Aldol Addition of Lithium and Boron Enolates of 1,3-Dioxan-5-ones to Aldehydes. A New Entry into Monosaccharide Derivatives

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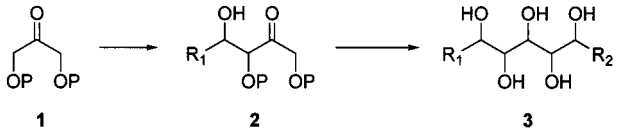
Methods allowing control of stereoselectivity in aldol reactions of enolates derived from 1,3-dioxan-5-ones (**4**) are described. Boron enolates, generated in situ, react with benzaldehyde to give the corresponding anti aldol selectively (the anti:syn ratio of up to 96:4) and in high yield. Lithium enolates give high anti selectivity only with aldehydes branched at the α-position. Enantioselective deprotonation of C_S symmetrical dioxanones (e.g., **4b**) can be accomplished efficiently, with enantiomeric excess of up to 90%, with chiral lithium amide bases of general structure PhCH(Me)N(Li)R (**9**, **10**) if the R group is sufficiently bulky (e.g, R = adamantyl) or is fluorinated (e.g., R = CH_2CF_3). Dioxanone boron and lithium enolates react readily with glyceraldehyde derivatives (**19**), yielding protected ketohexoses (**20** and **21**).

Aldol addition of ketone enolates to aldehydes provides one of the most useful synthetic tools for construction of carbon−carbon bonds. The reaction has been studied extensively during the past 3 decades, and a number of its mechanistic features and some effective methods for controlling diastereoselectivity have been elaborated.[1] More recently, the scope of the aldol addition reaction was expanded by chiral lithium amide bases which could be used to generate chiral enolates stereoselectively, thus affording another approach to synthesis of enantiomerically pure aldols.[2] Aldol reaction is very general, and, over the years, many diverse ketones were enolized and added to aldehydes. Protected 1,3-dihydroxyacetone (**1**) could be an interesting starting material for synthesis of polyoxygenated natural products of general structure **3** via the sequential aldol approach, if a number of stereoselectivity challenges were solved (Scheme 1). Some phenomena associated with the ketone structure affecting the course of the aldol reaction, e.g., selectivity problems due to the presence of a heteroatom at one of the α-carbon atoms, were described before.[3] When studying enolization of several C_S symmetrical ketones, we were intrigued by structural features of 1,3-dioxan-5-ones (**4**) that are potential synthetic equivalents of 1,3-dihydroxyacetone. An efficient control of both the diastereoselectivity and, ultimately, the enantioselectivity of the aldol reaction in the dioxanone system would be necessary if dioxanones were to become useful building blocks.[4] We described earlier a general method of synthesis of dioxanones and preliminary studies on their enolization.[5] Chemistry of these compounds proved nontrivial due to side reactions

Scheme 1



1 **2** **3**

and low stability of the dioxanone system, especially under acidic conditions. Below, we present results of recent studies on aldol addition reactions of lithium and boron enolates of 1,3-dioxanones to aldehydes and application of these results to synthesis of monosaccharide derivatives.[6]

Results and Discussion

As reported before,[5] early experiments with aldol addition of dioxanone lithium enolates were not very promising. The yields were rather low (55−77%) and, although the anti aldols were produced predominantly, in agreement with the Zimmerman−Traxler model,[1c] the selectivity in reactions with typical aldehydes (e.g., benzaldehyde) was low and the syn:anti ratio oscillated around 1:2. The aldol reaction could yield up to four different diastereoisomeric products: syn-cis, syn-trans, anti-cis, and anti-trans (Scheme 2; note that the trans products, which are possible when R and R′ are different, are not shown for brevity), and we hypothesized that the diastereoselectivity should be influenced by the size of the substituents R and R′ at the 2-position in the dioxanone molecule and by the structure of the R_1 group in the aldehyde−steric effects in the cyclic transition

(1) (a) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, U.K., 1991; Vol. 2, p 181. (b) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, U.K., 1991, Vol. 2, p 239. (c) Braun, M. In *Methods of Organic Chemistry (Houben-Weyl). Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: New York, 1996; Vol. E-21, p 1603.

(2) Review: O'Brien, P. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439.

(3) (a) Murray, D. H.; Albizati, K. F. *Tetrahedron Lett.* **1990**, *31*, 4109. (b) Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965.

(4) For other pertinent studies of reactions and synthetic applications of dioxanones see: (a) Enders, D. In *Stereoselective Synthesis*; Ottow, E., Schollkopf, K., Schulz, B.-G., Eds.; Springer: Berlin, 1994; p 63. (b) Enders, D.; Prokopenko, O. F.; Raabe, G.; Runsink, J. *Synthesis* **1996**, 1095. (c) Hirama, M.; Noda, T.; Ito, S. *J. Org. Chem.* **1988**, *53*, 706.

(5) Majewski, M.; Gleave, D. M.; Nowak, P. *Can. J. Chem.* **1995**, *73*, 1616.

(6) Preliminary communication: Majewski, M.; Nowak, P. *Synlett* **1999**, 1447.

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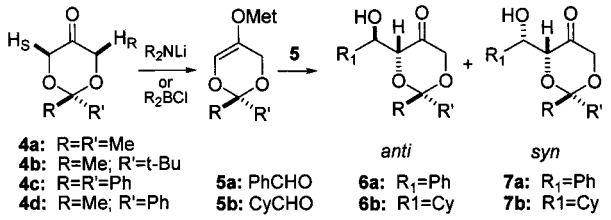
Table 1. Aldol Reaction of Boron Enolates of 4a with PhCHO[a]

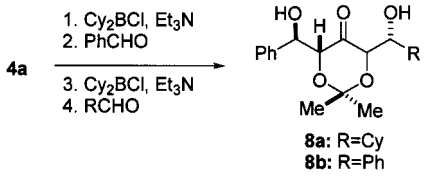
entry	reagent/amine	workup	anti:syn (**6aa**:**7aa**)	yield[b] (%)
1	BBNOTf/DIPEA	H_2O_2, pH 7	53:47	51
2	Bu_2BOTf/DIPEA	H_2O_2, pH 7	73:27	46
3	Cp_2BOTf/DIPEA	H_2O_2, pH 7	84:16	47
4	Cy_2BCl/Et_3N	H_2O_2, pH 7	96:4	64
5	Cy_2BCl/Et_3N	$HOCH_2CH_2NH_2$ (1 equiv)	92:8	60
6	Cy_2BCl/Et_3N	$HOCH_2CH_2NH_2$ (2 equiv)	70:30	64
7	Cy_2BCl/Et_3N	$HOCH_2CH_2NH_2$ (3 equiv)	71:29	47
8	Cy_2BCl/Et_3N	$NaBO_3$	94:6	31
9	Cy_2BCl/Et_3N	O_3	95:5	83
10	Cy_2BCl/Et_3N	DDO	96:4	81

[a] Lithium enolate of dioxanone **4a** gave **6aa** and **7aa** in a ratio of 65:35 and in 55% yield. [b] Combined yield of purified syn and anti products.

Scheme 2



Scheme 3



state should be maximized. In one promising experiment cyclohexanecarboxaldehyde **5b** had reacted with the lithium enolate of 2-*tert*-butyl-2-methyl-1,3-dioxan-5-one **4b** to give only one product, which had been identified by NMR and X-ray crystallography as the anti-cis isomer **6bb**.[5]

Further work on the aldol addition was clearly needed before this reaction could be used in synthesis. In an effort to optimize the reaction conditions we have examined the effect of lithium halide additives and the source of lithium enolate on the aldol reaction of dimethyldioxanone **4a**. Addition of LiCl or LiBr (3 times molar excess) to the solution of the lithium enolate did not affect diastereoselectivity (a small decrease in de was observed).[7] To generate the dioxanone lithium enolate, we used lithium diisopropylamide (LDA), LiTMP, or LiHMDS (HMDS = 1,1,1,3,3,3-hexamethyldisilane) and also amine-free conditions (the enolate was generated from the corresponding tetramethylsilane (TMS) enol ether by MeLi in Et_2O). In all cases the subsequent addition to benzaldehyde resulted in low diastereoselectivity (the anti isomer accounted for 56−65% of the purified product), but the yield was significantly higher under the amine-free conditions (86%). The potential for control of stereoselectivity in the dioxanone system seemed very limited at this stage.

Boron enolates are well-known to undergo addition to aldehydes with higher diastereoselectivity than the corresponding lithium enolates.[1b,8] We synthesized several boron enolates by treating dioxanone **4a** with dialkylboron triflate or halide in the presence of either triethylamine or *N*,*N*-diisopropylethanamine (DIPEA) and examined their reactions with benzaldehyde, the aldehyde which had shown little selectivity in previous studies mentioned above. The results are summarized in Table 1 and Scheme 2. Diastereoselectivity increased steadily with the increasing size of the ligands on boron (Table 1, entries 1−4). Dicyclohexylboron enolate afforded the aldol product **6a** in reasonably high purity (entry 4). Monitoring of the reaction by ^{1}H NMR indicated that the formation of boron enolates was fast, clean, and quantitative and the subsequent reaction with benzaldehyde was also fast and clean. Loss of the product, visible in low yields, occurred on workup, which turned out to be the critical factor. Dioxanones are sensitive to acids and bases, and some reagents commonly used for removal of boron byproducts at the workup stage (e.g., ethanolamine, sodium perborate) caused decomposition. Entries 5−7 in Table 1 illustrate how increasing amounts of ethanolamine adversely affected the reaction. Workup with a buffered hydrogen peroxide solution proved somewhat capricious with high concentration of the sodium phosphate buffer being an important variable (the more concentrated the better). Finally, both ozone and dimethyldioxirane (DDO) proved very good reagents for oxidative workup (entries 9 and 10), with the latter being much more convenient to use. To our knowledge, the use of DDO for working up reactions involving boron reagents is unprecedented and could offer a useful protocol in a more general sense, when labile compounds are involved. Conditions for highly diastereoselective reaction of dioxanone boron enolates were thus successfully developed. Next, we briefly explored the sequential bis-aldol reaction (Scheme 3).

The presence of two C−H acidic sites in a ketone at the α and α′ positions (one on each side of the carbonyl group) does not necessarily mean that two sequential aldol reactions would work efficiently, even if a single aldol was facile.[9] Diastereoselectivity is also an important issue in bis-aldol reactions because up to eight different isomers could be produced. We felt that a brief model study was necessary before planning a synthesis along the lines presented in Scheme 1. A "one pot" reaction of dioxanone **4a** with dicyclohexylboron chloride followed by addition of benzaldehyde, then by another equivalent of the boron reagent, and another equivalent of cyclo-

(7) LiBr and other additives greatly affect aldol diastereoselectivity in some systems: (a) Majewski, M.; Gleave, D. M. *Tetrahedron Lett.* **1989**, *30*, 5681. (b) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271.

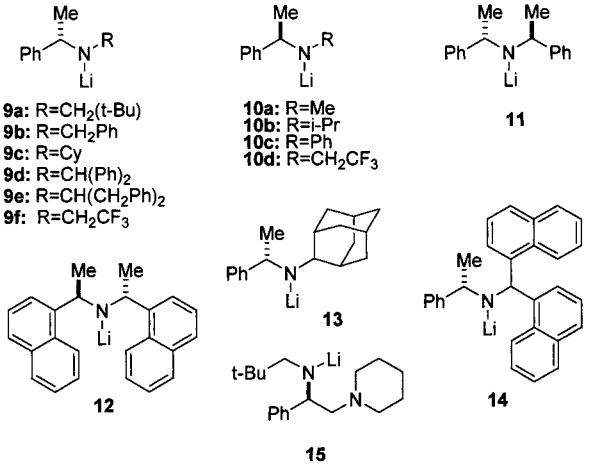
(8) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Toronto, 1984; Vol. 3, p 111.

(9) (a) McCarthy, P. A.; Kageyama, M. *J. Org. Chem.* **1987**, *52*, 4618. (b) Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013.

hexanecarboxaldehyde afforded a mixture of four compounds in the ratio of 83:9:6:2 (Scheme 3; the numbers were obtained by integration of the ^{1}H NMR spectrum of the crude product). Column chromatography yielded readily the pure major isomer **8a** (anti-trans-anti as shown in Scheme 3) in 64% yield. A similar experiment with the second aldehyde being PhCHO gave the analogous aldol **8b** in 60% yield. These results signify that, in general, the boron-mediated aldol and bis-aldol reactions of dioxanones can be controlled and should provide an efficient synthetic method.

Enantioselective Deprotonation. Treatment of achiral, C_S symmetrical ketones with chiral lithium amides leads to the formation of nonracemic lithium enolates.[2] The base discriminates between two enantiotopic protons H_R and H_S (cf., structure **4** in Scheme 2), and the resulting enolate could be trapped with electrophiles yielding ultimately chiral products. Enantioselective deprotonation has been applied successfully to synthesis of several natural products.[10] Although this method is now well-established and quite general, there is no "magic bullet". The stereoselectivity of deprotonation varies greatly with the structure of the starting ketone and the structure of lithium amide, and each new system has to be studied experimentally.

A brief study of enantioselective deprotonation of 2-*tert*-butyl-2-methyl-1,3-dioxan-5-one **4b** had demonstrated that the most popular chiral lithium amide reagents did not work very well with dioxanones (vide infra). We also observed that in all cases enantioselectivity increased when LiCl was used as additive. To develop a selective deprotonating reagent for dioxanones, we investigated a number of chiral lithium amides (**9**−**15**). The aldol



reaction of lithium enolate of **4b** with cyclohexanecarboxaldehyde (**5a**) was used as the model system (Scheme 2). This reaction gave only one diastereoisomer of the aldol, the anti-cis isomer **6bb** (out of four possible); thus, the measurement of enantiomeric excess was greatly simplified. Results of these enantioselective deprotonation studies are summarized in Table 2.

Table 2. Enantioselective Deprotonation of 4b with Chiral Lithium Amides 9−15 Followed by Reaction with Cyclohexanecarboxaldehyde (cf., Scheme 2)

entry	lithium amide	LiCl[a]	ee[b] (%)	yield[c] (%)
1	**9a**	1	(+) 19	63
2	**9b**	0	(+) 13	32
3	**9b**	0.5	(+) 39	56
4	**9c**	0.5	(+) 20	51
5	**9d**	1	(+) 70	60
6	**9e**	1	(+) 60	76
7	**9f**	1	(+) 90	61
8	**9f**	1	(+) 87[d]	86[d]
9	**10a**	0	(−) 10	43
10	**10a**	0.5	(−) 4	63
11	**10b**	0.5	(−) 16	55
12	**10c**	0	(+) 15	70
13	**10c**	0.5	(−) 32	53
14	**11**	0	(+) 18	58
15	**11**	0.5	(+) 60	51
16	**11**	1	(+) 59	49
17	**12**	0	(−) 50	41
18	**12**	0.5	(−) 60	43
19	**13**	1	(+) 80	91
20	**14**	1	(+) 90	95
21	**15**	0.5	(+) 20	51

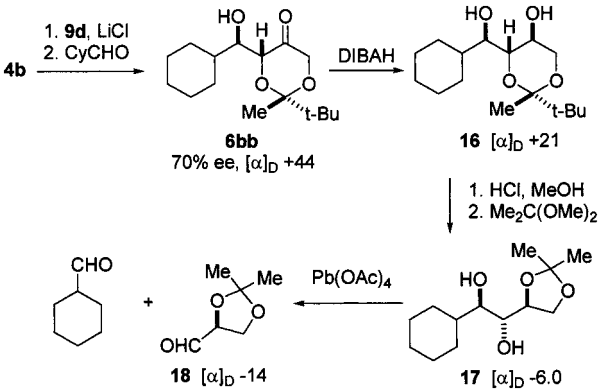
[a] Mmoles of LiCl per 1 mmol fo lithium amide. [b] The (+) and (−) refer to the dextrorotatory and the levorotatory product **6bb** (R_1 = cyclohexyl), respectively. [c] Yields refer to chromatographically purified **6bb**. [d] Lithium amide was generated in situ from the corresponding amine hydrochloride.

As mentioned above, chiral lithium amides **11** and **15** that are well-known for their ability to deprotonate cyclic symmetrical ketones with high enantioselectivity[2] did not work very well with dioxanones. Addition of LiCl did improve the selectivity in these cases, but the enantiomeric excess (ee) was still too low to be useful practically (Table 2, entries 14−16 and 21). In general, addition of LiCl to the solution of lithium amide almost always resulted in an increase of enantioselectivity (cf., entries 2 and 3, 9 and 10, 14 and 15, 17 and 18). In one remarkable case the additive caused the reversal of the absolute stereochemistry from the reaction favoring the dextrorotatory isomer to the levorotatory one (entries 12 and 13). We reported before that changing the amount of LiCl in this system caused a strong response and a monotonic plot of ee vs molar ratio of LiCl/lithium amide could be generated.[11] In most cases, the enantioselectivity did not increase further after 0.5 molar equiv of LiCl (per amide) were added. Toward the end of these studies we settled the lithium amide to LiCl-to-ketone ratio of 1:1:1 since we believed these conditions to be closest to the optimum for diverse systems. The results in Table 2 indicate that increasing the size of the R group in chiral lithium amides of general structure **9** (or **10**) is beneficial to selectivity. Entries 10, 11, 13, 3, 5, and 20 in Table 2 refer to the series of lithium amides where the size of the R group increases from methyl through isopropyl, neopentyl, and diphenylmethyl until, ultimately, the very bulky dinaphthylmethyl group in compound **14** yields excellent enantioselectivity. The electronic effects also seem to matter, and R groups having electron-withdrawing character result in more selective reagents (cf., entries 1 and 3, 4 and 13, 1 and 7). This is especially apparent in the reaction with fluorinated chiral amide **9f** (entries 7, 8) which, together with other fluorinated chiral lithium amides, was developed by Koga and proved an effective

(10) For earlier examples cf.: (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry*, **1991**, *2*, 1. Examples of recent syntheses: (b) Honda, T.; Kimura, N. Sato, S.; Kato, D.; Tominaga, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1043. (c) Honda, T.; Kimura, N.; Tsubuki, M. *Tetrahedron: Asymmetry* **1993**, *4*, 1475. (d) Muraoka, O.; Okumura, K.; Maeda, T.; Tanabe, G.; Momose, T. *Tetrahedron: Asymmetry* **1994**, *5*, 317. (e) Majewski, M.; Lazny, R.; Ulaczyk, A. *Can. J. Chem.* **1997**, *75*, 754. (f) Majewski, M.; Lazny, R. *J. Org. Chem.* **1995**, *60*, 5825.

(11) Majewski, M.; Lazny, R.; Nowak, P. *Tetrahedron Lett.* **1995**, *36*, 5465.

Scheme 4

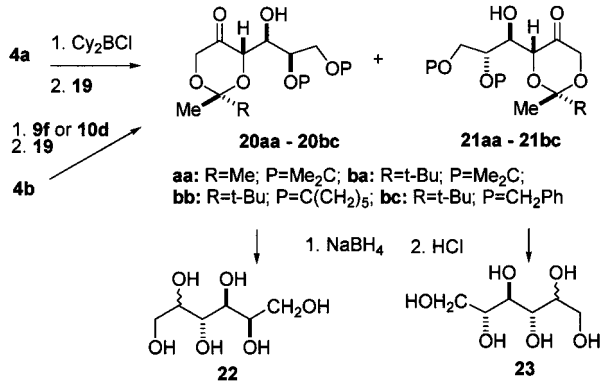


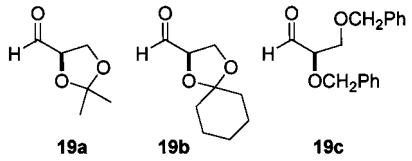
deprotonating reagent in several different systems.[12] Overall, we were able to find two very selective chiral lithium amide reagents, compounds **9e** and **14**, which deprotonated dioxanones with synthetically useful selectivity.

Absolute stereochemistry of dioxanone deprotonation deserves mention. To establish which chiral lithium amides abstracted the H_R proton and which one preferred the H_S one, we needed to correlate one of the aldol products with a compound of known absolute stereochemistry. We were able to accomplish that, somewhat indirectly, by degrading the aldol product **6bb** to a glyceraldehyde derivative (Scheme 4). Reduction of **6bb** with diisobutylaluminum hydride (DIBAH) afforded two diastereoisomeric diols in a ratio of 92:8. Diol **16** was the major product (isolated in 67% yield). The minor product, having the newly created OH group at the α face, was crystalline and provided us with a crystal structure, thus furnishing proof of relative stereochemistry.[5] Diol **16** was then subjected to transacetalization, which afforded compound **17** as the major product. Compound **17** was cleaved readily with lead tetraacetate to give *S*-isopropylideneglyceraldehyde **18**. Thus absolute configuration of the dextrorotatory isomer of compound **6bb**, originating from deprotonation of dioxanone **4b** with chiral lithium amide **9d**, was established to be as drawn in Scheme 4.

Synthesis of Carbohydrate Derivatives. Potential polyoxygenated synthetic targets were identified in Scheme 1 by structures **2** and **3**. The dioxanone-based methodology is readily amenable to synthesis of carbohydrates, and it should be noted that although the main themes in modern carbohydrate synthesis involve manipulation of readily available monosaccharides and synthesis of oligosaccharides, stereoselective total synthesis of "rare" sugars is a challenging and practically important undertaking.[13] To use dioxanones as building blocks for carbohydrate synthesis, a control of relative and absolute stereochemistry of aldol addition of dioxanone enolates is necessary. In the foregoing sections we have described the development of conditions for high diastereoselectivity using boron enolates and high enantioselectivity using lithium enolates. The former method did not offer an obvious potential for synthesizing enantiomerically pure compounds, while the latter suffered from lack of diastereoselectivity in a broad sense, only aldehydes branched at the α-carbon worked well. While dioxanone boron enolates do not provide obvious means to build chiral targets by manipulating the structure of the enolate, one could attempt to construct a system in which stereoselectivity rests in the chiral aldehyde reagent.[14] To explore this possibility, addition of the dicyclohexylboron enolate of **4a** to protected *R*-glyceraldehydes **19a,b** (Scheme 5) was tested. There are four diasteroisomeric aldol products which could form in this reaction corresponding to derivatives of four ketohexoses: D-tagatose, D-psicose, D-fructose, and D-sorbose. Isopropylidene glyceraldehyde **19a** afforded only two of

Scheme 5





these products in a ratio of 85:15 and in a modest yield of 59% (the DDO workup, described above, was used). The major product was subsequently identified as the D-tagatose derivative **20aa** and the minor isomer as the D-psicose derivative **21aa**. Isopropylidene glyceraldehyde is known to have a tendency to polymerize which could adversely affect the reactions involving this reagent. Trying to circumvent this potential problem, we tried another glyceraldehyde derivative **19b** having the diol functionality protected with a different group.[15] This reagent afforded a mixture of compounds **20aa** and **21aa** in 83% yield, but the stereoselectivity was somewhat diminished and the ratio of the products was 80:20.

A combination of a chiral dioxanone enolate with a chiral aldehyde could offer increased control of stereoselectivity due to double stereodifferentiation.[16] To investigate this possibility, we have conducted experiments with two enantiomeric lithium enolates of dioxanone **4b**, generated separately in high enantiomeric excess by using chiral lithium amides **9f** or **10d** (Scheme 5, Table 3). Three *R*-glyceraldehyde derivatives were used (**19a**−**c**), and it was noted that the isopropylidene-protected glyceraldehyde **19a** was the most selective reagent (but the yields were higher when **19b** was used). Treatment

(12) Aoki, K.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 2505, and references cited therein.

(13) (a) Jurczak, J.; Zamojski, A. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1997; p 593. (b) Collins, P.; Ferrier, R. *Monosaccharides: Their Chemistry and Their Roles in Natural Products*; Wiley: New York, 1995; p 53.

(14) C.f.: ref 1c, p 1713.

(15) Review: Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.

(16) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076.

Table 3. Double Stereoselection Involving Chiral Enolates of Dioxanone 4b and Protected *R*-Glyceraldehydes 19 (cf., Scheme 5)

entry	lithium amide	aldehyde	**20aa**:**21aa**:**(?)**[a]	yield[b] (%)
1	**10d**	**19a**	82:10: (8)	77
2	**10d**	**19b**	71:15: (14)	96
3	**10d**	**19c**	60:16: (14:10)	82
4	**9f**	**19a**	3:97	81
5	**9f**	**19b**	16:74: (10)	97
6	**9f**	**19c**	16:78: (6)	80

[a] The question mark symbolizes additional (not identified) byproduct(s). [b] Combined yields of all products after purification.

of **4b** with the chiral lithium amide **10d**, followed by addition of the protected glyceraldehyde **19a** yielded compound **20aa** as the major product (Table 3, entry 1), which was easily purified by column chromatography. The structure of **20aa** was assigned to be a derivative of D-tagatose by chemical correlation. A sample of **20aa** was reduced with $NaBH_4$ followed by removal of both acetonide groups to yield a mixture of two corresponding hexitols (**22**, Scheme 5), the spectra of which were compared with these obtained from a commercially available sample (cf., Experimental Section). The enantiomeric enolate, produced using base **9f**, yielded the corresponding D-psicose derivative **21aa** (entry 4). Stereoselective synthesis of ketohexose derivatives was thus successfully realized.

We reported previously that acetal dioxanones (R = H, R′ = alkyl) were much more difficult to work with then ketal dioxanones (R and R′ = alkyl groups).[5] Searching for a better starting material, we briefly investigated two dioxanones having the phenyl group at C-2 (compounds **4c** and **4d**). Compound **4c** did not offer significant advantages over compound **4a** (although the yields of aldol addition experiments were often higher with **4c** by up to 20%, as in the case of lithium enolate added to PhCHO). Compound **4d** displayed a significantly lower enantioselectivity in deprotonation experiments with chiral lithium amides, which could be attributed to the *A* value of the phenyl group being smaller than the *A* value of *tert*-butyl,[17] resulting in lower conformational stabilization of the starting material.[18]

Stereochemical Considerations. Reactions of dioxanones, described above, show some unusual features. We reported previously on striking electrophilicity of dioxanones; their high reactivity toward nucleophiles approaches the reactivity of aldehydes rather then ketones, and these compounds are very prone to reduction by LDA.[5] These features are related to inductive effects of the two oxygen atoms in the dioxanone ring. These two oxygen atoms also precipitate stereoelectronic effects which were used to rationalize the preference of 1,3-dioxane-5-carboxylate esters for equatorial alkylation.[19] Stereoselectivity of reactions involving dioxanone enolates also has some unusual aspects: aldehydes add to dioxanone enolates via equatorial attack (as exemplified by the transformation of **4b** to **6bb**), the reactions with protected glyceraldehydes follow the Cram chelate model,[20]

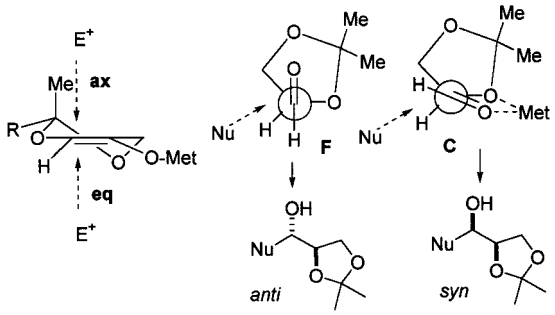


Figure 1. Relevant elements of stereocontrol. Comparison of axial (ax) and equatorial (eq) approach of an electrophile to dioxanone enolate and of the Felkin−Ahn (F) and Cram chelate (C) models applied to glyceraldehyde.

which results in the anti-syn isomers (**20**) being formed faster than the anti-anti isomers (**21**), and not the Felkin−Anh model (nucleophilic addition to glyceraldehyde usually favors the latter[15]), and addition of chiral lithium enolates of **4b** to glyceraldehyde derivatives is highly stereoselective and shows reversal of the sense of diastereoselectivity as the enolate is changed from the *R* isomer to the *S* isomer (cf., Scheme 5 and Table 3). We cannot fully rationalize all of these phenomena at this time; however, some comments can be made. Reactions of cyclic enolates with electrophiles were discussed in detail by Evans,[21] and it was pointed out that the axial attack of the electrophile, albeit favorable on stereoelectronic grounds, could be disadvantaged by steric effects. This is likely the case in our system, where the axial attack suffers an unfavorable 1,3-steric interaction from the pseudoaxial Me group (Figure 1).

Nucleophilic attack on *R*-isopropylidene glyceraldehyde usually favors the *si* face, in agreement with the Felkin−Anh model, and results in the relative stereochemistry of the two newly created stereogenic centers being anti.[15,22] Exceptions are known, however, and syn-selective addition was observed in several systems.[15,23] Dioxanones appear to be one of these exceptions; and the addition of achiral dioxanone enolates to **19a** proceeds predominantly to the *re* face of the aldehyde to afford tagatose derivative **20** as the major product (Scheme 5). Chiral enolates of dioxanones apparently obey the rules of a reagent-controlled system;[24] chirality of the enolate dominates reactivity. Examples of reagent-control systems of this type, where diastereotopic face selectivity of the aldehyde reagent was reversed, have been reported before.[25]

In summary, 1,3-dioxan-5-ones are promising synthetic building blocks. Their boron enolates were generated efficiently and provided good control of relative stereochemistry in the aldol addition reaction. Reagents for efficient enantioselective deprotonation of dioxanones in up to 90% ee were identified. Enantioselective deprotonation combined with the reaction of the resulting

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(18) The importance of "conformational anchoring" in cyclic ketones, related to the belief that, due to stereoelectronic effects, axial protons are abstracted by bases faster than equatorial protons was pointed out before. In some cases, however, the conformational bias seems to matter little; cf.: Majewski, M.; MacKinnon, J. *Can. J. Chem.* **1994**, *72*, 1699.

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lithium enolates with protected glyceraldehyde provided a quick synthetic entry into chiral polyoxygenated natural products. The utility of the method was demonstrated by synthesis of monosaccharide derivatives having all the OH groups protected differently, a feature which might be useful for further synthetic use of these sugars.

Experimental Section

General Methods. All air-sensitive reactions were carried out under nitrogen. Tetrahydrofuran (THF) and Et_2O were distilled under nitrogen from sodium and benzophenone. Dichloromethane and diisopropylamine were distilled from CaH_2. LiCl was dried at 130−150 °C under vacuum overnight, and it was used either as a solid or as a solution in THF.

Flash column chromatography (FCC)[26] and dry flash chromatography (DFC)[27] were carried out using Merck silica gel 60 (230−400 mesh) and Sigma silica gel type H (10−40 μm), respectively. Thin-layer chromatography (TLC) was performed on precoated glass plates (Merck, silica gel 60, F254). The spots were detected using UV light (254 nm) or with a developing solution prepared by dissolving concentrated H_2SO_4 (50 g), cerium(IV) sulfate (10 g), and phosphomolybdic acid hydrate (40 g) in water (1 L) followed by charring on a hot plate. Concentrated phosphate buffer, used to quench reactions, was prepared by dissolving Na_2HPO_4 (47 g) and NaH_2PO_4 (32 g) in H_2O (0.5 L). Optical rotations were measured on a Perkin-Elmer 241 polarimeter (1 dm, 1 mL cell); all concentrations are given in grams per 100 mL. Parent chiral amines of reagents **9**−**15** were synthesized by following the well-established literature procedures,[28] and the dioxanone substrates (**4**) were synthesized as described before.[5] Derivatives of glyceraldehyde (**19**) were synthesized according to literature procedures.[29]

General Procedures. Procedure A1. Enolization of Dioxanone and Aldol Addition. Diisopropylamine (0.17 mL, 1.20 mmol) was dissolved in THF (10 mL). The solution was cooled to 0 °C, and *n*-BuLi was added (0.44 mL, 1.10 mmol, 2.5 M solution in hexanes). After 0.5 h, the solution of the lithium amide was cooled to −78 °C and dioxanone **4** (1.00 mmol), dissolved in THF (0.5 mL), was added over 5 min. After stirring for an additional 5 min, the aldehyde (1.10 mmol) was added. The mixture was stirred for 5 min at −78 °C and then was quenched with a concentrated pH 7 buffer (20 mL) and extracted with Et_2O (3 × 50 mL). The combined extracts were washed with brine (20 mL) and dried with $MgSO_4$. The solvents were evaporated, and diastereoselectivity of the reaction was determined by ^{1}H NMR. The crude product was purified by DFC (hexane, then 4:1 hexane:ethyl acetate). The yields reported refer to the chromatographically pure material.

Procedure A2. Enantioselective Deprotonation in the Presence of Lithium Chloride (Added as Solid) Followed by Aldol Reaction. One of the chiral amines **9**−**15** (1.00 mmol) and LiCl (1.00 mmol, 42 mg) were dissolved in THF (10 mL). The solution was cooled to 0 °C, and *n*-BuLi was added (0.44 mL, 1.10 mmol, 2.5 M solution in hexanes). After 1 h, the solution was cooled to −78 °C, and dioxanone **4b** (172 mg, 1.00 mmol in 0.5 mL of THF) was added over 5 min. After stirring for 0.5 h, cyclohexanecarboxaldehyde **5b** (0.13 mL, 1.10 mmol) was added and the reaction mixture was stirred for 5 min at −78 °C. The reaction was then quenched with a concentrated pH 7 buffer (20 mL), and the mixture was extracted with Et_2O (3 × 50 mL). The extracts were washed with brine (20 mL) and dried with $MgSO_4$. The solvents were evaporated, and the enantioselectivity of the reaction was determined by ^{1}H NMR using a chiral shift reagent, (+)-Eu(hfc)$_3$. The crude product was purified by DFC (hexane followed by hexane:ethyl acetate, 4:1). The yields reported refer to the chromatographically pure material.

Procedure B: Boron-Mediated Aldol Reaction of 2-Substituted 1,3-Dioxan-5-one. This procedure was adapted from the literature.[30] A tertiary amine (either DIPEA or NEt_3; 2.00 mmol) was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to 0 °C. The dialkylboron halide or triflate (c.f, Table 1, 1.00 mmol) was added with stirring, followed by addition of the dioxanone (1.00 mmol), and the resulting mixture was stirred for 15 min. The aldehyde (1.10 mmol) was then added at 0 °C (procedure B1), or, alternatively, the reaction mixture was cooled to −78 °C and the aldehyde was added at this temperature (procedure B2). After an additional 15 min of stirring, the reaction was quenched with concentrated pH 7 buffer (20 mL) and extracted with Et_2O (3 × 50 mL). The combined extracts were washed with brine (2 × 10 mL) and dried with $MgSO_4$. The solvents were evaporated, and the residue was worked up in one of the following ways:

(a) The residue was dissolved in MeOH (9 mL) and cooled to 0 °C. Concentrated pH 7 buffer (3 mL) and H_2O_2 (3 mL, 30%) were next added. The solution was stirred at 0 °C for 3 h. Next, Et_2O (150 mL) was added, and the solution was washed with saturated $NaHCO_3$ (2 × 15 mL) and brine (15 mL) and was dried with $MgSO_4$. The solvents were then removed affording the crude product.

(b) The residue was dissolved in a cold (0 °C) acetone solution of dimethyldioxirane (30 mL, 0.1 M). After 1 h, acetone was removed and the mixture was dissolved in Et_2O (100 mL); the solution was washed with saturated $NaHCO_3$ (2 × 15 mL) and brine (15 mL) and was dried with $MgSO_4$. The solvents were then removed affording the crude product.

(c) The residue was dissolved in CH_2Cl_2 (50 mL). The solution was cooled to −78 °C and was saturated with ozone. The excess of ozone was removed with a stream of argon. Next, the solution was washed with saturated $NaHCO_3$ (2 × 15 mL) and was then dried with $MgSO_4$. The solvents were then removed, affording the crude product.

Diastereoselectivity of the reaction was determined by ^{1}H NMR on the crude product. The crude product was then purified by DFC (hexane, then 1:1 hexane:AcOEt). The yields reported refer to the combined yields of all isomers.

***anti*- and *syn*-4-(Hydroxyphenylmethyl)-2,2-dimethyl-1,3-dioxan-5-one (6aa, 7aa).**[5] Yields and selectivity of the boron-mediated aldol addition of dioxanone **4a** to PhCHO are summarized in Table 1. E.g., procedure A1 afforded the mixture of **6aa** and **7aa** as a colorless oil in 55% yield. The diastereoselectivity of the reaction was 65:35. The isomers were separated by DFC (hexane−hexane:ethyl acetate (4:1)) to provide the minor isomer **7aa** in 16% yield and the major isomer **6aa** in 27% yield. Procedure B2b afforded a mixture of **6aa** and **7aa** in 81% yield and in a ratio of 96:4. Spectral properties of **6a** and **7a** were in agreement with data published before.[5]

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4-(Cyclohexylhydroxymethyl)-6-(hydroxyphenylmethyl)-2,2-dimethyl-1,3-dioxan-5-one (8a). Triethylamine (0.28 mL, 2.00 mmol) was dissolved in CH_2Cl_2 (10 mL), and the solution was cooled to 0 °C. Dicyclohexylboron chloride (2.00 mL, 0.5 M solution in hexane, 1.00 mmol) was added, and the solution was stirred for 5 min. Next, dioxanone **4a** (0.130 g, 1.00 mmol) was added, and, after stirring for 15 min, PhCHO (0.10 mL, 1.00 mmol) was added. After stirring for another 15 min, NEt_3 (0.28 mL, 2.00 mmol) was added followed by addition of dicyclohexylboron chloride (2.00 mL, 0.5 M solution in hexane, 1.00 mmol) and, after 15 min, aldehyde **5b** (0.17 mL, 1.50 mmol). After stirring for 15 min, the reaction was quenched with concentrated pH 7 buffer (20 mL) and extracted with diethyl ether (3 × 50 mL). The extracts were washed with brine (2 × 10 mL) and dried with $MgSO_4$. The solvents were evaporated, and the residue was dissolved in methanol (18 mL) and cooled to 0 °C. Concentrated pH 7 buffer (6 mL) and hydrogen peroxide (6 mL, 30%) were next added. The solution was stirred at 0 °C for 3 h, Et_2O (150 mL) was added, and the solution was washed with saturated $NaHCO_3$ (2 × 15 mL) and brine (15 mL) and was dried with $MgSO_4$. The solvents were removed, and the mixture was analyzed by ^{1}H NMR. Four isomers were detected in the ratio of 83:09:6:2. The major product was isolated by DFC (9:1 hexane:CH_2Cl_2 followed by 9:1:2 hexane:CH_2Cl_2:AcOEt), which gave a colorless liquid (224 mg, 64%). Only the major product **8a** was characterized. Properties: R_f 0.35 (2:1 hexane:ethyl acetate); IR 3517, 1733, 1221 cm^{-1}; ^{1}H NMR 7.18−7.43 (m, 5H), 4.90 (d, J = 7.0 Hz, 1H), 4.33 (d, J = 7.0 Hz, 1H), 4.07 (d, J = 7.0 Hz, 1H), 3.64 (dd, J_1 = 7.0, J_2 = 2.5 Hz, 1H), 3.10 (br s, 2H), 1.42−1.89 (m, 6H), 1.37 (s, 3H), 1.25 (s, 3H), 1.02−1.40 (m, 5H); ^{13}C NMR 213.9, 139.1, 127.9, 127.1, 101.4, 76.3, 74.3, 73.7, 72.6, 38.5, 29.4, 26.4, 26.3, 26.0, 23.6, 23.4; MS (CI-NH_3) 366 (M + 18, 90), 260 (25), 254 (61), 243 (33), 240 (100), 219 (21), 184 (15), 165 (15), 161 (16); HRMS (CI-NH_3) 366.2281 (M + 18), calcd for $C_{20}H_{32}NO_5$ 366.2280.

4,6-Bis-(hydroxyphenylmethyl)-2,2-dimethyl-1,3-dioxan-5-one (8b). The procedure described above for compound **8a** was followed on the same scale. Five isomers were detected in the crude product in the ratio of 80:10:04:03:03. The major product was isolated by DFC (9:1 hexane:CH_2Cl_2 followed by 9:1:2 hexane:CH_2Cl_2:AcOEt) to provide a colorless liquid (206 mg, 60%). Only the major product **8b** was characterized. Properties: R_f 0.32 (2:1 hexane:ethyl acetate); IR 3530, 1738, 1224, 1027 cm^{-1}; ^{1}H NMR 7.20−7.39 (m, 10H), 4.88 (d, J = 6.5 Hz, 2H), 4.22 (d, J = 6.5 Hz, 2H), 3.39 (br s, 2H), 1.18 (s, 6H); ^{13}C NMR 212.1, 139.0, 128.0, 127.0, 101.7, 76.4, 72.6, 23.3; MS (CI-NH_3) 360 (M + 18, 21), 254 (57), 240 (16), 237 (16), 220 (15), 219 (100), 178 (31), 165 (25), 161 (35), 131 (91), 124 (32), 113 (17), 105 (44); HRMS (CI-NH_3) 360.1806 (M + 18), calcd for $C_{20}H_{26}NO_5$ 360.1811.

***cis*-2-*tert*-Butyl-4-(cyclohexylhydroxymethyl)-2-methyl-1,3-dioxan-5-one (6bb).** Procedure A1 afforded racemic compound **6bb** as a white solid in 61% yield. Only one diastereoisomer was detected. The spectral data were in agreement with values published before.[5] Compound **6bb** was also synthesized from the trimethylsilyl enol ether of 2-*tert*-butyl-2-methyl-1,3-dioxan-6-one as follows: TMS enol ether of **4b** (synthesized according to a general procedure published previously,[5] 122 mg, 0.50 mmol) was dissolved in THF (10 mL). The solution was cooled to −78 °C and *n*-BuLi was added (0.22 mL, 0.55 mmol, 2.5 M solution in hexanes). After 1 h, cyclohexanecarboxaldehyde (67 μL, 0.55 mmol) was added and, after an additional 5 min the reaction was quenched with concentrated pH 7 buffer (20 mL) and extracted with Et_2O (3 × 50 mL). The extracts were washed with brine (20 mL) and dried with $MgSO_4$. The solvents were evaporated, and the crude product was purified by SCC (4:1 hexane:ethyl acetate) to provide the pure aldol **6bb** (136 mg, 96%). Only one isomer was detected (^{1}H NMR).

The optically active (2*S*,4*R*)-**6bb** enantiomer was obtained by procedure A2: (*S*)-*N*-(2,2,2-trifluoroethyl)-1-phenylethylamine was used instead of diisopropylamine to generate the lithium amide **9f**. The reaction was performed in the presence of 1 equiv of LiCl. The pure compound (2*S*,4*R*)-**6bb**, having 90% ee, was obtained in 61% yield. The (2*R*,4*S*)-**6bb** enantiomer was obtained in an analogous way using the (*R*)-*N*-(2,2,2-trifluoroethyl)-1-phenylethylamine in 90% ee and 70% yield. Specific rotation: the 2*S*,4*R*-isomer of **6bb**, $[\alpha]^{25}_D$ +56.3 (c 0.8, MeOH, 90% ee); the 2*R*,4*S*-isomer had $[\alpha]^{25}_D$ −56.1 (c 1.0, MeOH, 90% ee).

***cis*-2-(Cyclohexylhydroxymethyl)-2-methyl-2-phenyl-1,3-dioxan-5-one (6db).** Procedure A1 afforded the racemic compound **6db** as a white solid in 55% yield. Only one diastereisomer was detected. The optically active (2*S*,4*R*)-**6db** was obtained by procedure A2: (*S*)-*N*-(2,2,2-trifluoroethyl)-1-phenylethylamine was used instead of diisopropylamine to generate the lithium amide. The reaction was performed in the presence of 1 equiv of LiCl. Pure compound **6db**, having 54% ee, was obtained in 64% yield. Properties: R_f 0.31 (4:1 hexane:ethyl acetate); $[\alpha]^{25}_D$ +35.9 (c 1.0 methanol, 54% ee, 2*S*,4*R*-**6db**); IR 3523, 1736, 1169 cm^{-1}; ^{1}H NMR 7.50−7.58 (m, 2H), 7.31−7.45 (m, 3H), 4.42 (dd, J_1 = 17.0, J_2 = 1.5 Hz, 1H), 4.18 (d, J = 17.0 Hz, 1H), 3.92 (d, J = 7.5 Hz, 1H), 3.65−3.75 (m, 1H), 3.09 (d, J = 2.0 Hz, 1H), 1.48−1.81 (m, 5H), 1.69 (s, 3H), 0.91−1.38 (m, 6H); ^{13}C NMR 211.3, 140.9, 128.5, 128.3, 125.9, 101.6, 74.7, 74.5, 67.1, 38.3, 29.7, 26.9, 26.5, 26.3, 26.0, 25.7; MS (CI-NH_3) 305 (M + 1, 31), 193 (100), 121 (18), 105 (27); HRMS (CI-N_3) 305.1753 (M + 1), calcd for $C_{18}H_{25}O_4$ 305.1753.

Reduction of Compound 6bb. Reduction of the ketone group in **6bb** was undertaken during structural assignment studies. It was established, that this compound could be reduced selectively to the cis-cis diol **16** by using DIBAH or to the cis−trans epimer of **16**, by using Raney nickel. The latter compound yielded well-defined crystals allowing crystallographic determination of the relative stereochemistry.[5]

Compound 16. Aldol **6bb** (0.860 g, 3.02 mmol) was dissolved in THF (25 mL) and cooled to −78 °C. DIBAH (2.00 mL, 1.5 M solution in toluene, 3.00 mmol) was added, and the reaction was stirred for 1 h. The reaction was quenched with MeOH (10 mL), and the mixture was warmed to room temperature. Saturated $NaHCO_3$ solution (5 mL) was added, followed by Celite (10 g), and Et_2O (100 mL). The slurry was stirred for 15 min and filtered. The filter cake was washed with Et_2O (2 × 50 mL). The resulting organic solution was washed with brine (2 × 20 mL) and dried with $MgSO_4$, and the solvents were evaporated. Two diastereoisomers were detected in the crude product in a ratio of 92:8 (^{1}H NMR). The major product was isolated by DFC (hexane followed by 1:1 hexane:AcOEt) which gave a white solid (0.579 g, 67%). The optically active 2*S*,4*R*,5*S*-**16** was prepared in the same way using the 2*S*,4*R*-**6bb** aldol having 70% ee as the starting material. Properties: R_f 0.38 (2:1 hexane:ethyl acetate); mp 96−99 °C; $[\alpha]^{25}_D$ +20.9 (c 0.7, chloroform, 70% ee, 2*S*,4*R*,5*S*-isomer); IR 3379, 1167, 1066 cm^{-1}; ^{1}H NMR 4.00−4.13 (br s, 1H), 3.75−3.90 (m, 1H), 3.50−3.70 (m, 4H), 2.94−3.03 (br s, 1H), 1.50−1.83 (m, 6H), 1.36 (s, 3H), 0.87−1.30 (m, 5H), 0.93 (s, 9H); ^{13}C NMR 102.2, 80.1, 71.2, 67.7, 63.7, 39.3, 39.1, 29.2, 26.5 (2×), 26.2, 25.6, 24.6, 12.1; MS (CI-N_3) 288 (M + 2, 26), 287 (M + 1, 100), 173 (16), 169 (11); Anal. Calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.55. Found: C, 67.89; H, 10.68.

Compound 17. Compound **16** (579 mg, 2.02 mmol, 70% ee) was dissolved in MeOH (25 mL). Water (1 mL) and concentrated HCl (0.5 mL) were added, and the resulting solution was refluxed for 15 min. Next, the solvent was evaporated, and the residual water was removed by evaporation with ethanol (2 × 50 mL) to provide a white solid (R_f 0.04, 1:1 hexane:ethyl acetate) in quantitative yield. The crude tetraol (413 mg, 2.02 mmol) was dissolved in THF (10 mL) and treated with 2,2-dimethoxypropane (1 mL), acetone (1 mL), and concentrated HCl (0.1 mL). After 0.5 h, when the TLC analysis indicated that all the starting material was consumed, the reaction was quenched with concentrated NH_4OH (1 mL). The solvent was evaporated, and the residue was dissolved in Et_2O (100 mL). The resulting solution was washed with brine (3 × 10 mL), dried with $MgSO_4$, and concentrated. The GC analysis indicated the presence of three products in the ratio of 20:54:26. DFC (hexane followed by 1:1 hexane:ethyl acetate) provided the three products in pure form as colorless oils.

Compound **17** (the 3,4-acetonide, side chain numbered from the cyclohexane ring) was the major product (eluted second) and was obtained in 50% yield. The other products were identified as the 1,2-acetonide (20%) and the bis-acetonide (13%). Properties: R_f 0.39 (1:1 hexane:ethyl acetate); $[\alpha]^{25}_D$ −6.0 (c 2.4, chloroform, sample having 70% ee); ^{1}H NMR 3.78−4.22 (m, 4H), 3.33−3.45 (m, 1H), 2.75 (br s, 2H), 0.91−2.00 (m, 11H), 1.38 (s, 3H), 1.33 (s, 3H); ^{13}C NMR 108.8, 108.3, 77.4, 70.8, 68.0, 65.6, 39.8, 27.7, 28.1, 26.7, 26.5, 26.2, 25.7.

Cleavage of compound **17** (0.27 mmol sample having 70% optical purity) with lead tetraacetate (0.30 mmol) in $CDCl_3$ (2 mL, room temperature, 30 min) yielded a sample of **18** having $[\alpha]^{25}_D$ −13.5 (c 3.3, $CHCl_3$).

(−)-1,3:5,6-Di-*O*-isopropylidene-D-tagatose (20aa) and (+)-1,3:5,6-Di-*O*-isopropylidene-D-psicose (21aa). Procedure A1 gave the mixture of aldols in 70% yield. Three diastereoisomers were formed in the ratio of 55:33:12. Only the two major isomers were isolated and characterized. Procedure B2a gave a mixture of aldols in 39% yield containing two diastereoisomers in the ratio of 85:15. Procedure B2b gave a mixture of aldols in 59% yield containing two diastereoisomers in the ratio of 87:13. Properties: Compound **20aa** (major product). Mp 103−105 °C (white solid); R_f 0.23 (2:1 hexane: ethyl acetate); $[\alpha]^{25}_D$ −167.2 (c 1.1, chloroform); ^{1}H NMR 4.26−4.32 (m, 3H), 3.98−4.10 (m, 2H), 3.83−3.91 (m, 2H), 3.17 (d, J = 3.5 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 3H), 1.24 (s, 3H), 1.07 (s, 3H); ^{1}H NMR (benzene-d_6) 4.25−4.32 (m, 2H), 3.98 (dd, J_1 = 8.0, J_2 = 7.5 Hz, 1H), 3.74−3.81 (m, 2H), 3.65 (m, 1H), 3.59 (d, J = 17.5 Hz, 1H), 3.16 (d, J = 3.0 Hz, 1H), 1.48 (s, 3H), 1.35 (s, 3H), 1.24 (s, 3H), 1.07 (s, 3H); ^{13}C NMR 210.4, 109.1, 101.3, 75.2, 73.4, 70.1, 66.7, 65.6, 26.3, 25.6, 23.6, 23.5; IR 3475, 1744, 1374, 1222, 1068 cm^{-1}; MS: (CI-NH_3) 278 (M + 18, 27), 261 (M + 1, 44), 243 (100), 220 (81), 203 (51), 131 (25), 101 (46); Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.57; H, 7.89.

Compound 21aa (Minor Product). Colorless oil; R_f 0.16 (2:1 hexane:ethyl acetate); $[\alpha]^{25}_D$ +144.7 (c 3.0, chloroform); ^{1}H NMR 4.46 (dd, J_1 = 3.5, J_2 = 1.5 Hz, 1H), 4.26−4.36 (m, 2H), 3.99−4.09 (m, 4H), 2.73 (d, J = 6.0 Hz, 1H), 1.45 (s, 6H), 1.35 (s, 3H), 1.32 (s, 3H); ^{13}C NMR 207.3, 109.2, 100.6, 75.9, 74.9, 71.9, 67.0, 66.1, 26.2, 25.2, 24.4, 23.2; IR 3469, 1747, 1374, 1223, 1069; MS (CI-NH_3) 278 (M + 18, 56), 261 (M + 1, 100), 243 (88), 220 (63), 203 (51), 101 (47); HRMS (FAB) 261.1333 (M + 1), calcd for $C_{12}H_{21}O_6$ 261.1338.

(+)−(2*S*,4*R*)-2-(*tert*-Butyl)-4-[(2*R*)-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl](hydroxy)methyl]-2-methyl-1,3-dioxan-5-one (21ba). Procedure A2, with **9f**, gave a colorless oil in 81% yield. The crude product consisted of two isomers in a ratio of 93:7. Only the major isomer was characterized. Properties: R_f 0.30 (2:1 hexane:ethyl acetate); $[\alpha]^{25}_D$ +59.6 (c 1.3, chloroform); ^{1}H NMR 4.24−4.51 (m, 3H), 3.93−4.21 (m, 4H), 2.55 (br s, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.06 (s, 9H); ^{13}C NMR 206.6, 109.6, 103.4, 78.3, 74.6, 74.1, 69.5, 68.5, 66.9, 40.1, 26.1, 25.1, 15.9; IR 3488, 1739, 1151, 1058 cm^{-1}; MS (CI-NH_3) 303 (M + 1, 100), 287 (20), 285 (20), 245 (71), 203 (30), 173 (21), 131 (24), 115 (18), 101 (57); HRMS (CI-NH_3) 303.181 (M + 1), calcd for $C_{15}H_{27}O_6$ 302.181.

(−)-(2*R*,4*S*)-2-(*tert*-Butyl)-4-[(2*S*)-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl](hydroxy)methyl]-2-methyl-1,3-dioxan-5-one (20aa). Procedure A2, with base **10d**, gave a colorless oil in 77% yield. The crude product consisted of three isomers in a ratio of 82:10:8. Only the major isomer was characterized. Properties: R_f 0.29 (2:1 hexane:ethyl acetate); $[\alpha]^{25}_D$ −45.8 (c 1.2, chloroform); ^{1}H NMR 4.12−4.50 (m, 4H), 4.06 (dd, J_1 = 8.0, J_2 = 6.5 Hz, 1H), 3.93 (dd, J_1 = 6.5, J_2 = 5.0 Hz, 1H), 3.84 (dd, J_1 = 7.5, J_2 = 0.5 Hz, 1H), 3.10 (br s, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.04 (s, 9H); ^{13}C NMR 209.1, 109.3, 104.2, 76.1, 75.1, 71.2, 69.6, 65.8, 40.2, 26.3, 25.4, 25.1, 16.2; IR 3485, 1738, 1158, 1058 cm^{-1}; MS (CI-NH_3) 303 (M + 1, 78), 245 (42), 220 (31), 203 (26), 173 (100), 148 (28), 131 (51), 115 (63), 101 (60); HRMS (CI-NH_3) 303.181 (M + 1), calcd for $C_{15}H_{27}O_6$ 302.181.

(+)−(2*S*,4*R*)-2-(*tert*-Butyl)-4-[(2*R*)-1,4-dioxaspiro[4.5]dec-2-yl(hydroxy)methyl]-2-methyl-1,3-dioxan-5-one (21bb). Procedure A2 with base **9f** gave a colorless oil. The crude product consisted of three isomers in a ratio of 74:16:10 (97% yield). Only the major isomer **21bb** was characterized. Properties: R_f 0.39 (2:1 hexane:ethyl acetate); $[\alpha]^{25}_D$ +62.9 (c 1.1, chloroform); ^{1}H NMR 4.34−4.46 (m, 1H), 4.18−4.30 (m, 1H), 3.85−4.15 (m, 5H), 2.65 (br s, 1H), 1.30−1.64 (m, 10H), 1.35 (s, 3H), 1.01 (s, 9H); ^{13}C NMR 206.0, 110.3, 103.3, 78.6, 74.3, 74.1, 69.4, 66.7, 40.2, 35.8, 34.5, 25.1, 25.0, 23.9, 23.7, 15.9; IR 3464, 1739, 1162, 1096, 1052 cm^{-1}; MS 342 (M$^+$, 20), 299 (32), 199 (21), 141 (70), 127 (100), 101 (26), 99 (25), 83 (24), 81 (20), 57 (23), 55 (29); HRMS (EI) 342.2041 (M), calcd for $C_{18}H_{30}O_6$ 342.2042.

(−)-(2*R*,4*S*)-2-(*tert*-Butyl)-4-[(2*S*)−(2*R*)-1,4-dioxaspiro-[4.5]dec-2-yl(hydroxy)methyl]-2-methyl-1,3-dioxan-5-one (20bb). Procedure A2 with base **10d** gave a colorless oil in 96% yield. The crude product consisted of three isomers in a ratio of 71:15:14. Only the major isomer **20bb** was characterized. Properties: R_f 0.38 (2:1 hexane:ethyl acetate); $[\alpha]^{25}_D$ −45.0 (c 1.0, chloroform); ^{1}H NMR 4.10−4.48 (m, 3H), 3.91−4.08 (m, 2H), 3.58−3.89 (m, 2H), 1.26−1.63 (m, 11H), 1.36 (s, 3H), 0.97 (s, 9H); ^{13}C NMR 209.0, 109.8, 104.2, 76.1, 74.5, 70.9, 69.6, 65.3, 40.2, 35.8, 34.8, 25.1, 25.0, 23.9, 23.7, 16.2; IR 3469, 1739, 1164, 1103, 1042 cm^{-1}; MS 342 (M, 14), 299 (30), 199 (23), 171 (22), 141 (60), 127 (100), 126 (49), 101 (37), 99 (37), 55 (20); HRMS (EI) 342.2042 (M), calcd for $C_{18}H_{30}O_6$ 342.2042.

(−)-(2*S*,4*R*)-4-[(1*R*,2*R*)-2,3-Bis(benzyloxy)-1-hydroxypropyl]-2-(*tert*-butyl)-2-methyl-1,3-dioxan-5-one (21bc). A modified procedure A2 with base **9f** (the aldehyde was used neat) gave a colorless oil in 80% yield. The crude product consisted of three isomers in a ratio of 78:16:6. Only the major isomer **21bc** was characterized. Properties: R_f 0.35 (2:1 hexane:ethyl acetate); $[\alpha]^{25}_D$ −33.0 (c 1.4, chloroform); ^{1}H NMR 7.18−7.40 (m, 10H), 4.8-−4.81 (m, 1H), 3.88−4.65 (m, 8H), 3.65−3.82 (m, 2H), 3.30 (br s, 1H), 1.30 (s, 3H), 0.99 (s, 9H); ^{13}C NMR 210.3, 138.3, 137.9, 128.2, 128.1, 127.5 (2×), 127.3, 127.2, 103.7, 76.2, 74.5, 73.3, 73.0, 71.4, 70.0, 69.2, 40.0, 25.1, 15.9; IR 3425, 1728, 1103 cm^{-1}; MS (CI-NH_3) 460 (M + 18, 44), 443 (M + 1, 16), 442 (M, 13), 425 (26), 335 (27), 317 (47), 288 (73), 181 (48), 173 (23), 108 (33), 91 (100); HRMS (EI) 442.2356 (M), calcd for $C_{26}H_{34}O_6$ 442.2355.

(+)−(2*R*,4*S*)-4-[(1*S*,2*R*)-2,3-Bis(benzyloxy)-1-hydroxypropyl]-2-(*tert*-butyl)-2-methyl-1,3-dioxan-5-one (20bc). A modified procedure A2 with base **10d** (the aldehyde was used neat) gave a colorless oil in 82% yield. The crude product consisted of four isomers in a ratio of 60:16:14:10. Only the major isomer **20bc** was characterized. Properties: R_f 0.34 (2:1 hexane:ethyl acetate); $[\alpha]^{25}_D$ +14.6 (c 1.2, chloroform); ^{1}H NMR 7.15−7.40 (m, 10H), 3.88−4.95 (m, 9H), 2.58−3.84 (m, 2H), 2.15 (s, 1H), 1.35 (s, 3H), 1.05 (s, 9H); ^{13}C NMR 205.7, 138.1, 137.8, 128.2, 128.1, 127.5 (2×), 127.3, 127.1, 102.8, 77.9, 77.2, 73.2, 72.9, 71.8, 69.8, 68.8, 39.7, 25.1, 15.0; IR 3427, 1732, 1105 cm^{-1}; MS (CI-NH_3) 460 (M + 18, 46), 443 (M + 1, 13), 442 (M, 11), 425 (29), 335 (20), 317 (30), 288 (60), 181 (26), 108 (32), 91 (100); HRMS (EI) 442.2357 (M), calcd for $C_{26}H_{34}O_6$ 442.2355.

Structure Determination of Ketohexose Derivatives 20 and 21. Samples of commercially available D-fructose, L-sorbose, D-psicose, and D-tagatose were converted to the corresponding alcohols by the following procedure (representative example):

D-Glucitol and D-Mannitol.[31] D-Fructose (0.500 g, 2.78 mmol) was dissolved in EtOH (25 mL), RaNi (0.500 g) was added, and the resulting slurry was refluxed overnight in hydrogen atmosphere. Next, the nickel catalyst was filtered off on a Celite pad, and the solvent was evaporated. The oily product (0.490 g, 98%) was dissolved in D_2O (1.0 mL), and the ^{13}C NMR spectrum was recorded. The methyl signal of the residual ethyl alcohol (17.4 ppm) was used as the internal standard. The product consisted of a mixture of two isomers, D-glucitol and D-mannitol, in the ratio of 85:15.

The ^{13}C NMR data (in D_2O), for different hexahexaols (hexitiols) thus obtained, were as follows: 2*S*,3*R*,4*R*,5*R*-isomer (D-glucitol): 73.4, 71.6, 71.5, 70.1, 63.4, 62.9; 2*R*,3*R*,4*R*,5*R*-isomer (D-mannitol): 71.3, 69.7, 63.8; 2*S*,3*R*,4*R*,5*S*-isomer (L-

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iditol): 72.2, 71.6, 63.2; 2*R*,3*R*,4*S*,5*S*-isomer (**23b**, D-allitol): 72.9, 72.8, 63.0; 2*R*,3*R*,4*S*,5*R*-isomer (**23a** = **22b**, D-talitol): 73.2, 72.1, 71.3, 71.0, 63.6, 62.6; 2*S*,3*R*,4*S*,5*R*-isomer (**22a**, D-galactitol): 70.8, 70.0, 63.8.

Hexitols from Compounds 20 and 21. The following two step procedure was used:

Step 1. A sample of **20aa** or **21aa** (0.40 mmol) was dissolved in methanol (5 mL). The solution was cooled to 0 °C, and sodium borohydride (15 mg, 0.40 mmol) was added. After strirring for 45 min, the reaction was quenched with a concentrated pH 7 buffer (2 mL), extracted with Et_2O (100 mL), washed with brine (2 × 15 mL), and dried with $MgSO_4$. The solvents were evaporated, and the residue was purified by SCC (3:1 hexane:dichloromethane → 3:1:3 hexane:dichloromethane:ethyl acetate).

Step 2. The resulting diol was next dissolved in MeOH. Concentrated hydrochloric acid (0.5 mL) was added, and the solution was refluxed for 1 h. Next, EtOH (50 mL) was added, and the solvents were evaporated. The residue was dissolved in D_2O (0.5 mL), and ^{13}C NMR spectrum was recorded. The methyl signal of residual ethyl alcohol (17.4 ppm) was used as the internal standard.

Compound **20aa** yielded initially (step 1) a mixture of two isomers having R_f's of 0.24 and 0.26 (1:1 hexane:ethyl acetate) in 86% yield. Step 2 provided a mixture of **22b** and **22a** in a ratio of 67:33 and in 99% yield.

Compound **21aa** yielded a mixture of two isomers having R_f's of 0.22 and 0.12 (1:1 hexane:ethyl acetate) in 78% in step 1. Step 2 provided a mixture of **23b** and **23a** in a ratio of 64:36 and in 92% yield.

Compounds **20ba**, **20bb**, **20bc** and **21ba**, **21bb**, **21bc** were converted to mixtures of the corresponding alcohols in the same way. In each case compound **20** yielded a mixture of **22a** and **22b**, and compound **21** afforded **23a** and **23b**.

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