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STEREOCONTROLLED SYNTHESES OF CHIRAL AND RACEMIC KEY INTERMEDIATES TO THIENAMYCIN FROM D-ALLO-THREONINE AND *TRANS*-CROTONIC ACID[1]

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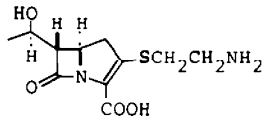
Abstract—Stereospecific and stereoselective syntheses of *cis*-**12**, and stereoselective synthesis of (±)-*trans*-**12** from D-allo-threonine and *trans*-crotonic acid, respectively, are described. The key steps in the syntheses are the formation of the β-lactam ring (**4**) by cyclization of the amide (**3**) via a complete S_N2 mechanism, and stereocontrolled conversion of the azetidinone (**4**) to **12**, **13**, and **14**, which are intermediates for the penems and the carbapenems.

To date in addition to the penicillins,[2] many kinds of β-lactam antibiotics have been discovered from naturally occurring organisms. In particular, thienamycin,[3] isolated from *Streptomyces* cattleya by a Merck research group, exhibits broad antibiotic activity against both gram-positive and gram-negative bacteria and also reveals activity against *Pseudomonas* spp. and resistance to bacterial β-lactamases. In addition, thienamycin has a unique structure, specifically the 1-carbapen-2-em nucleus and 6-(1-hydroxy)ethyl substituent in place of the traditional amide functionality. This intrigued many organic chemists to work towards the total synthesis of thienamycin. In practical synthesis of thienamycin there are four main problems to be solved: elaboration of the three contiguous chiral centers; construction of a carbapenem bicyclic system; and choice of a chiral source; choice of protective groups. However, Merck research groups have solved these problems.[4] In this paper, we wish to report other stereocontrolled syntheses of chiral or racemic key intermediates to thienamycin from D-*allo*-threonine or *trans*-crotonic acid.

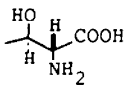
D-*allo*-Threonine was converted to (2*R*, 3*R*)-2-bromo-3-hydroxybutyric acid with retention of the configuration according to the method of Izumiya *et al.*[5] This was further transformed to (2*R*, 3*R*)-2-bromo-3-acetoxybutyryl chloride (**2**) by our previously reported method.[1a,1b] Reaction of the acid chloride (**2**) in the presence of triethylamine in THF with diethyl 2,4-dimethoxybenzylaminomalonate (**1**), which was obtained by the reductive amination of 2,4-dimethoxybenzaldehyde and diethyl aminomalonate with sodium cyanoborohydride[6], gave an amide (**3**) in 95% yield. Cyclization of **3** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at 20° for 15 hr proceeded with inversion of the configuration at the C connected to the Br atom to give an 2-azetidinone derivative (**4**) As an oil; $[\alpha]_D^{24}$ +39.5° (c = 2.03, EtOH); in 96% yield. This type of cyclization had already been reported by Sheehan and Bose in 1950.[7] The features of this reaction are easy manipulation, high yield of azetidin-2-one, the complete inversion of the configuration in the intramolecular nucleophilic substitution reaction and, if necessary, the possibility of utilization of one C of the malonic diester part. Judged from these points, this cyclization may be one of the most efficient thienamycin nucleus formation reactions discovered to date.[1a]

One of the malonic diesters in azetidin-2-one (**4**) was easily accesible to saponification, for conversion to a mono-carboxylic acid. The less hindered ester, the *trans* ester against the 3-(1-acetoxy)ethyl substituent, was stereospecifically saponified by 1 equiv of 1N NaOH to give **5** in 62% yield. The configuration of **5** was confirmed by transformation to t-butyl ester (±)-**32** from (±)-**5** (Scheme VI) as follows. The mono acid (±)-**5** was converted to an acid chloride by treatment with oxalyl chloride, and successive treatment of the acid chloride with t-butanol and pyridine gave t-butyl ester (±)-**30**. The t-butyl ester moiety of (±)-**30** revealed a greater resistance to saponification than either the ethyl ester part or the acetoxy group to give a hydroxy carboxylic acid (±)-**31** which was easily lactonized to (±)-**32**. If the configuration at the C-4 of **5** were opposite to that illustrated in Scheme I, it would be impossible for hydroxycarboxylic acid to produce lactonization. The fact that the lactone (±)-**32** was obtained reveals the relative configuration of (±)-**5** illustrated in Scheme I to be correct. In addition, the relative configuration between that at the C-3 and that at the 3-(1-acetoxy)ethyl group of (±)-**5** was also confirmed from the ^1H NMR study of the lactone (±)-**32**. The dihedral angle between the H on the lactone ring and the bridge head H is approx. 100° when measured using a Dreiding molecular model for the lactone (±)-**32** with the desired stereochemistry. The observed coupling constant (J = 1.5 Hz) supports the relative configuration of (±) – **32** as being correct. Since, the absolute configuration on the (1-acetoxy)ethyl side chain carbon of **5** is *R*, coherently, which is originated in D-*allo*-threonine, this result reveals that the absolute configuration of **5** is the same as that depicted in Scheme **I**.

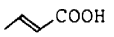
Decarboxylation of **5** with 2,4,6-collidine at 160° gave, stereoselectively, a mixture of *cis*- and *trans*-**6** (4:1, 75% yield) which was separable chromatographically. Saponification of the *cis* and *trans* mixture of **6** with 2.1 equiv of 1N NaOH–pyridine (2:1) produced a *cis*/*trans* mixture of two hydroxycarboxylic acids which was treated with a catalytic amount of concentrated hydrochloric acid to give a lactone (**7**), mp 87–89°; $[\alpha]_D^{24}$ −65.9° (c = 2.00, EtOH), in 62% yield from *cis* hydroxycarboxylic acid, and a *trans* carboxylic acid (**8**) in 14% yield. Grignard reaction of **7** with 1.8 equivalents of methylmagnesium bromide gave a 3:1 mixture of hemiketal (**9a**) and ketoalcohol (**9b**) in 98% yield, which



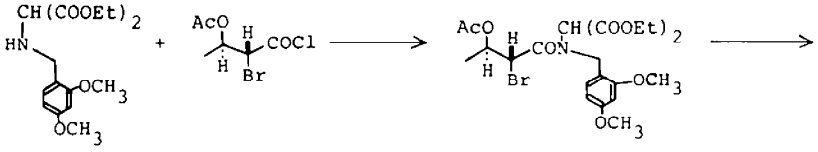
thienamycin



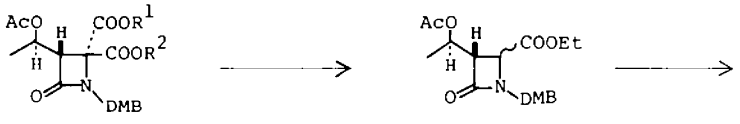
D-allo-threonine



trans-crotonic acid



1 2 3



4. $R^1=R^2=Et$

5. $R^1=Et$, $R^2=H$

6

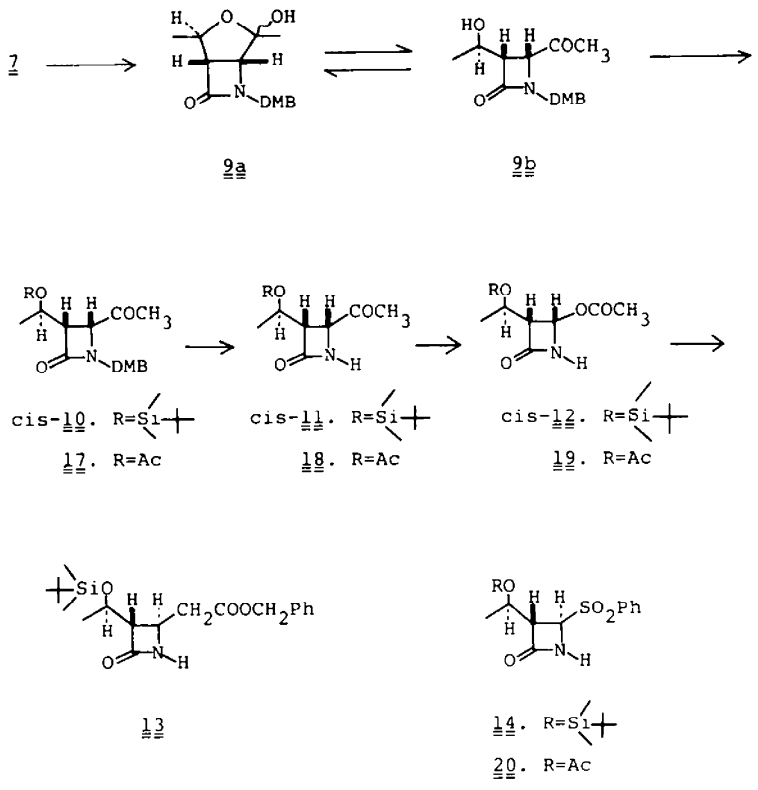
7 8

Scheme I.

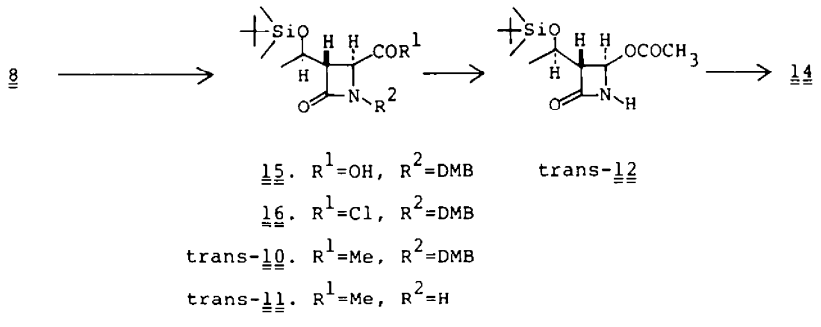
was further protected with a t-butyldimethylsilyl group to give a silyl ether (*cis*-**10**) in 88% yield; $[\alpha]_D^{25}$ − 20.7° (*c* = 1.96, EtOH). The 2,4-dimethoxybenzyl group, a protective group of 2-azetidinone nitrogen, was cleaved with potassium peroxodisulfate[8] in acetonitrile-water (1:1) at 65° to give *cis*-**11** in 74% yield prior to Baeyer-Villiger oxidation. Treatment of *cis*-**11** with m-chloroperbenzoic acid in chloroform gave *cis* **12**, m.p. 52–53°; $[\alpha]_D^{25}$ − 119.1° (*c* = 2.00, EtOH), in 96% yield. The reverse treatment of *cis*-**10**, i.e. oxidation of *cis*-**10** with m-chloroperbenzoic acid, yielded a phenolic compound without Baeyer-Villiger oxidation occurring. After trimethylsilylation of *cis*-**12**, reaction with trimethylsilylation of *cis*-**12**, reaction with trimethylsilyl enol ether of benzyl acetate according to Barrett's method[9] gave a *trans*-benzylester (**13**); m.p. 92–93°; $[\alpha]_D^{25}$ + 17.4° (*c* = 1.75, $CHCl_3$); in 58% yield. And treatment of *cis*-**12** with sodium benzenesulfinate in water-dioxane (1:1) gave a *trans* sulfone (**14**), m.p. 166–167°; $[\alpha]_D^{25}$ − 12.4° (*c* = 0.93, $CHCl_3$), in 63% yield. Thus D-*allo*-threonine was converted stereoselectively to *cis*-**12**, **13** and **14**, which were key intermediates for the synthesis of the carbapenems (Scheme II).

On the other hand, the hydroxycarboxylic acid (**8**) was converted to **14** as follows (Scheme III). The OH group of *trans* carboxylic acid (**8**) was silylated with *t*-butyldimethylsilyl chloride and dimethylaminopyridine to give a *trans* carboxylic acid (**15**) in 89% yield, which was treated with oxalyl chloride to give a *trans* acid chloride (**16**), and then successive treatment of **16** with dimethylcadmium gave a ketone (*trans*-**10**) in 66% yield from **15**. Deprotection of the 2,4-dimethoxybenzyl group gave *trans*-**11**, m.p. 72–73°, in 82% yield. Also, Baeyer-Villiger oxidation of *trans*-**11** afforded an acetoxy compound (*trans*-**12**), m.p. 101–103°; $[\alpha]_D^{25}$ + 47.9° (*c* = 1.00, $CHCl_3$) in 90% yield. These compounds, *cis*-**12**, *trans*-**12**, **13**, and **14** are useful as intermediates for the synthesis of the penems[10] and the carbapenems,[11,4a] and also antipodes of these compounds should be obtainable from L-*allo*-threonine. In addition, the racemic acetyl derivative of **14**, namely (±)-**20**, was obtained via the racemic 3:1 mixture of (±)-**9a** and (±)-**9b** from *trans* crotonic acid[1c,1d] (**9** → **17** → **18** → **19** → **20**) (Scheme II).

Alternatively, two stereospecific routes for the synthesis of the racemic intermediate (±)-**7** from the racemic compound (±)-**5** via lactone carboxylic acid (±)-**22**

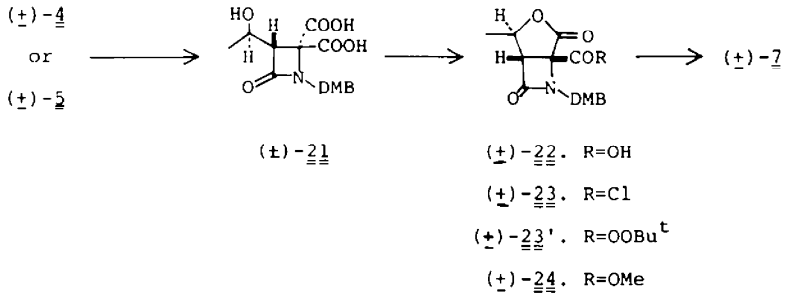


Scheme II.

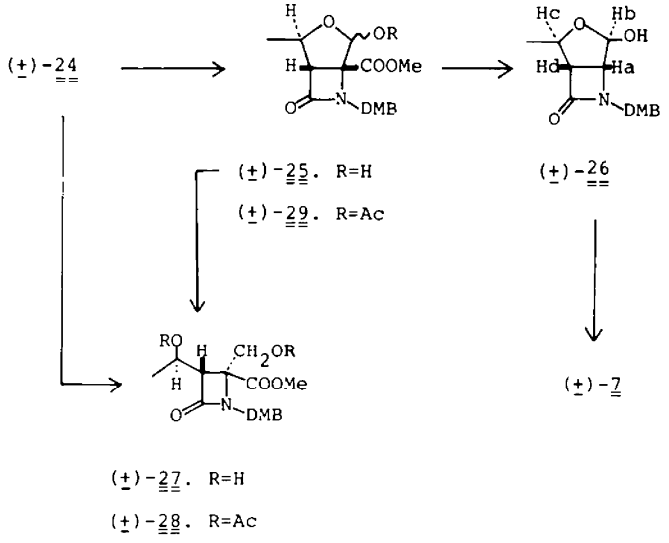


Scheme III.

was carried out. Saponification of (±)-**5** with 3 equiv of 1N NaOH afforded a hydroxy dicarboxylic acid (±)-**21** as a crystalline solid in 99% yield, which was easily transformed to a lactone carboxylic acid (±)-**22**, m.p. 162–165°, quantitatively (*cf* (−)−**22**, m.p. 180−184°; $[\alpha]_D^{23}$ − 77.9°(c = 2.00, THF)). Treatment of (±)-**22** with oxalyl chloride gave an acid chloride (±)-**23**, quantitatively, which was treated with t-butyl hydroperoxide and pyridine to give a peroxyester.[12] This crude peroxyester was heated in ethyl phenylacetate to give (±)-**7**, m.p. 74–76°, in 31% yield (Scheme IV). As this decarboxylation method resulted in rather a low yield, and a base catalized decarboxylation of (±)-**22** was not fruitful, another stereospecific method was attempted for the synthesis of the bicyclic lactone (±)-**7** from (±)-**22**. Esterification of (±)-**22** with ethereal diazomethane gave (±)-**24**, quantitatively, which was reduced with sodium borohydride at −50° to afford a 1:3 mixture of racemic diastereomers (±)-**25**, m.p. 113–117°, as a crystalline mixture accompanied by 11.4% recovery of the starting (±)-**24**. In this reaction, elevation of the temperature resulted in the formation of a more reduced diol (±)-**27**, which was characterized as its diacetate (±)-**28**, via the hemiacetal (±)-**25**. Acetylation of (±)-**25** with acetic anhydride-pyridine (1:2) gave a 4:5 mixture of diastereomers of (±)-**29**, quantitatively. Treatment of (±)-**25** with 1,8-diazabicyclo[5.4.0]undec-7-ene in THF-water (4:1) gave a demethoxycarbonylated product (±)-**26** in 96% yield. The relative configuration of this hemiacetal (±)-**26** was convinced as depicted in Scheme V, (±)-[1α, 2α, 4α, 5α], by the data of ^{1}H NMR of (±)-**26**. The fact that there are no couplings between either the C-1 bridge head proton and the C-2 hemiacetal constructing proton or between that of the C-5 bridge head and



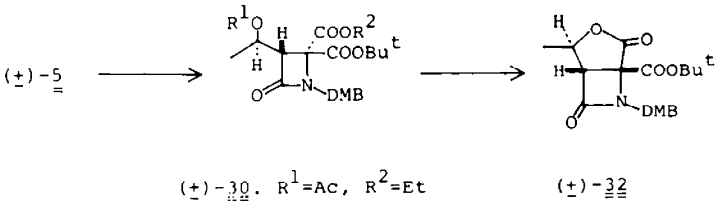
Scheme IV.



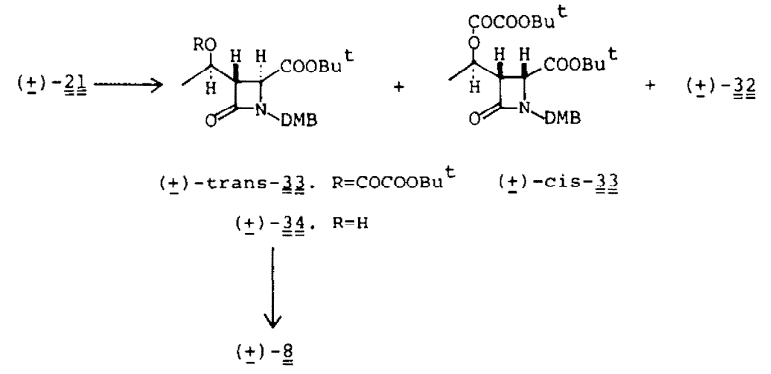
Scheme V.

the C-4 proton reveals that each of the dihedral angles of the two pairs are approx. 90°, and the relative configuration depicted in Scheme V is correct, the coupling constant between C-1 and C-5 being 4 Hz. Oxidation of (±)-**26** with Jones reagent gave a racemic lactone (±)-**7** in 62% yield. Thus, stereospecific conversion of (±)-**22** to lactone (±)-**7** was achieved by these two methods. Consequently, this means that stereospecific conversion of D-*allo*-threonine to *cis*-**12**, **13** and **14** was accomplished.

The stereoselective conversion of the hydroxy dicarboxylic acid (±)-**21** to *trans* hydroxycarboxylic acid (±)-**8** was accomplished as follows (Scheme VII). Treatment of (±)-**21** with 2 equiv of oxalyl chloride gave a mixture of acid chlorides which was further reacted with t-butanol pyridine to give a mixture of (±)-*trans*-**33**, (±)-*cis*-**33**, m.p. 125–127° and (±)-**32** in 40, 5, and 3% yield, respectively. The (±)-*trans*-**33**, was refluxed with 1,8-diazabicyclo[5, 4, 0]undec-7-ene in THF-water (2:1) to give an alcohol, (±)-*trans*-**34**, in 94% yield. Treatment of (±)-**34** with trifluoroacetic acid gave (±)-**8** in 77% yield, which was characterized as its methyl ester. This means that stereoselective conversion of D-*allo*-threonine to *trans*-**12** and **14** was accomplished.



Scheme VI.



Scheme VII.

EXPERIMENTAL

All m.ps are uncorrected. ^{1}H NMR spectra were obtained on a Hitachi R-24, Varian A-60 or HA-100 using tetramethylsilane as an internal standard, IR spectra on a Jasco IR A-2 spectrometer, and mass spectra on a JMS-01SG mass spectrometer. Preparative TLC was carried out using Merck Kieselgel 60 F_{254} plate.

Diethyl (N-2,4-*dimethoxybenzyl*) *aminomalonate* (1)

To a magnetically stirred suspension of diethylaminomalonate HCl (140 g, 0.661 mol) in 99.5% EtOH (450 ml) was added KOH (85% purity, 12 g) at room temp. After 2 hr, when a fair amount of the KOH pellets had dissolved, 2,4-dimethoxybenzaldehyde (99.6 g, 0.600 mol) was added. The resulting suspension was stirred for 15 min at 25°, and then a soln of $NaBH_3CN$ (13.5 g, 0.215 mol) in 99.5% EtOH (220 ml) was added dropwise to the stirred suspension over 30 min. After 30 min stirring, more KOH (85% purity, 36 g) was added, and stirring was continued for 1 hr until the pellets had dissolved completely. The mixture was filtered with suction and the filtrate was concentrated with a rotary evaporater. To this concentrate was added water (1 l.) and conc HCl (80 ml). The acidic aqueous layer was washed twice with ether (500 ml portion), brought to pH > 8 by addition of $NaHCO_3$ (*ca* 100 g), and then extracted 3 times with 500 ml portions of ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give a crude oily residue. Column chromatography on 2 kg of silica gel (eluate: PhH/EtOAc = 4/1) gave 162 g of **1** (83% yield) as an oil; NMR ($CDCl_3$) δ 1.20 (6H, t, J = 6.5 Hz), 2.05 (1H, s, NH), 2.35 (1H, d, J = 2 Hz), 3.66 (5H, s, OCH_3 and $ArCH_2$), 3.68 (3H, s), 3.92 (1H, s), 4.06 (4H, q, J = 6.5 Hz), 6.32 (1H, dd, J = 2, 9 Hz), 7.05 (1H, d, J = 9 Hz); MS *m/e* 325 (M^+).

(2R, 3R)-N-2,4-*Dimethoxybenzyl*-N-*bis*(*ethoxycarbonyl*)*methyl*-2-*bromo*-3-*acetoxybutylamide* (3)

To a soln of **1** (160 g, 0.492 mol) in THF (1.4 l.) was added a soln of **2**[1a,1b] (132 g, 0.542 mol) in THF (200 ml) with stirring at 20°. To this resulting soln was added gradually a soln of Et_3N (55 g, 0.545 mol) with stirring at 15°. The mixture was allowed to stand for 15 hr at 20°. Et_3N·HCl was removed by suction filtration, and the volume of the filtrate was reduced to approx. 0.6 l *in vacuo* while the bath temp was kept below 40°, and diluted with EtOAc (1.5 l.), washed twice with 10% HCl, sat $NaHCO_3$ aq and brine, dried over $MgSO_4$, decolorized with activated charcoal, and evaporated *in vacuo* to give 254 g of **3** (97% yield from **1**) as a viscous oil which was employed for the next reaction without further purification. NMR ($CDCl_3$) δ 1.14 (6H, t, J = 7 Hz), 1.40 (3H, d, J = 6 Hz), 2.03 (3H, s), 3.72 (3H, s), 3.76 (3H, s), 3.7–4.3 (2H + 1H, m), 4.60 (2H, bs), 4.88 (1H, s), 5.31 (1H, m), 6.35–6.55 (2H, m), 7.18 (1H, d, J = 9 Hz, aromatic).

[3S(R)]-1-(2,4-*Dimethoxybenzyl*)-3-(1-*acetoxyethyl*)-4,4-*bis*(*ethoxycarbonyl*)-2-*azetidinone* (4)

A soln of DBU (76 g, 0.50 mol) in benzene (200 ml) was added dropwise to a stirred soln of **2** (254 g, 0.477 mol) in benzene (1.6 l.) at 15–20°. The mixture was allowed to stand overnight at room temp, and the resulting DBU·HBr salt was filtered off with suction, and washed with EtOAc. The combined filtrate was washed with 10%HCl, sat $NaHCO_3$ aq and brine, dried over $MgSO_4$, and decolorized with activated charcoal. Evaporation of the solvent gave 206.5 g of **4** (95.9%) as an oil which was employed for the next reaction without further purification. NMR ($CDCl_3$) δ 1.10 (3H, t, J = 7 Hz), 1.15 (3H, t, J = 7 Hz), 1.37 (3H, d, J = 6 Hz), 1.93 (3H, s), 3.76 (6H, s), 3.7–4.4 (5H, m), 4.44 (2H, bs), 5.20 (1H, m), 6.45 (2H, m), 7.14 (1H, d, J = 9 Hz); IR ν_{max} (film) 1778, 1747 cm^{-1}; MS *m/e* 451 (M^+), 363, 252; $[\alpha]_D^{24}$ + 39.5° (*c* = 2.03, EtOH).

[3S-[3α(S*), 4α]]-1-(2, 4-*Dimethoxybenzyl*)-3-(1-*acetoxyethyl*)-4-*ethoxycarbonyl*-2-*azetidinone*-4-*carboxylic acid* (5)

To a stirred soln of **3** (206 g, 0.456 mol) in pyridine (250 ml) was added dropwise 1N NaOH (500 ml) at 5°. The mixture was allowed to stand overnight at 5°, diluted with sat $NaHCO_3$ (300 ml), and then washed twice with 500 ml portions of EtOAc. The aqueous layer was saturated with NaCl, acidified with conc HCl, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 120 g of **5** (62%) as a viscous oil which was employed for the next reaction without further purification. $[\alpha]_D^{25}$ + 37.7° (*c* = 2.14, EtOH); NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7 Hz). 1.33 (3H. d. J = 6 Hz), 1.89 (3H, s), 3.66 (3H, s), 3.76 (3H, s), 3.6 – 4.1 (2H + 1H, m), 4.28, 4.57 (2H, AB-q, J = 15 Hz), 5.08 (1H, m), 6.36 (1H, d, J = 2 Hz), 6.43 (1H, dd, J = 2, 9 Hz), 7.19 (1H, d, J = 9 Hz), 7.67 (1H, bs, COOH); MS *m/e* 423 (M^+), 379 (M^+-CO_2), 293; IR ν_{max} (film) 1750 (broad) cm^{-1}.

(±)-[3α(S*), 4α]-1-(2,4-*Dimethoxybenzyl*)-3-(1-*acetoxyethyl*)-4-*ethoxycarbonyl*-2-*azetidinone*-4-*carboxylic acid* ((±)-5)

The same successive treatment of (±)-*erythro*-2-bromo-3-acetoxybutyrylchloride[1a,1b] (±)-**2** as described above gave (±)-**5** as a viscous oil.

A mixture of [3S-[3α(S*), 4α]]-*and* [3S-[3α(S*), 4β]]-*ethyl* 1-(2,4-*dimethoxybenzyl*)-3-(1-*acetoxyethyl*)-2-*azetidinone*-4-*carboxylate*. (cis-**6**) *and* (trans-**6**)

A stirred soln of **5** (183.5 g, 0.433 mol) in 2,4,6-collidine (500 ml) was heated for 45 min at 160° and the collidine was removed under reduced pressure to give a residual oil which was diluted with EtOAc (2.5 l.). The soln was washed with 10% HCl, sat $NaHCO_3$ and brine, dried over $MgSO_4$, decolorized with activated charcoal, and then evaporated *in vacuo* to give 135.5 g of a mixture of *cis*-**6** and *trans*-**6** (82.5%), which was employed for the next reaction without further purification. The mixture of *cis*-**6** and *trans*-**6** (200 mg) was separated by chromatography on a preparative silica gel TLC plate. Development with PhH–EtOAc (3:1) gave 144 mg of *cis*-**6** as an oil; R_f = 0.40; NMR ($CDCl_3$) δ 1.20 (3H, t, J = 7 Hz), 1.33 (3H, d, J = 6.5 Hz), 1.90 (3H, s), 3.42 (1H, dd, J = 6, 11 Hz), 3.73 (3H, s), 3.77 (3H, s), 3.97 (1H, d, J = 6 Hz), 4.08 (2H, q, J = 7 Hz), 4.08, 4.56 (2H, AB-q, J = 15 Hz), 5.13 (1H, qd, J = 6.5, 11 Hz), 6.42 (1H, dd, J = 2, 9 Hz),

6.43 (1H, d, J = 2 Hz), 7.10 (1H, d, J = 9 Hz); IR ν_{max}(film) 1768, 1748, 1615, 1590 cm^{-1}; MS *m/e* 379 (M^+); and 37 mg of *trans*-**6** as an oil; R_f = 0.28; NMR ($CDCl_3$) δ 1.23 (3H, t, J = 7 Hz), 1.28 (3H, d, J = 6.5 Hz), 1.88 (3H, s), 3.21 (1H, dd, J = 2.5, 6.5 Hz), 3.79 (6H, s), 3.87 (1H, d, J = 2.5 Hz), 4.14, 4.65 (2H, AB-q, J = 15 Hz), 4.21 (2H, q, J = 7 Hz), 5.20 (1H, quintuplet, J = 6.5 Hz), 6.44 (1H, dd, J = 3, 9 Hz), 6.47 (1H, d, J = 3 Hz), 7.15 (1H, d, J = 9 Hz); IR ν_{max}(film) 1765, 1740, 1615, 1590 cm^{-1}; MS *m/e* 379 (M^+). The ratio of *cis*:*trans* was 3.89:1. The aqueous layer of sat $NaHCO_3$ washing was acidified with conc HCl, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give a crude crystalline solid which was recrystallized from EtOAc to give 10.5 g of an acid (**22**); m.p. 180–184. It is guessed that this lactone acid (**22**) had already existed in the starting acid (**5**) as an over-saponified by-product obtained from saponification of the acetoxy diester (**4**).

[1R-(1α, 4α, 5α)]-7-(2,4-Dimethoxybenzyl)-2,6-dioxo-4-methyl-3-oxa-7-azabicyclo[3.2.0]heptane (**7**) *and [3S-[3α(S*), 4β]]-1-(2,4-dimethoxybenzyl)-3-(1-hydroxyethyl)-2-azetidinone-4-carboxylic acid* (**8**)

To a stirred soln of **6** (283 g, 0.746 mol) in pyridine (780 ml) was added dropwise 1N NaOH (1560 ml, 1.56 mol) at 5° over a period of 40 min. The resulting soln was allowed to stand for 18 hr at 20–25°, concentrated *in vacuo* to a volume of 1.5 l. at a temp below 40°, and diluted with sat $NaHCO_3$ (11.). The aqueous soln was washed twice with EtOAc (0.8 l.) to recover 5.14 g of *cis*-**6**. The aqueous layer was acidified with conc HCl, sat with NaCl, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give 243.5 g of residue which was dissolved in THF (4 l.) and conc HCl (2 ml). The soln was allowed to stand for 18 hr at 20–25° and concentrated under reduced pressure to give a residual oil which was diluted with EtOAc (3 l.). The acidic materials were extracted with sat $NaHCO_3$ (0.6 l. × 3), and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give 90.0 g of **7** as a crystalline solid. The aqueous extract was treated several times in the same successive procedure as described above to give 34.9 g (2nd), 11.0 g (3rd) and 3.0 g (4 th) (total 138.9 g, 64% yield) of **7** and 31.9 g of **8** (14% yield) as a gum. **7**; m.p. 87–89° (from ether) (*cf* racemate m.p. 74–76°); $[\alpha]_D^{25}$ − 65.9° (*c* = 2.00, EtOH); NMR ($CDCl_3$) δ 1.32 (3H, d, J = 6.5 Hz), 3.45 (1H, dd, J = 2, 4.5 Hz), 3.77 (3H, s), 3.81 (3H, s), 4.03 (1H, d, J = 4.5 Hz), 4.08, 5.14 (2H, AB-q, J = 15 Hz), 4.93 (1H, qd, J = 6.5, 2 Hz), 6.44 (1H, dd, J = 2, 9 Hz), 6.45 (1H, d, J = 2 Hz), 7.19 (1H, d, J = 9 Hz). (Found: C, 61.94; H, 5.82; N, 4.76. Calc for $C_{15}H_{17}O_5N$: C, 61.85; H, 5.88, N, 4.81%.) A small quantity of **8** was characterized as its methyl ester: NMR ($CDCl_3$) δ 1.22 (3H, d, J = 6 Hz), 2.55 (1H, bs, OH), 3.15 (1H, dd, J = 2, 5 Hz), 3.70 (3H, s), 3.77 (3H, s), 3.78 (3H, s), 3.97 (1H, d, J = 2 Hz), 4.09 (1H, m), 4.11, 4.60 (2H, AB-q, J = 14.5 Hz), 6.37 (1H, dd, J = 2, 9 Hz), 6.37 (1H, d, J = 2 Hz), 7.10 (1H, d, J = 9 Hz).

A mixture of [1R-(1α, 2ξ, 4α, 5α)]-7-(2,4-dimethoxybenzyl)-2,4-dimethyl-2-hydroxy-3-oxa-6-oxo-7-azabicyclo[3.2.0]heptane (**9a**) *and [3S-[3α(S*), 4α]]-1-(2,4-dimethoxybenzyl)-3-(1-hydroxyethyl)-4-acetyl-2-azetidinone* (**9b**)

To a stirred soln of **7** (133.6 g, 0.459 mol) in THF (1.68 l.) was added a soln of MeMgBr (1M THF soln, 918 ml) in THF (420 ml) under N_2 at a temp range of −60–−45° over 15 min, and the stirring was continued for an additional 30 min at −60°. The mixture was quenched with 10% HCl (500 ml) at −60°, and diluted with EtOAc (7 l.). The resulting organic layer was washed with sat $NaHCO_3$ and brine, dried over $MgSO_4$, decolorized with activated charcoal, and evaporated under reduced pressure to give 138 g of a 3:1 mixture of **9a** and **9b** (98% yield); NMR δ ($CDCl_3$) 1.47 (9/4H, s, the Me protons of hemiketal **9a**), 2.14 (3/4H, s, the acetyl protons of keto-alcohol **9b**). This mixture was employed for the next reaction without further purification.

A mixture of (±)-**9a** *and* (±)-**9b**. By the same successive procedures as described above, a mixture of (±)-**9a** and (±)-**9b** was obtained from (±)-**5**.

[3S-[3α(S), 4α]]-1-(2,4-Dimethoxybenzyl)-3-(1-t-butyl dimethylsilyloxyethyl)-4-acetyl-2-azetidinone* (cis-**10**)

To a stirred soln of the mixture of **9a** and **9b** (138 g, 0.450 mol) in DMF (450 ml) was added t-butyldimethylsilyl chloride (135 g, 0.898 mol) and 4-dimethylaminopyridine (110 g, 0.898 mol). The resulting mixture was stirred for 2 days at 20–25°, diluted with EtOAc (4 l.), washed with cold 3% HCl, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The obtained residual oil (230 g) was purified by column chromatography (silica gel, 1.4 kg), which was eluted with PhH/EtOAc (9:1) to give 167 g of *cis*-**10** (88.4% yield) as an oil: $[\alpha]_D^{25}$ − 20.7° (*c* = 1.96, EtOH); NMR ($CDCl_3$) δ 0.05 (6H, s), 0.81 (9H, s), 1.19 (3H, d, J = 6 Hz), 2.12 (3H, s), 3.27 (1H, t, J = 6 Hz), 3.69 (3H, s), 3.73 (3H, s), 3.87 (1H, d, J = 6 Hz), 4.02, 4.64 (2H, AB-q, J = 15 Hz), 4.16 (1H, quintuplet, J = 6 Hz), 6.41 (1H, dd, J = 2, 9 Hz), 6.41 (1H, d, J = 2 Hz), 7.08 (1H, d, J = 9 Hz); MS *m/e* 421 (M^+), 394, 380, 364, 262.

[3S − [3α(S), 4α]]-3-(1-t-Butyldimethylsilyloxyethyl)-4-acetyl-2-azetidinone* (cis-**11**)

To a stirred soln of *cis*-**10** (64.3 g, 0.153 mol) in MeCN (2.2 l.) was added $K_2S_2O_8$ (360 g, 1.33 mol) and K_2HPO_4 (120 g, 0.69 mol) under argon atmosphere and the mixture was heated at 65° for 60 min with vigorous stirring, and then MeCN was removed under reduced pressure. The residual aqueous layer was extracted three times with EtOAc. The extract was washed with sat $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a residual oil (54.6 g) which was purified on a silica gel (800 g) column. Elution with PhH/EtOAc (7:3) gave 30.8 g of *cis*-**11** as a semisolid (*cf* m.p. of racemate: 74–76°, from ether/n-hexane); NMR ($CDCl_3$) δ 0.07 (6H, s), 0.82 (9H, s), 1.23 (3H, d, J = 6.5 Hz), 2.25 (3H, s), 3.52 (1H, dd, J = 4.5, 6 Hz), 4.21 (1H, d, J = 6 Hz), 4.28 (1H, dq, J = 4.5, 6.5 Hz), 6.82 (1H, bs, NH); MS *m/e* 256 ($M^+ - 15$), 214, 171, 170. (Found: C, 57.78; H, 9.34; N, 4.93. Calc for $C_{13}H_{25}O_3NSi$: c, 57.54; H, 9.29; N, 5.16%.)

[3R-[3α(R), 4α]]-3-(1-t-Butyldimethylsilyloxyethyl)-4-acetoxy-2-azetidinone* (cis-**12**)

A soln of *cis*-**11** (84.1 g, 0.139 mol) and *m*-chloroperbenzoic acid (80–90% purity, 280 g) in $CHCl_3$ (1.7 l.) was allowed to stand for 4 days at room temp in the dark, and concentrated under reduced pressure. The residual mixture was diluted with EtOAc (3 l.), and washed 3 times with 10% $NaHSO_3$, 7 times with sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 85.1 g of *cis*-**12** (95.6% yield) as a solid; m.p. 52–53° (needles from n-hexane), (*cf* m.p. of racemate, 78.5–80.5°); $[\alpha]_D^{23}$ − 119.1° (*c* = 2.00, EtOH); NMR($CDCl_3$) δ 0.09 (6H, s), 0.83 (9H, s), 1.30 (3H, d, J = 6.5 Hz), 2.07 (3H, s), 3.32 (1H, ddd, J = 2, 5, 9 Hz), 4.33 (1H, qd, J = 6.5, 9 Hz), 5.88 (1H, d, J = 5 Hz), 6.85 (1H, broad, NH); MS *m/e* 230 ($M^+ - 57$); IR ν_{max}(nujol) 3220, 1780, 1760, 1739 cm^{-1}. (Found: C, 54.22; H, 8.72; N, 4.77. Calc for $C_{13}H_{25}O_4NSi$: C, 54.33; H, 8.77; N, 4.87%.)

[3S-[3α(S), 4β]]-3-(1-t-Butyldimethylsilyloxy)ethyl-4-benzyloxycarbonylmethyl-2-azetidinone* (**13**)

To an ice-cooled soln of *cis*-**12** (287 mg, 1.0 mmol) in THF (10 ml), Me_3SiCl (141 mg, 1.3 mmol) and Et_3N (131 mg, 1.3 mmol) was added with stirring. After a time of 2 hr at 24°, the mixture was filtrated through celite. The celite was washed twice with a small portion of dry ether, and the combined organic layer was concentrated and dried *in vacuo* to give a viscous oil. The residue was dissolved in CH_2Cl_2 (10 ml). To this soln was added the trimethylsilyl enol ether of benzyl acetate (444 mg, 2 mmol) and trimethylsilyl trifluoromethanesulfonate (44 mg, 0.20 mmol) with stirring at room temp. After 20 hr, the mixture was diluted with EtOAc, washed with sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a viscous oil which was dissolved in 99% EtOH (10 ml). After addition of KF (10 ml), the suspension was stirred for 30 min, diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, and concentrated

in vacuo to give a viscous oil which was purified on a silica gel TLC plate. Development with cyclohexane/EtOAc = 2/1 (R_f = 0.40) gave 219 mg (58% yield) of **13** as a crystalline solid; m.p. 92–93° (leaflets from n-hexane); $[\alpha]_D^{25}$ + 17.4° (*c* = 1.75, $CHCl_3$); NMR ($CDCl_3$) δ 0.06 (6H, s), 0.87 (9H, s), 1.18 (3H, d, J = 6 Hz), 2.6–2.9 (2H + 1H, m), 3.8–4.4 (1H + 1H, m) 5.14 (2H, s), 6.14 (1H, bs, NH), 7.37 (5H, s). (Found: C, 63.96; H, 8.29; N, 3.68. Calc for $C_{20}H_{31}O_4NSi$: C, 63.62; H, 8.27; N, 3.71%.)

[3S-[3α(S*), 4β]]-3-(1-*t*-*Butyldimethylsilyloxyethyl*)-4-*phenylsulfonyl*-2-*azetidinone*(**14**)

(a) A soln of $PhSO_2Na\ 2\ H_2O$ (117 g, 0.585 mol) in H_2O (1.2 l.) was added to a soln of *cis*-**12** (84 g, 0.293 mol) in dioxane (1.2 l.), and the mixture was refluxed for 45 min, concentrated under reduced pressure to half volume, and extracted with EtOAc. The extract was washed with sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 68 g of **14** (63% yield) as a crystalline solid; m.p. 166–167° (from EtOAc/n-hexane); $[\alpha]_D^{25}$ − 12.4° (*c* = 0.93, $CHCl_3$); IR ν_{max} (nujol) 3160, 3090, 1780, 1740 cm^{-1}; NMR ($CDCl_3$) δ 0.05 (6H, s), 0.83 (9H, s), 1.10 (3H, d, J = 6.5 Hz), 3.40 (1H, t, J = 2 Hz), 4.23 (1H, dq, J = 2, 6.5 Hz), 4.75 (1H, d, J = 2 Hz), 6.22 (1H, bs, NH), 7.5–8.1 (5H, m). (Found: C, 55.14; H, 7.42; N, 4.03; S, 8.47. Calc for $C_{17}H_{27}O_4SNSi$: C, 55.28; H, 7.32; N, 3.79; S, 8.67%.)

(b) The same treatment of *trans*-**12** with $PhSO_2Na$ in THF–H_2O (1:1) gave **14** in 90% yield.

[3S-[3α(S*), 4β]]-1-(2,4-*Dimethoxybenzyl*)-3-(1-*t*-*butyldimethylsilyloxyethyl*)-2-*azetidinone*-4-*carboxylic acid* (**15**)

A soln of **8** (15 g, 48.5 mmol) in DMF (50 ml) was added 4-dimethylaminopyridine (17.5 g, 146 mmol) and t-butyldimethylsilyl chloride (22 g, 146 mmol). After 18 hr stirring at 20–25°, the mixture was adjusted to pH 3 with cold 5% HCl, adjusted with sat $NaHCO_3$ to pH 8, washed with EtOAc to remove non-acidic materials, and then reacidified to pH 3 with 15% HCl, and extracted with EtOAc. The extract was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 18.2 g of crude **15** (89% yield) which was employed for the next reaction without purification. NMR ($CDCl_3$) δ 0.06 (6H, s), 0.78 (9H, s), 1.24 (3H, d, J = 6 Hz), 3.26 (1H, t, J = 3 Hz), 3.84 (6H, s), 4.19 (1H, d, J = 3 Hz), 4.28, 4.62 (2H, AB-q, J = 14.5 Hz), 6.45 (1H, dd, J = 2, 9 Hz), 6.46 (1H, d, J = 4 Hz), 7.18 (1H, bs, COOH), 7.20 (1H, d, J = 9 Hz).

[3S - [3α(S*), 4β]] - 1 - (2,4 - *Dimethoxybenzyl*) - 3 - (1 - *t* - *butyldimethylsilyloxyethyl*)-2-*azetidinone*-4-*carboxylic acid chloride* (**16**)

To a stirred soln of the acid (**15**, 18 g) in THF (200 ml) was added oxalyl chloride (10 ml) at 20–25°. After a reaction time of 3 hr at 25°, the soln was concentrated *in vacuo* to give 18.7 g of **16** which was employed for the next reaction.

[3S-[3α(S*), 4β]]-1-(2,4-*Dimethoxybenzyl*)-3-(1-*t*-*butyldimethylsilyloxyethyl*)-4-*acetyl*-2-*azetidinone* (trans-**10**)

To a soln of MeMgBr (1M THF soln, 150 ml, 150 mmol) was added $CdCl_2$ (13.7 g, 75 mmol) with stirring at 5°. The mixture was stirred for an additional 1 hr at 24°. To this Me_2Cd soln was added a soln of **16** (18.7 g) in THF (200 ml) at 5° with stirring. After a time of 2 hr at 25°, the mixture was quenched with 10% aq $CuSO_4$, diluted with EtOAc, washed with sat $NaHCO_3$ and brine, dried over $MgSO_4$, decolorized with activated charcoal, and concentrated under reduced pressure to give a crude oil which was chromatographed on a silica gel (600 g) column. Elution with cyclohexane–EtOAc (2:1) gave 11.8 g of *trans*-**10** (65.9% yield from **15**) as a viscous oil; IR ν_{max} (film) 1760, 1718, 1616, 1590 cm^{-1}; NMR ($CDCl_3$) δ 0.04 (6H, s), 0.80 (9H, s), 1.20 (3H, d, J = 6 Hz), 2.05 (3H, s), 2.95 (1H, dd, J = 2.5, 4 Hz), 3.73 (3H, s), 3.78 (3H, s), 4.00 (1H, d, J = 2.5 Hz), 4.21 (1H, qd, J = 6, 4 Hz), 4.20, 4.54 (2H, AB-q, J = 15 Hz), 6.39 (1H, dd, J = 2, 9 Hz), 6.39 (1H, d, J = 2 Hz), 7.11 (1H, d, J = 9 Hz); MS *m/e* 421 (M^+), 364 (M^+ − 57).

[3S-[3α(S*), 4β]]-3-(1-*t*-*Butyldimethylsilyloxyethyl*)-4-*acetyl*-2-*azetidinone* (trans-**11**)

The same treatment of *trans*-**10** with $K_2S_3O_8$-K_2HPO_4 as described for the conversion of *cis*-**10** to *cis*-**11** gave *trans*-**11** in 82% yield as a crystalline solid: m.p. 72–73° (from n-hexane); NMR ($CDCl_3$) δ 0.11 (6H, s), 0.91 (9H, s), 1.30 (3H, d, J = 6 Hz), 2.26 (3H, s), 3.10 (1H, m), 4.1–4.5 (2H, m), 6.55 (1H, bs, NH). (Found: C, 57.61; H, 9.36; N, 5.02. Calc for $C_{13}H_{25}O_3NSi$: C, 57.54; H, 9.29; N, 5.16%.)

[3R-[3α(R*), 4β]]-3-(1-*t*-*Butyldimethylsilyloxyethyl*)-4-*acetoxy*-2-*azetidinone* (trans-**12**)

The same treatment of *trans*-**11** with *m*-chloroperbenzoic acid as described for the conversion of *cis*-**11** to *cis*-**12** gave *trans*-**12** in 84% yield as a crystalline solid; m.p. 101–103° (from n-hexane); $[\alpha]_D^{25}$ + 47.9° (*c* = 1.00, $CHCl_3$); IR ν_{max}(nujol) 3200, 1785, 1745 cm^{-1}; NMR ($CDCl_3$) δ 0.07 (6H, s), 0.85 (9H, s), 1.24 (3H, d, J = 6.5 Hz), 2.12 (3H, s), 3.22 (1H, dd, J = 1, 3 Hz), 4.24 (1H, dq, J = 3, 6.5 Hz), 5.89 (1H, d, J = 1 Hz); MS *m/e* 230 (M^+ − 57), 188, 144.

(±)-[3α(S*), 4α]-1-(2,4-*Dimethoxybenzyl*)-3-(1-*acetoxyethyl*)-4-*acetyl*-2-*azetidinone* ((±) − **17**)

A soln of the mixture of (±) − **9a** and (±) − **9b** (3.0 g, 3:1 mixture, 9.7 mmol) in pyridine (20 ml) and Ac_2O (10 ml) was allowed to stand for 18 hr at 25°, and then concentrated under reduced pressure to give a residual oil which was diluted with EtOAc. The soln was washed with 10% HCl, sat $NaHCO_3$ and brine, dried over $MgSO_4$, decolorized with activated charcoal, and concentrated under reduced pressure to give 3.10 g of (±)-**17** (91% yield) as a crystalline solid. An analytical sample was recrystallized from EtOAc-n-hexane; m.p. 108.5–109.5°; IR ν_{max} (nujol) 1759, 1745, 1712, 1613, 1585 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (3H, d, J = 6.5 Hz), 1.91 (3H, s), 2.05 (3H, s), 3.48 (1H, dd, J = 6, 10 Hz), 3.73 (3H, s), 3.78 (3H, s), 3.99 (1H, d, J = 6 Hz), 4.06, 4.65 (2H, AB-q, J = 15 Hz), 5.10 (1H, qd, J = 6.5, 10 Hz), 6.46 (1H, d, J = 2 Hz), 6.46 (1H, dd, J = 2, 9 Hz), 7.13 (1H, d, J = 9 Hz). (Found: C, 61.85; H, 6.61; N, 3.99. Calc. for $C_{18}H_{23}O_6N$: C, 61.88; H, 6.64; N, 4.01%).

(±)-[3α(S*), 4α]-3-(1-*Actoxyethyl*)-4-*acetyl*-2-*azetidinone* ((±)-**18**)

The same treatment of (±)-**17** as described for the formation of *cis*-**10** to *cis*-**11** gave (±)-**18** in 80% yield as a crystalline solid; m.p. 155–157° (changed to the crystalline form at 133–143°); MS *m/e* 199 (M^+): NMR (acetone-d_6) δ 1.31 (3H, d, J = 6 Hz), 1.97 (3H, s), 2.23 (3H, s), 3.72 (1H, dd, J = 5.5, 9.5 Hz), 4.46 (1H, d, J = 5.5 Hz), 4.87 (1H, qd, J = 6, 9.5 Hz), 7.50 (1H, bs, NH). (Found: C, 54.41; H, 6.67; N, 6.91. Calc for $C_9H_{13}O_4N$: 54.26; H, 6.58; N, 7.03%.)

(±)-[3α(R*), 4α]-3-(1-*Acetoxyethyl*)-4-*acetyl*-2-*azetidinone* ((±)-**19**)

The same treatment of (±)-**18** as described for the formation of *cis*-**12** from *cis*-**11** gave (±)-**19** in 83% yield; NMR ($CDCl_3$) δ 1.44 (3H, d, J = 6.5 Hz), 2.06 (3H, s), 2.12 (3H, s) 3.58 (1H, ddd, J = 2, 4, 10 Hz), 5.42 (1H, qd, J = 6.5, 10 Hz), 5.97 (1H, d, J = 4 Hz), 7.15 (1H, bs, NH).

(±)-[3α(S*), 4β]-3-(1-*Acetoxyethyl*)-4-*phenylsulfonyl*-2-*azetidinone* ((±)-**20**)

A soln of $PhSO_2Na$ (112 mg, 0.56 mmol) in H_2O (1 ml) was added to a soln of (±)-**19** in dioxane (1 ml), and the mixture was stirred for 1 hr at 60°, and diluted with EtOAc, washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give a residual oil which was purified on a preparative TLC plate. Development with cyclohexane/EtOAc (1:1) gave 70 mg of (±)-**20** (84.5% yield) as a viscous oil; NMR ($CDCl_3$) δ 1.30 (3H, d, J = 6 Hz), 1.94 (3H, s), 3.57 (1H, dd, J = 2, 6 Hz), 4.75 (1H, d, J = 2 Hz), 5.21 (1H, quintuplet, J = 6 Hz), 7.08 (1H, s, NH), 7.4–8.0 (5H, m).

(±)-(R*, S*)-1-(2,4-*Dimethoxybenzyl*)-3-(1-*hydroxyethyl*)-2-*azetidinone*-4,4-*bis*(*carboxylic acid*) ((±)-**21**)

A soln of (±)-**5** (11 g, 26 mmol) in pyridine (42 ml) and 1N NaOH (84 ml, 3.23 equiv) was allowed to stand for 20 hr at 0°, to which sat $NaHCO_3$ (200 ml) was added, and washed with EtOAc. The aqueous layer was acidified with dil HCl at 5–10°, and extracted with EtOAc. The extract was washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give 9.1 g of (±)-**21** (99% yield) as a crystalline solid; m.p. 124–125° (lactonization occured at this point, and then melting at 157–166°); IR ν_{max} (nujol) 3210, 3500–2400, 1770, 1742, 1660, 1608, 1585 cm^{-1}; NMR (acetone-d_6) δ 1.25 (3H, d, J = 6 Hz), 3.46 (1H, d, J = 9.5 Hz), 3.63 (6H, s), 4.00 (1H, qd, J = 6, 9.5 Hz), 4.35 (2H, s), 6.34 (1H, dd, J = 2, 10 Hz), 6.38 (1H, d, J = 2 Hz), 7.08 (1H, d, J = 10 Hz), 7.50 (3H, bs, COOH × 2 and OH). (Found: C, 54.66; H, 5.47; N, 3.87. Calc for $C_{16}H_{19}O_8N$: C, 54.39; H, 5.42; N, 3.96%.)

(±)-[1α, 4α, 5α]-7-(2, 4-*Dimethoxybenzyl*)-2,6-*dioxo*-4-*methyl*-3-*oxa*-7-*azabicyclo*[3.2.0]*heptane*-1-*carboxylic acid* ((±)-**22**)

A soln of (±)-**21** (3.53 g, 10 mmol) in THF (20 ml) containing conc HCl (0.5 ml) was allowed to stand for 16 hr at 25°. Evaporation of the solvent under reduced pressure gave a lactone (±)-**22** quantitatively as a crystalline solid; m.p. 162–165° (needles from EtOAc); IR ν_{max}(nujol) 1773, 1730 (broad), 1605, 1579 cm^{-1}.

[1S-(1α, 4α, 5α)]-7-(2, 4-*Dimethoxybenzyl*)-2, 6-*dioxo*-4-*methyl*-3-*oxa*-7-*azabicyclo* [3.2.0]*heptane*-1-*carboxylic acid*((−)-**22**)

The same successive treatment of **5** as described for the formation of (±)-**22** (via (±)-**21**) from (±)-**5** gave (−)-**22** as a crystalline solid; m.p. 180–184° (needles from EtOAc); $[\alpha]_D^{23}$ −77.9° (*c* = 2.00, THF); IR ν_{max} (nujol) 1785, 1745, 1730 (shoulder), 1613, 1588 cm^{-1}; NMR (acetone-d_6) δ 1.39 (3H, d, J = 6 Hz), 3.65, s), 3.88 (1H, d, J = 1 Hz), 4.33 (2H, s), 4.79 (1H, dq, J = 1, 6 hz), 5.98 (1H, bs, COOH), 6.33 (1H, dd, J = 2, 9 Hz), 6.40 (1H, d, J = 2 Hz), 7.08 (1H, d, J = 9 Hz). (Found: C, 57.49; H, 5.22; N, 4.18. Calc for $C_{16}H_{17}O_7N$: C, 57.31; H, 5.11; N, 4.18%.).

(±)-[1α, 4α, 5α]-7-(2,4-*Dimethoxybenzyl*)-2,6-*dioxo*-3-*oxa*-4-*methyl*-7-*azabicyclo*[3.2.0]*heptane*-1-*carboxylic acid chloride* ((±)-**23**)

A soln of (±)-**22** (1.35 g, 4.0 mmol) in THF (20 ml) and oxalyl chloride (2 ml) was allowed to stand for 18 hr at room temp, or refluxed for 1 hr, and concentrated under reduced pressure to give (±)-**23** quantitatively, which was employed for the next reaction without purification.

(±)-[1α, 4α, 5α]-7-(2,4-*Dimethoxybenzyl*)-2,6-*dioxo*-4-*methyl*-3-*oxa*-7-*azabicyclo*[3.2.0]*heptane* ((±)-**7**)

(a) To a soln of t-butyl hydroperoxide (270 mg, 3 mmol), and pyridine (240 mg, 3 mmol) in CH_2Cl_2 (4 ml) was added dropwise a soln of (±)-**23** (708 mg, 2 mmol) in CH_2Cl_2 (4 ml) at 0–5° over 20 min. The mixture was allowed to stand for 14 hr at 0°, diluted with CH_2Cl_2 (60 ml), washed with 2N H_2SO_4 and 2N Na_2CO_3, dried over $MgSO_4$, and concentrated under reduced pressure to give 654 mg of a crude oily (±)-**23** which was dissolved in ethyl phenylacetate (10 ml), and heated at 140° for 10 min under N_2. Ethyl phenylacetate was removed by silica gel column chromatography (elution with PhH), and elution with EtOAc gave a crude oil which was purified on a preparative TLC plate to give 181 mg of (±)-**7** (31% yield) as a crystalline solid; m.p. 74–76° (from ether). The same successive treatment of (−)-**22** as described above gave optically active (−)-**7**, m.p. 87–89°.

(b) Jones reagent (0.3 ml) was added to a stirred soln of (±)-**26** (125 mg) in acetone (4 ml) at 25°. After 30 min, the mixture was diluted with EtOAc, washed with sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue which was purified on a silica gel preparative TLC plate. Development with cyclohexane–EtOAc (1:1) gave 77 mg of (±)-**7** (R_f = 0.25, 62% yield) as a crystalline solid; m.p. 74–76° (from Et_2O); IR ν_{max} (nujol) 1780, 1763, 1720, 1590 cm^{-1}; MS *m/e* 291 (M^+).

(±)-[1α, 4α, 5α]-*Methyl* 7-(2,4-*dimethoxybenzyl*)-2,6-*dioxo*-4-*methyl*-3-*oxa*-7-*azabicyclo*(3,2,0)*heptane*-1-*carboxylate* ((±)-**24**)

Treatment of (±)-**22** with ethereal CH_2N_2 gave (±)-**24**, quantitatively, as a viscous oil; MS *m/e* 349 (M^+); NMR ($CDCl_3$) δ 1.46 (3H, d, J = 6.5 Hz), 3.64 (1H, d, J = 1 Hz), 3.77 (6H, s), 4.46 (2H, s), 4.83 (1H, dq, J = 1, 6.5 Hz), 6.32 (1H, d, J = 2 Hz), 6.33 (1H, dd, J = 2, 9 Hz), 7.08 (1H, d, J = 9 Hz).

A mixture of (±)-[1α, 2α, 4α, 5α]- *and* (±)-[1α, 2β, 4α, 5α]-*methyl* 7-(2,4-*dimethoxybenzyl*)-2-*hydroxy*-4-*methyl*-3-*oxa*-6-*oxo*-7-*azabicyclo*[3.2.0]*heptane*-1-*carboxylate* ((±)-**25**)

To a stirred soln of (±)-**24** (175 mg, 0.5 mmol) in MeOH (4 ml) was added three 40 mg portions of $NaBH_4$ at 20 min intervals at −50°. 20 Min after the last addition, the mixture was quenched with dil HCl, diluted with EtOAc, washed with sat $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent gave a crude residue which was purified on a preparative silica gel TLC plate to give 20 mg of the starting (±)-**24** (11.4% recovery) and 103 mg of (±)-**25** (59% yield) as a 1:3 mixture of crystalline solids; m.p. 113–117° (from ether); NMR ($CDCl_3$) δ 1.16 (3H/4, d, J = 6 Hz, CH_3CH of one isomer), 1.30 (9H/4, d, J = 6 Hz, CH_3CH of the other isomer), 4.94 (3H/4, d, J = 3.5 Hz, $\underline{CH}OH$, this signal changed to a singlet on addition of D_2O), 5.56 (1H/4, d, J = 10 Hz, this signal also changed to a singlet on addition of D_2O); MS *m/e* 351 (M^+).

(±)-[1α,2α,4α,5α]-7-(2,4-*Dimethoxybenzyl*)-2-*hydroxy*-4-*methyl*-3-*oxa*-6-*oxo*-7-*azabicyclo*[3.2.0]*heptane* ((±)-**26**)

To a soln of (±)-**25** (15 mg) in THF (4 ml) and H_2O (1 ml) was added DBU (10 mg). The mixture was refluxed for 2 hr and concentrated to give an oily residue which was chromatographed on a preparative TLC plate (developed with PhH/EtOAc = 2/1, R_f = 0.14) to give 12 mg of (±)-**26** (96% yield) as a viscous oil; IR ν_{max} (film) 3375, 2500, 1760–1720, 1610, 1588 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (3H, d, J = 6.5 Hz), 3.47 (1H, d, J = 4 Hz), 3.76 (3H, s), 3.78 (3H, s), 3.98 (1H, d, J = 4 Hz), 4.08, 4.38 (2H, AB-q, J = 14.5 Hz), 4.49 (1H, q, J = 6.5 Hz), 4.69 (1H, d, J = 3 Hz, $\underline{OH}$, D_2O exchanged), 5.21 (1H, d, J = 3 Hz, changed to a singlet on addition of D_2O), 6.33 (1H, dd, J = 2, 9 Hz), 6.38 (1H, d, J = 2 Hz), 7.03 (1H, d, J = 9 Hz); MS *m/e* 293 (M^+).

(±)-[3α(S*), 4β]-1-(2,4-*Dimethoxybenzyl*)-3-(1-*hydroxyethyl*)-4-*methoxycarbonyl*-4-*hydroxymethyl*-2-*azetidinone* ((±)-**27**

To a soln of (±)-**24** (210 mg, 0.60 mmol) in MeOH (4 ml) was added $NaBH_4$ (23 mg, 0.60 mmol) at 0° with stirring. After 1 hr, the mixture was quenched with 5% HCl, diluted with EtOAc, washed with sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a crude oily mixture which was chromatographed on a silica gel preparative TLC plate. Development with PhH/EtOAc (2:1) gave 76 mg of (±)-**27** (R_f = 0.167, 36% yield). NMR ($CDCl_3$ + D_2O) δ 1.33 (3H, d, J = 6 Hz), 3.38 (1H, d, J = 10.5 Hz), 3.58 (3H, s), 3.76 (6H, s), 3.77–4.40 (5H, m), 6.3–6.6 (2H, m), 7.16 (1H, d, J = 9 Hz).

(±)-[3α(S*), 4β]-1-(2,4-*Dimethoxybenzyl*)-3-(1-*acetoxyethyl*)-4-*methoxycarbonyl*-4-*acetoxymethyl*-2-*azetidinone* ((±)-**28**)

A soln of (±)-**27** (70 mg) in Ac_2O-pyridine (1:2, 3 ml) was allowed to stand overnight at room temp, and concentrated *in vacuo* to give an oily residue. Chromatography on a silica gel preparative TLC plate gave 46 mg of (±)-**28** in 53% yield. IR ν_{max} (film) 1170, 1748, 1615, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (3H, d, J = 6 Hz), 1.84 (3H, s), 1.95 (3H, s), 3.46 (1H, d, J = 11 Hz), 3.62 (3H, s), 3.77 (6H, s), 4.38 (4H, bs), 5.35 (1H, qd, J = 6, 11 Hz), 6.41 (1H, d, J = 2 Hz), 6.43 (1H, dd, J = 2, 9 Hz), 7.22 (1H, d, J = 9 Hz); MS *m/e* 437 (M^+), 378, 350.

A mixture of (±)-[1α, 2α, 4α, 5α]-*and* (±)-[1α, 2β, 4α, 5α]-1-*methoxycarbonyl*-2-*acetoxy*-3-*oxa*-4-*methyl*-6-*oxo*-7-(2,4-*dimethoxybenzyl*)-7-*azabicyclo*[3.2.0]*heptane* ((±)-**29**)

A soln of (±)-**25** (143 mg) in Ac_2O-pyridine (1:1, 2 ml) was allowed to stand overnight at room temp, diluted with EtOAc, washed with 15% HCl and sat $NaHCO_3$, dried over $MgSO_4$, and

concentrated *in vacuo* to give a viscous oil which was purified on a silica gel preparative TLC plate. Development with PhH-EtOAc (2:1) gave 174 mg of (±)-**29** (R_f = 0.47, 89% yield). NMR ($CDCl_3$) δ 1.24 (3H × 5/9, d, J = 6 Hz), 1.26 (3H × 4/9, d, J = 6 Hz), 1.80 (3H × 5/9, s, $OCOCH_3$), 1.90 (3H × 4/9, s, $OCOCH_3$), 3.38–3.90 (10H, m), 4.3–4.8 (3H, m), 6.07 (1H × 4/9, s, OCHOAc), 6.58 (1H × 5/9, s, OCHOAc), 6.35–6.53 (2H, m), 7.1–7.3 (1H, m); MS *m/e* 393 (M^-).

(±)-[3α(S*), 4β]-1-(2,4-*Dimethoxybenzyl*)-3-(1-*acetoxyethyl*)-4-*ethoxycarbonyl*-4-*t*-*butoxycarbonyl*-2-*azetidinone* ((±)-**30**)

To a soln of (±)-**5** (510 mg, 1.20 mmol) in THF (10 ml) was added oxalyl chloride (0.3 ml). The resulting soln was refluxed for 30 min, and concentrated under reduced pressure to give a viscous oily residue, which was mixed with THF (10 ml), pyridine (0.3 g) and t-BuOH (2 ml), and refluxed for 4 hr. The mixture was diluted with EtOAc, washed with dil HCl, sat $NaHCO_3$ (130 mg of the starting (±)-**5** was recovered from this washing layer) and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give an oily residue which was purified on preparative silica gel plates (developed with PhH/EtOAc = 4/1) to give 136 mg of (±)-**30** (23% yield) as a crystalline solid; m.p. 72–73° (from iso-Pr_2O); MS *m/e* 479 (M^+), 423, 393; IR ν_{max} (nujol) 1775, 1740, 1620, 1593 cm^{-1}; NMR ($CDCl_3$) δ 1.13 (3H, t, J = 7 Hz), 1.32 (9H, s), 1.38 (3H, d, J = 6.5 Hz), 1.92 (3H, s), 3.76 (6H, s), 3.8–4.3 (2H + 1H, m), 4.53 (2H, s), 5.28 (1H, dq, J = 9, 6.5 Hz, C_3-H), 6.48 (1H, d, J = 2 Hz), 6.48 (1H, dd, J = 2, 9 Hz), 7.19 (1H, d, J = 9 Hz).

(±)-[3α(S*), 4β]-1-(2,4-*Dimethoxybenzyl*)-3-(1-*hydroxyethyl*)-4-*t*-*butoxycarbonyl*-2-*azetidinone*-4-*carboxylic acid* ((±)-**31**)

A soln of (±)-**30**) (106 mg, 0.221 mmol) in pyridine (1.2 ml) and 0.1 N NaOH (2.4 ml) was allowed to stand overnight at 0°. The mixture was diluted with sat $NaHCO_3$ (20 ml), washed with EtOAc. The organic layer was washed with 10% HCl, H_2O and brine, dried over $MgSO_4$, and concentrated to recover the starting (±)-**30** (55 mg). The aqueous layer was adjusted to pH 2.5 with 10% HCl, and extracted with EtOAc. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated to give 36 mg of (±)-**31** as a viscous oil which was employed for the next reaction without purification. NMR ($CDCl_3$) δ 3.46 (1H, d, J = 10 Hz, C_3-H), 4.12 (1H, m, C_3-CH(OH)CH_3).

(±)-[1α, 4α, 5α]-*t*-*Butyl* 7-(2,4-*dimethoxybenzyl*)-2,6-*dioxo*-4-*methyl*-3-*oxa*-7-*azabicyclo*[3.2.0]*heptane*-1-*carboxylate* ((±)-**32**)

A soln of (±)-**31** (36 mg) in pyridine (0.5 ml) and Ac_2O (0.5 ml) was allowed to stand for 20 hr at 15°, diluted with EtOAc, washed with 10% HCl and brine, dried over $MgSO_4$, and concentrated to give an oily residue which was purified on a silica gel preparative TLC plate (developed with PhH/EtOAc = 4/1, R_f = 0.44) to give 29 mg of (±)-**32** (84% yield) as a viscous oil; IR ν_{max} (film) 1775, 1745, 1735 (shoulder), 1613, 1590 cm^{-1}; MS *m/e* 391 (M^+), 335 ($M^+ - C_4H_8$); NMR ($CDCl_3$) δ 1.44 (1H, d, J = 6.5 Hz), 1.49 (9H, s), 3.67 (1H, d, J = 1.5 Hz, C_4-H), 3.89 (6H, s), 4.62 (2H, s), 5.00 (1H, dq, J = 1.5, 6.5 Hz, C_4-H), 6.55 (1H, d, J = 2 Hz), 6.56 (1H, dd, J = 2, 14 Hz), 7.21 (1H, d, J = 14 Hz).

(±)-[3α(S*), 4β]- *and* (±)-[3α(S*), 4α]-*t*-*Butyl* 1-(2,4-*dimethoxybenzyl*)-3-(1-*t*-*butoxycarbonylcarboxyethyl*)-2-*azetidinone*-4-*carboxylate* ((±)-*trans*-**33**) *and* ((±)-cis-**33**).

A soln of (±)-**21** (335 mg, 0.95 mmol) in THF (5 ml) and oxalyl chloride (0.2 ml) was refluxed for 45 min, and concentrated under reduced pressure to give a residual oil, in which THF (4 ml), t-BuOH (1 ml) and pyridine (0.2 ml) was added, and then the resulting mixture was refluxed for 2 hr, diluted with EtOAc, washed with 5% HCl, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give a crude mixture of three products. They were separated on silica gel preparative TLC plates (developed with PhH/EtOAc = 4/1) to give 186 mg of (±)-*trans*-**33** (40% yield, R_f = 0.524) as a viscous oil; MS *m/e* 493 (M^-); IR ν_{max} (film) 1780–1720 (broad); NMR ($CDCl_3$) δ 1.40 (9H, s), 1.44 (3H, d, J = 6 Hz), 1.47 (9H, s), 3.23 (1H, dd, J = 2.5, 7.5 Hz), 3.75 (6H, s), 3.80 (1H, d, J = 2.5 Hz), 4.11, 4.59 (2H, AB-q, J = 14.5 Hz), 5.21 (1H, m), 6.36 (1H, dd, J = 2, 9 Hz), 6.43 (1H, d, J = 2 Hz), 7.09 (1H, d, J = 9 Hz); 24 mg of (±)-*cis*-**33** (5% yield, R_f = 0.570) as a crystalline solid; m.p. 125–127° (from diisopropyl ether; IR ν_{max} (nujol) 1765 (shoulder), 1753, 1721, 1610, 1587 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (9H, s), 1.49 (3H, d, J = 6 Hz), 1.50 (9H, s), 3.58 (1H, dd, J = 5.5, 10.5 Hz), 3.78 (6H, s), 3.94 (1H, d, J = 5.5 Hz), 4.06, 4.64 (2H, AB-q, J = 15 Hz), 5.20 (1H, m), 6.39 (1H, dd, J = 2, 9 Hz), 6.46 (1H, d, J = 2 Hz), 7.09 (1H, d, J = 9 Hz). (Found: C, 60.72; H, 7.13; N, 2.64. Calc for $D_{25}H_{35}O_9N$: C, 60.84; H, 7.15; N, 2.84%); and 12 mg of lactone (±)-**32** (3% yield, R_f = 0.446) as a viscous oil.

(±)-[3α(S*), 4β]-*t*-*Butyl* 1-(2,4-*dimethoxybenzyl*)-3-(1-*hydroxyethyl*)-2-*azetidinone*-4-*carboxylate* ((±)-**34**)

A soln of (±)-*trans*-**33** (135 mg, 027 mmol) in THF (2 ml), H_2O (1 ml) and DBU (50 mg) was refluxed for 1 hr, diluted with EtOAc, washed with 10% HCl, sat $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to give an oil which was purified on a silica gel TLC plate to give 94 mg of (±)-**34** (94% yield) as a viscous oil; IR ν_{max} (film) 3425, 1765, 1742, 1618, 1593 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (3H, d, J = 6 Hz), 1.41 (9H, s), 2.71 (1H, bs, OH), 3.01 (1H, dd, J = 2.5, 5 Hz), 3.70 (6H, s), 3.79 (1H, d, J = 2.5 Hz), 4.06, 4.58 (2H, AB-q, J = 15 Hz), 4.10 (1H, bm), 6.34 (1H, dd, J = 2, 9 Hz), 6.38 (1H, d, J = 2 Hz), 7.09 (1H, d, J = 9 Hz); MS *m/e* 365 (M^+), 337, 320, 308, 264, 236.

Methyl ester of (±)-**8**. A soln of racemic t-butyl ester (±)-**34** (366 mg, 1 mmol) in CH_2Cl_2 (3 ml) and CF_3COOH (3 ml) was stirred for 2 hr at 25°, and concentrated *in vacuo* to give a crude gum (±)-**8** which was further transformed to its methyl ester with ethereal CH_2N_2. Purification on a silica gel column gave 254 mg of methyl ester of (±)-**8** (77% yield) as a viscous oil.

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