Diallyldimethylgermane (38). To a stirred mixture of Mg turnings (107 g, 4.4 mol) and THF (2.5 L) was added a solution of methyl iodide (312 g, 2.2 mol), allyl bromide (266 g, 2.2 mol), and germanium tetrachloride (215 g, 1.0 mol) at a rate which was sufficient to maintain reflux temperature. After the addition was complete, the mixture was heated at reflux temperature for an additional 2 h and poured onto ice, and the organic layer was dried ($MgSO_4$) and distilled at 740 torr to give three fractions:[26] allyltrimethylgermane [bp 100-102 °C; 10.5 g (7%)], **38** [bp 147-148 °C; 37.4 g (20%)], and triallylmethylgermane [bp 188 °C; 18.3g (9%)]. For **38**: ^1H NMR (CCl_4) δ 0.17 (s, 6 H); 1.73 (d, 4 H, J = 8 Hz), 4.87 (m, 4 H), 5.84 (m, 2 H); MS, m/z (relative intensity 186 (4), 171 (7), 145 (100), 105 (23), 89 (20).

1,1-Dimethyl-1-germacyclooctan-5-one (39). This compound was prepared from **38** on a 12-mmol scale as in for **17a** (method A). Distillation gives 0.6 g (23%) of **39**: bp 70 °C (1.5 torr); IR (TF) 1705 cm^{-1} (C=O); MS, m/z (relative intensity) 216 (6), 188 (100); ^1H NMR (CCl_4) δ 0.05 (s, 6 H), 0.85 (m, 4 H), 1.98 (m, 4 H), 2.33 (m, 4 H). Anal. Calcd for $C_9H_{18}OGe$: C, 50.32; H, 8.45. Found: C, 50.40; H, 8.48.

Acknowledgment. The support of a William and Flora Hewlett Foundation Grant, of the Research Corp., and of the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. We also thank Eagle-Picher Industries and Laramie Chemical Co. for their generous gifts of several of the germanium compounds used in this study. Support by Grant CA-19203 to A.H. from the NIH is gratefully acknowledged.

Registry No. *meso*-**2**, 85337-66-2; *dl*-**2**, 85337-67-3; **3**, 85337-65-1; **4**, 85337-82-2; **9a**, 76240-84-1; **9b**, 85337-43-5; **9c**, 68561-25-1; **9d**, 72761-80-9; **9e**, 85337-44-6; **9f**, 85337-45-7; **9g**, 85337-46-8; **10**, 85337-47-9; *meso*-**11**, 85337-48-0; *dl*-**11**, 85337-68-4; *cis*-**12**, 85337-49-1; *trans*-**12**, 85337-50-4; *cis*-**13a**, 85337-51-5; *trans*-**13a**, 85337-52-6; *cis*-**13b**, 85337-69-5; *trans*-**13b**, 85337-70-8; *cis*-**13c**, 85337-71-9; *trans*-**13c**, 85337-72-0; **15**, 85337-54-8; **16**, 85337-53-7; *cis*-**17a**, 85337-55-9; *trans*-**17a**, 85337-56-0; *cis*-**17b**, 85337-73-1; *trans*-**17b**, 85337-74-2; *cis*-**17c**, 85337-75-3; *trans*-**17c**, 85337-76-4; *cis*-**17d**, 85337-77-5; *cis*-**17e**, 85337-78-6; *cis*-**17f**, 85337-79-7; *cis*-**17g**, 85337-80-0; **20**, 22146-25-4; **21**, 85337-57-1; **22**, 85337-58-2; **23**, 18001-18-8; **24**, 68469-62-5; **25**, 85337-59-3; **26**, 85337-60-6; **27**, 85337-61-7; **28**, 10325-26-5; **29**, 1450-29-9; **30**, 85337-62-8; **31**, 85337-63-9; **32**, 85337-81-1; **33**, 85337-64-0; **34**, 1113-12-8; **35**, 10325-32-3; **36**, 85354-83-2; **37**, 10325-31-2; **38**, 1793-69-7; **39**, 85354-84-3; α-bromostyrene, 98-81-7; styrene, 100-42-5; 2-bromopropene, 557-93-7; dichlorodimethylsilane, 75-78-5; dichlorodimethylgermane, 1529-48-2; dichlorodimethylstannane, 753-73-1; dichlorodiethylgermane, 13314-52-8; chlorodimethylvinylsilane, 1719-58-0; allyl bromide, 106-95-6; chlorodimethylphenylsilane, 768-33-2.

(26) Lesbre, M.; Mazerolles, P.; Stagé, J. "The Organic Compounds of Germanium"; Wiley: New York, 1971 and references cited therein.

Diels-Alder Reactions of Cycloalkenones. 2. Preparation and Structure of Cyclohexadienone Adducts[1]

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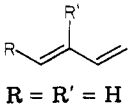
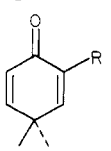
Uncatalyzed and aluminum chloride induced Diels-Alder reactions of 4,4-dimethyl-2,5-cyclohexadienone and 2,4,4-trimethyl-2,5-cyclohexadienone with 1,3-butadiene, isoprene, and (*E*)-piperylene are described. Structure analysis of the 1:1 adducts by standard means and ^{13}C NMR spectroscopy is presented.

In continuation of a broad study of the Diels-Alder reaction of cycloalkenones, especially under Lewis acid catalysis,[1] the reactions of 2,5-cyclohexadienones were investigated. These more highly functionalized dienophiles were expected to be more reactive than their 2-cyclohexenone equivalents and perhaps to reveal altered regio- and/or stereochemistry.

Three dienes, 1,3-butadiene (**1a**), isoprene (**1b**), and (*E*)-piperylene (**1c**), and two dienophiles, 4,4-dimethyl-2,5-cyclohexadienone (**2a**) and 2,4,4-trimethyl-2,5-cyclohexadienone (**2b**) were chosen for the investigation, and experiments on uncatalyzed, thermal reactions (at 160 °C for 70 h) and reactions under aluminum chloride catalysis (at 40 °C for less than 1 day, except for one case) were carried out under conditions of predominant 1:1 adduct formation. The structures of the products were determined by ^{13}C NMR spectroscopy.



1a, R = R' = H
b, R = H; R' = Me
c, R = Me; R' = H



2a, R = H
b, R = Me

As Table I, presenting the six sets of results, indicates, the acid-induced reactions, in contrast to their uncatalyzed counterparts, are high yielding.[4] The acid-catalyzed reactions of the unsymmetrical dienone **2b** yield ca. 4:1 mixtures of adducts favoring the products of reaction on the unsubstituted double bond of the dienone.[6] This regiochemical preference is in consonance with previous

(1) For previous papers see: Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *Synth. Commun.* **1979**, *9*, 391. Fringuelli, F.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1982**, *47*, 5056.

(2) (a) Università di Perugia. (b) Rice University.

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(4) For a recent report on the uncatalyzed addition of (*E*)-piperylene to 4,4-dimethyl-2,5-cyclohexadienone in high yield, presumably under different conditions, see ref 5.

(5) Liotta, D.; Saindane, M.; Barnum, C. *J. Am. Chem. Soc.* **1981**, *103*, 3224.

(6) Contrastingly, cyclohexadienones **2** (R = CHO or CO_2Me) show preference for diene addition on their substituted double bond.[5,7]

(7) Lui, H.-J.; Browne, E. N. C. *Can. J. Chem.* **1981**, *59*, 601.

0022-3263/83/1948-1810$01.50/0

Table I. Thermal and Aluminum Chloride Catalyzed Diels–Alder Reactions of Dienes 1 with Cyclohexadienones 2[a]

	thermal reaction			catalyzed reaction		
compd	yield, %	products	ratio	yield, %	products	ratio
1a–2a	5	3a, 4a[b]	1:1	95	3a, 4a[b]	200:1
1b–2a	c			63	3b, 4b[b]	3.5:1
1c–2a	20	3c, 4c	9:1	95	3c, 4c	200:1
1a–2b	c			90	3d, 4d,[b] 3e[d]	200:1:55
1b–2b	7	3f, 4f,[b] 3g	2:1:2	85	3f, 4f,[b] 3g	80:1:20
1c–2b	24	3h, 4h, 3i	150:1:50	88	3h, 4h, 3i	200:1:50

[a] Thermal reactions at 160 °C for 70 h. For temperature and time of catalyzed reactions see Table III. [b] Structure based on base-catalyzed equilibration of major cis adduct. [c] Less than 0.5% total yield. [d] Structure based on analogy with the structures 3g,i.

Table II. ^{13}C Chemical Shifts of Hexalones 3 and 4[a]

	chemical shift									
atom	3b	3c	3f	3g	3h	3i	4a	4c	4d	4h
C(1)	199.0	200.3	199.4	203.5	200.6	204.2	199.1	200.9	199.2	201.0
C(2)	125.8	126.4	131.5	123.7	131.8	126.6	125.7	126.0	131.3	131.5
C(3)	155.2	152.9	150.3	159.1	148.1	157.3	155.2	159.0	150.2	154.5
C(4)	36.1	36.7	35.6	35.8	36.2	35.6	36.2	35.3	35.7	35.1
C(4a)	42.7	46.6	43.0	43.5	46.9	44.2	42.9	43.5	43.1	43.8
C(5)	24.2	24.7	24.4	23.4	24.9	22.6	24.0	24.8	24.0	25.1
C(6)	118.9	123.5	119.1	119.1	123.5	123.3	124.9	122.8	124.9	122.8
C(7)	131.9	131.5	132.1	130.1	131.7	130.3	124.9	132.4	125.1	132.5
C(8)	28.4	33.8	28.8	37.1	34.0	36.7	23.7	30.8	24.0	31.2
C(8a)	42.0	47.4	42.0	43.5	47.3	45.6	41.6	48.6	41.5	48.6
2-Me			15.7		15.7				15.7	15.9
4α-Me	25.9	25.7	26.4	22.7	26.2	23.5	25.9	20.3	26.3	20.5
4β-Me	26.5	26.3	26.7	30.8	26.5	32.1	26.4	27.7	26.5	28.3
7-Me	23.0		23.1	23.5						
8-Me		18.7			18.8	26.6		22.8		22.9
8a-Me				22.1		17.5				

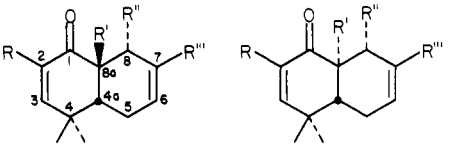
[a] The δ values are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm.

reports on the Diels–Alder reactions of unsymmetrical *p*-quinones[8] as well as with the lower reactivity of dienes in their acid-catalyzed reactions with 2-methyl-2-cyclohexenone than with 2-cyclohexenone.[1]

Whereas the reactions of isoprene (**1b**) with cycloalkenones has led predominantly to adducts wherein the isoprene methyl group is 1,4-oriented to the α-keto bridgehead,[1] the reactions of this diene with the cyclohexadienones (**2**) yield 1,3-oriented products. This latter regiochemical preference reflects also the behavior of *p*-quinones.[8b,9] The regiochemistry of the catalyzed isoprene–cyclohexadienone reactions was maintained even on replacement of the aluminum chloride catalyst by stannic chloride or boron trifluoride.[10]

The reactions of (*E*)-piperylene (**1c**) with the cyclohexadienones **2** led exclusively to products in which the piperylene methyl group is located vicinally to the α-keto bridgehead in analogy with the behavior of the diene in reactions with cycloalkenones[1] and thermal reactions of *p*-quinones.[8b,9] The regiochemistry of acid-catalyzed reactions of the latter with the same diene has been reported to be inverted.[8b,9] The stereochemistry of the cycloadditions of (*E*)-piperylene (**1c**) with the cyclohexadienones **2**, as with the cycloalkenones[1,11] and *p*-quinones,[8b] emanates from an endo transition state.

Even though the acid-induced Diels–Alder reactions of the 2-unsubstituted 2-cycloalkenones were accompanied by an isomerization leading to trans bicycles,[1] such stereochemical change was observed to occur only minimally in the reactions of the cyclohexadienones. Whereas thus the *cis*-hexalones **3** were the major products, they could



3 **4**

a, R = R′ = R″ = R‴ = H
b, R = R′ = R″ = H; R‴ = Me
c, R = R′ = R‴ = H; R″ = Me
d, R = Me; R′ = R″ = R‴ = H
e, R = R″ = R‴ = H; R′ = Me
f, R = R‴ = Me; R′ = R″ = H
g, R = R″ = H; R′ = R‴ = Me
h, R = R″ = Me; R′ = R‴ = H
i, R = R‴ = H; R′ = R″ = Me

be isomerized into the corresponding trans compounds **4** on base treatment. The equilibrium values at room temperature for the trans/cis mixtures were as follows: **4a/3a**, 2.5; **4b/3b**, 3.0; **4c/3c**, 40; **4d/3d**, 3.0; **4f/3f**, 3.0; **4h/3h**, 50.

A small investigation of the dependence of the reaction site of unsymmetrical cyclohexadienone **2b** on the nature of the catalyst was undertaken with dienes **1b,c**. The selectivity dependence was shown to be minor, as the **3f/3g** and **3h/3i** yield ratios changed from 4:1 to only 9:1 on replacement of aluminum chloride by stannic chloride or boron trifluoride.

(8) (a) Tishler, M.; Fieser, L. F.; Wendler, N. L. *J. Am. Chem. Soc.* **1940**, *62*, 2866. (b) Stojanak, Z.; Dickinson, R. A.; Stojanak, N.; Woznow, R. J.; Valenta, Z. *Can. J. Chem.* **1975**, *53*, 616.

(9) Kakushima, M.; Espinosa, J.; Valenta, Z. *Can. J. Chem.* **1976**, *54*, 3304.

(10) This result was in contrast to the dramatic change of regiochemistry of the reaction between isoprene (**1b**) and cyclohexadienone **2** (R = CO_2Me) under the influence of stannic chloride vs. that accelerated by boron trifluoride.[7]

(11) The reactions of (*E*)-piperylene (**1c**) with 2-methylcyclohexenone have yielded an adduct derived from an exo transition state as a minor product.[1]

Table III. Reaction Conditions of the Acid-Catalyzed Reactions of Dienes 1 with Cyclohexadienones 2[a,b]

compd	catalyst	ratios: diene/ketone	ratios: catalyst/ketone	ketone concn, M	reaction time, h	product yield, %
1a-2a	$AlCl_3$	3	0.9	0.20	15	95
1b-2a	$AlCl_3$	3	0.9	0.17	11	63
1c-2a	$AlCl_3$	3	0.25	0.10	21	95
1a-2b	$AlCl_3$	3	0.9	0.20	15	90
1b-2b[c]	$AlCl_3$	9	0.25	0.10	65	85
1c-2b	$AlCl_3$	3	0.5	0.10	4	88
1b-2b	$SnCl_4$	9	0.5	0.10	48	4
1c-2b	$SnCl_4$	3	0.5	0.10	23	70
1b-2b	Et_2OBF_3	9	0.5	0.10	92	22
1c-2b	Et_2OBF_3	3	0.5	0.10	13	90

[a] Ratios of equivalents; complexation temperature 22 °C; complexation time 60 min; reaction temperature 40 °C. [b] Product ratios listed in Table I. [c] Reaction temperature 25 °C.

Structure Analysis by ^{13}C NMR Spectroscopy. The carbon shift assignment of 10 of the 15 hexalones (3 and 4) followed a first-order analysis and is presented in Table II. It was aided by a $Yb(DPM)_3$-induced shift study on each ketone and by the available shift data for related octalones.[1] Among the angularly unsubstituted hexalones the cis bicycles could be differentiated readily from their trans isomers by the *gem*-dimethyl shift characteristics. Whereas in the conformationally rigid trans compounds one of the two methyl groups is quasi-axial, and thus shielded strongly with respect to its quasi-equatorial neighbor, the two groups in the conformationally loose cis substances are both conformationally and shiftwise closer to each other. The introduction of an angular methyl group into the *cis*-hexalone framework, however, decreases strongly the shift similarity of the geminal methyl functions.

The site of the isoprene methyl group in compounds **3b,f,g** is revealed by the allyl methylene shifts, thus settling the regiochemistry of the isoprene adducts. Both the site and stereochemistry of the secondary methyl group of substances **3c,h,i** and **4c,h** are determined by the δ values of the methyl groups, their methine attachments, and the allyl methylene unit, thereby yielding the configuration of the (*E*)-piperylene adducts.

Experimental Section

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra of carbon tetrachloride solutions were recorded on a Perkin-Elmer 257 spectrophotometer. ^1H NMR spectra of carbon tetrachloride solutions with Me_4Si as an internal standard (δ 0) were registered on a JEOL JNM-60 spectrometer. The ^{13}C NMR spectra were taken on a Varian XL-100-15 FT NMR spectrometer. With the use of *m*- and *p*-methoxyacetophenone and *p*-chloroacetophenone as internal standards and 1-, 2-, or 3-m 20% LAC 728 columns, GC analyses were performed on Carlo Erba GI and Hewlett-Packard 5880A chromatographs. The latter apparatus also was utilized with 50-m OV-101 (0.2-mm diameter) capillary columns and an "on-column" injection system. Absorption chromatography was executed on SILAL 13 and silica gel columns. All solid Diels–Alder adducts were crystallized from pentane and the 2,4-dinitrophenylhydrazones from absolute ethanol.

General Procedure. The thermal, uncatalyzed Diels–Alder reactions were carried out at 160 °C for 70 h by following a procedure described previously[1] for like reactions of cycloalkenones. All data are reported in Table I. The aluminum chloride induced Diels–Alder reactions also followed an earlier procedure,[1] their data being detailed in Table III. Isolated product yields were ca. 6% lower than the GC yields. Compounds **3b,c** are not described below in view of their earlier isolation.[12] Base-induced equilibria were established by treatment of a solution of 40 mg of ketone 3 in 3 mL of dry ethanol with an ethanolic sodium ethoxide solution (from 250 mg of sodium in 10 mL of dry ethanol), stirring under nitrogen at room temperature, and GC analysis.

4,4-Dimethyl-4aβ,5,8,8aβ-tetrahydro-1(4*H*)-naphthalenone (3a): mp 73–74 °C; IR 1690 (C=O, s), 1628 (C=C, w) cm^{-1}; ^1H NMR δ 1.10, 1.31 (s, 3 each, Me_2), 5.50 (m, 2, olefinic Hs), 5.75 (d, 1, J = 10 Hz, H-2), 6.25 (dd, 1, J = 10, 2 Hz, H-3). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.43; H, 9.20. 2,4-Dinitrophenylhydrazone,[13] mp 172–173 °C.

2,4,4-Trimethyl-4aβ,5,8,8aβ-tetrahydro-1(4*H*)-naphthalenone (3d): IR 1685 (C=O, s), 1635 (C=C, w) cm^{-1}; ^1H NMR δ 1.06, 1.28 (s, 3 each, Me_2), 1.67 (s, 3, olefinic Me), 5.47 (br s, 2, olefinic Hs), 5.97 (br s, 1, H-3). 2,4-Dinitrophenylhydrazone,[13] mp 158–160 °C. Anal. Calcd for $C_{19}H_{22}O_4N_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.70; H, 6.03; N, 15.10.

2,4,4,7-Tetramethyl-4aβ,5,8,8aβ-tetrahydro-1(4*H*)-naphthalenone (3f): mp 34–35 °C; IR 1675 (C=O, s), 1635 (C=C, w) cm^{-1}; ^1H NMR δ 1.05, 1.25 (s, 3 each, Me_2), 1.65, 1.67 (s, 3 each, olefinic Me_2), 5.17 (br s, 1, H-6), 6.03 (br s, 1, H-3). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.60; H, 9.82.

4,4,7,8aβ-Tetramethyl-4aβ,5,8,8a-tetrahydro-1(4*H*)-naphthalenone (3g): IR 1680 (C=O, s), 1650 (C=C, w) cm^{-1}; ^1H NMR δ 0.97, 1.10, 1.15 (s, 3 each, Me_3), 1.62 (s, 3, olefinic Me), 5.30 (br s, 1, H-6), 5.60 (d, 1, J = 10 Hz, H-2), 6.28 (d, 1, J = 10 Hz, H-3). 2,4-Dinitrophenylhydrazone, mp 172–173 °C. Anal. Calcd for $C_{20}H_{24}O_4N_4$: C, 62.49; H, 6.29; N, 14.58. Found: C, 62.75; H, 6.20; N, 14.61.

2,4,4,8α-Tetramethyl-4aβ,5,8,8aβ-tetrahydro-1(4*H*)-naphthalenone (3h): mp 43–44 °C; IR 1690 (C=O, s), 1650 (C=C, w) cm^{-1}; ^1H NMR δ 1.05, 1.30 (s, 3 each, Me_2), 1.38 (d, 3, J = 6 Hz, 8-Me), 1.65 (s, 3, olefinic Me), 5.42 (m, 2, olefinic Hs), 5.90 (br s, 1, H-3). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.43; H, 9.96.

4,4,8α,8aβ-Tetramethyl-4aβ,5,8,8a-tetrahydro-1(4*H*)-naphthalenone (3i): IR 1675 (C=O, s), 1635 (C=C, w) cm^{-1}; ^1H NMR δ 0.88, 1.00 (s, 3 each, Me_2), 1.08 (d, 3, J = 6 Hz, 8-Me), 1.28 (s, 3, olefinic Me), 5.52 (m, 2, olefinic Hs), 5.75 (d, 1, J = 10 Hz, H-2), 6.35 (d, 1, J = 10 Hz, H-3). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.43; H, 9.96. 2,4-Dinitrophenylhydrazone, mp 195–196 °C.

4,4,8α-Trimethyl-4aβ,5,8,8aα-tetrahydro-1(4*H*)-naphthalenone (4c): IR 1690 (C=O, s) cm^{-1}; ^1H NMR δ 1.06, 1.12 (s, 3 each, Me_2), 1.23 (d, 3, J = 6 Hz, 8-Me), 5.40 (m, 2, olefinic Hs), 5.62 (dd, 1, J = 10, 2 Hz, H-2), 6.40 (dd, 1, J = 10, 2 Hz, H-3). 2,4-Dinitrophenylhydrazone, mp 174–175 °C. Anal. Calcd for $C_{19}H_{22}O_4N_4$: C, 61.61; H, 5.99; N, 15.13. Found: C, 61.48; H, 5.94, N, 15.20.

2,4,4,8α-Tetramethyl-4aβ,5,8,8aα-tetrahydro-1(4*H*)-naphthalenone (4h): IR 1685 (C=O, s), 1645 (C=C, w) cm^{-1}; ^1H NMR δ 1.02, 1.10 (s, 3 each, Me_2), 1.18 (d, 3, J = 6 Hz, 8-Me), 1.70 (s, 3, olefinic Me), 5.43 (m, 2, olefinic Hs), 6.20 (br s, 1, H-3).

(12) Liu, H.-J.; Browne, E. N. C. *Can. J. Chem.* **1979**, *57*, 377.

(13) The bridgehead configuration of the bicycle may have undergone a change during derivative formation.

2,4-Dinitrophenylhydrazone, mp 200–201 °C. Anal. Calcd for $C_{20}H_{24}O_4N_4$: C, 62.49; H, 6.29; N, 14.58. Found: C, 62.57; H, 6.34; N, 14.70.

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Registry No. **1a**, 106-99-0; **1b**, 78-79-5; **1c**, 2004-70-8; **2a**, 1073-14-9; **2b**, 38441-63-3; **3a**, 65595-97-3; **3a**·DNP, 85407-52-9; **3d**, 85407-53-0; **3d**·DNP, 85407-54-1; **3f**, 85407-55-2; **3g**, 85407-56-3; **3g**·DNP, 85407-57-4; **3h**, 85407-58-5; **3i**, 85407-59-6; **3i**·DNP, 85407-60-9; **4c**, 78006-86-7; **4c**·DNP, 85407-61-0; **4h**, 85407-62-1; **4h**·DNP, 85407-63-2.

7α- or 7β-(4-Phenylbutyl)dihydrocodeine Derivatives[1]

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A lipophilic 4-phenylbutyl group was selectively incorporated into the 7α- or 7β-position of the morphine nucleus by use of 6,7-oxymethylene (oxetane) intermediates. 7,7-Bis[(tosyloxy)methyl]dihydroisocodeine (**2**) with dilute NaOH gave 6β,7β-(oxymethylene)-7α-[(tosyloxy)methyl] compound **3**. Displacement of the tosyloxy group with NaOAc followed by hydrolysis and oxidation gave 6β,7β-(oxymethylene)-7α-formyl derivative **6**. Wittig condensation with cinnamyltriphenylphosphorane and hydrogenation of the resulting diene **7** gave 6β,7β-(oxymethylene)-7α-(4-phenylbutyl)dihydroisocodeine (**8**). Oxidation of **2** to 6-oxo ditosylate **10** and then $NaBH_4$ reduction, yielding 6α-ol **11**, allowed ring closure to 6α,7α-(oxymethylene)-7β-[(tosyloxy)methyl] compound **12**. Reaction of **12** with NaOAc to give **13** followed by continuation of the reaction sequence as described above yielded the α-oxetane–7β-(4-phenylbutyl) derivative **17**. Reaction of 7,7-bis(hydroxymethyl)dihydroisocodeine (**1**) with acetone–*p*-TsOH gave predominantly isopropylidene derivative **23** with the 6β- and 7α-hydroxyl functions blocked. Oxidation of **23** to 7β-formyl derivative **33**, followed by condensation with cinnamyltriphenylphosphorane, hydrolysis of the isopropylidene group, and catalytic reduction gave 7α-(hydroxymethyl)-7β-(4-phenylbutyl)dihydroisocodeine (**36**). The 7β-arylalkyl derivatives were potent narcotic agonists in contrast to the 7α-substituted compound which was inactive.

We have been engaged during the past several years in a program to explore the chemistry of the morphine C ring.[2] The objective of these studies was to delineate what factors are responsible for the potent narcotic agonist activity found in a series of 6,14-*endo*-ethenotetrahydrooripavine derivatives.[3]

Our work led to the preparation of 7,7-dimethyldihydrocodeinones[4] from 7,7-bis(hydroxymethyl)dihydroisocodeine. This latter material was prepared via the aldol–crossed Cannizzaro reaction of dihydrocodeinone with formaldehyde as reported some time ago by Mannich and Schulte.[5] The transformation of the corresponding 8β-alkyl-7,7-bis(hydroxymethyl) compounds, by way of tosylated intermediates, to 8β-alkyl-7,7-dimethyl derivatives involved oxetane ring formation.[4] These oxymethylene compounds have now been used as synthetic tools for further study of morphine C-ring chemistry. This report details the use of these novel oxetane ring containing compounds for the selective preparation of some 7α- and 7β-(arylalkyl)dihydrocodeines.

The preparation of 7α-monoalkyl-substituted derivatives of dihydrocodeinone, by use of different methodology, was recently reported by us.[6] These compounds did not have potent narcotic agonist activity. The 7α-arylalkyl derivative **8**, prepared in the course of this present work, was likewise inactive. To further explore structure–activity relations, the corresponding 7β-arylalkyl derivative **17**, which has a 6α,7α-oxymethylene ring, was prepared. Unexpectedly, this compound was found to be a very potent narcotic agonist. In light of this result, other 7β-(4-phenylbutyl) derivatives were prepared with either a hydroxymethyl or methyl group in the 7α-position.

We previously reported that treatment of ditosylate **2** with $LiEt_3BH$ at reflux yielded 6β,7β-(oxymethylene)-7α-methyldihydroisocodeine.[4] More recently, we found that treatment of **2** with dilute NaOH in refluxing 2-butanone results in closure to a 6β,7β-oxetane ring with retention of the 7α-tosyloxy function to give **3** (Scheme I). Displacement of the tosyl group in **3** with NaOAc gave **4** which was hydrolyzed to 7α-hydroxymethyl compound **5**. Oxidation to formyl derivative **6** followed by Wittig condensation with cinnamyltriphenylphosphorane gave a moderate yield of diene **7**. Hydrogenation of **7**, in the presence of a trace of HCl, gave a mixture of the desired product **8** together with oxymethylene-cleaved material **9**.[7] Compound **8** did not show narcotic agonist activity at 10 mg/kg in the mouse writhing assay.

The introduction of the same arylalkyl group into the 7β-position was accomplished in the following manner. Ditosylate **2** was smoothly oxidized to crystalline 6-oxo compound **10** in good yield by using Me_2SO–trifluoroacetic anhydride (TFAA).[8] Sodium borohydride reduction of **10** gave predominantly the 6α-ol **11**, with only traces of the 6β isomer **2** being observed. Ring closure to the α-oxetane **12**, followed by tosylate displacement with acetate and hydrolysis, yielded **14**. Oxidation of **14** to **15** and, then, Wittig condensation gave diene **16**. Catalytic reduction of **16**, in the absence of HCl, proceeded very slowly to eventually give a moderate yield of saturated compound

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