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Stereoselective Total Syntheses of (-)-Desoxoprosopinine and (-)-Desoxoprosophylline : Palladium(0)-Catalyzed Intramolecular *N*-Alkylation for the Key Piperidine Ring Formation

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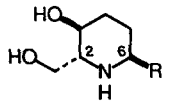
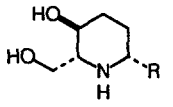
Abstract: Intramolecular *N*-alkylation of D-glucose-derived substrate **21*E*** proceeded in an S_N2' mode smoothly in the presence of a Pd(0) catalyst and *n*-Bu_4NI. The major cyclization product, a 2,6-dialkylated piperidine **22*t***, was effectively converted into the title alkaloids.

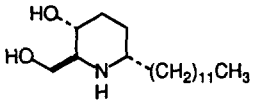
Alkaloids containing a 2,6-dialkylated piperidine ring are found abundantly in nature and many of them exhibit interesting biological activities.[1] Prosopis alkaloids, one of the subgroups of these piperidine alkaloids, were isolated from *Prosopis africana* Taub.[2] Some of these alkaloids, such as (+)-prosopinine (**1**) and (+)-prosopine (**2**) (Figure 1), possess local anesthetic activity.[3] Several endeavors directed towards total syntheses of these alkaloids have been reported to date,[4] including an efficient chemoenzymatic total synthesis of (+)-desoxoprosopinine (**3**),[5] reduction product of (+)-prosopinine (**1**). Stereoselective syntheses of *trans*-2,6-disubstituted piperidines are generally more difficult than those of *cis* isomers, besides, there are some reports concerning the stereoselective preparation of *cis*- and *trans*-2,6-dialkylated piperidine alkaloids from a common intermediate.[6] It is beneficial to overcome these difficulties from a synthetic point of view. In this paper, we describe enantiospecific and stereoselective total syntheses of (-)-desoxoprosopinine (**6**)[7] and (-)-desoxoprosophylline (**7**)[8] using a transition metal catalyzed approach.[9] Furthermore, the formal syntheses of (+)-enantiomers of **6** and **7**, *i. e.* **3** and **5**, are also presented.



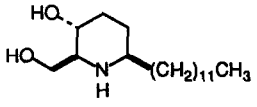
1 R = $(CH_2)_9COCH_2CH_3$ **(+)-prosopinine**
2 R = $(CH_2)_{10}CH(OH)CH_3$ **(+)-prosopine**
3 R = $(CH_2)_{11}CH_3$ **(+)-desoxoprosopinine**



4 R = $(CH_2)_9COCH_2CH_3$ **(±)-prosophylline**
5 R = $(CH_2)_{11}CH_3$ **(+)-desoxoprosophylline**



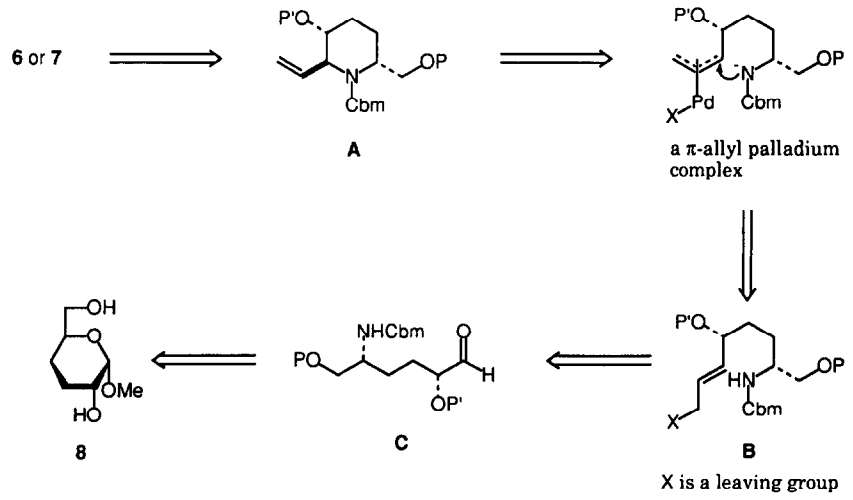
6 (-)-desoxoprosopinine



7 (-)-desoxoprosophylline

Figure 1

As shown in a retrosynthetic analysis illustrated in Scheme 1, we envisioned that the 2,6-dialkylated piperidine rings of **6** and **7** would be formed by palladium(0)-catalyzed intramolecular *N*-alkylation.[10] It was expected that the *N*-alkylation would proceed in an S_N2' fashion via an intermediary π-allyl palladium complex. The target compounds **6** and **7** would be derived from the cyclization product **A** by oxidative cleavage of the vinyl group at *C*-2 and carbon elongation at *C*-6 side chain. The substrate **B** of the *N*-alkylation would be prepared from the known pyranoside **8** via an acyclic amino-sugar **C**. The starting compound **8** is easily available derived from D-glucose in six steps by the known procedure.[11]

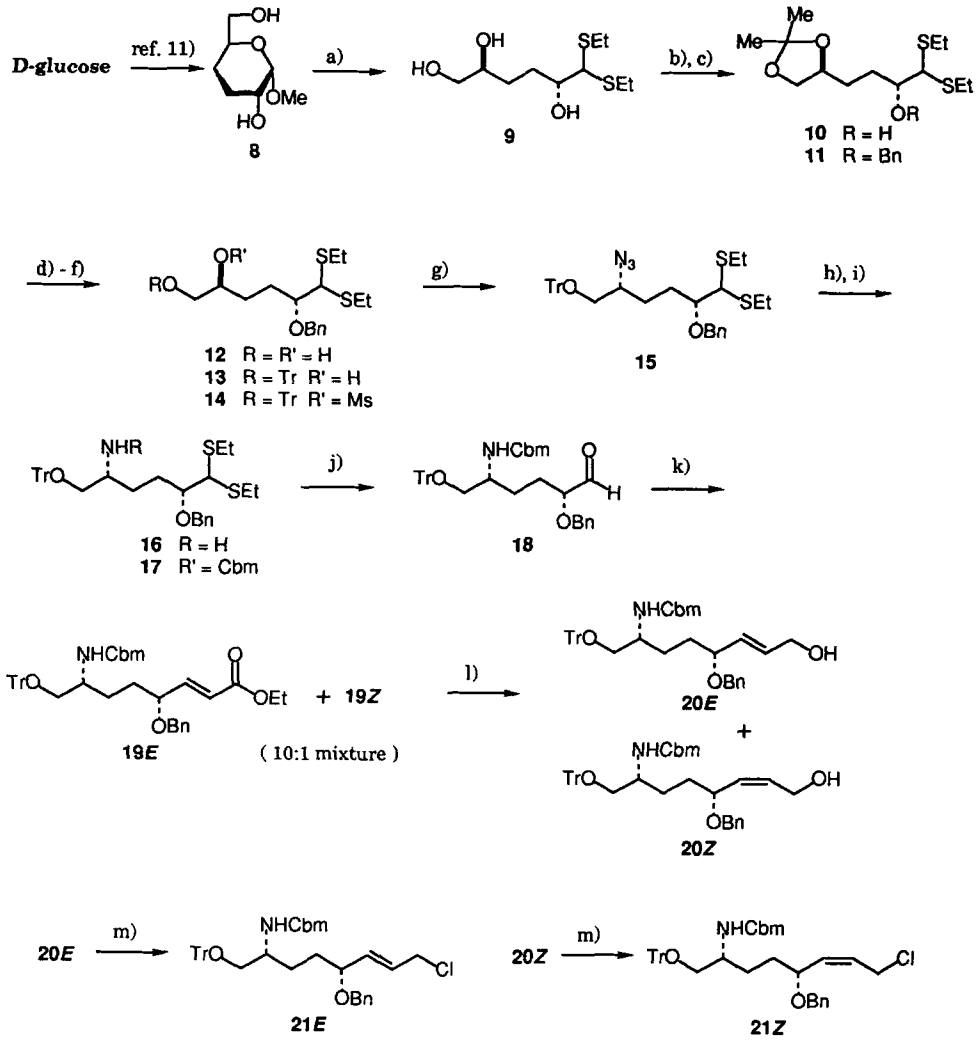


Scheme 1

RESULTS AND DISCUSSION

The substrate **B** = **21** for the key piperidine ring formation was prepared from methyl 3,4-dideoxy-α-D-*erythro*-hexopyranoside (**8**)[11] (Scheme 2). Thioacetalization (EtSH / conc. HCl) of **8** with concomitant pyranoside ring opening afforded an acyclic dithioacetal **9**. The terminal 1,2-diol moiety of **9** was protected as the isopropylidene ketal to give **10** in 84% yield for two steps. Protection of the hydroxyl group of **10** as a benzyl ether furnished a fully protected triol **11** in 98% yield. Removal of the *O*-isopropylidene group in **11** with 50% aqueous acetic acid and selective protection of the primary hydroxyl group of the resulting diol **12** by tritylation afforded the trityl ether **13**. By means of the standard procedure, **13** was converted into the mesylate **14** in 86% yield from **11**. Displacement of the mesyloxy group in **14** by an azido group in an S_N2 fashion provided the azide **15** in 91% yield. Chemoselective reduction of the azido group in **15** with hydrogen sulfide followed by protection of the resulting amine **16** gave a carbamate **17** in 94% yield. Dethioacetalization of **17** with $HgCl_2$ afforded an aldehyde **18**, which was subjected to a Horner-Emmons olefination with triethyl phosphonoacetate in the presence of NaH resulting in the formation of an inseparable mixture of *E*-α,β-unsaturated ester **19*E*** and the *Z*-isomer, in a ratio of 10:1, in a combined yield of 99%. Diisobutylaluminum hydride (Dibal-H) reduction of the mixture afforded an *E*,*Z*-mixture of allylic alcohols, which was cleanly separated by SiO_2 chromatography giving the *E*-isomer **20*E*** and the *Z*-isomer **20*Z*** in 83% and 3% yields, respectively. Treatment of **20*E*** with excess TsCl in the presence of 4-dimethylaminopyridine (DMAP) gave

allylic chloride **21*E***, the substrate of the piperidine ring formation, in 94% yield. Under the same conditions, the *Z*-isomer **21*Z*** was obtained in 80% yield from **20*Z***.



a) EtSH, conc. HCl, -15°C; b) $Me_2C(OMe)_2$, DL-camphorsulfonic acid, acetone; c) BnBr, NaH, THF; d) 50% aq. AcOH; e) TrCl, DMAP, pyridine, 70°C; f) MsCl, pyridine; g) NaN_3, DMF, 70°C; h) H_2S, aq. pyridine; i) MeOC(O)Cl, K_2CO_3, aq. acetone; j) $HgCl_2$, $CaCO_3$, aq. MeCN; k) $(EtO)_2P(O)CH_2COOEt$, NaH, THF; l) Dibal-H, CH_2Cl_2, -78°C; m) TsCl, DMAP, CH_2Cl_2.

Scheme 2

With the allylic chloride **21*E*** in hand, we explored the key intramolecular *N*-alkylation to construct a piperidine ring. Table 1 shows the results of the attempted cyclization of **21*E*** under various reaction conditions. In the earlier experiment, the substrate **21*E*** was treated with NaH in the presence of a catalytic amount of $Pd(PPh_3)_4$ in refluxing THF (run 1). Under these conditions, the cyclization proceeded with

moderate diastereoselectivity affording an inseparable mixture of two piperidine derivatives **22*t*** and **22*c*** (Scheme 3) in a combined yield of 59%. When **21*E*** was treated with NaH alone in THF or *t*-BuOK in THF, no *N*-alkylation proceeded and **21*E*** was recovered almost quantitatively (run 2 and 3). These facts verify that the Pd(0) catalyst is indispensable to realize the piperidine ring formation. Stereochemical assignment of the newly introduced stereogenic center (*C*-2) in **22*t*** and **22*c*** was confirmed by ^{1}H NMR analysis of advanced bicyclic oxazolidone derivatives **38** and **39** (*vide infra*). Switching the base (NaH) in the above conditions (run 1) to *t*-BuOK decreased the amount of cyclization products (run 4). The use of other solvents, such as acetonitrile (run 5), DMF (run 6) and benzene (run 7), did not improve the yield of the cyclization products. The combination of $Pd(OAc)_2$ and 1,2-bis(diphenylphosphino)ethane as a ligand led to much lower yield of the piperidine derivatives (run 8). Fortunately, it was found that addition of *n*-Bu_4NI,[12] a phase transfer agent, lowered the reaction temperature to rt, and improved the yield and the diastereoselectivity of the products significantly (run 9). These mild conditions gave the best result.[13] In order to examine the role of the double bond geometry on the stereochemical outcome of this cyclization, the *Z*-allylic chloride **21*Z*** was subjected to the Pd(0)-catalyzed *N*-alkylation under the same conditions optimized for **21*E***. The mixture **22*t*** and **22*c*** was obtained in a ratio of 13:1, although the yield of the products decreased significantly (48%). Thus, it is concluded that the diastereoselectivity of the *N*-alkylation is independent of the allylic geometry of the substrates.

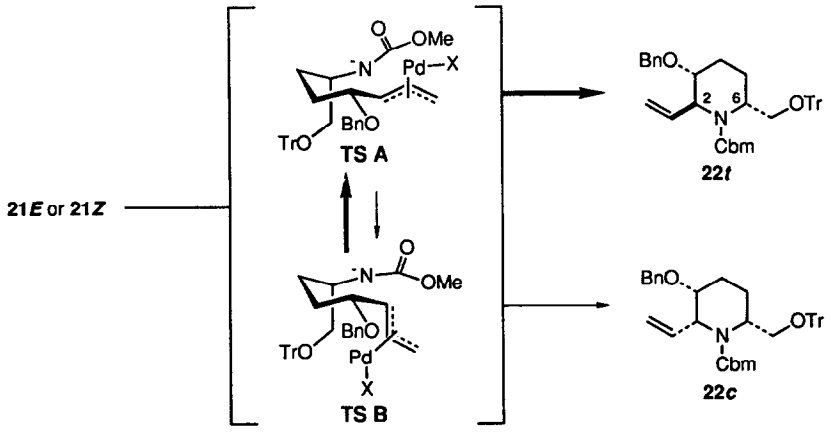
Table 1. Pd(0)-Catalyzed Intramolecular *N*-Cyclization of 21*E*

run	reaction conditions	yield[a] (**22*t*** : **22*c***)[b]
1	NaH (4eq), $Pd(PPh_3)_4$ (0.2eq) / THF, reflux	59% (3 : 1)
2	NaH (2eq) / THF, reflux	no reaction
3	*t*-BuOK (3eq) / THF, reflux	no reaction
4	*t*-BuOK (4eq), $Pd(PPh_3)_4$ (0.2eq) / THF, reflux	34% (3 : 1)
5	NaH (4eq), $Pd(PPh_3)_4$ (0.2eq) / MeCN, reflux	30% (3 : 1)
6	NaH (2eq), $Pd(PPh_3)_4$ (0.2eq) / DMF, rt	28% (nd[c])
7	NaH (4eq), $Pd(PPh_3)_4$ (0.2eq) / PhH, reflux	no reaction
8	NaH (4eq), $Pd(OAc)_2$ (0.4eq), $Ph_2P(CH_2)_2PPh_2$ (0.8eq) / THF, reflux	5% (nd[c])
9	NaH (2eq), $Pd(PPh_3)_4$ (0.2eq), *n*-Bu_4NI (1eq) / THF, rt	75% (12 : 1)

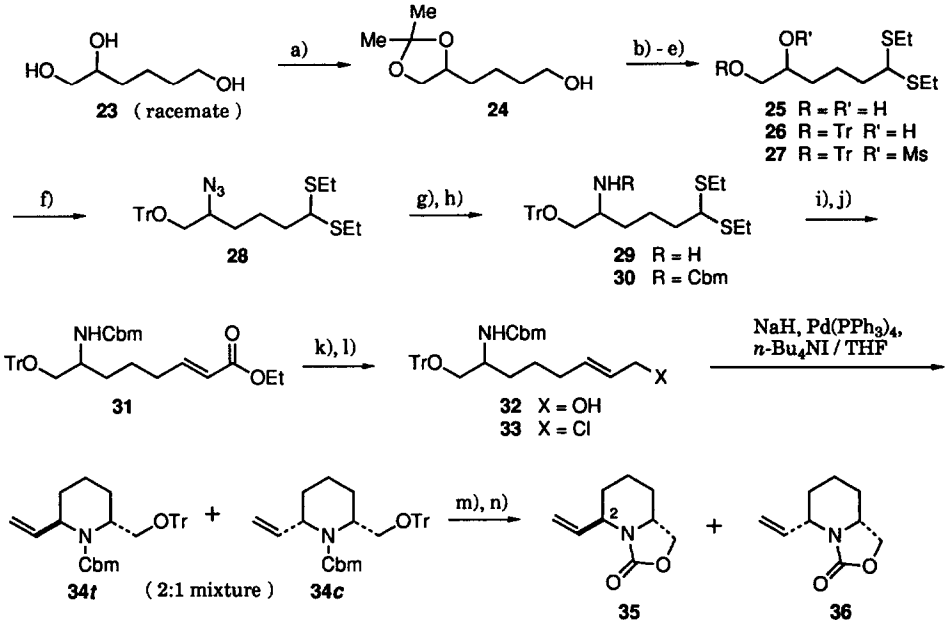
[a] Combined yield of **22*t*** and **22*c***. [b] Ratios were determined based on the 270 MHz ^{1}H NMR analysis of the mixture. [c] Not determined.

The chair-like transition states **A** and **B** with the (trityloxy)methyl group disposing an axial orientation, in which an $A^{1,3}$-strain like interaction is avoided,[14] are proposed for explanation of the stereochemical outcome of the cyclization (Scheme 3). Although the equatorially disposed π-allyl palladium complex in **TS A** may suffer from an $A^{1,3}$-strain between the benzyloxy group, **TS B** seems to be much more destabilized by non-bonded interactions between the axial π-allyl palladium complex and the (trityloxy)methyl group (1,3-diaxial repulsion) and the benzyloxy group. As a result, the *trans*-2,6-disubstituted piperidine **22*t*** was obtained as the major product via more advantageous **TS A**. In order to ensure the role of the benzyloxy group in the substrate **21*E***, we prepared allylic chloride **33** from racemic 1,2,6-hexanetriol (**23**) by a route analogous to that described for the conversion of **8** into **21*E*** (Scheme 4). Exposure of **33** to the same conditions employed for **21*E*** resulted in the formation of an approximately 2:1 inseparable mixture of **34*t*** and **34*c*** (79%). The mixture was converted

into bicyclic oxazolidones **35** and **36**, of which structures were unambiguously determined by ^{1}H NMR analysis.[15] Although the formation of the *trans*-2,6-substituted piperidine **34*t*** was preferential, this cyclization displayed a much lower level of diastereoselectivity. This leads a conclusion that the benzyloxy group in **21*E*** plays an important role for achieving the observed high stereoselectivity.



Scheme 3

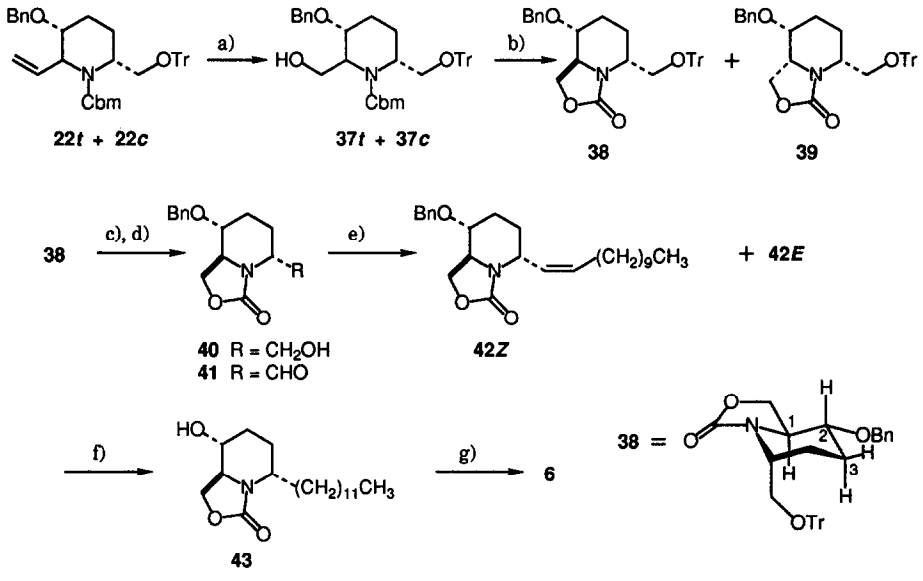


a) same as b) in Scheme 2; b) PCC, MS-4A, CH_2Cl_2; c) EtSH, conc. HCl, -15°C; d) - f) same as e) - g) in Scheme 2; g) $LiAlH_4$, THF; h) - l) same as i) - m) in Scheme 2; m) *p*-TsOH, MeOH; n) NaH, THF, reflux.

Scheme 4

The highly efficient methodology for constructing the *trans*-2,6-disubstituted piperidine ring via Pd(0)-catalyzed intramolecular *N*-alkylation was thus established. The cyclization product **22*t*** seems to be a useful precursor for the preparation of piperidine alkaloids, and its versatility was demonstrated by its transformation into (-)-desoxoprosopinine (**6**) and (-)-desoxoprosophylline (**7**) as follows.

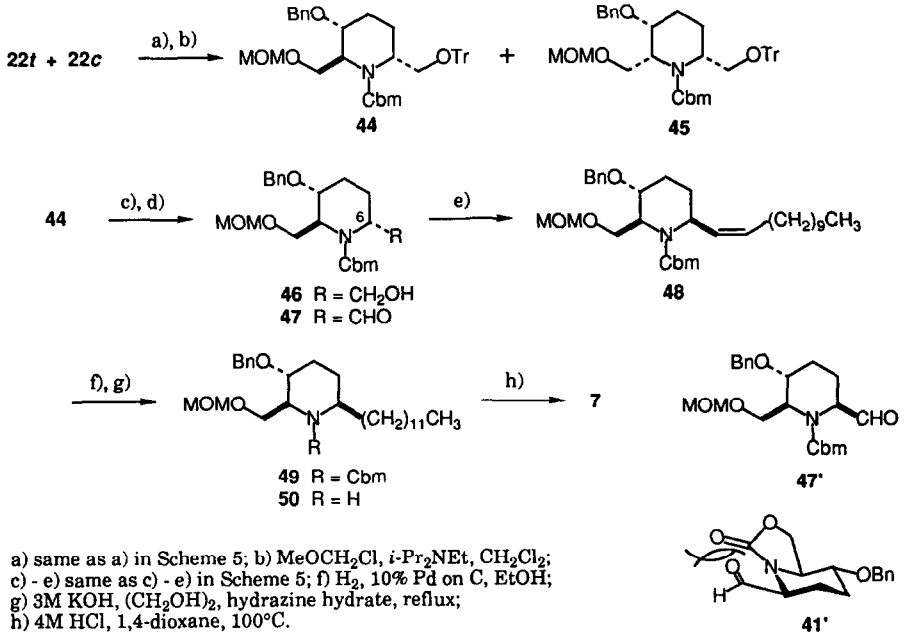
The total synthesis of **6** was executed as outlined in Scheme 5. Ozonolysis of the mixture of **22*t*** and **22*c*** followed by $NaBH_4$ reduction gave a mixture of **37*t*** and **37*c***, which was then converted into readily separable oxazolidones **38** (86%) and **39** (6%) by brief exposure to NaH. In the ^1H NMR spectrum of **38**, *H*-2 signal appears at δ 3.17 as a ddd with $J_{1,2}$=9.5, $J_{2,3ax}$=10.6 and $J_{2,3eq}$=4.0Hz. On the other hand, $J_{1,2}$=2.4Hz was observed in the case of **39**. From these observations, the structures of **38** and **39** were determined to be as depicted. Consequently, the major product **22*t*** is a *trans*-2,6-substituted piperidine. Acid hydrolysis of **38** with *p*-TsOH in MeOH removed the trityl group to afford **40** in 98% yield. Swern oxidation[16] of **40** and subsequent Wittig olefination of the resulting aldehyde **41** with $Ph_3P{=}CH(CH_2)_9CH_3$ (salt free) at 0°C gave *Z*-olefin **42*Z*** and *E*-olefin **42*E*** in 49% and 3% yields, respectively. Both olefins **42*Z*** and **42*E*** were hydrogenated separately in the presence of 10% Pd on C. Under these conditions, the benzyl group was also hydrogenolyzed to give **43** quantitatively from **42*Z***, or in 71% yield from **42*E***. Finally, the oxazolidone ring was cleaved efficiently by saponification of **43** in 8M KOH affording **6** in 80% yield. Mp and $[\alpha]_D$ of the synthetic **6** were identical with those reported.[7a,b] ^1H and ^{13}C NMR spectra of **6** coincided with those reported for synthetic **3**.[5]



a) O_3, CH_2Cl_2, MeOH, -78°C, PPh_3, then $NaBH_4$; b) NaH, THF, reflux; c) *p*-TsOH, MeOH; d) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, then Et_3N; e) $Ph_3P{=}CH(CH_2)_9CH_3$, THF, 0°C; f) H_2, 10% Pd on C, MeOH : conc.HCl (50:1); g) 8M KOH, EtOH, 100°C.

Scheme 5

Our next goal was to accomplish the total synthesis of the *cis*-2,6-dialkylated piperidine alkaloid, (-)-desoxoprosophylline (**7**), from the major *N*-alkylation product **22*t***. For this aim, it was necessary to invert the stereochemistry at *C*-6 of **22*t***. Compounds **44** and **45** were prepared from the mixture of **22*t*** and **22*c*** via **37*t*** and **37*c*** in 76% and 7% yields, respectively (Scheme 6). Detritylation of the major MOM ether **44** and subsequent Swern oxidation of the resulting alcohol **46** gave a monocyclic aldehyde **47**. Wittig olefination of **47** under the same conditions used for **41** proceeded with complete epimerization of *C*-6 giving a *cis*-2,6-disubstituted piperidine **48** exclusively in 59% yield. This result indicates that the monocyclic aldehyde **47** was prone to epimerize to **47'**, which is likely to be more thermodynamically stable than the 2,6-*trans* form,[14b] prior to the Wittig reaction. In contrast to **47'**, compound **41'** which might be derived from the aldehyde **41** by epimerization suffers from a disadvantageous interaction between the aldehydo group and the carbamate. Therefore, the bicyclic structure of **41** is indispensable for carbon elongation at *C*-6 without epimerization under the Wittig olefination conditions. Hydrogenation of the *cis*-2,6-disubstituted piperidine **48** afforded a 79% yield of **49**, which was subjected to deprotect the methyl carbamate with 3M KOH in ethylene glycol and hydrazine hydrate giving **50** in 61% yield, and **49** (27%) was recovered. Finally, removal of the methoxymethyl and benzyl groups in **50** by acid hydrolysis provided **7** in 81% yield. Mp, $[\alpha]_D$ and ^1H NMR of the synthetic **7** were identical with those reported.[7a,b]

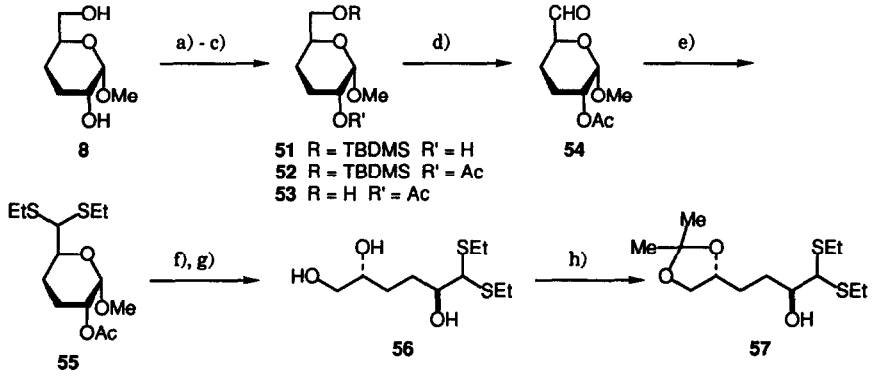


a) same as a) in Scheme 5; b) $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2;
c) - e) same as c) - e) in Scheme 5; f) H_2, 10% Pd on C, EtOH;
g) 3M KOH, $(CH_2OH)_2$, hydrazine hydrate, reflux;
h) 4M HCl, 1,4-dioxane, 100°C.

Scheme 6

Lastly, we expected to confirm a possibility to realize the formal syntheses of (+)-desoxoprosopinine (**3**) and (+)-desoxoprosophylline (**5**). For this purpose, we seeked an efficient synthetic route to compound **57**, the enantiomer of aforementioned **10**. The route to **57** from **8** is summarized in Scheme 7. Selective protection of the primary hydroxy group of the pyranoside **8** provided the silyl ether **51** in 77% yield, and crude **8** was recovered. By standard two-step transformations, **51** was converted into monoacetate **53** in 97% yield.

Swern oxidation of **53** and dithioacetalization of the resulting aldehyde **54** with EtSH in the presence of a catalytic amount of BF_3•OEt_2 gave dithioacetal **55** in 68% yield for two steps. Acid hydrolysis of **55** gave hemiacetal, direct $NaBH_4$ reduction of which afforded triol **56** in 67% yield, and **55** (22%) was recovered. Selective protection of the 1,2-diol moiety in **56** as an isopropylidene ketal gave **57** in 86% yield. $[\alpha]_D$ of the synthetic **57** was same as that of the enantiomer **10** in magnitude but opposite in sign, and ^1H NMR spectra were identical each other. Compound **57** would be converted into **3** and **5** using the exactly same transformation of **10** into **6** and **7**.



a) TBDMSCl, imidazole, DMF, 0°C; b) Ac_2O, pyridine; c) n-Bu_4NF, THF; d) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C, then Et_3N; e) EtSH, BF_3•Et_2O, CH_2Cl_2, 0°C; f) 2M HCl, 1,4-dioxane, 80°C; g) $NaBH_4$, MeOH; h) same as b) in Scheme 2.

Scheme 7

In conclusion, the D-glucose derived **21*E*** was found to be a suitable substrate for construction of *trans*-2,6-dialkylated piperidines under the Pd(0)-catalyzed intramolecular *N*-alkylation conditions. The effectiveness of this reaction was proved by the stereoselective total syntheses of (-)-desoxoprosopinine (**6**) and (-)-desoxoprosophylline (**7**) from the major *N*-alkylation product **22*t***. Furthermore, we presented the formal syntheses of (+)-desoxoprosopinine (**3**) and (+)-desoxoprosophylline (**5**). Accordingly, our present approaches constitute diastereo- and enantiodivergent total syntheses of both enantiomers of these piperidine alkaloids.

EXPERIMENTAL

Melting points are uncorrected. Specific rotations were measured using a JASCO Model DIP-4 or JASCO DIP-370 digital polarimeter in a 10 mm cell in $CHCl_3$ solution. IR spectra were recorded using a JASCO IR-810 (neat) or BIO-RAD DEGILAB FTS-65 ($CHCl_3$ and KBr) spectrometer. ^1H NMR spectra were recorded using a Varian EM-390 (90 MHz), JEOL EX-90 (90 MHz) or JEOL GX-270 (270 MHz) spectrometer and ^{13}C NMR spectra at 100 MHz were recorded using a JEOL JNM-GX 400 FT (400 MHz) spectrometer in $CDCl_3$ solution with tetramethysilane as an internal standard. High-resolution mass spectra (HRMS) were taken using a Hitachi M-80 mass spectrometer. Microanalyses were carried out by staffs of the Analytical Center in our university.

Thin-layer chromatography (TLC) was performed with a glass plate coated Kieselgel 60 GF_{254} (Merck). Crude reaction mixtures or extractive materials were chromatographed on silicagel 60 K070 (Katayama Chemicals).

Unless otherwise specified, reactions were carried out at room temperature (rt). Reagents and solvents were removed by concentration in vacuo using an evaporator with bath at 35-45 °C.

Solvents were dried (drying reagent in parenthesis) and distilled prior to use: tetrahydrofuran=THF ($LiAlH_4$, then Na/benzophenone ketyl), *N*,*N*-dimethylformamide=DMF (CaH_2), CH_2Cl_2 (CaH_2), dimethyl sulfoxide= DMSO (CaH_2), and pyridine (NaOH).

3,4-Dideoxy-5,6-*O*-isopropylidene-D-*erythro*-hexose Diethyldithioacetal (10). A solution of **8** (2.73 g, 16.8 mmol) in a mixture of EtSH (12.0 mL) and concentrated HCl (18.0 mL) was stirred at -15 °C for 5.5 h. The solution was neutralized with ammonia-water and concentrated in vacuo with aid of EtOH. To the residue was added EtOAc (200 mL), and the whole was stirred for 1 h. The resulting solids were removed by filtration, washed well with EtOAc. The combined filtrate and washing were concentrated in vacuo to give crude **9** (4.60 g), which was used without purification.

To a stirred solution of the crude **9** in acetone (60 mL) were added DL-camphorsulfonic acid (381 mg, 1.68 mmol) and 2,2-dimethoxypropane (4.13 mL, 33.6 mmol). The mixture was stirred for 12 h, and neutralized with saturated aqueous $NaHCO_3$. After the solvents were removed by concentration in vacuo, the residue was partitioned between EtOAc (200 mL) and H_2O (250 mL). The aqueous layer was extracted with EtOAc (200 mL x 2). The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:6) to give 4.19 g (84%) of **10** as a pale yellow oil: TLC R_f 0.26 (EtOAc/hexane, 1:4); $[\alpha]^{19}_D$ +57.6° (*c* 0.70); IR (neat) 3470, 2980, 2930, 2870, 1450, 1370, 1260, 1215 cm^{-1}; ^1H NMR (270 MHz) δ 1.28 (t, *J* = 7.3 Hz, 6 H), 1.36, 1.42 (2 s, 3H x 2), 1.48-2.02 (m, 4 H), 2.59-2.78 (m, 4 H), 2.89 (br, 1 H), 3.54 (t, *J* = 7.1 Hz, 1 H), 3.67-3.73 (m, 1 H), 3.79 (d, *J* = 5.9 Hz, 1 H), 4.03-4.16 (m, 2 H). Anal. Calcd for $C_{13}H_{26}O_3S_2$: C, 53.02; H, 8.90. Found: C, 52.77; H, 8.57.

2-*O*-Benzyl-3,4-dideoxy-5,6-*O*-isopropylidene-D-*erythro*-hexose Diethyldithioacetal (11). To a cold (0 °C) stirred solution of **10** (4.19 g, 14.2 mmol) in THF (60 mL) was added NaH (60% emulsion in mineral oil, 1.70 g, 42.6 mmol). After being stirred at room temperature for 1 h, benzyl bromide (3.40 mL, 28.4 mmol) was added to the mixture. This was stirred for 13 h. Excess NaH was decomposed by addition of MeOH. The mixture was concentrated in vacuo. The residue was partitioned between EtOAc (200 mL) and H_2O (200 mL). The aqueous layer was extracted with EtOAc (200 mL x 2). The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane, then EtOAc/hexane, 1:10) to give 5.36 g (98%) of **11** as a pale yellow oil: TLC, R_f 0.65 (EtOAc/hexane, 1:4); $[\alpha]^{20.5}_D$ +37.3° (*c* 2.18); IR (neat) 2980, 2930, 2870, 1455, 1370, 1260, 1210 cm^{-1}; ^1H NMR (90 MHz) δ 1.25, 1.27 (2 t, each *J* = 7.3 Hz, 3 H x 2), 1.37, 1.39 (2 s, 3 H x 2), 1.53-2.13 (m, 4 H), 2.65, 2.69 (2 q, each *J* = 7.3 Hz, 2 H x 2), 3.37-3.82 (m, 2 H), 3.87-4.14 (m, 3 H), 4.57, 4.71 (ABq, *J* = 11.4 Hz, 2 H), 7.17-7.43 (m, 5 H). Anal. Calcd for $C_{20}H_{32}O_3S_2$: C, 62.44; H, 8.37. Found: C, 62.82; H, 8.22.

2-*O*-Benzyl-3,4-dideoxy-6-*O*-trityl-D-*erythro*-hexose Diethyldithioacetal (13). A solution of **11** (5.36 g, 13.9 mmol) in 50% aqueous AcOH (70 mL) was stirred for 15 h. The solution was concentrated in vacuo with aid of toluene and EtOH to give crude **12** (4.92 g), which was used without purification.

To a stirred solution of the crude **12** in pyridine (80 mL) were added trityl chloride (7.75 g, 27.8 mmol) and DMAP (849 mg, 6.95 mmol). The mixture was stirred at 70 °C for 2.5 h. After removal of the solvent by concentration in vacuo, the residue was partitioned between EtOAc (200 mL) and H_2O (250 mL). The aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane + 1% Et_3N, then EtOAc/hexane, 1:10 + 1% Et_3N) to give 10.2 g of **13** as a pale yellow oil, which was contaminated by a small amount of trityl chloride but used for the next step. An analytical sample was obtained by further silica gel chromatography : TLC, R_f 0.40 (EtOAc/hexane, 1:4 with 1% Et_3N); $[\alpha]^{27}_D$ +12.4° (*c* 0.97); IR (neat) 3450, 3060, 3040, 2930, 2870, 1600, 1495, 1075 cm^{-1}; ^1H NMR (90 MHz) δ 1.23, 1.24 (2 t, each *J* =7.3 Hz, 3H x 2), 1.38-1.98 (m, 4H), 2.26-2.43 (br, 1H), 2.63, 2.67 (2 q, each *J* = 7.3 Hz, 2 H x 2), 2.88-3.27 (m, 2 H), 3.56-3.97 (m, 2 H), 3.93 (d, *J* = 4.2 Hz, 1 H), 4.55, 4.64 (ABq, *J* = 11.4 Hz, 2 H), 7.16-7.60 (m, 20 H). Anal. Calcd for $C_{36}H_{42}O_3S_2$: C, 73.63; H, 7.21. Found: C, 73.72; H, 7.23.

2-*O*-Benzyl-3,4-dideoxy-5-*O*-mesyl-6-*O*-trityl-D-*erythro*-hexose Diethyldithioacetal (14). To a cold (0 °C) stirred solution of **13** obtained above (10.2g) in pyridine (70 mL) was added mesyl chloride (1.60 mL, 20.9 mmol). After being stirred for 13 h at rt, the mixture was concentrated in vacuo. The residue was partitioned between EtOAc (300 mL) and H_2O (150 mL). The organic layer was washed with H_2O (150 mL x 2). The organic layer was dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:10 + 1% Et_3N) to give 7.96 g (86% from **11**) of **14** as a pale yellow oil: TLC, R_f 0.33 (EtOAc/hexane, 1:4 + 1% Et_3N); $[\alpha]^{28}_D$ +16.3° (*c* 0.87); IR (neat) 3060, 3040, 2970, 2940, 2870, 1600, 1490, 1450, 1355, 1260, 1220 cm^{-1}; ^1H NMR (90 MHz) δ 1.21, 1.22 (2 t, each *J* = 7.4 Hz, 3 H x 2), 1.56-1.87 (m 4 H), 2.63, 2.66 (2 q, each *J* = 7.4 Hz, 2 H x 2), 2.95 (s, 3 H), 3.08-3.43 (m, 2 H), 3.47-3.83 (m, 1 H), 3.90 (d, *J* = 4.3 Hz, 1 H), 4.49, 4.67 (ABq, *J* = 11.4 Hz, 2 H), 4.6-4.9 (m, 1 H), 7.03-7.63 (m, 20 H). Anal. Calcd for C $_{37}H_{44}O_5S_3$: C, 66.83; H, 6.67. Found: C, 66.48; H, 6.74.

5-Azido-2-*O*-benzyl-3,4,5-trideoxy-6-*O*-trityl-L-*threo*-hexose Diethyldithioacetal (15). A solution of **14** (7.96 g, 12.0 mmol) in DMF (80 mL) was heated at 70 °C for 24 h in the presence of sodium azide (3.90 g, 60.0 mmol) with vigorous stirring. The mixture was diluted with EtOAc (300 mL) and this was washed with H_2O (150 mL x 3). The organic layer was dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:80 +1% Et_3N) to give 6.65 g (91%) of **15** as a pale yellow oil: TLC, R_f 0.48 (EtOAc/hexane, 1:8 + 1% Et_3N); $[\alpha]^{27}_D$ +19.6° (*c* 0.98); IR (neat) 3060, 3040, 2970, 2940, 2870, 2100, 1600, 1490, 1450, 1375, 1340, 1265, 1220, 1155 cm^{-1}; ^1H NMR (90 MHz) δ 1.22, 1.24 (2 t, each *J* = 7.4 Hz, 3 H x 2), 1.46-1.97 (m, 4H), 2.63, 2.68 (2 q, each *J* =7.4 Hz, 2H x 2), 3.02-3.73 (m, 4 H), 3.91 (d, *J* = 4.2 Hz, 1 H), 4.51, 4.65 (ABq, *J* = 11.6 Hz, 2 H), 7.17-7.67 (m, 20 H). Anal. Calcd for $C_{36}H_{41}N_3O_2S_2$: C, 70.67; H, 6.57; N, 6.87. Found: C, 70.80; H, 6.77; N, 6.56.

2-*O*-Benzyl-5-(methoxycarbonyl)amino-3,4,5-trideoxy-6-*O*-trityl-L-*threo*-hexose Diethyldithioacetal (17). To a solution of **15** (6.65 g, 10.9 mmol) in a mixture of pyridine (70 mL) and H_2O (70 mL) was blown H_2S for 3 h. After the solution was kept standing for 2 days with a tight stopper, H_2S was bubbled again for 2 h. The solution was stirred for an additional 20 h. Then H_2S gas was excluded by blowing N_2 gas, and the mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (toluene + 1% Et_3N, then EtOH/toluene, 1:20 + 1% Et_3N) to give 6.05 g of amino derivative (**16**).

This crude **16** was dissolved in a mixture of acetone (90 mL) and H_2O (30 mL). To this solution were added K_2CO_3 (30 g) and methoxycarbonyl chloride (1.7 mL, 22 mmol). After being stirred for 2 h, the mixture was concentrated in vacuo. The residue was partitioned between EtOAc (200 mL) and H_2O (200 mL). The aqueous layer was extracted with EtOAc (200 mL x 2). The combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:7 + 1% Et_3N) to give 6.59 g (94%) of **17** as white crystals, mp 93.0-94.0 °C; TLC, R_f 0.32 (EtOAc/hexane, 1:4 + 1% Et_3N); $[\alpha]^{25}_D$ +36.0° (*c* 1.09); IR (KBr) 3300, 3080, 3050, 3020, 2960, 2940, 2920, 2880, 2840, 1695, 1530, 1490, 1440, 1330, 1300, 1280, 1250, 1220 cm^{-1}; ^1H NMR (90 MHz) δ 1.22, 1.24 (2 t, each *J* = 7.3 Hz, 3 H x 2), 1.43-1.97 (m, 4 H), 2.64, 2.68 (2 q, each *J* = 7.3 Hz, 2 H x 2), 2.97-3.15 (m, 2 H), 3.64 (s, 3 H), 3.6-3.7 (m, 2 H), 3.92 (d, *J* = 4.3 Hz, 1 H), 4.54, 4.68 (ABq, *J* = 11.6 Hz, 2 H), 4.79 (d, *J* = 9 Hz, 1H), 7.15-7.47 (m, 20 H). Anal. Calcd for $C_{38}H_{45}NO_4S_2$: C, 70.88; H, 7.04; N, 2.18. Found: C, 70.72; H, 7.00; N, 2.11.

***E* and *Z* Mixture of Ethyl (4*R*,7*R*)-4-benzyloxy-7-(methoxycarbonyl)amino-8-(trityloxy)oct-2-enoate (19*E* and 19*Z*).** To a cold (0 °C) stirred solution of **17** (1.48 g, 2.30 mmol) in a mixture of acetonitrile and H_2O (5:1, v/v, 30 mL) were added $CaCO_3$ (2.30 g, 23.0 mmol) and $HgCl_2$ (6.24 g, 23.0 mmol). After being stirred the mixture for 30 min , the resulting precipitates were removed by filtration through a Celite-pad, and washed well with EtOAc (200 mL). The combined filtrate and washing were washed with 1 N aqueous KI (80 mL x 3), 20% aqueous $Na_2S_2O_3$ (80 mL x 3), successively. The organic layer was dried and concentrated in vacuo to give crude **18** (1.36 g) as a pale yellow oil, which was subjected directly to the next step.

The following reaction was carried out under argon atmosphere. To a cold (0 °C) stirred suspension of NaH (60% emulsion in mineral oil, 166 mg, 6.90 mmol) in THF (10 mL) was added $(EtO)_2P(O)CH_2COOEt$ (1.37 mL, 6.90 mmol). After being stirred the mixture for 15 min, a solution of the crude **18** (1.36 g) in THF (20 mL) was added. The mixture was stirred for 30 min, and quenched by addition of saturated aqueous NH_4Cl (3 mL). The whole was diluted with EtOAc (200 mL), washed with H_2O (120 mL x 3). The organic layer was dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:5 + 1% Et_3N) to give 1.39 g (99%) of an inseparable mixture of **19*E*** and **19*Z*** as a colorless oil; TLC, R_f 0.60 (EtOAc/hexane, 1:2); IR (neat) 3350, 2950, 1715, 1655, 1445, 1260, 1090 cm^{-1}; ^1H NMR (270 MHz) for the major **19*E***; δ 1.29 (t, *J* = 7.1 Hz, 3 H), 1.50-1.75 (m, 4 H), 3.03 (dd, *J* = 4.0, 9.4 Hz, 1 H), 3.14 (dd, *J* = 4.0, 9.4 Hz, 1 H), 3.64 (s, 3 H), 3.68-3.73, 3.90-4.02 (2 m, 1 H x 2), 4.21 (q, *J* = 7.1 Hz, 2 H), 4.33, 4.57 (ABq, *J* = 11.7 Hz, 2 H), 4.81 (d, *J* = 8.8 Hz, 1 H), 6.00 (dd, *J* = 1.1, 15.8 Hz, 1 H), 6.81 (dd, *J* = 6.4, 15.8 Hz, 1 H), 7.15-7.50 (m, 20 H). Anal. Calcd for $C_{38}H_{41}NO_6$: C, 75.10; H, 6.80; N, 2.30. Found: C, 74.73; H, 6.77; N, 2.27.

(2*E*,4*R*,7*R*)-4-Benzyloxy-7-(methoxycarbonyl)amino-8-(trityloxy)oct-2-en-1-ol (20E) and the Z-isomer (20Z). The following reaction was carried out under argon atmosphere. To a cold (-78 °C) stirred solution of the mixture of **19*E*** and **19*Z*** (1.39 g, 2.29 mmol) obtained above in CH_2Cl_2 (30 mL) was added Dibal-H (1.5 M solution in toluene, 4.6 mL, 6.9 mmol). After being stirred for 90 min at -78 °C, the mixture was quenched with H_2O (2 mL). The whole was gradually warmed to rt. The resulting gels were removed by filtration, washed well with CH_2Cl_2. The combined filtrate and washing were washed with H_2O (120 mL). The aqueous layer was extracted with CH_2Cl_2 (100 mL x 2). The combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:2 + 1% Et_3N) to give 1.07 g (83%) of **20*E*** and 42 mg (3%) of **20*Z***. Compound **20*E*** as a pale yellow oil: TLC, R_f 0.39 (EtOAc/hexane, 1:1); $[\alpha]^{24}_D$ +26.6° (*c* 1.00); IR (neat) 3420, 3320, 3030, 2920, 2850, 1695, 1440, 1215 cm^{-1}; ^1H NMR (270 MHz) δ 1.17-1.85 (m, 5 H), 3.05 (dd, *J* = 4.4, 9.3 Hz, 1 H), 3.14 (dd, *J* = 3.8, 9.3 Hz, 1 H), 3.63 (s, 3 H), 3.58-3.83 (m, 2 H), 4.15 (dd, *J* = 1.3, 5.1 Hz, 2 H), 4.33, 4.55 (ABq, *J* = 11.7 Hz, 2 H), 4.85 (d, *J* = 9.2 Hz, 1 H), 5.58 (ddt, *J* = 7.7, 15.6, 1.3 Hz, 1 H), 5.82 (dt, *J* = 15.6, 5.1 Hz, 1 H), 7.17-7.45 (m, 20 H). Anal. Calcd for $C_{36}H_{39}NO_5$: C, 76.43; H, 6.95; N, 2.48. Found: C, 76.12; H, 6.89; N, 2.40. Compound **20*Z*** as a pale yellow oil: TLC, R_f 0.44 (EtOAc/hexane, 1:1); $[\alpha]^{23}_D$ +19.2° (*c* 1.07); IR (neat) 3425, 3320, 3010, 2940, 2920, 2850, 1690, 1500, 1440, 1215 cm^{-1}; ^1H NMR (270 MHz) δ 1.00-2.08 (m, 5 H), 3.06 (dd, *J* = 3.9, 9.3 Hz, 1 H), 3.13 (dd, *J* = 3.9, 9.3 Hz, 1H), 3.61 (s, 3 H), 3.64-4.26 (m, 4 H), 4.29, 4.54 (ABq, *J* = 11.7 Hz, 2 H), 4.92 (d, *J* = 8.8 Hz, 1 H), 5.42 (dd, *J* = 9.3, 11.3 Hz, 1 H), 5.84 (dt, *J* = 11.3, 7.0 Hz, 1 H), 7.18-7.49 (m, 20 H).

(2*E*,4*R*,7*R*)-4-Benzyloxy-1-chloro-7-(methoxycarbonyl)amino-8-(trityloxy)oct-2-ene (21*E*). To a stirred solution of **20*E*** (1.06 g, 1.87 mmol) in CH_2Cl_2 (20 mL) were added tosyl chloride (2.86 g, 15.0 mmol) and DMAP (914 mg, 7.48 mmol). After being stirred for 2 days, tosyl chloride (713 mg, 3.74 mmol) and DMAP (228 mg, 1.87 mmol) were added to the mixture. The mixture was stirred for additional 4 h, then diluted with CH_2Cl_2 (70 mL). The whole was washed with H_2O (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (70 mL x 2). The combined organic layers were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:8 + 1% Et_3N) to give 1.02 g (94%) of **21*E*** as a colorless oil: TLC, R_f 0.41 (EtOAc/hexane, 1:3); $[\alpha]^{24}_D$ + 32.9 ° (*c* 1.13) ; IR (neat) 3330, 3060, 3025, 2925, 2825, 1720, 1510, 1445, 1090 cm^{-1}; ^1H NMR (270 MHz) δ 1.26-1.70 (m, 4 H), 3.05 (dd, *J* = 4.0, 9.2 Hz, 1 H), 3.15 (dd, *J* = 3.3, 9.2 Hz, 1 H), 3.64 (s, 3 H), 3.74-3.82 (m, 2 H), 4.07 (d, *J* = 6.6 Hz, 2 H), 4.33, 4.56 (ABq, *J* = 11.9 Hz, 2 H), 4.81 (d, *J* = 8.4 Hz, 1 H), 5.66 (dd, *J* = 7.1, 15.0 Hz, 1 H), 5.81 (dt, *J* = 15.0, 6.6 Hz, 1 H), 7.17-7.45 (m, 20 H).

(2*Z*,4*R*,7*R*)-4-Benzyloxy-1-chloro-7-(methoxycarbonyl)amino-8-(trityloxy)oct-2-ene (21*Z*). As analogously described for **21*E***, 41.0 mg (74.1 μmol) of **20*Z*** was converted to the allylic chloride **21*Z*** by treatment of TsCl (totally 12 molar equivalents) in the presence of DMAP (totally 6 molar equivalents) for 2 days. Extractive workup and chromatography on silica gel gave 34.6 mg (80%) of **21*Z*** as a colorless oil: TLC, R_f 0.45 (EtOAc/hexane, 1:3); $[\alpha]\ ^{19}_D$ +23.9 ° (*c* 1.73); IR (neat) 3325, 3050, 3020, 2940, 2925, 2850, 1710, 1550, 1440, 1250, 1220 cm^{-1}; ^1H NMR (270 MHz) δ 1.20-1.80 (m, 4 H), 3.05 (dd, *J* = 4.0, 9.2 Hz, 1 H), 3.14 (dd, *J* = 4.0, 9.2 Hz, 1 H), 3.63 (s, 3 H), 3.67-3.80, 4.12-4.22 (2 m, 2 H x 2), 4.32,

4.57 (ABq, J = 11.7 Hz, 2 H), 4.81 (d, J = 8.4 Hz, 1 H), 5.52 (dd, J = 9.2, 10.8 Hz, 1 H), 5.82 (dt, J = 10.8, 8.1 Hz, 1 H), 7.20-7.48 (m, 20 H).

Inseparable Mixture of (2*S*,3*R*,6*R*)-3-Benzyloxy-1-(methoxycarbonyl)-6-(trityloxy)-methyl-2-vinylpiperidine (22*t*) and the 2*R* isomer (22*c*). From 21*E*. The following reaction proceeded most effectively in a 150 - 200 mg scale. Thus 345 mg of **21*E*** was divided into two portions. To a cold (0 °C) stirred solution of **21*E*** (173 mg, 296 μmol or 172 mg, 294 μmol) in THF (15 mL) were added NaH (60% emulsion in mineral oil, 28.4 mg, 0.71 mmol or 28.7 mg, 0.72 mmol), tetra-*n*-butylammonium iodide (113 mg, 307 μmol or 110 mg, 299 μmol), and tetrakis(triphenylphosphine)palladium (0) (70.5 mg, 61.0 μmol or 69.8 mg, 60.4 μmol). Each mixture was stirred for 4 days, and then combined. The reaction was quenched by addition of a few drops of H_2O, and the whole was diluted with EtOAc (100 mL). This was washed with 20% aqueous $Na_2S_2O_3$ (50 mL x 3). The organic layer was dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:10 + 1% Et_3N) to give 243 mg (75%) of the inseparable mixture of **22*t*** and **22*c*** as a colorless oil: TLC, R_f 0.58 (EtOAc/hexane, 1:3); IR (neat) 3075, 3050, 3020, 2950, 2850, 1690, 1480, 1440, 1380, 1310 cm^{-1}; ^1H NMR (270 MHz) for the major isomer **22*t*** δ 1.20-2.15 (m, 4 H), 3.43 (d, J = 7.3 Hz, 2 H), 3.58 (s, 3 H), 3.58-3.65, 4.00-4.15, 4.60-4.67 (3 m, 1 H x 3), 4.26, 4.33 (ABq, J = 12.1 Hz, 2 H), 5.14 (ddd, J = 1.1, 2.2, 17.2 Hz, 1 H), 5.18 (ddd, J = 1.1, 2.2, 10.6 Hz, 1 H), 5.79 (ddd, J = 4.8, 10.6, 17.2 Hz, 1 H), 7.08-7.48 (m, 20 H). Anal. Calcd for $C_{36}H_{37}NO_4$: C, 78.95; H, 6.81; N, 2.56. Found: C, 78.59; H, 6.80; N, 2.45.

From 21Z. As analogously, 25.9 mg (44 μmol) of **21Z** was converted into 11.7 mg (48%) of the mixture of **22*t*** and **22*c***.

***rac*-1,2-*O*-(Isopropylidene)hexan-1,2,6-triol (24).** To a stirred solution of 1,2,6-hexanetriol (**23**) (546 mg, 4.07 mmol) in acetone (10 mL) were added 2,2-dimethoxypropane (0.75 mL, 6.1 mmol) and DL-camphorsulfonic acid (193 mg, 0.830 mmol). The mixture was stirred for 30 min, and diluted with saturated aqueous $NaHCO_3$ (100 mL). This was extracted with CH_2Cl_2 (50 mL x 3). The combined extracts were dried and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:2) to give 637 mg (90%) of **24** as a colorless oil: TLC, R_f 0.50 (EtOH/toluene, 1:5); IR (neat) 3450, 2990, 2860, 1450, 1380, 1370, 1240, 1210, 1060 cm^{-1}; ^1H NMR (270 MHz) δ 1.36, 1.41 (2 s, 3 H x 2), 1.45-1.70 (m, 7 H), 3.51 (t, J = 6.9 Hz, 1 H), 3.66 (t, J = 6.2 Hz, 2 H), 4.02-4.14 (m, 2 H).

***rac*-6-Bis(ethylthio)-1,2-dihydroxyhexane (25).** To a cold (0 °C) stirred solution of **24** (625 mg, 3.59 mmol) in CH_2Cl_2 (12 mL) were added PCC (1.55 g, 7.19 mmol) and powdered molecular sieves 4A (0.97 g). The mixture was stirred for 30 min, and transferred to a short silica gel column. The column was eluted with excess Et_2O, and the elutes were concentrated to give 561 mg of aldehyde as a colorless oil, which was used for the next step.

To a cold (-15 °C) stirred solution of the above aldehyde (561 mg) in ethanethiol (4 mL) was added concentrated HCl (6 mL). The mixture was stirred at -15 °C for 4 h, then neutralized with aqueous ammonia, and diluted with H_2O (80 mL). This was extracted with CH_2Cl_2 (40 mL x 3). The combined extracts were dried and concentrated. The residue was chromatographed on silica gel (EtOH/toluene, 1:12) to give 541 mg (63%) of **25** as a colorless oil: TLC, R_f 0.41 (EtOH/toluene, 1:5); IR (neat) 3370, 2960, 2870, 1450, 1370,

1260, 1100 cm^{-1}; ^1H NMR (270 MHz) δ 1.26 (t, *J* = 7.3 Hz, 6 H), 1.42-1.88 (m, 6H), 2.17 (br s, 2 H), 2.59 (dq, *J* = 12.5 and 7.3 Hz, 2 H), 2.69 (dq, *J* = 12.5 and 7.3 Hz, 2 H), 3.45 (dd, *J* = 10.8 and 7.5 Hz, 1 H), 3.64-3.76 (m, 2 H), 3.79 (t, *J* = 6.8 Hz, 1 H). HRMS calcd for $C_{10}H_{22}O_2S_2$ (M^+) *m/z* 238.1060, found 238.1060.

***rac*-6-Bis(ethylthio)-2-hydroxy-1-(trityloxy)hexane (26).** To a stirred solution of **25** (527 mg, 2.21 mmol) in pyridine (10 mL) were added trityl chloride (1.23 g, 4.41 mmol) and DMAP (136 mg, 1.11 mmol). The mixture was stirred at 70 °C for 4 h and diluted with EtOAc (100 mL). This was washed with brine (50 mL x 3). The organic layer was dried and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:12 containing 1% Et_3N) to give 1.22 g (quantitatively) of **26** as a colorless oil: TLC, Rf 0.16 (EtOAc/hexane, 1:10); IR (neat) 3450, 3060, 2960, 2930, 2870, 1600, 1490, 1450, 1070 cm^{-1}; ^1H NMR (270 MHz) δ 1.23, 1.24 (2 t, each *J* = 7.5 Hz, 3 H x 2), 1.36-1.81 (m, 6 H), 2.30 (d, *J* = 2.6 Hz, 1 H), 2.55, 2.56 (2 dq, each *J* = 12.5 and 7.5 Hz, 1 H x 2), 2.64, 2.65 (2 dq, each *J* = 12.5 and 7.5 Hz, 1 H x 2), 3.03 (dd, *J* = 9.2 and 7.3 Hz, 1 H), 3.18 (dd, *J* = 9.2 and 3.3 Hz, 1 H), 3.70-3.82 (m, 1 H), 3.73 (t, *J* = 7.0 Hz, 1 H), 7.24-7.45 (m, 15 H).

***rac*-6-Bis(ethylthio)-2-(mesyloxy)-1-(trityloxy)hexane (27).** To a stirred solution of **26** (1.22 g) in pyridine (12 mL) was added mesyl chloride (0.34 mL, 4.4 mmol). The mixture was stirred for 2 h and diluted with EtOAc (100 mL). This was washed with brine (50 mL x 3). The organic layer was dried and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:15 containing 1% Et_3N) to give 1.07 g (86% from **25**) of **27** as a colorless oil: TLC, R_f 0.16 (EtOAc/hexane, 1:10); IR (neat) 3060, 3030, 2960, 2930, 2860, 1600, 1490, 1450, 1380, 1360, 1170 cm^{-1}; ^1H NMR (270 MHz) δ 1.23 (t, *J* = 7.5 Hz, 6 H), 1.46-1.82 (m, 6 H), 2.54, 2.55 (2 dq, each *J* = 12.5 and 7.5 Hz, 1 H x 2), 2.65, 2.66 (2 dq, each *J* = 12.5 and 7.5 Hz, 1 H x 2), 3.01 (s, 3 H), 3.27 (dd, *J* = 11.0 and 6.2 Hz, 1 H), 3.35 (dd, *J* = 11.0 and 3.5 Hz, 1 H), 3.71 (t, *J* = 7.1 Hz, 1 H), 4.71-4.78 (m, 1 H), 7.25-7.45 (m, 15 H). Anal. Calcd for $C_{30}H_{38}O_4S_3$: C, 64.48; H, 6.85. Found: C, 64.31; H, 6.97.

***rac*-2-Azido-6-bis(ethylthio)-1-(trityloxy)hexane (28).** To a solution of **27** (1.05 g, 1.88 mmol) in DMF (20 mL) was added sodium azide (612 mg, 9.41 mmol). The mixture was stirred at 70 °C for 15 h and diluted with EtOAc (100 mL). This was washed with brine (50 mL x 3), and the organic layer was dried and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:80 containing 1% Et_3N) to give 746 mg (79%) of **28** as a colorless oil: TLC, R_f 0.66 (EtOAc/hexane, 1:6); IR (neat) 3050, 3030, 2960, 2860, 2100, 1590, 1490, 1450, 1260, 1070 cm^{-1}; ^1H NMR (270 MHz) δ 1.23, 1.24 (2 t, each *J* = 7.5 Hz, 3 H x 2), 1.40-1.78 (m, 6 H), 2.55 (dq, *J* = 12.5 and 7.5 Hz, 2 H), 2.65, 2.66 (2 dq, each *J* = 12.5 and 7.5 Hz, 1 H x 2), 3.16 (dd, *J* = 9.5 and 6.6 Hz, 1 H), 3.22 (dd, *J* = 9.5 and 3.7 Hz, 1 H), 3.35-3.44 (m, 1 H), 3.71 (t, *J* = 7.0 Hz, 1 H), 7.24-7.48 (m, 15 H). Anal. Calcd for $C_{29}H_{35}N_3OS_2$: C, 68.87; H, 6.98; N, 8.31. Found: C, 69.08; H, 7.12; N, 7.96.

***rac*-6-Bis(ethylthio)-2-(methoxycarbonyl)amino-1-(trityloxy)hexane (30).** To a cold (0 °C) stirred solution of **28** (355 mg, 0.702 mmol) in THF (7 mL) was added $LiAlH_4$ (80.5 mg, 2.12 mmol). The mixture was stirred at rt for 90 min, quenched with H_2O (0.1 mL), and 10% aqueous NaOH (0.1 mL) and H_2O

(0.3 mL), successively. The resulting gels were removed by filtration and washed well with EtOAc. The combined filtrate and washings were washed with brine (50 mL). The aqueous layer was extracted with EtOAc (30 mL). The organic layers were combined, dried, and concentrated to give crude amine **29** (353 mg), which was used for the next step; TLC, R_f 0.53 (EtOH/toluene, 1:5).

To a cold (0 °C) stirred solution of the crude amine **29** (353 mg) in a mixture of H_2O (2 mL) and acetone (6 mL) were added K_2CO_3 (1.94 g, 14.0 mmol) and methyl chloroformate (0.11 mL, 1.4 mmol). The mixture was stirred at rt for 90 min and diluted with H_2O (80 mL). This was extracted with CH_2Cl_2 (40 mL x 3). The combined extracts were dried and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:12 containing 1% Et_3N) to give 274 mg (73%) of **30** as white crystals, mp 108-110 °C: TLC, R_f 0.35 (EtOAc/hexane, 1:4); IR (neat) 3320, 3050, 3020, 2920, 2860, 1710, 1590, 1500, 1480, 1440, 1220, 1080 cm^{-1}; ^1H NMR (270 MHz) δ 1.23, 1.24 (2 t, each J = 7.5 Hz, 3 H x 2), 1.45-1.86 (m, 6 H), 2.55, 2.56 (2 dq, each J = 12.5 and 7.5 Hz, 1 H x 2), 2.66 (dq, J = 12.5 and 7.5 Hz, 2 H), 3.10 (dd, J = 9.2 and 3.7 Hz, 1 H), 3.17 (dd, J = 9.2 and 3.7 Hz, 1 H), 3.65 (s, 3 H), 3.67-3.80 (m, 1 H), 3.72 (t, J = 7.0 Hz, 1 H), 4.81 (d, J = 8.4 Hz, 1 H), 7.23-7.43 (m, 15 H). Anal. Calcd for $C_{31}H_{39}NO_3S_2$: C, 69.24; H, 7.31; N, 2.60. Found: C, 69.14; H, 7.54; N, 2.58.

***rac*-(*E*)-Ethyl 7-(methoxycarbonyl)amino-8-(trityloxy)-2-octenoate (31).** To a cold (0 °C) stirred solution of **30** (244 mg, 0.453 mmol) in a mixture of H_2O and acetonitrile (1:5, 10 mL) were added $CaCO_3$ (458 mg, 4.58 mmol) and $HgCl_2$ (1.24 g, 4.57 mmol). The mixture was stirred at rt for 30 min. The resulting precipitates were removed by filtration through a Celite-pad and washed well with EtOAc. The combined filtrate and washings were washed with 1 M aqueous KI (30 mL x 3) and 20% aqueous $Na_2S_2O_3$ (30 mL x 3), successively. The organic layer was dried and concentrated to give crude aldehyde (203 mg), which was subjected directly to the next step.

To a cold (0 °C) stirred suspension of NaH (60% dispersion in mineral oil, 57 mg, 1.4 mmol) in THF (3 mL) was added triethyl phosphonoacetate (0.27 mL, 1.4 mmol) under Ar. The mixture was stirred at rt for 15 min, and a solution of the above aldehyde (203 mg) in THF (2 mL) was added at 0 °C. The mixture was stirred at rt for 30 min, quenched with saturated aqueous NH_4Cl (1 mL), and diluted with H_2O (60 mL). This was extracted with CH_2Cl_2 (30 mL x 3). The combined extracts were dried and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:6 containing 1% Et_3N) to give 228 mg (100%) of **31** as a colorless oil: TLC, R_f 0.16 (EtOAc/hexane, 1:4); IR (neat) 3340, 3050, 3020, 2980, 2950, 2860, 1710, 1650, 1590, 1530, 1450, 1270, 1190, 1090 cm^{-1}; ^1H NMR (270 MHz) δ 1.28 (t, J = 7.1 Hz, 3 H), 1.34-1.69 (m, 4 H), 2.14-2.22 (m, 2 H), 3.08 (dd, J = 9.2 and 3.7 Hz, 1 H), 3.18 (dd, J = 9.2 Hz and 3.7 Hz, 1 H), 3.66 (s, 3 H), 3.70-3.82 (m, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 4.81 (d, J = 8.4 Hz, 1 H), 5.78 (dt, J = 15.6 and 1.5 Hz, 1 H), 6.90 (dt, J = 15.6 and 7.0 Hz, 1 H), 7.23-7.42 (m, 15 H).

***rac*-(*E*)-7-(Methoxycarbonyl)amino-8-(trityloxy)-2-octen-1-ol (32).** To a cold (-78 °C) stirred solution of **31** (212 mg, 0.423 mmol) in CH_2Cl_2 (4 mL) was added Dibal-H (1.5 M solution in toluene, 0.59 mL, 0.89 mmol) under Ar. The mixture was stirred at -78 °C for 30 min and quenched with H_2O (0.5 mL). The resulting gels were removed by filtration through a Celite pad and washed with CH_2Cl_2. The combined filtrate and washing were washed with H_2O (60 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL x 2). The combined extracts were dried and concentrated. The residue was purified by chromatography on silica

gel (EtOAc/hexane, 1:2 containing 1% Et_3N) to give 171 mg (88%) of **32** as a colorless oil: TLC, R_f 0.10 (EtOAc/hexane, 1:2); IR (neat) 3450, 3330, 3050, 3020, 2940, 2850, 1700, 1590, 1530, 1490, 1450, 1220, 1090 cm^{-1}; ^1H NMR (270 MHz) δ 1.30-1.69 (m, 5 H), 1.98-2.07 (m, 2 H), 3.08 (dd, J = 9.2 and 3.8 Hz, 1 H), 3.17 (dd, J = 9.2 and 3.3 Hz, 1 H), 3.65 (s, 3 H), 3.72-3.82 (m, 1 H), 4.06 (d, J = 2.2 Hz, 2 H), 4.82 (d, J = 8.4 Hz, 1 H), 5.56-5.70 (m, 2 H), 7.23-7.43 (m, 15 H).

***rac*-(*E*)-1-Chloro-7-(methoxycarbonyl)amino-8-(trityloxy)-2-octene (33).** To a stirred solution of **32** (156 mg, 0.339 mmol) in CH_2Cl_2 (4 mL) were added tosyl chloride (650 mg, 3.41 mmol) and DMAP (209 mg, 1.71 mmol). The mixture was stirred for 64 h and diluted with H_2O (40 mL). This was extracted with CH_2Cl_2 (20 mL x 3). The combined extracts were dried and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:9 containing 1% Et_3N) to give 145 mg (90%) of **33** as a colorless oil: TLC, R_f 0.32 (EtOAc/hexane, 1:4); IR (neat) 3330, 3050, 3020, 2950, 2860, 1710, 1590, 1510, 1490, 1450, 1250, 1080 cm^{-1}; ^1H NMR (270 MHz) δ 1.26-1.66 (m, 4 H), 2.04 (q, J = 7.0 Hz, 2 H), 3.08 (dd, J = 9.3 and 4.0 Hz, 1 H), 3.17 (dd, J =9.3 and 3.7 Hz, 1 H), 3.66 (s, 3 H), 3.70-3.81 (m, 1 H), 4.01 (dd, J = 6.6 and 0.9 Hz, 2 H), 4.80 (d, J = 8.8 Hz, 1 H), 5.58 (dtt, J = 15.0, 7.0 and 0.9 Hz, 1 H), 5.72 (dt, J = 15.0 and 6.6 Hz, 1 H), 7.23-7.42 (m, 15 H).

Mixture of *rac-trans* and *cis*-1-(methoxycarbonyl)-2-(trityloxy)methyl-6-vinylpiperidines (34*t* and 34*c*). To a cold (0 °C) stirred solution of **33** (133 mg, 0.278 mmol) in THF (14 mL) were added sodium hydride (60% dispersion in mineral oil, 37 mg, 0.94 mmol), tetrabutylammonium iodide (105 mg, 0.284 mmol), and tetrakis(triphenylphosphine)palladium (68 mg, 0.059 mmol). The mixture was stirred for 27 h and quenched with H_2O (1 mL). This was diluted with EtOAc (50 mL), and the whole was washed with brine (20 mL x 3). The organic layer was dried and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:12 containing 1% Et_3N) to give 97.3 mg (79%) of the inseparable mixture of **34*t*** and **34*c*** as a colorless oil: TLC, R_f 0.39 (EtOAc/hexane, 1:4); IR (neat) 3050, 3020, 2950, 2860, 1690, 1590, 1490, 1440, 1380, 1310, 1070 cm^{-1}; ^1H NMR (270 MHz) δ 1.25-2.02 (m, 6 H), 2.91-3.37 (m, 2 H), 3.61 (s, 3 H x 2/3), 3.72 (s, 3 H x 1/3), 4.20-4.30, 4.55-4.68 (2 m, total 2 H), 4.73 (d, J = 10.6 Hz, 1 H x 1/3), 4.87 (d, J = 17.2 Hz, 1 H x 1/3), 5.07 (d, J = 17.2 Hz, 1 H x 2/3), 5.08 (d, J = 10.6 Hz, 1 H x 2/3), 5.46 (ddd, J = 17.2, 10.6, 4.9 Hz, 1 H x 1/3), 5.87 (ddd, J = 17.2, 10.6, 4.9 Hz, 1 H x 2/3), 7.23-7.42 (m, 15 H).

rac-trans* and *cis*-2-Vinyl-1-aza-8-oxabicyclo[4.3.0]nonan-9-ones (35 and 36).** To a stirred solution of the mixture of **34*t and **34*c*** (77.3 mg, 0.175 mmol) in MeOH (2 mL) was added *p*-toluenesulfonic acid (monohydrate, 34.0 mg, 0.179 mmol). The mixture was stirred for 1 h and diluted with saturated aqueous $NaHCO_3$ (30 mL). This was extracted with CH_2Cl_2 (15 mL x 3). The combined extracts were dried and concentrated to give 78 mg of a mixture of crude de-*O*-trityl derivatives as a colorless oil, which was used for the next step: TLC, R_f 0.21 (EtOAc/hexane, 1:2).

To a stirred solution of the above mixture (78 mg) in THF (2 mL) was added sodium hydride (60% dispersion in mineral oil, 21 mg, 0.52 mmol). The mixture was refluxed for 1 h and quenched with EtOH (0.2 mL). This was diluted with H_2O (20 mL). The whole was extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were dried and concentrated. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:3) to give 15.1 mg (52%) of **35** and 9.9 mg (34%) of **36** both as a colorless oil. Compound **35**: TLC, R_f 0.34

(EtOAc/hexane, 1:1); IR (neat) 2940, 2860, 1750, 1410, 1260, 1040 cm^{-1}; ^1H NMR (270 MHz) δ 1.25-1.84 (m, 6 H), 3.78-3.90 (m, 1 H), 3.90 (t, *J* = 7.3 Hz, 1 H), 4.42 (t, *J* = 7.3 Hz, 1 H), 4.56-4.62 (m, 1 H), 5.18 (dt, *J* = 16.9 and 1.1 Hz, 1 H), 5.26 (dt, *J* = 10.6 and 1.1 Hz, 1 H), 5.76 (ddd, *J* = 16.9, 10.6, 4.0 Hz, 1 H). HRMS calcd for $C_9H_{13}NO_2$ (M^+) *m/z* 167.0945, found 167.0937. Compound **36**: TLC, R_f 0.31 (EtOAc/hexane, 1:1); IR (neat) 2940, 2850, 1750, 1400, 1310, 1250, 1040 cm^{-1}; ^1H NMR (270 MHz) δ 1.25-1.98 (m, 6 H), 3.52-3.66 (m, 2 H), 3.83 (t, *J* = 8.4 Hz, 1 H), 4.36 (dd, *J* = 8.4 and 7.5 Hz, 1 H), 5.16 (dt, *J* = 10.3 and 1.1 Hz, 1 H), 5.20 (dt, *J* = 17.2 and 1.1 Hz, 1 H), 6.29 (ddd, *J* = 17.2, 10.3, 8.1 Hz, 1 H). HRMS calcd for $C_9H_{13}NO_2$ (M^+) *m/z* 167.0945, found 167.0939.

(1*S*,2*R*,5*R*)-2-Benzyloxy-5-(trityloxy)methyl-6-aza-8-oxabicyclo[4.3.0]nonan-7-one (38) and the 1*R* isomer (39). To a cold (-78 °C) stirred solution of the mixture of **22*t*** and **22*c*** (191 mg, 349 μmol) in a mixture of CH_2Cl_2 and MeOH (1:1, v/v, 6 mL) was blown ozone (ca.3% in O_2) for 30 min. Then triphenylphosphine (137 mg, 524 μmol) was added to the solution. After being stirred for 15 min, $NaBH_4$ (40.5 mg, 1.07 mmol) was added to the mixture. The mixture was stirred at 0 °C for 2h, and neutralized with Amberlite IR-120 [H^+]. The resin was removed by filtration and washed well with CH_2Cl_2. The combined filtrate and washing were concentrated in vacuo to give crude mixture of **37*t*** and **37*c***, which was used for the next step directly.

A solution of the mixture obtained above in THF (4 mL) was heated under reflux for 1 h in the presence of NaH (60% emulsion in mineral oil, 28.5 mg, 713 μmol). The mixture was quenched with EtOH (3 drops), diluted with H_2O (30 mL), and the whole was extracted with CH_2Cl_2 (20 mL x 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:4 + 1% Et_3N) to give 155 mg (86%) of **38** and 11 mg (6%) of **39**. Compound **38** as a pale yellow oil: TLC, R_f 0.57 (EtOAc/hexane, 1:2); $[\alpha]^{21.5}_D$ -32.0° (*c* 0.66); IR (neat) 3075, 3050, 3020, 2920, 2860, 1750, 1480, 1440, 1410, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 1.15-1.35, 1.61-1.72, 1.85-1.95, 2.00-2.10 (4 m, 1 H x 4), 3.13 (dd, *J* = 6.6, 9.2 Hz, 1 H), 3.17 (ddd, *J* = 4.0, 9.5, 10.6 Hz, 1 H), 3.27 (dd, *J* = 7.0, 9.2 Hz, 1 H), 3.34 (ddd, *J* = 4.8, 8.1, 9.5 Hz, 1 H), 4.00 (dd, *J* = 4.8, 8.8 Hz, 1 H), 4.18 (ddd, *J* = 6.6, 6.8, 7.0 Hz, 1 H), 4.31 (dd, *J* = 8.1, 8.8 Hz, 1 H), 4.37, 4.61 (ABq, *J* = 11.7 Hz, 2 H), 7.13-7.50 (m, 20 H). Compound **39** as white crystals, mp 163-164°C :TLC, R_f 0.41 (EtOAc/hexane, 1:2); $[\alpha]^{19}_D$ +24.0° (*c* 0.59); IR (neat) 3090, 3060, 3030, 2960, 2930, 2870, 1750, 1590, 1490, 1470, 1450, 1220 cm^{-1}; ^1H NMR (270 MHz) δ 1.35-2.30 (m, 4 H), 3.21-3.35 (m, 1 H), 3.42-3.47 (m, 1 H), 3.62 (ddd, *J* = 2.4, 5.7, 8.1 Hz, 1 H), 3.64 (dd, *J* = 9.2, 9.5 Hz, 1 H), 4.07 (dd, *J* = 4.0, 9.5 Hz, 1 H), 4.12 (t, *J* = 8.1 Hz, 1 H), 4.20 (dd, *J* = 5.7, 8.1 Hz, 1 H), 4.36, 4.67 (ABq, *J* = 12.3 Hz, 2 H), 7.13-7.50 (m, 20 H).

(1*S*,2*R*,5*R*)-2-Benzyloxy-5-hydroxymethyl-6-aza-8-oxabicyclo[4.3.0]nonan-7-one (40). To a cold (0 °C) stirred solution of **38** (155 mg, 299 μmol) in MeOH (3 mL) was added *p*-toluenesulfonic acid (monohydrate 58.8 mg, 309 μmol). After being stirred at rt for 90 min, the mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL). This was extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/toluene, 1:1) to give **40** (81.6 mg, 98%) as a colorless oil: TLC, R_f 0.13 (EtOAc/toluene, 1:1); $[\alpha]^{24}_D$ -74.5° (*c* 0.87); IR (neat) 3400, 2930, 2870, 1730, 1420, 1250, 1070 cm^{-1}; ^1H NMR (270 MHz) δ 0.70-1.92 (m, 3 H), 2.17 (dq, *J* = 12.5, 3.9 Hz, 1 H), 2.28 (br, 1 H), 3.25 (td, *J* = 10.0, 3.9 Hz, 1 H), 3.60-4.02 (m, 4 H), 4.05 (dd, *J* = 5.7,

9.0 Hz, 1 H), 4.45 (dd, J = 8.2, 9.0 Hz, 1 H), 4.43, 4.67 (ABq, J = 11.4 Hz, 2 H), 7.21-7.42 (m, 5 H). HRMS calcd for $C_{15}H_{20}NO_4$ ($M+H^+$) m/z 278.1390, found 278.1381.

(1*S*,2*R*,5*R*)-2-Benzyloxy-5-[(*Z*)-1-dodecenyl]-6-aza-8-oxabicyclo[4.3.0]nonan-7-one (42*Z*) and its *E*-isomer (42*E*). The following reaction was carried out under argon atmosphere. To a cold (-78 °C) stirred mixture of oxalyl chloride (0.16 mL, 1.8 mmol) and DMSO (0.25 mL, 3.2 mmol) in CH_2Cl_2 (1 mL) was added a solution of **40** (99.0 mg, 357 μmol) in CH_2Cl_2 (2 mL). After being stirred at -78 °C for 45 min, triethylamine (0.75 mL, 5.3 mmol) was added to the mixture. The mixture was warmed gradually to rt and stirred for 1 h. The mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were dried and concentrated in vacuo to give crude **41** as a pale yellow oil, which was used for the next step directly.

Undecyl(triphenylphosphonium) bromide was prepared as follows. A mixture of 1-bromoundecane (4.50 mL, 20.1 mmol) and triphenylphosphine (5.26 g, 20.1 mmol) was heated at 100 °C for 12 h. The mixture was diluted with H_2O (600 mL), and the aqueous solution was washed with Et_2O (200 mL x 2). The ethereal layer was extracted with H_2O (150 mL). The combined aqueous layers were concentrated in vacuo by coevaporation with EtOH to give the phosphonium salt (9.22 g, 92%) as a pale yellow oil, which was used for the next step: ^1H NMR (90 MHz) δ 0.86 (t, J = 6 Hz, 3 H), 1.21 (br s, 16 H), 1.60-1.66 (m, 2 H), 3.60-3.90 (m, 2 H), 7.70-8.00 (m, 15 H).

The ylide of the above phosphonium salt was prepared as follows. A suspension of the salt (1.50 g, 3.01 mmol) and sodium amide (122 mg, 3.13 mmol) in THF (10 mL) was heated under reflux for 2 h, and cooled to rt. The deep orange colored supernatant was transferred by syringe for the following Wittig reaction.

To a cold (0 °C) stirred solution of the crude **41** obtained above in THF (2 mL) was added the above ylide solution (5 mL). The mixture was stirred at 0 °C for 10 min, and quenched with saturated aqueous NH_4Cl (20 mL). This was extracted with Et_2O (10 mL x 3). The combined ethereal extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:9) to give 72.5 mg (49%) of **42*Z*** and 3.8 mg (3%) of **42*E***. Compound **42*Z*** as a colorless oil: TLC, R_f 0.38 (EtOAc/hexane, 1:3); $[\alpha]^{22}_D$ -84.9° (*c* 0.62); IR (neat) 2950, 2850, 1750, 1450, 1400, 1220, 1100, 1070 cm^{-1}; ^1H NMR (270 MHz) δ 0.88 (t, J = 6.8 Hz, 3 H), 1.26 (br s, 16 H), 1.15-1.40, 1.52-1.80, 2.08-2.24 (3 m, 6 H), 3.25 (td, J = 9.8, 4.0 Hz, 1 H), 3.65 (ddd, J = 4.8, 8.2, 9.8 Hz, 1 H), 4.06 (dd, J = 4.8, 8.9 Hz, 1 H), 4.35 (dd, J = 8.2, 8.9 Hz, 1 H), 4.44, 4.68 (AB q, J = 11.5 Hz, 2 H), 4.71-4.78 (m, 1 H), 5.50-5.62 (m, 2 H), 7.18-7.42 (m, 5 H). HRMS calcd for $C_{26}H_{40}NO_3$ ($M+H^+$) m/z 414.3006, found 414.3016. Compound **42*E*** as a colorless oil: TLC, R_f 0.28 (EtOAc/hexane, 1:3); $[\alpha]^{23.5}_D$ -88.1° (*c* 0.19); IR (neat) 2930, 2850, 1760, 1450, 1410, 1250, 1220, 1100 cm^{-1}; ^1H NMR (270 MHz) δ 0.88 (t, J = 6.4 Hz, 3 H), 1.26 (br s, 16 H), 1.70-1.86, 2.00-2.21 (2 m, 6 H), 3.24 (td, J = 10.1, 3.8 Hz, 1 H), 3.64 (ddd, J = 4.9, 8.8, 10.1 Hz, 1 H), 4.04 (dd, J = 4.9, 9.2 Hz, 1 H), 4.40 (dd, J = 8.8, 9.2 Hz, 1 H), 4.42, 4.67 (AB q, J = 11.7 Hz, 2 H), 4.46-4.51 (m, 1 H), 5.36 (dd, J = 4.2, 15.4 Hz, 1 H), 5.62 (dt, J = 15.4, 6.4 Hz, 1 H), 7.26-7.36 (m, 5 H). HRMS calcd for $C_{26}H_{38}NO_3$ ($M-H^+$) m/z 412.2849, found 412.2846.

(1*S*,2*R*,5*S*)-5-Dodecyl-2-hydroxy-6-aza-8-oxabicyclo[4.3.0]nonan-7-one (43). From 42*Z*. A solution of **42*Z*** (53.4 mg, 129 μmol) in MeOH containing conc. HCl solution (50:1, v/v, 1 mL) was hydrogenated under atmospheric H_2 gas in the presence of 10% palladium on charcoal (27 mg) for 1 h. The

catalyst was removed by filtration through a Celite-pad, and washed well with EtOAc. The combined filtrate and washing were washed with saturated aqueous $NaHCO_3$ (15 mL x 3). The organic layer was dried and concentrated in vacuo. The residue was chromatographed on silica gel (EtOAc/hexane, 1:2) to give 41.9 mg (quantitatively) of **43** as white crystals, mp 103-104 °C: TLC, R_f 0.27 (EtOAc/hexane, 1:1); $[\alpha]^{24}_D$ -18.6° (*c* 0.44); IR ($CHCl_3$) 3610, 3410, 3020, 2930, 2860, 1740, 1460, 1420, 1230 cm^{-1}; ^1H NMR (270 MHz) δ 0.88 (t, *J* = 6.4 Hz, 3 H), 1.26 (br s, 20 H), 1.39-1.47, 1.58-1.67, 1.90-1.95 (3 m, 7 H), 3.41-3.53, 3.85-3.92 (2 m, 3 H), 4.24 (dd, *J* = 3.8, 9.2 Hz, 1 H), 4.41 (dd, *J* = 7.9, 9.2 Hz, 1 H). HRMS calcd for $C_{19}H_{35}NO_3$ (M^+) *m/z* 325.2614, found 325.2610.

From 42*E*. As analogously, 3.5 mg (8.5 μmol) of **42*E*** was converted to 2.0 mg (71%) of **43**.

(2*S*,3*R*,6*S*)-6-Dodecyl-3-hydroxy-2-(hydroxymethyl)piperidine, (-)-Desoxoprosopinine (6). A solution of **43** (9.7 mg, 30 μmol) in a mixture of EtOH (1 mL) and 8 M aqueous KOH (1 mL) was heated at 100 °C for 24 h. The solution was diluted with H_2O (20 mL), and this was extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOH/toluene, 1:5, then EtOH/toluene, 1:5 + 3% Et_3N) to give 7.2 mg (80%) of **6** as white crystals, mp 89.0-89.5 °C [lit.[7a,b] 89.5 °C]: TLC, R_f 0.20 (CH_2Cl_2/MeOH, 5:1); $[\alpha]^{21.5}_D$ -15.9° (*c* 0.28) [lit.[7a,b] $[\alpha]_D$ -14.7° (*c* 0.30)]; IR ($CHCl_3$) 3600, 3380, 3020, 2930, 2860, 1470, 1240 cm^{-1}; ^1H NMR (270 MHz) δ 0.88 (t, *J* = 6.4 Hz, 3 H), 1.26 (br s, 22 H), 1.48-1.75 (m, 4 H), 2.54 (br s, 2 H), 2.77-2.90 (m, 2 H), 3.51-3.57 (m, 1 H), 3.61 (dd, *J* = 7.3, 10.4 Hz, 1 H), 3.67 (dd, *J* = 5.1, 10.4 Hz, 1 H); ^{13}C NMR (100 MHz) δ 14.1, 22.7, 26.3, 26.7, 26.8, 28.3, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 31.9, 33.5, 50.2, 58.3, 61.5, 67.3. HRMS calcd for $C_{18}H_{37}NO_2$ (M^+) *m/z* 299.2822, found 299.2840.

(2*S*,3*R*,6*R*)-3-Benzyloxy-1-(methoxycarbonyl)-2-(methoxymethoxy)methyl-6-(trityloxy)-methylpiperidine (44) and its 2*R*-isomer (45). To a cold (-78 °C) solution of mixture of **22*t*** and **22*c*** (133 mg, 242 μmol) in a mixture of MeOH and CH_2Cl_2 (1:1, v/v, 3 mL) was blown ozone for 15 min. To the solution was added triphenylphosphine (92.2 mg, 352 μmol), and the mixture was stirred at - 78 °C for 30 min. Then $NaBH_4$ (26.3 mg, 695 μmol) was added to the mixture. After being stirred for 0 °C for 3 h, the mixture was neutralized by addition of Amberlite IR-120 [H^+]. The resin was removed by filtration, washed well with CH_2Cl_2. The combined filtrate and washing were concentrated in vacuo to give 243 mg of crude mixture of **37*t*** and **37*c*** as a colorless oil, which was used for the next step directly.

To a cold (0°C) stirred solution of the crude mixture (243 mg) in CH_2Cl_2 (3 mL) were added chloromethyl methyl ether (0.19 mL, 2.4 mmol) and *i*-Pr_2NEt (0.85 mL, 4.9 mmol). The mixture was stirred at rt for 16 h, and diluted with brine (20 mL). This was extracted with CH_2Cl_2 (15 mL x 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:6 + 1% Et_3N) to give 110 mg (76%) of **44** and 9.5 mg (7%) of **45**. Compound **44** as a pale yellow oil: TLC, R_f 0.29 (EtOAc/hexane, 1:3); $[\alpha]^{17}_D$ +32.2° (*c* 0.56); IR (neat) 3060, 3020, 2950, 1700, 1600, 1490, 1450, 1380, 1320 cm^{-1}; ^1H NMR (270 MHz) δ 1.57-1.85, 2.08-2.17 (2 m, 4 H), 3.29 (s, 3 H), 3.42-3.68 (m, 4 H), 3.58 (s, 3 H), 3.72-3.75, 3.92-3.97, 4.14-4.21 (3 m, 1 H x 3), 4.27, 4.32 (ABq, *J* = 12.1 Hz, 2 H), 4.55, 4.60 (ABq, *J* = 6.6 Hz, 2 H), 7.10-7.45 (m, 20 H). Anal. Calcd for $C_{37}H_{41}NO_6$: C, 74.60; H, 6.94; N, 2.35. Found: C, 74.25; H, 6.86; N, 2.35. Compound **45** as a pale yellow oil: TLC, R_f 0.35 (EtOAc/hexane, 1:3); $[\alpha]^{17}_D$ +51.1° (*c* 0.48); IR (neat) 2950, 2880, 1700, 1490, 1450, 1360, 1340, 1320, 1290 cm^{-1}; ^1H NMR (270

MHz) δ 1.26-1.31, 1.57-1.64, 1.94-2.01 (3 m, 4 H), 3.01-3.23, 3.46-3.54 (2 m, 5 H), 3.11 (s, 3 H), 3.73 (s, 3 H), 4.27, 4.36 (ABq, J = 6.4 Hz, 2 H), 4.45, 4.60 (ABq, J = 11.7 Hz, 2 H), 4.47-4.68 (m, 2 H), 7.22-7.45 (m, 20 H).

(2*S*,3*R*,6*R*)-3-Benzyloxy-6-hydroxymethyl-1-(methoxycarbonyl)-2-(methoxymethoxy)-methylpiperidine (46). To a cold (0 °C) stirred solution of **45** (110 mg, 184 μmol) in MeOH (2 mL) was added *p*-toluenesulfonic acid (monohydrate 37.6 mg, 198 μmol). After being stirred at rt for 1 h, the mixture was diluted with saturated aqueous $NaHCO_3$ (20 mL). This was extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:2) to give 61.0 mg (94%) of **46** as a pale yellow oil: TLC, R_f 0.10 (EtOAc/hexane, 1:2); $[\alpha]^{24}_D$ +22.2° (*c* 0.91); IR (neat) 3450, 2930, 1700, 1460, 1260, 1100, 1030 cm^{-1}; ^1H NMR (270 MHz) δ 1.48-1.57, 1.75-2.07 (2 m, 5 H), 3.34 (s, 3 H), 3.50-3.74, 3.85-3.87, 4.54-4.63 (3 m, 7 H), 3.67 (s, 3 H), 4.51, 4.58 (ABq, J = 11.5 Hz, 2 H), 4.60 (s, 2 H), 7.26-7.34 (m, 5 H). HRMS calcd for $C_{18}H_{27}NO_6$ (M^+) *m/z* 353.1836, found 353.1854.

(2*S*,3*R*,6*S*)-3-Benzyloxy-6-[(*Z*)-1-dodecenyl]-1-(methoxycarbonyl)-2-(methoxymethoxy)-methylpiperidine (48). The following reaction was carried out under argon atmosphere. To a cold (-78 °C) stirred mixture of oxalyl chloride (0.085 mL, 0.97 mmol) and DMSO (0.14 mL, 2.0 mmol) in CH_2Cl_2 (1 mL) was added a solution of **46** (33.0 mg, 93 μmol) in CH_2Cl_2 (1 mL). After being stirred at -78 °C for 45 min, triethylamine (0.39 mL, 2.8 mmol) was added to the mixture. The mixture was warmed gradually to rt and stirred for 1 h. The mixture was diluted with H_2O (30 mL) and extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were dried and concentrated in vacuo to give crude **47** as a pale yellow oil, which was used for the next step directly.

To a cold (0 °C) stirred solution of the crude **47** obtained above in THF (1 mL) was added the aforementioned undecenetriphenylphosphorane solution (1.3 mL). The mixture was stirred at 0 °C for 10 min, and quenched with saturated aqueous NH_4Cl (20 mL). This was extracted with Et_2O (10 mL x 3). The combined ethereal extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:7) to give 27.1 mg (59%) of **48** as a pale yellow oil: TLC, R_f 0.37 (EtOAc/hexane, 1:6); $[\alpha]^{24}_D$ +56.5° (*c* 1.36); IR (neat) 2980, 2850, 1700, 1500, 1460, 1400, 1360, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 0.88 (t, J = 6.6 Hz, 3 H), 1.26 (br s, 16 H), 1.70-1.92 (m, 4 H), 2.11-2.19 (m, 2 H), 3.32 (s, 3 H), 3.51-3.54 (m, 2 H), 3.68 (s, 3 H), 3.68-3.73, 4.50-4.62 (2 m, 1 H x 2), 4.52, 4.60 (ABq, J = 12.1 Hz, 2 H), 4.58, 4.63 (ABq, J = 6.6 Hz, 2 H), 4.95-5.00 (m, 1 H), 5.38-5.41 (m, 2 H), 7.26-7.34 (m, 5 H). HRMS calcd for $C_{29}H_{47}NO_5$ (M^+) *m/z* 489.3451, found 489.3427.

(2*S*,3*R*,6*R*)-3-Benzyloxy-6-dodecyl-1-(methoxycarbonyl)-2-(methoxymethoxy)methyl-piperidine (49). A solution of **48** (14.0 mg, 29 μmol) in EtOH (1 mL) was hydrogenated under atmospheric H_2 gas in the presence of 10% palladium on charcoal (7.0 mg) for 2 h. The catalyst was removed by filtration through a Celite-pad, and washed well with EtOH. The combined filtrate and washing were concentrated in vacuo. The residue was chromatographed on silica gel (EtOAc/hexane, 1:12) to give 11.1 mg (79%) of **49** as a colorless oil: TLC, R_f 0.37 (EtOAc/hexane, 1:6); $[\alpha]^{21}_D$ +12.1° (*c* 1.28); IR (neat) 2940, 2850, 1690, 1460, 1400, 1360, 1150 cm^{-1}; ^1H NMR (270 MHz) δ 0.88 (t, J = 6.6 Hz, 3 H), 1.26 (br s, 22 H), 1.70-

1.92 (m, 4 H), 3.33 (s, 3 H), 3.48 (d, J = 7.3 Hz, 2 H), 3.69 (s, 3 H), 3.66-3.72, 4.07-4.15, 4.49-4.67 (3 m, 1 H x 3), 4.52, 4.59 (ABq, J = 11.6 Hz, 2 H), 4.57, 4.62 (ABq, J = 6.4 Hz, 2 H), 7.26-7.34 (m, 5 H). HRMS calcd for $C_{29}H_{49}NO_5$ (M^+) *m/z* 491.3607, found 491.3568.

(2*S*,3*R*,6*R*)-3-Benzyloxy-6-dodecyl-2-(methoxymethoxy)methylpiperidine (50). A solution of **49** (25.3 mg, 48 μmol) in 3 M KOH / ethylene glycol (1 mL) was heated under reflux for 2.5 h in the presence of hydrazine hydrate (12 μL, 0.25 mmol). The mixture was diluted with H_2O (20 mL). This was extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:6 + 1% Et_3N) to give 12.6 mg (61%) of **50** as white solids, and 6.3 mg (27%) of **49** was recovered. The recovered **49** was resubmitted to the same procedure. After two cycles, 18.2 mg (88%) of **50** was obtained: TLC, R_f 0.43 (EtOAc/toluene, 1:2); $[\alpha]^{22}_D$ -36.8° (*c* 0.63); IR (neat) 3340, 3030, 2930, 2850, 1500, 1460, 1450, 1440, 1210, 1150 cm^{-1}; ^1H NMR (270 MHz) δ 0.88 (t, J = 6.6 Hz, 3 H), 1.25 (br s, 22 H), 1.74-2.28 (m, 4 H), 2.47-2.53 (m, 1H), 2.79 (ddd, J = 10.0, 8.1, 2.6 Hz, 1 H), 3.19 (dt, J = 4.4, 10.0 Hz, 1 H), 3.36 (s, 3 H), 3.53 (dd, J = 9.2, 8.1 Hz, 1 H), 3.95 (dd, J = 9.2, 2.6 Hz, 1 H), 4.42, 4.62 (ABq, J = 11.5 Hz, 2 H), 4.61, 4.65 (ABq, J = 6.4 Hz, 2 H), 7.26-7.31 (m, 5 H). HRMS calcd for $C_{27}H_{47}NO_3$ (M^+) *m/z* 433.3553, found 433.3534.

(2*S*,3*R*,6*R*)-6-Dodecyl-3-hydroxy-2-(hydroxymethyl)piperidine, (-)-Desoxoprosophylline (7). A solution of **50** (16.2 mg, 37 μmol) in a mixture of 1,4-dioxane (1 mL) and 4 M HCl (1 mL) was heated at 100 °C for 17 h. The solution was diluted with 2 M aqueous NaOH (20 mL), and this was extracted with CH_2Cl_2 (10 mL x 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOH/toluene, 1:5, then EtOH/toluene, 1:5 + 3% Et_3N) to give 9.1 mg (81%) of **7** as white crystals, mp 90.5 °C [lit.[7a,b] 90.5 °C]: TLC, R_f 0.19 (EtOH/toluene, 1:4); $[\alpha]^{21}_D$ -13.9° (*c* 0.25) [lit.[7a,b] $[\alpha]_D$ -14° (*c* 0.24)]; IR ($CHCl_3$) 3570, 3370, 3070, 2990, 2880, 1420, 1200 cm^{-1}; ^1H NMR (270 MHz) δ 0.88 (t, J = 6.6 Hz, 3 H), 1.26 (br s, 22 H), 1.72-1.80 (m, 2 H), 1.85 (br, 2 H), 2.01-2.10 (m, 2 H), 2.50-2.61 (m, 2 H), 3.51 (dt, J = 4.4, 9.7 Hz, 1 H), 3.76 (dd, J = 10.8, 4.9 Hz, 1 H), 3.86 (dd, J = 10.8, 4.6 Hz, 1 H); ^{13}C NMR (100 MHz) δ 14.1, 22.7, 26.2, 29.4, 29.6, 29.7 x 4, 30.5, 30.6, 31.9, 33.6, 35.9, 56.4, 63.4, 63.6, 69.5. HRMS calcd for $C_{18}H_{37}NO_2$ (M^+) *m/z* 299.2821, found 299.2791.

Methyl 6-*O*-*t*-Butyldimethylsilyl-3,4-dideoxy-α-D-*erythro*-hexopyranoside (51). To a cold (0°C) stirred solution of **8** (253 mg, 1.56 mmol) in DMF (5 mL) were added TBDMSCl (259 mg, 1.72 mmol) and imidazole (233 mg, 3.43 mmol). After being stirred at 0°C for 1 h, the mixture was diluted with EtOAc (40 mL). The whole was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:6) to give 333 mg (77%) of **51** as a colorless oil, and **8** was recovered from the aqueous layer. The recovered **8** was resubmitted to the same procedure. After two cycles, 371 mg (86%) of **51** was obtained: TLC, R_f 0.37 (EtOAc/hexane, 1:3); $[\alpha]^{19}_D$ +78.4° (*c* 1.10); IR (neat) 3460, 2960, 2940, 2860, 1480, 1460, 1260, 1140 cm^{-1}; ^1H NMR (270 MHz) δ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.26-1.44, 1.60-1.76, 1.84-1.92 (3 m, 5 H), 3.43 (s, 3 H), 3.48-3.72 (m, 4 H), 4.67 (d, J = 3.7 Hz, 1 H). HRMS calcd for $C_{12}H_{25}O_3Si$ (M^+ - OCH_3) *m/z* 245.1571, found 245.1598.

Methyl 2-*O*-Acetyl-6-*O*-*t*-butyldimethylsilyl-3,4-dideoxy-α-D-*erythro*-hexopyranoside (52). To a stirred solution of **51** (311 mg, 1.12 mmol) in pyridine (3 mL) was added acetic anhydride (3 mL). The mixture was stirred for 17 h, then concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:20) to give 358 mg (quantitatively) of **52** as a colorless oil: TLC, R_f 0.52 (EtOAc/hexane, 1:3); $[\alpha]^{17}_D$ +74.6° (*c* 1.08); IR (neat) 2950, 2930, 2860, 1740, 1470, 1460, 1370, 1240 cm^{-1}; ^1H NMR (270 MHz) δ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.39-1.56, 1.73-1.97 (2 m, 4 H), 2.09 (s, 3 H), 3.42 (s, 3 H), 3.53 (dd, *J* = 10.6, 5.1 Hz, 1 H), 3.64 (dd, *J* = 10.6, 5.7 Hz, 1H), 3.75 (dddd, *J* = 11.7, 5.7, 5.1, 2.2 Hz, 1 H), 4.77 (d, *J* = 3.3 Hz, 1 H), 4.79 (ddd, *J* = 12.8, 5.1, 3.3 Hz, 1 H). HRMS calcd for $C_{14}H_{27}O_4Si$ (M^+ - OCH_3) *m/z* 287.1677, found 287.1646.

Methyl 2-*O*-Acetyl-3,4-dideoxy-α-D-*erythro*-hexopyranoside (53). To a cold (0°C) stirred solution of **52** (383 mg, 1.20 mmol) in THF (6 mL) was added *n*-Bu_4NF (1.8 mL, 1.8 mmol, 1.0 M solution in THF). The mixture was stirred at rt for 1 h, and diluted with saturated aqueous $NaHCO_3$ (40 mL). This was extracted with CH_2Cl_2 (20 mL x 3). The combined extracts were dried and concentrated. The residue was purified by chromatography on silica gel (EtOAc/toluene, 1:2) to give 238 mg (97%) of **53** as a colorless oil: TLC, R_f 0.22 (EtOAc/toluene, 1:1); $[\alpha]^{17}_D$ +138.8° (*c* 0.87); IR (neat) 3450, 2950, 1730, 1370, 1240 cm^{-1}; ^1H NMR (270 MHz) δ 1.51-1.72, 1.79-2.05 (2 m, 5 H), 2.09 (s, 3 H), 3.44 (s, 3 H), 3.48-3.67 (m, 2 H), 3.84 (dq, *J* = 14.3, 3.3 Hz, 1 H), 4.80 (ddd, *J* = 12.8, 4.8, 3.7 Hz, 1 H), 4.81 (d, *J* = 3.7 Hz, 1 H). HRMS calcd for $C_8H_{13}O_4$ (M^+ - OCH_3) *m/z* 173.0812, found 173.0808.

(2*S*,3*R*,6*S*)-3-Acetoxy-6-[bis(ethylthio)methyl]-2-(methoxy)tetrahydropyran (55). The following reaction was carried out under argon atmosphere. To a cold (-78 °C) stirred mixture of oxalyl chloride (0.42 mL, 4.8 mmol) and DMSO (0.68 mL, 9.6 mmol) in CH_2Cl_2 (3 mL) was added a solution of **53** (196 mg, 0.96 mmol) in CH_2Cl_2 (2 mL). After being stirred the mixture at -78 °C for 1 h, triethylamine (2.0 mL, 14 mmol) was added. The mixture was warmed gradually to rt and stirred for 1 h. The mixture was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (20 mL x 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:2) to give 184 mg (95%) of **54** as a pale yellow oil, which was used immediately.

To a cold (0 °C) stirred solution of the above aldehyde **54** (184 mg, 0.910 mmol) in CH_2Cl_2 (4 mL) were added EtSH (0.27 mL, 3.6 mmol) and $BF_3{\cdot}OEt_2$ (56 μL, 0.46 mmol). The mixture was stirred at 0°C for 1.5 h, then neutralized with ammonia-water. The mixture was diluted with H_2O (40 mL) and extracted with CH_2Cl_2 (20 mL x 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:12) to give 201 mg (72%) of **55** as a colorless oil: TLC, R_f 0.50 (EtOAc/hexane, 1:2); $[\alpha]^{20}_D$ +111.4° (*c* 0.86); IR (neat) 2960, 2350, 1740, 1450, 1370, 1240 cm^{-1}; ^1H NMR (270 MHz) δ 1.27 (t, *J* = 7.3 Hz, 6 H), 1.80-2.02 (m, 4 H), 2.08 (s, 3 H), 2.62-2.82 (m, 4 H), 3.46 (s, 3 H), 3.79 (d, *J* = 5.5 Hz, 1 H), 3.98 (ddd, *J* = 11.0, 5.5, 1.8 Hz, 1 H), 4.77-4.85 (m, 2 H). HRMS calcd for $C_{13}H_{24}O_4S_2$ (M^+) *m/z* 308.1113, found 308.1090.

3,4-Dideoxy-L-*erythro*-hexose Diethyldithioacetal (56). A solution of **55** (155 mg, 0.501 mmol) in a mixture of 1,4-dioxane (2 mL) and 2 M HCl (2 mL) was heated at 80 °C for 3 h. The solution was

diluted with H_2O (40 mL), and this was extracted with CH_2Cl_2 (20 mL x 3). The combined extracts were dried and concentrated in vacuo to give crude hemiacetal (119 mg), which was used without purification.

To a cold (0 °C) stirred solution of the crude hemiacetal (119 mg) in MeOH (3 mL) was added $NaBH_4$ (56.6 mg, 1.50 mmol). After being stirred for rt for 45 min, the mixture was neutralized by addition of Amberlite IR-120 [H^+]. The resin was removed by filtration, washed well with MeOH. The combined filtrate and washing were concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOH/toluene, 1:10 then 1:5) to give 84.9 mg (67%) of **56** as a colorless oil, and crude **55** (34.4 mg) was recovered. The recovered crude **55** was resubmitted to the same procedure. After two cycles, 97.9 mg (77%) of **56** was obtained: TLC, R_f 0.07 (EtOAc/toluene, 1:3); $[\alpha]^{21}_D$ -54.9° (*c* 0.65); IR (neat) 3400, 2970, 2930, 2860, 1460, 1330, 1260 cm^{-1}; ^1H NMR (270 MHz) δ 1.28 (t, *J* = 7.5 Hz, 6 H), 1.52-1.80, 1.95-2.05 (2 m, 4 H), 2.17 (br, 1 H), 2.58-2.78 (m, 4 H), 2.92 (br, 1 H), 3.21 (br, 1 H), 3.45-3.80, 4.03-4.43 (2 m, 5 H). HRMS calcd for $C_{10}H_{22}O_3S_2$ (M^+) *m/z* 254.1008, found 254.0996.

3,4-Dideoxy-5,6-*O*-isopropylidene-L-*erythro*-hexose Diethyldithioacetal (57). To a stirred solution of **56** (84.9 mg, 0.334 mmol) in acetone (2 mL) were added DL-camphorsulfonic acid (37.9 mg, 0.163 mmol) and 2,2-dimethoxypropane (82 μL, 0.67 mmol). The mixture was stirred for 1 h, and diluted with saturated aqueous $NaHCO_3$ (30 mL). The whole was extracted with CH_2Cl_2 (15 mL x 3). The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexane, 1:6) to give 84.1 mg (86%) of **57**: $[\alpha]^{20}_D$ -57.7° (*c* 0.60); ^1H NMR (270 MHz) spectrum was identical to that of **10**. HRMS calcd for $C_{13}H_{26}O_3S_2$ (M^+) *m/z* 294.1322, found 294.1326.

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