Formal Total Synthesis of Enantiopure (−)-Anisomycin, Antibiotic from *Streptomyces*

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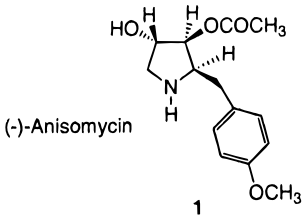
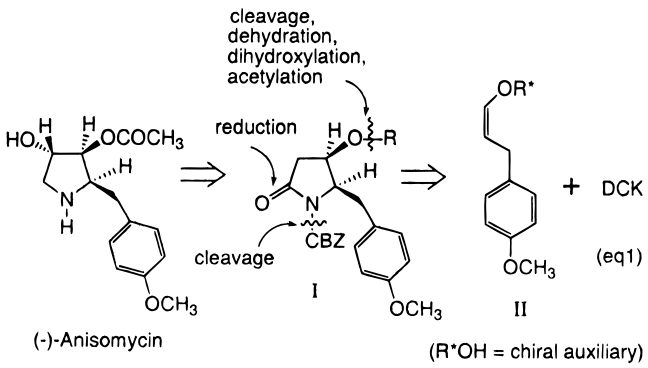
The antibiotic (−)-anisomycin was first isolated from the fermentation broths of *Streptomyces griseolus* and *Streptomyces roseochromogenes* by Pfizer, Inc., in 1954[1] and, subsequently, from those of *Streptomyces* sp. No. 638 and *SA* 3097 by groups in Japan.[2] Some 10 years after its initial isolation, its structure and relative stereochemistry were elucidated by chemical and spectroscopic means, which were later confirmed by X-ray crystallography.[3] The absolute stereochemistry of this alkaloid has been firmly established as 2*R*,3*S*,4*S* by chemical correlation with L-tyrosine.[4]



Anisomycin possesses strong and selective activity against pathogenic protozoa and fungi[5] and has clinically been used with success in the treatment of vaginitis due to *trichomonas vaginilis*[6] and for amoebic dysentery.[7] Both anisomycin and its deacetyl derivative have been employed as fungicides in the eradication of bean mildew and to inhibit other pathogenic fungi in plants.[8] Effectively inhibiting peptide bond formation on eukaryotic ribosomes, anisomycin has found additional use as a tool in molecular biology.[9]

To date, the preparation of (−)-anisomycin has almost invariably relied on chiral pool starting material, such as L-malic acid, L-tartaric acid, D-glucose, D-ribose, D-galactose, D-mannitol, D-tyrosine, or L-aspartic acid and has often proceeded in modest yield.[10] Given the sustained interest in this alkaloid, it was felt that it would be worthwhile to test our dichloroketene−chiral *O*-alkyl enol ether cycloaddition methodology[11] for potentially flexible access.[12]

The approach we hoped to develop is shown retrosynthetically in eq 1. The pyrrolidine derivative corresponding to I (eq 1, R = H), previously[10s,t] converted to anisomycin through formal syn elimination of water, trans dihydroxylation−monoacetylation, and N-deprotection, appeared to be available from I (R = R*) by carbonyl reduction and O−R* bond cleavage. This pyrrolidinone, it was felt, might be accessed through Beckmann ring expansion, dechlorination, and N-protection of the 2 + 2 cycloadduct derived from dichloroketene (DCK) and a chiral enol ether II. In this paper, we report an asymmetric formal synthesis of (−)-anisomycin through the successful realization of this approach.



For high face discrimination in the cycloaddition and the possibility to effect subsequently selective C−O bond cleavage, the easily available, enantiopure, dual purpose inductor (*S*)-1-(2,4,6-triisopropylphenyl)ethanol[13] (**2**, Scheme 1) appeared to be the one of choice. Both

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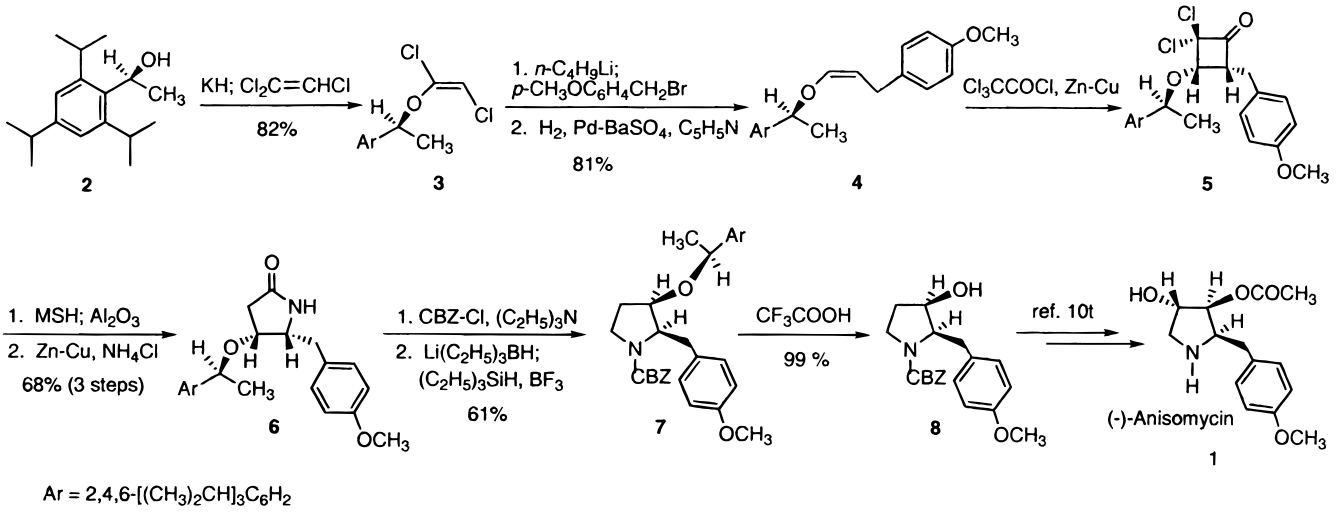
Scheme 1



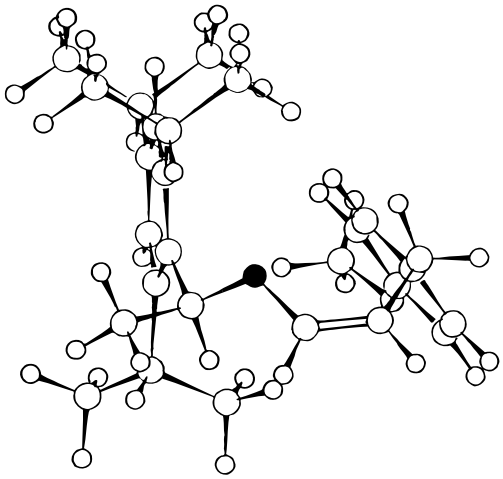


Figure 1. Global minimum-energy conformation of enol ether **4** (● = enol oxygen).

molecular modeling of enol ether **4**[14,15] (Figure 1) and synthetic results previously obtained with other enol ethers derived from this inductor[11e−h] clearly indicated the C_α-*re* face of enol ether **4** would be the more accessible, as required in the projected route to (−)-anisomycin, and this was eventually borne out.

Thus, this alcohol was transformed with potassium hydride and trichloroethylene to the *E* dichloro enol ether **3** (82% yield). The corresponding lithium acetylide, formed from **3** with *n*-butyllithium, was then treated with 4-methoxybenzyl bromide in THF−HMPA under carefully optimized conditions to yield the somewhat unstable alkylated acetylenic ether, which was converted without purification into the *Z* enol ether **4** in 81% yield for the two steps.[16]

In the presence of dichloroketene, generated in situ from trichloroacetyl chloride and zinc−copper couple,[17] enol ether **4** underwent clean and, as expected, face-selective cycloaddition to produce in high yield the desired dichlorocyclobutanone **5**, contaminated with only ca. 7% of diastereomeric material (^{1}H NMR). Because it was anticipated that removal of this contaminant would be more readily achieved at the pyrolidinone stage, the crude cycloadduct was converted with *O*-(mesitylenesulfonyl)hydroxylamine,[18] and apparently with complete regioselectivity, into the corresponding dichloropyrrolidinone, which was dechlorinated with zinc−copper couple in methanol saturated with ammonium chloride[19] to

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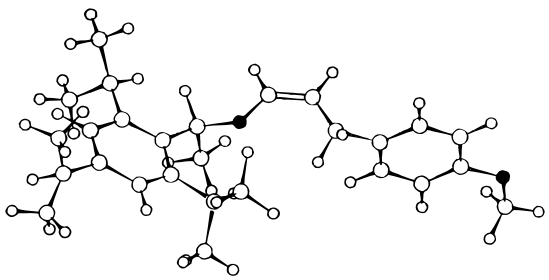
(14) Molecular modeling was performed on an IBM RS 6000 workstation running Insight II Discover 97.0 (MSI, San Diego). The structure was energy minimized with the force field cvff.frc. and the minimization algorithm VA09A. The molecular dynamics was performed at 500 K *in vacuo* (dielectric constant fixed at 1; 200 000 steps of 1 fs) and consisted of the generation of 200 structures. The depicted conformation is lowest in energy by 3.6 kcal/mol. (The next lowest in energy would also be expected to undergo cycloaddition largely on the C_α-*re* face.)

(15) The solid-state structure is shown below (crystal data for $C_{27}H_{38}O_2$, triclinic *P*-1, $a = 10.492(8)$ Å, $b = 13.428(3)$ Å, $c = 17.862(5)$ Å, $\alpha = 96.47(2)°$, $\beta = 100.41(4)°$, $\gamma = 90.03(4)°$, $V = 2459(2)$ Å^3, $Z = 4$, $d_{calcd} = 1.066$ Mg/M^3, $F(000) = 864$, 2θ range 2−59.9°, 12928 measured reflections. 12505 [R(int) = 0.01] independent reflections, 4896 with $I > 3\sigma$, $R = 0.065$, $R_w = 0.057$, GOF = 2.301):



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provide the highly crystalline pyrrolidinone **6**. Recrystallization of this material from pentane−dichloromethane afforded in 68% overall yield from enol ether **4** the stereochemically pure (^{1}H NMR; chiral HPLC of the free alcohol) pyrrolidinone **6**.

To intersect the previous synthesis at the above-mentioned chiral pyrrolidine, pyrrolidinone **6** was first treated with benzyl chloroformate (CBZ-Cl), which provided the expected imide in 98% yield after purification.[20] Reduction of the ring carbonyl could now be cleanly effected in yields of up to 78%, but generally somewhat lower, by using the excellent procedure recently described by Pedregal, Ruano, and co-workers,[21] namely, sequential reduction with super hydride and triethylsilane in the presence of boron trifluoride etherate. The resulting pyrrolidine **7** on brief treatment with trifluoroacetic acid gave in 99% yield (27% overall from **2**, 87%/step) the enantiopure hydroxy pyrrolidine **8** ($[\alpha]^{25}_D$ −6.0° (lit.[10t] $[\alpha]^{25}_D$ −4.99°)), which displayed a high-field ^{1}H NMR spectrum in perfect agreement with that kindly provided by Professor H. Takahata.[10t]

This highly enantioselective formal total synthesis, based on an effective asymmetric 2 + 2 cycloaddition, produces (−)-anisomycin in approximately 8% overall yield.

Experimental Section

The reaction mixture was generally poured into water, and the separated aqueous phase was then thoroughly extracted with the specified solvent. After being washed with 10% aqueous HCl and/or $NaHCO_3$ (if required), water, and saturated aqueous NaCl, the combined organic phases were dried over anhyd Na_2SO_4 or $MgSO_4$ and then filtered and concentrated under reduced pressure on a Büchi Rotovapor to yield the crude reaction product. Tetrahydrofuran and ether were distilled from sodium−benzophenone, and methanol was distilled from magnesium. Pentane, dichloromethane, pyridine, HMPA, and triethylamine were distilled from calcium hydride.

(+)-2-((1*S*)-1-((1*Z*)-3-(4-Methoxyphenyl)-1-propenyloxy)-ethyl)-1,3,5-triisopropylbenzene (4). An argon-flushed flask was charged with 4.40 g (38.4 mmol) of a 35% suspension of potassium hydride in mineral oil. The mineral oil was removed by washing with pentane, and the flask was charged with 50 mL of anhydrous tetrahydrofuran, capped with a rubber septum, and connected to a Nujol-filled bubbler by means of a syringe needle. The solid alcohol **2**[13] (4.36 g, 17.6 mmol) was then added portionwise. The mixture was stirred until hydrogen evolution was complete (ca. 2 h), cooled to −50 °C, and treated dropwise over 2 h with a solution of trichloroethylene (1.70 mL, 2.49 g, 19.0 mmol) in 3 mL of anhydrous tetrahydrofuran, after which the reaction mixture was allowed to warm to 20 °C over 1 h, whereupon it was poured into cold saturated aqueous ammonium chloride. The crude product was isolated with pentane in the usual way and purified by filtration through silica gel (200 mL, pretreated with 2.5% triethylamine, v/v) with pentane to afford 4.96 g (82%) of pure 2-((1*S*)-1-((1*E*)-1,2-dichloroethenyloxy)ethyl)-1,3,5-triisopropylbenzene (**3**).[11g]

To a solution of 4.80 g (14.0 mmol) of the above compound in 40 mL of anhydrous tetrahydrofuran at −78 °C was added dropwise 14.1 mL (32.4 mmol) of 2.3 M *n*-butyllithium in hexanes. After being stirred for 30 min at −78 °C, the reaction mixture was warmed to −40 °C over 30 min and treated dropwise with 8.40 g (41.8 mmol) of 4-methoxybenzyl bromide followed by 11.4 mL of hexamethylphosphoramide. The solution was stirred at −30 °C for 20 h, whereupon it was poured into cold saturated aqueous ammonium chloride. The product was isolated with pentane in the usual way to give crude 2-((1*S*)-1-(3-(4-methoxyphenyl)-1-propynyloxy)ethyl)-1,3,5-triisopropylbenzene: IR 2268 cm^{-1}.

A mixture of the above crude compound, 8.70 g (62.9 mmol) of potassium carbonate, and 1.5 g of 10% palladium on barium sulfate in 200 mL of dry pyridine was stirred under hydrogen for 48 h at 0 °C, whereupon the hydrogen was replaced with argon and the reaction mixture was diluted with pentane and filtered over Celite. The solvents were thoroughly washed with water, saturated aqueous copper sulfate, water, and saturated aqueous ammonium chloride, dried over sodium sulfate, and evaporated under reduced pressure. The resulting crude product was purified by dry silica gel chromatography (pretreated with 2.5% triethylamine, v/v) with 0−5% ether in pentane to afford 4.45 g (81% from **3**) of enol ether **4**: mp 51−52 °C (pentane); $[\alpha]^{20}_D$ +36.5° (*c* 1.4, chloroform); IR 3034, 1661, 1609, 1244 cm^{-1}; ^{1}H NMR (250 MHz) δ 1.20−1.40 (m, 18 H), 1.75 (d, J = 6.7 Hz, 3 H), 2.97 (hept, J = 6.7 Hz, 1 H), 3.52 (AB of ABX, δ_a = 3.44, δ_b = 3.61, J_{ab} = 15.5 Hz, J_{ax} = 7.1 Hz, J_{bx} = 7.9 Hz, 2 H), 3.50−3.75 (m, 2 H), 3.85 (s, 3 H), 4.57 (pseudo q, 1 H), 5.49 (q, J = 6.7 Hz, 1 H), 6.17 (dt, J = 6.3, 1.5 Hz, 1H), 7.08 (ABq, δ_a = 6.91, δ_b = 7.25, J_{ab} = 8.5 Hz, 4 H), 7.12 (s, 2 H); ^{13}C NMR (62.8 MHz) δ 22.5, 23.9, 24.6, 29.1, 29.5, 34.0, 55.2, 75.4, 105.4, 113.6, 121.9 (br), 129.1, 132.9, 134.0, 144.2, 146.8 (br), 147.7, 157.6; mass spectrum (EI) *m*/*z* 394 (M^+), 231 (100), 147.

Anal. Calcd for $C_{27}H_{38}O_2$: C, 82.18; H, 9.71. Found: C, 82.00; H, 9.65.

(−)-(2*R*,3*S*)-4,4-Dichloro-2-(4-methoxybenzyl)-3-((1*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)cyclobutanone (5). To a stirred mixture of 1.98 g (5.02 mmol) of enol ether **4** and 3.60 g (ca. 55 mmol) of Zn−Cu couple in 50 mL of ether under argon was added over 1.5 h 0.910 mL (1.34 g, 7.36 mmol) of freshly distilled trichloroacetyl chloride in 18 mL of ether. After an additional 1 h, the ether solution was separated from the excess couple and added to pentane, and the resulting mixture was partially concentrated under reduced pressure in order to precipitate the zinc chloride. The supernatant was decanted and washed successively with a cold aqueous solution of sodium bicarbonate, water, and brine and then dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure left 2.38 g of crude cyclobutanone **5** (containing ca. 7% of its diastereomer (δ 4.57 ppm)) as a white solid. Recrystallization from pentane of comparable material from a previous run gave analytically pure **5**: mp 102−103 °C; $[\alpha]^{20}_D$ −19.2° (*c* 1.6, chloroform); IR 3054, 3033, 1804, 1609, 1266, 1248 cm^{-1}; ^{1}H NMR (250 MHz) δ 1.13 (d, J = 6.7 Hz, 3 H), 1.21 (d, J = 6.7 Hz, 3 H), 1.25−1.31 (m, 9 H), 1.36 (d, J = 6.7 Hz, 3 H), 1.74 (d, J = 6.7 Hz, 3 H), 2.91 (hept, J = 6.7 Hz, 1 H), 3.10 (d, J = 7.9 Hz, 2 H), 3.33 (hept, J = 6.7 Hz, 1 H), 3.71 (pseudo q, 1 H), 3.79 (s, 3 H), 3.86 (hept, J = 6.7 Hz, 1 H), 4.40 (d, J = 9.1 Hz, 1 H), 5.52 (q, J = 6.7 Hz, 1 H), 6.98 (ABq, δ_a = 6.83, δ_b = 7.14, Jab = 8.7 Hz, 4 H), 7.04 (s, 1 H), 7.11 (s, 1 H); ^{13}C NMR (62.8 MHz) δ 22.6, 23.7, 23.9, 24.9, 25.2, 25.4, 28.3, 29.2, 30.7, 34.0, 55.2, 60.6, 73.5, 77.4, 88.3, 113.9, 120.8, 123.3, 129.9, 130.2, 130.4, 147.0, 148.3, 148.9, 158.3, 195.8; mass spectrm (CI) *m*/*z* 522 (M^+ + 18), 231 (100).

Anal. Calcd for $C_{29}H_{38}O_3Cl_2$: C, 68.90; H, 7.58. Found: 68.99; H, 7.67.

(−)-(4*R*,5*R*)-5-(4-Methoxybenzyl)-4-((1*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)-2-pyrrolidinone (6). A solution of the above crude cyclobutanone **5** in 50 mL of dichloromethane was treated with 1.30 g (6.04 mmol) of *O*-mesitylenesulfonylhydroxylamine and stirred at 20 °C for 40 min. The solvent was then removed under reduced pressure, and the resulting material in 10 mL of toluene was placed on a column of basic alumina (200 g, Merck activity 1) and eluted rapidly with methanol. The resulting crude (4*S*,5*R*)-3,3-dichloro-5-(4-methoxybenzyl)-4-((1*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)-2-pyrrolidinone (IR 1684 cm^{-1}) was used below.

The crude dichloro lactam in 65 mL of methanol previously saturated with ammonium chloride was stirred at 20 °C with 1.2 g (ca. 18 mmol) of zinc−copper couple under argon for 1 h, whereupon the mixture was filtered to remove the excess couple. The filtrate was concentrated under reduced pressure, and the residue was then processed with dichloromethane in the usual way to give 2.05 g of lactam **6**. Recrystallization of this material

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(20) Attempts to α-hydroxylate **6**, as well as several of its derivatives, led to unsatisfactory results.

(21) Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M. C.; Ruano, J. L. G. *Tetrahedron Lett.* **1994**, *35*, 2053−2056.

from pentane−dichloromethane provided 1.54 g (68% overall yield from **4**) of stereochemically pure **6**. (HPLC (Chiracel OD-H column, 5 mm, 2-propanol/hexane 20:80, 0.5 mL/min, t_R 19.6 min (vs 22.2 min)) of the free alcohol (10% trifluoroacetic acid in dichloromethane) showed an ee of ≥99%.) Pyrrolidinone **6**: mp 190−191 °C (pentane−dichloromethane); $[\alpha]^{20}_D$ −22.2° (*c* 1.5, chloroform); IR 3421, 3200, 3052, 1698, 1609, 1265, 1247 cm^{-1}; ^{1}H NMR (250 MHz) δ 1.1−1.4 (m, 18 H), 1.58 (d, J = 6.3 Hz, 3 H), 2.50 (AB of ABX, δ_a = 2.47, δ_b = 2.52, J_{ab} = 16.6 Hz, J_{ax} = 7.1 Hz, J_{bx} = 7.1 Hz, 2 H), 2.80 (AB of ABX, δ_a = 2.63, δ_b = 2.97, J_{ab} = 14.1 Hz, J_{ax} = 10.7 Hz, J_{bx} = 3.2 Hz, 2 H), 2.85 (hept, J = 6.7 Hz, 1 H), 3.16 (hept, J = 6.7 Hz, 1 H), 3.65−3.80 (m, 1 H), 3.76 (s, 3 H), 3.90 (hept, J = 6.7 Hz, 1 H), 4.25 (pseudo q, J = 7.1 Hz, 1 H), 5.09 (q, J = 6.3 Hz, 1 H), 5.49 (br s, 1 H), 6.92 (ABq, δ_a = 6.80, δ_b = 7.03, J_{ab} = 8.7 Hz, 4 H), 6.96 (s, 1 H), 7.06 (s, 1 H); ^{13}C NMR (50.3 MHz) δ 23.2, 23.9, 24.3, 25.0, 25.1, 28.1, 29.2, 34.0, 35.5, 36.3, 55.2, 59.4, 71.3, 72.4, 114.1, 120.6, 123.3, 130.1, 132.1, 145.9, 147.7, 148.7, 158.3, 174.3; mass spectrum (EI) *m*/*z* 452 (M$^+$), 231 (100).

Anal. Calcd for $C_{29}H_{41}NO_3$: C, 77.12; H, 9.15; N, 3.10. Found: C, 77.49; H, 9.16; N, 3.27.

(−)-(2*R*,3*R*)-1-(Benzyloxycarbonyl)-2-(4-methoxybenzyl)-3-((1*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidine (7). To a solution of lactam **6** (268 mg, 0.59 mmol) in 4.5 mL of dry tetrahydrofuran at −78 °C were added 0.29 mL (0.67 mmol) of a 2.3 M solution of *n*-butyllithum in hexane and, after 10 min, 0.205 mL (250 mg, 1.47 mmol) of benzyl chloroformate. The reaction mixture was then allowed to warm to 0 °C over 1 h. The crude product was isolated with ether in the usual manner and purified by dry silica gel chromatography with 5−20% ethyl acetate in cyclohexane to give 339 mg (98%) of (−)-(4*R*,5*R*)-1-(benzyloxycarbonyl)-5-(4-methoxybenzyl)-4-((1*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)-2-pyrrolidinone: mp 118−119 °C (pentane); $[\alpha]^{20}_D$ −99° (*c* 1.7, chloroform); IR 3053, 1787, 1753, 1719, 1609, 1292, 1265 cm^{-1}; ^{1}H NMR (200 MHz) δ 1.10−1.45 (m, 18 H), 1.65 (d, J = 6.9 Hz, 3 H), 2.41 (AB of ABX, δ_a = 2.25, δ_b = 2.57, J_{ab} = 16.8 Hz, J_{ax} = 10.6 Hz, J_{bx} = 7.5 Hz, 2 H), 2.85 (hept, J = 6.9 Hz, 1 H), 3.08 (AB of ABX, δ_a = 3.00, δ_b = 3.16, J_{ab} = 14.1 Hz, J_{ax} = 4.1 Hz, J_{bx} = 5.8 Hz, 2 H), 3.09−3.20 (m, 1 H), 3.70−3.80 (m, 1 H), 3.78 (s, 3 H), 4.11 (dt, J = 7.9, 10.6 Hz, 1 H), 4.40−4.50 (m, 1 H), 5.07 (q, J = 6.9, 1 H), 5.19 (ABq, δ_a = 5.15, δ_b = 5.23, J_{ab} = 12.3 Hz, 2 H), 6.94 (ABq, δ_a = 6.77, δ_b = 7.11, J_{ab} = 8.9 Hz, 4 H), 6.98 (s, 1 H), 7.06 (s, 1 H), 7.30−7.45 (m, 5 H); ^{13}C NMR (62.8 MHz) δ 23.1, 23.8, 24.1, 24.8, 25.0, 27.9, 29.0, 33.1, 33.9, 37.8, 55.0, 61.2, 68.0, 69.3, 71.3, 113.4, 120.6, 123.3, 128.2, 128.3, 128.4, 129.1, 131.3, 131.4, 135.0, 145.9, 147.7, 148.6, 150.8, 158.1, 170.5; mass spectrum (CI) *m*/*z* 586 (MH$^+$), 542, 231 (100).

Anal. Calcd for $C_{37}H_{47}NO_5$: C, 75.86; H, 8.09; N, 2.39. Found: C, 75.73; H, 8.24; N, 2.43.

To a stirred solution of this lactam (170 mg, 0.29 mmol) in 2.6 mL of THF at −78 °C under argon was added dropwise 0.45 mL (0.45 mmol) of a 1 M solution of lithium triethylborohydride in THF. The resulting solution was stirred for 30 min at −78 °C, quenched with saturated aqueous sodium bicarbonate (0.5 mL), and then allowed to warm to 0 °C. Ten drops of a 30% aqueous solution of hydrogen peroxide were added, and the mixture was then stirred for 1 h at 20 °C. The crude product was isolated with ether in the usual way to yield 166 mg of the corresponding α-hydroxypyrrolidine: IR 3424, 1691.

To a solution of this material in dry dichloromethane was added 0.034 mL (25 mg, 0.21 mmol) of triethylsilane followed by, at −78 °C, 0.030 mL (34 mg, 0.24 mmol) of boron trifluoride diethyl etherate. The same amounts of these two reagents were again added to the reaction mixture at −78 °C every 30 min until TLC (20% ethyl acetate in cyclohexane) showed total disappearance of starting material (six times). The reaction mixture was then poured into saturated aqueous sodium bicarbonate, and the crude product was isolated with dichloromethane in the usual way and purified by dry silica gel chromatography with 5% ethyl acetate in cyclohexane to afford 103 mg (62%) of pyrrolidine **7** as a white solid: mp 104−105 °C (pentane); $[\alpha]^{20}_D$ −48.1° (*c* 1, chloroform); IR 3061, 3029, 1703, 1607, 1247 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6, 65 °C) δ 1.19−1.26 (m, 20 H), 1.49 (dd, J = 11.8, 10.1 Hz, 1 H), 1.57 (d, J = 5.9 Hz, 3 H), 1.74−1.82 (m, 1 H), 2.82 (hept, J = 7.0, Hz, 1 H), 2.90−3.30 (m, 4 H), 3.45 (s, 3 H), 3.77 (dt, J = 10.6, 7.0 Hz, 1 H), 4.20 (br q, J = 5.9 Hz, 1 H), 5.06 (q, J = 7.0 Hz, 1 H), 5.10 (ABq, δ_a = 5.05, δ_b = 5.15, J_{ab} = 12.9 Hz, 2 H), 6.77 (A of ABq, J_{ab} = 9.4 Hz, 2 H), 7.05−7.25 (m, 9 H); ^{13}C NMR (75.5 MHz, rotamers) δ 24.1, 24.8, 24.9, 25.2, 25.7, 26.0, 28.5, 28.9, 29.4, 29.8, 34.7, 35.2, 35.6, 43.7, 43.9, 55.3, 60.8, 61.3, 67.1, 67.4, 71.7, 72.1, 75.8, 76.9, 114.2, 121.4, 124.4, 129.1, 129.2, 132.3, 132.4, 132.7, 133.7, 134.0, 138.2, 138.5, 146.8, 148.6, 150.0, 150.2, 155.0, 155.2, 159.2; mass spectrum (CI) *m*/*z* 572 (MH$^+$), 342, 231 (100).

Anal. Calcd for $C_{37}H_{49}NO_4$: C, 77.72; H, 8.64; N, 2.45. Found: C, 77.89; H, 8.74; N, 2.53.

(−)-(2*R*,3*R*)-1-(Benzyloxycarbonyl)-2-(4-methoxybenzyl)-3-hydroxypyrrolidine (8). To a solution of 73 mg (0.128 mmol) of pyrrolidine **7** in 1.2 mL of dichloromethane was added 0.090 mL (133 mg, 1.17 mmol) of trifluoroacetic acid. The reaction mixture was stirred at 20 °C for 1 h and then evaporated to dryness under reduced pressure. The residue was processed with dichloromethane in the usual way, and the crude product was purified by dry silica gel chromatography with 40% ethyl acetate in cyclohexane to give 43 mg (99%) of pyrrolidine **8** as an oil: $[\alpha]^{25}_D$ −6.0° (*c* 1.3, chloroform) (lit.[10t] $[\alpha]^{25}_D$ −4.99° (*c* 1.145, chloroform)); IR 3440, 3061, 3032, 1693, 1611, 1246 cm^{-1}; ^{1}H NMR (300 MHz) δ 1.72−1.83 (m, 1 H), 1.93−2.04 (m, 1 H), 2.84−2.92 (m, 1 H), 3.0−3.15 (br s, 1 H), 3.40−3.60 (m, 2 H), 3.75 (s, 3 H), 4.10 (br q, J = 6.3 Hz, 1 H), 4.32 (q, J = 6.0 Hz, 1 H), 5.10 (deformed ABq, δ_a = 5.07, δ_b= 5.13, J_{ab} = 12.0 Hz, 2 H), 6.93 (deformed ABq, δ_a = 6.77, δ_b = 7.09, J_{ab} = 8.5 Hz, 4 H), 7.30−7.36 (m, 5 H); ^{13}C NMR (50.3 MHz, C_6D_6, 65 °C) δ 32.8, 34.3, 44.9, 55.5, 63.6, 67.6, 72.3, 114.9, 129.2, 131.6, 132.6, 138.5, 155.9, 159.5. HPLC (Chiracel OD-H, 5 mm, 2-propanol/hexane 15:85, 0.5 mL/min, t_R 20.7 min (vs 24.5 min)) indicated an ee of ≥99%; the high-field ^{1}H NMR spectrum was in perfect agreement with that kindly provided by Professor H. Takahata.[10t] HRMS (FAB$^+$) *m*/*e* calcd for $C_{20}H_{23}NO_4$ (M$^+$) + H 342.1713, found 342.1705.

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