**(2*RS*,3*R*)-[3-[[(*tert*-Butyloxy)carbonyl]amino]-2-hydroxy-5-methylhexanoyl]-L-valyl-L-valyl-aspartic Acid Dibenzyl Ester (9a,b).** Boc-Val-Val-Asp(OBzl)$_2$ (8; 0.612 g, 1 mmol) was deprotected by using 4 N hydrochloric acid in dioxane (30 min, 25 °C). The salt (0.548 g, 1 mmol) was neutralized with triethylamine and coupled with Boc acids **5a,b** (0.261 g, 1 mmol) in 5 mL of methylene chloride with DCC (0.248 g, 1.2 mmol) and HOBt (0.23 g, 1.5 mmol) as coupling reagents. The product was isolated as described above for the tripeptide. Separation of diastereomers was achieved by chromatography over silica gel, eluting with 1% methanol in chloroform.

For **9a**: $R_f$ 0.51; NMR ($CDCl_3$) $\delta$ 0.83–1.01 (6 s, 18 H, $CH_3$), 1.44 (s, 9 H, $(CH_3)_3C$), 1.64–1.71 (m, 3 H), 2.03–2.31 (m, 2 H), 2.82–3.26 (AB, 2 H), 3.86–4.01 (m, 1 H), 4.18–4.29 (m, 1 H), 4.30–4.43 (m, 2 H), 4.87–4.96 (m, 1 H), 5.12–5.29 (m, 4 H), 5.35 (d, $J$ = 10 Hz, 1 H), 5.54 (d, $J$ = 10 Hz, 1 H), 6.83 (d, $J$ = 10 Hz, 1 H), 7.06 (d, $J$ = 10 Hz, 1 H), 7.38–7.61 (m, 10 H).

Anal. Calcd for $C_{40}H_{58}N_4O_{10}$: C, 63.64; H, 7.74; N, 7.42. Found: C, 63.57; H, 7.90; N, 7.46.

For **9b**: $R_f$ 0.56; NMR ($CDCl_3$) $\delta$ 0.77–1.11 (m, 18 H, 6 $CH_3$), 1.44 (s, 9 H, $(CH_3)_3C$), 1.58–1.81 (m, 3 H), 2.01–2.21 (m, 1 H), 2.28–2.45 (m, 1 H), 2.84–3.26 (AB, 2 H), 3.69–3.91 (m, 1 H), 4.04–4.33 (m, 2 H), 4.33–4.44 (m, 1 H), 4.96–5.07 (m, 1 H), 5.11–5.30 (m, 4 H), 5.75 (d, $J$ = 4 Hz, 1 H), 6.86 (d, $J$ = 8 Hz, 1 H), 6.76 (d, $J$ = 10 Hz, 1 H), 6.99 (d, $J$ = 10 Hz, 1 H), 7.35–7.58 (m, 10 H).

**(2*S*,3*R*)-(3-Amino-2-hydroxy-5-methylhexanoyl)-L-valyl-L-valyl-L-aspartic Acid (1, Amastatin).** Tetrapeptide **9a** (0.189 g, 0.25 mmol) was stirred in trifluoroacetic acid at room temperature for 30 min. After removal of the solvent, the residue was dissolved in methanol (15 mL) and hydrogenated (40 psi of hydrogen, 0.05 g of 10% palladium on carbon) for 24 h. The solution was filtered and amastatin (1) isolated by crystallization in 95% overall yield: mp 265–267 °C dec; $[\alpha]^{25}_D$ −40.0° ($c$ 0.44, acetic acid) (lit.[2] $[\alpha]^{22}_D$ −44.3°); $R_f$ 0.46 ($n$-butyl alcohol–acetic acid–water, 4:1:1) (lit.[2] $R_f$ 0.46); $IC_{50}$ (leucine aminopeptidase) = $4 \times 10^{-7}$ M (lit.[2] $IC_{50} = 1 \times 10^{-6}$ M).

**(2*R*,3*R*)-(3-Amino-2-hydroxy-5-methylheptanoyl)-L-valyl-L-valyl-L-aspartic Acid (10).** By use of the procedure described for the synthesis of 1, tetrapeptide **9a** was converted to epiamastatin (**10**) in 95% yield: mp 267–269 °C dec; $[\alpha]^{25}_D$ −26.23° ($c$ 0.44, acetic acid); $R_f$ 0.50 ($n$-butyl alcohol–acetic acid–water, 4:1:1).

**(2*R*,3*R*)-[3-[[(*tert*-Butyloxy)carbonyl]amino]-2-hydroxy-5-methylhexanoyl]-L-leucine Methyl Ester (7a).** Boc acid **5b** (0.20 g, 0.82 mmol) was coupled with L-leucine methyl ester hydrochloride (0.137 g, 0.82 mmol) by using DCC (0.202 g, 0.98 mmol) and HOBt (0.187 g, 1.23 mmol) in methylene chloride. The product was isolated in crude form without chromatography as described for peptide **9** and characterized by NMR and TLC data; $R_f$ 0.43 (5% methanol in chloroform). The presence of Boc-(2*S*,3*S*)-AHMHA-L-Leu-OMe compound **7b** was not detected in the crude isolate.

**(2*S*,3*S*)-[3-[[(*tert*-Butyloxy)carbonyl]amino]-2-hydroxy-5-methylhexanoyl]-L-leucine Methyl Ester (7b).** By use of the procedure developed for the synthesis of dipeptide **7a**, Boc acid **5c** was converted to dipeptide **7b**: $R_f$ 0.51 (5% methanol in chloroform). The presence of diastereomer **7a** was not detected in isolates of dipeptide **7b**.

**Acknowledgment.** This work was supported in part by a grant to D.H.R. from the National Institutes of Health (AM 20100-01) and a grant from Merck Sharp and Dohme, Inc., to Professor T. O. Goodfriend.

**Registry No.** 1, 67655-94-1; **2a**, 70853-11-1; **2b**, 70853-17-7; **2c**, 73397-20-3; **2d**, 73397-21-4; **4a**, 73397-23-6; **4b**, 73397-24-7; **5a**, 73397-25-8; **5b**, 73397-26-9; **5c**, 73397-27-0; **5d**, 73397-28-1; **6a**, 73397-29-2; **6b**, 73397-30-5; **6c**, 73397-31-6; **6d**, 73397-32-7; **7a**, 73397-33-8; **7b**, 73465-21-1; **8**, 70853-22-4; **9a**, 73397-34-9; **9b**, 73465-22-2; **10**, 73465-23-3; Asp(OBzl)$_2$ $p$-toluenesulfonate, 2886-33-1; Boc-L-Val, 13734-41-3; Boc-Val-Asp(OBzl)$_2$, 70853-19-9; Cbz-D-Leu-OMe, 73397-22-5; L-Leu-OMe hydrochloride, 7517-19-3; Boc-L-Leu-OMe, 63096-02-6.

# Lineatin: Regioselective Synthesis and Resolution Leading to the Chiral Pheromone of *Trypodendron lineatum*[1a]

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The aggregation pheromone of a major timber beetle pest, *Trypodendron lineatum* (Oliver), has been synthesized. Racemic lineatin (3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.0$^{4,7}$]nonane, **1**) has been prepared in 2.8% overall yield via an eight-step synthesis commencing from 5-hydroxy-3,5-dimethyl-3-hexenoic acid lactone (**2**), an easily obtainable condensation product of ketene and mesityl oxide. Dichlorocyclopropanation of **3** followed by low-temperature metalation–methylation gave the chlorobicyclo[4.1.0]heptane derivatives **5a** and **5b**, which upon treatment with potassium *tert*-butoxide in $Me_2SO$ gave the expected methylenebicyclo[4.1.0]heptanes **11a** and **11b**. Buffered epoxidation gave the tricyclic oxaspiropentane **12** which was converted to oxabicyclo[4.2.0]octanones **13** and **14**. Borohydride reduction of **13** and **14** gave *endo*-oxabicyclo[4.2.0]octanols **18** and **19**, respectively, which were easily separated by rapid-flow chromatography. Treatment of alcohol **18** with $p$-toluenesulfonic acid (PTSA) gave lineatin whereas **19** gave 3,3,7-trimethyl-2,9-dioxatricyclo[4.2.1.0$^{4,7}$]nonane (**20**), originally considered as one of the two probable structures of lineatin. Production of the optical isomers of lineatin was achieved by resolution of the penultimate synthetic intermediate in the sequence. Diastereomeric carbamates derived from bicyclic alcohol **18** and (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate were prepared and separated by preparative high-pressure LC on silica. LAH reduction of each diastereomer gave the optical isomers of **18** which were cyclized (PTSA) to the enantiomers of lineatin. Congruent arguments based on carbamate chromatographic properties and $^1$H NMR data as well as optical rotatory power of the chiral centers of lineatin led to the assignment of the 1*R*,4*S*,5*R*,7*R* configuration to the dextrorotatory enantiomer of lineatin, (+)-**1**, which was attractive in the field.

The ambrosia beetle, *Trypodendron lineatum* (Oliver), is a major timber pest in the northern hemisphere and primarily attacks fallen and sawn timber. Although both host- and beetle-produced volatiles[1b,2] stimulate attack by

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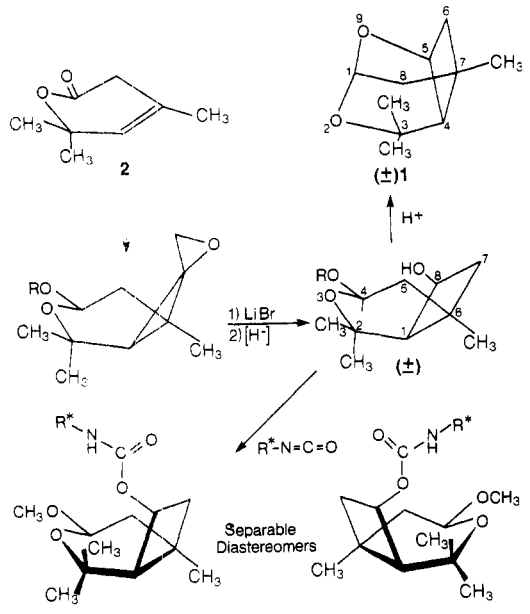
Scheme I

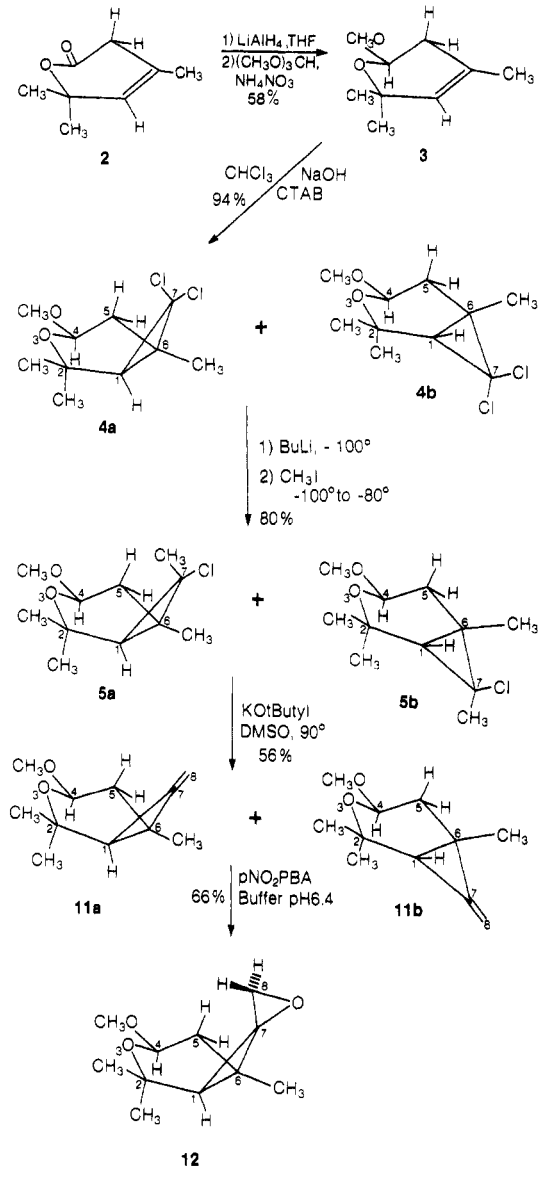



*T. lineatum*, secondary attraction can be elicited in the field[2] and the laboratory[3] solely by a female-produced, aggregation pheromone isolable from frass. The pheromone, lineatin, has recently been identified as 3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.0$^{4,7}$]nonane (**1**) on the basis of convergent spectroscopic data on the natural isolate[4] and biological properties of synthetic material from four independent routes.[5,6]

Three of the previous routes produced low yields of lineatin which was isolated in the final step by preparative GLC from complex mixtures while a fourth route[6] gave lineatin in <0.2% yield after 12 steps. The present route was devised to provide the quantities of lineatin required for field testing and to provide synthetic material for resolution of the pheromone. Pirkle's recent work[7] on resolution suggested that this could be accomplished with a synthetic intermediate near the end of the sequence containing an alcohol derivatizable under neutral or basic conditions with a chiral isocyanate (Scheme I).

The envisioned route to **1** utilizes an intermediate, **2**, previously converted by us[5] to lineatin in low yield by a sequence involving a [2 + 2] cycloaddition. This synthon is particularly attractive since it possesses the proper methyl and oxygen pattern and is available in high purity and good yield from large-batch, $BF_3$-catalyzed reaction of ketene with mesityl oxide.[8] Conversion to lineatin requires elaboration of a *cis*-cyclobutanol (possessing endo stereochemistry at $C_5$) fused to the olefinic carbons of **2** that eventually become $C_4$ and $C_7$ of lineatin. Of the several methods available for cyclobutanol elaboration (e.g., $\Delta$ and $h\nu$ cycloaddition, ring expansion) we chose rearrangement of the requisite oxaspiropentane since the regioselectivity of this process could be predicted to give the desired cyclobutyl oxygen substitution.[9]

Scheme II




## Results and Discussion

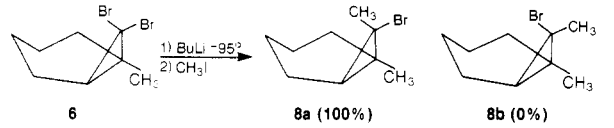
To prevent carbonyl-centered side reactions during carbenoid introduction of the cyclopropyl moiety, **2** was converted to the mixed acetal **3** by partial hydride reduction and catalyzed reaction[10] with trimethyl orthoformate. Reaction of **3** with dichlorocarbene gave isomeric dichlorocyclopropane derivatives **4a** and **4b** in a ratio of 2.1:1 (Scheme II).

The preferred conformation of both isomers can be ascertained to be a half-chair from the similar couplings of the acetal hydrogen to both hydrogens on the adjacent carbon. In a boat conformation both isomers would possess an equatorial methoxy, and the $C_4$–$C_{5a}$ dihedral angle would be approximately 90°. The relative stereochemistries of each isomer in the half-chair can be deduced from the relative shielding observed for the cyclopropyl hy-

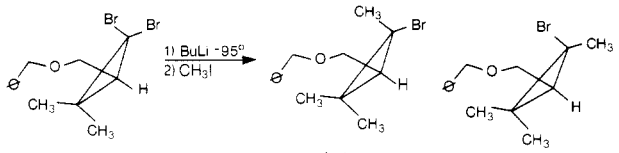
(1) (a) Presented at the 62nd Annual Conference of the CIC Pheromone Symposium, Vancouver, Canada, June 1979. (b) K. Graham, *Can. J. Zool.*, **46**, 905 (1968); H. A. Moeck, *Can. Entomol.*, **102**, 985 (1970).
(2) J. A. Rudinsky and G. E. Daterman, *Z. Angew. Entomol.*, **54**, 300 (1964); *Can. Entomol.*, **96**, 1339 (1964); J. A. Chapman, *ibid.*, **98**, 50 (1966).
(3) J. H. Borden, R. G. Brownlee, and R. M. Silverstein, *Can. Entomol.*, **100**, 629 (1968); J. H. Borden and C. E. Slater, *Ann. Entomol. Soc. Am.*, **62**, 454 (1969).
(4) J. G. MacConnell, J. H. Borden, R. M. Silverstein, and E. Stokkink, *J. Chem. Ecol.*, **3**, 549 (1977).
(5) J. H. Borden, J. R. Handley, B. D. Johnston, J. G. MacConnell, R. M. Silverstein, K. N. Slessor, A. A. Swigar, and D. T. W. Wong, *J. Chem. Ecol.*, **5**, 681 (1979).
(6) K. Mori and M. Sasaki, *Tetrahedron Lett.*, 1329 (1979).
(7) W. H. Pirkle and M. S. Holkstra, *J. Org. Chem.*, **39**, 3904 (1974); W. H. Pirkle and P. L. Rinaldi, *ibid.*, **44**, 1025 (1979).
(8) F. G. Young, *J. Am. Chem. Soc.*, **71**, 1346 (1949).
(9) D. H. Aue, M. J. Meshisknek, and D. F. Shellhamer, *Tetrahedron Lett.*, 4799 (1973).
(10) F. Korte, V. Claussen, and K. Gohring, *Tetrahedron*, **18**, 1257 (1962).
(11) E. V. Dehmlow, *Angew. Chem., Int. Ed. Engl.*, **16**, 493 (1977).

drogens. In the $^1H$ NMR of the major (anti) isomer the $C_1$ hydrogen ($\delta$ 1.24) is deshielded relative to that in the minor (syn) isomer ($\delta$ 1.06). The $C_1$ hydrogen of the anti isomer is expected to be deshielded relative to the syn isomer because of its proximity to the ring oxygen.

The mixture of dichlorocyclopropanes **4a** and **4b** was converted to the methylchlorocyclopropanes **5a** and **5b** by low-temperature lithiation and subsequent alkylation according to the procedure of Kitatani et al.[12] The $\alpha$-haloalkyllithium species derived from dihalocyclopropanes **6** and **7** undergo efficient alkylation at low temperatures upon treatment with excess alkyl halide.[12] Addition of methyl iodide after a short (~10 min) equilibrium period resulted in exclusive formation of endo-methylated products **8a** (vs. **8b**) and **9a** (vs. **9b**).

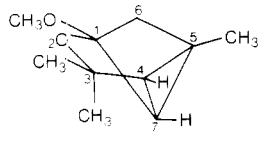



**6** **8a (100%)** **8b (0%)**




**7** **9a (100%)** **9b (0%)**

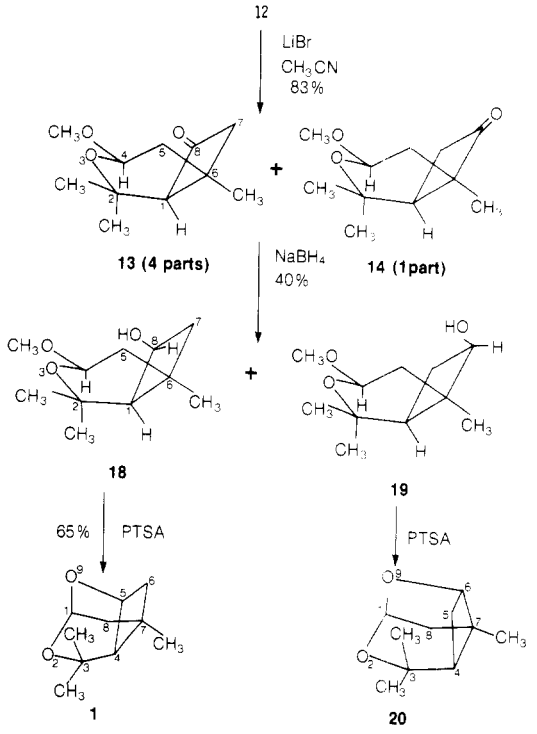
When the dichlorocyclopropanes **4a** and **4b** were subjected to low-temperature (−100 °C) lithiation and the chlorolithium intermediates allowed to equilibrate for a short time (30 min) prior to addition of methyl iodide, the *endo*-chloromethyl isomers **5a** and **5b** were formed as the major products. The only drawback to equilibration prior to alkylation was the formation of 10–20% carbene insertion products from decomposition of the chlorolithium intermediates. The major (83%) insertion product, isolated by preparative GLC, was assigned the tricyclic structure 1-methoxy-3,3,5-trimethyl-2-oxatricyclo-[2.2.1.$0^{5,7}$]heptane (**10**) on the basis of its molecular formula and the presence of three alkyl methyl signals and a methoxy resonance in its $^1H$ NMR spectrum. The $^1H$ NMR spectrum of **10** did not contain an acetal hydrogen but it did exhibit a high-field cyclopropyl hydrogen ($\delta$ 0.99). Intramolecular insertion of appropriately positioned carbenes into carbon hydrogen bonds flanked by oxygen[13] is known to be facile. If the solution derived from lithiation of **4a** and **4b** was allowed to warm above −90 °C *prior* to addition of methyl iodide, major quantities (up to 70%) of **10** and related products were formed at the expense of the major chloromethylcyclopropane isomer (**5a**) formed in the alkylation.



**10**

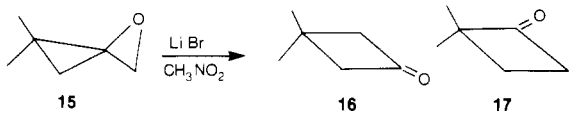
Separation of the chloromethylcyclopropanes **5a** and **5b** (and their $C_7$ isomers) by preparative GLC was thwarted by their facile thermal decomposition. Since subsequent elimination, epoxidation, and rearrangement of all four chloromethylcyclopropanes could be expected to lead to the same cyclobutyl precursor of lineatin, isomer separation was not achieved at this stage. Thus, treatment of the chloromethylcyclopropane isomer mixture with potassium *tert*-butoxide in $Me_2SO$[12] gave methylenecyclopropanes **11a** and **11b** in a 3:1 ratio. Assignment of syn and anti stereochemistry to **11a** and **11b**, respectively, followed from the deshielding of one alkyl methyl in the anti (**11b**) isomer ($\delta$ 1.24 vs. 1.33) and the deshielding of the $C_1$ hydrogen in the syn (**11a**) isomer ($\delta$ 1.18 vs. 1.08) in the $^1H$ NMR spectra of these olefins.

**Scheme III**




Treatment of the methylenecyclopropanes **11a** and **11b** with peracid gave a single isolable epoxide **12** in good yield. A variety of epoxidizing conditions were investigated by utilizing both *m*-chloroperbenzoic acid and *p*-nitroperbenzoic acid. The most suitable procedure involved use of excess *p*-nitroperbenzoic acid at 20–25 °C for 12–16 h in the presence of phosphate buffer (pH 6.4). Although GC/MS analysis of the crude epoxidation reaction mixture revealed that two epoxides were formed, the minor one (presumably arising from the anti olefin **11b**) was thermally unstable, and we did not isolate it in pure form.

Lithium bromide mediated rearrangement of epoxide **12** gave a mixture of cyclobutanones **13** and **14** (IR 1780 $cm^{-1}$) (Scheme III). Yields of **13** and **14** were high if lithium carbonate was present to ensure neutrality. In the absence of carbonate, yields of **13** and **14** decreased due to elimination of methanol from the acetal (as indicated by GC/MS of the crude reaction mixture). The predominance of **13** rather than **14** from the rearrangement of **12** is expected on the basis of rearrangement of **15** to give **16** and **17** in a 14:1 ratio.[7] In the present case analysis by GLC of the rearrangement reaction mixture indicated the **13**:**14** ratio was 4:1.



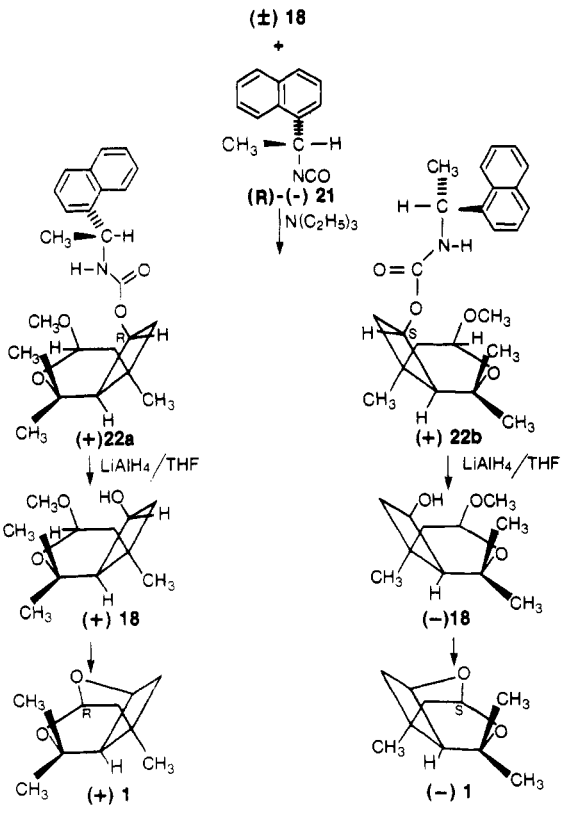

**15** **16** **17**

The structure of the major ketone (**13**) was easily assigned from its $^1H$ NMR spectrum. Thus, the signals due to the cyclobutyl methylene ($C_7$) gave a clean AB pattern

(12) K. Kitatani, T. Hiyama, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **50**, 3288 (1977).

(13) K. G. Taylor and J. Chaney, *J. Am. Chem. Soc.*, **94**, 8925 (1972); L. A. Paquette and R. T. Taylor, *ibid.*, **99**, 5708 (1977); L. A. Paquette, G. Zon, and R. T. Taylor, *J. Org. Chem.*, **39**, 2677 (1974).

Scheme IV




($\delta$ 2.70 and 2.59, $J_{AB}$ = 4 Hz). In the $^1$H NMR spectrum of **14** the pattern in this region was considerably more complex.

Sodium borohydride reduction of the mixture of cyclobutanones **13** and **14** gave the corresponding alcohols which were separated by using Still's rapid chromatographic procedure[14] on 40–63-$\mu$m silica gel. Hydride attack was expected to produce the endo alcohols in each case. The least polar alcohol isolated was assigned structure **18** on the basis of its $^1$H NMR spectrum and facile cyclization by PTSA to racemic lineatin ((±)-**1**). The latter exhibited $^1$H NMR and mass spectra identical with those reported[4,6] for the natural pheromone and was attractive to *T. lineatum* in field bioassays.[15]

A more polar secondary alcohol isolated from the reduction of the mixture of **13** and **14** was assigned structure **19** on the basis of its spectral properties and cyclization to 3,3,7-trimethyl-2,9-dioxatricyclo[4.2.1.0$^{4,7}$]nonane ((±)-**20**), the structure of which was assigned by comparison of its $^1$H NMR and mass spectra to that reported for this compound.[6] This tricyclic actal was not attractive to *T. lineatum* in field bioassays.[15]

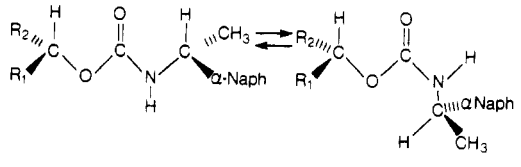
The separate reduction of **13** and **14** purified by GLC to **18** and **19**, respectively, confirmed the structure of the alcohols. In each reduction a small amount (~10%) of impurity thought to be the exo alcohol isomer was detected but not isolated.

(14) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
(15) J. H. Borden, A. C. Oehlschlager, K. N. Slessor, L. Chong, and H. D. Pierce, Jr., *Can. Entomol.*, **113**, 1099 (1980).
(16) The (*R*)-(+)-1-(1-naphthyl)ethylamine (Norse Chem. Co.) from which the isocyanate was derived had an optical rotation of $[\alpha]^{20}_D$ +75.8° (neat) which indicates its optical purity to be 92%. This conclusion can be reached by reference to J. Jacobus, M. Raban, and K. Mislow, *J. Org. Chem.*, **33**, 1142 (1968), who report $[\alpha]^{23}_D$ +81.7° (neat) for this amine, and ref 7 reports $[\alpha]^{28.3}_D$ +80.47 ± 0.05° (neat). Professor Pirkle independently determined the optical purity of the amine used in this study to be 92% by his recently developed high-pressure LC method.[17]
(17) W. H. Pirkle and D. W. House, *J. Org. Chem.*, **44**, 1957 (1979).

Resolution of alcohol **18** was achieved by preparation of diastereomeric carbamates with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (**21**, Scheme IV) in the presence of triethylamine.[7] The latter not only catalyzed the reaction but prevented elimination of methanol from the acid-sensitive alcohol. Separation of the diastereomeric carbamates from the reaction of (*R*)-(−)-**21** and racemic **18** was achieved by semipreparative high-pressure LC.

Each carbamate was cleaved to the alcohol by LAH reduction. Optical isomers of lineatin were generated by PTSA-catalyzed cyclization of the enantiomeric alcohols. The optical purity of both enantiomers was calculated to be 92% on the basis of the calculated[16] optical purity of 92% for the (*R*)-(−)-1-(1-naphthyl)ethylamine used to prepare the isocyanate and the observation that each carbamate was >99% pure as judged from analytical high-pressure LC.

Assignment of stereochemistry to the diasteromeric carbamates and hence configuration to the enantiomers of lineatin follows from general independent arguments. The first is based on the observation that **22a** elutes prior to **22b** on silica. Pirkle has developed a model[18] that allows the relative elution order of diastereomeric carbamates in chromatographic systems to be predicted from an examination of the relative abilities of groups appended to the carbinyl carbons to ward off the stationary phase. His predictions are based on the assumption that the carbamate linkage is the primary site of interaction and that the carbamate backbone in solution and while absorbed (*Z*) is as given in **22a** and **22b** with both carbinyl hydrogens eclipsed with the carbonyl due to carbinyl hydrogen bonding (CHB).




Z E

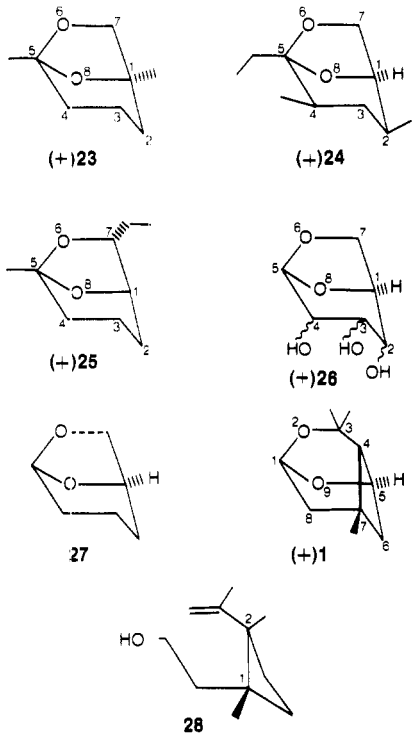
In the present case, the naphthyl ring and the *gem*-dimethyl group of the bicyclic acetal portion of the carbamate are the major groups interfering with carbamate–stationary phase interaction. These are threoid in **22a**, blocking interaction from both sides of the carbamate, whereas in **22b** they are erythroid, leaving one side of the carbamate relatively free for interaction. By Pirkle's arguments **22a** should be the faster eluting diastereomer of the pair since the carbamate is more shielded from a stationary phase.

Examination of the steric environment of the acetal oxygens reveals that in **22a** they are more shielded from interaction with a stationary phase than in **22b**. Although the ring acetal oxygens in both **22a** and **22b** suffer the same crowding due to the geminal methyls, the methoxyl of **22b** is more accessible to a stationary phase. This is due to the shielding of the methoxyl by a proximal naphthyl in **22a** and by a methyl in **22b**. Evaluation of these interactions suggests **22a** should be the faster eluting isomer.

A second and independent argument leading to the assignment of configuration to the carbamates **22a** and **22b** comes from the observation that the methoxyl resonance in the $^1$H NMR spectrum of **22b** is exchange broadened whereas that in **22a** is a sharp resonance. Pirkle has recently observed[19] that diastereomeric carbamates derived

(18) W. H. Pirkle and R. Hauska, *J. Org. Chem.*, **42**, 1839 (1977).
(19) W. H. Pirkle, K. A. Simmons, and C. W. Boeder, submitted for publication in *J. Org. Chem.*

Chart I




from **21** and racemic alcohols exhibit NMR line broadening in only one of the pair of diastereomers. The line broadening was shown by low-temperature $^{13}C$ and $^{1}H$ NMR studies to be due to hindered rotation about the amide portion of the carbamate *and* a nontrivial concentration of the *E* rotomer in the diasteromer exhibiting this phenomenon. Invariably, broadening was observed only in (*Z* rotomer) erythroid carbamates such as **22b**.

Comparison of the rotations of lineatin enantiomers and related dioxabicycles suggests the 1*R* configuration for the dextrorotatory enantiomer. Thus, in (+)-frontalin (**23**),[20] (+)-multistriatin (**24**),[21] and (+)-brevicomin (**25**)[22] as well as seven of the eight diasteromeric 1,6-anhydro-L-hexoses (**26**),[23] the dioxabicyclo system (**27**), common with (1*R*)-(+)-lineatin, apparently exhibits dextrorotatory power (see Chart I). That the same sense of rotatory power is probably exhibited by the $C_4$ (*S*) and $C_7$ (*R*) centers of (+)-**1** can be deduced from comparison of these centers with $C_1$ (*R*) and $C_2$ (*S*) of (+)-grandisol (**28**).[24] Thus, arguments based on the chromatographic and $^{1}H$ NMR properties of diasteromeric carbamates **22a** and **22b** as well as on the optical rotatory power of chiral centers in lineatin indicated that the dextrorotatory enantiomer of lineatin possesses the 1*R*,4*S*,5*R*,7*R* configuration.

Field tests of (+)-**1**, (−)-**1**, and (±)-**1** prepared herein revealed that *T. lineatum* responds to the dextrorotatory enantiomer of lineatin ((+)-**1**).

## Experimental Section

Analytical gas chromatography (GLC) was carried out on Varian Aerograph Model 1200 (packed columns) and Model 2100 (capillary columns) instruments employing flame-ionization detectors while preparative GLC was performed on the former instrument using a 10:1 splitter. Isomer ratios were not corrected for relative response.

Analytical chromatographic columns used in this work were as follows: column A, 33 m × 0.66 mm i.d., glass capillary, coated with SP-1000, linear velocity 20 cm/s at 100 °C, He; column B, 10 ft × $^{1}/_{8}$ in., 10% SP-1000 on Chromosorb W 100/120, 40 mL/min at 25 °C, He; column C, 5 ft × $^{1}/_{8}$ in., 5% SE-30 on Chromosorb W 100/120, 30 mL/min at 25 °C, He.

A Varian LC 5000 was used for high-pressure LC. A MicroPak Si-10 column (30 cm × 4 mm) was employed for analytical separations. A Whatman Magnum 9 Partisil 10/50 column was used for semipreparative separation. Rotations were determined at the sodium D line on a Rudolph Polarimeter Model 70 using a 0.5-dm microcell.

$^{1}H$ NMR spectra were measured in $CDCl_3$ or $CCl_4$ solutions on a Varian Associates XL100, A56/60, or EM360 spectrometer using $Me_4Si$ as an internal standard. Spectra are reported in $\delta$ units.

IR spectra were recorded on a Perkin-Elmer 457 grating spectrophotometer and were calibrated against a polystyrene film. Mass spectra were obtained with an Hitachi Perkin-Elmer RMU-6 operated at 70 eV coupled via a jet separator to a Varian Model 1400 gas chromatograph or on a HP5985B GC/MS/DS using column C. We are indebted to Mr. G. Owen for this service.

Analyses were performed by Mr. M. Yang of the Simon Fraser University, Department of Biological Sciences, on a Perkin-Elmer elemental analyzer, Model 240.

**Preparation of 5-Hydroxy-3,5-dimethyl-3-hexenoic Acid Lactone (2).** Ketene generated from acetone pyrolysis was passed into mesityl oxide (500 mL) containing 1% v/v $BF_3$·$Et_2O$ at 10 °C according to the procedure of Young.[8] After 19 h of continuous ketene generation the mesityl oxide solution was concentrated on a rotary evaporator (10 mmHg, 70 °C) and then distilled under vacuum to yield a forerun of mesityl oxide and 340 g of **2**, bp 70–72 °C (0.75 mm) [lit.[8] bp 92–93 °C (2 mm)]. Analysis by GLC on columns B and C at 100–150 °C programmed at 6 °C/min revealed that **2** was >95% pure: Mass spectrum, *m/e* (relative intensity) 140 (17), 125 (100), 97 (73).

**Preparation of 2,2,4-Trimethyl-6-methoxy-5,6-dihydro-2*H*-pyran (3).** A solution of 157 g (1.1 mol) of lactone **2** in 200 mL of dry THF containing 60 mL of $Et_2O$ was cooled to −20 to −30 °C by use of a dry ice/acetone bath. To this solution was added 11.2 g (.29 mol) of LAH slurried in 320 mL of dry THF over 15 min. The cooling bath was removed and the reaction allowed to warm to room temperature. After 30 min at room temperature the reaction was poured into 800 g of ice containing 33 mL of concentrated $H_2SO_4$. The ether layer was withdrawn and the aqueous portion extracted with two 200-mL portions of ether. The combined ether extracts were washed with 100 mL of 5% $NaHCO_3$ and 100 mL of saturated NaCl, dried ($Na_2SO_4$), and concentrated in vacuo. Thin-layer chromatography of this reaction mixture on silica gel G with toluene–$Et_2O$ (1:2 v/v) as the development solvent revealed one major component ($R_f$ 0.64) which was slightly more polar than the starting lactone ($R_f$ 0.73).

This concentrated reaction mixture was reacted without further purification with 100 mL of trimethyl orthoformate and 4 g of $NH_4NO_3$ in 40 mL of MeOH at room temperature for 12 h and at reflux for 4 h.[10] After this time the reaction mixture was poured into 300 mL of $H_2O$ and extracted with three 200-mL portions of $CHCl_3$. The extract was washed with 100 mL of saturated NaCl solution, dried ($MgSO_4$), filtered, and concentrated in vacuo. Distillation of the concentrate under vacuum gave 102 g (58%) of **3**, bp 62–67 °C (15 mm). Analysis by GLC on column A at 80 °C revealed **3** was >95% pure: mass spectrum, *m/e* (relative intensity) 156 (3), 141 (100), 109 (69), 96 (71), 81 (77).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.19; H, 10.33.

**Preparation of *syn*- and *anti*-2,2,6-Trimethyl-4-methoxy-7,7-dichloro-3-oxabicyclo[4.1.0]heptanes (4a and 4b).** To a solution of **3** (100 g, 0.64 mol) in 250 mL of $CHCl_3$ was added cetyltrimethylammonium bromide (2 g, 5.5 mmol) and a chilled 50% NaOH solution (250 g of NaOH and 250 mL of water). The two-phase reaction was stirred vigorously and analyzed periodically by GLC on column A at 100–150 °C with linear temperature programming at 6 °C/min. After 3 h the initially vigorous exothermic reaction subsided, and analysis by GLC revealed the

(20) K. Mori, *Tetrahedron*, **31**, 1381 (1975).
(21) K. Mori, *Tetrahedron*, **32**, 1979 (1976).
(22) K. Mori, *Tetrahedron*, **30**, 4223 (1974).
(23) Rotations have been given for the 1,6-anhydro-D-hexoses: D. Horton and J. D. Wander, *J. Org. Chem.*, **32**, 3780 (1967).
(24) P. D. Hobbs and P. D. Magnus, *J. Am. Chem. Soc.*, **98**, 4594 (1976).

reaction was 50% complete. Stirring was continued at room temperature for 16 h, after which time the reaction was >95% complete by GLC. The reaction solution was diluted with 1 L of water, the $CHCl_3$ layer separated, and the aqueous phase extracted with two 300-mL portions of $CH_2Cl_2$. The combined extracts were washed with two 500-mL portions of water with the addition of small amounts of $MgSO_4$ to break emulsions formed during washing. The extract was dried ($Na_2SO_4$), filtered, and concentrated in vacuo. Distillation from NaOH pellets yielded **4a** and **4b** in a 2.1:1 ratio (column A, 100–180 °C, programmed at 6 °C/min): 145 g (94%); bp 70–80 °C (0.1 mm). Preparative GLC on column B at 100–180 °C programmed at 6 °C/min yielded pure **4a** and **4b**.

For **4a**: $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 4.65 (1 H, $C_4$, dd, $J$ = 2, 6 Hz), 3.35 (3 H, $OCH_3$, s), 2.30 (1 H, $C_{5e'}$, dd, $J$ = 6, 16 Hz), 1.78 (1 H, $C_{5a'}$, dd, $J$ = 2, 16 Hz), 1.49 (6 H, $CH_3$, s), 1.44 (3 H, $CH_3$, s), 1.24 (1 H, $C_1$, s); mass spectrum, $m/e$ (relative intensity) 225 (1), 223 (1.4), 209 (4.8), 207 (7.6), 180 (15), 178 (19), 167 (15), 165 (22), 163 (10), 147 (70), 145 (100), 143 (78), 129 (20), 127 (10), 115 (15), 113 (25), 91 (32), 79 (21), 77 (35), 75 (11); chemical ionization ($CH_4$) $m/e$ 239, 241 ($M^+ + 1$).

Anal. Calcd for $C_{10}H_{16}O_2Cl_2$: C, 50.22; H, 6.74. Found: C, 49.94; H, 6.73.

For **4b**: $^1H$ NMR (100 MHz, $CDCl_3$) $\delta$ 4.54 (1 H, $C_4$, dd, $J$ = 4, 9 Hz), 3.40 (3 H, $OCH_3$, s), 1.6–2.1 (2 H, $C_5$, m), 1.57 (3 H, $CH_3$, s), 1.49 (3 H, $CH_3$, s), 1.40 (3 H, $CH_3$, s), 1.06 (1 H, $C_1$, s); mass spectrum, $m/e$ (relative intensity) 208 (12), 206 (19), 193 (10), 191 (14), 173 (18), 171 (49), 165 (12), 163 (20), 131 (34), 129 (100), 115 (21), 113 (58), 82 (48), 77 (89); chemical ionization ($CH_4$) $m/e$ 239, 241 ($M^+ + 1$).

Anal. Calcd for $C_{10}H_{16}O_2Cl_2$: C, 50.22; H, 6.74. Found: C, 49.97; H, 6.81.

**Preparation of 2,2,6,7-Tetramethyl-4-methoxy-7-chloro-3-oxabicyclo[4.1.0]heptanes (5).** A three-necked 500-mL flask fitted with a low-temperature thermometer, a mechanical stirrer, and a dropping funnel was flushed with dry $N_2$ and charged with 24 g (100 mmol) of **4a** and **4b** (2.1:1) in 300 mL of dry THF. The solution was cooled to −100 °C (ether/liquid $N_2$ bath), and BuLi (90 mL, 2.5 M in hexane, 250 mmol) was added dropwise over 30 min with the reaction temperature maintained at −100 °C. The reaction solution, which turned orange during this addition, was allowed to stand at −100 °C for 30 min, and then MeI (30.4 g, 210 mmol) was added over 20 min with the temperature maintained at −100 to −80 °C. During this addition the reaction solution changed in color to light yellow. The reaction mixture was allowed to warm to room temperature over 10–12 h. The solution was diluted with 1 L water and extracted with three 200-mL portions of petroleum ether (bp 30–60 °C). The extract was dried ($Na_2SO_4$) and concentrated in vacuo to give a liquid product which distilled under vacuum to yield two major fractions. The lowest boiling fraction [bp 35–45 °C (1 mm), 2 g] contained three major components in a 4.9:28.1:1 ratio on analysis by GLC on column A at 100–150 °C programmed at 6 °C/min. Preparative GLC on column C at 80–150 °C programmed at 6 °C/min yielded the major component **10**: $^1H$ NMR ($CDCl_3$) $\delta$ 3.37 (3 H, $OCH_3$, s), 2.66–1.50 (3 H, $C_6$, $C_7$, m), 1.42 (3 H, $CH_3$, s), 1.33 (3 H, $CH_3$, s), 1.27 (3 H, $CH_3$, s), 0.997 (1 H, $C_4$, s); mass spectrum, $m/e$ (relative intensity) 168 (7), 153 (14), 125 (17), 114 (14), 111 (16), 110 (41), 109 (100), 108 (15), 107 (15), 100 (17), 95 (47), 93 (46), 91 (20), 79 (22), 77 (20), 67 (62).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.63; H, 9.40.

The second fraction, [bp 55–60 °C (0.75 mm), 17.5 g (80%)] was shown by GC/MS analysis on column C at 100–180 °C programmed at 6 °C/min to be a mixture of four isomers of **5** of which the two major peaks constituted 82%. The $^1H$ NMR spectrum of the major isomer could be discerned from the spectrum of the center cut of the distillation fraction mixture: $^1H$ NMR ($CDCl_3$) $\delta$ 4.60 (1 H, $C_4$, dd, $J$ = 2, 6 Hz), 3.35 (3 H, $OCH_3$, s), 1.82 (2 H, $C_5$, m), 1.70 (3 H, $CH_3$, s), 1.43 (3 H, $CH_3$, s), 1.32 (3 H, $CH_3$, s), 0.98 (1 H, $C_1$, s); mass spectrum, $m/e$ (relative intensity) 205 (0.4), 203 (1.3), 189 (1.2), 187 (3.5), 160 (2), 158 (5), 147 (4), 145 (11), 125 (100), 123 (31), 109 (16), 107 (8), 93 (20), 91 (8), 81 (15).

Anal. Calcd for $C_{11}H_{18}O_2Cl$: C, 60.70; H, 8.33. Found: C, 60.41; H, 8.65.

**Preparation of *syn*- and *anti*-2,2,6-Trimethyl-4-methoxy-7-methylene-3-oxabicyclo[4.1.0]heptanes (11a and 11b).** To a suspension of 20 g (178 mmol) of potassium *tert*-butoxide in 60 mL of dry $Me_2SO$ under $N_2$ at 90 °C was added 12 g (55 mmol) of monochloride isomers **5a** and **5b** over a period of 10 min. The reaction turned dark upon this addition. Analysis by GLC on column A at 100 °C revealed the reaction was complete in 15 min. The reaction was cooled, diluted with 500 mL of $H_2O$, and continuously extracted with pentane for 24 h. The pentane was removed slowly through a Vigreux column and the residue distilled under vacuum to yield a 3:1 mixture of **11a** and **11b** (by GLC as above): 5.63 g (56%); bp 60–65 °C (7 mm). Preparative GLC on column B at 100–150 °C programmed at 6 °C/min yielded an analytical sample of **11a**: $^1H$ NMR ($CDCl_3$) $\delta$ 5.42 (1 H, $C_8$, s), 5.38 (1 H, $C_8$, s), 4.32 (1 H, $C_4$, dd, $J$ = 4, 8 Hz), 3.34 (3 H, $OCH_3$, s), 2.00 (1 H, $C_5$, dd, $J$ = 4, 13 Hz), 1.57 (1 H, $C_5$, dd, $J$ = 8, 13 Hz), 1.43 (3 H, $CH_3$, s), 1.24 (3 H, $CH_3$, s), 1.22 (3 H, $CH_3$, s), 1.18 (1 H, $C_1$, s); mass spectrum, $m/e$ (relative intensity) 167 (2), 139 (32), 124 (91), 107 (100), 91 (65), 81 (51), 79 (49).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.50; H, 9.97.

For **11b**: $^1H$ NMR ($CDCl_3$) $\delta$ 5.42 (1 H, $C_8$, d, $J$ = 2.2 Hz), 5.32 (1 H, $C_8$, m), 4.60 (1 H, $C_4$, dd, $J$ = 5.0, 7.5 Hz), 3.37 (3 H, $OCH_3$, s), 1.6–1.8 (2 H, $C_5$, m), 1.43 (3 H, $CH_3$, s), 1.33 (3 H, $CH_3$, s), 1.22 (3 H, $CH_3$, s), 1.08 (1 H, $C_1$, $J$ = 2.2 Hz); mass spectrum, $m/e$ (relative intensity) 167 (2), 139 (19), 124 (49), 107 (100), 91 (33), 81 (15), 79 (18).

**Preparation of 2,2,6-Trimethyl-4-methoxy-7,8-epoxy-3-oxabicyclo[4.1.0]heptane (12).** To 12.2 g (61.6 mmol) of *syn*- and *anti*-methylenebicycloheptanes **11a** and **11b** in 300 mL of $CH_2Cl_2$ was added 1 L of phosphate buffer (pH 6.4, 35.5 g of $Na_2HPO_4$ and 34 g of $KH_2PO_4$ in 1 L of $H_2O$). To this was added with stirring 21 g of *p*-nitroperbenzoic acid (98% pure by iodometric titration, 112 mmol) over 10 min. The reaction was stirred at room temperature for 14 h after which time all the oxidizing reagent had been consumed. The reaction phases were separated, and the aqueous phase was washed with 100 mL of $CH_2Cl_2$. The organic phase was dried ($MgSO_4$), concentrated in vacuo, and distilled under vacuum to yield epoxide **12**: 8.1 g (66%); bp 55–65 °C (0.4 mm); $^1H$ NMR ($CDCl_3$) $\delta$ 4.52 (1 H, $C_4$, dd, $J$ = 5.7, 7 Hz), 3.35 (3 H, $OCH_3$, s), 3.23 (2 H, $C_8$, m), 1.77 (2 H, $C_5$, m), 1.42 (3 H, $CH_3$, s), 1.30 (1 H, $C_1$, s), 1.23 (3 H, $CH_3$, s), 1.19 (3 H, $CH_3$, s); mass spectrum, $m/e$ (relative intensity) 141 (61), 125 (32), 109 (64), 95 (31), 81 (69), 67 (38), 55 (43), 45 (47), 43 (100), 41 (71); chemical ionization ($CH_4$): $m/e$ 199.2 (26, M + 1).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 66.64; H, 9.14. Found: C, 66.83; H, 9.28.

**Preparation of 2,2,6-Trimethyl-4-methoxy-3-oxabicyclo-[4.2.0]octan-8-one (13) and 2,2,6-Trimethyl-4-methoxy-3-oxabicyclo[4.2.0]octan-7-one (14).** To 5.8 g (29 mmol) of epoxide **12** in 75 mL of $CH_3CN$ (high-pressure LC grade) was added 250 mg of $Li_2CO_3$ and 10.2 g (117 mmol) of LiBr (dried at 125 °C for 12 h and used immediately). The solution was stirred to dissolve the LiBr and was maintained at 60 °C for 30 min, after which time analysis by GLC on column A revealed the reaction to be complete. The reaction was cooled to room temperature, diluted with 100 mL of $H_2O$, and extracted with four 100-mL portions of pentane. The extract was dried ($MgSO_4$), concentrated by removal of pentane through a Vigreux column, and distilled (~10 mg of $Li_2CO_3$ added to ensure neutrality): yield 4.8 g (83%); bp 55–60 °C (0.3 mm). Analysis by GLC on column A at 100–170 °C programmed at 6 °C/min revealed two major products in a ratio of 4:1 (IR 1780 $cm^{-1}$). Samples of the individual ketones were isolated by preparative GLC on column B (100–180 °C at 6 °C/min).

The faster eluting minor ketone (**14**) gave the following: $^1H$ NMR ($CDCl_3$) $\delta$ 4.70 (1 H, $C_4$, t, $J$ = 6.5 Hz), 3.37 (3 H, $OCH_3$, s), 3.3–1.5 (5 H, $C_1$, $C_5$, $C_7$, m), 1.39 (3 H, $CH_3$, s), 1.25 (3 H, $CH_3$, s), 1.18 (3 H, $CH_3$, s); mass spectrum, $m/e$ (relative intensity) 167 (9), 141 (83), 140 (11), 125 (11), 123 (14), 109 (58), 97 (39), 96 (14), 95 (15), 85 (100), 81 (40), 80 (15), 79 (16), 69 (21), 67 (11).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 66.64; H, 9.15. Found: C, 66.60; H, 9.07.

The slower eluting major ketone (**13**) gave the following: ($CDCl_3$) $\delta$ 4.87 (1 H, $C_4$, dd, $J$ = 6.5, 7.5 Hz), 3.37 (3 H, $OCH_3$,

s), 2.80 (1 H, $C_1$, s), 2.70 (1 H, $C_7$, d, $J$ = 4 Hz), 2.59 (1 H, $C_7$, d, $J$ = 4 Hz), 2.33 (1 H, $C_5$, dd, $J$ = 15, 6.5 Hz), 1.87 (1 H, $C_5$, dd, $J$ = 15, 7.5 Hz), 1.36 (3 H, $CH_3$, s), 1.30 (6 H, 2 $CH_3$, s), couplings confirmed by decoupling experiments.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 66.64; H, 9.15. Found: C, 66.20; H, 9.44.

**Preparation of 2,2,6-Trimethyl-4-methoxy-3-oxabicyclo-[4.2.0]octan-8-ol (18) and 2,2,6-Trimethyl-4-methoxy-3-oxabicyclo[4.2.0]octan-7-ol (19).** To 3.2 g (16 mmol) of the 4:1 mixture of bicyclic ketones **13** and **14** in 30 mL of 95% EtOH was added 0.611 g (16 mmol) of $NaBH_4$. The reaction was stirred overnight at room temperature, diluted with 150 mL of $H_2O$, and extracted with five 50-mL portions of $Et_2O$. The $Et_2O$ was dried ($Na_2SO_4$) and concentrated in vacuo to give 3.2 g of an oil. This product was shown by TLC to be a mixture of at least five components (silica gel G, developed in hexane–EtOAc, 1:1 v/v). The crude reaction mixture was chromatographed on 200 g (5 cm × 18 cm column) of silica gel 60, 230–400 mesh. The eluant was hexane–EtOAc (1:1 v/v) and was forced through the column at 5 cm/min according to the procedure of Still.[14] Fractions of 25 mL were collected. Fractions 1–10 were devoid of material. Fractions 11–19 contained nonalcohol impurities ($R_f$ 0.6–0.7, 0.39 g). Fractions 20–22 contained nonalcohol impurities ($R_f$ 0.6) and an alcohol (**18**, $R_f$ 0.55, 0.468 g) that cyclized to give lineatin (**1**) (see below). Fractions 23–29 contained 1.3 g (40%) of an alcohol (**18**, $R_f$ 0.55) that cyclized to give lineatin (**1**). Fractions 30–33 contained alcohol **18** ($R_f$ 0.55) and alcohol **19** ($R_f$ 0.40). Fractions 34–45 contained alcohol **19** ($R_f$ 0.40, 0.731 g) which cyclized to give the lineatin isomer **20**. The progress of the chromatography was followed by TLC and by withdrawing a 100-μL portion from each fraction, diluting it to 1 mL with pentane, and then treating the aliquot with a crystal of PTSA. Filtration through a short neutral alumina column (disposable pipette) was followed by analysis by GLC on column A at 100–180 °C programmed at 6 °C/min.

For alcohol **18**: $^1$H NMR δ 4.98 (1 H, $C_4$, t, $J$ = 7 Hz), 4.42 (1 H, $C_8$, m), 3.42 (3 H, $OCH_3$, s), 2.7–1.5 (6 H, OH, $C_1$, $C_5$, $C_7$, m), 1.41 (3 H, $CH_3$, s), 1.24 (3 H, $CH_3$, s), 1.16 (3 H, $CH_3$, s); mass spectrum, $m/e$ (relative intensity) 141 (49), 125 (15), 111 (20), 109 (59), 107 (19), 99 (34), 98 (11), 97 (19), 96 (33), 95 (12), 87 (20), 85 (100), 84 (28), 83 (34), 81 (41), 79 (18), 71 (11), 69 (23), 67 (23), 61 (18), 59 (37), 58 (45), 55 (43), 43 (66).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.56; H, 10.21.

For alcohol **19**: $^1$H NMR δ 4.80 (1 H, $C_4$, dd, $J$ = 4, 8 Hz), 4.13 (1 H, $C_7$, dd, $J$ = 7, 15 Hz), 3.38 (3 H, $OCH_3$, s), 2.4–1.5 (6 H, OH, $C_1$, $C_5$, $C_8$, m), 1.33 (6 H, 2$CH_3$, s), 1.22 (3 H, $CH_3$, s); chemical ionization ($CH_4$) mass spectrum, $m/e$ (relative intensity) 201 (1), 170 (11), 169 (100), 151 (42), 141 (12), 125 (99), 124 (10), 123 (49), 109 (15), 107 (12), 99 (17), 97 (11), 95 (36), 93 (26), 86 (58), 85 (23), 84 (81), 83 (10), 69 (15).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.58; H, 10.37.

**Preparation of (±)-3,3,7-Trimethyl-2,9-dioxatricyclo-[3.3.1.0$^{4,7}$]nonane (1).** To 1.3 g (6 mmol) of **18** dissolved in 20 mL of pentane containing 0.5 mL of MeOH were added a few crystals of PTSA (~1 mg). The reaction was stirred at room temperature for 1 h, filtered through neutral alumina (1 cm × 5 cm), concentrated in vacuo, and distilled under vacuum (with ~2 mg of $Li_2CO_3$ added) to yield 0.71 g of **1**: 65%; bp 70 °C (12 mm). Analysis by GLC on column A at 100–180 °C programmed at 6 °C/min revealed that **1** was 98% pure and well resolved from **20**. An analytical sample of **1** prepared by preparative GLC on column B at 100–180 °C programmed at 6 °C/min gave the following: $^1$H NMR ($CCl_4$) δ 4.91 (1 H, $C_1$, br s), 4.39 (1 H, $C_5$, m), 2.2–1.5 (5 H, $C_4$, $C_6$, $C_8$, m), 1.15 (6 H, 2 $CH_3$, s), 1.11 (3 H, $CH_3$, s); mass spectrum, $m/e$ (relative intensity) 168 (1.7), 153 (4), 140 (3), 126 (16), 125 (24), 124 (11), 113 (11), 111 (36), 109 (31), 107 (34), 97 (18), 96 (37), 95 (13), 91 (11), 85 (100), 84 (22), 83 (53), 81 (28), 79 (22), 69 (39), 67 (20), 57 (22), 56 (36), 55 (76), 53 (17), 43 (33), 41 (37).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.63; H, 9.40.

**Preparation of 3,3,7-Trimethyl-2,9-dioxatricyclo-[4.2.1.0$^{4,7}$]nonane (20).** A 355-mg portion of the chromatography fraction containing alcohol **19** was dissolved in 10 mL of pentane containing 1 mL of $Et_2O$ and a few crystals of PTSA. The reaction was allowed to stir for 1 h at room temperature and was then filtered through a 1 cm × 5 cm column of neutral alumina. The pentane was removed in vacuo and the concentrate distilled under vacuum to give **20**: 30 mg (10%); bp 70–73 °C (10 mm). An analytical sample isolated by preparative GLC on column B at 100–180 °C programmed at 6 °C/min gave the following: $^1$H NMR ($CCl_4$) δ 5.27 (1 H, $C_1$, d, $J$ = 3.3 Hz), 3.89 (1 H, $C_6$, t, $J$ = 4 Hz), 2.60–1.45 (5 H, $C_4$, $C_5$, $C_8$, m), 1.38 (3 H, $CH_3$, s), 1.21 (3 H, $CH_3$, s), 1.07 (3 H, $CH_3$, s); mass spectrum, $m/e$ (relative intensity) 168 (0.9), 153 (2), 124 (28), 110 (13), 109 (100), 83 (15), 81 (19), 79 (12), 71 (18), 69 (35), 67 (13), 55 (17), 43 (15), 41 (21).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.28; H, 9.64.

**Preparation of 2,2,6-Trimethyl-4-methoxy-3-oxabicyclo-[4.2.0]octan-7-yl *N*-[1-(1-Naphthyl)ethyl]carbamates (22a and 22b).** Alcohol **18** (217 mg, 1.08 mmol), 50 mg of triethylamine, and 213 mg (1.08 mmol) of (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (**21**)[7,16] were heated at 70 °C for 15 h in a sealed tube. The reaction mixture was chromatographed on 50 g (2.5 × 19 cm) of silica gel 60, 230–400 mesh. The eluant was hexane–THF (80:20), forced through the column at 5 cm/min, taking 15-mL fractions. Analysis by high-pressure LC of each fraction [Micropak column 90:10 hexane–THF, 3 mL/min, 280-nm monitor] indicated fractions 13 and 14 (207 mg) were a 60:40 mixture of the carbamates in which the faster running diastereomer predominated. Fractions 15 and 16 (174 mg) were a 50:50 mixture of the two carbamates and fractions 17–20 (50 mg) were a 20:80 mixture of two carbamates in which the slower eluting diastereomer predominated.

The pure diastereomeric carbamates were isolated from the first and third fractions on a Magnum 9 Partisil 10/50 semipreparative column (4–6-mg loading) by using 85:15 hexane–THF at 4 mL/min with 280-nm monitoring ($\alpha$ = 1.11). This chromatographic procedure was followed by preparative TLC of each diastereomer on 0.75 mm × 20 cm × 20 cm silica gel 60 GF 254 with hexane–EtOAc (1:1 v/v) as development solvent to remove slow-eluting contaminants.

The faster eluting carbamate, **22a**, was isolated as an oil: $^1$H NMR δ 8.2–7.2 (7 H, naph, m), 5.52 (1 H, $C_\alpha$, quin, $J$ = 6.8 Hz), 5.27 (1 H, $C_8$, t, $J$ = 7.5 Hz), 5.2–5.0 (1 H, NH, m), 4.71 (1 H, $C_4$, t, $J$ = 6.8 Hz), 3.38 (3 H, $OCH_3$, s), 2.3–1.7 (5 H, $C_1$, $C_5$, $C_7$, m), 1.62 (3 H, $CH_3$, d, $J$ = 6.8 Hz), 1.20 (9 H, 3 $CH_3$, m); $[\alpha]^{23}_D$ +8.0 ± 1.7° ($c$ 0.476, $CHCl_3$); mass spectrum, $m/e$ (relative intensity) 397 (15), 215 (12), 200 (14), 199 (13), 197 (32), 182 (15), 156 (22), 155 (100), 154 (16), 153 (15), 141 (12), 109 (16), 43 (11).

The slower eluting carbamate diastereomer, **22b**, was isolated as an oil: $^1$H NMR δ 8.2–7.2 (7 H, naph, m), 5.52 (1 H, $C_\alpha$, quin, $J$ = 6.8 Hz), 5.27 (1 H, $C_8$, t, $J$ = 7.5 Hz), 5.1–4.7 (2 H, NH, $C_4$, m), 3.33 (3 H, $OCH_3$, br s), 2.33–1.7 (5 H, $C_1$, $C_5$, $C_7$, m), 1.62 (3 H, d, $J$ = 6.8 Hz), 1.20 (9 H, 3 $CH_3$, s); $[\alpha]^{23}_D$ −32.3 ± 1° (c 0.82, $CHCl_3$); mass spectrum, $m/e$ (relative intensity) 397 (12), 215 (10), 200 (15), 199 (13), 197 (32), 182 (20), 156 (22), 155 (100), 154 (17), 153 (19), 141 (12), 109 (15).

**Reduction of Carbamate 22a to (+)-18.** To 5 mL of dry THF (distilled from LAH) were added 87.3 mg of **22a** (>99% one diastereomer by high-pressure LC) and 100 mg of LAH. The reaction was refluxed for 2 h, after which time analysis by TLC (silica gel 60, hexane–EtOAc, 50:50 v/v) revealed the **22a** had been consumed. The reaction was quenched by addition of 10 mL of 20% aqueous NaOH and then extracted four times with 15-mL portions of $Et_2O$ which were combined and dried ($MgSO_4$). The residue was chromatographed by preparative TLC [20 cm × 20 cm × 0.75 mm silica gel G-254, hexane–EtOAc (50:50 v/v)] to give (+)-**18** [25.9 mg (59%); $[\alpha]^{23}_D$ +32.6 ± 1.0° ($c$ 8.63, $CHCl_3$)] which gave a $^1$H NMR spectrum identical with racemic **18**.

**Reduction of Carbamate 22b to (−)-18.** By use of the above procedure, 73.9 mg of **22b** (>99% diasteromerically pure) was reduced by LAH in THF to yield 28.1 mg (75%) of (−)-**18** [$[\alpha]^{23}_D$ −32.8 ± 0.7° ($c$ 9.37, $CHCl_3$)] that gave a $^1$H NMR spectrum identical with that of racemic **18**.

**Cyclization of (+)-18 to (+)-1.** Alcohol (+)-**18** (25 mg, 0.12 mmol) in 0.5 mL of $CHCl_3$ was treated with a crystal of PTSA at room temperature for 1 h after which time TLC analysis (as above for reduction) revealed that the alcohol was consumed. The reaction was filtered through an 0.5 × 0.5 cm column of neutral alumina, concentrated in vacuo, and distilled to yield 12.5 mg

(59%) of (+)-1 [bp 70 °C (10 mm); $[\alpha]^{24}_D$ +66.3 ± 3.5° (c 3.1, $CHCl_3$)] which was >99% pure by GLC on column A at 150 °C.

**Cyclization of (−)-18 to (−)-1.** Alcohol (−)-18 (28 mg, 0.14 mmol) in 0.5 mL of $CHCl_3$ was cyclized as above with PTSA to yield after distillation (−)-1 [14.5 mg (62%); $[\alpha]^{23}_D$ −71.6 ± 2.0° (c 3.6, $CHCl_3$)] which was >99% pure by GLC on column A at 150 °C.

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**Registry No.** (+)-1, 65035-34-9; (−)-1, 73649-91-9; (±)-1, 71899-16-6; **2**, 22954-83-2; (±)-**3**, 73433-57-5; (±)-**4a**, 73433-58-6; (±)-**4b**, 73494-07-2; (±)-**5a**, 73433-59-7; (±)-**5b**, 73494-08-3; (±)-**11a**, 73433-60-0; (±)-**11b**, 73494-09-4; (±)-**12**, 73433-61-1; (±)-**13**, 73433-62-2; (±)-**14**, 73433-63-3; **15**, 52545-77-4; **16**, 1192-33-2; **17**, 1192-14-9; (+)-**18**, 73433-64-4; (−)-**18**, 73494-10-7; (±)-**18**, 73494-11-8; (±)-**19**, 73433-65-5; (±)-**20**, 71899-15-5; (+)-**22a**, 73433-66-6; (−)-**22b**, 73494-12-9; (±)-**10**, 73433-67-7.

# Synthesis of Chiral Conformationally Fixed Cyclohexanones[1]

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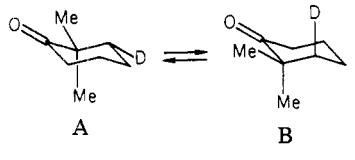
Two syntheses of (*R*)-(+)-2,2-dimethyl-4-*tert*-butylcyclohexanone (**1**) are presented. Related 4-alkylcyclohexanones (intermediates in the syntheses) bear other (potential) conformational anchoring groups. The key steps in the syntheses are the opening of the cyclobutane ring of (+)-3,3-dimethylnopinone (**10**) by either pyrolysis or reaction with $BBr_3$. The high optical purity of the final compound was determined by analysis of the $^{19}F$ NMR spectrum of the diastereomeric ester mixture obtained from the reaction of alcohol (+)-**14b** with (*S*)-(+)-MTPA chloride.

Since the original publication of the octant rule in 1961,[2] optical rotatory dispersion (ORD) and circular dichroism (CD) have been used to obtain important information about the absolute stereochemistry and/or conformation of chiral ketones[3] and, as such, have become important research tools. Recently, we[4] and others[5] have become interested in the effects of isotopic substituents on CD spectra. The data already obtained have led to a greater understanding of the nature and origins of the induced Cotton effect,[6] and variable-temperature circular dichroism has been used successfully to study the conformational demands of isotopic substituents in conformationally mobile cyclohexanone systems.[4d,e] Thus from equilibrium 1, where the molecule bears a *gem*-dimethyl "chiral probe",[4d] it was determined that deuterium prefers to occupy the axial position. The enthalpy difference between the two conformations was calculated to be in the range of 5 ± 2 cal/mol.




(1)

This type of enthalpy calculation depends upon a reasonable assumption of the rotational strengths ([*R*] values) of the individual conformers A and B. These [*R*] values are determined from the CD spectrum of a "reference" compound which, while bearing the particular substituent of interest, is held in a fixed conformation due to either (1) sufficient rigidity in the carbon skeleton to preclude conformational change (e.g., the adamantane[5] or the steroid[7] skeleton) or (2) excessive bias of one conformation over another due to a large potential-energy difference (e.g., the *tert*-butylcyclohexane skeleton[4c,8]). We felt that cyclohexanones with a γ-*tert*-butyl group would serve as the most convenient and appropriate models for the conformationally mobile systems we are investigating and, therefore, searched for a general synthetic path to such chiral ketones.

In this paper, we report two syntheses of (*R*)-(+)-2,2-dimethyl-4-*tert*-butylcyclohexanone (**1**). Several related 2,2-dimethylcyclohexanones with other 4-alkyl substituents which can be considered as conformational anchoring groups were prepared as intermediates to (+)-**1**. In a subsequent paper,[9] the syntheses of 4-*tert*-butylcyclohexanones having different substitution patterns will be presented, and the CD spectra of these reference ketones will be discussed in detail.

**Initial Considerations and Synthesis.** Generality was of paramount importance in the design of a synthesis of

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