Stereocontrolled Total Synthesis of the *Stemona* Alkaloid (−)-Stenine

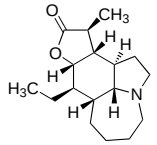
Yoshiki Morimoto,* Maki Iwahashi, Takamasa Kinoshita, and Koji Nishida[a]

Abstract: The *Stemona* alkaloid stenine (**1**), isolated from *Stemona tuberosa* of physiologically active stemonaceous plants, possesses the structurally novel and unique azepinoindole skeleton (B,C,D-ring system). We have achieved the asymmetric total synthesis of (−)-stenine (**1**), starting from 1,5-pentanediol (**10**). The key features are an intramolecular diastereoselective Diels–Alder reaction of the (*E*,*E*,*E*) triene **6**, prepared in a convergent fashion from three components—dienyl chloride **7**, dithiane **8**, and chiral phosphonate **9**—and efficient construction of the tricyclic A,B,D-ring system **29** through thermodynamically controlled regioselective enolization of the bicyclic ketone **25**. In this article, we describe in detail the highly stereocontrolled total synthesis of (−)-stenine (**1**). These results should be useful for the asymmetric total synthesis of another, more complex, molecule: tuberostemonine (**2**), the synthesis of which has never been reported.

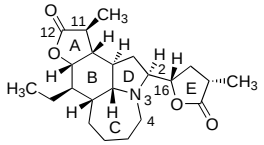
Keywords: alkaloids · asymmetric synthesis · cycloaddition · (−)-stenine · total synthesis

Introduction

Extracts from the roots and rhizomes of stemonaceous plants (*Stemona* and *Croomia*) have long been used in China and Japan as cough remedies for humans and as anthelmintics for domestic animals. A number of related *Stemona* alkaloids have been isolated from these extracts and their structures determined, mostly by X-ray diffraction studies.[1] In this family of alkaloids, stenine (**1**) and tuberostemonine (**2**),[2] isolated from *Stemona tuberosa*, possess the structurally novel and unique azepinoindole skeleton (B,C,D-ring system). Tuberostemonine (**2**) has also been shown to exhibit inhibitory activity on excitatory transmission at the crayfish neuromuscular junction.[3] These pharmacological properties indicate that some of the effects of the crude extracts may be attributable to **2** and that this alkaloid may be a useful tool in the field of neuropharmacology. These and other types of *Stemona* alkaloids have recently been the subject of several synthetic studies[4, 5] because of their stimulating structures and prominent physiological activities. However, the total synthesis of tuberostemonine (**2**) has never been reported.



stenine (**1**)



tuberostemonine (**2**)

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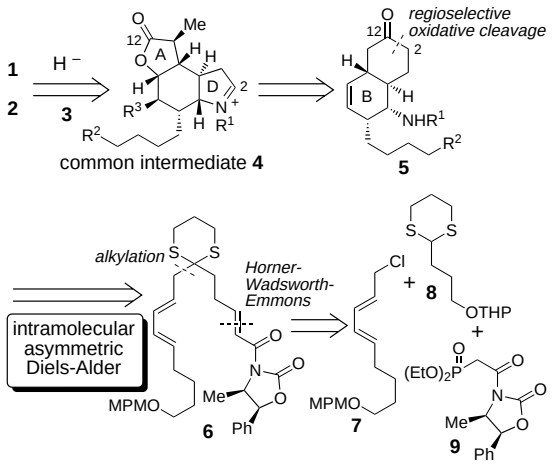
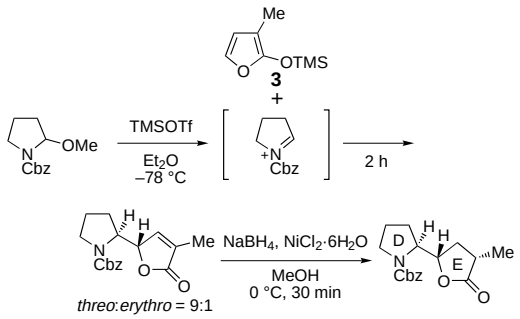
In the course of ongoing investigations into the efficient syntheses of both alkaloids **1** and **2**,[6] Hart and Chen first reported the total synthesis of racemic (±)-stenine (**1**).[7] The asymmetric total synthesis of optically active (−)-stenine (**1**) was afterwards achieved by Wipf et al.[8] and by our group.[9] In this article, we give details of the highly stereocontrolled total synthesis of (−)-stenine (**1**), directed toward the final goal of tuberostemonine (**2**).

Results and Discussion

The retrosynthetic analysis of both alkaloids **1** and **2** is outlined in Scheme 1. We have previously developed an efficient synthetic route to the D,E-ring system—a substructure characteristic of other types of *Stemona* alkaloids as well as of tuberostemonine (**2**)—based on the *threo*-selective addition reaction[10] of 3-methyl-2-trimethylsilyloxyfuran (**3**) to an *N*-acyliminium ion, followed by diastereoselective hydrogenation (Scheme 2).[11] In the context of these results, disconnections of the C(2)−C(16) and N(3)−C(4) bonds pointed to the iminium ion **4** as a conceivable common intermediate for both alkaloids **1** and **2**, in conjunction with hydride and silyl dienol ether **3**, respectively, as nucleophiles. It was anticipated that preparation of the tricyclic ring system **4** could be achieved from the bicyclic ketone **5** by regioselective oxidative cleavage of the C(2)−C(12) bond, followed by stereoselective cyclizations of the A- and D-rings. An intramolecular asymmetric Diels–Alder reaction[12] of the (*E*,*E*,*E*) triene **6**, containing an oxazolidinone chiral auxiliary,[13] was considered to be the most efficient method for simultaneous construction of the decalin skeleton and the four stereogenic centers on the B-ring in **5**. The desired Diels–



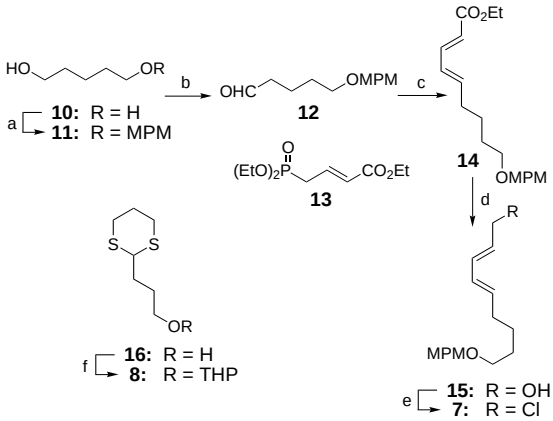
Scheme 1. Retrosynthetic analysis of the *Stemona* alkaloids **1** and **2**. MPM = 4-methoxyphenylmethyl; THP = tetrahydropyranyl.



Scheme 2. Synthetic route to the *Stemona* alkaloid D,E-ring system.

Alder precursor **6** was to be assembled in turn by convergent coupling of three readily available fragments (dienyl chloride **7**, dithiane **8**, and chiral phosphonate **9**[14]).

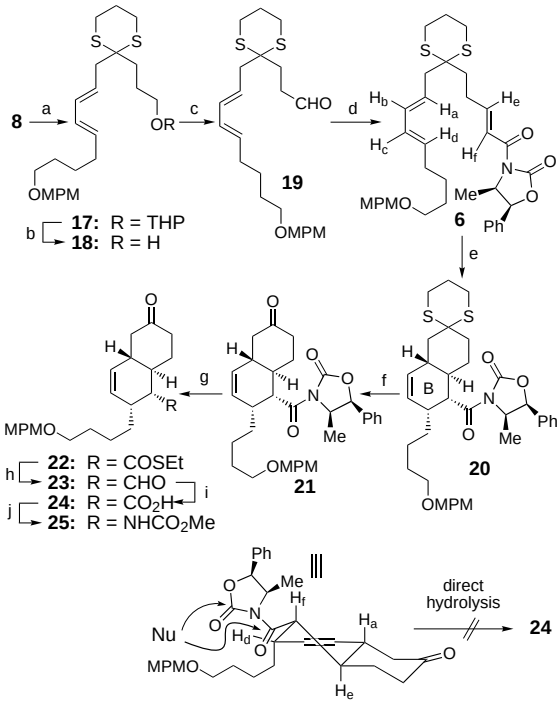
The two requisite fragments **7** and **8** were easily prepared as shown in Scheme 3. Monoprotection of commercially available 1,5-pentanediol (**10**) as an MPM ether and Swern oxidation[15] of the alcohol **11** afforded the aldehyde **12**.[16]



Scheme 3. a) NaH, MPMCl, *N*,*N*-dimethylformamide (DMF), room temperature (RT), 12 h, 73%; b) $(COCl)_2$, dimethyl sulfoxide (DMSO), CH_2Cl_2, then Et_3N, –78 to 0 °C, 25 min, 89%; c) lithium diisopropylamide (LDA), **13**, hexamethylphosphoric triamide (HMPA), THF, –78 °C to RT, 24 h, 70%; d) DIBALH, toluene, –15 °C, 20 min, 98%; e) *n*BuLi, methanesulfonyl chloride (MsCl), THF, –15 °C to RT, 20 h; f) 3,4-dihydro-2*H*-pyran (DHP), camphorsulfonic acid (CSA), CH_2Cl_2, 0 °C, 2 h, 99%.

Horner–Wadsworth–Emmons treatment of the aldehyde **12** with triethyl 4-phosphonocrotonate (**13**) yielded the (*E*,*E*) diene **14**, which was subjected to diisobutylaluminium hydride (DIBALH) reduction and subsequent chlorination to give the desired dienyl chloride **7**. The dithiane **8**[17] was prepared from the known 2-(3-hydroxypropyl)-1,3-dithiane (**16**)[18] by THP protection.

The convergent assembly of the Diels–Alder precursor **6** began with alkylation[19] of the dithiane **8** with the dienyl chloride **7** (Scheme 4). Subsequent removal of the tetrahydropyranyl group in **17** provided the alcohol **18**, which was



Scheme 4. a) *n*BuLi, THF, –25 °C, 4 h, then **7**, HMPA, –78 °C to RT, 20 h; b) 0.1 equiv *p*-TsOH·H_2O, MeOH/THF (7:3), RT, 1.5 h, 68% (three steps from **15**); c) SO_3·Py, DMSO, Et_3N, CH_2Cl_2, 0 °C to RT, 2 h, 85%; d) **9**,[14] LiCl, Et_3N, THF, 0 °C to RT, 24 h, 90%; e) 1.3 equiv Me_2AlCl, CH_2Cl_2, –20 °C, 72 h, 85%; f) $AgNO_3$, *N*-chlorosuccinimide (NCS), CH_3CN/H_2O (4:1), 0 °C, 20 min, 80%; g) LiSEt, THF, 0 °C, 1.5 h, 91%; h) Et_3SiH, 10% Pd/C, acetone, 0 °C to RT, 1.5 h, 100%; i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH/H_2O (5:2), 0 °C to RT, 1 h, 100%; j) diphenylphosphoryl azide (DPPA), Et_3N, DMF, 60 °C, 30 min, then 10 equiv MeOH, 0.2 equiv CuCl, RT, 40 h, 82%.

oxidized with sulfur trioxide/pyridine complex.[20] The modified Horner–Wadsworth–Emmons reaction[21] of the resulting aldehyde **19** with the readily available chiral phosphonate **9**[14] afforded the (*E*,*E*,*E*) triene **6**[22] in good overall yields. The key reaction—the intramolecular asymmetric Diels–Alder reaction of **6**—proceeded smoothly at –20 °C in the presence of 1.3 equivalents of dimethylaluminium chloride as a Lewis acid to produce the bicyclic compound **20** with good facial and complete *endo* selectivities (**20**/B-ring antipode 10:1).[13] The stereochemistry of **20** was assigned as shown on the basis of the diagnostic coupling constants in the ^1H NMR spectrum of **21** ($^3J(a,e) = 11.6$ Hz, $^3J(e,f) = 11.0$ Hz, $^3J(f,d) = 5.5$ Hz) obtained by oxidative hydrolysis of the dithio ketal.[23]

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This good diastereoselectivity in the intramolecular Diels–Alder reaction of **6** may be interpreted by consideration of the transition state as follows (Figure 1). First of all, it has been reported that a six-membered chelate structure between two carbonyl oxygens of an *N*-acyloxazolidinone and the aluminium metal is formed in the presence of more than a stoichiometric amount of dimethylaluminium chloride.[13, 24] In this case, an *s-cis* conformation predominates in the α,β-unsaturated carboximide moiety. When the diene approaches the dienophile from the less hindered side (back side), differentiating the diastereotopic olefinic face, there are *endo* or *exo* transition states. It is assumed that the *endo* transition state would be more favored than the *exo* one, due to a repulsive 1,3-diaxial-like interaction in the *exo* transition state, as shown in Figure 1.[25] Thus, the cycloadduct **20** with the desirable configuration would be produced.

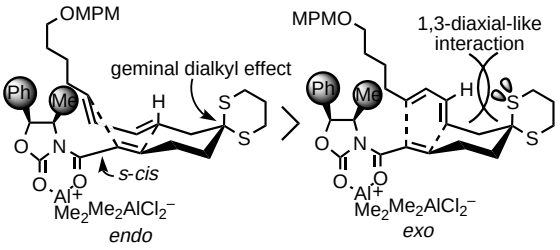
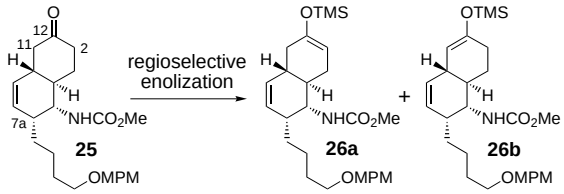


Figure 1. Plausible transition state (*endo* vs. *exo*) explaining the *endo* product **20**.

We encountered a little trouble in removing the chiral auxiliary from the carboximide **21**. It was found that direct hydrolysis of this carboximide **21** using lithium hydroxide resulted in cleavage of the oxazolidinone ring. Evans et al. have reported a new technique[26] for the nondestructive removal of 2-oxazolidinones from extremely hindered imides such as **21**, by employing basic hydrogen peroxide. Treatment of **21** with lithium hydrogen peroxide, however, resulted in hydrolysis both at the exocyclic and at the oxazolidinone carbonyl centers, providing the carboxylic acid **24** and the corresponding ring-opened amide as an inseparable 1:1 mixture. This problem was finally solved by means of a method using alkyl mercaptans.[25a, 27] Removal of the chiral auxiliary could be accomplished through nucleophilic attack of lithium ethanethiolate exclusively on the exocyclic carbonyl group, to afford the thioester **22** in 91% yield. The thioester **22** was converted into the carboxylic acid **24** in quantitative yield by reduction[28] of **22** to aldehyde **23** and oxidation of the resulting aldehyde **23** with sodium chlorite.[29] The introduction of a nitrogen functionality onto the carboxylic acid **24**, giving carbamate **25**, was carried out by the modified Curtius rearrangement according to Shioiri's method[30] in the presence of a catalytic amount of copper(I) chloride.[31]

The next stage involved the oxidative cleavage of the C(2)–C(12) bond in ketone **25** (Scheme 5). The enolization of **25** was examined primarily under kinetic conditions, by using lithium diisopropylamide or lithium hexamethyldisilazane (LHMDS) as a base, followed by addition of chlorotrimethylsilane,[32] to give silyl enol ethers **26a** and **26b** in a ratio of 3:1, with moderate regioselectivities. The regioselective



reaction conditions	**26a** : **26b**
1) LDA, THF, –78 °C 2) TMSCl	3 : 1
1) LHMDS, THF, –78 °C 2) TMSCl	3 : 1
TMSCl, NaI, Et_3N CH_3CN, 50 °C, 3 h	~ 6 : 1

Scheme 5. Regioselective enolization of **25** under kinetic or thermodynamic conditions.

enolization of **25** was, however, accomplished under thermodynamically controlled conditions[25a] to yield predominantly the preferred trimethylsilyl enol ether **26a** (**26a**/**26b** ≈ 6:1). In order to evaluate thermodynamic stabilities of the regioisomeric silyl enol ethers **26a** and **26b** energetically, semiempirical molecular orbital calculations were performed for the C(7a)-methyl counterparts **26a′** and **26b′**, to simplify the calculations. The results calculated by PM3[33] are shown in Figure 2.[34] The optimized structures revealed that **26a′**, with a C(2)=C(12) double bond, is more stable than **26b′**, with a C(11)=C(12) one, by 1.10241 kcal mol^{-1}. At the same time, the approximate populations of silyl enol ethers **26a′** and **26b′** at the reaction temperature (323 K) could be estimated on the basis of the thermodynamic difference as **26a′**/**26b′** ≈ 5.6:1,

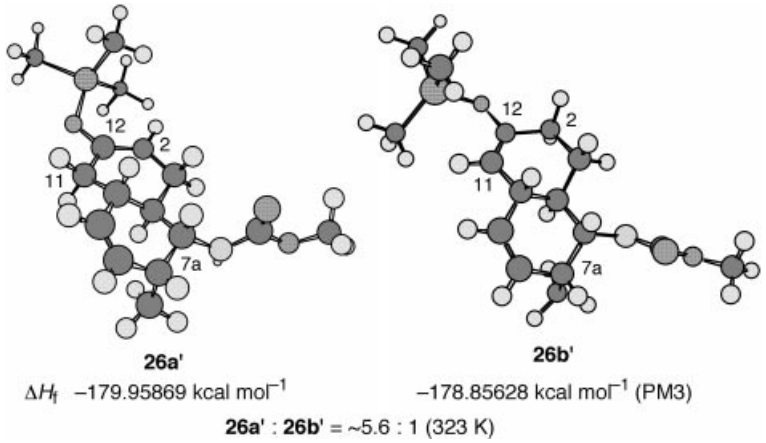
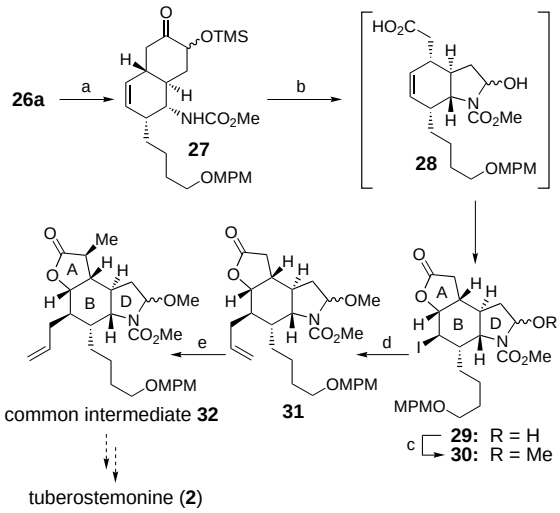


Figure 2. The optimized structures, heats of formation (ΔH_f), and populations at 50 °C of silyl enol ethers **26a′** and **26b′** calculated by PM3.

which is highly consistent with experimental observation (**26a**/**26b** ≈6:1).

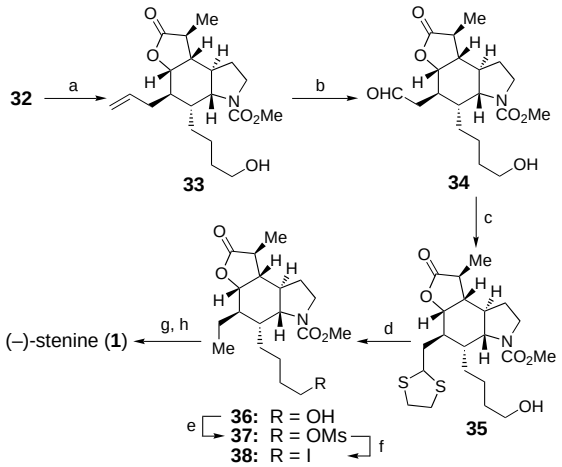
Treatment of the silyl enol ether **26a** with 1.1 equivalents of *m*-chloroperoxybenzoic acid (*m*-CPBA)[35] and subsequent oxidative cleavage of the resulting α-alkoxy ketone **27** with orthoperiodic acid afforded an intermediary carboxylic acid derivative **28**, in situ iodolactonization of which stereoselectively formed the A,B,D-ring system **29** in 50% overall yield from the bicyclic ketone **25** (Scheme 6). After protection of



Scheme 6. a) 1.1 equiv *m*-CPBA, hexane/CH_2Cl_2 (2:1), −15 °C to RT, 2 h; b) H_5IO_6, THF/H_2O (2:1), RT, 2 h, then I_2, $NaHCO_3$, RT, 40 h, 50% (three steps); c) 0.05 equiv CSA, $CH(OMe)_3$, MeOH, CH_2Cl_2, RT, 1 h, 90%; d) 3 equiv allyltributyltin, 0.15 equiv azobis(isobutyronitrile) (AIBN), toluene, 80 °C, 4 h, 80%; e) LDA, HMPA, THF, −78 °C, 30 min, then MeI, −78 °C, 1.5 h, 73%.

the hemiacetal in **29**, a suitably functionalized α-alkoxycarbamate **32**—a common intermediate for stenine (**1**) and tuberostemonine (**2**)—was constructed by stereocontrolled alkylation through a radical process and methylation at the convex side of the molecule by application of Hart's procedure[7] to the iodide **30**. Since α-alkoxycarbamates are in general precursors of *N*-acyliminium ions,[36] attachment of the E-ring to the common intermediate **32** for an approach to tuberostemonine (**2**) according to our methodology shown in Scheme 2 may be possible.

The residual tasks for the total synthesis of stenine (**1**) from the key intermediate **32** were: reduction of an acetal, removal of the terminal C_1 unit from an allylic group, and ring-closure to a perhydroazepine ring (C-ring). Concurrent reduction of the acetal group and the *p*-methoxybenzyl ether in **32** with an excess of triethylsilane in the presence of boron trifluoride etherate in acetonitrile at 0 °C gave the alcohol **33** in good yield (Scheme 7). The allylic group in **33** was converted to an ethyl group by a Lemieux–Johnson oxidation,[37] followed by conversion to the dithiolane **35**, and desulfurization with Raney nickel to provide the alcohol **36**. This was transformed into the iodide **38** in conventional manner, for formation of the perhydroazepine (C) ring. Finally, this C-ring was constructed by removal of the methoxycarbonyl group with trimethylsilyl iodide (TMSI),[7, 38] followed by intramolecular



Scheme 7. a) 5 equiv Et_3SiH, 2.2 equiv $BF_3 \cdot OEt_2$, CH_3CN, 0 °C, 50 min, 82%; b) cat. OsO_4, $NaIO_4$, THF/H_2O (2:1), RT, 1 h, 75%; c) 1,2-ethanedithiol, $BF_3 \cdot OEt_2$, CH_2Cl_2, −15 °C, 45 min, 81%; d) Raney Ni (W-2), EtOH, reflux, 2 h, 85%; e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 88%; f) NaI, acetone, reflux, 2 h, 98%; g) 10 equiv TMSI, CH_2Cl_2, RT, 5 h; h) CH_3CN, reflux, 1 h, 70% (two steps).

N-alkylation of the corresponding amine in refluxing acetonitrile to afford (−)-stenine (**1**) ($[\alpha]_D^{23} = -27.5$ ($c = 0.523$ in MeOH), lit.[2a] $[\alpha]_D = -30.2$ (in MeOH)). The spectroscopic (^{1}H NMR, ^{13}C NMR, IR) and mass spectrometric data of synthetic (−)-stenine (**1**) were consistent with the ^{1}H NMR spectrum of natural stenine (**1**) and the data reported for (±)-stenine (**1**).[7b]

In conclusion, the highly stereocontrolled total synthesis of (−)-stenine (**1**) has been accomplished; the key features being an intramolecular asymmetric Diels–Alder reaction of the triene **6**—prepared in a convergent fashion from three readily available components: dienyl chloride **7**, dithiane **8**, and chiral phosphonate **9**—and efficient construction of the tricyclic A,B,D-ring system **29** through thermodynamically controlled regioselective enolization of the bicyclic ketone **25**. To achieve the asymmetric total synthesis of tuberostemonine (**2**), a more complex target, application of our methodology shown in Scheme 2 to the common intermediate **32** is currently under investigation in our laboratory.

Experimental Section

General methods: Melting points are uncorrected. ^{1}H NMR spectra were recorded in deuteriochloroform and [D_6]benzene on Hitachi R-90H (90 MHz) and JEOL model JNM-GX 400 (400 MHz) spectrometers. ^{13}C NMR spectra were measured in [D_6]benzene on a JEOL model JNM-GX 400 (100 MHz) spectrometer. Infrared (IR) spectra were recorded on a JASCO A-102 spectrophotometer. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Low- and high-resolution (EI and FAB) mass spectra were determined on JEOL model AX-500 and SX-102 spectrometers. Elemental analyses were performed with a Perkin–Elmer 240 C elemental analyzer by the staff at our Analytical Division. Analytical thin-layer chromatography was carried out on precoated silica gel glass plates (Merck TLC plates, silica gel 60 F_{254}). The silica gel used for column chromatography was Merck silica gel 60 (70–230 mesh). All reactions were performed in oven-dried glassware. Tetrahydrofuran (THF) was distilled over sodium/benzophenone. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), diisopropylamine, toluene, acetonitrile (CH_3CN), and 1,1,1,3,3,3-hexamethyldisilazane (HMDS)

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were distilled over calcium hydride. Methanol (MeOH) and ethanol (EtOH) were distilled over magnesium. Acetone was distilled over potassium permanganate. *tert*-Butyl alcohol (*t*BuOH) was distilled over magnesium activated with iodine. Hexane was distilled over sodium metal. *N,N*-Dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and hexamethylphosphoric triamide (HMPA) were distilled over calcium hydride under reduced pressure.

Alcohol 11: 1,5-Pentanediol (**10**) (27.7 mL, 0.264 mol) was added dropwise at room temperature under a nitrogen atmosphere to a solution of sodium hydride (60% in oil suspension, 11.6 g, 0.290 mol) in *N,N*-dimethylformamide (500 mL), and the solution was stirred at this temperature for 1 h. 4-Methoxybenzyl chloride (25.0 mL, 0.185 mol) was added dropwise to the solution, which was stirred at room temperature for 12 h. Saturated aqueous ammonium chloride (50 mL) and water (1.5 L) were added sequentially, and the aqueous layer was extracted with diethyl ether (3 × 300 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (benzene/ethyl acetate 92:8 to 68:32) on silica gel (550 g) to give alcohol **11**[16] (30.5 g, 73.4%) as a colorless oil: $R_f = 0.37$ (benzene/ethyl acetate 70:30); ^{1}H NMR (90 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.26$ (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.62 (t, $J = 6.2$ Hz, 2H), 3.45 (t, $J = 6.0$ Hz, 2H), 1.85–1.15 (m, 7H); IR (film): $\tilde{\nu} = 3410$, 2950, 2870, 1619, 1520, 1470, 1370, 1305, 1250, 1180, 1100, 1039, 820 cm^{-1}; MS (EI): *m/z* (%): 224 (11) $[M]^+$, 137 (98), 122 (25), 121 (100); HR-MS (EI): found: 224.1391 $[M]^+$; $C_{13}H_{20}O_3$ calcd 224.1413; elemental analysis calcd (%) for $C_{13}H_{20}O_3$ (224.3): C 69.61, H 8.99; found: C 69.52, H 8.96.

Aldehyde 12: Dimethyl sulfoxide (12.6 mL, 0.178 mol) dissolved in dichloromethane (50 mL) was added dropwise at −78 °C under a nitrogen atmosphere to a solution of oxalyl chloride (11.6 mL, 0.133 mol) in dichloromethane (150 mL), and the solution was stirred at the same temperature for 10 min. Alcohol **11** (25.0 g, 0.111 mol) dissolved in dichloromethane (60 mL) was added dropwise to the solution, which was stirred at −78 °C for 30 min. Triethylamine (61.8 mL, 0.444 mol) was added to the solution at −78 °C, and the mixture was allowed to warm to 0 °C. After this had been vigorously stirred at 0 °C for an additional 25 min, water (300 mL) was added, and the aqueous layer was extracted with dichloromethane (300 mL and 2 × 100 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate 84:16 to 68:32) on silica gel (500 g) to afford aldehyde **12**[16] (22.1 g, 89.5%) as a colorless oil: $R_f = 0.56$ (hexane/ethyl acetate 70:30); ^{1}H NMR (90 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 9.69$ (t, $J = 1.7$ Hz, 1H), 7.26 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.39 (t, $J = 5.7$ Hz, 2H), 2.55–2.23 (m, 2H), 1.90–1.35 (m, 4H); IR (film): $\tilde{\nu} = 2955$, 2875, 1730, 1618, 1520, 1470, 1370, 1305, 1250, 1179, 1100, 1018, 820 cm^{-1}; MS (EI): *m/z* (%): 222 (6.0) $[M]^+$, 137 (24), 122 (22), 121 (100); HR-MS (EI): found: 222.1245 $[M]^+$; $C_{13}H_{18}O_3$ calcd 222.1256; elemental analysis calcd (%) for $C_{13}H_{18}O_3$ (222.3): C 70.24, H 8.16; found: C 70.30, H 8.12.

Ester 14: *n*-Butyllithium (1.6 M in hexane, 54.9 mL, 88.6 mmol) was added dropwise at 0 °C under a nitrogen atmosphere to a solution of diisopropylamine (12.4 mL, 88.6 mmol) in tetrahydrofuran (150 mL), and the solution was stirred at the same temperature for 30 min. After the solution had been cooled to −78 °C, triethyl 4-phosphonocrotonate (**13**) (19.7 mL, 88.6 mmol) was added dropwise, and the mixture was stirred at −78 °C for an additional 30 min. Aldehyde **12** (19.7 g, 88.6 mmol) dissolved in tetrahydrofuran (50 mL) and hexamethylphosphoric triamide (23.1 mL, 0.133 mol) was added dropwise at −78 °C to the solution, which was allowed to warm to room temperature over 24 h, with stirring. Saturated aqueous ammonium chloride (50 mL) and water (250 mL) were added consecutively to the reaction mixture, and the aqueous layer was extracted with ether (3 × 250 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Purification of the residue by column chromatography (hexane/ethyl acetate 88:12 to 76:24) on silica gel (600 g) yielded ester **14** (19.7 g, 70.0%) as a colorless oil: $R_f = 0.45$ (hexane/ethyl acetate 80:20); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.25$ (d, $J = 8.5$ Hz, 2H), 7.24 (dd, $J = 15.3$, 10.4 Hz, 1H), 6.87 (d, $J = 8.6$ Hz, 2H), 6.16 (dd, $J = 15.3$, 9.8 Hz, 1H), 6.09 (dt, $J = 15.0$, 6.3 Hz, 1H), 5.77 (d, $J = 15.3$ Hz, 1H), 4.42 (s, 2H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 3H), 3.44 (t, $J = 6.4$ Hz, 2H), 2.17 (q, $J = 6.9$ Hz, 2H), 1.68–1.46 (m, 4H), 1.29 (t, $J = 7.3$ Hz, 3H); IR (film): $\tilde{\nu} = 2955$, 2870, 1717, 1648, 1619, 1520, 1470, 1370, 1305, 1250, 1200, 1177, 1140, 1100, 1039, 1002, 872, 820 cm^{-1}; MS (EI): *m/z* (%): 318 (3.0) $[M]^+$, 121 (100); HR-MS (EI): found: 318.1831 $[M]^+$; $C_{19}H_{26}O_4$ calcd 318.1831; elemental analysis calcd (%) for $C_{19}H_{28}O_4$ (318.4): C 71.67, H 8.23; found: C 71.54, H 8.25.

Alcohol 15: Diisobutylaluminium hydride (0.95 M in hexane, 276 mL, 0.262 mol) was slowly added at −15 °C under a nitrogen atmosphere to a solution of ester **14** (38.0 g, 0.119 mol) in toluene (180 mL), and the solution was stirred at the same temperature for 20 min. Appropriate quantities of methanol and water were each carefully added to the solution at −15 °C, and the mixture was then vigorously stirred for 20 min. The resulting mixture was filtered through a pad of Celite, and the filtrates were concentrated under reduced pressure. The residue was purified by column chromatography (benzene/ethyl acetate 92:8 to 68:32) on silica gel (570 g) to give alcohol **15** (32.1 g, 97.6%) as a colorless oil: $R_f = 0.51$ (benzene/ethyl acetate 70:30); ^{1}H NMR (90 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.26$ (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 6.38–5.40 (m, 4H), 4.42 (s, 2H), 4.14 (d, $J = 5.7$ Hz, 2H), 3.80 (s, 3H), 3.39 (t, $J = 5.9$ Hz, 2H), 2.05 (q, $J = 6.6$ Hz, 2H), 1.75–1.15 (m, 5H); IR (film): $\tilde{\nu} = 3360$, 2920, 2880, 1605, 1505, 1452, 1356, 1296, 1241, 1170, 1092, 1030, 988, 819 cm^{-1}; MS (EI): *m/z* (%): 276 (1.5) $[M]^+$, 121 (100); HR-MS (EI): found: 276.1750 $[M]^+$; $C_{17}H_{24}O_3$ calcd 276.1725; elemental analysis calcd (%) for $C_{17}H_{24}O_3$ (276.4): C 73.88, H 8.75; found: C 73.67, H 8.71.

Tetrahydropyranyl ether 8: 3,4-Dihydro-2*H*-pyran (22.8 mL, 0.250 mol) was added dropwise at 0 °C under a nitrogen atmosphere to a solution of 2-(3-hydroxypropyl)-1,3-dithiane (**16**)[18] (42.4 g, 0.238 mol) and camphorsulfonic acid (553 mg, 2.38 mmol) in dichloromethane (350 mL), and the solution was stirred at the same temperature for 2 h. Saturated aqueous sodium hydrogen carbonate (20 mL) and water (400 mL) were added successively, and the aqueous layer was extracted with dichloromethane (350 mL and 2 × 100 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (hexane/ethyl acetate 96:4 to 68:32) on silica gel (640 g) to provide tetrahydropyranyl ether **8**[17] (62.1 g, 99.3%) as a colorless oil: $R_f = 0.48$ (hexane/ethyl acetate 80:20); ^{1}H NMR (90 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 4.55$ (br s, 1H), 4.25–3.25 (m, 5H), 3.10–2.60 (m, 4H), 2.30–1.35 (m, 12H); IR (film): $\tilde{\nu} = 2920$, 1430, 1410, 1340, 1265, 1190, 1130, 1110, 1070, 1025, 980, 900, 860, 805 cm^{-1}; MS (EI): *m/z* (%): 262 (6.0) $[M]^+$, 177 (100), 161 (18), 119 (12), 85 (29); HR-MS (EI): found: 262.1074 $[M]^+$; $C_{12}H_{22}O_2S_2$ calcd 262.1061; elemental analysis calcd (%) for $C_{12}H_{22}O_2S_2$ (262.4): C 54.92, H 8.45; found: C 54.84, H 8.42.

Alcohol 18: *n*-Butyllithium (1.6 M in hexane, 61.6 mL, 99.5 mmol) was added dropwise at −15 °C under a nitrogen atmosphere to a solution of alcohol **15** (26.2 g, 94.8 mmol) in tetrahydrofuran (250 mL), and the solution was stirred at the same temperature for 30 min. Methanesulfonyl chloride (7.70 mL, 99.5 mmol) was added dropwise at −15 °C, and the solution was allowed to warm to room temperature over 20 h, with stirring. Saturated aqueous ammonium chloride (30 mL) and water (300 mL) were added sequentially, and the aqueous layer was extracted with diethyl ether (3 × 200 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford the dienyl chloride **7** as a colorless oil [$R_f = 0.58$ (hexane/ethyl acetate 80:20)], which was used in the next step without further purification.

n-Butyllithium (1.6 M in hexane, 79.9 mL, 0.129 mol) was added dropwise at −25 °C under a nitrogen atmosphere to a solution of dithiane **8** (32.3 g, 0.123 mol) in tetrahydrofuran (250 mL), and the solution was stirred at the same temperature for 4 h. After the solution had been cooled to −78 °C, the above dienyl chloride **7** (27.9 g, 94.8 mmol), dissolved in tetrahydrofuran (50 mL) and hexamethylphosphoric triamide (19.8 mL, 0.114 mol), was added dropwise to the solution, which was allowed to warm to room temperature over 20 h, with stirring. Saturated aqueous ammonium chloride (30 mL) and water (300 mL) were added sequentially, and the aqueous layer was extracted with diethyl ether (3 × 200 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (hexane/ethyl acetate 88:12 to benzene/ethyl acetate 76:24) on silica gel (650 g) to furnish crude tetrahydropyranyl ether **17**, which was also used in the next step without further purification. To obtain physical data for the ether **17**, further purification of a small proportion of the crude product was carried out by column chromatography (hexane/ethyl acetate 88:12 to 76:24) on silica gel to provide the ether **17** as a

colorless oil: $R_f = 0.35$ (hexane/ethyl acetate 80:20); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.25$ (d, $J = 9.2$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 6.08 (dd, $J = 14.7$, 10.4 Hz, 1H), 6.02 (dd, $J = 15.0$, 10.7 Hz, 1H), 5.61 (dt, $J = 14.7$, 7.3 Hz, 1H), 5.60 (dt, $J = 13.8$, 6.9 Hz, 1H), 4.58 (t, $J = 3.4$ Hz, 1H), 4.42 (s, 2H), 3.85 (ddd, $J = 11.0$, 7.9, 3.1 Hz, 1H), 3.80 (s, 3H), 3.73 (dt, $J = 9.8$, 6.4 Hz, 1H), 3.43 (t, $J = 6.4$ Hz, 2H), 3.47 – 3.37 (m, 2H), 2.86 – 2.78 (m, 4H), 2.65 (d, $J = 7.3$ Hz, 2H), 2.07 (q, $J = 7.3$ Hz, 2H), 2.02 – 1.40 (m, 16H); IR (film): $\tilde{\nu} = 2940$, 2855, 1613, 1515, 1450, 1440, 1247, 1120, 1100, 1076, 1035, 990, 815 cm^{-1}; MS (EI): *m*/*z* (%): 520 (1.3) $[M]^+$, 261 (77), 177 (58), 159 (37), 121 (66), 85 (100); HR-MS (EI): found: 520.2684 $[M]^+$; $C_{29}H_{44}O_4S_2$ calcd 520.2681.

A quantity of *p*-toluenesulfonic acid monohydrate (902 mg, 4.74 mmol) was added at room temperature under a nitrogen atmosphere to a solution of the above crude ether **17** (49.4 g, 94.8 mmol) in tetrahydrofuran (90 mL) and methanol (210 mL), and the solution was stirred at the same temperature for 1.5 h. Saturated aqueous sodium hydrogen carbonate (30 mL) and water (400 mL) were added consecutively, and the aqueous layer was extracted with diethyl ether (3 × 200 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (benzene/ethyl acetate 88:12 to 76:24) on silica gel (500 g) to afford alcohol **18** (28.0 g, 67.7% from alcohol **15**) as a colorless oil: $R_f = 0.45$ (benzene/ethyl acetate 80:20); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.25$ (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 6.09 (dd, $J = 14.3$, 10.1 Hz, 1H), 6.02 (dd, $J = 14.6$, 10.4 Hz, 1H), 5.61 (dt, $J = 13.8$, 6.9 Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.65 (t, $J = 6.1$ Hz, 2H), 3.44 (t, $J = 6.4$ Hz, 2H), 2.88 – 2.78 (m, 4H), 2.67 (d, $J = 7.3$ Hz, 2H), 2.07 (q, $J = 7.1$ Hz, 2H), 2.00 – 1.89 (m, 4H), 1.79 – 1.67 (m, 3H), 1.66 – 1.56 (m, 2H), 1.55 – 1.41 (m, 2H); IR (film): $\tilde{\nu} =$ 3440, 2950, 2875, 1613, 1515, 1450, 1440, 1420, 1301, 1248, 1172, 1098, 1035, 990, 820 cm^{-1}; MS (EI): *m*/*z* (%): 436 (0.5) $[M]^+$, 207 (3.0), 177 (100), 159 (10), 121 (38); HR-MS (EI): found: 436.2119 $[M]^+$; $C_{24}H_{36}O_3S_2$ calcd 436.2106; elemental analysis calcd (%) for $C_{24}H_{36}O_3S_2$ (436.7): C 66.01, H 8.31; found: C 66.11, H 8.28.

Aldehyde 19: Dimethyl sulfoxide (40.2 mL, 0.567 mmol), triethylamine (55.4 mL, 0.397 mol), and a portion of sulfur trioxide/pyridine complex (27.1 g, 0.170 mol) were added sequentially at 0 °C under a nitrogen atmosphere to a solution of alcohol **18** (24.4 g, 56.7 mmol) in dichloromethane (150 mL), and the solution was allowed to warm to room temperature. After this had been stirred for 2 h, water (300 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 200 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was subjected to column chromatography (benzene/ethyl acetate 98:2 to 96:4) on silica gel (250 g) to give aldehyde **19** (21.0 g, 85.4%) as a colorless oil: $R_f = 0.55$ (benzene/ethyl acetate 90:10); ^{1}H NMR (90 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 9.80$ (s, 1H), 7.31 (d, $J = 8.6$ Hz, 2H), 6.92 (d, $J = 8.8$ Hz, 2H), 6.29 – 5.26 (m, 4H), 4.42 (s, 2H), 3.80 (s, 3H), 3.43 (t, $J = 5.9$ Hz, 2H), 3.00 – 2.51 (m, 8H), 2.40 – 1.20 (m, 10H); IR (film): $\tilde{\nu} = 2925$, 2840, 1716, 1605, 1507, 1440, 1356, 1298, 1244, 1170, 1098, 1032, 990, 820 cm^{-1}; MS (EI): *m*/*z* (%): 434 (1.2) $[M]^+$, 175 (100), 121 (35); HR-MS (EI): found: 434.1943 $[M]^+$; $C_{24}H_{34}O_3S_2$ calcd 434.1949; elemental analysis calcd (%) for $C_{24}H_{34}O_3S_2$ (434.7): C 66.32, H 7.88; found: C 66.18, H 7.91.

Triene 6: A quantity of lithium chloride (2.31 g, 54.5 mmol) was added at room temperature under a nitrogen atmosphere to a solution of phosphonate **9**[14] (17.9 g, 50.3 mmol) in tetrahydrofuran (180 mL), and the solution was stirred at the same temperature for 5 min. After the solution had been cooled to 0 °C, triethylamine (7.01 mL, 50.3 mmol) was added dropwise, and the solution was again allowed to warm to room temperature. After the solution had then been stirred at the same temperature for 30 min, aldehyde **19** (18.2 g, 41.9 mmol) dissolved in tetrahydrofuran (50 mL) was added dropwise at 0 °C, and the solution was allowed to warm to room temperature over 24 h, with stirring. Water (300 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 200 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate 76:24 to 68:32) on silica gel (364 g) to furnish triene **6** (23.9 g, 90.0%) as a colorless oil: $R_f = 0.47$ (hexane/ethyl acetate 70:30); $[\alpha]_D^{30} = +3.19$ ($c = 1.13$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.45 – 7.34$ (m, 3H), 7.34 – 7.22 (m, 5H), 7.16 (dt, $J = 15.3$, 6.7 Hz, 1H), 6.87 (d, $J = 8.5$ Hz, 2H), 6.10 (dd, $J = 14.7$, 10.4 Hz, 1H), 6.03 (dd, $J = 14.7$, 10.4 Hz, 1H), 5.67 (d, $J = 7.3$ Hz, 1H), 5.69 – 5.55 (m, 2H), 4.80 (quin, $J = 6.7$ Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.44 (t, $J = 6.7$ Hz, 2H), 2.92 – 2.72 (m, 4H), 2.72 – 2.58 (m, 2H), 2.53 – 2.44 (m, 1H), 2.12 – 2.01 (m, 3H), 2.01 – 1.91 (m, 2H), 1.67 – 1.55 (m, 4H), 1.52 – 1.42 (m, 2H), 0.92 (d, $J = 6.7$ Hz, 3H); IR (film): $\tilde{\nu} = 2930$, 2850, 1780, 1685, 1630, 1610, 1510, 1455, 1350, 1250, 1200, 1125, 1100, 1040, 995, 770, 740, 700 cm^{-1}; MS (EI): *m*/*z* (%): 635 (0.93) $[M]^+$, 514 (13), 121 (100); HR-MS (EI): found: 635.2755 $[M]^+$; $C_{36}H_{45}O_5NS_2$ calcd 635.2739; elemental analysis calcd (%) for $C_{36}H_{45}NO_5S_2$ (635.9): C 68.00, H 7.13, N 2.20; found: C 67.91, H 7.10, N 2.21.

Dithiane 20: Dimethylaluminium chloride (0.94 M in hexane, 41.0 mL, 38.5 mmol) was added dropwise at −20 °C under a nitrogen atmosphere to a solution of triene **6** (18.8 g, 29.6 mmol) in dichloromethane (250 mL), and the solution was stirred at the same temperature for 72 h. Water (20 mL) was added at −78 °C, and the mixture was allowed to warm to room temperature, with stirring. Aqueous hydrochloric acid (1.0 M, 200 mL) was added to the resulting mixture, which was stirred for some time. The aqueous layer was extracted with dichloromethane (3 × 250 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was subjected to column chromatography (hexane/ethyl acetate 76:24 to 68:32) on silica gel (380 g) to provide dithiane **20** (16.0 g, 85.1%) as a colorless oil: $R_f = 0.46$ (hexane/ethyl acetate 70:30); $[\alpha]_D^{30} = -50.0$ ($c = 1.21$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.45 – 7.34$ (m, 3H), 7.33 – 7.26 (m, 2H), 7.22 (d, $J = 8.5$ Hz, 2H), 6.85 (d, $J = 8.5$ Hz, 2H), 5.76 (ddd, $J = 9.8$, 4.3, 2.4 Hz, 1H), 5.64 (d, $J = 7.3$ Hz, 1H), 5.42 (d, $J = 9.8$ Hz, 1H), 4.80 (quin, $J = 6.7$ Hz, 1H), 4.38 (s, 2H), 3.80 (dd, $J = 9.8$, 6.1 Hz, 1H), 3.79 (s, 3H), 3.38 (t, $J = 6.1$ Hz, 2H), 2.97 – 2.64 (m, 5H), 2.44 – 2.33 (m, 2H), 2.06 – 1.92 (m, 2H), 1.83 (dd, $J = 12.5$, 2.8 Hz, 1H), 1.78 (dd, $J = 13.4$, 3.7 Hz, 1H), 1.68 – 1.24 (m, 10H), 0.87 (d, $J = 6.7$ Hz, 3H); IR (film): $\tilde{\nu} = 2950$, 2860, 1780, 1738, 1690, 1612, 1514, 1452, 1350, 1300, 1240, 1190, 1110, 1090, 1030, 765, 700 cm^{-1}; MS (EI): *m*/*z* (%): 635 (1.5) $[M]^+$, 528 (1.6), 514 (27), 121 (100), 91 (10); HR-MS (EI): found: 635.2716 $[M]^+$; $C_{36}H_{45}O_5NS_2$ calcd 635.2739; elemental analysis calcd (%) for $C_{36}H_{45}NO_5S_2$ (635.9): C 68.00, H 7.13, N 2.20; found: C 68.05, H 7.11, N 2.18.

Ketone 21: Dithiane **20** (15.9 g, 25.0 mmol) dissolved in acetonitrile (50 mL) was added at 0 °C to a solution of *N*-chlorosuccinimide (10.0 g, 75.0 mmol) and silver nitrate (14.0 g, 82.5 mmol) in acetonitrile (90 mL) and water (30 mL), and the solution was stirred at the same temperature for 20 min. Aqueous sodium thiosulfate (10%, 50 mL) and ether (150 mL) were added, and the resulting mixture was filtered through a pad of Celite. The filtrates were concentrated in vacuo, and the residue was poured into water (100 mL). The aqueous layer was extracted with dichloromethane (3 × 100 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (benzene/ethyl acetate 88:12 to 76:24) on silica gel (477 g) to afford ketone **21** (10.9 g, 80.0%) as a colorless oil: $R_f = 0.54$ (benzene/ethyl acetate 80:20); $[\alpha]_D^{26} = -96.3$ ($c = 0.922$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.45 – 7.35$ (m, 3H), 7.30 (d, $J = 6.7$ Hz, 2H), 7.22 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.5$ Hz, 2H), 5.84 (ddd, $J = 9.9$, 4.7, 1.7 Hz, 1H), 5.68 (d, $J = 7.9$ Hz, 1H), 5.43 (d, $J = 10.4$ Hz, 1H), 4.83 (quintet, $J = 6.9$ Hz, 1H), 4.39 (s, 2H), 3.82 (dd, $J = 11.0$, 5.5 Hz, 1H), 3.79 (s, 3H), 3.39 (t, $J = 6.1$ Hz, 2H), 2.87 – 2.77 (m, 1H), 2.51 – 2.37 (m, 3H), 2.31 – 2.12 (m, 3H), 2.03 (dq, $J = 2.8$, 11.6 Hz, 1H), 1.62 – 1.46 (m, 3H), 1.46 – 1.19 (m, 4H), 0.89 (d, $J = 6.7$ Hz, 3H); IR (film): $\tilde{\nu} = 2960$, 2880, 1790, 1720, 1620, 1521, 1462, 1390, 1360, 1310, 1255, 1233, 1199, 1156, 1125, 1100, 1040, 770, 739, 702 cm^{-1}; MS (FAB): *m*/*z* (%): 546 (22) $[M+H]^+$; HR-MS (FAB): found: 546.2808 $[M+H]^+$; $C_{33}H_{40}O_6N$ calcd 546.2855; elemental analysis calcd (%) for $C_{33}H_{39}NO_6$ (545.7): C 72.64, H 7.20, N 2.57; found: C 72.49, H 7.23, N 2.55.

Thioester 22: *n*-Butyllithium (1.6 M in hexane, 12.5 mL, 20.1 mmol) was added dropwise at 0 °C under a nitrogen atmosphere to a solution of ethanethiol (1.79 mL, 24.1 mmol) in tetrahydrofuran (50 mL), and the solution was stirred at the same temperature for 30 min. Ketone **21** (7.32 g, 13.4 mmol) dissolved in tetrahydrofuran (50 mL) was added dropwise at 0 °C, and the solution was stirred at the same temperature for 1.5 h. Aqueous hydrochloric acid (1.0 M, 10 mL) and brine (150 mL) were added sequentially, and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was subjected to column chromatography (hexane/ethyl acetate 84:16 to 68:32) on silica gel (220 g) to give thioester **22** (5.26 g, 91.1%) as a colorless oil: $R_f = 0.50$

0947-6539/01/0719-4112 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 19

(hexane/ethyl acetate 70:30); $[\alpha]_D^{24} = -114.6$ ($c = 1.04$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.25$ (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.81 (ddd, $J = 10.1$, 4.6, 1.5 Hz, 1H), 5.40 (d, $J = 9.8$ Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.48–3.37 (m, 2H), 2.96–2.81 (m, 3H), 2.58–2.32 (m, 4H), 2.22 (ddd, $J = 12.7$, 6.3, 3.2 Hz, 1H), 2.21–2.09 (m, 2H), 1.98 (dq, $J = 2.4$, 11.1 Hz, 1H), 1.68–1.44 (m, 3H), 1.44–1.25 (m, 4H), 1.25 (t, $J = 7.3$ Hz, 3H); IR (film): $\tilde{\nu} = 2945$, 2860, 1712, 1681, 1610, 1515, 1455, 1360, 1300, 1242, 1170, 1097, 1030, 980, 839, 808, 730 cm^{-1}; MS (EI): m/z (%): 430 (0.8) $[M]^+$, 122 (14), 121 (100); HR-MS (EI): found: 430.2180 $[M]^+$; $C_{25}H_{34}O_4S$ calcd 430.2178; elemental analysis calcd (%) for $C_{25}H_{34}O_4S$ (430.6): C 69.73, H 7.96; found: C 69.79, H 7.92.

Aldehyde 23: Triethylsilane (5.80 mL, 36.3 mmol) was added dropwise at 0 °C under a nitrogen atmosphere to a solution of thioester **22** (5.20 g, 12.1 mmol) and Pd/C (10%, 520 mg) in acetone (60 mL), and the solution was stirred at room temperature for 1.5 h. The reaction mixture was filtered through a pad of Celite, and the filtrates were concentrated under reduced pressure. The residue was purified by column chromatography (benzene/ethyl acetate 92:8 to 76:24) on silica gel (160 g) to provide aldehyde **23** (4.48 g, 100%) as a colorless oil: $R_f = 0.53$ (benzene/ethyl acetate 80:20); $[\alpha]_D^{23} = -104.0$ ($c = 0.924$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 9.80$ (d, $J = 3.1$ Hz, 1H), 7.25 (d, $J = 9.2$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.84 (ddd, $J = 10.1$, 4.6, 2.1 Hz, 1H), 5.44 (d, $J = 9.8$ Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.43 (t, $J = 6.1$ Hz, 2H), 2.69–2.61 (m, 1H), 2.55 (ddd, $J = 11.1$, 5.6, 2.9 Hz, 1H), 2.54–2.10 (m, 6H), 2.07–1.97 (m, 1H), 1.71–1.24 (m, 7H); IR (film): $\tilde{\nu} = 2945$, 2860, 1715, 1610, 1515, 1460, 1360, 1300, 1245, 1172, 1095, 1030, 818, 730 cm^{-1}; MS (EI): m/z (%): 370 (1.8) $[M]^+$, 137 (11), 122 (16), 121 (100); HR-MS (EI): found: 370.2145 $[M]^+$; $C_{23}H_{30}O_4$ calcd 370.2144; elemental analysis calcd (%) for $C_{23}H_{30}O_4$ (370.5): C 74.56, H 8.16; found: C 74.70, H 8.13.

Carboxylic acid 24: Sodium dihydrogen phosphate (6.60 g, 55.0 mmol), 2-methyl-2-butene (23.3 mL, 0.220 mol), and sodium chlorite (3.98 g, 44.0 mmol) were added consecutively, at 0 °C under a nitrogen atmosphere, to a solution of aldehyde **23** (4.06 g, 11.0 mmol) in *tert*-butyl alcohol (40 mL) and water (16 mL). The solution was stirred at room temperature for 1 h. Water (50 mL) was added, and the aqueous layer was adjusted to pH 2 with concentrated hydrochloric acid. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was subjected to column chromatography (chloroform/acetone 99:1 to 68:32) on silica gel (162 g) to furnish carboxylic acid **24** (4.25 g, 100%) as a colorless oil: $R_f = 0.48$ (chloroform/acetone 80:20); $[\alpha]_D^{24} = -121.3$ ($c = 0.838$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.40–5.00$ (br s, 1H), 7.24 (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.82 (ddd, $J = 10.2$, 4.7, 1.6 Hz, 1H), 5.41 (d, $J = 10.4$ Hz, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.51–3.38 (m, 2H), 2.65 (dd, $J = 11.6$, 5.5 Hz, 1H), 2.61–2.53 (m, 1H), 2.53–2.30 (m, 4H), 2.22–2.09 (m, 2H), 1.91–1.80 (m, 1H), 1.69–1.18 (m, 7H); IR (film): $\tilde{\nu} = 3500–2450$, 2930, 2850, 1725, 1710, 1610, 1510, 1460, 1418, 1360, 1300, 1246, 1215, 1173, 1115, 1100, 1035, 820, 735 cm^{-1}; MS (EI): m/z (%): 386 (2.5) $[M]^+$, 137 (18), 121 (100); HR-MS (EI): found: 386.2085 $[M]^+$; $C_{23}H_{30}O_5$ calcd 386.2093; elemental analysis calcd (%) for $C_{23}H_{30}O_5$ (386.5): C 71.48, H 7.82; found: C 71.60, H 7.78.

Carbamate 25: Triethylamine (1.49 mL, 10.7 mmol) and diphenylphosphoryl azide (2.30 mL, 10.7 mmol) were successively added dropwise at room temperature under a nitrogen atmosphere to a solution of carboxylic acid **24** (3.77 g, 9.75 mmol) in *N*,*N*-dimethylformamide (55 mL), and the solution was stirred at 60 °C for 30 min. After the solution had been cooled to room temperature, methanol (3.94 mL, 97.5 mmol) and a portion of copper(I) chloride (193 mg, 1.95 mmol) were added, and the solution was stirred at the same temperature for an additional 40 h. Water (250 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (benzene/ethyl acetate 76:24 to 68:32) on silica gel (151 g) to afford carbamate **25** (3.30 g, 81.5%) as a colorless oil: $R_f = 0.43$ (benzene/ethyl acetate 70:30); $[\alpha]_D^{28} = -82.4$ ($c = 0.745$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.26$ (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 5.77 (ddd, $J = 10.1$, 4.9, 2.7 Hz, 1H), 5.37 (d, $J = 10.4$ Hz, 1H), 4.82 (d, $J = 9.8$ Hz, 0.67H), 4.77 (d, $J = 9.2$ Hz, 0.33H), 4.43 (s, 2H), 3.88 (dt, $J = 5.8$, 10.7 Hz, 1H), 3.80 (s, 3H), 3.67 (s, 2H), 3.66 (s, 1H), 3.46 (t, $J = 6.1$ Hz, 2H), 2.53–2.36 (m, 2H), 2.36–2.19 (m, 2H), 2.19–2.02 (m, 2H), 1.98–1.16 (m, 9H); IR (film): $\tilde{\nu} = 3350$, 2950, 2870, 1712, 1615, 1550, 1532, 1515, 1460, 1360, 1302, 1250, 1180, 1170, 1113, 1100, 1039, 820, 736 cm^{-1}; MS (EI): m/z (%): 415 (3.0) $[M]^+$, 340 (2.4), 294 (17), 137 (22), 121 (100); HR-MS (EI): found: 415.2369 $[M]^+$; $C_{24}H_{33}O_5N$ calcd 415.2368; elemental analysis calcd (%) for $C_{24}H_{33}NO_5$ (415.5): C 69.37, H 8.00, N 3.37; found: C 69.41, H 7.98, N 3.34.

Hemiacetal 29: Triethylamine (5.69 mL, 40.8 mmol) and chlorotrimethylsilane (3.88 mL, 30.6 mmol) were added dropwise at room temperature under a nitrogen atmosphere to a solution of carbamate **25** (4.23 g, 10.2 mmol) and sodium iodide (3.06 g, 20.4 mmol) in acetonitrile (70 mL), and the solution was stirred at 50 °C for 3 h. After the solution had been cooled to room temperature, water (100 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 80 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give silyl enol ethers **26a** and **26b** in a ratio of ≈6:1, as a colorless oil that was used in the next step without further purification: $R_f = 0.80$ (benzene/ethyl acetate 70:30); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.25$ (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.73 (ddd, $J = 9.8$, 4.9, 2.4 Hz, 1H), 5.47 (d, $J = 9.8$ Hz, 1H), 4.85 (d, $J = 6.1$ Hz, 0.86H), 4.73 (s, 0.14H), 4.66 (d, $J = 9.8$ Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.73–3.60 (m, 4H), 3.44 (t, $J = 6.4$ Hz, 2H), 2.46–1.05 (m, 13H), 0.18 (s, 9H); IR (film): $\tilde{\nu} = 3340$, 2945, 2860, 1710, 1615, 1539, 1518, 1460, 1365, 1250, 1190, 1100, 1039, 899, 844 cm^{-1}; MS (EI): m/z (%): 487 (1.8) $[M]^+$, 366 (72), 293 (48), 291 (90), 121 (100), 73 (82).

A quantity of *m*-chloroperoxybenzoic acid (80% purity, 2.41 g, 11.2 mmol) was added at −15 °C under a nitrogen atmosphere to a solution of the above silyl enol ethers **26a** and **26b** (4.97 g, 10.2 mmol) in dichloromethane (25 mL) and hexane (50 mL), and the solution was allowed to warm to room temperature over 2 h, with stirring. Saturated aqueous sodium hydrogen carbonate (80 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 80 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to provide α-trimethylsilyloxy ketone **27** as a colorless oil [$R_f = 0.56$ (benzene/ethyl acetate 70:30)], which was also used in the next step without further purification.

Orthoperiodic acid (4.65 g, 20.4 mmol) was added at room temperature under a nitrogen atmosphere to a solution of the above α-trimethylsilyloxy ketone **27** (5.14 g, 10.2 mmol) in tetrahydrofuran (50 mL) and water (25 mL), and the solution was stirred at the same temperature for 2 h. Sodium hydrogen carbonate (4.28 g, 51.0 mmol) and iodine (7.22 g, 30.6 mmol) were added at room temperature, and the solution was stirred at the same temperature for 40 h. Aqueous sodium thiosulfate (10%, 25 mL) was added, and the resulting mixture was filtered through a pad of Celite. The filtrates were concentrated in vacuo, and the residue was poured into saturated aqueous sodium hydrogen carbonate (25 mL). The aqueous layer was extracted with diethyl ether (3 × 50 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (chloroform/acetone 92:8 to 76:24) on silica gel (206 g) to yield hemiacetal **29** (2.93 g, 50.0% yield from carbamate **25**) as a colorless oil: $R_f = 0.48$ (chloroform/acetone 80:20); $[\alpha]_D^{29} = -10.2$ ($c = 2.57$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.26$ (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.6$ Hz, 2H), 5.56 (br s, 1H), 4.99 (s, 1H), 4.86 (d, $J = 1.8$ Hz, 1H), 4.42 (s, 2H), 3.96 (br s, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 3.50–3.38 (m, 2H), 3.10–2.70 (m, 2H), 2.68 (dd, $J = 16.8$, 6.4 Hz, 1H), 2.44 (d, $J = 17.1$ Hz, 1H), 2.24–2.09 (m, 1H), 2.02 (dd, $J = 12.2$, 5.5 Hz, 1H), 1.79–1.67 (m, 2H), 1.67–1.32 (m, 6H); IR (film): $\tilde{\nu} = 3460$, 2950, 2880, 1800, 1720, 1628, 1530, 1468, 1390, 1375, 1340, 1320, 1262, 1190, 1170, 1150, 1110, 1040, 1015, 985, 950, 915, 832, 750 cm^{-1}; MS (FAB): m/z (%): 556 (26) $[M - OH]^+$; HR-MS (FAB): found: 556.1201 $[M - OH]^+$; $C_{24}H_{31}O_6NI$ calcd 556.1196; elemental analysis calcd (%) for $C_{24}H_{32}INO_7$ (573.4): C 50.27, H 5.62, N 2.44; found: C 50.15, H 5.58, N 2.46.

Methyl acetal 30: Methanol (3.67 mL, 90.6 mmol), trimethyl orthoformate (2.48 mL, 22.7 mmol), and a portion of camphorsulfonic acid (52.7 mg, 0.227 mmol) were added sequentially, at room temperature under a nitrogen atmosphere, to a solution of hemiacetal **29** (2.60 g, 4.53 mmol) in dichloromethane (30 mL), and the solution was stirred at the same temperature for 1 h. Saturated aqueous sodium hydrogen carbonate (5.0 mL) and water (50 mL) were added, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (benzene/ethyl

acetate 76:24 to 52:48) on silica gel (80 g) to furnish methyl acetal **30** (2.39 g, 90.0%) as a colorless oil: $R_f = 0.66$ (benzene/ethyl acetate 50:50); $[\alpha]_D^{27} = -12.6$ ($c = 0.943$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.26$ (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 9.2$ Hz, 2H), 5.20 (br s, 1H), 4.95 (br s, 1H), 4.88–4.84 (m, 1H), 4.42 (s, 2H), 3.98 (br d, $J = 9.2$ Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.43 (t, $J = 6.1$ Hz, 2H), 3.33 (br s, 3H), 2.85 (br s, 1H), 2.75 (ddd, $J = 11.6$, 6.7, 4.3 Hz, 1H), 2.67 (dd, $J = 17.1$, 6.7 Hz, 1H), 2.42 (d, $J = 17.1$ Hz, 1H), 2.16 (dq, $J = 4.0$, 11.9 Hz, 1H), 1.99 (dd, $J = 11.6$, 4.9 Hz, 1H), 1.69–1.32 (m, 7H); IR (film): $\tilde{\nu} = 2950$, 2875, 1790, 1710, 1615, 1517, 1445, 1374, 1305, 1248, 1200, 1155, 1130, 1098, 1083, 1035, 1000, 979, 939, 900, 820, 755, 736 cm^{-1}; MS (FAB): *m/z* (%): 586 (7.4) $[M-H]^+$, 556 (53); HR-MS (FAB): found: 586.1243 $[M-H]^+$; $C_{25}H_{33}O_7NI$ calcd 586.1302; elemental analysis calcd (%) for $C_{25}H_{34}INO_7$ (587.4): C 51.11, H 5.83, N 2.38; found: C 51.00, H 5.78, N 2.39.

Allylation product 31: Azobis(isobutyronitrile) (78.3 mg, 0.477 mmol) and allyltributyltin (3.45 mL, 11.1 mmol) were added at room temperature under a nitrogen atmosphere to a solution of methyl acetal **30** (1.87 g, 3.18 mmol) in toluene (7.0 mL), and the solution was stirred at 80 °C for 4 h. After the solution had been cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was subjected to column chromatography (benzene/ethyl acetate 76:24 to 52:48) on silica gel (112 g) to afford allylation product **31** (1.28 g, 80.0%) as a colorless oil: $R_f = 0.47$ (benzene/ethyl acetate 50:50); $[\alpha]_D^{27} = -52.5$ ($c = 1.20$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.25$ (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.80 (ddt, $J = 16.9$, 10.2, 7.0 Hz, 1H), 5.18 (br s, 1H), 5.12 (d, $J = 8.5$ Hz, 1H), 5.09 (d, $J = 16.5$ Hz, 1H), 4.42 (s, 2H), 4.38 (br s, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.42 (t, $J = 6.7$ Hz, 2H), 3.42–3.28 (m, 1H), 3.33 (br s, 3H), 2.66 (dd, $J = 17.4$, 7.0 Hz, 1H), 2.37 (d, $J = 16.5$ Hz, 1H), 2.45–2.12 (m, 6H), 1.97 (dd, $J = 12.2$, 4.9 Hz, 1H), 1.70–1.22 (m, 7H); IR (film): $\tilde{\nu} = 2950$, 2870, 1780, 1710, 1615, 1517, 1447, 1378, 1310, 1248, 1200, 1170, 1115, 1085, 1035, 996, 945, 897, 820, 780 cm^{-1}; MS (FAB): *m/z* (%): 500 (2.6) $[M-H]^+$, 470 (23); HR-MS (FAB): found: 500.2628 $[M-H]^+$; $C_{28}H_{38}O_7N$ calcd 500.2648; elemental analysis calcd (%) for $C_{28}H_{39}NO_7$ (501.6): C 67.04, H 7.84, N 2.79; found: C 66.99, H 7.90, N 2.76.

Lactone 32: *n*-Butyllithium (1.6 M in hexane, 0.886 mL, 1.43 mmol) was added dropwise at 0 °C under a nitrogen atmosphere to a solution of diisopropylamine (0.201 mL, 1.43 mmol) in tetrahydrofuran (5.0 mL), and the solution was stirred at the same temperature for 30 min. After the solution had been cooled to −78 °C, hexamethylphosphoric triamide (1.54 mL, 8.88 mmol) and lactone **31** (359 mg, 0.716 mmol) dissolved in tetrahydrofuran (6.0 mL) were added dropwise, and the solution was stirred at the same temperature for 30 min. Iodomethane (0.469 mL, 7.52 mmol) was added dropwise at −78 °C, and the solution was stirred at the same temperature for an additional 1.5 h. Saturated aqueous ammonium chloride (3.0 mL) was added at −78 °C, and the resulting mixture was allowed to warm to room temperature, with stirring. The reaction mixture was poured into water (30 mL), and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (benzene/ethyl acetate 76:24 to 68:32) on silica gel to give lactone **32** (268 mg, 72.6%), an intermediate common to stenine (**1**) and tuberostemonine (**2**), as a colorless oil: $R_f = 0.49$ (benzene/ethyl acetate 70:30); $[\alpha]_D^{29} = -58.7$ ($c = 1.32$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.25$ (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.83 (ddt, $J = 17.1$, 9.8, 7.3 Hz, 1H), 5.20 (br s, 1H), 5.12 (d, $J = 9.8$ Hz, 1H), 5.11 (d, $J = 16.5$ Hz, 1H), 4.46 (t, $J = 6.4$ Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 3.42 (t, $J = 6.7$ Hz, 2H), 3.44–3.30 (br s, 1H), 3.33 (br s, 3H), 2.46 (dq, $J = 5.5$, 7.3 Hz, 1H), 2.41–2.15 (m, 4H), 2.08–1.95 (m, 3H), 1.64–1.53 (m, 2H), 1.49–1.22 (m, 5H), 1.28 (d, $J = 7.3$ Hz, 3H); IR (film): $\tilde{\nu} = 2945$, 2860, 1775, 1710, 1612, 1515, 1423, 1375, 1310, 1245, 1197, 1170, 1085, 1030, 1003, 990, 947, 820 cm^{-1}; MS (FAB): *m/z* (%): 514 (0.5) $[M-H]^+$, 484 (3.5) $[M-OMe]^+$; HR-MS (FAB): found: 484.2638 $[M-OMe]^+$; $C_{28}H_{38}O_6N$ calcd 484.2699; elemental analysis calcd (%) for $C_{29}H_{41}NO_7$ (515.6): C 67.55, H 8.01, N 2.72; found: C 67.43, H 7.99, N 2.70.

Alcohol 33: Triethylsilane (0.415 mL, 2.60 mmol) and boron trifluoride etherate (0.140 mL, 1.14 mmol) were added dropwise at 0 °C under a nitrogen atmosphere to a solution of lactone **32** (268 mg, 0.520 mmol) in acetonitrile (7.0 mL), and the solution was stirred at the same temperature for 50 min. Saturated aqueous sodium hydrogen carbonate (15 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (chloroform/acetone 84:16 to 76:24) on silica gel to provide alcohol **33** (156 mg, 82.1%) as a colorless oil: $R_f = 0.40$ (chloroform/acetone 80:20); $[\alpha]_D^{27} = -105.0$ ($c = 0.855$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 5.90-5.75$ (m, 1H), 5.13 (d, $J = 8.5$ Hz, 1H), 5.10 (d, $J = 15.9$ Hz, 1H), 4.51 (br s, 1H), 3.90–3.60 (m, 1H), 3.68 (s, 3H), 3.67–3.57 (m, 2H), 3.38–3.24 (m, 1H), 3.25 (dt, $J = 5.8$, 11.2 Hz, 1H), 2.70–2.33 (m, 1H), 2.52 (dq, $J = 2.6$, 7.5 Hz, 1H), 2.32–2.14 (m, 3H), 2.04 (ddd, $J = 11.3$, 5.5, 2.8 Hz, 1H), 1.99 (dt, $J = 11.3$, 5.7 Hz, 1H), 1.93–1.20 (m, 8H), 1.39 (dq, $J = 8.3$, 11.7 Hz, 1H), 1.31 (d, $J = 7.3$ Hz, 3H); IR (film): $\tilde{\nu} = 3475$, 2950, 1775, 1690, 1640, 1458, 1380, 1297, 1200, 1160, 1113, 1055, 1013, 990, 920, 775, 730 cm^{-1}; MS (EI): *m/z* (%): 365 (16) $[M]^+$, 322 (42), 306 (33), 292 (33), 260 (30), 167 (100), 141 (23), 81 (21), 69 (29), 55 (23); HR-MS (EI): found: 365.2184 $[M]^+$; $C_{20}H_{31}O_5N$ calcd 365.2202; elemental analysis calcd (%) for $C_{20}H_{31}NO_5$ (365.5): C 65.73, H 8.55, N 3.83; found: C 65.85, H 8.50, N 3.81.

Aldehyde 34: A catalytic amount of osmium tetroxide was added at room temperature to a solution of alcohol **33** (156 mg, 0.427 mmol) and sodium metaperiodate (274 mg, 1.28 mmol) in tetrahydrofuran (4.0 mL) and water (2.0 mL), and the solution was vigorously stirred at the same temperature for 1 h. Water (25 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (chloroform/methanol 96:4 to 92:8) on silica gel to yield aldehyde **34** (117 mg, 74.5%) as a colorless oil: $R_f = 0.48$ (chloroform/methanol 90:10); $[\alpha]_D^{27} = -103.1$ ($c = 1.04$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 9.79$ (s, 1H), 4.45 (br s, 1H), 3.85–3.60 (m, 1H), 3.68 (s, 3H), 3.61 (t, $J = 5.8$ Hz, 2H), 3.43–3.18 (m, 2H), 2.80–2.40 (m, 2H), 2.52 (dq, $J = 4.9$, 7.3 Hz, 1H), 2.15–1.20 (m, 11H), 2.04 (dt, $J = 11.6$, 5.8 Hz, 1H), 1.43 (dq, $J = 8.5$, 12.0 Hz, 1H), 1.30 (d, $J = 7.3$ Hz, 3H); IR (film): $\tilde{\nu} = 3450$, 2950, 2880, 1775, 1690, 1460, 1452, 1383, 1357, 1335, 1270, 1205, 1160, 1125, 1025, 990, 930, 775, 733, 700 cm^{-1}; MS (EI): *m/z* (%): 367 (19) $[M]^+$, 294 (16), 168 (17), 167 (100), 69 (16), 55 (20); HR-MS (EI): found: 367.2010 $[M]^+$; $C_{19}H_{29}O_6N$ calcd 367.1995; elemental analysis calcd (%) for $C_{19}H_{29}NO_6$ (367.4): C 62.11, H 7.96, N 3.81; found: C 62.19, H 7.94, N 3.77.

Dithiolane 35: 1,2-Ethanedithiol (32.1 μL, 0.382 mmol) and boron trifluoride etherate (47.0 μL, 0.382 mmol) were added dropwise at −15 °C under a nitrogen atmosphere to a solution of aldehyde **34** (117 mg, 0.318 mmol) in dichloromethane (4.0 mL), and the solution was stirred at the same temperature for 45 min. Water (10 mL) was added at −15 °C, and the resulting mixture was allowed to warm to room temperature with stirring. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (chloroform/methanol 98:2 to 96:4) on silica gel to furnish dithiolane **35** (114 mg, 80.9%) as a colorless oil: $R_f = 0.56$ (chloroform/methanol 90:10); $[\alpha]_D^{29} = -73.7$ ($c = 1.14$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 4.66$ (t, $J = 6.4$ Hz, 1H), 4.52–4.45 (m, 1H), 3.90–3.64 (m, 1H), 3.69 (s, 3H), 3.62 (t, $J = 6.1$ Hz, 2H), 3.33–3.18 (m, 6H), 2.64–2.28 (m, 2H), 2.53 (dq, $J = 2.0$, 7.4 Hz, 1H), 2.05 (ddd, $J = 11.6$, 4.9, 2.1 Hz, 1H), 1.99 (dt, $J = 11.6$, 6.1 Hz, 1H), 2.08–1.22 (m, 10H), 1.38 (dq, $J = 9.2$, 11.8 Hz, 1H), 1.31 (d, $J = 7.3$ Hz, 3H); IR (film): $\tilde{\nu} = 3475$, 2940, 1770, 1690, 1452, 1382, 1355, 1270, 1202, 1160, 1115, 1056, 1000, 775, 734 cm^{-1}; MS (EI): *m/z* (%): 443 (20) $[M]^+$, 325 (23), 324 (87), 167 (22), 119 (34), 118 (72), 105 (100); HR-MS (EI): found: 443.1798 $[M]^+$; $C_{21}H_{33}O_5NS_2$ calcd 443.1800; elemental analysis calcd (%) for $C_{21}H_{33}NO_5S_2$ (443.6): C 56.86, H 7.50, N 3.16; found: C 56.58, H 7.44, N 3.17.

Alcohol 36: A solution of dithiolane **35** (114 mg, 0.257 mmol) and Raney nickel (W-2) (1.14 g) in ethanol (3.0 mL) was stirred and refluxed under a nitrogen atmosphere for 2 h. After the solution had been cooled to room temperature, the reaction mixture was filtered through a pad of Celite, and the filtrates were concentrated in vacuo. The residue was purified by column chromatography (chloroform/methanol 98:2 to 96:4) on silica gel to afford alcohol **36** (77.4 mg, 85.2%) as a colorless oil: $R_f = 0.56$ (chloroform/methanol 90:10); $[\alpha]_D^{27} = -122.2$ ($c = 1.39$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 4.51-4.44$ (br s, 1H), 3.89–3.64 (m, 1H), 3.69 (s, 3H), 3.62 (t, $J = 6.1$ Hz, 2H), 3.35–3.22 (m, 1H), 3.25 (dt, $J = 5.8$, 11.2 Hz, 1H), 2.72–2.32 (m, 1H), 2.52 (dq, $J = 2.4$, 7.5 Hz, 1H), 2.14–2.00 (m, 1H),

0947-6539/01/0719-4114 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 19

2.04 (ddd, $J = 11.6$, 4.9, 2.4 Hz, 1H), 1.98 (dt, $J = 11.6$, 5.8 Hz, 1H), 1.91–1.22 (m, 10H), 1.37 (dq, $J = 8.3$, 11.7 Hz, 1H), 1.31 (d, $J = 7.3$ Hz, 3H), 1.03 (t, $J = 7.3$ Hz, 3H); IR (film): $\tilde{\nu} = 3480$, 2950, 2890, 1775, 1695, 1462, 1450, 1383, 1205, 1161, 1122, 1052, 985, 772, 755 cm^{-1}; MS (EI): *m/z* (%): 353 (8.0) $[M]^+$, 167 (100), 81 (23), 69 (40), 55 (24); HR-MS (EI): found: 353.2194 $[M]^+$; $C_{19}H_{31}O_5N$ calcd 353.2203; elemental analysis calcd (%) for $C_{19}H_{31}NO_5$ (353.5): C 64.56, H 8.84, N 3.96; found: C 64.48, H 8.82, N 3.98.

Mesylate 37: Triethylamine (32.4 μL, 0.232 mmol) and methanesulfonyl chloride (13.4 μL, 0.174 mmol) were added dropwise at 0 °C under a nitrogen atmosphere to a solution of alcohol **36** (41.1 mg, 0.116 mmol) in dichloromethane (3.0 mL), and the solution was stirred at the same temperature for 30 min. Water (10 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to column chromatography (benzene/ethyl acetate 68:32 to 52:48) on silica gel to give mesylate **37** (44.3 mg, 88.4%) as a colorless oil: $R_f = 0.42$ (benzene/ethyl acetate 50:50); $[\alpha]_D^{27} = -107.1$ ($c = 1.48$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 4.51–4.45$ (m, 1H), 4.26–4.16 (m, 2H), 3.90–3.70 (br s, 1H), 3.69 (s, 3H), 3.35–3.25 (m, 1H), 3.25 (dt, $J = 5.8$, 11.4 Hz, 1H), 3.02 (s, 3H), 2.73–2.32 (m, 1H), 2.53 (dq, $J = 1.8$, 7.5 Hz, 1H), 2.12–2.00 (m, 1H), 2.05 (ddd, $J = 11.3$, 5.5, 2.1 Hz, 1H), 1.99 (dt, $J = 11.6$, 5.7 Hz, 1H), 1.90–1.23 (m, 9H), 1.38 (dq, $J = 8.5$, 11.9 Hz, 1H), 1.32 (d, $J = 7.9$ Hz, 3H), 1.04 (t, $J = 7.3$ Hz, 3H); IR (film): $\tilde{\nu} = 2970$, 2950, 2890, 1775, 1700, 1451, 1383, 1355, 1202, 1175, 1123, 980, 950, 930, 775, 750 cm^{-1}; MS (EI): *m/z* (%): 431 (14) $[M]^+$, 167 (100); HR-MS (EI): found: 431.1985 $[M]^+$; $C_{20}H_{33}O_7NS$ calcd 431.1978; elemental analysis calcd (%) for $C_{20}H_{33}NO_7S$ (431.5): C 55.66, H 7.71, N 3.25; found: C 55.72, H 7.67, N 3.24.

Iodide 38: A solution of mesylate **37** (43.8 mg, 0.101 mmol) and sodium iodide (75.7 mg, 0.505 mmol) in acetone (3.0 mL) was stirred and heated under reflux under a nitrogen atmosphere for 2 h. After the solution had been cooled to room temperature, water (10 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography (benzene/ethyl acetate 84:16 to 76:24) on silica gel to provide iodide **38** (46.0 mg, 98.3%) as a colorless oil: $R_f = 0.62$ (benzene/ethyl acetate 70:30); $[\alpha]_D^{31} = -99.7$ ($c = 1.53$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 4.48$ (t, $J = 4.0$ Hz, 1H), 3.89–3.58 (m, 1H), 3.70 (br s, 3H), 3.35–3.12 (m, 4H), 2.70–2.32 (m, 1H), 2.52 (dq, $J = 2.1$, 7.5 Hz, 1H), 2.12–2.00 (m, 1H), 2.04 (ddd, $J = 11.6$, 4.9, 2.4 Hz, 1H), 1.98 (dt, $J = 11.3$, 5.7 Hz, 1H), 1.90–1.22 (m, 9H), 1.37 (dq, $J = 8.5$, 11.6 Hz, 1H), 1.31 (d, $J = 7.3$ Hz, 3H), 1.04 (t, $J = 7.3$ Hz, 3H); IR (film): $\tilde{\nu} = 2975$, 2950, 1775, 1700, 1450, 1382, 1202, 1163, 1120, 985, 774, 750 cm^{-1}; MS (EI): *m/z* (%): 463 (6.0) $[M]^+$, 336 (40), 167 (100); HR-MS (EI): found: 463.1220 $[M]^+$; $C_{19}H_{30}O_4NI$ calcd 463.1219; elemental analysis calcd (%) for $C_{19}H_{30}INO_4$ (463.4): C 49.25, H 6.53, N 3.02; found: C 49.07, H 6.48, N 3.03.

(−)-Stenine (1): Iodotrimethylsilane (0.162 mL, 1.14 mmol) was added dropwise at room temperature under a nitrogen atmosphere to a solution of iodide **38** (52.9 mg, 0.114 mmol) in dichloromethane (2.5 mL), and the solution was stirred at the same temperature for 5 h. Methanol (0.5 mL) was added, and the solution was stirred for some time. Saturated aqueous sodium hydrogen carbonate (1.0 mL) and aqueous sodium thiosulfate (10%, 2.0 mL) were added sequentially, and the resulting mixture was stirred for some time. The mixture was poured into saturated aqueous sodium hydrogen carbonate (5.0 mL), and the aqueous layer was extracted with dichloromethane (3 × 5.0 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield crude product, which was used in the next step without further purification.

A solution of the above crude product in acetonitrile (3.0 mL) was stirred and refluxed under a nitrogen atmosphere for 1 h. After the solution had been cooled to room temperature, aqueous sodium carbonate (10%, 5.0 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 5.0 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (chloroform/methanol 96:4 to 92:8) on silica gel to furnish (−)-stenine (**1**) (22.1 mg, 70.0% yield from iodide **38**) as a colorless solid: $R_f = 0.43$ (chloroform/methanol 90:10); m.p. 62–63 °C; $[\alpha]_D^{23} = -27.5$ ($c = 0.523$ in MeOH); ^1H NMR (400 MHz, [D$_6$]benzene, 25 °C, TMS): $\delta = 3.98$ (dd, $J = 11.6$, 9.2 Hz, 1H), 3.01–2.89 (m, 1H), 2.64 (dt, $J = 12.6$, 4.4 Hz, 1H), 2.20 (dt, $J = 6.1$, 9.2 Hz, 1H), 2.08 (ddd, $J = 12.8$, 10.7, 2.1 Hz, 1H), 1.90–1.79 (m, 1H), 1.73 (dq, $J = 10.1$, 7.0 Hz, 1H), 1.37 (q, $J = 9.6$ Hz, 1H), 1.03 (d, $J = 6.7$ Hz, 3H), 0.90 (t, $J = 7.6$ Hz, 3H), 1.79–0.80 (m, 13H); ^{13}C NMR (100 MHz, [D$_6$]benzene, 25 °C, TMS): $\delta = 178.0$, 79.6, 67.3, 54.9, 52.8, 47.3, 43.0, 42.7, 40.3, 40.1, 30.2, 30.0, 27.8, 26.4, 23.1, 15.1, 10.2; IR (CH_2Cl_2): $\tilde{\nu} = 2945$, 1770, 1455, 1382, 1350, 1330, 1200, 1175, 1158, 1018, 1000 cm^{-1}; MS (EI): *m/z* (%): 277 (40) $[M]^+$, 276 (100) $[M-H]^+$; HR-MS (EI): found: 277.2042 $[M]^+$; $C_{17}H_{27}O_2N$ calcd 277.2042; elemental analysis calcd (%) for $C_{17}H_{27}NO_2$ (277.4): C 73.61, H 9.81, N 5.05; found: C 73.52, H 9.77, N 5.03.

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