1985

Search for New Membrane Active Substances: synthesis of 3-tropanols with alkyl, alkenyl and alkenynyl group at the bridgehead

Ramalinga Murty Dharanipragada
West Virginia University

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

Part of the [Organic Chemistry Commons](#)

Recommended Citation

Dharanipragada, Ramalinga Murty, "Search for New Membrane Active Substances: synthesis of 3-tropanols with alkyl, alkenyl and alkenynyl group at the bridgehead" (1985). *Graduate Theses, Dissertations, and Problem Reports*. 10148.
<https://researchrepository.wvu.edu/etd/10148>

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.

8523763

PLEASE NOTE

Dharanipragada, Ramalinga Murty

The negative microfilm copy of this dissertation was prepared and deposited at the University of Microfilms International, 300 N. Zeeb Road, Ann Arbor, MI 48106, for the purpose of making the film available to the public. It is not to be used for any other purpose without the written permission of the University of Microfilms International.

SEARCH FOR NEW MEMBRANE ACTIVE SUBSTANCES: SYNTHESIS OF 3-TROPANOLS WITH ALKYL, ALKENYL AND ALKENYNYL GROUP AT THE BRIDGEHEAD

INFORMATION TO USERS

West Virginia University

PH.D. 1985

**University
Microfilms
International**

300 N. Zeeb Road, Ann Arbor, MI 48106

The negative microfilm copy of this dissertation was prepared and inspected by the school granting the degree. We are using this film without further inspection or change. If there are any questions about the content, please write directly to the school.

INFORMATION TO USERS

The following explanation of techniques is provided to help clarify markings or notations which may appear on this reproduction.

1. The sign or "target" for pages apparently lacking from the document photographed is "Missing Page(s)". If it was possible to obtain the missing page(s) or section, they are spliced into the film along with adjacent pages. This may have necessitated cutting through an image and duplicating adjacent pages to assure complete continuity.
2. When an image on the film is obliterated with a round black mark, it is an indication of either blurred copy because of movement during exposure, duplicate copy, or copyrighted materials that should not have been filmed. For blurred pages, a good image of the page can be found in the adjacent frame. If copyrighted materials were deleted, a target note will appear listing the pages in the adjacent frame.
3. When a map, drawing or chart, etc., is part of the material being photographed, a definite method of "sectioning" the material has been followed. It is customary to begin filming at the upper left hand corner of a large sheet and to continue from left to right in equal sections with small overlaps. If necessary, sectioning is continued again—beginning below the first row and continuing on until complete.
4. For illustrations that cannot be satisfactorily reproduced by xerographic means, photographic prints can be purchased at additional cost and inserted into your xerographic copy. These prints are available upon request from the Dissertations Customer Services Department.
5. Some pages in any document may have indistinct print. In all cases the best available copy has been filmed.

University
Microfilms
International

300 N. Zeeb Road
Ann Arbor, MI 48106

SEARCH FOR NEW MEMBRANE ACTIVE SUBSTANCES:

SYNTHESIS OF 3-TROPANOLS WITH ALKYL, ALKENYL AND ALKENYNYL
GROUP AT THE BRIDGEHEAD

DISSERTATION

Submitted To The College of Arts and Sciences
of
West Virginia University
In Partial Fulfillment Of The Requirement For
The Degree Of Doctor Of Philosophy

by

Ramalinga Murty Dharanipragada, M.S.

Morgantown
West Virginia

1985

PHYS. SCI. LIB.

w

378.7543

Chem.

D536s

C. 2

TO

my mother on the occasion of her sixtieth birthday

and

to the memory of my father.

ACKNOWLEDGEMENTS

It is my pleasure to thank my research advisor, Dr. G. Fodor for sharing his expertise on tropane alkaloids with me. I particularly would like to thank him for giving me the opportunity to co-author several review articles on the chemistry of tropane alkaloids. My stay with him has been a learning experience.

I would like to thank two of my teachers, Drs. W. R. Moore and D. W. H. MacDowell, who "baptised" me into organic chemistry. I would like to thank the other members of my committee Drs. N. S. Dalal and J. P. O'Donnell for their cooperation. I thank Dr. K. Wang for several "chalk-fest" sessions which proved very useful.

Several people in Dr. Fodor's research group deserve my gratitude. I thank Mrs. Jyothsna Venkat for years of warm friendship. Her help in proof-reading this manuscript is deeply appreciated. I thank Dr. J. Case and the late Dr. J. Butterick for refining my techniques in the laboratory. I thank Drs. R. Arnold and K. Fang for their friendship and pleasant company. I thank Dr. K. Sussangkarn and Dr. Hansie Mathelier for their cooperation in the laboratory. I thank Ms. Krystal Berry for her help with some of the drawings.

Several undergraduate students have contributed to the success of this project. I would like to thank Mr. Craig Abshire, Mr. Dale Carpenter, Ms. Karen Clark, Mr. Sam Colombo,

Mr. Mark Herman, Mr. Jeff Jackson, Mr. Tony Piscopio, Mr. Ely J. Salon, Mr. Stan Wasilewski, and Mr. Robert Yepundich for their contributions in terms of maintaining a steady supply of some of the key intermediates. Tony Piscopio was instrumental in the preparation of en-yne Wittig salts.

Over the years, I had the privilege to assist more than 700 students in the undergraduate chemistry laboratories. These students have helped me to strengthen the foundations of my chemistry. I thank the department of chemistry for giving me such an opportunity and also for uninterrupted financial support all these years.

Several friends among the staff of the chemistry department have made me feel at home. They helped me find a home "away from home". Particular mention should be made of Mr. Forrest Ferrell whose sense of humor, fatherly advice and warm friendship kept me sane from time to time. I thank Mrs. Georgetta Cobun, Mrs. Siobhan Byrne, Mrs. Marleen Dewitt, Mrs. Dorothy Nagy, Ms. Eloise McNair, Ms. Michell Cobun, Ms. Debbie Koon, Mrs. Bev Matheny, Mr. Mike Naugle, Mr. Bob Victor, Mr. Carl Wise, and Mr. Sherman Adams for their cooperation and cheerful disposition at all times.

At this point I would like to reminisce and thank a lot of my friends whose friendship I value very much. I acknowledge Mr. Jamshed Bapasola, Mr. Bobby Adams, Dr. Mahendra Suryan, Dr. Sham Nikam, Dr. Jagadeesh Moodera, Mrs. Sharada Shenvi Labadie, Mrs. Shahin Ravangard, Mr. Jalil Shojae, Mr. Wee Lerthusnee, Mrs. Malvina Marciano, Ms. Sujitra Dhumrongvaraporn,

Mr. Hongbum Kim, Ms. Nancy Crowley, Ms. Donna Carmesi and Ms. Stephanie Ware for their friendship. I thank my roommate Mr. Vijay Waghray for putting up with me all these years.

I thank my cousins Dr. Babu Paidipaty and Dr. Sudha Paidipaty of Detroit for the good times I had with them every Christmas.

I thank Mrs. Duana Nacarate for typing this manuscript. She impressed me with her professionalism, speed and her ability to decipher my handwriting, which is no easy task.

There have been times, while in the process of trying to run, I was unable to walk, and I did many "moonwalks" in the chemical sense; with none of the reactions proceeding in the desired direction. I thank God many of the problems have been solved towards the end.

Finally the most important person I would like to thank is my friend Alex who defined friendship in her own special way. When she talks I listen. No matter where I go, her friendship, affection and love will always be cherished.

TABLE OF CONTENTS

	Page
TITLE PAGE	i
DEDICATION	ii
ACKNOWLEDGEMENTS	iii
TABLE OF CONTENTS	vi
LIST OF FIGURES	xii
 1. INTRODUCTION AND LITERATURE SURVEY	 1
2. STATEMENT OF THE PROBLEM	8
3. SYNTHETIC STRATEGY	9
4. RESULTS AND DISCUSSION	11
Part A - Construction of Tropane Skeleton	11
4.1.1 Building Blocks	11
4.1.2 Synthetic Efforts Towards Ketoaldehyde <u>26</u>	13
4.1.3 Hydrogenation of <u>32</u>	17
4.1.4 Robinson Condensation	18
4.1.5 Mechanism of Robinson Condensation	20
4.1.6 Synthesis of related Tropinones	20
4.1.7 Stereoselective Reduction of (+) 1-Methoxy- methyl-3-tropanone (<u>17</u>)	24
4.1.8 Configuration of C-3 Hydroxyl of <u>43</u>	25
4.1.9 Structure Determination of <u>43</u> -Chemical Methods	26
4.1.10 Protection of C-3 Hydroxyl in <u>43</u>	31
4.1.11 Improvement of Yields of <u>60</u> : Use of 4-N,N-Dimethylaminopyridine (DMAP) as Acetylation Catalyst	32
4.1.12 Reasons for Improved Yields - Mechanism of DMAP Action	33
4.1.13 Cleavage of Methyl Ether of <u>60</u>	35
4.1.14 Structure Determination of the Monoacetate <u>55</u>	39

Part B - Elaboration of the Side Chain by Wittig Route	41
4.2.1 Search for Oxidizing Agent	41
4.2.2 Dimethylsulfoxide-Dicyclohexylurea Oxidation	43
4.2.3 Structure of the Tropan-1-Aldehyde (<u>56</u>) - Spectral Data	45
4.2.4 Chemical Proof for the Structure of Aldehyde <u>56</u>	46
4.2.5 Mechanism of DMSO-DCC Oxidation	46
4.2.6 Constraints of the Oxidation	47
4.2.7 DMSO-Acetic Anhydride as Oxidants	47
4.2.8 Mechanism of Oxidation	51
4.2.9 Possible Mechanism for Acetate Formation	52
4.2.10 Oxidation using DMSO/Pyridine-SO ₃	54
4.2.11 Oxidation using DMSO-P ₂ O ₅	55
4.2.12 DMSO-Thionyl Chloride	56
4.2.13 Swern Oxidation: DMSO-Oxalyl Chloride Complex as Oxidizing Agent	56
4.2.14 Mechanism of DMSO-Oxalyl Chloride Oxidation	58
4.2.15 Wittig Reaction: Extension of the Side Chain.	60
4.2.16 Structure Determination of 1-Pentenyl-3 β -tropanol	63
4.2.17 Interpretation of Mass Spectra of 1-Pentenyl-3 β -Tropanol	64
4.2.18 Removal of Acetate by Transesterification	67
4.2.19 Stereochemistry of Wittig Olefination	68
4.2.20 Mechanism of Wittig Reaction	69
4.2.21 Attempted Preparation of Crystalline Salts of <u>14</u>	71
4.2.22 Chemical Confirmation of Structure of Alkene <u>14</u>	72
4.2.23 Reduction of Alkene <u>14</u> to (+) 1-n-Pentyl-3 β -tropanol (<u>15</u>)	72
4.2.24 Attempted Removal of N-CH ₃ of 1-Pentenyl-3 β -tropanol	74
Part C - Scope and Limitations of the Wittig Route	80
4.3.1 Retrosynthesis Analysis of Skipped En-yne <u>136</u>	80
4.3.2 Comparison of Scheme 99 and Scheme 100	83

4.3.3	Attempted Condensation of Aldehyde <u>56</u> with ylide <u>139</u>	83
4.3.4	Alternate Approaches to Skipped En-yne Sidechain	88
4.3.5	Preparation of Wittig Salt <u>149</u>	88
4.3.6	Attempted Preparation of $H-C\equiv C-CH_2CH_2PPh_3Br$ <u>49</u>	89
4.3.7	Attempted Preparation of Phosphonium Tosylate <u>158</u>	91
4.3.8	One Step Preparation of 4-Bromo-1-butyne	94
4.3.9	Wittig Condensation Leading to En-yne <u>151</u>	96
4.3.10	Studies on Aldehyde Homologation	98
Part D - Attempted Organometallic Route to 1-Alkyl Tropanols		103
4.4.1	Attempted Preparation of Bromide <u>176</u>	103
4.4.2	Attempted Preparation of Chloride <u>177</u>	105
4.4.3	Preparation of Mesylate <u>180</u>	107
4.4.4	Attempted Carbon-Carbon Bond Formation using Mesylates	112
4.4.5	Formation of Sulfones - Steric Factors Raise their Ugly Heads	113
4.4.6	Preparation of Iodide <u>193</u>	115
4.4.7	Mechanism of Formation of Iodide	117
5.	SUMMARY	121
6.	EXPERIMENTAL	123
	Instrumentation	123
	Solvents	124
	Reagents	124
	General Remarks	127
	Preparations	127
6.1	Preparation of Furfuryl methyl ether (<u>31</u>)	127
6.2	Preparation of 2,5-Dimethoxy 2-methoxymethyl- 2,5-dihydrofuran (<u>32</u>)	129
6.3	Preparation of Raney Nickel W-2	130
6.4	Preparation of 2,5-Dimethoxy-2-methoxymethyl tetrahydrofuran (<u>34</u>)	131
6.5	(+) 1-Methoxymethyl-3-tropanone (<u>17</u>)	132

6.6	Preparation of 1-Methoxymethyl-3 β -tropanol (43)	134
6.7	Preparation of 1-Methoxymethyl pseudotropine hydrochloride (45)	135
6.8	Preparation of 1-Methoxymethyl-3 β -acetoxytropane Hydrochloride (60)	136
6.9	Preparation of 1-Hydroxymethyl-3 β -acetoxytropane (55)	137
6.10	Preparation of Tetraphenyl borate salt of 3 β -Hydroxymethyl-3 β -acetoxytropane	138
6.11	Preparation of Methyl-2-furoate (27)	141
6.12	Preparation of 1-Hydroxymethyl-3 β -tropanol (52)	142
6.13	Swern Oxidation of 1-Hydroxymethyl-3 β -acetoxytropane (55) to 3 β -acetoxytropane-1-aldehyde (56)	143
6.14	Chemical conformation of structure of 3 β -acetoxytropane-1-aldehyde (56) by reduction to 1-hydroxymethyl-3 β -acetoxytropane (55)	145
6.15	Pfizzner-Moffatt Oxidation of 1-hydroxymethyl-3 β -acetoxytropane	146
6.16	Attempted Oxidation of 55 using dimethyl sulfoxide in presence of acetic anhydride. Preparation of 1-acetoxymethyl-3 β -acetoxytropane (86)	147
6.17	Preparation of Sulfur Trioxide-Pyridine Complex	148
6.18	Oxidation of 1-Hydroxymethyl-3 β -acetoxytropane by Dimethyl Sulfoxide in Presence of Pyridine-Sulfur Trioxide Complex	148
6.19	Preparation of n-Butyl triphenyl phosphonium bromide (98)	149
6.20	Wittig condensation of aldehyde 56, with n-butyridene triphenylphosphorane: Preparation of 1-pentyl-3 β -hydroxytropane (14)	150
6.21	Preparation of 1-(1-Pentenyl)-3-acetoxytropane (103)	152
6.22	Deacetylation of 1-(1-pentenyl)-3 β -acetoxytropane	153
6.23	Addition of n-Butyllithium to 3 β -Acetoxytropane-1-aldehyde	154
6.24	Preparation of Potassium Azo Dicarboxylate	155
6.25	Attempted Diimide Reduction of Alkene 14	155
6.26	Preparation of (+) 1-n-amyl-3 β -tropanol (15)	155
6.27	Preparation of (+) 1-n-amyl-3 β -tropanol hydrochloride (122)	156
6.28	Preparation of 4-Trimethylsilyl but-3yn-1-ol	156

6.29	Tosylation of 4-trimethylsilyl but-3yn-1-ol . . .	158
6.30	Displacement of Tosylate <u>146</u> by Iodide	158
6.31	Preparation of Triphenyl (1-Trimethyl silyl but-3-ynyl) phosphonium iodide (<u>138</u>)	159
6.32	Preparation of 3-Butynyl tosylate	160
6.33	Preparation of 1-Bromo-3-butyne (<u>152</u>)	160
6.34	Attempted improvement of yields of PBr_3 reaction: use of LiBr as co-reactant	162
6.35	Preparation of 1-Bromo-3-butyne using Carbon Tetrabromide and Triphenylphosphine	163
6.36	Attempted Preparation of 1-Bromo-3-butyne by utilizing N-bromosuccinimide/triphenyl phosphine as brominating reagents	164
6.37	Preparation of triphenyl(but-3-ynyl) phosphonium bromide <u>149</u>	164
6.38	Attempted preparation of triphenyl(but-3-ynyl) phosphonium tosylate	165
6.39	Attempted Wittig condensation of neopentyl aldehyde <u>56</u> with triphenyl (1-trimethylsilyl but-3-ynyl) phosphonium iodide (<u>138</u>)	166
6.40	Wittig reaction of triphenyl (3-butynylidene) phosphorane (<u>150</u>) with 3 β -acetoxytropene-1-aldehyde (<u>56</u>)	169
6.41	Aldehyde homologation - attempted Wittig reaction of neopentyl aldehyde <u>56</u> with methoxymethylene triphenylphosphorane	170
6.42	Successful homologation of aldehyde <u>56</u> to 1-(3 β -acetoxytropene)acetaldehyde Wittig reaction using 2 eq of potassium butoxide as base	172
6.43	Cleavage of enol ethers <u>173</u> and <u>174</u> with boron tribromide	173
6.44	Attempted Preparation of 1-chloromethyl-3 β -acetoxytropene (<u>177</u>)	175
6.45	1-Methanesulfonyloxymethyl-3 β -acetoxytropene (<u>180</u>)	176
6.46	Conversion of acetoxy mesylate <u>180</u> into 1-methane sulfonyloxymethyl-3 β -tropanol (<u>181</u>)	177
6.47	Hydrogenolysis of mesylate <u>180</u> into 1-methyl-3 β -tropanol (<u>183</u>)	178
6.48	Attempts to couple 1-mesyloxymethyl-3 β -acetoxytropene (<u>186</u>) with allyl magnesium bromide	179
6.49	Attempted coupling of mesylate <u>180</u> with ethyl magnesium bromide	180

6.50	Attempted coupling of mesylate <u>180</u> with ethyl magnesium bromide using Li_2CuCl_4 as catalyst . .	180
6.51	Attempted coupling of mesylate <u>180</u> with di n-butyl copper lithium	181
6.52	Preparation of di-n-butyl methyl carbinol	182
6.53	Conversion of mesylate <u>180</u> into iodide <u>193</u> . . .	183
6.54	Attempted Coupling of Allylmagnesium bromide with 1-iodomethyl-3 β -acetoxytropane	184
REFERENCES		186
APPENDIX		196
ABSTRACT		285
VITA		286
APPROVAL PAGE		288

LIST OF FIGURES

Figure		Page
1	^1H NMR spectrum of 1-methoxymethylfuran (<u>31</u>) . . .	198
2	Infrared spectrum of 1-methoxymethylfuran (<u>31</u>) . . .	199
3	^1H NMR spectrum of 1-methoxymethyl-2,5-dimethoxy-2,5-dihydrofuran (<u>32</u>)	201
4	Infrared spectrum of 1-methoxymethyl-2,5-dimethoxy-2,5-dihydrofuran (<u>32</u>)	202
5	^1H NMR spectrum of 1-methoxymethyl-2,5-dimethoxytetrahydrofuran (<u>34</u>)	204
6	Infrared spectrum of 1-methoxymethyl-2,5-dimethoxytetrahydrofuran (<u>34</u>)	205
7	^1H NMR spectrum of 1-methoxymethyl tropane 3-one (<u>17</u>)	207
8	Infrared spectrum of 1-methoxymethyl tropane 3-one (<u>17</u>)	208
9	^1H NMR spectrum of 1-methoxymethyl 3 β -hydroxytropane (<u>43</u>)	210
10	Infrared spectrum of 1-methoxymethyl 3 β -hydroxytropane (<u>43</u>)	211
11	^1H NMR spectrum of 1-methoxymethyl 3 β -acetoxytropane hydrochloride (<u>60</u>)	213
12	Infrared spectrum of 1-methoxymethyl 3 β -acetoxytropane hydrochloride (<u>60</u>)	214
13	^1H NMR spectrum of 1-methoxymethyl 3 β -acetoxytropane	216
14	^1H NMR spectrum of 1-hydroxymethyl 3 β -acetoxytropane (<u>55</u>)	218
15	Infrared spectrum of 1-hydroxymethyl 3 β -acetoxytropane (<u>55</u>)	219
16	^1H NMR spectrum of 1-hydroxymethyl 3 β -hydroxytropane (<u>52</u>)	221
17	Infrared spectrum of 1-hydroxymethyl 3 β -hydroxytropane (<u>52</u>)	222
18	^1H NMR spectrum of 3 β -acetoxytropane 1-aldehyde (<u>56</u>)	224

INTRODUCTION AND LITERATURE SEARCH

19	Infrared spectrum of 3 β -acetoxytropone 1-aldehyde (<u>56</u>)	225
20	^1H NMR spectrum of 1-acetoxymethyl 3 β -acetoxytropone (<u>86</u>)	227
21	^1H NMR spectrum of 1-(1-pentenyl)-3 β - acetoxytropone (<u>103</u>)	229
22	^1H NMR spectrum of 1-(1-pentenyl)-3 β - hydroxytropone (<u>14</u>). Solvent: CDCl_3	231
23	^1H NMR spectrum of 1-(1-pentenyl)-3 β - hydroxytropone (<u>14</u>). Solvent: $\text{CDCl}_3 + \text{D}_2\text{O}$	232
24	Infrared spectrum of 1-(1-pentenyl)-3 β - hydroxytropone (<u>14</u>)	233
25	^{13}C NMR spectrum of 1-(1-pentenyl)-3 β - hydroxytropone (<u>14</u>)	234
26	Mass spectrum of 1-(1-pentenyl)-3 hydroxytropone (<u>14</u>)	235
27	^1H NMR spectrum of 1-pentenyl 3 β -hydroxytropone (<u>15</u>)	237
28	^1H NMR spectrum of 1-pentenyl 3 β -hydroxytropone hydrochloride (<u>122</u>)	239
29	Mass spectrum of 1-pentenyl 3 β -hydroxytropone hydrochloride (<u>122</u>)	240
30	^1H NMR spectrum of 1-(1-hydroxypentyl)-3 β - hydroxytropone (<u>118</u>)	242
31	^1H NMR spectrum of mixture of geometric isomers of 1-(2-methoxyvinyl)-3 β -acetoxytropone (<u>173</u> + <u>174</u>).	244
32	^1H NMR spectrum of 1-(3 β -hydroxytropenyl) acetaldehyde (<u>164</u>)	246
33	^1H NMR spectrum of 1-bromo-3-butyne (<u>152</u>)	248
34	Infrared spectrum of 1-bromo-3-butyne (<u>152</u>)	249
35	^1H NMR spectrum of 4-butyryl triphenyl phosphonium bromide (<u>149</u>)	251
36	^1H NMR spectrum of triphenylphosphine oxide	253
37	^1H NMR spectrum of 1-(1-penten-4-ynyl)-3 β - acetoxytropone (<u>151</u>)	255

38	Infrared spectrum of 1-(1-penten-4-ynyl)-3 β -acetoxytropene (<u>151</u>)	256
39	Mass spectrum of 1-(1-penten-4-ynyl)-3 β -acetoxytropene (<u>151</u>)	257
40	^1H NMR spectrum of 4-trimethylsilyl but-3yn-1-ol (<u>143</u>)	259
41	Infrared spectrum of 4-trimethylsilyl but-3yn-1-ol (<u>143</u>)	260
42	^1H NMR spectrum of 4-trimethylsilyl but-3yn-1-tosylate (<u>146</u>)	262
43	Infrared spectrum of 4-trimethylsilyl but-3yn-1-tosylate (<u>146</u>)	263
44	^1H NMR spectrum of 1-Iodo-4-trimethylsilyl-3-butyne (<u>144</u>)	265
45	Infrared spectrum of 1-Iodo-4-trimethylsilyl-3-butyne (<u>144</u>)	266
46	^1H NMR spectrum of 3-butyne 1-tosylate (<u>153</u>)	268
47	^1H NMR spectrum of 1-methanesulfonyloxymethyl 3 β -acetoxytropene (<u>180</u>)	270
48	Infrared spectrum of 1-methanesulfonyloxymethyl 3 β -acetoxytropene (<u>180</u>)	271
49	^1H NMR spectrum of 1-methanesulfonyloxymethyl 3 β -hydroxytropene (<u>181</u>)	273
50	^1H NMR spectrum of 1-iodomethyl 3 β -acetoxytropene (<u>193</u>)	275
51	Infrared spectrum of 1-iodomethyl 3 β -acetoxytropene (<u>193</u>)	276
52	^1H NMR spectrum of Di-n-butyl methyl carbinol (<u>185</u>)	278
53	Infrared spectrum of Di-n-butyl methyl carbinol (<u>185</u>)	279
54	^1H NMR spectrum of 1-methyl-3 β -hydroxytropene (<u>183</u>)	281
55	^1H NMR spectrum of allyl methylsulfone (<u>186a</u>)	283
56	Infrared spectrum of allyl methylsulfone (<u>186a</u>)	284

INTRODUCTION AND LITERATURE SEARCH

In recent years, Witkop and coworkers have isolated^{1,2} several structurally unique alkaloids from the colombian frog belonging to the genera Dendrobates. These alkaloids, which occur in the defensive skin secretions of the frog have been found to be highly active venoms as well as mucosal tissue irritants towards both mammals and reptiles. Among them are three important alkaloids histrionicotoxin, isodihydrohistrionicotoxin and octahydrohistrionicotoxin.

1

1a Histrionicotoxin

1b Isodihydrohistrionicotoxin

1c Octahydrohistrionicotoxin

1d Perhydrohistrionicotoxin

The C_{19} alkaloids histrionicotoxin (abbreviated as HTX) 1a and gephyrotoxin (2) (Dendrobates histrionicus) share common cis enyne side chains, while pumiliotoxin-C (3) (Dendrobates Pumilio) and gephyrotoxin (2) are both elaborated cis-decahydroquinolines.

Both histrionicotoxin (1a) (HTX) and its semisynthetic derivative perhydrohistrionicotoxin (1d) (H_{12} -HTX) have attracted considerable interest from the standpoint of total synthesis, and while a total synthesis of HTX is yet to be accomplished, several different approaches to the construction of H_{12} -HTX (1d) have been reported.³ The attention given to these objectives stems from their unique properties as neurotoxins in conjunction with the scarcity of HTX (ca. 200 μ g per frog). It has been shown^{4b} that both HTX 1a and H_{12} -HTX 1d selectively bind to the acetyl choline receptor and interrupt transsynaptic transmission of neuromuscular impulses. Both 1a and 1d block postsynaptic membrane depolarization while not interfering with acetylcholine binding. It has been postulated^{4a} that these toxins prevent membrane depolarization by reversible binding to the receptor ion channel or "ion conductance modulator". HTX-12 (1d) has biological activity similar to HTX (1a) in the *in vitro* assay in nerve muscle preparation of frogs and therefore provides a biochemical standard.

Histrionicotoxin HTX (1a) appears to act quite similarly to its completely reduced form HTX-12 (1d). This alkaloid reduces the sensitivity of denervated skeletal-muscle to repetitive applications of acetylcholine and blocks the increase in ionic conductance resulting from co-innervation of acetylcholine with its own receptor. In addition, HTX specifically inhibits the increase of potassium conductance that normally occurs during an action potential.

Perhydrohistrionicotoxin has been shown to inhibit muscarinic cholinergic sites in neuroblastoma cells.^{4c} The structurally related compounds dihydro-adaline, (4), granatan-3 α -ol (5), grantan-3 β -ol (6) have also been tested for their receptor affinity. Inhibition of [³H] scopolamine binding was studied by carrying out displacement experiments with [³H] scopolamine as the labelled ligand. Fifty percent inhibition of [³H] scopolamine binding was obtained by either 70 μ M H₁₂ HTX, 250 μ M dihydro-adaline, 4 mM granatan-3 β -ol or >10 mM granatan-3 α -ol. All these compounds have similar bicyclic structural elements with a secondary amino and a secondary alcohol function. While in H₁₂ HTX, two aliphatic side chains are attached to the ring system, dihydro-adaline has only one aliphatic side chain, and the granatanols have none. Thus, the observed order of receptor affinity suggests that lipophilic side chains contribute to the receptor binding of these compounds.

As can be seen from molecular models, the amino and hydroxyl groups of HTX (1a) and dihydro-adaline (4) are in very similar and

close conformational arrangements, permitting a hydrogen bond interaction. The hydroxyl group of granatan-3 β -ol (6) has the same conformation as in dihydro-adaline whereas, in granatan-3 α -ol (5) it points in the opposite direction and cannot interact with the amino group. Since granatan-3 α -ol (5) has a lower affinity to the receptor than granatan-3 β -ol (6), a certain orientation of the hydroxyl group, probably in relation to the amino group, appears to be important for causing receptor blockade.

Adaline 7, isolated⁵ from the defensive secretion of European ladybug Adalia bipunctata, has a secondary amino and hydroxyl moieties and an amyl side chain. It has insect antifeeding properties. Several groups⁶ have accomplished the total synthesis of adaline.

An elegant route to racemic adaline, using an intramolecular nitronc cyclo-addition has been achieved by Gössinger and Winkop, affording adaline in 30% overall yield in eight steps from N-hydroxy-piperidine^{6a} (Scheme 1).

An alternative approach by Hill^{6b}, using double Michael

Scheme 1

addition of benzylamine to 3-alkyl-2,7-cyclooctadienones lead to racemic adaline (Scheme 2). Asymmetric induction was achieved by using (+)- α -methyl benzylamine (Scheme 3).

Scheme 2

Scheme 3

A biomimetic synthesis of adaline has been accomplished by Hussen^{6d} and coworkers. The key step of their synthetic route was an intramolecular Mannich reaction of the intermediate iminium-enol 13' derived from the enamine equivalents, aminonitrile 13 (Scheme 4).

Scheme 4

2. STATEMENT OF THE PROBLEM

Since histrionicotoxin (1a) and dihydroadaline (4) inhibit muscarinic cholinergic sites, and both of them have alkyl or alkenyl sidechains, it was suggested^{88a} that synthesis of 1-alkyl or 1-alkenyl tropanols and nortropanols (which would be expected to have similar conformational arrangement as 1a and 4) might be profitable in order to explore structure activity relationships.

The target compounds are:

14

15

206

207

3. SYNTHETIC STRATEGY

A retrosynthetic analysis of the target compounds 14 and 15 would suggest two conceivable routes (Schemes 5 and 6). Although different in nature (as to the method of elaboration of side chain), both these routes share a common precursor such as 1-carbomethoxy-3-tropanone (16) or 1-methoxymethyl-3-tropanone (17).

Scheme 5

3.1 Route I: Wittig Route

Scheme 6

3.2 Route II: Organometallic Route

4. RESULTS AND DISCUSSION

Part A. Construction of the Tropane Skeleton

4.1.1 Building Blocks

A classical way to build a tropane skeleton⁷ is by the condensation of succinic dialdehyde 18, methylamine hydrochloride 19 and acetone dicarboxylic acid 20 (Scheme 7).

Scheme 7^{8a}

This "one pot" procedure, known as the Robinson condensation^{8a} (first used for the synthesis of tropinone 21), has been extended^{8b} to the synthesis of 1-methyltropinone 23 (Scheme 8).

Scheme 8^{8b}

Unfortunately, generalization of this method to higher homologues⁹ seemed to be difficult, owing to the problems in synthesizing the key intermediates and to the diminished reactivity of long-chain keto aldehydes (Scheme 9).

Scheme 9

Therefore a more intricate study seemed desirable.

A search of literature showed that 1-carbomethoxy-3-tropanone (16) and 1-methoxymethyl-3-tropanone (17) have been synthesized by Kehrle and Karrer.¹⁰ We envisioned that either of these compounds could be elaborated to our synthetic targets 14 and 15 by methods outlined in our retrosynthesis analysis (Schemes 5 and 6).

1-Carbomethoxy-3-tropanone (16) has been synthesized by Karrer¹⁰ from the ketoaldehyde 26, methylamine hydrochloride (19) and acetone dicarboxylic acid (20). When keto aldehyde 33 was used in place of 26, 1-methoxymethyl-3-tropanone (17) was obtained (Scheme 10).

Scheme 10

4.1.2 Synthetic Efforts Towards Ketoaldehyde 26:

2,5-Dimethoxydihydrofurans have been utilized as synthetic precursors of keto aldehydes. Karrer¹⁰ obtained keto aldehyde 26 on hydrolysis of 2,5-dimethoxy-2-carbomethoxy tetrahydrofuran 28 (Scheme 11).

Scheme 11

We planned to synthesize the tetrahydrofuran derivative 28 using Karrer's procedure.¹⁰ Thus 2-furoic acid was esterified using absolute methanol and a cat. amount of sulfuric acid to give methyl 2-furoate (27) in 60% yield (Scheme 12).

Scheme 12

In our hands, attempted electrolytic methoxylation of 27 gave the desired dimethoxy dihydrofuran 29 in only 10-15% yield (Scheme 13). We could never obtain the reported^{11a} yields of 68%.

Scheme 13

Even a chemical variation of this method involving electrophilic addition of bromine followed by nucleophilic

displacement using methanol did not improve our yields
(Scheme 14).

Scheme 14

Although it was very disheartening to face these setbacks at that time, in retrospect, it is not surprising that we obtained poor yields, since an electron-withdrawing group like the carbomethoxy would reduce the electron density on the furan ring and would render it less susceptible to electrophilic attack by bromine.

Since such serious problems were encountered in synthesizing 29 (and in turn obtaining 26 and 16), we abandoned all hopes of making this compound and turned our attention to the synthesis of 1-methoxymethyl-3-tropanone (17). We speculated (correctly as it turned out) that the precursors to 17, namely the dihydrofuran derivative 32 and keto aldehyde 33 would be more easily accessible.

Thus furfuryl alcohol (30) was methylated by methyl iodide following Tollens' procedure¹² (Scheme 15).

Scheme 15¹²

Electrophilic addition of bromine to 2-methoxymethylfuran (31), followed by nucleophilic displacement of the resulting bromide by methanol gave 2,5-dimethoxy-2-methoxymethyl-2,5-dihydrofuran (32) in 66% yield (Scheme 16).

Scheme 16

To our knowledge this is the first chemical synthesis of 32 by this procedure (the previous methods¹⁰ were electrochemical). Furan and several other furan derivatives (but not 31) have been converted by similar procedures¹³⁻¹⁵ to the corresponding dimethoxydihydrofurans.

4.1.3 Hydrogenation of 32:

In the literature^{11,13,14} hydrogenation of dihydrofurans of type 32 has been accomplished by using catalytic amounts of Raney nickel (W-2) at 1700-2000 psi and/or heating to 80°C (Scheme 17).

Scheme 17

As these conditions appeared too drastic to us, we tried to find a different catalyst that would allow the same hydrogenation at much milder conditions. Unfortunately using PtO_2 or Pd/black at 1-2 atmospheres (16-32 psi) and carrying out the reduction at room temperature resulted in hydrogenolysis of methoxy group (Scheme 18).

Scheme 18

Finally, after several trials, we found that by increasing the amount of Raney nickel (1 equivalent of Raney nickel by weight to 1 equivalent of 32), the hydrogenation can be carried out under very mild conditions (1-2 atm, 20°) without any hydrogenolysis (Scheme 19).

Scheme 19

Under these conditions, the uptake of hydrogen was sufficiently rapid. In fact, even using 0.5 equivalent of Raney nickel would maintain a sufficient rate of hydrogenation.

4.1.4 Robinson condensation:

The hydrolysis of the above-hydrogenated product 34 to the keto aldehyde 33 was achieved by heating it with 1 N hydrochloric acid at 75°C for 20 min (Scheme 20).

Scheme 20

The resulting ketoaldehyde 33 was cooled rapidly to 10°C and condensed with acetonedicarboxylic acid and methylamine hydrochloride in water at room temperature for two days in the presence of sodium citrate as buffer. The reaction was carried out at pH 5. At the end, the pH was adjusted to 10 and the reaction mixture was heated to 60°C to effect decarboxylation of the intermediate keto acid 35 (Scheme 21). The desired product, 1-methoxymethyl-3-tropinone (17) was thus obtained in 55-60% yield (yields based on 34).

Our yields of 17 are 15-20% higher than Karrer's yields.¹⁰
 We believe that the improved yields are due to the use of sodium citrate as a buffer.¹⁶

4.1.5 Mechanism of Robinson Condensation:

The mechanism of Robinson condensation has been elucidated by Paquette.¹⁷ It is summarized in Scheme 22.

Paquette's mechanism explains the formation of 3-tropanone (36). We can safely assume that the same mechanism operates for the formation of 1-methoxymethyl-3-tropanone (17) from the keto aldehyde 33, methylamine hydrochloride (19) and acetone dicarboxylic acid 20 (Scheme 22).

4.1.6 Synthesis of Related Tropanones:

Since we were able to synthesize 17 successfully, we were curious to see if we could synthesize a related compound 1-hydroxymethyl-3-tropanone (37) by similar procedures. Scheme 23 summarizes the sequence of synthetic events performed to obtain 37.

Unfortunately the yields we obtained for some of the intermediates on our way to 37 (Scheme 23) were far from satisfactory. As a consequence, 37 was never used in the subsequent steps of our synthesis.

Instead compound 17 was carried on for further synthetic elaborations.

Scheme 23

4.1.7 Stereoselective Reduction of

(+) 1-Methoxymethyl-3-tropanone (17):

Since the configuration of the C-3 hydroxyl is equatorial (β) in our target compounds 14 and 15, we needed to adopt conditions that would reduce the carbonyl of 17 stereospecifically to the β -hydroxy group.

Several studies on the stereochemistry of tropanone reductions have been carried out in the past.^{18,19} Conditions have been developed¹⁹ (Scheme 24) whereby one gets predominantly the β isomer (thermodynamically controlled) or predominantly the α isomer (kinetically controlled).

Scheme 24¹⁹

By using known¹⁹ procedures (Scheme 25) for such reactions, we were able to reduce ketone 17 in 90% crude yield (70% distilled product) exclusively to (+) 1-methoxymethyl pseudotropine (43).

Scheme 25

The crude compound was sufficiently pure (no impurities could be seen in ^1H NMR) and could be used "as is" in the subsequent steps. The loss of yields on distillation is due to the partial decomposition of the compound at higher temperatures (b.p. 105°C at 0.4 mm). One could avoid distillation altogether and purify the compound by column chromatography (basic alumina).

4.1.8 Configuration of C-3 Hydroxyl of 43:

The configuration of the hydroxyl group was determined to be equatorial (β) based on ^1H NMR. This conclusion was based on the coupling constant of the C-3 axial hydrogen with the axial hydrogens of C_2 and C_4 (base width = 40 Hz). Fodor, Katrizky^{20,21} et al. determined the conformation of tropine (44) and pseudotropine (42), from ^1H NMR. They observed that the C-3 methine signal in tropine (44) has a band width of 17 Hz whereas in pseudotropine (42), the band width is 40 Hz.

42

(pseudotropine)

43 44

(tropine)

Axial-Axial coupling of C-3 hydrogen in 42 is 10.2 Hz.

Axial-Axial coupling of C-3 hydrogen in 43 is 10 Hz.

Axial-Equatorial coupling of C-3 hydrogen in 44 is 5 Hz.

Since the band width for the C-3 hydrogen in 43 is close to the band width for C-3 hydrogens in 42, we can assume that both 43 and 42 have the same configuration at C-3.

4.1.9 Structure Determination of 43 - Chemical Methods:

Since 43 was one of the key intermediates, we felt the need for an unequivocal determination of its structure. The hydrochloride salt of this amine was prepared by bubbling dry hydrogen chloride gas through an ethereal solution of 43 (Scheme 26). The elemental analysis of the corresponding crystalline hydrochloride salt 45 was satisfactory.

Scheme 26

To support the structure of 43, chemical reactions were contemplated. It was felt that the cleavage of the methyl ether would be a good start.

Ethers have been cleaved by 48% aqueous hydrobromic acid. Sperber²² cleaved the neopentyl amino ethyl ether 46 to the corresponding hydroxy derivative 47 in 95% yield by using this reagent (Scheme 27).

Scheme 27

Nineham²³ cleaved the primary dimethyl ether **48** to the corresponding dibromide **49** by the same method (Scheme 28).

Scheme 28

Among tropanes, Fodor²⁴ et al. cleaved 6 β -methoxytropine (**50**) to the corresponding diol **51** (Scheme 29).

Scheme 29

Following Fodor's procedure²⁴, the methyl ether **43** was cleaved to the diol **52** by refluxing in 48% aqueous hydrogen bromide for two days and neutralizing the resulting hydrobromide

salt with sodium carbonate (Scheme 30). The diol 52 was obtained as a gum, which on chromatography over basic alumina gave a yellow solid.

It did not come as a surprise that diol 52 was formed exclusively and the bromide 53 was not formed at all. The reason for such immediate acceptance of this result is that the methyl ether functionality in 43 is neopentyllic in nature and formation of bromide 53 would require nucleophilic displacement on a neopentyllic carbon which would not be expected to be very facile (path B, Scheme 31). On the other hand, attack by bromide ion on the 1° carbon (path A, Scheme 31) would be expected to be more easy and that happens to be the preferred path for the reaction.

The evidence for the transformation of 43 into diol 52 was obtained from the ^1H NMR spectra of these compounds. The sharp singlet for the methoxy group at δ 3.3 (CH_2OCH_3) in 43 was absent

Scheme 31

in case of 52 indicating loss of methoxy group. Also the methylene protons CH_2OCH_3 in 43 give a signal at δ 3.4, whereas in the product 52 (CH_2OH), they give a signal at δ 3.6.

The tetraphenyl borate (Scheme 32) and the hydrobromide salts of the diol 52 have been prepared (Scheme 33), both of which gave satisfactory elemental analysis.

Scheme 32

Scheme 33

All these chemical reactions and physical determinations supported the structure of methyl ether 43. All data pointed to the fact that the compound in hand indeed was 43.

The next item on the agenda was to return to the mainstream synthesis and to convert 43 to 55 (Scheme 34). In principle 55 could be used as a common intermediate for both the Wittig and Grignard routes.

Scheme 34

4.1.10 Protection of C-3 Hydroxyl in 43:

So far the basic skeleton of our compound is made. What needs to be done is to functionalize the side chain for further elaboration. One needs to protect the C-3 hydroxyl to avoid any interference from a free hydroxyl group. One of the hydroxyl protecting groups that can be added on and removed very easily is an acetate.

Protection of C-3 hydroxyl in tropanes is a known reaction.

Fodor²⁵ protected the 2° hydroxyl of 58 as an acetate (Scheme 35).

Scheme 35

Following Fodor's procedure we were able to protect the 2° hydroxyl of 45 as an acetate in 50% yield (Scheme 36).

Although this reaction was successful, the yields needed improvement. The following section describes how an improvement of the yields has been accomplished.

4.1.11 Improvement of Yields of 60: Use of 4-N,N-Dimethylamino-pyridine (DMAP) as Acetylation Catalyst:

4-N,N-Dimethylamino pyridine (DMAP), (61), has been introduced to organic synthesis as a super acylation catalyst by Steglich and Höfle²⁶ in 1969. When compared to pyridine, it was found that DMAP can increase the rates of acetylation by 10^4 times. Since then DMAP has been used with ever-increasing frequency^{27,29} for acetylation reactions which proceed with reluctance in pyridine. Even hindered alcohols have been acetylated very smoothly by using DMAP as catalyst.

In our case, using DMAP as catalyst had a remarkable effect

on the yields, which increased from 50% (cf Scheme 36) to 85-90% (Scheme 37).

Scheme 37

4.1.12 Reasons for Improved Yields - Mechanism of DMAP Action:

When treated with acetic anhydride, DMAP forms a stable N-acyl pyridinium salt 62 (Scheme 38).

Scheme 38

It has been estimated²⁸, that 62 is ca 25 kJ/mole lower in energy than the starting materials. The pyridinium salt 62 is resonance stabilized and one could write several mesomeric forms (Scheme 39).

Scheme 39

Because of this charge delocalization, the N-acyl 4-dialkylamino pyridinium salt 62 is present as a loosely-bound ion pair, thus greatly facilitating nucleophilic attack on the activated acyl group with general base catalysis by the neighboring acetate group (Scheme 40).

Scheme 40

The regenerated catalyst repeats its action over and over again, so one needs very little (ca. 0.05 eq. of cat to 1 eq. of R-OH) of the catalyst.

4.1.13 Cleavage of Methyl Ether of 60:

The next problem we had to address was selective cleavage of the methyl ether functionality in 60 without affecting the acetate at C-3 (Scheme 41).

Recently, Corey³⁰ converted the methyl ether 63 into the alcohol 64 by using two equivalents of iodotrimethylsilane, generated in situ from chlorotrimethylsilane and sodium iodide (Scheme 42).

Following Corey's procedure, 60 was treated with freshly generated iodotrimethylsilane. Heating this mixture either in acetonitrile or in chloroform led to complete recovery of starting material (Scheme 43).

Scheme 43

Although disappointed by this failure, our search for ether-cleaving reagents continued. Among reagents that looked promising for the problem at hand, boron tribromide caught our attention. Bossi³¹ cleaved the arylmethylether 65 into the phenol 66 by treating with a thirty-fold excess of boron tribromide in chloroform at -70°C (Scheme 44).

Corey³², in his first synthesis of prostaglandins, cleaved the methyl ether in 63 by treating with excess BBr_3 at 0°C (Scheme 45), without affecting the acetate functionality.

Scheme 45

The only disturbing example in the literature³³ was in the case of carbohydrate 67 where all the acetate functionalities in the molecule were cleaved on treatment with BBr_3 at room temperature (Scheme 46).

Scheme 46

Keeping these precedents in mind, methyl ether 60 was treated with 5.5 eq of BBr_3 at 0°C . Unfortunately there was no reaction at 0°C or below 0°C . However, carrying out the same reaction at room temperature, resulted in almost quantitative cleavage of methyl ether functionality (Scheme 47) and the acetate was untouched.

Scheme 47

The amount of BBr_3 used deserves some comment. The reason for using such a large excess of the reagent is that each nucleophile in the molecule would tie up one equivalent of BBr_3 . Since we have three oxygen atoms and one chloride, we need at least four equivalents of BBr_3 . The additional 1.25 equivalents was to make sure that we have enough reagent.

The best aspect of this reaction is that the acetate was untouched in our case (cf Scheme 46), although we carried out the reaction at room temperature (Scheme 47).

The yields and ease of isolation of product seemed to depend a lot on the method of work-up. The best yields were obtained when concentrated ammonium hydroxide was used during the work-up. After the reaction was complete, the mixture was poured onto ice and the pH was brought to 11 with ammonium hydroxide. The yields dropped when the pH was taken to 12 and beyond. One can speculate that at higher hydroxide ion concentrations, the acetate would be attacked resulting in the formation of the water-soluble diol 52 (Scheme 48).

Scheme 48

Another important attribute of the reaction that deserves comment is the dependence of the yields on the scale of the

reaction. When the reaction was done on a 5 g scale, the yields were extremely good. However, when it was scaled up to 10 g, the yields were much lower (50-60%) and highly inconsistent. The reason for this discrepancy is not very clear. However we got around this problem by carrying out three or four sets of reactions at the same time on a 5 g scale and combining the product from all the sets.

4.1.14 Structure Determination of the Monoacetate 55:

The ^1H NMR and IR of 55 were as expected. 55 had an IR absorption at 3500 cm^{-1} indicating OH functionality. ^1H NMR showed lack of methoxy group but presence of CH_2OH (δ 3.5) and D_2O exchangeable O-H at δ 4.5.

The hydrochloride and tetraphenylborate salts of 55 have been prepared and both of them gave satisfactory elemental analyses (Scheme 49).

TABLE I

STARTING MATERIAL:

<u>Reagents</u>	<u>Conditions</u>	<u>Result</u>
1.5 PCC	CH_2Cl_2 , r.t., 5 hrs	no reaction
4 PCC	CH_2Cl_2 , r.t., 24 hrs	no reaction
1.5 PCC	CHCl_3 , Δ^b , 24 hrs	nothing recovered
1.2 PCC	CH_2Cl_2 , Δ^b , 1 hr	nothing recovered
1.5 PCC/crushed mol. sieves	CH_2Cl_2 , r.t., 2 hrs	nothing recovered
1.6 PCC/alumina	CH_2Cl_2 , r.t., 2 hrs	nothing recovered
1.3 PCC/0.2 NaOAc	CH_2Cl_2 , r.t., 2 hrs	very little reaction
1.5 PDC	CH_2Cl_2 , r.t., 24 hrs	nothing recovered
Collins reagent (CrO_3 -pyridine)	CH_2Cl_2 , r.t., 24 hrs	nothing recovered
8x active MnO_2	CH_3CN , r.t., 10 hrs	very little reaction
8x active MnO_2	CH_3CN , Δ^b , 6 hrs	very little reaction

Part B. Elaboration of the Side Chain by Wittig Reaction

The successful synthesis of the diol monoacetate 55 has been a break-through as far as our methodology was concerned. We considered it to be a very versatile intermediate. Successful oxidation of the hydroxyl group would give aldehyde 56 (Scheme 50), which sets the stage for Wittig reaction.

Scheme 50

4.2.1 Search for Oxidizing Agent:

Our search started with transition metal oxidants. A variety of chromium-based oxidizing agents were employed. Among them were pyridinium chlorochromate (PCC)^{34,35}, pyridinium dichromate (PDC)³⁶, PCC/crushed molecular sieves³⁷, PCC/alumina³⁸, PCC/sodium acetate³⁹, Collin's reagent (CrO_3 -pyridine)^{40,41}, active manganese dioxide^{42,43}, all of which consistently gave unsatisfactory results (Table I). Although it is not clear as to why we did not recover any meaningful products in some cases, one could speculate that perhaps the N-methyl group is also oxidized and the resulting product may be soluble

in water. This speculation is based on an analogy in the literature, where an N-methyl was oxidized to an N-formyl group by Collins' reagent in the laboratories of Corey^{44,45} (Scheme 51).

Scheme 51

If a similar reaction occurred in our case, then we would end up with 71, which may be water soluble (Scheme 52).

Scheme 52

The next type of oxidizing agent we have looked at are those that utilized dimethyl sulfoxide (DMSO) as an oxidant.

4.2.2 Dimethylsulfoxide-Dicyclohexylurea Oxidation:

Dimethylsulfoxide has been used very widely as an oxidizing agent, in organic synthesis. It has been used with various electrophiles which activate the DMSO. One of the first activators used was dicyclohexylcarbodiimide (DCC).⁴⁶ This oxidation now known as Pfitzner-Moffatt oxidation,⁴⁷ is carried out by using DMSO and DCC in the presence of 1.5 molar equivalents of anhydrous phosphoric acid or trifluoroacetic acid. Many alkaloids have been oxidized by utilizing this method. Büchi⁴⁸ oxidized the 2° hydroxyl of the indole alkaloid 72 to the corresponding ketone 73 (Scheme 53) in 66% yield by this method.

Weisner⁵⁰ oxidized the tricyclic compound 76 to aldehyde 77 (Scheme 55-A).

Scheme 55-A

We have found only one reported example⁵¹ where such an oxidation failed in case of a neopentyl alcohol 78 (Scheme 55-B).

Scheme 55-B

From these examples one can conclude that neopentyl alcohols can be oxidized by this method as long as they are held by a bicyclic system (e.g. 74, 76). This observation was very encouraging to us, since the compound we planned to oxidize, 55, happened to be a neopentyl alcohol held by a bicyclic system.

Keeping these precedents in mind, the alcohol 55 was treated with 3 equivalents of DCC, 1.5 equivalents of trifluoroacetic acid and the reaction was carried out in DMSO at room temperature for 2 days. After work-up, 40% yield of the product 56 was isolated (Scheme 56).

Scheme 56

The work-up of the reaction was simplified by the possibility of freeing the product from excess DCC and dicyclohexylurea by extraction of the amine salt into water followed by regeneration of the free base.

The yields could be improved to 50% (and the reaction was cleaner) when 1.5 equivalents of 2,2-dichloropropionic acid were used instead of trifluoroacetic acid. Very poor yields (20%) were obtained when anhydrous phosphoric acid was used as an acid catalyst.

4.2.3 Structure of the Tropan-1-Aldehyde (56)-Spectral Data:

The ^1H NMR of aldehyde 56 showed a sharp singlet for the aldehyde proton $-\text{C}(=\text{O})\text{H}$ at δ 9.5. The IR spectra showed absence of hydroxyl, which proved that the alcohol was oxidized.

4.2.4 Chemical Proof for the Structure of Aldehyde 56:

Apart from the spectral proof, it was our desire to have a definite chemical proof for the structure of aldehyde 56.

This was accomplished by reducing the aldehyde 56 back to the alcohol 55, using NaBH_4 in anhydrous ether (Scheme 57).

Scheme 57

The ^1H NMR spectrum of product from this reduction was superimposable with that of an authentic sample of 55. This result confirmed that 56 indeed was the desired aldehyde.

4.2.6 Mechanism of DMSO-DCC Oxidation^{47,52}:

The mechanism of this oxidation involves formation of intermediate A (Scheme 58) by nucleophilic attack of DMSO on the carbodiimide, followed by reaction of this species with the alcohol. A major part of the driving force for the reaction is derived from the conversion of the carbodiimide to urea D, with formation of an amide carbonyl. The role of the DCC is to activate DMSO towards nucleophilic attack by the alcohol on DMSO.

Scheme 58

4.2.6 Constraints of the Oxidation:

Although the reaction worked well, separation of the product from the byproduct dicyclohexylurea involved tedious chromatography. To avoid it, we looked for other DMSO based oxidizing agents. What followed was a systematic experimental investigation of a variety of DMSO based oxidizing agents as to their potential to effect clean oxidation of our neopentyl alcohol 55 to the corresponding aldehyde 56.

4.2.7 DMSO-Acetic Anhydride as Oxidants:

Following their work on the application of the DMSO-DCC method to the oxidation of the indole alkaloids, Albright and Goodman⁵³ have developed a very useful alternative reaction using DMSO and acetic anhydride. The advantage of this reaction is that the byproduct from the reaction is predominantly acetic acid, which can be removed by aqueous extraction together with DMSO. Another feature that makes this method attractive is a suggestion in the literature⁴⁶ that DMSO-Ac₂O oxidations are well suited for oxidation of highly hindered alcohols.

Reported oxidations⁵⁴⁻⁵⁵, of hindered primary alcohols 80 and 82 are particularly encouraging (Scheme 59).

Scheme 59

In the alkaloid area, the reported⁵⁶ oxidation of neopentyl indole alkaloid 84 to the aldehyde 85 (Scheme 60) raised our hopes of accomplishing a similar oxidation in our case too.

Scheme 60⁵⁶

Adopting a similar procedure to our case and treating 55 with DMSO and acetic anhydride at room temperature for 40 hrs gave, to our total disbelief, the corresponding diacetate 86 as the exclusive product (Scheme 61).

Scheme 61

To understand this anomalous result, we have to look at the supposed mechanistic pathway by which DMSO-Ac₂O oxidations occur.

4.2.8 Mechanism of Oxidation:

Scheme 62 describes the mechanism of DMSO-Ac₂O oxidation.

Scheme 62

The first step is attack of sulfoxide on acetic anhydride to form species A, which is very susceptible to nucleophilic attack by the alcohol to give species B, which on loss of proton to acetate anion gives C. The species C, collapses to the aldehyde and dimethyl sulfide.

4.2.9 Possible Mechanism for Acetate Formation:

Since in our case, acetate formation (instead of oxidation) took place, it is obvious that at least some of the events described in Scheme 62 did not occur. We can speculate on how the diacetate 86 could have formed in this reaction. In principle, we can postulate three different pathways.

(i) Once species A is formed, the alcohol could attack A at the carbonyl rather than the sulfur (Scheme 63), thus giving the acetate and regenerating DMSO.

Scheme 63

We can justify such an attack by the alcohol in the above scheme (equation ii) on the carbonyl rather than the sulfur by contending that the carbonyl group is sterically less hindered than the sulfur.

(ii) The second possible pathway would be competitive

nucleophilic attack by the alcohol on acetic anhydride (Scheme 64).

Scheme 64

But this possibility is very remote since we have forty equivalents of DMSO per each equivalent of alcohol and also DMSO would be expected to be a better nucleophile than alcohol.

(iii) The third path one can imagine would be as follows (Scheme 65).

The alcohol attacks the activated intermediate species A (as described in Scheme 62) to form species B. The acetate anion, instead of abstracting a proton from B, acts as a nucleophile and displaces DMSO (Scheme 65).

Scheme 65

This possibility can also be ruled out with some degree of confidence because nucleophilic displacement on a neopentyllic

carbon would not be expected to go with such ease (considering the fact that the reaction was done at room temperature) and especially by a poor nucleophile like acetate anion.

From these three possibilities we can conclude that the first pathway we considered (Scheme 63) is the most likely one by which the formation of acetate occurred during the attempted oxidation of alcohol 55 by DMSO-Ac₂O.

4.2.10 Oxidation using DMSO/Pyridine-SO₃:

Parikh and Doering⁵⁷ have shown that the pyridine complex of sulfur trioxide provides excellent activation of DMSO in the presence of triethylamine. The oxidation is usually performed by the addition of the pyridine-SO₃ complex⁵⁸ (three molar equivalents) to a DMSO solution of the alcohol and triethylamine (ten molar equivalents) at room temperature. This method has been applied to several steroidal alcohols.

Applying Doering's procedure⁵⁷, to our case resulted in the oxidation of alcohol 55 to the aldehyde 56 in 35% yield (Scheme 66).

Scheme 66

This method did not provide us with any substantial advantages over other methods we attempted. So our search for a better oxidant continued.

4.2.11 Oxidation using DMSO-P₂O₅:

When DMSO-phosphorus pentoxide⁵⁹ was tried as the oxidizing mixture, neither the starting material nor any product was obtained. In analogy with the DMSO-acetate anhydride reaction (Scheme 61), one could speculate that a water-soluble phosphate is probably formed (Scheme 67).

Scheme 67

This speculation is based on the fact that phosphorus pentoxide is an anhydride of phosphoric acid, just as Ac₂O is anhydride of acetic acid.

4.2.12 DMSO-Thionyl Chloride:

When DMSO-SOCl₂ mixture⁶⁰ or DMSO-trifluoroacetic anhydride mixture^{61,62} were used as oxidizing agents, alcohol 55 was recovered unchanged (Scheme 68).

Scheme 68

4.2.13 Swern Oxidation: DMSO-Oxalyl Chloride Complex as Oxidizing Agent:

Swern⁶⁰⁻⁶⁴ has systematically studied the scope and limitations of oxidation of alcohols using DMSO activated by various activators. In his study of relative effectiveness of DMSO activators in this oxidation, he discovered that oxalyl chloride^{60,63-64} is the most effective activator. Currently, the combination of DMSO-oxalyl chloride has become a common reagent in the organic laboratory. Also known as Swern oxidation, this method has three advantages: (i) no over-oxidation occurs; (ii)

even hindered alcohols such as neopentyl alcohol 88 (Scheme 69)

can be oxidized very smoothly to the corresponding aldehydes;

(iii) the formation of unwanted side-products is minimal.

Scheme 69

Following Swern's procedure⁶⁰ (Scheme 70) our neopentyl alcohol 55 was oxidized to the aldehyde 56 very smoothly in 95% yield (1 g scale).

Scheme 70

The reaction was typically done by forming the activated complex between DMSO and oxalyl chloride at -60°C , which spontaneously loses CO and CO_2 (Scheme 71). Addition of alcohol to this reactive species, followed by treatment with a base like triethylamine or N-methylpiperidine and warming to room

temperature, followed by basic (NH_4OH , $\text{pH} = 10-11$) aqueous extractive work-up gave the crude aldehyde (which was essentially pure for all practical purposes) in 95% yield.

4.2.14 Mechanism of DMSO-Oxalyl Chloride Oxidation:

The mechanism of Swern oxidation is believed to be as follows (Scheme 71).

Scheme 71

The mechanism of this oxidation deserves some comment. DMSO reacts with oxalyl chloride even at -60°C and forms species A, which spontaneously loses one mole each of carbon monoxide and carbon dioxide (the loss of these gases can be observed if the escaping gases are bubbled through mineral oil). Species B, being a very powerful electrophile, is attacked by the nucleophile alcohol and forms species C. The base abstracts a proton from species C, thus forming the desired aldehyde with extrusion of dimethyl sulfide. Overall the alcohol is oxidized to the aldehyde and DMSO is reduced to dimethyl sulfide.

An observation we made during the oxidation of our alcohol 55 is that the yields dropped down to 85% when the reaction was done on a large scale (5 g). Also N-methylpiperidine seems to be the most suitable base for the reaction. Using a highly hindered base like 2,6-lutidine seemed to promote formation of methylthiomethyl ether as by-product (Scheme 72).

Scheme 72

The product 90 should be coming from Pummerer rearrangement⁶⁵⁻⁶⁶ of species C (Scheme 73).

Scheme 73

4.2.15 Wittig Reaction: Extension of the Side Chain:

In 1953, Wittig⁷⁰ observed that when methyltriphenylphosphonium bromide (91) was treated with phenyllithium, an ylide 92 was formed that could react with benzophenone to give triphenylphosphine oxide (94) and 1,1-diphenylethylene (93) in 84% yield (Scheme 74). This discovery led to the development of a new method of preparation of alkenes, which has since found widespread application in organic synthesis and is now generally known as the Wittig reaction.⁶⁷⁻⁶⁹

Scheme 74

One could generalize this reaction in the following way

(Scheme 75).

Scheme 75

A similar Wittig reaction on our aldehyde 56, in principle

should give access to a variety of compounds (Scheme 76).

Scheme 76

There are many instances in literature where the Wittig reaction has been used in the alkaloid area.

Rapoport⁷¹ utilized this method to synthesize 6-methylene dihydrodesoxycodeine 96 from dihydrocodeinone 95 (Scheme 77).

Scheme 77

In the indole series, neopentyl aldehyde 85 was converted⁵⁶ to the olefin 97 (Scheme 78).

Scheme 78

Keeping these analogies in mind, we carried out the Wittig reaction utilizing the aldehyde 56 and the ylide 99 generated from *n*-butyltriphenylphosphonium bromide. *n*-Butylphosphonium bromide was prepared from *n*-butyl bromide and triphenylphosphine in refluxing benzene according to the procedure of Sondheimer⁷² (Scheme 79).

Scheme 79

It was very pleasing to find that the desired compound 14 was formed as a single product to the exclusion of the trans isomer 100.

4.2.16 Structure Determination of 1-Pentenyl-3β-tropanol:

Spectral data (^1H NMR, IR and mass) supported the structure of 14.

^1H NMR showed olefinic protons at δ 5.5 (m), hydroxyl at δ 4.7 (exchangeable with D_2O) and the C-3 methine proton at δ 4.0 (m), indicating loss of acetate. In case of acetate 103, the same proton gives a signal at δ 5.0 (m). This is a clear indication that the compound underwent deacetylation during the reaction. The coupling constant for vinylic protons was about 6 Hz, indicating cis relationship between the olefinic protons. Infrared absorption at 685 cm^{-1} also supported cis olefinic geometry. There was no absorption at 965 cm^{-1} corresponding to trans olefinic geometry. Absence of absorption at 1720 cm^{-1} (corresponding to acetate carbonyl stretch) and presence of a band at 3500 cm^{-1} for O-H indicated that acetate was hydrolysed.

^{13}C NMR showed 13 signals corresponding to 13 different carbon atoms in the compound. If there were any trans alkene present, it would have showed more than 13 peaks. The assignment of ^{13}C NMR signals was based on known ^{13}C NMR absorption signals for tropanes.⁷⁴

4.2.17 Interpretation of Mass Spectra of 1-Pentenyl-3 β -Tropanol:

The mass spectrum of the compound 14 showed molecular ion (M^+) peak at 208.8 (mol. wt. of 14 = 209). Several years ago Fodor⁷⁵ and Djerassi studied the mass spectra of tropine and several other tropane alkaloids. The fragmentation pattern of our compound 14 fell in line with Fodor's study. Scheme 81 shows the various fragments.

Two surprising events came about during the Wittig reaction: (i) the conversion of acetate into hydroxyl and (ii) the exclusive formation of cis olefin.

The reaction of acetates with Wittig reagents has precedence in literature. Sondheimer⁷⁶ found that 7-keto chloesteryl acetate 101 on treatment with excess methylene triphenyl phosphine in refluxing THF produced 7-methylene-cholesterol 102 (Scheme 80).

Scheme 81

Under these vigorous conditions (refluxing THF), the Wittig reagent attacks the acetate. We reasoned that if this is true, then by carrying out the reaction at milder conditions we may be able to preserve the acetate. The acetate could then be removed in a subsequent step, by transesterification with methanol. When the aldehyde 56 was treated with 1.3 eq of ylide solution (1.4 eq of n-butyolphosphonium bromide + 1.3 eq. of n-butyllithium) at room temperature for 24 hrs, we obtained alkene 103, with the acetate functionality intact (Scheme 82).

Scheme 82

Alkene 103 was purified by silica gel chromatography. Once again the stereochemical outcome of the Wittig reaction was *cis*. There was no formation of *trans* alkene 104 at all.

4.2.18 Removal of Acetate by Transesterification:

The acetate functionality in 103 was removed⁷⁷ by treatment with methanolic potassium carbonate at room temperature for 12 hr (Scheme 83).

Scheme 83

Scheme 84 summarizes the two different ways of obtaining 14 from the Wittig reaction.

We found that path A is a much cleaner path than path B. There were less side products to worry about in path A than in path B.

In both cases, the work-up was simplified by virtue of having a basic nitrogen atom in the molecule. In either case, after the Wittig reaction, the mixture was acidified and the non-basic side products (mainly PPh_3O), were removed by extraction with benzene and ether. The mixture was basified and the free amine extracted with ether. The last traces of PPh_3O could easily be separated (even before chromatography) by dissolving the crude alkene in pentane (triphenyl phosphine oxide is insoluble in pentane), cooling to 0°C , filtering and removing pentane. The residue which was essentially pure was further purified by silica gel chromatography.

4.2.19 Stereochemistry of Wittig Olefination:

The cis stereochemical outcome of the Wittig products 103 and 14 deserves some comment.

The amount of Z isomer is known⁷⁸⁻⁸⁰ to increase with the bulkiness of the aldehyde component. In general, the unstabilized ylides like the one we used, are known⁸¹ to react with aldehydes to give predominantly Z-alkene while stabilized ylides give predominantly E-alkenes. The following examples⁷⁴ illustrate this generalization.

Scheme 85

Corey⁸² has carried out a similar Z specific Wittig reaction by using neopentyl aldehyde 107 (Scheme 86).

Scheme 86

4.2.20 Mechanism of Wittig Reaction:

The mechanism of Wittig reaction is controversial.

Mechanisms based on betaine formation have been proposed.⁸³

However, there is no experimental evidence for betaines. There are other mechanisms based on oxaphosphetanes. Oxaphosphetanes have been observed by Vedejs^{78,84} by using low-temperature ^{31}P NMR spectroscopy. Very recently^{85,86} evidence has been presented for cis- and trans-oxaphosphetanes by Marayanoff who resolved the corresponding ^{31}P NMR signals. The following mechanistic pathway is proposed by Marayanoff (Scheme 87).

Scheme 87

Both cis and trans oxaphosphetanes are formed. The cis oxaphosphetane 112 gives cis olefin 114 whereas the trans oxaphosphetane 113 gives trans olefin 115. The cis oxaphosphetane 112 is formed faster than the trans. The cis oxaphosphetane decomposes faster than the trans. The cis and trans oxaphosphetanes could equilibrate via reversible interconversion of oxaphosphetanes and starting materials. The current view⁸⁵ is that the relative stereochemical preference for cis and trans

olefins in the Wittig reaction may be dictated not by what happens during the reaction of aldehydes and ylides but by what can happen to the oxaphosphetanes afterwards.

4.2.21 Attempted Preparation of Crystalline Salts of 14:

All attempts at preparing crystalline derivatives of 14 have failed. Treating 14 with hydrochloric or hydrobromic acids gave oily salts which could never be crystallized. A white crystalline tetraphenylborate salt could be prepared but it decomposed at room temperature in 24 hr (Scheme 88).

Scheme 88

4.2.22 Chemical Confirmation of Structure of Alkene 14:

To confirm chemically that the product from the Wittig reaction (Scheme 79) is not just an addition product of *n*-butyllithium to the aldehyde 56, an alternate reaction was done. Pure aldehyde 56 was refluxed with 6 equivalents of *n*-butyllithium (Scheme 89). The resulting product was identified by ^1H NMR as 118.

Scheme 89

4.2.23 Reduction of Alkene 14 to (+) 1-n-Pentyl-3 β -tropanol (15):

Attempted reduction of olefin 14 by diimide 121 (generated⁸⁷ in situ from potassium azo-dicarboxylate⁸⁸ and acetic acid) resulted in complete recovery of starting material (Scheme 90).

Scheme 90

However successful reduction of 14 to the saturated amine 15 was accomplished by catalytic hydrogenation over Raney Nickel (W-2) (Scheme 91).

Scheme 91

^1H NMR of 15 showed lack of unsaturation which proved that the reduction was successful. A crystalline hydrochloride salt of 15, which gave a satisfactory elemental analysis, was prepared⁸⁹ by bubbling hydrogen chloride gas through an ethereal solution of 15.

Scheme 92

The mass spectrum of the hydrochloride salt **122** showed molecular ion peak M^+ at 210.8 (molecular weight of **15** = 211). When injected in the mass spectrometer, the hydrochloride salt **122** loses one mole of HCl and the molecular ion peak of the salt corresponds to $M^+ - 36.5$, which corresponds to the molecular ion peak of free base **15**.

4.2.24 Attempted Removal of N-CH₃ of 1-Pentenyl-3 β -Tropanol:

Since dihydroadalinine **4** and perhydrohistrionicotoxin **1d** are 2° amines, we planned to convert our compound **14**, which is a 3° amine to the 2° amine **123** by N-demethylation (Scheme 93).

Scheme 93

In the tropane series, a variety of amine demethylation procedures have been developed. Most of these involve treatment

Scheme 94⁹³

Scheme 95

Scheme 96

of 3° amine with acylating agents.⁹⁰⁻⁹⁴ Scheme 94 describes one of the most effective methods, developed by Olofsson.⁹³ There are other methods that use 2,2,2-trichloroethyl chloroformate⁹¹ or ethyl chloroformate⁹⁰ (Scheme 95). Unfortunately all attempts to N-demethylate 14 using these procedures failed.

The possible reason for failure of these reactions in our case could be the steric hindrance involved in nucleophilic attack of our 3° amine 103 (which is also neopentylic in nature) on the chloroformates.

To our knowledge, there is not a single case in the literature where a neopentylic 3° nitrogen has been demethylated.

The other methodologies we have looked at were oxidative⁹⁵⁻⁹⁸ N-demethylation. Scheme 97-A describes one such example.⁹⁸ Scheme 97-A

To our chagrin this methodology did not work in our case

(Scheme 97-B).

Scheme 97-B

No further attempts were made to effect N-demethylation.

However, it would be interesting to see if cyanogen bromide⁹⁹⁻¹⁰¹ can effect N-demethylation.

Part C. Scope and Limitations of the Wittig Route

Having succeeded in the synthesis of our target compounds 14 and 15, the next item on our agenda was to explore the potential and limitations of the Wittig route.

Since histrionicotoxin 1a has a en-yne side chain, it would be worthwhile to synthesize tropanes with similar sidechains. Aldehyde 56, in principle, could be elaborated to en-yne 136 and 137.

136

137

136 has a skipped en-yne side chain whereas 137 contains a conjugated en-yne side chain.

4.3.1 Retrosynthesis Analysis of Skipped En-yne 136:

Scheme 98 depicts a possible retro synthetic route for 136.

Scheme 98

Wittig salt **138** was synthesized by Jones¹⁰² in modest yields.

Scheme 99 describes Jones methodology.

The overall yields of Wittig salt **138** were 27% over three steps. The step that definitely needs improvement is the first step where the trimethylsilyl acetylene derivative **143** was prepared. Jones followed the procedure of Shostakovski¹⁰³ and obtained 39% yield of this compound.

It occurred to us that the reason for low yields could lie in (low-yield) formation of ethylmagnesium bromide which was generated in situ. We used commercially available ethylmagnesium bromide (Aldrich, 2 M solution in tetrahydrofuran) and obtained **143** in 91% yield. This is a major improvement over Jones' procedure.^{102,103}

Apart from improving the yields of **143**, we completely renovated Jones' methodology and developed a new protocol for Wittig salt **138**: Scheme 100 describes our methodology.

Scheme 99 (Jones's methodology¹⁰²)

143 (39%)

144 (72%)

138 (95%)

Overall yields of 138 are 27%.

4.3.2 Comparison of Scheme 99 and Scheme 100:

Our protocol for Wittig salt 138 (Scheme 100) has several advantages worth mentioning and no pretense is made about the superiority of our methodology over Jones' (Scheme 99).

Scheme 100

1. Yields of 143 are 91%
2. Yields of iodide 144 are 89%
(based on 143)
3. Iodide 144 purified by
distillation
4. Isolation of Wittig salt is
very easy; since the
reaction was done in benzene,
the Wittig salt separates out
from the reaction as the
reaction proceeds.
5. Overall yields of Wittig salt
138 are 77% (based on 141).

Scheme 99

- Yields of 143 are 39%
- Yields of iodide 144 are 72%
(based on 143)
- Iodide 144 purified by
tedious chromatography
- The reaction done in ethanol
in which the Wittig salt is
soluble. Isolation is
somewhat non-trivial.
- Overall yields of Wittig salt
138 are 27% (based on 141).

4.3.3 Attempted Condensation of Aldehyde 56 with ylide 139:

It was gratifying to develop a synthetic methodology for Wittig salt 138. The next task was to utilize it in the Wittig

Scheme 100 (our methodology)

Overall yields of 138 are 77%.

condensation as planned in Scheme 98.

The ylide 139 could be generated by a variety of bases (Scheme 102). However, to our total dismay, it proved very intransigent as far as addition to the aldehyde was concerned (Scheme 103). Every attempt at effecting the Wittig condensation resulted only in recovery of unreacted aldehyde. Ylide 139 is known to add to unhindered aldehydes very smoothly even at 0°C (Scheme 101).

We can attribute the lack of reactivity of ylide 139 in our case to the neopentyllic nature of our aldehyde. This is in contrast to the reactivity of ylide 99, generated from n-butyltriphenylphosphonium bromide which added very smoothly to aldehyde 56 (see Scheme 79). It is surprising that the bulky trimethylsilyl group (which was absent in ylide 99, but present in ylide 139), although remote from the reaction site, apparently hampers the reactivity of ylide 139, by imposing severe steric restraints.

Scheme 102

Scheme 103

2 eq of 139 generated
from n BuLi
-10°C, 40 hrs
0°C, 2 hrs

1.1 eq of 139 generated
from NaH
23°C, 60 hr

1.1 eq of 139
generated from
KOtBu
23°C, 60 hr

4.3.4 Alternate Approaches to Skipped En-yne Sidechain:

At this point, we postulated that replacing the bulky trimethylsilyl group by a much smaller group like hydrogen would increase the reactivity of the corresponding ylide 150 and give access to en-yne 151 (Scheme 104).

4.3.5 Preparation of Wittig Salt 149:

Wittig salt 149 is an unknown compound; we have found no report of it in the literature. It can, in principle, be prepared from bromide 152 and triphenyl phosphine. This synthetic plan demanded a steady and facile supply of bromide 152.

4.3.6 Attempted Preparation of $\text{H-C}\equiv\text{C-CH}_2\text{CH}_2\text{PPh}_3$ ⁴⁹:

3-Butyn-1-ol was converted¹⁰⁴ to its tosylate ¹⁵³

(Scheme 105) by treating with p-toluenesulfonyl chloride in presence of 2,6-lutidine¹⁰⁵ (which acts as solvent as well as proton trap).

Scheme 105

Tosylate ¹⁵³ was purified by silica gel chromatography.

A variety of attempted nucleophilic displacements of this tosylate by chloride, bromide or iodide ions failed to give the corresponding halides (Scheme 106). It is surprising that none of these reactions worked in our hands.¹⁰⁶

It is our speculation that these halides (which seem to be highly volatile) are heat-sensitive and any attempted (Scheme 107) distillation would result in their disintegration into corresponding hydrogen halide and vinylacetylene (bp 15°C).

Scheme 107

Scheme 106

4.3.7 Attempted Preparation of Phosphonium Tosylate 158:

There are few instances¹⁰⁷⁻¹¹⁰ in literature where phosphonium ylides are generated from alkyl phosphonium tosylates. Scheme 108 represents one such example.

Since we had seemingly insurmountable problems in the preparation of bromide 152 (and in turn Wittig salt 149), we planned to take recourse to 4-butyntriphenylphosphonium tosylate (158), an unknown compound in literature. The phosphonium salt 158 could be visualized as a precursor to ylide 150 (Scheme 109).

Scheme 109

Scheme 110-A

Scheme 110-B

Refluxing tosylate 153 with triphenylphosphine in benzene, to our total surprise and disappointment gave (as the only identified product) triphenylphosphoxide but none of the desired, Wittig salt 158 (Scheme 110-A). The structure of the product triphenylphosphine oxide was clear from ^1H NMR and also from the molecular ion peak M^+ at 277.69 (mol. wt. of $\text{PPh}_3 \rightarrow 0 = 278$) in the mass spectrum of the compound. It is conceivable, as suggested by Dr. Moore that tosylate 153 undergoes a thermal decomposition to give vinyl acetylene and p-toluene sulphonic acid. Triphenylphosphene is then oxidized by p-toluene sulphonic acid to give triphenylphosphine oxide and p-toluenesulphonic acid is reduced to p-toluene sulphinic acid (Scheme 110-B).

There is one instance in literature¹¹¹ where triphenylphosphine oxide was isolated when octyl tosylate was refluxed with triphenyl phosphine (Scheme 111).

Scheme 111

159

The only other alternative to prepare alkyl phosphonium tosylates is by using high pressures. Recently Dauben¹¹² developed conditions to prepare alkyl phosphonium tosylates (and mesylates) by using high pressures at ambient temperatures (Scheme 112).

Scheme 112

We could not attempt these conditions since we didn't have Dauben's high-pressure apparatus. But, if possible, it certainly would be interesting to see if the desired Wittig salt 158 could be prepared using Dauben's conditions.

4.3.8 One Step Preparation of 4-Bromo-1-butyne:

Since tosylate 153 did not prove useful either in the preparation of 4-bromo-1-butyne 152 or 4-butyntriphenylphosphonium tosylate 158, we had to take recourse to procedures that would directly convert 4-butyne-1-ol in one step to 4-bromo-1-butyne, thus bypassing use of tosylate 153 completely (Scheme 113).

Scheme 113

A variety of reagents were utilized by us in attempts to bring about this transformation. Utilizing carbon tetrabromide-triphenylphosphine mixture ¹¹³⁻¹¹⁴ gave the desired bromide 152 in 10% yield along with unidentified olefinic compound(s) (Scheme 114).

Scheme 114

Employing N-bromosuccinimide-triphenylphosphine mixture ¹¹⁵ gave none of the desired compound 152 but only olefinic impurities which were not identified (Scheme 115).

Scheme 115

However, a 15% yield of the desired bromide 152 was obtained, When phosphorus tribromide ¹⁰⁴ was used (Scheme 116).

Scheme 116

Attempted improvement¹¹⁶ of yields of this reaction by adding lithium bromide did not prove useful (Scheme 117).

Scheme 117

4.3.9 Wittig Condensation Leading to En-yne 151:

The bromide 152 obtained from the PBr_3 reaction (Scheme 116) was used to generate Wittig salt 149 (Scheme 118). The phosphonium salt, 149 was treated with n-butyllithium to generate ylide 150, which was condensed with aldehyde 56. The spectral data were in agreement with the assigned structure for en-yne 151. The mass spectrum showed a molecular ion peak M^+ at 247 (calculated molecular weight of 151 = 247).

Although the Wittig condensation is successful in obtaining en-yne 151, there is a need for improved preparation of the bromide 152 and the Wittig salt 149. No further studies were carried out in that direction.

Scheme 118

THF, 23°C, 12 hr

4.3.10 Studies on Aldehyde Homologation:

Our neopentylidic aldehyde 56 is quite sluggish in its reactivity compared to unhindered aldehydes. This fact became apparent when it failed to react with acetylenic ylide 139 (Scheme 102) as discussed before. It was then felt that extension of the aldehyde by one carbon would give the homologous aldehyde 164 (Scheme 119), which being unhindered, should be more reactive.

Initial attempts at aldehyde homologation utilizing Magnus's¹¹⁷ reductive nucleophilic acylation procedure did not yield any meaningful product(s) (Scheme 120).

Aldehyde and ketone extensions have been carried out in literature¹¹⁸⁻¹²⁴ via Wittig condensations. Danishefsky¹¹⁸ homologated the neopentyl steroidal ketone 168 by Wittig condensation with ylide generated from methoxymethyltriphenyl phosphonium chloride (Scheme 121).

Scheme 121

Attempted condensation of aldehyde 56 with methoxymethylene triphenylphosphorane 171 under a variety of conditions gave unreacted starting material (Scheme 122).

Finally conditions were developed for successful condensation of ylide 171 with aldehyde 56. Thus, treating 2.1 equiv of ylide 171, generated from methoxymethyltriphenylphosphonium chloride 172 and potassium tert-butoxide with aldehyde

Scheme 122

56 at ambient temperature for 3 days resulted in isolation of a mixture of Z and E enol ethers 173 and 174 respectively (Scheme 123).

The above mixture of isomers could be hydrolysed to the homologated aldehydes 164 and 175 in poor yields by using either 70% aqueous perchloric acid (Scheme 124-A) or by treating with a large excess of boron tribromide (Scheme 124-B).

Scheme 124-A

No attempts were made to optimize the yields on these reactions.

No further chemistry was done with the homologated aldehydes 175 and 164.

Scheme 124-B

Part D. Attempted Organometallic Route to 1-Alkyl Tropanols

An alternative route for Wittig condensation in carbon-carbon bond formation is coupling of alkyl halides or mesylates with carbon nucleophiles such as cuprate or Grignard reagents.¹²⁵⁻¹³⁷

When applied to suitably functionalized tropanes, such coupling should give access to the desired 1-alkyltropanols (Scheme 125).

4.4.1 Attempted Preparation of Bromide 176:

Triphenylphosphine dibromide¹³⁸⁻¹³⁹ has been used to cleave ethers to the corresponding bromides (Scheme 126).

Scheme 126

Scheme 127

Treatment of methyl ether 60 with this reagent, either in refluxing DMF or chlorobenzene, resulted in only recovery of starting materials and none of the desired bromide 176 was obtained (Scheme 127).

4.4.2 Attempted Preparation of Chloride 177:

The next goal was to convert alcohol 55 into the chloride 177 (Scheme 128).

Scheme 128

Fodor¹⁴⁰ converted diol 178 into chloride 179 by using thionyl chloride (Scheme 129).

Scheme 129¹⁴⁰

Scheme 130

Applying the same procedure to our case did not prove useful (Scheme 130), due to the neopentyllic nature of the hydroxy group.

4.4.3 Preparation of Mesylate 180:

Since all attempts at converting the neopentyl alcohol 55 into the corresponding halides failed, we turned our attention to the preparation of mesylates. When 55 was treated with methane sulfonyl chloride at room temperature in the presence of 2,6-lutidine, mesylate 180 was obtained as a yellow crystalline solid (Scheme 131).

Scheme 131

The spectral data of mesylate 180 were in agreement with the assigned structure. The structure received further support from the following chemical transformations.

- (i) Treatment of mesylate 180 with sodium methoxide in methanol or with anhydrous potassium carbonate in methanol resulted in

Scheme 132

cleavage of acetate, while leaving the methanesulfonyl group intact (Scheme 132).

In fact, the mesylate 181 was inert to methoxide even in refluxing methanol (Scheme 133).

Scheme 133

(ii) Mesylates and tosylates are known¹⁴³⁻¹⁴⁴ to be easily reduced by lithium aluminum hydride. Reduction of mesylate 180 with three equiv of LiAlH_4 in refluxing ether gave 1-methylpseudotropine 133 (Scheme 134).

Scheme 134

These chemical transformations confirmed the structure of mesylate 180.

Scheme 135

Scheme 136

4.4.4 Attempted Carbon-Carbon Bond Formation using Mesylates:

The successful preparation of mesylates 180 and 181 set the stage for carbon-carbon bond formation via Grignard/cuprate coupling.

Unfortunately, treatment of mesylate 180 with either lithium n-butylcuprate or n-butylmagnesium bromide in the presence of cuprous iodide resulted in isolation of sulfone 186(c) and diol 52 (Schemes 135 and 136). None of the desired alkylated tropanol 15 was obtained in either case.

The structure of 3° alcohol 185 was confirmed by independent synthesis from ethyl acetate (Scheme 137).

Scheme 137

Treatment of mesylate 181 with several Grignard reagents in presence of cuprous iodide gave corresponding sulfones 186(a-c) (Scheme 138).

Scheme 138

R = allyl (a)
R = ethyl (b)
R = n butyl (c)

The structure of sulfones 186(a-c) was very clear from the ^1H NMR. For example, in case of alkylmethyl sulfone 186a, the methylene protons next to sulfur gave a signal at δ 3.8 as a doublet, which is typical¹⁴⁶ of an allyl sulfone.

4.4.5 Formation of Sulfones - Steric Factors Raise their Ugly Heads:

The formation of these sulfones is a result of attack of nucleophile (Grignard or cuprate reagent) on sulfur rather than on neopentyllic carbon (Scheme 139).

Scheme 139

There are two isolated incidents in literature where sulfones are formed in similar reactions.

Johnson¹³⁰ and Dutra, during their pioneering study on

carbon-carbon bond formation via organometallic coupling, found that when cyclopentyl tosylate was treated with lithium dimethyl cuprate, a side product, believed to be dicyclopentyl ether (190) was obtained in minor amounts (Scheme 140).

These authors¹³⁰ proposed the following mechanistic rationale (involving sulfones) for the formation of ether 190 (Scheme 141).

There is another precedent from the recent literature¹³⁶ (Scheme 142).

Scheme 142

4.4.6 Preparation of Iodide 193:

When there are two reactive centers in a molecule, the reaction always occurs at the more reactive site. Such was the case with mesylate 180, in which sulfur being sterically less hindered was more open (compared to neopentyl carbon) to attack by carbon nucleophiles (Grignard/cuprate reagents).

To get around this problem, we planned to convert mesylate 180 to iodide 193.

Attempted preparation of iodide 193 from mesylate 180 by refluxing with sodium iodide failed (Scheme 143).

Scheme 143

Magnesium iodide (MgI_2) is known¹⁵⁰⁻¹⁵¹ to work in cases where sodium iodide has failed. Scheme 144 represents typical examples.

Scheme 144

Neopentyl tosylates are known to undergo such substitutions with rearrangement to give 3° iodides (Scheme 145).

Scheme 145

Application of similar experimental procedures to our case resulted, to our delight, in isolation of the desired iodide 193, unaccompanied by products of rearrangement (Scheme 146).

Scheme 146

4.4.7 Mechanism of Formation of Iodide:

It was speculated¹⁵⁰ that magnesium coordinates to one of the oxygens of the sulfonate group, thereby assisting the displacement of sulfonate anion by iodide.

In our case, it is conceivable that magnesium being a bidentate ligand, coordinates not only to the oxygen of the sulfonate group but also to the lone pair of nitrogen and forms a seven membered chelate (Scheme 147).

Scheme 147

We believe that chelation of nitrogen prevents any rearrangements, since rearrangement would lead to a 3° carbonium ion (**200b**), that would be next to a positively charged nitrogen, thereby creating an unfavorable situation.

There are examples in literature^{134,135} where neopentyl type and other hindered halides have been displaced by carbon nucleophiles. Schemes 148 and 149 represent a few examples.

Scheme 148¹³⁴

Scheme 149¹³⁵

In our hands, all attempts at carbon-carbon bond formation by displacement of iodide functionality in 193 resulted in complete recovery of starting material (Scheme 150).

At this point it became clear that we have come to a blind alley. So this route was abandoned and we took recourse to the Wittig route as described previously (Chapter 4, Part B).

Scheme 150

5. SUMMARY

The synthetic methodology we have developed^{153,154} for bridgehead substituted tropane-3 β -ols is summarized in Scheme 151.

wavenumbers (cm^{-1}) and were described by the following abbreviations: *vs* = very strong, *s* = strong, *m* = medium, *w* = weak, *br* = broad, and *sh* = sharp.

¹H NMR spectra were recorded on a Varian EM-360 (60 MHz).

Scheme 151

6. EXPERIMENTAL

INSTRUMENTATION:

Melting points were determined on a Electrothermal melting point apparatus. Both melting and boiling points are uncorrected.

Infrared spectra were recorded on a Beckman IR-8, IR-10 or IR-20A spectrophotometers. The absorptions are expressed in wavenumbers (cm^{-1}) and were described by the following abbreviations: vs = very strong, s = strong, m = medium, w = weak, br = broad, and sh = sharp.

^1H NMR spectra were recorded on a Varian EM-360 (60 MHz) spectrometer. The chemical shifts were expressed in ppm (δ) and the letter code describes the multiplicities of the resonance signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The coupling constants, J are reported in Hertz.

The carbon-13 NMR spectra were taken on a Varian CFT-20 spectrometer at 20 MHz. Tetramethylsilane (TMS) was used as internal standard for both ^1H NMR and ^{13}C recordings.

Mass spectra were obtained on Finnigan 4021 mass spectrometer with an INCOS data system. The ionizing voltage was 70 eV unless otherwise indicated in the text.

Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, Tennessee. All the hydrogenations were carried out on a Parr low-pressure reaction apparatus.

SOLVENTS:

"Dry" solvents were obtained by distillation from an appropriate drying agent shortly before use.

Tetrahydrofuran (THF) was distilled from CaH_2 followed by distillation over LiAlH_4 under N_2 . In some instances, it was distilled under N_2 from sodium metal in the presence of benzophenone ketyl. The distilled THF was stored over 4 Å molecular sieves under N_2 atmosphere. Benzene was distilled from sodium metal and stored over sodium wire. Toluene was distilled from CaH_2 . Anhydrous ether was distilled from CaH_2 . Dimethyl sulfoxide (DMSO), dimethylformamide and hexamethylphosphoramide were stirred overnight with NaOH pellets, decanted and distilled twice over CaH_2 under high vacuum. They were stored over 3 Å molecular sieves under N_2 . Glyme and diglyme were distilled over CaH_2 . Methanol was distilled from magnesium methoxide. Chloroform and methylene chloride were stirred with anhydrous CaCl_2 , decanted and distilled over P_4O_{10} . Ethyl acetate was distilled from P_4O_{10} .

REAGENTS:

The following chemicals were purchased from Fisher Chemical Company and were purified as mentioned.

Oxalyl chloride was distilled under N_2 . Acetic anhydride was distilled under N_2 . Acetyl chloride was used from a freshly

opened bottle. Methanesulfonyl chloride was distilled under vacuum (water aspirator) just before use. Triethylamine, pyridine, N-methylpiperidine and 2,6-lutidine were distilled twice from CaH_2 and stored over 3 Å molecular sieves under N_2 . Chlorotrimethylsilane (Me_3SiCl) was distilled from CaH_2 under N_2 . Lithium bromide, lithium chloride, sodium iodide, cuprous chloride, carbon tetrabromide and phosphorous tribromide were used without purification.

Thionyl chloride was purified by distilling over triphenyl phosphite, according to the procedure of Fieser.¹⁵² Li_2CuCl_4 was prepared according to the procedure of Kochi.¹⁵³

Furfuryl alcohol was distilled prior to use. Methyl iodide was used from a freshly opened bottle. Methylamine hydrochloride was used without any purification. 1-Bromobutane was distilled from P_2O_5 . Triphenylphosphine (PPh_3), sulfur trioxide (SO_3), 2-furoic acid, sodium citrate, sodium tetraphenylborate were used without any purification. p-Toluenesulfonyl chloride was used from a freshly opened bottle. Hydrogen chloride gas was generated from sodium chloride and concentrated sulfuric acid. Hydrogen bromide was used as a 48% aqueous solution. Perchloric acid (HClO_4) was used as a 70% aqueous solution.

Sodium hydride (NaH) was purchased as a 59% suspension in mineral oil and was washed with dry pentane just before use.

The following chemicals were purchased from Aldrich Chemical Company:

Boron tribromide (BBr_3) was supplied as a 1 M solution in

dichloromethane.

n-Butyllithium (n-BuLi) was used as a 1.6 M solution in hexane.

n-Butylmagnesium chloride (n-BuMgCl) was used as a 2 M solution in diethyl ether.

Allylmagnesium chloride was used as a 2 M solution in tetrahydrofuran.

Ethylmagnesium bromide (EtMgBr) was used as a 2 M solution in tetrahydrofuran.

Propylmagnesium chloride was used as a 2 M solution in diethyl ether.

Methoxymethyltriphenylphosphonium chloride and potassium t-butoxide were used without purification. Raney nickel was prepared from Aluminum-nickel catalyst according to the procedure of Mozingo.^{11b}

Proton sponge [1,8-bis(dimethyl amino)naphthalene] and dicyclohexylcarbodiimide (DCC) were used without purification.

Pyridinium chlorochromate³⁴ (PCC) and pyridinium dichromate²⁶ (PDC) were prepared according to the procedure of Corey.

Eastman chromatogram sheets, either silica gel or alumina with fluorescent indicator, were used for thin-layer chromatography (TLC). Spots were detected by visualization under ultraviolet light (254 nm). Silica gel 60 (Merck) was used for flash vacuum chromatography. Solvents were evaporated on a Buchi Rotavapor-R.

General Remarks:

The symbol r.t. refers to room temperature and r.b. refers to round bottom flask. Ether refers to diethyl ether unless otherwise noted. Air- and moisture-sensitive reactions were carried out under on N_2 atmosphere. The glassware was flame-dried before use in such reactions. Air-sensitive reagents were transferred either via double ended cannula or by syringes equipped with needles. The solvents were freshly distilled just before use and were transferred to the reaction flask via double ended needles under positive pressure of N_2 . The symbol Δ^b refers to heated to reflux.

PREPARATIONS:6.1 Preparation of Furfuryl methyl ether (31):

In a 1-L three-necked flask equipped with a mechanical stirrer, a reflux condenser and a stopper, 225 mL of furfuryl alcohol (2.6 mol, 255.3 g, $d = 1.135$) and 162 mL of iodomethane (2.6 mol, 369.3 g, $d = 2.28$) were taken. The mixture was stirred well and cooled in an ice-salt bath to -10°C . To this cooled mixture, 148 g of finely powdered potassium hydroxide pellets (2.6 mol) were added in small portions. During the addition, the temperature was maintained below 25°C . When all the potassium hydroxide had been added, the ice-bath was removed and the mixture stirred for another 6 hr at 23°C . At the end of this period,

200 mL of ice-cold distilled water was added to the reaction mixture. The aqueous and organic layers were separated. The organic layer was extracted three times with 300 mL portions of ether each time. The organic extracts were combined, dried (anhyd. Na_2SO_4) and the solvent evaporated. Distillation of the residual oil at 1 atm (b.p. 130-134°C) gave 192 g (66%) of furfuryl methyl ether, as a colorless liquid.

NMR (CDCl_3): δ 3.25 (s, 3H), δ 4.3 (s, 2H), δ 6.3 (s, 2H), δ 7.4 (s, 1H).

IR (neat): 3100, 3000, 1600, 1500, 1450, 1350, 1150, 1000, 950, 750 cm^{-1} .

Notes:

1. Using dimethyl sulfoxide (DMSO) as solvent resulted in only a 4% increase of yields (66 → 70%).
2. Using anhydrous ether as solvent decreased the yield from 66% to 50%.
3. When necessary the reaction was scaled up to two times the amounts used in the above procedure without any serious problems.
4. Using NaH/DME gave only 43% yield of product.

6.2 Preparation of 2,5-Dimethoxy 2-methoxymethyl-

2,5-dihydrofuran (32):

The procedure by Kebrle and Karrer¹⁰ has been modified for larger scale work. In a four-necked 1-L reaction kettle (equipped with a mechanical stirrer, low-temperature thermometer, drying tube filled with drierite and a dropping funnel) 400 mL of absolute methanol, 100 mL of dry benzene, 208 g of anhydrous sodium carbonate (2.2×0.892 mol) and 100 g of 2-methoxymethylfuran (0.892 mol) were placed. The slurry was cooled to -15°C and stirred. Meanwhile, to 100 mL of absolute methanol 47.4 mL of bromine (0.892 moles) were added dropwise, below -10°C . The methanolic bromine solution was then added slowly to the reaction mixture maintained below -10°C in about 2 hr. The mixture was stirred for another 5 hr. at -10°C . Then, 50 g of anhydrous sodium sulfate was added, the cooling bath was removed and the mixture was stirred for 0.5 hr at room temperature. The salts were filtered off and washed with dry ether and benzene. The filtrate was placed into the reaction kettle and stirred with 50 g of anhydrous K_2CO_3 for 8 hr. After filtration, the solvent was evaporated; then a total of 1000 mL of anhydrous ether was added until no more solids precipitated. After filtration and evaporation a brownish oil was obtained which was distilled at 0.1 mm (bp $45-50^{\circ}\text{C}$) to give 111.6 g (72%) of the diastereoisomeric mixture of (+) 2-methoxymethyl-2,5-dimethoxy-2,5-dihydrofurans as a colorless oil.

NMR (CDCl_3): δ 3.2 (s, 2H), δ 3.5-3.8 (OCH_3 , (several

singlets, 9H), δ 5.6 (s, 1H), δ 5.9-6.2 (m, 2H, C=C-H).

IR (neat): 3000, 1640 (C=C), 1450, 1350, 850, 750 cm^{-1} .

Notes:

1. Bromine reacts with methanol very violently above 0°C. So the temperature of bromine-methanol solution should always be kept at or below -10°C for safety reasons.
2. Bromine should be added as fast as it is consumed.
3. Before distilling the product, a pinch of an anti-oxidant such as hydroquinone should be added to avoid decomposition of the product.
4. If the product is kept for too long, it becomes yellow. It may be necessary to redistill it prior to use.

6.3 Preparation of Raney Nickel W-2:

Raney nickel W-2 was prepared from nickel-aluminium alloy (50/50) according to the procedure of Mozingo,^{11b} as described in Organic Synthesis. It was stored in bottles filled completely with 95% ethanol.

Notes:

1. Raney nickel is extremely pyrophoric when it is dry. So every precaution should be taken while handling it.
2. Even the used catalyst should be stored and disposed of in bottles filled with water.

6.4 Preparation of 2,5-Dimethoxy-2-methoxymethyl
tetrahydrofuran (34):

2-methoxymethyl-2,5-dimethoxydihydrofuran (35 g, 0.201 mol) were dissolved in 100 mL of absolute ethanol in a Pyrex hydrogenation bottle. 20 g of Raney nickel were added and the compound was hydrogenated at 2 atm until the calculated amount of hydrogen (145 psi) was consumed. The hydrogen uptake was rapid (about 15 min for the total consumption of hydrogen). The catalyst was filtered and the solvent evaporated. Distillation of the residual oil (b.p. 45-48°C at .1 mm) gave 32 g (90%) of the expected cyclic acetate ketal of 4-keto-5-methoxypentanol (34).

NMR (CDCl₃): δ 1.9-2 (m, 4H), δ 3.1-3.3 (m, 11H), δ 5.0 (m, 1H).

IR (neat): 3000, 1450, 1350, 850, 720 cm⁻¹.

Notes:

1. Raney nickel W-2 can be purchased as a suspension in water from Aldrich. However using this commercially available catalyst resulted in slowdown of hydrogenation by at least ten times.
2. Ethyl acetate was a poor solvent for this hydrogenation. The rate was too slow.
3. Using PtO_2 or 10% Pd/C resulted in hydrogenolysis of the methoxy groups.
4. The same hydrogenation was done by Clauson-Kaas¹⁴ at 2000 psi and 100°C by using a catalytic amount of Raney nickel.

6.5 (+) 1-Methoxymethyl-3-tropanone (17):

2,5-dimethoxy-2-methoxymethyltetrahydrofuran (100 g, 0.568 mol) were dissolved in 550 mL 1N HCl and kept at 80°C for 20 min. The mixture was rapidly cooled in ice and the ketoaldehyde was used immediately in the Robinson condensation.

In a 3-necked 2-L flask equipped with a mechanical stirrer, reflux condenser, addition funnel, 133 g (1.6 x 0.568 mol) of acetonedicarboxylic acid were added to the solution of the keto-aldehyde and the solution adjusted to pH = 5 with solid potassium carbonate very carefully (foam!!) while cooling. Then 600 mL 12% sodium citrate solution followed by 80 g

methylammonium chloride (2.1×0.568 mol) were added. The total volume of the solution was adjusted to 1000 mL by water. The resulting solution was stirred for 40 h at room temperature when release of carbon dioxide ceased. At the end the pH was brought to 10 by solid potassium carbonate.

Subsequently the mixture was heated to 60°C and cooled down. The volume of the solution was evaporated to 300 mL and extracted with ether in a continuous liquid-liquid extractor for 24 hr. The ethereal extract was dried (Na_2SO_4) and the solvent removed by evaporation. The resulting crude oil was distilled at 0.4 mm, bp $65\text{--}70^{\circ}\text{C}$. Yield 62 g (60%). Light yellowish colored viscous oil. Kebrle and Karrer¹⁰ reported 40% yield when no citrate buffer was used.

NMR (CDCl_3): δ 1.5–2.9 (m, 11H), δ 3.5 (m, 6H, CH_2OCH_3 , 1-H).

IR (neat): 3000, 1710 (br, C=O), 1450, 1410, 1350, 1200, 1150, 100.

For analytical purposes the picrate was prepared from 500 mg distilled 6 tropanone 6 and 5 mL of a saturated alcoholic solution of picric acid. Washing with absolute methanol and drying gave a product. m.p. $170\text{--}171^{\circ}\text{C}$.

Anal. for $\text{C}_{16}\text{H}_{20}\text{O}_9\text{N}_4$: Calcd.: C, 46.60; H, 4.89; N, 13.59.

Found: C, 46.71; H, 4.99; N, 13.52.

Notes:

1. The reported¹⁰ yield of this compound was only 40% (sodium citrate was not used as buffer by these workers).
2. If the continuous extraction was not done, the yields dropped down to 42%. This is due to the fact that the product is fairly soluble in water. The carbonyl and the 3° amine functionalities allow for extensive hydrogen bonding.

6.6 Preparation of 1-Methoxymethyl-3 β -tropanol (43):

In a 3-necked 2-L r.b. flask equipped with a mechanical stirrer, reflux condenser and dropping funnel, a suspension 23 g (1 mol) of Na in 500 mL of dry toluene was brought to reflux. A mixture of 85 g of 1-methoxymethyltropinone (0.46 mol) and 21 mL of absolute ethanol (1.25×0.46 mol) and 100 mL of dry toluene was added dropwise, enough to keep the mixture refluxing. The mixture was refluxed for 12 hr. At the end of this period, it was cooled in an ice bath. 200 mL of absolute ethanol was added, followed by 200 mL of water. The organic and aqueous layers were separated. The aqueous layer was extracted with (3 x 200 mL) ether. The combined organic layers were washed with saturated sodium chloride solution, dried (Na_2SO_4), filtered and the solvents evaporated. The resulting brown oil was distilled at 0.4 mm (b.p. 110-112°C) to give 75 g (90%) of 1-methoxymethyl-3 β -tropanol.

NMR (CDCl_3): δ 1.5-1.8 (m, 8H), δ 2.4 (s, 3H), δ 3.3 (m, 6H), δ 4.1 (m, 1H).

IR (film): 3400, 1450, 1250, 1100, 1050, 900 cm^{-1} .

Notes:

1. The compound could also be purified by chromatography on silica gel (MeOH + 1% Na_4OH).
2. During the vacuum distillation, an air-cooled condenser was used. The compound would solidify when a water cooled condenser was used.
3. The yields drop down to 75-80% if good vacuum (less than 0.5 mm) is unattainable. Reproducibility was better if the vacuum was good.

6.7 Preparation of 1-Methoxymethyl pseudotropine hydrochloride (45):

10 g of 43 were (0.054 mol) dissolved in 200 mL of absolute ethanol and dry HCl gas was bubbled through the solution until pH = 2-3 was reached. Ethanol was evaporated and the resulting solid dried under vacuum for 6 hrs. Yield 11.9 g (100%).

Anal. Calcd. for $\text{C}_{10}\text{H}_{20}\text{NO}_2\text{Cl}$: C, 54.77; H, 9.03; N, 6.32; O, 14.44; Cl, 16.03. Found: C, 54.22; H, 9.00; N, 6.21; O, 14.61; Cl, 16.03.

m.p. 177-179°C.

6.8 Preparation of 1-Methoxymethyl-3 β -acetoxytropine

Hydrochloride (60):

Amine 45 (7.00 g, 0.032 mol) was dissolved in 125 mL of freshly distilled acetic anhydride and 50 mL of acetyl chloride, in a 500 mL r.b. flask. To this magnetically stirred solution, 0.26 g (0.002 mol) of dimethylaminopyridine (DMAP) was added and the mixture was refluxed overnight. Acetyl chloride and acetic anhydride were removed by evaporation. To the brown oily residue, 20 mL of acetone was added and the sides of the flask scratched with a glass rod. White crystals were obtained, which were washed with 5 mL of cold acetone. Yield 7 g (85%).

m.p. 153-156°C.

NMR (CDCl₃): δ 2.2-2.5 (m, 11H), δ 2.9 (s, 3H), δ 3.3 (s, 5H), δ 4.9-5.2 (m, 1H).

IR (KBr): 2900, 1720, 1370, 1240, 1020 cm⁻¹.

Anal. Calcd. for C₁₂H₂₂O₃NCl: C, 54.64; H, 8.37; N, 5.31;

Cl, 13.47; O, 18.21. Found: C, 54.53; H, 8.52; N, 5.25;

Cl, 13.60; O, 17.99.

Notes:

1. The amount of DMAP needed is only 1/15 of the alcohol.
2. The yields drop down from 85 → 50% if the catalyst (DMAP) is not used.
3. Instead of using HCl salt of the starting amino alcohol 43, one could use the free base. Since one mole of hydrogen chloride is liberated during the reaction, we still end up with the hydrochloride salt of the acylated amine. However, it is convenient to use the hydrochloride salt of the starting amino alcohol 45 which is a solid rather than the free base which is a syrup.

6.9 Preparation of 1-Hydroxymethyl-3B-acetoxytropane (55):

In a 3-necked 500 mL r.b. flask equipped with a mechanical stirrer, addition funnel with septum, reflux condenser with a nitrogen inlet, 5 g (0.019 mol) of 60 were taken and dissolved in 200 mL of dry chloroform. 100 mL of 1 M solution of boron tribromide (5.25 x 0.019 mol) in methylene chloride were transferred via cannula to the addition funnel by using a positive pressure of nitrogen. It was added dropwise from the addition funnel to the reaction mixture at 23°C. The mixture was stirred for 16 hr. It was then poured onto crushed ice and less adjusted to pH 11 by ammonium hydroxide solution. The organic

and aqueous layers were separated. The aqueous layer was extracted with (2 x 100 mL) chloroform. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was evaporated. The crude compound was pure enough for the next step and was used in most cases without any purification. Yield 4 g (99%).

However for analytical purposes, a small amount was chromatographed (CHCl_3 as eluent) over silica gel.

^1H NMR (CDCl_3): δ 1.5–1.9 (m, 8H); δ 2.1 (s, 3H); δ 2.3 (s, 3H); δ 3.3 (m, 1H), δ 3.5 (s, 2H); δ 4.4 (s, 1H, exchangeable with D_2O); δ 5.1 (m, 1H).

IR (CDCl_3): 3400 (br, OH), 2950, 1720 (s, $\text{O}-\overset{\text{O}}{\parallel}\text{CCH}_3$), 1450, 1300, 1200, 1020, 900, 800 cm^{-1} .

Notes:

1. The reaction does not proceed below room temperature.
2. For optimization of yields, see Table I.

6.10 Preparation of Tetraphenyl borate salt of 3-Hydroxymethyl-38-acetoxypentane:

To a solution of 1 g of 55 in 30 ml of water diluted hydrochloric acid was added until pH of 2 was reached. A 7% aqueous solution of a sodium tetraphenyl boron was added

Table I

OPTIMIZATION OF YIELDS

Amt. of CH_2OCH_3	Amt. of BBr_3	Conditions	Work-up	% Yield
1 g	5X	RT, 24 hr	10% Na_2CO_3 ; pH = 10	80%
1 g	7.6X	RT, 36 hr	conc. NH_3 , pH = 10	50%
2 g	5X	-30° → RT; 24 hr at RT	10% Na_2CO_3 , pH = 10	62%
2 g	5.25X	0° → RT; 28 hr at RT	10% Na_2CO_3 + conc. NH_3 pH = 10	100%
5 g	5.25X	0° → RT; 24 hr at RT	10% Na_2CO_3 + conc. NH_3 pH = 10	80%
5 g	5.25X	0° → RT; 24 hr at RT	10% Na_2CO_3 + conc. NH_3 pH = 10	75%
4 g	6.6X	RT, 24 hr	10% Na_2CO_3 , pH = 10	84%
4 g	6.6X	RT, 18 hr	10% Na_2CO_3 + dil. NH_3 pH = 10	89%
8 g	6.6X	RT, 24 hr	10% Na_2CO_3 , pH = 10	75%
8 g	6.6X	RT, 24 hr	10% Na_2CO_3 , NH_3 , pH = 12	85%
8 g	6.6X	RT, 15 hr	10% Na_2CO_3 , pH = 10	65%
0 g	5.25X	RT, 24 hr	10% Na_2CO_3 , pH = 10	42%

5 g	5.25X	RT, 24 hr	10% Na_2CO_3 , pH = 10	65%
4 g	6.6X	RT, 24 hr	10% Na_2CO_3 , pH = 10	65%
5 g	5.25X	RT, 24 hr	10% Na_2CO_3 , pH = 12	51%
5 g	5.25X	RT, 24 hr	dil. NaOH, pH = 10	89%
5 g	5.25X	RT, 24 hr	dil. NH_4 , pH = 8-9	80%
4 g	5.25X	RT, 24 hr	conc. NH_4OH , pH = 10	100%
4 g	5.25X	RT, 24 hr	conc. NH_4OH , pH = 12	75%
5 g	5.25X	RT, 24 hr	conc. NH_4OH , pH = 10-11	100%
4 g	5.25X	RT, 24 hr	conc. NH_4OH	98%
5 g	5.25X	RT, 24 hr	conc. NH_4OH	95%
5 g	5.25X	RT, 24 hr	conc. NH_4OH	98%
5 g	5.25X	RT, 24 hr	conc. NH_4OH	95%

Notes: Consistent yields of (95-100%) are obtained by using:

1. 5.25 equiv. of BBr_3 at room temperature for 24 hours.
2. Chloroform as solvent.
3. Using concentrated NH_4OH in work up (pH = 10).
4. At higher pH, acetate is hydrolysed.

dropwise, with cooling and stirring. An immediate precipitation occurred. After the precipitation was complete, the precipitate was filtered on suction, washed well with distilled water and dried under vacuum at 40°C for 6 hrs.

m.p. 108-110°C.

Anal. Calcd. for $C_{35}H_{40}O_3BN$: C, 78.877; H, 7.01.

Found: C, 78.60; H, 7.50.

6.11 Preparation of Methyl-2-furoate (27):

In a 1-L one-neck r.b. flask, 112 g of 2-furoic acid (1 mol) were dissolved in 300 mL of dry methanol. 5 mL of conc. sulfuric acid were added and the flask was equipped with a soxhlet charged with 3 Å molecular sieves. A reflux condenser was attached on top of the soxhlet and the reaction mixture was refluxed for 20 hrs. At the end of the reflux period, the mixture was cooled, and poured into 200 mL of ice-cold water. The aqueous solution was extracted with ether. The ether layer was washed with 10% sodium bicarbonate solution, followed by water and finally with saturated salt solution. It was dried (Na_2SO_4), filtered and then evaporated. The residue was distilled (b.p. 40°C at 5 mm) to give 80 g (60%) of colorless liquid.

1H NMR ($CDCl_3$): δ 3.8 (s, 1H), δ 6.5 (m, 1H), δ 7.2 (d, 1H), δ 7.8 (d, 1H).

6.12 Preparation of 1-Hydroxymethyl-3 β -tropanol (52):

In a 1-L r.b. flask equipped with a magnetic stirrer and reflux condenser, 26.0 g (0.14 mol) of 1-methoxymethyl-3 β -tropanol (43) were dissolved in 160 mL of 48% aqueous HBr and the mixture heated to reflux for 36 hr. At the end of this heating period, the mixture was cooled in an ice-bath, neutralized carefully with 10% sodium hydroxide solution and water was evaporated. To the crude solid 100 mL of hot acetone added and the insoluble solids filtered. Acetone was evaporated and the crude product was chromatographed on a column of basic alumina. 20 g (90%) of 52 was obtained as a yellow solid.

NMR (D_2O): δ 1.5-1.8 (m, 8H), δ 2.5 (s, 3H), δ 3.6 (3H).

IR ($CHCl_3$): 3500 (br, OH), 3000, 1450, 1020 cm^{-1} .

The tetraphenylborate salt was prepared using the procedure outlined in section 6.10.

m.p. 194-196°C.

Anal. Calcd. for $C_{33}H_{38}NO_2$: C, 80.65; H, 7.73; N, 2.85; B, 2.24; O, 6.52. Found: C, 79.85; H, 8.03; N, 2.75; B, 2.09; O, 7.10.

The HBr salt of the diol 52 was prepared by dissolving the compound in 48% HBr solution and azeotroping the water with benzene.

Anal. Calcd. for $C_9H_{18}NO_2Br$: C, 43.20; H, 6.4; N, 5.60;

Br, 32.0; O, 12.80. Found: C, 43.05; H, 6.6; N, 5.39; Br, 32.6; O, 12.65.

6.13 Swern Oxidation of 1-Hydroxymethyl-38-acetoxytropane (55)
to 38-acetoxytropane-1-aldehyde (56):

A solution of 3.6 mL (2.2×0.019 mol) of oxalyl chloride in 50 mL dichloromethane was placed in a flask equipped with mechanical stirrer, a low-temperature thermometer, a Claisen-adapter with dropping funnels, one containing 6.5 mL (4.8×0.0188 mol) dimethyl sulfoxide diluted with 20 mL methylene chloride and the other containing 4 g (0.019 mol) of 1-hydroxymethyl-38-acetoxytropane (8a) dissolved in 20 mL of the same solvent. The flask was cooled to -60°C . First the dimethyl sulfoxide solution was added dropwise under nitrogen to the oxalyl chloride solution. The reaction mixture was stirred for additional 30 min at -60°C . The methylene chloride solution of 8a was then added dropwise and the solution stirred for additional 1 hr between 40°C and -60°C . Finally 11 mL (5×0.019 mol) of N-methylpiperidine were added and the solution stirred for additional 15 min and the mixture was allowed to warm to 20° . 30 mL of water added and the pH adjusted to 11 with dil. ammonium hydroxide solution. The organic and aqueous phases were separated and the aqueous layer extracted 3 times with 100 mL methylene chloride. The combined organic layers were washed with water, by saturated salt solution, dried (Na_2SO_4). Filtration followed by evaporation of solvent gave 3.8 g (95%) of aldehyde 11 as a light yellow oil. It was characterized by its ^1H NMR and mass spectra.

NMR (CDCl_3): δ 1.5-1.8 (m, 8H), δ 2.0 (s, 3H), δ 2.3 (s,

3H, N-CH₃), δ 3.3 (m, 1H), δ 5.1-5.4 (m, 1H, H-3), δ 9.7 (s, 1H, -C-H).

IR (film): 2900, 1750, 1350, 1250, 1070, 900, 720 cm⁻¹.

Mass spectrum: m/e 211.1 (M⁺), 196.1, 185.1, 168.1, 152.1, 122.1, 111.1, 96.1 (base peaks, 82.1, 67.1, 55.0).

Notes:

1. Evaporation of solvent should be carried out in a well ventilated hood.
2. When triethylamine was used in place of N-methylpiperidine, there was evidence for another product, amino sulfide 90. Using 2,6-lutidine increased the amounts of this by-product at the cost of desired aldehyde 56. Thus the most suitable base was determined to be N-methylpiperidine.
3. When the reaction was carried out on a smaller scale (1 gm of starting alcohol), the crude yields were found to be much better (95-100%).

6.14 Chemical conformation of structure of 3 β -acetoxytropane
1-aldehyde (56) by reduction to 1-hydroxymethyl-3 β -
acetoxytropane (55):

To 1.00 g of the crude aldehyde 56 in 25 mL of ether were added 2.00 g of NaBH_4 (0.053 mol) and the mixture was stirred for 12 hr in a 100 mL r.b. flask at 23°C. After this time, the solids were filtered, and the pH of the solution was adjusted to 3 by dilute hydrochloric acid. It was then basified with dilute ammonium hydroxide (pH = 10). The water layer was extracted with chloroform. Drying (Na_2SO_4) and removal of chloroform gave alcohol 55 as the only product.

NMR (CDCl_3): δ 1.5-1.9 (m, 8H), δ 2.1 (s, 3H), δ 2.3 (s, 3H), δ 3.3 (m, 1H), δ 3.5 (m, 2H), δ 4.9 (s, 1H), δ 5.0 (t, 1H).

IR (CHCl_3): 3500 (br, O-H), 3000, 1450, 1020 cm^{-1} .

Notes:

1. Methanol or any other alcohol was not used deliberately to avoid loss of acetate by trans esterification.
2. Notice the appearance of signals for CH_2OH at δ 3.5 and disappearance of signals at δ 9.5 corresponding to aldehyde proton in ^1H NMR.

6.15 Pfizzner-Moffatt oxidation of 1-hydroxymethyl-38-

acetoxytropane:

Alcohol 55 (0.80 g, 0.0037 mol) was dissolved in 100 mL of ethyl acetate in a one necked 100 mL r.b. flask. Then 25 mL of dimethyl sulfoxide (DMSO), 2.25 g of (3 x 0.0037 mol) dicyclohexylcarbodiimide (DCC) and 0.4 mL of trifluoroacetic acid (1.5 x 0.0037 mol) were added. The mixture was stirred at 23°C for 48 hr. Ethyl acetate was evaporated on rotovap. Dimethyl sulfoxide was removed by vacuum distillation. To the residue 50 mL of water was added. Ether extraction of the aqueous layer gave dicyclohexyl urea after removal of ether. The water layer was basified with dilute NH_4OH (pH = 11) and extracted with chloroform. Removal of chloroform gave the aldehyde 56. Yield 0.3 g (40%).

NMR (CDCl_3): δ 1.9-2.3 (m, 11H), δ 2.3 (s, 3H), δ 3.3 (m, 1H), δ 4.9-5.3 (m, 1H), δ 9.6 (s, 1H).

IR (neat): 2900, 1750, 1350, 1250, 1070, 900, 720 cm^{-1} .

Notes:

1. The yields could be improved to 50% when 2,2-dichloro-propionic acid was used in place of trifluoroacetic acid.
2. The product could be purified by silica gel chromatography (acetone as eluent).

3. The reaction could be done even without using ethyl acetate as solvent.
4. Poor yields were obtained when anhydrous phosphoric acid was used as acid catalyst.
5. It is important that strictly anhydrous conditions be maintained for the success of the reaction.

6.16 Attempted Oxidation of 55 using dimethyl sulfoxide in presence of acetic anhydride. Preparation of 1-acetoxymethyl-3 β -acetoxo tropane (86):

To 2.00 g of alcohol (0.009 mol) 55 in 28 mL of dry DMSO, 4.8 mL (5.5 x 0.009 mol) of dry acetic anhydride were added and the mixture stirred at 23°C for 40 hr. At the end of this period, dimethyl sulfoxide and acetic anhydride were vacuum distilled. Water was added and the mixture made basic with dilute ammonium hydroxide (pH = 10). Extraction by chloroform, followed by drying (Na₂SO₄) and evaporating the solvent gave 1 g of diacetate 86 as the only product (42% yield).

NMR (CDCl₃): δ 1.5-1.8 (m, 8H), δ 1.9 (s, 3H), δ 2.0 (s, 3H), δ 2.3 (s, 3H), δ 3.2 (m, 1H), δ 4.5 (m, 1H).

6.17 Preparation of Sulfur Trioxide-Pyridine Complex⁵⁸:

In a 250 mL erlenmeyer flask, cooled in an ice bath 12.3 mL of sulfur trioxide (0.3 mol) were dissolved in 40 mL of carbon tetrachloride. To this stirred mixture, 24 mL of (0.3 mol) dry pyridine were added slowly. The crystalline product that separated out was collected and washed with 5 mL of ice cold water to remove traces of pyridine and sulfuric acid. The compound was dried under vacuum for 6 hrs. Yield 37 g (78%). m.p. 172-175°C.

Notes:

1. Sulfur trioxide-pyridine complex is commercially available.
2. Sulfur trioxide used was from a freshly opened bottle.

6.18 Oxidation of 1-Hydroxymethyl-3 β -acetoxytropine by Dimethyl Sulfoxide in Presence of Pyridine-Sulfur Trioxide Complex:

To a solution of 2.00 g (0.0094 mol) of alcohol 55 in 20 mL of dry DMSO and 14 mL of dry triethylamine (11 x 0.0094 mol) was added, a solution of 7.5 g of py-SO₃ (5 x 0.0094 mol) complex in 20 mL of dry DMSO (exothermic reaction). The mixture was stirred at 23°C for 12 hrs. After this period, triethyl amine was removed on rotovap and dimethyl sulfoxide by vacuum distillation.

To the residue, water was added and pH adjusted to 3 with diluted HCl. Extraction with ethyl acetate removed the side products. The aqueous layer was basified with dilute ammonium hydroxide (pH = 10) and extracted with chloroform. Evaporation of chloroform gave 0.7 g (35%) of aldehyde 56.

The ^1H NMR and IR spectra are superimposable with those of aldehyde 56 obtained from previous methods (cf section 6.13).

6.19 Preparation of n-Butyl triphenyl phosphonium bromide (98):

In a 100 mL r.b. flask equipped with a condenser, 10.0 g of triphenyl (0.038 mol) and 30 mL of 1-bromobutane (8 x 0.038 mol) were dissolved in 10 mL of dry benzene. The mixture was magnetically stirred and heated to reflux for 8 hr. A white solid precipitated out during that time. It was collected on a Buchner funnel. The solid was washed with 20 mL of dry benzene. It was then dried under vacuum for 6 hr to give 12 g (79%) of white powder. m.p. 233-235°C.

Mass spectrum (70 eV): m/e 319.1 ($\text{M}^+ - \text{HBr}$), 289.1 (base peak), 262.1, 199.1, 183.1, 152.1, 108.1, 91.4, 65.0, 57.0.

6.20 Wittig condensation of aldehyde 56, with
n-butyldiene triphenylphosphorane: Preparation of
1-Pentyl-3 β -hydroxytropene (14):

A 3-necked flask was equipped with a reflux condenser, a septum, addition funnel and nitrogen adapter, and a stirring bar. 5.45 g of n-butyl triphenylphosphonium bromide (1.6×0.008 mol) was dissolved in 25 mL dry tetrahydrofuran and ultimately 8 mL of a 1.6 M n-butyllithium solution in tetrahydrofuran (1.5×0.0085 mol) was added dropwise via syringe. A deep red color developed. The mixture was stirred at 20° for 30 min. It was refluxed for 45 min. Then 1.8 g of aldehyde 10 (0.0085 mol) in 25 mL dry tetrahydrofuran was added dropwise and the mixture refluxed for 40 hr. 10 mL of water added dropwise at 0°, followed by 10 mL of dil. hydrochloric acid and the mixture stirred for 30 min. The solvent was evaporated in a rotavapor and the pH was adjusted to 2 with dil. hydrochloric acid. 100 mL water was added and the water layer was extracted with 500 mL benzene followed by 500 mL ether to remove triphenylphosphine oxide. The aqueous layer was made alkaline (pH 10) with dil. ammonium hydroxide and extracted with ether. The ethereal layer was washed with water and saturated sodium chloride solution. Drying (Na_2SO_4), followed by evaporation in vacuo gave 1.78 g of a crude liquid. This was purified on a column of silica gel. Pure 1-(1-pentenyl)-3 β -hydroxytropene (14) was eluted with methanol and 1% ammonium hydroxide solution. Yield 0.9 g (50%). The TLC of the product 14 gave one spot: R_f (CHCl_3): 0.39.

NMR (CDCl_3): δ 0.9 (t, 3H, CH_3), δ 1.2-2.1 (m, 12H), δ 2.3 (s, 3H, N-CH_3), δ 3.3 (m, 1H), δ 3.8-4.1 (m, 1H), δ 4.3 (br s, 1H, exchangeable with D_2O), δ 5.3 (m, 2H, C=C).

IR (film): 3200 (br, OH), 2900, 1680 (m), 1400, 1200, 675 (cis alkene).

Mass spectrum: m/e 208.9 (M^+), 191.8, 179.8, 163.8, 149.8 (base peak), 135.8, 121.8, 109.8, 95.8, 80.8, 67.8, 54.8.

^{13}C NMR (CDCl_3): 132.98, 131.25, 66.0, 63.69, 60.33, 57.28, 42.58, 36.63, 34.65, 34.08, 33.71, 30.91, 27.55, 23.70, 18.8, 13.8.

Anal. Calcd. for $\text{C}_{13}\text{H}_{23}\text{NO}$: C, 74.64; H, 11.00; N, 6.69.

Found: C, 74.03; H, 10.24; N, 6.69.

Notes:

1. The deep red color of the ylide solution starts getting lighter as soon as aldehyde is added. The color change is almost like a titration. At the end of the addition, the solution turns light yellow.
2. Triphenyl phosphine oxide is extremely soluble in benzene. It is advantageous to extract the aqueous layer with as much benzene as possible. Since the amine is in the aqueous layer as an amine salt, which is insoluble in benzene, there is no danger of losing it to benzene or ether.
3. When chloroform was used in the final extraction of the free amine, unidentifiable phosphorus-containing side products

were obtained. However when ether was used, the crude product was essentially pure.

4. The reaction failed when dimethyl anion ($\text{CH}_2\text{SCH}_3/\text{CH}_3\text{SCH}_3$) generated from sodium hydride and DMSO was used as base instead of n-butyl lithium. The reason for this failure is not clear.

5. Attempted preparation of crystalline hydrochloride or hydrobromide of the amine 14 gave only oils.

6.21 Preparation of 1-(1-Pentenyl)-3-acetoxytropane (103):

Same procedure as in 6.20 was used except only 1.4 eq of Wittig salt and 1.3 eq of n-butyl lithium were used for 1 eq of aldehyde. The reaction was carried out at 23°C for 40 hr. The crude was purified by chromatography on silica gel (84% CHCl_3 + 15% MeOH + 1% NH_4OH) to give 103 as a light yellow colorless liquid. Yield 1.0 g (50%).

NMR (CDCl_3): δ 0.9 (t, 3H), δ 1.5-2.0 (m, 15H), δ 2.3 (s, 3H), δ 3.3 (m, 1H), δ 4.9 (m, 1H), and δ 5.5 (m, 2H).

Notes:

1. The amounts of Wittig salt and n-butyl lithium used are the minimum amounts required for the reaction to go to completion. Using lower amounts (1.3 eq Wittig salt and 1.2 eq of n-butyllithium), left some starting aldehyde unreacted.
2. Although the yields were only 50%, the crude product mixture did not show any unreacted aldehyde.

6.22 Deacetylation of 1-(1-pentenyl)-3 β -acetoxytropene

Acetate 103 (0.8 g, 0.0032 mol) was dissolved in 50 mL of anhydrous methanol and 4.5 g (10 x 0.003 mol) of anhydrous K_2CO_3 were added and the mixture stirred at 23°C for 10 hr. At the end of this period, the solids were filtered, methanol evaporated and pH adjusted to 2 by dilute hydrochloric acid. Then 25 mL of water was added and the aqueous layer extracted with ether. The water layer was basified with diluted NH_4OH and extracted with chloroform. Evaporation of chloroform gave a crude oil which was purified by silica gel chromatography (methanol + 1% NH_4OH).

The desired compound was obtained 0.5 g (75%) as a light yellow oil.

1H NMR ($CDCl_3$): δ 0.9 (t, 3H), δ 1.2-2.1 (m, 12H), δ 2.3 (s, 3H), δ 3.3 (m, 1H), δ 3.8-4.1 (m, 1H), δ 4.3 (br s, 1H,

exchangeable with D_2O), δ 5.3 (m, 2H).

IR (neat): 3200 (br, OH), 2900, 1680 (m), 1400, 1200, 600.

Notes:

The 1H NMR and IR spectra of this compound obtained from this two-step procedure were superimposable to the spectra obtained from the one-step procedure.

6.23 Addition of n-Butyllithium to 3 β -Acetoxytropane-1-aldehyde.

In a two-necked 100 mL r.b. flask equipped with a condenser, septum, and magnetic stirrer, 1.2 g (0.0056 mol) of aldehyde 56 in 50 mL of ether was dissolved. Then 21.3 mL (6 x 0.0056 mol) of 1.6 M solution of n-butyl lithium in hexane added via syringe. The mixture was heated to reflux under N_2 for 12 hr. Then it was cooled, poured onto ice and made acidic (pH = 2) with diluted HCl. The aqueous layer was extracted with ether (2 x 50 mL) to remove non-nitrogenous side products. The aqueous layer was made alkaline with dilute ammonium hydroxide. It was then extracted with chloroform and chloroform evaporated. The residue was dried under vacuum to give 0.6 g (47%) of crude diol 118.

1H NMR ($CDCl_3$): δ 0.9 (t, 3H), δ 2.3 (s, 3H), δ 1.5-1.8 (m, 14H), δ 3.3 (m, 1H), δ 3.9-4.2 (m, 2H).

6.24 Preparation of Potassium Azo Dicarboxylate:

This compound was prepared according to the procedure by Curry.⁸⁸

6.25 Attempted Diimide Reduction of Alkene 14:

In a three necked 100 mL r.b. flask equipped with a condenser, N₂ adapter, mechanical stirrer, 2.3 g of potassium azocarboxylate (3 x 0.004 mol) were suspended in 10 mL of absolute methanol. To this slurry, 0.8 g of alkene 14 in 10 mL of absolute methanol were added. Then 1.6 mL of glacial acetic acid was added dropwise. The mixture stirred at r.t. for 14 hrs after which 10 mL of acetic acid and 30 mL of water were added. The mixture was poured into diluted NH₄OH (pH = 11). Extraction with ether, followed by drying (Na₂SO₄) and evaporation the solvent left 0.75 g (90% recovery) of unreacted starting alkene 14.

6.26 Preparation of (+) 1-n-amyl-3 β -tropanol (15):

1-pentenyl-3 β -tropanol (14) (0.75 g, 0.0036 mol) was dissolved in 50 mL of absolute methanol and 1 g of Raney nickel (W-2) was added. The mixture was hydrogenated at 2 atm for 3 hrs. Filtration of the catalyst followed by evaporation of the solvent left 0.7 g (93%) of (+) 1-n-amyl-3 β -tropanol (15) as a

light yellow oil.

^1H NMR (CDCl_3): δ 0.9 (t, 3H), δ 1.5–2.1 (m, 19H), δ 2.5 (s, 3H), δ 3.4–3.6 (m, 2H), δ 6.5 (br s, 1H, exchangeable with D_2O).

Mass spectrum (20 eV): m/e 211.2 (M^+), 194.2, 182.1, 166.1, 152.1, 138.1, 126.1, 111.1, 96.1 (base peak), 82.0, 67.0.

6.27 Preparation of (+) 1-n-amy-3 β -tropanol hydrochloride (122):

Through the solution of amine (15) in 20 mL of dry chloroform, dry hydrogen chloride gas was bubbled through until the solution was acidic. Evaporation of the solvent left a foam which turned into a fine powder. m.p. 139–142°C.

^1H NMR (CDCl_3): δ 0.9 (t, 3H), δ 1.4 (m, 11H), δ 2.1–2.3 (m, 8H), δ 2.9 (d, 3H), δ 3.9 (br m, 1H).

Anal. Calcd. for $\text{C}_{13}\text{H}_{26}\text{ClNO}$: C, 63.03; H, 10.50, N, 5.60.

Found: C, 62.20; H, 10.48; N, 5.53.

6.28 Preparation of 4-Trimethylsilyl but-3yn-1-ol (143):

In a three-necked 100 mL r.b. flask, equipped with a condenser, N_2 adapter, low-temperature thermometer, and a septum, 45 mL (2 x 0.045 mol) of ethyl magnesium bromide (2 M solution in THF) in 15 mL of dry tetrahydrofuran was cooled to -10°C with ice-salt bath. 3 g (0.043 mol) of 3-butyne-1-ol was added

dropwise via syringe. After stirring for 1.5 hr below 0°C , the cooling bath was removed and the mixture was heated to 50°C for 1 hr. It was then stirred at 23°C for 12 hr. At the end of this period, 80 mL of saturated ammonium chloride solution was added. Extraction with ether, followed by evaporation of ether left an oily residue, which was stirred with 10 mL of 95% ethanol and 3 drops of conc. hydrochloric acid for 1 hr. The solution was then extracted with ether, washed with 10% sodium carbonate solution, dried (Na_2SO_4) and evaporated. The resulting oil was distilled under vacuum (water aspirator). b.p. $87-89^{\circ}\text{C}$. Yield 5.4 g (91%). Clean, colorless oil.

^1H NMR (CDCl_3): δ 0.9 (s, 9H), δ 2.3 (t, 2H), δ 3.5 (q, 2H), δ 4.3 (t, 1H).

IR (neat): 3400, 3000, 2100, 1410, 1250, 1170, 900, 850, 750 cm^{-1} .

Notes:

1. When Jones procedure¹⁰² was followed the yields dropped down to 50%.
2. Commercially available (Aldrich) ethylmagnesium bromide tends to precipitate out from the tetrahydrofuran solution in the bottle. More tetrahydrofuran was added to the bottle to dissolve the reagent before transferring it to the reaction pot.

3. When allylmagnesium chloride was used instead of ethylmagnesium bromide, the yields dropped down to 84%.

6.29 Tosylation of 4-trimethylsilyl but-3yn-1ol:

Freshly-distilled 4-trimethylsilyl but-3yn-1ol (143), (5.0 g, 0.035 moles) was dissolved in 50 mL of dry, freshly distilled pyridine in a 100 mL one-necked r.b. flask. The mixture was stirred and cooled below 0°C in ice-salt bath. 7.4 g (0.039 mol) of p-toluene sulfonyl chloride was added in one portion and the mixture stirred for 2 hr at 0°C. It was then poured onto 50 mL of cold water. Extraction with ether followed by washing with 10% sodium carbonate solution and evaporation of ether left crude tosylate (146) as a colorless oil. It was used in the next step without any purification. Yield 10.1 g (98%).

$^1\text{H NMR}$ (CDCl_3): δ 0.1 (s, 9H), δ 2.3-2.5 (m, 5H), δ 4.0 (t, 2H), δ 7.2 (d, 2H), δ 7.8 (d, 2H).

6.30 Displacement of Tosylate 146 by Iodide:

Tosylate 146 (18.6 g, 0.063 mol) and 47 g (5 x 0.063 mol) were dissolved in 500 mL of dry acetone. The mixture was brought to reflux and kept there for 48 hr. It was then cooled to 23°C, acetone evaporated and 300 mL of water was added. Extraction with methylene chloride followed by drying (CaCl_2) and

evaporation gave a crude oil which was distilled under vacuum

(b.p. 73°C at 0.04 mm) to give 14.2 g (90%) of iodide 144.

$^1\text{H NMR}$ (CDCl_3): δ 0.1 (s, 9H), δ 2.5 (t, 2H), δ 3.2 (t, 2H).

IR (neat): 3000, 2200, 1410, 1250, 1170, 900, 850, 750 cm^{-1} .

Notes:

1. The displacement of the tosylate by iodide occurs very slowly at room temperature.

6.31 Preparation of Triphenyl (1-Trimethyl silyl but-3-ynyl) phosphonium iodide (138):

Iodide 138 (7 g, 0.028 mol) in 50 mL of dry benzene was mixed with 7.25 g (0.028 mol) of triphenylphosphine and the mixture refluxed for 68 hrs. A heavy oily layer separated out. The mixture was cooled, the layers separated and the bottom layer extracted with benzene (2 x 50 mL) to remove unreacted starting materials. The bottom layer was dried under vacuum to remove any traces of benzene. Addition of anhydrous ether resulted in a white foam, which was dried on a freeze dryer. It was crushed to a fine powder. m.p. 132-133°C. Yield 13.9 g (95%).

6.32 Preparation of 3-Butynyl tosylate:

A solution of 45.6 g (1.2 x 0.2 mol) of p-toluene sulfonyl chloride in 31 mL (1.3 x 0.1 mol) of 2,6-lutidine was placed in a 3-necked 250 mL r.b. flask equipped with a low-temperature thermometer and N₂ adapter. The mixture was cooled in an ice bath. 14 g (0.2 mol) of 3-butyne-1-ol was added dropwise. The ice bath was removed and the mixture stirred magnetically for 18 hr. The mixture was then poured into 100 mL water. It was then extracted with 300 mL of ether. The ether layer was then washed with 10% sulfuric acid (to remove traces of lutidine), followed by 10% sodium bicarbonate, water and saturated salt solution. Evaporative removal of ether left 38.3 g (81%) of tosylate 158, which was purified by silica gel chromatography (80% pet. ether + 20% ethyl acetate).

¹H NMR (CDCl₃): δ 2.0 (t, 1H), δ 2.5 (m, 5H), δ 4.2 (t, 2H), δ 7.4 (d, 2H), δ 7.9 (d, 2H).

For attempted displacement of tosylate 158 by halide ions, see Table II.

6.33 Preparation of 1-Bromo-3-butyne (152):

In a 3-necked 250 mL r.b. flask equipped with a mechanical stirrer, low-temperature thermometer, addition funnel with N₂ adapter, 35 g (0.4993 mol) of but-3yn-1-ol and 4 mL (0.49 mol) of dry pyridine were stirred. The temperature was maintained

Table II

Attempted displacement of tosylate 153 by iodide, bromide
and chloride

Reactant	Reagents	Conditions	Result
$\text{H-C}\equiv\text{C-CH}_2\text{CH}_2\text{OTS}$	5 eq NaI	acetone, 23°C, 18 hr aqueous-work up	nothing recovered
$\text{H-C}\equiv\text{C-CH}_2\text{CH}_2\text{OTS}$	5 eq NaI	acetone, 23°C, 18 hr nonaqueous work-up	nothing recovered
$\text{H-C}\equiv\text{C-CH}_2\text{CH}_2\text{OTS}$	5 eq LiBr	0°C → 23°C, acetone, 12 hr	nothing recovered
$\text{H-C}\equiv\text{C-CH}_2\text{CH}_2\text{OTS}$	5 eq LiBr	23°C, DMF, 12 hr	nothing recovered
$\text{H-C}\equiv\text{C-CH}_2\text{CH}_2\text{OTS}$	LiCl	DMF-ether stirred for 18 hr followed by addition of PPh_3	nothing recovered
$\text{H-C}\equiv\text{C-CH}_2\text{CH}_2\text{OTS}$	5 eq LiCl	DMF, 23°C	nothing recovered

between -20°C and -10°C with acetone/liq. N_2 bath. A solution of 16.6 mL ($1/3 \times 0.49$ mol) of PBr_3 in 20 mL of anhydrous ether added dropwise. The temperature was maintained between -20°C and -15°C . After the addition was complete, the mixture was stirred at -20°C for 30 min. The product was distilled from reaction pot "as is" at 1 atm.

Fraction 1	b.p. $75-90^{\circ}\text{C}$	9.85 g
------------	------------------------------	--------

Fraction 2	b.p. $95-104^{\circ}\text{C}$	8.56 g
------------	-------------------------------	--------

Fraction 1 was found to be 1-bromo-3-butyne (152). Yield 15%.

NMR (CDCl_3): δ 2.1 (t, 1H), δ 2.9 (m, 2H), δ 3.5 (t, 2H).

IR (neat): 3300, 3000, 1400, 1260, 1210, 900, 740 cm^{-1} .

Fraction 2 was found to be a mixture of undesired olefinic impurities which were not identified.

6.34 Attempted improvement of yields of PBr_3 reaction: use of LiBr as co-reactant:

In a 3-necked 250 mL r.b. flask equipped with a mechanical stirrer, low-temperature thermometer and N_2 adapter, a mixture of 15 g (0.21 mol) of 3-butyne-1-ol, 20 mL of anhydrous ether, 18 mL (1.5×0.21 mol) of 2,6-lutidine and 36.8 g (2×0.21 mol) of anhydrous lithium bromide was cooled to -40°C . Then 10 mL (0.5 x 0.21 mol) of phosphorous tribromide was added dropwise. The mixture was warmed to 0°C , stirred at 23°C for 2 hr and 0°C

after which 15 mL of 2,6-lutidine were added. The mixture was poured onto water, layers separated. The organic layer was dried over 3 Å molecular sieves and distilled at 1 atm. The fraction boiling at 75-90°C was collected. Yield 3.4 g (10%).

^1H NMR (CDCl_3): δ 2.1 (t, 1H), δ 2.9 (m, 2H), δ 3.5 (t, 2H).

6.35 Preparation of 1-Bromo-3-butyne using Carbon Tetrabromide and Triphenylphosphine:

To a magnetically stirred solution of 5 g (0.071 mol) of 3-butyne-1-ol and 26 g (0.071 mol) of carbon tetrabromide in 50 mL of dry methylene chloride was added 20.5 g (1.1 x 0.071 mol) of PPh_3 in small portions at 23°C. The reaction mixture was stirred at 23°C for 24 hr. The product was distilled from the reaction pot.

Fraction 1 40-60°C (mainly methylene chloride)

Fraction 2 65-85°C (fairly pure)

Fraction 3 90-110°C (impure, contains olefinic compounds)

Fraction 2 was redistilled to give 1.5 g (15%) of

1-bromo-3-butyne. b.p. 75-90°C at 1 atm.

^1H NMR (CDCl_3): δ 2.0 (t, 1H), δ 2.9 (m, 2H), δ 3.5 (t, 2H).

6.36 Attempted Preparation of 1-Bromo-3-butyne by utilizing N-bromosuccinimide/triphenyl phosphine as brominating reagents:

In a 3-necked 100-mL r.b. flask equipped with a magnetic stirrer, addition funnel and condenser, 7 g (1.1×0.357 mol) of N-bromosuccinimide in 40 mL of dry tetrahydrofuran was stirred under nitrogen. A solution of 10.25 g (1.1×0.357 mol) of triphenylphosphine in 20 mL of anhydrous ether added dropwise. An exothermic reaction occurred with separation of a solid. To this suspension, a solution of 2.5 g (0.3566 mol) of 3-butyne-1-ol in 10 mL of anhydrous ether was added. The mixture was stirred at 23°C for 6 hr. The compound was distilled at 1 atm., b.p. $75-88^\circ\text{C}$. Yield 2 g.

^1H NMR indicates this compound to be a mixture of olefins. There was no evidence for acetylinic protons. The structure of the olefin was not determined.

NMR (CDCl_3): δ 1.9 (m), δ 3.3 (m), δ 5.2-6.9 (m).

6.37 Preparation of triphenyl(but-3-ynyl) phosphonium bromide 149:

In a one-necked 250 mL r.b. flask equipped with a magnetic stirrer and condenser, 9.85 g (0.074 mol) of 1-bromo-3-butyne and 29.4 g (1.5×0.074 mol) of PPh_3 were dissolved in 100 mL of dry benzene. The mixture was heated to reflux for 24 hr. Two layers were formed. The top layer was decanted. The heavier

bottom layer was extracted with 100 mL of benzene to remove any unreacted starting material. The bottom layer was kept under vacuum. A yellow solid 4.5 g (15%) was obtained.

^1H NMR (CDCl_3): δ 2.0 (m, 1H), δ 2.8-2.9 (m, 4H), δ 7.9-8.0 (m, 15H).

6.38 Attempted preparation of triphenyl(but-3-ynyl) phosphonium tosylate:

In a 250 mL one-necked r.b. flask equipped with a magnetic stirrer and condenser 5 g (0.026 mol) of but-3-ynyl tosylate and 21 g (3 x 0.026 mol) of triphenyl phosphine in 100 mL of benzene were dissolved. The mixture was stirred at 23°C for 5 hr and later on heated to reflux for 48 hr. Later it was cooled to 23°C, solvent evaporated. An oil was obtained which was repeatedly washed with anhydrous ether (500 mL) to give 2.8 g of a solid which was identified as the phenyl phosphonine oxide based on its melting point, ^1H NMR spectrum and mass spectrum. m.p. 153-155°C.

NMR (CDCl_3): δ 7.2-7.9 (m).

Mass spectrum: m/e 277.69 (M^+), 262.1, 201.1, 183.0, 170.0, 152.1, 128.0, 95.0, 77.0, 55.8.

The molecular ion 277.69 correspond to triphenyl phosphine oxide ($\text{PPh}_3 \rightarrow \text{O}$, mol. wt. = 278).

Notes:

1. Both the ^1H NMR and mass spectrum indicate that the only isolated product is $\text{PPh}_3 \rightarrow 0$.
2. At no stage during the reaction, there was a separation of two layers. This indicates that the desired phosphonium salt is not formed. One would expect the phosphonium salt to be insoluble in benzene.

6.39 Attempted Wittig condensation of neopentyl aldehyde 56 with triphenyl (1-trimethylsilyl but-3-ynyl) phosphonium iodide (138):

a. Potassium tert-butoxide:

In a one-necked 50 mL r.b. flask equipped with a side-arm with septum, 4.5 g (1.3×0.007 mol) of triphenyl (1-trimethyl silyl but-3-ynyl) phosphonium iodide (138) was suspended in 30 mL of dry tetrahydrofuran and cooled to 0°C with an ice bath. To this magnetically stirred suspension, a solution of 1 g (1.3×0.07 mol) of potassium butoxide in 10 mL of dry tetrahydrofuran added via syringe. A brick red color developed very slowly. The mixture was stirred at 0°C for 1 hr and at 23°C for 2 hrs. To this ylide solution, 1.5 g (0.007 mol) of aldehyde 56 in 10 mL of dry tetrahydrofuran was added via syringe. The mixture stirred at 23°C for 80 hr. After this period, 20 mL of

water was added. Tetrahydrofuran was removed by evaporation. Addition of dilute hydrochloric acid and extraction of the resulting acidic ($\text{pH} = 3$) solution with benzene was done to remove non-nitrogenous side products. The aqueous layer was adjusted to $\text{pH} 10$ by dilute ammonium hydroxide and extracted three times with ether. The combined ether layers were dried (Na_2SO_4) and evaporated to give 1.2 g of unreacted aldehyde 56 (80% recovery).

Notes:

1. The brick red color of ylide did not change even after 80 hr .

b. NaOH as base:

In a one-necked 50 mL r.b. flask equipped with a side arm for septum, 0.37 g (1.3×0.007 mol) of 59% sodium hydride (suspension in mineral oil) was taken. Dry pentane was added and after stirring for a few min., pentane was removed. 30 mL of dry tetrahydrofuran was added. To this 4.5 g of phosphonium salt 138 in 30 mL of dry tetrahydrofuran added dropwise at 0°C . To this suspension, the aldehyde 56 in 10 mL of tetrahydrofuran was added via a syringe. The mixture was allowed to warm to 23°C and stirred for 60 hr. The reaction was worked up in the same way

as the previous experiment. 1.2 g (80% recovery) of unreacted aldehyde 56 was recovered from the reaction.

c. n-butyllithium as base:

In a two-necked 250 mL r.b. flask with a nitrogen adapter and septum, 10.1 g (2.2×0.0095 mol) of Wittig salt 138 in 50 mL of dry tetrahydrofuran was taken. The mixture was cooled to -78°C using acetone/liq. N_2 bath. Then 12.4 mL (2.1×0.0095 mol) of 1.6 M n-butyl lithium added dropwise via a syringe. The mixture was warmed to -20°C and stirred at -20°C for 5 hr. Then 2 g (0.0095 mol) of aldehyde 56 in 20 mL of dry tetrahydrofuran added via syringe. The mixture was stirred at -15°C for 40 hr. It was then warmed to 23°C and stirred for another 2 hr. The reaction was worked up as in the previous experiment. 1.5 g of unreacted aldehyde 56 (75% recovery) was obtained from the reaction.

Notes:

1. The deep red color of ylide did not change throughout the length of the reaction.
2. The color disappears only after addition of water. It indicates that the ylide was formed but it did not add to the aldehyde.

3. If the ylide did not form, butyl lithium would have added to the aldehyde. But the only product isolated was the unreacted aldehyde.

6.40 Wittig reaction of triphenyl (3-butynylidene) phosphorane (150) with 3 β -acetoxytropene-1-aldehyde (56):

In a 3-necked 250 mL r.b. flask equipped with magnetic stirrer, addition funnel, reflux condenser with N₂ adapter, 4.32 g (1.3 x 0.0085 mol) of triphenyl (3-butynyl) phosphonium bromide in 75 mL of dry tetrahydrofuran was suspended and cooled to 0°C. Then 6.3 mL (1.18 x 0.0085 mol) of 1.6 M n-BuLi added dropwise via a syringe. Mixture stirred at 0°C for 2 hr. It was warmed up to 23°C and stirred for another 1 hr. A solution of 1.8 g (0.008 mol) of aldehyde in 25 mL of dry tetrahydrofuran added dropwise and the mixture stirred at 23°C for 24 hr. and worked up to give 0.7 g (33%) of a light yellow liquid. The spectral data are in agreement with the structure of 1-(1-penten-4-ynyl)-3 β -acetoxytropene (151).

NMR (CDCl₃): δ 1.8-2.0 (m, 11H), δ 2.3 (s, 3H).

IR (film): 3300 (H-C $\equiv$ C), 3000, 2250 (C $\equiv$ C), 1720 (O-C(=O)-CH₃),
1250, 1020, 900, 750 cm⁻¹.

Mass spectrum: m/e 247 (M⁺).

6.41 Aldehyde homologation - attempted Wittig reaction of
neopentyl aldehyde 56 with methoxymethylene
triphenylphosphorane:

a. Dimsylanion $\text{(CH}_2\text{S}^-\text{CH}_3\text{)}$ as base:

In a 3-necked 100 mL r.b. flask equipped with a reflux condenser, N₂ adapter and thermometer, a magnetically stirred solution of 0.2 g (0.005 mol) of sodium hydride (59% suspension in mineral oil) was washed with dry pentane. Then 5 mL of dry dimethylsulfoxide (DMSO) was added and the mixture was heated to 55°C and kept there under N₂ for 40 min. There was evolution of gas (H₂) and the solution turned green. To this mixture, a solution of 1.72 g (0.005 mol) of methoxymethyl triphenyl phosphonium chloride in 10 mL of dimethylsulfoxide was added dropwise at 55°C. The mixture was stirred at that temperature for 30 min. and cooled to 23°C. To this 1 g (0.0047 mol) of aldehyde 56 in 10 mL of dimethylsulfoxide was added dropwise and the mixture stirred at 23°C for 24 hr. The solvent was removed by vacuum distillation. To the residue 50 mL of water added. The pH was brought to 2 with dilute hydrochloric acid. The aqueous layer was extracted with benzene (2 x 50 mL) followed by ether (2 x 50 mL). The aqueous layer made alkaline (pH = 10) with dilute ammonium hydroxide and extracted with ether. Evaporation of ether gave 0.8 g (80% recovery) of unreacted aldehyde 56.

b. n-Butyl lithium as base - reaction at 23°C:

In a 3-necked 100 mL r.b. flask equipped with a reflux condenser, addition funnel and septum, 2.1 g (1.3×0.0047 mol) of methoxy methyl triphenyl-phosphonium chloride was suspended in 30 mL of dry THF. Then 3.5 mL (1.2×0.0047 mol) of 1.6 M n-BuLi was added via syringe at 23°C. The mixture was stirred at 23°C for 30 min. and heated to reflux for 1 hr. It was cooled to 23°C. Then 1 g (0.0047 mol) of aldehyde 56 in 10 mL of dry tetrahydrofuran added and the solution stirred at 23°C for 48 hr. At the end of this period, 20 mL of water was added. Tetrahydrofuran was evaporated. The solution was made acidic (pH = 2) with diluted hydrochloric acid. The aqueous layer was extracted with benzene (2 x 50 mL) followed by ether (2 x 50 mL). The aqueous layer was made alkaline (pH = 10) with dilute ammonium hydroxide solution. Extraction with ether and removal of ether gave 0.85 g (85% recovery) of unreacted aldehyde 56.

c. n-Butyl lithium as the base - reaction done at reflux:

Same procedure as above was followed except the reaction mixture was heated to reflux. Work-up as above yielded unreacted aldehyde 56 as the only product.

6.42 Successful homologation of aldehyde 56 to1-(3 β -acetoxytropene)acetaldehyde Wittig reaction using2 eq of potassium butoxide as base:

In a 3-necked r.b. flask equipped with a reflux condenser, addition funnel, septum and a magnetic stirrer, 5.1 gm (2.1 x 0.007 mol) of methoxy methyl phosphonium chloride was suspended in 50 mL of dry tetrahydrofuran. A solution of 1.67 g (2.1 x 0.007 mol) of KOtBu in 20 mL of dry tetrahydrofuran was added dropwise. The mixture was stirred at 23°C for 1 hr. A deep red color developed. Then 1.5 g (0.007 mol) of aldehyde 56 in 10 mL of tetrahydrofuran was added dropwise. The color changed from deep red to light yellow. The mixture was stirred at 23°C for 72 hrs. After that time, 20 mL of water was added and tetrahydrofuran evaporated. Work-up as in the previous experiment gave 1.1 g of crude mixture of gemoeetric isomers of 1-(2-methoxyvinyl)-3 β -acetoxytropene.

$^1\text{H NMR}$ (CDCl_3): δ 1.6-1.8 (m, 8H), δ 2.0 (s, 3H), δ 2.3 and δ 2.35 (s, 3H), δ 3.5 and δ 3.6 (s, 3H), δ 3.3 (m, 1H), δ 4.3 and 5.9 (d, 2H as J = 8 Hz), δ 4.7 and δ 6.4 (d, 2H, trans J = 15 Hz).

The crude mixture of enol ethers was used for hydrolysis without any purification. It was dissolved in a solution of 20 mL of ether + 5 mL of 70% perchloric acid and stirred at 23°C for 10 hrs. It was poured onto crushed ice and the resulting solution made alkaline (pH = 10) with dilute ammonium hydroxide. Extraction with ethyl acetate and removal of solvent left 0.14 g

(10% yield) of crude 1-(3 β -hydroxytropanyl)acetaldehyde (175).

^1H NMR (CDCl_3): δ 1.2-1.8 (m, 8H), δ 2.3 (s, 3H), δ 2.5 (d, 2H), δ 3.3 (m, 1H). δ 3.9 (m, 1H), and δ 9.8 (t, 1H).

Notes:

1. No effort was made to separate the olefins in the Wittig condensation. The crude mixture of trans and cis olefins was used in the hydrolysis since both of them yield the same homologated aldehyde.

6.43 Cleavage of enol ethers 173 and 174 with boron tribromide:

In a 250 mL 3-necked r.b. flask equipped with a mechanical stirrer, condenser and addition funnel, 1 g of mixture of enol ethers 173 and 174 (0.004 mol) was dissolved in 100 mL of methylene chloride. To this 22 mL of 1 M solution of boron tribromide (5.25×0.004 mol) in methylene chloride was added dropwise, at 0°C . The solution was then warmed up to 23°C and stirred for 24 hr at 23°C . It was then poured onto crushed ice and made alkaline ($\text{pH} = 10$) with dilute ammonium hydroxide solution. Extraction with chloroform and evaporation of solvent gave 0.18 g (20%) of crude 1-(3 β -acetoxytropanyl)-acetaldehyde (164):

Table III

Attempted N-demethylations

<u>Reactant</u>	<u>Reagents</u>	<u>Conditions</u>	<u>Result</u>
amine <u>103</u>	2,2,2-trichloroethyl- chloro formate	benzene, reflux for 18 hr	no reaction
amine <u>103</u>	2,2,2-trichloroethyl chloroformate + dimethyl amino pyridine (DMAP)	benzene, reflux for 18 hr	no reaction
amine <u>103</u>	vinyl chloroformate	ether, reflux for 24 hr	no reaction
amine <u>103</u>	vinyl chloroformate + BaO	ether, reflux for 24 hr	no reaction
amine <u>103</u>	vinyl chloroformate + proton sponge	methylene chloride 23°C, 24 hr	no reaction
amine <u>103</u>	Pt, air	24 hr, 23°C	no reaction

6.45 Attempted Preparation of 1-chloromethyl-3 β -acetoxytropine

(177):

In a 100 mL r.b. flask equipped with a reflux condenser and nitrogen in-out let, 1 g of amino alcohol 55 (0.005 mol) was dissolved in 30 mL of distilled thionylchloride. The mixture was stirred under nitrogen at 23°C for 10 hr. It was heated to reflux for 1 1/2 hr and then cooled to 23°C. The solvent was evaporated. To the residue 10% sodium carbonate solution was added until pH adjusted to 10. Extraction with chloroform, followed by drying (Na_2SO_4) and evaporation of the solvent gave 1 g of unreacted 1-hydroxymethyl-3 β -acetoxytropine (55).

Notes:

1. The lack of reactivity can be attributed to the neopentyllic nature of the hydroxyl group.
2. The same reaction was repeated with the hydrochloride salt of amino alcohol 55. Refluxing this salt with thionyl chloride for 15 hr and working up as above, resulted in total recovery of starting material.
3. Addition of cat amount of dimethylamino pyridine (DMAP) had no effect on the reaction.

6.46 1-Methanesulfonyloxymethyl-3 β -acetoxytropane (180):

In a 100 mL one-neck r.b. flask, equipped with a magnetic stirrer, 4.88 g of 1-hydroxymethyl-3 β -acetoxytropane (55) (0.023 mol), 1.9 mL of freshly distilled methane sulfonyl chloride (1.1 x 0.023 mol), 2.7 mL (0.023 mol) of 2,6-lutidine were dissolved in 50 mL of dry chloroform. The mixture was stirred at 20°C for 24 hr. It was poured onto water. The solution was made alkaline (pH = 10) with dilute ammonium hydroxide solution. The chloroform layer was washed with water and brine. It was dried (Na₂SO₄), filtered and solvent evaporated. Trituration with petroleum ether and carbon tetrachloride resulted in precipitation of 180 as a solid. Yield 3.5 g (53%).

m.p. 89°C-91°C.

NMR (CDCl₃): δ 1.5-2 (m, 8H), δ 2.3 (s, 3H), δ 3.4 (m, 1H), δ 4.2 (s, 2H), δ 3.1 (s, 3H), δ 2.0 (s, 3H), δ 5.2 (q, 1H).

IR (KBr): 3000, 1720, 1360, 1170 cm⁻¹.

Anal. Calcd. for C₁₂H₂₁NO₅S: C, 49.48; H, 7.25; N, 4.81; S, 10.99.

Found: C, 49.52; H, 7.33; N, 4.80; S, 10.74.

Notes:

1. The tosylate was prepared by essentially following the same procedure. However the yields were much lower and reaction was very slow.

2. Although the isolated yields of the pure compound were only 53%, there was no evidence for any unreacted starting material in the crude product (absence of OH at 3400 cm^{-1} in IR).

3. It is essential that 2,6-lutidine be used as a proton trap. In the absence of 2,6-lutidine, substantial amounts of unreacted starting material were seen in the crude product mixture.

6.47 Conversion of acetoxy mesylate 180 into 1-methane sulfonyloxymethyl-3 β -tropanol (181):

In a one-necked 250 mL r.b. flask, equipped with a reflux condenser and nitrogen adapter, 0.52 g of mesylate 180 (0.002 mol) and 0.24 g of sodium methoxide ($2.5 \times 0.002\text{ mol}$) were dissolved in 100 mL of absolute methanol. The mixture was stirred at 23°C for 6 hrs and brought to reflux for 1 hr and cooled. Methanol was evaporated and the residue was poured into ice-water. Extraction with ether followed by drying (Na_2SO_4) and evaporation of ether gave 0.3 g (76%) of crude deacetylated product.

NMR (CDCl_3): δ 1.3-1.8 (m, 8H), δ 2.3 (s, 3H), δ 3.1 (s, 3H), δ 3.3 (m, 1H), δ 4.2 (m, 3H).

Notes:

1. In the NMR, there is no evidence for OCH_3 group. The signals for mesylate (δ 4.2, δ 3.1) were still present. This lead us to conclude that the mesylate was not displaced.
2. If more stringent conditions are used (5 eq. of sodium methoxide, reflux for 48 hrs), the methoxide ion seems to attack the sulfur of mesylate giving the diol (which is water soluble).
3. Using potassium carbonate/methanol instead of sodium methoxide also resulted in the isolation of 1-methane sulfonyloxymethyl-3 β -tropanol (181).

6.48 Hydrogenolysis of mesylate 180 into 1-methyl-3 β -tropanol
(183):

A solution of 0.5 g of mesylate 180 (0.0018 mol) in 50 mL of anhydrous ether was added to 0.2 g (3 x 0.0018 mol) of lithium alanate at 0°C in a 100 mL r.b. flask, equipped with a condenser. The mixture was magnetically stirred and warmed to 23°C, and then heated to reflux for 3 hr. It was cooled to 23°C and poured onto ice-water. Dilute hydrochloric acid was added to adjust the pH to 3, organic and aqueous layers separated. Aqueous layer was made alkaline (pH = 10) by dilute ammonium hydroxide and extracted with ether. Washing with water followed by saturated

salt solution, drying (Na_2SO_4) and evaporating left 0.2 g (74%) of an oil which proved by ^1H NMR to be 1-methyl-3 β -tropanol (183).

NMR (CDCl_3): δ 1.1 (s, 3H), δ 1.5-2 (m, 8H), δ 2.3 (s, 3H), δ 3.3 (m, 1H), δ 3.9 (m, 1H).

Notes:

1. Notice the appearance of signal due to bridgehead methyl group at δ 1.1 (s, 3H). Also the signals due to the mesylate have disappeared. (δ 4.2, δ 3.1).

6.49 Attempts to couple 1-mesyloxymethyl-3 β -acetoxytropine (186) with allyl magnesium bromide:

In a 3 necked 250 mL r.b. flask equipped with low-temperature thermometer, a reflux condenser, addition funnel, magnetic stirrer, 1.89 g (0.0076 mol) of mesylate 180 were dissolved in 50 mL of dry tetrahydrofuran. 0.72 g (1/2 x 0.0076 mol) of copper(I) iodide were added. At -30°C , 38 mL of 1 M solution of allyl magnesium bromide (9.5 x 0.0076 mol) added dropwise and the mixture was stirred at -30°C for 1 hr and then at 23°C for 16 hr. Work up by adding water and extraction with chloroform gave a residue, 0.49 g which gave spectral data expected for allyl methyl sulfone.

NMR (CDCl_3): δ 2.9 (s, 3H), δ 3.8 (d, 2H), δ 5.3-5.8 (m,

3H).

IR (film): 1640 cm^{-1} (C=C), 1350 cm^{-1} (v, SO_2), 1120 cm^{-1} (v, SO_2).

Notes:

1. The ^1H NMR was compared with that of an authentic ^1H NMR of allyl phenyl sulfone. This comparison proved that the compound in hand was allyl methyl sulfone.

6.50 Attempted coupling of mesylate 180 with ethyl magnesium bromide:

Similar procedure as in section 6.49 was used except ethyl magnesium bromide was used in place of allyl magnesium bromide. Work up by similar procedure gave a mixture of compounds which appeared to be ethyl methyl sulfone and methyl diethyl carbinol.

NMR (CDCl_3): δ 1.2-1.5 (m), δ 2.3 (m), δ 2.8 (s).

6.51 Attempted coupling of mesylate 180 with ethyl magnesium bromide using Li_2CuCl_4 as catalyst:

Same procedure as above was obtained except 0.5 mL of 1 M solution of Li_2CuCl_4 in dry THF was used as catalyst, instead of CuI . Work up as above gave similar results.

Notes:

1. The procedure of Kochi¹³³ was used for the preparation of

6.52 Attempted coupling of mesylate 180 with di n-butyl copper lithium:

In a 100 mL 3-necked flask equipped with a N₂ adapter and two septums, 1.62 g of CuI (2.5 x 0.0035 mol) were taken in 25 mL of distilled THF. The suspension was cooled to -40°C with ethyl acetate/liq. N₂ bath. To this magnetically stirred suspension, 6.9 mL of 2.46 M n-BuLi (5 x 0.0035 mol) was added dropwise via syringe. The solution turned deep blue. 0.85 g (0.0035 mol) of mesylate 180 in 20 mL of tetrahydrofuran added dropwise. The mixture was maintained at -30°C for 1 hr and at 23°C for another 1 hr. Water was added and the end of this period and the aqueous layer extracted with chloroform. Removal of CHCl₃ left an oil which proved to be methyl butyl sulfone by ¹H NMR. The other product, diol 52 being soluble in water was never recovered.

NMR (CDCl₃): δ 0.9 (m), δ 1.3 (m), δ 2.5 (m).

6.53 Preparation of di-n-butyl methyl carbinol:

In a 3-necked 250 mL r.b. flask equipped with addition funnel (a septum was attached to the addition funnel), condenser, magnetic stirrer, 2 g of ethyl acetate (0.0023 mol) were taken. To the addition funnel 25 mL (2.1 x 0.0023 mol) of n-butyl magnesium chloride (2 M solution in ether) was transferred by a cannula. The Grignard reagent was added with stirring at 23°C, to the ethyl acetate solution. The mixture was refluxed for 3 hr under N_2 . It was then cooled, poured into 100 mL of ice-cold water. The pH was adjusted to 5 with 10% ammonium chloride solution extracted with ether. Drying (Na_2SO_4) and evaporation of ether left 3.3 g (92%) of crude di-n-butyl methyl carbinol 135.

NMR ($CDCl_3$): δ 0.9 (t), δ 1.3 (s), δ 1.5 (m), (all these together integrate for 21 H), δ 3.5 (m, 1H).

IR ($CDCl_3$): 3400 (br, OH), 2900, 1480, 1360, 1150, 1000, 900 cm^{-1} .

Notes:

1. The only purpose of making this compound was to compare this product with the side products we got during the attempted coupling reaction of mesylate 180 with n-butyl magnesium bromide or n-butyl copper lithium.

6.54 Conversion of mesylate 180 into iodide 193:

Magnesium iodide was prepared as follows. In a one-neck 50 mL r.b. flask equipped with a reflux condenser, a side arm with septum, 0.62 g of Mg (5 x 0.0053 mol) in 25 mL of anhydrous ether was taken. 6.75 g of I_2 (5 x 0.0053 mol) was added portion wise. When the brown color of I_2 has disappeared, the condenser was removed and replaced by a septum.

In another one-necked 100 mL r.b. flask equipped with a condenser and a sidearm with septum, 1.5 g of mesylate 180 were dissolved in 25 mL of chloroform. The magnesium iodide solution was transferred by a double ended needle under a positive pressure of N_2 . The reaction mixture was refluxed for 24 hr. It was then cooled, the solvent evaporated and the residue was adjusted with dilute ammonium hydroxide solution to pH 10 and extracted with chloroform. The organic layer was washed with 5% sodium bisulfite solution and later with saturated salt solution. Drying (Na_2SO_4) and evaporating the solvent left 0.8 g of an oil (39%) which proved to be 1-iodomethyl-3 β -acetoxytropine 193.

NMR ($CDCl_3$): δ 1.5-1.8 (m, 8H), δ 2.0 (s, 3H), δ 2.3 (s, 3H), δ 3.2 (s, 1H), δ 3.3 (m, 1H), δ 4.9-5.2 (m, 1H).

IR (film): 2900, 1720, 1250, 1000 cm^{-1} .

Notes:

1. The mesylate could not be displaced by sodium iodide.
2. Using ether-tetrahydrofuran mixture as solvent system slowed down the reaction. There was some unreacted starting material in the product. It is conceivable that tetrahydrofuran coordinates to magnesium iodide and renders it ineffective.
3. Although the isolated yields of pure iodide were only 39% when ether-chloroform was used as solvent system, the crude product showed complete absence of starting mesylate.

6.55 Attempted Coupling of Allylmagnesium bromide with
1-Iodomethyl-3 β -acetoxytropene:

In a 100 mL 3-necked r.b. flask equipped with a magnetic stirrer, condenser with N₂ adapter, low-temperature thermometer, 0.6 g of CuI (0.003 mol) was taken. A solution of 1 g of iodide 193 (0.003 mol) dissolved in 25 mL of tetrahydrofuran and 25 mL of hexamethylphosphoramide and transferred via syringe into the reaction flask. The reaction mixture was cooled to -10°C. 15.5 mL (5 x 0.003 mol) of allyl magnesium bromide (2 M solution in THF) was added via syringe. The mixture was brought to 23°C and stirred for 72 hr. At the end it was heated to reflux for 0.5 hr.

The mixture was poured onto ice, dilute hydrochloric acid

was added to adjust pH to 2 and extracted with ether. The water layer was made alkaline (pH 10) with dilute ammonium hydroxide and extracted with chloroform. Evaporation of solvent gave unreacted 1-iodomethyl-3 β -tropanylacetate 193 as the sole product.

References

1. a. J. W. Daly, I. Karle, C. W. Myers, T. Tokuyama, J. A. Waters and B. Witkop, Proc. Nat. Acad. Sci., U.S.A., 1971, 68, 1870.
b. T. Tokuyama, K. Uenoyama, G. Brown, J. W. Daly and B. Witkop, Helv. Chim. Acta, 1974, 57, 2597.
c. I. L. Karle, J. Am. Chem. Soc., 1973, 95, 4036.
d. J. W. Daly, T. Tokuyama, T. Fujiwara, R. J. Highet, and I. L. Karle, J. Am. Chem. Soc., 1980, 102, 830.
e. J. W. Daly, B. Witkop, T. Tokuyama, T. Nishikawa, and I. L. Karle, Helv. Chim. Acta, 1977, 60, 1128.
2. J. Inubushi and I. Ibuka, Heterocycles, 1977, 8, 633.
3. a. M. Aratani, L. V. Dunkerton, T. Fukuyama, Y. Kishi, H. Kakoi, S. Sugiura and S. Inoue, J. Org. Chem., 1975, 40, 2009.
b. T. Fukuyama, L. V. Dunkerton, M. Aratani and Y. Kishi, J. Org. Chem., 1975, 40, 2011.
c. E. J. Corey, J. F. Arnett and G. N. Widiger, J. Am. Chem. Soc., 1975, 97, 430.
d. E. J. Corey, M. Petrzilka and Y. Ueda, Helv. Chim. Acta, 1977, 60, 2294.
e. D. A. Evans, E. W. Thomas, and R. E. Cherpeck, J. Am. Chem. Soc., 1982, 104, 3695.
f. S. A. Godleski, D. J. Heacock, J. D. Meinhart and S. V. Wallendaal, J. Org. Chem., 1983, 48, 2101.
g. K. Takahashi, B. Witkop, A. Brossi, M. A. Maleque and E. X. Albuquerque, Helv. Chim. Acta, 1982, 65, 252.
4. a. J. Elliott and m. A. Raftery, Biochemistry, 1979, 18, 1968.
b. A. J. Lapa, E. X. Albuquerque, M. J. Sarvey, J. Daly and B. Witkop, Exp. Neurol., 1975, 47, 558.
c. W. Burgermeister, W. L. Klein, M. Nirenberg and B. Witkop, Mol. Pharmacol., 1978, 14, 751.
5. B. Tursch, J. C. Braekman, D. Daloze, C. Hootele, D. Losman, R. Karlsson, and J. M. Pasteels, Tetrahedron Letters, 1973, 201.
6. For total syntheses of adaline, see
a. E. Gossinger and B. Witkop, Monatsh. Chem., 1980, 111, 803.
b. R. K. Hill and L. A. Renbaum, Tetrahedron, 1982, 38, 1959.
c. D. H. Gnecco Medina, D. S. Grierson and H. P. Husson, Tetrahedron Lett., 1983, 2099.

7. For extensive reviews on the chemistry of tropanes, see:
 - a. G. Fodor, in "The Alkaloids" (R. H. F. Manske, ed.), 1960, 6, 145.
 - b. G. Fodor, in "The Alkaloids" (R. H. F. Manske, ed.), 1967, 9, 269.
 - c. G. Fodor, in "The Alkaloids" (R. H. F. Manske, ed.), 1971, 13, 351.
 - d. G. Fodor, in "Chemistry of the Alkaloids" (S. W. Pelletier, ed.), p. 431, Van Nostrand-Reinhold, Princeton, New Jersey, 1970.
 - e. R. L. Clarke, in "The Alkaloids" (R. H. F. Manske, ed.), 1977, 16, 84.
 - f. G. Fodor, in "The Alkaloids" (M. F. Grundon, ed.), Specialist Periodical Reports, The Royal Society of Chemistry, London, 1978, 8.
 - g. G. Fodor, in "The Alkaloids" (M. F. Grundon, ed.), Specialist Periodical Reports, The Royal Society of Chemistry, London, 1979, 9.
 - h. G. Fodor and J. Butterick, in "The Alkaloids" (M. F. Grundon, ed.), Specialist Periodical Reports, The Royal Society of Chemistry, London, 1980, 10.
 - i. G. Fodor and R. Dharanipragada, in "The Alkaloids" (M. F. Grundon, ed.), Specialist Periodical Reports, The Royal Society of Chemistry, London, 1981, 11, 36.
 - j. G. Fodor and R. Dharanipragada, in "The Alkaloids" (M. F. Grundon, ed.), Specialist Periodical Reports, The Royal Society of Chemistry, London, 1982, 12, 45.
 - k. G. Fodor and R. Dharanipragada, in "The Alkaloids" (M. F. Grundon, ed.), Specialist Periodical Reports, The Royal Society of Chemistry, London, 1983, 13, 55.
 - l. G. Fodor and R. Dharanipragada, in "The Alkaloids" (M. F. Grundon, ed.), Natural Product Reports, The Royal Society of Chemistry, London, 1984, 1, 231.
 - m. G. Fodor and R. Dharanipragada, in "The Alkaloids" (M. F. Grundon, ed.), Natural Product Reports, The Royal Society of Chemistry, London, 2, manuscript in print.
8.
 - a. R. Robinson, J. Chem. Soc., 1917, 762.
 - b. B. K. Blount and R. Robinson, J. Chem. Soc., 1933, 1511.
9. J. Case, unpublished results.
10. J. Kebrle and P. Karrer, Helv. Chim. Acta, 1954, 37, 484.
11.
 - a. N. Clauson-Kaas and F. Limborg, Acta Chem. Scand., 1952, 6, 551.
 - b. R. Mozingo, Org. Syn. Coll. Vol. III, 1955, 181.
12. L. Wessell and B. Tollens, Ann., 1892, 272, 291.
13. D. M. Burness, Org. Syn. Coll. Vol. V, 1973, 403.
14. N. Clauson-Kaas, F. Limborg and J. Fakstorp, Acta Chem. Scand., 1948, 2, 109.

15. J. Fakstorp, D. Raleigh and L. E. Schniepp, J. Am. Chem. Soc., 1950, 72, 869.
16. G. Gal, I. Simonyi and G. Tokar, Acta. Chem. Acad. Sci. Hung., 1955, 6, 365.
17. L. Paquette and J. Heimaster, J. Am. Chem. Soc., 1966, 88, 763.
18. A. H. Beckett, N. J. Harper, A. D. J. Balon, and T. H. E. Watts, Tetrahedron, 1959, 6, 319.
19. A. Nickon and L. Fieser, J. Am. Chem. Soc., 1952, 74, 5566.
20. R. J. Bishop, G. Fodor, A. R. Katrizsky, F. Soti, L. E. Sutton, and F. J. Swinbourne, J. Chem. Soc. (C), 1966, 74.
21. For an elaborate discussion of PMR studies on tropanes, see A. F. Casy, "PMR Spectroscopy in Medicinal and Biological Chemistry", 1971, p. 240.
22. N. Sperber, M. Sherlock and D. Papa, J. Am. Chem. Soc., 1953, 75, 1122.
23. A. W. Nineham, J. Chem. Soc., 1953, 2601.
24. G. Fodor, S. Kiss and J. Rakoczi, Chim & Ind. (Paris), 1963, 90, No. 36, 225.
25. G. Fodor and O. Kovacs, J. Chem. Soc., 1953, 724.
26. W. Steglich and G. Hofle, Angew. Chem. Int. Ed. (Engl.), 1969, 8, 981.
27. G. Hofle and W. Steglich, Synthesis, 1972, 619.
28. G. Hofle, W. Steglich and H. Vorbruggen, Angew. Chem. Int. Ed. (Engl.), 1978, 17, 569.
29. E. F. V. Scriven, Chemical Society Reviews, 1983, 12, 129.
30. E. J. Corey and K. Shimoji, J. Am. Chem. Soc., 1983, 105, 1662.
31. A. Brossi, F. Hsu and K. Rice, J. Org. Chem., 1982, 47, 5214.
32. E. J. Corey, N. M. Weinsheker, T. K. Schaaf, W. Huber, J. Am. Chem. Soc., 1969, 91, 5676.
33. T. G. Bonner, E. J. Bourne and S. McNally, J. Chem. Soc., 1960, 2929.

34. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 1975, 2647.
35. G. Piancatelli, A. Scettri and M. D'Auria, Synthesis, 1982, 245.
36. E. J. Corey and G. Schmidt, Tetrahedron Lett., 1979, 399.
37. J. Herscovici and K. Antonakis, J. Chem. Soc. Chem. Commun., 1980, 561.
38. Y. S. Cheng, W. L. Liu and S. Chen, Synthesis, 1980, 223.
39. G. Melvyn and R. W. Rickards, J. Chem. Soc. Perkin Trans. I, 1981, 599.
40. J. C. Collins and W. W. Hess, Org. Syn., 1972, 52, 5.
41. R. Ratcliffe and R. Rodehorst, J. Org. Chem., 1970, 35, 4000.
42. J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Janesen and T. Walker, J. Chem. Soc., 1952, 1094.
43. The activated manganese dioxide used in these experiments has been kindly provided by Dr. K. Fang.
44. E. J. Corey and R. D. Balanson, J. Am. Chem. Soc., 1974, 96, 6516.
45. A. Cave, C. Kan-Fan, P. Potier, J. Le Men and M. M. Janot, Tetrahedron, 1967, 23, 4691.
46. J. G. Moffatt in "Oxidation", Vol. 2, R. L. Augustine and D. L. Trecker (eds.), Marcel Dekker Inc., New York (1971).
47. a. K. E. Pfitzner and J. G. Moffatt, J. Am. Chem. Soc., 1965, 87, 5661, (1965).
b. K. E. Pfitzner and J. G. Moffatt, J. Am. Chem. Soc., 1965, 87, 5670.
48. G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet and F. E. Ziegler, J. Am. Chem. Soc., 1966, 88, 3099.
49. J. Karliner and C. Djerassi, J. Org. Chem., 1966, 31, 1945.
50. K. Wiesner, A. Phillip and P. T. Ho, Tetrahedron Lett., 1968, 1209.
51. J. Meinwald and R. A. Schneider, J. Am. Chem. Soc., 1967, 89, 2023.
52. J. G. Moffatt, J. Org. Chem., 1971, 36, 1909.
53. J. D. Albright and L. Goldman, J. Am. Chem. Soc., 1967, 89, 2416.

54. K. T. Joseph and C. S. Krishna Rao, Tetrahedron, 1967, 23, 3215.
55. G. Eggart, C. Pascual and H. Wehrli, Helv. Chim. Acta, 1967, 50, 985.
56. E. Houghton and J. E. Saxton, J. Chem. Soc. (C), 1969, 595.
57. J. R. Parikh and W. von E. Doering, J. Am. Chem. Soc., 1967, 89, 5505.
58. L. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley and Sons, Inc., New York, NY, Vol. I, 1967, p. 1127.
59. K. Onodera, S. Hirano and N. Kashimura, Carbohydr. Res., 1968, 6, 276.
60. K. Omura and D. Swern, Tetrahedron, 1978, 34, 1651.
61. S. L. Huang, K. Omura and D. Swern, Synthesis, 1978, 297.
62. S. L. Huang, K. Omura and S. Swern, J. Org. Chem., 1976, 41, 3329.
63. A. J. Mancuso, S. L. Huang and D. Swern, J. Org. Chem., 1978, 43, 2480.
64. A. J. Mancuso and D. Swern, Synthesis, 1981, 165.
65. C. R. Johnson, J. C. Sharp and W. G. Phillips, Tetrahedron Lett., 1967, 5299.
66. C. R. Johnson and W. G. Phillips, J. Am. Chem. Soc., 1969, 91, 682.
67. A. Maercker, Org. React., 1965, 14, 270.
68. H. J. Bestmann and O. Vostrowsky, Topics in Current Chemistry, 1983, 109, 86.
69. I. Gosney and A. G. Rowley in "Organophosphorus Reagents in Organic Synthesis", Ch. 2, J. G. Cadogan (ed.), Academic Press (1979), p. 17.
70. G. Wittig and G. Geissler, Ann., 1953, 580, 44.
71. H. Rapoport and M. S. Chadha, J. Am. Chem. Soc., 1957, 79, 5730.
72. R. Mechoulam and F. Sondheimer, J. Am. Chem. Soc., 1958, 80, 4386.
73. D. J. Pasto and C. R. Jhonson, Laboratory Text for Organic Chemistry, pp. 137-138, Prentice-Hall, Inc., Englewood Cliffs, NJ (1979).

74. E. Wenkert, J. S. Bindra, C. Chang, D. W. Cochran and F. M. Schell, Accts. Chem. Res., 1974, 7, 46.
75. E. L. Blosssey, H. Budzikiewicz, M. Ohashi, G. Fodor and C. Djerassi, Tetrahedron, 1964, 20, 585.
76. F. Sondheimer and R. Mechoulam, J. Am. Chem. Soc., 1957, 79, 5029.
77. C. B. Reese in Protective Groups in Organic Chemistry (J. W. Mcomie, ed.) Plenum Press, New York (1973), p. 109.
78. E. Vedejs and K. A. J. Snoble, J. Am. Chem. Soc., 1973, 95, 5778.
79. W. P. Schneider, J. Chem. Soc. Chem. Commun., 1969, 785.
80. U. Axen, F. H. Lincoln, J. L. Thompson, J. Chem. Soc. Chem. Commun., 1969, 303.
81. M. Schlosser, Top. Stereochem., 1970, 5, 1.
82. E. J. Corey and E. Hamanaka, J. Am. Chem. Soc., 1967, 89, 2758.
83. R. Holler and H. Lischka, J. Am. Chem. Soc., 1980, 102, 4632.
84. E. Vedejs, G. P. Meier and K. A. J. Snoble, J. Am. Chem. Soc., 1981, 103, 2823.
85. Chemical and Engineering News, p. 30, March 26, 1984.
86. A. B. Reitz, M. S. Mutter and B. E. Maryanoff, J. Am. Chem. Soc., 1984, 106, 1873.
87. J. W. Hamersma and E. I. Snyder, J. Org. Chem., 1965, 30, 3985.
88. D. C. Curry, B. C. Uff and N. D. Ward, J. Chem. Soc. (C), 1967, 1120.
89. a. Suggestion from Dr. B. Witkop of NIH to Dr. G. Fodor.
b. The unsaturated amino alcohol 14 and the saturated amine hydrochloride salt 93 have been sent to Dr. B. Witkop at NIH for biological evaluations.
90. G. Kraiss and N. Nador, Tetrahedron Lett., 1971, 57.
91. T. A. Montzka, J. D. Matiskella and R. A. Partyka, Tetrahedron Lett., 1974, 1325.
92. J. D. Hobson and J. G. McCluskey, J. Chem. Soc. (C), 1967, 2015.

93. R. A. Olofson, R. C. Schnur, L. Bunes and J. P. Pepe, Tetrahedron Lett., 1977, 1567.
94. R. A. Olofson, J. T. Martz, J. P. Senet, M. Piteau and T. Malfroot, J. Org. Chem., 1984, 49, 2081.
95. R. D. Birkenmeyer and L. A. Dolak, Tetrahedron Lett., 1970, 5049.
96. G. T. Davis and D. H. Rosenblatt, Tetrahedron Lett., 1968, 4085.
97. R. C. Thomas, J. Antibiotics, 1982, 35, 1202.
98. S. F. Martin and S. K. Davidsen, J. Am. Chem. Soc., 1984, 106, 6431.
99. H. A. Hageman, Org. React., 1953, 7, 198.
100. G. Fodor, S. Abidi and T. C. Carpenter, J. Org. Chem., 1974, 39, 1507.
101. A. Nickon and L. F. Fieser, J. Am. Chem. Soc., 1952, 74, 5566.
102. A. G. Fallis, M. T. W. Hearn, E. R. H. Jones, V. Thaller and J. Turner, J. Chem. Soc. Perkin Trans. I, 1973, 743.
103. M. F. Shostakovskii, A. S. Atavin and N. V. Egorov, J. Gen. Chem. (USSR), 1965, 35, 813.
104. G. Eglinton and M. C. Whiting, J. Chem. Soc., 1950, 3650.
105. This result is in contrast to Eglinton's claim¹⁰⁴ that the reaction proceeds only in pyridine and not in 2,6-lutidine.
106. None of the published procedures¹⁰⁴ of Eglinton could be reproduced by us.
107. I. Ernest, A. Main and R. Manasse, Tetrahedron Lett., 1982, 167.
108. D. Klamann and P. Weyerstahl, Chem. Ber., 1964, 97, 2534.
109. E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson and S. Hammarstrom, J. Am. Chem. Soc., 1980, 102, 1436.
110. Reference 68, p. 130.
111. D. Klamann and P. Weyerstahl, Angew. Chem. Int. Ed. (Engl.), 1963, 2, 43.
112. W. G. Dauben, J. M. Gerdes and R. A. Bunce, J. Org. Chem., 1984, 49, 4293.

113. S. Chen and M. M. Joullie, Synth. Commun., 1984, 14, 591.
114. J. Hooz and S. Gilani, Can. J. Chem., 1968, 46, 86.
115. A. K. Bose and B. Lal, Tetrahedron Lett., 1973, 3937.
116. W. S. Johnson and T. K. Schaaf, J. Chem. Soc. Chem. Commun., 1969, 611.
117. C. Burford, F. Cooke, E. Ehlinger and P. Magnus, J. Am. Chem. Soc., 1977, 4536.
118. S. Danishefsky, K. Nagasawa and N. Wang, J. Org. Chem., 1975, 40, 1989.
119. S. G. Levine, J. Am. Chem. Soc., 1958, 80, 6150.
120. D. R. Coulson, Tetrahedron Lett., 1964, 3323.
121. J. D. Brewer and J. A. Elix, Aust. J. Chem., 1972, 25, 545.
122. G. Wittig and M. Schlosser, Chem. Ber., 1961, 94, 1373.
123. N. R. Natale, B. E. Marron, E. J. Evain and C. D. Dodson, Synth. Commun., 1984, 14, 599.
124. K. C. Nicolaou, R. L. Magolda and D. A. Claremon, J. Am. Chem. Soc., 1980, 102, 1404.
125. E. J. Corey and G. H. Posner, J. Am. Chem. Soc., 1967, 89, 3911.
126. G. Posner, Org. React., 1972, 19, 1.
127. G. Posner, Org. React., 1975, 22, 253.
128. F. Derguini-Boumechal and G. Linstumelle, Tetrahedron Lett., 1976, 3225.
129. G. Fouquet and M. Schlosser, Angew. Chem. Int. Ed. (Engl.), 1974, 13, 82.
130. C. R. Johnson and G. A. Dutra, J. Am. Chem. Soc., 1973, 95, 7777.
131. C. R. Johnson and G. A. Dutra, J. Am. Chem. Soc., 1973, 95, 7783.
132. G. M. Whitesides, W. F. Fischer, Jr., J. S. Filippo, Jr., R. W. Bashe, and H. O. House, J. Am. Chem. Soc., 1969, 91, 4871.
133. M. Tamura and J. Kochi, Synthesis, 1971, 303.

134. F. Derguini, Y. Bessiere and G. Linstrumelle, Synth. Commun., 1981, 11, 859.
135. M. S. Kharasch and C. F. Fuchs, J. Org. Chem., 1944, 9, 359.
136. B. H. Lipshutz, D. Parker and J. Kozlowski, J. Org. Chem., 1983, 48, 3334.
137. B. H. Lipshutz, R. S. Wilhelm and J. Kozlowski, Tetrahedron, 1984, 40, 5005.
138. A. G. Anderson, Jr. and F. J. Freenor, J. Am. Chem. Soc., 1964, 86, 5037.
139. A. G. Anderson, Jr. and F. J. Freenor, J. Org. Chem., 1972, 37, 626.
140. O. Kovacs, G. Fodor, and I. Weisz, Helv. Chim. Acta, 1954, 37, 892.
141. R. S. Tipson, J. Org. Chem., 1944, 9, 235.
142. R. K. Crossland and K. L. Servis, J. Org. Chem., 1970, 35, 3195.
143. A. C. Cope and G. L. Woo, J. Am. Chem. Soc., 1963, 85, 3601.
144. A. Eschenmoser and A. Frey, Helv. Chim. Acta, 1952, 35, 1660.
145. R. C. Ebersole and F. C. Chang, J. Org. Chem., 1973, 38, 2713.
146. Compared with ^1H NMR spectrum of allyl phenyl sulfone
Sadler ^1H NMR spectra # 20468M.
147. A. I. Meyers, A. Nabeya, H. W. Adickes and I. R. Politzer, J. Am. Chem. Soc., 1969, 91, 763.
148. It has been observed that treatment of norbornyl brosylates with strong bases yields dinorbornyl ethers.¹⁴⁹
149. W. Huckel, W. Toppe and G. Legutke, Ann., 1940, 543, 191.
150. P. Place, M. Roumestant and J. Gore, Bull. Chim. Soc. Fr., 1976, 169.
151. W. Kraus and H. Graf, Angew. Chem. Int. Ed. (Engl.), 1975, 14, 824.
152. L. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley and Sons, Inc., New York, NY, Vol. I, p. 1158 (1967).

153. G. Fodor and R. Dharanipragada, Abstract MEDI 106, 188th National Meeting of the American Chemical Society, Philadelphia, PA (1984).
154. R. Dharanipragada and G. Fodor, "Search for New Membrane Active Substances: Synthesis of 3-Tropanols with Alkyl, Alkenyl and Alkenynyl Group at the Bridgehead", submitted to Chem. Soc. for publication.

APPENDIX

31

Figure 1. ^1H NMR spectrum of 1-methoxymethylfuran (31).

Figure 2. Infrared spectrum of 1-methoxymethyl furan (31).

Figure 3. ^1H NMR spectrum of 1-methoxymethyl furan (31).
1,3-dihydrofuran (32).

32

Figure 3. ^1H NMR spectrum of 1-methoxymethyl-2,5-dimethoxy-2,5-dihydrofuran (32).

Figure 4. Infrared spectrum of 1-methoxymethyl-2,5-dimethoxy-2,5-dihydrofuran (32).

34

Figure 5. ^1H NMR spectrum of 1-methoxymethyl 2,5-dimethoxy tetrahydrofuran (34).

Figure 6. Infrared spectrum of 1-methoxymethyl-2,5-dimethoxy tetrahydrofuran (34).

17

Figure 7. ^1H NMR spectrum of 1-methoxymethyl tropane 3-one (17).

Figure 8. Infrared spectrum of 1-methoxymethyl tropane-3-one (17).

43

Figure 9. ^1H NMR spectrum of 1-methoxymethyl 3 β -hydroxytropolane (43).

Figure 10. Infrared spectrum of 1-methoxymethyl 3β-hydroxytropolane (43).

Figure 11. ^1H NMR spectrum of 1-methoxymethyl 3β-hydroxytropolane hydrochloride (50).

Figure 11. ^1H NMR spectrum of 1-methoxymethyl 3 β -acetoxytropane hydrochloride (60).

Figure 12. Infrared spectrum of 1-methoxymethyl-3 β -acetoxytropine hydrochloride (60).

55

Figure 14. ^1H NMR spectrum of 1-hydroxymethyl 3 β -acetoxytropane (55).

Figure 15. Infrared spectrum of 1-hydroxymethyl-3 β -acetoxytropane (55).

Figure 16. ^1H NMR spectrum of 1-hydroxymethyl-3 β -acetoxytropane (55).

32

Figure 16. ^1H NMR spectrum of 1-hydroxymethyl 3 β -hydroxytropine (52).

Figure 17. Infrared spectrum of 1-hydroxymethyl 3 β -hydroxytropine (52).

Figure 19. Infrared spectrum of 10-acetylmethyl-10-norbornene-2-carboxylate (56).

Figure 18. ^1H NMR spectrum of 3 β -acetoxytropane 1-aldehyde (56).

Figure 19. Infrared spectrum of 3 β -acetoxytropane-1-aldehyde (56).

Figure 20. ¹H NMR spectrum of 3 β -acetoxytropane-1-aldehyde (56).

103

14

Figure 22. ^1H NMR spectrum of 1-(1-pentenyl) 3 β -hydroxytropolene (14).
Solvent: CDCl_3

Figure 23. ^1H NMR spectrum of 1-(1-pentenyl) 38-hydroxytropine (14).
Solvent: $\text{CDCl}_3 + \text{D}_2\text{O}$

Figure 24. Infrared spectrum of 1-(1-pentenyl)-30-hydroxytropine
(14).

FILE: CHL7531#3

07-05-84 11:07:00 + 0:22
SAMPLE: DM-3-232

235

15

Figure 27. ^1H NMR spectrum of

Figure 27. ^1H NMR spectrum of 1-pentenyl 3 β -hydroxytropene (15).

122

Figure 28. ^1H NMR spectrum of 1-pentyl 3B-hydroxytropine hydrochloride (122).

07-05/84 10:36:00 + 2:00
SHIP: DM3-300

149504

240

118

Figure 30. ^1H NMR spectrum of 1-(1-hydroxypentyl)-3 β -hydroxytropine (118).

173 174

164

Figure 32. ^1H NMR spectrum of 1-(3 β -hydroxytropanyl) acetaldehyde (164).

152

Figure 33. ^1H NMR spectrum of 1-bromo-3-butyne (152).

Figure 34. Infrared spectrum of 1-bromo-3-butyne (152).

Figure 35. ^1H NMR spectrum of 1-bromo-3-butyne (152).

149

Figure 35. ^1H NMR spectrum of 4-butynyl triphenyl phosphonium bromide (149).

$\text{PPh}_3 \rightarrow 0$

151

Figure 37. ^1H NMR spectrum of 1-(1-penten-4-ynyl)-38-acetoxytropane (151).

Figure 38. Infrared spectrum of 1-(1-penten-4-ynyl)-3 β -acetoxytropane (151).

03/20/84 10:21:00
SAMPLE: OH-10-141

CHLIP C-122004

250420

24288

5.0%

187.9

100.0

50.0

M-E

143

Figure 41. Infrared spectrum of 4-trimethylsilyl but-3yn-1-ol (143).

146

Figure 43. Infrared spectrum of 4-trimethylsilyl but-3yn-1-tosylate (146).

144

Figure 44. ^1H NMR spectrum of 1-Iodo-4-trimethylsilyl-3-butyne (144).

Figure 45. Infrared spectrum of 1-Iodo-4-trimethylsilyl-3-butyne (144).

153

Figure 46. ^1H NMR spectrum of 3-butynyl 1-tosylate (153).

180

Figure 47. ^1H NMR spectrum of 1-methanesulfonyloxymethyl 3 β -acetoxytropane (180).

Figure 48. Infrared spectrum of 1-methanesulfonyloxymethyl-3β-acetoxytropane (180).

Figure 49. ¹H NMR spectrum of 1-methanesulfonyloxymethyl-3β-acetoxytropane (180).

181

Figure 49. ^1H NMR spectrum of 1-methanesulfonyloxymethyl
38-hydroxytropine (181).

193

Figure 50. ^1H NMR spectrum of 1-iodomethyl 38-acetoxytropane (193).

Figure 51. Infrared spectrum of 1-iodomethyl-3 β -acetoxytropane (193).

185

Figure 52. ^1H NMR spectrum of Di-n-butyl methyl carbinol (185).

Figure 53. Infrared spectrum of Di-n-butyl methyl carbinol (185).

183

Figure 54. ^1H NMR spectrum of 1-methyl-3 β -hydroxytropane (183).

Figure 55. ^1H NMR spectrum of allyl-3 β -hydroxytropane (184).

186a

ABSTRACT

The synthesis of β -tranyptol and α -tranyptol, with alkyl, alkenyl and alkynyl groups at the bridgehead was elaborated. The new compounds have been characterized by their physical and chemical substances that would serve as model compounds for the synthesis of β -tranyptol. In order to avoid confusion in obtaining individual long-chain β -tranyptol for the synthesis

Figure 55. ^1H NMR spectrum of allyl methylsulfone (186a).

Figure 56. Infrared spectrum of allyl methyl sulfone (186a).

ABSTRACT

The synthesis of 3-tropanols and nortropanols, with alkyl, alkenyl and alkynyl groups at the bridgehead was elaborated. The new compounds have been considered as new membrane active substances that would serve as model compounds for histrionicotoxin (1a). In order to avoid difficulties in obtaining individual long-chain 4-ketoaldehydes for the Robinson condensation of each new model compound, a key tropane intermediate 55 was prepared instead. The first attempts to extend the chains of the mesyl ester 180 and iodomethyltropanol (193) by Grignard-type coupling failed. Therefore we embarked on a Wittig reaction of the tropane-1-aldehyde 56 we synthesized in high yield from 55. Indeed, both 1-pentenyl and 1-pentyl-tropanols were obtained. Coupling with an acetylenic phosphorane led to 1-pentenynyltropanol. A further new key compound, namely 3 β -acetoxy-1-tropanylacetaldehyde (164) was also synthesized that shall give access to conjugated tropanyl enynes which would more closely resemble 1a.

VITA

Ramalinga Murty Dharanipragada was born in Vijayawada, India on November 9, 1956. He received his early education at Vivekananda Centenary High School. He graduated from Andhra Loyola College in 1975. He obtained his Master's degree in chemistry from the Indian Institute of Technology, Bombay in 1977. After working as a research scholar for a year at the same school, he came to the United States to pursue research in synthetic organic chemistry under the direction of Dr. Gabor Fodor at West Virginia University. He is currently a candidate for the degree of Doctor of Philosophy in Chemistry.

PUBLICATIONS

1. G. Fodor and R. Dharanipragada in "Tropane Alkaloids", M. F. Grundon, Ed. (Specialist Periodical Reports), The Royal Society of Chemistry, London, 1981, Vol. 11, p. 36-43.
2. G. Fodor and R. Dharanipragada in "Tropane Alkaloids", M. F. Grundon, Ed. (Specialist Periodical Reports), The Royal Society of Chemistry, London, 1982, Vol. 12, p. 45-52.
3. G. Fodor and R. Dharanipragada in "Tropane Alkaloids", M. F. Grundon, Ed. (Specialist Periodical Reports), The Royal Society of Chemistry, London, 1983, Vol. 13, p. 55-64.
4. G. Fodor and R. Dharanipragada in "Tropane Alkaloids", M. F. Grundon, Ed. (Natural Products Reports), The Royal Society of Chemistry, London, 1984, Vol. 1 (#3), pp. 231-234.
5. G. Fodor and R. Dharanipragada in "Tropane Alkaloids", M. F. Grundon, Ed. (Natural Products Reports), The Royal Society of Chemistry, London, 1985, Vol. 2, manuscript in print.
6. G. Fodor and R. Dharanipragada in "Tropane Alkaloids", M. F. Grundon, Ed. (Natural Products Reports), The Royal Society of Chemistry, London, 1986, Vol. 3, manuscript in preparation.

7. G. Fodor and R. Dharanipragada, Abstract MEDI 106, 188th National Meeting of the American Chemical Society, Philadelphia, PA (1984).
8. R. Dharanipragada and G. Fodor, "Search for New Membrane Active Substances: Synthesis of 3-Tropanols with Alkyl, Alkenyl and Alkenynyl Group at the Bridgehead", submitted to Chem. Soc. for publication.

APPROVAL OF THE EXAMINING COMMITTEE

Naresh Dalal
Naresh Dalal, Ph.D.

Denis W. H. MacDowell
Denis W. H. MacDowell, Ph.D.

William R. Moore
William R. Moore, Ph.D.

John P. O'Donnell
John P. O'Donnell, Ph.D.

April 16, 1985
Date

Gabor B. Fodor
Gabor B. Fodor, Ph.D., Chairman