 15.1; HRMS (CI): Calculated for [C₁₁H₁₆O₅+Na]⁺ 251.0890, Found 251.0883.

1-(*tert*-butyldimethylsilyloxy)-pen-4-yne (I-11a):²

² H. Guo; O'Doherty, G.A. *Org. Lett.* **2005**; 7(18); 3921-3924.

To a magnetically stirred solution of 4-pentynol **I-11** (5.0 g, 59.4 mmol) and imidazole (10.1 g, 148.6 mmol) in dry DMF (100 mL), was added dropwise *tert*-butyldimethylsilyl chloride (9.4 g, 62.4 mmol) in DMF (50 mL) over 10 min at 0 °C under an atmosphere of nitrogen. The reaction mixture was warmed to room temperature and stirred overnight. Water (300 mL) was added and then the reaction mixture was extracted with Et₂O (3 x 300 mL), dried (Na₂SO₄), and evaporated under reduced pressure to leave a light yellow oil. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/hexane to give TBS-ether **I-11a** (11.8 g, 147.1, 99%) as a colorless oil; *R_f* = 0.89 (30% EtOAc/hexane); IR (thin film, cm⁻¹) 3314, 2954, 2930, 2858, 1473, 1256, 1106, 835, 776; ¹H NMR (600 MHz, CDCl₃) δ 3.68 (t, *J* = 6.6 Hz, 2H), 2.26 (td, *J* = 7.2, 2.4 Hz, 2H), 1.90 (t, *J* = 2.4, 1H), 1.71 (tt, *J* = 7.2, 6.6 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 84.3, 68.3, 61.5, 31.6, 26.0, 18.4, 14.9, -5.3.

(+/-)-7-(*tert*-butyldimethylsilyloxy)-hept-3-yne-2-ol (I-11b**):²**

A solution of BuLi in hexane (24.71 mL, 59.3 mmol) was added dropwise to the magnetically stirred solution of TBS-ether **I-11a** (11.8 g, 59.3 mmol) in dry THF (59.3 mL) at -78 °C under the atmosphere of argon. After 30 min, acetaldehyde (1.54 g, 35.1 mmol) was added and stirred for 10 min at 0 °C and then the resulting solution was warmed to room temperature for 50 min. 100 mL of CH₂Cl₂ was added to the reaction

mixture followed by addition of 100 mL of pH = 7.0 phosphate buffer. The aqueous phase was separated and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 6% EtOAc/hexane to give propargyl alcohol **I-11b** (8.4 g, 34.6 mmol, 98%): light yellow oil; R_f = 0.42 (20% EtOAc/hexane); IR (thin film, cm⁻¹), 3364, 2953, 2930, 2858, 1740, 1472, 1254, 1103, 1071, 835, 775; ¹H NMR (600 MHz CDCl₃) δ 4.65 (qd, J = 6.6, 1.8 Hz, 1H), 3.64 (t, J = 6.0 Hz, 2H), 2.24 (td, J = 7.2, 1.8 Hz, 2H), 1.66 (tt, J = 7.2, 6.6 Hz, 2H), 1.38 (d, J = 6.6 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 84.0, 82.5, 61.6, 58.4, 31.7, 25.9, 24.7, 18.3, 15.1, -5.0; CIHRMS: Calculated for [C₁₃H₂₆O₂SiNa⁺]: 265.1594, found: 265.1630.

7-(*tert*-butyldimethylsilyloxy)-hept-3-yne-2-one (I-8):²

To a solution of alcohol **I-11b** (2 g, 8.23 mmol) in THF (82.3 mL), was added activated MnO₂ (10 g) and left to stir for 30 h, the reaction mixture was filtered and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 5% EtOAc/hexane to yield propargyl ketone **I-8** (1.96 g, 8.13 mol, 98%): R_f = 0.85 (30% EtOAc/hexane); IR (thin film, cm⁻¹) 2955, 2930, 2858, 2210, 1678, 1472, 1226, 1103, 966, 8345, 775; ¹H NMR (600 MHz, CDCl₃) δ 3.64 (t, J = 6.0 Hz, 2H), 2.40 (t, J = 7.2 Hz, 2H), 2.25 (s, 3H), 1.71 (tt, J = 7.2, 6.0 Hz, 2H), 0.84 (s,

9H), 0.02 (s, $J = 0.05$ Hz, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 184.5, 93.5, 81.4, 61.1, 32.6, 30.7, 25.8, 18.2, 15.3, -5.4 .

(*R*)-7-(*tert*-butyldimethylsilyloxy)-hept-3-yne-2-ol (I-12**):²**

To a 20 mL flask was added propargyl ketone **I-8** (704 mg, 2.92 mmol), CH_2Cl_2 (1.48 mL), formic acid/triethylamine (1:1, 5.38 mL) and Noyori asymmetric transfer hydrogenation catalyst (*S*)- $\text{Ru}(\eta^6\text{-mesitylene})$ -(*R,R*)-TsDPEN (8.9 mg, 0.5 mol%). The resulting solution was stirred at room temperature for 24 h. Water (10 mL) was added to dilute and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with saturated NaHCO_3 , dried over Na_2SO_4 , and concentrated under reduced pressure to afford crude oil. The crude product was purified by silica gel flash chromatography eluting with 6% EtOAc/hexane to give propargyl alcohol **I-12** (605 mg, 2.49 mmol, 86%): colorless oil; $R_f = 0.42$ (20% Et₂O/hexane); $[\alpha]_D^{25} = +16$ ($c = 1.1$, CH_2Cl_2); IR (thin film, cm^{-1}) 3346, 2954, 2930, 2858, 1739, 1472, 1253, 1103, 1070, 835, 775; ^1H NMR (600 MHz CDCl_3) δ 4.43 (qd, $J = 6.0, 1.8$ Hz, 1H), 3.64 (t, $J = 6.0$ Hz, 2H), 2.71 (s, 1H), 2.22 (td, $J = 7.2, 1.8$ Hz, 2H), 1.63 (tt, $J = 7.2, 6.0$ Hz, 2H), 1.34 (d, $J = 6.0$ Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 83.8, 82.5, 61.5, 58.2, 31.6, 25.9, 24.7, 18.3, 15.0, -5.3 ; CI HRMS: Calculated for $[\text{C}_{13}\text{H}_{26}\text{O}_2\text{SiNa}^+]$: 265.1594, found: 265.1630.

(*R*)-7-(*tert*-butyldimethylsilyloxy) –heptan-2-ol (I-6):²

To a solution of propargyl alcohol **I-12** (2 g, 8.23 mmol) in dry EtOAc (33 mL), was carefully added Pd/C (20 mg) and the resulting suspension was stirred under H₂ (1 atm) for 5 min at room temperature. The catalyst was filtered off through a short pad of celite, concentrated under reduced pressure to afford colorless oil. The crude product was purified by silica gel flash chromatography eluting with 6% EtOAc/hexane to give alcohol **I-6** (1.73 g, 6.75 mmol, 82%): colorless oil; R_f = 0.40 (20% Et₂O/hexane); $[\alpha]_D^{25}$ = +8 (c = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3363, 2929, 2857, 1472, 1254, 1096, 835, 774; ¹H NMR (600 MHz, CDCl₃) δ 3.74 (ddq, J = 6.0, 6.0, 6.0, 1H), 3.56 (t, J = 6.6 Hz, 2H), 1.85(s, 1H), 1.49 (m, 2H), 1.43 (m, 2H), 1.39 (m, 2H), 1.31(m, 2H), 1.14 (d, J = 6.0 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 68.0, 63.2, 39.4, 32.8, 26.0, 25.9, 25.6, 23.5, 18.4, -5.3; CIHRMS: Calculated for [C₁₃H₃₀O₂Si+Na]⁺: 269.1907, found: 269.1903.

(2*S*, 6*R*)-6-((*R*)-7-(*tert*-butyldimethylsilyloxy)heptan-2-yloxy)-2-methyl-2H-pyran-3(6H)-one (I-14):²

To a solution of pyranone **I-5** (473 mg, 2.07 mmol) and alcohol **I-6** (430 mg, 1.74 mmol) in dry CH_2Cl_2 (1 mL), was added a CH_2Cl_2 (1 mL) solution of $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ (43.9 mg, 2.5 mol%) and PPh_3 (45.6 mg, 10 mol%) at 0 °C under argon atmosphere. After stirring for 3 h at 0 °C to room temperature, the reaction mixture was quenched with 15 mL of saturated NaHCO_3 , extracted (3 x 25 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 4% EtOAc /hexane to give pyranone **I-14** (656 mg, 1.64 mmol, 94%): $R_f = 0.64$ (20% EtOAc /hexane); $[\alpha]_D^{25} = +13$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 2930, 2857, 1701, 1463, 1375, 1254, 1097, 1023, 836; ^1H NMR (600 MHz, CDCl_3) δ 6.77 (dd, $J = 10.2, 3.6$ Hz, 1H), 6.04 (d, $J = 10.2$ Hz, 1H), 5.25 (d, $J = 3.6$ Hz, 1H), 4.56 (q, $J = 6.6$ Hz, 1H), 3.89 (ddq, $J = 6.0, 6.0, 6.0$ Hz, 1H), 3.58 (t, $J = 6.6$ Hz, 2H), 1.58 (m, 2H) 1.49 (m, 2H), 1.47 (m, 2H), 1.41 (m, 2H), 1.35 (d, $J = 6.6$ Hz, 3H), 1.17 (d, $J = 6.6$ Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 197.2, 144.2, 127.1, 90.8, 73.8, 70.4, 63.2, 37.3, 32.8, 26.0, 25.8, 25.6, 19.5, 18.3, 15.2, -5.3; CIHRMS: Calculated for $[\text{C}_{19}\text{H}_{36}\text{O}_4\text{SiNa}]^+$: 379.2275, found: 379.2277.

(1S, 3S, 5R, 6R)-5-((R)-7-(tert-butyldimethylsilyloxy)heptan-2-yloxy)-3-methyl-4,7-dioxabicyclo[4.1.0]heptan-2-one (I-15):²

To the solution of pyranone **I-14** (440 mg, 1.18 mmol) in methanol (3.93 mL) at 0 °C, 30% aqueous hydrogen peroxide (0.553 mL, 4.7 mmol) was added dropwise, followed by aqueous sodium hydroxide (0.236 mL, 0.5 M). The reaction mixture was warmed to room temperature. After stirring for 5 h, the reaction mixture was quenched using saturated NaHCO₃ (25 mL), extracted with diethyl ether (5 x 20 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 4% EtOAc/hexane to give 656 mg (1.64 mmol, 94%) of epoxy-enone **I-15**: R_f = 0.62 (20% EtOAc/hexane); $[\alpha]_D^{25}$ = -103 (c = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2930, 2858, 1726, 1463, 1380, 1254, 1143, 1094, 1057, 833; ¹H NMR (600 MHz, CDCl₃) δ 5.28 (d, J = 0.6 Hz, 1H), 4.19 (q, J = 7.0 Hz, 1H), 3.86 (ddq, J = 6.0, 6.0, 6.0 Hz, 1H), 3.60 (t, J = 6.6 Hz, 2H), 3.48 (dd, J = 4.2, 0.6 Hz, 1H), 3.42 (d, J = 4.2 Hz, 1H), 1.54 (m, 2H), 1.51 (m, 2H), 1.37 (d, J = 6.6 Hz, 3H), 1.32 (m, 2H), 1.24 (m, 2H), 1.20 (d, J = 7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 203.3, 91.3, 73.7, 71.9, 63.1, 54.3, 53.0, 37.1, 32.8, 26.0, 25.8, 25.5, 19.2, 18.4, 16.8, -5.2; CIHRMS: Calculated for [C₁₉H₃₆O₅SiNa⁺]: 395.2224, found: 379.2228.

(1R, 2S, 3S, 5R, 6R)-5-((R)-7-(tert-butyldimethylsilyl)heptan-2-yloxy)-3-methyl-4, 7-dioxa-bicyclo[4.1.0]heptan-2-ol (I-16):²

A CH_2Cl_2 (0.46 mL) solution of epoxy enone **I-15** (181 mg, 0.46 mmol) and $\text{CeCl}_3/\text{MeOH}$ (0.3 mL, 0.4 M) was cooled to $-78\text{ }^\circ\text{C}$. NaBH_4 (38.4 mg, 10.2 mmol) was added and the reaction mixture was stirred at -78 to $-20\text{ }^\circ\text{C}$ for 4 h. The reaction mixture was diluted with ether (5 mL) and quenched with 2.5 mL of saturated NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% $\text{EtOAc}/\text{hexane}$ to give 170 mg (0.43 mmol, 93%) of epoxy alcohol **I-16**: $R_f = 0.34$ (40% $\text{EtOAc}/\text{hexane}$); $[\alpha]_D^{25} = -54$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3441, 2930, 2857, 1463, 1387, 1254, 1097, 1055, 834; ^1H NMR (600 MHz, CDCl_3) δ 5.02 (s, 1H), 3.84 (ddq, $J = 6.0, 6.0, 6.0$ Hz 1H), 3.60 (t, $J = 6.6$ Hz, 2H), 3.59-3.55 (m, 1H), 3.50 (m, 1H), 3.26 (d, $J = 3.6$ Hz, 1H), 3.05 (d, $J = 3.6$ Hz, 1H), 1.61-1.53 (m, 2H) 1.52 (m, 2H), 1.49-1.40 (m, 2H), 1.38-1.31 (m, 2H), 1.23 (d, $J = 6.6$ Hz, 3H), 1.16 (d, $J = 6.6$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 92.5, 73.1, 68.0, 65.6, 63.3, 56.0, 50.6, 37.3, 32.8, 26.0, 25.8, 25.5, 19.4, 18.4, 18.3, -5.2 ; CIHRMS: Calculated for $[\text{C}_{19}\text{H}_{38}\text{O}_5\text{SiNa}^+]$: 397.2380, found: 397.2386.

(2R, 3R, 5R, 6S)-2-((R)-7-(tert-butyldimethylsilyloxy)heptan-2-yloxy)-tetrahydro-6-methyl-2H-pyran-3,5-diol (I-4):²

To a solution of epoxy ketone **I-16** (35 mg, 0.09 mmol) in dry THF (0.15 mL) at $-78\text{ }^{\circ}\text{C}$, was added dropwise the suspension solution of LiAlH_4 (6.8 mg, 0.18 mmol) in dry THF (0.15 mL) under argon atmosphere. After stirring 2 h, the resulting solution was warmed to the room temperature and LiAlH_4 (6.8 mg, 0.18 mmol) in dry THF (0.15 mL) was added dropwise again, keeping reaction overnight. Water (1 mL) was added dropwise with cooling. Then the mixture was extracted with EtOAc (3 x 3 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexane to give 30.5 mg (0.078 mmol, 86%) of diol **I-4**: $R_f = 0.21$ (50% EtOAc/hexane); $[\alpha]_D^{25} = -67$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3360, 2929, 2857, 1463, 1378, 1255, 1098, 1028, 984, 835; ^1H NMR (600 MHz, CD_3OD) δ 4.69 (s, 1H), 3.83 (ddq, $J = 6.0, 6.0, 6.0$ Hz, 1H), 3.76 (m, 1H), 3.69 (t, $J = 6.6$ Hz, 2H), 3.66 (m, 1H), 3.56 (ddd, $J = 11, 11, 4.2$ Hz, 1H), 2.00 (ddd, $J = 13.2, 3.6, 3.6$ Hz, 1H), 1.82 (ddd, $J = 13.2, 11.4, 3$ Hz, 1H), 1.58 (m, 2H), 1.51 (m, 2H), 1.43 (m, 2H), 1.34 (m, 2H), 1.26 (d, $J = 6.6$ Hz, 3H), 1.17 (d, $J = 6.0$ Hz, 3H), 0.95 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (150 MHz, CD_3OD) δ 96.3, 72.5, 71.2, 70.0, 68.8, 63.1, 38.6, 36.1, 34.0, 27.1, 26.7, 26.6, 19.5, 19.3, 18.3, -4.9 ; CIHRMS: Calculated for $[\text{C}_{19}\text{H}_{40}\text{O}_5\text{SiNa}^+]$: 399.2537, found: 399.2539.

(2*R*, 3*R*, 5*R*, 6*S*)-2-((*R*)-7-(*tert*-butyldimethylsilyloxy)heptan-2-yloxy)-tetrahydro-6-methyl-2*H*-pyran-3,5-diol (I-17**):²**

To a solution of diol **I-4** (752 mg, 2 mmol) in pyridine (2 mL), was added Ac₂O (1 mL) and DMAP (35 mg). The reaction mixture was stirred for 12 h. Water was added to destroy the excess acetic anhydride, extracted (3 x 50 mL) with Et₂O washed with 40 mL of saturated CuSO₄ solution for three times, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% ether/hexane to give acetate **I-17** (912 mg, 1.98 mmol, 99%); a clean oil; R_f = 0.49 (10% EtOAc/hexane); $[\alpha]_D^{25} = -66$ ($c = 1.1$, CH₂Cl₂); IR (thin film, cm⁻¹) 2934, 2958, 1743, 1371, 12309, 1037, 835; ¹H NMR (600 MHz, CDCl₃) δ 4.74 (m, 1H), 4.70 (ddd, $J = 11.4, 10.2, 4.2$ Hz, 1H), 4.65 (s, 1H), 3.85 (dq, $J = 9.6, 6.6$ Hz, 1H), 3.76 (m, 1H), 3.60 (t, $J = 6.6$ Hz, 2H), 2.11 (ddd, $J = 13.2, 3.6, 3.6$ Hz, 1H), 2.10 (s, 3H), 2.05 (s, 3H), 1.93 (ddd, $J = 13.2, 11.4, 3$ Hz, 1H), 1.58 (m, 2H), 1.54 (m, 2H), 1.43 (m, 2H), 1.34 (m, 2H), 1.17 (d, $J = 6.6$ Hz, 3H), 1.12 (d, $J = 6.0$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 170.4, 170.1, 93.7, 72.4, 70.7, 70.0, 68.8, 63.3, 37.2, 32.9, 29.5, 26.1, 26.0, 25.9, 25.6, 21.3, 21.2, 19.1, 18.4, 17.7, -5.2; CIHRMS: Calculated for [C₂₃H₄₄O₇SiNa⁺]: 483.2754, found: 483.2755.

2-((*R*)-7-hydroxyheptan-2-yloxy)-tetrahydro-6-methyl-2H-pyran-3, 5-diacetate (I-18):²

To a solution of TBS-ether **I-17** (460.6 mg, 1 mmol) in dry MeOH (2 mL), 6 N HCl (2 mL) was added at room temperature under the argon atmosphere. After 4 h, the reaction mixture was diluted with ether (20 mL) and quenched with saturated NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified by passing a silica gel pad eluting with pure ether to give alcohol **I-18** (350 mg, 0.97 mmol, 97%); a colorless oil, $[\alpha]_D^{25} = -86$ ($c = 1.12$, CH₂Cl₂); IR (thin film, cm⁻¹) 2975, 2935, 2861, 1739, 1230, 1105, 1032, 983; ¹H NMR (600 MHz, CDCl₃) δ 4.81 (m, 1H), 4.77 (ddd, $J = 11.4, 10.2, 4.2$ Hz, 1H), 4.72 (s, 1H), 3.84 (dq, $J = 9.6, 6.6$ Hz, 1H), 3.74 (m, 1H), 3.62 (t, $J = 6.6$ Hz, 2H), 2.10 (ddd, $J = 13.2, 3.6, 3.6$ Hz, 1H), 2.09 (s, 3H), 2.03 (s, 3H), 1.92 (ddd, $J = 13.2, 11.4, 3$ Hz, 1H), 1.57 (m, 2H), 1.54 (m, 2H), 1.43 (m, 2H), 1.36 (m, 2H), 1.15 (d, $J = 6.6$ Hz, 3H), 1.11 (d, $J = 6.0$ Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 170.4, 170.1, 93.7, 72.3, 70.7, 70.0, 66.8, 62.7, 37.1, 32.7, 29.4, 25.8, 25.5, 21.2, 21.1, 19.1, 17.7; CIHRMS: Calculated for [C₁₇H₃₀O₇Na⁺]: 369.1889, found: 369.1891.

2-methyl-6-((*R*)-7-oxoheptan-2-yloxy)-tetrahydro-2H-pyran-3, 5-yl diacetate (I-19):

A solution of alcohol **I-18** (240 mg, 0.693 mmol) and trichloroisocyanuric acid (171.2 mg, 1.386 mmol) in ethyl ether (30 ml) was stirred at $-30\text{ }^{\circ}\text{C}$, and then 2,2,6,6-tetramethylpiperidinoxy was added in one portion. The mixture was stirred for 20 min and then quenched with 30 ml saturated sodium carbonate. The organic layer was separated and the aqueous layer was extracted with ether. Combined the organic layer and washed with brine, dried (Na_2SO_4), filtered and concentrated. Chromatography on silica gel (20% EtOAc/Hexane) gave aldehyde **I-19** (210 mg, 0.61 mmol, 88%) as colorless oil; R_f (40% EtOAc/Hexane) = 0.66; $[\alpha]_D^{25} = -41$ ($c = 1.0$, MeOH); IR (thin film, cm^{-1}), 2929, 1741, 1234, 1040; ^1H NMR (600 MHz, CD_3Cl) δ 9.76 (t, $J = 1.8$ Hz, 1H), 4.82 (m, 1H), 4.78 (ddd, $J = 11.4, 10.2, 4.8$ Hz, 1H), 4.72 (s, 1H), 3.82 (dq, $J = 12.6, 6$ Hz, 1H), 3.76 (ddq, $J = 6.0, 6.0, 6.0$ Hz, 1H), 2.44 (dt, $J = 7.2, 1.8$ Hz, 1H), 2.09 (m, 3H), 2.04 (m, 3H), 1.91 (ddd, $J = 13.8, 11.4, 3$ Hz, 1H), 1.68-1.46 (m, 8H), 1.33 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (150 MHz, CD_3Cl) δ 202.6, 170.6, 170.3, 93.8, 72.3, 70.8, 70.0, 67.0, 44.003, 37.01, 29.6, 25.4, 22.3, 21.4, 21.3, 19.19, 17.9. CIHRMS: Calculated for $[\text{C}_{17}\text{H}_{28}\text{O}_7\text{Na}^+]$: 367.1227, Found: 367.1733.

(8R,E)-ethyl 8-(3,5-diacetoxy-6-methyl-tetrahydro-2H-pyran-2-yloxy)non-2-enoate (I-20):

Ylide (396.7 mg, 1.14 mmol) was dissolved in 0.6 ml of CH_2Cl_2 , into which aldehyde **I-19** (190 mg, 0.55 mmol) was added. The reaction was stirred vigorously at room temperature for 12 hrs before solvent was removed in vacuum. Chromatography on silica gel (30% EtOAc/Hexane) gave ethyl ester **I-20** (220 mg, 0.53 mmol, 96.5%) as colorless oil. R_f (40% EtOAc/Hexane) = 0.57; $[\alpha]_D^{25} = -22$ ($c = 1.0$, MeOH); IR (thin film, cm^{-1}), 2936, 1743, 1233, 1038; ^1H NMR (600 MHz, CD_3Cl) δ 6.96 (dt, $J = 13.8, 7.2$ Hz, 1H), 5.82 (dt, $J = 15.6, 1.8$ Hz, 1H), 4.83 (m, 1H), 4.79 (ddd, $J = 10.8, 9.6, 4.2$ Hz, 1H), 4.73 (s, 1H), 4.18 (q, $J = 7.2$ Hz, 2H), 3.84 (dq, $J = 12, 6$ Hz, 1H), 3.76 (ddq, $J = 6.0, 6.0, 6.0$ Hz, 1H), 2.22 (dt, $J = 7.2, 1.2$ Hz, 1H), 2.11 (m, 3H), 2.06 (m, 3H), 1.93 (ddd, $J = 13.8, 11.4, 3$ Hz, 1H), 1.60-1.35 (m, 8H), 1.28 (t, $J = 7.2$ Hz, 3H); 1.17 (d, $J = 6.6$ Hz, 3H), 1.13 (d, $J = 6$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 170.3, 170.1, 166.7, 148.9, 121.5, 93.6, 72.2, 70.6, 69.8, 66.8, 60.4, 60.2, 36.8, 32.2, 29.3, 27.9, 25.3, 21.2, 19.0, 17.6, 14.3; CIHRMS: Calculated for $[\text{C}_{21}\text{H}_{34}\text{O}_8\text{Na}^+]$: 437.2146, Found: 437.2151.

(8R,E)-methyl 8-(3,5-dihydroxy-6-methyl-tetrahydro-2H-pyran-2-yloxy)non-2-enoate (I-21):

To a 20 ml flask was added ethyl ester **I-20** (136 mg, 0.328 mmol), MeOH (3 ml), Lithium hydroxide (30 mg, 1.25 mmol). The resulting solution was stirred at room temperature for 24 hrs. Aqueous HCl (0.5 M, 3 ml) was added before solvent was removed in vacuum. Chromatography on silica gel (80% EtOAc/Hexane) gave ethyl ester **I-21** (103 mg, 0.309 mmol, 99%) as colorless oil. R_f (EtOAc) = 0.58; $[\alpha]_D^{25} = -81$ ($c = 1.0$, MeOH); IR (thin film, cm^{-1}), 3404, 2934, 2180, 1991, 1723, 1655, 1438, 1273, 1203, 1101, 1128, 1029, 984, 854; ^1H NMR (600 MHz, CD_3Cl) δ 6.96 (dt, $J = 15.6$, 6.6 Hz, 1H), 5.83 (dt, $J = 15.6$, 1.2 Hz, 1H), 4.69 (s, 1H), 3.80-3.77 (m, 1H), 3.72 (s, 3H), 3.65 (dt, $J = 6.6$, 3.0 Hz, 1H), 3.59-3.57 (m, 1H), 2.22 (ddd, $J = 9.0$, 7.2, 1.8 Hz, 1H), 1.88-1.72 (m, 2H), 1.61 (s, 1H), 1.55-1.35 (m, 6H), 1.27 (d, $J = 6$ Hz, 3H), 1.22 (d, $J = 6$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 167.3, 149.5, 121.7, 96.1, 71.3, 70.0, 69.3, 69.1, 51.5, 36.9, 35.2, 32.0, 27.8, 25.0, 20.0, 17.7; CIHRMS: Calculated for $[\text{C}_{16}\text{H}_{28}\text{O}_6\text{Na}^+]$: 339.1778, Found: 339.1784.

(8R,E)-8-(3,5-dihydroxy-6-methyl-tetrahydro-2H-pyran-2-yloxy)non-2-enoic acid (I-1)

To a 20 ml flask was added methyl ester **I-21** (13 mg, 0.04 mmol), THF/ H_2O (4:1, 0.4 ml), Lithium hydroxide (1.44 mg, 0.06 mmol). The resulting solution was stirred at room temperature for 24 hrs. Aqueous HCl (0.5 M, 0.4 ml) was added to make the pH equal to 7, and then the solvent was removed in vacuum. Chromatography on silica gel (5%

MeOH/EtOAc) gave acid **I-1** (12 mg, 0.0397 mmol, 99%) as colorless oil. R_f (EtOAc) = 0.28; $[\alpha]_D^{25} = -62$ ($c = 1.0$, MeOH); IR (thin film, cm^{-1}), 3703, 3364, 2930, 2357, 2164, 2084, 2010, 1954, 1696, 1272, 1127, 981, 667; ^1H NMR (600 MHz, CD_3Cl) δ 6.93 (dt, $J = 15.6, 7.2$ Hz, 1H), 5.79 (dt, $J = 15.6, 1.2$ Hz, 1H), 4.62 (s, 1H), 3.78-3.75 (m, 2H), 3.69 (s, 1H), 3.63-3.58 (m, 1H), 3.49 (ddd, $J = 10.8, 9.6, 4.8$ Hz, 1H), 2.23-2.21 (m, 2H), 2.05-1.91 (m, 2H), 1.74 (ddd, $J = 12.6, 11.4, 2.4$ Hz, 1H), 1.58-1.23 (m, 8H), 1.19 (d, $J = 6.6$ Hz, 3H), 1.11 (d, $J = 6$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 169.9, 148.8, 122.4, 96.4, 71.3, 70.0, 68.8, 67.2, 36.9, 34.8, 31.9, 28.0, 25.2, 18.2, 16.9; CIHRMS: Calculated for $[\text{C}_{15}\text{H}_{26}\text{O}_6\text{Na}^+]$: 325.1622, Found: 325.1627.

(8R,E)-8-(3,5-dihydroxy-6-methyl-tetrahydro-2H-pyran-2-yloxy)-N-(2-(2-(7-(dimethylamino)-2-oxo-2H-chromen-4-yl)acetamido)ethyl)non-2-enamide (I-23)

To a solution of amine (6 mg, 0.015 mmol) in THF (0.125 ml), was added Et_3N (3 μL), HBTU (4.7 mg, 0.0125 mmol) and acid **I-1** (5 mg, 0.0125 mmol). The reaction mixture was stirred overnight, concentrated under reduced pressure, purified using silica gel flash chromatography eluting with 10% MeOH/EtOAc to give amide **I-23** (5 mg, 0.00872 mmol, 69%); R_f (10% MeOH/EtOAc) = 0.55; $[\alpha]_D^{25} = -30$ ($c = 0.5$, MeOH); IR (thin

film, cm^{-1}), 3781, 3358, 2933, 2252, 2149, 1997, 1699, 1615, 1531, 1453, 1403, 1252, 1128, 1030, 983, 834; ^1H NMR (600 MHz, CD_3Cl) δ 7.32 (d, $J = 9$ Hz, 1H), 6.92 (dt, $J = 15.6, 7.2$ Hz, 1H), 6.77-6.71 (m, 1H), 6.54 (d, $J = 3$ Hz, 1H), 6.03 (s, 1H), 5.81 (dt, $J = 15.6, 1.2$ Hz, 1H), 4.63 (s, 1H), 3.79-3.78 (m, 1H), 3.70 (s, 1H), 3.67-3.60 (m, 2H), 3.41 (t, $J = 6.0$ Hz, 2H), 3.34 (t, $J = 6.0$ Hz, 2H), 3.06 (s, 6H), 2.26-2.22 (m, 1H), 1.97-1.88 (m, 2H), 1.78-1.73 (m, 1H), 1.58-1.54 (m, 1H), 1.50-1.45 (m, 2H), 1.43-1.38 (m, 1H), 1.28 (m, 2H), 1.20 (d, $J = 6.6$ Hz, 3H), 1.11 (d, $J = 6$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 170.3, 167.9, 163.1, 156.0, 153.6, 151.4, 149.2, 144.6, 125.7, 123.5, 121.9, 109.5, 108.7, 97.6, 96.4, 71.2, 70.0, 68.8, 67.2, 39.3, 39.0, 38.7, 36.9, 34.8, 31.8, 28.1, 28.0, 25.2, 18.1, 16.9; CIHRMS: Calculated for $[\text{C}_{30}\text{H}_{43}\text{O}_8\text{N}_3\text{Na}^+]$: 596.2942, Found: 596.2948.

(2*S*, 6*R*)-6-(benzyloxy)-2-methyl-2*H*-pyran-3(6*H*)-one (II-20)³

To a solution of Boc-protected pyranone **II-23** (22.8 g, 100 mmol) and benzyl alcohol (21.6 g, 200.0 mmol) in dry CH_2Cl_2 (100 mL) was added $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ (257 mg, 0.25 mol% Pd) and PPh_3 (262 mg, 0.5 mol%) at 0 °C under argon atmosphere. After stirring for 2 h from 0 °C to room temperature, the reaction mixture was quenched with of

³ Guo, H.; O'Doherty, G. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 5206-5208.

saturated aqueous NaHCO_3 (300 mL), extracted with Et_2O (300 mL $\times$ 3), dried over Na_2SO_4 , and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 4% EtOAc /hexane to give Bn-ether **II-20** (19.6 g, 90 mmol, 90%); colorless oil; $R_f = 0.71$ (30% EtOAc /hexane); $[\alpha]_D^{25} = +46$ ($c = 1.11$, CH_2Cl_2); IR (thin film, cm^{-1}) 2985, 2939, 2873, 1697, 1231, 1022, 953; ^1H NMR (270 MHz, CDCl_3) δ 7.32-7.38 (m, 5H), 6.85 (dd, $J = 10.2, 3.6$ Hz, 1H), 6.11 (d, $J = 10.2$ Hz, 1H), 5.28 (d, $J = 3.6$ Hz, 1H), 4.86 (d, $J = 11.4$ Hz, 1H), 4.70 (d, $J = 11.4$ Hz, 1H), 4.57 (q, $J = 6.7$ Hz, 1H), 1.36 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 197.0, 143.5, 137.2, 126.6, 128.2, 128.1, 127.5, 92.4, 70.8, 70.5, 15.3; HRMS (CI): Calculated for $[\text{C}_{13}\text{H}_{14}\text{O}_3 + \text{Na}]^+$: 241.0835, found: 241.0843.

(1*R*,2*R*,4*S*,6*S*)-2-(benzyloxy)-4-methyl-3,7-dioxabicyclo-[4.1.0]heptan-5-one (II-24).

To the solution of pyranone **II-20** (220 mg, 1.0 mmol) in methanol (3 mL) at 0 °C, 30% aqueous hydrogen peroxide (0.26 mL, 2.5 mmol) was added dropwise, followed by aqueous sodium hydroxide (0.1 mL, 0.5 M). The reaction mixture was stirred at RT for 4 h and then the reaction mixture was extracted with diethyl ether. The extracts were washed with saturated aqueous NaHCO_3 , dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography

to give epoxide **II-24** (207 mg, 0.88 mmol, 88%) as colorless oil: R_f (20% EtOAc/hexane) 0.47; $[\alpha]_D^{20} = -59.3$ (c 1.0, MeOH); IR (thin film, cm^{-1}) ν 3034, 2937, 1726, 1455, 1369, 1256, 1146, 1060, 996, 859, 699; ^1H NMR (270 MHz, CDCl_3) δ 7.36 (m, 5H), 5.30 (d, $J = 1.2$ Hz, 1H), 4.80 (d, $J = 11.6$ Hz, 1H), 4.64 (d, $J = 11.6$ Hz, 1H), 4.17 (q, $J = 6.9$ Hz, 1H), 3.59 (dd, $J = 3.9, 1.2$ Hz, 1H), 3.46 (d, $J = 4.0$ Hz, 1H), 1.38 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl_3) δ 203.1, 136.6, 128.7, 128.4, 128.2, 93.3, 93.2, 72.0, 70.8, 53.8, 53.1; HRMS: Calculated for $[\text{C}_{13}\text{H}_{14}\text{O}_4 + \text{Na}]^+$: 257.0784, Found: 257.0784.

(1R,2R,4S,5S,6R)-2-(benzyloxy)-4-methyl-3,7-dioxabicyclo[4.1.0]heptan-5-ol (II-18).

To a solution of epoxide **II-20** (672 mg, 2.87 mmol) in CH_2Cl_2 (3 mL) was added a solution of $\text{CeCl}_3/\text{MeOH}$ (3 mL, 0.4 M). The mixture was cooled to -78 °C. NaBH_4 (130 mg, 3.4 mmol) was added and the reaction mixture was stirred at -78 to -20 °C for 4 h. The reaction was quenched with saturated aqueous NaHCO_3 . The mixture was extracted with Et_2O , and the organic layer was washed with saturated brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give epoxide **II-18** (576 mg, 2.44 mmol, 85%) as colorless oil: R_f (80% EtOAc/hexane) 0.47; $[\alpha]_D^{20} = -62.8$ (c 1.0, MeOH); IR (thin film, cm^{-1}) ν 3430, 2911, 1454, 1370, 1241, 1114, 1054, 980, 848, 805, 738, 698; ^1H NMR (600 MHz,

CDCl₃) δ 7.34 (m, 5H), 5.03 (s, 1H), 4.75 (d, J = 11.4 Hz, 1H), 4.57 (d, J = 11.4 Hz, 1H), 3.58 (dq, J = 9.0, 6.0 Hz, 1H), 3.45 (d, J = 9.0 Hz, 1H), 3.23 (d, J = 3.6 Hz, 1H), 3.12 (d, J = 3.6 Hz, 1H), 1.21 (d, J = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 137.5, 128.8, 128.4, 128.3, 94.5, 70.3, 68.0, 65.8, 56.1, 50.5, 18.5; HRMS: Calculated for [C₁₃H₁₆O₄+H]⁺: 237.1121, Found: 237.1121.

(2R,3R,4S,5R,6S)-2-(benzyloxy)-6-methyltetrahydro-2H-pyran-3,4,5-triol (II-25).

To a round bottom flask was added epoxide **II-18** (13 mg, 0.055 mmol), HOAc (0.5 ml) and Sc(OTf)₃ (5 mg, 0.01 mmol). The reaction solution was stirred for 1 h at RT. The reaction mixture was diluted with EtOAc and saturated aqueous NaHCO₃ was added at 0 °C. The mixture was extracted with EtOAc, and the EtOAc layer was washed with saturated brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was dissolved in THF/H₂O (0.4 mL, 3:1) at RT, and lithium hydroxide monohydrate (5 mg, 0.13 mmol) was added to the solution. The reaction mixture was stirred at RT for 5 h. Then the reaction mixture was directly loaded onto silica gel column to give α -6-deoxy-altrose **II-25** (9.6 mg, 0.038 mmol, 69%) as colorless oil: R_f (EtOAc) 0.49; $[\alpha]_D^{20}$ -73.3 (c 1.0, MeOH); IR (thin film, cm⁻¹) ν 3384, 2930, 1455, 1375, 1259, 1127, 1061, 1014, 970, 852, 737, 698; ¹H NMR (600 MHz, CDCl₃) δ 7.35 (m, 5H), 4.81 (s, 1H), 4.75 (d, J = 12 Hz, 1H), 4.55 (d, J = 12 Hz, 1H), 3.98 (dd, J = 3.6, 1.8 Hz, 1H),

3.89 (dd, $J = 3.6, 3.6$ Hz, 1H), 3.79 (dq, $J = 9.0, 6.0$ Hz, 1H), 3.51 (dd, $J = 9.6, 3.6$ Hz, 1H), 1.21 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 136.5, 128.9, 128.6, 128.4, 99.0, 70.9, 70.1, 69.8, 69.6, 65.8, 17.8; HRMS: Calculated for $[\text{C}_{13}\text{H}_{18}\text{O}_5 + \text{Na}]^+$: 277.1046, Found: 277.1047.

(2*R*,3*S*,4*S*,5*S*,6*S*)-2-(benzyloxy)-4-bromo-6-methyltetrahydro-2*H*-pyran-3,5-diol (II-27).

To a round bottom flask was added epoxide **II-18** (96 mg, 0.41 mmol), HOAc (0.5 mL) and $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ (106 mg, 0.41 mmol). The reaction mixture was stirred at RT for 1 h. The reaction mixture was diluted with EtOAc and saturated aqueous NaHCO_3 was added at 0 °C. The mixture was extracted with EtOAc, and the organic layer was washed with saturated brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give bromide **II-27** (137 mg, 0.4 mmol, 98%) as colorless oil: R_f (50% EtOAc/hexane) 0.28; $[\alpha]_D^{25} -57.2$ (c 1.0, MeOH); IR (thin film, cm^{-1}) ν 3402, 2919, 1718, 1454, 1245, 1055, 994, 739; ^1H NMR (600 MHz, CDCl_3) δ 7.34 (m, 5H), 4.80 (d, $J = 12.0$ Hz, 1H), 4.72 (d, $J = 3.6$ Hz, 1H), 4.54 (d, $J = 12.0$ Hz, 1H), 4.35 (dd, $J = 6.0, 3.6$ Hz, 1H), 4.12 (dd, $J = 6.0, 3.6$ Hz, 1H), 4.08 (qd, $J = 6.6, 6.6$ Hz, 1H), 3.67 (dd, $J = 6.0, 3.6$ Hz, 1H), 1.27 (d, $J = 6.6$ Hz, 3H);

^{13}C NMR (150 MHz, CDCl_3) δ 137.2, 128.4, 127.8, 127.7, 99.0, 71.8, 70.4, 69.8, 68.5, 56.0, 16.9; HRMS: Calculated for $[\text{C}_{13}\text{H}_{17}\text{BrO}_4+\text{Na}]^+$: 339.0202, Found: 339.0204.

(2*R*,3*R*,5*R*,6*S*)-2-(benzyloxy)-6-methyltetrahydro-2*H*-pyran-3,5-diol (II-26).

To a solution of bromide **II-27** (17 mg, 0.05 mmol) in dry toluene (0.5 ml), tris(trimethylsilyl)silane (TTMSS) (0.033 ml, 0.1 mmol) and AIBN (4 mg, 0.025 mmol) was added at 0 °C. At this stage reaction mixture was degassed using freeze-pump-thaw technique three times. Then the reaction mixture was stirred at 80 °C for 4 h under Ar. The mixture was directly loaded onto silica gel column for purification to give α -ascarylose **II-28** (10 mg, 0.038 mmol, 76%) as colorless oil.

Alternative procedure for (II-26): To a round bottom flask was added epoxide **18** (23 mg, 0.094 mmol), THF (0.5 ml) and LiAlH_4 (7.1 mg, 0.19 mmol) at 0 °C. The reaction solution was stirred for 30 min at 0 °C. Water was added dropwise to quench the reaction, then the mixture was extracted with EtOAc. The organic layer was washed with saturated brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give α -ascarylose **26** (19 mg, 0.08 mmol, 85%) as colorless oil: R_f (60% EtOAc/hexane) 0.17; $[\alpha]_D^{20}$ -90.8 (c 1.0, MeOH); IR (thin film, cm^{-1}) ν 3405, 2935, 1718, 1686, 1256, 1123, 1080, 995; ^1H NMR (600 MHz, CDCl_3) δ 7.34 (m, 5H), 4.74 (d, J = 12.0 Hz, 1H), 4.68 (s, 1H), 4.53 (d, J =

12.0 Hz, 1H), 3.91 (dd, $J = 4.8, 3.0$ Hz, 1H), 3.70 (dq, $J = 9.6, 6.0$ Hz, 1H), 3.61 (ddd, $J = 10.8, 9.0, 4.2$ Hz, 1H), 2.09 (ddd, $J = 13.2, 3.6, 3.6$ Hz, 1H), 1.89 (ddd, $J = 13.2, 11.4, 3.0$ Hz, 1H), 1.30 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 137.4, 128.5, 127.9, 127.8, 98.2, 69.8, 69.0, 68.8, 68.1, 35.2, 17.7; HRMS: Calculated for $[\text{C}_{13}\text{H}_{18}\text{O}_4+\text{H}]^+$: 239.0202, Found: 239.0204.

(+/-) undec-3-yn-2-ol (III-22a)

A solution of *n*-BuLi in hexane (48 mL, 121 mmol) was added dropwise to the solution of 1-nonyne **III-22** (20 mL, 121 mmol) in dry THF (120 mL) at $-78\text{ }^{\circ}\text{C}$ under argon. After 30 min, acetaldehyde (6.7 mL, 120 mmol) was added. The reaction was stirred for 10 min at $0\text{ }^{\circ}\text{C}$ and then the resulting solution was warmed to room temperature for 50 min. Additional CH_2Cl_2 (80 mL) was added to the reaction mixture followed by addition of 80 mL saturated aqueous NH_4Cl (80 mL). The aqueous phase was separated and extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. Chromatography on silica gel (10% EtOAc/hexane) gave alcohol **III-22a** (16.8 g, 96.8 mmol, 80%)⁴ as a colorless oil; R_f (20% EtOAc/hexane) = 0.32; IR (thin film, cm^{-1}), 3345, 2930, 2857, 2227, 1467, 1156, 1078; ^1H NMR (600 MHz, CDCl_3) δ 4.48 (qdt, $J = 6.6, 4.8, 1.8$ Hz 1H), 4.15 (td, $J = 7.2, 1.8$

⁴ James, S. A.; Edward, R. D.; Antonio, Z. *J. Org. Chem.* **1989**, 54, 5854-5

Hz, 2H), 1.93 (d, $J = 4.8$ Hz, 1H), 1.46 (tt, $J = 7.2, 7.2$ Hz, 2H), 1.38 (d, $J = 6.6$ Hz, 3H), 1.35-1.25 (m, 8H), 0.85 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 84.9, 82.5, 58.8, 31.9, 29.0, 28.9, 28.8, 25.0, 22.8, 18.8, 14.2.

undec-3-yn-2-one (III-21)

To a solution of alcohol **III-22a** (22 g, 131 mmol) in THF (100 mL) at room temperature was added activated MnO_2 (65 g). The reaction mixture was stirred for 24 h and then filtered through celite and concentrated under pressure to give ketone **III-21** (18.7 g, 116 mmol, 86%)⁵ as a colorless oil. R_f (20% EtOAc/hexane) = 0.70; IR (thin film, cm^{-1}), 2926, 2213, 1750, 1358, 1228; ^1H NMR (600 MHz, CDCl_3) δ 2.35 (t, $J = 7.2$ Hz, 1H), 2.32 (s, 3H), 1.57 (tt, $J = 7.2, 7.2$ Hz, 2H), 1.41-1.26 (m, 8H), 0.89 (t, $J = 7.2$, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 184.9, 94.2, 81.4, 32.7, 31.6, 28.8, 28.7, 27.7, 22.6, 18.9, 14.0.

(R)-undec-3-yn-2-ol (III-23)

⁵ Marshall, J. A.; Robinson, E. D.; Antonio, Z. *J. Org. Chem.* **1989**, 54, 5854-5

To a flask was added ketone **III-21** (0.136 g, 0.82 mmol), CH₂Cl₂ (0.42 mL), formic acid/Et₃N (5:4, 1.5 mL) and Noyori asymmetric transfer hydrogenation catalyst (*S*)-Ru(η^6 -mesitylene)-(*R,R*)-TsDPEN (2.5 mg, 0.0016 mmol, 0.2 mol%). The resulting solution was stirred at room temperature for 24 h, water was added to dilute and the reaction mixture was extracted with saturated NaHCO₃, dried over Na₂SO₄ and concentrated under reduced pressure to afford a crude oil. The crude product was purified by silica gel flash chromatography eluting with 10% EtOAc/hexane to give alcohol **III-23** (0.118 g, 0.71 mmol, 86%)⁶ as a colorless oil. *R*_f (20% Et₂O/hexane) = 0.32; [α]_D²⁵ = +18 (MeOH); IR (thin film, cm⁻¹), 3303, 2926, 2856, 2253, 1458, 1376, 1076, 889; ¹H NMR (600 MHz, CDCl₃) δ 4.48 (qdt, *J* = 6.6, 4.8, 1.8 Hz 1H), 4.15 (td, *J* = 7.2, 1.8 Hz, 2H), 1.93 (d, *J* = 4.8 Hz, 1H), 1.46 (tt, *J* = 7.2, 7.2 Hz, 2H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.35-1.25 (m, 8H), 0.85 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 84.9, 82.5, 58.8, 31.9, 29.0, 28.9, 28.8, 25.0, 22.8, 18.8, 14.2.

(*R*)-undec-10-yn-2-ol (III-23a)

A 30% suspension of KH in mineral oil (171 mg, 4.28 mmol) was washed three times under Argon with dry ether and then the excess solvent was removed under vacuum, Dry 1,3-diaminopropane (1.14 mL) was added with cooling (15 °C). After the mixture was

⁶ Marshall, J. A.; Wang, X.; *J. Org. Chem.* **1990**, 55, 2995-6

stirred for 1 h, the alkynol **III-23** (172 mg, 1.02 mmol) was added dropwise (10 min) at (10-15 °C) to the mixture and the resulting slurry was stirred further under argon for 2 hrs. With cooling (0 °C), water (11 mL) was added dropwise and the mixture was extracted with ether, the combined extracts were washed with 1 N HCl, saturated aqueous sodium bicarbonate and brine, and then dried with anhydrous sodium sulfate. Flash chromatography gave (*R*)-undec-10-yn-2-ol **III-23a** (143 mg, 85%) as a colorless oil: $[\alpha]_D^{25} = -4$ (CH₂Cl₂); *R_f* (30% EtOAc/Hexane) = 0.32; IR (thin film, cm⁻¹) 3296, 2931, 2856, 2116, 1611, 1512, 1244, 1034, 821; ¹H NMR (600 MHz, CDCl₃) δ 3.79 (t, *J* = 5.4 Hz, 1H), 2.18 (td, *J* = 7.2, 2.4 Hz, 2H), 1.93 (t, *J* = 2.4 Hz, 1H), 1.57~1.25 (m, 12H), 1.18 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 84.7, 68.2, 68.1, 39.3, 29.5, 29.0, 28.7, 28.4, 25.7, 23.5, 18.4; ESI HRMS Calcd for [C₁₁H₂₀O+H]⁺: 169.1587, Found: 169.1586.

(*R*)-tert-butyldimethyl(undec-10-yn-2-yloxy)silane (III-24**)**

To a magnetically stirred solution of alcohol **III-23a** (300 mg, 1.79 mmol) and imidazole (304 mg, 4.48 mmol) in dry CH₂Cl₂ (3 mL) was added dropwise TBSCl (281 mg, 1.87 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. Water was added and then the reaction mixture was extracted with Et₂O, dried with Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash chromatography to give alkyne **III-24** (490 mg,

1.74 mmol, 97%) as a colorless oil. R_f (5% Et₂O/hexane) = 0.68; $[\alpha]_D^{25} = -13$ (CH₂Cl₂); IR (thin film, cm⁻¹), 3314, 2929, 2857, 2253, 1463, 1374, 1254, 1134, 1069, 1005, 834, 807, 773; ¹H NMR (600 MHz, CDCl₃) δ 3.76 (qdd, $J = 6.0, 6.0, 6.0$ Hz, 1H), 2.16 (td, $J = 6.6, 2.4$ Hz, 2H), 1.92 (t, $J = 2.4$ Hz, 1H), 1.58-1.26 (m, 12H), 1.11 (d, $J = 6.0$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ¹³C NMR (150 MHz, CD₃Cl) δ 84.8, 68.6, 68.0, 39.7, 29.5, 29.2, 29.0, 28.7, 28.5, 26.0, 25.7, 23.8, 18.4, 18.2, -4.37, -4.69; ESI HRMS Calcd for [C₁₇H₃₄OSi+H]⁺: 283.2452, Found: 283.2453.

(*R*)-ethyl 11-(tert-butyldimethylsilyloxy)dodec-2-ynoate (III-24a**)**

To a solution of alkyne **III-24** (358 mg, 1.27 mmol) in THF (2.5 mL) at -78 °C was added *n*-BuLi (0.5 mL, 1.4 mmol) dropwise and the reaction mixture was stirred for 1h. Ethylchloroformate (0.15 mL, 1.55 mmol) was added at -78 °C and the reaction mixture was stirred for another 1h. The reaction mixture was then warmed to 0 °C and stirred for 15 min. The reaction was quenched with saturated aqueous NH₄Cl (10 mL) and then extracted with Et₂O, washed with brine and dried with Na₂SO₄. Evaporated under reduced pressure gave the crude product which was then purified using silica gel flash chromatography to give ester **III-24a** (373 mg, 1.05 mmol, 83%) as a colorless oil. R_f (10% Et₂O/hexane) = 0.65; $[\alpha]_D^{25} = -7$ (CH₂Cl₂); IR (thin film, cm⁻¹), 2930, 2857, 2235, 1713, 1366, 1246, 1134, 1070, 1005, 834, 807, 773, 752; ¹H NMR (600 MHz, CDCl₃) δ

4.20 (q, $J = 7.2$ Hz, 2H), 3.75 (qdd, $J = 6.0, 6.0, 6.0$ Hz, 1H), 2.31 (t, $J = 7.2$ Hz, 2H), 1.57 (tt, $J = 7.2, 7.2$ Hz, 2H), 1.44-1.22 (m, 10H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.10 (d, $J = 6.0$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 153.9, 89.4, 73.2, 68.6, 61.7, 39.7, 29.4, 29.0, 28.8, 27.5, 25.9, 25.7, 23.8, 18.6, 18.1, 14.0, - 4.20, - 4.51; ESI HRMS Calcd for $[\text{C}_{20}\text{H}_{38}\text{O}_3\text{Si}+\text{H}]^+$: 355.2663, Found: 355.2665.

(*R*, 2*E*, 4*E*)-ethyl 11-(tert-butyldimethylsilyloxy)dodeca-2, 4-dienoate (III-25**)**

In to a round bottom flask were added ester **III-24a** (276 mg, 0.78 mmol), PPh_3 (204 mg, 0.78 mmol), phenol (73 mg, 0.78 mmol) and benzene (1.5 mL). The mixture was stirred at 50 °C for 12 h. The solution was diluted with ether (1 mL) and 1 N NaOH (1 mL). The layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed (water, brine), dried (Na_2SO_4) and concentrated. The residue was dissolved in ether (3 mL) and MeI (0.06 mL) was added to the solution. The reaction mixture was refluxed for 12 hrs. Then the solution was filtered, concentrated and purified by flash chromatography on silica gel to give diene **III-25** (249 mg, 0.70 mmol) as a light yellow oil. R_f (10% Et_2O /hexane) = 0.64; $[\alpha]_D^{25} = -14$ (CH_2Cl_2); IR (thin film, cm^{-1}), 2930, 2857, 2200, 1717, 1643, 1368, 1255, 1138, 1047, 1001, 836, 774; ^1H NMR (600 MHz, CDCl_3) δ 7.25 (dd, $J = 15.6, 10.2$ Hz, 1H), 6.16 (dd, $J = 15.0, 10.2$ Hz, 1H), 6.11 (dt, $J = 15.0, 6.6$ Hz, 1H), 5.77 (d, $J = 15.6$ Hz, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 3.76 (qdd, $J = 6.0, 6.0, 6.0$ Hz, 1H), 2.16 (dt, $J = 6.6, 6.6$ Hz, 2H), 1.44-1.26 (m, 8H), 1.29 (t, $J = 7.2$

Hz, 3H), 1.10 (d, $J = 6.0$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, CD_3Cl) δ 167.3, 145.1, 144.6, 128.4, 119.2, 68.6, 60.1, 39.6, 32.9, 29.2, 28.7, 26.0, 23.8, 18.2, 14.3, - 4.40, - 4.69; ESI HRMS Calcd for $[\text{C}_{20}\text{H}_{38}\text{O}_3\text{Si}+\text{H}]^+$: 355.2663, Found: 355.2664.

(4*R*,5*R*,11*R*,*E*)-ethyl11-(tert-butyldimethylsilyloxy)-4,5-dihydroxydodec-2-enoate

(III-19)

In a round bottom flask were added *t*-BuOH (40 mL), water (40 mL), $\text{K}_3\text{Fe}(\text{CN})_6$ (8.29 g, 25.31 mmol), K_2CO_3 (3.49 g, 35.31 mmol), MeSO_2NH_2 (806 mg, 8.48 mmol), (DHQD)₂-PHAL (130 mg), and OsO_4 (3 mg.). The reaction mixture was stirred at room temperature for about 15 min. and then cooled to 0 °C. To this solution was added diene **III-25** (3.00 g, 8.48 mmol) and the reaction was stirred at 0 °C overnight. The reaction was quenched with saturated aqueous sodium sulfite (30 mL) at room temperature and then extracted with ethyl acetate, washed with 2 N NaOH and brine to remove methanesulfonamide. After removal of solvents in vacuum, flash chromatography on silica gel gave diol **III-19** (2.70 g, 6.95 mmol, 82%) as a colorless oil. R_f (30% Et_2O /hexane) = 0.40; $[\alpha]_D^{25} = -14$ (CH_2Cl_2); IR (thin film, cm^{-1}), 3406, 2932, 2859, 1720, 1463, 1370, 1256, 1177, 1047, 836, 774; ^1H NMR (600 MHz, CDCl_3) δ 6.93 (dd, $J = 15.6, 5.4$ Hz, 1H), 6.14 (dd, $J = 15.6, 1.8$ Hz, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 4.12 (ddd, $J = 5.4, 5.4, 1.8$ Hz, 1H), 3.76

(qdd, $J = 6.0, 6.0, 6.0$ Hz, 1H), 3.55 (ddd, $J = 5.4, 4.2, 3.6$ Hz, 1H), 1.54-1.25 (m, 10H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.11 (d, $J = 6.0$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (150 MHz, CD_3Cl) δ 166.2, 146.6, 122.6, 74.1, 74.0, 68.9, 60.6, 39.6, 33.1, 29.6, 25.9, 25.7, 25.6, 23.8, 18.1, 14.2, - 4.42, - 4.75; ESI HRMS Calcd for $[\text{C}_{20}\text{H}_{40}\text{O}_5\text{Si}+\text{H}]^+$: 389.2718, Found: 389.2719.

(4S,5S,11R,E)-ethyl 11-(tert-butyldimethylsilyloxy)-4,5-dihydroxydodec-2-enoate
(III-20)

In a round bottom flask were added *t*-BuOH (2 mL), water (2 mL), $\text{K}_3\text{Fe}(\text{CN})_6$ (649 mg, 1.97 mmol), K_2CO_3 (272 mg, 1.97 mmol), MeSO_2NH_2 (71.8 mg, 0.65 mmol), $(\text{DHQ})_2\text{-PHAL}$ (10 mg), and OsO_4 (4 mg.). The reaction mixture was stirred at room temperature for about 15 min. and then cooled to 0 °C. To this solution was added diene **III-25** (233 mg, 0.65 mmol) and the reaction was stirred at 0 °C overnight. The reaction was quenched with saturated aqueous sodium sulfite (3 mL) at room temperature and then extracted with ethyl acetate, washed with 2 N NaOH, and brine to remove methanesulfonamide. After removal of solvents in vacuum, flash chromatography on silica gel gave diol **III-20** (202 mg, 0.52 mmol, 80%) as a colorless oil. R_f (30% $\text{Et}_2\text{O}/\text{hexane}$) = 0.40; $[\alpha]^{25}_{\text{D}} = -31$ (CH_2Cl_2); IR (thin film, cm^{-1}), 3402, 2930, 2857, 1721, 1658, 1370, 1254, 1133, 1040, 835, 774; ^1H NMR (600 MHz, CDCl_3) δ 6.91 (dd, J

= 15.6, 4.8 Hz, 1H), 6.14 (dd, J = 15.6, 1.2 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.11 (ddd, J = 5.4, 5.4, 1.2 Hz, 1H), 3.76 (qdd, J = 6.0, 6.0, 6.0 Hz, 1H), 3.53 (ddd, J = 4.8, 4.8, 4.8 Hz, 1H), 1.54-1.25 (m, 10H), 1.28 (t, J = 7.2 Hz, 3H), 1.11 (d, J = 6.0 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 166.4, 146.9, 122.4, 74.1, 74.0, 68.6, 60.6, 39.6, 33.1, 29.6, 25.9, 25.7, 25.6, 23.8, 18.1, 14.2, - 4.43, - 4.74; ESI HRMS Calcd for $[\text{C}_{20}\text{H}_{40}\text{O}_5\text{Si}+\text{H}]^+$: 389.2718, Found: 389.2720.

(*E*)-ethyl-3-((4*R*,5*R*)-5-((*R*)-6-hydroxyheptyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-acrylate (III-19a**)**

The monohydrate of *p*-toluenesulfonic acid (100 mg, 5.27 mmol) was added to a solution of diol **III-19** (2.05 g, 5.27 mmol), 2,2-dimethoxypropane (1.5 mL, 10.54 mmol) and CH_2CH_2 (4 mL). The solution was stirred for 5 h. The reaction mixture was diluted with CH_2CH_2 and washed with 1 N NaOH. The organic layer was dried over Na_2SO_4 , filtered and concentrated to give the crude product. The crude product was further purified by column chromatography to give alcohol **III-19a** (1.33 g, 4.25 mmol, 81%) as a colorless oil. R_f (30% Et_2O /hexane) = 0.40; $[\alpha]_{\text{D}}^{25} = +24$ (CH_2Cl_2); IR (thin film, cm^{-1}), 3473, 2934, 2861, 1722, 1661, 1371, 1259, 1174, 1036, 979; ^1H NMR (600 MHz, CDCl_3) δ 6.85 (dd, J = 15.6, 6.0 Hz, 1H), 6.10 (dd, J = 15.6, 1.2 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 4.11 (ddd, J = 6.6, 6.0, 1.2 Hz, 1H), 3.78 (qdd, J = 6.0, 6.0, 6.0 Hz, 1H), 3.72 (ddd, J =

6.6, 5.4, 3.0 Hz, 1H), 1.61-1.24 (m, 10H), 1.43 (s, 3H), 1.40 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.17 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 166.0, 144.1, 122.8, 109.4, 80.6, 80.2, 68.0, 60.6, 39.2, 31.9, 29.5, 27.2, 26.7, 25.9, 25.5, 23.5, 14.2; ESI HRMS Calcd for $[\text{C}_{17}\text{H}_{30}\text{O}_5 + \text{Na}]^+$: 337.1986, Found: 337.1987.

(*E*)-ethyl-3-((4*S*,5*S*)-5-((*R*)-6-hydroxyheptyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate
(III-20a)

The monohydrate of *p*-toluenesulfonic acid (2.3 mg, 0.012 mmol) was added to a solution of diol **III-20** (95.5 mg, 0.246 mmol), 2,2-dimethoxypropane (0.06 mL, 0.492 mmol) and CH_2CH_2 (0.2 mL). The solution was stirred for 5 h. The reaction mixture was diluted with CH_2CH_2 and washed with 1 N NaOH. The organic layer was dried over Na_2SO_4 , filtered and concentrated to give the crude product. The crude product was further purified by column chromatography to give alcohol **III-20a** (60 mg, 0.19 mmol, 78%) as a colorless oil. R_f (30% Et_2O /hexane) = 0.40; $[\alpha]_D^{25} = -20$ (CH_2Cl_2); IR (thin film, cm^{-1}), 3443, 2934, 2860, 1722, 1662, 1460, 1371, 1261, 1173, 1036, 979, 877; ^1H NMR (600 MHz, CDCl_3) δ 6.84 (dd, $J = 15.6, 6.0$ Hz, 1H), 6.10 (dd, $J = 15.6, 1.2$ Hz, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 4.13 (ddd, $J = 8.4, 6.0, 1.2$ Hz, 1H), 3.78 (qdd, $J = 6.0, 6.0, 6.0$ Hz, 1H), 3.72 (ddd, $J = 8.4, 6.0, 6.0$ Hz, 1H), 1.61-1.27 (m, 10H), 1.42 (s, 3H), 1.40 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.17 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 166.0, 144.1,

122.7, 109.3, 80.5, 80.2, 68.0, 60.6, 39.1, 31.9, 29.5, 27.2, 26.6, 25.9, 25.5, 23.5, 14.2;
ESI HRMS Calcd for $[C_{17}H_{30}O_5+Na]^+$: 337.1986, Found: 337.1987.

**(*E*)-3-(((4*R*,5*R*)-5-((*R*)-6-hydroxyheptyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylic acid
(**III-19b**)**

LiOH (452 mg, 10.78 mmol) was added to a solution of alcohol **III-19a** (1.35 g, 4.31 mmol), THF (4 mL) and H₂O (1 mL). The reaction mixture was stirred for 5 h, then diluted with CH₂CH₂ and washed with 1 N HCl and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated to give the crude product. The crude product was further purified by column chromatography to give acid **III-19b** (1.12 g, 3.92 mmol, 91%) as a colorless oil. *R_f* (50% Et₂O/hexane) = 0.26; $[\alpha]_D^{25} = +22$ (CH₂Cl₂); IR (thin film, cm⁻¹), 3450, 2933, 2862, 1701, 1380, 1261, 1238, 1111, 1054, 980; ¹H NMR (600 MHz, CDCl₃) δ 6.96 (dd, *J* = 15.6, 5.4 Hz, 1H), 6.13 (dd, *J* = 15.6, 1.2 Hz, 1H), 4.17 (ddd, *J* = 8.4, 5.4, 1.2 Hz, 1H), 3.80 (qdd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 3.72 (ddd, *J* = 8.4, 6.0, 6.0 Hz, 1H), 1.63-1.32 (m, 10H), 1.44 (s, 3H), 1.41 (s, 3H), 1.18 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 170.3, 146.6, 121.8, 109.5, 80.5, 80.1, 68.2, 39.0, 31.9, 29.5, 27.2, 26.6, 25.9, 25.5, 23.4; ESI HRMS Calcd for $[C_{15}H_{25}O_5+H]^+$: 287.1853, Found: 287.1854.

(*E*)-3-((4*S*,5*S*)-5-((*R*)-6-hydroxyheptyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylic acid
(III-20b)

LiOH (19.4 mg, 0.463 mmol) was added to a solution of alcohol **III-20a** (58 mg, 0.185 mmol), THF (1.7 mL) and H₂O (0.3 mL). The reaction mixture was stirred for 5 h, then diluted with CH₂CH₂ and washed with 1 N HCl and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated to give the crude product. The crude product was further purified by column chromatography to give acid **III-20b** (48 mg, 0.167 mmol, 90%) as a colorless oil. *R_f* (50% Et₂O/hexane) = 0.26; [α]_D²⁵ = - 22 (CH₂Cl₂); IR (thin film, cm⁻¹), 3311, 2934, 2860, 1702, 1373, 1240, 1169, 1052, 980, 863; ¹H NMR (600 MHz, CDCl₃) δ 6.95 (dd, *J* = 15.6, 5.4 Hz, 1H), 6.13 (dd, *J* = 15.6, 1.2 Hz, 1H), 4.17 (ddd, *J* = 8.4, 5.4, 1.2 Hz, 1H), 3.80 (qdd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 3.73 (ddd, *J* = 8.4, 6.0, 6.0 Hz, 1H), 1.63-1.32 (m, 10H), 1.44 (s, 3H), 1.41 (s, 3H), 1.18 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 170.3, 146.6, 121.8, 109.5, 80.5, 80.1, 68.2, 39.0, 32.0, 29.5, 27.2, 26.6, 25.9, 25.5, 23.4; ESI HRMS Calcd for [C₁₅H₂₆O₅+H]⁺: 287.1853, Found: 287.1854.

(3*aR*,8*R*,13*aR*,*E*)-2,2,8-trimethyl-9,10,11,12,13,13*a*-hexahydro-3*aH*-[1,3]dioxolo[4,5-*e*][1]oxacyclododecin-6(8*H*)-one (III-19c)

(3a*R*,8*R*,13a*R*,*Z*)-2,2,8-trimethyl-9,10,11,12,13,13a-hexahydro-3aH-[1,3]dioxolo[4,5-e][1]oxacyclododecin-6(8H)-one (**III-19d**)

To a solution of acid **III-19b** (47.5 mg, 0.17 mmol) and Et₃N (0.028 mL, 0.2 mmol) in THF (0.83 mL) was added 2,4,6-trichlorobenzoyl chloride (0.029 mL, 0.18 mmol) dropwise. The reaction mixture was stirred at room temperature for 2 h, followed by dilution with dry toluene (20 mL) and added dropwise to a refluxing solution of DMAP (646 mg, 5.3 mmol) in dry toluene (50 mL). After addition, the mixture was refluxed for 10 h and then concentrated in vacuum. The residue was dissolved in EtOAc (30 mL) and washed with 1 N HCl (20 mL), saturated NaHCO₃, brine, dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel to give the macrolactone **III-19c** (28.5 mg, 0.10 mmol, 60%)⁷ and macrolactone **III-19d** (4.74 mg, 0.017 mmol, 10%).

⁷ These known compounds were characterized based on the comparison of ¹H and ¹³C NMR data with the published ones: Chou, C.-Y. Hou, D.-R. *J. Org. Chem.* **2006**, *71*, 9887.

III-19c: colorless oil; R_f (10% Et₂O/hexane) = 0.33; $[\alpha]_D^{25} = +6$ (MeOH); IR (thin film, cm⁻¹), 2982, 2934, 2866, 1718, 1463, 1371, 1252, 1163, 1050, 988, 857; ¹H NMR (600 MHz, CDCl₃) δ 6.77 (dd, $J = 15.6, 9.6$ Hz, 1H), 6.22 (d, $J = 15.6$ Hz, 1H), 4.98 (dq, $J = 9.6, 6.0, 4.2$ Hz, 1H), 4.04 (dd, $J = 9.6, 8.4$ Hz, 1H), 3.91 (ddd, $J = 11.4, 8.4, 4.2$ Hz, 1H), 1.96 (ddt, $J = 13.8, 13.8, 4.2$ Hz, 1H), 1.68 (dddd, $J = 15.6, 9.0, 4.2, 1.8$ Hz, 1H), 1.61-1.35 (m, 8H), 1.44 (s, 3H), 1.42 (s, 3H), 1.30 (d, $J = 6.0$ Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 166.6, 143.8, 125.9, 109.3, 80.4, 80.1, 75.4, 35.4, 29.5, 27.8, 27.1, 26.8, 25.1, 24.9, 20.6; ESI HRMS Calcd for [C₁₅H₂₄O₄ + Na]⁺: 291.1567, Found: 291.1568.

III-19d: colorless oil; R_f (10% Et₂O/hexane) = 0.41; $[\alpha]_D^{25} = +53$ (MeOH); IR (thin film, cm⁻¹), 2982, 2939, 2866, 1718, 1380, 1206, 1047, 861; ¹H NMR (600 MHz, CDCl₃) δ 5.97 (d, $J = 12.0$ Hz, 1H), 6.22 (dd, $J = 12.0, 8.4$ Hz, 1H), 5.08 (qdd, $J = 6.0, 4.2, 3.0$ Hz, 1H), 4.87 (dd, $J = 9.0, 9.0$ Hz, 1H), 3.87 (ddd, $J = 9.0, 5.4, 1.8$ Hz, 1H), 1.85-1.41 (m, 8H), 1.42 (s, 3H), 1.41 (s, 3H), 1.25 (d, $J = 6.6$ Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 166.3, 139.1, 125.3, 109.3, 79.9, 75.1, 72.9, 30.8, 27.4, 27.2, 26.4, 25.4, 18.3, 18.2, 17.9; ESI HRMS Calcd for [C₁₅H₂₄O₄ + H]⁺: 269.1747, Found: 269.1748.

(3aS,8R,13aS,E)-2,2,8-trimethyl-9,10,11,12,13,13a-hexahydro-3aH-[1,3]dioxolo[4,5-e][1]oxacyclododecin-6(8H)-one (III-20c)

(3aS,8R,13aS,Z)-2,2,8-trimethyl-9,10,11,12,13,13a-hexahydro-3aH-[1,3]dioxolo[4,5-e][1]oxacyclododecin-6(8H)-one (III-20d)

To a solution of acid **III-20b** (180 mg, 0.63 mmol) and Et₃N (0.1 mL) in THF (3.1 mL) was added 2,4,6-trichlorobenzoyl chloride (0.11 mL, 0.65 mmol) dropwise. The reaction mixture was stirred at room temperature for 2h, followed by dilution with dry toluene (76 mL) and added dropwise to a refluxing solution of DMAP (169 mg, 20.16 mmol) in dry toluene (190 mL). After addition, the mixture was refluxed for 10 h and then concentrated in vacuum. The residue was dissolved in EtOAc (100 mL) and washed with 1 N HCl, saturated NaHCO₃, brine, dried over Na₂SO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel to give the macrolactone **III-20c** (108 mg, 0.39 mmol, 62%) and macrolactone **III-20d** (17 mg, 0.06 mmol, 10%)⁸

III-20c: colorless oil. *R_f* (10% Et₂O/hexane) = 0.56; [α]_D²⁵ = + 30 (MeOH); IR (thin film, cm⁻¹), 2983, 2937, 2870, 1717, 1465, 1230, 1163, 1057, 993, 848; ¹H NMR (600 MHz, CDCl₃) δ 6.86 (dd, *J* = 16.2, 6.6 Hz, 1H), 6.20 (dd, *J* = 16.2, 1.2 Hz, 1H), 5.02 (qdd, *J* = 6.0, 5.4, 5.4 Hz, 1H), 4.11 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H), 3.63 (ddd, *J* = 10.8, 8.4, 3.6 Hz, 1H), 1.99-1.44 (m, 8H), 1.44 (s, 3H), 1.43 (s, 3H), 1.28 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 166.8, 143.9, 123.7, 109.5, 83.0, 81.2, 73.1, 33.3, 29.0, 27.4, 27.3,

⁸ Sharma, G. V. M.; Reddy, J. J.; Reddy, K. L. *Tetrahedron Lett.* **2006**, 47, 6531-6535.

26.9, 25.3, 24.2, 20.2; ESI HRMS Calcd for $[C_{15}H_{24}O_4+Na]^+$: 291.1567, Found: 291.1568.

III-20d: colorless oil. R_f (10% Et₂O/hexane) = 0.38; $[\alpha]^{25}_D = -50$ (MeOH); IR (thin film, cm⁻¹), 2941, 2937, 1710, 1460, 1379, 1298, 1211, 1074, 1045, 993, 833; ¹H NMR (600 MHz, CDCl₃) δ 6.14 (dd, $J = 12.0, 8.4$ Hz, 1H), 6.22 (dd, $J = 12.0, 1.2$ Hz, 1H), 5.31 (ddd, $J = 9.0, 8.4, 1.2$ Hz, 1H), 4.89 (dq, $J = 12.0, 6.0, 3.6$ Hz, 1H), 3.87 (dd, $J = 8.4, 6.0$ Hz, 1H), 1.75-1.31 (m, 16H), 1.45 (s, 3H), 1.42 (s, 3H), 1.27 (d, $J = 6.0$ Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 165.8, 144.7, 123.7, 109.3, 79.5, 74.2, 74.0, 32.5, 27.3, 27.0, 26.5, 24.4, 20.8, 20.1, 17.1; ESI HRMS Calcd for $[C_{15}H_{24}O_4+Na]^+$: 291.1567, Found: 291.1568.

(5*R*,6*R*,12*R*,*E*)-5,6-dihydroxy-12-methyloxacyclododec-3-en-2-one (Cladospolide C)

To a solution of lactone **III-19c** (140 mg, 0.50 mmol) and acetonitrile/water (2:1, v/v, 5 mL) was added trifluoroacetic acid (3.75 mL) at 0 °C. Then the reaction was stirred at room temperature for another 2 h, diluted with ether acetate, washed with sat. NaHCO₃(aq), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to give the **Cladospolide C** (91 mg, 0.40 mmol, 80%)

as a colorless solid.⁹ R_f (50% Et₂O/hexane) = 0.27; Mp 91-92 °C; $[\alpha]_D^{25} = -90$ (MeOH); IR (thin film, cm⁻¹), 3415, 2940, 2864, 1705, 1650, 1460, 1258, 1035; ¹H NMR (600 MHz, CDCl₃) δ 6.81 (dd, $J = 15.6, 9.0$ Hz, 1H), 6.05 (d, $J = 15.6$ Hz, 1H), 4.98 (dq, $J = 8.4, 6.0, 1.8$ Hz, 1H), 3.98 (dd, $J = 8.4, 7.8$ Hz, 1H), 3.57 (ddd, $J = 7.8, 7.8, 1.8$ Hz, 1H), 1.30 (d, $J = 6.0$ Hz, 3H) 1.69-1.11 (m, 10H); ¹³C NMR (150 MHz, CD₃Cl) δ 166.7, 145.3, 124.5, 77.5, 76.5, 74.3, 33.9, 32.1, 27.3, 24.5, 24.1, 20.8; ESI HRMS Calcd for [C₁₂H₂₀O₄+H]⁺: 229.1434, Found: 229.1435.

(5*R*, 6*R*, 12*R*, *Z*)-5,6-dihydroxy-12-methyloxacyclododec-3-en-2-one (III-17)

To a solution of lactone **III-19d** (58 mg, 0.21 mmol) and acetonitrile/water (2:1, v/v, 2 mL) was added trifluoroacetic acid (1.58 mL) at 0 °C. Then the reaction was stirred at room temperature for another 2 h, diluted with ether acetate, washed with sat. NaHCO₃(aq), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to give the lactone **III-17** (48 mg, 0.17 mmol, 81%) as a colorless oil; R_f (50% Et₂O/hexane) = 0.33; $[\alpha]_D^{25} = +1$ (MeOH); IR (thin film, cm⁻¹), 3272, 2943, 2862, 1710, 1461, 1278, 1050; ¹H NMR (600 MHz, CDCl₃) δ 6.12 (dd, $J = 12.0, 8.4$ Hz, 1H), 6.05 (dd, $J = 12.0, 1.2$ Hz, 1H), 5.10 (qdd, $J = 6.0, 5.4, 3.0$ Hz, 1H),

⁹ These known compounds were characterized based on the comparison of ¹H and ¹³C NMR data with the published ones: Chou, C.-Y. Hou, D.-R. *J. Org. Chem.* **2006**, *71*, 9887.

4.97 (ddd, $J = 8.4, 4.8, 1.2$ Hz, 1H), 3.87 (ddd, $J = 9.0, 4.8, 3.0$ Hz, 1H), 2.04-1.35 (m, 10H), 1.25 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 166.7, 145.3, 124.5, 77.5, 76.5, 74.3, 33.9, 32.1, 27.3, 24.5, 24.1, 20.8; ESI HRMS Calcd for $[\text{C}_{12}\text{H}_{20}\text{O}_4+\text{H}]^+$: 229.1434, Found: 229.1435.

(5*S*, 6*S*, 12*R*, *E*)-5, 6-dihydroxy-12-methyloxacyclododec-3-en-2-one (III-18)

To a solution of lactone **III-20c** (68 mg, 0.24 mmol) and acetonitrile/water (2:1, v/v, 2.5 mL) was added trifluoroacetic acid (1.83 mL) at 0 °C. Then the reaction was stirred at room temperature for another 2 h, diluted with ether acetate, washed with sat. $\text{NaHCO}_3(\text{aq})$, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography on silica gel to give the lactone **III-18** (45 mg, 0.20 mmol, 83%) as a colorless oil; R_f (50% Et_2O /hexane) = 0.41; $[\alpha]_D^{25} = -10$ (MeOH); IR (thin film, cm^{-1}), 3396, 2937, 2870, 1711, 1464, 1247, 1028; ^1H NMR (600 MHz, CDCl_3) δ 6.94 (dd, $J = 15.6, 6.0$ Hz, 1H), 6.12 (dd, $J = 15.6, 1.2$ Hz, 1H), 4.96 (dq, $J = 6.6, 6.0, 3.0$ Hz, 1H), 4.12 (ddd, $J = 7.2, 6.0, 1.2$ Hz, 1H), 3.32 (ddd, $J = 9.6, 7.8, 1.8$ Hz, 1H), 1.74-1.20 (m, 10H), 1.28 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 167.2, 146.9, 122.5, 78.0, 77.8, 73.1, 33.2, 32.6, 28.3, 25.0, 22.8, 19.0; ESI HRMS Calcd for $[\text{C}_{12}\text{H}_{20}\text{O}_4+\text{Na}]^+$: 251.1254, Found: 251.1254.

(5*S*,6*S*,12*R*,*Z*)-5,6-dihydroxy-12-methyloxacyclododec-3-en-2-one (Cladospolide B)

To a solution of lactone **III-20d** (34 mg, 0.12 mmol) and acetonitrile/water (2:1, v/v, 1.2 mL) was added trifluoroacetic acid (0.90 mL) at 0 °C. Then the reaction was stirred at room temperature for another 2 h, diluted with ether acetate, washed with sat. NaHCO₃(aq), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to give the **Cladospolide B** (27 mg, 0.10 mmol, 81%) as a white solid;¹⁰ *R_f* (50% Et₂O/hexane) = 0.57; Mp 108-109 °C; [α]_D²⁵ = + 5 (MeOH); IR (thin film, cm⁻¹), 3345, 2934, 2865, 1707, 1461, 1280, 1046; ¹H NMR (600 MHz, CDCl₃) δ 6.23 (dd, *J* = 12.0, 8.4 Hz, 1H), 5.77 (dd, *J* = 12.0, 1.2 Hz, 1H), 5.26 (ddd, *J* = 8.4, 4.2, 1.2 Hz, 1H), 4.88 (dq, *J* = 10.2, 6.0, 1.8 Hz, 1H), 3.77 (ddd, *J* = 9.0, 4.2, 2.4 Hz, 1H), 1.84-1.35 (m, 10H), 1.28 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 165.8, 148.5, 121.9, 74.4, 73.9, 67.5, 32.0, 30.6, 25.7, 24.1, 21.3, 19.7; ESI HRMS Calcd for [C₁₂H₂₀O₄+H]⁺: 229.1434, Found: 229.1435.

¹⁰ These known compounds were characterized based on the comparison of ¹H and ¹³C NMR data with the published ones: Austin, K. A. B.; Banwell, M. G.; Loong, D. T. J.; Rae, A. D.; Willis, A. C. *Org. Biomol. Chem.* **2005**, *3*, 1081.

(5*R*,6*R*,12*R*,*E*)-6-(tert-butyldimethylsilyloxy)-5-hydroxy-12-methyloxacyclododec-3-en-2-one (III-3a)

(5*R*,6*R*,12*R*,*E*)-5-(tert-butyldimethylsilyloxy)-6-hydroxy-12-methyloxacyclododec-3-en-2-one (III-3a1)

To a magnetically stirred solution of **Cladospolide C** (10 mg, 0.044 mmol) and imidazole (7.5 mg, 0.11 mmol) in dry CH₂Cl₂ (0.5 mL) was added dropwise TBSCl (19 mg, 0.13 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. Water was added and then the reaction mixture was extracted with Et₂O, dried with Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash chromatography to give alcohol **III-3a** (4.5 mg, 0.013 mmol, 30%) and alcohol **III-3a1** (9 mg, 0.026 mmol, 60%).

III-3a: colorless oil; *R*_f (10% Et₂O/hexane) = 0.20; [α]_D²⁵ = 50 (CH₂Cl₂); IR (thin film, cm⁻¹), 3457, 2930, 2858, 1722, 1463, 1255, 1048, 998, 776 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.84 (dd, *J* = 15.6, 9.0 Hz, 1H), 6.07 (d, *J* = 15.6 Hz, 1H), 5.02 (dq, *J* = 9.0,

6.0, 3.0 Hz, 1H), 4.04 (dd, $J = 9.0, 7.2$ Hz, 1H), 3.64 (ddd, $J = 8.4, 7.2, 1.2$ Hz, 1H), 1.70-1.10 (m, 10H), 1.28 (d, $J = 6.0$ Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 167.2, 145.4, 123.7, 77.2, 76.8, 73.7, 33.5, 32.1, 27.6, 25.8, 24.4, 23.4, 20.3, 18.0, - 4.49, - 4.78; ESI HRMS Calcd for $[\text{C}_{18}\text{H}_{34}\text{O}_4\text{Si}+\text{H}]^+$: 343.2299, Found: 343.2300.

III-3a1: colorless oil; R_f (10% Et_2O /hexane) = 0.08; $[\alpha]_D^{25} = + 34$ (CH_2Cl_2); IR (thin film, cm^{-1}), 3482, 2931, 2859, 1721, 1463, 1254, 1039, 997, 778; ^1H NMR (600 MHz, CDCl_3) δ 6.77 (dd, $J = 16.2, 9.0$ Hz, 1H), 6.01 (dd, $J = 16.2, 0.6$ Hz, 1H), 4.99 (dq, $J = 10.2, 6.0, 2.4$ Hz, 1H), 3.93 (ddd, $J = 9.0, 7.2, 0.6$ Hz, 1H), 3.54 (ddd, $J = 7.2, 7.2, 2.4$ Hz, 1H), 1.70-1.11 (m, 10H), 1.30 (d, $J = 6.0$ Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 167.0, 146.6, 123.8, 78.3, 76.6, 74.2, 33.8, 30.4, 27.5, 25.8, 24.4, 24.0, 20.7, 18.1, - 4.50, - 4.82; ESI HRMS Calcd for $[\text{C}_{18}\text{H}_{34}\text{O}_4\text{Si}+\text{H}]^+$: 343.2299, Found: 343.2300.

(6*R*,12*R*,*E*)-6-(tert-butyldimethylsilyloxy)-12-methyloxacyclododec-3-ene-2,5-dione

(III-3b)

To a magnetically stirred solution of alcohol **III-3a** (5 mg, 0.015 mmol) in dry CH₂Cl₂ (0.2 mL) was added Dess-Martin periodinane (16 mg, 0.038 mmol) at room temperature. The reaction mixture was stirred for 1 h. CH₂Cl₂ was added to dilute the reaction solution and then the reaction mixture was washed with NaHCO₃, extracted with ether acetate, dried with Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash chromatography to give ketone **III-3b** (4.6 mg, 0.014 mmol, 95%) as a colorless oil; *R_f* (10% Et₂O/hexane) = 0.33; [α]_D²⁵ = - 12 (CH₂Cl₂); IR (thin film, cm⁻¹), 2931, 2858, 1721, 1463, 1251, 1078, 838, 779; ¹H NMR (600 MHz, CDCl₃) δ 7.21 (d, *J* = 16.8 Hz, 1H), 6.90 (d, *J* = 16.8 Hz, 1H), 4.89 (dq, *J* = 7.8, 6.0, 4.8 Hz, 1H), 4.41 (dd, *J* = 6.0, 4.2 Hz, 1H), 1.78-1.15 (m, 10H), 1.34 (d, *J* = 6.0 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 200.8, 166.8, 138.2, 131.3, 79.2, 75.3, 35.1, 34.1, 27.7, 25.8, 23.9, 20.6, 18.1, - 4.79, - 5.25; ESI HRMS Calcd for [C₁₈H₃₂O₄Si+Na]⁺: 363.1962, Found: 363.1964.

(6*R*,12*R*,*E*)-6-hydroxy-12-methyloxacyclododec-3-ene-2,5-dione (III-28)

To a plastic flask were added **III-3b** (4 mg, 0.012 mmol) and 5% HF in CH₃CN (15 μ L) at room temperature. The reaction mixture was stirred for 2 h and then ether acetate was added to dilute the reaction solution. The reaction mixture was washed with NaHCO₃,

extracted with ether acetate, dried with Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash chromatography to give ketone **III-28** (2.3 mg, 0.102 mmol, 85%) as a colorless oil; *R_f* (50% Et₂O/hexane) = 0.33; [α]_D²⁵ = - 23 (CH₂Cl₂); IR (thin film, cm⁻¹), 3501, 2931, 1719, 1249, 1156; ¹H NMR (600 MHz, CDCl₃) δ 7.37 (d, *J* = 16.2 Hz, 1H), 6.67 (d, *J* = 16.2 Hz, 1H), 4.94 (dq, *J* = 9.6, 6.0, 3.0 Hz, 1H), 4.34 (dd, *J* = 9.6, 3.0 Hz, 1H), 2.01 (m, 1H), 1.67-1.17 (m, 9H), 1.42 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 201.5, 165.6, 137.5, 131.2, 77.3, 75.2, 35.1, 33.5, 27.8, 24.5, 23.3, 20.8; ESI HRMS Calcd for [C₁₂H₁₈O₄+H]⁺: 227.1278, Found: 227.1278.

(5*S*,6*S*,12*R*,*E*)-6-(tert-butyldimethylsilyloxy)-5-hydroxy-12-methyloxacyclododec-3-en-2-one (III-18a)

(5*S*,6*S*,12*R*,*E*)-5-(tert-butyldimethylsilyloxy)-6-hydroxy-12-methyloxacyclododec-3-en-2-one (III-18a1)

To a magnetically stirred solution of diol **III-18** (20 mg, 0.088 mmol) and imidazole (15 mg, 0.22 mmol) in dry CH₂Cl₂ (1 mL) was added dropwise TBSCl (38 mg, 0.26 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. Water was added and then the reaction mixture was extracted with Et₂O, dried with Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash chromatography to give alcohol **III-18a** (18 mg, 0.053 mmol, 60%) and alcohol **III-18a1** (9 mg, 0.027 mmol, 30%).

III-18a: colorless oil; *R_f* (10% Et₂O/hexane) = 0.17; [α]_D²⁵ = + 7 (CH₂Cl₂); IR (thin film, cm⁻¹), 3484, 2931, 2858, 1716, 1464, 1252, 1004, 837, 776; ¹H NMR (600 MHz, CDCl₃) δ 6.95 (dd, *J* = 15.6, 5.4 Hz, 1H), 6.10 (dd, *J* = 15.6, 1.8 Hz, 1H), 5.08 (qdd, *J* = 6.0, 6.0, 2.4 Hz, 1H), 4.04 (ddd, *J* = 7.2, 5.4, 1.8 Hz, 1H), 3.30 (dd, *J* = 7.2, 7.2, Hz, 1H), 1.60-1.20 (m, 10H), 1.28 (d, *J* = 6.0 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 6H); ¹³C NMR (150 MHz, CD₃Cl) δ 166.9, 146.8, 121.9, 78.9, 77.3, 72.6, 33.7, 32.4, 28.0, 25.8, 24.5, 22.9, 19.0, 18.0, - 4.20, - 4.19; ESI HRMS Calcd for [C₁₈H₃₄O₄Si+Na]⁺: 365.2189, Found: 365.2120.

III-18a1: colorless oil; *R_f* (10% Et₂O/hexane) = 0.20; [α]_D²⁵ = + 30 (CH₂Cl₂); IR (thin film, cm⁻¹), 3508, 2932, 2858, 1716, 1464, 1251, 1229, 1004, 837, 778; ¹H NMR (600 MHz, CDCl₃) δ 6.94 (dd, *J* = 16.2, 6.0 Hz, 1H), 6.05 (dd, *J* = 16.2, 1.2 Hz, 1H), 5.11 (dq, *J* = 6.6, 6.0, 3.0 Hz, 1H), 4.03 (ddd, *J* = 7.2, 6.0, 1.2 Hz, 1H), 3.29 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 1.75-1.20 (m, 10H), 1.28 (d, *J* = 6.0 Hz, 3H), 0.93 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 166.9, 147.9, 122.4, 78.7, 77.9, 72.7, 32.3,

31.6, 28.0, 25.8, 24.8, 22.6, 18.8, 18.1, -5.35, -5.36; ESI HRMS Calcd for $[C_{18}H_{34}O_4Si + H]^+$: 343.2119, Found: 343.2301.

(6*S*,12*R*,*E*)-6-(tert-butyldimethylsilyloxy)-12-methyloxacyclododec-3-ene-2,5-dione
(III-18b)

To a magnetically stirred solution of alcohol **III-18a** (10 mg, 0.03 mmol) in dry CH_2Cl_2 (0.4 mL) was added Dess-Martin periodinane (32 mg, 0.076 mmol) at room temperature. The reaction mixture was stirred for 1 h. CH_2Cl_2 was added to dilute the reaction solution and then the reaction mixture was washed with $NaHCO_3$, extracted with ether acetate, dried with Na_2SO_4 and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash chromatography to give ketone **III-18b** (9.2 mg, 0.028 mmol, 95%) as a colorless oil; R_f (10% Et_2O /hexane) = 0.64; $[\alpha]_D^{25} = + 31$ (CH_2Cl_2); IR (thin film, cm^{-1}), 2932, 2858, 1723, 1464, 1254, 1095, 847, 779; 1H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, $J = 16.8$ Hz, 1H), 6.93 (d, $J = 16.8$ Hz, 1H), 4.63 (qdd, $J = 6.0, 6.0, 6.0$ Hz, 1H), 4.34 (dd, $J = 6.0, 1.6$ Hz, 1H), 1.90-1.06 (m, 10H), 1.34 (d, $J = 6.0$ Hz, 3H), 0.92 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 201.3, 167.5, 134.2, 132.0, 77.2, 74.9, 34.8, 34.2, 27.9, 25.7, 24.1, 21.4, 20.6, 18.1, - 4.91, - 4.90; ESI HRMS Calcd for $[C_{18}H_{32}O_4Si + H]^+$: 341.2143, Found: 341.2144.

(6*S*,12*R*,*E*)-6-hydroxy-12-methyloxacyclododec-3-ene-2,5-dione (III-29)

To a plastic flask was added **III-18b** (8 mg, 0.024 mmol) and 5% HF in CH₃CN (30 μ L) at room temperature. The reaction mixture was stirred for 2 hrs and then ether acetate was added to dilute the reaction solution. The reaction mixture was washed with NaHCO₃, extracted with ether acetate, dried with Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash chromatography to give ketone **III-29** (4.6 mg, 0.2 mmol, 85%) as a colorless oil; *R*_f (50% Et₂O/hexane) = 0.56; [α]_D²⁵ = -10 (CH₂Cl₂); IR (thin film, cm⁻¹), 3508, 2936, 1714, 1256, 1194, cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 7.12 (d, *J* = 16.2 Hz, 1H), 6.82 (d, *J* = 16.2 Hz, 1H), 4.92 (qdd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 4.52 (dd, *J* = 8.4, 4.2 Hz, 1H), 1.90 (m, 1H), 1.72-1.18 (m, 9H), 1.36 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 203.0, 166.3, 138.0, 130.9, 75.1, 74.6, 35.0, 34.8, 26.7, 24.0, 23.3, 20.7; ESI HRMS Calcd for [C₁₂H₁₈O₄+H]⁺: 227.1278, Found: 227.1278.

(6*S*,12*R*,*Z*)-6-(tert-butyldimethylsilyloxy)-12-methyloxacyclododec-3-ene-2,5-dione
(III-2a)

(A) To a magnetically stirred solution of **Cladospolide B** (5 mg, 0.022 mmol) and imidazole (4 mg, 0.05 mmol) in dry CH₂Cl₂ (0.2 mL) was added dropwise TBSCl (9 mg, 0.06 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. Water was added and then the reaction mixture was extracted with Et₂O, dried with Na₂SO₄ and evaporated under reduced pressure to leave the inseparable 1:2 mixture of alcohol (6.8 mg, 0.02 mmol). To a magnetically stirred solution of mixture of (2 mg, 0.006 mmol) in dry CH₂Cl₂ (0.06 mL) was added Dess-Martin periodinane (6 mg, 0.015 mmol) at room temperature. The reaction mixture was stirred for 1 h. CH₂Cl₂ was added to dilute the reaction solution and then the reaction mixture was washed with NaHCO₃, extracted with ether acetate, dried with Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash chromatography to give ketone **III-2a** (0.6 mg, 0.0018 mmol, 27% in 2 steps)

(B) To a plastic flask was added **III-18b** (8 mg, 0.024 mmol) and 5% HF/Py. (2:1) in CH₃CN (30 µL) at room temperature. The reaction mixture was stirred for 2 h and then ether acetate was added to dilute the reaction solution. The reaction mixture was washed with NaHCO₃, extracted with ether acetate, dried with Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash

chromatography to give ketone **III-2a** (7.4 mg, 0.22 mmol, 90%) as a colorless oil; *R_f* (10% Et₂O/hexane) = 0.37; [α]_D²⁵ = - 80 (CH₂Cl₂); IR (thin film, cm⁻¹), 2931, 2860, 1726, 1464, 1251, 1164, 1119, 839, 778; ¹H NMR (600 MHz, CDCl₃) δ 6.73 (d, *J* = 12.6 Hz, 1H), 6.23 (d, *J* = 12.6 Hz, 1H), 4.91 (dq, *J* = 9.6, 6.0, 3.0 Hz, 1H), 4.32 (dd, *J* = 7.8, 4.2 Hz, 1H), 1.93-1.26 (m, 10H), 1.27 (d, *J* = 6.0 Hz, 3H), 0.93 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 203.2, 166.3, 133.6, 130.6, 76.4, 73.9, 33.3, 330.5, 26.3, 25.8, 22.1, 21.2, 20.0, 18.1, -4.91, -5.07; ESI HRMS Calcd for [C₁₈H₃₂O₄Si+H]⁺: 341.2143, Found: 341.2144.

(6*S*,12*R*,*Z*)-6-hydroxy-12-methyloxacyclododec-3-ene-2,5-dione ((*ent*)-Cladospolide D **III-31)**

To a plastic flask was added **III-2a** (5 mg, 0.015 mmol) and 5% HF in CH₃CN (17 μ L) at room temperature. The reaction mixture was stirred for 2 h and then ether acetate was added to dilute the reaction solution. The reaction mixture was washed with NaHCO₃, extracted with ether acetate, dried with Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash chromatography to give (*ent*)-Cladospolide D **III-31** (3 mg, 0.013 mmol, 87%) as a colorless oil;¹¹ *R_f* (30%

¹¹ Zhang, H.; Tomoda, H.; Tabata, N.; Miura, H.; Namikoshi, M.; Yamaguchi, Y.; Masuma, R.; Omura, S. *J. O. Anti.* **54**, 635-641

Et₂O/hexane) = 0.36; $[\alpha]_D^{25} = -28$ (CH₂Cl₂); IR (thin film, cm⁻¹), 3467, 2936, 1720, 1224, 1167, 1083; ¹H NMR (600 MHz, CDCl₃) δ 6.40 (d, *J* = 13.2 Hz, 1H), 6.31 (d, *J* = 13.2 Hz, 1H), 5.22 (dq, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4.66 (ddd, *J* = 8.4, 6.0, 5.4 Hz, 1H), 3.16 (d, *J* = 6.0 Hz, 1H), 1.95 (m, 1H), 1.72-1.18 (m, 9H), 1.30 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 203.5, 165.4, 133.3, 130.9, 73.5, 71.5, 33.2, 31.1, 23.0, 21.6, 21.5, 20.6; ESI HRMS Calcd for [C₁₂H₁₈O₄+H]⁺: 227.1278, Found: 227.1278.

(5*R*,6*R*,12*R*,*Z*)-6-(tert-butyldimethylsilyloxy)-5-hydroxy-12-methyloxacyclododec-3-en-2-one (III-17a)

(5*R*,6*R*,12*R*,*Z*)-5-(tert-butyldimethylsilyloxy)-6-hydroxy-12-methyloxacyclododec-3-en-2-one (III-17a1)

To a magnetically stirred solution of diol **III-17** (15 mg, 0.066 mmol) and imidazole (11.2 mg, 0.16 mmol) in dry CH₂Cl₂ (0.7 mL) was added dropwise TBSCl (30 mg, 0.2 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. Water was added and then the reaction mixture was extracted with Et₂O, dried with

Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash chromatography to give alcohol **III-17a** (6.7 mg, 0.02 mmol, 30%) and alcohol **III-17a1** (13.4 mg, 0.04 mmol, 60%).

III-17a: colorless oil; *R_f* (20% Et₂O/hexane) = 0.39; [α]²⁵_D = -56 (CH₂Cl₂); IR (thin film, cm⁻¹), 3482, 2931, 2858, 1713, 1463, 1217, 1075, 835, 778; ¹H NMR (600 MHz, CDCl₃) δ 6.14 (dd, *J* = 12.0, 7.2 Hz, 1H), 6.93 (dd, *J* = 12.0, 1.2 Hz, 1H), 5.14 (qdd, *J* = 6.0, 6.0, 3.0 Hz, 1H), 4.94 (dd, *J* = 7.2, 1.2 Hz, 1H), 3.98 (ddd, *J* = 10.2, 3.0, 1.2 Hz, 1H), 2.06-1.26 (m, 10H), 1.39 (d, *J* = 6.0 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 165.8, 148.7, 121.0, 74.3, 72.5, 67.4, 31.9, 29.3, 25.8, 24.4, 21.5, 21.2, 18.0, 16.8, - 4.70, - 5.09; ESI HRMS Calcd for [C₁₈H₃₄O₄Si +H]⁺: 343.2299, Found: 343.2300.

III-17a1: colorless oil; *R_f* (20% Et₂O/hexane) = 0.6; [α]²⁵_D = + 40 (CH₂Cl₂); IR (thin film, cm⁻¹), 3570, 2931, 2857, 1713, 1464, 1199, 1073, 836, 779; ¹H NMR (600 MHz, CDCl₃) δ 6.14 (d, *J* = 12.0, 8.4 Hz, 1H), 6.93 (dd, *J* = 12.0, 1.2 Hz, 1H), 5.13 (qdd, *J* = 6.0, 4.8, 3.6 Hz, 1H), 5.02 (ddd, *J* = 9.0, 3.6, 1.2 Hz, 1H), 3.75 (ddd, *J* = 9.6, 7.2, 3.6, Hz, 1H), 2.03-1.25 (m, 10H), 1.27 (d, *J* = 6.0 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 166.1, 146.9, 121.6, 73.6, 72.6, 69.0, 31.5, 29.9, 26.0, 24.9, 20.9, 20.7, 18.3, 17.3, - 4.66, - 4.68; ESI HRMS Calcd for [C₁₈H₃₄O₄Si +H]⁺: 343.2299, Found: 343.2301.

(6*R*,12*R*,*Z*)-6-(tert-butyldimethylsilyloxy)-12-methyloxacyclododec-3-ene-2,5-dione
(III-17b)

To a magnetically stirred solution of alcohol **III-17a** (8 mg, 0.023 mmol) in dry CH₂Cl₂ (0.3 mL) was added Dess-Martin periodinane (24 mg, 0.058 mmol) at room temperature. The reaction mixture was stirred for 1 h. CH₂Cl₂ was added to dilute the reaction solution and then the reaction mixture was washed with NaHCO₃, extracted with ether acetate, dried with Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash chromatography to give ketone **III-17b** (7.4 mg, 0.022 mmol, 95%) as a colorless oil; *R_f* (10% Et₂O/hexane) = 0.50; [α]_D²⁵ = + 18 (CH₂Cl₂); IR (thin film, cm⁻¹), 2932, 2857, 1717, 1464, 1285, 1098, 838, 778; ¹H NMR (600 MHz, CDCl₃) δ 6.78 (d, *J* = 12.6 Hz, 1H), 5.95 (d, *J* = 12.6 Hz, 1H), 4.87 (dq, *J* = 9.0, 6.0, 3.0 Hz, 1H), 4.14 (dd, *J* = 9.6, 3.0 Hz, 1H), 1.84-1.24 (m, 10H), 1.25 (d, *J* = 6.0 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ¹³C NMR (150 MHz, CD₃Cl) δ 204.3, 164.5, 140.4, 125.9, 78.8, 73.9, 31.9, 31.3, 27.1, 25.7, 20.7, 19.5, 19.3, 18.0, - 4.80, - 5.13; ESI HRMS Calcd for [C₁₈H₃₂O₄Si+Na]⁺: 363.1962, Found: 363.1964.

(6*R*,12*R*,*Z*)-6-hydroxy-12-methyloxacyclododec-3-ene-2,5-dione (III-30)

To a plastic flask was added **III-17b** (6 mg, 0.018 mmol) and 5% HF in CH₃CN (20 μ L) at room temperature. The reaction mixture was stirred for 2 h and then ether acetate was added to dilute the reaction solution. The reaction mixture was washed with NaHCO₃, extracted with ether acetate, dried with Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash chromatography to give alcohol **III-30** (3.4 mg, 0.015 mmol, 86%) as a colorless oil; *R*_f (30% Et₂O/hexane) = 0.32; [α]_D²⁵ = + 4 (CH₂Cl₂); IR (thin film, cm⁻¹), 3453, 2934, 1712, 1284, 1083; ¹H NMR (600 MHz, CDCl₃) δ 6.56 (d, *J* = 13.2 Hz, 1H), 6.20 (d, *J* = 13.2 Hz, 1H), 4.96 (dq, *J* = 9.6, 6.0, 3.6 Hz, 1H), 4.44 (m 1H), 2.01 (m, 1H), 1.82-1.18 (m, 9H), 1.27 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 203.2, 165.3, 134.8, 130.3, 76.0, 74.0, 31.2, 31.0, 27.3, 25.6, 21.5, 18.7; ESI HRMS Calcd for [C₁₂H₁₈O₄+H]⁺: 227.1278, Found: 227.1278.

(*R,E*)-12-methyloxacyclododec-3-ene-2,5,6-trione (III-26)

A solution of diol **III-3** (6 mg, 0.026 mmol) and trichloroisocyanuric acid (6.1 mg, 0.026 mmol) in ethyl ether (0.3 ml) was stirred at $-30\text{ }^{\circ}\text{C}$, then 2,2,6,6-tetramethylpiperidinoxy was added in one portion. The mixture was stirred for 60 min and then quenched with saturated sodium carbonate. The organic layer was separated and the aqueous layer was extracted with ether. Combined the organic layer, washed with brine, dried (Na_2SO_4), filtered and concentrated. Chromatography on silica gel gave **III-26** (3.8 mg, 0.017 mmol, 67%) as colorless oil.

A solution of diol **III-18** (12 mg, 0.052 mmol) and trichloroisocyanuric acid (12.3 mg, 0.053 mmol) in ethyl ether (0.5 ml) was stirred at $-30\text{ }^{\circ}\text{C}$, then 2,2,6,6-tetramethylpiperidinoxy was added in one portion. The mixture was stirred for 60 min and then quenched with saturated sodium carbonate. The organic layer was separated and the aqueous layer was extracted with ether. Combined the organic layer, washed with brine, dried (Na_2SO_4), filtered and concentrated. Chromatography on silica gel gave **III-26** (7.6 mg, 0.034 mmol, 65%) as colorless oil.

III-16: $R_f = 0.67$ (7:3 (v/v) hexane/EtOAc); $[\alpha]_D^{20} = -2$ ($c = 0.1$, MeOH); IR (thin film, cm^{-1}) 3373, 2934, 1715, 1134, 1040, 987, 706; ^1H NMR (600 MHz, CDCl_3) ^1H spectra shows a mixture of diketone **16** and its hydrate, peaks associated with the diketone: δ 6.87 (d, $J = 15.6$ Hz, 1H), 6.36 (d, $J = 15.6$ Hz, 1H), 5.05 (m, 1H), 3.05 (ddd, $J = 13.2$, 7.8, 3.0 Hz, 1H), 2.36 (ddd, $J = 13.2$, 12.0, 3.0 Hz, 1H), 1.41 (d, $J = 7.8$ Hz, 3H), peaks associated with the hydrate: 7.00 (s, 2H), 4.60 (m, 1H), 4.14 (s, 1H), 3.73 (s, 1H), 2.69

(m,1H), 2.54 (m,1H), 1.41 (d, $J = 6.6$ Hz, 3H), peaks associated with the mixture: 1.67-1.54 (m); ^{13}C NMR (150 MHz, CD_3Cl) diketone **16**: δ 204.2, 195.6, 164.9, 136.6, 136.0, 75.5, 39.5, 34.8, 24.8, 23.4, 21.8, 20.8; ESI HRMS Calcd for $[\text{C}_{12}\text{H}_{16}\text{O}_4 + \text{H}]^+$: 225.1121, Found: 225.1122.

(*R,Z*)-12-methyloxacyclododec-3-ene-2,5,6-trione (III-27)

A solution of diol **III-17** (6 mg, 0.026 mmol) and trichloroisocyanuric acid (6.0 mg, 0.026 mmol) in ethyl ether (0.3 ml) was stirred at $-30\text{ }^{\circ}\text{C}$, then 2,2,6,6-tetramethylpiperidinoxy was added in one portion. The mixture was stirred for 40 min and then quenched with saturated sodium carbonate. The organic layer was separated and the aqueous layer was extracted with ether. Combined the organic layer, washed with brine, dried (Na_2SO_4), filtered and concentrated. Chromatography on silica gel gave **III-27** (5.0 mg, 0.022 mmol, 86%) as colorless oil.

A solution of diol **III-2** (15 mg, 0.066 mmol) and trichloroisocyanuric acid (15.3 mg, 0.066 mmol) in ethyl ether (0.6 ml) was stirred at $-30\text{ }^{\circ}\text{C}$, then 2,2,6,6-tetramethylpiperidinoxy was added in one portion. The mixture was stirred for 40 min and then quenched with saturated sodium carbonate. The organic layer was separated and the aqueous layer was extracted with ether. Combined the organic layer, washed with

brine, dried (Na₂SO₄), filtered and concentrated. Chromatography on silica gel gave **III-27** (12 mg, 0.056 mmol, 85%) as colorless oil.

III-27: R_f = 0.34 (9:1 (v/v) hexane/EtOAc); $[\alpha]_D^{25} = +2$ (c = 0.5, CH₂Cl₂); IR (thin film, cm⁻¹), 2931, 1710, 1377, 1284, 995; ¹H NMR (600 MHz, CDCl₃) δ 6.49 (d, J = 12.6 Hz, 1H), 6.29 (d, J = 12.6 Hz, 1H), 5.02 (dq, J = 6.0, 6.0, 2.4 Hz, 1H), 3.13 (ddd, J = 15.6, 10.2, 2.4 Hz, 1H), 2.44 (ddd, J = 15.6, 9.6, 2.4 Hz, 1H), 1.98 (m, 1H), 1.83 (m, 1H), 1.59-1.61 (m, 6H), 1.18 (d, J = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 199.1, 190.4, 163.8, 135.7, 129.6, 73.2, 34.6, 31.6, 26.5, 21.4, 21.0, 19.0; ESI HRMS Calcd for [C₁₂H₁₆O₄ + H]⁺: 225.1121, Found: 225.1122.

(6S,12R,Z)-6-hydroxy-12-methoxacyclododec-3-ene-2,5-dione (III-31)

To a solution of **III-34** (1.0 mg) in 3.0 ml D₆-benzene, 0.1 mg I₂ was added, the solution was irradiated with 300 nm UV light through a Pyrex filter for 20 min, the chromatography gave double bond isomer **III-35** (0.95 mg, 95%) was formed. To a plastic flask was added **III-35** (5 mg, 0.015 mmol) 0.1 mL CH₃CN and 5% HF in CH₃CN (17 μ L) at room temperature. The reaction mixture was stirred for 2 h and then ether acetate was added to dilute the reaction solution. The reaction mixture was washed with NaHCO₃, extracted with EtOAc, dried with Na₂SO₄ and evaporated under reduced pressure to leave the crude product which was then purified using silica gel flash

chromatography to give (*ent*)-cladospolide D **III-31** (3 mg, 0.013 mmol, 87%) as a colorless oil;

III-31: *R_f* (30% Et₂O/hexane) = 0.36; $[\alpha]_D^{25} = -57$ (*c* = 0.1, CH₂Cl₂); IR (thin film, cm⁻¹), 3467, 2936, 1720, 1224, 1167, 1083; ¹H NMR (600 MHz, CDCl₃) δ 6.40 (d, *J* = 13.2 Hz, 1H), 6.31 (d, *J* = 13.2 Hz, 1H), 5.22 (dq, *J* = 9.0, 6.0, 6.0 Hz, 1H), 4.66 (ddd, *J* = 8.4, 6.0, 5.4 Hz, 1H), 3.16 (d, *J* = 6.0 Hz, 1H), 1.95 (m, 1H), 1.72-1.18 (m, 9H), 1.30 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 203.5, 165.4, 133.3, 130.9, 73.5, 71.5, 33.2, 31.1, 23.0, 21.6, 21.5, 20.6; ESI HRMS Calcd for [C₁₂H₁₈O₄+H]⁺: 227.1278, Found: 227.1278.

Photo equilibration of TBS-protected (*E*)-5-bis-cladospolide D (III-32**) and TBS-protected (*Z*)-5-bis-cladospolide D (**III-33**)**

A solution of **III-32** (1.5 mg) in 3.5 ml D₆-benzene was irradiated with 300 nm UV light through a Pyrex filter. After 24 h, a photo equilibrium (1.3:1, **III-33**/ **III-32**) was established with the *Z*-isomer **III-33** being slightly favored, **III-32** and **III-33** could be separated by chromatography.

Pure **III-33** (1.0 mg) was irradiated in 3.0 ml D₆-benzene solution with 300 nm UV light through a Pyrex filter, the same photo equilibrium (1.3:1, **III-33**/ **III-32**) was established with the *Z*-isomer **III-33** being slightly favored, **III-32** and **III-33** could be separated by chromatography.

III-32: *R_f* (10% Et₂O/hexane) = 0.33; [α]_D²⁵ = - 12 (*c* = 0.5, CH₂Cl₂); IR (thin film, cm⁻¹), 2931, 2858, 1721, 1463, 1251, 1078, 838, 779; ¹H NMR (600 MHz, CDCl₃) δ 7.21 (d, *J* = 16.8 Hz, 1H), 6.90 (d, *J* = 16.8 Hz, 1H), 4.89 (dq, *J* = 7.8., 6.0, 4.8 Hz, 1H), 4.41 (dd, *J* = 6.0, 4.2 Hz, 1H), 1.78-1.15 (m, 10H), 1.34 (d, *J* = 6.0 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 200.8, 166.8, 138.2, 131.3, 79.2, 75.3, 35.1, 34.1, 27.7, 25.8, 23.9, 20.6, 18.1, - 4.79, - 5.25; ESI HRMS Calcd for [C₁₈H₃₂O₄Si + Na]⁺: 363.1962, Found: 363.1964.

III-33: *R_f* (10% Et₂O/hexane) = 0.50; [α]_D²⁵ = + 18 (*c* = 0.4, CH₂Cl₂); IR (thin film, cm⁻¹), 2932, 2857, 1717, 1464, 1285, 1098, 838, 778; ¹H NMR (600 MHz, CDCl₃) δ 6.78 (d, *J* = 12.6 Hz, 1H), 5.95 (d, *J* = 12.6 Hz, 1H), 4.87 (dq, *J* = 9.0, 6.0, 3.0 Hz, 1H), 4.14 (dd, *J* = 9.6, 3.0 Hz, 1H), 1.84-1.24 (m, 10H), 1.25 (d, *J* = 6.0 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H); ¹³C NMR (150 MHz, CD₃Cl) δ 204.3, 164.5, 140.4, 125.9, 78.8, 73.9, 31.9, 31.3, 27.1, 25.7, 20.7, 19.5, 19.3, 18.0, - 4.80, - 5.13; ESI HRMS Calcd for [C₁₈H₃₂O₄Si + Na]⁺: 363.1962, Found: 363.1964.

Iodine promoted photochemical equilibration of TBS-protected (*E*)-5-bis-cladospolide D (III-32**) and TBS-protected (*Z*)-5-bis-cladospolide D (**III-33**)**

To a solution of **III-32** (1.5 mg) in 3.5 ml D_6 -benzene, 0.1 mg I_2 was added, the solution was irradiated with 300 nm UV light through a Pyrex filter. After 50 min, a photochemical equilibrium ($K_{eq} = 4$, **III-33/ III-32**) was established with the *Z*-isomer **III-33** being favored, **III-32** and **III-33** could be separated by chromatography.

To a solution of **III-33** (1.0 mg) in 3.0 ml D_6 -benzene, 0.1 mg I_2 was added, the solution was irradiated with 300 nm UV light through a Pyrex filter. After 50 min, the same photochemical equilibrium ($K_{eq} = 4$, **III-33/ III-32**) was established with the *Z*-isomer **III-33** being favored, **III-32** and **III-33** could be separated by chromatography.

Photo equilibration of TBS-protected (*E*)-cladospolide D (III-34**) and TBS-protected (*Z*)-cladospolide D (**III-35**)**

A solution of **III-34** (1.0 mg) in 3.0 ml D₆-benzene was irradiated with 300 nm UV light through a Pyrex filter. After 24 h, a photo equilibrium (1:2, **III-34/III-35**) was established with the *Z*-isomer **III-35** being slightly favored, **III-34** and **III-35** could be separated by chromatography.

When pure **III-35** (1.0 mg) was irradiated in 3.0 ml D₆-benzene solution with 300 nm UV light through a Pyrex filter, the same photo equilibrium (1:2, **III-34/III-35**) was established with the *Z*-isomer **III-35** being slightly favored, **III-34** and **III-35** could be separated by chromatography.

III-34: *R_f* (10% Et₂O/hexane) = 0.64; [α]_D²⁵ = + 31 (*c* = 0.4, CH₂Cl₂); IR (thin film, cm⁻¹), 2932, 2858, 1723, 1464, 1254, 1095, 847, 779; ¹H NMR (600 MHz, CDCl₃) δ 7.41 (d, *J* = 16.8 Hz, 1H), 6.93 (d, *J* = 16.8 Hz, 1H), 4.63 (qdd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 4.34 (dd, *J* = 6.0, 1.6 Hz, 1H), 1.90-1.06 (m, 10H), 1.34 (d, *J* = 6.0 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 201.3, 167.5, 134.2, 132.0, 77.2, 74.9, 34.8, 34.2, 27.9, 25.7, 24.1, 21.4, 20.6, 18.1, - 4.91, - 4.90; ESI HRMS Calcd for [C₁₈H₃₂O₄Si+H]⁺: 341.2143, Found: 341.2144.

III-35: *R_f* (10% Et₂O/hexane) = 0.37; [α]_D²⁵ = - 80 (*c* = 0.5, CH₂Cl₂); IR (thin film, cm⁻¹), 2931, 2860, 1726, 1464, 1251, 1164, 1119, 839, 778; ¹H NMR (600 MHz, CDCl₃) δ 6.73 (d, *J* = 12.6 Hz, 1H), 6.23 (d, *J* = 12.6 Hz, 1H), 4.91 (dqdd, *J* = 9.6, 6.0, 3.0 Hz, 1H), 4.32 (dd, *J* = 7.8, 4.2 Hz, 1H), 1.93-1.26 (m, 10H), 1.27 (d, *J* = 6.0 Hz, 3H), 0.93 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 203.2, 166.3, 133.6, 130.6,

76.4, 73.9, 33.3, 330.5, 26.3, 25.8, 22.1, 21.2, 20.0, 18.1, -4.91, -5.07; ESI HRMS Calcd for $[C_{18}H_{32}O_4Si + H]^+$: 341.2143, Found: 341.2144.

Iodine promoted photochemical equilibration of TBS-protected (*E*)-cladospolide D (III-34**) and TBS-protected (*Z*)-cladospolide D (**III-35**)**

To a solution of **III-34** (1.0 mg) in 3.0 ml D_6 -benzene, 0.1 mg I_2 was added, the solution was irradiated with 300 nm UV light through a Pyrex filter. After 20 min, a photochemical equilibrium ($K_{eq} > 20$, **III-35/III-34**) was established with the *Z*-isomer **III-35** being favored.

To the other solution of **III-35** (1.0 mg) in 3.0 ml D_6 -benzene, 0.1 mg I_2 was added, the solution was irradiated with 300 nm UV light through a Pyrex filter. After 20 min, the same photochemical equilibrium ($K_{eq} > 20$, **III-35/III-34**) was established with the *Z*-isomer **III-35** being favored.

Iodine promoted photochemical equilibration of cladospolide C (III-3**) and 4,5-bis-
epi-cladospolide B (**III-7**)**

To a solution of **III-3** (1.0 mg) in 3.0 ml D₆-benzene, 0.1 mg I₂ was added, the solution was irradiated with 300 nm UV light through a Pyrex filter. After 24 h, a photochemical equilibrium ($K_{eq} = 1$, **III-3/III-7**) was established, **III-3** and **III-7** were separated by chromatography (SiO₂, 50% Et₂O/hexane).

To the other solution of **III-7** (1.0 mg) in 3.0 ml D₆-benzene, 0.1 mg I₂ was added, the solution was irradiated with 300 nm UV light through a Pyrex filter. After 24 h, the same photochemical equilibrium ($K_{eq} = 1$, **III-3/ III-7**) was established, **III-3** and **III-7** were separated by chromatography (SiO₂, 50% Et₂O/hexane).

III-3: *R_f* (50% Et₂O/hexane) = 0.27; Mp 91-92 °C; $[\alpha]_D^{25} = +53$ ($c = 0.4$, MeOH); IR (thin film, cm⁻¹), 3415, 2940, 2864, 1705, 1650, 1460, 1258, 1035; ¹H NMR (600 MHz, CDCl₃) δ 6.81 (dd, $J = 15.6, 9.0$ Hz, 1H), 6.05 (d, $J = 15.6$ Hz, 1H), 4.98 (dq, $J = 8.4, 6.0, 1.8$ Hz, 1H), 3.98 (dd, $J = 8.4, 7.8$ Hz, 1H), 3.57 (ddd, $J = 7.8, 7.8, 1.8$ Hz, 1H), 1.30 (d, $J = 6.0$ Hz, 3H) 1.69-1.11 (m, 10H); ¹³C NMR (150 MHz, CD₃Cl) δ 166.7, 145.3, 124.5, 77.5, 76.5, 74.3, 33.9, 32.1, 27.3, 24.5, 24.1, 20.8; ESI HRMS Calcd for [C₁₂H₂₀O₄ + H]⁺: 229.1434, Found: 229.1435.

III-7: R_f (50% Et₂O/hexane) = 0.33; $[\alpha]_D^{25} = -1$ ($c = 0.2$, MeOH); IR (thin film, cm⁻¹), 3272, 2943, 2862, 1710, 1461, 1278, 1050; ¹H NMR (600 MHz, CDCl₃) δ 6.12 (dd, $J = 12.0, 8.4$ Hz, 1H), 6.05 (dd, $J = 12.0, 1.2$ Hz, 1H), 5.10 (qdd, $J = 6.0, 5.4, 3.0$ Hz, 1H), 4.97 (ddd, $J = 8.4, 4.8, 1.2$ Hz, 1H), 3.87 (ddd, $J = 9.0, 4.8, 3.0$ Hz, 1H), 2.04-1.35 (m, 10H), 1.25 (d, $J = 6.0$ Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 166.7, 145.3, 124.5, 77.5, 76.5, 74.3, 33.9, 32.1, 27.3, 24.5, 24.1, 20.8; ESI HRMS Calcd for [C₁₂H₂₀O₄+H]⁺: 229.1434, Found: 229.1435.

Isomerization of cladospolide B (III-2) and 4,5-bis-epi-cladospolide C (III-8)

To a solution of **III-8** (1.0 mg) in 3.0 ml D₆-benzene, 0.1 mg I₂ was added, the solution was irradiated with 300 nm UV light through a Pyrex filter. After 24 h, a photochemical equilibrium ($K_{eq} = 0.3$, **III-2/III-8**) was established, **III-8** and **III-2** were separated by chromatography (SiO₂, 50% Et₂O/hexane).

To the other solution of **III-2** (1.0 mg) in 3.0 ml D₆-benzene, 0.1 mg I₂ was added, the solution was irradiated with 300 nm UV light through a Pyrex filter. After 24 h, a photochemical equilibrium ($K_{eq} = 6$, **III-2/ III-8**) was established, **III-8** and **III-2** were separated by chromatography (SiO₂, 50% Et₂O/hexane).

III-8: R_f (50% Et₂O/hexane) = 0.41; $[\alpha]^{25}_D = -13$ (c = 0.1, MeOH); IR (thin film, cm⁻¹), 3396, 2937, 2870, 1711, 1464, 1247, 1028; ¹H NMR (600 MHz, CDCl₃) δ 6.94 (dd, J = 15.6, 6.0 Hz, 1H), 6.12 (dd, J = 15.6, 1.2 Hz, 1H), 4.96 (dq, J = 6.6, 6.0, 3.0 Hz, 1H), 4.12 (ddd, J = 7.2, 6.0, 1.2 Hz, 1H), 3.32 (ddd, J = 9.6, 7.8, 1.8 Hz, 1H), 1.74-1.20 (m, 10H), 1.28 (d, J = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 167.2, 146.9, 122.5, 78.0, 77.8, 73.1, 33.2, 32.6, 28.3, 25.0, 22.8, 19.0; ESI HRMS Calcd for [C₁₂H₂₀O₄ + Na]⁺: 251.1254, Found: 251.1254.

III-2: R_f (50% Et₂O/hexane) = 0.57; Mp 108-109 °C; $[\alpha]^{25}_D = +24$ (c = 0.1, MeOH); IR (thin film, cm⁻¹), 3345, 2934, 2865, 1707, 1461, 1280, 1046; ¹H NMR (600 MHz, CDCl₃) δ 6.23 (dd, J = 12.0, 8.4 Hz, 1H), 5.77 (dd, J = 12.0, 1.2 Hz, 1H), 5.26 (ddd, J = 8.4, 4.2, 1.2 Hz, 1H), 4.88 (dq, J = 10.2, 6.0, 1.8 Hz, 1H), 3.77 (ddd, J = 9.0, 4.2, 2.4 Hz, 1H), 1.84-1.35 (m, 10H), 1.28 (d, J = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 165.8, 148.5, 121.9, 74.4, 73.9, 67.5, 32.0, 30.6, 25.7, 24.1, 21.3, 19.7; ESI HRMS Calcd for [C₁₂H₂₀O₄ + H]⁺: 229.1434, Found: 229.1435.

Methyl 3-(furan-2-yl)-3-oxopropanoate (IV-28)

Sodium hydride (5.71 g, 0.24 mol) was placed in a flask and washed with dry hexane three times, dimethyl carbonate (15.9 g, 0.177 mol) and 60 mL THF was added to this flask. The mixture was heated to 50 °C, a solution of 2-acetyl furan **IV-30** (6.54g, 0.059 mol) in 60 mL THF was added dropwise. The mixture was stirred for 1 h at 50 °C and then cooled to 0 °C. After addition of glacial acetic acid followed by cold water, the mixture was extracted with ether acetate. The extracts were washed with cold water, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give furan ketone **IV-28** (7.23 g, 0.043 mol, 73%) as colorless oil: *R_f* (10% EtOAc/hexane) = 0.15; IR (thin film, cm⁻¹) 3135, 2956, 1740, 1674, 1571, 1467, 1328, 1153, 1017, 883, 768; ¹H NMR (600 MHz, CDCl₃) δ 7.61 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.27 (dd, *J* = 3.6, 0.6 Hz, 1H), 6.57 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.86 (s, 2H), 3.75 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 180.8, 167.4, 152.0, 147.0, 118.3, 112.7, 52.5, 45.2

(S)-Methyl 3-(furan-2-yl)-3-hydroxypropanoate (IV-28a)

To a flask was added furan ketone **IV-28** (173 mg, 1.03 mmol), 2 M NaCOOH in water (10 mL), cetyl trimethylammonium bromide (37.5 mg, 0.10 mmol). The mixture was stirred at RT. for 5 min, then Noyori catalyst (*S, S*) (1.3 mg, 0.002 mmol) was added. The reaction mixture was allowed to stir for 24 hr. Water was added to dilute and the mixture was extracted with Et₂O, dried (Na₂SO₄) and concentrated under reduced pressure. The

crude product was purified using silica gel flash chromatography to give 148 mg (0.88 mmol, 85%) of furan alcohol **IV-28a** as colorless oil: R_f (30% EtOAc/hexane) = 0.18; $[\alpha]_D^{25} = -24$ ($c = 1.0$, MeOH); IR (thin film, cm^{-1}) 3450, 2956, 1733, 1439, 1362, 1284, 1163, 1011, 884, 805, 741; ^1H NMR (600 MHz, CDCl_3) δ 7.37 (dd, $J = 1.8, 0.6$ Hz, 1H), 6.33 (dd, $J = 3.0, 1.8$ Hz, 1H), 6.277 (ddd, $J = 3.0, 0.6, 0.6$ Hz, 1H), 5.14 (ddd, $J = 9.0, 4.2, 0.6$ Hz, 1H), 3.75 (s, 3H), δ 2.91 (dd, $J = 16.8, 9.0$ Hz, 1H), 2.83 (dd, $J = 16.8, 4.2$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 172.2, 154.7, 142.2, 110.2, 106.3, 64.1, 51.9, 39.6

(S)-Methyl 2-(6-hydroxy-3-oxo-3,6-dihydro-2H-pyran-2-yl)acetate (IV-32)

To a solution of furan alcohol **IV-28a** (100 mg, 0.59 mmol) in 4 mL THF- H_2O (3:1) was added NaHCO_3 (98.8 mg, 1.18 mmol), $\text{NaOAc} \cdot 3\text{H}_2\text{O}$ (80 mg, 0.59 mmol) and NBS (105 mg, 0.59 mmol) at 0°C . The reaction mixture was kept stirring at this temperature for 1h, then saturated NaHCO_3 was added to quench the reaction. The reaction mixture was extracted with EtOAc, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give 87 mg (0.47 mmol, 80%) of pyranone alcohol **IV-32** as colorless oil: R_f (30% EtOAc/hexane) = 0.14

Methyl-2-((2*S*,6*S*)-6-(tert-butoxycarbonyloxy)-3-oxo-3,6-dihydro-2H-pyran-2-yl)acetate (IV-33**)**

To a solution of pyranone alcohol **IV-32** (70 mg, 0.376 mmol) in 3 mL CH₂Cl₂ was added DMAP (4.6 mg, 0.0376 mmol) at -78 °C, a pre-cooled solution of (Boc)₂O (164 mg, 0.75mmol) in 2 mL CH₂Cl₂ was added dropwise. The reaction mixture was stirred at -78 °C for 12 hr. The reaction mixture was diluted with EtOAc and quenched with saturated NaHCO₃, extracted with EtOAc, washed (NaCl), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give Boc-pyranone **IV-33** 76 mg (0.27 mmol, 71%) as light yellow oil: *R_f*(35% EtOAc/hexane) = 0.71; [α]_D²⁵ = + 34.2 (*c* = 1.0, MeOH); IR (thin film, cm⁻¹) 2919, 1744, 1702, 1371, 1275, 1159, 946, 849; ¹H NMR (600 MHz, CDCl₃) δ 6.87 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.33 (d, *J* = 3.6 Hz, 1H), 6.25 (d, *J* = 10.2 Hz, 1H), 4.91 (dd, *J* = 6.0, 4.2 Hz, 1H), 3.68 (s, 3H), 2.95 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.85 (dd, *J* = 16.8, 6.0 Hz, 1H), 1.52 (s, *J* = 9H); ¹³C NMR (150 MHz, CDCl₃) δ 193.8, 170.3, 151.7, 140.8, 128.5, 88.9, 83.7, 72.4, 51.9, 35.1, 27.6; CIHRMS: Calculated for [C₁₃H₁₈O₇ + Na⁺]: 309.0945, Found: 309.0946

Methyl-2-((2*S*,6*R*)-6-(tert-butoxycarbonyloxy)-3-oxo-3,6-dihydro-2H-pyran-2-yl)acetate (IV-34)

To a solution of pyranone alcohol **IV-32** (70 mg, 0.376 mmol) in 3 mL CH₂Cl₂ was added DMAP (4.6 mg, 0.0376 mmol) at -78 °C, a pre-cooled solution of (Boc)₂O (164 mg, 0.75mmol) in 2 mL CH₂Cl₂ was added dropwise. The reaction mixture was stirred at -78 °C for 12 hr. The reaction mixture was diluted with EtOAc and quenched with saturated NaHCO₃, extracted with EtOAc, washed (NaCl), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give Boc-pyranone **IV-34** 9 mg (0.03 mmol, 8%) as light yellow oil: *R_f*(35% EtOAc/hexane) = 0.66; [α]_D²⁵ = - 64.8 (*c* = 1.0, MeOH); IR (thin film, cm⁻¹) 2919, 1748, 1700, 1371, 1275, 1164, 1064, 945, 851; ¹H NMR (600 MHz, CDCl₃) δ 6.91 (dd, *J* = 10.2, 2.4 Hz, 1H), 6.40 (dd, *J* = 1.8, 1.8 Hz, 1H), 6.26 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.73 (dd, *J* = 7.8, 5.4 Hz, 1H), 3.71 (s, 3H), 2.91 (dd, *J* = 16.8, 4.8 Hz, 1H), 2.88 (dd, *J* = 16.8, 7.8 Hz, 1H), 1.52 (s, *J* = 9H); ¹³C NMR (150 MHz, CDCl₃) δ 193.6, 170.1, 151.4, 143.5, 128.8, 90.0, 83.9, 75.8, 52.0, 37.4, 27.6; CIHRMS: Calculated for [C₁₃H₁₈O₇ + Na⁺]: 309.0945, Found: 309.0943

Methyl-2-((2*S*,3*R*,6*S*)-6-(tert-butoxycarbonyloxy)-3-hydroxy-3,6-dihydro-2H-pyran-2-yl)acetate (IV-48**)**

To a solution of pyranone **IV-32** (62 mg, 0.22 mmol) in 0.5 mL CH₂Cl₂ was added 0.5 mL CeCl₃ in MeOH (0.4 M) and NaBH₄ (16 mg, 0.43 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 3 hr. The reaction mixture was diluted with EtOAc and quenched with saturated NaHCO₃, extracted with EtOAc, washed (NaCl), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give allylic alcohol **IV-48** 57 mg (0.20 mmol, 90%) as colorless oil: *R_f*(30% EtOAc/hexane) = 0.28; [α]²⁵_D = - 73.0 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3483, 2981, 1744, 1438, 1371, 1275, 1164, 1057, 938, 847; ¹H NMR (600 MHz, CDCl₃) δ 6.07 (ddd, *J* = 10.2, 1.2, 1.2 Hz, 1H), 6.03 (ddd, *J* = 2.4, 1.2, 1.2 Hz, 1H), 5.78 (ddd, *J* = 10.2, 3.0, 2.4 Hz, 1H), 4.13-4.09 (m, 2H), 3.69 (s, 3H), 2.83 (dd, *J* = 16.2, 4.2 Hz, 1H), 2.63 (dd, *J* = 16.2, 7.2 Hz, 1H), 1.51 (s, *J* = 9H); ¹³C NMR (150 MHz, CDCl₃) δ 171.7, 152.2, 134.8, 124.2, 90.3, 82.8, 70.3, 67.2, 51.9, 37.6, 27.7; CIHRMS: Calculated for [C₁₃H₂₀O₇+Na⁺]: 311.1101, Found: 311.1092

Methyl-2-((2*S*,3*R*,6*S*)-6-(tert-butoxycarbonyloxy)-3-(tert-butyldimethylsilyloxy)-3,6-dihydro-2H-pyran-2-yl)acetate (IV-50**)**

To a solution of alcohol **IV-48** (50 mg, 0.17 mmol) in 1 mL CH₂Cl₂ was added imidazol (24 mg, 0.35 mmol) and TBSCl (53 mg, 0.35 mmol) at 0 °C. The reaction mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc and quenched with saturated NaHCO₃, extracted with EtOAc, washed (NaCl), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give TBS-alcohol **IV-50** 63 mg (0.16 mmol, 92%) as colorless oil: R_f (10% EtOAc/hexane) = 0.5; $[\alpha]_D^{25}$ = - 83.5 (c = 1.3, CH₂Cl₂); IR (thin film, cm⁻¹) 2960, 2932, 2859, 1748, 1370, 1254, 1139, 1096, 838; ¹H NMR (600 MHz, CDCl₃) δ 6.01 (dd, J = 1.8, 1.2 Hz, 1H), 5.96 (ddd, J = 10.2, 1.2, 1.2 Hz, 1H), 5.70 (ddd, J = 10.2, 3.0, 1.8 Hz, 1H), 4.18 (ddd, J = 9.6, 9.0, 2.4 Hz, 1H), 4.08 (ddd, J = 9.0, 3.0, 1.2 Hz, 1H), 3.67 (s, 3H), 2.77 (dd, J = 15.6, 2.4 Hz, 1H), 2.43 (dd, J = 15.6, 9.6 Hz, 1H), 1.51 (s, J = 9H), 0.87 (s, J = 9H), 0.10 (s, J = 6H), 0.07 (s, J = 6H); ¹³C NMR (150 MHz, CDCl₃) δ 171.0, 152.3, 135.9, 123.4, 90.5, 82.6, 70.4, 67.0, 51.6, 36.6, 27.7, 25.6, 17.8, -4.29, -4.88; CIHRMS: Calculated for [C₁₉H₃₄O₇Si+Na⁺]: 425.1966, Found: 425.1970

(2*S*,3*S*,6*S*)-6-(tert-butoxycarbonyloxy)-2-(2-methoxy-2-oxoethyl)-3,6-dihydro-2H-pyran-3-yl 4-nitrobenzoate (IV-48a)

To a solution of alcohol **IV-48** (100 mg, 0.35 mmol) in 5 mL THF was added PPh₃ (182 mg, 0.69 mmol), *p*-Nitrobenzoic acid (116 mg, 0.69 mmol) and DIAD (0.14 mL, 0.69 mmol) at 0 °C. The reaction mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc and quenched with saturated NaHCO₃, extracted with EtOAc, washed (NaCl), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give **IV-48a** 125 mg (0.29 mmol, 82%) as colorless oil: *R_f* (10% EtOAc/hexane) = 0.25; [α]_D²⁵ = 148.4 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2990, 2957, 1747, 1530, 1263, 1167, 942, 847; ¹H NMR (600 MHz, CDCl₃) δ 8.29 (d, *J* = 9.0, 2H), δ 8.21 (d, *J* = 9.0, 2H), 6.36 (ddd, *J* = 10.2, 6.0, 1.2 Hz, 1H), 6.21 (dd, *J* = 3.0, 0.6 Hz, 1H), 6.13 (ddd, *J* = 10.2, 3.0, 0.6 Hz, 1H), 5.32 (dd, *J* = 6.0, 2.4 Hz, 1H), 4.75 (ddd, *J* = 8.4, 6.0, 2.4 Hz, 1H), 3.66 (s, 3H), 2.77 (dd, *J* = 16.2, 8.4 Hz, 1H), 2.66 (dd, *J* = 16.2, 6.0 Hz, 1H), 1.53 (s, *J* = 9H); ¹³C NMR (150 MHz, CDCl₃) 170.1, 164.0, 152.0, 150.8, 134.8, 130.9, 129.1, 126.4, 123.7, 90.0, 83.1, 67.4, 64.8, 51.9, 35.5, 27.7; CIHRMS: Calculated for [C₂₀H₂₃NO₁₀ + Na⁺]: 460.1214, Found: 460.1169

Methyl-2-((2*S*,3*S*,6*S*)-6-(tert-butoxycarbonyloxy)-3-hydroxy-3,6-dihydro-2H-pyran-2-yl)acetate (IV-52**)**

To a solution of nitrobenzoate **IV-48a** (34 mg, 0.08 mmol) in 0.8 mL MeOH was added K_2CO_3 (1 mg, 10% mmol) at 0 °C. The reaction mixture was stirred at RT for 15 min. The reaction mixture was diluted with EtOAc and quenched with H_2O , extracted with EtOAc, washed (NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give allylic alcohol **IV-52** 12 mg (0.04 mmol, 50%) as colorless oil: R_f (30% EtOAc/hexane) = 0.26; $[\alpha]_D^{25} = 2.4$ ($c = 1.0$, MeOH); IR (thin film, cm^{-1}) 3472, 2934, 1744, 1279, 1259, 1030, 938, 848; 1H NMR (600 MHz, $CDCl_3$) δ 6.30 (ddd, $J = 9.6, 6.0, 0.6$ Hz, 1H), 6.11 (dd, $J = 3.0, 0.6$ Hz, 1H), 5.94 (ddd, $J = 9.6, 3.0, 1.2$ Hz, 1H), 4.48 (ddd, $J = 7.2, 6.0, 1.2$ Hz, 1H), 3.87 (m, 1H), 3.70 (s, 3H), 2.76 (d, $J = 7.2$, 2H), 1.51 (s, $J = 9H$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 152.1, 131.0, 126.2, 90.4, 82.9, 69.4, 63.0, 51.8, 35.3, 27.7; CIHRMS: Calculated for $[C_{13}H_{20}O_7 + Na^+]$: 311.1101, Found: 311.1092

Methyl-2-((2*S*,3*S*,6*S*)-6-(tert-butoxycarbonyloxy)-3-(tert-butyldimethylsilyloxy)-3,6-dihydro-2*H*-pyran-2-yl)acetate (IV-54**)**

To a solution of alcohol **IV-52** (4 mg, 0.014 mmol) in 0.1 mL CH₂Cl₂ was added imidazol (2 mg, 0.028 mmol) and TBSCl (4 mg, 0.028 mmol) at 0 °C. The reaction mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc and quenched with saturated NaHCO₃, extracted with EtOAc, washed (NaCl), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give TBS-alcohol **IV-54** 5 mg (0.013 mmol, 90%) as colorless oil: *R_f*(10% EtOAc/hexane) = 0.52; [α]_D²⁵ = 12.4 (*c* = 0.8, CH₂Cl₂); IR (thin film, cm⁻¹) 2960, 2932, 2859, 1748, 1368, 1256, 1139, 1096, 941, 838; ¹H NMR (600 MHz, CDCl₃) δ 6.13 (dd, *J* = 10.2, 5.4 Hz, 1H), 6.12 (d, *J* = 3.0 Hz, 1H), 5.89 (dd, *J* = 10.2, 3.0, Hz, 1H), 4.43 (ddd, *J* = 7.2, 6.6, 2.4 Hz, 1H), 3.96 (dd, *J* = 5.4, 2.4 Hz, 1H), 3.67 (s, 3H), 2.71 (dd, *J* = 16.8, 7.2 Hz, 1H), 2.68 (dd, *J* = 16.8, 6.6 Hz, 1H), 1.51 (s, *J* = 9H), 0.88 (s, *J* = 9H), 0.07 (s, *J* = 6H), 0.05 (s, *J* = 6H); ¹³C NMR (150 MHz, CDCl₃) δ 171.3, 152.2, 131.0, 125.4, 90.7, 82.6, 69.6, 62.3, 51.6, 35.4, 27.8, 25.7, 18.1, -4.27, -4.89; CIHRMS: Calculated for [C₁₉H₃₄O₇Si+Na⁺]: 425.1966, Found: 425.1970

(2*S*,6*S*)-6-(2-methoxy-2-oxoethyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl pivalate (IV-43)

To a solution of pyranone alcohol (**IV-32**) (55 mg, 0.3 mmol) in 3 mL CH₂Cl₂ was added PivCl (0.07 mL, 0.6 mmol), pyridine (0.07 mL, 0.9 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 12 hr. The reaction mixture was diluted with EtOAc and quenched with saturated NaHCO₃, extracted with EtOAc, washed (NaCl), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give Piv-pyranone **IV-43** 61 mg (0.23 mmol, 75%) as light yellow oil: R_f (10% EtOAc/hexane) = 0.25; $[\alpha]_D^{25} = +52.8$ ($c = 0.5$, CH₂Cl₂); IR (thin film, cm⁻¹) 2976, 1742, 1702, 1370, 1174, 1127, 1094, 936; ¹H NMR (600 MHz, CDCl₃) δ 6.89 (dd, $J = 10.2, 3.6$ Hz, 1H), 6.48 (d, $J = 3.6$ Hz, 1H), 6.26 (d, $J = 10.2$ Hz, 1H), 4.89 (dd, $J = 7.2, 4.2$ Hz, 1H), 3.69 (s, 3H), 3.00 (dd, $J = 16.8, 4.2$ Hz, 1H), 2.89 (dd, $J = 16.8, 7.2$ Hz, 1H), 1.25 (s, $J = 9$ H); ¹³C NMR (150 MHz, CDCl₃) δ 194.0, 176.9, 170.5, 141.8, 128.3, 86.6, 72.5, 52.0, 39.3, 35.0, 27.0; CIHRMS: Calculated for [C₁₃H₁₈O₆ + Na⁺]: 293.0996, Found: 309.0996

(2*R*,6*S*)-6-(2-methoxy-2-oxoethyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl pivalate (IV-44)¹²

To a solution of pyranone alcohol (**IV-32**) (55 mg, 0.3 mmol) in 3 mL CH₂Cl₂ was added PivCl (0.07 mL, 0.6 mmol), pyridine (0.07 mL, 0.9 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 12 hr. The reaction mixture was diluted with EtOAc and quenched with saturated NaHCO₃, extracted with EtOAc, washed (NaCl), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give Piv-pyranone **IV-44** 5 mg (0.02 mmol, 6%) as light yellow oil.

(2*S*,5*R*,6*S*)-5-hydroxy-6-(2-methoxy-2-oxoethyl)-5,6-dihydro-2H-pyran-2-yl pivalate (IV-56)

To a solution of pyranone **IV-43** (56 mg, 0.21 mmol) in 0.5 mL CH₂Cl₂ was added 0.5 mL CeCl₃ in MeOH (0.4 M) and NaBH₄ (24 mg, 0.63 mmol) at -78 °C. The reaction mixture was stirred at -78 °C for 3 hr. The reaction mixture was diluted with EtOAc and

¹² This compound is not characterized.

quenched with saturated NaHCO₃, extracted with EtOAc, washed (NaCl), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give allylic alcohol **IV-56** 50 mg (0.18 mmol, 88%) as colorless oil: R_f (30% EtOAc/hexane) = 0.25; $[\alpha]_D^{25} = -45.5$ ($c = 0.29$, MeOH); IR (thin film, cm⁻¹) 3480, 2974, 1741, 1439, 1280, 1122, 1035, 926; ¹H NMR (600 MHz, CDCl₃) δ 6.21 (d, $J = 2.4$ Hz, 1H), 6.06 (dd, $J = 10.8, 1.2$ Hz, 1H), 5.78 (ddd, $J = 10.2, 1.8, 1.2$ Hz, 1H), 4.09-4.08 (m, 2H), 3.70 (s, 3H), 2.84 (dd, $J = 15.6, 4.2$ Hz, 1H), 2.60 (dd, $J = 15.6, 7.8$ Hz, 1H), 1.23 (s, $J = 9$ H); ¹³C NMR (150 MHz, CDCl₃) δ 177.3, 171.7, 134.2, 124.9, 89.3, 87.7, 70.6, 67.2, 39.0, 37.6, 27.0; CIHRMS: Calculated for [C₁₃H₂₀O₆+Na⁺]: 295.1152, Found: 295.1166

(2*S*,3*S*,6*S*)-2-(2-methoxy-2-oxoethyl)-6-(pivaloyloxy)-3,6-dihydro-2H-pyran-3-yl 4-nitrobenzoate (IV-56a)

To a solution of alcohol **IV-56** (46 mg, 0.17 mmol) in 1 mL THF was added PPh₃ (262 mg, 0.25 mmol), *p*-Nitrobenzoic acid (167 mg, 0.25 mmol) and DIAD (0.05 mL, 0.25 mmol) at 0 °C. The reaction mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc and quenched with saturated NaHCO₃, extracted with EtOAc, washed (NaCl), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give **IV-56a** 57 mg (0.14

mmol, 80%) as colorless oil: R_f (10% EtOAc/hexane) = 0.29; $[\alpha]_D^{25} = 147.0$ ($c = 1.0$, MeOH); IR (thin film, cm^{-1}) 2981, 2879, 1728, 1530, 1270, 1113, 932, 718; ^1H NMR (600 MHz, CDCl_3) δ 8.29 (d, $J = 9.0$, 2H), δ 8.21 (d, $J = 9.0$, 2H), 6.38 (dd, $J = 3.0$, 1.2 Hz, 1H), 6.35 (ddd, $J = 10.2$, 6.0, 1.2 Hz, 1H), 6.11 (ddd, $J = 10.2$, 3.0, 0.6 Hz, 1H), 5.33 (dd, $J = 6.0$, 2.4 Hz, 1H), 4.71 (ddd, $J = 8.4$, 4.8, 2.4 Hz, 1H), 3.67 (s, 3H), 2.75 (dd, $J = 16.2$, 9.0 Hz, 1H), 2.62 (dd, $J = 16.2$, 4.8 Hz, 1H), 1.25 (s, $J = 9\text{H}$); ^{13}C NMR (150 MHz, CDCl_3) 177.1, 170.3, 164.1, 150.8, 134.8, 130.9, 129.7, 125.9, 123.7, 87.5, 67.7, 65.1, 52.0, 39.1, 35.7, 27.0; CIHRMS: Calculated for $[\text{C}_{20}\text{H}_{23}\text{NO}_9 + \text{Na}^+]$: 444.1265, Found: 444.1248

(2*S*,5*S*,6*S*)-5-hydroxy-6-(2-methoxy-2-oxoethyl)-5,6-dihydro-2*H*-pyran-2-yl pivalate (IV-58)

To a solution of nitrobenzoate **IV-56a** (18 mg, 0.043 mmol) in 0.5 mL MeOH was added NEt_3 (3 L) at 0 °C. The reaction mixture was stirred at RT for 3 hr. The reaction mixture was diluted with EtOAc and quenched with H_2O , extracted with EtOAc, washed (NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give allylic alcohol **IV-58** 6 mg (0.024 mmol, 60%) as colorless oil: R_f (30% EtOAc/hexane) = 0.25; $[\alpha]_D^{25} = 37$ ($c = 1.0$, MeOH); IR (thin film, cm^{-1}) 3467, 2976, 2812, 1737, 1439, 1280, 1070, 919; ^1H NMR (600 MHz,

CDCl₃) δ 6.30 (ddd, J = 10.2, 6.0, 1.2 Hz, 1H), 6.28 (d, J = 3.6 Hz, 1H), 5.92 (ddd, J = 10.2, 3.6, 0.6 Hz, 1H), 4.46 (ddd, J = 7.8, 6.0, 2.4 Hz, 1H), 3.85 (m, 1H), 3.69 (s, 3H), 2.75 (dd, J = 16.2, 7.8 Hz, 1H), 2.71 (dd, J = 16.2, 6.0 Hz, 1H), 1.23 (s, J = 9H); ¹³C NMR (150 MHz, CDCl₃) 177.2, 171.3, 130.7, 126.8, 87.9, 69.6, 62.3, 51.8, 39.0, 35.6, 27.0; CIHRMS: Calculated for [C₁₃H₂₀O₆ + Na⁺]: 295.1152, Found: 295.1143

Hept-3-yn-2-ol (IV-31a)

A solution of *n*-BuLi in hexane (11.1 mL, 26.5 mmol) was added dropwise to the solution of 1-heptyn **IV-31** (1.5 g, 22.1 mmol) in dry THF (44 mL) at -78 °C under argon. After 30 min, acetaldehyde (1.2 mL, 22.1 mmol) was added. The reaction was stirred for 10 min at 0 °C and then the resulting solution was warmed to room temperature for 50 min. Additional CH₂Cl₂ (10 mL) was added to the reaction mixture followed by addition of saturated aqueous NH₄Cl (20 mL). The aqueous phase was separated and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated. Chromatography on silica gel gave alcohol **IV-31a** (2.03 g, 18.1 mmol, 82%) as a colorless oil; *R*_f(10% EtOAc/hexane) = 0.28; IR (thin film, cm⁻¹), 3340, 2958, 2869, 2244, 1458, 1291, 1155, 1074, 893; ¹H NMR (600 MHz, CDCl₃) δ 4.45 (qt, J = 6.6, 1.8 Hz, 1H), 2.10 (td, J = 6.6, 1.8 Hz, 2H), 1.45 (qt, J = 7.2, 6.6 Hz, 2H), 1.35 (d, J =

6.6 Hz, 3H), 0.91 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 84.1, 82.4, 58.2, 24.5, 21.9, 20.5, 13.2

Hept-3-yn-2-one (IV-35)

To a solution of alcohol (**IV-31a**) (4.0 g, 35.7 mmol) in THF (100 mL) at room temperature was added activated MnO_2 (20 g). The reaction mixture was stirred for 24 h and then filtered through celite and concentrated under pressure to give ketone **IV-35** (3.73 g, 33.9 mmol, 95%) as a colorless oil. R_f (10% EtOAc/hexane) = 0.40; IR (thin film, cm^{-1}), 2960, 2871, 2210, 1675, 1358, 1226; ^1H NMR (600 MHz, CDCl_3) δ 2.30 (t, $J = 7.2$ Hz, 2H), 2.28 (s, 3H), 1.57 (qt, $J = 7.2, 7.2$ Hz, 2H), 0.98 (t, $J = 7.2$, 3H); ^{13}C NMR (150 MHz, CD_3Cl) δ 184.8, 93.8, 81.4, 32.6, 21.1, 20.7, 13.3

(S)-Hept-3-yn-2-ol (IV-36)

To a flask was added ketone **IV-35** (10.8 g, 86.9 mmol), 2 M NaCOOH in water (400 mL), cetyl trimethylammonium bromide (3.17 g, 8.69 mmol). The mixture was stirred at RT. for 5 min, then Noyori catalyst (S, S) (105 mg, 0.174 mmol) was added. The reaction

mixture was allowed to stir for 24 hr. Water was added to dilute and extracted with Et₂O, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give 9.5 g (84.8 mmol, 97%) of alcohol **IV-36** as colorless oil: *R_f* (10% EtOAc/hexane) = 0.28; [α]_D²⁵ = - 10.3 (*c* = 0.29, MeOH); IR (thin film, cm⁻¹), 3340, 2958, 2869, 2244, 1458, 1291, 1155, 1074, 893; ¹H NMR (600 MHz, CDCl₃) δ 4.45 (qt, *J* = 6.6, 1.8 Hz, 1H), 2.10 (td, *J* = 6.6, 1.8 Hz, 2H), 1.45 (qt, *J* = 7.2, 6.6 Hz, 2H), 1.35 (d, *J* = 6.6 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CD₃Cl) δ 84.1, 82.4, 58.2, 24.5, 21.9, 20.5, 13.2

(S)-Hept-6-yn-2-ol (IV-36a)

A 30% suspension of KH in mineral oil (5.62 g, 140 mmol) was washed three times under Argon with dry ether and then the excess solvent was removed under vacuum, dry 1,3-diaminopropane (28 mL) was added with cooling (15 °C). After the mixture was stirred for 1 h, the alkynol **IV-36** (3.15 g, 28.1 mmol) was added dropwise (20 min) at (10-15 °C) to the mixture and the resulting slurry was stirred further under argon for 2 hrs. With cooling (0 °C), water was added dropwise and the mixture was extracted with ether, the combined extracts were washed with 1 N HCl, saturated aqueous sodium bicarbonate and brine, and then dried with anhydrous sodium sulfate. Flash chromatography gave alkynol **IV-36a** (2.71 g, 24.2 mmol, 85%) as a colorless oil: [α]_D²⁵ = 8 (*c* = 1.0, CHCl₃); *R_f* (20% EtOAc/Hexane)= 0.28; IR (thin film, cm⁻¹) 3309, 2934,

2862, 2117, 1460, 1432, 1374, 1128, 1093, 937, 821; ^1H NMR (600 MHz, CDCl_3) δ 3.83 (qt, $J = 6.0, 6.0$ Hz, 1H), 2.23 (td, $J = 7.2, 3.0$ Hz, 2H), 1.95 (t, $J = 3.0$ Hz, 1H), 1.67~1.56 (m, 4H), 1.20 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 84.3, 68.5, 67.6, 38.2, 24.7, 23.6, 18.4

(S)-Hept-6-yn-2-yl pivalate (IV-29)

To a flask was added alkynol **IV-36a** (1.55 g, 13.8 mmol), PivCl (2.06 mL, 16.6 mmol), pyridine (5.6 mL, 6.9 mmol) at 0 °C. The mixture was then stirred at RT. for 3 hr. NaHCO_3 was added and the mixture was extracted with Et_2O , dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give 2.57 g (13.1 mmol, 95%) of pivalate alcohol **IV-29** as colorless oil: R_f (10% EtOAc /hexane) = 0.5; $[\alpha]_D^{25} = 27.8$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3300, 2976, 2874, 2244, 1725, 1288, 1166, 1088; ^1H NMR (600 MHz, CDCl_3) δ 4.90 (qt, $J = 6.6, 6.0$ Hz, 1H), 2.20 (td, $J = 7.2, 2.4$ Hz, 2H), 1.95 (t, $J = 2.4$ Hz, 1H), 1.70~1.51 (m, 4H), 1.20 (d, $J = 6.6$ Hz, 3H), 1.19 (s, 9H); ^{13}C NMR (150 MHz, CD_3Cl) δ 178.1, 84.0, 70.0, 68.6, 38.7, 34.9, 27.1, 24.4, 19.9, 18.3; CIHRMS: Calculated for $[\text{C}_{12}\text{H}_{20}\text{O}_2 + \text{Na}^+]$: 219.1356, Found: 219.1355

(S)-6-Oxoheptan-2-yl pivalate (IV-37)

To a flask was added [(*i*-Pr)AuCl] (21.9 mg, 0.035 mmol) and small amount of AgSbF₆ (covering the tip of a spatula) in 3 mL MeOH, the mixture was stirred at RT for 1 min. Alkyne **IV-29** (135 mg, 0.69 mmol) was added followed by addition of 1 mL water. The reaction mixture was heated at 65 °C for 12 hr. The solvent was removed by vacuum, the crude product was purified using silica gel flash chromatography to give ketone **IV-37** 126 mg (0.59 mmol, 85%) as colorless oil: *R*_f(10% EtOAc/hexane) = 0.35; [α]_D²⁵ = 34.7 (*c* = 0.8, CH₂Cl₂); IR (thin film, cm⁻¹) 2976, 1721, 1481, 1367, 1284, 1166, 1088; ¹H NMR (600 MHz, CDCl₃) δ 4.90 (qt, *J* = 6.0, 6.0 Hz, 1H), 2.42 (t, *J* = 7.2 Hz, 2H), 2.11 (s, 3H), 1.65~1.48 (m, 4H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.17 (s, 9H); ¹³C NMR (150 MHz, CD₃Cl) δ 208.7, 178.4, 70.2, 43.4, 38.9, 35.4, 30.1, 27.3, 20.0, 19.7; CIHRMS: Calculated for [C₁₂H₂₂O₃ + Na⁺]: 237.1461, Found: 237.1460

(S)-7-Bromo-6-oxoheptan-2-yl pivalate (IV-38)

Bromine (0.035 mL, 0.67 mmol) was added to a solution of ketone **IV-37** (120 mg, 0.56 mmol) in 3 mL MeOH at RT. for 10 min under N₂. After the addition was completed, the reaction mixture was stirred for 2 hr. Then the MeOH was removed from the reaction

mixture under reduced pressure. The residue was partitioned between ether and water. The PH of the resulting solution was adjusted to 8.0 by adding NaHCO₃. The ether layer was washed with NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated to yield crude product, the crude product was purified using silica gel flash chromatography to give bromo-ketone **IV-38** 114 mg (0.39 mmol, 70%) as colorless oil.

To a flask was added [(*i*-Pr)AuCl] (50 mg) and small amount of AgSbF₆ (covering the tip of a spatula) in 3 mL anhydrous MeOH, the mixture was stirred at RT for 1 min. Alkyne **IV-29** (494 mg, 4.4 mmol) was added. The reaction mixture was heated at 65 °C for 5 hr. NBS (801mg, 4.5 mmol) was added to the reaction solution. After another 5 hr, the solvent was removed by vacuum, the crude product was purified using silica gel flash chromatography to give ketone **IV-38** 1.1 g (0.59 mmol, 85%) as colorless oil.

IV-38: *R*_f (10% EtOAc/hexane) = 0.53; [α]_D²⁵ = 0.60 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2974, 1716, 1460, 1397, 1284, 1166, 1127; ¹H NMR (600 MHz, CDCl₃) δ 4.89 (qt, *J* = 6.0, 6.0 Hz, 1H), 3.86 (s, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 1.65~1.48 (m, 4H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.19 (s, 9H); ¹³C NMR (150 MHz, CD₃Cl) δ 201.7, 178.1, 69.8, 39.3, 38.7, 35.0, 34.1, 27.2, 19.8, 19.6; CIHRMS: Calculated for [C₁₂H₂₁BrO₃ +Na⁺]: 317.0566, Found: 317.0544

(S)-6-oxo-7-(1-phenyl-1H-tetrazol-5-ylthio)heptan-2-yl pivalate (IV-38a)

To the solution of ketone **IV-38** (113 mg, 0.39 mmol) in MeOH (2 mL), PT-SH (68 mg, 0.39 mmol) and KOH (21 mg, 0.39 mmol) was added at RT. The mixture was then stirred at RT for 3 hr. 1 M HCl was added and extracted with Et₂O, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give 129 mg (0.33 mmol, 85%) of sulfide **IV-38a** as colorless oil: *R_f* (20% EtOAc/hexane) = 0.24; [α]_D²⁵ = 42.3 (*c* = 0.65, CH₂Cl₂); IR (thin film, cm⁻¹) 2976, 2939, 2874, 1718, 1500, 1169, 698; ¹H NMR (600 MHz, CDCl₃) δ 7.62~7.55 (m, 5H), 4.89 (qt, *J* = 6.0, 6.0 Hz, 1H), 4.32 (s, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 1.65~1.48 (m, 4H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.19 (s, 9H); ¹³C NMR (150 MHz, CD₃Cl) δ 209.2, 178.1, 133.0, 131.0, 130.1, 124.4, 121.2, 69.7, 68.1, 38.7, 37.8, 35.2, 27.1, 19.8, 19.4; CIHRMS: Calculated for [C₁₉H₂₆N₄O₃S+Na⁺]: 413.1678, Found: 413.1618

(S)-6-oxo-7-(1-phenyl-1H-tetrazol-5-ylsulfonyl)heptan-2-yl pivalate (IV-27)

A solution of sulfide **IV-38a** (66 mg, 0.17 mmol) in ethanol (1 mL) at 0 °C was treated with ammonium heptamolybdate tetrahydrate (31 mg, 0.025 mmol) and 30% aqueous

hydrogen peroxide solution (0.17 ml, 1.7 mmol), The reaction mixture was warmed to ambient temperature over 5 hr, stirred for additional 7 hr and then brine was added. The mixture was extracted with Et₂O, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give sulfone **IV-27** 50 mg (0.12 mmol, 70%) as colorless oil: *R*_f(30% EtOAc/hexane) = 0.54; $[\alpha]_D^{25} = 3.5$ (*c* = 1.2, CH₂Cl₂); IR (thin film, cm⁻¹) 2974, 2941, 2876, 1720, 1450, 1356, 1164, 764; ¹H NMR (600 MHz, CDCl₃) δ 7.67~7.58 (m, 5H), 4.85 (qt, *J* = 6.0, 6.0 Hz, 1H), 4.71 (s, 2H), 2.67 (t, *J* = 6.6 Hz, 2H), 1.65~1.48 (m, 4H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.19 (s, 9H); ¹³C NMR (150 MHz, CD₃Cl) δ 196.0, 178.2, 153.4, 132.9, 131.6, 129.6, 125.5, 69.6, 64.8, 43.7, 38.7, 34.7, 27.1, 19.7, 19.7; CIHRMS: Calculated for [C₁₉H₂₆N₄O₅S+Na⁺]: 445.1516, Found: 445.1517

**(2*S*)-5-((5*S*,7*aS*)-3-(sulfonyl)-5-(2-methoxy-2-oxoethyl)-6-oxo-5,6
7,7*a*-tetrahydro-3*aH*-furo[3,2-*b*]pyran-2-yl)pentan-2-yl-pivalate (IV-42)**

To a solution of Boc-pyranone **IV-33** (10 mg, 0.024 mmol) and sulfone **IV-27** (7 mg, 0.024 mmol) in dry CH₂Cl₂ (0.3 mL), was added Pd₂(DBA)₃•CHCl₃ (2.5 mg, 10 mol%) and PPh₃ (2.5 mg, 40 mol%) at 0 °C under argon atmosphere. After stirring for 3 h at 0

°C, the reaction mixture was quenched with saturated NaHCO₃, extracted with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give 12 mg **IV-42** (0.02 mmol, 85%) as colorless oil.

To a solution of Piv-pyranone **IV-43** (11 mg, 0.026 mmol) and sulfone **IV-27** (7 mg, 0.026 mmol) in dry CH₂Cl₂ (0.3 mL), was added Pd₂(DBA)₃•CHCl₃ (2.5 mg, 10 mol%) and PPh₃ (2.5 mg, 40 mol%) at 0 °C under argon atmosphere. After stirring for 3 h at 0 °C, the reaction mixture was quenched with saturated NaHCO₃, extracted with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give 14 mg **IV-42** (0.02 mmol, 85%) as colorless oil.

IV-42: *R*_f (20% EtOAc/hexane) = 0.44; [α]_D²⁵ = -172.1 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2975, 2957, 2873, 1739, 1596, 1369, 1172, 1083, 764, 632; ¹H NMR (600 MHz, CDCl₃) δ 7.71 (m, 2H), 7.61 (m, 3H), 5.57 (d, *J* = 7.2 Hz, 1H), 5.31 (dt, *J* = 7.2, 3.6 Hz, 1H), 4.85 (qt, *J* = 6.0, 6.0 Hz, 1H), 4.29 (t, *J* = 4.2 Hz, 1H), 3.61 (s, 3H), 3.26 (dd, *J* = 16.2, 3.0 Hz, 1H), 3.04 (dd, *J* = 16.2, 3.0 Hz, 1H), 3.02 (dd, *J* = 17.4, 4.2 Hz, 1H), 2.78 (t, *J* = 7.2 Hz, 2H), 2.54 (dd, *J* = 17.4, 4.2 Hz, 1H), 1.71~1.50 (m, 4H), 1.17 (d, *J* = 6.0 Hz, 3H), 1.16 (s, 9H); ¹³C NMR (150 MHz, CD₃Cl) δ 206.2, 182.0, 178.0, 170.3, 156.0, 133.3, 131.3, 129.6, 125.4, 106.9, 82.1, 76.6, 73.3, 69.6, 51.9, 38.7, 38.6, 35.7, 35.2, 27.8, 27.1, 22.6, 19.7; CIHRMS: Calculated for [C₂₇H₃₄ N₄O₉S+Na⁺]: 613.1939, Found: 613.1940

(*S,E*)-7-((2*S*,5*R*,6*S*)-5-hydroxy-6-(2-methoxy-2-oxoethyl)-5,6-dihydro-2H-pyran-2-yl)hept-6-en-2-yl pivalate (IV-41**)**

To a solution of allylic alcohol **IV-48** (15 mg, 0.052 mmol) and sulfone **IV-27** (22 mg, 0.052 mmol) in dry CH_2Cl_2 (0.3 mL), was added $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ (2.5 mg, 5 mol%) and PPh_3 (2.5 mg, 20 mol%) at 0 °C under argon atmosphere. After stirring for 3 h at 0 °C, the reaction mixture was cooled to -78 °C and MeOH was added to the solution. Then NaBH_4 was added to the reaction solution, the reaction mixture was allowed to stir at -78 °C for 5 hr. The reaction was then quenched with saturated NaHCO_3 , extracted with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give 5 mg **IV-41** (0.013 mmol, 26%) as colorless oil: R_f (30% EtOAc /hexane) = 0.50; $[\alpha]_D^{25} = 57.0$ ($c = 0.75$, CH_2Cl_2); IR (thin film, cm^{-1}) 3485, 2978, 2936, 1723, 1456, 1167, 1070, 1132; ^1H NMR (600 MHz, CDCl_3) δ 5.85 (ddd, $J = 10.8, 1.8, 1.8$ Hz, 1H), 5.79 (ddd, $J = 10.8, 3.0, 1.8$ Hz, 1H), 5.63 (dtd, $J = 15.6, 7.2, 1.2$ Hz, 1H), 5.53 (dd, $J = 15.6, 5.4$ Hz, 1H), 4.85 (qt, $J = 6.0, 6.0$ Hz, 1H), 4.63 (dddd, $J = 5.4, 3.0, 1.8, 1.2$ Hz, 1H), 3.94 (ddd, $J = 7.2, 1.8, 1.8$ Hz, 1H), 3.89 (ddd, $J = 7.8, 7.2, 4.8$ Hz, 1H), 3.71 (s, 3H), 2.81 (dd, $J = 15.6, 4.8$ Hz, 1H), 2.57 (dd, $J = 15.6, 7.8$ Hz, 1H), 2.08 (dt, $J = 7.2, 7.2$ Hz, 2H), 1.64~1.38 (m, 4H), 1.19 (d, $J = 6.0$ Hz, 3H), 1.18 (s, 9H); ^{13}C NMR (150 MHz, CD_3Cl) δ 178.3, 172.1, 133.9, 129.5, 128.6,

127.9, 72.5, 70.5, 67.2, 57.0, 51.8, 38.7, 37.9, 35.0, 32.1, 27.1, 24.5, 19.7; CIHRMS:

Calculated for $[C_{20}H_{32}O_6 + Na^+]$: 391.2091, Found: 391.2079

(*S,Z*)-7-((2*S*,5*R*,6*S*)-5-hydroxy-6-(2-methoxy-2-oxoethyl)-5,6-dihydro-2H-pyran-2-yl)hept-6-en-2-yl pivalate (**IV-49**)¹³

To a solution of allylic alcohol **IV-48** (15 mg, 0.052 mmol) and sulfone **IV-27** (22 mg, 0.052 mmol) in dry CH_2Cl_2 (0.3 mL), was added $Pd_2(DBA)_3 \cdot CHCl_3$ (2.5 mg, 5 mol%) and PPh_3 (2.5 mg, 20 mol%) at 0 °C under argon atmosphere. After stirring for 3 h at 0 °C, the reaction mixture was cooled to -78 °C and MeOH was added to the solution. Then $NaBH_4$ was added to the reaction solution, the reaction mixture was allowed to stir at -78 °C for 5 hr. The reaction was then quenched with saturated $NaHCO_3$, extracted with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give 2 mg **IV-49** (0.006 mmol, 13%) as colorless oil. 1H NMR (600 MHz, $CDCl_3$) δ 5.84 (ddd, $J = 10.2, 2.4, 2.4$ Hz, 1H), 5.71 (ddd, $J = 10.8, 3.0, 1.8$ Hz, 1H), 5.55 (m, 2H), 4.92 (ddd, $J = 4.8, 2.4, 1.8$ Hz, 1H), 4.86 (qt, $J = 6.0, 6.0$ Hz, 1H), 3.97 (ddd, $J = 7.8, 6.6, 4.8$ Hz, 1H), 3.92 (ddd, $J = 6.6, 3.0, 2.4$ Hz, 1H), 3.71 (s, 3H), 2.77 (dd, $J = 15.6, 4.8$ Hz, 1H), 2.59 (dd, $J = 15.6, 7.8$ Hz, 1H),

¹³ This compound is not fully characterized.

2.33 (ddd, $J = 6.0, 4.8, 1.8$ Hz, 2H), 1.64~1.38 (m, 4H), 1.19 (d, $J = 6.0$ Hz, 3H), 1.18 (s, 9H);

(2*R*,7*R*)-7-(sulfonyl)-7-((2*R*,6*S*)-6-(2-methoxy-2-oxoethyl)-5-oxo-5,6-dihydro-2H-pyran-2-yl)-6-oxoheptan-2-yl pivalate (IV-25)¹⁴

To three round bottle flasks, **IV-42** in THF (0.5 M) was added. NaOMe, KO*t*-Bu and NaH (catalytic to 5 equivalent) was added to the three bottles respectively. The reaction solutions were allowed to stir for 24 hr at R.T. No desired product **IV-25** can be isolated.

(2*S*)-5-((3*S*,3*aR*,5*S*,7*aS*)-3-(sulfonyl)-5-(2-methoxy-2-oxoethyl)-6-oxohexahydro-2H-furo[3,2-*b*]pyran-2-yl)pentan-2-yl pivalate (IV-46)¹⁴

To a solution of **IV-42** in dry CH₂Cl₂ was carefully added Pd/C (3 equivalents) and the resulting suspension was stirred under H₂ (1 atm) for 24 hr at room temperature. TLC

¹⁴ This compound was not obtained.

showed there was still starting materials. The reaction solution was allowed to stir under H₂ (3 atm) for 24 hr, starting materials was fully recovered.

To a solution of **IV-42** in dry CH₂Cl₂ was carefully added Wilkinson's catalyst (20 mol %) and the resulting suspension was stirred under H₂ (1 atm) for 24 hr at room temperature. TLC showed there was still starting materials. The reaction solution was allowed to stir under H₂ (3 atm) for 24 hr, starting materials was fully recovered.

(2*R*,7*R*)-7-(sulfonyl)-7-((2*R*,5*R*,6*S*)-5-(tert-butyldimethylsilyloxy)-6-(2-methoxy-2-oxoethyl)-5,6-dihydro-2H-pyran-2-yl)-6-oxoheptan-2-yl pivalate (IV-51)¹⁴

To a solution of **IV-50** and sulfone **IV-27** in dry CH₂Cl₂ (0.5 M), was added Pd₂(DBA)₃·CHCl₃ (5 mol%) and PPh₃ (20 mol%) at 0 °C under argon atmosphere. After stirring for 3 h at 0 °C, the reaction mixture was warmed up to R.T. and allowed to stir for 5 hr, desired product **IV-51** was not observed.

(2*R*,7*R*)-7-(sulfonyl)-7-((2*R*,5*S*,6*S*)-5-hydroxy-6-(2-methoxy-2-oxoethyl)-5,6-dihydro-2H-pyran-2-yl)-6-oxoheptan-2-yl pivalate (IV-53)¹⁴

To a solution of **IV-52** and sulfone **IV-27** in dry CH_2Cl_2 (0.5 M), was added $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ (5 mol%) and PPh_3 (20 mol%) at 0°C under argon atmosphere. After stirring for 3 h at 0°C , the reaction mixture was warmed up to R.T. and allowed to stir for 5 hr, desired product **IV-53** was not observed.

To a solution of **IV-58** and sulfone **IV-27** in dry CH_2Cl_2 (0.5 M), was added $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ (5 mol%) and PPh_3 (20 mol%) at 0°C under argon atmosphere. After stirring for 3 h at 0°C , the reaction mixture was warmed up to R.T. and allowed to stir for 5 hr, desired product **IV-53** was not observed.

(2*R*,7*R*)-7-(sulfonyl)-7-((2*R*,5*S*,6*S*)-5-(tert-butyldimethylsilyloxy)-6-(2-methoxy-2-oxoethyl)-5,6-dihydro-2*H*-pyran-2-yl)-6-oxoheptan-2-yl pivalate (IV-55)¹⁴

To a solution of **IV-54** and sulfone **IV-27** in dry CH_2Cl_2 (0.5 M), was added $\text{Pd}_2(\text{DBA})_3 \cdot \text{CHCl}_3$ (5 mol%) and PPh_3 (20 mol%) at 0 °C under argon atmosphere. After stirring for 3 h at 0 °C, the reaction mixture was warmed up to R.T. and allowed to stir for 5 hr, desired product **IV-55** was not observed.

Appendix

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

¹H NMR (600 MHz)

¹³C NMR (150 MHz)

¹H NMR (600 MHz)

¹³C NMR (150 MHz)

^1H NMR (270 MHz, CDCl_3)

X : parts per Million : ^1H

^{13}C NMR (67.5 MHz, CDCl_3)

□ X : parts per Million : ^{13}C

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

¹³C NMR (150 MHz, CDCl₃)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

¹³C NMR (150 MHz, CDCl₃)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

¹H NMR (600 MHz, CDCl₃)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

¹³C NMR (150 MHz, CDCl₃)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

¹³C NMR (150 MHz, CDCl₃)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

¹H NMR (600 MHz, CDCl₃)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

¹H NMR (600 MHz, CDCl₃)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

¹³C NMR (150 MHz, CDCl₃)

^1H NMR (600 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz, CDCl_3)

^{13}C NMR (150 MHz, CDCl_3)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

^{13}C NMR (150 MHz)

^1H NMR (600 MHz)

¹H NMR (600 MHz)

¹³C NMR (150 MHz)

¹H NMR (600 MHz)

¹³C NMR (150 MHz)

^1H NMR (600 MHz)