Cycloaddition of Dimethyl Acetylenedicarboxylate to 24. Into an NMR tube was placed a solution of **24** (54.9 mg, 0.298 mmol) and dimethyl acetylenedicarboxylate (46.6 mg, 0.328 mmol) in 0.5 mL of CD_2Cl_2 and the tube was sealed in vacuo. After 18 h at room temperature, reaction was complete (^1H NMR analysis) and a 4:1 mixture of **25** and **26** was produced. When exposed to the air, both adducts were oxidized. The following spectra were derived from the mixture.

For **25**: ^1H NMR (80 MHz, CD_2Cl_2) δ 6.29 (t, J = 1.7 Hz), 3.59 (s), 3.50 (s), 3.43 (t, J = 1.7 Hz), 2.25-1.13 (series of m); ^{13}C NMR (75 MHz, CD_2Cl_2) ppm 172.33, 166.52, 150.33, 140.65, 90.22, 69.12, 63.44, 51.99, 50.75, 34.31, 32.84, 25.88, 25.51.

For **26**: ^1H NMR (80 MHz, CD_2Cl_2) δ 6.78 (t, J = 1.8 Hz), 3.76-3.54 (m), 3.65 (s), 2.25-1.13 (series of m); ^{13}C NMR (75 MHz, CD_2Cl_2) ppm 171.41, 166.39, 153.69, 143.81, 100.92, 78.96, 61.81, 52.03, 51.08, 34.87, 34.07, 25.70, 25.40.

Benzyne Addition to 24. A 155-mg (0.841-mmol) sample of **24** was reacted with benzenediazonium 2-carboxylate hydrochloride and propylene oxide in ethylene dichloride exactly as described above. Analogous purification afforded 106 mg of a pale yellow viscous oil, which consisted of a 4:3 mixture of syn and anti adducts. This mixture was separated by MPLC on silica gel (elution with petroleum ether) to give 29.7 mg (14%) of **27** and 39.1 mg (18%) of **28**, both as colorless oils.

For **27**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.88-6.67 (m, 4 H), 5.76 (t, J = 1.7 Hz, 2 H), 3.45 (s, 2 H), 3.36 (m, 2 H), 2.12-1.28 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 169.27, 148.97, 136.70, 123.42, 123.11, 84.60, 67.11, 60.21, 49.82, 33.26, 32.60, 25.64, 25.20.

For **28**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.10-6.78 (m, 6 H), 3.49 (m, 4 H), 2.18-1.21 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 170.73, 153.07, 143.60, 123.63, 121.22, 93.39, 79.32, 59.18, 50.13, 34.14, 33.60, 25.47, 25.19; MS m/z (M^+) calcd 260.1565, obsd 260.1532.

Diels-Alder Reaction of Cyclooctyne with 24. Into an NMR tube was placed a solution of **24** (67.4 mg, 0.37 mmol) and cyclooctyne (42.9 mg, 0.40 mmol) in 0.5 mL of toluene-d_8, and the tube was sealed in vacuo. After 14.5 h of heating at 120 °C, reaction was shown to be complete (^1H NMR analysis) and to consist of a 6.5:1 mixture of **29** and **30**. The following spectra were derived from the mixture.

For **29**: ^1H NMR (300 MHz, toluene-d_8) δ 6.34 (t, J = 1.7 Hz), 3.42 (t, J = 1.6 Hz), 2.79 (s), 2.28-1.35 (series of m); ^{13}C NMR (75 MHz, toluene-d_8) ppm 170.98, 142.64, 140.12, 86.11, 69.62, 67.81, 50.62, 34.76, 33.92, 30.23, 26.41, 26.10, 25.80 (1 C not observed).

For **30**: ^1H NMR (300 MHz, toluene-d_8) δ 6.79 (t, J = 1.7 Hz), 3.53 (t, J = 1.7 Hz), 2.77 (s), 2.28-1.35 (series of m); ^{13}C NMR (75 MHz, toluene-d_8) ppm 170.48, 147.04, 143.92, 96.98, 77.15, 65.17, 50.83, 35.26, 35.23, 29.48, 27.01, 26.41, 25.89 (1 C not observed).

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Registry No. 8, 119594-09-1; **9**, 60526-44-5; **11**, 119594-06-8; **12**, 119594-07-9; **13**, 119594-08-0; **14**, 119677-31-5; **23**, 124382-48-5; **34**, 85222-07-7; **25**, 85222-29-3; **26**, 85280-15-5; **27**, 124382-50-9; **28**, 124440-58-0; **29**, 124382-51-0; **30**, 124440-59-1; $Ph_3P^+(CH_2)_3P^+Ph_3 \cdot 2Br^-$, 7333-67-7; 1,4-dibromobutane, 110-52-1; (*Z*)-1,2-bis(phenylsulfonyl)ethylene, 963-15-5; benzenediazonium-2-carboxylate hydrochloride, 124382-49-6; tricyclo[5.2.1.$0^{2,6}$]deca-2,5,8-triene, 6675-71-4; dimethyl acetylenedicarboxylate, 762-42-5; cyclooctyne, 1781-78-8.

Supplementary Material Available: Tables VII-X, listing positional parameters and anisotropic thermal parameters for **8** (4 pages); Table XI listing structure factors for **8** (8 pages). Ordering information can be found on any current masthead page.

Asymmetric Total Synthesis of Atisine via Intramolecular Double Michael Reaction

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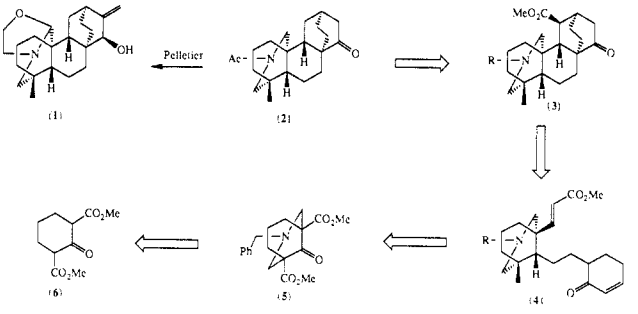
Contribution from the Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan, and Instrumental Analysis Center for Chemistry, Faculty of Science, Tohoku University, Aobayama, Sendai 980, Japan. *Received June 26, 1989*

Abstract: The bridged, pentacyclic intermediate **2** for atisine (**1**) was synthesized in a naturally occurring enantiomeric form from dimethyl cyclohexanone-2,6-dicarboxylate (**6**). The synthesis is composed of the following key steps: (1) formation of the azabicyclo[3.3.1]nonane by a double Mannich reaction, (2) enantioselective conversion by a lipase-catalyzed acylation, (3) stereoselective hydroboration in the presence of $BF_3 \cdot Et_2O$, and (4) construction of the bicyclo[2.2.2]octane ring system by an intramolecular double Michael reaction.

Diterpene alkaloids[1] are widely distributed in the plant world and have long been of interest due to their physiological properties and architectural features. Atisine (**1**), the predominant alkaloid of *Aconitum heterophyllum*,[2] has a relatively uncomplicated hexacyclic structure including azabicyclo[3.3.1]nonane and bicyclo[2.2.2]octane rings. The absolute stereochemistry was elucidated by interrelating the degradation products with those of the related diterpene alkaloids and diterpenes.[3,4] Since the stereostructure had been determined, the alkaloid has attracted the attention of organic chemists as a target molecule. Three different routes[5,6] have been successful in reaching Pelletier's synthetic intermediates[7] for atisine, although only racemates were synthesized. A major obstacle in the synthesis is the problem of constructing azabicyclo[3.3.1]nonane and bicyclo[2.2.2]octane ring systems. We envisioned assembly of the bicyclo[2.2.2]octane

Scheme I



[†] Pharmaceutical Institute, Tohoku University.
[‡] Instrumental Analysis Center for Chemistry, Tohoku University.

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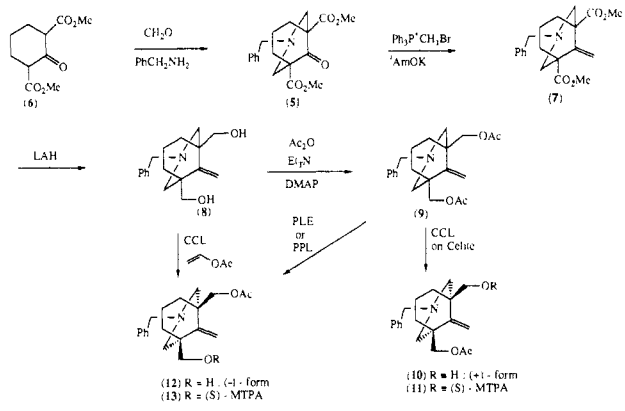
Scheme II



system **3**, convertible to a synthetic intermediate **2**, by an intramolecular double Michael reaction developed by us.[8,9] It was further considered that the substrate **4** of the key step could be constructed in an optically active form from a symmetrical azabicyclo[3.3.1]nonane **5** prepared by a double Mannich condensation of dimethyl cyclohexanone-2,6-dicarboxylate (**6**). We have completed the synthesis of the intermediate **2** of atisine (**1**) in the naturally occurring enantiomeric form and provide here a full account of this work.[10]

Synthesis of Chiral Azabicyclo[3.3.1]nonane. The azabicyclononane **5**, mp 121–122 °C, corresponding to the AE part of atisine (**1**) was synthesized in 97% yield by double Mannich reaction from diester **6**[11a] with use of benzylamine and formaldehyde.[11b] Although such Robinson–Schöpf condensations were precedented with cyclic keto-diesters, this appears to be their first application in a complex synthesis. The product **5** possesses the meso structure, which is of advantage of performing the enzyme-catalyzed, enantioselective transformation.[12] Therefore, keeping in mind the

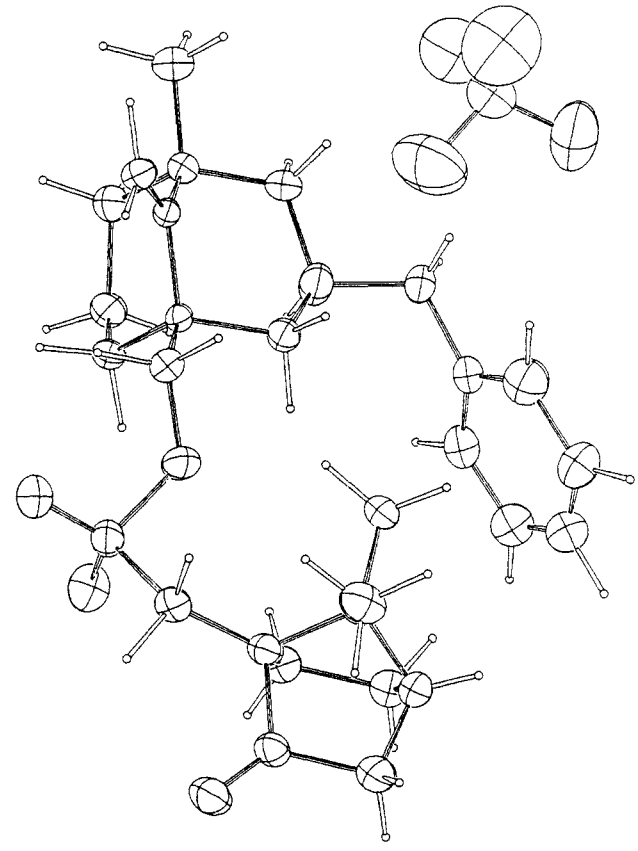
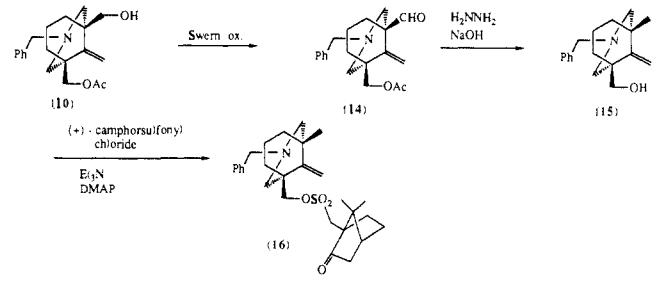


Figure 1. Molecular structure of the perchlorate of **16**.

Scheme III



asymmetric synthesis, introduction of a carbon unit at the C-9 position was examined, by using a Wittig-type reaction. Although direct introduction of a phenethyl group failed, reaction of **5** with an ylid prepared from methyltriphenylphosphonium bromide and potassium *tert*-pentoxide in hot benzene gave in 78% yield the *exo*-methylene **7**, mp 89–90 °C. Reduction of the diester **7** with $LiAlH_4$ afforded, in 93% yield, the diol **8**, which was quantitatively converted into the diacetate **9**. Enzymatic hydrolysis of the diacetate **9** was first studied utilizing porcine liver esterase (PLE), porcine pancreas lipase (PPL), and *Candida cylindracea* lipase (CCL) in a mixture of phosphate buffer and MeOH. Although yields of monoacetates in the above enzymatic reactions were poor, the optical purities of the products, determined by 500 MHz ^1H NMR spectroscopy, after conversion to the MTPA esters,[13] ranged between 64 and 80% ee. It was also noteworthy that hydrolysis

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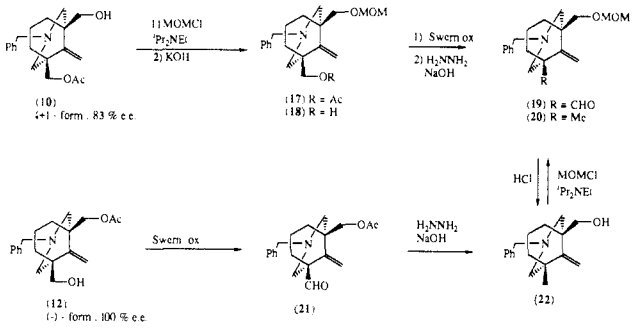
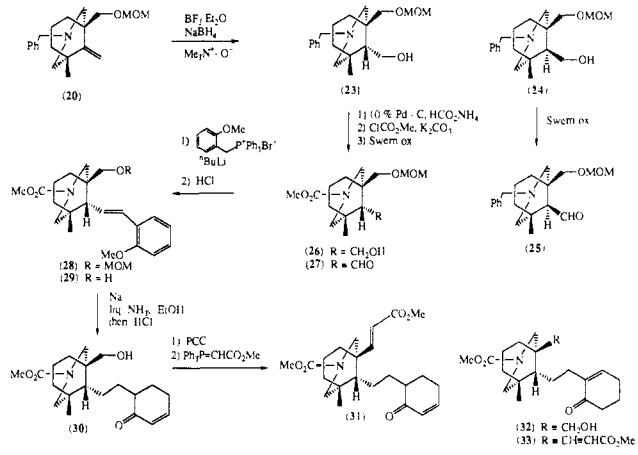
Scheme IV



Scheme V



of **9** with PLE or PPL produced the (−)-acetate **12**, while the (+)-enantiomer **10** was obtained on hydrolysis with CCL. The major product of the enzyme-catalyzed reactions was the diol **8**, formed by hydrolysis of two acetyl groups. Therefore hydrolysis of **9** was examined by using enzymes immobilized with Celite in an organic solvent. When **9** was treated with CCL on Celite in isooctane[14] for 2 days at 35 °C, the (+)-monoacetate **10**, $[\alpha]_D^{26}$ +4.23° (*c* 2.87, MeOH), was produced in 26% yield. ^{1}H NMR analysis of the MTPA ester **11** indicated an 83% ee for the optical purity.

Next, lipase-catalyzed irreversible transesterification[15] was tested for the diol **8**, and the (−)-enantiomer **12** was obtained in a high optical purity by using CCL. Thus, the reaction of **8** in the presence of CCL and vinyl acetate in benzene for 11 h at 28 °C gave a 32% yield of (−)-**12**, $[\alpha]_D^{28}$ −5.10° (*c* 0.96, MeOH). A 100% ee of this product **12** was confirmed by the ^{1}H NMR spectrum of its MTPA ester **13**. The above reaction also gave the diacetate **9** in 1% yield, and the starting diol **8** was recovered in 66% yield. Both materials were reused for the enzyme-catalyzed reaction.

Determination of Absolute Configuration. In order to determine the absolute configuration by X-ray analysis, transformation of the monoacetate **10** or **12** into a crystalline derivative having, in part, known asymmetric centers was investigated. Thus the absolute stereochemistries of both enantiomers **10** and **12** were established as depicted. Namely, the (+)-acetate **10**, obtained in 83% ee by CCL catalyzed hydrolysis, was oxidized by the Swern method to the aldehyde **14**, which was then subjected to the Wolff–Kishner reduction to give the methyl derivative **15**. Recrystallization of the hydrochloride, derived from **15**, produced crystals, mp 190–192 °C. Optical purity (100% ee) of the recovered free base **15**, $[\alpha]_D^{20}$ −4.38° (*c* 1.13, MeOH), was established by ^{1}H NMR analysis of the MTPA ester. Condensation of **15** with (+)-camphorsulfonyl chloride in the presence of 4-*N*,*N*-(dimethylamino)pyridine (DMAP) and Et_3N, followed by conversion of the resulting sulfonate **16** to the perchlorate, furnished a crystalline compound, mp 189–192 °C, $[\alpha]_D^{20}$ +25.32° (*c* 0.12, MeOH). The crystal structure of the perchlorate of **16**, determined by X-ray analysis, is shown in Figure 1. This result made clear the absolute stereochemistry of **16** and eventually the absolute configurations of both enantiomers **10** and **12**.

Since the absolute configurations of the monoacetates have now been determined, both enantiomers **10** and **12** were transformed into the same intermediate **20**, required for synthesis of atisine (**1**) in the natural absolute configuration. Protection of **10** with the methoxymethyl (MOM) group, followed by basic hydrolysis of the acetyl group of its product **17**, afforded the alcohol **18**, which was converted as above into the methyl derivative **20** via the aldehyde **19**, in excellent yield. Acid hydrolysis of **20** formed the carbinol, which was purified via recrystallization of the hydrochloride to give pure **22**, $[\alpha]_D^{26}$ +4.31° (*c* 1.77, MeOH). On the other hand, the optically pure (−)-isomer **12**, prepared by enzyme-catalyzed acylation, was transformed into the (+)-methyl compound **22**, $[\alpha]_D^{25}$ +4.30° (*c* 0.73, MeOH), through the aldehyde **21**. Blocking the hydroxyl group of **22**, obtained in optically pure form from both enantiomers **10** and **12**, with the MOM group produced the optically pure (+)-**20**, $[\alpha]_D^{27}$ +8.10° (*c* 2.02, $CHCl_3$).

Stereoselective Synthesis of the Chiral Substrate for the Intramolecular Double Michael Reaction. For the synthesis of atisine (**1**), a hydrogen atom must be introduced from the si-face of intermediate **20** at the C-9 position. Hydroboration[16] of **20**, using the borane–dimethyl sulfide complex, followed by oxidation with trimethylamine *N*-oxide,[17] gave a mixture of (9*R*)- and (9*S*)-isomers, **23** and **24**, in a ratio of 1.2:1. A reaction using dicyclohexylborane, instead of the borane–dimethyl sulfide complex, produced the 1:1.2 mixture of **23** and **24**. The desired asymmetric induction was achieved in a stereoselective manner by reaction with a mixture of $NaBH_4$ and BF_3·Et_2O.[18] When the hydroboration was carried out by addition of BF_3·Et_2O into the mixture of **20** and $NaBH_4$ in diglyme, the ratio of two diastereoisomers **23** and **24** was about 14:1. The ratio was further improved by the reverse addition of reagents. Thus, to a stirred solution of **20** and BF_3·Et_2O in diglyme was added a solution of $NaBH_4$ in diglyme at −23 °C, and the resulting product was oxidized with trimethylamine *N*-oxide to afford the desired isomer **23**, $[\alpha]_D^{28}$ +1.87° (*c* 0.63, $CHCl_3$), in 78% yield and the diastereoisomer **24**, $[\alpha]_D^{27}$ −3.55° (*c* 0.88, $CHCl_3$), in 2% yield. It is therefore considered that these reagents generate borane in situ, while coordination of BF_3 to the amine hinders one face of the double bond. The stereochemistry of **23** was assigned by ^{1}H NMR NOE experiments. Positive NOE effects were observed between the $-N(CH_2)_2$ and carbinol CH_2 groups of **23**, while the isomer **24** showed no NOE between those functions. The relative stereochemistry of **23** was further supported by chemical reactivity. Namely, oxidation of **23** into the corresponding aldehyde failed, but Swern oxidation of the isomer **24** readily produced the aldehyde **25**. This fact indicates that the free tertiary amino group is in close proximity to the primary hydroxyl group and interferes with the oxidation. Thus, it was necessary, at this juncture, to remove the *N*-benzyl group by hydrogenolysis[19] and to reprotect the secondary amine as a methyl carbamate. Swern oxidation of the carbamate **26**, obtained in 88% yield from **23**, gave the aldehyde **27**, in 86% yield. The aldehyde **27** was efficiently converted to the substrate **31** of the key cyclization reaction as follows. Thus **27** was treated with a Wittig reagent, generated from (2-methoxybenzyl)triphenylphosphonium bromide and ^{n}BuLi, to afford the styrene **28** in 99% yield as an *E* isomer. After removal of the MOM group of **28**, the resulting carbinol **29** was subjected to Birch reduction, by using metallic Na in the presence of EtOH in a mixture of NH_3 and THF, followed by acid hydrolysis, to give the mixture of the enones **30** and **32** in 73% overall

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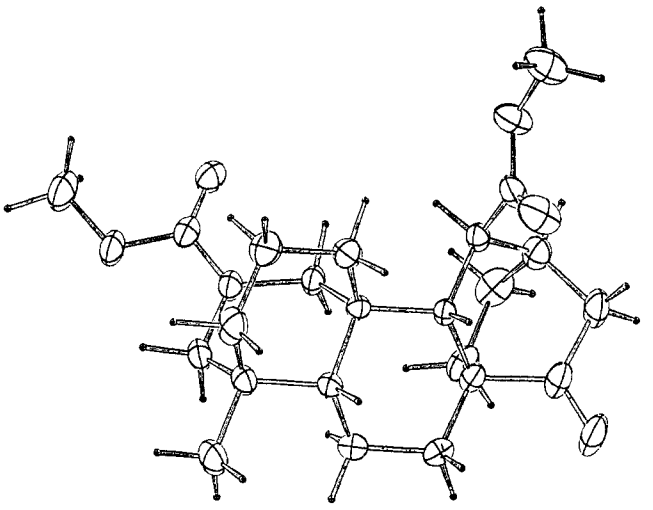


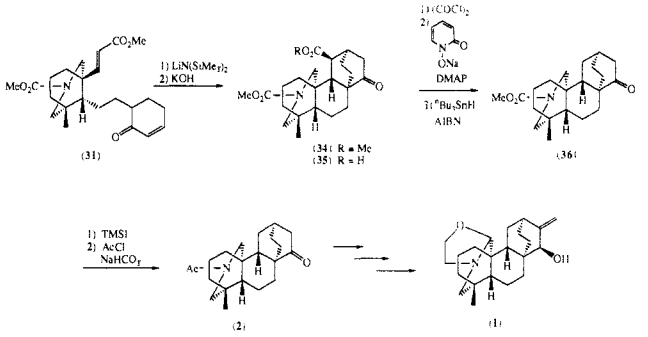
Figure 2. Molecular structure of the racemate of the compound **34**.

yield, in the ratio of 6:1. Oxidation of the mixture **30** and **32** with pyridinium chlorochromate (PCC), followed by reaction of the resulting aldehydes with (methoxycarbonylmethylene)triphenylphosphorane in hot MeCN and a subsequent separation, furnished the required α,β-unsaturated ester **31**, $[\alpha]_D^{29}$ −44.84° (*c* 1.52, $CHCl_3$), in 69% overall yield and the undesired isomer **33** in 12% overall yield.

Intramolecular Double Michael Reaction and Formal Total Synthesis of Atisine. Now the starting material **31** for the key step, the intramolecular double Michael reaction, was accessible in the optically active form. The tandem conjugate addition was conducted by using $LiN(SiMe_3)_2$[8] in a mixture of hexane and Et_2O. The desired pentacyclic compound **34** was obtained as a major product together with a small amount of one diastereoisomer. The ratio of the two products varied with the reaction conditions. When the annulation was carried out for 30 min at −78 °C and then for 1.5 h at ambient temperature, the ketoester **34**, $[\alpha]_D^{24}$ +9.35° (*c* 1.27, $CHCl_3$), was produced in 58% yield without formation of the stereoisomer. The relative stereochemistry of the product **34** was established by X-ray analysis of the corresponding racemate, whose spectral properties and TLC behaviors were identical with those of (+)-**34**. The molecular structure of the racemate of **34** is pictured in Figure 2.

The unnecessary methoxycarbonyl group of **34** was removed by Barton's free-radical decarboxylation procedure.[20] Thus alkaline hydrolysis of **34** gave the carboxylic acid **35**, $[\alpha]_D^{29}$ +4.01° (*c* 0.86, $CHCl_3$), in 90% yield. After conversion of **35** into the acid chloride, its treatment with 2-mercaptopyridine-1-oxide sodium salt in the presence of DMAP, followed by radical reduction using $^nBu_3SnH$ and azoisobutyronitrile (AIBN), gave the carbamate **36**, mp 120–123 °C, $[\alpha]_D^{24}$ −20.84° (*c* 0.87, $CHCl_3$), $[\theta]^{25}$ +4416 (293 nm) (positive maximum, MeOH), in 64% yield. Finally, the carbamate group of **34** was converted to the acetamide function **2**, mp 172–172.5 °C (lit.,[7b] mp 170.5–171 °C), $[\alpha]_D^{23}$ −18.58° (*c* 0.34, MeOH), $[\theta]^{25}$ +6294 (292 nm) (positive maximum, MeOH), in 83% overall yield by exposure to Me_3SI[21] followed by acetylation. IR data of the product **2** were identical with reported ones,[7b] and the 500 MHz ^1H NMR data well-supported structure **2**, although the spectrum was complicated because of rotational isomers. Both ketones **36** and **2** showed a rather large positive Cotton effect[22] in their CD spectra supporting their absolute configurations as depicted in Scheme VI. Since **2** has been correlated with atisine (**1**) by Pelletier and co-workers,[7] the present work represents a formal total synthesis of atisine.

Scheme VI



In summary, the following four key steps, (1) formation of the AE ring system by double Mannich condensation, (2) enantioselective acylation catalyzed with lipase, (3) stereoselective hydroboration using $NaBH_4$–BF_3·Et_2O, and (4) construction of the DE ring system by intramolecular double Michael reaction, effected an efficient asymmetric synthesis of the natural enantiomer of atisine (**1**).

Experimental Section

General Procedure. All reactions were carried out under a positive atmosphere of dry N_2 unless indicated. Solvents were freshly distilled prior to use: THF and Et_2O were distilled from sodium benzophenone; CH_2Cl_2 was distilled over P_2O_5 and kept over 4 Å molecular sieves; DMSO was distilled over CaH_2 under reduced pressure and kept over 4 Å molecular sieves. Unless otherwise noted, all reaction mixtures were dried, after workup, over anhydrous K_2CO_3. Silica gel column chromatography was carried out with Wako gel C-200, while Merck Kieselgel 60 Art. 9385 was used for flash chromatography. High-performance liquid chromatography (HPLC) was carried out with a Gilson HPLC system Model 302/303 equipped with 10 × 250 mm column of Dynamax microsorb silica 5 μm and monitored by using UV and refractive index detectors.

Dimethyl 3-Benzyl-3-azabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylate (5). To a solution of dimethyl cyclohexanone-2,6-dicarboxylate (**6**)[11a] (35.0 g, 0.16 mol) in MeOH (1.2 L) were added benzylamine (21.4 mL, 0.2 mol) and 35% CH_2O (60.6 mL, 0.65 mol), and the mixture was stirred for 24 h at ambient temperature. After concentration of the mixture under reduced pressure, the residue was taken up into CH_2Cl_2 and then washed with H_2O three times. After drying, followed by evaporation of the mixture, the resulting solid was recrystallized from MeOH to give the amino ketone **5** (53.7 g, 97%) as colorless plates: mp 121–122 °C; IR ($CHCl_3$) 1710, 1725 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.54 (2 H, s, NCH_2Ph), 3.70 (6 H, s, $2CO_2Me$), 7.21 (5 H, s, Ph); mass spectrum, *m/z* 345 (M^+). Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.12; H, 6.72; N, 4.02. Found: C, 66.02; H, 6.85; N, 4.15.

Dimethyl 3-Benzyl-9-methylene-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate (7). To a suspension of methyltriphenylphosphonium bromide (105.7 g, 0.30 mol) in dry benzene (400 mL) was added a mixture of KH (11.3 g, 0.28 mol) and *tert*-pentyl alcohol (33.9 mL, 0.31 mol) in dry benzene (700 mL), and the mixture was stirred for 1 h at ambient temperature. To the resulting mixture was added dropwise a solution of the above amino ketone **5** (34.4 g, 0.1 mol) in dry benzene (400 mL). After having been heated at reflux for 1.5 h, the reaction mixture was washed twice with H_2O and dried. Evaporatiopn of the solvent gave a residue, which was subjected to silica gel column chromatography. Elution with hexane–AcOEt (19:1 v/v), followed by recrystallization of the residue from MeOH, afforded the exo olefin **7** (26.8 g, 78%) as colorless pillars: mp 89–90 °C; IR ($CHCl_3$) 1725 (C=O), 905 (=CH_2) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.46 (2 H, s, NCH_2Ph), 3.71 (6 H, s, $2CO_2Me$), 4.54 (2 H, s, >C=CH_2), 7.27 (5 H, s, Ph); mass spectrum, *m/z* 343 (M^+). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 70.00; H, 7.34; N, 4.08. Found: C, 69.90; H, 7.15; N, 4.16.

3-Benzyl-1,5-(dihydroxymethyl)-9-methylene-3-azabicyclo[3.3.1]nonane (8). To a suspension of $LiAlH_4$ (5 g, 0.13 mol) in dry THF (250 mL) was slowly added a solution of the exo olefin 7 (20.8 g, 0.06 mol) in dry THF (250 mL) at ambient temperature, and the mixture was stirred for 1.5 h at the same temperature. After addition of H_2O (5 mL) followed by 15% aqueous NaOH solution (5 mL) and H_2O (5 mL), the resulting mixture was filtered though Celite, dried, and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (7:3 v/v) as eluant to give the diol **8** (17.4 g, 93%) as a colorless oil: IR ($CHCl_3$) 3460 (OH), 905 (=CH_2) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.37 (2 H, s, NCH_2Ph), 3.50 (4 H, s, 2 × CH_2OH), 4.67 (2 H, s, >C=CH_2), 7.23 (5 H, s, Ph); mass spectrum, *m/z* 287 (M^+). Anal. Calcd for

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(21) Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315.
(22) Moffitt, W.; Woodward, R. B.; Moscowitz, A.; Klyne, W.; Djerassi, C. *J. Am. Chem. Soc.* **1961**, *83*, 4013.
(23) Jia-Xing, Y. *Acta Crystallogr., Sect. A* **1981**, *37*, 642; **1983**, *39*, 35.

$C_{18}H_{25}NO_2 \cdot H_2O$: C, 70.83; H, 8.93; N, 4.59. Found: C, 71.08; H, 8.91; N, 4.33.

1,5-(Diacetoxymethyl)-3-benzyl-9-methylene-3-azabicyclo[3.3.1]nonane (9). To a solution of the diol **8** (1.15 g, 3.77 mmol) in dry CH_2Cl_2 (30 mL) were added DMAP (5 mg, 0.04 mmol), Et_3N (5.3 mL, 37.7 mmol), and Ac_2O (1.4 mL, 15.1 mmol), and the mixture was stirred for 4 h at ambient temperature. After dilution with CH_2Cl_2, the mixture was washed with 10% NH_4OH and saturated aqueous NaCl solution, dried, and evaporated. The residue was purified by silica gel column chromatography with hexane–ether (3:1 v/v) as eluant to afford the diacetate **9** (1.40 g, 100%) as a colorless oil: IR ($CHCl_3$) 1733 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.04 (6 H, s, 2 × OAc), 2.87 and 2.99 (each 2 H, each br s, 2 × Bn-N-CH_2), 3.40 (2 H, s, NCH_2Ph), 4.00 (4 H, s, 2 × AcOCH_2), 4.63 (2 H, s, >C=CH_2), 7.29 (5 H, s, Ph); mass spectrum, m/z 371.2095 (M^+), found 371.2097.

Enzymatic Hydrolysis of the Diacetate 9. (A) To a solution of the diacetate **9** (50 mg, 0.13 mmol) in MeOH (1 mL) were added 0.1 *N*-phosphate buffer (pH 7.5, 9 mL) and an enzyme (Sigma: porcine liver esterase, porcine pancreas lipase-type II, or *Candida cylindracea* lipase-type VII; 120 units). After having been shaken for 3 days at 30 °C under normal atmosphere followed by addition of 10% aqueous NaOH solution (5 mL), the mixture was extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl solution, dried, and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–Et_2O (3:1 v/v) afforded the starting diacetate **9**. The next elution with hexane–Et_2O (3:2 v/v) gave the monoacetate **10** or **12** as a colorless oil: IR ($CHCl_3$) 3600 (OH), 1717 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.04 (3 H, s, OAc), 2.85–3.00 (4 H, m, 2 × Bn-N-CH_2), 3.31 and 3.49 (each 1 H, each d, each J = 13 Hz, NCH_2Ph), 3.57 (2 H, br s, HOCH_2), 4.02 (2 H, s, AcOCH_2), 4.66 and 4.70 (each 1 H, each s, >C=CH_2), 7.30 (5 H, s, Ph); mass spectrum, m/z 329 (M^+); exact mass calcd for $C_{20}H_{27}NO_3$ 329.1989 (M^+), found 329.1991. Further elution with hexane–Et_2O (1:1 v/v) gave the diol **8**.

(B) To a solution of the diacetate **9** (3.72 g, 10.0 mmol) in isooctane (400 mL) was added a mixture of Celite (9.67 g) and *Candida cylindracea* lipase-type VII (3.7 g) in H_2O (7.4 mL), and the mixture was shaken for 2 days at 35 °C under normal atmosphere. The mixture was filtered through Celite, and the immobilized enzyme was washed with CH_2Cl_2. The combined filtrates were dried and evaporated to give a residue, which was chromatographed on silica gel. Elution with hexane–Et_2O (3:2 v/v) afforded the (+)-monoacetate **10** (0.87 g, 26%) as a colorless oil: $[\alpha]_D^{26}$ +4.23° (c 2.87, MeOH), whose spectral data were identical with those of the above specimen, prepared by method A. The starting diacetate **9** (2.30 g, 62%) and the diol **8** (0.12 g, 4%) were obtained from the elutions with hexane–Et_2O (3:1 v/v) and (1:1 v/v), respectively.

Enzymatic Acetylation of Diol 8. To a solution of diol **8** (330 mg, 1.08 mmol) in benzene (10 mL) were added *Candida cylindracea* lipase-type VII (330 mg) and vinyl acetate (0.25 mL, 2.70 mmol), and the mixture was shaken for 11 h at 28 °C under normal atmosphere. After filtration through Celite, followed by washing the enzyme with CH_2Cl_2, the combined filtrates were dried and evaporated. The crude product was purified by silica gel column chromatography. Elution with hexane–Et_2O (3:2 v/v) gave the (−)-monoacetate **12** (115 mg, 32%) as a colorless oil, $[\alpha]_D^{28}$ −5.10° (c 0.96, MeOH), whose spectral data were identical with those of the above compound. The diacetate **9** (3 mg, 1%) and the starting diol **8** (219 mg, 66%) were obtained from the elutions with hexane–ether (3:1 v/v) and (1:1 v/v), respectively.

Conversion of the Monoacetates 10 and 12 into the MTPA Esters. To a solution of the acetate **10** or **12** (5 mg, 0.015 mmol) in dry CH_2Cl_2 (2 mL) were added DMAP (5 mg, 0.04 mmol), Et_3N (7 μL, 0.02 mmol), and (−)-(*S*)-α-methoxy-α-((trifluoromethyl)phenyl)acetyl chloride (5 μL, 0.023 mmol), and the mixture was stirred for 1 h at ambient temperature. After dilution with CH_2Cl_2, the resulting mixture was washed with 10% NH_4OH and saturated aqueous NaCl solution, dried, and evaporated. The residue was purified by silica gel column chromatography, eluating with hexane–AcOEt (9:1 v/v) to afford the MTPA ester (8 mg, 100%) as a colorless oil. The optical purity (% ee) was determined from the intensities at 4.21 and 4.24 ppm [J = 11 Hz, for (+)-monoacetate **11**] and at 4.20 and 4.27 ppm [J = 11 Hz, for (−)-monoacetate **13**] due to CH_2-OMTPA on 500 MHz ^1H NMR spectrum.

(−)-(1*R*,5*S*)-5-(Acetoxymethyl)-3-benzyl-1-formyl-9-methylene-3-azabicyclo[3.3.1]nonane (14). To a stirred solution of $(COCl)_2$ (0.016 mL, 0.19 mmol) in dry CH_2Cl_2 (0.7 mL) was added a solution of DMSO (0.02 mL, 0.28 mmol) in dry $CHCl_2$ (0.3 mL) at −78 °C under Ar. After having been stirred for 2 min at −78 °C, a solution of the (+)-acetate **10** (50.9 mg, 0.16 mmol), prepared by the enzymatic hydrolysis using CCL in dry CH_2Cl_2 (1 mL) was added during 5 min. After having been stirred for 15 min followed by addition of Et_3N (0.108 mL, 0.77 mmol), the mixture was stirred for 5 min at −78 °C, and the stirring was continued until the reaction temperaure rose to room temperature. After dilution with CH_2Cl_2, the resulting mixture was washed with 10% NH_4OH and saturated aqueous NaCl solution, dried, and evaporated. The residue was chromatographed on silica gel with hexane–AcOEt (9:1 v/v) as eluant to give the aldehyde **14** (43.4 mg, 86%) as a yellowish oil: $[\alpha]_D^{26}$ −13.41° (c 0.74, $CHCl_3$); IR ($CHCl_3$) 1725 (C=O), 905 (=CH_2) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.05 (3 H, s, OAc), 2.70–3.15 (4 H, m, 2 × Bn-N-CH_2), 3.37 and 3.55 (each 1 H, each d, each J = 13 Hz, NCH_2Ph), 4.01 (2 H, s, AcOCH_2), 4.60 and 4.71 (each 1 H, each s, >C=CH_2), 7.29 (5 H, s, Ph), 9.63 (1 H, s, CHO); mass spectrum, m/z 327 (M^+); exact mass calcd for $C_{20}H_{25}NO_3$ 327.1833 (M^+), found 327.1834.

(−)-(1*S*,5*S*)-3-Benzyl-5-(hydroxymethyl)-1-methyl-9-methylene-3-azabicyclo[3.3.1]nonane (15). A mixture of the aldehyde **14** (119 mg, 0.36 mmol) and $H_2NNH_2 \cdot H_2O$ (1.06 mL, 21.8 mmol) in triethylene glycol (5 mL) was heated at 120 °C for 2 h and cooled to room temperature. After addition of NaOH (1.45 g, 36.3 mmol), the mixture was first heated at 150 °C until H_2O had distilled off and heated further at 170 °C for 18 h. After having been cooled, followed by addition of H_2O and CH_2Cl_2, the CH_2Cl_2 layer was washed with saturated aqueous NaCl, dried, and evaporated. The residue was purified by silica gel column chromatography eluating with hexane–Et_2O (4:1 v/v) to give the methyl compound **15** (89 mg, 90%) as a yellowish oil, which was converted as usual into the hydrochloride. Recrystallization from MeOH–ether afforded colorless pillars: mp 190–192 °C. The crystalline hydrochloride was partitioned between 10% NH_4OH and CH_2Cl_2, and the CH_2Cl_2 layer was washed with saturated aqueous NaCl solution, dried, and evaporated to give the optically pure (−)-**15** as colorless oil: $[\alpha]_D^{20}$ −4.38° (c 1.13, MeOH); IR ($CHCl_3$) 3640 (OH), 905 (=CH_2) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.95 (3 H, s, 1-Me), 3.35 (2 H, br s, NCH_2Ph), 3.53 (2 H, br s, 5-CH_2O), 4.60 and 4.72 (each 1 H, each s, C=CH_2), 7.28 (5 H, s, Ph); mass spectrum, m/z 271 (M^+); exact mass calcd for $C_{18}H_{25}NO$ 271.1935 (M^+), found 271.1936.

(+)-(1*S*,5*S*)-3-Benzyl-5-[(1′*S*,4′*R*)-((camphorsulfonyl)oxy)methyl]-1-methylene-3-azabicyclo[3.3.1]nonane (16). To a stirred solution of the above (−)-**15** (32.2 mg, 0.12 mmol) in dry CH_2Cl_2 (2 mL) were added DMAP (5 mg, 0.04 mmol), Et_3N (0.08 mL, 0.59 mmol), and (+)-camphorsulfonyl chloride (44.0 mg, 0.18 mmol), and the mixture was stirred for 1 h at ambient temperature. After dilution with CH_2Cl_2, the mixture was washed with 10% NH_4OH and saturated aqueous NaCl solution, dried, and evaporated. The residue was subjected to silica gel column chromatography eluating with hexane–AcOEt (4:1 v/v) to give the ester **16** (57.7 mg, 100%) as a colorless oil: IR ($CHCl_3$) 1745 (C=O), 1360 and 1167 (SO_2) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.88 and 1.11 (each 3 H, each s, 2 × Me), 0.95 (3 H, s, 5-Me), 4.22 (2 H, s, SO_2CH_2), 4.57 and 4.74 (each 1 H, each s, C=CH_2), 7.92 (5 H, s, Ph); mass spectrum, m/z 485 (M^+); exact mass calcd for $C_{28}H_{39}NO_4S$ 485.2598 (M^+), found 485.2600. After conversion into the perchlorate, recrystallization from MeOH–ether gave colorless plates: mp 189–192 °C, $[\alpha]_D^{20}$ +25.32° (c 0.12, MeOH), one of which was submitted to X-ray analysis.

(−)-(1*R*,5*S*)-5-(Acetoxymethyl)-3-benzyl-1-[((methoxymethyl)oxy)methyl]-9-methylene-3-azabicyclo[3.3.1]nonane (17). To a stirred solution of the (+)-acetate **10** (7.28 g, 22.1 mmol), prepared by the enzymatic hydrolysis using CCL in dry CH_2Cl_2 (200 mL) were added $^iPr_2NEt$ (13.5 mL, 77.4 mmol) and MOMCl (3.4 mL, 44.2 mmol) at 0 °C, and the mixture was stirred for 20 h at ambient temperature. After dilution with CH_2Cl_2, the mixture was washed with 10% NH_4OH and saturated aqueous NaCl solution, dried, and evaporated to afford a residue, which was subjected to silica gel column chromatography. Elution with hexane–Et_2O (3:1 v/v) gave the MOM ether **17** (8.04 g, 98%) as a colorless oil: $[\alpha]_D^{20}$ −4.05° (c 1.77, MeOH); IR ($CHCl_3$) 1735 (C=O), 1105 (O—CH_2—O), 905 (=CH_2) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.03 (3 H, s, OAc), 3.31 (3 H, s, OMe), 3.39 (2 H, s, NCH_2Ph), 3.43 (2 H, s, 1-CH_2O), 4.01 (2 H, s, 5-CH_2OAc), 4.59 (2 H, s, OCH_2O), 4.63 and 4.69 (each 1 H, each s, C=CH_2), 7.29 (5 H, s, Ph); mass spectrum, m/z 373 (M^+); exact mass calcd for $C_{22}H_{31}NO_4$ 373.2251 (M^+), found 373.2253.

(+)-(1*R*,5*S*)-3-Benzyl-5-(hydroxymethyl)-1-[((methoxymethyl)oxy)methyl]-9-methylene-3-azabicyclo[3.3.1]nonane (18). A mixture of the MOM ether **17** (4.10 g, 11.0 mmol) and 7.5% KOH–EtOH (120 mL) was heated at reflux for 5 h. After evaporation of the solvent, the residue was partitioned between H_2O and CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl solution, dried, and evaporated. The residue was purified by silica gel column chromatography, eluating with hexane–Et_2O (7:3 v/v) to give the alcohol **18** (3.72 g, 100%) as a colorless oil: $[\alpha]_D^{20}$ +1.52° (c 1.44, $CHCl_3$); IR ($CHCl_3$) 3400 (OH), 1100 (O—CH_2—O), 905 (=CH_2) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.32 (3 H, s, OMe), 3.39 (2 H, br s, NCH_2Ph), 3.43 (2 H, s, 1-CH_2O),

3.53 (2 H, d, J = 2 Hz, 5-CH_2OH), 4.59 (2 H, s, OCH_2O), 4.68 and 4.69 (each 1 H, each s, C=CH_2), 7.29 (5 H, s, Ph); mass spectrum, m/z 331 (M^+). Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.52; H, 8.83; N, 4.23. Found: C, 72.70; H, 9.05; N, 4.02.

(+)-(1*R*,5*S*)-3-Benzyl-5-formyl-1-[((methoxymethyl)oxy)methyl]-9-methylene-3-azabicyclo[3.3.1]nonane (19). The alcohol **18** (3.42 g, 10.3 mmol) was subjected to the Swern oxidation as in the case of **10**, and the product was purified by silica gel column chromatography with hexane–AcOEt (9:1 v/v) as eluant to give the aldehyde **19** (3.19 g, 94%) as a yellowish oil: $[\alpha]_D^{24}$ +11.48° (c 2.91, $CHCl_3$); IR ($CHCl_3$) 1725 (C=O), 1100 (O—CH_2—O), 9.05 (=CH_2) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.30 (3 H, s, OMe), 3.42 (4 H, s, NCH_2Ph and 1-CH_2O), 4.56 (2 H, s, OCH_2O), 4.56 and 4.72 (each 1 H, each s, C=CH_2), 7.27 (5 H, s, Ph), 9.57 (1 H, s, CHO); mass spectrum, m/z 329 (M^+); exact mass calcd for $C_{20}H_{27}NO_3$ 329.1989 (M^+), found 329.1991.

(+)-(1*R*,5*R*)-3-Benzyl-1-[((methoxymethyl)oxy)methyl]-5-methyl-9-methylene-3-azabicyclo[3.3.1]nonane (20). (A) The aldehyde **19** (3.19 g, 9.69 mmol) was subjected to the Wolff–Kishner reduction as in the case of **14**, and the product was purified by silica gel column chromatography. Elution with hexane–AcOEt (19:1 v/v) yielded the 5-methyl compound **20** (2.74 g, 81%) as a yellowish oil: $[\alpha]_D^{24}$ +7.51° (c 2.16, $CHCl_3$); IR ($CHCl_3$) 1110 (O—CH_2—O), 905 (=CH_2) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.93 (3 H, s, 5-Me), 3.31 (3 H, s, OMe), 3.24 and 3.43 (each 1 H, each d, each J = 12 Hz, 1-CH_2O), 3.42 (2 H, s, NCH_2Ph), 4.59 (2 H, s, OCH_2O), 4.59 and 4.71 (each 1 H, each s, C=CH_2), 7.28 (5 H, s, Ph); mass spectrum, m/z 315 (M^+). Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.14; H, 9.27; N, 4.44. Found: C, 75.74; H, 9.56; N, 4.47.

(B) To a stirred solution of the optically pure (+)-**22** (1.63 g, 6.01 mmol) in dry CH_2Cl_2 (40 mL) were added $^iPr_2NEt$ (3.68 mL, 21.0 mmol) and MOMCl (0.91 mL, 12.0 mmol) at 0 °C, and the mixture was stirred for 20 h at ambient temperature. The same workup as in the case of **17**, followed by purification using silica gel column chromatography with hexane–AcOEt (19:1 v/v) as eluant, yielded the optically pure **20** (1.83 g, 93%) as colorless oil: $[\alpha]_D^{27}$ +8.10° (c 2.02, $CHCl_3$), spectral data of which were identical with those of the above product.

(+)-(1*R*,5*S*)-1-(Acetoxymethyl)-3-benzyl-5-formyl-9-methylene-3-azabicyclo[3.3.1]nonane (21). The Swern oxidation of the (−)-acetate **12** (167 mg, 0.51 mmol), prepared by the enzymatic acetylation using CCL and vinyl acetate, was carried out as above to give the (+)-aldehyde **21** (118 mg, 71%) as a yellowish oil, $[\alpha]_D^{25}$ +13.63° (c 1.18, $CHCl_3$), whose spectral data were identical with those of the (−)-enantiomer **21**.

(+)-(1*R*,5*R*)-3-Benzyl-1-(hydroxymethyl)-5-methyl-9-methylene-3-azabicyclo[3.3.1]nonane (22). (A) Wolff–Kishner reduction of the aldehyde **21** (59.5 mg, 0.18 mmol) was carried out as above to give the (+)-methylated compound **22** (36.7 mg, 74%) as a yellowish oil, $[\alpha]_D^{25}$ +4.30° (c 0.73, MeOH), whose spectral properties were superimposable on those of the (−)-enantiomer **15**.

(B) A mixture of the above 5-methyl compound **20** (2.78 g, 8.82 mmol), prepared via the enzymatic hydrolysis, and concentrated HCl (14 mL) in MeOH (80 mL) was stirred for 15 h at 60 °C. After basification by addition of 10% NH_4OH under cooling, the mixture was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2, and the extract was washed with saturated aqueous NaCl solution, dried, and evaporated to give a residue, which was chromatographed on silica gel. Elution with hexane–AcOEt (9:1 v/v) afforded **22** (2.39 g, 100%) as a colorless oil, $[\alpha]_D^{25}$ +3.47° (c 0.94, MeOH), which was converted into the corresponding hydrochloride. Recrystallization of the salt from MeOH-ether gave colorless pillars, mp 190–192 °C, which were reconverted, as in the case of the enantiomer **15**, into the free base, as a colorless oil: $[\alpha]_D^{26}$ +4.31° (c 1.77, MeOH). Its properties were identical with those of the above compound, prepared by method A.

Conversion of the 1-Hydroxymethylated Compounds 15 and 22 into the MTPA Esters. The above alcohols **15** and **22** (6 mg each) were treated with (−)-(*S*)-α-methoxy-α-((trifluoromethyl)phenyl)acetyl chloride in the presence of Et_3N and DMAP, as above, and the products were purified by silica gel column chromatography. Elution with hexane–AcOEt (19:1 v/v) gave the MTPA esters (11 mg, 100% each) as a colorless oil. The optical purity (% ee) was determined from the ^1H NMR signal intensities at 4.21 and 4.24 ppm (J = 11 Hz; derived from **22**) and at 4.20 and 4.27 ppm (J = 11 Hz; derived from **15**) due to CH_2-OMTPA at 500 MHz.

(+)-(1*R*,5*R*,9*R*)-3-Benzyl-9-(hydroxymethyl)-1-[((methoxymethyl)oxy)methyl]-5-methyl-3-azabicyclo[3.3.1]nonane (23). To a stirred solution of the optically pure olefin (+)-**20** (2.35 g, 7.14 mmol) and BF_3·Et_2O (3.51 mL, 28.6 mmol) in dry diglyme (25 mL) was slowly added a solution of $NaBH_4$ (0.92 g, 24.3 mmol) in dry diglyme (45 mL) at −23 °C under Ar, and the mixture was stirred for 18 h at −23 °C. To the resulting mixture was added Me_3NO (11.1 g, 99.9 mmol) at room temperature, and the mixture was stirred for 11 h at 120 °C. After addition of 10% NH_4OH under cooling with ice, the mixture was extracted with ether. The extract was washed with saturated aqueous NaCl solution, dried, and evaporated to give a residue, which was subjected to flash chromatography. Elution with benzene–AcOEt (17:3 v/v) afforded the (+)-(9*S*)-hydroxymethyl compound **24** (0.04 g, 2%) as a colorless oil: $[\alpha]_D^{27}$ −3.55° (c 0.88, $CHCl_3$); IR ($CHCl_3$) 3475 (OH), 1110 (O—CH_2—O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (3 H, s, 5-Me), 3.24 and 3.38 (each 1 H, each d, J = 10 Hz, 1-CH_2O), 3.33 (2 H, br s, NCH_2Ph), 3.34 (3 H, s, OMe), 3.72 (1 H, d, J = 11 Hz, 9-CH_2OH), 3.80 (1 H, dd, J = 7 and 11 Hz, 9-CH_2OH), 4.58 (2 H, s, OCH_2O), 7.27 (5 H, s, Ph); mass spectrum, m/z 333 (M^+).

Further elution with benzene–AcOEt (17:3 v/v) gave the (+)-(9*R*)-hydroxymethyl compound **23** (1.86 g, 78%) as a colorless oil: $[\alpha]_D^{28}$ +1.87° (c 0.63, $CHCl_3$); IR ($CHCl_3$) 3450 (OH), 1110 (OCH_2O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (3 H, s, 5-Me), 3.30 (3 H, s, OMe), 3.29 and 3.45 (each 1 H, each d, J = 10 Hz, 1-CH_2O), 3.41 (2 H, s, NCH_2Ph), 3.69 (1 H, d, J = 11 Hz, 9-CH_2OH), 3.80 (1 H, dd, J = 3 and 11 Hz, 9-CH_2OH), 4.57 (2 H, s, OCH_2O), 7.26 (5 H, s, Ph); mass spectrum, m/z 333 (M^+). Anal. Calcd for $C_{20}H_{31}NO_3$: C, 72.02; H, 9.38; N, 4.20. Found: C, 72.05; H, 9.35; N, 3.84.

(−)-(1*R*,5*R*,9*R*)-9-(hydroxymethyl)-3-(methoxycarbonyl)-1-[((methoxymethyl)oxy)methyl]-5-methyl-3-azabicyclo[3.3.1]nonane (26). To a solution of the (9*R*)-hydroxymethyl compound **23** (1.73 g, 5.19 mmol) in MeOH (29 mL) were added 10% Pd-C (1.7 g) and anhydrous HCO_2NH_4 (1.62 g, 25.6 mmol), and the mixture was heated at reflux for 10 min. After being cooled, the mixture was filtered through Celite, and the catalyst was washed with $CHCl_3$ and hexane. The combined filtrates and washings were evaporated to give the crude amine, which was used for the next reaction without purification.

To a rigorously stirred solution of the above amine in benzene (72 mL) were added 44% aqueous K_2CO_3 solution (48 mL) and methyl chloroformate (7.9 mL, 0.103 mol), and the stirring was continued for 16 h at ambient temperature. The organic layer was washed with saturated aqueous NaCl solution, dried, and evaporated to give a residue, which was chromatoraphed on silica gel. Elution with hexane–AcOEt (7:3 v/v) gave the carbamate **26** (1.37 g, 88%) as a yellowish oil: $[\alpha]_D^{26}$ −4.06° (c 1.17, $CHCl_3$); IR ($CHCl_3$) 3450 (OH), 1680 (NC=O), 1100 (O—CH_2—O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.98 (3 H, s, 5-Me), 3.38 (3 H, s, OMe), 3.16–3.60 (2 H, m, 1-CH_2O), 3.70 (3 H, s, CO_2Me), 4.63 (2 H, s, OCH_2O); mass spectrum, m/z 301 (M^+). Anal. Calcd for $C_{15}H_{27}NO_5$: C, 59.76; H, 9.03; N, 4.65. Found: C, 59.99; H, 9.39; N, 4.35.

(−)-(1*R*,5*R*,9*R*)-9-Formyl-3-(methoxycarbonyl)-1-[((methoxymethyl)oxy)methyl]-5-methyl-3-azabicyclo[3.3.1]nonane (27). The carbamate **26** (1.10 g, 3.65 mmol) was subjected to the Swern oxidation as above, and the crude product was purified by silica gel column chromatography with hexane–AcOEt (4:1 v/v) as eluant to afford the aldehyde **27** (0.94 g, 86%) as a colorless oil: $[\alpha]_D^{25}$ −14.82° (c 1.13, $CHCl_3$); IR ($CHCl_3$) 1710 (C=O), 1685 (NC=O), 1110 (O—CH_2—O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.92 (3 H, s, 5-Me), 3.30 (3 H, s, OMe), 3.20 and 3.35 (each 1 H, each d, each J = 10 Hz, 1-CH_2O), 3.73 (3 H, s, CO_2Me), 4.52 (2 H, s, OCH_2O), 10.00 (1 H, d, J = 5 Hz, CHO); mass spectrum, m/z 299 (M^+); exact mass calcd for $C_{15}H_{25}NO_5$ 299.1731 (M^+), found 299.1732.

(*E*)-(−)-(1*R*,5*R*,9*R*)-3-(Methoxycarbonyl)-1-[((methoxymethyl)oxy)methyl]-9-(2-methoxystyryl)-5-methyl-3-azabicyclo[3.3.1]nonane (28). To a stirred suspension of (2-methoxybenzyl)triphenylphosphonium bromide (3.95 g, 8.51 mmol) in dry THF (47 mL) was added 1.82 M ^{n}BuLi–hexane (3.78 mL, 6.81 mmol) under Ar. After having been stirred for 30 min at room temperture, a solution of the aldehyde **27** (1.02 g, 3.41 mmol) in dry THF (24 mL) was slowly added to the resulting mixture with stirring. The mixture was stirred for 3 h at room temperature and then partitioned between H_2O and ether. The organic layer was washed with saturated aqueous NaCl solution, dried, and evaporated. The residue was subjected to silica gel column chromatography, eluting with hexane–AcOEt (4:1 v/v), to give the (*E*)-styrene **28** (1.36 g, 99%) as a colorless oil: $[\alpha]_D^{24}$ −4.47° (c 1.49, $CHCl_3$); IR ($CHCl_3$) 1680 (NC=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.80 (3 H, s, 5-Me), 3.30 (3 H, s, OMe), 3.10 and 3.36 (each 1 H, each d, each J = 11 Hz, 1-CH_2O), 3.73 (3 H, s, CO_2Me), 3.83 (3 H, s, ArO*Me*), 4.54 (2 H, s, OCH_2O), 6.22 (1 H, dd, J = 10 and 16 Hz, CH=CHAr), 6.86 (1 H, d, J = 16 Hz, CH=C*H*Ar); mass spectrum, m/z 403 (M^+); exact mass calcd for $C_{23}H_{33}NO_5$ 403.2357 (M^+), found 403.2359.

(*E*)-(−)-(1*R*,5*R*,9*R*)-1-(Hydroxymethyl)-3-(methoxycarbonyl)-9-(2-methoxystyryl)-5-methyl-3-azabicyclo[3.3.1]nonane (29). A mixture of the (*E*)-styrene **28** (1.29 g, 3.20 mmol) and concentrated HCl (6 mL) in MeOH (30 mL) was heated for 12 h at 55 °C. After basification by addition of 10% NH_4OH under ice cooling, the mixture was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2, and the extract was washed with saturated aqueous NaCl solution, dried, and evaporated. The crude product was purified by silica gel column chro-

matography on silica gel with hexane–AcOEt (3:2 v/v) as eluant to afford the olefinic alcohol **29** (1.15 g, 100%) as a colorless oil: $[\alpha]_D^{25}$ −20.67° (*c* 1.76, $CHCl_3$); IR ($CHCl_3$) 3500 (OH), 1685 (NC=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.80 (3 H, s, 5-Me), 3.73 (3 H, s, CO_2Me), 3.84 (3 H, s, ArOMe), 6.32 (1 H, dd, *J* = 10 and 16 Hz, C*H*=CHAr), 6.91 (1 H, d, *J* = 16 Hz, CH=C*H*Ar); mass spectrum, *m/z* 359 (M^+); exact mass calcd for $C_{21}H_{29}NO_4$ 359.2095 (M^+), found 359.2097.

(−)-(1*S*,5*R*,9*R*)-1-(2-(Methoxycarbonyl)ethenyl)-3-(methoxycarbonyl)-5-methyl-9-{2′-[1″-(2″-oxo)cyclohex-3″-enyl]ethyl}-3-azabicyclo[3.3.1]nonane (31). To dry liquid NH_3 (10 mL) were added a solution of the olefinic alcohol **29** (56.2 mg, 0.16 mmol) in dry THF (1 mL), Na (22 mg, 0.94 mmol), and EtOH (0.09 mL) under stirring, and the mixture was stirred at −33 °C. Na and EtOH were added, and the reaction was monitored by TLC analysis until the reaction was completed. After evaporation of liquid NH_3 at ambient temperature, the resulting mixture was neutralized with saturated aqueous NH_4Cl solution. After concentration under reduced pressure, the residue was taken up into CH_2Cl_2, and the organic solution was washed with saturated aqueous NaCl solution, dried, and evaporated. The mixture of the above product and 3 N HCl (2.4 mL) in MeOH (3.0 mL) was heated with stirring for 3 h at 60 °C. After basification with saturated aqueous $NaHCO_3$ solution, under ice cooling, the mixture was concentrated under reduced pressure. The residue was taken up into CH_2Cl_2 and the organic layer was washed with saturated aqueous NaCl solution, dried, and evaporated. The residue was chromatographed on silica gel, eluting with hexane–AcOEt (3:2 v/v) to afford a mixture of enones **30** and **32** (40 mg, 73%) in the ratio of 6:1 as a colorless oil [$[\alpha]_D^{26}$ −4.17° (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 3470 (OH), 1680 (C=O), 1670 (N—C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.86 (3 H, s, 5-Me), 3.68 (3 H, s, CO_2Me), 5.98 (1 H, d, *J* = 11 Hz, COC*H*=CH), 6.70–7.20 (1 H, m, COCH=C*H*); mass spectrum, *m/z* 349 (M^+); exact mass calcd for $C_{20}H_{31}NO_4$ 349.2251 (M^+), found 349.2253] which was used for the following reaction without further purification.

To a solution of the mixture of enones **30** and **32** (385 mg, 1.10 mmol) in dry CH_2Cl_2 (12 mL) were added Florisil (475 mg) and PCC (475 mg, 2.20 mmol), and the mixture was stirred for 2 h. After filtration through alumina (grade III), followed by washing with ether, the combined filtrates were evaporated to give a residue, which was taken up into ether. The organic solution was washed with 1 N − HCl and saturated aqueous NaCl solution, dried over $MgSO_4$, and evaporated. The residue was subjected to column chromatography on silica gel with hexane–AcOEt (3:1 v/v) as eluant to give the corresponding aldehydes (358 mg, 93%) as a colorless oil: $[\alpha]_D^{27}$ −10.79° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 1718 and 1684 (C=O) cm^{-1}; mass spectrum, *m/z* 347 (M^+); exact mass calcd for $C_{20}H_{29}NO_4$ 347.2095 (M^+), found 347.2096.

A mixture of the above aldehydes (302 mg, 0.87 mmol) and (methoxycarbonylmethylene)triphenylphosphorane (867 mg, 2.59 mmol) in dry MeCN (6 mL) was heated at reflux for 3 days under Ar. After dilution with benzene, the mixture was washed with H_2O and saturated aqueous NaCl solution, dried, and evaporated. The residue was chromatographed on silica gel, eluating with hexane–AcOEt (3:2 v/v) to give an oil, which was further purified by HPLC with hexane–AcOEt (4:1 v/v) as eluant. The first crop gave the isomer **33** (43 mg, 12%) as a colorless oil: $[\alpha]_D^{29}$ −60.90° (*c* 1.54, $CHCl_3$); IR ($CHCl_3$) 1709 and 1690 (C=O), 1678 (NC=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.92 (3 H, s, 5-Me), 3.72 (3 H, s, >NCO_2Me), 3.75 (3 H, s, CO_2Me), 5.71 (1 H, d, *J* = 17 Hz, CH=C*H*CO_2), 6.77 (1 H, d, *J* = 17 Hz, C*H*=$CHCO_2$), 6.74–7.00 (1 H, m, =CH—); mass spectrum, *m/z* 403 (M^+). The second crop afforded the enone ester **31** (241 mg, 69%) as a colorless oil: $[\alpha]_D^{29}$ −44.84° (*c* 1.52, $CHCl_3$); IR ($CHCl_3$) 1709 and 1690 (C=O), 1678 (NC=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.92 (3 H, s, 5-Me), 2.77–2.88, 2.91–3.06, and 3.61–4.09 (4 H, m, CH_2NCH_2), 3.72 (3 H, s, NCO_2Me), 3.75 (3 H, s, CO_2Me), 5.71 (1 H, d, *J* = 17 Hz, C*H*=$CHCO_2$), 5.93 (1 H, d, *J* = 10 Hz, CH=C*H*CO), 6.77 (1 H, d, *J* = 17 Hz, C*H*=$CHCO_2$), 6.74–7.00 (1 H, m, C*H*=CHCO); mass spectrum, *m/z* 403 (M^+); exact mass calcd for $C_{23}H_{33}NO_5$ 403.2357 (M^+), found 403.2359.

(+)-8α,12α-Ethano-16,17-imino-*N*,11β-bis(methoxycarbonyl)-14-oxo-5β,9β,10α-podocarpane (34). To a stirred solution of 1.45 M ^{n}Bu-Li–hexane (0.11 mL, 0.16 mmol) in hexane (1 mL) was added HN-$(SiMe_3)_2$ (0.034 mL, 0.16 mmol) at 0 °C under Ar, and the mixture was stirred for 10 min at 0 °C and for 10 min at ambient temperature. After having been cooled at −78 °C, a solution of the enone ester **31** (43.8 mg, 0.11 mmol) in a mixture of hexane–Et_2O (8:3 v/v; 1.1 mL) was added to the stirred mixture. The resulting mixture was stirred for 30 min at −78 °C and for 1.5 h at room temperature and then poured onto silica gel (5 g) under ice cooling. After elution using AcOEt, followed by evaporation of the eluate, the residue was subjected to HPLC with hexane–AcOEt (4:1 v/v) as eluant to give the pentacyclic ketone **34** (25.2 mg, 58%) as a colorless oil: $[\alpha]_D^{24}$ +9.35° (*c* 1.27, $CHCl_3$); IR ($CHCl_3$) 1728 and 1717 (C=O), 1675 (NC=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 and 0.87 [3 H (2.5:1), s, 4-Me], 3.69 and 3.72 [3 H (1:2.5), s, NCO_2Me), 3.72 and 3.74 [3 H (2.5:1), s, CO_2Me], 3.20–4.20 (4 H, m, CH_2NCH_2); mass spectrum, *m/z* 403 (M^+); exact mass calcd for $C_{23}H_{33}NO_5$ 403.2357 (M^+), found 403.2359. The spectral data were identical with those of the racemate of **34** as colorless pillars, mp 172–173 °C, whose structure was determined by X-ray analysis.[10]

(+)-8α,12α-Ethano-16,17-imino-*N*-(methoxycarbonyl)-14-oxo-5β,9β,10α-podocarpane-11β-carboxylic Acid (35). A mixture of the keto ester **34** (63.4 mg, 0.16 mmol) and 5% KOH–EtOH (3 mL) was heated at reflux for 4 h and then concentrated under reduced pressure. The residue was partitioned between H_2O and ether, and the aqueous layer was acidified with 10% HCl under ice cooling. Extraction with CH_2Cl_2, followed by drying and evaporation of the solvent gave a residue, which was purified by silica gel column chromatography. Elution with MeOH–$CHCl_3$ (1:24 v/v) afforded the carboxylic acid **35** (55.1 mg, 90%) as a yellowish oil: $[\alpha]_D^{29}$ +4.01° (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 3200–2400 (OH), 1720 and 1695 (C=O), 1675 (NC=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.85 (3 H, s, 4-Me), 3.30–4.10 (4 H, m, CH_2NCH_2), 3.74 (3 H, s, CO_2Me); mass spectrum, *m/z* 389 (M^+); exact mass calcd for $C_{22}H_{31}NO_5$ 389.2200 (M^+), found 389.2202.

(−)-8α,12α-Ethano-16,17-imino-*N*-(methoxycarbonyl)-14-oxo-5β,9β,10α-podocarpane (36). To a stirred solution of the carboxylic acid **35** (48.1 mg, 0.12 mmol) in dry benzene (2 mL) were added DMF (2 drops) and $(COCl)_2$ (0.05 mL, 0.1 mmol), and the mixture was stirred for 2 h at ambient temperature. After evaporation, the residue was taken up into dry benzene, and the mixture was further evaporated to give the acid chloride, which was used in the following reaction without purification.

A mixture of 2-mercaptopyridine-1-oxide sodium salt (22 mg, 0.148 mmol) and DMAP (5 mg, 0.04 mmol) in dry toluene (6 mL) was heated at reflux in a Dean–Stark apparatus to remove H_2O. To the resulting mixture was added a solution of the above acid chloride in dry toluene (2 mL), and the mixture was heated at reflux for 15 min. After addition of a solution of ^{n}Bu$_3$SnH (108 mg, 0.371 mmol) and AIBN (3 mg) in dry toluene (3 mL) during 10 min, the mixture was heated at reflux for 3 days. After addition of CCl_4 (20 mL) followed by heating for 1 h at 80 °C, evaporation of the mixture gave a residue, to which were added saturated aqueous KF (9 mL) solution and saturated I_2 in CH_2Cl_2 (9 mL) solution. After having been stirred vigorously for 12 h, the mixture was filtered through Celite and washed with CH_2Cl_2. The organic layer of the filtrate was washed with 2 M aqueous $Na_2S_2O_3$ solution and saturated aqueous NaCl solution, dried over Na_2SO_4, and evaporated. The residue was subjected to chromatography on silica gel with hexane–AcOEt (4:1 v/v) as eluant, to yield the carbamate **36** (27.5 mg, 64%) as a colorless solid: mp 120–123 °C; $[\alpha]_D^{24}$ −20.84° (*c* 0.87, $CHCl_3$); IR ($CHCl_3$) 1713 (C=O), 1680 (NC=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.83 and 0.85 [3 H (2.5:1), s, 4-Me], 3.08–4.20 (4 H, m, CH_2NCH_2), 3.72 and 3.74 [3 H (5:1), s, CO_2Me]; mass spectrum, *m/z* 345 (M^+); exact mass calcd for $C_{21}H_{31}NO_3$ 345.2302 (M^+), found 345.2304; CD (MeOH) $[\theta]^{25}$ +4416 (293 nm) (positive maximum).

(−)-*N*-Acetyl-8α,12α-ethano-16,17-imino-14-oxo-5β,9β,10α-podocarpane (2). To a solution of the carbamate **36** (8.6 mg, 0.025 mmol) in dry $CHCl_3$ (1 mL) was added Me_3SiI (0.005 mL, 0.037 mmol), and the mixture was heated in a sealed tube at 60 °C for 2 h. After addition of MeOH (0.004 mL, 0.01 mmol), evaporation of the mixture gave a residue, which was dissolved in 0.25 M MeONa in MeOH (2 mL). Evaporation of the solvent gave the crude amine, which was used in the next reaction without purification.

To a vigorously stirred solution of the amine in CH_2Cl_2 (1 mL) were added saturated aqueous $NaHCO_3$ solution (1 mL) and AcCl (0.01 mL, 0.13 mmol) at ambient temperature, and the mixture was stirred for 12 h at the same temperature. After extraction with CH_2Cl_2, the extract was washed with saturated aqueous NaCl solution, dried, and evaporated. The product was purified by silica gel column chromatography eluting with MeOH–$CHCl_3$ (1:19 v/v) to give the acetamide **2** as a colorless oil, recrystallization of which from ether–hexane afforded colorless pillars (6.8 mg, 83%): mp 172–172.5 °C (lit.[7b] mp 170.5–171 °C; $[\alpha]_D^{23}$ −18.58° (*c* 0.34, MeOH); IR ($CHCl_3$) 1714 (C=O), 1630 (NC=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 and 0.88 [3 H (1:3), s, 4-Me], 2.10 and 2.14 [3 H (3:1), s, NAc], 3.11 and 3.16, 2.76 and 3.61 [each 1 H (3:1), each dd, each *J* = 15 and 1 Hz, NCH_2), 3.34 and 4.55, 3.68 and 4.17 [each 1 H (3:1), each d, each *J* = 15 Hz, NCH_2]; mass spectrum, *m/z* 329 (M^+); exact mass calcd for $C_{21}H_{31}NO_2$ 329.2353 (M^+), found 329.2355; CD (MeOH) $[\theta]^{25}$ +6294 (292 nm) (positive maximum).

X-ray Crystallographic Study of the Perchlorate of 16. A colorless crystal with dimensions of 0.20 × 0.25 × 0.25 mm was used for the data collection on Rigaku automated four-circle diffractometer, equipped with

a rotating anode (50 kV, 200 mA), with use of graphite monochromated Mo Kα radiation (λ = 0.71069 Å). Crystal data are as follows: molecular formula, $C_{28}H_{40}NO_8SCl$; molecular weight, 586.1; orthorhombic space group, $P2_12_12_1$, a = 13.494 (4) Å, b = 18.833 (4) Å, c = 11.323 (8) Å, V = 2877.5 (10) Å^3, Z = 4, D_c = 1.35 g/cm^3; μ(Mo K); 2.48 cm^{-1}. A total of 2808 reflections within 2θ = 52°. The structure was solved by the direct method with a RANTAN81 program with some modification.[23] After the block-diagonal least-squares refinement for non-hydrogen atoms with anisotropic temperature factors, the hydrogen atoms were calculated geometrically and also verified from the difference Fourier map and then included in the refinement with isotropic temperature factors. The final R factor was 0.089 (R_w = 0.087) for 1789 reflections with $|F_o| > 3\sigma(|F_o|)$.

X-ray Crystallographic Study of the Racemate of 34. A colorless crystal,[10] mp 172-173 °C (from Et_2O-hexane), with dimensions of 0.20 × 0.20 × 0.25 mm was used for data collection on the above diffractometer. Crystal data are as follows: $C_{23}H_{33}NO_5$, molecular weight, 403.5; monoclinic space group, $P2_1/c$, a = 18.991 (1) Å, b = 7.651 (1) Å, c = 14.707 (1) Å, β = 93.71 (1)°, V = 2132.4 (3) Å^3, Z = 4, D_c = 1.26 g/cm^3; μ(Mo K), 0.82 cm^{-1}. A total of 4055 reflections within 2θ = 55°. The structure was solved as above, and the final R factor was 0.059 (R_w = 0.051) for 3370 reflections with $|F_o| > 3\sigma(|F_o|)$.

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Supplementary Material Available: Listing of final atomic coordinates, temperature factors, and bond lengths and angles for the perchlorate of **16** and for the racemate of **34** (14 pages). Ordering information is given on any current masthead page.

Monohalogenation of Alkyl Phenyl Ethers in Micellar and Vesicular Media

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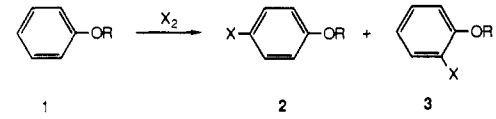
Abstract: The rates and regioselectivities of monohalogenation of C_6H_5OR (**1**: **a**, R = C_5H_{11}; **b**, R = C_9H_{19}; **c**, R = $C_{12}H_{25}$) by chlorine water and bromine water to give 4-XC_6H_4OR (**2**) and 2-XC_6H_4OR (**3**) (X = Cl, Br) have been determined in micellar sodium dodecyl sulfate (**4**) and vesicular sodium 3-[(2,2-diheptadecyl-1,3-dioxolan-4-yl)methoxy]-1-propanesulfonate (**5**) and *dl*-α-dipalmitoylphosphatidylcholine (**6**) in a pH 7.30 phosphate buffer. The **2**/**3** ratios for **1a** were greater in the surfactant media than in buffer/water alone and increased in the order **1a** < **1b** < **1c**. In general the second-order rate constants, k_2, for **1a** were less in the surfactant media than in buffer alone and decreased in the order **1a** > **1b** ≥ **1c**. The combination of kinetic and regioselectivity data indicated that the three ethers, which differ in hydrophilic/hydrophobic character, have different solubilization sites in the surfactant aggregates and react at these sites. The quantitative isolation of products and unreacted starting material from vesicular **5**, a cleavable surfactant, involved acid-catalyzed hydrolysis of **5**, followed by straightforward extractive workup.

There have been numerous studies of organic reactions in surfactant-based organized media.[2] Generally, the focus has been either regio/stereoselectivity or, more often, kinetics. Both factors have been investigated in relatively few systems.[3] But the combination of the two allows a determination of the relationship between solubilization and reaction sites within a surfactant aggregate. We and others have previously reported that micelles can influence the regioselectivity of electrophilic aromatic substitution reactions, including the halogenation and nitration of alkyl phenyl ethers,[4] phenol,[4c,5] and bromobenzene.[6] Herein we report a study of the relative abilities of aqueous micelles and vesicles to control *both* the regioselectivities and rates of monochlorination and monobromination of alkyl phenyl ethers **1** to give para (**2**) and ortho products (**3**) (eq 1).



(1)

1 2 3

1a, R = *n*-C_5H_{11}
b, R = *n*-C_9H_{19}
c, R = *n*-$C_{12}H_{25}$

X = Cl, Br

Results

Halogenations were performed with chlorine water and bromine water in micellar sodium dodecyl sulfate (**4**) and vesicular sodium 3-[(2,2-diheptadecyl-1,3-dioxolan-4-yl)methoxy]-1-propane-

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