An Efficient Stereospecific Total Synthesis of (±)-Anisomycin and Related New Synthetic Antibiotics

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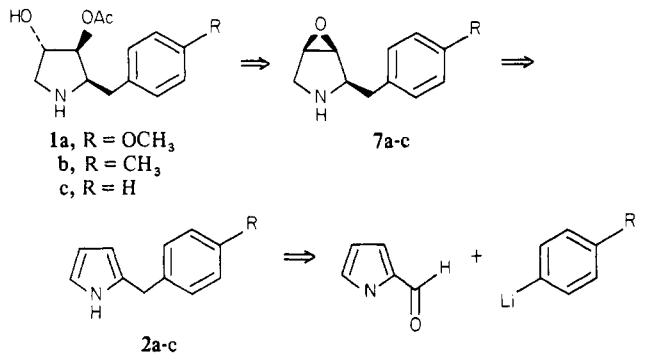
Abstract: Herein an efficient stereospecific total synthesis of (±)-anisomycin is reported. The synthetic sequence from pyrrole-2-carboxaldehyde required 13 reactions in which the overall isolated yield of anisomycin (**1a**) was 40%. The key intermediates in the synthesis were 2-(*p*-methoxybenzyl)pyrrole (**2a**) and 3,4β-oxido-2β-(*p*-methoxybenzyl)pyrrolidine (**7a**). The crucial reaction was the regioselective, stereospecific ring opening of the syn epoxide **7a** to the trans diol 3β,4α-dihydroxy-2β-(*p*-methoxybenzyl)pyrrolidine (**8a**), followed by a selective protection–acetylation–deprotection reaction sequence to complete the synthesis. This same selective synthetic procedure was used to prepare two new synthetic analogues, 3β-acetoxy-4α-hydroxy-2β-(*p*-methylbenzyl)pyrrolidine (**1b**) and 3β-acetoxy-2β-benzyl-4α-hydroxypyrrolidine (**1c**). The new synthetic antibiotics showed similar activity to that of (±)-anisomycin (**1a**) in biological screens.

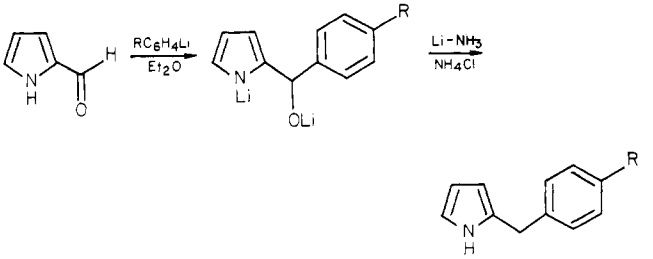
The antibiotic anisomycin (**1a**) was originally isolated from culture filtrates of two *Streptomyces* species (*S. griseolus* and *S. roseochromogenes*) by Sobin and Tanner of Pfizer Inc. in the early fifties[2] and more recently from *Streptomyces* sp. No. 638.[3] The gross structure was elucidated by Beereboom et al.,[4] and subsequently the relative stereochemistry was established by NMR[5] and X-ray analysis[6] and the absolute configuration by chemical correlation studies.[7] Because the antibiotic specifically blocks peptide bond formation on eukaryotic ribosomes, anisomycin has become a valuable tool in molecular biology and exhibits selective action against protozoa and several strains of fungi.[8] The drug has been used with some success in clinical trials for the treatment of both amoebic dysentery[9] and vaginitis[10] caused by *Trichomonas vaginalis* and as a fungicide to eradicate bean mildew and to inhibit other pathogenic fungi in plants.[11]

Previous syntheses of (±)- and (−)-anisomycin have been described, but each depended on random acylation sequences followed by separation of isomers, procedures that in all cases resulted in overall isolated yields of ca. 1% or less.[12] Recently a selective chiral synthesis of (−)-anisomycin was reported with a much improved overall isolated yield of ca. 8% starting from a simple glucofuranose derivative.[13] We report herewith a convenient and efficient stereospecific total synthesis of (±)-anisomycin from pyrrole-2-carboxaldehyde where the overall isolated yield was consistently better than 40%. The entire synthesis required 13 reactions (6 are functional-group-protecting and -deprotecting manipulations) and was performed in 10 reaction vessels by using tandem procedures. This synthetic sequence was then used to stereospecifically prepare two new synthetic antibiotic analogues, 3β-acetoxy-4α-hydroxy-2β-(*p*-methylbenzyl)pyrrolidine (**1b**) and 3β-acetoxy-2β-benzyl-4α-hydroxypyrrolidine (**1c**), of anisomycin (**1a**).

Scheme I



The strategy chosen for this total synthesis of anisomycin (**1a**) evolved from the retrosynthetic reasoning outlined in Scheme I. The first phase of the synthesis involved the elaboration of the entire carbon skeleton of anisomycin that is embodied in 2-(*p*-methoxybenzyl)pyrrole (**2a**) by utilizing our tandem alkylation–reduction techniques. By this procedure, the 2-benzylpyrroles **2a–c** required for the syntheses described herein could be prepared from pyrrole-2-carboxaldehyde in a two-reaction, one-pot sequence by arylation–reduction in isolated yields of 97–99%.[14]



With the carbon skeleton thus rapidly assembled, the subsequent two phases of the synthesis involved the introduction of the correct (and crucial for activity)[5a,8b,12c] stereochemical functionality assembled in the antibiotic. In the retrosynthetic analysis (Scheme I), the formation of the syn epoxide **7a** and its regioselective,

(1) Taken in part from the Ph.D. Thesis of D.P.S., Rutgers University, May 1981. H. Martin Friedman Thesis Award (Rutgers University), May 1981. Paper presented in part at New York and North Jersey Sections of the American Chemical Society, Metrochem '82, June 6–8, 1982, Piscataway, NJ.

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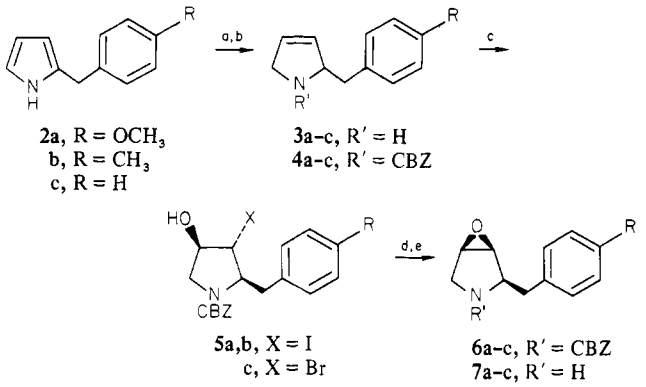
Scheme II[a]



2a, R = OCH_3
b, R = CH_3
c, R = H

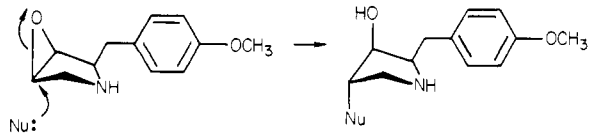
3a-c, R′ = H
4a-c, R′ = CBZ

5a,b, X = I
c, X = Br

6a-c, R′ = CBZ
7a-c, R′ = H

[a] (a) Zn/aqueous HCl/EtOH or MeOH; (b) $C_6H_5CH_2OCOCl$/toluene/2 N NaOH or $NaHCO_3$ (MeOH); (c) NIS or NBA/aqueous $HClO_4$/THF; (d) 5-10% KOH (EtOH or MeOH); (e) H_2/10% Pd-C/MeOH or EtOH.

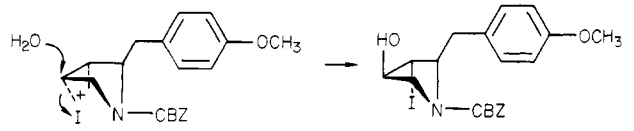
stereospecific opening are fundamental to this synthetic approach. During structural elucidation studies,[4,6] the syn epoxide **7a** demonstrated remarkable regioselective, stereospecific ring-opening reactions with a variety of nucleophiles. In such studies the nucleophile was involved in a trans opening of the epoxide by attacking exclusively at the C-4 position, establishing all of the



7a

stereocenters of the antibiotic. The selective ring opening, it should be emphasized, must be performed on the free-amine epoxide **7a** since the regioselectivity is lost with the N-protected syn epoxide **6a**.[12c,15]

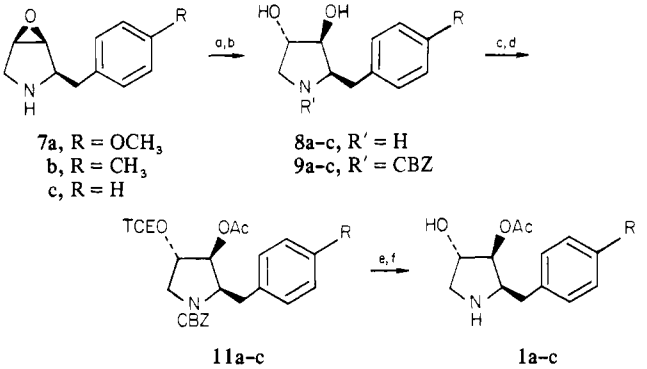
The syn epoxides **7a–c** were stereospecifically prepared as outlined in Scheme II. Reduction of 2-(*p*-methoxybenzyl)pyrrole (**2a**) with zinc in HCl resulted in a 67% yield of 2-(*p*-methoxybenzyl)-3-pyrroline (**3a**). Although this step ultimately turned out to be the lowest yield in the synthesis, this McElvain procedure[16] was the method of choice. Treatment of *N*-((benzyloxy)carbonyl)-2-(*p*-methoxybenzyl)-3-pyrroline (**4a**), prepared from benzyl chloroformate in toluene–2 N NaOH (94% yield), with *N*-iodosuccinimide in perchloric acid–THF at 0 °C gave only *one* iodohydrin, *N*-((benzyloxy)carbonyl)-4β-hydroxy-3α-iodo-2β-(*p*-methoxybenzyl)pyrrolidine (**5a**). This regioselective,



5a

stereospecific reaction must again reflect the dominating influence of the bulky (*p*-methoxybenzyl) group at the C-2 position. *N*-Iodosuccinimide rather than *N*-bromoacetamide had to be used to prepare the halohydrins **5a** (R = OCH_3) and **5b** (R = CH_3) to avoid halogenation of the activated aromatic ring; however, for the preparation of halohydrin **5c** (R = H), this side reaction was not a problem, and *N*-bromoacetamide could be used. The halohydrins **5a–c** were then converted to the corresponding N-

Scheme III[a]



7a, R = OCH_3
b, R = CH_3
c, R = H

8a-c, R′ = H
9a-c, R′ = CBZ

11a-c

1a-c

[a] (a) CF_3CO_2H/CF_3CO_2Na/120 °C; (b) 10% Na_2CO_3/THF/$C_6H_5CH_2OCOCl$; (c) Cl_3CCH_2OCOCl/pyridine/CH_2Cl_2; (d) Ac_2O/pyridine; (e) Zn/HOAc–THF, then 2 N NaOH; (f) H_2/10% Pd-C/MeOH.

protected syn epoxides **6a–c** in 5–10% KOH (alcohol). The yield of crystalline **6a** was 92% from **5a** and 75% from **4a**. When the crude intermediate iodohydrin **5a** was not purified, but immediately treated with base, the overall isolated yield of **6a** (from **4a**) improved to 85%. The *N*-((benzyloxy)carbonyl) protecting group was then removed by catalytic hydrogenation to yield 2β-(*p*-methoxybenzyl)-3,4β-oxidopyrrolidine (**7a**) quantitatively. The overall isolated yield of this key intermediate syn epoxide **7a**[17] from the starting material pyrrole-2-carboxaldehyde was an impressive 53%.[18]

The last phase of the synthesis involved the regioselective, stereospecific ring opening of the *syn*-2-benzyl-3-pyrrolidine epoxides **7a–c** and subsequent selective manipulations to convert the resultant 3β,4α-dihydroxy-2β-benzylpyrrolidines **8a–c** by the protection–acetylation–deprotection sequence outlined in Scheme III to the anisomycins **1a–c**. The syn epoxide **7a** was cleaved in refluxing trifluoroacetic acid containing sodium trifluoroacetate and then the acid removed in vacuo.[19] The residue was then dissolved in THF, the solution adjusted to pH 9 with 10% Na_2CO_3, and benzyl chloroformate added slowly to selectively protect the

(15) In this study we also found that treatment of *N*-((benzyloxy)-carbonyl)-2β-(*p*-methoxybenzyl)-3,4β-oxidopyrrolidine (**6a**) in sodium trifluoroacetate–trifluoroacetic acid yielded, after subsequent cosmetic manipulations, a 1:1 mixture of **1a** and 4β-acetoxy-3α-hydroxy-2β-(*p*-methoxybenzyl)pyrrolidine (**12a**), indicating no regioselectivity during the ring opening (see ref 17).

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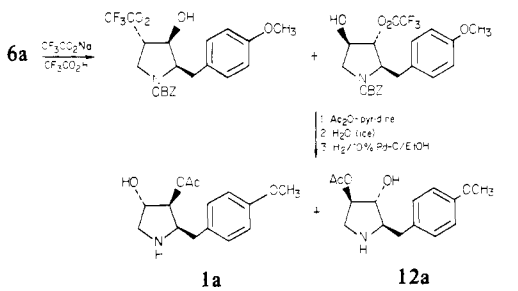
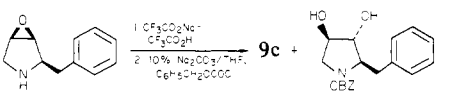
(17) To ensure that our structural assignments were correct and that we in fact had the syn epoxides **6a–c**, we converted *N*-((benzyloxy)carbonyl)-2β-(*p*-methoxybenzyl)-3,4β-oxidopyrrolidine (**6a**) to a 1:1 mixture of anisomycin (**1a**) and 4β-acetoxy-3α-hydroxy-2β-(*p*-methoxybenzyl)pyrrolidine (**12a**) by the general procedure of Oida and Ohki.[12c]



1a 12a

(18) The corresponding overall isolated yields of the syn epoxides **7b** and **7c** were 43% and 33%, respectively. No attempt was made to repeat these sequences to optimize these yields.

(19) The regioselectivity of the epoxide ring opening in sodium trifluoroacetate–trifluoroacetic acid was extremely dependent on the reaction conditions. For example, with syn epoxide **7c**, when the reaction mixture was placed in an oil bath at 25 °C, heated to boiling, and refluxed for 16 h, a 2:1 mixture of the desired diol **9c** and the diastereomer **13c** was formed. If the mixture



7c 13c

was heated in a warm oil bath (45 °C) for 16 h instead, the ratio improved (4:1). Best results (at least 20:1) were obtained by lowering the reaction mixture into a hot-oil bath at ca. 120 °C so that boiling started immediately and then allowing the mixture to reflux for 16 h.

amine group of the trans diol **8a** to produce *N*-((benzyloxy)carbonyl)-3β,4α-dihydroxy-2β-(*p*-methoxybenzyl)pyrrolidine (**9a**) in 97% yield.

The remaining four steps of the synthesis were performed in tandem without purification of intermediates. The less hindered 4α-hydroxy group was selectively protected in methylene chloride containing pyridine by the slow addition of an excess of 2,2,2-trichloroethyl chloroformate. After 30 min, the methylene chloride was removed in vacuo and acetic anhydride added to acetylate the free 3β-hydroxy group. The anisomycin derivative **11a** was then sequentially deprotected with zinc in HOAc–THF and catalytic hydrogenation (H_2/Pd–C). The overall isolated yield of (±)-anisomycin (**1a**) from the syn epoxide **7a** was 75%. The isolated yields of the anisomycin analogues **1b** and **1c** from the corresponding syn epoxides **7b** and **7c** were equally gratifying (71% and 75%, respectively).

Comparison of the crystalline synthetic (±)-anisomycin product with authentic natural (−)-anisomycin[20] indicated total identity with ^{1}H NMR (100 and 360 MHz), ^{13}C NMR, IR, UV, and mass spectroscopy. In addition, in vitro tube-dilution biological testing against protoza (*Trichomonas vaginalis*, *T. foetus*, and *Entamoeba hystolytica*), yeasts (*Candida albicans* and *Saccharomyces cerevisiae*), and dermatophytes (*Trichophyton mentogrophytes* and *Epidermophyton floccosum*) indicated the synthetic (±)-anisomycin to possess half the activity as that of the natural (−)-anisomycin. The new synthetic analogues **1b** and **1c** were also effective antibiotics against these microorganisms, with the general trend of (±)-**1a** > (±)-**1b** > (±)-**1c**. These studies, along with the synthesis and screening results of other synthetic analogues of anisomycin, will be described elsewhere.

Experimental Section

2-(*p*-Methoxybenzyl)-3-pyrroline (3a). To a stirring, refluxing slurry of 10 g of zinc dust and 3.20 g (17.1 mmol) of 2-(*p*-methoxybenzyl)-pyrrole (**2a**)[14] in 13 mL of absolute ethanol was slowly added (dropwise) 16 mL of a solution of 20% aqueous HCl over 1 h, followed by the addition of 10 mL of a solution of 30% aqueous HCl over 30 min. After an additional 1.5 h of refluxing, the mixture was cooled and filtered. After the filtrate was adjusted to pH 10 with a solution of 20% aqueous NaOH and extracted with CH_2Cl_2, the organic layer was dried ($MgSO_4$), filtered, and concentrated at reduced pressure (88 torr). Following column chromatography (30 g of silica gel, 60–200 mesh, 5–20% MeOH in CH_2Cl_2), 2.20 g (11.4 mmol, 67%) of **3a** was obtained as a colorless oil:[12c] n^{21}_D 1.5588 (lit.[12b] n^{25}_D 1.5502); IR (film) 3400–3100, 3075, 3000, 2910, 2840, 1620, 1520, 1250, 1180, 1040 cm^{-1}; UV (MeOH) λ_{max} 224 nm (ϵ 11 470), 276 (1770), 282 (1460); ^{1}H NMR (79.5 MHz) δ 7.10 (2 H, d, J = 9 Hz), 6.80 (2 H, d, J = 9 Hz), 5.86 (1 H, d with further fine splitting, J = 10 Hz), 5.72 (1 H, d with further fine splitting, J = 10 Hz), 4.38–3.97 (1 H, br m), 3.78 (3 H, s) superimposed on a complex multiplet at 3.80–3.57 (2 H), 2.69 (2 H, d, J = 7 Hz), 2.14 (1 H, br s, exchanges with D_2O); mass spectrum, m/e (relative intensity) 189 (M^+, 1), 188 (7), 187 (50), 186 (36), 156 (15), 121 (12), 80 (45), 68 (100). Anal. Calcd for $C_{12}H_{15}NO$): C, 76.15; N, 7.40. Found: C, 73.53; N, 6.64.

2-(*p*-Methylbenzyl)-3-pyrroline (3b). Reduction of 4.20 g (24.6 mmol) of 2-(*p*-methylbenzyl)pyrrole (**2b**)[14] as described for **3a** yielded 3.00 g (17.3 mmol, 71%) of **3b** as a colorless oil: n^{23}_D 1.5458; IR (film) 3475–3050, 3070, 3050, 3020, 2925, 2850, 1520, 1415, 1095, 815, 720 cm^{-1}; UV (MeOH) λ_{max} 211 nm (ϵ 10 095), 217 (9390, sh); ^{1}H NMR (79.5 MHz) δ 7.08 (4 H, superficial s), 5.85 (1 H, d with further fine splitting, J = 7 Hz), 5.72 (1 H, d with further fine splitting, J = 7 Hz), 4.35–3.94 (1 H, br m), 3.94–3.66 (2 H, complex m), 2.70 (2 H, d, J = 7 Hz), 2.30 (3 H, s), 2.20 (1 H, s, exchanges with D_2O); mass spectrum, m/e (relative intensity) 173 (M^+, 1), 172 (4), 171 (25), 170 (18), 156 (9), 80 (22), 68 (100). Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.09. Found: C, 79.30; H, 7.61; N, 7.35.

2-Benzyl-3-pyrroline (3c). To a cooled (3–5 °C, ice–water bath), stirred slurry of 67 g of zinc dust and 10.3 g (65.6 mmol) of 2-benzylpyrrole (**2c**)[14] in 85 mL of methanol was added 380 mL of a solution of 10% aqueous HCl over 30 min, followed by the slow addition (30 min) of 85 mL of concentrated HCl. After an additional 3 h of stirring, the mixture was filtered and the filtrate adjusted to pH 10 with a solution of 20% aqueous NaOH. The solution then was extracted with Et_2O and the organic phase dried ($MgSO_4$), filtered, and concentrated at reduced pressure (88 torr). Following column chromatography (100 g of silica gel, 5–20% MeOH in CH_2Cl_2), 6.80 g (42.8 mmol, 65%) of **3c** was obtained as a colorless oil: n^{14}_D 1.5560; IR (film) 3540–3100, 3050, 3025, 2900, 2840, 1600, 1490, 1450, 1090, 1030, 700 cm^{-1}; UV (MeOH) λ_{max} 204 nm (ϵ 10 500); ^{1}H NMR (79.5 MHz) δ 7.23 (5 H, superficial s), 5.85 (1 H, d with further fine splitting, J = 9 Hz), 5.74 (1 H, d with further fine splitting, J = 9 Hz), 4.43–4.05 (1 H, br m), 3.80–3.60 (2 H, complex m), 2.78 (2 H, d, J = 7 Hz), 2.10 (1 H, br s); mass spectrum, m/e (relative intensity) 159 (M^+, 2), 158 (6), 157 (33), 156 (28), 91 (20), 80 (38), 68 (100). Anal. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 77.33; H, 7.67; N, 7.91.

***N*-((Benzyloxy)carbonyl)-2-(*p*-methoxybenzyl)-3-pyrroline (4a).** To a cooled (3–5 °C ice–water bath), stirred mixture of 3.00 g (15.87 mmol) of 2-(*p*-methoxybenzyl)-3-pyrroline (**3a**) in 30 mL of toluene and 30 mL of 2 N NaOH was added 3.0 mL (21 mmol) of benzyl chloroformate. After 1 h, the organic phase was separated, washed with water, dried ($MgSO_4$), filtered, and then concentrated at vacuum-pump pressure. Following column chromatography (30 g of silica gel, 2–10% Et_2O in hexane), 4.80 g (14.86 mmol, 94%) of **4a** was obtained as a colorless oil:[5b,12c] n^{25}_D 1.5647; IR (film) 3065, 3030, 2950, 2860, 1710, 1615, 1520, 1420, 1255, 1110, 700 cm^{-1}; UV (MeOH) λ_{max} 225 nm (ϵ 13 050), 275 (1625), 282 (1480); ^{1}H NMR (79.5 Hz) δ 7.37 (5 H, superficial s), 7.69–7.30 (4 H, complex m), 5.71 (1 H, d, J = 8 Hz), 5.56 (1 H, d, J = 8 Hz), 5.18 (2 H, apparent s), 4.93–4.52 (1 H, br m), 4.33–3.99 (1 H, complex m), 3.76 (3 H, s) superimposed on a complex m at 3.95–3.65 (1 H), 3.12–2.64 (2 H, complex m); mass spectrum, m/e (relative intensity) 323 (M^+, 0.3), 202 (25), 158 (35), 122 (25), 121 (32), 91 (100). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

***N*-((Benzyloxy)carbonyl)-2-(*p*-methylbenzyl)-3-pyrroline (4b).** Treatment of 1.00 g (5.80 mmol) of 2-(*p*-methylbenzyl)-3-pyrroline (**3b**) as described for **4a** yielded 1.67 g (5.40 mmol, 93%) of **4b** as a colorless oil: n^{14}_D 1.5629; IR (film) 3025, 2950, 2925, 2870, 1710, 1625, 1520, 1415, 1365, 1330, 1110, 700 cm^{-1}; UV (MeOH) λ_{max} 207 nm (ϵ 20 960, sh); ^{1}H NMR (79.5 MHz) δ 7.32 (5 H, superficial s), 6.98 (4 H, superficial s), 5.69 (1 H, d, J = 8 Hz), 5.60 (1 H, d, J = 8 Hz), 5.19 (2 H, apparent s), 4.9–4.5 (1 H, br m), 4.4–4.0 (1 H, complex m), 4.0–3.6 (1 H, complex m), 3.3–2.5 (2 H, complex m), 2.30 (3 H, s); mass spectrum, m/e (relative intensity) 307 (M^+, 0.3), 202 (29), 158 (27), 105 (22), 91 (100). Anal. ($C_{20}H_{21}NO_2$) C, H, N.

***N*-((Benzyloxy)carbonyl)-2-benzyl-3-pyrroline (4c).** To a stirred slurry containing 13.0 g (82.0 mmol) of 2-benzyl-3-pyrroline (**3c**), 13 g of $NaHCO_3$, and 5 mL of methanol in 130 mL of toluene was added 14 mL (98 mmol) of benzyl chloroformate. After 30 min, the mixture was poured over ice and extracted with toluene. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated at vacuum-pump pressure. Following column chromatography (100 g of silica gel, 2–10% Et_2O in hexane), 21.0 g (72.0 mmol, 88%) of **4c** was obtained as a colorless oil: n^{14}_D 1.5662; IR (film) 3050, 3025, 2950, 2915, 2850, 1700, 1620, 1495, 1455, 1410, 1360, 1320, 1100, 700 cm^{-1}; UV (MeOH) λ_{max} 207 nm (ϵ 20 280, sh); ^{1}H NMR (79.5 MHz) δ 7.36 (5 H, superficial s), 7.17 (5 H, superficial s), 5.71 (1 H, d, J = 8 Hz), 5.57 (1 H, d, J = 8 Hz), 5.21 (2 H, apparent s), 5.0–4.6 (1 H, br m), 4.40–3.99 (1 H, complex m), 3.99–3.57 (1 H, complex m), 3.37–2.52 (2 H, complex m); mass spectrum, m/e (relative intensity) 293 (M^+, 0.3), 202 (56), 158 (47), 91 (100), 65 (24). Anal. ($C_{19}H_{19}NO_2$) C, H, N.

***N*-((Benzyloxy)carbonyl)-4β-hydroxy-3α-iodo-2β-(*p*-methoxybenzyl)pyrrolidine (5a).** To a cooled (3–5 °C ice–water bath), stirred solution of 1.60 g (4.95 mmol) of *N*-((benzyloxy)carbonyl)-2-(*p*-methoxybenzyl)-3-pyrroline (**4a**) in 40 mL of THF was added dropwise a solution of 1.4 g of 70% perchloric acid in 4 mL of H_2O, followed by the slow addition of 3.60 g (16.0 mmol) of crystalline *N*-iodosuccinimide over a 1-h period. During an additional hour of stirring, the temperature was allowed to slowly rise to ambient and then a saturated Na_2SO_3 solution was added until the mixture on testing gave a negative peroxide test with KI–starch test paper. The mixture was then extracted with Et_2O and the organic phase separated, dried ($MgSO_4$), and concentrated at reduced pressure (88 torr). Following column chromatography (20 g of silica gel, 5–20% Et_2O in hexane), 1.90 g (4.07 mmol, 82%) of **5a** was obtained as a white solid, which crystallized from EtOAc–Et_2O (1:1): mp 134–135 °C; IR (Nujol) 3400–3200, 1675, 1620, 1520, 1505, 1260, 1190, 1150, 1080, 1020, 740 cm^{-1}; UV (MeOH) λ_{max} 223 nm (ϵ 11 900), 275 (2020), 283 (1570); ^{1}H NMR (79.5 MHz) δ 7.36 (5 H, superficial s), 7.27–6.64 (4 H, complex m), 5.16 (2 H, s), 4.68–4.22 (2 H, m, $w_{1/2}$ = 16 Hz), 3.97 (1 H, superficial t, J = 4 Hz) superimposed on a complex m at 4.22–3.85 (1 H), 3.80 (3 H, s), 3.52–2.77 (3 H, complex overlapping multiplets), 2.82 (1 H, br superficial d, exchanges with D_2O); mass spectrum, m/e (relative intensity) 467 (M^+, 0.5), 346 (5), 175 (8), 158 (6), 122 (10), 121 (97), 91 (100). Anal. ($C_{20}H_{22}NO_4I$) C, H, N, I.

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***N*-((Benzyloxy)carbonyl)-4β-hydroxy-3α-iodo-2β-(*p*-methylbenzyl)-pyrrolidine (5b).** Treatment of 1.80 g (5.80 mmol) of *N*-((benzyloxy)-carbonyl)-2-(*p*-methylbenzyl)-3-pyrroline (**4b**) as described for **5a** yielded 2.03 g (4.50 mmol, 78%) of **5b** as a white solid, which crystallized from EtOAc–Et_2O (1:1): mp 123–124 °C; IR ($CHCl_3$) 3600, 3550–3150, 2955, 1695, 1520, 1500, 1420, 1360, 1115 cm^{-1}; UV (MeOH) λ_{max} 207 nm (ε 24 290, sh); ^1H NMR (79.5 Hz) δ 7.35 (5 H, superficial s), 7.03 (4 H, superficial s), 5.17 (2 H, s), 4.62–4.28 (2 H, m, $w_{1/2}$ = 14 Hz), 3.98 (1 H, superficial t, J = 3 Hz) superimposed on a broad complex m at 4.20–3.82 (1 H), 3.47–2.61 (4 H, complex overlapping multiplets; one proton exchanges with D_2O), 2.29 (3 H, s); mass spectrum, *m/e* (relative intensity) 451 (M^+, 0.3), 346 (15), 219 (29), 175 (25), 158 (18), 105 (49), 91 (100), 65 (15). Anal. ($C_{20}H_{22}NO_3I$) C, H, N, I.

***N*-((Benzyloxy)carbonyl)-3α-bromo-4β-hydroxy-2β-benzylpyrrolidine (5c).** To a cooled (3–5 °C ice–water bath), stirred solution of 10 g (34.0 mmol) of *N*-((benzyloxy)carbonyl)-2-benzyl-3-pyrroline (**4c**) in 180 mL of THF was slowly added a solution of 5.8 g of 70% perchloric acid in 20 mL of H_2O, followed by the slow addition of 12.0 g (87.0 mmol) of *N*-bromoacetamide (recrystallized from CH_2Cl_2, mp 110–111 °C) over a 30-min period. During an additional 1 h of stirring, the temperature was allowed to slowly rise to ambient temperature, and then the product was isolated as described for **5a**. Following column chromatography (125 g of silica gel, 5–10% Et_2O in hexane), 9.80 g (25.1 mmol, 74%) of **5c** was obtained as a white solid, which crystallized from EtOAc–Et_2O (1:1): mp 114–115 °C; IR ($CHCl_3$) 3610, 3550–3250, 3065, 2950, 2880, 1700, 1600, 1500, 1460, 1420, 1360, 1120 cm^{-1}; UV (MeOH) λ_{max} 204 nm (ε 14 520), 207 (14 615); ^1H NMR (79.5 MHz) δ 7.37 (5 H, superficial s), 7.22 (5 H, superficial s), 5.18 (2 H, s), 4.6–4.2 (2 H, m, $w_{1/2}$ = 14 Hz), 4.00 (1 H, superficial t, J = 4 Hz) superimposed on a broad complex m at 4.2–3.8 (1 H), 3.52–2.97 (3 H, complex overlapping multiplets), 2.65 (1 H, broad superficial d, J = 3 Hz, exchanges with D_2O); mass spectrum, *m/e* (relative intensity) 391 (M^+, 0.3), 389 (M^+, 0.3), 300 (35), 298 (36), 256 (32), 254 (32), 92 (45), 91 (100), 77 (12), 65 (62), 51 (13), 41 (18), 39 (25). Anal. ($C_{19}H_{20}NO_3Br$) C, H, N, Br.

***N*-((Benzyloxy)carbonyl)-2β-(*p*-methoxybenzyl)-3,4β-oxidopyrrolidine (6a).** After a solution containing 3.80 g (8.14 mmol) of *N*-((benzyloxy)carbonyl)-4β-hydroxy-3α-iodo-2β-(*p*-methoxybenzyl)-pyrrolidine (**5a**) in 40 mL of 5% KOH (EtOH) was stirred for 30 min, water was added and the solution extracted with CH_2Cl_2. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated at reduced pressure (88 torr). Following column chromatography (60 g of silica gel, 5–20% Et_2O in hexane), 2.53 g (7.46 mmol, 92%) of **6a** was obtained as a white solid, which crystallized from Et_2O: mp 74–75 °C;[5b,12c] IR (film) 3035, 2950, 2880, 2840, 1710, 1615, 1520, 1430, 1395, 1330, 1255, 1120, 1040, 880, 700 cm^{-1}; UV (MeOH) λ_{max} 223 nm (ε 11 905), 275 (1725), 282 (1410); ^1H NMR (100 MHz) δ 7.36 (5 H, apparent s) superimposed on a multiplet from 7.5–7.0 (2 H), 6.84 (2 H, d, J = 8.4 Hz), 5.15 (2 H, s), 3.78 (3 H, s) superimposed on complex overlapping multiplets at 4.05–3.55 (4 H), 3.49 (1 H, d, J = 3 Hz) overlapping 3.46 (1 H, d, J = 3 Hz), 2.74 (1 H, apparent t, J = 11 Hz); mass spectrum, *m/e* (relative intensity) 339 (M^+, 9), 248 (8), 218 (15), 174 (25), 121 (69), 91 (100), 77 (9), 65 (12). Anal. ($C_{20}H_{21}NO_4$) C, H, N.

***N*-((Benzyloxy)carbonyl)-2β-(*p*-methylbenzyl)-3,4β-oxidopyrrolidine (6b).** Similar treatment of 5.05 g (11.2 mmol) of *N*-((benzyloxy)-carbonyl)-4β-hydroxy-3α-iodo-2β-(*p*-methylbenzyl)pyrrolidine (**5b**) in 100 mL of 5% KOH (MeOH), as described for **6a**, yielded, after column chromatography (50 g of silica gel, 1–5% Et_2O in toluene), 3.24 g (10.0 mmol, 90%) of **6b** as a white solid, which crystallized from Et_2O: mp 92–93 °C; IR ($CHCl_3$) 3020, 3000, 2945, 2880, 1675, 1510, 1500, 1450, 1420, 1385, 1355, 1315, 1110, 870 cm^{-1}; UV (MeOH) λ_{max} 207 nm (ε 19 500), 211 (18 150), 221 (9025, sh); ^1H NMR (100 MHz) δ 7.39 (5 H, s), 7.30–7.00 (4 H, complex m), 5.18 (2 H, s), 4.06–3.58 (4 H, complex overlapping multiplets), 3.53 (1 H, d, J = 3 Hz), 3.49 (1 H, d, J = 3 Hz), 2.76 (1 H, apparent t, J = 11 Hz), 2.34 (3 H, s); mass spectrum, *m/e* (relative intensity) 323 (M^+, 8), 232 (34), 218 (84), 174 (93), 105 (99), 92 (50), 91 (100), 79 (16), 77 (18), 65 (27). Anal. ($C_{20}H_{21}NO_3$) C, H, N.

***N*-((Benzyloxy)carbonyl)-2β-benzyl-3,4β-oxidopyrrolidine (6c).** Similar treatment of 13.80 g (35.3 mmol) of *N*-((benzyloxy)-carbonyl)-3α-bromo-4β-hydroxy-2β-benzylpyrrolidine (**5c**) in 150 mL of 10% KOH (EtOH), as described for **6a**, yielded, after column chromatography (120 g of silica gel, 5–20% Et_2O in hexane), 8.70 g (28.2 mmol, 80%) of **6c** as a white solid, which crystallized from Et_2O: mp 68–69 °C; IR ($CHCl_3$) 3080, 3070, 2945, 2880, 1695, 1500, 1455, 1420, 1390, 1325, 1115, 870, 700 cm^{-1}; UV (MeOH) λ_{max} 205 nm (ε 18 710), 207 (18 785); ^1H NMR (79.5 MHz) δ 7.36 (5 H, superficial s) overlapping 7.28 (5 H, br s), 5.13 (2 H, s), 4.05–3.51 (4 H, complex overlapping multiplets), 3.45 (1 H, d, J = 3 Hz) overlapping 3.41 (1 H, d, J = 3 Hz), 2.75 (1 H, apparent t, J = 11 Hz); mass spectrum, *m/e* (relative intensity) 309 (M^+, 2), 218 (63), 174 (39), 91 (100), 65 (35), 39 (15). Anal. ($C_{19}H_{19}NO_3$) C, H, N.

2β-(*p*-Methoxybenzyl)-3,4β-oxidopyrrolidine (7a). A slurry containing 2.15 g (6.34 mmol) of *N*-((benzyloxy)carbonyl)-2β-(*p*-methoxybenzyl)-3,4β-oxidopyrrolidine (**6a**) and 200 mg of 10% Pd/C in 250 mL of MeOH was stirred under a hydrogen atmosphere for 2 h and then filtered. The filtrate was concentrated at reduced pressure (88 torr) and the residue, following column chromatography (20 g of silica gel, 2% MeOH in CH_2Cl_2), yielded 1.30 g (6.34 mmol, 100%) of **7a** as a colorless oil, which solidified on standing: IR (film) 3330, 3275 (br), 3030, 2925, 2865, 1620, 1590, 1520, 1470, 1445, 1305, 1255, 1180, 1040, 915, 870, 840, 820 cm^{-1}; UV (MeOH) λ_{max} 223 nm (ε 10 810), 276 (1800), 282 (1530); ^1H NMR (90 MHz) δ 7.29 (2 H, d with further fine splitting, J = 9 Hz), 6.96 (2 H, d with further fine splitting, J = 9 Hz), 3.83 (3 H, s), 3.69 (1 H, d, J = 3 Hz), 3.39 (1 H, d, J = 3 Hz), 3.34–3.00 (2 H, overlapping complex multiplets), 3.00–2.59 (3 H, overlapping complex multiplets), 1.53 (1 H, s, exchanges with D_2O); mass spectrum, *m/e* (relative intensity) 205 (M^+, 2), 122 (45), 121 (37), 91 (10), 84 (100), 78 (11), 77 (16), 56 (43). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.11; H, 7.37; N, 6.83. Found: C, 67.73; H, 6.82; N, 6.32.

2β-(*p*-Methylbenzyl)-3,4β-oxidopyrrolidine (7b). Treatment of a mixture of 4.00 g (12.3 mmol) of *N*-((benzyloxy)carbonyl)-2β-(*p*-methylbenzyl)-3,4β-oxidopyrrolidine (**6b**) and 400 mg of 10% Pd/C in 200 mL of absolute EtOH under a hydrogen atmosphere for 1.5 h, as described for **7a**, yielded, following column chromatography (20 g of silica gel, 2–5% MeOH in CH_2Cl_2), 2.20 g (11.6 mmol, 95%) of **7b** as a colorless oil.

2β-Benzyl-3,4β-oxidopyrrolidine (7c). Treatment of a mixture of 5.00 g (16.2 mmol) of *N*-((benzyloxy)carbonyl)-2β-benzyl-3,4β-oxidopyrrolidine (**6c**) and 500 mg of 10% Pd/C in 250 mL of absolute EtOH under a hydrogen atmosphere for 1.5 h, as described for **7a**, yielded, following column chromatography (50 g of silica gel, 2–5% MeOH in CH_2Cl_2), 2.80 g (16.0 mmol, 98%) of **7c** as a colorless oil, which solidified on standing: IR (film) 3330, 3270 (br), 3085, 3065, 3030, 2920, 2860, 1600, 1580, 1500, 1455, 1090, 1030, 920, 865, 700 cm^{-1}; UV (MeOH) λ_{max} 205 nm (8655), 207 (8700); ^1H NMR (79.5 MHz) δ 7.27 (5 H, s), 3.52 (1 H, d, J = 3 Hz), 3.32 (1 H, d, J = 3 Hz), 3.28–2.98 (2 H, complex overlapping multiplets), 2.98–2.52 (3 H, complex overlapping multiplets), 1.82 (1 H, s, exchanges with D_2O); ^{13}C NMR (25.2 MHz) δ 138.580 (ipso), 128.990 (m), 128.528 (o), 126.435 (p), 60.684 (C-2), 57.077 and 56.255 (C-3 and C-4), 48.231 (C-5), 36.772 (benzyl C); mass spectrum, *m/e* (relative intensity) 175 (M^+, 0.6), 91 (17), 84 (100), 65 (9), 56 (46). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 8.00. Found: C, 73.49; N, 7.48.

***N*-((Benzyloxy)carbonyl)-3β,4α-dihydroxy-2β-(*p*-methoxybenzyl)-pyrrolidine (9a).** A solution of 800 mg (3.90 mmol) of 2β-(*p*-methoxybenzyl)-3,4β-oxidopyrrolidine (**7a**) and 800 mg of sodium trifluoroacetate in 20 mL of trifluoroacetic acid was cautiously lowered into a hot-oil bath (ca. 120 °C) so that boiling started immediately.[19] After 16 h of refluxing the solution was allowed to cool, and the solvent was then removed at reduced pressure (88 torr). Tetrahydrofuran (50 mL) was added to the residue, and a solution of 10% Na_2CO_3 was added to adjust the solution to pH 9. To the cold (3–5 °C ice–water bath), stirred solution was slowly added (dropwise) 1.70 mL (11.9 mmol) of benzyl chloroformate, and after 1 h the mixture was extracted with CH_2Cl_2. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated at reduced pressure (88 torr). Following column chromatography on 120 g of silica gel and elution with toluene–CH_2Cl_2–MeOH–MeOH saturated with NH_3 gas (32:8:3:1), 1.35 g (3.78 mmol, 97%) of **9a** was obtained as a colorless oil, which solidified on standing: IR (film) 3600–3150, 3070, 3040, 2950, 2840, 1680, 1620, 1520, 1430, 1360, 1255, 1130, 1110, 1040, 760, 710 cm^{-1}; ^1H NMR (79.5 MHz) δ 7.35 (5 H, superficial s), 7.11 (2 H, d with further fine splitting, J = 9 Hz), 6.74 (2 H, dd, J = 9, 2 Hz), 5.11 (2 H, apparent s), 3.75 (3 H, s) superimposed on 4.3–3.6 (3 H, complex m), 3.6–2.6 (4 H, complex overlapping multiplets), 2.6–2.0 (2 H, m, exchanges with D_2O); mass spectrum, *m/e* (relative intensity) 357 (M^+, 1.3), 236 (11), 192 (15), 121 (27), 91 (100), 65 (7). Anal. ($C_{20}H_{23}NO_5$) C, H, N.

(±)-Anisomycin (1a). To a stirred and cooled (3–5 °C ice–water bath) solution of 1.35 g (3.78 mmol) of *N*-((benzyloxy)carbonyl)-3β,4α-dihydroxy-2β-(*p*-methoxybenzyl)pyrrolidine (**9a**) in 20 mL of CH_2Cl_2 and 2 mL of pyridine was added (dropwise) 0.70 mL (5.1 mmol) of 2,2,2-trichloroethyl chloroformate. After 30 min, the CH_2Cl_2 was removed at reduced pressure (88 torr) and the residue treated in situ with a solution of 20 mL of pyridine containing 1.00 mL (10.6 mmol) of acetic anhydride. After 18 h, the solution was poured onto ice and extracted with CH_2Cl_2. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated at reduced pressure (88 torr). The residue was dissolved in 50 mL of acetic acid–THF (1:4) and 6.0 g of zinc powder added. After stirring for 1 h, the slurry was filtered and the filtrate

adjusted to pH 9 with 2 N NaOH. The solution was then extracted with CH_2Cl_2 and the organic phase concentrated at reduced pressure (88 torr). To the residue was added 100 mL of MeOH and 100 mg of 10% Pd/C and the mixture stirred under a hydrogen atmosphere for 2 h. The catalyst was then removed by filtration and the filtrate concentrated at reduced pressure (88 torr). Column chromatography of the residue on 150 g of silica gel and elution with toluene–CH_2Cl_2–MeOH–MeOH saturated with NH_3 gas (32:8:3:1) yielded 770 mg (2.91 mmol, 77%) of **1a** as a white solid, which crystallized from EtOAc:[5b] mp 126–127 °C (lit.[12c] mp 127–128.5 °C); $[\alpha]^{26}_D$ 0° (*c* 0.3, EtOH); IR ($CHCl_3$) 3585, 3600–3100, 2955, 2935, 2835, 1726, 1612, 1515, 1375, 1248, 1175, 1035 cm^{-1}; UV (MeOH) λ_{max} 223 nm (ϵ 10995), 276 (1780), 282 (1530); ^1H NMR (100 MHz) δ 7.11 (2 H, d with further fine splitting, J = 8.6 Hz), 6.82 (2 H, d with further fine splitting, J = 8.5 Hz), 4.72 (1 H, dd, J = 4.6, 1.2 Hz), 4.16 (1 H, ddd, J = 6.3, 4.8, 1.2 Hz), 3.78 (3 H, s), 3.41 (1H, dd, J = 11.4, 6.2 Hz) superimposed on 3.58–3.38 (1 H, complex m), 2.79 (2 H, d, J = 6.1 Hz) superimposed on 2.75 (1 H, dd, J = 11.4, 5.0 Hz), 2.37 (2 H, s, exchanges with D_2O), 2.14 (3 H, s); ^1H NMR (360 MHz) δ 7.108 (2 H, d, J = 8.545), 6.827 (2 H, d, J = 9.155 Hz), 4.712 (1 H, d, J = 3.662 Hz), 4.168 (1 H, t with further fine splitting, J = 4.883 Hz), 3.780 (3 H, s), ca. 3.51 (1 H, dd, J = ca. 10, 4 Hz), 3.416 (1 H, dd, J = 11.597, 6.714 Hz), ca. 2.85–2.70 (3 H, overlapping complex multiplets), 2.412 (2 H, br s, exchanges with D_2O), 2.142 (3 H, s); ^{13}C NMR (20 MHz) δ 171.19, 158.40, 131.18, 129.81 (2 C), 114.15 (2 C), 82.09, 77.17, 61.65, 55.19, 52.77, 34.68, 21.02; mass spectrum, *m/e* (relative intensity) 266 (0.9), 265 (M^+, 0.8), 144 (62), 126 (19), 122 (16), 121 (31), 84 (100), 43 (24). Anal. ($C_{14}H_{19}NO_4$) C, H, N.

(−)-Anisomycin:[20] $[\alpha]^{26}_D$ −26.0° (*c* 0.3, EtOH); IR ($CHCl_3$) 3585, 3600–3100, 2950, 2935, 2830, 1725, 1615, 1515, 1375, 1250, 1175, 1035 cm^{-1}; ^1H NMR (100 MHz) δ 7.12 (2 H, d with further fine splitting, J = 8.8 Hz), 6.82 (2 H, d with further fine splitting, J = 8.8 Hz), 4.70 (1 H, dd, J = 4.6, 1.2 Hz), 4.18 (1 H, ddd, J = 6.6, 5.1, 1.2 Hz), 3.78 (3 H, s), 3.43 (1 H, dd, J = 11.6, 6.7 Hz) superimposed on 3.59–3.31 (1 H, complex m), 2.79 (2 H, d, J = 6.6 Hz) superimposed on 2.72 (1 H, dd, J = 11, 4.9 Hz), 2.14 (3 H, s) superimposed on 2.01 (2 H, br s, exchanges with D_2O); ^1H NMR (360 MHz) δ 7.113 (2 H, d, J = 8.545 Hz), 6.830 (2 H, d, J = 8.540 Hz), 4.721 (1 H, d, J = 3.662 Hz), 4.182 (1 H, t with further fine splitting, J = ca. 4 Hz), 3.780 (3 H, s), ca. 3.53 (1 H, dd, J = ca. 12, 6 Hz), 3.427 (1 H, dd, J = 11.597, 6.714 Hz), ca. 2.86–2.72 (3 H, overlapping complex multiplets), 2.522 (2 H, br s, exchanges with D_2O), 2.146 (3 H, s); ^{13}C NMR (20 MHz) δ 171.26, 158.31, 131.12, 129.75 (2 C), 114.09 (2 C), 82.09, 77.26, 61.61, 55.23, 52.67, 34.60, 21.02; mass spectrum, *m/e* (relative intensity) 266 (0.3), 265 (M^+, 0.1), 144 (27), 126 (11), 122 (8), 121 (19), 84 (100), 43 (17).

3β-Acetoxy-4α-hydroxy-2β-(*p*-methylbenzyl)pyrrolidine (1b). A solution of 2.00 g (10.6 mmol) of 2β-(*p*-methylbenzyl)-3,4β-oxidopyrrolidine (**7b**) and 2.00 g of sodium trifluoroacetate in 50 mL of trifluoroacetic acid was cautiously lowered into a hot-oil bath (ca. 120 °C) so that boiling started immediately.[19] After 16 h of refluxing the solution was allowed to cool, and the solvent was then removed at reduced pressure (88 torr). Tetrahydrofuran (100 mL) was added to the residue, and a solution of 10% Na_2CO_3 was added to adjust the solution to pH 9. To the cold (3–5 °C ice–water bath), stirred solution was slowly added (dropwise) 3.50 mL (24.6 mmol) of benzyl chloroformate, and after 1 h, the mixture was extracted with CH_2Cl_2. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated at reduced pressure (88 torr). Following column chromatography on 250 g of silica gel and elution with toluene–$CHCl_2$–MeOH–MeOH saturated with NH_3 gas (32:8:3:1), 3.51 g of **9b** was obtained as a colorless oil, which solidified on standing. To a cooled (3–5 °C ice–water bath) solution of the entire sample of **9b** in 50 mL of CH_2Cl_2 containing 5 mL of pyridine was added (dropwise) 1.60 mL (11.7 mmol) of 2,2,2-trichloroethyl chloroformate. After 30 min, the CH_2Cl_2 was removed at reduced pressure (88 torr) and the residue treated in situ with a solution of 50 mL of pyridine containing 2.00 mL (21.2 mmol) of acetic anhydride. After 18 h, the solution was poured onto ice and extracted with CH_2Cl_2. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated at reduced pressure (88 torr). The residue was dissolved in 100 mL of acetic acid–THF (1:4) and 10.0 g of zinc powder added. After stirring 1 h, the slurry was filtered and the filtrate adjusted to pH 9 with 2 N NaOH. The solution was then extracted with CH_2Cl_2 and the organic phase concentrated at reduced pressure (88 torr). To the residue was added 250 mL of MeOH and 250 mg of 10% Pd/C and the mixture stirred vigorously under a hydrogen atmosphere for 2 h. The catalyst was then removed by filtration and the filtrate concentrated at reduced pressure (88 torr). Column chromatography of the residue on 300 g of silica gel and elution with toluene–CH_2Cl_2–MeOH–MeOH saturated with NH_3 gas (32:8:3:1) yielded 1.88 g (7.55 mmol, 71%) of **1b** as a white solid, which crystallized from EtOAc: mp 125–126 °C; IR (Nujol) 3290, 3400–3050, 1740, 1725, 1520, 1250, 1070, 1030, 960, 950, 815, 765 cm^{-1}; UV (MeOH) λ_{max} 207 nm (ϵ 8355, sh), 211 (9085), 216 (8355, sh), 240 (7025, sh); ^1H NMR (100 MHz) δ 7.09 (4 H, s), 4.71 (1 H, dd, J = 4.8, 1.4 Hz), 4.17 (1 H, ddd, J = 6, 4, 1.5 Hz), 3.42 (1 H, dd, J = 11.3, 6.6 Hz) superimposed on 3.66–3.34 (1 H, complex m), 2.81 (2 H, d, J = 6.3 Hz) superimposed on 2.72 (1 H, dd, J = 11.5, 4.5 Hz), 2.31 (3 H, s) superimposed on 2.5–2.1 (2 H, br s, exchanges with D_2O), 2.14 (3 H, s); mass spectrum, *m/e* (relative intensity) 250 (M^+ + 1, 0.3), 144 (31), 126 (11), 105 (16), 91 (7), 84 (100), 43 (18). Anal. ($C_{14}H_{19}NO_3$) C, H, N.

3β-Acetoxy-2β-benzyl-4α-hydroxypyrrolidine (1c). A solution of 1.00 g (5.71 mmol) of 2β-benzyl-3,4β-oxidopyrrolidine (**7c**) and 1.00 g of sodium trifluoroacetate in 20 mL of trifluoroacetic acid was cautiously lowered into a hot-oil bath (ca. 120 °C) so that boiling started immediately.[19] After the solution was refluxed for 16 h, it was allowed to cool, and the solvent was then removed at reduced pressure (88 torr). Tetrahydrofuran (50 mL) was added to the residue, and a solution of 10% Na_2CO_3 was added to adjust the solution to pH 9. To the cold (3–5 °C ice–water bath), stirred solution was added (dropwise) 1.50 mL (10.5 mmol) of benzyl chloroformate, and after 1 h, the mixture was extracted with CH_2Cl_2. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated at reduced pressure (88 torr). Following column chromatography on 120 g of silica gel and elution with toluene–CH_2Cl_2–MeOH–MeOH saturated with NH_3 gas (32:8:3:1), 1.81 g of **9c** was obtained as a colorless oil, which solidified on standing. To a cooled (3–5 °C ice–water bath) solution of the entire sample of **9c** in 20 mL of CH_2Cl_2 containing 2 mL of pyridine was added (dropwise) 0.80 mL (5.84 mmol) of 2,2,2-trichloroethyl chloroformate. After 30 min, the CH_2Cl_2 was removed at reduced pressure (88 torr) and the residue treated in situ with a solution of 20 mL of pyridine containing 1.00 mL (10.6 mmol) of acetic anhydride. After 18 h, the solution was poured onto ice and extracted with CH_2Cl_2. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated at reduced pressure (88 torr). The residue[21] was dissolved in 50 mL of acetic acid–THF (1:4) and 6.0 g of zinc powder added. After being stirred for 1 h, the slurry was filtered and the filtrate adjusted to pH 9 with 2 N NaOH. The solution was then extracted with CH_2Cl_2 and the organic phase concentrated at reduced pressure (88 torr). To the residue was added 100 mL of MeOH and 200 mg of 10% Pd/C and the mixture stirred vigorously under a hydrogen atmosphere for 2 h. The catalyst was then removed by filtration and the filtrate concentrated at reduced pressure (88 torr). Column chromatography of the residue on 100 g of silica gel and elution with toluene–CH_2Cl_2–MeOH–MeOH saturated with NH_3 gas (32:8:3:1) yielded 1.00 g (4.26 mmol, 75%) of **1c** as a white solid, which crystallized from EtOAc: mp 112–113 °C; IR (film) 3340, 3600–3050, 3090, 3070, 3025, 2930, 2875, 1740, 1600, 1500, 1460, 1375, 1240, 1035, 960, 705 cm^{-1}; UV (MeOH) λ_{max} 207 nm (ϵ 8890); ^1H NMR (100 MHz) δ 7.29–7.17 (5 H, complex m), 4.71 (1 H, dd, J = 4.7, 1.3 Hz), 4.16 (1 H, ddd, J = 6, 4, 1.5 Hz), 3.41 (1 H, dd, J = 11.5, 6.5 Hz) superimposed on 3.70–3.37 (1 H, complex m), 2.84 (2 H, d, J = 7.5 Hz) superimposed on 2.72 (1 H, dd, J = 11.5, 4.7 Hz), 2.17 (2 H, br s, exchanges with D_2O), 2.13 (3 H, s); mass spectrum, *m/e* (relative intensity) 236 (M^+ + 1, 0.3), 144 (28), 126 (10), 91 (20), 84 (100), 43 (20). Anal. ($C_{13}H_{17}NO_3$) C, H, N.

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Registry No. (±)-**1a**, 21497-40-5; (±)-**1b**, 82892-50-0; (±)-**1c**, 82892-51-1; **2a**, 1963-42-4; **2b**, 79499-34-6; **2c**, 33234-48-9; (±)-**3a**, 22862-67-5; (±)-**3b**, 82892-36-2; (±)-**3c**, 82892-37-3; (±)-**4a**, 82892-38-4; (±)-**4b**, 82892-39-5; (±)-**4c**, 82892-40-8; (±)-**5a**, 82892-41-9; (±)-**5b**, 82892-42-0; (±)-**5c**, 82892-43-1; (±)-**6a**, 34869-05-1; (±)-**6b**, 82892-44-2; (±)-**6c**, 82892-45-3; (±)-**7a**, 82916-85-6; (±)-**7b**, 82892-46-4; (±)-**7c**, 82892-47-5; (±)-**9a**, 82916-86-7; (±)-**9b**, 82892-48-6; (±)-**9c**, 82892-49-7; (±)-**12a**, 82916-87-8; (±)-**13c**, 82892-52-2.

(21) The order of removing the protecting groups is important since treatment of **11c** with H_2/10% Pd–C/MeOH, followed by Zn/HOAc–THF (then 2 N NaOH), failed to yield **1c**.