42.50; H, 6.20. The isomers of R_f 0.4 (15 mg) and R_f 0.3 (4 mg) were separated by chromatography on silica (eluant hexanes/Et_2O 1:1). The major isomer **19** (R_f 0.4) was obtained as a colorless syrup: $[\alpha]_D$ -94° (c = 1.15, $CHCl_3$); IR (neat) 1460, 1413, 1390, 1380, 1255, 1216, 1160, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (d, 1 H, J = 7.6 Hz), 4.68 (d, 1 H, J = 5.6 Hz), 4.57 (dd, 1 H, J = 2.8, 5.6 Hz), 4.43-4.38 (m, 1 H), 3.76 (d, 1 H, J = 10.0 Hz), 3.67-3.41 (m, 5 H), 3.62 (s, 3 H) 3.53 (s, 3 H), 3.52 (s, 3 H), 3.42 (s, 3 H), 3.41 (s, 3 H), 3.29-3.04 (m, 4 H), 1.53 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 113.3, 109.4, 95.4, 87.4, 86.9, 85.8, 83.5, 82.1, 79.4, 74.7, 72.7, 71.5, 60.8, 60.5, 60.4, 59.6, 58.9, 26.9, 25.6, 5.8; mass spectrum (EI), m/e 547 (M^+ - Me), 403, 371, 328, 327, 235, 175, 157, 147, 115, 101. The minor isomer **20** (R_f 0.3) was obtained as a colorless syrup: $[\alpha]_D$ +37° (c = 0.90, $CHCl_3$); IR (CCl_4) 1728, 1691, 1676, 1650, 1555, 1377, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.85 (d, 1 H, J = 7.2 Hz), 4.68-4.65 (m, 1 H), 4.62 (dd, 1 H, J = 4.0, 7.2 Hz), 4.58 (d, 1 H, J = 8.0 Hz), 3.63 (s, 3 H), 3.58 (s, 3 H), 3.52 (s, 3 H), 3.40 (s, 3 H), 3.37 (s, 3 H), 3.63-2.95 (m, 10 H), 1.61 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 116.5, 103.1, 96.3, 87.0, 84.7, 83.5, 82.4, 81.4, 79.6, 74.8, 72.2, 71.5, 61.2, 60.8, 60.3, 59.5, 59.4, 26.4, 26.2, 6.6; mass spectrum (EI), m/e 547 (M^+ - Me), 371, 328, 327, 285, 235, 207, 187, 175, 147.

2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl 1-Deoxy-3-*epi*-1-iodo-3,4-isopropylidene-α-D-fructofuranoside (22) and 2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl 1-Deoxy-3-*epi*-1-iodo-3,4-isopropylidene-β-D-fructofuranoside (23). Treatment of the α-vinyl ether **21b** (50 mg) with Bu_4NF in THF (1.0 M; 1.5 mL) followed by ^{t}BuOK (35 mg) and I_2 (55 mg), as described above for **18b**, gave the disaccharides **22** and **23** (24 mg, 65%) as a 2:1 mixture, after chromatography on silica (eluant hexanes/Et_2O 1:4): $[\alpha]_D$ +86° (c = 1.15, $CHCl_3$); TLC R_f 0.5 (silica, hexanes/Et_2O 1:4): IR (neat) 1460, 1385, 1260, 1220, 1200, 1170, 1110 cm^{-1}; mass spectrum (EI), m/e 547 (M^+ - Me), 371, 343, 327, 285, 235, 207, 187, 175, 157, 147, 115, 101. Anal. Calcd for $C_{20}H_{35}IO_{10}$: C, 42.71; H, 6.27. Found: C, 42.74; H, 6.17. The two anomers respectively showed the following NMR data. α-Anomer **22**: ^1H NMR (400 MHz, C_6D_6) δ 5.45 (d, 1 H, J = 3.6 Hz), 4.69 (d, 1 H, J = 8.0 Hz), 4.62-4.58 (m, 1 H), 4.49 (dd, 1 H, J = 4.8, 8.0 Hz), 4.27-4.22 (m, 1 H), 3.90 (dd, 1 H, J = 9.4 Hz, J = 9.4 Hz), 3.70-3.44 (m, 2 H), 3.65 (s, 3 H), 3.56 (s, 3 H), 3.54 (d, 1 H, J = 11.2 Hz), 3.40 (d, 1 H, J = 11.2 Hz), 3.37-3.08 (m, 4 H), 3.19 (s, 3 H), 3.15 (s, 3 H), 3.04 (s, 3 H), 1.74 (s, 3 H), 1.25 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.8, 103.7, 90.1, 85.8, 82.9, 81.9, 81.7, 81.1, 78.8, 72.3, 71.3, 70.7, 60.7, 60.4, 59.6, 59.2, 58.6, 26.7, 26.4, 8.2. β-Anomer **23**: ^1H NMR (400 MHz, C_6D_6) δ 5.46 (d, 1 H, J = 3.6 Hz), 4.98 (d, 1 H, J = 5.6 Hz), 4.93 (dd, 1 H, J = 5.0, 5.6 Hz), 4.36-4.31 (m, 1 H), 4.23-4.18 (m, 1 H), 3.84 (dd, 1 H, J = 9.2 Hz, J = 9.2 Hz), 3.70-3.08 (m, 8 H), 3.63 (s, 3 H), 3.49 (s, 3 H), 3.25 (s, 3 H), 3.16 (s, 3 H), 3.01 (s, 3 H), 1.35 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.6, 108.2, 91.1, 84.6, 83.6, 83.2, 81.7, 81.5, 79.2, 72.6, 71.1, 60.8, 59.2, 58.7, 27.0, 25.4, 5.9.

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Supplementary Material Available: Full experimental details describing the preparation and authentication of all new compounds (40 pages). Ordering information is given on any current masthead page.

Asymmetric Synthesis with α,β-Bis[(methoxymethyl)oxy] Ketones. Enantioselective Total Synthesis of Natural (+)-Indolizidine 195B (Bicyclic Gephyrotoxin 195B) and (-)-Pinidine and Their Enantiomers from a Common Chiral Synthon

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Abstract: The first enantioselective total synthesis of naturally occurring (+)-indolizidine 195B (bicyclic gephyrotoxin 195B) and (-)-pinidine and their enantiomers has been achieved starting from 4-*O*-benzyl-2,3-*O*-bis(methoxymethyl)-L-threitol as a single and common chiral synthon, readily available from L-tartaric acid. This synthesis establishes the absolute stereochemistry of (+)-indolizidine 195B as 3*S*,5*S*,9*S*. The strategy for the synthesis of the alkaloids in both enantiomeric forms is based on the process involving a combination of the creation of new stereogenic centers by 1,2-asymmetric induction and destruction of the original chirality inducing group, i.e., *threo*-bis(methoxymethyl) ether. Actually, these processes consist of highly diastereoselective hydride addition to α,β-bis(methoxymethyl)oxy ketones via chelation or nonchelation control by using a variety of borohydride reagents and stereospecific transformation of *threo*-vicinal diols into both *E* and *Z* olefins.

Stereocontrolled addition of hydride from metal hydride reagents to acyclic ketones has been widely used for the preparation of optically active acyclic secondary alcohols. One of the most widely studied processes for this is the enantioselective hydride addition to prochiral ketones by metal hydride reagents modified with chiral ligands (reagent control).[1] Alternative efforts have been focused on the diastereoselective hydride addition of achiral metal hydride reagents (1,2- or 1,3-asymmetric induction) to ketone substrates having a stereogenic center or linked with a chiral auxiliary (substrate control).[2] Often there is a need for the preparation of molecules in both enantiomeric forms for studies, for example, on their physical or biological properties. In obtaining both enantiomers of a molecule by the methods for asymmetric induction mentioned above, both enantiomers of chiral reagents, chiral building blocks, or chiral auxiliaries are required. In many cases, however, one of the enantiomers of the chiral agents is not readily accessible from commercial sources or may have a high cost (for example, D- vs. L-sugars and L- vs. D-amino acids). To

(1) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2A.

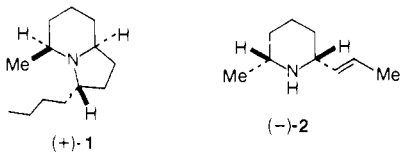
(2) (a) Eliel, E. L., in ref 1, Chapter 5. (b) Ohishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 388.

0002-7863/89/1511-1396$01.50/0

overcome these problems we envisioned the selective preparation of both enantiomers from a *single* enantiomeric source readily available at low cost, which involves diastereoselective hydride addition to a chiral substrate to create the new stereogenic center followed by destroying the original stereogenic center(s) via some sort of cleavage. In this paper we demonstrate the effectiveness of such a process in the stereoselective preparation of some alkaloids in both enantiomeric forms. Thus a key element in the initial stage of a general approach to alkaloid synthesis is producing a new stereogenic center based on chelation or nonchelation controlled hydride addition to chiral acyclic α,β-bis[(methoxymethyl)oxy] ketones leading to the opposite sense of diastereoselectivity; this problem of stereocontrol is simply solved by careful selection of borohydride reagents. This approach resulted in highly stereocontrolled syntheses of naturally occurring (+)-indolizidine 195B (bicyclic gephyrotoxin 195B) [(+)-**1**][3,4] and (−)-pinidine [(−)-**2**][6,7] and their enantiomers for the first time from a *single* and *common* chiral synthon. Also, our findings led to the establishment of the absolute configuration of (+)-indolizidine 195B as (+)-**1**.

Synthetic Strategy

Our synthetic strategy for a general approach to both enantiomers of indolizidine 195B (**1**) and pinidine (**2**) is illustrated in Figure 1. Starting from the L-threitol building block **3**,



diastereofacially selective hydride addition to ketone **4** with the *threo*-bis(methoxymethyl) ether (bis-MOM ether) as the "chirality inductor" leads to the creation of a new stereogenic center, affording the *syn*- or *anti*-alcohol **5**. After conversion of **5** to the corresponding *threo*-vicinal diol **6**, the chirality inductor group (bis-MOM ether) is destroyed in the next stage by appropriate methods to produce both enantiomers of the *Z* and *E* olefins **7**. These enantiomeric olefins (*R*)-**7** and (*S*)-**7** can be utilized as chiral building blocks for the synthesis of (+)-indolizidine 195B [(+)-**1**] and (−)-pinidine [(−)-**2**], and their enantiomers (−)-**1** and (+)-**2**, respectively.

In the above sequence, the elimination of the *threo*-vicinal dihydroxy groups can be performed *stereospecifically* in two different ways according to eq 1 via deoxygenation of the epoxides[8] and desulfurization–decarboxylation of the cyclic 1,2-thionocarbonates[9] to yield the *Z* and *E* olefins, respectively.

As a result of this planning, diastereoselective preparation of the *syn*- and *anti*-secondary alcohols by hydride addition to α,β-bis(methoxymethyl)oxy ketones became the first important problem for our synthetic venture.

Diastereoselective Hydride Addition to α,β-Bis[(methoxymethyl)oxy] Ketones

In diastereoselective addition of metal hydride reagents to acyclic chiral α-alkoxy ketones, two stereochemical courses of addition of hydride nucleophiles are possible, leading to the opposite sense of diastereoselectivity predicted by chelation or nonchelation models. With this in mind, the chiral ketone **9** bearing vicinal MOM ethers in α and β positions with threo configuration was initially chosen to develop the method to gain efficient syn and anti selectivity. Thus, L-threitol derivative **3**, readily available in bulk from diethyl L-tartrate in 3 steps,[10] was converted to **9** by the sequence of Swern oxidation (**3** → **8**)[11] followed by Grignard reaction (*n*-BuMgBr) and Swern oxidation (Scheme I). The α,β-bis[(methoxymethyl)oxy] ketone **9** obtained was subjected to hydride addition with use of a variety of borohydride reagents. The results are summarized in Table I (entries 1–3).

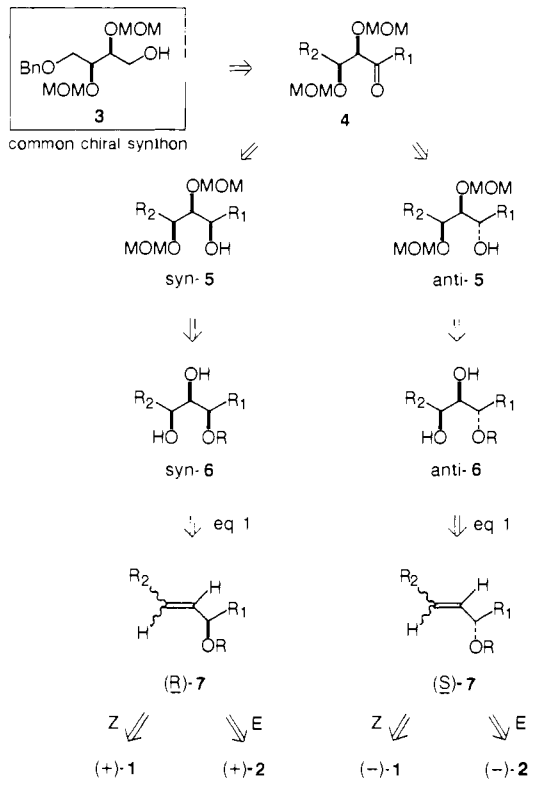
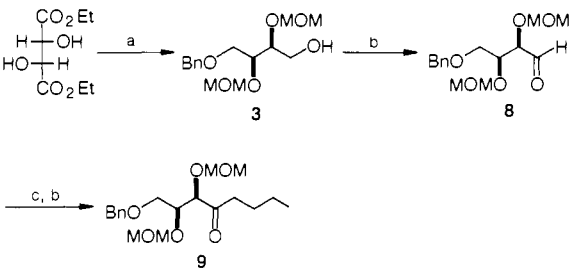


Figure 1.

Scheme I[a]

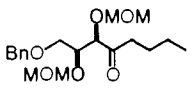
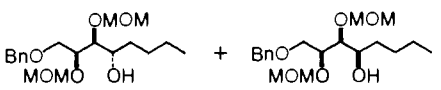
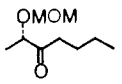
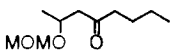


[a] (a) reference 10. (b) Me_2SO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C. (c) *n*-BuMgBr, Et_2O.

The stereochemical outcome of hydride addition to **9** can be accounted for as follows: the formation of anti isomer **10** would be predicted by an α-coordination transition-state model[12] (A) in which the *re* face of the carbonyl would be exposed to the reagent, while in β-chelation (B) and nonchelate Felkin–Anh[13] (C) transition states both would make the opposite diastereotopic face (*si* face) more accessible leading to syn isomer **11** (Figure 2). Actually, employment of zinc borohydride[2b] provided high anti selectivity of >99:1 yielding **10** in accordance with the α-

(3) Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *42*, 3453.
(4) We comply with the proposal by Daly[5] that the term gephyrotoxin is preferable to no longer use for the simple indolizidine class of dendrobatid alkaloids for some reason, but to refer to it simply as indolizidines. Thus gephyrotoxin 195B will be termed indolizidine 195B in this article.
(5) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1986; Vol. 4, Chapter 1.
(6) (a) Tallent, W. H.; Stromberg, V. L.; Horning, E. C. *J. Am. Chem. Soc.* **1955**, *77*, 6361. (b) Tallent, W. H.; Horning, E. C. *Ibid.* **1956**, *78*, 4467.
(7) Hill, R. K.; Chan, T. H.; Joule, J. A. *Tetrahedron* **1965**, *21*, 147.
(8) For one-step conversion of vicinal diols into olefins, see: Garegg, P. J.; Samuelson, B. *Synthesis* **1979**, 469, 813.
(9) (a) Corey, E. J.; Winter, R. A. E. *J. Am. Chem. Soc.* **1963**, *85*, 2677. (b) Corey, E. J.; Carey, F. A.; Winter, R. A. E. *Ibid.* **1965**, *87*, 934.
(10) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 1069.
(11) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(12) Still, W. C.; Mcdonald, J. H., III *Tetrahedron Lett.* **1980**, *21*, 1031.
(13) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.

Table I

entry	substrate	borohydride	products: anti/syn ratio[a] (yield,[b] %)
			
	9		**10** (anti) + **11** (syn)
1		$Zn(BH_4)_2$	>99:1 (95)
2		$LiBH_4$	46:54 (97)
3		$LiBH(\underline{sec}\text{-}Bu)_3$	8:92 (85)
			
	12		**13** (anti) + **14** (syn)
4		$Zn(BH_4)_2$	83:17 (83)
5		$LiBH_4$	57:43 (78)
6		$LiBH(\underline{sec}\text{-}Bu)_3$	11:89 (88)
			
	15		**16** (anti) + **17** (syn)
7		$Zn(BH_4)_2$	29:71 (89)
8		$LiBH_4$	34:66 (76)
9		$LiBH(\underline{sec}\text{-}Bu)_3$	31:69 (94)

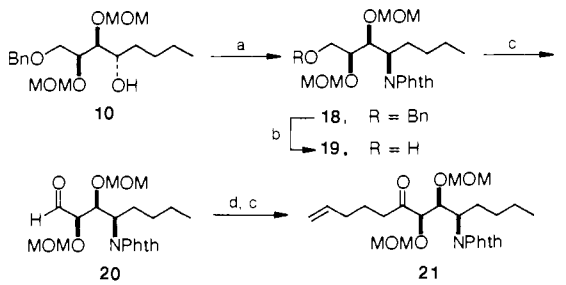
[a]Anti:syn ratios were determined by 400 MHz ^1H NMR. [b]Yield after purification by chromatography on silica gel.

chelation model A. In this model the metal ion will fit in a pocket formed from the carbonyl oxygen and the MOM ether oxygens. Thus the predominance of α-chelation over β-chelation in this case is probably due to such "crown ether effect" which may facilitate the α-chelate structure.

In marked contrast to this, reduction with a trialkylborohydride such as lithium tri-*sec*-butylborohydride (L-Selectride) displayed excellent syn selectivity (leading to **11**) of 92:8 consistent with the β-chelation (B) and/or Felkin–Anh model (C). In an effort to judge these reaction modes, we then carried out hydride addition with chiral α-(methoxymethyl)oxy ketone **12**[14] (entries 4–6, Table I). In contrast to the α-chelate controlled anti addition with zinc borohydride providing **13** (83:17 selectivity), syn selectivity (89:11) was obtained with L-Selectride to afford **14**. For the latter case, the reaction mode via the nonchelate process is the only explanation, which suggests that the trialkylborohydrides having no Lewis acidity[15] are of low coordinating ability, but they would be characterized as "bulky naked hydrides",[16] thus affording the *syn*-alcohol predicted by the nonchelate Felkin–Anh model (C, R = Me).

We next investigated borohydride reduction of β-(methoxymethyl)oxy ketone **15**.[17] The results are summarized in Table I (entries 7–9). In all these cases the syn preference predicted by the β-chelation model D leading to **17** was observed, albeit in modest to poor selectivity ranging between 71:29 and 66:34. For

Scheme II[a]



[a](a) Phthalimide, Ph_3P, $(=NCO_2Et)_2$, THF. (b) H_2, 10% Pd/C, MeOH. (c) Me_2SO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C. (d) $CH_2{=}C\text{-}H(CH_2)_3MgBr$, THF.

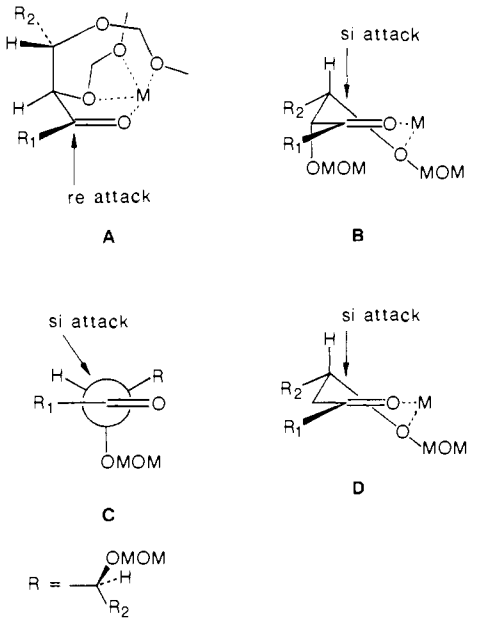


Figure 2.

(14) The α-(methoxymethyl)oxy ketone **11** was prepared from ethyl L-lactate according to: Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1987**, 746.

(15) Negishi, E. *Organometallics in Organic Synthesis*; Wiley-Interscience: New York, 1980; Vol. 1, Chapter 5.

(16) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1984**, *106*, 4629.

(17) The β-(methoxymethyl)oxy ketone **15** was prepared from racemic ethyl 3-hydroxybutyrate (i) by the following scheme.

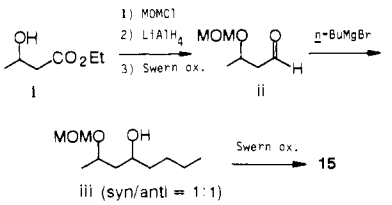
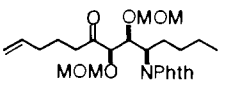
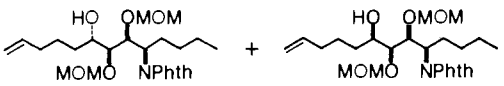
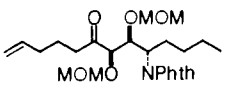
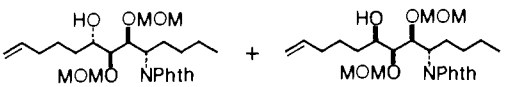
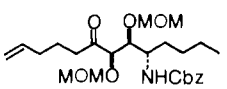
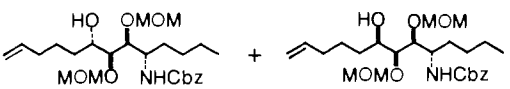


Table II

entry	substrate	borohydride	products: anti/syn ratio[a] (yield,[b] %)
	 **21**		 **22** (anti) + **23** (syn)
1		$Zn(BH_4)_2$	96:4 (72)
2		$NaBH_4$	63:37 (99)
3		$LiBH_4$	58:42 (88)
4		$LiBH(\underline{sec}\text{-}Bu)_3$	1:99 (86)
5		$LiBH(Sia)_3$	3:97 (69)
	 **28**		 **31** (anti) + **32** (syn)
6		$Zn(BH_4)_2$	98:2 (75)
	 **30**		 **33** (anti) + **34** (syn)
7		$Zn(BH_4)_2$	>99:1 (77)
8		$LiBH(\underline{sec}\text{-}Bu)_3$	1:>99 (72)

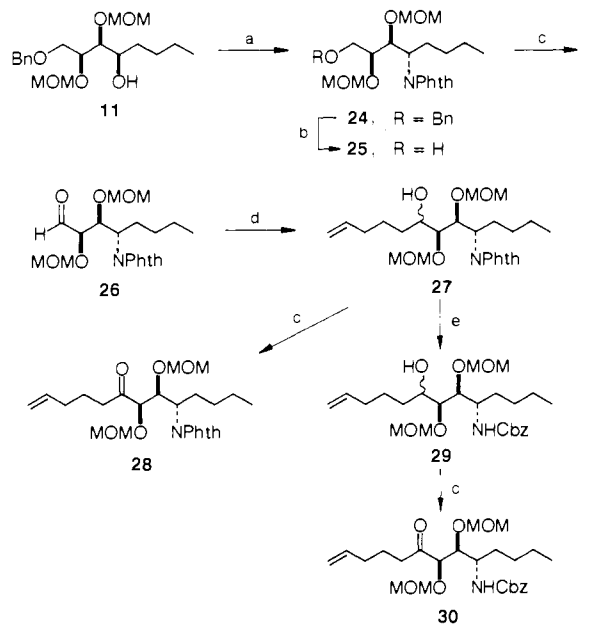
[a]Anti:syn ratios were determined by 400 MHz ^1H NMR. [b]Yield after purification by chromatography on silica gel.

both α- and β-(methoxymethyl)oxy ketones **12** and **15**, use of L-Selectride resulted in syn selectivity; however, the degree of selectivity in the case of β-(methoxymethyl)oxy ketone **15** (69:31) was lower than that in the case of α-(methoxymethyl)oxy ketone **12** (89:11). These facts indicate that in the competition between β-chelation and nonchelation processes the latter process is an important contribution to emergence of the syn selectivity. Thus, it is postulated that in the case of α,β-bis(methoxymethyl)oxy ketone **9** the syn selectivity with L-Selectride predominantly arises from the effect of the α-(methoxymethyl)oxy group via nonchelate Felkin–Anh model C and is enhanced to 92:8 by the β-MOM group which facilitates the syn-directed control due to β-chelation.

We next envisaged the preparation of the key chiral intermediates with the correct configurations required for the synthesis of the title alkaloids by application of the above observations. To this end, *anti*-alcohol **10** was converted to α,β-bis(methoxymethyl)oxy ketone **21** as outlined in Scheme II. The Mitsunobu reaction of **10** with phthalimide gave **18** in 61% yield with stereoinversion. Compound **18** was then converted to aldehyde **20** by debenzylation (H_2, Pd/C) followed by Swern oxidation in 67% yield from **18**. The Grignard reaction of **20** proceeded in a nonstereoselective manner, resulting in the formation of a 46:54 mixture of the *syn*/*anti*-alcohols, which were converted by Swern oxidation to form ketone **21** (78% yield). The same diastereoselective behavior with borohydride reagents as that for **9** was seen in the reaction of **21**, following the predicted pattern. Thus, as shown in Table II (entries 1–5), *anti,syn,syn*- and *syn,syn,syn*-alcohols **22** and **23** were obtained by employing zinc borohydride and L-Selectride or lithium trisiamylborohydride (LS-Selectride), respectively, with excellent facial selectivity.

In the same manner, *syn*-alcohol **11** was converted to ketone **28** via alcohol **27**, formed by nonstereoselective (syn/anti = 50:50) Grignard reaction, as outlined in Scheme III. Alcohol **27** was transformed to ketone **30** via the sequence involving removal of the phthaloyl group, benzyloxycarbonylation, and Swern oxidation (Scheme III). Results of hydride addition to these ketones **28** and **30** are presented in Table II. Excellent syn selectivity for the formation of anti,syn,anti products **31** and **33** was obtained with zinc borohydride (entries 6 and 7) in accordance with that observed in entry 1. In sharp contrast to this the use of L-Selectride (entry 8) offered virtually complete syn selectivity.

Scheme III[a]

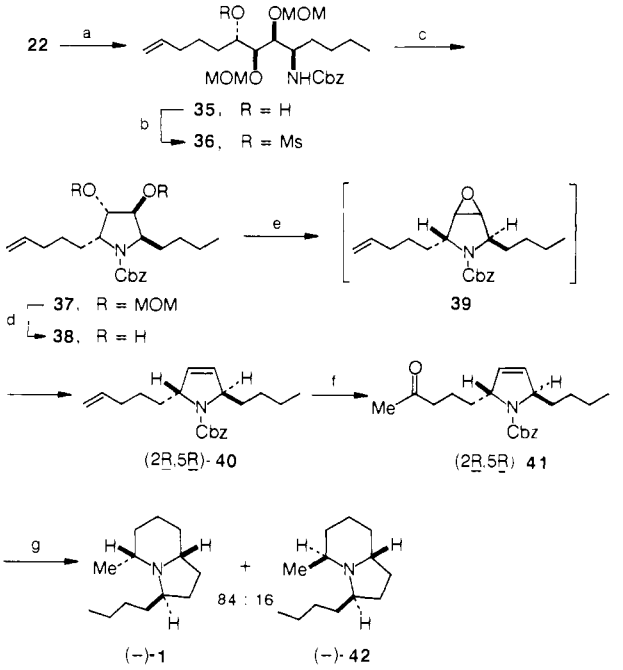


[a](a) Phthalimide, Ph_3P, $(=NCO_2Et)_2$, THF. (b) H_2, 10% Pd/C, MeOH. (c) Me_2SO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C. (d) $CH_2{=}C\text{-}H(CH_2)_3MgBr$, THF. (e) $(NH_2)_2{\cdot}H_2O$, EtOH, reflux, then $PhCH_2OCOCl$, aqueous Na_2CO_3, CH_2Cl_2, 0 °C.

Synthesis of (+)- and (−)-Indolizidine 195B

The highly diastereoselective preparation of the amino alcohol derivatives with appropriate configurations was now established. We envisaged the utilization of the anti,syn,syn (**22**) and syn,syn,anti (**32** or **34**) isomers as key building blocks, which are enantiomeric at C-6 and C-9, for the enantioselective synthesis of both (−)- and (+)-enantiomers of indolizidine 195B [(−)-**1** and (+)-**1**], respectively. (+)-Indolizidine 195B has recently been extracted from the skin of the Columbian poison-frog *Dendrobates histrionicus* as a new alkaloidal component and its structure has been determined as (5*E*,9*E*)-3-butyl-5-methylindolizidine on the

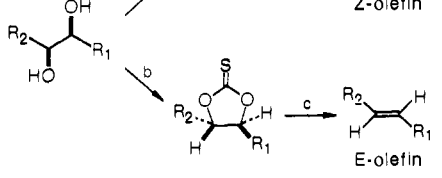
Scheme IV[a]



[a](a) $(NH_2)_2{\cdot}H_2O$, EtOH, reflux, then $PhCH_2OCOCl$, aqueous Na_2CO_3, CH_2Cl_2, 0 °C. (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C. (c) *t*-BuOK, THF, 0 °C → room temperature. (d) Concentrated HCl, MeOH, reflux. (e) 2,4,5-Triiodoimidazole, imidazole, Ph_3P, Zn, toluene, reflux. (f) O_2, $PdCl_2$, $CuCl_2$, DMF–H_2O, 70 °C. (g) H_2, 10% Pd/C, MeOH.

basis of NMR spectral analysis by Daly et al.[3] The absolute stereochemistry for this alkaloid has tentatively been proposed to be 3*S*,5*S*,9*S* by comparison of its optical rotation to those reported for the naturally occurring congeners by the same group.[3] In order to confirm the gross structure of indolizidine 195B and to establish its absolute stereochemistry, we envisaged the total synthesis of indolizidine 195B in both enantiomeric forms [(+)-**1** and (−)-**1**] based on a general strategy illustrated in Figure 1.

With the anti,syn,syn building block **22** in hand, we initially synthesized (−)-indolizidine 195B [(−)-**1**] as outlined in Scheme IV. Removal of the phthaloyl group with hydrazine followed by *N*-benzyloxycarbonylation gave **35** in 73% overall yield, which underwent mesylation and subsequent base-prompted cyclization (*t*-BuOK, THF) to provide as a single diastereomer the (2*R*,5*R*)-*cis*-pyrrolidine **37** with complete inversion of the C-6 configuration (*S* to *R*) in 72% yield from **35**. The subsequent formation of the olefin was performed on the basis of eq 1 after removal of the chirality inducing groups. Thus, deprotection of

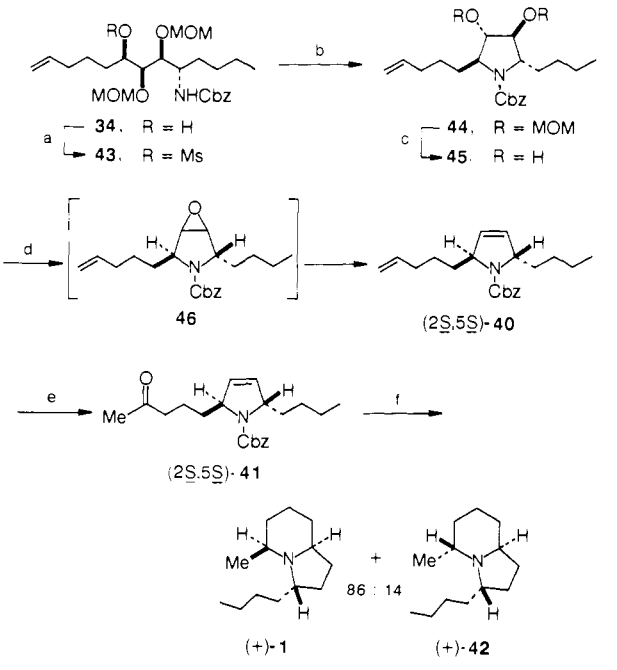


(1)

(a) 2,4,5-Triiodoimidazole, imidazole, Ph_3P, Zn, toluene, reflux; (b) thiocarbonyldiimidazole, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, reflux; (c) $(MeO)_3P$, reflux.

the MOM groups, without cleavage of the carbamate, occurred on treatment of **37** with concentrated hydrochloric acid in refluxing methanol in 95% yield. The resulting *trans*-diol **38** was converted to *Z* olefin (2*R*,5*R*)-**40** via epoxide (2*R*,5*R*)-**39** in 79% overall yield by treatment with triiodoimidazole, triphenylphosphine, and zinc in refluxing toluene. The Wacker process (O_2, $PdCl_2$, $CuCl_2$)[18] was applied to the site selective oxidation of the terminal

Scheme V[a]



[a](a) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C. (b) *t*-BuOK, THF, 0 °C → room temperature. (c) Concentrated HCl, MeOH, reflux. (d) 2,4,5-Triiodoimidazole, imidazole, Ph_3P, Zn, toluene, reflux. (e) O_2, $PdCl_2$, $CuCl_2$, DMF–H_2O, 70 °C. (f) H_2, 10% Pd/C, MeOH.

olefin, affording methyl ketone (2*R*,5*R*)-**41** in 79% yield, which on hydrogenation over palladium on carbon provided (−)-indolizidine 195B [(−)-**1**] along with its C-5 epimer (−)-**42** in a ratio of 84:16 (total yield: 91%). Synthetic (−)-**1** having spectral data (^1H and ^{13}C NMR) identical with those of the natural product showed $[\alpha]^{22}_D$ −97.1° while the natural product is reported[3] to be dextrorotatory ($[\alpha]^{16}_D$ +65°).[19] It follows, therefore, that naturally occurring indolizidine 195B has the absolute configuration opposite to that of synthetic (−)-**1** and should be illustrated by (+)-**1**.

For the synthesis of (+)-**1**, we chose to utilize *syn,syn,anti*-amino alcohol **34** previously obtained from **30** (Table II, entry 8). Thus, following the same route as that described above, **34** was subjected to mesylation, base-prompted cyclization, and removal of the MOM groups to provide **45** in 71% overall yield (Scheme V). *trans*-Diol **45** was converted to methyl ketone (2*S*,5*S*)-**41** via deoxygenation of epoxide **46** followed by Wacker oxidation of the resulting (2*S*,5*S*)-**40** in the same manner as described above (66% overall yield). Hydrogenation of (2*S*,5*S*)-**41** over palladium on carbon resulted in completion of the first asymmetric synthesis of (+)-indolizidine 195B [(+)-**1**], $[\alpha]^{24}_D$ +98.0°, along with its C-5 epimer (+)-**42** in an 86:14 ratio (97% yield). Synthetic (+)-indolizidine 195B had the same sign of optical rotation (dextrorotatory) as that published[3] for the natural product and its spectra (^1H and ^{13}C NMR) proved identical with those of the natural material.

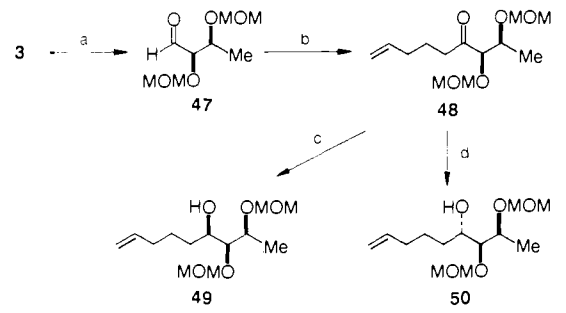
In conclusion, the preparation of both the (+)- and (−)-enantiomers of indolizidine 195B was thus achieved starting from the common chiral synthon **3** and our synthesis establishes the absolute stereostructure of the naturally occurring (+)-enantiomer as 3*S*,5*S*,9*S* as shown in formula (+)-**1**.

Synthesis of (+)- and (−)-Pinidine

To demonstrate further the general utility of the present synthetic strategy for the synthesis of natural products, we next envisioned the application of this methodology to the enantioselective synthesis of both (+)- and (−)-enantiomers of pinidine (**2**).

(18) For a review, see: Hüttel, R. *Synthesis* **1970**, 225.
(19) The reported value in ref 3 for natural (+)-indolizidine 195B would be somewhat tentative because of the very small quantity of natural material available.

Scheme VI[a]



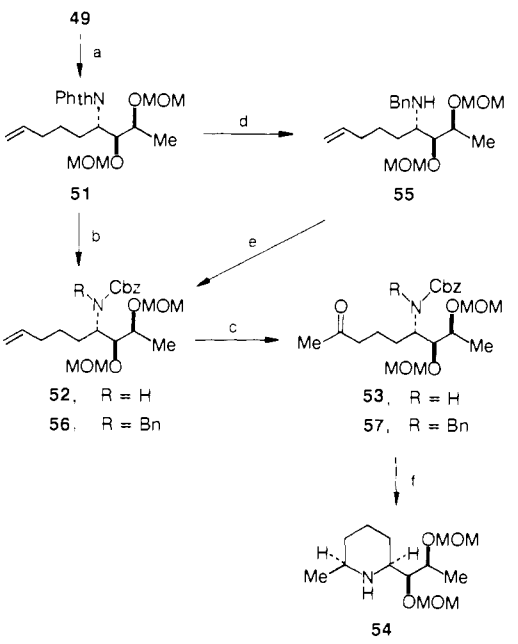
[a] (a) Reference 22. (b) $CH_2{=}CH(CH_2)_3MgBr$, THF, then Me_2SO, $(COCl)_2$, Et_3N, −78 °C. (c) $LiBH(sec\text{-}Bu)_3$, THF, −78 °C. (d) $Zn(BH_4)_2$, Et_2O, −20 °C → 0 °C.

The alkaloid (−)-pinidine [(−)-**2**] has been isolated from various species of *Pinus*.[6] The assignment of the absolute configuration of (−)-**2** has been made by chemical correlation studies.[7] While several syntheses of pinidine in racemic form[20] and dihydropinidine (racemic and optically active)[21] have been reported, asymmetric synthesis of pinidine remains unexplored. Our approach to both natural (−)- and unnatural (+)-enantiomers of pinidine employed a *common* precursor and was based on an asymmetric synthesis involving a combination of diastereoselective hydride addition to α,β-bis[(methoxymethyl)oxy] ketones and stereospecific transformation of *threo*-vicinal diols into olefins as demonstrated above in the synthesis of (+)- and (−)-indolizidine 195B.

The L-threitol building block **3** was converted to aldehyde **47** by the method developed in our laboratory[22] and was subsequently subjected to Grignard reaction with 4-pentenylmagnesium bromide followed by Swern oxidation to provide α,β-bis[(methoxymethyl)oxy] ketone **48** in 90% yield from **47** (Scheme VI). The *syn*- and *anti*-alcohols **49** and **50**, required for the syntheses of (+)- and (−)-pinidine, respectively, could be prepared by the procedure based on chelation or nonchelation controlled hydride addition, which proceeded in highly stereoselective and predictable manner along lines established in the synthesis of indolizidine 195B. Thus reduction of **48** with L-Selectride provided **49** with 91:9 syn selectivity in 90% yield. Alternatively, with zinc borohydride the *anti*-alcohol **50** was obtained with >99:1 selectivity in 70% yield (Scheme VI).

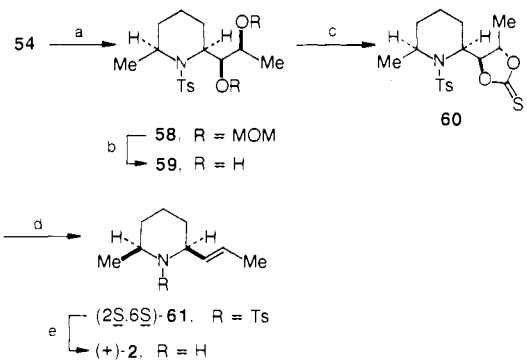
With *syn*-alcohol **49** in hand, the synthesis of unnatural (+)-pinidine was accomplished as follows. Mitsunobu reaction of **49** with phthalimide gave **51** (60% yield), which was converted to carbamate **52** by removal of the phthaloyl protecting group followed by *N*-benzyloxycarbonylation in 83% overall yield (Scheme VII). When ketone **53**, prepared from **52** via the Wacker process (O_2, $PdCl_2$, $CuCl_2$), was hydrogenated over palladium on carbon cyclization occurred in 89% yield to afford cis 2,6-disubstituted piperidine **54** as a single product. In this sequence (**52** → **53** → **54**), the yield of the Wacker process varied and was sometimes very poor (5–50%). To avoid this problem, protection of the NH group of **52** was envisioned. Accordingly, **51** underwent dephthaloylation followed by N-benzylation (benzyl bromide, aqueous Na_2CO_3) to give **55** (75% yield), which was converted to carbamate **56** in 80% yield. Wacker oxidation of **56** resulted in methyl ketone **57** in 60% yield. Subsequent ring formation of **57** by catalytic hydrogenation provided exclusively **54** in 94% yield (Scheme VII). Tosylation followed by removal of the MOM groups by acid treatment of the resulting tosylate **58** afforded *threo*-diol **59** (52% overall yield), which was then stereospecifically transformed into the *E* olefin by the method based on eq 1. Accordingly, **59** was converted to cyclic thionocarbonate **60** by treatment with thiocarbonyldiimidazole in the presence of diisopropylethylamine in 85% yield. Compound **60** was then heated with trimethyl phosphite to generate (2*S*,6*S*)-**61** with *E* geometry in the 2-alkyl side chain as a single product in 97% yield. Birch reduction of (2*S*,6*S*)-**61** resulted in detosylation with the olefin moiety intact, furnishing (+)-pinidine [(+)-**2**] in 81% yield (Scheme VIII). Synthetic (+)-**2** had identical optical rotation ($[\alpha]^{24}_D$ +10.2°) and spectra (^1H and ^{13}C NMR and mass) as those of authentic material prepared via resolution of racemic pinidine by Leete et al.[20a]

Scheme VII[a]



[a] (a) Phthalimide, Ph_3P, $(=NCO_2Et)_2$, THF. (b) (**51** → **52**) $(NH_2)_2{\cdot}H_2O$, EtOH, reflux, then $PhCH_2OCOCl$, aqueous Na_2CO_3, CH_2Cl_2, 0 °C. (c) O_2, $PdCl_2$, $CuCl_2$, DMF–H_2O, 70 °C. (d) $(NH_2)_2{\cdot}H_2O$, EtOH, reflux, then $PhCH_2Br$, aqueous Na_2CO_3, CH_2Cl_2, reflux. (e) (**55** → **56**) $PhCH_2OCOCl$, aqueous Na_2CO_3, CH_2Cl_2, 0 °C. (f) H_2, 10% Pd/C, MeOH.

Scheme VIII[a]



[a] (a) TsCl, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, room temperature. (b) Concentrated HCl, MeOH, reflux. (c) Thiocarbonyldiimidazole, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, reflux. (d) $(MeO)_3P$, reflux. (e) Na, liquid NH_3, EtOH, −78 °C.

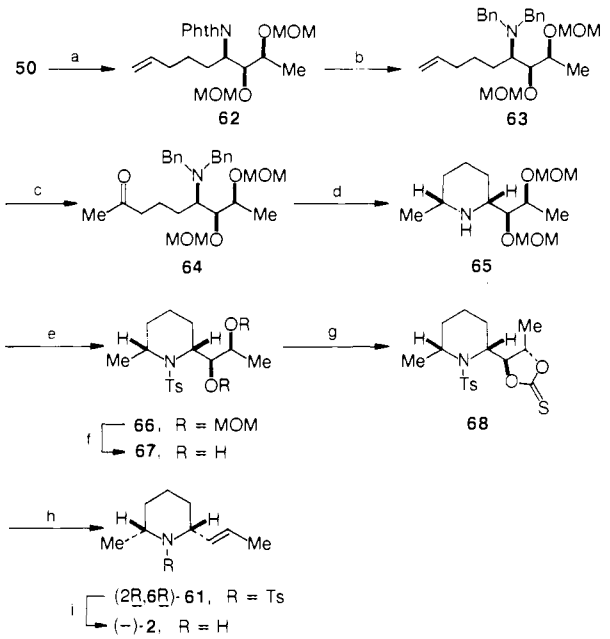
Alternatively, the natural (−)-enantiomer of pinidine [(−)-**1**] was constructed from *anti*-alcohol **50** (Scheme IX) utilizing the above sequence for the preparation of (+)-pinidine. The Mitsunobu reaction of **50** gave phthalimide **62** (57% yield), which was converted to **63** in 81% yield by dephthaloylation and N,N-dibenzylation. Wacker oxidation of **63** (68% yield) followed by hydrogenation over palladium on carbon of the resulting methyl ketone **64** resulted in in situ ring construction affording **65** as a single diastereomer in 95% yield. N-Protection by the tosyl group and removal of the MOM groups led to *threo*-diol **67** (43% overall yield), which was stereospecifically transformed into *E* olefin

(20) (a) Leete, E.; Carver, R. A. *J. Org. Chem.* **1975**, *40*, 2151. (b) Arseniyadis, S.; Sartoretti, J. *Tetrahedron Lett.* **1985**, *26*, 729.

(21) (a) Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569. (b) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 3369. (c) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P.; *J. Am. Chem. Soc.* **1983**, *105*, 7754.

(22) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 4245.

Scheme IX[a]



[a] (a) Phthalimide, Ph_3P, ($=NCO_2Et$), THF. (b) $(NH_2)_2 \cdot H_2O$, EtOH, reflux, then $PhCH_2Br$, aqueous Na_2CO_3, CH_2Cl_2, reflux. (c) O_2, $PdCl_2$, $CuCl_2$, DMF–H_2O, 70 °C. (d) H_2, 10% Pd/C, MeOH. (e) TsCl, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, room temperature. (f) Concentrated HCl, MeOH, reflux. (g) Thiocarbonyldiimidazole, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, reflux. (h) $(MeO)_3P$, reflux. (i) Na, liquid NH_3, EtOH, −78 °C.

(2*R*,6*R*)-**61** via cyclic thionocarbonate **68** in 78% overall yield. Finally, the tosyl protective group was removed by Birch reduction to provide (−)-pinidine [(−)-**2**] in 79% yield. Synthetic (−)-**2** had $[\alpha]^{25}_D$ −10.8° (*c* 0.07, EtOH) identical with that published for the natural alkaloid [$[\alpha]^{25}_D$ −10.5° (*c* 1.880, EtOH)][6a] and exhibited spectral data (^1H and ^{13}C NMR and mass) identical with those of (+)-pinidine previously prepared via resolution of the racemate by Leete et al.[20a]

Conclusion

In conclusion, the feasibility of regulating the stereochemical course of reduction of α,β-bis[(methoxymethyl)oxy] ketones by borohydride reduction with significant differences in chelation or nonchelation processes and subsequent stereospecific transformation of *threo*-vicinal diols into olefins provides a general synthetic method for alkaloid synthesis. Also, this approach has allowed us to demonstrate the marked versatility of the L-threitol building block **3** as a synthetically very flexible common chiral synthon and, by exploiting it, to accomplish an efficient preparation of both (+)- and (−)-enantiomers of indolizidine and piperidine alkaloids and their congeners in a highly stereocontrolled manner.

Experimental Section

General Methods. Melting points (uncorrected) were determined by using a Yanagimoto micro melting point apparatus. Optical rotations were measured with a JASCO DIP-360 digital polarimeter in a 1-dm cell. IR spectra were determined on a Hitachi 260-30 or a Perkin-Elmer 1710 FTIR spectrometer. ^1H NMR spectra were recorded on a Bruker AM-400 (400 MHz), a JEOL JNM-PS-100 (100 MHz), or a Varian EM-390 (90 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer at 100.6 MHz and the degree of substitution of each carbon atom was determined by complete decoupling and DEPT composed 90° and 135° pulsed sequence experiments. Mass spectra were obtained with a Hitachi RMU-7L double-focusing mass spectrometer at an ionizing potential of 70 eV. TLC was run on Wako precoated silica gel 70 FM plates. Merck silica gel 60 (230–400 mesh) and aluminum oxide 90 (basic, activity I, 70–230 mesh) were used for column chromatography.

(2*S*,3*R*)-1-(Benzyloxy)-2,3-bis[(methoxymethyl)oxy]octan-4-one (9). To a stirred ice-cold ethereal solution (100 mL) of *n*-butylmagnesium bromide, prepared from 4.3 g (176 mmol) of magnesium and 30.1 g (220 mmol) of 1-bromobutane, was added dropwise a solution of 4-*O*-benzyl-2,3-*O*-bis(methoxymethyl)-L-threose (**8**)[10] (26.2 g, 88 mmol) in ether (100 mL) under nitrogen over 10 min. The reaction was allowed to warm to room temperature, stirred for 14 h, and quenched with water (5 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 50 mL). The organic layers were dried ($MgSO_4$), the solvent was removed by evaporation, and the residue was purified by silica gel chromatography with hexane–ethyl acetate (3:1) to give a diastereomeric mixture of the alcohols (**10** and **11**) (30.8 g, 98%) as a colorless oil. To a stirred −78 °C solution of oxalyl chloride (7.33 g, 57.8 mmol) in dichloromethane (40 mL) was added dropwise a solution of dimethyl sulfoxide (9.02 g, 115.6 mmol) in dichloromethane (35 mL) over a period of 5 min, and the mixture was stirred for another 10 min at −78 °C. To this mixture was added dropwise a solution of the above diastereomeric mixture of the alcohols (**10** and **11**) (10.30 g, 28.9 mmol) in dichloromethane (35 mL) over 5 min, and stirring was continued at −78 °C. After 1 h, triethylamine (17.54 g, 173.3 mmol) was added to the reaction mixture, and the reaction was allowed to warm to ambient temperature. After addition of dichloromethane (500 mL) the mixture was washed with water (100 mL), dried ($MgSO_4$), and evaporated in vacuo. Chromatography of the resulting residue on silica gel with hexane–ethyl acetate (5:1 to 3:1) afforded **9** (9.68 g, 95%) as a colorless oil: $[\alpha]^{20}_D$ +24.2° (*c* 1.33, $CHCl_3$); IR ($CHCl_3$) 2950, 1710, 1445, 1145, 1095, 1020, 910, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.89 (3 H, t, *J* = 7.4 Hz), 1.30 (2 H, sext, *J* = 7.4 Hz), 1.54 (2 H, quint, *J* = 7.4 Hz), 2.58 (2 H, td, *J* = 7.4, 1.1 Hz), 3.30 (3 H, s), 3.37 (3 H, s), 3.61 (1 H, dd, *J* = 9.6, 5.6 Hz), 3.66 (1 H, dd, *J* = 9.6, 6.9 Hz), 4.16 (1 H, ddd, *J* = 6.8, 5.7, 3.3 Hz), 4.28 (1 H, d, *J* = 3.3 Hz), 4.52 (2 H, s), 4.59 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.66 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.69 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.70 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 7.25–7.40 (5 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 13.94, 22.38, 25.21, 39.86, 55.97, 56.41, 69.06, 73.55, 76.60, 82.15, 96.97, 97.49, 127.83 (2 carbons), 127.86 (2 carbons), 128.50, 137.88, 210.04; mass spectrum, *m/z* (relative intensity) 322 (M^+ − 32, 0.3), 309 (0.6), 277 (1.0), 239 (2.4), 204 (20), 163 (14), 117 (22), 92 (28), 91 (100), 85 (55). Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.39; H, 8.53. Found: C, 64.12; H, 8.58.

General Procedure for Reduction of Ketones 9, 12, and 15. A. With $Zn(BH_4)_2$. To a stirred cooled (−20 °C) solution of ketone (2 mmol) in ether (10 mL) was added dropwise a 0.14 M solution of $Zn(BH_4)_2$ (4 mmol) in ether under nitrogen over 15 min and the mixture was stirred at 0 °C for 45 min. The reaction mixture was quenched by addition of water (2 mL) and the layers were separated. The organic layer was washed with brine (2 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification of the resulting residue by silica gel chromatography with hexane–ethyl acetate (2:1) gave a mixture of the *anti*- and *syn*-alcohols (see Table I).

B. With $LiBH_4$. To a stirred cooled (−20 °C) solution of the ketone (0.2 mmol) in THF (5 mL) was added $LiBH_4$ (0.4 mmol) and the mixture was stirred at −20 °C for 1 h. After the reaction was quenched by addition of water (1 mL), ether (25 mL) was added to the reaction mixture. The resulting mixture was filtered through Celite, and the filtrate was dried ($MgSO_4$) and concentrated in vacuo. The residue was worked up by procedure A (see Table I).

C. With L-Selectride. To a stirred cooled (−78 °C) solution of the ketone (1.7 mmol) in THF (10 mL) was added a 1 M solution of L-Selectride (3.4 mmol) in THF via a syringe and the mixture was stirred at −78 °C for 1 h. After the reaction was quenched with water (2 mL), ether (50 mL) was added to the reaction mixture and the resulting mixture was worked up by procedure B (see Table I).

(2*S*,3*S*,4*S*)-1-(Benzyloxy)-2,3-bis[(methoxymethyl)oxy]octan-4-ol (10). Pure **10** was obtained as follows: The diastereomeric mixture (6.88 g) of **10** and **11** (>99:1) obtained by reduction of **9** with $Zn(BH_4)_2$ was separated by chromatography on silica gel with ether acetate–hexane (5:1 to 3:1) to provide **10** (6.70 g, 93% from **9**) as a colorless oil: $[\alpha]^{20}_D$ −25.7° (*c* 0.27, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.90 (3 H, t, *J* = 7.2 Hz), 1.21–1.62 (6 H, m), 3.30 (1 H, d, *J* = 6.1 Hz), 3.39 (3 H, s), 3.40 (3 H, s), 3.55–3.73 (4 H, m), 4.02 (1 H, td, *J* = 5.5, 4.1 Hz), 4.52 (1 H, $^1/_2$ AB q, *J* = 12.0 Hz), 4.55 (1 H, $^1/_2$ AB q, *J* = 12.0 Hz), 4.66 (1 H, $^1/_2$ AB q, *J* = 6.7 Hz), 4.70 (1 H, $^1/_2$ AB q, *J* = 6.7 Hz), 4.73 (1 H, $^1/_2$ AB q, *J* = 6.7 Hz), 4.80 (1 H, $^1/_2$ AB q, *J* = 6.7 Hz), 7.20–7.40 (5 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 14.12, 22.79, 28.10, 32.70, 56.08, 56.18, 70.10, 70.97, 76.89, 82.42, 97.43, 98.19, 127.77 (3 carbons), 128.46 (2 carbons), 137.95; mass spectrum, *m/z* (relative intensity) 163 (16), 91 (91), 45 (100). Anal. Calcd for $C_{19}H_{32}O_6$: C, 64.02; H, 9.05. Found: C, 64.26; H, 9.22.

(2*S*,3*S*,4*R*)-1-(Benzyloxy)-2,3-bis[(methoxymethyl)oxy]octan-4-ol (11). Pure **11** was obtained as follows: The diastereomeric mixture (510 mg) of **11** and **10** (92:8) obtained by reduction of **9** with L-Selectride was chromatographed on silica gel with hexane–ethyl acetate (5:1 to 3:1) to provide **11** (455 mg, 75% from **9**) as a colorless oil: $[\alpha]^{20}_D$ −11.9° (*c* 1.35, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.91 (3 H, t, *J* = 7.2

Hz), 1.25–1.60 (6 H, m), 2.85 (1 H, d, J = 5.4 Hz), 3.36 (3 H, s), 3.40 (3 H, s), 3.57 (1 H, t, J = 4.5 Hz), 3.60–3.70 (2 H, unresolved), 3.70–3.77 (1 H, m), 3.94 (1 H, dd, J = 9.7, 5.1 Hz), 4.53 (2 H, s), 4.67 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.70 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.73 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.77 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 7.22–7.40 (5 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 14.07, 22.77, 27.92, 33.42, 55.84, 56.28, 69.64, 70.28, 73.52, 76.84, 82.24, 96.89, 98.60, 127.77 (2 carbons), 127.80 (2 carbons), 128.43, 137.92; mass spectrum, m/z (relative intensity) 357 (M^+ + 1, 0.6), 339 (2), 307 (1), 293 (15), 201 (45), 163 (40), 91 (100). Anal. Calcd for $C_{19}H_{32}O_6$: C, 64.02; H, 9.05. Found: C, 63.88; H, 8.98.

(2*S*,3*S*,4*R*)-1-(Benzyloxy)-4-(1,3-dioxo-2-azaindan-2-yl)-2,3-bis[(methoxymethyl)oxy]octane (18). To a stirred, ice-cold solution of **10** (1.25 g, 3.51 mmol), phthalimide (1.03 g, 7.00 mmol), and triphenylphosphine (1.84 g, 7.01 mmol) in THF (15 mL) was added diethyl azodicarboxylate (1.22 g, 7.00 mmol). The mixture was allowed to warm to room temperature and stirred for 14 h. After the solvent was evaporated, the residue was subjected to chromatography on silica gel with hexane–ethyl acetate (4:1) to remove most of the triphenylphosphine oxide from the reaction product. To the oily product obtained was added benzene (15 mL), and a separated solid [$(NHCO_2Et)_2$] was filtered. The filtrate was evaporated and the residue was chromatographed on silica gel with hexane–ethyl acetate (5:1 to 4:1) to give **18** (1.04 g, 61%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.82 (3 H, t, J = 7.2 Hz), 1.11–1.39 (4 H, m), 1.68–1.80 (1 H, m), 2.07–2.20 (1 H, m), 2.81 (3 H, s), 3.46 (3 H, s), 3.64 (1 H, dd, J = 9.5, 6.6 Hz), 3.70 (1 H, dd, J = 9.5, 6.1 Hz), 4.00 (1 H, td, J = 6.3, 1.8 Hz), 4.38 (1 H, dd, J = 9.9, 1.9 Hz), 4.47 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 4.48 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 4.53 (2 H, s), 4.56 (1 H, ddd, J = 12.1, 9.9, 3.9 Hz), 4.70 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 4.87 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 7.20–7.40 (5 H, m), 7.69 (2 H, dd, J = 5.4, 3.0 Hz), 7.83 (2 H, dd, J = 5.4, 3.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 13.98 (CH_3), 22.43 (CH_2), 27.34 (CH_2), 28.69 (CH_2), 52.85 (CH), 56.01 (CH_3), 56.25 (CH_3), 69.70 (CH_2), 73.61 (CH_2), 76.00 (CH), 80.24 (CH), 96.98 (CH_2), 99.30 (CH_2), 122.97 (CH), 127.80 (CH), 127.86 (CH), 128.48 (CH), 132.26 (C), 133.71 (CH), 137.95 (C), 169.03 (C); mass spectrum, m/z (relative intensity) 408 (5), 332 (10), 290 (25), 216 (75), 160 (78), 91 (100).

(2*S*,3*S*,4*R*)-4-(1,3-Dioxo-2-azaindan-2-yl)-2,3-bis[(methoxymethyl)oxy]octanol (19). A solution of **18** (710 mg, 1.46 mmol) in methanol (10 mL) was hydrogenated over 10% palladium on carbon (700 mg) at atmospheric pressure for 3 h. After filtration, the catalyst was washed with methanol (5 mL) and the resulting methanol solution was evaporated in vacuo. Chromatography on silica gel with hexane–ethyl acetate (2:1 to 1:1) gave **19** (410 mg, 71%) as a colorless oil: $[\alpha]^{22}_D$ −44.6° (c 1.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.81 (3 H, t, J = 7.2 Hz), 1.10–1.40 (4 H, m), 1.58–1.68 (1 H, m), 1.83 (1 H, br s), 2.09–2.21 (1 H, m), 3.02 (3 H, s), 3.31 (1 H, dd, J = 8.0, 4.2 Hz), 3.48 (3 H, s), 3.68–3.85 (2 H, unresolved), 4.33 (1 H, dd, J = 9.6, 1.7 Hz), 4.45 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.50 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.56 (1 H, ddd, J = 12.2, 9.7, 3.8 Hz), 4.71 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 4.84 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 7.71 (1 H, dd, J = 5.4, 3.1 Hz), 7.83 (1 H, dd, J = 5.4, 3.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 13.92, 22.31, 27.43, 28.50, 52.73, 56.27 (2 carbons), 62.55, 80.03, 80.68, 97.57, 99.00, 123.15 (2 carbons), 132.00, 133.91 (2 carbons), 168.97; mass spectrum, m/z (relative intensity) 332 (2), 290 (30), 216 (85), 160 (100). Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.75; H, 7.39; N, 3.54. Found: C, 60.82; H, 7.30; N, 3.24.

(2*R*,3*S*,4*R*)-4-(1,3-Dioxo-2-azaindan-2-yl)-2,3-[bis(methoxymethyl)oxy]octanal (20). To a stirred solution of oxalyl chloride (0.80 g, 6.30 mmol) in dichloromethane (5 mL) at −78 °C was added dropwise a solution of dimethyl sulfoxide (0.98 g, 12.55 mmol) in dichloromethane (5 mL) over a period of 5 min, and the mixture was stirred for another 10 min at −78 °C. To this mixture was added dropwise a solution of **19** (1.25 g, 3.16 mmol) in dichloromethane (3 mL) over a period of 5 min, and stirring was continued at −78 °C. After 1 h, triethylamine (1.91 g, 18.87 mmol) was added to the reaction mixture, and the reaction mixture was warmed to ambient temperature and stirred for 15 min. The mixture was washed with water (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by silica gel chromatography with hexane–ethyl acetate (5:1 to 3:1) afforded **20** (1.17 g, 94%) as a colorless oil, which solidified on standing: mp 80–83 °C; $[\alpha]^{24}_D$ −11.1° (c 1.01, $CHCl_3$); IR ($CHCl_3$) 2950, 1765, 1725 (sh), 1705, 1385, 1140, 1015, 525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.81 (3 H, t, J = 7.1 Hz), 1.14–1.40 (4 H, m), 1.50–1.65 (1 H, m), 2.10–2.23 (1 H, m), 2.91 (3 H, s), 3.50 (3 H, s), 4.19 (1 H, d, J = 1.6 Hz), 4.38 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 4.43 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 4.55–4.70 (2 H, unresolved), 4.81 (1 H, $^1/_2$ AB q, J = 7.1 Hz), 4.86 (1 H, $^1/_2$ AB q, J = 7.1 Hz), 7.71 (2 H, dd, J = 5.4, 3.0 Hz), 7.83 (2 H, dd, J = 5.4, 3.0 Hz), 9.72 (1 H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 13.92 (CH_3), 22.33 (CH_2), 27.41 (CH_2), 28.49 (CH_2), 52.45 (CH), 56.05 (CH_3), 56.72 (CH_3), 79.64 (CH), 82.33 (CH), 97.56 (CH_2), 98.89 (CH_2), 123.19 (2 carbons, CH), 132.02 (2 carbons, C), 133.96 (2 carbons, CH), 168.83 (2 carbons, C), 201.99 (CH); mass spectrum, m/z (relative intensity) 303 (8), 300 (30), 258 (10), 246 (15), 216 (60), 160 (100). Anal. Calcd for $C_{20}H_{27}NO_7$: C, 61.06; H, 6.92; N, 3.56. Found: C, 61.31; H, 6.95; N, 3.58.

(7*R*,8*S*,9*R*)-9-(1,3-Dioxo-2-azaindan-2-yl)-7,8-bis[(methoxymethyl)oxy]tridec-1-en-6-one (21). To a stirred solution of 4-pentenylmagnesium bromide, prepared from 1.39 g (9.33 mmol) of 4-pentenyl bromide and 453 mg (18.6 mmol) of Mg, in THF (10 mL) was added dropwise at −78 °C a solution of **20** (1.22 g, 3.10 mmol) in THF (5 mL) under nitrogen. After the reaction mixture was stirred at −78 °C for 30 min, the resulting dark greenish blue solution was quenched with water (2 mL) and extracted with ether (90 mL). The extract was dried ($MgSO_4$) and concentrated in vacuo. Purification by chromatography on silica gel with hexane–ethyl acetate (3:1) gave a diastereomeric mixture (1.33 g, 93%) of **22** and **23** in a ratio of 54:46 (determined by ^{1}H NMR) as a colorless oil, which was subjected to Swern oxidation in a similar manner to that described for the preparation of 9 to afford **21** (1.13 g, 85% from the mixture of **22** and **23**, 78% from **20**) as a colorless oil: $[\alpha]^{20}_D$ −16.4° (c 0.28, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.82 (3 H, t, J = 7.2 Hz), 1.11–1.40 (4 H, m), 1.60–1.74 (3 H, m), 2.07 (2 H, dd, J = 14.1, 7.2 Hz), 2.10–2.23 (1 H, m), 2.52–2.69 (2 H, unresolved), 2.82 (3 H, s), 3.49 (3 H, s), 4.28 (1 H, d, J = 1.7 Hz), 4.29 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.38 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.51–4.66 (2 H, m), 4.70 (1 H, $^1/_2$ AB q, J = 7.1 Hz), 4.79 (1 H, $^1/_2$ AB q, J = 7.1 Hz), 4.92–5.07 (2 H, m), 5.76 (1 H, ddt, J = 17.0, 10.3, 6.7 Hz), 7.70 (2 H, dd, J = 5.4, 3.0 Hz), 7.83 (2 H, dd, J = 5.4, 3.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 13.98, 22.28, 22.44, 27.25, 28.62, 33.09, 39.31, 52.73, 56.17, 56.88, 81.07, 82.74, 97.37, 99.03, 115.36, 123.10 (2 carbons), 132.14 (2 carbons), 133.87 (2 carbons), 137.99, 168.89 (2 carbons), 209.92; mass spectrum, m/z (relative intensity) 364 (5), 288 (50), 258 (30), 246 (20), 216 (100), 160 (100). Anal. Calcd for $C_{25}H_{35}NO_7$: C, 65.06; H, 7.64; N, 3.03. Found: C, 64.84; H, 7.59; N, 3.04.

(2*S*,3*S*,4*S*)-1-(Benzyloxy)-4-(1,3-dioxo-2-azaindan-2-yl)-2,3-bis[(methoxymethyl)oxy]octane (24). In the same manner as described above for the preparation of **18**, **11** was subjected to Mitsunobu reaction. Thus, from 10.0 g (28.05 mmol) of **11** was obtained 6.9 g (51%) of **24** as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.82 (3 H, t, J = 7.2 Hz), 1.09–1.41 (4 H, m), 1.87–1.99 (1 H, m), 2.05–2.19 (1 H, m), 3.23 (3 H, s), 3.41 (3 H, s), 3.65 (1 H, dd, J = 9.9, 7.2 Hz), 3.72 (1 H, dd, J = 9.9, 4.8 Hz), 3.83 (1 H, ddd, J = 7.2, 4.8, 2.8 Hz), 4.32 (1 H, ddd, J = 11.4, 9.9, 3.6 Hz), 4.40–4.53 (4 H, m), 4.57 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.78 (2 H, s), 7.20–7.39 (5 H, m), 7.70 (2 H, dd, J = 5.4, 3.0 Hz), 7.81 (2 H, dd, J = 5.4, 3.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 14.00, 22.41, 28.34, 28.45, 51.60, 55.76, 56.48, 70.01, 73.29, 76.81, (2 carbons), 97.23, 98.48, 123.22 (2 carbons), 127.53, 127.64 (2 carbons), 128.33 (2 carbons), 132.01 (2 carbons), 133.91 (2 carbons), 138.32, 168.61 (2 carbons).

(2*S*,3*S*,4*S*)-4-(1,3-Dioxo-2-azaindan-2-yl)-2,3-bis[(methoxymethyl)oxy]octanol (25). In the same manner as described above for the preparation of **19**, **24** (5.2 g, 10.7 mmol) was hydrogenated to give **25** (3.2 g, 76%) as a colorless oil: $[\alpha]^{22}_D$ −36.9° (c 1.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.81 (3 H, t, J = 7.2 Hz), 1.08–1.40 (4 H, m), 1.77 (1 H, br s), 1.81–1.92 (1 H, m), 2.05–2.19 (1 H, m), 3.26 (3 H, s), 3.45 (3 H, s), 3.45–3.52 (1 H, m), 3.68–3.79 (2 H, m), 4.36 (1 H, dd, J = 9.8, 2.2 Hz), 4.40–4.49 (1 H, m, containing 1 H, $^1/_2$ AB q, J = 7.2 Hz at δ 4.44), 4.57 (1 H, $^1/_2$ AB q, J = 7.2 Hz), 4.75 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.83 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 7.72 (2 H, dd, J = 5.4, 3.1 Hz), 7.81 (2 H, dd, J = 5.4, 3.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 13.93, 22.32, 27.87, 28.37, 51.53, 55.84, 56.58, 63.02, 77.77, 82.66, 98.50, 98.82, 123.29 (2 carbons), 131.77 (2 carbons), 134.11 (2 carbons), 168.49 (2 carbons); mass spectrum, m/z (relative intensity) 332 (3), 290 (40), 246 (20), 216 (70), 160 (100). Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.75; H, 7.39; N, 3.54. Found: C, 60.90; H, 7.30; N, 3.72.

(2*R*,3*S*,4*S*)-4-(1,3-Dioxo-2-azaindan-2-yl)-2,3-bis[(methoxymethyl)oxy]octanal (26). In the same manner as described above for the preparation of **20**, **25** was subjected to Swern oxidation. Thus, from 928 mg (2.35 mmol) of **25** was obtained 790 mg (86%) of **26** as a colorless oil: $[\alpha]^{23}_D$ −24.6° (c 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.83 (3 H, t, J = 7.2 Hz), 1.09–1.40 (4 H, m), 1.87–1.98 (1 H, m), 2.08–2.20 (1 H, m), 3.35 (3 H, s), 3.38 (3 H, s), 3.81 (1 H, br s), 4.47–4.57 (1 H, m, containing 1 H, $^1/_2$ AB q, J = 6.9 Hz at δ 4.54), 4.63 (1 H, dd, J = 9.6, 1.8 Hz), 4.69 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.71 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 4.80 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 7.74 (2 H, dd, J = 5.4, 3.1 Hz), 7.84 (2 H, dd, J = 5.4, 3.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 13.92, 22.32, 27.96, 28.43, 51.81, 56.38, 56.50, 77.57, 82.69, 98.29, 98.47, 123.46 (2 carbons), 131.70 (2 carbons),

134.26 (2 carbons), 168.39 (2 carbons), 201.76; mass spectrum, *m/z* (relative intensity) 364 (0.2), 332 (1), 331 (1), 290 (10), 289 (10), 286 (12), 274 (18), 258 (15), 246 (21), 216 (54), 160 (100). Anal. Calcd for $C_{20}H_{27}NO_7$: C, 61.06; H, 6.92; N, 3.56. Found: C, 60.76; H, 6.80; N, 3.62.

(7*R*,8*S*,9*S*)-9-(1,3-Dioxo-2-azaindan-2-yl)-7,8-bis[(methoxymethyl)oxy]tridec-1-en-6-one (28). In the same manner as described above for the preparation of **21** from **20**, **26** (396 mg, 1.01 mmol) underwent Grignard reaction to give alcohol **27** (328 mg, 70%) as a diastereomeric mixture of the anti (**31**) and syn (**32**) isomers in a 50:50 ratio, which was subsequently oxidized via Swern procedure to afford **28** (294 mg, 90% from **27**) as a colorless oil: $[\alpha]^{23}_D$ −37.3° (*c* 0.73, $CHCl_3$); IR (neat) 3076, 1775, 1713, 1641, 1613, 1468, 1386, 1216, 1029, 920, 795, 724, 631, 531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.82 (3 H, t, *J* = 7.2 Hz), 1.07–1.40 (4 H, m), 1.65 (2 H, quint, *J* = 7.4 Hz), 1.86–1.96 (1 H, m), 2.00–2.11 (3 H, m), 2.46 (1 H, dt, *J* = 17.9, 7.4 Hz), 2.61 (1 H, dt, *J* = 17.9, 7.4 Hz), 3.29 (3 H, s), 3.34 (3 H, s), 3.93 (1 H, d, *J* = 1.9 Hz), 4.45–4.53 (1 H, m, containing 1 H, $^1/_2$ AB q, *J* = 6.8 Hz at δ 4.49), 4.59 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.65 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 4.71 (1 H, dd, *J* = 9.5, 1.9 Hz), 4.75 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 4.88–5.01 (2 H, m), 5.73 (1 H, ddt, *J* = 17.1, 10.3, 6.7 Hz), 7.74 (2 H, dd, *J* = 5.4, 3.1 Hz), 7.84 (2 H, dd, *J* = 5.4, 3.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 13.86, 22.31, 22.34, 28.30, 28.43, 32.98, 38.72, 52.20, 56.67 (2 carbons), 78.17, 82.43, 97.90, 98.48, 115.09, 123.38 (2 carbons), 131.69 (2 carbons), 134.18 (2 carbons), 138.02, 168.41 (2 carbons), 208.33; mass spectrum, *m/z* (relative intensity) 400 (0.5), 364 (5), 288 (45), 216 (100), 160 (95); mass spectrum (isobutane CI), *m/z* (relative intensity) 430 (5), 400 (20), 368 (60), 288 (30), 216 (100). Anal. Calcd for $C_{25}H_{35}NO_7$: C, 65.06; H, 7.64; N, 3.03. Found: C, 65.18; H, 7.80; N, 3.20.

(7*R*,8*S*,9*S*)-9-[[(Benzyloxy)carbonyl]amino]-7,8-bis[(methoxymethyl)oxy]tridec-1-en-6-one (30). A solution of **27** (88 mg, 0.19 mmol) and hydrazine hydrate (48 mg, 0.96 mmol) in ethanol (4 mL) was refluxed for 2 h. Ether (20 mL) was added to the reaction mixture after cooling, and the resulting phthalhydrazide was filtered. The filtrate was concentrated in vacuo to give the crude amine as an oil, which was dissolved in dichloromethane (2 mL). To the resulting solution was added an aqueous solution of Na_2CO_3 (41 mg, 0.39 mmol in 1 mL of water), and to this at 0 °C with stirring was added dropwise a solution of benzyl chloroformate (32 mg, 0.19 mmol) in dichloromethane (0.1 mL) via syringe. After being stirred at 0 °C for 5 min, the mixture was extracted with dichloromethane (10 mL) and dried ($MgSO_4$). Removal of the solvent in vacuo followed by purification by silica gel chromatography with hexane–ethyl acetate (5:1 to 3:1) gave carbamate **29** (58 mg, 65% from **27**) as a colorless oil as a diastereomeric mixture (**33** + **34**). This product **29** was subsequently subjected to Swern oxidation in the same manner as described in the preparation of **21**, providing **30** (46 mg, 80% from **29**) as a colorless oil: IR (neat) 3341, 2955, 1641, 1510, 1235, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.89 (3 H, t, *J* = 6.7 Hz), 1.19–1.77 (8 H, m), 2.07 (2 H, q, *J* = 7.1 Hz), 2.58 (2 H, t, *J* = 7.4 Hz), 3.28 (3 H, s), 3.40 (3 H, s), 3.90–4.04 (2 H, m), 4.26 (1 H, d, *J* = 3.1 Hz), 4.51 (1 H, $^1/_2$ AB q, *J* = 7.0 Hz), 4.67 (1 H, $^1/_2$ AB q, *J* = 7.0 Hz), 4.70 (1 H, $^1/_2$ AB q, *J* = 7.0 Hz), 4.72 (1 H, $^1/_2$ AB q, *J* = 7.0 Hz), 4.90–5.10 (2 H, m, containing 1 H, $^1/_2$ AB q, *J* = 12.2 Hz at δ 5.05), 5.10 (1 H, $^1/_2$ AB q, *J* = 12.2 Hz), 5.53 (1 H, d, *J* = 8.7 Hz), 5.76 (1 H, ddt, *J* = 17.1, 10.3, 6.7 Hz), 7.20–7.42 (5 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 14.00, 22.23, 22.65, 28.40, 31.15, 33.06, 38.67, 51.83, 56.31, 56.91, 66.62, 78.16, 83.52, 96.49, 97.62, 115.33, 128.05 (2 carbons), 128.18, 128.50 (2 carbons), 136.85, 137.99, 156.63, 209.67; mass spectrum, *m/z* (relative intensity) 396 (1), 368 (2), 358 (1), 294 (2), 292 (2), 264 (5), 220 (18), 176 (30), 91 (100).

Reduction of 21 with Borohydrides. A. With $Zn(BH_4)_2$. Reduction of **21** was run under the conditions described above in General Procedure A. The result is summarized in Table II. The product (96:4 anti/syn mixture) was chromatographed on silica gel with chloroform–methanol (50:1) to give (6*S*,7*S*,8*S*,9*R*)-9-(1,3-dioxo-2-azaindan-2-yl)-7,8-bis-[(methoxymethyl)oxy]tridec-1-en-6-ol (**22**) (68% from **21**) as a colorless oil: $[\alpha]^{20}_D$ −45.0° (*c* 1.45, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.83 (3 H, t, *J* = 7.2 Hz), 1.10–1.80 (9 H, m), 2.05–2.24 (3 H, m), 3.09 (3 H, s), 3.22 (1 H, d, *J* = 5.2 Hz), 3.51–3.60 (1 H, unresolved, containing 3 H, s at δ 3.55), 3.81 (1 H, dd, *J* = 12.8, 5.7 Hz), 4.45–4.53 (1 H, unresolved, containing 1 H, $^1/_2$ AB q, *J* = 6.8 Hz at δ 4.50), 4.55 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.63 (1 H, ddd, *J* = 11.9, 9.9, 3.7 Hz), 4.76 (1 H, $^1/_2$ AB q, *J* = 7.0 Hz), 4.82 (1 H, $^1/_2$ AB q, *J* = 7.0 Hz), 4.93–5.07 (2 H, m), 5.83 (1 H, ddt, *J* = 17.1, 10.3, 6.7 Hz), 7.72 (2 H, dd, *J* = 5.4, 3.1 Hz), 7.84 (2 H, dd, *J* = 5.4, 3.1 Hz); mass spectrum, *m/z* (relative intensity) 303 (67), 290 (55), 258 (38), 246 (92), 216 (100), 160 (95).

B. With $NaBH_4$. To a stirred solution of **21** (16 mg, 0.035 mmol) in ethanol (1 mL) was added $NaBH_4$ (3 mg, 0.08 mmol) at 0 °C. After 30 min at 0 °C, the reaction mixture was diluted with chloroform (10 mL) and water (1 mL) was added to this solution. The organic phase was separated and dried ($MgSO_4$). Evaporation of the solvent followed by purification by preparative TLC on silica gel with chloroform–methanol (40:1) afforded a diastereomeric mixture (15.9 mg, 99%) of alcohols **23** and **22** as a colorless oil (see Table II).

C. With $LiBH_4$. Reduction was run under the conditions described above in General Procedure B. The result is summarized in Table II.

D. With L-Selectride. Reduction was carried out under the conditions described above in General Procedure C. The product (99:1 syn/anti mixture) was chromatographed on silica gel with chloroform–methanol (50:1) to give (6*R*,7*S*,8*S*,9*R*)-9-(1,3-dioxo-2-azaindan-2-yl)-7,8-bis-[(methoxymethyl)oxy]tridec-1-en-6-ol (**23**) (83% from **21**) as a colorless oil: $[\alpha]^{20}_D$ −28.5° (*c* 2.24, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.81 (3 H, t, *J* = 7.2 Hz), 1.10–1.39 (4 H, m), 1.41–1.80 (5 H, m), 2.00–2.21 (3 H, m), 2.94 (1 H, d, *J* = 4.4 Hz), 2.96 (3 H, s), 3.50 (3 H, s), 3.54 (1 H, dd, *J* = 6.0, 2.5 Hz), 3.82 (1 H, br m), 4.27 (1 H, dd, *J* = 9.5, 2.5 Hz), 4.46 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.51 ($^1/_2$ AB q, *J* = 6.8 Hz), 4.56 (1 H, ddd, *J* = 11.8, 9.5, 3.7 Hz), 4.79 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.85 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.91–5.05 (2 H, m), 5.80 (1 H, ddt, *J* = 17.0, 10.3, 6.6 Hz), 7.69 (2 H, dd, *J* = 5.4, 3.0 Hz), 7.82 (2 H, dd, *J* = 5.4, 3.0 Hz); mass spectrum, *m/z* (relative intensity) 400 (2), 303 (20), 290 (30), 258 (28), 246 (60), 216 (92), 160 (100). Anal. Calcd for $C_{25}H_{37}NO_7$: C, 64.77; H, 8.05; N, 3.02. Found: C, 64.43; H, 8.13; N, 2.93.

Reduction of 28 with $Zn(BH_4)_2$. Reduction of **28** with $Zn(BH_4)_2$ was run under the conditions described above in General Procedure A. The result is summarized in Table II. The product (98:2 anti/syn mixture) was separated by chromatography on silica gel with chloroform–methanol (50:1). The first fraction contained (6*S*,7*S*,8*S*,9*S*)-9-(1,3-dioxo-2-azaindan-2-yl)-7,8-bis[(methoxymethyl)oxy]tridec-1-en-6-ol (**31**) as a colorless oil: $[\alpha]^{25}_D$ −32.7° (*c* 1.87, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.83 (3 H, t, *J* = 7.2 Hz), 1.08–1.50 (5 H, m), 1.50–1.72 (4 H, m), 1.80–1.92 (1 H, m), 1.97–2.21 (3 H, m), 3.31–3.36 (1 H, unresolved, containing 3 H, s at δ 3.34), 3.46 (3 H, s), 3.70–3.79 (1 H, m), 4.45–4.56 (2 H, m), 4.59 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 4.64 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 4.82 (1 H, $^1/_2$ AB q, *J* = 6.5 Hz at δ 4.88), 4.87–5.00 (2 H, m, containing 1 H, $^1/_2$ AB q, *J* = 6.5 Hz), 5.78 (1 H, ddt, *J* = 17.1, 10.2, 6.7 Hz), 7.72 (2 H, dd, *J* = 5.5, 3.0 Hz), 7.82 (2 H, dd, *J* = 5.5, 3.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 14.01, 22.43, 25.20, 27.93, 28.50, 32.81, 33.77, 52.13, 56.36, 56.76, 71.15, 78.04, 82.11, 98.42, 99.14, 114.45, 123.38 (2 carbons), 131.84 (2 carbons), 134.14 (2 carbons), 138.99, 168.61 (2 carbons); mass spectrum, *m/z* (relative intensity) 400 (3), 303 (29), 290 (55), 258 (35), 246 (85), 216 (90), 160 (100). Anal. Calcd for $C_{25}H_{37}NO_7$: C, 64.77; H, 8.05; N, 3.02. Found: C, 64.98; H, 7.96; N, 3.05.

The second fraction contained (6*R*,7*S*,8*S*,9*S*)-9-(1,3-dioxo-2-azaindan-2-yl)-7,8-bis[(methoxymethyl)oxy]tridec-1-en-6-ol (**32**) as a colorless oil: $[\alpha]^{25}_D$ −24.8° (*c* 1.01, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ Me_4Si 0.82 (3 H, t, *J* = 6.0 Hz), 0.90–2.40 (12 H, m), 3.22 (1 H, br, d, *J* = 7.8 Hz), 3.38 (3 H, s), 3.44 (3 H, s), 3.45–3.95 (2 H, m), 4.30–5.18 (8 H, m), 5.57–6.09 (1 H, m), 7.65–7.98 (4 H, m); mass spectrum, *m/z* (relative intensity) 400 (2), 365 (3), 303 (21), 290 (36), 258 (32), 246 (70), 216 (86), 160 (100). Anal. Calcd for $C_{25}H_{37}NO_7$: C, 64.77; H, 8.05; N, 3.02. Found: C, 64.80; H, 7.81; N, 3.13.

Reduction of 30 with Borohydrides. A. With $Zn(BH_4)_2$. Reduction of **30** with $Zn(BH_4)_2$ was run under the conditions described above in General Procedure A. The result is summarized in Table II. The product (>99:1 anti/syn mixture) was subjected to chromatography on silica gel with hexane–ethyl acetate (5:1 to 3:1) to give (6*S*,7*R*,8*S*,9*S*)-9-[[(benzyloxy)carbonyl]amino]-7,8-bis[(methoxymethyl)oxy]tridec-1-en-6-ol (**33**) (77%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.89 (3 H, t, *J* = 6.7 Hz), 1.19–1.80 (10 H, m), 2.01–2.21 (2 H, m), 3.30–3.38 (1 H, unresolved), 3.40 (3 H, s), 3.43 (3 H, s), 3.52–3.89 (4 H, m), 4.66 (1 H, $^1/_2$ AB q, *J* = 6.6 Hz), 4.70 (1 H, $^1/_2$ AB q, *J* = 6.6 Hz), 4.74 (1 H, $^1/_2$ AB q, *J* = 6.6 Hz), 4.77 (1 H, $^1/_2$ AB q, *J* = 6.6 Hz), 4.90–5.06 (2 H, m), 5.06 (1 H, $^1/_2$ AB q, *J* = 12.3 Hz), 5.13 (1 H, $^1/_2$ AB q, *J* = 12.3 Hz), 5.57 (1 H, br d, *J* = 9.0 Hz), 5.83 (1 H, ddt, *J* = 17.0, 10.3, 6.6 Hz), 7.20–7.40 (5 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 14.07, 22.70, 25.31, 28.48, 29.99, 31.79, 33.71, 51.65, 56.37 (2 carbons), 66.56, 70.56, 80.80, 84.50, 97.98, 98.56, 114.64, 127.99 (3 carbons), 128.51 (2 carbons), 136.90, 138.84, 156.52.

B. With L-Selectride. Reduction of **30** with L-Selectride was run under the conditions described above in General Procedure C. The result is summarized in Table II. The reduction product (>99:1 syn/anti mixture) was subjected to chromatography on silica gel with hexane–ethyl acetate (5:1 to 3:1) to give (6*R*,7*S*,8*S*,9*S*)-9-[[(benzyloxy)-carbonyl]amino]-7,8-bis[(methoxymethyl)oxy]tridec-1-en-6-ol (**34**) (71%) as a colorless oil: $[\alpha]^{23}_D$ −49.9° (*c* 0.93, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.88 (3 H, t, *J* = 6.7 Hz), 1.15–1.69 (9 H, m),

1.79 (1 H, s), 2.00–2.18 (2 H, unresolved), 2.91 (1 H, d, J = 5.4 Hz), 3.37 (3 H, s), 3.42 (3 H, s), 3.49 (1 H, t, J = 4.7 Hz), 3.66–3.79 (2 H, unresolved), 3.84–3.94 (1 H, m), 4.61 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.64–4.78 (2 H, unresolved), 4.80 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.91–5.06 (2 H, m), 5.07 (1 H, d, J = 12.4 Hz), 5.11 (1 H, $^1/_2$ AB q, J = 12.4 Hz), 5.62 (1 H, d, J = 9.4 Hz), 5.81 (1 H, ddt, J = 17.0, 10.2, 6.7 Hz), 7.20–7.42 (5 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 14.02, 22.68, 25.09, 26.26, 28.49, 30.36, 33.20, 33.72, 51.67, 56.20, 56.49, 66.60, 70.79, 81.32, 82.27, 97.70, 98.65, 114.73, 127.97 (2 carbons), 127.99, 128.48 (2 carbons), 136.91, 138.66, 156.75; mass spectrum, m/z (relative intensity) 404 (1.5), 360 (2), 314 (10), 264 (15), 250 (14), 220 (35), 176 (44), 91 (100). Anal. Calcd for $C_{25}H_{41}NO_7$: C, 64.22; H, 8.84; N, 3.00. Found: C, 64.42; H, 8.91; N, 3.07.

(6*S*,7*S*,8*S*,9*R*)-9-[[(Benzyloxy)carbonyl]amino]-7,8-bis[(methoxymethyl)oxy]tridec-1-en-6-ol (35). A solution of **22** (468 mg, 1.01 mmol) and hydrazine hydrate (253 mg, 5.05 mmol) in ethanol (5 mL) was refluxed for 2 h. After being cooled, the reaction mixture was diluted with ether (70 mL), and the resulting phthalhydrazide was filtered. The filtrate was concentrated in vacuo to give an oily product that was dissolved in dichloromethane (7 mL). To the resulting solution was added a solution of Na_2CO_3 (214 mg, 2.02 mmol) in water (3 mL), and to this at 0 °C with stirring was added dropwise a solution of benzyl chloroformate (172 mg, 1.01 mmol) in dichloromethane (2 mL) via syringe. The mixture was stirred at 0 °C for 5 min, extracted with dichloromethane, and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by chromatography on silica gel with hexane–ethyl acetate (5:1 to 3:1) to give **35** (345 mg, 73%) as a colorless oil: $[\alpha]^{23}_D$ −53.4° (c 1.62, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.89 (3 H, t, J = 6.8 Hz), 1.19–1.76 (10 H, m), 2.02–2.17 (2 H, m), 3.04 and 3.09 (total 1 H, 2 sets of d, J = 7.7 Hz each, 2:3 integral ratio), 3.38 (3 H, s), 3.40 (3 H, s), 3.55–3.67 (2 H, m), 3.67–3.78 (2 H, m), 4.62 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.64 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.68 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.81 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.90–5.20 (5 H, m), 5.81 (1 H, ddt, J = 17.0, 10.3, 6.7 Hz), 7.25–7.49 (5 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ (2 sets of signals appeared depend on the rotamers) 13.97 and 14.06 (total 1 carbon, CH_3), 22.60 and 22.66 (total 1 carbon, CH_2), 25.03 and 25.56 (total 1 carbon, CH_2), 28.13 and 31.40 (total 1 carbon, CH_2), 31.94 and 32.15 (total 1 carbon, CH_2), 33.36 (CH_2), 33.63 (CH_2), 51.91 (CH), 56.09 (CH_3), 56.44 (CH_3), 66.86 and 67.89 (total 1 carbon, CH_2), 70.59 and 70.91 (total 1 carbon, CH), 79.19 and 79.26 (total 1 carbon, CH), 85.34 and 85.52 (total 1 carbon, CH), 98.54 and 98.75 (total 2 carbons, CH_2), 114.66 (CH_2), 128.15 and 128.42 (total 3 carbons, CH), 128.56 and 128.62 (total 2 carbons, CH), 136.72 (C), 138.80 (CH), 156.25 (C); mass spectrum (isobutane CI), m/z (relative intensity) 468 (M^+ + 1, 3), 436 (25), 406 (22), 405 (18), 404 (65), 392 (10), 374 (20), 362 (25), 361 (24), 360 (100).

(2*R*,3*S*,4*S*,5*R*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-3,4-bis[(methoxymethyl)oxy]-2-(4-pentenyl)pyrrolidine (37). To a stirred, ice-cold solution of **35** (137 mg, 0.293 mmol) and triethylamine (148 mg) in dichloromethane (2 mL) was added a solution of mesyl chloride (67 mg, 0.59 mmol) via syringe. After 10 min at 0 °C, the mixture was diluted with ether (30 mL) and filtered to remove the salt separated. The filtrate was concentrated in vacuo to give crude mesylate **36** as an oil which was dissolved in THF (2 mL). The resulting solution was cooled (0 °C) and to this was added potassium *tert*-butoxide (66 mg, 0.59 mmol) with stirring. After being stirred at 0 °C for 10 min and room temperature for 10 min, the mixture was diluted with benzene (30 mL) and quenched with water (3 mL) under cooling. The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on silica gel with hexane–ethyl acetate (10:1 to 5:1) to give **37** (95 mg, 72% from **35**) as a colorless oil: $[\alpha]^{23}_D$ +3.5° (c 1.07, MeOH); ^{1}H NMR (90 MHz, $CDCl_3$) δ Me_4Si 0.83 (3 H, br t, J = 6.0 Hz), 0.95–2.25 (12 H, m), 3.35 (6 H, s), 3.70–4.15 (2 H, m), 4.17 (2 H, dd, J = 5.7, 2.4 Hz), 4.50–5.30 (8 H, m), 5.30–6.10 (1 H, m), 7.37 (5 H, s).

(2*R*,3*S*,4*S*,5*R*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-3,4-dihydroxy-2-(4-pentenyl)pyrrolidine (38). A solution of **37** (170 mg, 0.378 mmol) in methanol (2 mL) and concentrated HCl (0.3 mL) was refluxed for 30 min. The mixture was concentrated in vacuo, basified by addition of 10% Na_2CO_3, and extracted with chloroform (2 × 5 mL). The chloroform extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Chromatography on silica gel with hexane–ethyl acetate (1:1 to 1:2) followed by recrystallization from chloroform–hexane afforded **38** (130 mg, 95%) as colorless needles: mp 88–89 °C; $[\alpha]^{23}_D$ −12.3° (c 0.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.84 (3 H, br s), 1.05–1.80 (10 H, unresolved), 1.85–2.13 (2 H, unresolved), 2.72–2.88 (2 H, unresolved), 3.85 (2 H, br s), 4.19 (2 H, apparent br s, but top of the peak is split by 3.0 Hz), 4.90 (1 H, d, J = 10.3 Hz), 4.95 (1 H, d, J = 17.4 Hz), 5.06 (1 H, $^1/_2$ AB q, J = 12.2 Hz), 5.19 (1 H, $^1/_2$ AB q, J = 12.2 Hz), 5.72 (1 H, br s), 7.23–7.50 (5 H, m); mass spectrum, m/z (relative intensity) 363 (0.5), 361 (M^+, 1), 306 (4), 292 (4), 270 (5), 262 (5), 260 (5), 248 (10), 226 (5), 91 (100); exact mass calcd for $C_{21}H_{31}NO_4$ (M^+) 361.2251, found 361.2256.

(2*R*,5*R*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-2-(4-pentenyl)-3-pyrroline [(2*R*,5*R*)-40]. A mixture of **38** (106 mg, 0.293 mmol), triphenylphosphine (308 mg, 1.17 mmol), imidazole (40 mg, 0.59 mmol), 2,4,5-triiodoimidazole (523 mg, 1.17 mmol), and zinc dust (77 mg, 1.17 mmol) in toluene (2 mL) was refluxed for 4 h. The resulting brown gum (solidified on standing at room temperature) was removed by decantation and washed with benzene (10 mL). The combined solution was washed with 10% sodium thiosulfate, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel with hexane–ethyl acetate (30:1) to give (2*R*,5*R*)-**40** (76 mg, 79%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.80 and 0.88 (total 3 H, t, J = 7.2 Hz each, depending on the rotamers), 1.00–1.38 (6 H, m), 1.55–2.09 (6 H, m), 4.49–4.62 (2 H, m), 4.86–5.03 (2 H, m), 5.08 (1 H, dd, J = 12.3, 2.1 Hz), 5.24 (1 H, dd, J = 12.3, 1.5 Hz), 5.60–5.86 (3 H, m), 7.26–7.48 (5 H, m).

In this reaction, when the reaction time was 30 min the intermediate epoxide **39** was isolated.

(2*R*,5*R*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-2-(4-oxopentyl)-3-pyrroline [(2*R*,5*R*)-41]. To a mixture of $PdCl_2$ (20 mg, 0.11 mmol) and $CuCl_2$ (15 mg, 0.11 mmol) in 2 mL of dimethylformamide–water (3:1) was added a solution of (2*R*,5*R*)-**40** (76 mg, 0.23 mmol). The mixture was stirred at 70 °C with bubbling of oxygen at a flow rate of 150 mL/min for 40 min. The reaction mixture was concentrated in vacuo and the residue was extracted with benzene (50 mL). The benzene solution was filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel with hexane–ethyl acetate (8:1 to 5:1) to give (2*R*,5*R*)-**41** (63 mg, 79%) as a colorless oil: $[\alpha]^{23}_D$ −235.1° (c 0.88, $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ Me_4Si 0.80 and 0.87 (total 3 H, t, J = 6.3 Hz each, depending on the rotamers), 0.75–2.55 (12 H, m, containing total 3 H, s × 2 at δ 2.03 and 2.10, depending on the rotamers), 4.57 (2 H, br s), 5.03 (1 H, $^1/_2$ AB q, J = 12.0 Hz), 5.23 (1 H, $^1/_2$ AB q, J = 12.0 Hz), 5.50–5.85 (2 H, unresolved), 7.37 (5 H, s); mass spectrum, m/z (relative intensity) 343 (M^+, 3), 286 (4), 258 (10), 242 (38), 214 (32), 208 (61), 91 (100); exact mass for $C_{21}H_{28}NO_3$ (M^+ − 1) 342.2066, found 342.2047.

Preparation of (−)-Indolizidine 195B [(−)-1]. A solution of (2*R*,5*R*)-**41** (60 mg, 0.175 mmol) in methanol (5 mL) was hydrogenated over 10% palladium on carbon (55 mg) at atmospheric pressure for 2 h. The catalyst was washed with methanol (2 mL) containing methanolic ammonia (0.5 mL) and the filtrate was concentrated at below 30 °C at 20 mmHg. The oily residue was chromatographed on aluminum oxide with hexane–chloroform (3:1). The first fractions gave (−)-**1** (26 mg, 76%) as a pale yellow oil: $[\alpha]^{22}_D$ −97.1° (c 0.12, MeOH); IR (neat) 2960, 2928, 2871, 2857, 2788, 2695, 1456, 1375, 1316, 1227, 1190, 1134 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.90 (3 H, t, J = 7.2 Hz), 0.95–1.94 (16 H, m, containing 3 H, d, J = 6.2 Hz at δ 1.10), 2.32–2.46 (1 H, m), 2.46–2.59 (1 H, m), 3.28 (1 H, br t, J = 8.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 14.27, 20.49, 23.08, 24.81, 25.02, 26.43, 29.25, 30.10, 32.44, 34.60, 52.12, 58.94, 59.05; mass spectrum, m/z (relative intensity) 195 (M^+, 1), 194 (M^+ − 1, 1), 180 (10), 138 (100); mass spectrum (isobutane CI), m/z (relative intensity) 196 (M^+ + 1, 40), 195 (M^+, 17), 194 (18), 155 (15), 138 (100).

The second fractions gave (−)-5-epiindolizidine 195B [(−)-**42**] (5 mg, 15%) as a pale yellow oil: $[\alpha]^{25}_D$ −36.4° (c 0.14, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.89 (3 H, t, J = 7.0 Hz), 1.02–1.83 (15 H, m, containing 3 H, d, J = 6.7 Hz, at δ 1.18), 1.95–2.09 (1 H, m), 2.81–3.01 (2 H, unresolved), 3.32 (1 H, br s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 14.21, 19.11, 20.56, 23.10, 27.05, 27.11, 28.66, 29.02, 29.16, 36.18, 48.99, 55.52, 60.01.

(2*S*,3*S*,4*S*,5*S*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-3,4-bis[(methoxymethyl)oxy]-2-(4-pentenyl)pyrrolidine (44). In the same manner as described above for the preparation of **37**, **34** was subjected to cyclization. From 392 mg (0.838 mmol) of **34** was obtained 320 mg (85%) of **44** as a colorless oil: $[\alpha]^{23}_D$ +48.2° (c 0.34, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.83 and 0.91 (total 3 H, 2 sets of t, J = 6.7 and 6.6 Hz each, depending on the rotamer), 1.14–2.20 (12 H, m), 3.36 (6 H, s), 3.70–3.86 (2 H, m), 4.00 (2 H, s), 4.55–4.69 (4 H, m), 4.87–5.01 (2 H, m), 5.05 (1 H, $^1/_2$ AB q, J = 12.4 Hz), 5.21 (1 H, $^1/_2$ AB q, J = 12.4 Hz), 5.71 and 5.82 (total 1 H, 2 sets of ddt, J = 17.0, 10.2, 6.7 and 17.0, 10.3, 6.6 Hz each, depending on the rotamers), 7.20–7.40 (5 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ (the duplicate sets of signals belonging to the two rotamers are given in square brackets) [13.95 and 14.08], [22.41 and 22.60], 25.88, 28.62, 30.18, 31.43, [33.45 and 33.64], 55.52 (2 carbons), [64.68 and 64.80], [65.15 and 65.24], 66.72, [81.59 and 81.72], [82.36 and 82.46], 95.13 (2 carbons), [114.60 and 114.89], [127.96 and 128.14 (total 3 carbons)], 128.46 (2 carbons), 136.91,

[138.46 and 138.69], 154.50; mass spectrum, m/z (relative intensity) 449 (M^+, 0.2), 392 (3), 380 (4), 348 (10), 336 (10), 313 (4), 91 (100). Anal. Calcd for $C_{25}H_{39}NO_6$: C, 66.79; H, 8.74; N, 3.12. Found: C, 66.48; H, 8.87; N, 3.07.

(2*S*,3*S*,4*S*,5*S*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-3,4-dihydroxy-2-(4-pentenyl)pyrrolidine (45). In a manner similar to that described above for the preparation of **38**, **44** (320 mg, 0.712 mmol) was treated with HCl to provide **45** (215 mg, 84%) as a colorless oil: $[\alpha]^{24}_D$ +39.5° (*c* 0.65, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.70–1.03 (3 H, unresolved), 1.09–2.23 (14 H, unresolved), 3.71 (2 H, br s), 4.06 (2 H, br s), 4.84–5.10 (2 H, unresolved), 5.06 (1 H, $^1/_2$ AB q, J = 12.3 Hz), 5.21 (1 H, $^1/_2$ AB q, J = 12.3 Hz), 5.60–5.90 (1 H, unresolved), 7.20–7.44 (5 H, m); mass spectrum, m/z (relative intensity) 361 (1), 292 (2), 270 (6), 260 (8), 248 (11), 226 (6), 91 (100).

(2*S*,5*S*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-2-(4-pentenyl)-3-pyrroline [(2*S*,5*S*)-40]. In the manner described above for the preparation of (2*R*,5*R*)-**40**, **45** (213 mg, 0.589 mmol) underwent dehydroxylation to give (2*S*,5*S*)-**40** (180 mg, 93%).

(2*S*,5*S*)-*N*-[(Benzyloxy)carbonyl]-5-butyl-2-(4-oxopentyl)-3-pyrroline [(2*S*,5*S*)-41]. In the same manner used for the preparation of (2*R*,5*R*)-**41**, (2*S*,5*S*)-**40** (161 mg, 0.491 mmol) was converted to (2*S*,5*S*)-**41** (120 mg, 71%): $[\alpha]^{24}_D$ +234.5° (*c* 1.50, $CHCl_3$); exact mass for $C_{21}H_{29}NO_3$ (M^+) 343.2145, found 343.2136.

Preparation of (+)-Indolizidine 195B [(+)-1]. Compound (2*S*,5*S*)-**41** (91 mg, 0.265 mmol) was treated in the same manner used for the preparation of (−)-indolizidine 195B [(−)-**1**] to afford (+)-**1** (43 mg, 83%), $[\alpha]^{24}_D$ +98.0° (*c* 0.30, MeOH) [lit.[3] $[\alpha]^{16}_D$ +65° (*c* 0.41, MeOH)], and (+)-5-epiindolizidine 195B [(+)-**42**] (7 mg, 14%), $[\alpha]^{24}_D$ +37.9° (*c* 0.10, MeOH). The spectral data of these products were identical with those of (−)-**1** and (−)-**42** previously synthesized. The ^1H (100 MHz) and ^{13}C NMR spectra of synthetic (+)-**1** were superimposable to those of natural (+)-indolizidine 195B.

(2*S*,3*R*)-2,3-Bis[(methoxymethyl)oxy]-8-nonen-4-one (48). In the manner described for the preparation of **21**, (2*S*,3*R*)-2,3-bis[(methoxymethyl)oxy]butanal (**47**)[22] (1.78 g, 9.26 mmol) was converted to **48** (2.17 g, 90%) as a colorless oil: $[\alpha]^{25}_D$ +68.6° (*c* 3.29, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.23 (3 H, d, J = 6.4 Hz), 1.66 (2 H, quint, J = 7.4 Hz), 2.05 (2 H, td, J = 7.3, 7.0 Hz), 2.58 (2 H, t, J = 7.4 Hz), 3.29 (3 H, s), 3.39 (3 H, s), 3.95 (1 H, d, J = 3.7 Hz), 4.09 (1 H, qd, J = 6.4, 3.7 Hz), 4.56 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.63 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.66 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.69 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.91–5.02 (2 H, m), 5.75 (1 H, ddt, J = 17.0, 10.3, 6.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 16.51 (CH_3), 22.13 (CH_2), 33.09 (CH_2), 39.38 (CH_2), 55.67 (CH_3), 56.34 (CH_3), 73.57 (CH), 85.54 (CH), 95.40 (CH_2), 97.35 (CH_2), 115.20 (CH_2), 138.05 (CH), 210.35 (C); mass spectrum, m/z (relative intensity) 216 (10), 133 (60), 97 (70), 87 (100). Anal. Calcd for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29. Found: C, 59.81; H, 9.55.

(2*S*,3*S*,4*R*)-2,3-Bis[(methoxymethyl)oxy]-8-nonen-4-ol (49). In the manner described in General Procedure C, **48** (105 mg, 0.403 mmol) was reduced with L-Selectride to give a 91:9 mixture (95 mg, 90%) of **49** and **50**. The mixture was chromatographed on silica gel with hexane–ethyl acetate (5:1 to 4:1) to give **49** (85 mg, 75%) as a more polar component: $[\alpha]^{24}_D$ −8.2° (*c* 2.43, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.20 (3 H, d, J = 6.4 Hz), 1.39–1.69 (4 H, m), 2.00–2.11 (2 H, m), 2.70 (1 H, d, J = 5.5 Hz), 3.24 (1 H, t, J = 4.6 Hz), 3.34 (3 H, s), 3.41 (3 H, s), 3.71 (1 H, td, J = 8.7, 4.9 Hz), 3.89 (1 H, qd, J = 6.3, 4.4 Hz), 4.60 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.67 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.75 (2 H, s), 4.89–5.01 (2 H, m), 5.78 (1 H, ddt, J = 17.1, 10.3, 6.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 16.63 (CH_3), 24.96 (CH_2), 33.41 (CH_2), 33.71 (CH_2), 55.63 (CH_3), 56.25 (CH_3), 70.61 (CH), 73.68 (CH), 85.08 (CH), 95.49 (CH_2), 98.63 (CH_2), 114.55 (CH_2), 138.69 (CH); mass spectrum, m/z (relative intensity) 199 (5), 111 (30), 102 (100); mass spectrum (isobutane CI), m/z (relative intensity) 263 (M^+ + 1, 1), 231 (5), 199 (100), 169 (20), 155 (30), 102 (40). Anal. Calcd for $C_{13}H_{26}O_5$: C, 59.52; H, 9.99. Found: C, 59.18; H, 10.03.

(2*S*,3*S*,4*S*)-2,3-Bis[(methoxymethyl)oxy]-8-nonen-4-ol (50). In the manner described in General Procedure A, **48** (134 mg, 0.515 mmol) was reduced with $Zn(BH_4)_2$ to afford as a single diastereomer **50** (95 mg, 70%) as a colorless oil: $[\alpha]^{24}_D$ −16.8° (*c* 1.19, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.18 (3 H, d, J = 6.5 Hz), 1.36–1.72 (4 H, m), 1.95–2.12 (2 H, m), 2.97–3.40 (2 H, unresolved, containing 3 H, s at δ 3.35 and 3 H, s at δ 3.38), 3.62–3.71 (1 H, m), 3.90 (1 H, qd, J = 6.4, 4.9 Hz), 4.63 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.64 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.65 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.70 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.87–5.00 (2 H, m), 5.77 (1 H, ddt, J = 17.1, 10.3, 6.7 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 16.36 (CH_3), 25.05 (CH_2), 32.10 (CH_2), 33.72 (CH_2), 55.72 (CH_3), 56.04 (CH_3), 70.58 (CH), 73.87 (CH), 85.21 (CH), 95.74 (CH_2), 98.16 (CH_2), 114.49 (CH_2), 138.79 (CH); mass spectrum, m/z (relative intensity) 199 (2), 111 (20), 102 (100).

(6*S*,7*S*,8*S*)-7,8-Bis[(methoxymethyl)oxy]-6-(1,3-dioxo-2-azaindan-2-yl)-1-nonene (51). In the manner described for the preparation of **18**, **49** (3.35 g, 12.8 mmol) was subjected to Mitsunobu reaction to give **51** (3.01 g, 60%) as a pale yellow oil: ^1H NMR (90 MHz, $CDCl_3$) δ Me_4Si 1.00–1.51 (2 H, unresolved, containing 3 H, d, J = 6.6 Hz at δ 1.23), 1.75–2.32 (4 H, m), 3.15 (3 H, s), 3.43 (3 H, s), 3.83 (1 H, qd, J = 6.6, 2.1 Hz), 4.15–4.55 (2 H, m, containing 2 H, s at δ 4.37), 4.65–5.10 (2 H, m, containing 2 H, s at δ 4.78), 5.73 (1 H, ddt, J = 17.1, 10.2, 6.8 Hz), 7.52–7.91 (4 H, m).

(6*S*,7*S*,8*S*)-6-[[(Benzyloxy)carbonyl]amino]-7,8-bis[(methoxymethyl)oxy]non-1-ene (52). In the manner described above for the preparation of **29**, **51** (768 mg, 1.96 mmol) was converted to **52** (644 mg, 83%): colorless oil; $[\alpha]^{24}_D$ −27.4° (*c* 1.39, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.24 (3 H, d, J = 6.3 Hz), 1.35–1.60 (4 H, m), 1.92–2.15 (2 H, m), 3.38 (3 H, s), 3.39 (3 H, s), 3.46 (1 H, dd, J = 4.9, 4.0 Hz), 3.84–3.94 (2 H, m), 4.65 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.67 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.70 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.76 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.90–5.04 (2 H, m), 5.06 (1 H, $^1/_2$ AB q, J = 12.4 Hz), 5.12 (1 H, $^1/_2$ AB q, J = 12.4 Hz), 5.69 (1 H, br d, J = 9.3 Hz), 5.77 (1 H, ddt, J = 17.0, 10.3, 6.7 Hz), 7.20–7.40 (5 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 16.89 (CH_3), 25.45 (CH_2), 29.98 (CH_2), 33.61 (CH_2), 51.65 (CH), 55.88 (CH_3), 56.13 (CH_3), 66.48 (CH_2), 73.82 (CH), 83.77 (CH), 95.59 (CH_2), 97.85 (CH_2), 114.85 (CH_2), 127.96 (CH, 3 carbons), 128.47 (CH, 2 carbons), 137.05 (C), 138.53 (CH), 156.65 (C); mass spectrum, m/z (relative intensity) 276 (10), 232 (18), 188 (14), 91 (100). Anal. Calcd for $C_{21}H_{33}NO_6$: C, 63.78; H, 8.41; N, 3.54. Found: C, 63.52; H, 8.35; N, 3.53.

(6*S*,7*S*,8*S*)-6-[[(Benzyloxy)carbonyl]amino]-7,8-bis[(methoxymethyl)oxy]nonan-2-one (53). In the manner described above for the preparation of (2*R*,5*R*)-**41**, **52** was converted to **53**. The yield varied from 5 to 50%. **53**: colorless oil; $[\alpha]^{24}_D$ −30.6° (*c* 0.87, $CHCl_3$); IR (neat) 3523, 3349, 2938, 2894, 1714, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.23 (3 H, d, J = 6.4 Hz), 1.36–1.80 (4 H, m), 2.10 (3 H, s), 2.30–2.58 (2 H, m), 3.37 (3 H, s), 3.39 (3 H, s), 3.46 (1 H, dd, J = 5.0, 3.9 Hz), 3.82–3.92 (2 H, m), 4.64 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.66 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.69 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.75 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 5.06 (1 H, $^1/_2$ AB q, J = 12.4 Hz), 5.11 (1 H, $^1/_2$ AB q, J = 12.4 Hz), 5.74 (1 H, br d, J = 9.2 Hz), 7.20–7.45 (5 H, m); mass spectrum, m/z (relative intensity) 348 (1), 304 (2), 260 (25), 248 (30), 204 (40), 146 (26), 91 (100). Anal. Calcd for $C_{21}H_{33}NO_7$: C, 61.30; H, 8.08; N, 3.40. Found: C, 61.55; H, 8.21; N, 3.65.

(6*S*,7*S*,8*S*)-6-(Benzylamino)-7,8-Bis[(methoxymethyl)oxy]-2-nonene (55). To a solution of **51** (5.38 g, 13.7 mmol) in ethanol (70 mL) was added hydrazine hydrate (3.44 g, 68.7 mmol) and the mixture was refluxed. After 2.5 h, the reaction mixture was cooled and diluted with ether (100 mL) and filtered to remove resulting phthalhydrizide. The filtrate was concentrated in vacuo to give an oily product that was dissolved in dichloromethane (20 mL). To the resulting solution was added a solution of Na_2CO_3 (3.00 g, 28.3 mmol) in water (10 mL) and benzyl bromide (2.39 g, 14.0 mmol) and the mixture was refluxed for 3 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (10 mL × 2). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated in vacuo. The crude product was purified by chromatography on silica gel with hexane–ethyl acetate (10:1 to 6:1) to give **55** (3.64 g, 75%) as a colorless oil: $[\alpha]^{20}_D$ −86.6° (*c* 0.97, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.12 (3 H, d, J = 6.4 Hz), 1.35–1.48 (3 H, m), 1.60–1.75 (2 H, m), 1.97–2.05 (2 H, m), 2.50–2.61 (1 H, m), 3.38 (3 H, s), 3.39 (3 H, s), 3.61 (1 H, dd, J = 6.7, 3.3 Hz), 3.70 (1 H, d, J = 13.0 Hz), 3.82 (1 H, quint, J = 6.5 Hz), 3.89 (1 H, d, J = 13.0 Hz), 4.68 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.70 (1 H, $^1/_2$ AB q, J = 6.8 Hz), 4.73 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.81 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.91–5.02 (2 H, m), 5.80 (1 H, ddt, J = 17.1, 10.3, 6.6 Hz), 7.20–7.38 (5 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 17.44 (CH_3), 25.84 (CH_2), 29.71 (CH_2), 33.94 (CH_2), 51.58 (CH_2), 55.53 (CH_3), 56.02 (CH_3), 57.17 (CH), 75.07 (CH), 82.95 (CH), 96.07 (CH_2), 98.63 (CH_2), 114.44 (CH_2), 126.81 (CH), 128.28 (CH, 2 carbons), 128.39 (CH, 2 carbons), 139.01 (CH), 141.05 (C); mass spectrum, m/z (relative intensity) 320 (2), 232 (2), 202 (2), 188 (100), 91 (80). Anal. Calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46; N, 3.98. Found: C, 68.06; H, 9.40; N, 3.88.

(6*S*,7*S*,8*S*)-6-[*N*-[(Benzyloxy)carbonyl]benzylamino]-7,8-bis[(methoxymethyl)oxy]-1-nonene (56). To a stirred 0 °C solution of **55** (3.60 g, 10.2 mmol) in dichloromethane (10 mL) at 0 °C was added all at once an aqueous solution of Na_2CO_3 (2.17 g, 20.5 mmol in 5 mL of water), and then a solution of benzyl chloroformate (1.75 g, 10.3 mmol) in dichloromethane (3 mL) was added dropwise over 10 min. Stirring was continued for 5 min at 0 °C and the reaction mixture was extracted with dichloromethane (3 × 10 mL). After the solution was dried ($MgSO_4$), the solvent was evaporated in vacuo and the residue was purified by

chromatography on silica gel with hexane–ethyl acetate (10:1 to 6:1) to give **56** (4.0 g, 80%) as a colorless oil: $[\alpha]^{20}_D$ −26.0° (*c* 0.66, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.00 and 1.13 (total 3 H, 2 sets of d, *J* = 5.4 and 6.2 Hz each, depending on the rotamers), 0.95–1.31 (2 H, unresolved), 1.49–2.00 (4 H, m), 3.22–3.70 (8 H, unresolved), 4.13–4.41 (2 H, unresolved), 4.41–4.80 (5 H, m), 4.80–4.95 (2 H, unresolved), 5.09–5.29 (2 H, unresolved), 5.50–5.70 (1 H, m), 7.10–7.50 (10 H, m); mass spectrum, *m/z* (relative intensity) 454 (1), 410 (2), 322 (88), 278 (100). Anal. Calcd for $C_{28}H_{39}NO_6$: C, 69.25; H, 8.09; N, 2.88. Found: C, 69.36; H, 8.23; N, 2.90.

(6*S*,7*S*,8*S*)-6-[*N*-[(Benzyloxy)carbonyl]benzylamino]-7,8-bis[(methoxymethyl)oxy]nonan-2-one (57). In the manner described above for the preparation of (2*R*,5*R*)-**41**, **56** (2.10 g, 4.32 mmol) was oxidized by the Wacker procedure. The crude product was purified by chromatography of silica gel with hexane–ethyl acetate (4:1 to 3:1) to give **57** (1.30 g, 60%) as a colorless oil: $[\alpha]^{20}_D$ −23.9° (*c* 1.28, $CHCl_3$); IR (neat) 1695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ Me_4Si 0.70–2.50 (12 H, m), 3.20–3.90 (2 H, unresolved, containing 6 H, s at δ 3.33), 3.90–4.90 (7 H, unresolved), 5.17 (2 H, br s), 7.30 (10 H, br s).

[2*S*,6*S*,2(1*S*,2*S*)]-2-[[1,2-Bis(methoxymethyl)oxy]propyl]-6-methylpiperidine (54). A. From 53. A solution of **53** (176 mg, 0.428 mmol) in methanol (1 mL) was hydrogenated over 10% palladium on carbon (176 mg) at atmospheric pressure for 1 h. The reaction mixture was worked up in a manner similar to that previously described for the preparation of (−)-indolizidine 195B [(−)-**1**]. The crude product was purified by chromatography on silica gel with ethyl acetate–5% methanolic ammonia (10:1) to provide **54** (100 mg, 89%) as a colorless oil: $[\alpha]^{20}_D$ −4.3° (*c* 1.45, $CHCl_3$); IR (neat) 3349, 2929, 2855, 2823, 1443, 1378, 1213, 1148, 1105, 1034, 919 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.82–1.19 (2 H, m, containing 3 H, d, *J* = 6.3 Hz at δ 0.97, and 3 H, d, *J* = 6.4 Hz at δ 1.12), 1.27 (1 H, qt, *J* = 13.1, 3.8 Hz), 1.51 (1 H, dd, *J* = 12.8, 2.5 Hz), 1.66 (1 H, dd, *J* = 12.7, 2.5 Hz), 1.74 (1 H, d quint, *J* = 13.2, 3.3 Hz), 1.98 (1 H, br s), 2.54 (1 H, dtd, *J* = 17.2, 6.3, 2.6 Hz), 2.69 (1 H, ddd, *J* = 11.1, 6.3, 2.5 Hz), 3.26 (1 H, dd, *J* = 6.3, 4.6 Hz), 3.29 (3 H, s), 3.32 (3 H, s), 3.82 (1 H, qd, *J* = 6.4, 4.6 Hz), 4.57 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 4.60 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 4.63 (2 H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 16.26 (CH_3), 22.96 (CH_3), 24.57 (CH_2), 27.58 (CH_2), 34.47 (CH_2), 52.06 (CH), 55.49 (CH_3), 55.99 (CH_3), 57.15 (CH), 73.23 (CH), 84.79 (CH), 95.37 (CH_2), 98.44 (CH_2); mass spectrum, *m/z* (relative intensity) 230 (3), 98 (100).

B. From 57. In the manner described above in A, **57** (600 mg, 1.20 mmol) was converted to **54** (295 mg, 94%) by hydrogenation.

[2*S*,6*S*,2(1*S*,2*S*)]-2-[[1,2-Bis(methoxymethyl)oxy]propyl]-6-methyl-*N*-(*p*-tolylsulfonyl)piperidine (58). A mixture of **54** (310 mg, 1.19 mmol) and tosyl chloride (454 mg, 2.38 mmol) in dichloromethane (2 mL) containing diisopropylethylamine (2 mL) was stirred at ambient temperature for 5 days. The reaction mixture was diluted with dichloromethane (10 mL), washed with water (2 mL), and dried ($MgSO_4$). After the solvent was evaporated, the residue was chromatographed on silica gel with hexane–ethyl acetate (4:1 to 3:1) to give **58** (270 mg, 55%) as a pale yellow oil: $[\alpha]^{20}_D$ −61.3° (*c* 1.53, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.99–1.30 (4 H, m, containing 3 H, d, *J* = 7.1 Hz at δ 1.25), 1.37 (3 H, d, *J* = 6.6 Hz), 1.48–1.62 (1 H, unresolved), 1.84 (1 H, br d, *J* = 15.0 Hz), 2.38 (3 H, s), 3.38 (3 H, s), 3.40 (3 H, s), 3.64 (1 H, dd, *J* = 9.2, 1.3 Hz), 4.10 (2 H, qd, *J* = 6.7, 1.4 Hz), 4.29 (1 H, td, *J* = 7.2, 1.4 Hz), 4.72 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.77 (1 H, $^1/_2$ AB q, *J* = 6.8 Hz), 4.78 (1 H, $^1/_2$ AB q, *J* = 7.3 Hz), 4.96 (1 H, $^1/_2$ AB q, *J* = 7.3 Hz), 7.25 (2 H, d, *J* = 8.3 Hz), 7.68 (2 H, d, *J* = 8.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 14.41 (CH_2), 19.44 (CH_3), 21.47 (CH_3), 22.63 (CH_3), 22.79 (CH_2), 27.99 (CH_2), 48.54 (CH), 52.74 (CH), 55.41 (CH_3), 56.46 (CH_3), 73.93 (CH), 82.88 (CH), 98.51 (CH_2), 99.03 (CH_2), 127.13 (CH, 2 carbons), 129.64 (CH, 2 carbons), 138.15 (C), 143.01 (C); mass spectrum, *m/z* (relative intensity) 338 (1), 252 (100), 155 (15), 84 (35), 83 (58).

[2*S*,6*S*,2(1*S*,2*S*)]-2-[1,2-Dihydroxypropyl]-6-methyl-*N*-(*p*-tolylsulfonyl)piperidine (59). A solution of **58** (222 mg, 0.534 mmol) in methanol (4 mL) containing concentrated HCl (0.6 mL) was refluxed for 30 min. After concentration of the reaction mixture in vacuo, the residue was basified by 10% aqueous Na_2CO_3, extracted with chloroform (5 mL × 2), and dried ($MgSO_4$). Removal of the solvent in vacuo followed by chromatography on silica gel with hexane–ethyl acetate (2:1) gave **59** (165 mg, 94%) as a colorless oil: $[\alpha]^{20}_D$ −16.4° (*c* 1.67, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.93–1.16 (2 H, m), 1.20–1.34 (2 H, unresolved, containing 3 H, d, *J* = 7.1 Hz at δ 1.22, and 3 H, d, *J* = 6.5 Hz at δ 1.29), 1.57 (1 H, qt, *J* = 13.5, 3.0 Hz), 2.07 (1 H, d, *J* = 13.8 Hz), 2.42 (3 H, s), 2.46 (1 H, d, *J* = 10.7 Hz), 3.49 (1 H, t, *J* = 10.6 Hz), 3.60 (1 H, d, *J* = 4.3 Hz), 3.72 (1 H, dd, *J* = 10.3, 5.9 Hz), 4.15 (1 H, quint, *J* = 6.6 Hz), 4.39 (1 H, qd, *J* = 6.6, 4.4 Hz), 7.29 (2 H, d, *J* = 8.2 Hz), 7.70 (2 H, d, *J* = 8.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 13.50 (CH_2), 19.00 (CH_3), 21.56 (CH_3), 22.10 (CH_3), 23.34 (CH_2), 28.67 (CH_2), 48.46 (CH), 54.66 (CH), 64.13 (CH), 73.29 (CH), 126.60 (CH, 2 carbons), 129.95 (CH, 2 carbons), 137.94 (C), 143.50 (C); mass spectrum, *m/z* (relative intensity) 266 (1), 265 (1), 252 (100), 155 (25), 91 (30); mass spectrum (isobutane CI), *m/z* (relative intensity) 328 (M^+ + 1, 100), 310 (15), 252 (95).

[2*S*,6*S*,2(4*S*,5*S*)]-2-(4-Methyl-2-thioxo-1,3-dioxolan-5-yl)-6-methyl-*N*-(*p*-tolylsulfonyl)piperidine (60). A mixture of **59** (319 mg, 0.974 mmol), thiocarbonyldiimidazole (520 mg, 2.92 mmol), and diisopropylethylamine (1.26 g, 9.74 mmol) in dichloromethane (4 mL) was refluxed for 2 h. The reaction mixture was diluted with dichloromethane (15 mL), washed with water, and dried ($MgSO_4$). Evaporation of the solvent in vacuo and chromatography on silica gel with hexane–ethyl acetate (6:1 to 5:1) afforded a solid, which was recrystallized from chloroform–hexane to give **60** (304 mg, 84%) as colorless needles: mp 171–172 °C; $[\alpha]^{24}_D$ −148.1° (*c* 1.32, $CHCl_3$); IR ($CHCl_3$) 1315, 1282, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.10–1.21 (2 H, m), 1.28–1.40 (2 H, m, containing 3 H, d, *J* = 7.1 Hz), 1.50–1.60 (1 H, m), 1.62 (3 H, d, *J* = 6.3 Hz), 1.94 (1 H, d and unresolved, *J* = 14.3 Hz), 2.44 (3 H, s), 4.10–4.21 (2 H, m), 4.61 (1 H, dd, *J* = 9.7, 6.5 Hz), 5.34 (1 H, quint, *J* = 6.4 Hz), 7.33 (2 H, d, *J* = 8.2 Hz), 7.70 (2 H, d, *J* = 8.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 13.27 (CH_2), 19.91 (CH_3), 21.63 (CH_3), 22.92 (CH_3), 23.76 (CH_2), 28.25 (CH_2), 48.45 (CH), 53.53 (CH), 82.58 (CH), 85.96 (CH), 126.89 (CH, 2 carbons), 130.13 (CH, 2 carbons), 137.43 (C), 143.98 (C), 190.75 (C); mass spectrum, *m/z* (relative intensity) 252 (100), 155 (20), 91 (30); mass spectrum (isobutane CI), *m/z* (relative intensity) 370 (M^+ + 1, 25), 252 (100). Anal. Calcd for $C_{17}H_{23}NO_4S_2$: C, 55.26; H, 6.27; N, 3.79. Found: C, 54.97; H, 6.26; N, 3.76.

(2*S*,6*S*)-6-Methyl-2-[(*E*)-1-propenyl]-*N*-(*p*-tolylsulfonyl)piperidine [(2*S*,6*S*)-61]. A mixture of **60** (273 mg, 0.739 mmol) and trimethyl phosphite (2 mL) was refluxed for 14 h. The reaction mixture was diluted with chloroform (20 mL), washed with water, and dried ($MgSO_4$). Concentration in vacuo and purification by chromatography on silica gel with hexane–ethyl acetate (20:1 to 10:1) gave (2*S*,6*S*)-**61** (210 mg, 97%) as a colorless oil: $[\alpha]^{24}_D$ −36.7° (*c* 1.67, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.24 (3 H, d, *J* = 7.1 Hz), 1.28–1.42 (4 H, m), 1.63–1.78 (5 H, m), 2.41 (3 H, s), 4.11–4.22 (1 H, m), 4.58 (1 H, br s), 5.56–5.70 (2 H, m), 7.26 (2 H, d, *J* = 8.1 Hz), 7.70 (2 H, d, *J* = 8.1 Hz); mass spectrum, *m/z* (relative intensity) 293 (3), 279 (8), 278 (62), 252 (16), 155 (38), 138 (38), 122 (28), 91 (68), 81 (100); exact mass calcd for $C_{16}H_{23}NO_2S$ 293.1448, found 293.1463.

Preparation of (+)-Pinidine [(+)-2]. A solution of (2*S*,6*S*)-**61** (220 mg, 0.750 mmol) in ethanol (6 mL) was added to liquid ammonia (20 mL) with stirring at −78 °C. To this mixture was added sodium (1.0 g, 43.5 mmol) in small portions with stirring at −78 °C and the reaction was allowed to warm to room temperature. After 14 h, the reaction mixture was diluted with ether (30 mL) and quenched with a saturated aqueous solution of ammonium chloride (3 mL). The solid that separated was filtered and rinsed with ether (10 mL). The combined solution was dried ($MgSO_4$) and concentrated below 30 °C at 20 mmHg. The residual oil was purified by chromatography on silica gel with ether–5% methanolic ammonia (200:1) to give (+)-**2** (85 mg, 81%) as a colorless oil: $[\alpha]^{24}_D$ +10.2° (*c* 0.32, EtOH) [lit.[20a] $[\alpha]^{23}_D$ +10.2° (*c* 6.0, EtOH)]; ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.02 (1 H, tdd, *J* = 13.0, 11.0, 3.9 Hz), 1.06 (3 H, d, *J* = 6.2 Hz), 1.15 (1 H, tdd, *J* = 13.0, 11.1, 3.9 Hz), 1.35 (1 H, qt, *J* = 13.1, 3.8 Hz), 1.50–1.65 (2 H, m), 1.65 (3 H, dd, *J* = 6.0, 0.8 Hz), 1.76 (1 H, d quint, *J* = 13.2, 3.0 Hz), 2.65 (1 H, dtd, *J* = 17.2, 6.3, 2.5 Hz), 3.04 (1 H, ddd, *J* = 11.0, 6.9, 1.9 Hz), 5.45 (1 H, ddd, *J* = 15.3, 6.8, 1.4 Hz), 5.57 (1 H, dq, *J* = 15.3, 6.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 17.83 (CH_3), 23.12 (CH_3), 24.79 (CH_2), 32.41 (CH_2), 33.97 (CH_2), 52.34 (CH), 59.52 (CH), 124.99 (CH), 135.22 (CH). This material was treated with methanolic HCl, affording (+)-pinidine hydrochloride [(+)-**2**·HCl], which was recrystallized from ethanol–ether to give colorless needles: mp 246–248 °C (lit.[20a] mp 243–244 °C); $[\alpha]^{24}_D$ +9.5° (*c* 0.20, EtOH); mass spectrum, *m/e* (relative intensity) 139 (M^+ − HCl, 38), 138 (20), 124 (100), 111 (18), 110 (25), 98 (25), 96 (82), 82 (64), 81 (48), 68 (63).

^1H and ^{13}C NMR spectra and TLC behavior of synthetic (+)-**2** were identical with those of authentic (±)-**2**. Furthermore synthetic (+)-**2**·HCl had a mass spectrum identical with that of authentic (±)-**2**·HCl.

(6*R*,7*S*,8*S*)-7,8-Bis[(methoxymethyl)oxy]-6-(1,3-dioxo-2-azaindan-2-yl)-1-nonene (62). In the manner described for the preparation of **18**, **50** (9.50 g, 36.22 mmol) was subjected to Mitsunobu reaction to give **62** (8.10 g, 57%) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ $CDCl_3$ 1.22–1.39 (2 H, m, containing 3 H, d, *J* = 6.4 Hz at δ 1.29), 1.73–1.84 (1 H, m), 1.97–2.21 (3 H, m), 2.87 (3 H, s), 3.45 (3 H, s), 3.99 (1 H, qd, *J* = 6.4, 2.1 Hz), 4.13 (1 H, dd, *J* = 9.7, 2.1 Hz), 4.49 (1 H, $^1/_2$ AB q, *J* = 6.9 Hz), 4.52–4.62 (1 H, m, containing 1 H, $^1/_2$ AB q, *J* = 6.9 Hz at δ 4.57), 4.68 (1 H, $^1/_2$ AB q, *J* = 7.0 Hz), 4.78 (1 H, $^1/_2$ AB q, *J* = 7.0 Hz), 4.87–5.01 (2 H, m), 5.72 (1 H, ddt, *J* = 17.0,

10.3, 6.7 Hz), 7.71 (2 H, dd, J = 5.4, 3.0 Hz), 7.84 (2 H, dd, J = 5.4, 3.0 Hz).

(6*R*,7*S*,8*S*)-6-(*N*,*N*-Dibenzylamino)-7,8-bis[(methoxymethyl)oxy]-non-1-ene (63). A mixture of **62** (6.49 g, 16.6 mmol) and hydrazine hydrate (4.15 g, 82.8 mmol) in ethanol (70 mL) was refluxed for 2.5 h. Ether (30 mL) was added to the reaction mixture after cooling, and the resulting phthalhydrazide was filtered. The filtrate was concentrated in vacuo to give the crude amine as an oil, which was dissolved in dichloromethane (40 mL). To the resulting solution was added an aqueous solution of Na_2CO_3 (7.03 g, 66.3 mmol in 20 mL of water) and benzyl bromide (5.67 g, 33.2 mmol) at once and the mixture was refluxed for 3 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (15 mL × 2). The combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and purification by chromatography on silica gel with hexane–ethyl acetate (10:1) gave **63** (5.9 g, 81%) as a colorless oil: $[\alpha]^{25}_D$ −85.0° (c 0.51, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.46 (3 H, d, J = 6.1 Hz), 1.21–1.36 (1 H, m), 1.50–1.65 (1 H, m), 1.78 (2 H, q, J = 7.3 Hz), 2.13 (2 H, q, J = 7.3 Hz), 2.43–2.53 (1 H, m), 3.26–3.44 (3 H, unresolved, containing 3 H, s at δ 3.37 and 3 H, s at δ 3.39), 4.10 (2 H, br d, J = 13.1 Hz), 4.18 (1 H, ddt, J = 8.8, 6.2, 6.1 Hz), 4.65 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.66 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.70 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.80 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.97–5.12 (2 H, m), 5.88 (1 H, ddt, J = 17.0, 10.2, 6.7 Hz), 7.15–7.46 (10 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 16.98 (CH_3), 22.79 (CH_2), 26.82 (CH_2), 34.13 (CH_2), 55.35 (CH_3), 55.78 (CH_2, 2 carbons), 56.31 (CH_3), 57.19 (CH), 75.10 (CH), 84.68 (CH), 96.10 (CH_2), 99.35 (CH_2), 114.72 (CH_2), 126.69 (CH, 2 carbons), 128.20 (CH, 4 carbons), 129.54 (CH, 4 carbons), 138.93 (CH), 140.82 (C, 2 carbons); mass spectrum, m/z (relative intensity) 410 (2), 278 (100), 91 (85); mass spectrum (isobutane CI), m/z (relative intensity) 442 (M^+ + 1, 15), 410 (23), 278 (100), 91 (97). Anal. Calcd for $C_{27}H_{39}NO_4$: C, 73.44; H, 8.90; N, 3.17. Found: C, 73.57; H, 8.94; N, 3.20.

(6*R*,7*S*,8*S*)-6-(*N*,*N*-Dibenzylamino)-7,8-bis[(methoxymethyl)oxy]-nonan-1-one (64). In the manner described previously for the preparation of (2*R*,5*R*)-**41**, **63** (1.30 g, 2.94 mmol) was oxidized by the Wacker process. The crude product was purified by chromatography on silica gel with hexane–ethyl acetate (5:1 to 4:1) to give **64** (920 mg, 68%) as a colorless oil; $[\alpha]^{25}_D$ −65.0° (c 0.22, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 0.43 (3 H, d, J = 6.2 Hz), 1.45–1.60 (1 H, m), 1.63–1.81 (3 H, m), 2.18 (3 H, s), 2.41–2.55 (3 H, m), 3.25–3.43 (3 H, m, containing 2 sets of 3 H, s at δ 3.37 and δ 3.39), 4.09 (2 H, br d, J = 13.0 Hz), 4.18 (1 H, ddt, J = 8.7, 6.2, 6.1 Hz), 4.65 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.66 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.69 (1 H, $^1/_2$ AB, q, J = 6.6 Hz), 4.79 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 7.15–7.42 (10 H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 16.88 (CH_3), 21.65 (CH_2), 22.76 (CH_2), 29.88 (CH_3), 43.89 (CH_2), 55.31 (CH_3), 55.64 (CH_2, 2 carbons), 56.26 (CH_3), 57.06 (CH), 74.98 (CH), 84.80 (CH), 96.04 (CH_2), 99.44 (CH_2), 126.89 (CH, 2 carbons), 128.19 (CH, 4 carbons), 129.51 (CH, 4 carbons), 140.61 (C, 2 carbons), 208.70 (C); mass spectrum, m/z (relative intensity) 426 (1), 294 (65), 278 (22), 91 (100); mass spectrum (isobutane CI), m/z (relative intensity) 458 (M^+ + 1, 9), 426 (12), 294 (82), 278 (25), 91 (100). Anal. Calcd for $C_{27}H_{39}NO_5$: C, 70.87; H, 8.59; N, 3.06. Found: C, 70.80; H, 8.66; N, 3.15.

[2*R*,6*R*,2(1*S*,2*S*)]-2-[1,2-Bis[(methoxymethyl)oxy]propyl]-6-methylpiperidine (65). In the manner described previously for the preparation of **54** from **53** (procedure A), **64** (918 mg, 2.01 mmol) was hydrogenated. The crude product was purified by chromatography on silica gel with ethyl acetate–5% methanolic ammonia (10:1) to give **65** (500 mg, 95%) as a colorless oil: $[\alpha]^{25}_D$ −8.6° (c 0.28, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.05–1.40 (3 H, m, containing 3 H, d, J = 6.3 Hz at δ 1.09 and 3 H, d, J = 6.5 Hz at δ 1.22), 1.58 (1 H, br dd, J = 12.8, 2.5 Hz), 1.75 (1 H, br dd, J = 12.7, 2.5 Hz), 1.82 (1 H, d quint, J = 13.1, 3.1 Hz), 2.56–2.68 (1 H, m), 2.82 (1 H, ddd, J = 11.1, 8.0, 2.4 Hz), 3.25–3.35 (1 H, m), 3.36 (3 H, s), 3.42 (3 H, s), 3.94 (1 H, ddd, J = 12.9, 6.4, 3.0 Hz), 4.60 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.69 (1 H, $^1/_2$ AB q, J = 6.9 Hz), 4.73 (1 H, $^1/_2$ AB q, J = 6.6 Hz), 4.79 (1 H, $^1/_2$ AB q, J = 6.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 16.56 (CH_3), 22.84 (CH_3), 24.67 (CH_2), 27.91 (CH_2), 33.83 (CH_2), 52.55 (CH), 55.76 (CH_3), 56.16 (CH_3), 57.73 (CH), 72.55 (CH), 86.46 (CH), 95.31 (CH_2), 99.03 (CH_2); mass spectrum, m/z (relative intensity) 262 (M^+ + 1, 2), 230 (10), 198 (10), 142 (18), 140 (27), 112 (65), 98 (100); exact mass for $C_{12}H_{24}NO_3$ (M^+ − MeO) 230.1755, found 230.1775.

[2*R*,6*R*,2(1*S*,2*S*)]-2-[1,2-Bis[(methoxymethyl)oxy]propyl]-6-methyl-*N*-(*p*-tolylsulfonyl)piperidine (66). In the manner described for the preparation of **58**, **65** (480 mg, 1.84 mmol) was subjected to tosylation. The crude product was purified by chromatography on silica gel with hexane–ethyl acetate (6:1 to 5:1) to give **67** (390 mg, 51%) as a pale yellow oil: $[\alpha]^{25}_D$ +29.5° (c 0.22, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.18–1.40 (4 H, m, containing 3 H, d, J = 6.6 Hz at δ 1.31, and 3 H, d, J = 7.3 Hz at δ 1.33), 1.46–1.60 (1 H, m), 2.02 (1 H, br d, J = 13.9 Hz), 2.41 (3 H, s), 3.38 (3 H, s), 3.43 (3 H, s), 3.76 (1 H, dd, J = 9.5, 3.2 Hz), 3.99–4.09 (2 H, m), 4.35–4.41 (1 H, unresolved), 4.65 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.69 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.69 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 4.69 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 4.83 (1 H, $^1/_2$ AB q, J = 7.0 Hz), 7.26 (2 H, d, J = 8.2 Hz), 7.73 (2 H, d, J = 8.2 Hz); mass spectrum, m/z (relative intensity) 252 (10), 86 (66), 84 (100).

[2*R*,6*R*,2(1*S*,2*S*)]-2-[1,2-Dihydroxypropyl]-6-methyl-*N*-(*p*-tolylsulfonyl)piperidine (67). In the manner described for the preparation of **59**, **66** (338 mg, 0.813 mmol) underwent acidic hydrolysis. The crude product was purified by chromatography on silica gel with hexane–ethyl acetate (2:1) to give **67** (225 mg, 85%) as a colorless oil: $[\alpha]^{25}_D$ +51.4° (c 0.21, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.08–1.68 (6 H, m, containing 3 H, d, J = 6.4 Hz at δ 1.33, and 3 H, d, J = 7.1 Hz at δ 1.40), 1.98 (1 H, d, J = 10.6 Hz), 2.43 (3 H, s), 3.02 (1 H, dd, J = 4.0, 0.4 Hz), 3.53 (1 H, ddd, J = 10.2, 4.2, 0.8 Hz), 3.63–3.73 (1 H, m), 4.07 (1 H, dd, J = 9.7, 6.4 Hz), 4.36 (1 H, quint d, J = 7.1, 2.4 Hz), 7.30 (2 H, d, J = 8.4 Hz), 7.73 (2 H, d, J = 8.4 Hz); mass spectrum, m/e (relative intensity) 282 (5), 252 (100), 155 (30), 91 (45); mass spectrum (isobutane CI), m/z (relative intensity) 328 (M^+ + 1, 35), 252 (100), 155 (25), 91 (34).

[2*R*,6*R*,2(4*S*,5*S*)]-2-(4-methyl-2-thioxo-1,3-dioxolanyl)-6-methyl-*N*-(*p*-tolylsulfonyl)piperidine (68). In the manner described for the preparation of **60**, **67** (209 mg, 0.638 mmol) was converted to the crude product of **68**, which was purified by chromatography on silica gel with hexane–ethyl acetate (5:1 to 4:1) to give **68** (208 mg, 88%) as a pale yellow gum: $[\alpha]^{25}_D$ −30.2° (c 0.58, $CHCl_3$); IR ($CHCl_3$) 1317, 1278, 1200, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ $CHCl_3$ 1.11–1.88 (6 H, m, containing 3 H, d, J = 7.1 Hz at δ 1.28, and 3 H, d, J = 6.2 Hz at δ 1.61), 2.43 (3 H, s), 4.02 (1 H, quint d, J = 6.7, 2.4 Hz), 4.33 (1 H, ddd, J = 7.9, 4.6, 1.8 Hz), 4.42 (1 H, dd, J = 9.2, 4.6 Hz), 5.06 (1 H, ddt, J = 9.2, 6.2, 6.2 Hz), 7.32 (2 H, d, J = 8.0 Hz), 7.72 (2 H, d, J = 8.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ $CDCl_3$ 15.00, 18.17, 21.63, 21.69, 25.98, 28.33, 48.44, 50.27, 81.41, 91.12, 127.15 (2 carbons), 130.00 (2 carbons), 137.20, 143.84, 190.78; mass spectrum, m/z (relative intensity) 369 (M^+, 0.1), 294 (1), 252 (100), 155 (28), 91 (56).

(2*R*,6*R*)-6-Methyl-2-[(*E*)-1-propenyl]-*N*-(*p*-tolylsulfonyl)piperidine [(2*R*,6*R*)-61]. Compound **68** (187 mg, 0.506 mmol) was transformed into (2*R*,6*R*)-**61** (132 mg, 89%) in the same manner as described for the preparation of (2*S*,6*S*)-**61**; $[\alpha]^{25}_D$ +35.7° (c 0.96, $CHCl_3$). Anal. Calcd for $C_{16}H_{23}NO_2S$: C, 65.49; H, 7.90; N, 4.77. Found: C, 65.23; H, 7.84; N, 4.77.

Preparation of (−)-Pinidine [(−)-2]. In the same manner as described for the preparation of (+)-**2**, (2*R*,6*R*)-**61** (85 mg, 0.29 mmol) was subjected to detosylation. The same workup afforded 32 mg (79%) of (−)-**2**; $[\alpha]^{25}_D$ −10.8° (c 0.07, EtOH) [lit.[6a] $[\alpha]^{25}_D$ −10.5° (c 1.880, EtOH)]. For (−)-**2**·HCl: mp 244–246 °C (lit.[6a] mp 244–246 °C); $[\alpha]^{24}_D$ −9.6° (c 0.25, EtOH) [lit.[20a] $[\alpha]^{23}_D$ −9.5° (c 5.3, EtOH)].

Synthetic (−)-**2** was found to be identical with both authentic (±)-**2** and synthetic (+)-**2** by ^1H and ^{13}C NMR spectroscopy as well as TLC behavior. Furthermore, synthetic (−)-**2**·HCl had a mass spectrum identical with those of both (±)-**2**·HCl and (+)-**2**·HCl.

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Registry No. (+)-**1**, 118015-64-8; (−)-**1**, 53447-41-3; (−)-**2**, 501-02-0; (+)-**2**, 55448-42-5; (+)-**2**·HCl, 55399-24-1; **3**, 99891-37-9; **8**, 99878-63-4; **9**, 117941-00-1; **10**, 117941-01-2; **11**, 118014-58-7; **12**, 106513-37-5; **13**, 117941-02-3; **14**, 117941-03-4; (±)-**15**, 117941-04-5; (±)-**16**, 117941-05-6; (±)-**17**, 117941-06-7; **18**, 117941-07-8; **19**, 117941-08-9; **20**, 117941-09-0; **21**, 117941-10-3; **22**, 117941-11-4; **23**, 118014-59-8; **24**, 118014-60-1; **25**, 118015-65-9; **26**, 118014-61-2; **28**, 118014-62-3; **30**, 117941-12-5; **31**, 118014-63-4; **32**, 118014-64-5; **33**, 117941-13-6; **34**, 118014-65-6; **35**, 118014-66-7; **36**, 117941-14-7; **37**, 118015-66-0; **38**, 117941-15-8; (2*R*,5*R*)-**40**, 118014-67-8; (2*S*,5*S*)-**40**, 117940-99-5; (2*R*,5*R*)-**41**, 118014-68-9; (2*S*,5*S*)-**41**, 117940-98-4; (−)-**42**, 92841-44-6; (+)-**42**, 53447-42-0; **43**, 118014-69-0; **44**, 117941-16-9; **45**, 118014-70-3; **47**, 104465-59-0; **48**, 117941-18-1; **49**, 117941-19-2; **50**, 118014-71-4; **51**, 117941-20-5; **52**, 117941-21-6; **53**, 117941-22-7; **54**, 118015-67-1; **55**, 117941-23-8; **56**, 117941-24-9; **57**, 117941-25-0; **58**, 117941-26-1; **59**, 117941-27-2; **60**, 117941-28-3; (2*S*,6*S*)-**61**, 118015-63-7; (2*R*,6*R*)-**61**, 117941-17-0; **62**, 118014-72-5; **63**, 117958-78-8; **64**, 117941-29-4; **65**, 117941-30-7; **66**, 118014-73-6; **67**, 118014-74-7; **68**, 118014-75-8; CH_2=$CH(CH_2)_3MgBr$, 34164-50-6.