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Double Diastereoselection in Aldol Reactions Mediated by Dicyclohexylchloroborane between Chiral Aldehydes and a Chiral Ethyl Ketone Derived from L-Erythrulose. Synthesis of a C_1-C_9 Fragment of the Structure of the Antifungal Metabolite Soraphen $A_{1\alpha}$

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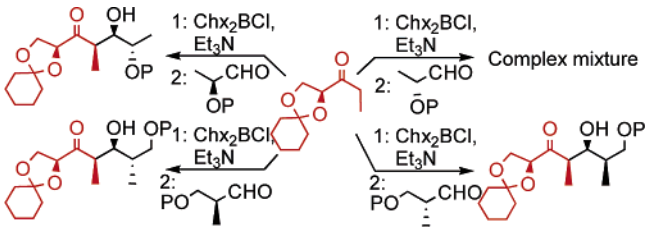

Both matched and mismatched diastereoselections have been observed in the aldol reactions of a range of chiral aldehydes with the dicyclohexylboron enolate of a chiral ethyl ketone related to L-erythrulose. As was previously observed in the corresponding aldol reactions with L-erythrulose derivatives, the Felkin−Anh model provides an adequate explanation for the stereochemical outcome of reactions with chiral α-methyl aldehydes. However, a satisfactory account of the results observed with α-oxygenated aldehydes was only possible with the Cornforth model. As a practical application of the methodology described herein, a C_1-C_9 fragment of the structure of the antifungal macrolide soraphen $A_{1\alpha}$ has been prepared in a convergent and stereoselective way.

Introduction

The aldol reaction is a powerful and general method for the stereocontrolled construction of carbon−carbon bonds.[1] Among the many enolate types used for this kind of reaction thus far, boron enolates are particularly versatile because of their good reactivity and excellent stereoselectivity.[2] In recent years, we have investigated the outcome of the aldol reactions of boron enolates generated from dicyclohexylboron chloride, Chx_2BCl, with either the L-erythrulose derivative **1**[3] or the structurally related ketone **2**.[4] This line of research has led to several different findings, with each result prompting us to expand our investigative efforts. One of our first findings concerning reactions with achiral aldehydes, for example, was that, in contrast to the previously documented behavior of Chx_2BCl, ketones **1** and **2** give rise to syn aldols **3** and **4**, respectively, with almost total stereoselectivity.[5] In the case of **1**, we were able to demonstrate that this is due to the fact that Chx_2BCl promotes the formation of the boron *Z*-enolate rather than the expected *E*-enolate[3c] (although not experimentally investigated, it is reasonable to assume for **2** the same behavior and thus the selective formation of the *Z*-enolate). We further concluded that the boron *Z*-enolate of each ketone has a distinct stereofacial bias for attacking the *Re* aldehyde carbonyl face. These results are of interest because when the aldol adducts are appropriately manipulated, **1** and **2** may be viewed as synthetic equivalents of chiral d^2, d^3, and d^4 synthons (see Scheme 1), the latter two of which were reported for the first time in our study.[3] These synthons, in turn, greatly facilitate the synthesis of polyoxygenated, sugar-like chains and polypropionate fragments, which are present in many biologically relevant natural products.[6]

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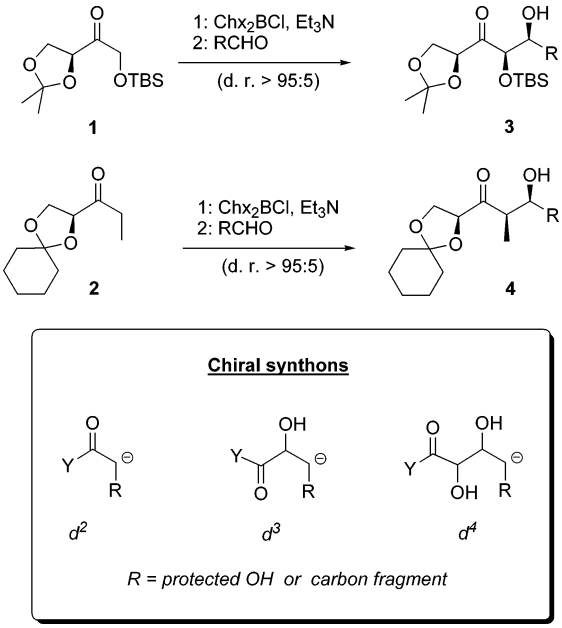
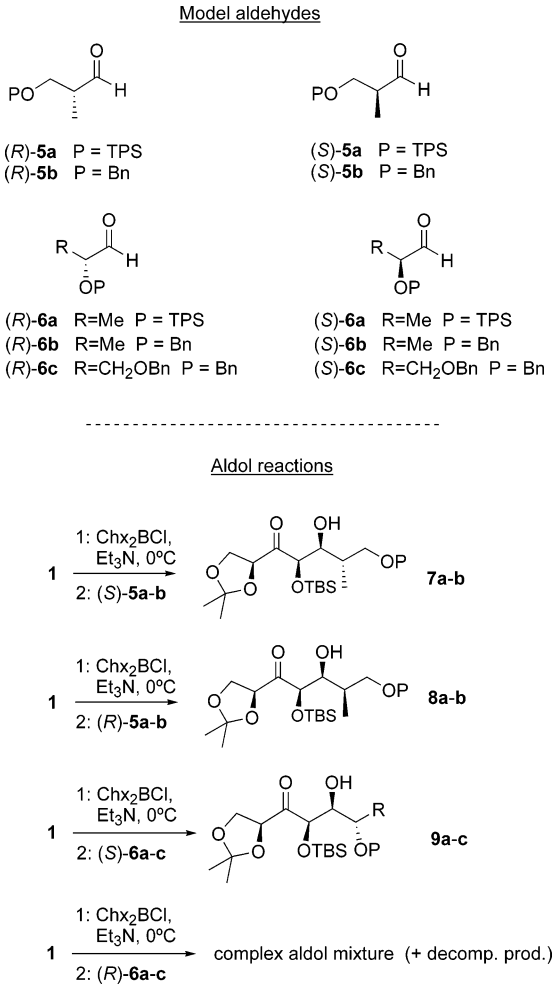
SCHEME 1. Aldol Additions of the Boron *Z*-Enolates of 1 and 2 to Achiral Aldehydes



After obtaining these results, we extended our study to the doubly diastereoselective[1c] aldol reactions of ketone **1** with α-chiral aldehydes (Scheme 2). We found that in the case of α-methyl aldehydes **5a**,**b** of either configuration, the boron *Z*-enolate of **1** was able to exert the stereocontrol over the reaction.[7] As with achiral aldehydes, the boron *Z*-enolate of **1** selectively attacked the *Re* aldehyde carbonyl face. Thus, aldols **7a**,**b** and **8a**,**b** were obtained as essentially single stereoisomers after reaction with the (*S*) and (*R*) enantiomers, respectively, of the aforementioned aldehydes (Scheme 2).[8] In contrast, a distinct match/mismatch dichotomy was found when α-oxygenated aldehydes were used. Thus, while a highly stereoselective aldol reaction occurred with aldehydes (*S*)-**6a**−**c**,[9] leading to aldols **9a**−**c**, only complex aldol mix-

SCHEME 2. Aldol Additions of the Boron *Z*-Enolate of 1 to α-Chiral Aldehydes



(1) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem*. **1982**, *13*, 1−115. (b) Mukaiyama, T. *Org. React*. **1982**, *28*, 203−331. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−30. (d) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, pp 111−212. (e) Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99−111. (f) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1993; Vol. 2. (g) Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1993; Vol. 2, pp 99−131. (h) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1993; Vol. 2, pp 133−179, 181−238. (i) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1993; Vol. 2, pp 239−275. (j) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1993; Vol. 2, pp 277−299. (k) Paterson, I. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1993; Vol. 2, pp 301−319. (l) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth*. **1994**, *1*, 317−338. (m) Braun, M. In *Houben-Weyl's Methods of Organic Chemistry, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1996; Vol. 3, pp 1603−1666, 1713−1735. (n) Mahrwald, R. *Chem. Rev*. **1999**, *99*, 1095−1120. (o) Palomo, C.; Oiarbide, M.; García, J. M. *Chem.-Eur. J*. **2002**, *8*, 36−44. (p) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev*. **2004**, *33*, 65−75. (q) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004.

(2) Cowden, C. J.; Paterson, I. *Org. React*. **1997**, *51*, 1−200.

(3) (a) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron* **2000**, *56*, 677−683. (b) Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron: Asymmetry* **2002**, *13*, 2317−2327. (c) Murga, J.; Falomir, E.; González, F.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 9697−9707. (d) The d^3 synthon of ketone **1** is conceptually related to dihydroxyacetone enolates. See: Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem., Int. Ed*. **2005**, *44*, 1304−1325.

(4) Carda, M.; Murga, J.; Falomir, E.; González, F.; Marco, J. A. *Tetrahedron: Asymmetry* **2000**, *11*, 3211−3220.

(5) This stereochemical outcome of aldol reactions mediated by dicyclohexylboron chloride may be general in α-oxygenated ketones: Murga, J.; Falomir, E.; Carda, M.; González, F.; Marco, J. A. *Org. Lett*. **2001**, *3*, 901−904.

(6) (a) *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990. (b) Norcross, R. D.; Paterson, I. *Chem. Rev*. **1995**, *95*, 2041−2114. (c) Thirsk, C.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 999−1023. (d) Yeung, K.-S.; Paterson, I. *Angew. Chem., Int. Ed*. **2002**, *41*, 4632−4653. (e) Suenaga, K. *Bull. Chem. Soc. Jpn*. **2004**, *77*, 443−451.

(7) Marco, J. A.; Carda, M.; Díaz-Oltra, S.; Murga, J.; Falomir, E.; Roeper, H. *J. Org. Chem.* **2003**, *68*, 8577−8582.

(8) In the aldol reaction of ketone **1** with (*R*)-**5b**, an approximately 4:1 mixture of syn aldols was formed, according to the NMR data of the mixture. In our previous publication,[7] we assumed that the not isolated, minor stereoisomer was the "anti-Felkin" stereoisomer, which resulted from attack to the aldehyde *Si* face. However, we later found that aldehyde **5b** is much more prone to racemization than its analogue **5a**. We thus believe that the minor stereoisomer, which appears in the reaction mixture in variable proportions, is formed from the small proportion of the undesired enantiomer, generated adventitiously during the synthesis and isolation of the aldehyde. The preparation of aldehydes **5** has to be performed with extreme care, to keep racemization to a minimum (the results presented in this paper and in refs 7 and 9 are part of the Ph.D. thesis of S.D.-O., Universidad Jaume I, July 2005).

tures and extensive decomposition resulted when the (*R*) enantiomers were used.

These results were not adequately explained with the Felkin−Anh paradigm alone,[10] as this mechanistic model worked satisfactorily only in the reactions with α-methyl aldehydes **5**, but not with those involving α-oxygenated aldehydes **6**. Relying on recent results,[11] we then proposed Cornforth's dipolar model as offering a more adequate explanation for the stereochemical outcome of aldol reactions of **1** with chiral aldehydes bearing polar α-heteroatoms.[12] This was the first time that this model had been applied to a doubly diastereoselective aldol reaction.[1c] In the present Article, we have extended the same approach to chiral ethyl ketone **2** in the belief that stereoselective aldol reactions of **2** with α-methyl aldehydes and α-oxygenated aldehydes will provide efficient access to polypropionate fragments such as those present in macrolides, polyether antibiotics, and related bioactive metabolites.[6]

Results and Discussion

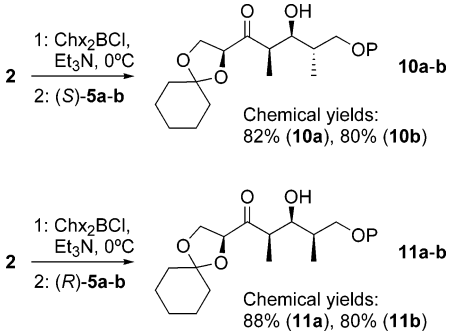
Aldol Reactions with α-Methyl Aldehydes. To accomplish our objective, standard procedures were used to prepare the four enantiomerically pure aldehydes **5a**,**b** and **6a**,**b** that we had employed in our previous study (Scheme 2).[13] The aldol additions were performed under the conditions described in our earlier reports.[3,14−17] We started with the aldol reactions of ketone **2** and α-methyl aldehydes (*R*)-**5** and (*S*)-**5**. The results are shown in Scheme 3 and Table 1. The reactions with aldehydes (*S*)-**5** were comparatively rapid at 0 °C (total conversion in 5 h) and completely diastereoselective, taking into account the detection limits of NMR spectroscopic methods (dr > 95:5). Aldols **10** were thus formed via enolate attack to the *Re* aldehyde carbonyl face. For aldehydes (*R*)-**5**, the reactions were also completely diastereoselective and gave rise to aldols **11**, again resulting from enolate attack to the *Re* aldehyde face.

TABLE 1. Stereochemical outcome of Aldol Additions of Ketone 2 with Aldehydes (*R*)- and (*S*)-5

entry	aldehyde	% yield	dr[a]
1	(*S*)-**5a**	95	>95:5[b]
2	(*S*)-**5b**	75	>95:5[b]
3	(*R*)-**5a**	86	>95:5[c]
4	(*R*)-**5b**	62	>95:5[c]

[a] dr > 95:5 means that the minor diastereoisomer was not detected by means of ^{1}H and ^{13}C NMR. [b] The only diastereoisomer detected was **10a**,**b**. [c] The only diastereoisomer detected was **11a**,**b**.

SCHEME 3. Aldol Additions of the Boron *Z*-Enolate of 2 to Aldehydes (*R*)-5 and (*S*)-5



These results lead to the conclusion that the facial bias of this ketone enolate (attack to aldehyde *Re* faces) is strong enough to overcome the inherent facial Felkin preference of the carbonyl group in α-methyl aldehydes **5**, a fact which greatly enhances the synthetic value of this methodology.[6] This can be understood within the same mechanistic framework presented in our recent publications.[3c,7] Scheme 4 presents a proposal of favorable cyclic transition structures (TSs) of the Zimmerman−Traxler type,[18,19] in which the different, previously discussed energetically relevant features[7] are taken into account. In order of increasing quantitative importance, these factors are: (a) the inherent Felkin−Anh bias of the aldehyde (nucleophilic attack *anti*-coplanar to either the bulkiest aldehyde C_α substituent or that having the

(9) The methodology described in ref 7 has been applied to the stereoselective synthesis of the natural lactone anamarine: Díaz-Oltra, S.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2004**, *60*, 2979−2985.

(10) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. **1968**, *9*, 2199−2204. (b) Anh, N. T. *Top. Curr. Chem*. **1980**, *88*, 145−162. (c) Mengel, A.; Reiser, O. *Chem. Rev*. **1999**, *99*, 1191−1223. See also, however: Smith, R. J.; Trzoss, M.; Bühl, M.; Bienz, S. *Eur. J. Org. Chem*. **2002**, 2770−2775.

(11) Shortly before we concluded our investigation with ketone **1**, a paper by Evans and co-workers appeared in which the Cornforth model was resurrected to provide a good explanation of the sterochemical outcome of aldol reactions of achiral ketones with α-heteroatom-substituted aldehydes: Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed*. **2003**, *42*, 1761−1765.

(12) Cornforth's model has been previously applied to reactions of α-oxygenated aldehydes with achiral allylboron compounds: (a) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc*. **1986**, *108*, 3422−3434. (b) Brinkmann, H.; Hoffmann, R. W. *Chem. Ber*. **1990**, *123*, 2395−2401. (c) Thadani, A. N.; Batey, R. A. *Tetrahedron Lett*. **2003**, *44*, 8051−8055. (d) The higher stability of Cornforth-like transition structures in some additions of allylboron reagents to α-oxygenated aldehydes has also received theoretical support: Gung, B. W.; Xue, X. *Tetrahedron: Asymmetry* **2001**, *12*, 2955−2959. (e) For more detailed accounts of the diastereoselective reactions of allylboron compounds, see: Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1993; Vol. 2, pp 1−54. Roush, W. R. In *Houben-Weyl's Methods of Organic Chemistry, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1996; Vol. 3, pp 1410−1486, and references therein. (f) For a related situation in the addition of an allenylstannane, see: Marshall, J. A.; Wang, X.-J. *J. Org. Chem*. **1991**, *56*, 3211−3213.

(13) See pertinent citations in our previous publication.[7] Because aldehydes **6c** gave essentially the same results as **6b** in aldol reactions with **1**, only the latter were used in the present work.

(14) The stereostructures of the aldol products were established with the aid of the chemical correlation methodology used in our previous papers[3] and, in two cases, by means of X-ray diffraction analysis.[15] Aldol adducts were reduced in situ with $LiBH_4$ to yield the expected *syn*-1,3-diols.[16] These were subsequently converted into acetonides, which were then studied by means of NMR.[17] Standard manipulations of the protecting groups further permitted the preparation of other cyclic derivatives suitable for similar NMR studies. Descriptions of these chemical correlations and analytical data for correlation products are given in the Supporting Information.

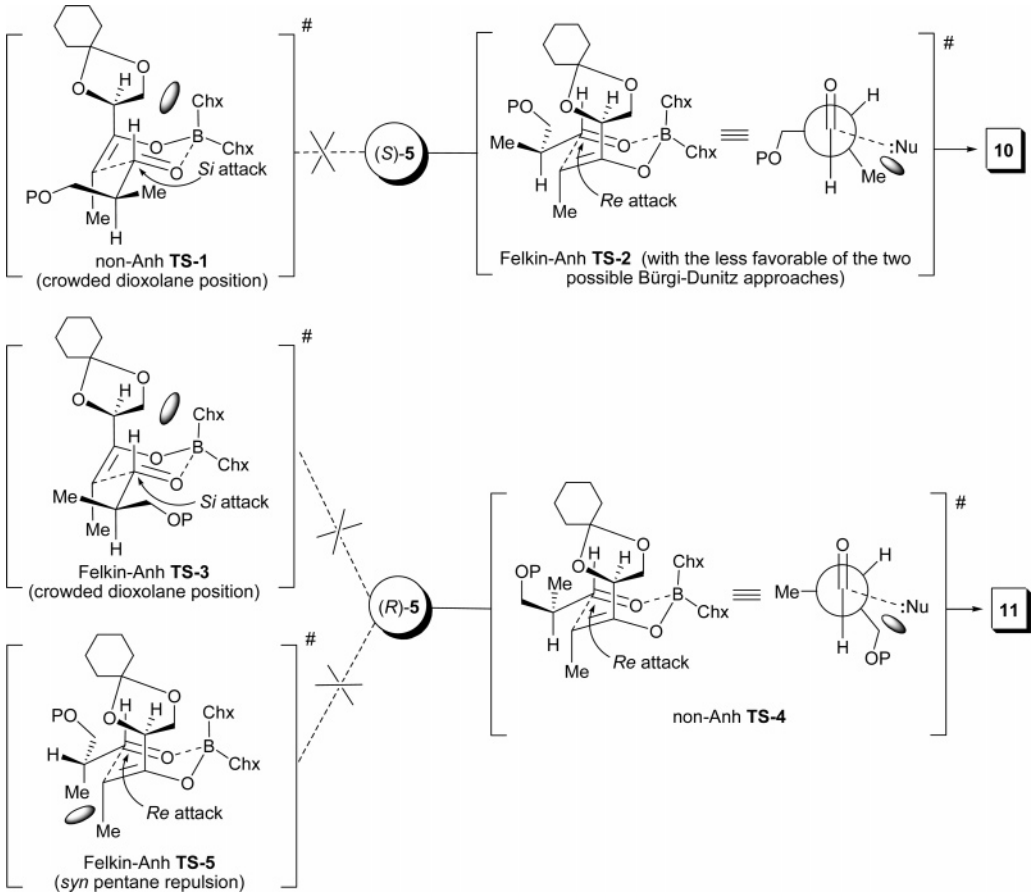
(15) The stereostructures of two correlation compounds related to aldols **10a** and **11a** (see Supporting Information) were established by means of X-ray diffraction analyses. Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Center as supplementary material with references CCDC-269222 and CCDC-269772. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax, +44(0)-1223-336033 or e-mail, deposit@ccdc.cam.ac.uk].

(16) Paterson, I.; Channon, J. A. *Tetrahedron Lett*. **1992**, *33*, 797−800.

(17) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res*. **1998**, *31*, 9−17.

(18) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc*. **1957**, *79*, 1920−1923.

SCHEME 4. Felkin−Anh TSs for Aldol Additions of the Boron *Z*-Enolate of 2 to Aldehydes (*R*)-5 and (*S*)-5



lowest lying σ^*_{C-X} orbital), including the most favorable Bürgi−Dunitz trajectory (approach nearer to the smallest C_α substituent, usually an H atom);[10,20,21] (b) anticoplanar orientation of the $C-O_{enolate}$ and $C_\alpha-O$ bonds (minimized dipolar repulsion)[1e,22] and the spatial allocation of the dioxolane ring away from the bulky boron ligands (minimized steric crowding); and (c) avoidance of syn pentane repulsive interactions between the Me group at the enolate C=C bond and one substituent at the stereogenic α-aldehyde carbon.[1a,12,23,24]

For the reactions of aldehydes (*S*)-**5** yielding solely syn aldols **10**, we may assume a TS such as **TS-2**, which is still of the Felkin−Anh-type (enolate attack anti to the bulky CH_2OP group), but in which the enolate approaches along a less favorable Bürgi−Dunitz trajectory that pushes the nucleophile toward the methyl group rather than to the hydrogen atom, a feature of quantitatively minor importance.[7] The alternative, and unobserved, attack of the enolate to the aldehyde *Si* face must take place, under the assumed avoidance of syn pentane interactions, through **TS-1**, which shows an unfavorable steric crowding between the dioxolane ring and one of the bulky boron ligands. This particular hindrance may be alleviated by means of bond rotation, but only at the cost of increasing the dipolar repulsion between the $C-O_{enolate}$ and $C_\alpha-O$ bonds.[22] In contrast, the aldol reaction with aldehydes (*R*)-**5** led mainly to the Felkin stereoisomer **11** (Scheme 4). This stereochemical outcome can be explained only if the aldol process occurs via the "non-Anh" rotamer **TS-4**,[21] again under avoidance of the syn pentane interaction present in the Felkin−Anh rotamer **TS-5**. Moreover, enolate attack to the aldehyde *Si* face to yield the (not detected) epimer of **11** through

(19) For theoretical studies on boron aldol reactions, see: (a) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem*. **1990**, *55*, 481−493. (b) Goodman, J. M.; Kahn, S. D.; Paterson, I. *J. Org. Chem*. **1990**, *55*, 3295−3303. (c) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem*. **1990**, *55*, 3576−3581. (d) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991**, *47*, 3471−3484. (e) Bernardi, F.; Robb, M. A.; Suzzi-Valli, G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem*. **1991**, *56*, 6472−6475. (f) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992**, *48*, 4439−4458. (g) Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, *49*, 685−696. See also ref 3c.

(20) Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*; Pergamon: New York, 1996; Chapters 4 and 5.

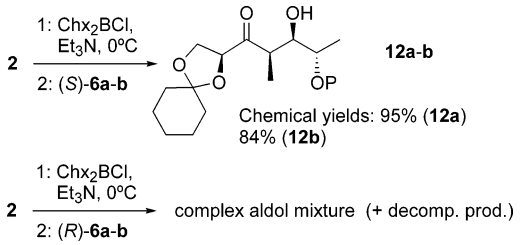
(21) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc*. **1987**, *109*, 3353−3361. The "non-Anh" label in Schemes 4 and 6 refers to transition structures in which attack takes place anti to a substituent, which neither has the lowest lying σ^*_{C-X} orbital (for α-heteroatom-substituted aldehydes) nor is the sterically bulkiest one (for aldehydes not bearing α-heteroatoms). See also ref 20.

(22) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem*. **1991**, *56*, 2499−2506. For another example of the importance of dipole alignment in aldol TSs, see: Boeckman, R. K., Jr.; Connell, B. T. *J. Am. Chem. Soc*. **1995**, *117*, 12368−12369.

(23) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151−4157. The quantitative importance of the syn pentane interaction in these reactions is underscored by the fact that pivalaldehyde does not react with the boron *Z*-enolates of ketones **1** and **2**.[3,4] In fact, if a TS is drawn for aldol reactions with this aldehyde, a steric interaction of the aforementioned type will always be present for all rotamers around the *t*Bu−CO bond.

(24) The various factors that may influence the stereochemical outcome of aldol reactions have been very lucidly analyzed by Danishefsky and co-workers in a recent publicaction: Lee, C. B.; Wu, Z.; Zhang, F.; Chappell, M. D.; Stachel, S. J.; Chou, T.-C.; Guan, Y.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2001**, *123*, 5249−5259.

SCHEME 5. Aldol Additions of the Boron *Z*-Enolate of 2 to Aldehydes (*R*)-6 and (*S*)-6



TS-3 would suffer from steric crowding between the dioxolane ring and one of the B-cyclohexyl groups.

Aldol Reactions with α-Oxygenated Aldehydes. We then investigated the aldol reactions of ketone **2** and α-oxygenated aldehydes (*R*)-**6** and (*S*)-**6**. The results are given in Scheme 5. The reactions with aldehydes (*S*)-**6** were highly diastereoselective and gave aldols **12a**,**b** (dr > 95:5), once again through enolate attack to the aldehyde *Re* face. In contrast, the reactions of aldehydes (*R*)-**6** were very slow (less than 50% conversion after 12 h) and not only yielded complex mixtures of 3−4 stereoisomeric aldols but were also accompanied by extensive decomposition.[25]

These results parallel those previously observed with ketone **1**[7] and may be explained within the same mechanistic framework. Again, the Felkin−Anh model proves unable to provide a satisfactory explanation of this stereochemical outcome, as shown on the left-hand side of Scheme 6.[26,27] Reasonable explanations may be formulated, however, by invoking the Cornforth model.[11,12,28] This is illustrated on the right-hand side of Scheme 6, where the proposed transition structures are reexamined within this paradigm. Thus, the unfavorable non-Anh **TS-7** now becomes favorable within the framework of the Cornforth model. Dipolar repulsions between the C=O and C_α−OP bonds are minimized in this TS, in which nucleophilic attack takes place from the less hindered carbonyl face. The alternative **TS-6** not only deviates from the Cornforth geometry, an unfavorable feature in this case, but also shows a syn pentane repulsion between the two methyl groups. As regards the aldol reactions of **2** with aldehydes (*R*)-**6**, a Cornforth transition structure **TS-9** may be formulated, but it suffers from steric crowding between the dioxolane ring and the boron cyclohexyl ligands. For its part, the Felkin−Anh **TS-8** deviates from the Cornforth geometry. The fact that both alternative TSs display energetically unfavorable features explains why the corresponding aldol reaction is slow and nonstereoselective.

All results therefore can be explained within the framework of the same unified general concept we put forth in our recent publication.[7] Energetic factors in order of decreasing quantitative importance are: (a) for α-heteroatom-substituted aldehydes and in contrast to α-methyl aldehydes, Cornforth TSs are markedly preferred to those of the Felkin−Anh type; (b) syn pentane repulsions between the enolate Me group and one aldehyde nonhydrogen α-substituent (Me in the lactaldehyde derivatives used here) are energetically important interactions that must be avoided through C−C bond rotation; (c) steric crowding between the dioxolane ring and one B-cyclohexyl group arises when attack takes place from the enolate *Si* face; while suitable C−C bond rotation relieves this interaction, it simultaneously increases the dipolar repulsion between the $C-O_{enolate}$ and C_α−O bonds; and (d) because the Felkin−Anh π-facial bias is not very strong for aldehydes bearing only carbon α-substituents (dr's rarely ≥3:1),[1,20] stereocontrol is frequently exerted by the chiral enolate rather than by the aldehyde.

In summary, we propose that α-methyl aldehydes (*S*)-**5** react with the dicyclohexylboron enolate of **2** to yield aldols **10** selectively through **TS-2** whereas aldehydes (*R*)-**5** generate aldols **11** through **TS-4** (Scheme 4), with stereocontrol coming from the chiral enolate in both cases. The α-oxygenated aldehydes (*S*)-**6**, on the other hand, react to yield aldols **12** through the Cornforth transition state **TS-7** (Scheme 6). Their enantiomers (*R*)-**6** react sluggishly and nonstereoselectively because the energy of the Cornforth-type **TS-9** (Scheme 6) is increased by factor c. The energy of the alternative **TS-8** is also increased by its deviation from the Cornforth geometry, that is, dominance of factor a. Once again, the Cornforth model proves useful in explaining the stereochemical outcome of aldol additions to α-heteroatom-substituted carbonyl groups.[28−30]

Synthesis of the C_1−C_9 Soraphen $A_{1\alpha}$ Fragment. As noted above, the unprecedented d^3 and d^4 synthons depicted in Scheme 1 may be particularly useful for the synthesis of polyhydroxy and polypropionate chains such as those present in bioactive, natural polyketides. To

(25) This was established upon examination of NMR data for the crude aldol mixtures. In view of this synthetically useless result, we did not attempt to isolate individual compounds.

(26) Provided that chelation is not involved in the transition state, achiral enolates react with α-oxygenated aldehydes to yield predominantly, albeit with variable diastereoselectivity, the Felkin aldols. See refs 1 and 2. For more recent cases, see, for example: (a) Esteve, C.; Ferrerò, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett*. **1999**, *40*, 5079−5082. (b) Lu, L.; Chang, H.-Y.; Fang, J.-M. *J. Org. Chem*. **1999**, *64*, 843−853. However, it is worth noting that Felkin aldols have been found to predominate in some reactions where chelation is likely to occur: Grandel, R.; Kazmaier, U.; Rominger, F. *J. Org. Chem*. **1998**, *63*, 4524−4528.

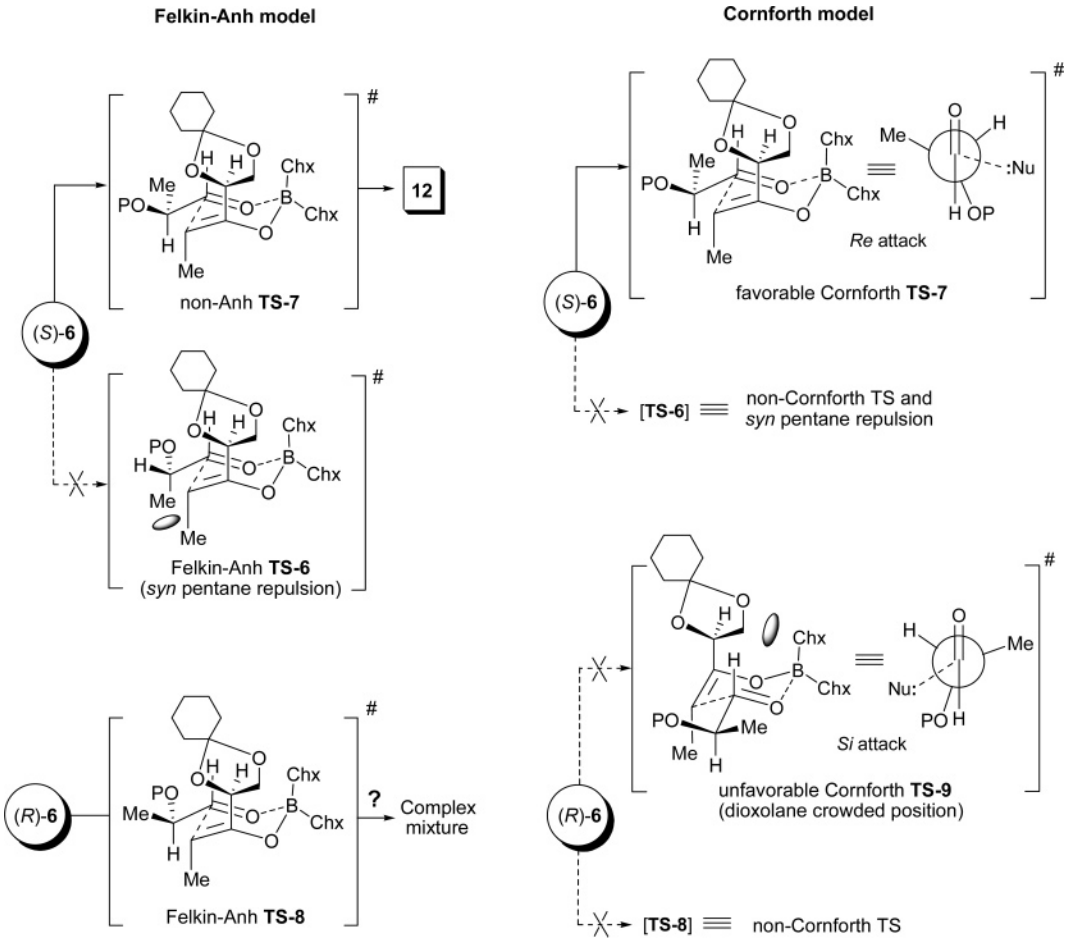
(27) For nucleophilic additions to aldehydes bearing α-heteroatoms other than oxygen, see, for example: (a) Reetz, M. T. *Chem. Rev*. **1999**, *99*, 1121−1162 (α-amino aldehydes). (b) Enders, D.; Piva, O.; Burkamp, F. *Tetrahedron* **1996**, *52*, 2893−2908 (α-sulphenyl aldehydes). (c) Enders, D.; Adam, J.; Klein, D.; Otten, T. *Synlett* **2000**, 1371−1384 (α-silyl aldehydes). See also: Enders, D.; Burkamp, F. *Collect. Czech. Chem. Commun*. **2003**, *68*, 975−1006.

(28) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc*. **1959**, 112−127. See also: Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc*. **1982**, *104*, 7162−7166.

(29) Doubly diastereoselective aldol reactions of chiral enolates with chiral α-oxygenated aldehydes are not extensively documented in the literature. Matched and mismatched processes have been reported, with the full range from total stereocontrol by the enolate to complete dominance of the aldehyde being observed. See refs 1 and 2 and, for further cases: (a) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem.-Eur. J*. **1995**, *1*, 318−333. (b) Sibi, M. P.; Lu, J.; Edwards, J. *J. Org. Chem*. **1997**, *62*, 5864−5872. (c) Kobayashi, S.; Furuta, T. *Tetrahedron* **1998**, *54*, 10275−10294. (d) Esteve, C.; Ferrerò, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett*. **1999**, *40*, 5083−5086. (e) Nicolaou, K. C.; Pihko, P. M.; Diedrichs, N.; Zou, N.; Bernal, F. *Angew. Chem., Int. Ed*. **2001**, *40*, 1262−1265. (f) Forsyth, C. J.; Hao, J.; Aiguade, J. *Angew. Chem., Int. Ed*. **2001**, *40*, 3663−3667. (g) Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Org. Biomol. Chem*. **2004**, *2*, 3385−3400. For a recent review on doubly and multiply stereoselective reactions, see: Kolodiazhnyi, O. I. *Tetrahedron* **2003**, *59*, 5953−6018.

(30) Excluded from this discussion are chiral enolates in which the chirality resides in the ligands bound to the heteroatom. In these cases, stereocontrol by the chiral auxiliary is usually observed. See, for example: Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem*. **1995**, *60*, 6248−6249.

SCHEME 6. Felkin−Anh and Cornforth TSs for Aldol Additions of the Boron *Z*-Enolate of 2 to Aldehydes (*R*)-6 and (*S*)-6



illustrate this, we have prepared a fragment of the molecular structure of the antifungal metabolite soraphen $A_{1\alpha}$ (Scheme 7). This naturally occurring compound is the main member of a macrolide family isolated from cultures of a strain of the myxobacterium *Sorangium cellulosum*. It exhibits a marked antifungal activity due to its ability to inhibit the fungal acetyl-CoA carboxylase.[31] Recent studies have established that the product is basically a polyketide as regards its biosynthetic origin, even though the presence of an unsubstituted phenyl ring also relates it to the shikimic acid pathway.[32] Only a total synthesis has been reported thus far for soraphen $A_{1\alpha}$,[33] but other synthetic approaches to fragments of its structure or analogues thereof have recently appeared in the literature.[34]

Our main retrosynthetic concept for soraphen $A_{1\alpha}$ is depicted in Scheme 7. The macrolide system is to be constructed by means of a Julia olefination-macrolactonization sequence. This retrosynthetic cleavage gives rise to fragments **A** and **B**, the latter comprising carbon atoms C-1 to C-9. In this paper, we present a stereoselective synthesis of compound **13** (depicted in Scheme 7 in both the cyclic hemiacetal and the open form), a precursor to fragment **B**. Functional modification of compound **13** produces intermediate **C** (Scheme 8), the disconnection of which via retro-aldol reaction generates **D**. Compound **D** in turn is easily available via our aldol methodology from ketone **2** and one of the aldehydes (*S*)-**5** (depending on the protective group selected), whereby the former product functions as a chiral d^4 synthon, thus maximizing atom economy.[35] The process is highly convergent and leads to compound **13**, which has six stereocenters (seven in the hemiacetal form), from two chiral precursors, **2** and (*S*)-**5**, with one stereocenter each.

The specific steps of the synthesis are depicted in Scheme 9. Thus, aldol reaction of **2** with aldehyde (*S*)-**5b**, followed by in situ reduction[16] with $LiBH_4$, afforded *syn*-1,3-diol **14**, which was subsequently transformed into its benzylated derivative **15**.[36] Cleavage of the cyclohex-

(31) (a) Bedorf, N.; Schomburg, D.; Gerth, K.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem*. **1993**, 1017−1021. (b) Gerth, K.; Bedorf, N.; Irschik, H.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1994**, *47*, 23−31. (c) Gerth, K.; Pradella, S.; Perlova, O.; Beyer, S.; Müller, S. *J. Biotechnol*. **2003**, *106*, 233−253.

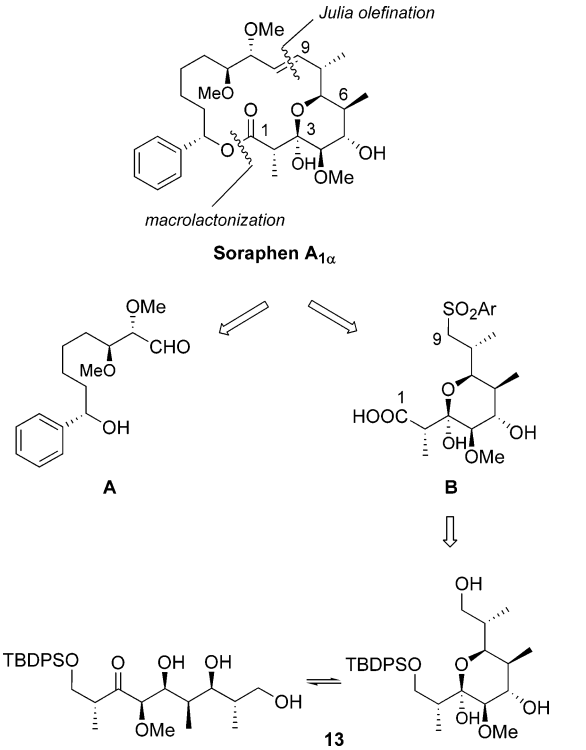
(32) (a) Hill, A. M.; Thompson, B. L.; Harris, J. P.; Segret, R. *Chem. Commun*. **2003**, 1358−1359. (b) Hill, A. M.; Thompson, B. L. *Chem. Commun*. **2003**, 1360−1361.

(33) Abel, S.; Faber, D.; Hüter, O.; Giese, B. *Synthesis* **1999**, 188−197.

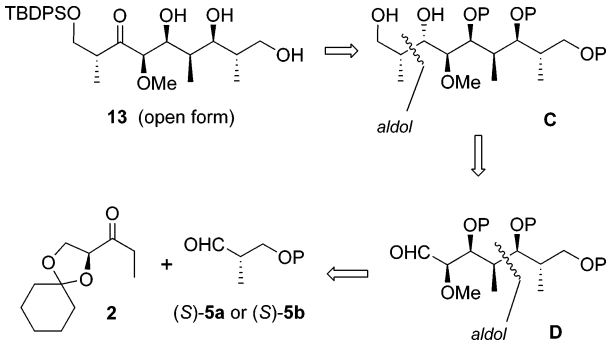
(34) (a) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C.; Winkler, T. *J. Org. Chem*. **1995**, *60*, 953−959. (b) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 521−525. (c) Gurjar, M. K.; Mainkar, A. S.; Srinivas, P. *Tetrahedron Lett*. **1995**, *36*, 5967−5968. (d) Cao, Y.; Eweas, A. F.; Donaldson, W. A. *Tetrahedron Lett*. **2002**, *43*, 7831−7834. (e) Park, S. H.; Lee, H. W.; Park, S.-U. *Bull. Korean Chem. Soc*. **2004**, *25*, 1613−1614.

(35) (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 259−281. (b) Trost, B. M. *Acc. Chem. Res*. **2002**, *35*, 695−705. See also: Eissen, M.; Mazur, R.; Quebbemann, H.-G.; Pennemann, K.-H. *Helv. Chim. Acta* **2004**, *87*, 524−535.

SCHEME 7. Structure and Retrosynthetic Analysis of Soraphen $A_{1\alpha}$



SCHEME 8. Retrosynthetic Analysis of Intermediate 13, a C_1–C_9 Fragment of Soraphen $A_{1\alpha}$



anone acetal was initially attempted under the usual aqueous acidic conditions, but yields were only moderate.[37] An excellent 87% yield was obtained, however, under aprotic conditions with anhydrous $ZnBr_2$ in CH_2Cl_2.[38] Diol **16** was selectively silylated in its primary alcohol group and then methylated in the secondary hydroxyl with trimethyloxonium tetrafluoroborate[39] to **18**. Desilylation of the latter compound with TBAF followed by Swern oxidation[40] afforded aldehyde **20**. The absolute configurations of all five stereocenters present in compounds **14**–**20** were unequivocally established as described in the Supporting Information.[14] The remaining carbon chain, which comprises two stereocenters, was added with the aid of the asymmetric Evans aldol methodology.[41] Thus, oxazolidinone **21** was transformed into its boron *Z*-enolate and added to aldehyde **20**. This provided adduct **22**, which has seven consecutive stereocenters, as an essentially single diastereomer. The configurations of the two new stereocenters were predicted on the basis of the reliable outcome of Evans aldol methodology, aided here in a matched way by the intrinsic Felkin bias of the aldehyde.[29b,42] Reductive cleavage of the chiral auxiliary followed by selective protection and oxidation with Dess–Martin periodinane[43] afforded ketone **25** in good yield. Ketone **25** was then converted into the targeted intermediate **13**,[44] precursor to one of the key fragments of soraphen $A_{1\alpha}$.

Experimental Section

General Features. These are described in detail in the Supporting Information.

General Experimental Procedure for Aldol Additions of Ketone 2 Mediated by Dicyclohexyl Boron Chloride. Chx_2BCl (neat, 395 μL, ca. 1.8 mmol) was added under N_2 via syringe to an ice-cooled solution of Et_3N (280 μL, 2 mmol) in anhydrous Et_2O (5 mL). Ketone **2** (198 mg, 1 mmol) was dissolved in anhydrous ether (5 mL) and added dropwise via syringe to the reagent solution. The reaction mixture was then stirred for 30 min. After addition of a solution of the appropriate aldehyde (1.5 mmol) in ether (6 mL), the reaction mixture was stirred at 0 °C for 5 h. Phosphate buffer solution (pH 7, 6 mL) and MeOH (6 mL) were then added, followed by 30% aq H_2O_2 solution (3 mL). After being stirred for 1 h at room temperature, the mixture was worked up (extraction with Et_2O). Solvent removal in vacuo and column chromatography of the residue on silica gel (hexanes–EtOAc mixtures) afforded the corresponding aldol addition product. Chemical yields and dr's (the latter determined by means of ^1H and ^{13}C NMR) are given in the text.

(36) In our first approach to **13**, MOM protecting groups were used for the hydroxyl functions of diol **14**. However, they proved incompatible with the acidic reaction conditions necessary for the deprotection of the cyclohexanone acetal: a great amount of decomposition was observed under a variety of conditions, as well as formation of formaldehyde acetals as byproducts.

(37) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999; pp 215–217. (b) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme Verlag: Stuttgart, 2004; pp 133–137. For instance, acidic conditions such as 80% aq AcOH or PPTS/MeOH gave yields of around 50–60% (based on recovered starting material), together with ill-defined byproducts.

(38) Ribes, C.; Falomir, E.; Murga, J. Submitted for publication.

(39) Meerwein, H. *Organic Syntheses*; Wiley: New York, 1973; Coll. Vol. V, pp 1096–1098. See also: Pichlmair, S. *Synlett* **2004**, 195–196.

(40) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297–572.

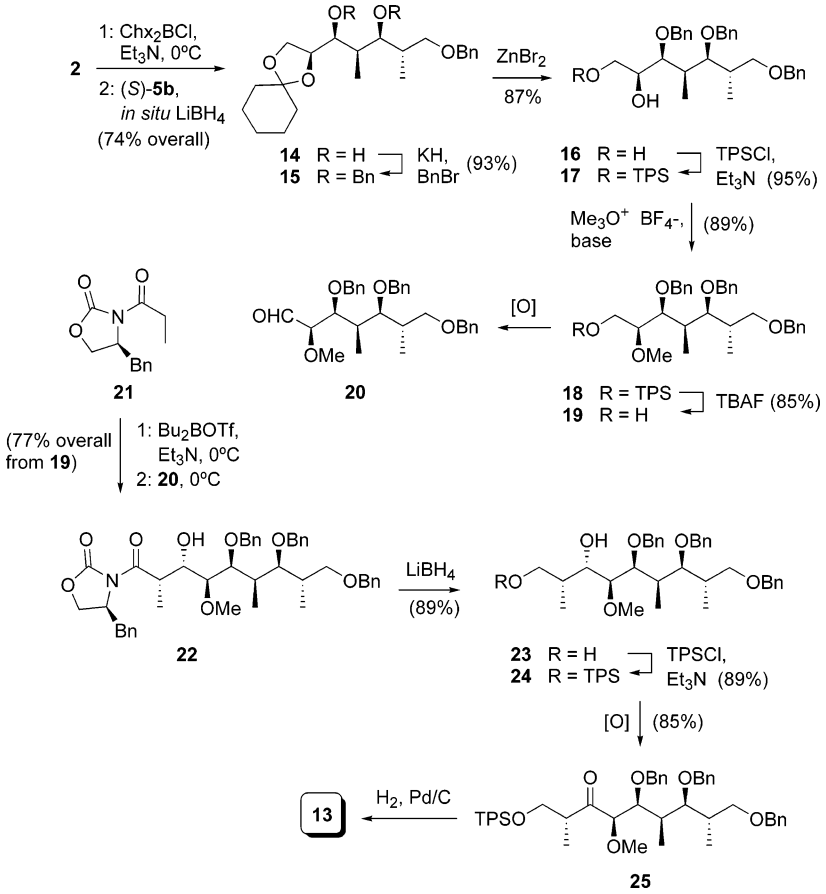
(41) (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23–32. (b) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1993; Vol. 2, pp 239–276. See also ref 2.

(42) At least one case is known where the strong Felkin stereofacial bias of an α-oxygenated aldehyde forced the formation of an anti aldol from the *Z*-boron enolate of a chiral *N*-acyloxazolidinone: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc*. **1990**, *112*, 7001–7031. In the present case, however, a matched double diastereoselection can be expected between the known facial preference of the boron enolate of **21** and the Felkin bias of aldehyde **20**: both factors predict here a predominant enolate attack to the aldehyde carbonyl *Si* face. For a very similar situation, see ref 29b.

(43) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277–7287.

(44) Our efforts to perform hydrogenolytic debenzylation of **25**, while providing the desired **13** (as its hemiacetal form in the assumedly most stable anomer), have not yet given satisfactory and reproducible yields (<30%), even if various reaction conditions have been tried. Unfortunately, many otherwise useful debenzylating reagents (e.g., Na in liquid NH_3 or Li di-*tert*-butyldiphenylide) are precluded here due to the presence of the α-alkoxy ketone moiety. We are presently investigating other methods to improve the yield of this critical deprotection step, as well as the use of alternative protecting groups.

SCHEME 9. Stereoselective Synthesis of Intermediate 13



(2*R*,3*S*,4*S*)-5-(*tert*-Butyldiphenylsilyloxy)-1-[(2*S*)-(1,4-dioxaspiro[4.5]dec-2-yl)]-3-hydroxy-2,4-dimethylpentan-1-one (10a). Oil, $[\alpha]_D$ −36.5 (*c* 1.4; $CHCl_3$). IR 3490 (br), 1715 cm^{-1}. ^1H NMR (500 MHz) δ 7.70−7.65 (4H, br m), 7.45−7.35 (6H, br m), 4.64 (1H, dd, J = 7.7, 5.7 Hz), 4.24 (1H, dt, J = 8.8, 3 Hz), 4.20 (1H, dd, J = 8.5, 7.7 Hz), 4.10 (1H, dd, J = 8.5, 5.7 Hz), 3.84 (1H, dd, J = 10.2, 4 Hz), 3.74 (1H, dd, J = 10.2, 7.2 Hz), 3.60 (1H, br d, J = 3 Hz, OH), 3.27 (1H, dq, J = 3, 7 Hz), 1.84 (1H, m), 1.65−1.55 (8H, br m), 1.40 (2H, m), 1.10 (3H, d, J = 7 Hz), 1.07 (9H, s), 0.87 (3H, d, J = 7 Hz); ^{13}C NMR (125 MHz) δ 212.8, 132.9, 132.8, 111.3, 19.1 (C), 135.6, 135.5, 129.9, 129.8, 127.7, 127.6, 79.1, 74.7, 45.1, 37.7 (CH), 68.8, 66.3, 35.8, 34.6, 25.1, 24.0, 23.8 (CH_2), 26.9 (×3), 13.4, 7.5 (CH_3). HR FABMS *m/ z* 525.3043 (M + H^+). Calcd for $C_{31}H_{45}O_5Si$, 525.3036. Anal. Calcd for $C_{31}H_{44}O_5Si$: C, 70.95; H, 8.45. Found: C, 70.80; H, 8.49.

(2*R*,3*S*,4*S*)-5-Benzyloxy-1-[(2*S*)-(1,4-dioxaspiro[4.5]dec-2-yl)]-3-hydroxy-2,4-dimethylpentan-1-one (10b). Oil; $[\alpha]_D$ −42.6 (*c* 1.5; $CHCl_3$). IR 3480 (br), 1718 cm^{-1}. ^1H NMR (500 MHz) δ 7.35−7.25 (5H, br m), 4.59 (1H, dd, J = 8, 5.5 Hz), 4.52, 4.49 (2H, AB system, J = 11.7 Hz), 4.16 (1H, t, J = 8 Hz), 4.10 (1H, br dd, J = 8.5, 3 Hz), 4.05 (1H, dd, J = 8, 5.5 Hz), 3.62 (1H, dd, J = 9, 4 Hz), 3.55−3.50 (2H, m), 3.25 (1H, dq, J = 3.5, 7 Hz), 1.94 (1H, m), 1.65−1.50 (8H, br m), 1.40 (2H, m), 1.05 (3H, d, J = 7 Hz), 0.92 (3H, d, J = 7 Hz); ^{13}C NMR (125 MHz) δ 212.8, 137.7, 111.4 (C), 128.5, 127.9, 127.7, 79.1, 75.2, 45.1, 36.1 (CH), 75.5, 73.6, 66.3, 35.8, 34.6, 25.1, 24.0, 23.9 (CH_2), 13.7, 7.8 (CH_3). HR EIMS *m/z* (rel int.) 376.2227 (M^+, 1), 198 (12), 141 (50), 91 (100). Calcd for $C_{22}H_{32}O_5$, 376.2249. Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.09; H, 8.70.

(1*S*,2*R*,3*S*,4*S*)-5-Benzyloxy-1-[(2*S*)-1,4-dioxaspiro[4.5]-dec-2-yl]-2,4-dimethylpentane-1,3-diol (14). Chx_2BCl (neat, 4 mL, ca. 18 mmol) was added under N_2 via syringe to an ice-cooled solution of Et_3N (2.8 mL, 20 mmol) in anhydrous Et_2O (50 mL). Ketone **2** (1.98 g, 10 mmol) was dissolved in anhydrous ether (50 mL) and added dropwise via syringe to the reagent solution. The reaction mixture was then stirred for 30 min. After addition of a solution of freshly prepared aldehyde (*S*)-**5b** (2.67 g, 15 mmol) in ether (60 mL), the reaction mixture was stirred at 0 °C for 5 h. The solution was cooled to −78 °C and treated dropwise with a 2 M solution of $LiBH_4$ in THF (15 mL, 30 mmol). The stirring was then continued at −78 °C for 2 h. The reaction was quenched with pH 7 phosphate buffer (60 mL) and MeOH (60 mL), followed by a 30% aq H_2O_2 solution (30 mL). After being stirred for 1 h at room temperature, the mixture was poured into saturated aq $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine and dried on anhydrous Na_2SO_4. Solvent removal in vacuo afforded an oily residue, which was chromatographed on silica gel (hexanes−EtOAc mixtures) to yield *syn*-1,3-diol **14** (2.8 g, 74% overall): oil; $[\alpha]_D$ +15.8 (*c* 3.1, $CHCl_3$); IR 3470 (br) cm^{-1}; ^1H NMR δ 7.35−7.25 (5H, br m), 4.52 (2H, s), 4.20 (1H, dt, J = 8, 6 Hz), 4.00 (1H, dd, J = 8, 6 Hz), 3.70 (3H, m), 3.57 (1H, dd, J = 10, 5 Hz), 3.54 (1H, dd, J = 10, 7 Hz), 3.10 (2H, br s, OH), 1.96 (1H, m), 1.65−1.55 (9H, br m), 1.40 (2H, m), 0.97 (3H, d, J = 6.5 Hz), 0.81 (3H, d, J = 6.5 Hz); ^{13}C NMR δ 137.9, 110.1 (C), 128.5, 127.8, 127.7, 79.3, 76.9, 76.7, 37.3, 36.0 (CH), 75.5, 73.5, 65.9, 36.4, 35.1, 25.2, 24.1, 23.9 (CH_2), 13.5, 6.3 (CH_3). HR EIMS *m/z* (rel int.) 378.2350 (M^+, 1), 141 (20), 91 (100). Calcd for $C_{22}H_{34}O_5$, 378.2406.

(2*S*)-2-[(1*S*,2*R*,3*S*,4*S*)-1,3,5-Tris(benzyloxy)-2,4-dimethylpentyl]-1,4-dioxaspiro[4.5]decane (15). A 30% commercial suspension of potassium hydride in mineral oil (3.2 g, equivalent to ca. 24 mmol of KH) was stirred under N_2 with dry hexane (20 mL). The suspension was decanted, and the supernatant liquid was removed with a syringe. This operation was repeated once more with dry hexane and then again with dry THF. After addition of dry THF (20 mL), the flask was

cooled in an ice bath. A solution of diol **14** (2.27 g, 6 mmol) in dry THF (20 mL) was then added via syringe and stirred for 30 min at the same temperature. Benzyl bromide (5.7 mL, ca. 48 mmol, 8 equiv) and tetra-*n*-butylammonium iodide (185 mg, 0.5 mmol) were then added to the reaction mixture, which was stirred for 2 h at room temperature. Workup (extraction with CH_2Cl_2) and column chromatography on silica gel (hexanes−Et_2O, 19:1) furnished **15** (3.11 g, 93%): oil; $[\alpha]_D$ −11.1 (*c* 1.8, $CHCl_3$); ^{1}H NMR δ 7.40−7.25 (15H, br m), 4.82 (1H, d, J = 12 Hz), 4.63 (1H, d, J = 12 Hz), 4.58 (2H, AB system, J = 11.5 Hz), 4.44 (2H, s), 4.28 (1H, m), 3.87 (1H, dd, J = 8, 6 Hz), 3.58 (1H, dd, J = 9, 5.5 Hz), 3.50 (1H, dd, J = 7.3, 3 Hz), 3.45−3.40 (2H, m), 3.34 (1H, dd, J = 9, 6.3 Hz), 2.00 (1H, m), 1.83 (1H, m), 1.65−1.25 (10H, br m), 1.05 (3H, d, J = 7 Hz), 0.99 (3H, d, J = 7 Hz); ^{13}C NMR δ 139.2, 139.1, 138.6, 109.8 (C), 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 83.9, 80.8, 79.0, 38.7, 36.2 (CH), 75.2, 73.5, 73.1, 72.0, 65.9, 36.5, 35.5, 25.3, 24.1, 24.0 (CH_2), 16.2, 10.7 (CH_3). HR EIMS *m/z* (rel int.) 558.3380 (M^+, 1), 309 (10), 269 (16), 181 (42), 91 (100). Calcd for $C_{36}H_{46}O_5$, 558.3345.

(2*S*,3*S*,4*R*,5*S*,6*S*)-3,5,7-Tris(benzyloxy)-4,6-dimethylheptane-1,2-diol (16). Anhydrous $ZnBr_2$ (6.75 g, 30 mmol) was added under N_2 to a solution of acetal **15** (2.8 g, ca. 5 mmol) in dry CH_2Cl_2 (60 mL). The mixture was stirred at room temperature until consumption of the starting material (ca. 3 h, TLC monitoring!). Workup (extraction with CH_2Cl_2) and column chromatography on silica gel (hexanes−EtOAc, 7:3) provided diol **16** (2.08 g, 87%): oil; $[\alpha]_D$ +7.7 (*c* 1.8, $CHCl_3$); IR 3440 (br) cm^{-1}; ^{1}H NMR δ 7.40−7.25 (15H, br m), 4.67 (1H, d, J = 11.5 Hz), 4.63 (1H, d, J = 11.5 Hz), 4.60−4.55 (4H, m), 3.80 (1H, m), 3.65 (1H, dd, J = 9, 5 Hz), 3.60−3.55 (3H, m), 3.53 (1H, dd, J = 11.5, 4.5 Hz), 3.48 (1H, dd, J = 7, 4 Hz), 2.80 (1H, br s, OH), 2.30 (1H, br s, OH), 2.25 (2H, m), 1.14 (3H, d, J = 7 Hz), 1.09 (3H, d, J = 7 Hz); ^{13}C NMR δ 138.9, 138.4, 138.1 (C), 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 81.2, 80.8, 72.3, 37.4, 36.6 (CH), 74.5, 74.0, 73.2, 72.4, 64.5 (CH_2), 15.0, 10.4 (CH_3). HR FAB MS *m/z* 479.2824 $(M + H)^+$. Calcd for $C_{30}H_{39}O_5$, 479.2797.

(2*S*,3*S*,4*R*,5*S*,6*S*)-3,5,7-Tris(benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)-4,6-dimethylheptan-2-ol (17). A solution of alcohol **16** (1.92 g, ca. 4 mmol) and imidazole (680 mg, 10 mmol) in dry CH_2Cl_2 (15 mL) was treated dropwise under N_2 with a solution of TPS chloride (1.55 g, 6 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred overnight at rt, then diluted with CH_2Cl_2 and worked up. Column chromatography on silica gel (hexanes−EtOAc, 9:1) afforded **17** (2.72 g, 95%): oil; $[\alpha]_D$ −9.6 (*c* 2.1, $CHCl_3$); IR 3500 (br) cm^{-1}; ^{1}H NMR δ 7.75−7.70 (4H, m), 7.45−7.25 (21H, br m), 4.71 (1H, d, J = 11.5 Hz), 4.66−4.58 (3H, m), 4.55 (2H, AB system, J = 12 Hz), 4.05 (1H, m), 3.81 (1H, dd, J = 10, 6.5 Hz), 3.75−3.70 (2H, m), 3.65−3.60 (3H, m), 2.60 (1H, d, J = 7 Hz, OH), 2.32 (1H, m), 2.23 (1H, m), 1.19 (3H, d, J = 7 Hz), 1.16 (9H, s), 1.13 (3H, d, J = 6.5 Hz); ^{13}C NMR δ 139.1, 138.7, 138.4, 133.3, 133.2, 19.2 (C), 135.6, 135.5, 129.7, 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 127.2, 81.1, 80.0, 72.0, 37.2, 37.0 (CH), 74.6, 74.0, 73.1, 72.5, 65.2 (CH_2), 26.9 (×3), 15.0, 10.5 (CH_3). HR FAB MS *m/z* 717.3998 $(M + H)^+$. Calcd for $C_{46}H_{57}O_5Si$, 717.3970.

(2*S*,3*S*,4*R*,5*S*,6*S*)-3,5,7-Tris(benzyloxy)-1-(*tert*-butyldiphenylsilyloxy)-2-methoxy-4,6-dimethylheptane (18). Alcohol **17** (2.15 g, ca. 3 mmol) and 1,8-bis(*N*,*N*-dimethylamino)-naphthalene (3.9 g, ca. 18 mmol) were dissolved under N_2 in dry CH_2Cl_2 (50 mL) and treated with trimethyloxonium tetrafluoroborate (2.22 g, ca. 15 mmol). The solution was stirred for 3 h at rt. Workup (extraction with CH_2Cl_2) and column chromatography on silica gel (hexanes−EtOAc, 19:1) yielded methyl ether **18** (1.95 g, 89%): oil; $[\alpha]_D$ −17.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 7.75−7.70 (4H, m), 7.45−7.30 (21H, br m), 4.72 (1H, d, J = 11.3 Hz), 4.66 (2H, d, J = 11.3 Hz), 4.60 (1H, d, J = 11.3 Hz), 4.52 (2H, AB system, J = 12 Hz), 3.91 (1H, dd, J = 10.5, 6 Hz), 3.87 (1H, dd, J = 10.5, 5.7 Hz), 3.71 (1H, dd, J = 7.4, 4 Hz), 3.65−3.60 (3H, m), 3.52 (1H, dd, J = 7.4, 3.4 Hz), 3.49 (3H, s), 2.30 (1H, m), 2.18 (1H, m), 1.16 (3H, d, J = 7 Hz), 1.13 (9H, s), 1.08 (3H, d, J = 7 Hz); ^{13}C NMR δ 139.2, 138.8, 138.7, 133.4, 133.3, 19.2 (C), 135.6, 135.5, 129.7, 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 127.2, 83.0, 82.0, 80.5, 37.2, 37.1 (CH), 74.7, 74.3, 73.0, 72.4, 63.3 (CH_2), 59.2, 26.9 (×3), 15.4, 10.3 (CH_3). HR EIMS *m/z* (rel int.) 730.4010 (M^+, 1), 639 (M^+ − Bn, 1), 269 (36), 181 (100), 91 (84). Calcd for $C_{47}H_{58}O_5Si$, 730.4053.

(2*S*,3*S*,4*R*,5*S*,6*S*)-3,5,7-Tris(benzyloxy)-2-methoxy-4,6-dimethylheptan-1-ol (19). Compound **18** (1.83 g, ca. 2.5 mmol) was dissolved under N_2 in dry THF (9 mL). Tetra-*n*-butylammonium fluoride trihydrate (TBAF, 788 mg, 3 mmol) dissolved in dry THF (3 mL) was then added. The reaction mixture was stirred at rt until consumption of the starting material (TLC monitoring). After addition of an aq saturated NH_4Cl solution (5 mL), the mixture was stirred for 5 min, worked up, and chromatographed on silica gel (hexanes−EtOAc mixtures). This furnished **19** (1.05 g, 85%): oil; $[\alpha]_D$ −2.7 (*c* 3.3, $CHCl_3$); IR 3450 (br) cm^{-1}; ^{1}H NMR δ 7.40−7.30 (15H, br m), 4.82 (1H, d, J = 11.5 Hz), 4.66 (1H, d, J = 11.5 Hz), 4.62 (2H, AB system, J = 11.5 Hz), 4.55 (2H, AB system, J = 12 Hz), 3.76 (1H, dd, J = 12, 4 Hz), 3.69 (2H, m), 3.59 (1H, dd, J = 12, 5 Hz), 3.50 (3H, s), 3.50−3.45 (3H, m), 2.30 (1H, br s, OH), 2.20 (2H, m), 1.16 (3H, d, J = 7 Hz), 1.05 (3H, d, J = 7 Hz); ^{13}C NMR δ 139.1, 138.8, 138.4 (C), 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 127.2, 83.3, 82.8, 80.2, 37.4, 36.5 (CH), 74.5, 74.3, 72.9, 72.0, 61.1 (CH_2), 58.4, 15.6, 10.2 (CH_3). HR FAB MS *m/z* 493.2919 $(M + H)^+$. Calcd for $C_{31}H_{41}O_5$, 493.2948.

Oxidation of Alcohol 19 to Aldehyde 20. DMSO (350 μL, 5 mmol) was dissolved under N_2 in dry CH_2Cl_2 (10 mL), cooled to −78 °C, and treated with oxalyl chloride (330 μL, 2.5 mmol). After the mixture was stirred at this temperature for 15 min, a solution of alcohol **19** (985 mg, 2 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise. The stirring was continued by further 15 min, followed by addition of triethylamine (1.4 mL, 10 mmol). The reaction mixture was then heated to 0 °C and stirred for 15 min at this temperature. Workup (CH_2Cl_2) and evaporation in vacuo provided **20** as an oily product, which was directly used in the next step. For weight calculations in the next step, the oxidation is assumed to be quantitative.

Oxazolidinone 22. A solution of **21** (466 mg, 2 mmol) in dry CH_2Cl_2 (2 mL) was cooled to −78 °C under N_2 and treated successively with triethylamine (560 μL, 4 mmol) and di-*n*-butylboron triflate (3.6 mL of a 1 M solution in CH_2Cl_2, 3.6 mmol, 1.8 equiv). The mixture was stirred for 30 min at the same temperature, then for 1 h at 0 °C, and recooled to −78 °C. The crude aldehyde **20** from above was dissolved in dry CH_2Cl_2 (10 mL) and added dropwise at −78 °C to the boron enolate mixture. The reaction was then heated to −20 °C and stirred for 14 h at this temperature. The reaction was quenched through sequential addition of pH 7 buffer solution (15 mL), MeOH (15 mL), and 30% aqueous H_2O_2 (8 mL), followed by stirring for 30 min at room temperature. The reaction mixture was subsequently worked up (extraction with CH_2Cl_2) and chromatographed on silica gel (hexanes−EtOAc, 4:1) to yield compound **22** (1.11 g, 77% overall yield from **19**): oil; $[\alpha]_D$ +8.1 (*c* 1.2, $CHCl_3$); IR 3490 (br), 1781, 1694 cm^{-1}; ^{1}H NMR δ 7.40−7.25 (20H, br m), 4.72 (1H, d, J = 11.3 Hz), 4.66 (1H, d, J = 11.3 Hz), 4.65−4.50 (5H, m), 4.24 (1H, m), 4.13 (1H, dd, J = 9, 2.7 Hz), 4.05 (2H, m), 3.92 (1H, dd, J = 7.7, 2.8 Hz), 3.61 (2H, m), 3.51 (1H, dd, J = 7.8, 2.8 Hz), 3.47 (1H, overlapped m), 3.46 (3H, s), 3.30 (1H, br s, OH), 3.25 (1H, dd, J = 13.5, 3.5 Hz), 2.80 (1H, dd, J = 13.3, 9.5 Hz), 2.40 (1H, m), 2.14 (1H, m), 1.37 (3H, d, J = 7 Hz), 1.19 (3H, d, J = 7 Hz), 1.10 (3H, d, J = 7 Hz); ^{13}C NMR δ 177.1, 152.8, 139.2, 138.8, 138.4, 135.2 (C), 129.4, 128.9, 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 127.3, 81.8, 81.0, 80.0, 71.0, 55.0, 39.6, 37.4, 37.2 (CH), 74.5, 74.1, 73.0, 72.6, 66.0, 37.8 (CH_2), 59.6, 15.3, 12.1, 10.1 (CH_3). HR FAB MS *m/z* 724.3770 $(M + H)^+$. Calcd for $C_{44}H_{54}NO_8$, 724.3849.

Alcohol 23. A solution of $LiBH_4$ (2 M in THF, 0.9 mL, 1.8 mmol) was cooled under N_2 to −10 °C and treated with

absolute EtOH (105 μL, 1.8 mmol). After the mixture was stirred for 10 min at this temperature, a solution of compound **22** (1.08 g, ca. 1.5 mmol) in dry Et_2O (20 mL) was added dropwise via syringe, followed by stirring for 2 h at −10 °C. The reaction was quenched through addition of 1 M NaOH (4 mL), with continued stirring for further 15 min at 0 °C. Workup (extraction with Et_2O) and column chromatography on silica gel (hexanes−EtOAc, 4:1) furnished compound **23** (735 mg, 89%): oil; $[\alpha]_D$ −27.2 (*c* 2.6, $CHCl_3$); IR 3430 (br) cm^{-1}; ^1H NMR δ 7.40−7.30 (15H, m), 4.70 (1H, d, J = 11.5 Hz), 4.66 (1H, d, J = 11.5 Hz), 4.61 (1H, d, J = 11.5 Hz), 4.58 (1H, d, J = 11.5 Hz), 4.55 (2H, s), 4.04 (1H, dd, J = 9, 1.7 Hz), 3.88 (1H, dd, J = 6.6, 3.4 Hz), 3.73 (1H, dd, J = 10.6, 4 Hz), 3.66 (2H, m), 3.57 (2H, m), 3.43 (3H, s), 3.41 (1H, dd, J = 9, 3.4 Hz), 3.30 (1H, br s, OH), 2.70 (1H, br s, OH), 2.38 (1H, m), 2.16 (1H, m), 2.00 (1H, m), 1.20 (3H, d, J = 7 Hz), 1.09 (3H, d, J = 7 Hz), 1.03 (3H, d, J = 7 Hz); ^{13}C NMR δ 139.2, 138.5, 138.1 (C), 128.3, 128.2, 128.1, 127.7, 127.5, 127.4, 127.2, 82.1, 80.3, 79.7, 73.1, 37.0, 36.8, 35.5 (CH), 73.9, 73.8, 73.0, 72.5, 67.6 (CH_2), 59.4, 15.4, 10.1, 9.6 (CH_3). HR FAB MS *m/z* 551.3405 $(M + H)^+$. Calcd for $C_{34}H_{47}O_6$, 551.3372.

Alcohol 24. This was obtained in 89% yield through silylation of **23** under the conditions described above for **17**: oil; $[\alpha]_D$ −24 (*c* 2, $CHCl_3$); IR 3500 (br) cm^{-1}; ^1H NMR δ 7.75−7.70 (4H, m), 7.50−7.30 (21H, br m), 4.82 (1H, d, J = 11.6 Hz), 4.71 (1H, d, J = 11.6 Hz), 4.69 (1H, d, J = 11.4 Hz), 4.60 (1H, d, J = 11.4 Hz), 4.56 (2H, br s), 4.23 (1H, br d, J = 8.8 Hz), 3.98 (1H, dd, J = 7.4, 2.8 Hz), 3.85−3.80 (2H, m), 3.68 (1H, dd, J = 8.8, 3.8 Hz), 3.64 (1H, dd, J = 8.8, 5.8 Hz), 3.60 (1H, dd, J = 7.7, 3.1 Hz), 3.50 (1H, overlapped m), 3.50 (3H, s), 3.10 (1H, br s, OH), 2.42 (1H, m), 2.20 (1H, m), 2.10 (1H, m), 1.23 (3H, d, J = 7 Hz), 1.15 (9H, s), 1.12 (3H, d, J = 7 Hz), 1.10 (3H, d, J = 7 Hz); ^{13}C NMR δ 139.3, 138.7, 138.6, 133.3, 133.2, 19.2 (C), 135.6, 135.5, 129.7, 128.3, 128.2, 128.1, 128.0, 127.8, 127.5, 127.4, 127.3, 127.2, 127.1, 82.1, 80.8, 80.0, 72.2, 37.3, 37.2, 35.6 (CH), 74.4, 74.2, 73.0, 72.6, 69.1 (CH_2), 59.7, 26.9 (×3), 15.3, 10.0, 9.8 (CH_3). HR FAB MS *m/z* 789.4546 $(M + H)^+$. Calcd for $C_{50}H_{65}O_6Si$, 789.4550.

Ketone 25. Alcohol **24** (552 mg, 0.7 mmol) was dissolved under N_2 in dry CH_2Cl_2 (5 mL). After successive addition of solid $NaHCO_3$ (0.12 g, ca. 1.4 mmol) and Dess−Martin periodinane (0.6 g, ca. 1.4 mmol), the mixture was stirred at room temperature until consumption of the starting material (ca. 45 min, TLC monitoring!). Workup (extraction with CH_2Cl_2) and column chromatography on silica gel (hexanes−EtOAc, 19:1) afforded compound **25** (468 mg, 85%): oil; $[\alpha]_D$ −62.2 (*c* 0.8, $CHCl_3$); IR 1725 cm^{-1}; ^1H NMR δ 7.65−7.60 (4H, m), 7.45−7.20 (21H, br m), 4.62 (1H, d, J = 11.6 Hz), 4.58 (1H, d, J = 11.6 Hz), 4.55−4.45 (4H, m), 4.35 (1H, d, J = 3.4 Hz), 4.07 (1H, dd, J = 8.3, 3.4 Hz), 3.80 (1H, dd, J = 9.3, 8.3 Hz), 3.60−3.55 (3H, m), 3.50 (1H, dd, J = 8.3, 2.5 Hz), 3.42 (3H, s), 3.05 (1H, m), 2.36 (1H, m), 2.10 (1H, m), 1.10 (3H, d, J = 6.8 Hz), 1.04 (3H, d, J = 7 Hz), 1.03 (9H, s), 0.95 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 212.1, 139.3, 138.8, 138.3, 133.1, 133.0, 19.2 (C), 135.5, 135.4, 129.8, 128.3, 128.2, 128.1, 128.0, 127.8, 127.5, 127.4, 127.3, 127.2, 127.1, 88.3, 81.4, 80.0, 45.4, 37.4, 36.1 (CH), 74.2, 73.1, 72.6, 70.8, 67.6 (CH_2), 59.1, 26.9 (×3), 15.1, 12.8, 9.8 (CH_3). HR FAB MS *m/ z* 787.4353 $(M + H)^+$. Calcd for $C_{50}H_{63}O_6Si$, 787.4393.

Hemiacetal 13. A solution of compound **25** (393 mg, 0.5 mmol) in EtOAc (100 mL) was mixed with 10% Pd/C (1.6 g) and placed under H_2 in a pressure flask at 35 atm. After being stirred for 16 h, the crude mixture was filtered through Celite, all volatiles were removed in vacuo, and the residue was chromatographed on silica gel (hexanes−EtOAc, 7:3). This gave **13** in very variable and not reproducible yields (always <30%) as a somewhat unstable oil. R_f on silica gel, 0.2 (elution with hexanes−EtOAc, 1:1): oil; $[\alpha]_D$ −3.3 (*c* 0.2, $CHCl_3$); IR 3430 (br) cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 7.70−7.65 (4H, m), 7.40−7.30 (6H, br m), 4.03 (1H, dd, J = 9.4, 3.6 Hz), 3.76 (1H, m), 3.65−3.65 (1H, m), 3.56 (3H, s), 3.50−3.45 (2H, m), 3.05 (2H, m), 2.25 (1H, m), 1.88 (2H, m), 1.15 (3H, d, J = 7 Hz), 1.05 (9H, s), 0.97 (3H, d, J = 6.7 Hz), 0.80 (3H, d, J = 6.8 Hz); ^{13}C NMR δ 134.1, 134.0, 100.4, 19.2 (C), 135.7, 135.6, 129.5, 129.4, 127.5, 127.3, 84.4, 78.3, 73.6, 42.4, 40.3, 29.6 (CH), 63.6, 63.5 (CH_2), 61.1, 26.9 (×3), 18.0, 12.1, 11.5 (CH_3). HR EIMS *m/z* (rel int.) 441.1928 ($M^+ - H_2O - t$Bu, 6), 423 ($M^+ - 2H_2O - t$Bu, 11), 391 ($M^+ - 2H_2O$ − MeOH − *t*Bu, 6), 285 (41), 265 (62), 199 (100). Calcd for $C_{29}H_{44}O_6Si-H_2O-t$Bu, 441.2091.

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Supporting Information Available: Description of the general features and chemical correlations, including reaction conditions, used to establish the configurations of the aldols and spectral data of some selected correlation products. Graphical NMR spectra of compounds **10a**, **10b**, **11a**, **11b**, **12a**, **12b**, **13**−**19**, and **22**−**25**, as well as of some correlation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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