$C_{2:6}$, $C_{3a:4a:7a:8a}$ is obvious (Figure 8).

Conclusions

The charge alternation concept is presented, and its application to cyclic doubly charged conjugated systems is discussed. The charge density was deduced from calculation and compared with experimental data ($\Delta\delta^{13}C$ in the carbon NMR spectra). It can be concluded that charge alternation is indeed a characteristic feature of this type of compounds. It seems that in order to reduce Coulombic repulsions, the charge is not spread uniformly but is concentrated at certain positions in *an alternating mode*. This alternation leads to a donor-acceptor type interaction which is more stabilizing than a simple uniform charge distribution. Interestingly, it has been found that the more the negative charge is located on two carbons, the more is the *positive* charge concentrated on the atom in between them. We have presented rules which permit the prediction of the location of the main charges either on the starred or on the nonstarred set of subsystems. In the case of the charged annulenes there is no exception to the charge alternation rules, while in polycyclic systems the deviations, if any, are found particularly in the inner carbons of pericondensed systems.

In our study we describe examples in which the charge alternation prevails covering a wide range of K_c values from -1 ppm/e for $\mathbf{14}^{2-}$ up to the biphenylene case (**17**) for which K_c is equal to 174 ppm/e.[7b] Therefore, it can be concluded that the charge alternation which is a basic characteristic of these systems prevails regardless of the magnitude of K_c.

The approach presented here is very simple and empirical and seemingly rather naïve. The charges in a dianion of an alternant hydrocarbon depend mainly on the HOMO of this dianion, and thus such a simple treatment as the one presented here cannot always be correct. However, one has to consider to what extent the HOMO of the dianion depends on the eventual distribution of the charges in the dianion, since it is the charge alternation stabilization that is the physical effect, and the MO's are only a manifestation of these effects. The fact that charge alternation does take place in diatropic and paratropic π-conjugated charged systems and that the charges there are distributed nonuniformly proves that this is a powerful and fundamental effect in chemistry.

Experimental Section

The procedure for the metal reduction process was as described previously.[3c,d,15,16] The 2D NMR spectra were obtained on a Bruker SY-200 pulsed FT spectrometer equipped with a pulse programmer operating at 200.133 and 50.32 MHz for ^1H and ^{13}C NMR, respectively. Field frequency regulations were maintained by ^2H locking. The free induction decay (FID) signals were digitized and accumulated on an Aspect-2000 computer. All 2D NMR experiments (such as COSY, NOESY, and $^{13}C/^1H$ correlation spectroscopy) used for assignment of spectra were carried out according to standard pulse sequences appearing in the Bruker Library (DISN 85). The MO calculations were performed by the "$\omega\beta$" technique[9] amplified by the habitual parameters. For =N- and the aromatic C-N and N-N bonds we used the following parameters:[9c] $\alpha(N) = \alpha(C) + 0.4\beta(C-C)$, $\beta(C-N) = \beta(-C-C)$, $\beta(N-N) = \beta(C-C)$. For $\mathbf{2a}^{2+}$ the parameters were $\alpha(C_{9:10}) = \alpha(C) - 0.1\beta(C-C)$ and for the CH_3 substituents $\alpha(C) = \alpha(C) - 0.2\beta(C-C)$, $\alpha(\equiv H_3) = \alpha(C) - 0.5\beta(C-C)$, $\beta(C_{9:10}-C) = 0.7\beta(C-C)$, and $\beta(C\equiv H_3) = 2.5\beta(C-C)$. For $\mathbf{2b}^{2+}$ the $\beta(C-C)$ for the bond connecting the phenyl substituents was taken as $0.5\beta(C-C)$.

Registry No. **1**, 85-01-8; $\mathbf{1}^{2-}$, 113584-95-5; **2**, 120-12-7; $\mathbf{2}^{2-}$, 113584-96-6; $\mathbf{2}^{2+}$, 34531-06-1; **2a**, 781-43-1; $\mathbf{2a}^{2+}$, 38418-02-9; **2b**, 1499-10-1; $\mathbf{2b}^{2+}$, 70470-09-6; **3**, 216-00-2; $\mathbf{3}^{2+}$, 113685-58-8; **4**, 216-01-3; $\mathbf{4}^{2-}$, 113584-97-7; **5**, 230-17-1; $\mathbf{5}^{2-}$, 94370-25-9; **6**, 92-24-0; $\mathbf{6}^{2+}$, 38418-05-2; **7**, 129-00-0; $\mathbf{7}^{2-}$, 95596-53-5; $\mathbf{7}^{2+}$, 60670-21-5; **8**, 113597-87-8; $\mathbf{8}^{2-}$, 113597-89-0; **9**, 113597-88-9; $\mathbf{9}^{2-}$, 113597-90-3; **10**, 14458-51-6; $\mathbf{10}^{2-}$, 113685-61-3; $\mathbf{10}^{2+}$, 113685-60-2; **11**, 208-96-8; $\mathbf{11}^{2-}$, 113584-98-8; **12**, 201-06-9; $\mathbf{12}^{2-}$, 113584-99-9; **13**, 206-44-0; $\mathbf{13}^{2-}$, 113685-59-9; **14**, 194-32-1; $\mathbf{14}^{2-}$, 69743-13-1; **15**, 10474-65-4; $\mathbf{15}^{2-}$, 113585-00-5; **16**, 217-22-1; $\mathbf{16}^{2-}$, 66560-56-3; **17**, 259-79-0; $\mathbf{17}^{2-}$, 72843-96-0; $\mathbf{17}^{2+}$, 62157-22-6; **18**, 248-58-8; $\mathbf{18}^{2-}$, 65583-99-5; **19**, 275-51-4; $\mathbf{19}^{2-}$, 78851-03-3; **20**, 70600-15-6; $\mathbf{20}^{2-}$, 113585-01-6.

Electrophilic Additions to 3-*C*-[(Methoxycarbonyl)methyl]-3-deoxy-D-ribofuranose Enolates: A Case of Unusually Efficient Non-Chelate-Enforced Chirality Transfer†

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Contribution from Institut für Organische Chemie der Freien Universität, Takustrasse 3, D-1000 Berlin 33, FRG, Institut für Kristallographie der Freien Universität, Takustrasse 6, D-1000 Berlin 33, FRG, and Institut für Anorganische Chemie der Freien Universität, Fabeckstrasse 34-36, D-1000 Berlin 33, FRG. *Received August 7, 1987*

Abstract: The enolates **4a,b** obtained from ester **3a** on deprotonation with lithium diisopropylamide in THF and THF/HMPA, respectively, add alkyl halides and benzaldehyde with >99% diastereoselectivity to form **3c-f**. The structure of **3b** was established by X-ray crystallography via the corresponding 5,6-diol **3i**. This unusually high chirality transfer is not due to a chelate-controlled mechanism, as the partially deoxygenated derivatives **9d**, **10d**, and **11c** show the same or a slightly diminished selectivity on deprotonation/methylation. The steric course of the enolate alkylation may be described as a "frontside" attack of the electrophile on reactive conformation A. Furthermore, the stereochemistry of the deprotonation of **3a,b** was investigated by using the stereospecifically deuteriated model compounds **21a-d** and **22**. It was shown that the amide base attacks from the "front side" of the molecule, the reactive conformation of the substrate now being of type B, in contrast to the alkylation.

Chirality may be incorporated into ester enolates by means of the alcohol (O-chiral case) or the carboxylic acid (C-chiral case) component. In either case, efficient stereocontrol of electrophilic additions to a prochiral enolate carbon may be exerted by chelate-enforced chirality transfer, particularly in chelate rings of sizes 5-7.[1] In contrast to the configurationally unrestricted O-chiral case, chelate formation in C-chiral ester enolates requires *E* geometry around the double bond. This demand contradicts Ireland's rule,[2] according to which *Z*-enolates are generated with

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.
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⊥ Institut für Anorganische Chemie der Freien Universität.

(1) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3B, p 1-110.

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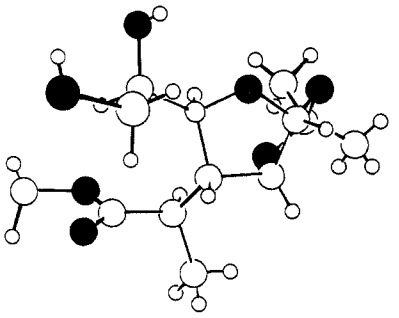
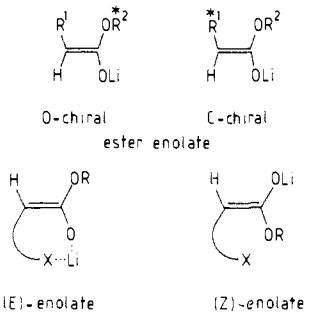
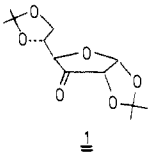


Figure 1. Crystal structure of **3i** (oxygens, large black circles; carbons, large white circles; hydrogens, small white circles).

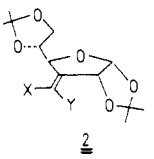
high selectivity under the very conditions inducing chelate formation. This means either that Ireland's rule does not apply in this situation or that chelate formation is of no relevance to the chirality transfer mechanism. Both alternatives apparently have been realized under appropriate circumstances. Thus, the presence of a β-alkoxide substituent induces the formation of an *E*-enolate and a chelate-enforced chirality transfer mechanism,[3] whereas a β-silicon function leads to the formation of a nonchelate *Z*-enolate.[4a] Chelate participation has also been disputed for systems with β-tin and γ-alkoxy groups.[4b]



To gain more insight into the influence of "intramolecular" ether and acetal functions on the steric course of enolate formation and alkylation and to define the reactive conformations in both processes more precisely, we chose the highly oxygenated ester derivatives **3a,b**, readily available[5] from ulose **1** via the unsaturated esters **2a–d**. The stereochemistry of the Horner olefination **1** → **2** highly depends on the size of the ester group. So we found a ratio of **2a**:**2b** = 2.7:1 (^{1}H NMR analysis) whereas for **2c**:**2d** the ratio was raised to 90:10. The configuration of **2c** was secured by X-ray analysis. Catalytic hydrogenation of **2** proceeded from the β-face of the allofuranose exclusively,[5] generating **3a,b** in diastereomerically pure form.

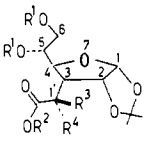


1



2

2	X	Y
a	H	CO_2Me
b	CO_2Me	H
c	H	CO_2-*t*-Bu
d	CO_2-*t*-Bu	H



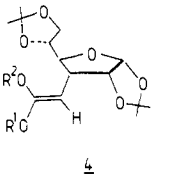
3

3	R^1	R^2	R^3	R^4
a	$-CMe_2-$	Me	H	H
b	$-CMe_2-$	*t*-Bu	H	H
c	$-CMe_2-$	Me	Me	H
d	$-CMe_2-$	Me	$CH_2CH{=}CH_2$	H
e	$-CMe_2-$	Me	CH_2Ph	H
f	$-CMe_2-$	Me	CH(OH)Ph	H
g	$-CMe_2-$	*t*-Bu	Me	H
h	$-CMe_2-$	Me	H	Me
i	H	Me	Me	H
j	H	*t*-Bu	H	H
k	H	Me	H	H
l	H	*t*-Bu	Me	H
m	$-CMe_2-$	Me	Me	$CH_2CH{=}CH_2$
n	$-CMe_2-$	Me	$CH_2-CH{=}CH_2$	Me

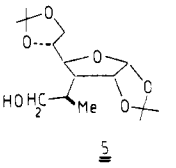
Stereochemical Results

On treatment with lithium diisopropylamide (LDA, 3 molar equiv) at −78 °C, **3a** quantitatively formed an enolate **4a,b** whose double-bond geometry was determined by Corey's internal quench procedure.[6] The (*E*/*Z*)-*O*-silyl ketene acetals **4c,d** were formed in the expected[2] highly solvent dependent ratio, which was **4c**:**4d** = 97:3 in THF and 15:85 in THF/HMPA (4/1). The *E*/*Z* assignments of **4c,d** are based on the ^{1}H NMR data reported by Ireland for simpler systems.[2] On studying the steric course of electrophilic additions to **4**, we found that **4a**, generated from **3a** in THF at −78 °C, adds alkyl halides and benzaldehyde to form compounds **3c–f** with >99% diastereoselectivity according to ^{1}H and ^{13}C NMR and HPLC analysis. This selectivity was also observed for the *tert*-butyl ester **3b**, which furnished pure **3g** on analogous deprotonation/methylation. Compound **3g** was correlated with **3c** by reducing both compounds to the same alcohol **5** and proving the identity of the material obtained from both sources by ^{1}H and ^{13}C NMR and HPLC data and optical rotation.

Compound **4b**, generated in THF/HMPA (4/1), also gave stereochemically pure (>99%) **3c** (**3d**) on treatment with methyl iodide (allyl bromide), which indicates that the sense and the magnitude of the asymmetric induction is independent of the enolate geometry and only results from the overall structure of the molecule. This behavior is characteristic of a C-chiral enolate and in contrast to the O-chiral type where the facial selectivity is reversed with the change of the enolate configuration.



4



5

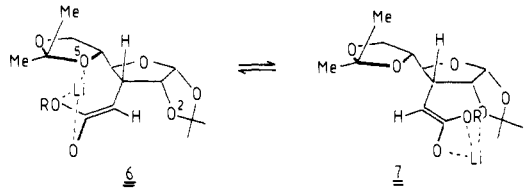
4	R^1	R^2
a	Li	Me
b	Me	Li
c	$SiMe_3$	Me
d	Me	$SiMe_3$

The 1′*R* configuration of **3c** was established via the corresponding 5,6-diol **3i**, which was submitted to a crystal structure analysis (Figure 1). On the basis of this assignment, the configurations of **3d,e** could be deduced from the ^{1}H NMR spectra. Compounds **3a–e** uniformly show a coupling constant of $J_{1',3}$ = 10 Hz, indicating an antiperiplanar arrangement of H-1′ and H-3. The C-2–C-3–C-1′–C-2′ all-anti conformation present in the crystal structure of **3i** may be assumed for **3a–e** as well, which in combination with $J_{1',3}$ means a 1′*R* configuration for these

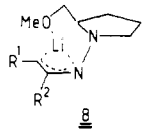
(2) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(3) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825. Frater, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269. Kurth, M. J.; Yu, Ch.-M. *J. Org. Chem.* **1985**, *50*, 1840.
(4) (a) Bernhard, W.; Fleming, I.; Waterson, D. J. *J. Chem. Soc., Chem. Commun.* **1984**, 28. (b) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435.
(5) Rosenthal, A.; Nguyen, L. *J. Org. Chem.* **1969**, *34*, 1029.
(6) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

compounds. As an additional confirmation, **3c** was epimerized (LDA, then MeOH) to give a 1:1 mixture of **3c** and **3h** with clearly distinguishable ^1H NMR spectra. Compound **3h** shows a coupling constant for $J_{1',3} = 6.5$ Hz, consistent with a syn arrangement of H-1′ and H-3 and, hence, a 1′*S* configuration. Moreover, with the required analytical data in hand, we were able to confirm the absence of **3h** in the formation of **3c**. The structure of the benzaldehyde adduct **3f** has not been established; only one out of four possible stereoisomers was formed, indicating that both the enolage (**4a**) and the aldehyde show high facial selectivity in the aldol type addition.

The Question of Chelate-Induced Chirality Transfer. The diastereoselectivity exhibited by **4a,b** toward electrophiles ranks among the highest ever found for exocyclic ester enolates.[1] On looking for mechanistic interpretations, it was quite natural to consider some sort of chelate intermediate, at least in the case of **4a**, where no HMPA is involved.[7] In view of the *Z*-enolate structure, however, such chelate species cannot be of the regular σ-type, with an essentially coplanar arrangement of the lithium cation and two chelating oxygen donors. Instead, the π-type sandwich complexes **6/7** had to be envisaged, analogous to species **8**, which has been postulated by Enders[8] for prolinol derived azaallyl derivatives.

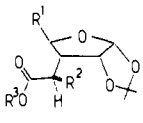


6 **7**



8

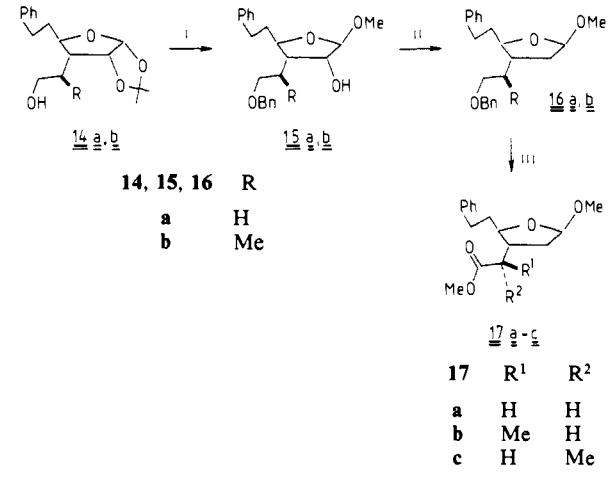
In **6/7**, O-2 and O-5 only may be used for chelate formation, as O-1, O-6, and the endocyclic O-7 are too far away from a lithium attached to the *Z*-enolate oxygen. To test the possibility of O-5 chelation, we prepared the 5-deoxygenated model compounds **9d,e** from **3a** via **3k** and **9a–c** as intermediates. Analogously, the 1′(*R*)-methyl derivatives **10d,e** were synthesized from **3c**, via **3i** and **10a-c**. Methylation of **9d** and **9e** under the usual conditions (LDA; THF, −78 °C, and then MeI) furnished stereochemically pure **10d,e**, respectively, identical in every respect (^1H and ^{13}C NMR, HPLC, and optical rotation) with the material directly obtained from **3c**. The same result was obtained for the pair **11/12c**, analogously prepared from **3b,g** via **3i,l** and **11/12a,b**. The synthesis of the 2,5-dideoxygenated model compounds **17a,b** (Scheme I) required some additional operations. We were unable to open the 1,2-acetonide ring of **9**, **10e** without immediate formation of the 2,3-annulated γ-lactones **13a,b**, even when starting from the *tert*-butyl esters **11/12c**. Hence, it was necessary to reduce **9**, **10e** and **11/12c** to **14a,b** and after O-benzylation open the acetonide with methanol and acid. In the resulting alcohols **15a,b**, the unprotected 2-OH function could straightforwardly be removed to give **16a,b** by using the Barton–McCombie protocol.[9] Compounds **16a,b** had to be debenzylated with sodium in ammonia; the use of hydrogen and a palladium catalyst led to anomerization at C-1. Two-step oxidation of the alcohol, first to the aldehyde by the Pfitzner–Moffat procedure[10] and then with buffered potassium permanganate[11] to the carboxylic acid and treatment with diazomethane afforded **17a,b**.



9 - **12**

	R^1	R^2	R^3
9a	CH=O	H	Me
9b	CH=CHCH=CH_2	H	Me
9c	CH=CHPh	H	Me
9d	*n*-Bu	H	Me
9e	CH_2CH_2Ph	H	Me
10a	CH=O	Me	Me
10b	CH=CHCH=CH_2	Me	Me
10c	CH=CHPh	Me	Me
10d	*n*-Bu	Me	Me
10e	CH_2CH_2Ph	Me	Me
11a	CH=O	H	*t*-Bu
11b	CH=CHPh	H	*t*-Bu
11c	CH_2CH_2Ph	H	*t*-Bu
12a	CH=O	Me	*t*-Bu
12b	CH=CHPh	Me	*t*-Bu
12c	CH_2CH_2Ph	Me	*t*-Bu

Scheme I[a]



14, 15, 16 R

a H

b Me

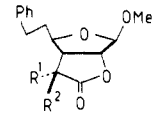
17 R^1 R^2

a H H

b Me H

c H Me

[a] i, (1) NaH, DMF, BnCl, 22 °C, 4 h; (2) *p*-TsOH, MeOH, 22 °C, 24 h. ii, NaH, CS_2, MeI, reflux in Et_2O, and then *n*-Bu_3SnH, AIBN, toluene, 100 °C, 1 h. iii, (1) Na, NH_3, −50 °C, 3 min; (2) DMSO, pyridine, CF_3CO_2H, DCC in toluene, 22 °C, 18 h; (3) $KMnO_4$ in H_2O-1-butanol, phosphate buffer, 22 °C, 10 min; (4) CH_2N_2, Et_2O–MeOH, 22 °C.



13 R^1 R^2

a H H

b Me H

c H Me

Methylation as usual converted **17a** into an 85:15 mixture of **17b** and **17c**, separable by HPLC. In conclusion, although O-2 shows a minor effect, neither the presence of this oxygen nor that of O-5/6 is essential for the diastereocontrol of the enolate methylation. The efficient chirality transfer observed in our case clearly belongs to the non-chelate-induced type, where high stereoselectivity has seldom been achieved so far.[1]

Reactive Confirmations of Enolate Alkylation. Having discarded the chelated species **6/7**, we may now generalize the discussion

(7) This assumption was made without any further investigation by Georges, M.; Tam, F. T.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 5747 for K-4.

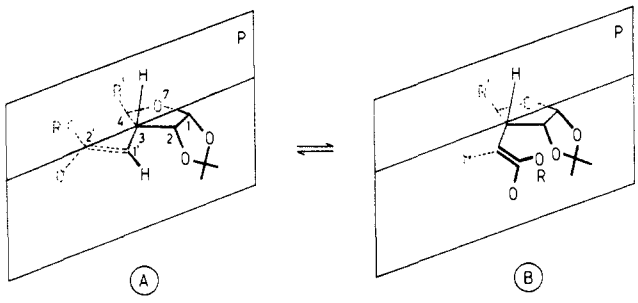
(8) Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3B, p 275–341.

(9) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574.

(10) Pfitzner, K. E.; Moffat, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661 and 5670.

(11) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

of the reactive confirmations. With respect to a plane P laid through C-1′, C-3, and H-3 and bisecting the O-7–C-1 bond, **4a** may adopt any confirmation out of the two magnitudes A and B. In A, C-2′ is on the C-4–O-7 side and in B on the C-1–C-2

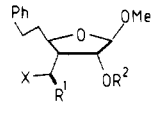


side of *P*. The observed sense of the asymmetric induction may then either be interpreted in terms of a "frontside" attack on an A confirmation or of a "backside" attack on a B confirmation. To avoid steric repulsion between the incoming electrophile and the rest of the molecule, a large dihedral angle of the enolate side chain and *P* would be desirable; on the other hand, too severe of an interaction with the substituents at C-4 and C-2 should be avoided. A dihedral angle of ca. 70° appears optimal. The A conformer with C-2′ located exactly within P would also be predicted to undergo "frontside attack" due to the steric shielding from the C-4 appendage. The B conformer with C-2′ in *P*, however, appears too severely hindered by interaction with the 1,2-acetonide.

To decide upon "frontside" vs "backside" directionality, we used lactones **13a,b** obtained from **9/10e** on acid catalyzed methanolysis, as model compounds. Usual deprotonation/methylation converted **13a** into a single stereoisomer **13c**, which was clearly nonidentical (^{1}H and ^{13}C NMR, melting point, and optical rotation) with **13b**.

As **13a** implicates a conformationally rigid B-type confirmation, the stereochemical result of the alkylation proves "frontside" attack, probably induced by the basketlike structure of the molecule.[12] Applied to **4a**, this result means that A and not B is the reactive conformation, throughout all substitution patterns examined thus far.

The preference for conformation A is the result of steric and/or dipole-type repulsions, which drive the enolate side chain away from C-2. To clarify the steric component a little further, the bulky 1,2-acetonitride moiety in **9/10e** was exchanged for the small 2-OMe substituent by preparing the model compounds **18/19c** from **13a,b** by reductive methylenation (**18/19a**), 2-OH methylation (**18/19b**), and oxidation of the olefin to the ester.

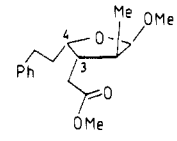


18 : **19**

	R^1	R^2	X
18a	H	H	$CH{=}CH_2$
18b	H	Me	$CH{=}CH_2$
18c	H	Me	CO_2Me
19a	Me	H	$CH{=}CH_2$
19b	Me	Me	$CH{=}CH_2$
19c	Me	Me	CO_2Me

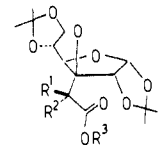
Under the usual deprotonation/methylation conditions **18c** was cleanly converted into **19c** with >99% selectivity. Thus, the bulk of the O-2 substituent is meaningless, and we may further draw the conclusion that the slight decrease in selectivity from >99% in **9e** to 85:15 in the 2-deoxygenated analogue **17a** goes mainly back to the polar repulsion of the 2-OR group. Anyway, irrespective of its substituent, O-2 does not contribute much to the conformational situation, and the propensity toward conformation A cannot primarily be due to a *vicinal* steric or polar repulsion. More likely, it is the strong dipole-type interaction of the negatively charged enolate oxygen and the acetal function on C-1 that has to be held responsible. The enolate side chain tries to move as far away from the anomeric center as possible and hence adopts conformation A. Interestingly, the α or β arrangement of O-1 does not matter in this respect, as **18c** exhibits undiminished selectivity.

It may be well expected that the conformational situation described so far should switch if additional steric effects are introduced, which destabilize A. For example, a substituent in the 1′-position should interact with a bulky group at O-2 and enforce a higher participation of conformers B. A similar effect should originate from a C-4 substituent, cis located to the 3 side chain. In fact, the enolates derived from **3c** and from **20**[13] add allyl bromide and methyl iodide, respectively, in a totally unselective manner, indicating an about equal participation of conformers A and B.

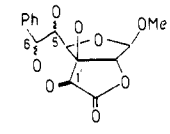


20

Reactive Conformation in the Deprotonation Step. It seemed interesting to compare the reactive conformation of the enolate addition with that adopted in the deprotonation step. To this end, esters **3a,b** had to be labeled in order to differentiate between the *pro-R* and *pro-S* hydrogens at C-1′. Consequently, **2c** and **2d** were separated by HPLC and deuteriated with D_2 over an Rh/Al_2O_3 catalyst. Compound **2c** gave stereochemically pure **21a** with >97% D at C-1′ and C-3 (^{1}H NMR analysis). The 1′-D must be in the *pro-S* position, as the hydrogenation of **2** is known to occur from the β-face exclusively.[5] Likewise, the (*pro-R*)-1′-D derivative **21b** and the methyl esters **21c,d** were obtained from stereochemically pure **2d**, **2a**, and **2b**.



21



22

21	R^1	R^2	R^3
a	D	H	*t*-Bu
b	H	D	*t*-Bu
c	D	H	Me
d	H	D	Me

As reactive conformations in the deprotonation step, again the two basic types A and B have to be considered, which may be attacked by the base from the "frontside" or the "backside" of the molecule. Thus we synthesized the conformationally locked γ-lactone **22** containing >97% D in the 3,5,6- and (*pro-S*)-1′-position by a route essentially analogous to that used for the unlabeled compound **13a**, except that the two hydrogenation steps in the synthesis were now performed with $D_2/Rh/Al_2O_3$. The 5,6-dideuteriation was felt advisable to simplify the ^{1}H NMR spectrum in the critical region between 2 and 3 ppm. On deprotonation/methylation **13c** was obtained from **22** with <3% D at C-1′ (^{1}H NMR analysis). Allowing for the deuterium isotope effect, this means that LDA has an enormous preference for the "frontside" attack. Deprotonation/methylation of **21a** furnished **3g** with a D/H ratio of 59:41 at C-1′ (^{1}H NMR analysis), whereas the analogous experiment with **21b** gave **3g** with a D/H ratio of 94:6. Similar D/H ratios have also been obtained from the deprotonation/allylation of **21a,b** and from the deprotonation/

(12) Cf. Wood, W. W.; Rashid, A. *Tetrahedron Lett.* **1987**, *28*, 1933.

(13) This compound has been prepared in racemic form. Details will be reported separately.

methylation of the methyl esters **21c,d**. Assuming exclusive frontside attack of the base, these data may be evaluated in terms of eq 1 and 2, in which [A] and [B] represent the concentrations

$$[B]/[A] = k_{H/D}(1/r_1) \quad (r_1 = 59{:}41) \qquad (1)$$

$$[B]/[A] = r_2(1/k_{H/D}) \quad (r_2 = 94{:}6) \qquad (2)$$

of conformers A and B, $k_{H/D}$ the kinetic primary isotope effect of the deprotonation step, and r_1 and r_2 the D/H ratios.

It follows that $k_{H/D} = 4.8$ and $[B]/[A] = 3.3$. Both values deserve some comment. (1) The primary kinetic isotope effect of LDA deprotonations is hard to measure by direct kinetic experiments, due to the extremely fast reaction, even at low temperature. Our indirect method provides a value quite in agreement with those obtained from kinetic measurements of E2 and E1cB reactions, where $k_{H/D}$ was found to be in the range from 3.0 to 6.3 in protic solvents.[14] (2) The deprotonation prefers conformation B, in contrast to the alkylation, although the preference in the latter case is far more distinct. Thus, both the ester **3** (crystal structure analysis!) and the enolate **4** adopt conformation A, whereas during the deprotonation, i.e. at the borderline between **3** and **4**, conformation B is favored. This surprising result may be interpreted by Ireland's model[2] according to which proton abstraction from C-1′ and lithium delivery at the enolate O occur in a concerted fashion. The resulting LDA–substrate complex requires considerable space on the "frontside" of the molecule and, as long as conformation A prevails, leads to considerable steric interactions with the 4-appendage. To avoid this, the side chain switches over to conformation B, in which the deprotonation then occurs. As soon as the base leaves, the substrate conformation A may again be restored.

Conclusion

Despite the presence of suitably located oxygen functions, chelate effects cannot be observed in the formation or alkylation or ester enolate **4**. This may be due to the fact that the optimum chelate ring size of 5 or 6 cannot be obtained, and hence, external enolate oxygens, with their full negative charge, are better ligands for the lithium cation than the neutral oxygen functions within the same molecule, so that the usual dimeric or tetrameric aggregates may be formed.[15] It is remarkable that despite this lack of any chelate-mediated chirality transfer **4** shows such a high diastereoselectivity on alkylation. Obviously, the dipole type repulsions enforcing reactive conformation A are fully equivalent to any chelate stabilization in this case. It is further astonishing that for deprotonation and enolate alkylation, different reactive conformations are used, which means that under the influence of the base–substrate–electrophile interactions repeated changes of conformation may occur. It remains the object of ongoing experiments to show how the relative participation of conformations A and B in deprotonation and alkylation and hence the steric course of the overall reaction may be controlled by the choice of substituents.

Experimental Section

All optical rotations in $CHCl_3$; NMR in $CDCl_3$ at 270 MHz (^1H) and 62.5 MHz (^{13}C). Compounds **1**, **2a,b**, **2c,d**, **3a**, **3b**, **3j**, and **3k** were prepared according to or in analogy to the literature.[5] Compounds **2c,d** were separated by HPLC (hexane/ethyl acetate, 9:1, Nucleosil 7 μm, 30 bar).

2c: $[\alpha]^{20}_D$ 110° (*c* 1.0); mp 88–89 °C; ^1H NMR δ 1.38, 1.41, 1.45, 1.53 (12 H, 4 s, Me), 1.53 (9 H, s, *t*-Bu), 3.92–4.16 (3 H, m, H-5, H-6), 4.66 (1 H, ddd, *J* = 7 Hz, *J* = 2 Hz, *J* = 1.5 Hz, H-4), 5.68 (1 H, ddd, *J* = 4 Hz, H-1), 6.23 (1 H, t = dd, *J* = 2 Hz, H-1′); ^{13}C NMR δ 25.10, 26.34, 26.76, 27.00, 27.74, 66.83, 76.55, 78.05, 79.55, 80.65, 104.56, 109.67, 112.17, 119.47, 153.51 (C-3), 163.95; IR (KBr) 2990 (vs), 2945 (s), 2900 (m, C—H), 1720 (vs, C=O), 1675 (s, C=C), 1455 (s, C—H), 1375 (vs, Me), 1315 (m), 1240 (vs), 1210 (vs), 1160 (vs), 1105 (s), 1065 (vs), 1025 (vs), 985 (vs), 910 (s), 885 (s), 855 (vs), 795 (m), 770 (m), 735 (m), 695 (w), 610 (w), 630 (m), 565 (m), 515 (m), 495 (w), 470 (w), 440 (w), 415 (w) cm^{-1}. Anal. Calcd for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92. Found: C, 60.74; H, 8.10.

2d: ^1H NMR δ 1.34, 1.40, 1.44 (12 H, 3 s, Me), 1.49 (9 H, s, *t*-Bu), 3.55 (1 H, dd, *J* = 8 Hz, *J* = 8.5 Hz, H-6a), 3.97 (1 H, dd, *J* = 6 Hz, *J* = 8.5 Hz, H-6b), 4.35 (1 H, ddd, *J* = 3 Hz, *J* = 8 Hz, *J* = 6 Hz, H-5), 5.08 (1 H, mc, H-4), 5.78 (1 H, mc, H-2), 5.93 (1 H, d, *J* = 5 Hz, H-1), 6.13 (1 H, t, *J* = 2 Hz, H-1′).

Crystal Structure Data of 2c. The crystal structure analysis was performed on a STOE diffractometer, Cu Kα radiation with Ni-Filter, $2.8° < \theta < 60°$, $w/2\theta$ scan, at 20°, 1718 reflections were collected, 245 of which were $<2\sigma(I)$. Space group $P2_12_12_1$, calcd density 1.60 g cm^{-3}, cell dimensions *a* = 32.068 (8) Å, *b* = 10.550 (3) Å, *c* = 5.744 (2) Å, *V* = 1943.3 Å^3, *Z* = 4, *R* = 0.048. A table of atomic coordinates and bond angles/distances may be found in the supplementary material.

Deprotonation and Alkylation of 3a. General Procedure. Diisopropylamine (12 mL, 86 mmol) in THF (500 mL) was treated with *n*-butyllithium (1.6 M in hexane, 52 mL, 84 mmol) at 0 °C for 15 min and then at 22 °C for 30 min. Then the solution was cooled to −35 °C and **3a** (20.0 g, 63 mmol) in THF (100 mL) was added dropwise. After 3 h at −35 °C, the neat electrophile (2–5-fold molar excess) was added, and the mixture was stirred for 1 h at −35 °C. After hydrolytic workup and extraction with ether, the products **3c–e**, were purified by column chromatography with ethyl acetate/hexane, 1:5. The products were analyzed by HPLC (ethyl acetate/hexane, 1:9; column Knauer 5 μm 50, 4 × 250, 25–30 bar, flow 2–5 mL/min.

3-*C*-[1′(*R*)-Methyl(methoxycarbonyl)methyl]-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (3c): $[\alpha]^{20}_D$ 27.2° (*c* 2.4); ^1H NMR δ 1.30, 1.50, 1.60, 1.61 (isopropylidene methyl, s), 1.42 (d, *J* = 5 Hz, 1′-Me), 2.24 (dt, *J* = 10 and 5 Hz, H-3), 2.75 (dq, *J* = 10 Hz, *J* = 7 Hz, H-1′), 3.68 (s, OMe), 3.81–4.12 (m, H-4, 5, 6), 4.70 (dd, *J* = 4.5 Hz, *J* = 5 Hz, H-2), 5.47 (d, *J* = 4 Hz, H-1); ^{13}C NMR δ 16.50 (1′-Me), 25.26–26.45, 37.00, 50.00, 51.30, 66.80, 76.65, 80.68, 81.31, 103.87, 109.15, 111.60, 175.83 (C=O); IR (neat) 2950, 1735 (ss), 1445, 1375 cm^{-1}. Anal. Calcd for $C_{16}H_{26}O_7$: C, 58.17; H, 7.90. Found: C, 58.09.

Epimerization of 3c to 3h. Compound **3c** (2.00 g, 6.40 mmol) was deprotonated with LDA as described for **3a**, and the reaction was quenched with methanol (5 mL) at −78 °C. Usual workup furnished a 1:1 mixture (1.70 g, 85%) of **3c** and **3h**: ^1H NMR δ 1.26–1.40 (s, isopropylidene Me), 2.16 (ddd, *J* = 10 Hz, *J* = 4.5 Hz, *J* = 5 Hz, H-3), 2.97 (dq, *J* = 6.5 Hz, *J* = 7 Hz, H-1′), 3.69 (s, OMe), 3.88–4.14 (m, H-5, 6), 4.28 (dd, *J* = 5 Hz, *J* = 10 Hz, H-4), 4.74 (dd, *J* = 4 Hz, *J* = 5 Hz, H-2), 5.77 (d, *J* = 4 Hz, H-1); ^{13}C NMR δ 16.17 (1′-Me), 25.18–26.54 (isopropylidene Me), 36.38, 49.96, 51.46, 66.86, 77.46, 79.95, 81.74, 104.48, 111.97, 175.36 (C=O). Anal. Calcd for $C_6H_{26}O_7$: C, 58.17; H, 7.93. Found: C, 58.23; H, 7.79.

Allylation of 3c. Compound **3c** (4.00 g, 12.10 mmol) was deprotonated as described for **3a** and then treated with allyl bromide (4.00 g, 33.3 mmol) for 1 h at −65 °C. Usual workup furnished **3m,n** (3.20 g, 75%) as a colorless oil. The configuration at C-1′ was assigned arbitrarily. **3m**: ^1H NMR δ 1.37 (s, Me), 2.42–2.72 (m, H-3), 3.63 (s, OMe), 3.87–4.11 (m, H-4), 4.78 (dd, *J* = 5 Hz, *J* = 4 Hz, H-2), 5.70 (d, *J* = 4 Hz, H-1). **3n**: ^1H NMR δ 1.36 (s, Me), 2.20 (dd, *J* = 10 Hz, *J* = 5 Hz, H-3), 3.67 (s, OMe), 4.22 (dd, *J* = 10 Hz, *J* = 6.5 Hz, H-4), 4.72 (dd, *J* = 4 Hz, *J* = 5 Hz, H-2), 5.67 (d, *J* = 4 Hz, H-1). Anal. Calcd for $C_{19}H_{30}O_7$: C, 61.61; H, 8.16. Found: C, 61.37; H, 8.07.

Hydrolysis of the 5,6-Acetonide Moiety in 3a–c,g. Compounds **3a–c,g** (1.0 mol) in HOAc/water (60%, 300 mL) was stirred for 37 h at 22 °C. The solution was neutralized with sodium carbonate and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated to give a colorless oil, which was purified by column chromatography (ethyl acetate/hexane 1:1): yields 80–95%.

3-*C*-[1′(*R*)-Methyl(methoxycarbonyl)methyl]-3-deoxy-1,2-isopropylidene-α-D-allofuranose (3i): $[\alpha]^{20}_D$ 19.2° (*c* 1.8); mp 90–91 °C (hexane/ether); ^{13}C NMR δ 16.8, 26.3, 26.6, 37.6, 49.1, 51.8, 63.4, 72.3, 81.4, 82.4, 103.8, 112.0, 176.8; IR (KBr) 3440, 1750 (s), 1735 (w), 1155 (m) cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_7$: C, 53.78; H, 7.60. Found: C, 53.01; H, 7.40. Crystal structure analysis of **3i**: performed on a STOE diffractometer at 22°, as described for **2c**. A total of 1370 reflections were collected. Space group $P2_12_12_1$, cell parameters *a* = 8.061 Å, *b* = 8.487 Å, *c* = 21.172 Å, *V* = 1448.455 Å^3, calcd density 1.331 g cm^{-3}, *R* = 0.044, R_w = 0.021. Tables of atomic coordinates and bond angles/distances may be found in the supplementary material.

Silylation of the Ester Enolates 4a,b. A mixture of diisopropylamine (360 mg, 3.5 mmol), *n*-butyllithium (1.6 M in hexane, 2.2 mL, 3.5 mmol), and trimethylsilyl chloride (640 mg, 3.5 mmol) in (a) THF (25

(14) See, for example: Saunders, W. H.; Edison, D. H. *J. Am. Chem. Soc.* **1960**, *82*, 138. Shiner, V. J. *Ibid.* **1952**, *74*, 5285. Shiner, V. J.; Smith, M. L. *Ibid.* **1958**, *80*, 4095. Brown, K. C.; Saunders, W. H. *Ibid.* **1970**, *92*, 4292. Finley, K. T.; Saunders, W. H. *Ibid.* **1967**, *89*, 898. Willi, A. V. *J. Phys. Chem.* **1966**, *70*, 2705; *Helv. Chim. Acta* **1966**, *49*, 1725. McLennan, D. J.; Wong, R. J. *J. Chem. Soc., Perkin Trans. II* **1974**, 526 and 1373; *Tetrahedron Lett.* **1972**, 2887 and 2891.

(15) Seebach, D.; Amstutz, R.; Laube, Th.; Schweizer, B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403.

mL) or (b) THF (20 mL) + HMPA (7.5 mL) was treated with **3a** (1.00 g, 3.2 mmol) in THF (10 mL) for 4 h at −78 °C. The volatile components were condensed into a trap kept at −196 °C, and the slimy residue was distilled at 130 °C (0.2 mm): yield (a) 1.11 g (90%) of **4c,d** in a ratio of 97:3 (^{1}H NMR analysis) and (b) 1.05 g (85%) of **4c,d** (17:83). **4c**: ^{1}H NMR: δ 0.27 (s, Me_3Si), 1.31, 1.37, 1.44, 1.51 (s, Me), 2.73 (dt, J = 4 Hz, J = 8 Hz, J = 10 Hz, H-3), 3.53 (s, OMe), 3.65 (d, J = 10 Hz, H-1′), 3.96 (mc, H-4, H-6), 4.22 (dt, J = 4 Hz, J = 10 Hz, H-5), 4.53 (t, J = 4 Hz, H-2), 5.80 (d, J = 4 Hz, H-1). **4d**: ^{1}H NMR δ 0.14 (s, Me_3Si), 1.26, 1.35, 1.45 (s, Me), 2.70 (mc, H-3), 3.48 (d, J = 10 Hz, H-1′), 3.65 (s, OMe), 3.89 (mc, H-4, H-6), 4.04 (dt, J = 2 Hz, J = 5 Hz, J = 8 Hz, H-5), 4.74 (t, J = 4 Hz, H-2), 5.70 (d, J = 4 Hz, H-1). Anal. Calcd for $C_{18}H_{31}O_7Si$: C, 54.67; H, 7.83. Found: C, 55.12; H, 8.41.

Synthesis of 9d,e, 10d,e, 11c, and 12c. General Procedure. The diol (**3i–l**, 80–200 mmol) in CH_2Cl_2 (500–2000 mL) was treated with lead tetraacetate (1 molar equiv) for 2 h at 22 °C. The mixture was filtered, and the filtrate was stirred with potassium carbonate (50–120 g) for 1 h. After filtration the mixture was evaported to give a quantitative yield of crude aldehyde (**9–12a**), which was added in THF (200–500 mL) to a solution of the ylide prepared from the phosphonium chloride and LDA in THF (100 mL/10 g of phosphonium salt). The mixture was stirred at 22 °C for 13 h, quenched with water (2–5 mL), filtered, and concentrated under reduced pressure. The residue was diluted with ether and filtered to remove the phosphine oxide. The mother liquor was purified by column chromatography (ethyl acetate/hexane, 1:4) to give an E/Z mixture of the olefins in 70–85% yield, which was hydrogenated in methanol (10 mL/g of olefin) over Pd/C (10%, 1 g/10 g of olefin) at 2 bar. After filtration and evaporation of the solvent under reduced pressure, the residue was purified by column chromatography (ethyl acetate/hexane, 1:3) to give **9d,e**, **10d,e**, **11c**, and **12c** in 95–99% yield.

3-*C*-[(Methoxycarbonyl)methyl]-3,5-dideoxy-5-*C*-propyl-1,2-*O*-isopropylidene-α-D-ribofuranose (9d): $[\alpha]^{20}_D$ 66.1° (*c*, 0.85); ^{1}H NMR δ 0.89 (t, J = 7 Hz, 1′-Me), 1.24–1.67 (m, isopropylidene Me + H-5, 6, 7, 8), 2.04 (m, H-3), 2.31 and 2.65 (AB part of ABM spectrum, J_{AB} = 17 Hz, J_{AM} = 10 Hz, J_{BM} = 4 Hz, H-1′), 3.64–3.78 (m, OMe and H-4), 4.73 (dd, J = 4 and 4.5 Hz, H-2), 5.78 (d, J = 4 Hz, H-1); IR (neat) 2990, 2960, 2930, 2870, 1735 (s), 1380, 1370, 1020, 870 cm^{-1}. Anal. calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.32; H, 8.67. For data of **9e**, **10d**, **10e**, **11c**, **and 12c**, see the supplementary material.

Enolate Methylation. Compound **9d,e** and **11c** were converted into the enolates and treated with methyl iodide as described for **3a,b**. The products (**10d,e** and **12c**) were identical according to the ^{1}H and ^{13}C NMR and HPLC data with the compounds described above.

Synthesis of Lactones 13a–c. Compound **9e** (6.88 g, 190 mmol) in methanol (150 mL) and water (3 mL) was treated with *p*-toluenesulfonic acid (250 g) for 8 h. The mixture was neutralized with sodium carbonate and concentrated under reduced pressure. The residue was diluted with water and extracted with ether. The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (ethyl acetate/hexane, 1:1) to furnish **13a** (2.73 g, 55%) as pure β-anomer according to ^{13}C and ^{1}H NMR (colorless crystals with mp 66 °C (hexane/ether)). Additionally, 0.38 g (8%) of the α-anomer (mp 59–61 °C) was isolated. **13a**: $[\alpha]^{20}_D$ −54.6° (*c* 1.07); ^{1}H NMR δ 1.80–1.93, 1.97–2.11 (2 m, H-5), 2.41 (d, J = 16 Hz, H-1′), 2.62–2.89 (m, H-3, H-6), 2.78 (d, J = 16 Hz, H-1′), 3.42 (s, OMe), 3.96 (ddd, J = 10 Hz, J = 5.5 Hz, J = 4 Hz, H-4), 4.86 (d, J = 6 Hz, H-2), 5.09 (s, H-1), 7.14–7.34 (5 H, m, phenyl); ^{13}C NMR δ 32.22, 33.74, 38.89, 42.09, 54.60, 87.15, 87.23, 106.96, 125.77, 128.10, 128.22, 140.9u, 175.30; IR (KBr) 3100 (w), 3070 (m), 3030 (m), 2960 (s), 2940 (s), 2020 (s, C-H), 2840 (m, OMe), 1785 (vs, C=O), 1600 (m), 1580 (w), 1500 (m, C=), 1490 (m), 1470 (m), 1455 (m), 1430 (m, C-H, 1380 (s, Me, 1335 (m), 1320 (m), 1285 (m), 1220 (m), 1180 (vs), 1110 (vs), 1070 (s), 1050 (s), 1020 (s), 995 (s), 970 (s), 925 (m), 910 (m), 890 (s), 870 (m), 805 (m), 760 (s), 700 (vs), 670 (m), 610 (m), 680 (m), 540 (m), 505 (s), 470 (m) cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H 6.92. Found: C, 68.61; H, 7.17. Analogously, **10e** (9.00 g, 26.9 mmol) was converted into **13b** (6.00 g, 81%): $[\alpha]^{20}_D$ 45.2° (*c* 1.0); mp 89 °C; ^{1}H NMR δ 1.20 (d, J = 7 Hz, 1′-Me), 1.84 and 1.99 (mc, H-5), 2.64–2.95 (m, H-1′, H-3, H-6), 3.43 (s, OMe), 4.15 (ddd, J = 9 and 4.5 and 4 Hz, H-4), 4.77 (d, J = 5 Hz, H-2), 5.08 (s, H-1), 7.2–7.4 (m, phenyl-H); ^{13}C NMR δ 11.11 (1′Me), 32.46, 37.13, 39.89, 47.02, 54.76, 79.83, 85.13, 106.31, 126.28, 128.45, 141.13, 177.44 (C=O); IR (KBr) 2940, 1770 (s), 1745, 1170, 1025 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.88; H, 7.23.

Deprotonation/methylation of **13a** (3.00 g, 10.9 mmol) as described for **3a,b** furnished **13c** (2.69 g, 85%), diastereomerically pure according to ^{1}H and ^{13}C NMR and HPLC: $[\alpha]^{20}_D$ −74.5° (*c* 1.0); mp 74.5 °C; ^{1}H NMR δ 1.30 (d, J = 7 Hz, 1′-Me), 1.89 and 2.03 (mc, H-5), 2.48–2.88 (m, H-1′/H-3, 6), 3.43 (s, OMe), 4.00 (ddd, J = 8 Hz, J = 6 Hz, J = 4 Hz, H-4) 4.88 (d, J = 6.5 Hz, H-2), 5.07 (s, H-1), 7.2–7.4 (m, phenyl H); ^{13}C NMR δ 16.89 (1′-Me), 32.51, 39.05, 40.68, 50.82, 55.01, 82.42, 85.89, 107.28, 126.57, 128.31, 128.50, 140.94, 178.74 (C=O); IR (KBr) 2930, 1770, 1190, 1110, 1060, 965, 750, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.65; H, 7.27.

Synthesis of Compounds 14–17. A mixture of **14a,b** and **9e** (17.6 g, 48.6 mmol) in THF (50 mL) was added dropwise to a suspension of lithium aluminum hydride (1.02 g, 26.9 mmol) in THF (100 mL), and the mixture was refluxed for 1 h. Hydrolytic workup and purification of the crude product by column chromatography (ethyl acetate/hexane, 1:1) furnished **14a** (12.3 g, 87%): $[\alpha]^{20}_D$ +76.6° (*c* 1.2); ^{1}H NMR δ 1.33, 1.49 (2 s, Me), 1.55–1.99 (m, H-3, H-5, H-1′, OH), 2.63–2.75, 2.83–2.95 (2 m, H-6), 3.74 (mc, H-2′), 3.83 (dt, ddd, J = 9.5 Hz, J = 9.5 Hz, J = 2, 5 Hz, H-4), 4.69 (t, dd, J = 4 Hz, H-2), 5.85 (1 H, d, J = 4 Hz, H-1), 7.15–7.34 (5 H, m, phenyl H); ^{13}C NMR δ 26.13, 26.28, 27.50, 32.03, 34.41, 45.65, 60.47, 80.23, 80.90, 104.48, 110.91, 125.52, 28.04, 128.10, 141.68; IR (film) 3440 (vs, OH), 3090 (w), 3060 (w), 3030 (m), 2980 (s), 2940 (vs), 2870 (s, C—H), 1600 (m), 1580 (vw), 1500 (m, C=C), 1455 (s), 1435 (m, C—H), 1380 (s), 1370 (s, Me), 1330 (m), 1310 (m), 1245 (s), 1215 (vs), 1165 (vs), 1130 (s), 1105 (vs), 1045 (vs), 1020 (vs), 945 (w), 910 (m), 880 (s), 795 (w), 750 (m), 700 (s), 650 (w), 580 (w), 545 (w), 510 (m) cm^{-1}; MS, m/e calcd for M^+ 292.1674, found 292.1677.

Compound 14a (7.80 g, 26.7 mmol) was benzylated in DMF (130 mL) with sodium hydride (50% in mineral oil, 2 g) was benzyl chloride (10 mL, 86.9 mmol) at 22 °C for 4 h. Usual workup and column chromatography yielded the benzyl ether (9.2 g, 90%), which was stirred with *p*-toluenesulfonic acid (3 g) in methanol (100 mL) at 22 °C for 24 h. Workup as described for **13a** including column chromatography (ethyl acetate/hexane, 1:3) furnished **15a** (6.15 g, 73%) as pure β-anomer. Additionally, 80 mg of the α-anomer was isolated.

15a: $[\alpha]^{20}_D$ −26.4° (*c* 1.24); ^{1}H NMR δ 1.60–1.96, 2.04 (m, mc, H-3, H-5, H-1′), 2.62–2.75, 2.83–2.95 (2 m, H-6), 3.05 (d, J = 3 Hz, OH), 3.39 (s, OMe), 3.48 (dt, J = 10 Hz, J = 2.5 Hz, H-2′), 3.62–3.69 (m, H-2′), 3.88 (dt, ddd, J = 9 Hz, J = 3.5 Hz, H-4), 4.15 (dd, J = 4 Hz, J = 3 Hz, H-2), 4.52 (s, H-3′), 4.88 (s, H-1), 7.14–7.39 (m, phenyl H); ^{13}C NMR δ 25.96, 32.52, 37.99, 46.24, 54.12, 69.45, 73.35, 76.73, 83.23, 108.70, 125.60, 127.57, 127.70, 128.18, 128.22, 128.35, 137.50, 142.05; IR (film) 3440 (vs, OH), 3090 (w), 3060 (m), 3030 (m), 2930 (vs), 2860 (s, C—H), 1950 (w), 1870 (w), 1810 (w), 1750 (w, Aromaten), 1600 (m), 1580 (w), 1495 (s, C=C), 1455 (vs, C—H), 1360 (s, Me), 1310 (m), 1210 (m), 1190 (m), 1140 (s), 1100 (vs), 1035 (vs), 975 (vs), 955 (vs), 910 (m), 880 (m), 820 (vw), 800 (w), 780 (w), 745 (s), 700 (vs), 620 (w), 605 (w), 560 (w), 510 (w) cm^{-1}. Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.40; H, 8.05.

Deoxygenation of 15a. Compound **15a** (5.00 g, 14.0 mmol) in ether (50 mL) was added dropwise to NaH (50% in mineral oil, 1.3 g) in ether (50 mL). The mixture was refluxed for 2 h, and then carbon disulfide (5 mL, 83 mmol) was added, and refluxing was continued for 2 h. Then methyl iodide (10 mL) was added, and the mixture was refluxed for another 4 h. Hydrolytic workup and column chromatography (ethyl acetate/hexane, 1:4) gave the xanthate (5.4 g, 86%), which was heated with Bu_3SnH (9.0 mL, 33.9 mmol) and a catalytic amount of AIBN in toluene (180 mL) to 100 °C for 1 h. Evaporation of the solvent and column chromatography (ethyl acetate/hexane, 1:5) yielded **16a** (2.40 g, 58%): $[\alpha]^{20}_D$ −15.6° (*c* 1.1); ^{1}H NMR δ 1.48–2.31 (m, H-2, H-3, H-5, H-1′), 2.62–2.75, 2.82–2.94 (2 m, H-6), 3.36 (s, OMe), 3.46 (t, J = 6.5 Hz, H-2′), 3.69 (dt, ddd, J = 8 Hz, J = 4 Hz, H-4), 4.48 (s, H-3′), 4.96 (d, J = 5 Hz, H-1), 7.14–7.37 (m, phenyl H); ^{13}C NMR δ 32.76, 33.34, 38.38, 39.69, 39.96, 54.26, 69.13, 72.98, 84.82, 104.73, 125.65, 127.50, 127.54, 128.29, 128.37, 138.38, 142.27; MS m/e calcd for M^+ − OMe 309.185468 found 309.18524.

Synthesis of the Methyl Esters 17a–c. Compound **16a** (2.00 g, 5.87 mmol) in ammonia (300 mL) and THF (100 mL) was treated with sodium (300 mg, 13 mmol) in small portions at −50 °C for 3 min. The blue color was discharged with solid ammonium chloride, and the ammonia was evaporated. The residue was treated with aqueous sodium bicarbonate, extracted with ether, and dried ($MgSO_4$). Evaporation of the solvent and column chromatography (ethyl acetate/hexane, 1:1) furnished the alcohol (1.00 g, 77%), which was treated in toluene (14 mL) with DMSO (14 mL), pyridine (0.72 mL, 0.99 mmol), trifluoroacetic acid (0.40 mL, 4.8 mmol), and DCC (5.04 g, 26.2 mmol) at 22 °C for 18 h. Ether (150 mL), methanol (15 mL), and oxalic acid (1.5 g) were added, and after 1 h, water (150 mL), was added. The mixture was filtered to remove the urea, and the organic phase was washed with sodium bicarbonate and water, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography (ethyl acetate/hexane, 1:4) to give the aldehyde (0.72 g, 71%), which was oxidized with potassium permanganate (saturated aqueous solution 20 mL) in *tert*-butyl alcohol (20 mL) and phosphate buffer (12 mL, pH 6.5), at 22 °C for 10

min. Bisulfite was added, and the MnO_2 was dissolved with ice-cold 2 N HCl. The mixture was extracted with ether, washed with water, and dried ($MgSO_4$), and evaporated to give a yellow oil, which was treated in methanol (30 mL) with an ethereal solution of diazomethane until the yellow color persisted. Evaporation of the solvent and column chromatography (ethyl acetate/hexane, 1:4) furnished **17a** (720 mg, 93%) as a colorless oil.

5-*C*-Benzyl-3-*C*-[(methoxycarbonyl)methyl]-2,3,5-trideoxy-β-D-methylribofuranoside (17a): $[\alpha^{20}]_D$ −28.0° (*c* 0.9); ^{1}H NMR δ 1.68–2.00 (m, H-2, H-5), 2.18–2.32, 2.38–2.60 (2 m, H-2, H-3, H-1′), 2.64–2.77, 2.86–2.94 (2 m, H-6), 3.38 (s, OMe), 3.68 (s, COOMe), 3.68–3.75 (m, H-4), 4.99 (d, *J* = 5 Hz, H-1), 7.16–7.33 (5 H, m, phenyl H); ^{13}C NMR δ 32.50, 37.55, 37.93, 38.86, 39.55, 51.42, 54.35, 83.91, 104.54, 125.66, 128.24, 128.30, 141.96, 172.30; IR (film) 3090 (w), 3070 (w), 3030 (m), 3000 (m), 2950 (vs), 2860 (w), 2830 (m, C—H), 1735 (vs, C=O), 1600 (m), 1580 (w), 1495 (m), 1450 (m), 1435 (s, C—H), 1360 (m), 1290 (w), 1260 (m), 1195 (vs), 1155 (vs), 1100 (vs), 1060 (s), 1030 (s), 1000 (m), 960 (s), 940 (m), 920 (w), 905 (w), 885 (m), 850 (w), 750 (s), 700 (vs), 670 (w), 580 (w), 545 (vw), 520 (w), 490 (w) cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.80; H, 7.92.

By an analogous sequence of steps **12c** was converted via **14b**, **15b**, and **16b** into **17b**. For data of these compounds, see the supplementary material.

Deprotonation/Methylation of 17a. The experiment was performed as described for **3a**. Analytically pure **17a** (510 mg, 2.04 mmol) gave an 85:15 mixture (518 mg, 88%) of **17b**, identical in the ^{1}H and ^{13}C NMR spectra with the compound described above, and **17c**; both components were separated by HPLC (column Knauer 5 μm 50, 4 × 250, ethyl acetate/hexane, 1:9, 25 bar, flow 2 mL/min). **17c**: ^{1}H NMR δ 1.14 (d, *J* = 7 Hz, Me), 1.78–1.94 (m, H-2a, H-5), 2.07 (dd, *J* = 13 Hz, *J* = 7.5 Hz, H-2), 2.32 (mc, H-1′), 2.45 (mc, H-3), 2.65–2.77 (2.86–2.97 (2 m, H-6), 3.38 (s, OMe), 3.64 (s, COOMe), 3.83 (q, dt, *J* = 6.5 Hz, H-4), 4.97 (d, *J* = 5 Hz, H-1), 7.14–7.32 (5 H, m, phenyl H); ^{13}C NMR δ 15.93, 32.94, 37.57, 39.60, 42.37, 45.60, 51.48, 54.38, 82.15, 104.89, 125.76, 128.35, 128.43, 142.08, 175.48.

Synthesis of Compounds 18 and 19a–c. Compound **13a** (9.00 g, 34.4 mmol) in toluene (200 mL) was treated dropwise with diisobutylaluminum hydride (1 M in toluene, 41.3 mL, 41.3 mmol) at −95 °C for 20 min. After 30 min at −65 °C, water (100 mL) and sodium fluoride (20 g) were added, and the mixture was stirred at 0 °C for 1 h. After filtration and extraction with ether, the organic phase was dried ($MgSO_4$) and evaporated to give a yellow oil, which was purified by column chromatography (ethyl acetate/hexane, 1:3). Pure lactol (7.20 g, 79%) was obtained as a 1:1 mixture of the anomers. The lactol in ether (30 mL) was added at 0 °C to methylidenetriphenylphosphorane prepared from the phosphonium bromide (24.4 g, 68.3 mmol) and *n*-butyllithium (1.6 M in hexane, 42.7 mL, 68.3 mmol) in ether (170 mL). The mixture was stirred at 22 °C for 12 h, diluted with water (5 mL), filtered, and evaporated to dryness. The residue was purified by column chromatography (ethyl acetate/hexane, 1:7) to furnish **18a** (3.60 g, 50%) as a colorless oil: $[\alpha]^{20}_D$ +5.7° (*c* 1.1); ^{1}H NMR δ 1.67 (s, OH), 1.79, 1.95 (2 m, H-5), 2.06–2.37 (m, H-3, H-1′), 2.70, 2.90 (2 m, H-6), 3.37 (s, OCH_3), 3.87 (dt, ddd, *J* = 9.5 Hz, *J* = 3 Hz, H-4), 4.10 (d, *J* = 4 Hz, H-2), 4.82 (s, H-1), 5.06 (ddd, *J* = 10 Hz, *J* = 3 Hz, *J* = 2 Hz, H-3′ trans), 5.11 (ddd, *J* = 17 Hz, *J* = 3 Hz, *J* = 2 Hz, H-3′ cis), 5.82 (dddd, *J* = 10 Hz, *J* = 17 Hz, *J* = 7 Hz, *J* = 6 Hz, H-2′), 7.15–7.33 (m, 5 H); IR (film) 3440 (s, O—H), 3080 (m), 3070 (m), 3030 (m), 2980 (m), 2930 (s), 2910 (s), 2830 (m), 1640 (m, C=C), 1600 (m), 1570 (vw), 1495 (m), 1450 (s), 1350 (m), 1190 (m), 1100 (s), 1035 (s), 980 (s), 915 (s), 750 (m), 700 (s) cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.14; H, 8.44.

O-Methylation. Compound **18a** (3.60 g, 13.7 mmol) in THF (20 mL) was added to a suspension of sodium hydride (80% in mineral oil, 620 mg, 20.6 mmol) in THF (100 mL). The mixture was stirred at 22 °C for 2 h, and then methyl iodide (1.9 mL, 30.5 mmol) was added. After 2 h at 22 °C the mixture was filtered and evaporated to give a yellow oil, which was purified by column chromatography to furnish **18b** (3.50 g, 93%): $[\alpha]^{20}_D$ 102° (*c* 2.7): ^{1}H NMR δ 1.74, 1.94 (2 m, H-5), 2.00–2.40 (2 m, H-3, H-1′), 2.70, 2.88 (2 m, H-6), 3.40 (2 s, OCH_3), 3.58 (d, *J* = 4 Hz, H-2), 3.85 (dt, ddd, *j* = 9 Hz, *J* = 3 Hz, H-4);, 4.89 (s, H-1), 5.00 (ddd, *J* = 11 Hz, *J* = 2 Hz, *J* = 1 Hz, H-3′ trans), 5.06 (dt, ddd, *J* = 17 Hz, *J* = 2 Hz, H-3′ cis), 5.78 (ddt, *J* = 11 Hz, *J* = 17 Hz, *J* = 7 Hz, H-2′), 7.15–7.35 (m, 5 H, phenyl H); IR (film) 3080 (m), 3065 (m), 3030 (m), 2980 (m), 2930 (s), 2910 (s), 2830 (m), 1640 (m), 1600 (m), 1580 (vw), 1495 (m), 1450 (s), 1370 (m), 1190 (s), 1100 (s), 1040 (s), 995 (m), 920 (s), 750 (m), 700 (m) cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.99; H, 8.79.

Lemieux Oxidation. Compound **18b** (3.40 g, 12.3 mmol) in acetone (5 mL) was added to sodium periodate (10.5 g, 49 mmol) in water (40 mL) and acetone (40 mL). The solution was cooled to 5 °C, and potassium permanganate (0.32 g, 2.0 mmol) in water (4 mL) and acetone (4 mL) were added dropwise over a period of 1 h. The mixture was stirred at 5–10 °C for 20 h, filtered, concentrated, and extracted with ether. The organic phase was evaporated and the residue was dissolved in 1 N sodium hydroxide, washed with ether, acidified, and extracted with ether. The ether phase was dried ($MgSO_4$) and treated with ethereal diazomethane until the evolution of nitrogen has ceased. Then the solvent was evaporated, and the residue was chromatographed (ethyl acetate/hexane, 1:3) to give **18c** (1.53 g, 41%) as a colorless oil.

5-*C*-Benzyl-3-*C*-[(methoxycarbonyl)methyl]-3,5-dideoxy-2-*O*-methyl-β-D-methylribofuranoside (18c): $[\alpha]^{20}_D$ 43.3° (*c* 1.1); ^{1}H NMR δ 1.69–1.99 (m, H-5), 2.29 and 2.64 (AB part of ABM spectrum, J_{AB} = 16 Hz, J_{aM} = 10 Hz, J_{BM} = 5 Hz, H-1′), 2.50 (dddd, M part of ABM spectrum, *J* = 10 Hz, *J* = 5 Hz, *J* = 8.5 Hz, H-3), 2.70 and 2.87 (mc, H-6), 3.40 and 3.42 (s, OMe), 3.70 (s, OMe), 3.77 (d, *J* = 5 Hz, H-2), 3.84 (ddd, *J* = 8 Hz, *J* = 8.5 Hz, *J* = 4 Hz, H-4), 4.90 (s, H-1), 7.2–7.4 (m, phenyl H); IR (film) 2940, 2910, 1735 (s), 1455, 1435, 1190, 1100, 1040, 955, 700 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 65.98; H, 7.82.

By an analogous sequence of steps, **13b** was converted into **19c**, via **19a** and **19b**. For data of these compounds, see the supplementary material.

Deprotonation/Methylation. Compound **18c** (500 mg, 1.62 mmol) was deprotonated and methylated as described for **3a** to give **19c** (495 mg, 95%) identical in ^{1}H and ^{13}C NMR data with the compound described above.

Synthesis of Compounds 21. Compound **2c** (5.00 g, 17.8 mmol) in methanol-*d* (50 mL) was deuteriated with D_2 (>99.9% d_2) over Rh/Al_2O_3 at 22 °C/(3 bar). Usual workup furnished **3b** (5.30 g, 94%) containing 99% deuterium at C-3 and C-1′, according to ^{1}H NMR analysis. Similarly **2a**, **2b**, and **2d** were deuterated; **3b**-d_2 (5.00 g, 13.9 mmol) was converted into **11c**-d_4 as described, except that the hydrogenation in the last step was performed with D_2/Rh/Al_2O_3 as described above. The conversion of **11c**-d_4 into **22** followed the procedure described for **13a**. Deprotonation/methylation of **21a–d** and of **22** was performed as described for **3a**. The deuterium analysis of the products was performed by comparing the intensity of the ^{1}H NMR signals of H-1′ and H-1. Accuracy ca. ±3%.

Acknowledgment. This work was financially supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We also thank the Schering AG, Berlin, Bergkamen, and the BASF AG, Ludwigshafen, for solvents and fine chemicals.

Supplementary Material Available: Procedures and analytical data of compounds not described in detail in the Experimental Section and tables of atomic coordinates and bond angles/distances of the crystal structure analysis of compounds **2c** and **3i** (25 pages). Ordering information is given on any current masthead page.