(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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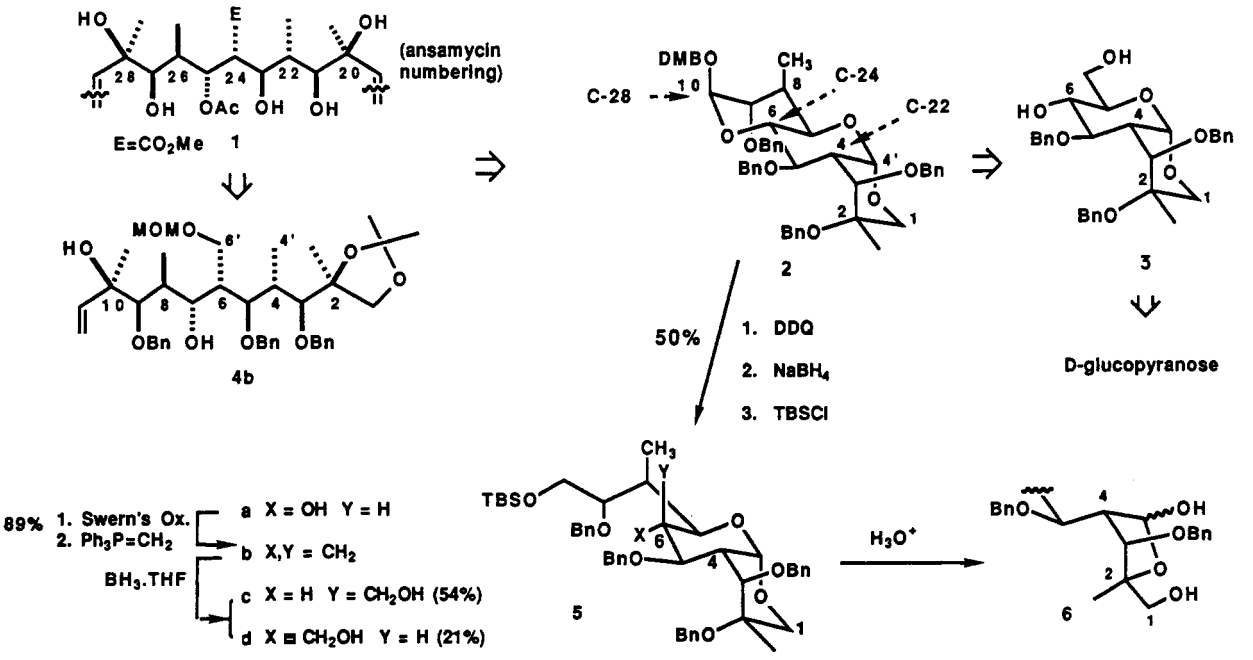
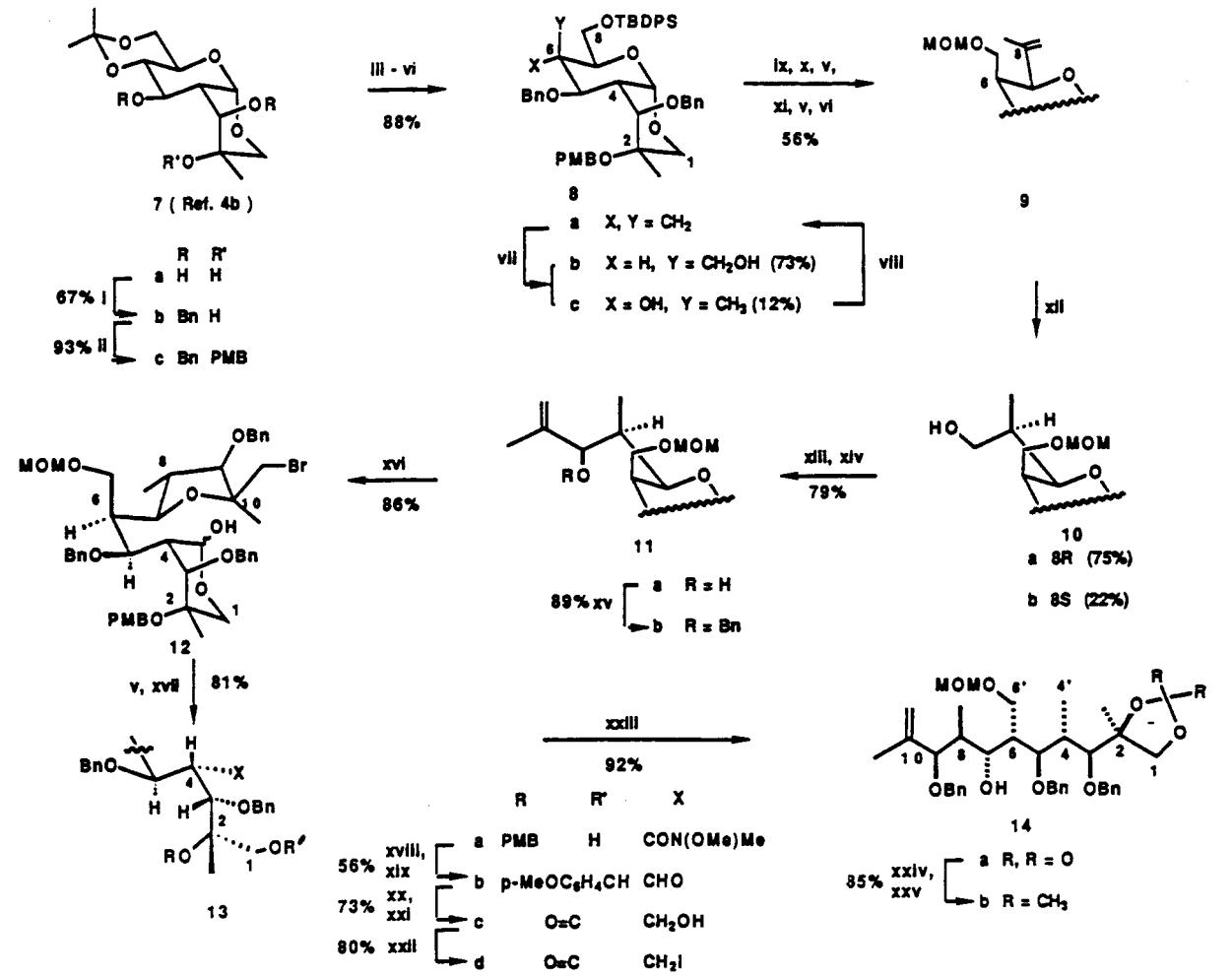
Scheme I

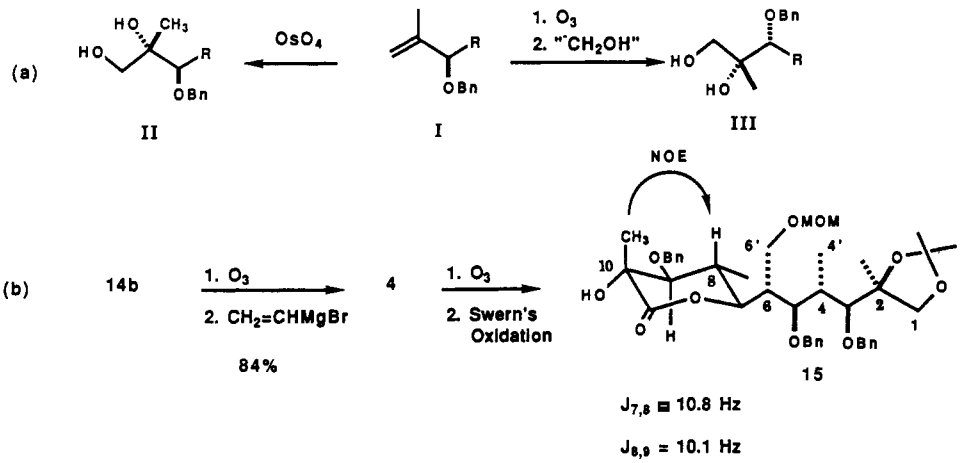


Scheme II[a]



[a] (i) NaH, BnBr, THF–DMF (10:1); (ii) NaH, PMBCl, DMF, *n*-Bu_4NI; (iii) THF–H_2O, HCl; (iv) TBDPSCl, Et_3N, DMAP, CH_2Cl_2; (v) Swern's Oxid.; (vi) $Ph_3P{=}CH_2$; (vii) BH_3–THF, 0 °C, then Na_2O_2; (viii) $SOCl_2$, py, 0 °C; (ix) MOMCl, Hunig's base, CH_2Cl_2; (x) CsF, 18-crown-6, DMSO, 60 °C; (xi) MeMgCl, THF, −78 °C; (xii) 9-BBN, THF then Na_2O_2; (xiii) PCC, Celite, Florisil, NaOAc, CH_2Cl_2; (xiv) isopropenylmagnesium bromide, THF, −90 °C; (xv) NaH, BnBr, DMF, *n*-Bu_4NI; (xvi) NBS, $NaHCO_3$, CH_3CN; (xvii) $Me_2Al(NMe)OMe$, CH_2Cl_2; (xviii) DDQ, MS 4 Å, CH_2Cl_2; (xix) LAH, ether; (xx) $NaBH_4$, EtOH, then H_3O^+; (xxi) $COCl_2$, py, CH_2Cl_2; (xxii) I_2, Ph_3Ph, imidazole, PhH; (xxiii) Zn, NH_4Cl, EtOH, reflux; (xxiv) MeLi, ether, −78 °C; (xv) 2,2-dimethoxypropane, CSA, CH_2Cl_2.

Scheme III



arose when the sequence involving oxidation, olefination, and hydroboration[7] was found to be poorly selective, giving a 3:1 mixture of the epimers **5c** and **5d**. A second problem was encountered when it was found that pyranose to furanose (e.g., **5** → **6**) rearrangement occurred readily.

Fortuitously, both problems could be solved consecutively. Thus, it transpired that the rearrangement **5** → **6** was related to the electrophilic nature of the C2-oxygen[8a] and could therefore be overcome by changing the O2 protecting group. This task was facilitated by the fact that the key dipyranosidic triol **7a**[5b] afforded the di-*O*-benzyl ether **7b** selectively,[5b] thereby enabling formation of the C2 *p*-methoxybenzyl derivative **7c**. It was then found that, unlike the case of **5b**, hydroboration of the derived alkene **8a** gave the axial product **8b** as the only primary alcohol.[7] A byproduct in this case was the tertiary alcohol **8c**, which could be recycled through dehydration to olefin **8a**.

The C-8 primary center of **8b** was converted into the alkene **9** via a series of routine operations; hydroboration gave the primary alcohol **10** as the major product,[7] and addition of isopropenylmagnesium bromide to the derived aldehyde gave the allylic alcohol **11a**, which upon benzylation gave the desired alkene **11b**.[9]

Structure **11b**, after removal of the C2 *p*-methoxybenzyl group and treatment with benzyl bromide, was identical with the material obtained from **5c** by desilylation, oxidation, and reaction with isopropenylmagnesium bromide. This observation therefore establishes the link with the advanced pyranosidic homologation product **5**.

The remaining tasks were (a) opening of the internal acetal, and (b) creation of the C-10 tertiary alcohol. Task (a) could have been a major obstacle; however, a recent serendipitous observation in our laboratory has shown that a remote electrophilic center can provide a gentle, nonacidic implement for cleavage of an acetal.[8] Indeed, treatment of alkene **11b** with *N*-bromosuccinimide afforded the (bromomethyl)tetrahydrofuran derivative **12**.

In view of the aforementioned acid-catalyzed rearrangement **5** → **6**, nonacidic conditions were desirable for further processing of **12**. The best protocol examined[9] proved to be based on Weinreb's strategy for amination of lactones.[10] Thus, oxidation of **12** to the lactone and cleavage with $Me_2AlN(OMe)Me$ afforded the amide **13a**. Oxidation with DDQ led to the 1,2-cyclic acetal, which, upon reduction with lithium aluminum hydride, afforded the aldehyde **13b**. Reduction of the latter to the primary alcohol and replacement of the *p*-methoxybenzyl group at O-2 were carried out via standard procedures to give the hydroxy carbonate **13c**. Reaction of the derived bis-halo compound **13d** with zinc and ammonium chloride furnished the C4-CH_3 and simultaneously restored the isopropenyl moiety in **14**.

The remaining task was to generate the C-10 tertiary alcohol, and for this, we relied on the principles of acyclic stereoselection. Two complementary pathways from alkene I, summarized in Scheme IIIa, should lead to the epimers, II and III, based on the empirical observations in the laboratories of Kishi,[11] Cram,[12] and Still.[13]

Clearly, it was the latter pathway that would be required here. Accordingly, after minor adjustments in the protecting groups, ozonolysis of **14** (Scheme IIIb), followed by addition of vinylmagnesium bromide, afforded compound **4**, whose C-10 configuration was verified by conversion into lactone **15** for ^1H NMR analysis. Thus, the parameters shown in Scheme III establish conclusively that (a) the conformation of the lactone ring was as depicted, and (b) the configuration at C-10 was indeed *R*, as desired for **2b**.

Compound **4**, possessing characteristics (i) → (iv) outlined earlier, is therefore ready for attachment to a suitable synthon for the pseudoaromatic portion of streptovaricin A. Further developments in this plan will be described in due course.

Supplementary Material Available: Details for the preparation of **4**, **5**, **9–12**, **13a,d**, **14b**, and **15** (11 pages). Ordering information is given on any current masthead page.

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