Convenient Method for the Synthesis of Lineatin, a Pheromone Component of *Trypodendron lineatum*

Peter Baeckström,* Lanna Li, Iwona Polec, C. Rikard Unelius, and Weerappuli R. Wimalasiri

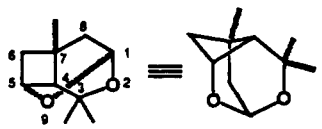
Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

Received April 18, 1990

Synthesis of racemic lineatin (1), a pheromone component of *Trypodendron lineatum*, is described. Condensation of 5-methyl-5-hexen-2-one (2) and triethyl phosphonoacetate with $LiN(SiMe_3)_2$ gave esters 3, which upon hydrolysis gave acids **4a-f**. The bicyclo[3.2.0] ring compounds **5** and **6** were obtained via an intramolecular [2 + 2] addition by refluxing underivatized carboxylic acids **4a-f** with NaOAc and Ac_2O. Compound **5** was isomerized to the thermodynamically more stable isomer **6** using a Pd/C catalyst activated with hydrogen. Reduction of **6** with $LiAlH_4$ gave the endo and exo isomers **7a** and **7b** (4:1). Isolation of the alcohol **7a** followed by acetylation gave **8**. Subsequent oxidation with OsO_4 and methylmorpholine *N*-oxide gave diol **9**. Cleavage of **9** with H_5IO_6 in diethyl ether gave keto aldehyde **10**, which was converted to keto acetal **11**. Treatment of **11** with MeMgBr followed by acidic workup gave 1. The overall efficiency is ~20%.

Introduction

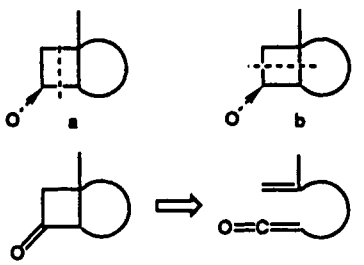
The striped ambrosia beetle, *Trypodendron lineatum* (Olivier), which bores tunnels into the sapwood of a number of species of coniferous trees, is a forest pest both in Europe and in North America. The commercial lures, i.e., Linoprax or Biolure, sold for mass-trapping of the female of *T. lineatum*, contain lineatin (1)[1] as their most expensive component.[2] The compound is essential in the aggregation pheromone as shown in both laboratory[3] and field trials.[4]



1

The absolute configuration of the biologically active (+)-enantiomer of lineatin has been determined to be 1*R*,4*S*,5*R*,7*R* (1);[5] however, the racemic mixture can also be used in lures since the (-)-enantiomer does not posses and inhibitory effect.[6]

A number of syntheses of racemic and optically active lineatin have been described in the literature.[5,7,8] With one exception,[8] all [2 + 2] cycloadditions to form the cyclobutane ring have been of type a, as shown in eq 1. We have developed a convenient method for the synthesis of



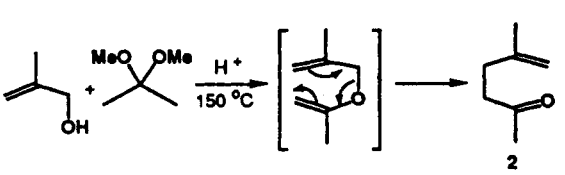
(1)

racemic lineatin utilizing the b-type cyclization. It is based on inexpensive reagents and has the advantage of placing oxygen in the desired corner of the cyclobutane ring in a one-step procedure as depicted in the lower part of eq 1 and Scheme I.

Results and Discussion

Intramolecular [2 + 2] additions of ketenes to double bonds leading to carbocycles has recently been reviewed.[9] It has been shown that the ideal tether length between the ketene and the double bond is three carbon atoms. The most commonly used ketene precursors are acid chlorides or amides derived from the corresponding carboxylic acids. A reference is also made to a reaction type whereby underivatized acids undergo cyclizations when heated in a mixture of anhydrous NaOAc and Ac_2O, i.e., Beereboom's reinvestigation of the cyclization of geranic acid.[10] A mixed anhydride is probably formed in situ, yielding a vinyl ketene on elimination of acetic acid.[11] This appealingly simple method for ring closure was successfully used as the key step in our approach to lineatin (Scheme I).

Ketone 2 was prepared by a Claisen rearrangement using methallyl alcohol (2-methyl-2-propenol) and acetone dimethyl acetal (2,2-dimethoxypropane) (eq 2). Although



2

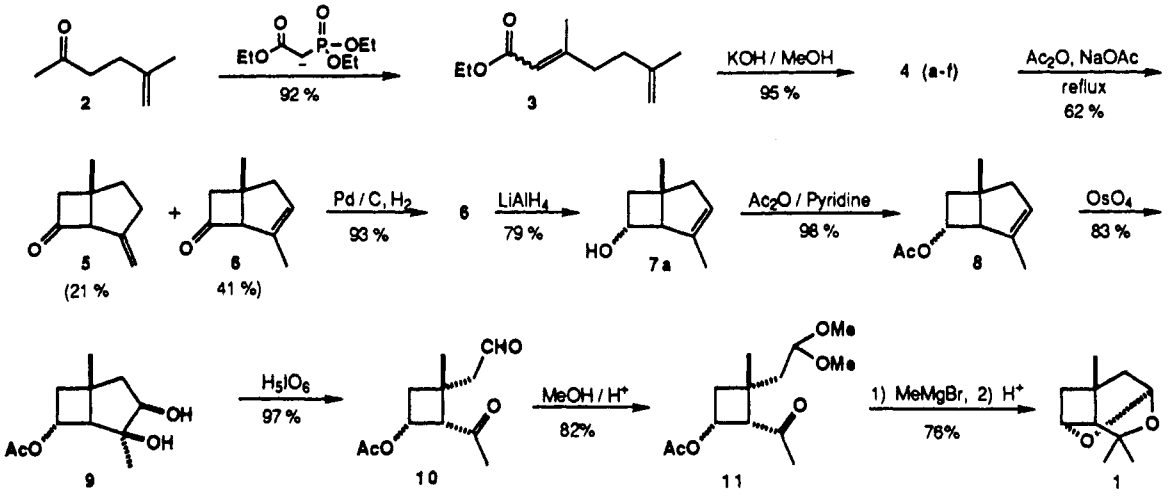
(2)

this type of reaction has previously been published,[12]

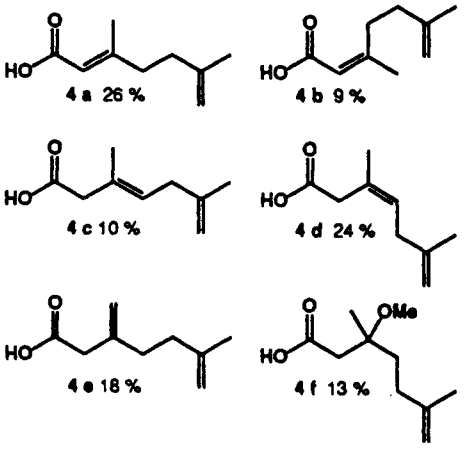
(1) MacConnell, J. G.; Borden, J. H.; Silverstein, R. M.; Stokkink, E. *J. Chem. Ecol.* **1977**, *3*, 549.
(2) (a) McLean, J. A.; Bakke, A.; Niemeyer, H. *Can. Entomol.* **1987**, *119*, 273. (b) König, E. *J. Appl. Entomol.* **1988**, *106*, 262.
(3) (a) Borden, J. H.; Brownlee, R. G.; Silverstein, R. M. *Can. Entomol.* **1968**, *100*, 629. (b) Borden, J. H.; Slater, C. E. *Ann. Entomol. Soc. Am.* **1969**, *62*, 454.
(4) (a) Rudinsky, J. A.; Daterman, G. E. Z. *Angew. Entomol.* **1964**, *54*, 300. (b) Rudinsky, J. A.; Daterman, G. E. *Can. Entomol.* **1964**, *96*, 1339. (c) Chapman, J. A. *Can. Entomol.* **1966**, *98*, 50.
(5) (a) Mori, K.; Uematsu, T.; Minobe, M.; Yanagi, K. *Tetrahedron Lett.* **1982**, *23*, 1921. (b) Mori, K.; Uematsu, T.; Minobe, M.; Yanagi, K. *Tetrahedron* **1983**, *39*, 1735.
(6) (a) Borden, J. H.; Oehlschlager, A. C.; Slessor, K. N.; Chong, L.; Pierce, H. D. *Can. Entomol.* **1980**, *112*, 107. (b) King, C. J.; Oehlschlager, A. C.; Borden, J. H. Z. *Angew. Entomol.* **1983**, *95*, 531.
(7) (a) Borden, J. H.; Handley, J. R.; Johnston, B. D.; MacConnell, J. G.; Silverstein, R. M.; Slessor, K. N.; Swigar, A. A.; Wong, D. T. W. *J. Chem. Ecol.* **1979**, *5*, 681. (b) Slessor, K. N.; Oehlschlager, A. C.; Johnston, B. D.; Pierce, H. D., Jr.; Grewal, S. K.; Wickremasinghe, L. K. G. *J. Org. Chem.* **1980**, *45*, 2290. (c) Mori, K.; Sasaki, M. *Tetrahedron* **1980**, *36*, 2197. (d) McKay, W. R.; Ounsworth, J.; Sum, P. E.; Weiler, L. *Can. J. Chem.* **1982**, *60*, 872. (e) White, J. D.; Avery, M. A.; Carter, J. P. *J. Am. Chem. Soc.* **1982**, *104*, 5486. (f) Kandil, A. A.; Slessor, K. N. *J. Org. Chem.* **1985**, *50*, 5649. (g) Kametani, T.; Toya, T.; Ueda, K.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2433.
(8) Skatteböl, L.; Stenström, Y. *Tetrahedron Lett.* **1983**, *24*, 3021.
(9) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793.
(10) (a) Beereboom, J. J. *J. Org. Chem.* **1965**, *30*, 4230. (b) Beereboom, J. J. *J. Am. Chem. Soc.* **1963**, *85*, 3525.
(11) Erman, W. F.; Treptow, R. S.; Bazukis, P.; Wenkert, E. *J. Am. Chem. Soc.* **1971**, *93*, 657.

0022-3263/91/1956-3358$02.50/0

Scheme I. Synthesis of Lineatin (for 4a–f, See Text)



considerable time was spent in finding the proper reaction conditions to achieve a reasonable yield (caution: the reaction has to be performed in a metal autoclave; an explosion occurred when the reaction was performed in sealed glass tubes). The starting material for the cyclization was made by condensation of 5-methyl-5-hexen-2-one (**2**) and triethyl phosphonoacetate at low temperature. An excellent yield of ethyl 3,6-dimethyl-2,6-heptadienoates (**3**; 92%, E:Z ≈4:1) was achieved when $LiN(SiMe_3)_2$ was used as the base in the condensation reaction.[13] When LDA was used, the yield of esters **3** was 64% (E:Z ≈ 3:1). The esters were subsequently hydrolyzed with 10% KOH/MeOH under reflux conditions. This gave a mixture of acids in 95% yield. The mixture consisted of five isomers **4a–e** (~3:1:1:3:2) and the acid **4f** (~13% of the mixture) derived from conjugate addition of MeOH to the double bond.



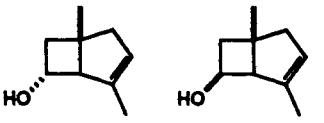
Treatment of the unseparated mixture of acids **4a–f**, in two installments, with anhydrous NaOAc and Ac_2O under reflux conditions resulted in the bicyclo[3.2.0] ring compounds **5**[13] and **6** (~1:2) in 62% total yield. Compound **5** was isomerized to the thermodynamically more stable isomer **6** using a Pd/C catalyst activated with hydrogen. In order to minimize the competing reduction of the double bonds, the reaction was monitored by GC. The catalyst $Pd/CaCO_3$ was also tried for this type of isomerization, as suggested in the literature.[14] However, our specimen

Table I. Reduction of 6 to 7a and 7b with Different Reducing Agents

reducing agent	yield (%)	ratio (7a:7b)
$LiAlH_4$	99	80:20
$(i\text{-}Bu)_2AlH$	90	76:24
$NaAlH_2(OC_2H_4OMe)_2$	81	65:35
$LiBEt_3H$	47	>99:1

of this catalyst, when used in pentane at room temperature, did not induce isomerization; neither did $Pd(Ph_3P)_4$ and $PdCl_2(PhCN)_2$ under the same conditions.

In order to get the highest yield of the endo alcohol **7a** from compound **6**, $LiAlH_4$ was selected after testing DIBAL, $NaAlH_2(OC_2H_4OMe)_2$ (Red-Al, Aldrich)[15] and $LiB(C_2H_5)_3H$ (Super-Hydride, Aldrich)[16] as reducing agents. The results are shown in Table I.



To determine the anti and syn relationship between the hydroxyl group and the methyl group on the four-membered ring of compounds **7a** and **7b**, NOE measurements were performed. The methyl protons on C-1 were irradiated. For compound **7a**, enhanced signals were observed for the protons on C-5 and C-6 and the proton with the lower shift (δ 2.32) on C-7. In compound **7b**, enhanced signals were observed for the proton on C-5 and the proton with the higher shift (δ 1.75) on C-7, but not for the proton attached to C-6. From these experiments, we conclude that for compound **7a** the methyl and the hydroxyl group have an anti configuration, whereas for compound **7b** the corresponding substituents have a syn configuration.

The next step in the sequence was to obtain the keto aldehyde **10** by cleavage of the double bond. The aldehyde was then to be selectively protected as the dimethyl acetal in order to enable a Grignard reaction with the keto function. A published one-pot reaction for this sequence,[17] i.e., ozonolysis in methanol using dimethyl sulfide and a catalytic amount of p-toluenesulfonic acid during workup, was tried. Although this method works well as stated for limonene, it was not successful for compound **8**. In fact,

(12) Saucy, G.; Marbet, R. *Helv. Chim. Acta.* **1967**, *50*, 2091.
(13) Snider, B. B.; Ron, E.; Burbaum, B. W. *J. Org. Chem.* **1987**, *52*, 5413.
(14) Kulkarni, Y. S.; Niwa, M.; Ron, E.; Snider, B. B. *J. Org. Chem.* **1987**, *52*, 1568.
(15) Cerny, M.; Malek, J. *Tetrahedron Lett.* **1969**, 1739.
(16) Corey, E. J.; Carney, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 7319.
(17) Heath, R. R.; Doolittle, R. E.; Sonnet, P. E.; Tumlinson, J. H. *J. Org. Chem.* **1980**, *45*, 2910.

Table II. ^1H and ^{13}C NMR Data (δ) of Acids 4a–f

	4a	4b	4c[a]	4d	4e	4f
2-H	5.71 (br s)	5.71 (s)	3.08 (s, 2 H)	3.10 (s, 2 H)	3.11 (s, 2 H)	2.61 (d, J = 14.5 Hz) 2.49 (d, J = 14.5 Hz)
4-H	2.33–2.29 (2 H, m)	2.78 (2 H, t, J = 8.0 Hz)	5.39 (br t, J = 6.9 Hz)	5.45 (t, J = 7.4 Hz)	2.28 (2 H, m)	1.75–1.70 (2 H, m)
5-H	2.21–2.17 (m, 2 H)	2.18 (2 H, t, J = 8.0 Hz)	2.73 (2 H, d, J = 6.9 Hz)	2.72 (2 H, d, J = 7.4 Hz)	2.18 (2 H, m)	2.10–1.90 (2 H, m)
7-H	4.75 (s) 4.70 (s)	4.74 (s) 4.72 (s)	4.73 (s) 4.70 (s)	4.72 (s) 4.70 (s)	4.73 (s) 4.70 (s)	4.71 (s) 4.69 (s)
6-Me	1.74 (s)	1.75 (s)	1.74 (s)	1.72 (s)	1.74 (s)	1.73 (s)
3-Me	2.19 (d, J = 1.1 Hz)	1.94 (d, J = 1.2 Hz)	1.73 (s)	1.84 (s)	4.98 (s) 4.96 (s)	1.31 (s)
3-OMe						3.27 (s)
C-1	172.4	171.2	177.5	177.9	177.5	174.5
C-2	115.3	115.7	44.8	37.1	41.7	43.2
C-3	162.7	163.4	129.2	128.9	141.6	76.1
C-4	39.3	32.1	127.5	127.4	33.9	31.5
C-5	35.5	36.2	37.1	36.5	35.6	35.4
C-6	144.4	145.2	145.1	144.5	145.1	145.2
C-7	110.7	110.4	110.3	110.5	110.3	110.0
6-Me	22.3	22.2	22.6	22.5	22.4	22.6 (or 22.5)
3-Me	19.1	25.5	16.2	23.9	114.4	22.5 (or 22.6)
3-OMe						49.2

[a] Data from a spectrum of a mixture of 4c and 4e.

our attempts to obtain keto aldehyde **10** by ozonolysis and subsequent workup with dimethyl sulfide failed. When the reaction was performed in dichloromethane with tetrabutylammonium borohydride (n-Bu_4NBH_4) present during ozonolysis, the keto aldehyde **10** could be isolated in ~30% yield.

Hence, compound **8** was converted to diol **9** with osmium tetraoxide and N-methylmorpholine N-oxide[18] in 83% yield after chromatography on silica gel. A rapid and clean reaction occurred when the diol was treated with periodic acid in diethyl ether.[19] The desired keto aldehyde **10** was obtained in excellent yield. The cleavage reaction with sodium periodate in water using a phase-transfer catalyst (n-Bu_4NBr) dissolved in methylene chloride gave less satisfactory results.

Conversion of the aldehyde group of compound **10** with p-TsOH in methanol gave the keto acetal **11** in 82% yield. The acetal **11** was then treated with methylmagnesium bromide, and on acidic workup, lineatin (**1**) was formed in good yield. Calculated from ketone **2**, the overall efficiency of the sequence is ~20%.

Experimental Section

All reactions of air- and water-sensitive materials were performed under N_2 or Ar. Liquid chromatography (LC) was performed on silica gel (Merck 60, 0.040–0.063 mm) dry-packed in 15- or 25-mm inner diameter (i.d.) glass columns. Gradient elution with hexane and increasing amounts of ethyl acetate, unless otherwise stated, was performed as described by Baeckström et al.[20] TLC was performed on silica gel (Merck 60, HF precoated aluminium foil) with 20% ethyl acetate in hexane as the eluant unless otherwise stated. The plates were developed with vanillin and H_2SO_4 in ethanol. NMR spectra were recorded in $CDCl_3$ on Bruker WP 200 and AM 400 spectrometers. Analytical GC was performed with an FID detector by use of a 30-m DB-23 or a 30-m DB-FFAP fused silica capillary column. Mass spectra (70 eV) were recorded on a GC–MS instrument supplied with a Superox FA fused silica capillary column. Melting points are uncorrected. ^1H and ^{13}C NMR data of acids **4a–f** and compounds **5–9** are shown in Tables II and III, respectively.

5-Methyl-5-hexen-2-one (2). 2-Methyl-2-propenol (14.4 g, 0.20 mol) was treated with 2,2-dimethoxypropane (62.4 g, 0.60 mol) at 150 °C in a sealed metal cylinder for 24 h in the presence of formic acid (1 mL) and 85% H_3PO_4 (40 μL). The mixture was cooled to room temperature, and the organic layer was washed with 5% $NaHCO_3$ (20 mL) and H_2O (20 mL). The aqueous layer was reextracted with Et_2O (3 × 15 mL), and the combined organic phase was dried ($MgSO_4$). The solvent was removed by distillation at atmospheric pressure, and the residue was distilled under reduced pressure (54–55 °C (30 mmHg)) to afford compound **2** (12.0 g, 54%). ^1H NMR: δ 4.69 (s, 6-1 H), 4.62 (s, 6-1 H), 2.54 (t, J = 7.5 Hz, 3-2 H), 2.25 (t, J = 7.5 Hz, 4-2 H). 2.12 (s, 1-3 H), 1.70 (br s, 5-Me). ^{13}C NMR: δ 208.2 (C-2), 144.3 (C-5), 110.0 (C-6), 41.7 (C-3), 31.3 (C-4), 29.7 (C-1), 22.4 (5-Me).

Ethyl (*E*)- and (*Z*)-3,6-Dimethyl-2,6-heptadienoate (3). To a stirred solution of hexamethyldisilazane (44.0 g, 0.27 mol) in THF (270 mL) at −4 °C (ice and NaCl) was added dropwise a solution of n-BuLi in hexane (2.43 M, 110 mL, 0.27 mol) during 1.5 h. The mixture was cooled to a temperature below −60 °C 1 h after completed addition, and triethyl phosphonoacetate (60.0 g, 0.27 mol) in THF (250 mL) was added dropwise to the mixture during 2 h. After continued stirring for 1.5 h, 5-methyl-5-hexen-2-one (**2**; 20.0 g, 0.18 mol) in THF (150 mL) was added dropwise over a period of 2 h while the temperature was maintained below −60 °C. The mixture was then allowed to reach room temperature overnight. The reaction mixture was washed with saturated NH_4Cl (400 mL), and the aqueous phase was reextracted with Et_2O (3 × 100 mL). Product **3** (30.0 g, 92%) was obtained after LC as a 2*E* and 2*Z* isomeric mixture (4:1 by GC).

(*E*)-**3**. ^1H NMR: δ 5.66 (br s, 2-1 H), 4.72 (s, 7-1 H), 4.67 (s, 7-1 H), 4.13 (q, J = 7.1 Hz, OCH_2–), 2.27–2.24 (m, 4-2 H), 2.18–2.15 (m, 5-2 H), 2.16 (d, J = 1.2 Hz, 3-Me), 1.72 (s, 6-Me), 1.26 (t, J = 7.1 Hz, OCH_2CH_3). ^{13}C NMR: δ 166.8 (C-1), 159.4 (C-3), 144.6 (C-6), 115.7 (C-2), 110.5 (C-7), 59.4 (OCH_2), 39.0 (C-4), 35.5 (C-5), 22.4 (6-Me), 18.7 (3-Me), 14.3 (OCH_2CH_3).

(*Z*)-**3**. ^1H NMR: δ 5.67 (br s, 2-1 H), 4.72 (s, 7-2 H), 4.14 (q, J = 7.1 Hz, OCH_2–), 2.76 (t, J = 8.0 Hz, 4-2 H), 2.17 (t, J = 8.0 Hz, 5-2 H), 1.89 (d, J = 1.3 Hz, 3-Me), 1.77 (s, 6-Me), 1.27 (t, J = 7.1 Hz, OCH_2CH_3). ^{13}C NMR: δ 166.3 (C-1), 159.9 (C-3), 145.3 (C-6), 116.4 (C-2), 110.2 (C-7), 59.5 (OCH_2), 36.1 (C-5), 31.8 (C-4), 25.1 (3-Me), 22.3 (6-Me) 14.3 (OCH_2CH_3).

3,6-Dimethyl-2,6-heptadienoic Acids 4a–f. The *E*/*Z* mixture of **3** (30.0 g, 0.17 mol) was treated with 10% KOH/MeOH (100 mL) under reflux for 4 h. The reaction mixture was cooled to room temperature, and methanol was removed in vacuo. The residue was dissolved in water (100 mL) and extracted with Et_2O (3 × 100 mL) to remove nonacidic materials. The aqueous layer was then neutralized with H_2SO_4 (50%) and extracted with Et_2O (4 × 100 mL) to give a mixture of six acids **4a–f** (26:9:10:24:18:13)

(18) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(19) Fieser, L. F.; Fieser, M. *Reagents For Organic Synthesis*; John Wiley and Sons: New York, 1967; Vol. 1, 817.
(20) Baeckström, P.; Stridh, K.; Li, L.; Norin, T. *Acta Chem. Scand. B* **1987**, *41*, 442.

Table III. ^1H and ^{13}C NMR Data (δ) of Compounds 5–9

	5	6	7a	7b	8	9
2-H	1.95 (ddd, J = 12.7, 5.3, 2.0 Hz)	2.56–2.55 (m, 2 H)	2.24–2.21 (m, 2 H)	2.26–2.18 (m, 2 H)	2.29–2.23 (m, 2 H)	1.93 (dd, J = 12.0, 6.8 Hz)
	1.77 (ddd, J = 12.7, 12.7, 8.0 Hz)					1.68–1.62 (dd, J = 12.0, 10.1 Hz)
3-H	2.59–2.46 (m, 2 H)	5.43 (br s)	5.49 (s)	5.28 (s)	5.45 (br s)	4.23 (dd, J = 10.1, 6.8 Hz)
5-H	3.47–3.45 (m)	3.58 (br, s)	2.94 (br s)	2.53 (br s)	3.04 (br, s)	2.48 (dd, J = 9.1, 2.4 Hz)
6-H			4.51 (ddd, J = 8.2, 7.5 4.7 Hz)	4.00 (ddd, J = 6.8, 2.9, 1.9 Hz)	5.27 (ddd, J = 8.2, 8.2, 7.8 Hz)	5.23 (ddd, J = 9.1, 9.1, 7.0 Hz)
7-H	2.97 (dd, J = 18.2, 2.6 Hz)	3.04 (dd, J = 17.7, 3.0 Hz)	2.32 (ddd, J = 11.9, 8.2, 2.4 Hz)	1.78 (ddd, J = 13.0, 2.9, 1.9 Hz)	2.27 (ddd, J = 11.7, 8.3, 3.3 Hz)	2.25 (ddd, J = 13.2, 9.1, 2.4 Hz)
	2.87 (dd, J = 18.2, 4.6 Hz)	2.87 (dd, J = 17.7, 4.8 Hz)	1.75 (ddd, J = 11.9, 7.5, 1.0 Hz)	2.27 (ddd, J = 13.0, 6.8, 1.2 Hz)	1.98 (ddd, J = 11.7, 8.3, 1.1 Hz)	1.78 (dd, J = 13.2, 7.0 Hz)
1-Me	1.45 (s)	1.38 (s)	1.19 (s)	1.34 (s)	1.24 (s)	1.23 (s)
4-Me	4.95 (d, J = 1.2 Hz)	1.73 (s)	1.82 (s)	1.73 (s)	1.72 (s)	1.32 (s)
(=CH_2)	4.90 (d, J = 1.2 Hz)					
6-OH(OAc)			1.94 (br s)	1.87 (br s)	2.03 (s)	2.02 (s)
C-1	33.9	35.5	36.6	40.0	38.4	36.1
C-2	33.4	47.2	48.6	47.4	48.0	46.5
C-3	39.4	127.0	127.7	125.7	127.1	78.3
C-4	148.0	135.4	139.2	139.4	139.4	80.2
C-5	75.5	80.1	60.9	64.3	58.8	57.3
C-6	207.1	207.8	68.0	71.5	69.5	63.7
C-7	56.8	59.0	45.2	44.4	40.8	40.0
1-Me	24.9	24.2	25.0	27.5	24.4	26.7
4-Me(CH_2)	109.1	15.5	17.3	14.7	16.6	21.6
OAc					21.1	21.1
C=O					170.7	170.2

in 95% yield (24.1 g). The elution order on the FFAP column of the GC was **4b**, **4d**, **4a**, **4c**, **4e**, and **4f**. The isolation of each acid was achieved by LC.

1-Methyl-4-methylenebicyclo[3.2.0]heptan-6-one (5) and 1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-one (6). A solution of the six acids **4a–f** (24.1 g, 0.16 mol) and anhydrous NaOAc (9.88 g, 0.12 mol) in 75 mL of acetic anhydride was heated to reflux for 4 h. The reaction mixture was cooled to room temperature and poured into 100 mL of ice–water and stirred for 2 h. The suspension was extracted with ether (4 × 100 mL). The combined organic phase was washed with saturated Na_2CO_3 (200 mL) and water (100 mL) and dried ($MgSO_4$). The endo- and exocyclic isomers **6** and **5** and unreacted acids (11.5 g) were obtained after concentration. The yield of **5** and **6**, after purification by LC, was 54% (*endo*/*exo* (2:1)). The recovered unreacted acids were once again subjected to cyclization affording **6** and **5** (2.20 g) and increasing the total yield to 62%. MS of **5**: m/z (relative intensity) 121 (M – Me), 95 (7), 94 (97), 93 (21), 91 (13), 80 (8), 79 (100), 77 (25), 65 (5), 53 (9), 51 (7), 41 (10). MS of **6**: m/z (relative intensity) 136 (M^+, 1), 121 (1), 107 (2), 95 (11), 94 (100), 93 (35), 91 (24), 79 (93), 77 (32), 65 (8), 53 (9), 51 (10).

1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-one (6). Pd/C (5%; 1 g) was activated by passing H_2 (500 mL) through the flask while stirring, and then the H_2 atmosphere was replaced by Ar. A solution of the isomeric mixture of ketones **5** and **6** (11.5 g, 84.6 mmol) in *n*-pentane (35 mL) was added. The mixture was stirred at room temperature, and the reaction was monitored by GC in 20-min intervals. After 3 h, the solution was filtered to remove the catalyst, and the filtrate was evaporated in vacuo. The product (11.4 g, 99%) contained 94% of isomer **6** as determined by GC.

***endo*- and *exo*-1,4-Dimethylbicyclo[3.2.0]hept-3-en-6-ol (7a and 7b).** A solution (20 mL) of $LiAlH_4$ in diethyl ether (1.0 g of $LiAlH_4$ in 26 mL of diethyl ether, 1 M) was added to an ether solution (5 mL) of ketone **6** (5.50 g, 94% by GC, 40.4 mmol) at room temperature. The solution was stirred for 30 min, and an excess of a mixture of $Na_2SO_4 \cdot (H_2O)_{10}$ and Celite 545 (4:1, by weight) was added and stirred until the color changed to white. The solution was filtered and concentrated to obtain **7a** and **7b** (5.30 g, 4:1 by GC). The isomers were separated by LC and the endo isomer **7a** was obtained in 79% yield (4.15 g). MS: m/z (relative intensity) 123 (M – 15, 4), 95 (18), 94 (100), 93 (12), 91 (11), 86 (11), 84 (17), 79 (84), 77 (16), 67 (6), 51 (12), 49 (24).

6-Acetoxy-1,4-dimethylbicyclo[3.2.0]hept-3-ene (8). The alcohol **7a** (3.10 g, 22.5 mmol) was added to acetic anhydride (3 mL) and pyridine (15 mL) at room temperature and left overnight. The mixture was then poured into ice–water, extracted with Et_2O (3 × 100 mL), dried over $MgSO_4$, and chromatographed on silica gel to give **8** (3.95 g, 98%). MS: m/z (relative intensity) 138 (M – 42, 1), 120 (5), 105 (9), 94 (100), 93 (12), 91 (9), 80 (5), 79 (52), 77 (11), 67 (5), 53 (4), 43 (41).

6-Acetoxy-1,4-dimethylbicyclo[3.2.0]heptane-3,4-diol (9). To a stirred mixture of *N*-methylmorpholine *N*-oxide·H_2O (189 mg, 1.2 mmol), H_2O (1 mL), acetone (0.4 mL), and OsO_4 (5.0 mg, 0.02 mmol) in 2-methyl-2-propanol (0.5 mL) was added acetate **8** (200 mg, 1.1 mmol). The reaction mixture was kept under Ar for 24 h at room temperature. Sodium hydrosulfite (20.0 mg), magnesium silicate (1.0 g), and H_2O (2 mL) were added, and the reaction mixture was filtered. The filtrate was neutralized to pH 7 with 1 N H_2SO_4, the acetone was evaporated, and the pH was further adjusted to pH 2. The solution was saturated with NaCl and extracted with EtOAc, and the organic layer was dried ($MgSO_4$). Product **9** was purified by LC (192 mg, 83%) and recrystallized from diethyl ether/hexane (50:50), mp 69–71 °C (uncorrected). MS: m/z (relative intensity) 154 (M – 60, 1), 136 (5), 121 (4), 111 (17), 110 (13), 95 (12), 93 (15), 87 (39), 84 (12), 71 (11), 58 (11), 43 (100).

1-[4-Acetoxy-2-methyl-2-(2-oxoethyl)cyclobutyl]ethanone (10). To a stirred solution of diol **9** (67.5 mg, 0.32 mmol) in Et_2O (3 mL) was added $H_5IO_6 \cdot H_2O$ (84.0 mg, 0.32 mmol) at room temperature. After 20 min, the solution was neutralized by adding saturated $NaHCO_3$ (5 mL) and then extracted with Et_2O. The ether solution was dried ($MgSO_4$) and concentrated to give **10** (65.0 mg, 97%). ^1H NMR: δ 9.65 (s, CHO), 5.23 (dt, J = 7.7 Hz, 3-1 H), 3.70 (d, J = 7.7 Hz, 2-1 H), 3.17 (d, J = 18.6 Hz, CH_2CHO-1 H), 2.68 (br d, J = 18.6 Hz, CH_2CHO-1 H), 2.26 (d, J = 7.7 Hz, 4-2 H), 2.00 (s, OAc), 2.11 (s, 2-COMe), 1.29 (s, 1-Me). ^{13}C NMR:

δ 207.2 (COMe), 201.3 (CHO), 170.6 (OCOMe), 66.8 (C-3), 59.4 (C-2), 51.3 (CH_2CHO), 40.5 (C-4), 33.5 (C-1), 32.5 (COMe), 27.7 (1-Me), 20.8 (OCOMe). MS: *m/z* (relative intensity) 170 (M - 42), 137 (3), 127 (6), 124 (8), 111 (5), 109 (13), 87 (99), 84 (7), 81 (9), 58 (7), 55 (4), 43 (100).

Acetate 8 (250 mg, 1.39 mmol) and *n*-Bu_4NBH_4 (308 mg, 1.25 mmol) were dissolved in 4 mL of CH_2Cl_2, and ozone was passed through the solution at -78 °C for 20 min. After the solution had been purged with N_2, the solvent was removed and a KI solution (1 M, in water) was added, which caused *n*-Bu_4NI to precipitate. The solution was filtered and extracted with Et_2O, and the Et_2O solution was dried ($MgSO_4$). TLC was run in 100% ethyl acetate. Product **10** (98.5 mg, 33%) was purified by LC with gradient elution with hexane and ethyl acetate (20–100%) then ethyl acetate and increasing amounts of MeOH.

1-[4-Acetoxy-2-(2,2-dimethoxyethyl)-2-methylcyclobutyl]ethanone (11). To a stirred solution of **10** (98.5 mg, 0.46 mmol) in methanol (0.5 mL) was added *p*-TsOH (0.36 mg, 0.002 mmol) at room temperature. After 1.5 h, saturated $NaHCO_3$ (5 mL) was added to the mixture and the product was extracted with Et_2O, dried ($MgSO_4$), and concentrated to give acetal **11** (97 mg, 82%). TLC was run in 2% methanol in CH_2Cl_2. ^1H NMR: δ 5.07 (dt, *J* = 7.8, 7.8 Hz, 3-1 H), 4.38 (dd, *J* = 7.3, 4.6 Hz, CH-$(OMe)_2$), 3.48 (dd, *J* = 7.5, 3.2 Hz, 2-1 H), 3.27 (s, OMe), 3.23 (s, OMe), 2.35 (dd, *J* = 11.4, 8.3 Hz, 4-CH_2-1 H), 2.17–2.08 (m, 4-1 H and $HCOCH_2$-1 H), 2.08 (s, COMe), 1.99 (s, OAc), 1.64 (dd, *J* = 14.2, 4.6 Hz, $HCOCH_2$-1 H), 1.26 (s, 1-Me). ^{13}C NMR: δ 206.4 (CO), 170.9 (CO), 102.3 ($CH(OMe)_2$), 66.5 (C-3), 60.1 (C-2), 53.8 (OMe), 51.5 (OMe), 39.9 (1-CH_2), 39.8 (C-4), 34.9 (C-1), 33.2 (COMe), 27.1 (1-Me), 20.8 (OCOMe). MS: *m/z* (relative intensity) 201 (M - 57, 2), 169 (3), 141 (6), 127 (5), 125 (8), 109 (19), 87 (8), 83 (7), 75 (98), 58 (14), 55 (5), 43 (100).

3,3,7-Trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane (Lineatin, 1). To a solution of acetal **11** (15.0 mg, 0.06 mmol) in dry Et_2O (1 mL) was gradually added MeMgBr (3.0 M solution in Et_2O, 70 μL, 0.21 mmol) at 0 °C (ice bath). The mixture was stirred at room temperature for 1 h, poured into 10% HCl (1 mL, with ice added), and extracted with *n*-pentane (4 × 10 mL). The combined organic phase was washed with saturated $NaHCO_3$ (10 mL), saturated $Na_2S_2O_3$ (5 mL), and H_2O (5 mL) and then dried ($MgSO_4$) and concentrated at atmospheric pressure to give a product (9.0 mg, 92%) containing 83% of compound **1** as determined by GC. TLC was run in 40% ethyl acetate in hexane. Chromatography on silica gel using gradient elution with pentane and increasing amounts of Et_2O gave pure lineatin. ^1H NMR: δ 5.12 (d, *J* = 3.2 Hz, 1-1 H), 4.52 (dd, *J* = 4.2, 3.2 Hz, 5-1 H), 2.12 (dd, *J* = 12.6, 3.2 Hz, 8-1 Hz), 1.99 (dd, *J* = 12.6, 2.3 Hz 8-1 H), 1.93 (dd, *J* = 4.2, 1.3 Hz, 4-H), 1.76 (ddd, *J* = 10.2, 3.2, 2.3 Hz, 6-1 H), 1.68 (d, *J* = 10.2 Hz, 6-1 H), 1.27 (s, 7-Me), 1.20 (s, 3-Me), 1.19 (s, 3-Me). ^{13}C NMR: δ 92.8 (C-1), 72.5 (C-3), 71.5 (C-5), 48.1 (C-4), 43.5 (C-8), 42.1 (C-6), 37.8 (C-7), 29.0 (7-Me), 27.9 (3-Me), 26.3 (3-Me). MS: *m/z* (relative intensity) 168 (M^+, 1), 153 (5), 140 (4), 125 (34), 111 (61), 107 (51), 100 (5), 96 (65), 91 (14), 85 (100), 69 (51), 55 (96), 41 (91). The spectra are consistent with those in the literature.[21]

Acknowledgment. We thank Professor Torbjörn Norin for helpful discussions and Dr. Ulla Jacobsson for running the NOE experiments and being helpful with the NMR work in general. Fina Liotta has been very helpful in correcting the English. We also thank the Swedish Council for Planning and Coordination for Research and the Swedish Science Research Council for financial support.

Supplementary Material Available: ^1H and ^{13}C NMR spectra of intermediates **6–11** and the final product, lineatin (17 pages). Ordering information is given on any current masthead page.

(21) Some previously published ^1H NMR data on lineatin are found in refs 5b, 7d–f.

Synthesis and Complexation Properties of a Water-Soluble Optically Active Cyclophane Incorporating a 4-Naphthyl-1,2,3,4-tetrahydroisoquinoline Unit as a Chiral Spacer

Taxiarchis M. Georgiadis, Millie M. Georgiadis, and François Diederich*

Department of Chemistry and Biochemistry, University of California Los Angeles, California 90024-1569

Received October 22, 1990

The unnatural alkaloid 6-methoxy-4-[2-(6-methoxynaphthalenyl)]-1,2,3,4-tetrahydroisoquinoline (**5**) was prepared as a chiral spacer for optically active cyclophane receptors. Optical resolution of the building block was accomplished through diastereomeric salt formation with dibenzoyltartaric acid. The *S* configuration was assigned by X-ray crystallographic methods to the hydrochloride salt of (-)-**5**. Starting from enantiomerically pure **5**, the optically active cyclophanes (*R*)- and (*S*)-**4** were prepared. These cyclophanes, in which the chiral alkaloid spacer is bridged to an achiral diphenylmethane unit, are efficient binders of naphthalene derivatives in D_2O/CD_3OD (60:40, v/v) and show a modest degree of chiral recognition in the inclusion complexation of naproxen derivatives.

In efforts to generate optically active cyclophane receptors[1] for the enantioselective complexation of naproxen derivatives, we had prepared the macrocycle (+)-**1** which incorporates the 4-phenyl-1,2,3,4-tetrahydroisoquinoline unit **2** as a chiral spacer.[2,3] In D_2O/CD_3OD (60:40, v/v), cyclophane (+)-**1** and the enantiomers of naproxen (**3a**) or its methyl ester (**3b**)[4] form diastereomeric inclusion complexes with different geometries. However, these complexes possess only moderate stability ($K_a \approx 50$–300 L mol^{-1} at 303 K), and MM2 force field calculations

(1) Recent examples of enantioselective complexation of organic guest molecules: (a) Jeong, K.-S.; Muehldorf, A. V.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 6144–6145. (b) Liu, R.; Sanderson, P. E. J.; Still, W. C. *J. Am. Chem. Soc.* **1990**, *55*, 5184–5186. (c) Bradshaw, J. S.; Huszthy, P.; McDaniel, C. W.; Zhu, C. Y.; Dalley, N. K.; Izatt, R. M.; Lifson, S. *J. Org. Chem.* **1990**, *55*, 3129–3137. (d) Castro, P. P.; Georgiadis, T. M.; Diederich, F. *J. Org. Chem.* **1989**, *54*, 5835–5838. (e) Echavarren, A.; Galán, A.; Lehn, J.-M.; De Mendoza, J. *J. Am. Chem. Soc.* **1989**, *111*, 4994–4995. (f) Pirkle, W. H.; Pochapsky, T. *Chem. Rev.* **1989**, 347–362. (g) Petti, M. A.; Shepodd, T. J.; Barrans, R. E., Jr.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 6825–6840.

(2) Dharanipragada, R.; Ferguson, S. B.; Diederich, F. *J. Am. Chem. Soc.* **1988**, *110*, 1679–1690.

(3) There exists no correlation between the arbitrarily chosen absolute configuration in the perspective drawing of (+)-**1** and the experimentally determined sign of optical rotation. The absolute configuration of (+)-**1** is not known.

(4) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203–205.

0022-3263/91/1956-3362$02.50/0