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Design, Synthesis, and Structure-Cytotoxicity Relationships of Aza-Steganes[1]

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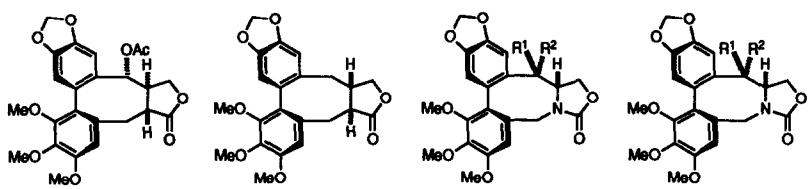
Abstract Optically active and racemic azaisopicrostegane (3), azapicrostegane (4), and all of four stereoisomers of racemic azaisopicrosteganols and azapicrosteganols (5, 6, 8, 9) were successfully synthesized by oxidative coupling of dibenzylurethanes (12, 18, 19)

In our program aimed at the creation of new compounds with antitumor activity based on natural lignans, podophyllotoxin[2,3] and steganacin (–)-1[4,5,6], we have shown that isopicrostegane (-)-2,[7] one of the four stereoisomers, shows a potent cytotoxicity higher than natural steganacin (-)-1.[8] The mechanism of action of 2 was shown to be based on the inhibition of microtuble assembly. Expecting to develop a new leading structure for anticancer drugs we started a next stage study We describe herein design, synthesis, and absolute configuration-antitumor activity relationships of new artificial aza-analogues based on (-)-2 [9] Furthermore, a boat-chair conformation of dibenzocyclooctadiene is proposed to be a biologically active form



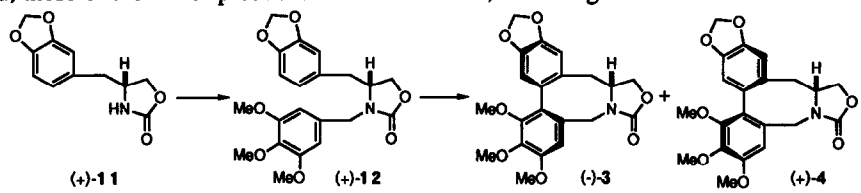
Design of Azaisopicrostegane

The guidelines we set for the creation of the candidate are categorized as follows: (1) the stereochemical structure has the most similarity to (-)-2, (2) carbonyl oxygen should have enough electron density to form a hydrogen-bond, (3) the compounds have minimum stereoisomers, (4) the synthetic route is as short as possible; (5) optically pure compounds are readily available

On the basis of the guidelines we designed 3 as an aza-analogue of (-)-2 [8] Atropisomerism and the carbon center at the β-position of the carbonyl group of 3 have the same relative configuration with (-)-2 and the center α to the carbonyl is an sp^2 nitrogen, reducing one asymmetric center and rendering enough electron density on the carbonyl oxygen in forming a hydrogen bond The isomeric compound 4 is, however, an analogue of picrostegane which showed weak cytotoxicity [8]

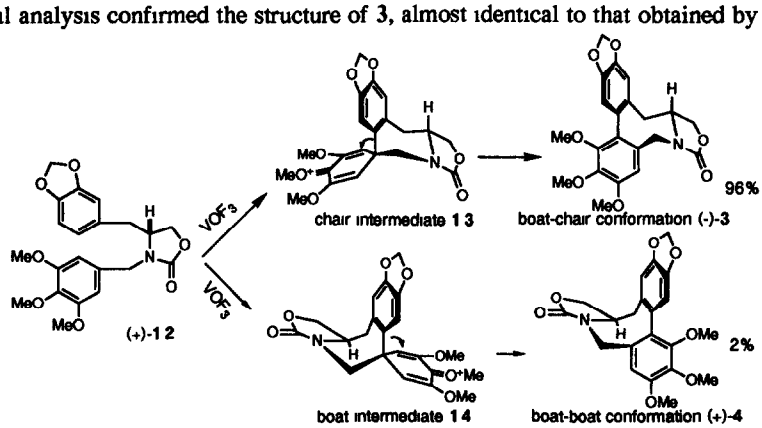
Synthesis of Azaisopicrostegane

The racemate and both enantiomers of **11** were prepared by the same way used in the synthesis of podophyllotoxin aza-analogues [3] Alkylation of (+)-**11** with trimethoxybenzyl bromide furnished (+)-**12** Nonphenolic oxidative intramolecular coupling of (+)-**12** by the action of VOF_3 in methylene chloride-trifluoroacetic acid[5] gave rise to a mixture of separable two diastereoisomers (-)-**3** and (+)-**4** in a ratio of 60 1 (determined by HPLC of the crude products) in 98% combined yield The major product was assigned to **3** on the basis of NMR spectroscopic analysis Thus, coupling constants between the methine proton α to nitrogen and benzylic methylene protons are 0 and 9 9 Hz, indicating the structure **3** On the other hand, those of the minor product are 2 0 and 6 6 Hz, indicating the structure **4**.



Heating of **3** over the melting point established a constant equilibrium to afford a mixture of **3** and **4** in a ratio of 40·1 In turn, heating of **4** also provided a mixture in the same ratio These thermodynamic behaviors of the two isomers come from the isomerization of a pivotal bond of biphenyl skeleton [7] The preferred stability of **3** to **4** is attributed to the boat-chair conformation of dibenzocyclooctadiene of **3** rather than the boat-boat conformation of **4**

Molecular mechanics calculations using Allinger's MM2 force field[10] reproduce the stability of **3** rather than **4** by 3 kcal/mol, consisting with the established equilibrium ratio Dihedral angles of the calculated structure also support the assignment of the structure on the basis of NMR. Dihedral angles for the corresponding bond arrangements described above, -72 and +172 deg for **3** and -90 and +24 deg for **4** obtained by calculation are in good agreement with the coupling constants observed Furthermore, X-ray structural analysis confirmed the structure of **3**, almost identical to that obtained by calculation [11]



Preferred formation of **3** rather than **4** is attributed to stability difference between the two conformers of the intermediate of the reaction The favorable intermediate **13**, in which seven-membered ring maintains chair conformation, leads to **3** through spirodienone-phenol-type rearrangement On the

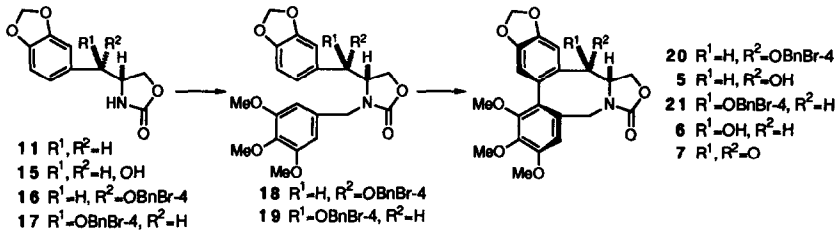
other hand, unfavorable intermediate **14**, in which seven-membered ring maintains boat conformation, leads to **4**

The compounds (+)-, (±)-**3** and (-)-, (±)-**4** were prepared starting from the corresponding amino acids,[11] respectively, without any event

It is noteworthy that **3** was readily prepared in quantity from the known amino acid, 3,4-methylenedioxyphenylalanine,[12] in four steps in high overall yield

Synthesis of Azaisopicrosteganol

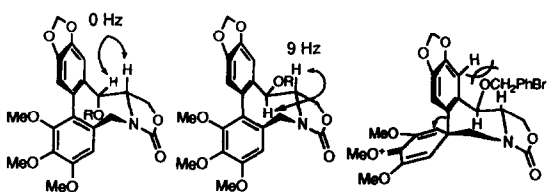
Since introduction of glucose moiety onto the benzylic position of **3** would be important for exerting better pharmacological behaviors as shown in podophyllotoxin-based antitumor pharmaceuticals,[2] it is highly desirable to introduce oxygen functionality onto the benzylic position of **3**



Although oxidative introduction of oxygen functionality onto **3** seems to be a straightforward method to afford **5**~**10**, attempted benzylic oxidation of **3** with NBS[5] and other reagents gave rise to a mixture of intractable products Inadequate orientation of the benzylic C-H bonds, having no possibility to take enough conjugation with aromatic π-orbital, seems to be the reason for this failure [13] The stereostructure of **3** obtained by MM2 calculations and by X-ray crystallography demonstrated the non-parallel orientation of the corresponding C-H bonds with aromatic π-orbital [14]

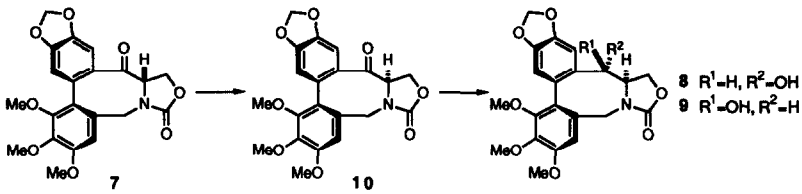
Then we examined oxidative coupling of **18** and **19**, possessing oxygen functionality protected by 4-bromobenzyl group inert toward oxidative coupling conditions, to **20** and **21** Protection of the benzylic OH of **15**[3] with 4-bromobenzyl group under the conditions of Tf_2O-4-bromobenzyl alcohol in dioxane at rt for 1 h provided the corresponding **16** and **17** in 99% combined yield Dibenzylurethanes **18** (63%) and **19** (36%) were obtained by treating a mixture of **16** and **17** with 3,4,5-trimethoxybenzyl bromide-NaH in DMF

Intramolecular coupling of **18** and **19** with VOF_3 in TFA-CH_2Cl_2 at -40 °C for 2 5 h provided **20** and **21** in 66 and 22% yields, respectively [15] Stereochemistries of **20** and **21** were determined by NMR analysis (coupling constants) as shown The unfavorable interactions between the benzylic OCH_2PhBr and aromatic group in the intermediate (**22** from **19**) explain higher (**20**) and lower (**21**) yields of the oxidative coupling



As we expected, hydrogenation of **20** and **21** with H_2-10% Pd/C in AcOEt-EtOH at rt smoothly provided **5** and **6** both in 94% yields, respectively The selective benzylic C-O bond fission of **20** and **21** to **5** and **6**, not to **3**, is ascribed to the unfavorable orientation of the benzylic C-O bond on the skeleton with respect to the methylenedioxyphenyl π-orbital as described above.[16]

The alcohols **5** and **6** were oxidized with PCC in CH_2Cl_2 to give the same ketone **7** in 79 and 75% yields, respectively IR spectrum of **7** (1722 cm^{-1}) indicates no conjugation of C-O double bond with aromatic group Reduction of **7** with $NaBH_4$ in methanol stereoselectively gave **5** in 85% yield.



7 **10**

On the other hand, treatment of **7** with DBU in CH_2Cl_2 at rt for 5 min smoothly provided an isomerized ketone **10** in 89% isolated yield IR spectrum (1676 cm^{-1}) of **10** in turn indicates the presence of conjugation between C-O double bond and aromatic group

Reduction of **10** with $NaBH_4$ in methanol gave a 3 to 7 mixture of isomeric alcohols **8** and **9** in 94% combined isolated yield, which were separated through their acetates Selective reduction of **10** with L-Selectride afforded **9** in 73% yield as a single isomer

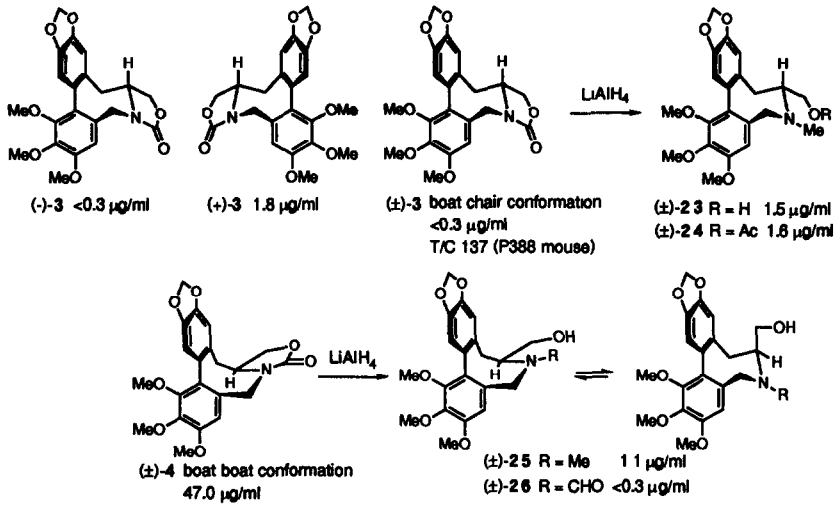
In conclusion we have succeeded in the preparation of all of four stereoisomers **5**, **6**, **8**, and **9** through oxidative coupling and subsequent regioselective hydrogenative cleavage of the benzyl protecting group and further isomerization as a key sequence of reactions

Antitumor Activity

We are very pleased to find that (±)-**3** showed promising *in vitro* cytotoxic activity (ED_{50} <0 3 μg/ml against KB cell) as well as *in vivo* activity (T/C 137) against experimental tumor in P388 mouse The activity is superior to those of natural lignan (-)-steganacin **1** as the leading compound [8] On the other hand, marginal cytotoxicity was observed in the assay of **4** (47 μg/ml) It is also important to note that (-)-**3** shows stronger cytotoxicity than (+)-**3**, clearly indicating the necessity of *R* pivotal absolute configuration Cytotoxicities of azaisopicrosteganol series (**5**, **6**, **7** <0 3 μg/ml) are higher than those of azapicrosteganol series (**8** 14 1, **9** 40 7, **10** 0 57 μg/ml), indicating that the parent skeleton **3** is essential for activity

Lithium aluminium hydride reduction of **3** and **4** provided the corresponding amino alcohols **23** and **25** *N*-Formyl alcohol **26** was obtained as a side-product by the reduction of **4** The amino alcohol **23** was acetylated to **24** The amino alcohols **23**, **25**, and acetyl amine **24** showed the similar potency of activity (ED_{50} 1 1-1 65 μg/ml) It is quite interesting that *N*-formyl alcohol **26** showed an activity (ED_{50} <0 3 μg/ml) higher than the parent compound **4**

These variations in biological activity suggest that the boat-chair conformation is an essential structure for biological activity The boat-boat conformation of inactive **4** is converted to the boat-chair conformation by releasing rigidity through reductive opening of the five-membered ring, and then **25** and **26** recovered activity Furthermore, the presence of the carbonyl group in a specific orientation is advantageous to show activity, and then **3** and **26** are of the potent compounds



We believe that conformation-activity relationships revealed by this work are useful in the development of the future anticancer pharmaceuticals

Further studies along this line are now in progress in our laboratories [17]

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Experimental[18]

(+)-(*R*)-4-(3,4-Methylenedioxybenzyl)-3-(3,4,5-trimethoxybenzyl)-1,3-oxazolidin-2-one (+)-12 A mixture of (+)-11 (2 56 g, 11 6 mmol)[2] and NaH (0 42 g, 17 4 mmol) in THF (25 ml) was stirred under reflux for 0 5 h After addition of a solution of 3,4,5-trimethoxybenzyl bromide (3 63 g, 13 9 mmol) in THF (20 ml) at rt, the whole was stirred under reflux for 4 5 h. After addition of satd aq NH_4Cl (15 ml), the mixture was extracted with ethyl acetate (50 ml x 3). The extracts were washed with 10% aq HCl (50 ml), satd aq $NaHCO_3$ (50 ml), and brine (50 ml), and then dried over Na_2SO_4 Concentration and following purification by column chromatography (benzene-acetone (4 1)) provided (+)-12 (4.59 g, 99%) as a colorless caramel. $[\alpha]_D^{20}$ +12 4 °(c=1 10, $CHCl_3$) IR (neat) 1750 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 2.60 (1H, dd, J=8 6, 13 7 Hz), 3 02 (1H, dd, J=4 9, 13 7 Hz), 3.81 (1H, dddd, J=4 9, 6 2, 8.6, 8.8 Hz), 8.85 (9H, s), 4 01 (1H, dd, J=6 2, 8 8 Hz), 4 01 (1H, d, J=15 0 Hz), 4 17 (1H, dd, J=8 8, 8 8 Hz), 4.78 (1H, d, J=15 0 Hz), 5 94 (2H, s), 6 47 (2H, s), 6 53-6 75 (3H, m) MS m/z 401. Anal ($C_{21}H_{23}NO_7$)

(-)-12. $[\alpha]_D^{20}$ -11.9 °(c=1.09, $CHCl_3$)

(±)-12: Colorless plates of mp 94 5-96 5 °C (ethyl acetate-hexane)

(-)-Azaisopicrostegane (-)-3 and (+)-Azapicrostegane (+)-4 A solution of (+)-12 (2 40 g, 5 98 mmol) in CH_2Cl_2 (60 ml) was added to a suspension of VOF_3 (6 0 g, 48 4 mmol) in CF_3CO_2H (14 ml) and CH_2Cl_2 (80 ml) at -42 °C The whole was stirred at -42 °C for 1 h and then at -30 °C for 3 h After addition of satd aq $NaHCO_3$ (70 ml), the mixture was extracted with CH_2Cl_2 (100 ml x 2) The extracts were washed with 10% HCl (160 ml), satd $NaHCO_3$ (160 ml), and brine (200 ml), and then dried over $MgSO_4$ Concentration and purification by column chromatography (hexane-benzene-acetone (5 5 2)) provided (-)-3 (2 30 g, 96%) and (+)-4 (48 mg, 2%)

(-)-3. Colorless caramel $[\alpha]_D^{24}$ -174 6 °(c=1 094, $CHCl_3$) IR (neat) 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2 48 (1H, dd, J=9 9, 13 7 Hz), 2 63 (1H, d, J=13.7 Hz), 3 36 (1H, d, J=14 3 Hz), 3 63, 3 90, and 3 91(each 3H, s), 3 72-3 88 (2H, m), 4.50-4 56 (1H, m), 4 64 (1H, d, J=14 3 Hz), 6 01 and 6 04 (each 1H, d, J=1 5 Hz), 6 72, 6 76, and 6 99 (each 1H, s) ^{13}C-NMR ($CDCl_3$) δ 39 6 (t), 44 9 (t), 55 9 (q),

57 4 (d), 60.8 (q), 60.8 (q), 67 4 (t), 101.1 (t), 108 5 (d), 109.1 (d), 110.8 (d), 125.9 (s), 128.9 (s), 129 8 (s), 131.9 (s), 141.8 (s), 145.8 (s), 147 6 (s), 150 8 (s), 152.9 (s), 156.9 (s) Anal. ($C_{21}H_{21}NO_7$)

(+)-4: White powder of mp 154-156 °C (benzene-ether) $[\alpha]_D^{22}$ +125 6 °(c=1 17, $CHCl_3$). IR (KBr) 1737 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 2.43 (1H, dd, J=2.0, 14.3 Hz), 2 89 (1H, dd, J=6.6, 14.3 Hz), 3.54, 3 89, and 3 90 (each 3H, s), 4 0 (1H, m), 4 09 (1H, dd, J=5.7, 8.9 Hz), 4.40 (1H, dd, J=8 6, 8.9 Hz), 4.78 (1H, d, J=14.7 Hz), 5.98 and 6 02 (each 1H, d, J=1.5 Hz), 6 59, 6.71, and 6 77 (each 1H, s). ^{13}C-NMR ($CDCl_3$) δ 38 2 (t), 48.8 (t), 54 4 (q), 56.0 (d), 60.6 (q), 61 0 (q), 68.3 (t), 101.2 (t), 108 3 (d), 109.2 (d), 111.0 (d), 127.4 (s), 127.6 (s), 129 1 (s), 129 6 (s), 142 2 (s), 146 6 (s), 147 3 (s), 151 5 (s), 152 7 (s), 157 5 (s). Anal ($C_{21}H_{21}NO_7$)

(+)-3 Colorless caramel $[\alpha]_D^{24}$ +174 7 °(c=1.578, $CHCl_3$)

(-)-4· White powder of mp 153 5-155 °C (benzene-ether) $[\alpha]_D^{24}$ -124 6 °(c=1.00, $CHCl_3$).

(±)-3 Colorless prisms of mp 185-186 °C (benzene-ether)

(±)-4 Colorless needles of mp 167-168 °C (ethyl acetate)

Thermal equilibration of 3 and 4

From (±)-3 Under argon atmosphere (±)-3 (2.10 g, 5 3 mmol) was heated at 205 °C for 3 h HPLC analysis (Waters radial PAK 5 μ, AcOEt-hexane (3·1), 3 0 ml/min, 264 nm) indicates the presence of (±)-3 (Rt 2 9 min) and (±)-4 (Rt 7 3 min) in a ratio of 40.1. Purification by column chromatography (benzene-hexane-acetone (5:5:2)) provided (±)-3 (2.02 g, 96%) and (±)-4 (74 mg, 3 5%)

From (±)-4 Heating of (±)-4 at 180 °C for 3 h provided a mixture in a ratio of 40·1

(±)-4-[Hydroxy-(3,4-methylenedioxyphenyl)methyl]-1,3-oxazolidin-2-one (±)-15. A suspension of (±)-11[3] (1 26 g, 5 7 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.73 g, 11 6 mmol) in AcOH (12 ml) was stirred at 60 °C for 50 h. After concentration and following dilution with CH_2Cl_2 (300 ml), the whole was washed with 10% NaOH (200 ml x 2) and brine (100 ml), and then dried over $MgSO_4$ Concentration provided a mixture of (±)-11 and acetate (1 29 g). The mixture and $NaHCO_3$ (480 mg, 5 7 mmol) in MeOH (20 ml) was stirred at rt for 3 days After filtration, the whole was concentrated. Purification by column chromatography (MeOH-$CHCl_3$ (1:10)) provided (±)-11 (314 mg, 25% recovery) and (±)-15 (570 mg, 42%) as a 1·1 mixture of diastereomers of mp 124-125 5 °C (colorless prisms) IR (KBr) 3310, 1743 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2 1 (1H, brs), 3 98 (1H, ddd, J=5 5, 8 1, 9.0 Hz), 4.07 (1H, dd, J=5 5, 9 0 Hz), 4.21 (1H, dd, J=9.0, 9 0 Hz), 4 52 (1H, d, J=8.1 Hz), 5 85 (1H, brs), 5.99 (2H, s), 6 78-6 87 (3H, m) ^{1}H-NMR ($CDCl_3$) δ 2 0 (1H, brs), 3.92-4 00 (1H, m), 4 43 (1H, dd, J=7 7, 9 2 Hz), 4 45 (1H, dd, J=5 9, 9 2 Hz), 4 60 (1H, d, J=6 6 Hz), 5 23 (1H, brs), 5.99 (2H, s), 6 77-6.87 (3H, m) MS m/z· 237 Anal ($C_{11}H_{11}NO_5$)

(±)-4-[4-Bromobenzyloxy-(3,4-methylenedioxyphenyl)methyl]-1,3-oxazolidin-2-one (±)-16 and (±)-17· A mixture of (±)-15 (22 4 mg, 0 094 mmol), 4-bromobenzyl alcohol (177 mg, 0 94 mmol), and triflic anhydride (26 6 mg, 0.094 mmol) in 1,4-dioxane (0.5 ml) was stirred at rt for 50 min After addition of satd aq $NaHCO_3$ (4 ml), the mixture was extracted with $CHCl_3$ (25 ml x 3) The extracts were washed with brine (50 ml) and dried over Na_2SO_4 Concentration and purification by column chromatography (benzene-acetone (9 1)) gave (±)-16 (23 9 mg, 62%) and (±)-17 (14 1 mg, 37%)

(±)-16 Colorless needles of mp 122-123 5 °C (AcOEt-hexane) IR ($CHCl_3$) 3450, 1761 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 3.94-4 00 and 4 10-4 16 (each 2H, m), 4 19 and 4 39 (each 1H, d, J=11 7 Hz), 5 93 (1H, brs), 6 00 and 6.01 (each 1H, d, J=1 5 Hz) 6 76 (1H, dd, J=1,8, 7 7 Hz), 6 80 (1H, d, J=1,8 Hz), 6 83 (1H, d, J=7 7 Hz), 7 14 and 7 46 (each 2H, d-like, J=8 4 Hz) MS m/z 405. Anal ($C_{18}H_{16}NO_5Br$)

(±)-17· Colorless oil IR ($CHCl_3$)· 3450, 1763 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ: 3 91 (1H, ddd, J=4.8, 8 1, 8 1 Hz), 4 13 (1H, d, J=8 1 Hz), 4 20 and 4 44 (each 1H, d, J=11 7 Hz), 4 34 (1H, dd, J=4.8, 9 2 Hz), 4 51 (1H, dd, J=8.1, 9 2 Hz), 4 65 (1H, brs), 6 016 and 6 022 (each 1H, d, J=1 5 Hz), 6 77 (1H, dd, J=1 5, 8 1 Hz), 6 83 (1H, d, J=1 5 Hz), 6 85 (1H, d, J=8 1 Hz), 7 12 and 7 48 (each 2H, d-like, J=8 4 Hz) MS m/z· 405, 407. Anal ($C_{18}H_{16}NO_5Br$)

(±)-4-[4-Bromobenzyloxy-(3,4-methylenedioxyphenyl)methyl]-3-(3,4,5-trimethoxybenzyl)-1,3-oxazolidin-2-one (±)-18 and (±)-19 A mixture of (±)-16 and (±)-17 (780 mg, 1 92 mmol) and NaH (69 1 mg, 2 88 mmol) in DMF (5 ml) was stirred at rt for 30 min After addition of 3,4,5-trimethoxybenzyl bromide (600 mg, 2 30 mmol) in DMF (5 ml), the mixture was stirred at rt for 25 min The mixture was diluted with satd aq NH_4Cl (20 ml) and then extracted with benzene (50 ml x 3) The extracts were washed with water (100 ml x 3) and brine (100 ml), and then dried over

Na_2SO_4 Concentration and purification by column chromatography (benzene-AcOEt (4·1)) provided (±)-**18** (685 mg, 61%) and (±)-**19** (425 mg, 38%)

(±)-**18**: Colorless prisms of mp 128 5-130 °C (AcOEt-hexane) IR (KBr): 1749 cm^{-1} ^{1}H-NMR ($CDCl_3$, TMS) δ· 3 69 (6H, s), 3.83 (3H, s), 3.77-3.91 (3H, m), 4 13 and 4.29 (each 1H, d, J=11.0 Hz), 4 36 (1H, d, J=7 7 Hz), 4.44 and 4.80 (each 1H, d, J=14 5 Hz), 5 99 and 6.01 (each 1H, d, J=1.5 Hz), 6.44 (2H, s), 6.74-6 76 (2H, m), 6.82 (1H, d, J=8 4 Hz), 7.13 and 7 48 (each 2H, d-like, J=8 4 Hz). ^{13}C-NMR ($CDCl_3$) δ: 48.22 (t), 55 92 (q), 58.14 (d), 60.80 (q), 63 95 (t), 69 59 (t), 84.94 (d), 101 46 (t), 105.52 (d), 107.04 (d), 108 56 (d), 121 72 (d), 122 01 (s), 129.89 (d), 129 98 (s), 131 67 (d), 132 14 (s), 136.32 (s), 137.34 (s), 148 43 (s), 148 60 (s), 153 26 (s), 158 79 (s). MS m/z 585, 587 Anal ($C_{28}H_{28}NO_8Br$)

(±)-**19** Colorless oil. IR ($CHCl_3$)· 1744 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ: 3 47 (1H, d, J=14 8 Hz), 3 73 (1H, ddd, J=4 8, 4 8, 8.8 Hz), 3 78 (6H, s), 3 82 (3H, s), 4 09 (1H, d, J=11 2 Hz), 4 11 (1H, dd, J=8 8, 8.8 Hz), 4.32 (1H, d, J=4.8 Hz), 4.37 (1H, dd, J=4.8, 8.8 Hz), 4 47 (1H, d, J=11 2 Hz), 4 64 (1H, d, J=14 8 Hz), 5.99 and 6.00 (each 1H, d, J=1 5 Hz), 6.27 (2H, s), 6 68 (1H, dd, J=1.5, 8 1 Hz), 6 72 (1H, d, J=1 5 Hz), 6 83 (1H, d, J=8 1 Hz), 7 14 and 7 49 (each 2H, d-like, J=8 4 Hz) ^{13}C-NMR ($CDCl_3$) δ 47.08 (t), 56.07 (q), 58 67 (d), 60.80 (q), 63 98 (t), 69 50 (t), 78 87 (d), 101 40 (t), 105 08 (d), 106 92 (d), 108 70 (d), 120.93 (d), 122 01 (s), 129 69 (d), 130.42 (s), 131 50 (s), 131 65 (d), 136.17 (s), 137 57 (s), 148 11 (s), 148 49 (s), 153 39 (s), 158 76 (s) MS m/z· 585, 587 Anal ($C_{28}H_{28}NO_8Br$)

Starting from (±)-**16**, (±)-**18** was obtained quantitatively.

(±)-Azaepiisopicrosteganol 4-bromobenzyl ether (±)-20 A solution of (±)-**18** (1 50 g, 2 56 mmol) in CH_2Cl_2 (85 ml) was added over a period of 20 min to a suspension of VOF_3 (3 17 g, 25 6 mmol), CF_3CO_2H (5.9 ml) in CH_2Cl_2 (32 ml) at -42 °C The whole was stirred at -23 °C for 2 h After addition of satd aq $NaHCO_3$ (100 ml), the mixture was extracted with CH_2Cl_2 (100 ml x 3) The extracts were washed with 10% HCl (100 ml x 2), satd $NaHCO_3$ (100 ml), and brine (100 ml), and then dried over $MgSO_4$. Concentration and purification by column chromatography (hexane-AcOEt (4·5)) gave (±)-**20** (1 13 g, 76%) as colorless prisms of mp 137-138 °C (benzene-EtOH) IR ($CHCl_3$) 1743 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 3 42 (1H, d, J=14 5 Hz), 3 47, 3 82 and 3 92 (each 3H, s), 3 81 (1H, ddd, J=0, 5 9, 8 8 Hz), 4 01 (1H, dd, J=5 9, 8 8 Hz), 4 03 (1H, d, J=12 6 Hz), 4 22 (1H, s), 4 26 (1H, d, J=12 6 Hz), 4.38, (1H, dd, J=8 8, 8 8 Hz), 4 65 (1H, d, J=14 5 Hz), 6 03 and 6 06 (each 1H, s), 6 59, 6 68 and 7 05 (each 1H, s), 6 75 and 7 12 (each 2H, d-like, J=8 4 Hz) ^{13}C-NMR ($CDCl_3$) δ. 45 74 (t), 56 07 (q), 59.69 (d), 59 87 (q), 61 24 (q), 65 65 (t), 68 86 (t), 82 11 (d), 101 58 (t), 108 15 (d), 109 37 (d), 112 15 (d), 121 14 (s), 126 42 (s), 128 40 (d), 128 70 (s), 129 19 (s), 130 24 (s), 131 24 (d), 136 32 (s), 141 19 (s), 146 91 (s), 147 64 (s), 149 86 (s) 152 81 (s), 157 86 (s) MS m/z 583, 585 Anal ($C_{28}H_{26}NO_8Br$)

(±)-Azaisopicrosteganol 4-bromobenzyl ether (±)-21: By the same way for (±)-**20**, (±)-**19** was converted to (±)-**21** in 22% yield Colorless prisms of mp 135-136 °C (AcOEt-hexane) IR ($CHCl_3$) 1743 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 3 20 (1H, d, J=14 5 Hz), 3 76, 3 89 and 3 92 (each 3H, s), 3 82 (1H, ddd, J=8 1, 8 8, 8 8 Hz), 3 99 (1H, d, J=8 8 Hz), 4 01 (1H, d, J=11 2 Hz), 4 17 (1H, dd, J=8 1, 9 3 Hz), 4 38 (1H, d, J=11 2 Hz), 4 46 (1H, dd, J=8 8, 9 3 Hz), 4 60 (1H, d, J=14 5 Hz), 6 04 and 6 09 (each 1H, d, J=1 5 Hz), 6 76, 6 94 and 7 08 (each 1H, s), 7 06 and 7 42 (each 2H, d-like, J=8 4 Hz) ^{13}C-NMR ($CDCl_3$) δ 44 60 (t), 56 07 (q), 60 25 (d), 61 00 (q), 61 09 (q), 65 94 (t), 69 67 (t), 79 51 (d), 101 52 (t), 104 61 (d), 109 08 (d), 110 74 (d), 122 10 (s), 124 55 (s), 129 28 (s), 129 78 (d), 131 62 (s), 131 67 (d), 132 70 (s), 135 73 (s), 142 04 (s), 146 91(s), 148 60 (s), 150 62 (s), 153 63 (s), 157 57 (s) MS m/z 583, 585 Anal ($C_{28}H_{26}NO_8Br$)

(±)-Azaepiisopicrosteganol (±)-5 A mixture of (±)-**20** (10 mg, 0 017 mmol) and 10% Pd/C (5 mg) in AcOEt-EtOH (1·1, 0 5 ml) was stirred for 3 h under hydrogen atmosphere Filtration and concentration gave a brown oil (10 mg) Purification by column chromatography (CH_2Cl_2-acetone (5 1)) gave (±)-**5** (6 7 mg, 94%) as colorless prisms of mp 222-223 °C (benzene) IR ($CHCl_3$) 3535, 1743 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 1 57 (1H, d, J=11 7 Hz), 3 38 (1H, d, J=14 3 Hz), 3 66, 3 91 and 3 93 (each 3H, s), 3 91 (1H, ddd, J=0, 7 3, 9 5 Hz), 4 23 (1H, dd, J=7 3, 8 4 Hz), 4 49 (1H, dd, J=8 4, 9 5 Hz), 4 57 (1H, d, J=11 7 Hz), 4 69 (1H, d, J=14 3 Hz), 6 02 and 6 06 (each 1H, d, J=1 5 Hz), 6 62, 6 70 and 7 04 (each 1H, s) ^{13}C-NMR ($CDCl_3$) δ 45 62 (t), 56 10 (q), 60 65 (d), 60 77 (q), 61 06 (q), 65 38 (t), 76 33 (d), 101 61 (t), 107 53 (d), 109 55 (d), 112 38 (d) 125 31 (s), 126 48 (s), 130 36 (s), 132 37 (s),

142 45 (s), 146,68 (s), 147 67 (s), 150 91 (s), 153 89 (s), 157.95 (s). MS m/z· 415 Anal ($C_{21}H_{21}NO_8$ 1/8C_6H_6)

(±)-Azaisopicrosteganol (±)-6 By the same way for (±)-5, (±)-21 was converted to (±)-6 in 94% yield Colorless needles of mp 252 5-253 5 °C (AcOEt-hexane) IR ($CHCl_3$): 3340, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2 03 (1H, d, J=2 6 Hz), 3 20 (1H, d, J=14.3 Hz), 3.77 (1H, ddd, J=8.1, 9.2, 9 2 Hz), 3 75, 3 89 and 3 90 (each 3H, s), 4 32 (1H, dd, J=8.1, 9.2 Hz), 4 33 (1H, dd, J=2.6, 9.2 Hz), 4 48 (1H, dd, J=9 2, 9.2 Hz), 4.60 (1H, d, J=14.3 Hz), 6 03 and 6.06 (each 1H, d, J=1 5 Hz), 6.70, 6.96 and 7 18 (each 1H, s). ^{13}C-NMR ($CDCl_3$) δ 44 51 (t), 56.10 (q), 60.68 (d), 60 89 (q), 61.24 (q), 65.82 (t), 72.77 (d), 101.49 (t), 104.70 (d), 108 96 (d), 110.34 (d), 124 55 (s), 127 59 (s), 128.52 (s), 132 78 (s), 135.06 (s), 146 74 (s), 148 34 (s), 150 62 (s), 153 63 (s), 157 74 (s) MS m/z 415 Anal ($C_{21}H_{21}NO_8$)

(±)-Azaisopicrosteganone (±)-7 A solution of (±)-5 (6.0 mg, 0 014 mmol) in CH_2Cl_2 (1 ml) was added to a suspension of PCC (43.5 mg, 0 20 mmol) in CH_2Cl_2 (1 ml) The mixture was stirred at rt for 41 h. After addition of CH_2Cl_2-ether (1.1, 5 ml), the whole was stirred for 20 min, and then filtered through florisile Concentration of the filtrate gave a brown oil (8 mg). Purification by column chromatography (CH_2Cl_2-acetone (20 1)) gave (±)-7 (4 5 mg, 75%) as white solids of mp 167-168 °C (CH_2Cl_2-hexane) IR ($CHCl_3$). 1746, 1720, 1596 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ: 3.60, 3 87 and 3.90 (each 3H, s), 3.70 and 4.78 (each 1H, d, J=14 5 Hz), 4 36 (1H, dd, J=8 6, 8 6 Hz), 4 62 (1H, dd, J=6 6, 8 6 Hz), 4 78 (1H, dd, J=6.6, 8.6 Hz), 6.088 and 6 091 (each 1H, s), 6 64, 6 86 and 6 97 (each 1H, s) ^{13}C-NMR($CDCl_3$) δ· 45 50 (t), 55 98 (q), 60 81 (q), 60 99 (q), 60 99 (d), 61.64 (t), 101 89 (t), 103 13 (d), 110 24 (d), 111.72 (d), 124 67 (s), 125 27 (s), 129 58 (s), 135 33 (s), 142 44 (s), 147.67 (s), 148 25 (s), 151 25 (s), 153 55 (s), 156.30 (s), 201 11 (s) MS m/z: 413 Anal ($C_{21}H_{19}NO_8$)

By the same way for (±)-7 from (±)-5, (±)-6 was converted to (±)-7 in 78% yield

Reduction of (±)-7 to (±)-5: To a solution of (±)-7 (0 6 mg, 0 0015 mmol) in MeOH (0.1 ml) was added $NaBH_4$ (0 2 mg, 0 0053 mmol) The mixture was stirred for 40 min at rt After dilution with CH_2Cl_2 (10 ml), the whole was washed with brine (10 ml) and then dried over Na_2SO_4 Concentration and purification by column chromatography (CH_2Cl_2-acetone (20 1)) gave (±)-5 (0 5 mg, 83%)

(±)-Azapicrosteganone (±)-10· A solution of (±)-7 (57 mg, 0 133 mmol) and DBU (20 mg, 0.133 mmol) in CH_2Cl_2 (2 ml) was stirred at rt for 5 min After addition of satd aq oxalic acid (3 ml), the whole was extracted with CH_2Cl_2 (10 ml x 3) The extracts were washed with brine (20 ml) and then dried over Na_2SO_4 Concentration and purification by column chromatography ($CHCl_3$-AcOEt (5 1)) gave (±)-**10** (51 mg, 89%) as colorless needles of mp 160-161 °C (benzene-ether) IR ($CHCl_3$) 1744, 1667, 1597 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ· 3 87 (1H, dd, J=5 3, 9 2 Hz), 3 58, 3 90 and 3 91 (each 3H, s), 4 06 and 4 55 (each 1H, d, J=12 5 Hz), 4 29 (1H, dd, J=8.9, 9 2 Hz), 4 84 (1H, dd, J=5 3, 8 9 Hz), 6.07 and 6 08 (each 1H, s), 6 64, 6 70 and 7 24 (each 1H, s) ^{13}C-NMR ($CDCl_3$) δ 46 85 (t), 56 10 (q), 60.99 (d), 60 99 (q), 64.22 (t), 102 19 (t), 107 93 (d), 109.04 (d), 111.64 (d), 126 72 (s), 128 25 (s), 131 11 (s), 133.30 (s), 142 68 (s), 147 94 (s), 151 20 (s), 151 90 (s), 154 16 (s), 156 53 (s), 196 10 (s) MS m/z 413 Anal ($C_{21}H_{19}NO_8$ 1/4C_6H_6 1/4H_2O)

(±)-Azaepipicrosteganol (±)-9 A solution of L-Selectride (0 04 mmol) in THF (0 04 ml) was added to a solution of (±)-**10** (3.4 mg, 0 008 mmol) in THF (0 1 ml) The mixture was stirred at rt for 20 min. After addition of 1N-HCl (0 5 ml), the mixture was stirred for 10 min, and then extracted with CH_2Cl_2 (10 ml x 3) The extracts were washed with water (1 ml), satd aq $NaHCO_3$ (10 ml), and brine (10 ml), and then dried over Na_2SO_4 Concentration and purification by column chromatography (CH_2Cl_2-acetone (5·1)) gave (±)-9 (2 5 mg, 73%) as white solids of mp 212-213 °C IR (KBr): 3400, 1710 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 2.20 (1H, brd, J=3 6 Hz), 3 56, 3 86 and 3 90 (each 3H, s), 4 04 and 5 02 (each 1H, d, J=16 0 Hz), 4 08-4 19 (2H, m), 4 59-4 67 (1H, m), 4 93 (1H, dd, J=3 6, 6 3 Hz), 5 98 and 6.04 (each 1H, d, J=1 3 Hz), 6 52, 6 73 and 7 09 (each 1H, s) ^{13}C-NMR ($CDCl_3$) δ· 48 82 (t), 56 01 (q), 58 37 (d), 60 85 (q), 60 88 (q), 61 30 (t), 69 00 (d), 101 26 (t), 104.35 (d), 107 28 (d), 110 85 (d), 125 18 (s), 126.36 (s), 130 15 (s), 130 80 (s), 142 05 (s), 146.95 (s), 147 55 (s), 151.61 (s), 152 88 (s), 157 59 (s) MS m/z· 415 Anal. ($C_{21}H_{21}NO_8$ 1/6C_6H_6)

(±)-Azapicrosteganol (±)-8 and (±)-9 A solution of (±)-**10** (27 mg, 0.065 mmol) and $NaBH_4$ (7 mg, 0.196 mmol) in MeOH (3 ml) was stirred at rt for 10 min After concentration , the residue was diluted with water and then extracted with $CHCl_3$ (20 ml x 3) The extracts were washed with brine and then dried over Na_2SO_4. Concentration gave a mixture of (±)-8 and (±)-9 (26 mg) in a ratio of 27·73

A solution of the mixture, Ac_2O (19 mg) and DMAP (7 4 mg) in pyridine (1 ml) was stirred at rt for 1 h. After dilution with $CHCl_3$ (100 ml), the whole was washed with satd. aq $CuSO_4$, brine, satd $NaHCO_3$, and brine, and then dried over Na_2SO_4 Concentration and purification by column chromatography (hexane-acetone (3 2)) gave the acetate of (±)-8 (7 8 mg, 27%) and the acetate of (±)-9 (21 mg, 72 %)

The acetate of (±)-8 Colorless oil IR ($CHCl_3$) 1752, 1744, 1592 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 2 10, 3 47, 3 886 and 3 894 (each 3H, s), 4 06 and 5 06 (each 1H, d, J=15 8 Hz), 4 17-4.25 (2H, m), 4 51-4 59 (1H, m), 5 79 (1H, d, J=6 3 Hz), 5 99 and 6 03 (each 1H, d, J=1 3 Hz), 6 52, 6.78 and 6 86 (each 1H, s) ^{13}C-NMR ($CDCl_3$) δ 20.85 (q), 48 88 (t), 55 98 (q), 56.64 (d), 60 65 (q), 60 99 (q), 61 64 (t), 71 12 (d), 101 38 (t), 103.67 (d), 107 48 (d), 111.50 (d), 124 94 (s), 126.27 (s), 126 95 (s), 130 24 (s), 142 43 (s), 147 26 (s), 147 53 (s), 151 88 (s), 152 97 (s), 157 21 (s), 169 20 (s) MS m/z 457. Anal ($C_{23}H_{23}NO_9$).

The acetate of (±)-9 White solid of mp 215-216 °C (benzene-ether) IR ($CHCl_3$) 1751, 1742, 1596 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ· 1 85 (3H, s), 3 57 (1H, ddd, J=5 0, 6 9, 8.9 Hz), 3 74, 3.91 and 3 94 (each 3H, s), 3 92 and 4 29 (each 1H, d, J=12 5 Hz), 4 23 (1H, dd, J=5.0, 8 9 Hz), 4 40 (1H, dd, J=8 9 , 8 9 Hz), 5 74 (1H, d, J=6.9 Hz), 6.03 and 6 04 (each 1H, s), 6 63, 6.66 and 6 91 (each 1H, s) ^{13}C-NMR ($CDCl_3$) δ 20 81 (q), 47 44 (t), 56 12 (q), 58 01 (d), 60 77 (q), 60 99 (q), 69.36 (t), 80 11 (d), 101 74 (t), 108 30 (d), 112 06 (d), 112 49 (d), 128 45 (s), 128 84 (s), 129.00 (s), 129 67 (s), 142 55 (s), 147.17 (s), 148 21 (s), 151 77 (s), 153.46 (s), 157 09 (s), 169.88 (s) MS m/z: 457 Anal ($C_{23}H_{23}NO_9$)

A mixture of the acetate of (±)-8 (7 0 mg, 0 015 mmol) and K_2CO_3 (6 3 mg, 0 046 mmol) in MeOH-CH_2Cl_2 (1 1, 2 ml) was stirred at 35 °C for 15 min After concentration, the residue was purified by column chromatography (CH_2Cl_2-acetone (5 1)) to give (±)-8 (6 3 mg, 99%) as colorless prisms of mp 189-190 °C (CH_2Cl_2-hexane) IR($CHCl_3$) 3410, 1730 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 1 99 (1H, brs), 3 48 (1H, ddd, J=5 3, 8 5, 8 9 Hz), 3.73, 3 91 and 3 93 (each 3H, s), 3 83 and 4 38 (each 1H, d, J=12 5 Hz), 4 20 (1H, dd, J=5.3, 8 9 Hz), 4 42 (1H, dd, J=8 6, 8 9 Hz), 4 57 (1H, brd, J=8 5 Hz), 6 03 and 6 04 (each 1H, s), 6 61, 6 63 and 6 82 (each 1H, s) ^{13}C-NMR ($CDCl_3$) δ 46 78 (t), 56 12 (q), 57 47 (d), 61 08 (q), 61 15 (q), 69 31 (t), 79 07 (d), 101 67 (t), 108 16 (d), 111 52 (d), 112.83 (d), 127 84 (s), 128 00 (s), 128 90 (s), 133 26 (s), 142 57 (s), 147 46 (s), 147 71 (s), 151 46 (s), 153 66 (s), 157 30 (s) MS m/z 415 Anal ($C_{21}H_{21}NO_8$)

By the same way for (±)-8, the acetate of (±)-9 was converted to (±)-9 in 92% yield

Reduction of (±)-3 to (±)-23 A mixture of (±)-3 (15 7 mg, 0 39 mmol), $LiAlH_4$ (39 0 mg, 1 02 mmol) in THF 10 ml was stirred under reflux for 2 h Usual workup gave a colorless oil (144 mg) Purification by column chromatography (Al_2O_3 II-III, $CHCl_3$) gave (±)-23 (125 mg, 82%) as white powder of mp 88-90 °C (benzene-hexane) IR (KBr) 3400 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 2.31 (3H, s), 2 2-2 6 (3H, m), 2 60 (1H, s, OH), 3 28 and 3 56 (each 1H, d, J=13 Hz), 3 4-3 8 (2H, m), 3 53 (3H, s), 3 86 (6H, s), 5 91 and 5 94 (each 1H, d, J=1 Hz), 6 68 (2H, s), 6 74 (1H, s) MS m/z 387 Anal ($C_{21}H_{25}NO_6$ 1/2C_6H_6)

Acetylation of (±)-23 to (±)-24 A mixture of (±)-23 (22 0 mg, 0 057 mmol) and Ac_2O (8 μl, 0 085 mmol) in pyridine (0 5 ml) was stirred at rt for 2 h The whole was diluted with $CHCl_3$ (30 ml) and then washed with satd $CuSO_4$, satd $NaHCO_3$, and brine, and then dried with Na_2SO_4 Concentration and purification by column chromatography (AcOEt-hexane-$CHCl_3$ (3 1·1)) gave (±)-24 (22 3 mg, 91%) as a colorless oil IR ($CHCl_3$) 1740 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 2 08 (3H, s), 2 32 (3H, s), 2 4-2 5 (2H, m), 2 67 (1H, m), 3 21 and 3 54 (each 1H, d, J=13 Hz), 3 54 (3H, s), 3 87 (6H, s), 3 91 (1H, dd, J=7, 11 Hz), 5 92 and 5 95 (each 1H, d, J=1 Hz), 6 65, 6 67, and 6 75 (each 1H, s) MS m/z 429 Hydrochloride of (±)-24 Colorless needles of mp 199-201°C (AcOEt) Anal ($C_{23}H_{27}NO_7$ HCl)

Reduction of (±)-4 to (±)-25 and (±)-26 (±)-4 was reduced under the same condition with (±)-3 Purification by preparative tlc (AcOEt-MeOH (9 1)) gave (±)-26 (13%) and (±)-25 (23%)

(±)-26 Colorless oil IR ($CHCl_3$) 3380, 1658 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 2 58 (1H, dd, J=3, 15 Hz), 2 99 (1H, dd, J=5, 15 Hz), 3 17 (1H, d, J=15 Hz), 3 56, 3 88, and 3 89 (each 3H, s), 3 4-4 2 (4H, m), 4 98 (1H, d, J=15 Hz), 5 97 and 6 00 (each 1H, d, J=1 Hz), 6 6-6 9 (2H, m), 7 14 (1H, s), 8 12 (1H, s) MS m/z 401 High MS ($C_{21}H_{23}NO_7$)

(±)-25 Colorless oil IR ($CHCl_3$) 3390 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ 2 48 (1H, d, J=19 Hz), 2 49 (3H, s), 2 70 (1H, dd, J=2, 19 Hz), 2 94 (1H, m), 3 1-3 6 (2H, m), 3 48 and 3 62 (each 1H, d, J=5 Hz),

3 52 (3H, s), 3.91 (7H, s, OCH_3 x 2, OH), 5 95 and 5 98 (each 1H, d, J=1 Hz), 6.60, 6.63, and 6 70 (each 1H, s) MS m/z 387 High MS ($C_{21}H_{25}NO_6$)

References and Notes

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10 Since biphenyl is not conjugated in the present system, usual parameters were used in the calculation We are grateful to Prof. E Osawa for providing the MM2 program

11 The details will be reported elsewhere We are grateful to Dr T Kawai, Eisai Co Ltd , for X-ray crystallography

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14 The dihedral angles (C=C-C-H) are around 30 °

15 Treatment of **18** with less reactive oxidizing agent in acidic conditions resulted in the production of isoquinoline-type cyclization products in high yield

16 Benzyl ether protection, instead of 4-bromobenzyl, also provided **5** and **6** by hydrogenolysis

17 We are grateful to financial support from the Japan Research Foundation for Optically Active Compounds and Grant in Aid for Scientific Research, Ministry of Education, Japan.

18 Satisfactory analytical data (±0 3% for C,H,N) were obtained for new compounds described in the experimental section SiO_2 column chromatography was used unless otherwise stated Melting points were measured using a Buchi 510 melting point apparatus and are not corrected Optical rotations were taken with a Jasco DIP-181 polarimeter IR spectra were taken with a Jasco infrared spectrometer model DS-402G ^1H NMR spectra were taken with a JEOL GX-400 spectrometer at 400 MHz, a JNM-PS 100 spectrometer, a JEOL-FX 100 spectrometer at 100 MHz, or with a Hitachi R-24 spectrometer at 60 MHz ^{13}C NMR spectra were taken with a JEOL GX-400 spectrometer at 100 MHz Chemical shift values are expressed in ppm relative to internal tetramethylsilane Abbreviations are as follows s, singlet, d, doublet, t, triplet, m, multiplet MS were taken with a JEOL-01, SG-2 mass spectrometer or a JEOL DX-300 mass spectrometer