A Carbohydrate Approach to the Enantioselective Synthesis of 1,3-Polyols

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Treatment of per-*O*-benzoyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**2**) with tertiary amines afforded selectively and with good yields the (5*H*)-furan-2-one derivatives **3**, **4**, and **5**, formed by controlled elimination of one, two, or three molecules of benzoic acid, respectively. The stereochemistry for the exocyclic double bonds of **4** and **5** was determined by means of NMR techniques. Particularly, the furanone **4** was obtained from **2** (∼90% yield) as a mixture of the *E* and *Z* diastereoisomers, which were separated by column chromatography or, more efficiently, by HPLC. The catalytic hydrogenation of compounds **4**-*E* and **4**-*Z* took place diastereoselectively, due to the chiral induction of the stereocenter located in the lateral chain. Thus, hydrogenation of **4**-*E* led to a mixture of the 4,5-dihydro-(3*H*)-furan-2-ones having 3*R*,5*S*,2′*S* (D-*xylo*, **6**) and 3*S*,5*R*,2′*S* (D-*arabino*, **7**) configurations, with **6** as the major product; whereas the **4**-*Z* isomer gave the same mixture, but being **7** preponderant. On hydrogenation of the original **4**-*E*/*Z* mixture, compound **6** was obtained pure after recrystallization. *O*-Debenzoylation of **6** gave **9**, which was reduced with $NaBH_4$ to the 3,5-dideoxy-*meso*-*xylo*-heptitol (**11**). The peracetate (**12**) and perbenzoate (**13**) of the latter were prepared, and the 1-(*tert*-butyldiphenylsilyl)oxy derivative (**16**) was also synthesized *via* the 3′-(silyloxy)-4,5-dihydro-(3*H*)-furan-2-one **14**. Chemoselective reduction of the lactone function of **6** with diisoamylborane gave the 2,5,6-tri-*O*-benzoyl-3,6-dideoxy-D-*xylo*-heptofuranose (**17**). The 3,5-dideoxy-D-*arabino*-heptitol (**18**), a diastereoisomer of **11**, was also isolated and characterized.

Introduction

In recent years, diverse strategies for the synthesis of extended 1,3-polyol chains have been developed.[1,2] The interest in pursuing such studies arises from the occurrence of a complex array of 1,3-polyhydroxyl functions in polyene macrolide antibiotics, which are employed in the treatment of systemic fungal infections.[3] Those studies culminate in the total synthesis of some members of such a class of antibiotics, as amphotericin B,[4] pimarolide,[5] mycoticin A,[6] and roxaticin.[7]

Hanessian *et al.*[8] used the "replicating chiron" procedure for the synthesis of seven carbon subunits having a predictable 1,3-substitution pattern. The sequence employs (*S*)-glutamic acid as chiral template, and 3,5-dideoxyheptonolactones are involved as intermediates. The attraction of using a carbohydrate as a chiral template resides in its appropriate functionalization, its flexibility in the length of carbon chains, and that its manipulation usually provides stereochemical control. Furthermore, previous work from our laboratory[9] has shown that 3,5-dideoxylactones are readily prepared from aldonolactones. Particularly, starting from an aldoheptono-1,4-lactone, such as commercially available D-*glycero*-D-*gulo*-heptono-1,4-lactone (**1**), a furanone (**4**), and hence a 3,5-dideoxylactone (**6** or **7**), similar to those involved as intermediates in the Hanessian's procedure,[8] could be obtained. The chiral center in the furanone is expected to induce stereoselection during the hydrogenation.

We describe here the above-mentioned carbohydrate approach to the enantioselective synthesis of 1,3-polyol fragments.

Results and Discussion

Benzoylation of D-*glycero*-D-*gulo*-heptono-1,4-lactone (**1**) at room temperature for 2 h afforded the per-*O*-benzoyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**2**) in good yield.[10] However, the benzoylation of **1** with a large excess of benzoyl chloride and pyridine, for long periods (16 h), led to a mixture of furanone derivatives (**3**−**5**), resulting from successive eliminations of benzoic acid.[11] The extent of the elimination can be controlled by adjusting the reaction conditions. Thus, treatment of **2** with 1 mol equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane (−15 °C, 15 min) gave crystalline **3** in 67% yield.[12] Under optimized conditions (20% triethylamine in chloroform, room temperature, 45 min) the furanone

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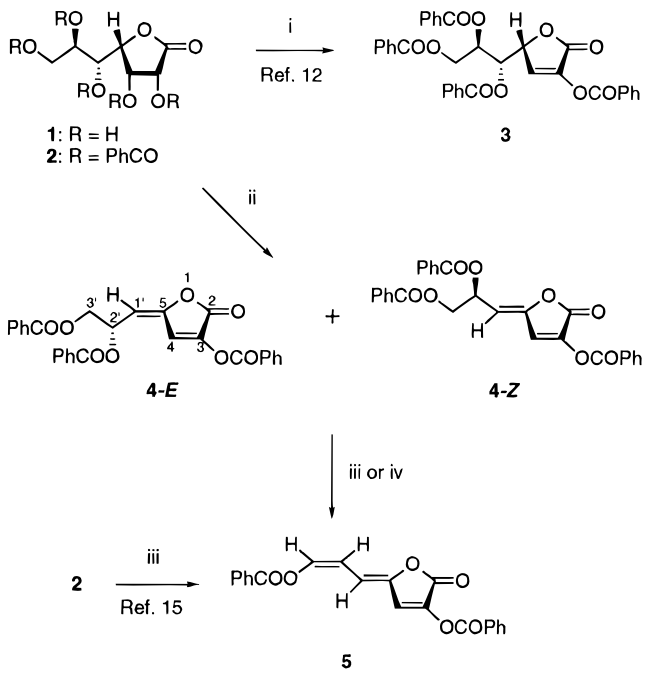
Scheme I[a]



[a] (i) DBU, CH_2Cl_2, −15 °C 15 min (67%); (ii) Et_3N, $CHCl_3$, rt, 45 min (90% from **2**); (iii) Et_3N, $CHCl_3$, rt, 6−10 h (60−80% from **2**); (iv) $SnCl_4$, CH_2Cl_2, rt.

4 was now obtained in ∼90% yield from **2**. The product showed two close spots by TLC, and its spectral data indicated that the two theoretically possible diastereoisomers for the C-5−C-1′ double bond had been formed. The mixture was partially separated by column chromatography. The ^{1}H NMR spectrum (Table 1) of the less polar product showed the H-1′ resonance at lower field (5.91 ppm) than that of the other isomer (5.49 ppm), suggesting a *cis* disposition for H-1′ and the furanone-ring oxygen atom,[13] and hence an *E* configuration for the exocyclic double bond. Furthermore, this compound showed, in agreement with the assigned structure, a long-range coupling constant $^4J_{4,1'}$ (0.8 Hz)—not observed for the other isomer—characteristic of a *transoid* disposition[14] for H-4 and H-1′. The identity of both diastereoisomers was firmly established by nuclear Overhauser effect difference spectroscopy (NOEDS). Selective saturation of the H-1′ signal (5.49 ppm) of the more polar isomer gave rise to a positive NOE (23%) over the H-4 signal (7.53 ppm), indicating a *Z* configuration. On the other hand, on saturation of H-1′ (5.91 ppm) of the other isomer, no enhancement of the H-4 signal was observed.

Once the structure of the furanones **4**-*E* and **4**-*Z* were established, their ratio in the original mixture was determined by the integral of the H-1′ signal for each diastereoisomer. Thus, the **4**-*Z*:**4**-*E* ratio was estimated as 1.2:1. Similar proportions were obtained by HPLC separation of **4**-*E*,*Z*. This procedure allowed us to recover, almost quantitatively, each of the pure diastereoisomers.

The elimination of benzoic acid from the perbenzoylated aldoheptonolactone **2**, which leads to the furanones **3**−**5**, takes place in successive steps. The H-3, vicinal to the carbonyl group in 4,5-dihydro-(3*H*)-furan-2-one derivatives, is acidic, as on removal produces a resonance-stabilized carbanion, which may rearrange with elimination of the benzoyloxy group at C-4. We have proposed[15] an E1cB mechanism for the formation of (5*H*)-furan-2-ones, such as **3**. The introduction of an endocyclic double bond favors the abstraction of H-5, being the resulting carbanion stabilized by conjugation with an α,β-unsaturated carbonyl group, and also an E1cB mechanism would operate during the second elimination, which leads to **4**. A further elimination of benzoic acid from **4** afforded the triunsaturated derivative **5**. However, the elimination from **4** to give **5** follows a different pathway, as the benzoyloxy group remains on C-3′, and that on C-2′ is eliminated. A mechanism similar to that proposed for the elimination of the allylic substituents in pyran-2-ones[16] could be involved. This process would start with the formation of an incipient allylic carbocation on C-2′, by breaking of the C-2′−OCOPh bond, followed by abstraction of H-3′ by a base. Since allylic esters produce carbocation intermediates on treatment with hard Lewis acids,[17] the furanone **4** was allowed to react with tin(IV) chloride in dichloromethane. Gradual conversion of **4** into **5** was observed, although tarry polymeric byproducts were formed. On the other hand, **5** can be readily prepared by prolonged treatment of **2** with triethylamine.[15]

The spectral data of the furanone **5** showed that we were dealing with a single stereoisomer. The ^{1}H NMR spectrum was completely assigned by single-frequency resonance (SFD) experiments. The coupling constant between H-2′ and H-3′ ($J_{2',3'}$ 6.2 Hz) suggests a *cis* relationship for those protons, whereas the large $J_{1',2'}$ value (11.8 Hz) would indicate a *s-trans* conformation along the C-1′−C-2′ bond. The stereochemistry for the exocyclic double bonds was conclusively confirmed by NOEDS experiments. Thus, selective irradiation at the H-1′ frequency (6.42 ppm) afforded positive NOE (20%) over the H-4 signal (7.62 ppm), indicating a *Z* configuration for the double bond on C-5. Similarly, saturation of the H-2′ signal resulted in an enhancement (18%) of the H-3′ signal (7.59 ppm), dictating also a *Z* configuration for the C-2′−C-3′ double bond. Interestingly, the **5** (*Z*,*Z*) was the only crystalline isomer (60−80% yield) isolated on reaction of **2** with 20% triethylamine in chloroform for 6 h. Also, when pure **4**-*E* and **4**-*Z* were treated separately with triethylamine, the **5** (*Z*,*Z*) isomer was obtained. This result indicates that **4**-*E* undergoes isomerization of the exocyclic double bond during (or before) the last elimination. In fact, we have observed that the isomerization of **4**-*E* into **4**-*Z* (and *vice versa*) is faster than the elimination of the allylic benzoyloxy group.

Hydrogenation of **4**-*E*,*Z* with Pd/charcoal as a catalyst afforded a syrup, which crystallized from ethanol. After successive recrystallizations from methanol, a single isomer from the four theoretically possible was obtained. The 500 MHz ^{1}H NMR spectrum of this product showed nicely resolved signals, which were readily assigned. The assignments were confirmed by a homonuclear 2D NMR COSY experiment. As we have previously described,[18] and in agreement with earlier studies on the elucidation

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Table 1. ^{1}H NMR Data for Compounds 4−12 and 14−18

	δ (ppm), J (Hz)								
compd	H-3 ($J_{3,4}$) ($J_{3,4'}$)	H-4 ($J_{4,5}$)	H-4′ ($J_{4',5}$) ($J_{4,4'}$)	H-5 ($J_{5,1'}$) ($J_{5,1''}$)	H-1′ ($J_{1',2'}$)	H-1″ ($J_{1'',2'}$) ($J_{1',1''}$)	H-2′ ($J_{2',3'}$)	H-3′ ($J_{3',3''}$)	H-3″ ($J_{2',3''}$)
4-*E*		7.60 ($J_{4,1'}$ 0.8 Hz)			5.91 (9.8)		6.22 (5.3)	4.68	
4-*Z*		7.53			5.49 (8.3)		6.43 (5.2)	4.70	
5		7.62 ($J_{4,1'}$ 0.5 Hz)			6.42 (11.8)		6.23 (6.2)	7.59 ($J_{1',3'}$ 1.0 Hz)	
6	5.70 (8.6) (10.6)	2.97 (5.6)	2.15 (10.4) (12.7)	4.73 (9.9) (4.6)	2.31		5.72 (3.8)	4.68 (12.0)	4.54 (5.7)
7	5.69 (8.6) (10.5)	3.06 (5.5)	2.17 (10.5) (12.7)	∼4.73 (∼7.5) (4.8)	2.52 (∼7.5)	2.24 (5.8) (14.7)	5.66 (3.5)	4.64 (12.1)	4.61 (5.6)
8		*a* (1.8)		5.31 (9.4) (3.8)	2.49 (9.1)	2.12 (3.9) (14.8)	5.78 (3.9)	4.72 (12.0)	4.56 (5.4)
9[b]	∼4.70 (8.0)	2.80 (5.0)	1.85[c]	∼4.70	1.85[c]		3.89 (3.8)	3.60 (11.7)	3.49 (6.2)
10	5.45 (8.6) (10.6)	2.79 (5.5)	2.01[c] (10.5) (12.7)	4.50	2.01[c]		5.22 (3.7)	4.31 (12.0)	4.05 (5.4)
14	4.54 (8.4) (10.9)	2.71 (5.2)	1.89 (10.8) (13.3)	4.66	1.74[c]		4.01 (3.6)	3.69 (10.2)	3.52 (7.0)
15	4.46 (8.1) (10.7)	2.28 (5.3)	1.90 (10.7) (12.6)	4.40	1.65		3.95 (3.5)	3.69 (10.2)	3.49 (7.0)

	H-1 ($J_{1,2}$)	H-1′ ($J_{1',2}$) ($J_{1,1'}$)	H-2 ($J_{2,3}$) ($J_{2,3'}$)	H-3 ($J_{3,4}$)	H-3′ ($J_{3,3'}$)	H-5	H-5′	H-4 ($J_{3',4}$)	H-6	H-7	H-7′
11[b]	3.61 (4.0)	3.49 (6.8) (11.6)	3.94		1.59[c]			4.05	3.94	3.61	3.49
12	4.23 (4.0)	3.95 (6.0) (12.0)	5.06[c]		1.83[c]			5.06[c]		4.23	3.95
16	3.67−3.43		4.00		1.57			4.19	4.00	3.67−3.43	
17[d]	5.58 (<1)		5.33 (6.0) (2.2)	2.66 (8.0)	1.82 (14.0)	2.20		4.60[c] (6.0)	5.70	4.60[c]	
18[b]	3.67−3.35		3.89[c]		1.68−1.59			4.01	3.89[c]	3.67−3.35	

[a] Overlapped with *H*-aromatic. [b] In D_2O. [c] Center of a complex multiplet. [d] Data for the β anomer.

of the geometry of 4,5-dihydro-3,5-disubstituted-(3*H*)-furan-2-ones,[19] the large values for the coupling constants between H-4,4′ with H-3 and H-5 indicate a *threo* relationship for the substituents on C-3 and C-5. Therefore, the chiral centers of the compound should have a 3*R*,5*S*,2′*S* (D-*xylo*) or 3*S*,5*R*,2′*S* (D-*arabino*) configuration. As described later, the absolute configuration was established as D-*xylo* (**6**), as chemical transformations performed on the compound led to a *meso* alditol.

The mother liquors of recrystallization of **6** showed by TLC two spots, the major product having R_f 0.35 (as **6**) and the other R_f 0.43. The mixture was separated by column chromatography. The NMR spectral data demonstrated that, against our expectations, the less polar component was not the D-*arabino* isomer **7** but the (5*H*)-furan-2-one **8**, produced by saturation of the exocyclic double bond of **4**. The ^{1}H NMR spectrum of **8** clearly showed the ABX pattern of the lateral chain-methylene groups at C-1′ and C-3′ coupled with H-2′. The configuration for **8** was established as *threo*, as on hydrogenation the dideoxylactone **6** was exclusively obtained. Therefore, the addition of hydrogen to the double bond of **8** took place with excellent diastereofacial selectivity from the side opposite to the exocyclic chain. This result agrees with previous observations from this[18] and other laboratories[20] on the stereochemistry of the hydrogenation of analogous (5*H*)-substituted-furan-2-ones.

Table 2. ^{13}C NMR Data for Compounds 4−18

	δ (ppm) (50.3 MHz)						
compd	C-2	C-3	C-4	C-5	C-1′	C-2′	C-3′
4-*E*	162.5	140.2	120.1	150.4	108.5	67.6	65.1
4-*Z*	162.5	139.4	122.7	147.8	109.3	67.7	64.8
5	162.6	138.4	123.5	145.4	107.2	106.0	137.9
6	171.4	69.2*	37.7#	73.5	35.5#	68.9*	65.2
7	171.6	68.8	36.9#	73.4	35.2#	68.8	65.1
8	162.6	137.9	*a*	75.8	36.0	69.1	65.1
9[b]	180.4	69.1*	39.0#	76.1	37.9#	68.9*	66.3
10	171.3	68.0*	36.3#	73.0	34.4#	67.9*	64.2
14	177.3	68.5	38.9*	74.1	37.5*	68.5	67.9
15	175.0	69.8	39.0*	72.8	38.7*	68.5	67.9

	C-1	C-2	C-3	C-4	C-5	C-6	C-7
11[b]	66.8	69.5	41.1	65.3	41.1	69.5	66.8
12	64.9	67.4	35.6	65.6	35.6	67.4	64.9
13	65.3	68.6	35.6	67.8	35.6	68.6	65.3
16[c]	68.0#	68.6#	42.1*	63.8	42.3*	68.8#	66.7#
17[d]	106.6	74.6	38.2*	79.2	35.9*	70.2	65.9
18[b]	66.8*	69.3	40.9#	66.2*	40.4#	70.6	66.6*

[a] Overlapped with *C*-aromatic. [b] In D_2O. [c] In DMSO-d_6. [d] Data for the β anomer. * and # signals may be interchanged.

The second component of the mixture isolated from the column, which had the same R_f as **6**, gave more complex NMR spectra than **6**. For example, the 500 MHz ^{1}H NMR spectrum showed additional signals at δ 3.06 (ddd, H-4), 2.17 (q, H-4′), 2.52 (ddd, H-1′), and 2.24 (ddd, H-1″). In the ^{13}C NMR spectrum (Table 2) of the product, distinctive signals appeared in the region of the methylene carbons (C-4,1′). The presence of the D-*arabino* isomer **7** was therefore established.

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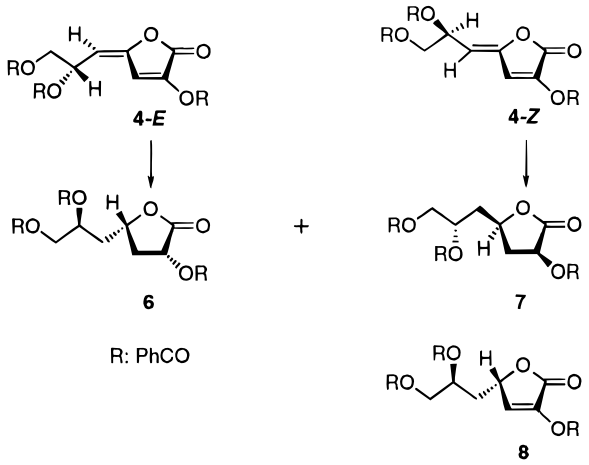
Scheme 2



In order to determine the ratio of **6** and **7**, the crude mixture of hydrogenation of **4**-*E*,*Z* was subjected to quantification on the basis of the NMR integral of the characteristic signals for each isomer. The data were confirmed by HPLC quantification of the free alditols, which were obtained by *O*-debenzoylation followed by $NaBH_4$ reduction of **6** and **7** (see later), as the alditols could be readily separated by that technique. Thus, on catalytic hydrogenation (10% Pd/C) of **4**-*E*,*Z*, a 1.4:1 ratio for **6**:**7** was obtained. This result indicates that the stereocenter at C-2′ exerts some stereocontrol during the hydrogenation. When **4**-*E* was hydrogenated under conditions identical to those employed for **4**-*E*,*Z*, a moderately higher diastereoselectivity was observed (ratio **6**:**7**, 2:1). Interestingly, although less selective, hydrogenation of **4**-*Z* led to the D-*arabino* (**7**) as the major stereoisomer (ratio **7**:**6**, 1.2:1). When the furanones **4**-*E* and **4**-*Z* were hydrogenated using $Pd/BaSO_4$ as catalyst a somewhat higher selectivity was observed. Thus, **4**-*E* afforded **6** and **7** in a 3:1 ratio, whereas **4**-*Z* gave a 1:1.4 ratio for the same products. However, attempted hydrogenations in homogeneous phase with a rhodium catalyst (Wilkinson catalyst) were extremely slow, and starting material was found to remain unreacted even after 40 h of reaction.

The diastereofacial selectivity observed for the furanones having a different configuration for the exocyclic double bond may be explained if the hydrogenation occurs under conformational control. Conformations having the C−H bond eclipsing the C=C bond are known to be preferred for allylic systems.[21,22] The large value for $J_{1',2'}$ in **4**-*E* and **4**-*Z* is indicative that they adopt preferentially such a conformation, as depicted in Scheme 2. Assuming that this conformational preference is reflected in the transition state, the stereochemistry of the major product would arise from the preferential approach of hydrogen to the face of the exocyclic double bond opposite to that containing the allylic benzoyloxy group. This explanation agrees with the fact that the stereoselection is higher for **4**-*E* than for **4**-*Z*; since the smaller $J_{1',2'}$ value for the latter suggests the presence of other eclipsed rotamers in the conformational equilibrium, which might react by a different reagent approach. Our results are in excellent agreement with the Kishi's empirical rule[23] for the osmylation of allylic alcohol systems.

The *O*-debenzoylation of **6** was accomplished with sodium methoxide in methanol, to afford syrupy heptonolactone **9**. Conventional acetylation of **9** afforded the tri-*O*-acetyl derivative **10** in 92% yield (from **6**). Direct reduction of **6** with lithium aluminum hydride led to the corresponding polyol (**11**) in 89% yield. The ^{13}C NMR spectrum of the product showed only four signals, indicating a symmetric structure for the 3,5-dideoxyheptitol **11** and, hence, a *meso-xylo* absolute configuration. The conversion of **6** into **11** was also performed by employing lithium borohydride in tetrahydrofurane,[24] affording a yield similar to that obtained in the reaction with lithium aluminum hydride. On the other hand, reduction of the free dideoxyheptonolactone **9** with excess of sodium borohydride in methanol gave **11** in 99% yield.

In order to facilitate the spectroscopic characterization of **11**, some derivatives were synthesized. Thus, acetylation of **11** afforded the *meso*-1,2,4,6,7-pentaacetoxypentane (**12**). The ^{13}C NMR spectrum of **11** showed three close signals in the region of 64−69 ppm, which were assigned by a ^{13}C NMR-APT experiment. Signals at 64.9 and 35.6 ppm, having inverse phase, were atributed to C-1,7 and C-3,5, respectively. The normal phase signals at 67.4 and 65.6 ppm, with an intensity ratio of aproximately 2:1, were identified as the resonances of C-2,6 and C-4, respectively. The benzoylated polyol **13** was also prepared, and its ^{13}C NMR spectrum was assigned by comparison with that of **11**.

A polyol derivative having one of the primary hydroxyl groups selectively protected would be useful for the elongation of the polyol chain from the opposite extreme. Such a derivative could be readily achieved by selective protection of the primary hydroxyl group (HO-3′) of **9** by silylation, followed by reduction of the lactone function. Thus, treatment of **9** with 1.2 equiv of *tert*-butylchlorodiphenylsilane and imidazole gave mainly the 3′-*O*-silyl derivative **14**, together with the 3,3′-di-*O*-silyl derivative **15** as a byproduct. Besides the primary hydroxyl group, the HO-3 of saturated furanones is also reactive, and disubstituted products are usually obtained on silylation[25] or esterification.[26] The lactone function of **14** was reduced with $NaBH_4$, to give the desired 1-*O*-silylated polyol **16**. As expected, the ^{13}C NMR spectrum of **16** showed differentiated resonances for the seven carbons of the polyol chain.

On the other hand, the lactone group of **6** may be selectively reduced to give a benzoylated derivative of the 3,5-dideoxy-D-*xylo*-heptofuranose (**17**), having the anomeric hydroxyl group unprotected. The reduction of the carbonyl lactone of **6** was chemoselectively performed with diisoamylborane,[27] affording the lactol derivative **17** with a very good yield (∼80%). The ^1H NMR spectrum of **17** showed a singlet ($J_{1,2}$ < 1 Hz) in the anomeric region (5.58 ppm). The small value for $J_{1,2}$ indicates[28] a β-con-

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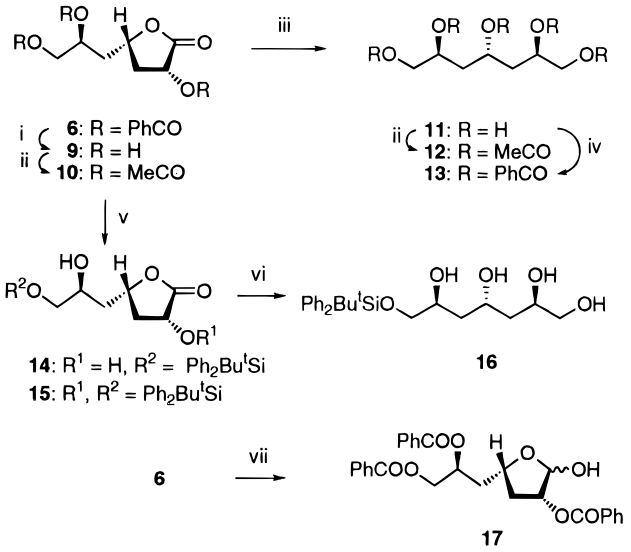
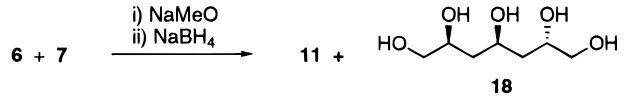
Scheme 3[a]



[a] (i) NaMeO−MeOH, 2 h, rt; (ii) $(MeCO)_2O$, C_5H_5N, 16 h, rt; (iii) $LiAlH_4$, THF, 6 h, rt (from **6**); or $LiBH_4$, THF, 6 h, reflux (from **6**); or $NaBH_4$, MeOH, 2 h, rt (from **9**); (iv) PhCOCl, C_5H_5N, 2 h, rt; (v) Ph_2Bu^tSiCl, imidazole, DMF, 14 h, rt; (vi) $NaBH_4$, MeOH, 4 h, rt; (vii) $(Me_2CHCHMe)_2BH$, THF, 20 h, rt.

Scheme 4



figuration for the major anomer. This assignment was confirmed by the ^{13}C NMR spectrum of **17**, which showed two signals at 100.6 and 94.6 ppm, in a 7:1 ratio, due to the resonances of C-1β and C-1α. Compound **17** also constitutes a synthetic equivalent of an alternate *anti*, *anti* polyol fragment with a different functionalization on each extreme.

In order to obtain the free alditol having the D-*arabino* configuration (**18**), the crude mixture of hydrogenation of **4**-*E*,*Z*, containing almost equal proportions of **6** and **7**, was subjected to *O*-debenzoylation followed by sodium borohydride reduction. The separation of the resulting mixture of *meso*-*xylo*- (**11**) and D-*arabino*- (**18**) 3,5-dideoxyalditols could be readily accomplished by HPLC. Compound **11** showed the same physical and spectroscopic properties as the product previously synthesized from pure **6**. The ^1H and ^{13}C NMR spectra of **18** were more complex than those of **11**, as expected for an asymmetric compound.

In summary, we report here easy routes for the access to 1,3-polyol chains of defined stereochemistry. Particularly, compound **11**, which was readily prepared from furanones **4**-*E*/*Z* can be identified in the C-16−C-22 and C-18−C-24 fragment constituents of the polyene macrolide antibiotics roxaticin[7] and mycoticin A and B,[6] respectively. Those fragments may undergo chain elongation from each of the extremes by procedures already described[1,7] to generate the required *syn* or *anti* geometry between hydroxyl groups.

Experimental Section

General Procedures. All NMR spectra were performed in $CDCl_3$, unless otherwise indicated. Column chromatography was carried out on silica gel 60, 240−400 mesh (Merck). Analytical TLC was performed on silica gel 60 F_{254} (Merck) precoated plates (0.2 mm), with 9:1 toluene−EtOAc as solvent, except when otherwise specified. Visualization of the spots was effected by exposure to UV light or charring with a solution of 10% sulfuric acid in EtOH, containing 0.5% *p*-anisaldehyde.

(5E)-3-(Benzoyloxy)-5-[(2′*S*)-2′,3′-bis(benzoyloxy)propylidene]-(5*H*)-furan-2-one (4-*E*) and (5*Z*)-3-(Benzoyloxy)-5-[(2′*S*)-2′,3′-bis(benzoyloxy)propylidene]-(5*H*)-furan-2-one (4-*Z*). To a solution of 2,3,5,6,7-penta-*O*-benzoyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone[10] (**2**, 2.20 g, 3.02 mmol) in dry chloroform (20 mL) was added triethylamine (1.9 mL, 13.3 mmol) under nitrogen. The mixture was stirred in the dark, at room temperature (rt) for 45 min, when monitoring by TLC showed two main spots (R_f 0.56 and 0.61) and no starting material (R_f 0.37). The solution was diluted with CH_2Cl_2 (300 mL), washed with 1 M aqueous HCl (2 × 100 mL), saturated aqueous NaCl (100 mL), and saturated aqueous $NaHCO_3$ (100 mL), dried ($MgSO_4$), and concentrated. The ^1H NMR spectrum of the resulting syrup showed almost exclusively the presence of the *E*- and *Z*-furanone derivatives (**4**). The mixture was partially separated by column chromatography, employing 10:1 hexane−EtOAc.

Fractions containing the faster moving product (R_f 0.61) were combined and concentrated to afford syrupy **4**-*E* (0.29 g, 20%), which gave the following: $[\alpha]_D = -97.2$ (*c* 1.3, $CHCl_3$); IR (film, cm^{-1}) 1780 (CO-1,4-lactone), 1740 (CO-enolic benzoate), 1710 (CO-benzoate); UV (methanol) λ_{max} (nm) 232 (ϵ 38 000), 276 (ϵ 31 000). Anal. Calcd for $C_{28}H_{20}O_8$: C, 69.42; H, 4.16. Found: C, 69.58; H, 4.19.

On concentration of the fractions which gave a single spot having R_f 0.56, syrupy compound **4**-*Z* (0.37 g, 25%) was obtained: $[\alpha]_D = -61.1$ (*c* 1.9, $CHCl_3$); IR (film, cm^{-1}) 1780, 1740, 1710; UV (methanol) λ_{max} (nm) 230 (ϵ 37 000), 275 (ϵ 30 000). Anal. Calcd for $C_{28}H_{20}O_8$: C, 69.42; H, 4.16. Found: C, 69.50; H, 4.21.

From intermediate fractions of the column was obtained a mixture **4**-*E*,*Z* (0.59 g, overall yield 85%) was obtained.

HPLC separation of the original **4**-*E*,*Z* mixture (0.50 g) was carried out employing an Ultrasphere ODS 5 μm (Alltech) column, with 15% MeOH−water (3 mL/min). The products were eluted as follows: **4**-*E* (t_R 15.2 min, 0.19 g, 38%), **4**-*Z* (t_R 20.2 min, 0.25 g, 50%), and a mixture **4**-*E*,*Z* (0.05 g, 10%).

(5Z)-3-(Benzoyloxy)-5-[(*Z*)-3′-(benzoyloxy)-2′-propenylidene]-(5*H*)-furan-2-one (5). **(a) By Treatment of 2 with Tertiary Amines.** It was synthesized[15] by reaction of **2** with 20% Et_3N in $CHCl_3$ for 6 h (mp 151−152 °C). Other amines, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or pyridine, were also effective for the preparation of **5**, but the yields were lower than when Et_3N was used.

(b) By Tin(IV) Chloride-Promoted Elimination from 4. To a solution of **4**-*E*/*Z* (0.10 g, 0.21 mmol) in CH_2Cl_2 (2 mL) was added $SnCl_4$ (0.051 mL, 0.42 mmol) at 0 °C under nitrogen. The mixture was stirred at rt, and TLC showed gradual conversion of **4** (R_f 0.56 and 0.61) into **5** (R_f 0.71). After 15 h, spots of similar intensity, corresponding to **4** and **5**, were observed, but the solution darkened and a tarry precipitate (R_f 0.0) appeared. After 24 h of reaction, complete decomposition was observed.

(3*R*,5*S*)-3-(Benzoyloxy)-5-[(2′*S*)-2′,3′-bis(benzoyloxy)propyl]-4,5-dihydro-(3*H*)-furan-2-one (6), Its (3*S*,5*R*,2′*S*) Diastereomer (7), and (5*S*)-3-(Benzoyloxy)-5-[(2′*S*)-2′,3′-bis(benzoyloxy)propyl]-(5*H*)-furan-2-one (8). (a) Hydrogenation of 4-*E*/*Z*. The diastereomeric mixture **4**-*E*/*Z* (3.14 g, 6.48 mmol) dissolved in EtOAc (20 mL) was hydrogenated in the presence of 10% Pd/C (0.30 g) at atmospheric pressure for 12 h. The catalyst was filtered, and the filtrate concentrated to a syrup, which slowly crystallized upon addition of EtOH (2.22 g, 70%). After four successive recrystallizations from MeOH, compound **6** was obtained as white needles (0.950 g, 30% yield): mp 139−140 °C; $[\alpha]_D = -50$ (*c* 1, $CHCl_3$); R_f 0.35; IR (Nujol, cm^{-1}) 1790, 1720. Anal. Calcd for $C_{28}H_{24}O_8$: C, 68.85; H, 4.95. Found: C, 68.96; H, 5.20.

The mother liquors of crystallization and recrystallization were combined and concentrated. The resulting syrup showed by TLC a main product, having the same R_f (0.35) as **6**, and a

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small proportion of a faster migrating component (R_f 0.43). The mixture was chromatographed using 12:1 toluene−EtOAc as eluent. The compound having R_f 0.43 was obtained as an amorphous solid (0.022 g, 0.7%), and it was characterized as (5*S*)-3-(benzoyloxy)-5-[(2′*S*)-2′,3′-bis(benzoyloxy)propyl]-(5*H*)-furan-2-one (**8**): $[\alpha]_D = -19$ (*c* 1.3, $CHCl_3$); IR (Nujol, cm^{-1}) 1775, 1735, 1720. Anal. Calcd for $C_{28}H_{22}O_8$: C, 69.13; H, 4.56. Found: C, 69.03; H, 4.67.

Evaporation of the solvent from the fractions that contained the product of R_f 0.35 gave a syrup (0.28 g) which did not crystallized from EtOH. The ^1H and ^{13}C NMR spectra of the product revealed that **6** was mixed with another fully saturated furanone, which was further identified as the (3*S*,5*R*,2′*S*) diastereoisomer **7**.

The mixture of **6** and **7** could not be separated at this stage by chromatographic techniques, including HPLC. However, the proportions of **6** and **7** in the crude mixtures of hydrogenation were determined by the integral of differentiated signals in the ^1H and ^{13}C NMR spectra of such mixtures. The ratio of **6** and **7** was also established by the sequence of *O*-debenzoylation followed by lactone reduction, which led to the corresponding alditols **11** and **18**. The proportions of both polyols in the mixtures was determined by HPLC, since they gave peaks having different t_R, as described below.

(b) Hydrogenation of 4-*E*. Compound **4**-*E* (0.593 g, 1.224 mmol) was hydrogenated in the presence of 10% Pd/C under the conditions described above. The crude product showed a **6**:**7** ratio of 2:1. Two recrystallizations from MeOH afforded **6** (0.281 g, 47%), which gave the same physical constants as those reported in a.

(c) Hydrogenation of 4-*Z*. Compound **4**-*Z* (0.402 g, 0.83 mmol) was hydrogenated as described in a. The ratio of **6**:**7** in the crude product was determined as 1:1.2. The product did not crystallize. After chromatographic purification with solutions of increasing polarity of hexane−EtOAc, a syrupy mixture of **6** and **7** (0.29 g, 71%) was obtained.

Hydrogenations of pure **4**-*E* and **4**-*Z* and of the original mixture **4**-*E*/*Z* were also performed by employing 10% Pd/$BaSO_4$. The hydrogenation mixtures were processed and quantified as described above. The following ratios for **6**:**7** were obtained: 3:1 (from **4**-*E*), 1:1.4 (from **4**-*Z*), 1.5:1 (from **4**-*E*/*Z*).

(3*R*,5*S*)-3-Hydroxy-5-[(2′*S*)-2′,3′-dihydroxypropyl]-4,5-dihydro-(3*H*)-furan-2-one (9). To a suspension of **6** (1.135 g, 2.317 mmol) in anhydrous MeOH (30 mL) was added a 1.18 M solution of NaOMe in MeOH (5.9 mL) at 0 °C. The mixture was allowed to reach rt, and it was stirred until complete consumption of **6** (2 h). The solution was made neutral upon addition of Dowex 50W (H^+) resin suspended in MeOH. The resin was filtered and the filtrate concentrated to a syrup, which showed by TLC an intense spot having R_f 0.45 (4:1 EtOAc−EtOH). The syrup was dissolved in water (100 mL), and the solution was extracted with 2:1 toluene−Et_2O (45 mL, twice). Upon evaporation of the water, the colorless oil obtained (0.40 g, 98%) was purified by column chromatography (4:1 EtOAc−EtOH) to give syrupy **9** (0.36 g, 88%): $[\alpha]_D = -55.1$ (*c* 0.9, H_2O). Anal. Calcd for $C_7H_{12}O_5$: C, 47.58; H, 6.87. Found: C, 47.36; H, 7.00.

(3*R*,5*S*)-3-Acetoxy-5-[(2′*S*)-2′,3′-diacetoxypropyl]-4,5-dihydro-(3*H*)-furan-2-one (10). Compound **6** (0.15 g, 0.85 mmol) was *O*-debenzoylated as described above. The crude syrup obtained was dissolved in pyridine (5 mL), and acetic anhydride (4 mL) was added at 0 °C. The mixture was stirred overnight at rt and then poured into ice−water (120 mL). After 0.5 h, it was extracted with CH_2Cl_2 (4 × 50 mL) and the extract washed with 2 M aqueous HCl (60 mL), water (60 mL), and saturated aqueous $NaHCO_3$ (60 mL), dried ($MgSO_4$), and concentrated. The residue (R_f 0.44, 9:1 toluene−*i*PrOH) was chromatographed with 15:1 chloroform−acetone, affording syrupy **10** (0.21 g, 81% from **6**): $[\alpha]_D = -26.3$ (*c* 2.5, $CHCl_3$). Anal. Calcd for $C_{13}H_{18}O_5$: C, 51.65; H, 6.00. Found: C, 51.72; H, 6.17.

3,5-Dideoxy-*meso*-*xylo*-heptitol (11). (a) By $LiAlH_4$ Reduction of 6. To a 0.5 M solution of $LiAlH_4$ in THF (18 mL), cooled at 0 °C was slowly added a solution of **6** (0.532 g, 1.09 mmol) in THF (8 mL) under nitrogen. The reaction mixture was allowed to reach rt, and it was stirred for 6 h, when the starting material (**6**) had been completely converted into a product of R_f 0.45 (2:2:1 *n*PrOH−EtOH−water). The solution was cooled at 0 °C and wet Et_2O was added, in order to destroy the remaining $LiAlH_4$. The mixture was carefully diluted with water (100 mL) and filtered. The solid residue was washed with water (3 × 30 mL) and then with boiling methanol (5 × 40 mL). The filtrate and washings were combined, concentrated to ∼20 mL, and desalted with Amberlite MB-3 resin. Compound **11** was obtained as a colorless oil (0.186 g, 95%): R_f 0.45 (2:2:1 *n*PrOH−EtOH−water), essentialy pure according to its NMR spectra. Column chromatography (1.5:1 EtOAc−MeOH) of a portion of the crude oil (0.08 g) afforded an analytical sample of **11** (0.071 g, 89%): $[\alpha]_D = 0.0$ (*c* 1.7, H_2O); HPLC t_R 9.3 min in a LiChrospher 100 NH_2 5 μm (Merck) column, with 8:1 acetonitrile−water (1.5 mL/min). Anal. Calcd for $C_7H_{16}O_5$: C, 46.66; H, 8.95. Found: C, 46.55; H, 9.11.

(b) By $LiBH_4$ Reduction of 6. Compound **6** (0.89 g, 1.82 mmol) was added, under nitrogen, to a freshly prepared 0.36 M solution of $LiBH_4$ in THF (10 mL). The mixture was heated under reflux for 6 h and then stirred at rt for an additional 12 h. Anhydrous MeOH (2 mL) was added, and after 1 h of stirring, the solution was treated with Dowex 50W (H^+) resin, filtered, and concentrated. The residue was dissolved in MeOH and the solvent evaporated, in order to eliminate the boric acid. This procedure was repeated 5 times. The polyol **11** was obtained as an essentially pure, colorless syrup (0.308 g, 94%), with the same properties as the product described in a.

(c) By $NaBH_4$ Reduction of 9. To a solution of **9** (0.364 g, 2.066 mmol) in MeOH (6 mL) was added an excess of $NaBH_4$ (0.20 g). The mixture was stirred for 2 h at rt, when TLC showed complete conversion of **9** (R_f 0.68, 3:2 $CHCl_3$−MeOH) into a more polar compound (R_f 0.48). The solution was neutralized with Dowex 50W (H^+) resin, filtered, and evaporated twice with MeOH, to give syrupy **11** (0.368 g, 99%), whose NMR spectrum was identical to that of the product described in a.

Isolation of 11 and 3,5-Dideoxy-D-*arabino*-heptitol (18) from the Mixtures of 6 and 7. The crude mixture of hydrogenation of **4**-*E*/*Z* was treated with 0.15 M NaOMe, followed by decationization with Dowex 50W (H^+) resin, and then reduced with an excess of $NaBH_4$ in MeOH (2 h). The solution was neutralized again with resin and concentrated to a syrup, which was redissolved in a small volume of MeOH and filtered through a C-8 MAXI-CLEAN cartridge (Alltech). The resulting mixture of polyols **11** and **18** was separated by HPLC, employing a LiChrospher 100 NH_2 5 μm (Merck) column, with 8:1 acetonitrile−water (1.5 mL/min). Compounds **18** and **11** gave peaks having t_R 7.9 and 9.3 min, respectively. Syrupy **18** gave $[\alpha]_D = -22$ (*c* 0.7, H_2O).

(3*R*,5*S*)-3-Hydroxy-5-[(2′*S*)-3′-*tert*-[(butyldiphenylsilyl)-oxy]-2′-hydroxypropyl]-4,5-dihydro-(3*H*)-furan-2-one (14) and (3*R*,5*S*)-3[(*tert*-Butyldiphenylsilyl)oxy]-5-[(2′*S*)-3′-[(*tert*-butyldiphenylsilyl)oxy]-2′-hydroxypropyl]-4,5-dihydro-(3*H*)-furan-2-one (15). Compound **6** (1.20 g, 2.46 mmol) was *O*-debenzoylated as described above. The resulting crude syrup was dissolved in anhydrous DMF (3 mL), and imidazole (0.42 g, 6.15 mmol) and *tert*-butylchlorodiphenylsilane (TBDPSCl, 0.39 mL, 1.48 mmol) were added. The mixture was stirred for 4 h at rt, and an equal amount of TBDPSCl was added. The stirring was maintained for a further 10 h, when TLC (3:2 hexane−acetone) showed two main spots having R_f 0.41 and 0.80. The mixture was diluted with CH_2Cl_2 (100 mL), and the solution was washed with dilute aqueous HCl (100 mL) and water (2 × 100 mL), dried ($MgSO_4$), filtered, and evaporated, to yield a colorless oil (1.19 g). The oil was subjected to column chromatography, employing mixtures of increassing polarity of toluene−EtOAc (from 5:1 to 1:1). Compound **15** (0.353 g, 22%) was isolated first. Further fractions from the column afforded the lower moving component (R_f 0.41), which was characterized as **14** (0.612 g, 60%). It gave $[\alpha]_D = -5.0$ (*c* 1, $CHCl_3$). Anal. Calcd for $C_{23}H_{30}O_5Si$: C, 66.64, H; 7.29. Found: C, 66.53; H, 7.60.

1-*O*-(*tert*-Butyldiphenylsilyl)-3,5-dideoxy-L-*xylo*-heptitol (16). Lactone **14** (93 mg, 0.224 mmol) was reduced under the same conditions as described for **9**, to give a colorless syrup (97 mg) of R_f 0.18 (3:2 hexane−acetone). After purification by column chromatography (2:1 hexane−acetone), pure **16** (47 mg, 50%) was obtained. It gave $[\alpha]_D = -0.7$ (*c* 1.3, $CHCl_3$). Anal. Calcd for $C_{23}H_{34}O_5Si$: C, 65.99; H, 8.19. Found: C, 66.20; H, 8.38.

2,6,7-Tri-*O*-benzoyl-3,5-dideoxy-α,*β*-D-*xylo*-heptofuranose (17). To a freshly prepared solution of bis(3-methyl-2-butyl)borane[27] (10 mmol) in THF (8 mL), cooled at −10 °C, was added compound **6** (1.20 g, 2.4 mmol) dissolved in THF (5 mL). The solution was stirred for 20 h at rt, and water (1 mL) was added dropwise. The mixture was stirred for an additional 0.5 h and then cooled at 0 °C; 30% H_2O_2 was slowly added, while the pH was maintained between 7 and 8 with 1 M NaOH. The THF was evaporated, and the residue was extracted with CH_2Cl_2 (3 × 75 mL); the extract was washed with saturated aqueous NaCl (80 mL), dried ($MgSO_4$), and concentrated. The resulting syrup was dissolved in methanol, followed by evaporation, in order to eliminate boric acid. The procedure was repeated four times, affording **17** (1.14 g, 95%) as a chromatographically homogeneous syrup (R_f 0.33, 4:1 toluene−EtOAc). Column chromatography led to syrup **17** (0.94 g, 78%): $[\alpha]_D = -16$ (*c* 2.5, $CHCl_3$). The ^{13}C NMR spectrum (25 MHz, $CDCl_3$) showed the two signals for the β and α anomers at 106.6 and 94.6 ppm, respectively, in a 7:1 ratio. Anal. Calcd for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.71; H, 5.42.

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