An Expeditious Route to the Northern Part of Retigeranic Acid *A* from (*R*)-(−)-Carvone[1]

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Favorskii rearrangement of the bromo ester **10a** readily obtainable from (*R*)-(−)-carvone is the key transformation in the preparation of the functionalized cyclopentane **2** required as the synthon for the northern half of retigeranic acid, **1**. Eight steps are required, the first four of which can be carried out without isolation, thereby affording a 40% overall yield of **12**.

Retigeranic acid **1** is a unique pentacyclic triquinane sesterterpene, which was isolated by Seshadri[3] in 1965 from *Lotaria retigera* lichens and whose structure was elucidated by Shibata[4] in 1972. Three successful syntheses have been described to date. The first one by Corey[5] in 1985 afforded the racemic compound. The second, by Paquette's group in 1987, afforded optically active **1** as well as some of its diastereomers.[6] The third, by Hudlicky's group, also gave the polyquinane in optically active form.[7] These accomplishments have confirmed Shibata's observation that natural retigeranic acid is a mixture of two isomeric substances, the minor component (retigeranic acid *A*) possessing structure **1**, while the major constituent (retigeranic acid *B*) is the epimer at the isopropyl bearing carbon.[6b]

We plan to obtain **1** in a convergent manner by coupling **2** to a triquinane **3a** or **3b**, and in this sense our retrosynthetic scheme parallels the successful approach of Paquette.[6] As indicated in Scheme I, the triquinane segment is to be derived from the bis-annulated pyranoside **4** whose efficient preparation, via radical cyclization strategy, we have recently described.[8] Paquette's experience[6b] made it clear that synthesis of the northern fragment **2** could present severe challenges, and hence we have given this segment priority. We report here the synthesis of the northern fragment **2** of retigeranic acid *A* in eight steps and 25% overall yield, starting from commercially available (*R*)-(−)-carvone.

It occurred to us that the 1,1,2,3-tetrasubstituted cyclopentane **2** could be prepared from a conveniently functionalized α-bromocyclohexanone, such as **7a** or **7b**, through a Favorskii type rearrangement (Scheme I). In view of the steric effect of the isopropyl group and the stereoelectronic factors involved in this rearrangement,[9] the reaction would be predicted to afford mainly cyclopentane **5**, through a disrotatory ring closure of the oxyallyl intermediate **6**.

Application of Mander's methoxycarbonylation[10] to (*R*)-(−)-carvone afforded the α-keto ester **8** in quantitative yield, which was hydrogenated over $Rh(Al_2O_3)$ to give **9** as a 85:15 mixture (^1H NMR) of epimers at C-3. The major component of this mixture was shown by ^1H NMR spectroscopy to have the methyl group in equatorial orientation. Bromination of **9** at C-1 did not occur by use of the method described by Vul'fson and co-workers[11] for ethyl 2-oxo-3-methylcyclohexanecarboxylate at −20 °C, and when the reaction mixture was allowed to reach room temperature, bromination took place exclusively at C-3, yielding the epimers **10a** and **10b** in a 2.5:1 ratio. Apparently the isopropyl group in **9** hinders enolization at C-1 and thus the reaction gives the unexpected regioisomers. In this context it should be noted that the mixture **9** does not exhibit an enol signal in ^1H NMR or IR spectra while ethyl 2-oxo-cyclohexanecarboxylate exists as a 61.5% in the enolized form.[12]

The major component of this mixture, **10a**, was obtained as a solid by fractional crystallization of the crude mixture from hot hexane. The configurations at C-3 in **10a** and **10b** were determined by ^1H NMR and IR spectroscopy: (a) the C-3 methyl signal is 0.12 ppm upfield in **10a** with respect to **10b**, (b) the axial H-1 proton is 0.41 ppm more deshielded in **10a**, (c) the ketone $\nu_{C=O}$ band absorption for **10a** is found at the same wavelength as that of the parent compound **9**, which is consistent with axial orientation of bromine.[13]

With **10a** in hand the "normal" Favorskii rearrangement was tried. Treatment with a methanolic solution of sodium methoxide at 0 °C afforded a 2:1 mixture of α-methoxy ketones **11** in 80% yield (Scheme II). The configuration at C-3 of the epimers was assigned by ^1H NMR spectroscopy, which showed that the major isomer is the one with equatorial methoxy group (axial methyl) **11a**. Thus: (a) the C-3 methoxy resonance was 0.23 ppm downfield in **11a**, (b) the axial H-1 proton was 0.20 ppm more deshielded in **11b** with respect to **11a**, (c) the C-3 methyl signal was 0.17 ppm upfield in the isomer **11b** where it is equatorial. The formation of these undesired products may be attributed to steric hindrance in removing H-1 of **10a**, the first step in the desired Favorskii rearrangement, by the adjacent isopropyl group.

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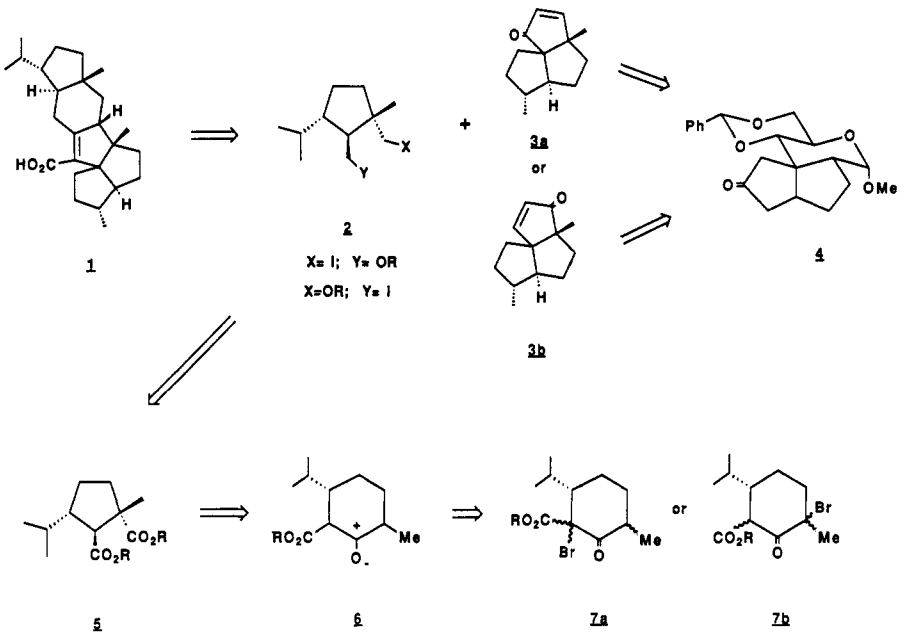
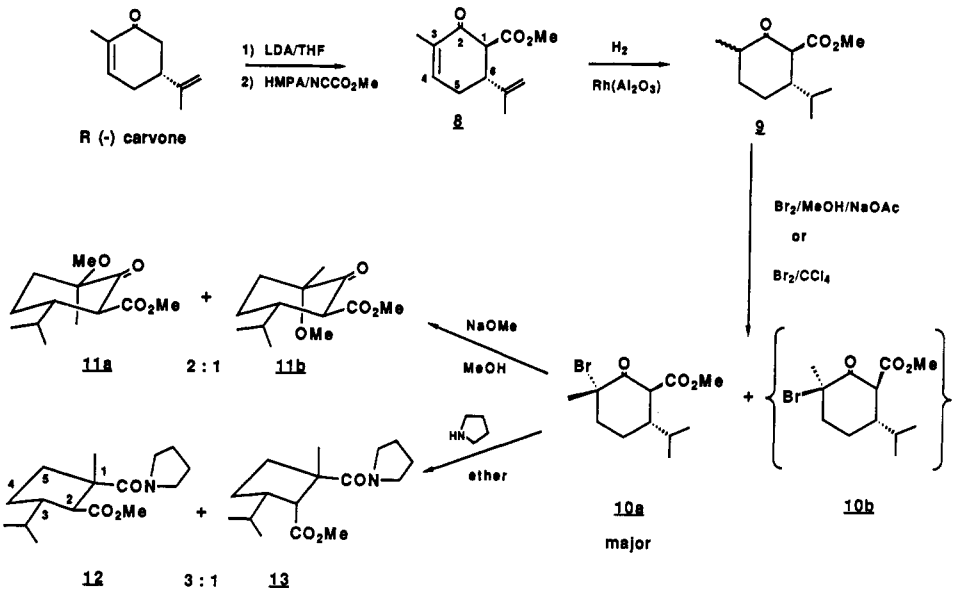
Scheme I

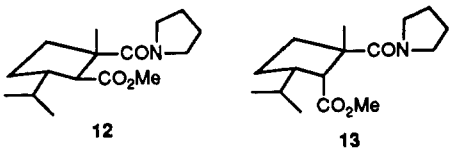


Scheme II



Bordwell and co-workers have shown that secondary amines promote Favorskii rearrangements provided that the α-halocyclohexanone possesses a group that enables formation of an enamine.[9,14] Our derivative **10a** meets this condition. Thus, treatment of **10a** with pyrrolidine in Et_2O for 5 min afforded the Favorskii products **12** and **13** in 3:1 ratio (Scheme II). The stereochemistry of these derivatives was assigned on the basis of the proposed reaction mechanism,[9,14] as depicted in Scheme III. According to Bordwell, opening of intermediate **14** should occur with retention of the configuration at the "activating group for enamine formation". However, the "activating group" used by Bordwell was phenyl, whereas in **10a** it was COOMe, which, being more enolizable, could lead to mixtures of **12** and **13**. Indeed, when **10a** was treated with pyrrolidine in a variety of solvents, using molecular sieves in some cases to remove the water produced in the first step of the

Table I. Favorskii Rearrangement of 10a with Pyrrolidine under Various Conditions

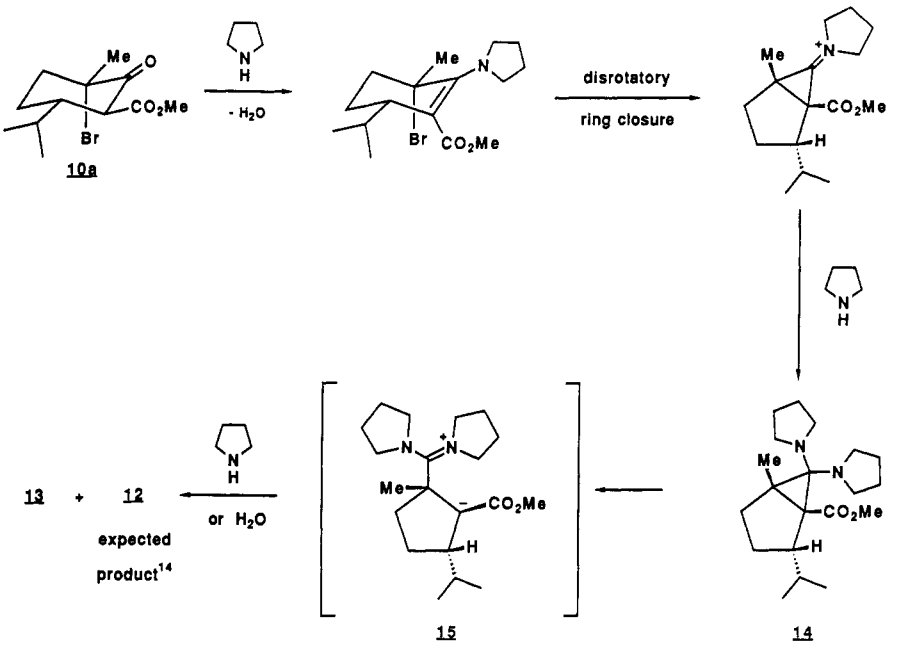


solvent	% 12	% 13
MeOH	60	40
AcOEt	80	20
AcOEt[a]	78	22
CH_2Cl_2	77	23
CH_2Cl_2[a]	77	23
Et_2O	75	25
Et_2O[a]	78	22
CCl_4	60	40
hexane	45	55
hexane[a]	69	31

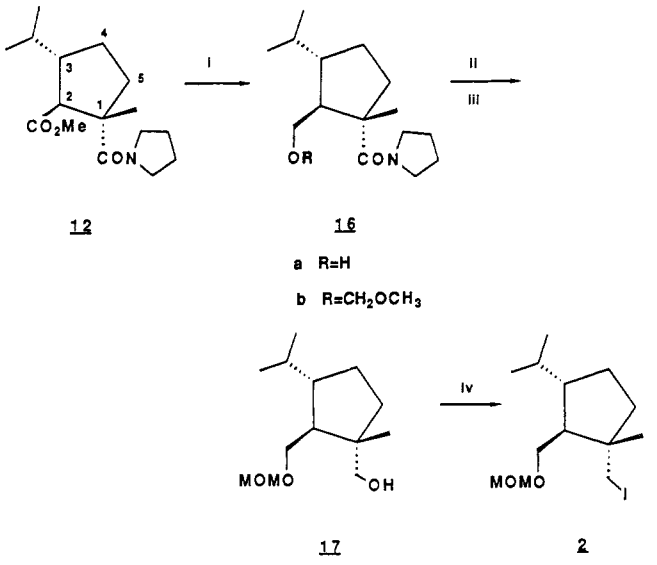
[a] In the presence of molecular sieves.

(14) Bordwell, F. G.; Almy, J. *J. Org. Chem.* **1973**, *38*, 573.

Scheme III

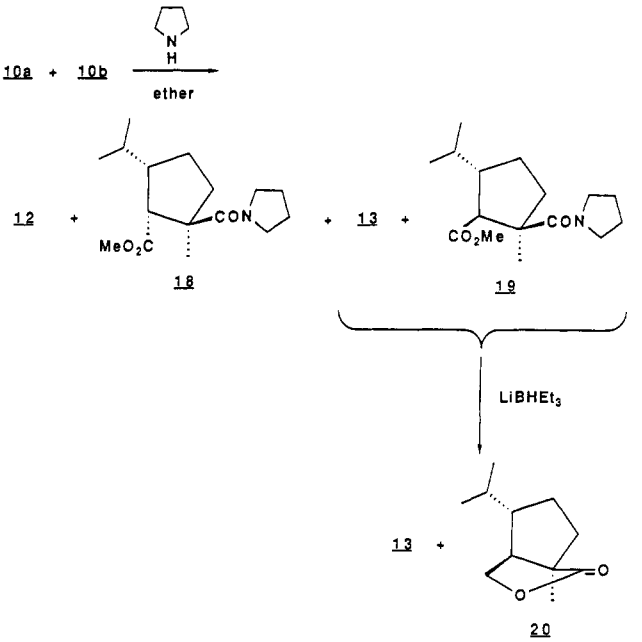


Scheme IV[a]



[a] (i) $LiBHEt_3/THF$; (ii) ClMOM; (iii) $LiBHEt_3$; (iv) I_2/PPh_3/imidazole.

Scheme V



reaction, the ratio of 12:3 was found to be solvent dependent (Table I). These results are in agreement with the differing extents of solvation of intermediate **15**.

The configurational assignment of **12** and **13** was confirmed by NOE experiments. Irradiation of the methyl signal provoked enhancement of H(2), and vice-versa, in **13** while this effect was not observed for **12**. All attempts at equilibration of **12** or **13** under basic conditions left each isomer unchanged in keeping with observations reported by Paquette on a similar system.[6b]

Ester–amide **12**, is therefore the isomer required, and the compound can be obtained in 40% overall yield from (R)-(−)-carvone by performing the first four steps without any purification. Conversion into the desired cyclopentane derivative **2** was carried out as shown in Scheme IV. Thus, selective reduction of **12** with 2.2 equiv of lithium triethylborohydride afforded the alcohol–amide **16a** in 96% yield. Protection of the alcohol followed by reduction of the amide to alcohol yielded **17** in 70% overall yield. The iodide **2** was then obtained in 93% yield under the iodination conditions described by Garegg.[15]

Although we had achieved our objective in the formation of **2**, it was desirable to gain a better understanding of the vagaries of the Favorskii rearrangement in these systems. Accordingly, we wished to examine the isomeric bromide **10b** (Scheme II), but since this compound could not be obtained in pure form, the crude mixture of mixture **10a** and **10b**, obtained from bromination of **9**, was used. There was obtained a mixture of four isomeric products, **12**, **13**, **18**, and **19**, in 3:1:1:1 ratio (^1H NMR estimation) (Scheme V).

Structural assignments for the new isomers, **18** and **19**, were made as follows. Firstly, we had found earlier that **13** did not react with lithium triethylborohydride. How-

(15) (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866. (b) Garegg, P. J.; Johansson, R.; Orthega, C.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 681.

ever, when a 1:1 mixture of **13** and a new isomer (obtained as such by flash chromatography) was treated with this reagent and the product subjected to oxidative work up, unreacted **13** was obtained in addition to a lactone. The latter must necessarily be **20** and the isomer which co-eluted with **13** must be **19**.

Since three disastereomers (**12**, **13**, **19**) have been assigned, the fourth must be **18**.

The procedure described in this paper shows that Favorskii type rearrangements such as **10a** → **12** (Scheme II) can be used for the stereoselective preparation of heavily functionalized cyclopentane derivatives such as **2**. The use of the latter in our synthesis of **1** is under way and will be described in due course.

Experimental Section

General Procedures. Melting points were determined in capillary tubes and are uncorrected. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ). IR spectra were recorded with use of sodium chloride plates for thin films of liquids, syrups, or solids in Nujol mulls. Optical rotations were determined at the sodium D line. ^{1}H NMR spectra were recorded at 300 MHz using $CDCl_3$ with internal tetramethylsilane or $CHCl_3$ as the standard. The coupling constants were verified by homonuclear decoupling experiments. The progress of all reactions was monitored by thin-layer chromatography (TLC), which was performed on aluminum plates precoated with silica gel HF-254 (0.2 mm layers) containing a fluorescent indicator. Detection was by UV (254 nm), followed by charring with sulfuric acid spray, or with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g), and cerium sulfate hydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Flash chromatography was performed using Kieselgel 60 (230–400 mesh, Merck) silica gel.

(1*S*,6*R*)-Methyl 3-Methyl-6-(1-methylethenyl)-2-oxocyclohex-3-enecarboxylate (8). *n*-Butyllithium (16 mL, 2.5 M in hexane) was added to 5.60 mL of diisopropyl amine (40 mmol) in dry THF (50 mL) at −20 °C under argon. After 30 min the temperature was lowered to −78 °C, and a solution of (*R*)-(−)-carvone (5 g, 33 mmol) in THF (25 mL) was added. The reaction mixture was stirred at 0 °C for 1 h, lowered to −78 °C, and HMPA (5.8 mL) was added followed by methyl cyanoformate (3.402 g, 3.174 mL, 40 mmol). After 10 min the reaction mixture was poured into water and extracted twice with ether, and the organic layer was dried over sodium sulfate and concentrated. Purification by flash chromatography (petroleum ether–ethyl acetate, 14:1) afforded 6.9 g (quantitative yield) of **8** as a colorless oil, bp 142–4 °C (15 mmHg): $[\alpha]^{20}_D$ −49.08° (*c* 1.63, $CHCl_3$); IR (neat) 1730, 1680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77 (m, 1 H, H-4), 4.84 (m, 2 H, H-8), 3.73 (s, 3 H, CO_2CH_3), 3.51 (d, $J_{1,6}$ = 12.9 Hz, 1 H, H-1), 3.13 (ddd, $J_{1,6}$ = 12.9 Hz, $J_{6,5}$ = 10.7 Hz, $J_{6,5'}$ = 4.9 Hz, 1 H, H-6), 2.55–2.28 (m, 2 H, H-5, H-5′), 1.81 (m, 3 H, CH_3), 1.75 (m, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.74, 170.32, 144.66, 144.59, 134.78, 112.85, 58.57, 52.03, 45.69, 30.71, 19.69, 15.78. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.99; H, 7.83.

(1*S*,3*S*,6*S*)-Methyl 3-Bromo-6-isopropyl-3-methyl-2-oxocyclohexanecarboxylate (10a). Keto ester **8** (6.9 g, 33 mmol) in ethanol (80 mL) was hydrogenated at 50 psi for 10 min, using 5% rhodium on alumina. The catalyst was filtered, and the solvent was removed to afford 7 g (99.5%) of a 85:15 mixture of **9** epimeric at C-3: IR (neat) 1730, 1715 cm^{-1}. For the major isomer **9a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3 H, CO_2CH_3), 3.31 (d, $J_{1,6}$ = 11.7 Hz, 1 H, H-1), 2.34 (m, 1 H, H-3), 2.23–2.06 (m, 2 H, H-4, H-6), 1.85 (m, 1 H, H-5), 1.70–1.30 (m, 3 H, H-4′, H-5′, H-7), 1.40 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.96 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.85 (d, *J* = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.95, 170.44, 61.96, 51.81, 47.33, 45.13, 34.09, 29.93, 23.31, 21.08, 15.71, 14.28; LRMS *m*/*z* (M^+ + H) 213. Selected signals for **9b** from the mixture: δ 3.73 (s, 3 H, CO_2CH_3), 3.49 (d, *J* = 11.6 Hz, 1 H, H-1), 2.68 (m, 1 H, H-3), 1.20 (d, *J* = 6.8 Hz, CH_3).

A solution of bromine (1.5 mL, 4.7 g, 29.21 mmol) in CCl_4 (15 mL) was added dropwise to a solution of 6.2 g (29.21 mmol) of the mixture of keto esters **9** in CCl_4 (50 mL). The reaction mixture was neutralized with a saturated solution of sodium bicarbonate and extracted with ether. The organic phase was dried (Na_2SO_4) and concentrated to yield 8.1 g (95%) of a mixture of epimers at C-3 which was dissolved in hot hexane and cooled to afford 4 g of pure **10a** as a white solid: mp 81–2 °C. $[\alpha]^{20}_D$ +234.25° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 1740, 1715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (d, $J_{1,6}$ = 12.7 Hz, 1 H, H-1), 3.77 (s, 3 H, CO_2CH_3), 2.38 (m, 1 H, H-4), 2.13 (m, 1 H, H-6), 1.96–1.72 (m, 3 H, H-4′, H-5, H-5′), 1.83 (s, 3 H, CH_3), 1.63 (m, 1 H, H-7), 0.97 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.90 (d, *J* = 6.9 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.70, 170.25, 64.42, 56.42, 52.07, 46.42, 41.32, 29.86, 27.78, 20.99, 20.20, 15.61. Anal. Calcd for $C_{12}H_{19}BrO_3$: C, 49.49; H, 6.58; Br, 27.44. Found: C, 49.43; H, 6.58; Br, 27.57.

(1*S*,2*S*,3*S*)- and (1*S*,2*R*,3*S*)-3-Isopropyl-2-(methoxycarbonyl)-1-methyl-1-(pyrrolidinylcarbonyl)cyclopentane (12 and 13). To 4 g of bromide **10a** (13.74 mmol) in dry ether (20 mL) at 0 °C was added 100 mL of a 1.2 M solution of pyrrolidine in dry ether (10 mL of pyrrolidine, 8.52 g, 0.12 mol). The mixture was stirred at 0 °C for 10 min and diluted with water, and the organic phase was separated, washed with 10% HCl, saturated $NaHCO_3$ solution, and water, dried, and evaporated to yield 3.9 g (97%) of a 3:1 mixture of **12** and **13**, which were separated by flash chromatography (petroleum ether–ethyl acetate, 2:1). For **12**: white solid; mp 59–60 °C; $[\alpha]^{20}_D$ +53.26° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 1725, 1620 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (s, 3 H, CO_2CH_3), 3.55 (m, 4 H, H-7), 3.22 (d, *J* = 9.3 Hz, H-2), 2.23 (m, 2 H, H-3, H-5), 1.88 (m, 5 H, H-8, H-5′), 1.72–1.56 (m, 2 H, H-4, H-9), 1.44 (m, 1 H, H-4′), 1.32 (s, 3 H, CH_3), 0.88 (t, *J* = 6.3 Hz, $C(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.71, 174.72, 54.41, 53.99, 51.45, 46.68, 47.71, 47.61, 37.42, 31.35, 27.21, 21.20, 20.24, 19.21. Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.40; H, 9.57; N, 5.00.

For **13**: white solid; mp 87–8 °C; $[\alpha]^{20}_D$ +48.6° (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 1710, 1600 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3 H, CO_2CH_3), 3.45 (m, 4 H, H-7), 2.99 (d, *J* = 6.1 Hz, 1 H, H-2), 2.59 (m, 1 H, H-5), 2.00–1.60 (m, 8 H, H-8, H-3, H-4, H-4′, H-5′), 1.32 (s, 3 H, CH_3), 1.31 (m, 1 H, H-9), 1.05 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.99 (d, *J* = 6.5 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.33, 175.26, 57.95, 55.81, 50.89, 48.19, 47.42, 46.76, 33.94, 30.82, 28.62, 26.89, 25.96, 23.33, 22.24, 21.96. Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.30; H, 9.62; N, 5.09.

(1*S*,2*S*,3*S*)-2-(Hydroxymethyl)-3-isopropyl-1-methyl-1-(pyrrolidinylcarbonyl)cyclopentane (16a). To the ester–amide **12** (1.62 g, 5.77 mmol) in THF (25 mL) was added lithium triethylborohydride (1 M in THF, 12.66 mmol, 12.66 mL) at room temperature. After 5 min the reaction was quenched by slow addition of 5 mL of 3 N sodium hydroxide, followed by 5 mL of 30% hydrogen peroxide solution, and stirred for 2 h at room temperature. The mixture was extracted into methylene chloride, and the organic phase was washed with brine, dried, and evaporated. The residue was purified by column chromatography (petroleum ether–EtOAc, 1:2) to yield 1.394 g (95.6%) of alcohol **16a**, as a white solid: mp 79–90 °C; $[\alpha]^{20}_D$ +46.0° (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) 3250, 1570 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (dd, *J* = 4.6, *J* = 3.4 Hz, 1 H, OH), 3.74–3.42 (m, 6 H, H-9, H-7), 2.47 (ddd, *J* = 3.8, *J* = 10.3, *J* = 10.26 Hz, 1 H, H-2), 2.10–1.32 (m, 10 H, H-3, H-4, H-5, H-8, H-10), 1.25 (s, 3 H, CH_3), 0.89 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.84 (d, *J* = 6.8 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.60, 61.75, 53.20, 50.40, 48.28, 47.42, 44.59, 36.07, 29.52, 26.98, 23.48, 23.16, 21.86, 17.35, 16.91. Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.27; H, 10.72; N, 5.49.

(1*S*,2*S*,3*S*)-1-Methyl-2-[(methoxymethoxy)methyl]-3-isopropyl-1-(pyrrolidinylcarbonyl)cyclopentane (16b). The alcohol **16a** (1.1 g, 4.341 mmol) was dissolved in dry methylene chloride (15 mL), diisopropylethylamine (1.512 mL, 8.683 mmol, 1.122 g) was added, and the mixture was treated with methoxymethyl chloride (6.512 mmol, 0.524 g, 495 μL) at room temperature and stirred for 10 h. The reaction mixture was diluted with methylene chloride and washed successively with dilute solutions of hydrochloric acid, sodium bicarbonate, and brine. The organic phase was dried and evaporated, and the residue was purified by column chromatography (petroleum ether–EtOAc, 2:1) to afford 1.25 g (97%) of the title compound **16b** as a colorless oil: $[\alpha]^{20}_D$ +32.80° (*c* 1.0, $CHCl_3$); IR (neat) 1620 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.61 (s, 2 H, OCH_2O), 3.67–3.41 (m, 6 H, H-7, H-9), 3.36 (s, 3 H, OCH_3), 2.43 (m, 1 H, H-2), 2.09 (m, 1 H, H-5), 1.90–1.30

(m, 9 H, H-4, H-5′, H-3, H-12, H-8), 1.24 (s, 3 H, CH_3), 0.90 (d, J = 6.6 Hz, 3 H, CH_3), 0.81 (d, J = 6.6 Hz, 3 H, CH_3). Anal. Calcd for $C_{17}H_{31}NO_3$: C, 68.65; H, 10.50; N, 4.71. Found: C, 68.48; H, 10.44; N, 4.67.

(1*S*,2*S*,3*S*)-1-Methyl-1-(2-hydroxyethyl)-2-[(methoxymethoxy)methyl]-3-isopropylcyclopentane (17). The amide **16b** (774 mg, 2.6 mmol) in THF (15 mL) was treated with lithium triethylborohydride (6.5 mmol, 6.5 mL). After 8 h at room temperature, the reaction mixture was quenched by slow addition of 3 M sodium hydroxide (3 mL) and 30% hydrogen peroxide (3 mL) and stirred for 2 h. The reaction mixture was taken up in methylene chloride, and the organic layer was washed successively with 10% solutions of hydrochloric acid, sodium bicarbonate, and brine and dried. Evaporation of the solvent followed by flash chromatography (petroleum ether–EtOAc, 4:1) yielded 433 mg (72.3%) of **17** as a colorless oil: $[\alpha]^{20}_D$ −58.87° (c 1.04, $CHCl_3$); IR (neat) 3450 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 2 H, OCH_2O), 3.69 (dd, J = 9.0 and 2.7 Hz, 1 H, OH), 3.55–3.30 (m, 4 H, H-6, H-7), 3.37 (s, 3 H, OCH_3), 1.72–1.22 (m, 7 H, H-2, H-3, H-4, H-5, H-8), 0.96 (s, 3 H, CH_3), 0.88 (d, J = 6.6 Hz, 3 H, CH_3), 0.82 (d, J = 6.6 Hz, 3 H, CH_3). Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 67.79; H, 11.32.

(1*S*,2*S*,3*S*)-1-Methyl-1-(2-iodoethyl)-2-[(methoxymethoxy)methyl]-3-isopropylcyclopentane (2). A mixture of the alcohol **17** (40 mg, 0.174 mmol), triphenylphosphine (183 mg, 0.696 mmol), and imidazole (47 mg, 0.696 mmol) in toluene (5 mL) under argon was treated with iodine (133 mg, 0.522 mmol). The reaction mixture was stirred at 80 °C for 5 h, followed by addition of saturated aqueous sodium bisulfite solution (2 mL). After all solids had dissolved, ethyl acetate (10 mL) was added, and the organic layer was washed with saturated aqueous sodium bicarbonate solution and brine and then dried. Evaporation of the solvent, followed by flash chromatography (petroleum ether–EtOAc, 29:1), gave **2** as a coloreless oil (55 mg, 93%): $[\alpha]^{20}_D$ −3.65° (c 1.37, $CHCl_3$); IR (neat) 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 s, (2 H, OCH_2O), 3.52–3.29 (m, 4 H, CH_2O, CH_2I), 3.34, (s, 3 H, OCH_3), 1.81 (m, 1 H, H-2), 1.70–1.30 (m, 6 H, H-3, H-4, H-5, H-8), 1.04 (s, 3 H, CH_3), 0.87 (d, J = 6.3 Hz, 3 H, CH_3), 0.83 (d, J = 6.4 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.62, 68.95, 55.43, 48.79, 48.37, 44.94, 40.75, 30.67, 25.45, 23.69, 21.91, 20.81, 17.72. Anal. Calcd for $C_{13}H_{25}O_2I$: C, 45.89; H, 7.41. Found: C, 46.06; H, 7.43.

The Nine Contiguous Chiral Centers in Streptovaricin A via Pyranosidic Homologation[1]

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A tripyranoside **2** has been prepared whose 10-carbon chain is folded so as to afford mutual internal protection of acetal groups. A cis-anti-trans stereosurface is thereby provided which allows for stereocontrolled development of eight of the nine contiguous asymmetric centers of the ansa chain of streptovaricin A. The "upper" acetal ring is cleaved, and the ninth stereocenter is installed in intermediate **10** by using acyclic stereocontrol principles. The remaining acetal is then opened, and the functional groups exposed thereby are manipulated. All nine stereocenters are created with high stereoselectivity, and the termini of the resulting array, **14b**, are suitably differentiated for eventual coupling with the pseudoaromatic residue.

We have recently reported a strategy termed "pyranosidic homologation" for the rational synthesis of structures with multiple contiguous asymmetric centers.[3] The polychiral arrays of the ansamycins, exemplified by the ansa chain of streptovaricin A, **1**,[4] are targets of choice, and in this context, the first plateau was attained with the conversion of a D-glucopyranose derivative into dipyranoside **3**[5a] and thence tripyranoside **2**,[5b] as outlined in Scheme I. The tandem advantages of these systems for (a) stereocontrol resulting from their conformational bias, and (b) ease of configurational assignments via ^{1}H NMR studies, which has been the raison d'etre of the pyranosidic homologation strategy,[3c] were fully realized in the synthesis and verification of **2**.[5b]

The acetals of **2**, which had provided reciprocal internal protection of functional groups while concomitantly defining the cis-anti-trans stereochemical surface, now had to be destroyed as a prelude to further elaboration toward compound **1**, which is, to our knowledge, the most complex assembly of *contiguous* chiral centers in the chemical literature[6] and was therefore chosen for that reason. In this paper, we describe the realization of the 12-carbon array **4** as an advanced precursor for **1**. In **4**: (i) all nine contiguous stereocenters have been created, (ii) all stereocenters have been verified without the need for X-ray analysis, (iii) the termini are differentiated so as to facilitate eventual connection to the prefabricated *pseudo*-aromatic moiety of streptovaricin A, (iv) the C-7 oxygen is differentiated from other hydroxyl groups so that eventually it can be uniquely acetylated, as required in **1**.

Treatment of tripyranoside **2**[5b] with 1 equiv of DDQ caused selective cleavage of the glycosidic 2,4-dimethoxybenzyl groups, and the resulting hemiacetal was reduced, paving the way to the C6-alcohol, **5a**. However, a problem

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