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Articles

Stereoselective Synthesis of Conformationally Constrained Cyclohexanediols: A Set of Molecular Scaffolds for the Synthesis of Glycomimetics

Anna Bernardi,*,† Daniela Arosio,† Leonardo Manzoni,† Fabrizio Micheli,‡ Alessandra Pasquarello,‡ and Pierfausto Seneci‡,§

Universita' di Milano, Dipartimento di Chimica Organica e Industriale, via Venezian 21, 20133 Milano, Italy, GlaxoWellcome SpA, Medicines Research Centre, via Fleming 4, 37100 Verona, Italy

anna.bernardi@unimi.it

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The practical, stereoselective synthesis of the three diastereoisomeric 1,2-*trans*-dicarboxy-4,5-cyclohexanediols **1**−**3** (DCCHDs) is described, starting from a common precursor, easily available in both enantiomeric forms. The regioselective derivatization of all functional groups of **1** is also reported. The three DCCHDs are locked in a single chair conformation and thus can be used to mimic vicinally disubstituted monosaccharides of any relative configuration.

Introduction

In recent years much interest has been devoted to the synthesis of so-called glycomimetics, i.e., functional and structural mimics of oligosaccharides, as promising therapeutic agents.[1] Analysis of the characteristic properties of sugar-binding sites shows that many of the lectins bind carbohydrates weakly, using shallow depressions exposed to the solvent on the protein surface. Thus, despite the great structural complexity of many bioactive oligosaccharides, often only small portions of these molecules are actually recognized by their receptors. The remaining part appears to act as a scaffold that orients the binding determinants in the appropriate conformation and provides a connection to the aglycons. This analysis suggests that functional mimics of carbohydrates may be designed by replacing these seemingly inactive fragments with simpler, non-carbohydrate scaffolds. Such replacements could decrease the molecular, and hence synthetic, complexity of the construct and simultaneously increase its metabolic stability.[2] In particular, carbocyclic diols of the appropriate configuration can be used as substitutes of branching units in complex oligosaccharides. For instance, the 3,4-disubstituted *N*-acetyl glucosamine (GlcNAc) of the sialylLewisX tetrasaccharide (sLex, Chart 1), a residue that does not contain any groups critical for binding to the sLex target, has been successfully replaced using 1,2-*trans*-cyclohexanediol in the synthesis of a highly effective mimic.[3]

The use of simple cyclohexanediols, though, is limited by two factors. First and foremost, simple 1,2-cyclohexanediols are conformationally flexible. Hence, they cannot be used to replace those branching motifs that incorpo-

* Corresponding author.
† Universita' di Milano.
‡ GlaxoWellcome.
§ Present address: Nucleotide Analog Design AG, Landsbergerstrasse 50, 80339 München, Germany.

(1) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300−2324.

(2) Simanek, E. E.; McGarvey, G. J.; Jablonowski, J. A.; Wong, C.-H., *Chem. Rev.* **1998**, *98*, 833−862, and references therein.

(3) Kolb, H. C.; Ernst, B. *Chem. Eur. J.* **1997**, *3*, 1571−1578.

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Chart 1. High-Activity Mimics of Oligosaccharides Built on Cyclohexanediol Scaffolds

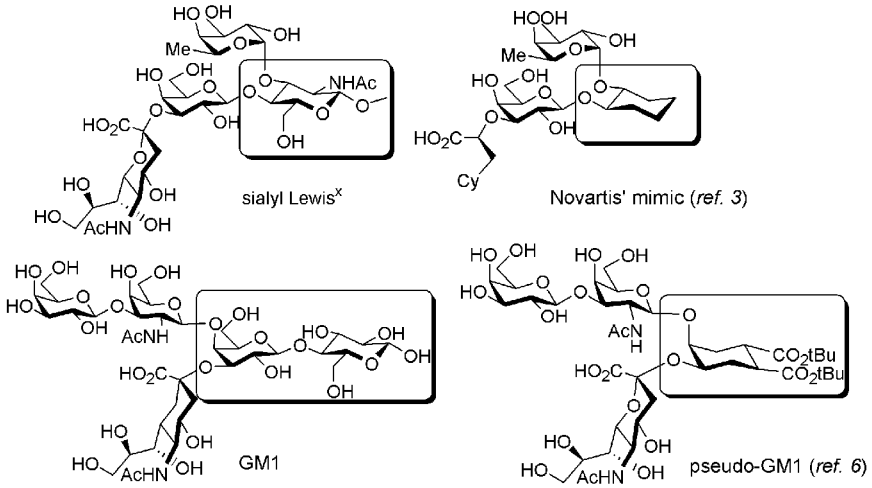


Chart 2. Common Arrays of Branching Units in Bioactive Oligosaccharides

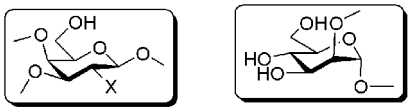
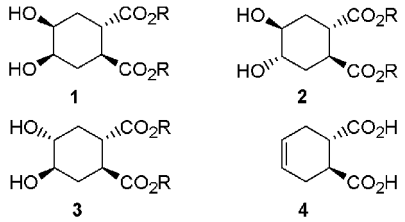


Chart 3. Conformationally Constrained Dicarboxy Cyclohexanediols (DCCHD) 1−3 and Their Common Precursor 4

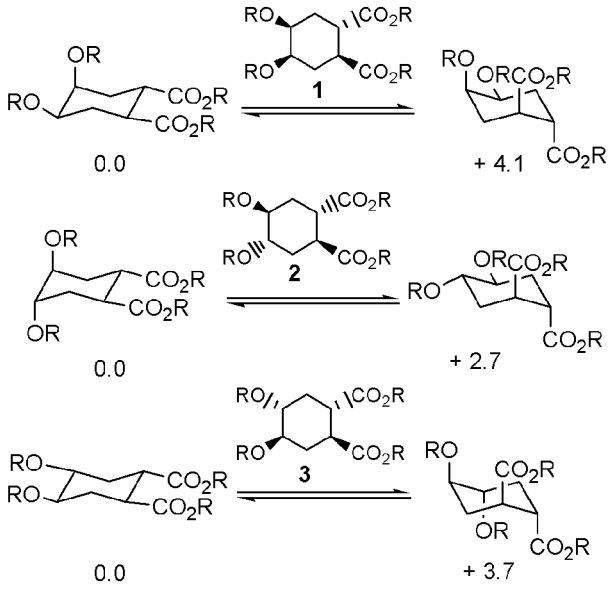


rate one or more axial substituents, and that are frequently encountered in bioactive oligosaccharides (see Chart 2). Such motifs include, for example, the 3,4-galacto and 2-Manα-1 arrays shown in Chart 2, that are commonly found in glycolipids and glycopeptides. Second, in biological systems the bioactivity of oligosaccharides is often expressed by multivalent clusters of glycoconjugates (glycoside cluster effect).[4] Simple cyclohexanediols that cannot be conjugated to polyvalent aglycons thus lack an important attribute, which could help to produce highly effective and specific ligands.

The stereoisomeric 1,2-*trans*-dicarboxy-4,5-cyclohexanediols (DCCHDs) **1**−**3** (Chart 3 and Scheme 1) overcome both the above-mentioned drawbacks and thus appear a very attractive alternative as mimics of scaffold monosaccharides.

Indeed, DCCHDs are highly conformationally stable, thanks to the 1,2-*trans*-dicarboxy substitution that acts as a conformational lock for the cyclohexane ring. MM3* calculations show (Scheme 1) that for all isomers the chair featuring two equatorial carboxy groups is at least 2.7 kcal/mol more stable than the isomeric one, diaxially

Scheme 1. Conformational Equilibria of DCCHDs 1−3 (MM3* relative energies in kcal/mol)



substituted.[5] This was experimentally confirmed for **1**[6] and **2**[7] by analysis of their ^{1}H NMR spectra. Accordingly, the diol functionality is also locked in the lowest energy conformation shown in Scheme 1 and can be used to reproduce vicinally disubstituted monosaccharides of any relative configuration.

In fact, we recently succeeded in mimicking the cis diol of the 3,4-disubstituted galactose residue in the GM1 oligosaccharide (Chart 1) using diol **1**, and the resulting pseudo-GM1 molecule (Chart 1) was shown to accurately replicate the three-dimensional structure and cholera toxin-binding activity of its natural model.[6,8] In addition,

(4) Lee, Y. C.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 1−327. Lis, H.; Sharon, N. *Chem. Rev.* **1998**, *98*, 637−674. Kiessling, L. L.; Pohl, N. L. *Chem. Biol.* **1996**, *3*, 71−77. Roy, R. *Curr. Opin. Struct. Biol.* **1996**, *6*, 692−702.

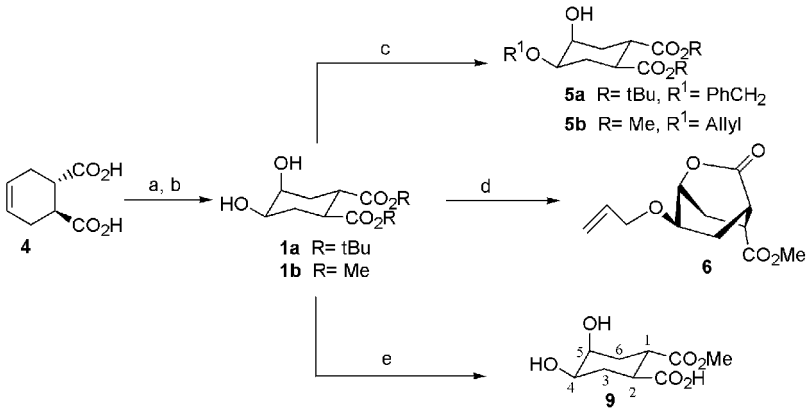
(5) Calculations were run in vacuo, using MacroModel 5.5: Mohamadi, F., Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

(6) Bernardi, A.; Checchia, A.; Brocca, P.; Sonnino, S.; Zuccotto, F. *J. Am. Chem. Soc.* **1999**, *121*, 2032−2036.

(7) Samoshin, V. V.; Chertkov, V. A.; Vatlina, L. P.; Dobretsova, E. K.; Simonov, N. A.; Kastorsky, L. P.; Gremyachinsky, D. E.; Schneider, H.-J. *Tetrahedron Lett.* **1996**, *37*, 3981−3984.

(8) (a) Bernardi, A.; Boschin, G.; Checchia, A.; Lattanzio, M.; Manzoni, L.; Potenza, D.; Scolastico, C. *Eur. J. Org. Chem.* **1999**, 1311−1317. (b) Bernardi, A.; Carrettoni, L.; Grosso Ciponte, A.; Monti, D.; Sonnino, S. *Bioorg., Med. Chem. Lett.* **2000**, *10*, 2197−2200.

Scheme 2[a]



[a] Conditions: (a) For **1a**: $Me_2NCH(OtBu)_2$, benzene; $OsCl_3/Et_3NO$. (b) For **1b**: $MeOH/H_2SO_4$; $OsCl_3/Et_3NO$. (c) Bu_2SnO, refl. benzene; R^1Br. (d) From **1b**: Bu_2SnO; allylBr, CsF, refl. toluene. (e) From **1b**: LiOH (2.5 mol equiv) or NaOH, (1.5 mol equiv).

the carboxy groups of DCCHDs could be exploited for conjugation to various supports, thus allowing the synthesis of polyvalent pseudo-glycoconjugates.

The three diastereisomeric diols should be easily synthesized from a common precursor, the 1,2-dicarboxy-4-cyclohexene **4**. Since we have recently described the facile, large-scale synthesis of both enantiomers of 1,2-dicarboxy-4-cyclohexene,[9] the three diols could, in principle, be synthesized in both enantiomeric forms.

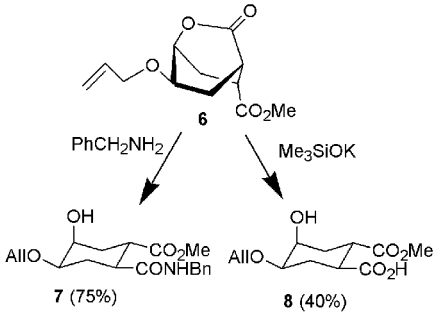
Here we report the stereoselective synthesis of DCCHD **1**−**3** starting from **4**, and some regioselective manipulations of their functional groups.

Results and Discussion

Synthesis and Regioselective Functionalization of the *cis*-Diol 1. We have described the synthesis of the *cis*-diol **1a** as an intermediate en route to pseudo-GM1.[8a] Starting from **4**, the *tert*-butyl ester was synthesized with dimethylformamide di-*tert*-butyl acetal (Scheme 2), and OsO_4 dihydroxylation gave **1a**. Likewise, the methyl ester **1b** can be obtained by Fischer esterification in MeOH, followed by dihydroxylation using Poli's protocol[10] (Scheme 2).

Selective alkylation of the equatorial hydroxy group can be achieved via the intermediate stannylene.[11] The Bu_2SnO-mediated synthesis of the monobenzyl ether **5a** from the di-*tert*-butyl ester **1a** (Scheme 2, route c) has already been described.[8a] The same procedure was also effective for the synthesis of the equatorial allyl ether **5b** from the dimethyl ester **1b**, using allyl bromide and Bu_2SnO (Scheme 2). In this case the alkylation step must be carried out at room temperature, to avoid the Sn-assisted lactonization[11] of the methyl ester. The latter reaction becomes prevalent in refluxing toluene, leading to lactone **6** as the only product, in 60% yield (Scheme 2, route d). This compound provides an easy entry to carboxy group differentiation in DCCHD **1**. In fact, reaction of **6** with 1 mol equiv of benzylamine in CH_2Cl_2 at room temperature selectively occurs on the lactone carboxy group, affording the amide **7** in 75% yield (Scheme 3). Similarly, Me_3SiOK hydrolysis preferentially

Scheme 3. Selective Opening of Lactone 6



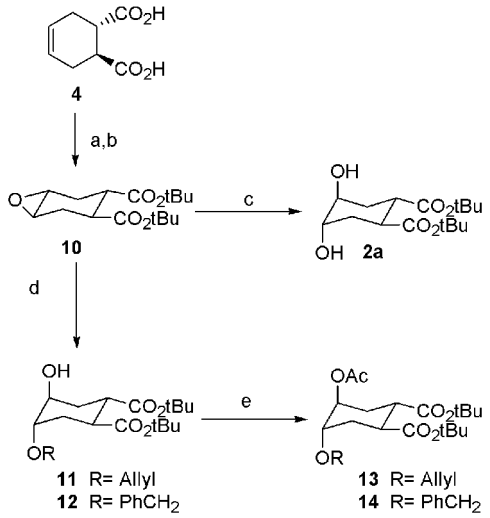
takes place on the lactone, leaving the methyl ester unchanged and yielding the monoacid **8** as the major product (40%) (Scheme 3).

Alternatively, carboxy group differentiation can also be achieved by direct, regioselective hydrolysis of **1b** with 2.5 mol equiv of LiOH in $MeOH/H_2O$ (Scheme 2, route e). This reaction appears to proceed initially to yield a 70:30 ratio of the regioisomeric monoacids, which cannot be separated by flash chromatography. However, if the reaction is protracted for 5−6 h at room temperature, the minor isomer is preferentially consumed to give the diacid, and the monoacid **9** is isolated in 64% yield and 90−95% isomeric purity after flash chromatography. The identity of this compound was established on the basis of its NOESY spectrum in D_2O, which showed medium-intensity cross-peaks between the methyl ester protons and both $H\text{-}_{6eq}$ and $H\text{-}_{6ax}$ (see Scheme 2 for numbering). Eventually, the same selective transformation was more efficiently achieved with 1.5 mol equiv of 0.07 M NaOH at room temperature for 45 min. Under these conditions, only the monoacid **9** is formed and can be isolated in 80% yield.

Synthesis of the Trans-Diaxial Diol 2. The trans-diaxial diol **2** was obtained by acid-catalyzed hydrolysis of the epoxide **10**,[7] which in turn was synthesized by MCPBA oxidation of the bis *tert*-butyl ester of **4** (Scheme 4). Selective trans-diaxial opening of **10** could also be achieved by catalyzed alcoholysis, using either allyl alcohol as the solvent (to give the allyl ether **11**), or excess $PhCH_2OH$ in dioxane or CH_2Cl_2 (to give the benzyl ether **12**) (Scheme 4). The diastereoisomeric composition of the mixture and the product characterization were determined after acetylation of the crude with Ac_2O/DMAP to give **13** and **14**, respectively.

(9) Bernardi, A.; Arosio, D.; Dellavecchia, D.; Micheli, F. *Tetrahedron: Asymmetry* **1999**, *40*, 3403−3407.
(10) Poli, G. *Tetrahedron Lett.* **1989**, *30*, 7385−7388
(11) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643−663.

Scheme 4. Synthesis of the Diaxial Diol 2 and of Its Monoethers 11 and 12[a]



[a] Conditions: (a) $Me_2NCH(OtBu)_2$; (b) MCPBA; (c) H_2O, H^+; (d) ROH, cat.; (e) Ac_2O, DMAP.

Table 1. Catalyzed Reaction of Epoxide 10 with Allyl Alcohol as Solvent

entry	catalyst	temperature	time	yield (%)
1	$FeCl_3$[a]	rt	2 h	60[b]
2	TCNE[c]	rt	2 h	74
3	DDQ[d]	rt	3 days	64
4	CAN[c]	rt	15 h	43[e]
5	$Cu(OTf)_2$[d]	rt	3 h	75
6	$Ce(OTf)_4$[f]	rt	4 h	67
7	$Mg(OTf)_2$[a]	60 °C → 80 °C	15 h + 4 h	69
8	$Yb(OTf)_3$[f]	rt	5 h	4[e]

[a] See ref 12a. [b]10% of inseparable chloride opening product was also obtained. [c]See ref 12c. [d]See ref 12b. [e]Byproducts were also obtained (see text). [f]See ref 12e.

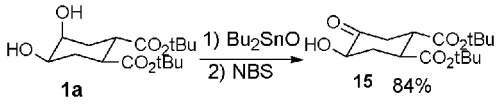
The alcoholysis of epoxides can be catalyzed by a number of Lewis acids, or by electron-transfer catalysts,[12] and some of these were examined in order to achieve maximum yield and selectivity in the allyl alcohol opening reaction (Table 1). Owing to the conformational stability of the 1,2-*trans*-dicarboxycyclohexane framework, only the ether arising from axial attack was obtained under all sets of conditions. $FeCl_3$ catalysis[12a] led to rapid reaction of the epoxide at room temperature, but, in addition to the desired allyl ether **11**, ca. 20% of inseparable chloride opening product was also formed. (Table 1, entry 1). Better results were achieved using other electron-transfer catalysts, such as tetracyanoethylene[12d] (TCNE, Table 1, entry 2) or DDQ[12b] (Table 1, entry 3). However, with the latter catalyst the alcoholysis reaction became sluggish and required 3 days at room temperature. CAN-catalyzed opening[12c] was also slow and gave a number of byproducts (Table 1, entry 4). Good reactivity and selectivity were obtained using 10% $Cu(OTf)_2$ (Table 1, entry 5) or 5% $Ce(OTf)_4$ (Table 1,entry 6) at room temperature. Lewis acidic conditions were also explored. $Mg(OTf)_2$ (Table 1, entry 7) did promote the reaction, but required high temperatures and prolonged reaction times. $Yb(OTf)_3$[12e] (Table 1, entry 8) catalyzed rapid epoxide opening, but also resulted in extensive decomposition of the *tert*-butyl esters.

Table 2. Synthesis of Benzyl Ether 12 from Epoxide 10

entry	catalyst	solvent	temperature	time (h)	yield (%)
1	DDQ[a]	dioxane	rt	72	0
2	TCNE[b]	dioxane	rt	48	0
3	TCN[b]	CH_2Cl_2	rt	15	22
4	$Cu(OTf)_2$[b]	CH_2Cl_2	rt	24	83
5	$Mg(OTf)_2$[c]	$ClCH_2CH_2Cl$	80 °C	24	60

[a] See ref 12a. [b]See ref 12d. [c]See ref 12a.

Scheme 5. Synhesis of Ketone 15



The best promoters were then tested in the synthesis of the benzyl ether **12**. In this case, only 5 mol equiv of nucleophile were employed, and the reaction was carried out in an inert solvent. Using dioxane as the solvent the opening reaction did not take place in the presence of either DDQ or TCNE (Table 2, entries 1 and 2). In CH_2Cl_2, TCNE does catalyze the reaction, but after 15 h only 22% of ether is formed (entry 3). On the contrary, good results were achieved using $Cu(OTf)_2$ (entry 4) or $Mg(OTf)_2$ (entry 5).[13]

Synthesis of the Trans-Diequatorial Diol 3. For the synthesis of the diequatorial diol **3**, Mitsunobu inversion[14] of the alcohol **5a** was initially attempted. However, using benzoic acid or the more reactive picolinic acid,[15] no reaction occurred, and the starting material was recovered unchanged. Therefore the ketone **15** was prepared by Sn-mediated selective oxidation of diol **1a** with NBS (Scheme 5),[16] and its stereoselective reduction was studied.

The steric outcome of the hydride reduction of simple cyclohexanones is known to depend on the size of the reducing agent.[17] Axial attack of the hydride is normally favored for torsional (Felkin)[18] or electronic (Cieplak)[19] reasons and leads to the equatorial alcohol with modest stereoselectivity. This selectivity is overridden by steric effects when using sterically hindered reducing agents, such as the selectrides.[17] In this case, equatorial attack of the hydride efficiently leads to the axial alcohol. Steric hindrance from the α-substituents of the carbonyl group is also known to favor equatorial attack. Accordingly, ketone **15** exhibited a modest preference for axial hydride attack in the reactions with $NaBH_4$ (Table 3, entry 2, 60:40 *trans:cis* ratio), with BH_3.THF (Table 3, entry 3, 66:34 *t:c*), and exclusive equatorial attack in the reaction with Li-selectride (Table 3, entry 1), which led to the starting *cis*-diol **1a**.

(12) (a) Iranpoor, N.; Salehi, P. *Synthesis* **1994**, 1152. (b) Iranpoor, N.; Baltork, I. M. *Tetrahedron Lett.* **1990**, *31*, 735. (c) Iranpoor, N.; Baltork, I. M. *Synth. Commun.* **1990**, *20*, 2789. (d) Masaki, Y.; Miura, T.; Ochiai, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 195. (e) Iranpoor, N.; Shekarriz, M.; Shirini, F. *Synth. Commun.* **1998**, *28*, 347. (f) De, A.; Ghosh, S.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 8379.

(13) The $Cu(OTf)_2$-promoted reaction appears to be rather general, as exemplified by cyclohexanol opening of **10**, which occurs in 40 h at RT in 60% yield.

(14) Mitsunobu, O. *Synthesis* **1981**, 1. Hughes, D. L. *Org. React.* **1992**, Chapter 2.

(15) Sammakia, T.; Jacobs, J. S. *Tetrahedron Lett.* **1999**, *40*, 2685.

(16) Kong, X.; Grindley, T. B. *J. Carbohydr. Chem.* **1993**, *12*, 557−571.

(17) Greeves, N. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds., 1991; vol. 8, chap. 1.1. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry B*; Plenum Press: New York, 1990.

(18) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2205. Wu, Y.-D.; Houk, K. *J. Am. Chem. Soc.* **1987**, *109*, 908.

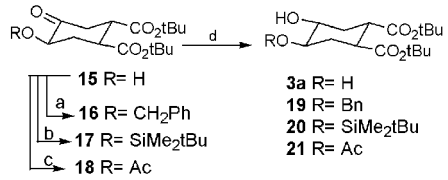
(19) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

Table 3. Reduction of Ketones 15−19. Synthesis of the Trans-Diequatorial Diol 3a

entry	substrate	reducing agent	solvent	*T* (°C)	*t* (h)	*t:c* ratio[a]	yield (%)
1	15	Li-selectride	THF	−78	2.5	0:100	98
2	15	$NaBH_4$	MeOH	0 → 25	0.5	60:40	94
3	15	BH_3	THF	0	5	66:34	81
4	15	$NaBH(OAc)_3$	MeCN/AcOH	−40	22	62:38	89
5	15	$NaBH(OAc)_3$	MeCN	−20	5	74:26	77
6	15	$Me_4NBH(OAc)_3$	MeCN	25	20	70:30	50[b]
7	16	$NaBH_4$	MeOH	0	1.5	40:60	85
8	16	$NaBH(OAc)_3$	MeCN/AcOH	−40	1.5	84:16	95
9	16	$NaBH(OAc)_3$	MeCN	−20	17	81:19	96
10	17	$NaBH_4$	MeOH	0	0.5	50:50	80
11	17	$NaBH(OAc)_3$	MeCN/AcOH	−40	6.5	82:18	85
12	18	$NaBH_4$	MeOH	0	2	60:40[c]	81[c]
13	18	$NaBH(OAc)_3$	MeCN/AcOH	−40	36	98: 2	70

[a] As determined by ^{1}H NMR at 300 MHz. [b]Reaction is incomplete. [c]Deacetylation occurs. Diastereomeric ratio and yields determined after peracetylation of the reduction crude.

Scheme 6. Stereoselective Reduction of Ketones 15−18: Synthesis of the Trans-Diequatorial Diol 3[a]



[a] Conditions: (a) BnBr, Ag_2O (70%); (b) TBSCl, DMF, imidazole (64%); (c) Ac_2O, DCM, pyridine, DMAP (86%); (d) reducing agents, see Table 3.

Directing effects from hydroxy groups have been reported by Evans and Chapman in the stereoselective reduction of *β*-hydroxy ketones, using $NaBH(OAc)_3$ or $Me_4NBH(OAc)_3$.[20] Their results are consistent with displacement of one of the OAc ligands by the substrate hydroxy group, followed by internal delivery of the hydride through a six-membered transition state. Indeed, a modest improvement of the trans selectivity was achieved upon treating **15** with $NaBH(OAc)_3$ (Table 3, entry 5, 74:26 *t:c*) or $Me_4NBH(OAc)_3$ (Table 3, entry 6, 70:30 *t:c*) in MeCN at −20 °C. Addition of AcOH to the reaction mixture, as in the original Evans−Chapman protocol, allowed the reaction to proceed at −40 °C, but was detrimental for the stereoselectivity (Table 3, entry 4, 62:38 *t:c*). Thus it appears that internal hydride delivery from the α-hydroxy group, which would require a five-membered transition structure, is occurring much less efficiently than from the *β* position. In an effort to improve the trans selectivity, the effect of different hydroxy protecting groups was examined, in the series **16**−**18** (Scheme 6, Table 3). Protection of the alcohol did not have any influence on the $NaBH_4$ reduction, which remained essentially stereorandom (Table 3, entries 2, 7 10, 12). On the contrary, the trans selectivity of $NaBH(OAc)_3$ reduction increased upon protection of the hydroxy group going from 3:1 for the free alcohol **15** to 5:1 for the benzyl ether **16** (Table 3, entry 8) and the silyl ether **17** (Table 3, entry 11) and reached synthetically useful values (98:2, Table 3, entry 13) for the acetate **18**.[21]

(20) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939.

(21) The reduction of **16** with chiral oxazaborolidines was also studied, using (*R*) or (*S*) diphenylprolinol (Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. Quallich, G. J.; Woodall, T. M. *Synth. Lett.* **1993**, 929). Both reagents yielded a 85:15 *trans:cis* ratio. For the enantioselective reduction of hydroxymethylene ketones with oxazaborolidine, see: Cho, B. T.; Chun, Y. S. *J. Org. Chem.* **1998**, *63*, 5280. *Tetrahedron: Asymmetry* **1999**, *10*, 1843.

In conclusion, we have described the straightforward stereoselective synthesis of enantiomerically pure, conformationally constrained DCCHD **1**−**3**, starting from an easily available common precursor, which can be readily synthesized in both enantiomeric forms.[9] These molecules should be useful as building blocks in the synthesis of mimics of complex oligosaccharides in solution or on solid phase, either using classical synthetic methods or applying parallel or combinatorial methodologies leading to oligosaccharide libraries. Their use in the design and synthesis of glycomimetics is underway in our laboratories[6,8] and will be reported in due course.

Experimental Section

General. Solvents: pyridine, DMF, CCl_4, and dichloroethane were dried over 4-A molecular sieves. The other dry solvents were distilled under nitrogen shortly before use. THF, Et_2O, dioxane, benzene, and toluene were distilled from Na; MeCN, EtCN, MeOH, Et_3N, CH_2Cl_2 were distilled from CaH_2. Flash chromatography: Silica gel (Kieselgel 60, 230−400 mesh). Mps: Kleinfeld Labortechnik apparatus, uncorrected values. NMR: Bruker Ac-200, Ac-300, and Avance-400, for ^{13}C spectra only selected values are reported, internal standard TMS. IR: Perkin-Elmer FTIR 1600 spectrometer. Optical rotations: Perkin-Elmer 241 at 589 nm, using 1 mL cells. Known compounds: **1a**,[8a] **4**,[9] **5a**.[8a]

Synthesis of (1*S*,2*S*)-Cyclohex-4-ene-1,2-dicarboxylic Acid Dimethyl Ester. To a solution of the diacid **4** (7.02 g, 0.041 mol, 1 mol equiv) in dry MeOH (100 mL) was added H_2SO_4 (0.5 mL, 0.009 mol, 0.2 mol equiv). The solution was stirred at reflux for ca. 20 h and then concentrated under vacuum to about half of the original volume. AcOEt was added, the organic phase was washed with saturated $NaHCO_3$ and dried with Na_2SO_4, and the solvent was evaporated under reduced pressure to yield 7.8 g of dimethyl ester (95%). $[\alpha]^{20}_D$: +127.3 (*c* = 1.23, $CHCl_3$); Microanalysis: Found, C 60.62%, H 7.10%; $C_{10}H_{14}O_4$ requires C 60.59%, H 7.12%. ^{1}H NMR (200 MHz, $CDCl_3$): 2.6−2.1 (m, 4H, CH_2), 2.85 (m, 2H, H_1, H_2), 3,7 (s, 6H, OCH_3), 5,7 (m, 2H, H_4, H_5); ^{13}C NMR (50.3 MHz, $CDCl_3$): 24.5, 40.96, 51.45, 124.66, 174.79.

Synthesis of (1*S*,2*S*)-Cyclohex-4-ene-1,2-dicarboxylic Acid Di-*tert*-Butyl Ester. To a refluxing solution of the diacid **4** (1.0 g, 5.88 mmol, 1 mol equiv), under N_2, in dry benzene (15 mL), was added *N*,*N*-dimethylformanide di-*tert*-butyl acetal (8.5 mL, 35.4 mmol, 1 mol equiv). The solution was refluxed for 36 h monitoring by TLC. The organic phase was washed with H_2O (20 mL) and then with saturated $NaHCO_3$ and finally with brine. The solvent, dried with Na_2SO_4, was evaporated under reduced pressure. The crude was used for the following reactions with no further purification. ^{1}H NMR (200 MHz, $CDCl_3$): 1.5 (s, 18H, $COOC(CH_3)_3$); 2.0−2.52 (m, 4H, H_{3ax}, H_{3eq}, H_{6ax}, H_{6eq}); 2.6−2.78 (m, 2H, H_1, H_2); 5.65 (d, 2H, H_4, H_5, J_{4-5} = 3.7 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 28.01, 28.22, 42.16, 80.12, 124.59, 174.18.

Synthesis of the *cis*-Diol 1b. To a solution of the dimethyl ester of **4** (208 mg, 1.05 mmol, 1 mol equiv) in wet CH_2Cl_2 (5 mL) were added trimethylamine *N*-oxide (152 mg, 1.37 mmol, 1.3 mol equiv) and osmium(III) chloride (5 mg,0.02 mmol, 0.02 mol equiv). The solution was stirred at room temperature for ca. 15 h. After reaction completion, the solvent was evaporated under reduced pressure. The crude can be used for the following reactions with no further purification (99%). An analytical sample was purified by flash chromatography (3:7 hexane:AcOEt). $[\alpha]^{20}_D$: +18.3 (c = 1, $CHCl_3$); Microanalysis: Found, C 51.31%, H 7.19%; $C_{10}H_{16}O_6$ requires C 51.72%, H 6.94%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.6−1.4 (m, 1H, H_{6ax}), 1.8 (q, 1H, H_{6ax}), 2.0 (dt, 1H, H_{3eq}), 2.0 (bm, 1H, OH), 2.1 (bm, 1H, OH), 2.25 (dt, 1H, H_{6eq}), 2.7 (m, 1H, H_2), 3.0 (m, 1H, H_1), 3.69 (s, 3H, OCH_3),), 3.7 (s, 3H, OCH_3), 3.7 (m, 1H, H_4), 4.0 (m, 1H, H_5); ^{13}C NMR (50.3 MHz, $CDCl_3$): 29.9, 32.9, 38.2, 42.9, 51.9, 52.0, 67.7, 70.1, 174.3, 175.4.

Synthesis of the Monoallyl Ether 5b. A solution of dimethyl ester **1b** (1.32 g, 5.69 mmol, 1 mol equiv) in dry benzene (30 mL) was refluxed for 6 h under N_2, in the presence of Bu_2SnO (1.42 g, 5.69 mmol, 1 mol equiv), and the water was continuously removed. After concentrating to 10 mL, allyl bromide (0.46 mL, 6.83 mmol, 1.2 mol equiv), Bu_4NI (2.07 g, 5.69 mmol, 1 mol equiv), and CsF (1.21 g, 7.96 mmol, 1.4 mol equiv) were added, and the suspension was stirred at room-temperature monitoring by TLC. After completion (ca. 48 h), the solvent was evaporated under reduced pressure and the crude was purified by flash chromatography on silica gel (hexane/AcOEt 6:4) to yield pure **5b** (73%). $[\alpha]^{20}_D$: −7.36 (c = 1.25, $CHCl_3$); Microanalysis: Found, C 57.55%, H 7.26%; $C_{13}H_{20}O_6$ requires C 57.34%, H 7.40%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.4−1.6 (m, 1H, H_{6ax}), 1.7−1.9 (q, 1H, H_{3ax}), 2.0−2.1 (dm, 1H, H_{6eq}), 2.2−2.3 (dm, 1H, H_{3eq}), 2.6−2.7 (tm, 1H, H_2), 3.0−3.1 (m, 1H, H_1), 3.4 (dq, 1H, H_4), 3.69 (s, 3H, OCH_3), 3.7 (s, 3H, OCH_3), 4.0 (m, 1H, H_5), 4.1 (m, 2H, OCH_2), 5.1−5.4 (m, 2H, CH_2CHCH_2O), 5.7−6.0 (m, 1H, $CHCH_2O$); ^{13}C NMR (50.3 MHz, $CDCl_3$): 27.27, 32.25, 38.19, 42.78, 51.82, 51.90, 65.62, 69.29, 76.77, 117.18, 134.33, 173.86, 155.33.

Synthesis of the Lactone 6. A solution of dimethyl ester **1b** (406 mg, 1.75 mmol, 1 mol equiv) in dry toluene (10 mL) was refluxed for 6 h under N_2, in the presence of Bu_2SnO (436 mg, 1.75 mmol, 1 mol equiv), and the water was continuously removed. After concentrating to 5 mL, allyl bromide (0.18 μL, 2.1 mmol, 1.2 mol equiv), Bu_4NI (638 mg, 1.75 mmol, 1 mol equiv), and CsF (372 mg, 2.45 mmol, 1.4 mol equiv) were added, and the suspension was refluxed monitoring by TLC. After completion (ca. 5 h), the reaction mixture was filtered, and the collected salts were washed with Et_2O. The organic phase was evaporated under reduced pressure, and the crude was purified by flash chromatography on silica gel (toluene/AcOEt 8:2) to yield 240 mg of pure lactone **6** (60%). Microanalysis: Found, C 59.73%, H 7.05%; $C_{12}H_{16}O_5$ requires C 59.99%, H 6.71%. IR (Nujol): ν 1735 cm^{-1}; ν 1758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): 1.82 (m, 1H, H_{3eq}); 2.13 (ddd, 1H, H_{6ax}, J_{6ax-5} = 5 Hz, $J_{6ax-6eq}$ = 14.6 Hz); 2.2−2.3 (m, 2H, H_{3ax}, H_{6eq}); 2.98 (m, 1H, H_1); 3.03 (dd, 1H, H_2, J_{2-1} = 3 Hz, J2$_{-3eq}$ = 5.5 Hz); 3.62−3.74 (dq, 1H, H_4, J_{4-5} = 1.5 Hz, J_{4-3eq} = 3 Hz, J_{4-3ax} = 10 Hz); 3.76 (s 3H, $COOCH_3$); 4.0−4.1 (m, 2H, CH_2=$CHCH_2O$); 4.82 (d, 1H, H_5, J_{5-4} = 1.5 Hz, J_{5-6ax} = 5 Hz); 5.15−5.35 (m, 2H, CH_2=$CHCH_2O$); 5.89 (m, 1H, CH_2=$CHCH_2O$); ^{13}C NMR (125.7 MHz, $CDCl_3$): 25.0; 25.9; 37.9; 38.1; 52.9; 69.6; 73.1; 76.3; 117.8; 134.4; 172.7; 173.6.

Synthesis of the Amide 7. To a solution of lactone **6** (22 mg, 0.092 mmol, 1 mol equiv) in CH_2Cl_2 (0,5 mL) was added benzylamine (10 mg, 0.092 mmol, 1 mol equiv) under N_2. The reaction mixture was stirred at room-temperature monitoring by TLC. After reaction completion (ca. 20 h), the solvent was evaporated, and the crude was taken up with AcOEt. The organic phase was washed with 6 N HCl and H_2O, dried with Na_2SO_4, and evaporated under reduced pressure to yield **7** as a yellow oil (75%). Microanalysis: Found, C 65.34%, H 7.40%; $C_{19}H_{25}NO_5$ requires C 65.69%, H 7.25%, N 4.03%. ^{1}H NMR (200 MHz, $CDCl_3$): 1.25 (m, 1H, H_{6ax}); 1.4−1.6 (m, 1H, H_{3ax}); 1.8−1.95 (m, 1H, H_{3eq}); 2.1−2.5 (m, 2H, H_{6eq}, H_2); 3.0−3.2 (m, 1H, H_1); 3.3−3.45 (m, 1H, H_4); 3.6 (s, 3H, $COOCH_3$); 4.04 (m, 2H, CH_2=$CHCH_2O$); 4.1 (m, 1H, H_5); 4.4 (d, 2H, $NHCH_2C_6H_5$, J_{gem} = 6 Hz); 5.1−5.35 (m, 2H, CH_2=$CHCH_2O$); 5.8−6.08 (m, 2H, CH_2=$CHCH_2O$, NH); 7.2−7.4 (m, 5H, C_6H_5); ^{13}C NMR (75.4 MHz, $CDCl_3$): 28.0, 33.2, 38.9, 43.5, 45.1, 51.8, 65.6, 69.3, 77.0, 117.2, 127.4, 127.8, 128.6, 134.5.

Synthesis of the Monoacid 8. To a suspension of potassium trimethylsilanoate (9 mg, 0.07 mmol, 1 mol equiv) in dry CH_2Cl_2 (0.25 mL) was added a solution of lactone **6** (16 mg, 0.07 mmol, 1 mol equiv) in dry CH_2Cl_2 (0.25 mL) under N_2. The reaction mixture was stirred at room temperature for 4 h. After completion, the solution was diluted with AcOEt. The organic phase was washed with 6 N HCl and then with H_2O, dried with Na_2SO_4, and evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel (hexane/AcOEt 3:7 + 1% AcOH) to yield pure **8** (40%). Microanalysis: Found, C 60.08%, H 7.17%; $C_{12}H_{18}O_6$ requires C 59.81%, H 7.02%. ^{1}H NMR (200 MHz, $CDCl_3$): 1.3−1.5 (m, 1H, H_6ax); 1.4−1.6 (m, 1H, H_3ax); 1.8−2.2 (m, 2H, H_6eq, H_{3eq}); 2.5 (m, 1H, H_2); 2.9 (m, 1H, H_1); 3.2 (dm, 1H, H_4); 3.5 (s, 3H, OCH_3); 3.9 (s, 3H, H_5, OCH_2); 5.0−5.2 (m, 2H, CH_2CHCH_2O); 5.6−5.9 (m, 1H, $CHCH_2O$).

Synthesis of the Monoacid 9. (1) Selective Hydrolysis with LiOH. To a solution of dimethyl ester **1b** (505 mg, 2.17 mmol, 1 mol equiv) in a 4:1 mixture of MeOH/H_2O (10 mL) was added LiOH·H_2O (228 mg, 5.34 mmol, 2.5 mol equiv). The solution was stirred at rt for 5.5 h. After this time, 6 N HCl was added to pH 1, and then the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel ($CHCl_3$/MeOH 9:1 + 1% AcOH) to yield 300 mg of **9** (60%) as 20:1 mixture with the regioisomeric monomethyl ester.

(2) Selective Hydrolysis with NaOH. To a solution of dimethyl ester **1b** (505 mg, 2.17 mmol, 1 mol equiv) was added a 0.07 M solution of NaOH (46.5 mL, 3.26 mmol, 1.5 mol equiv). The solution was stirred at rt for 45 min, 6 N HCl was added to pH 1, and the solvent evaporated under reduced pressure. The crude was purified as described above, to yield 378 mg (80%) of pure **9**.

$[\alpha]^{20}_D$ +17.5 (c = 1.05, MeOH); Microanalysis: Found, C 49.78%, H 6.12%; $C_9H_{14}O_6$ requires C 49.54%, H 6.47%. ^{1}H NMR (400 MHz, D_2O): 1.6−1.8 (m, 2H, H_{3ax}, H_{6ax}); 2.0 (m, 1H, H_{3eq}); 2.1 (m, 1H, H_{6eq}); 2.08 (m, 1H,); 2.71 (m, 1H, H_2); 2.88 (m, 1H, H_1); 3.65 (m, 1H, OCH_3); 3.71 (m, 1H, H_4); 3.74 (m, 1H, H_5); 4; ^{13}C NMR (50.3 MHz, $CDCl_3$) : 29.8; 33.2; 39.2; 44.0; 53.3; 68.3; 70.5; 178.4;179.0.

Synthesis of the Epoxide 10. To a solution of the di-*tert*-butyl ester of **4** (1.5 g, 5.5 mmol, 1 mol equiv) in CH_2Cl_2 (13 mL) was added MCPBA (1.85 g, 7.6 mmol, 1.4 mol equiv). The solution was stirred at room temperature for 3 h, and then the organic phase was washed with saturated $NaHCO_3$, dried with Na_2SO_4, and evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel (hexane/AcOEt 85:15) to yield 1.54 g of pure **10** as a white solid (97%). Mp: 98 °C. $[\alpha]^{20}_D$: +55.78 (c = 1.01, $CHCl_3$);[22] Microanalysis: Found, C 64.58%, H 8.50%; $C_{16}H_{26}O_5$ requires C 64.41%, H 8.78%. IR (Nujol): ν 3005 cm^{-1}; ν 1722 cm^{-1}. ^{1}H NMR (300 MHz, C_6D_6): 1.4 (s, 18 H, $COOC(CH_3)_3$); 1.58 (m, 1H, H_{6ax}, J_{6ax-5} = 2.1 Hz, J_{6ax-1} = 10.9 Hz, $J_{6ax-6eq}$ = 14.5 Hz); 1.95−2.06 (m, 2H, H_{3ax}, H_{6eq}); 2.35 (ddd, 1H, H_{3eq}, J_{3eq-4} = 1.7 Hz, J_{3eq-2} = 10.9 Hz, $J_{3eq-3ax}$ = 14.5 Hz); 2.52 (dt, 1H, H_2, J_{2-1} ≅ J_{2-3eq} = 2.7 Hz, J_{2-3ax} = 10.3 Hz); 2.71 (m, 1H, H_4); 2.79 (m, 1H, H_5); 3.0 (dt, 1H, H_1, J_{1-2} ≅ J_{1-6ax} = 10.6 Hz, J_{1-6eq} = 4.8 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): 26.4; 27.2; 27.8; 38.5; 41.0; 50.4; 51.9; 90.4; 172.9; 173.9.

Synthesis of the Trans-Diaxial Diol 2a. To a solution of the epoxide **10** (41 mg, 0.14 mmol, 1mol equiv) in 1:1 CH_3CN:H_2O (1 mL) was added $Ce(OTf)_4$ (7 mg, 0.013 mmol, 0.09 mol equiv). The solution was stirred at room temperature for ca. 15 h, monitoring by TLC. After reaction completion, water was added, and the crude extracted with AcOEt. The organic layer, dried with Na_2SO_4, was evaporated under reduced pressure.

(22) This compound was prepared starting from a batch of **4** with 82% ee.

The crude was purified by flash chromatography on silica gel (hexane/AcOEt 4:6) to yield 39 mg of pure **2a** (89%). $[\alpha]^{20}_D$: +16.2 (c = 1.8, EtOH),[22] Microanalysis: Found, C 61.03%, H 8.60%; $C_{16}H_{28}O_6$ requires C 60.74%, H 8.92%. ^{1}H NMR (200 MHz, $CDCl_3$): 1.45 (s, 18H, $COOC(CH_3)_3$); 1.6−1.8 (m, 2H, H_{3ax}, H_{6ax}); 2.08−2.24 (m, 2H, H_{3eq}, H_{6eq}); 2.4 (bs, 1H, OH); 2.9−3.05 (m, 2H, H_1, H_2); 3.55−3.72 (m, 1H, H_4, H_5). ^{13}C NMR (50.3 MHz, $CDCl_3$): 27.88; 30.53; 40.73; 70.36; 80.84; 173.45.

Synthesis of (1*S*,2*S*,4*S*,5*S*)-4-Allyloxy-5-hydroxy-cyclohexane-1,2-dicarboxylic Acid Di-*tert*-butyl Ester 11. To a solution of the epoxide **10** (15 mg, 0.05 mmol, 1 mol equiv) in allyl alcohol (150 μL, 2.2 mmol, 44 mol equiv) was added the catalyst. The reaction mixture was stirred at the indicated temperature, for the indicated time (Table 1), monitoring by TLC. After reaction completion, water (or a saturated solution of NH_4Cl and NH_3) was added, and the mixture was extracted with Et_2O. The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure.

The crude mixtures were purified by flash chromatography on silica gel (hexane/AcOEt 8:2) to give **11** with the yield reported in Table 1. $[\alpha]^{20}_D$: +14.2 (c = 1.1, $CHCl_3$);[22] Microanalysis: Found, C 64.17%, H 8.83%; $C_{19}H_{32}O_6$ requires C 64.02%, H 9.05%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.4 (s, 18H, $COOC(CH_3)_3$); 1.7−1.8 (m, 4H, H_{3ax}, H_{6ax},);2.0−2.16 (m, 2H, H_{3eq}, H_{6eq}); 2.95−3.0 (m, 2H, H_1, H_2); 3.35 (dt, 1H, H_4, $J_{4-5} \cong J_{4-3eq}$ = 3.4 Hz, J_{4-3ax} = 9.95 Hz), 3.75 (dt, 1H, H_5, $J_{5-4} \cong J_{5-6eq}$ = 3.4 Hz, J_{5-6ax} = 10.1); 3.8−4.15 (m, 2H, CH_2=$CHCH_2O$); 5.1−5.3 (m, 2H,CH_2=$CHCH_2O$); 5.8−6 (m, 1H, CH_2=$CHCH_2O$). ^{13}C NMR (50.3 MHz, $CDCl_3$): 27.3; 27.9; 30.2; 40.2; 40.6; 68.1; 68.8; 76.9; 80.8; 116.7; 134.9; 173.5.

Synthesis of (1*S*,2*S*,4*S*,5*S*)-4-Benzyloxy-5-hydroxy-cyclohexane-1,2-dicarboxylic Acid Di-*tert*-butyl Ester 12. To a solution of the epoxide **10** (20 mg, 0.067 mmol, 1 mol equiv) and benzyl alcohol (35 μL, 0.34 mmol, 5 mol equiv) in dry solvent (100 μL) was added the catalyst (Table 2). The reaction mixture was stirred at the indicated temperature, for the indicated time (Table 2), monitoring by TLC. After reaction completion, water (or a saturated NH_4Cl/NH_3 buffer) was added, and the mixture was extracted with Et_2O. The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The crude mixtures were purified by flash chromatography on silica gel (hexane/AcOEt 8:2) to give **12** with the yield reported in Table 2. $[\alpha]^{20}_D$: +7.5 (c = 1.32, $CHCl_3$);[22] Microanalysis: Found, C 67.74%, H 8.72%; $C_{23}H_{34}O_6$ requires C 67.96%, H 8.43%. ^{1}H NMR (200 MHz, $CDCl_3$): 1.45 (m, 18H, $COOC(CH_3)_3$); 1.6−1.95 (m, 2H, H_{3ax},H_{6ax}); 2.0−2.3 (m, 2H, H_{3eq}, H_{6eq}); 3.2−3.3 (m, 2H, H_1, H_2); 3.38 (m, 1H, H_4); 3.75 (m, 1H, H_5); 4.22 (d, 1H, $CH_2C_6H_5$, J_{gem} = 11.5 Hz);4.42 (d, 1H, $CH_2C_6H_5$, J_{gem} = 11.5 Hz) 7.3−7.5 (m, 5H, C_6H_5); ^{13}C NMR (50.3 MHz, $CDCl_3$): 27.2; 27.9; 30.7; 40.3; 40.7; 68.2; 70.8; 77.2; 90.6; 127.6; 128.3; 173.5.

Syntesis of the Acetates 13 and 14. To a solution of product **11** or **12** (12.3 mg, 0.035 mmol, 1 mol equiv) in dry CH_2Cl_2 (0.25 mL) were added Ac_2O (60 μL, 0.54 mmol, 15 mol equiv), TEA (30 μL, 0.22 mmol, 6 mol equiv), and a catalytic amount of DMAP. The solution was stirred at room temperature for ca. 2 h. After reaction completion, the organic phase was washed first with saturated $NaHCO_3$ and then with H_2O, dried with Na_2SO_4, and evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel (hexane/AcOEt 9:1) to yield the desired product (95%).

13: $[\alpha]^{20}_D$: +8.26 (c = 1.32, $CHCl_3$);[22] Microanalysis: Found, C 63.52%, H 8.24%; $C_{21}H_{34}O_7$ requires C 63.30%, H 8.60%. ^{1}H NMR (300 MHz, C_6D_6): 1.4 (s, 18H, $COOC(CH_3)_3$); 1.75−1.9 (m, 2H, H_{3ax}, H_{6ax}); 2.1−2.25 (m, 5H, H_{3eq}, H_{6eq}, $OCOCH_3$); 3.1−3.3 (m, 2H, H_1, H_2); 3.5 (m, 1H, H_4); 3.95−4.1 (m, 2H, CH_2=$CHCH_2O$); 4.98 (m, 1H, H_5); 5:15−5.32 (m, 2H, CH_2=$CHCH_2O$); 5.6 (m, 1H, CH_2=$CHCH_2O$); ^{13}C NMR (50.3 MHz, $CDCl_3$):21.1; 27.8; 27.9; 28.3; 39.7; 40.4; 68.6; 69.9; 72.4; 77.5; 116.8; 134.6.

14: $[\alpha]^{20}_D$: +7.5(c = 1.32, $CHCl_3$);[22] Microanalysis: Found, C 66.74%, H 8.13%; $C_{25}H_{36}O_7$ requires C 66.94%, H 8.09%. ^{1}H NMR (300 MHz, C_6D_6): 1.4 (s, 18H, $COOC(CH_3)_3$); 1.65−1.9 (m, 2H, H_{3ax}, H_{6ax}); 2.0−2.3 (m, 5H, H_{3eq}, H_{6eq}, $OCOCH_3$); 3.1−3.4 (m, 2H, H_1, H_2); 3.55 (m, 1H, H_4); 4.3 (m, 2H, $CH_2C_6H_5$); 5.2 (m, 1H, H_5); 7.0−7.3 (m, 5H, C_6H_5);^{13}C NMR (50.3 MHz, $CDCl_3$): 21.2; 27.9; 28.3; 39.8; 40.4; 68.5; 70.9; 72.6; 80.4; 80.5; 104.5; 127.4; 127.6; 128.3; 174.0.

Synthesis of Ketone 15. The diol **1a** (201 mg,0.64 mmol, 1 mol equiv) was refluxed with Bu_2SnO (159 mg, 0.64 mmol, 1 mol equiv) for 12 h in anhydrous toluene (14 mL) while continuously removing water. After this time, toluene was evaporated, and the residue was dried for 30 min under reduced pressure. The residue was taken up in dry chloroform (7 mL), and *N*-bromosuccinimide (123 mg, 0.69 mg, 1.1 mol equiv) was added. The reaction mixture was stirred at room temperature for ca. 1.5 h, the solvent was evaporated, and the crude was purified by flash chromatography on silica gel (hexane/AcOEt 7:3) to yield 169 mg of pure **15** (84%) as a white solid. Mp: 120 °C. $[\alpha]^{20}_D$: +26.9 (c = 1.1, $CHCl_3$);[23] Microanalysis: Found, C 61.35%, H 8.12%; $C_{16}H_{26}O_6$ requires C 61.13%, H 8.34%. IR (Nujol): ν 3502 cm^{-1}; ν 1725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 1.4 (m, 18H, $COOC(CH_3)_3$); 2.45 (t, 1H, H_1, $J_{1-2} \cong J_{1-6ax}$ = 13.9 Hz); 2.62−2.76 (m, 2H, H_{3ax}, H_{3eq}); 2.82 (dd, 1H, H_{6ax}, $J_{6ax-1} \cong J_{6ax-6eq}$ = 13.9 Hz);2.9 (dt, 1H, H_2, J_{2-1} = 13.9 Hz, J_{2-3ax} = 9.2 Hz, J_{2-3eq} = 2.2 Hz); 3.2 (dt, 1H, H_{6eq}, J_{6eq-1} = 3.3 Hz, $J_{6eq-6ax}$ = 12.9 Hz); 3.52 (d, 1H, OH, J = 4.9 Hz); 4.2 (m, 1H, H_4, $J_{4-3ax} \cong J_{4-3eq}$ = 9.05 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$): 27.8; 36.9; 39.9; 43.3; 46.3; 73.5; 81.5; 171.3; 207.6.

Synthesis of (1*S*,2*S*,4*R*)-4-Benzyloxy-5-oxocyclohexane-1,2-dicarboxylic Acid Di-*tert*-butyl Ester 16. To a solution of ketone **15** (100 mg, 0.32 mmol, 1 mol equiv) and benzyl bromide (60 μL, 0,5 mmol, 1.6 mol equiv) in dry Et_2O (3.5 mL) was slowly added Ag_2O (118 mg, 0.5 mmol, 1.6 mol equiv), heating after the first addition to start the reaction. The reaction mixture was refluxed for 5 h. After this time the salts were filtered and washed several times with AcOEt. The organic layer was evaporated under reduced pressure, and the crude was purified by flash chromatography on silica gel (toluene:Et_2O 95:5) to yield 100 mg of pure **16** (76%) as a white solid. Mp:137 °C; $[\alpha]^{20}_D$: +49.8 (c = 1.0, $CHCl_3$);[23] Microanalysis: Found, C 68.37%, H 8.06%; $C_{23}H_{32}O_6$ requires C 68.29%, H 7.97%. IR (Nujol): ν 1721 cm^{-1}; ν 1606 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): 1.5 (s, 18H, $COOC(CH_3)_3$); 1.7−2.0 (m, 1H, H_{3ax}); 2.3−2.65 (m, 2H, H_{6ax}, H_{3eq}); 2.75 (m, 1H, H_{6eq}); 2.84−3.1 (m, 2H, H_1, H_2); 4.0 (m, 1H, H_4); 4.5 (d, 1H, $CH_2C_6H_5$, J_{gem} =10 Hz); 4.85 (d, 1H, $CH_2C_6H_5$, J_{gem} = 10 Hz); 7.3−7.5 (m, 5H, C_6H_5); ^{13}C NMR (50.3 MHz, $CDCl_3$): 27.8; 34.9; 41.3; 43.8; 46.0; 72.0; 79.4; 81.3; 81.4; 127.8; 128.4; 173:3; 205.7.

Synthesis of (1*S*,2*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-5-oxocyclohexane-1,2-dicarboxylic Acid Di-*tert*-butyl Ester 17. To a solution of ketone **15** (29 mg, 0.092 mmol, 1 mol equiv) and imidazole (34 mg, 0.5 mmol, 5.5 mol equiv) in dry DMF (500 μL) was added $tBuMe_2SiCl$ (21 mg, 0.14 mmol, 1.5 mol equiv) under N_2. The reaction mixture was stirred at room temperature for ca. 15 h (monitoring by TLC), the solvent was evaporated under reduced pressure, and the residue was dissolved in AcOEt. The organic phase was washed first with saturated NH_4Cl and then with H_2O, dried with Na_2SO_4, and evaporated. The crude was purified by flash chromatography on silica gel (hexane/AcOEt 95:5) to yield 25 mg of pure **17** (64%).[23] Microanalysis: Found, C 61.20%, H 9.57%; $C_{22}H_{40}O_6Si$ requires C 61.65%, H 9.41%. ^{1}H NMR (200 MHz, $CDCl_3$): 0.08 (s, 3H, $OSi(CH_3)_2C(CH_3)_3$);0.16 (s, 3H, $OSi(CH_3)_2C(CH_3)_3$) 0.93 (s, 9H, $Si(CH_3)_2C(CH_3)_3$); 1.45 (s, 18H, $COOC(CH_3)_3$); 1.82 (m, 1H, H_{3ax}); 2.35−2.5 (m, 2H, H_{6ax}, H_{3eq}); 2.68 (m, 1H, H_{6eq}); 2.85−3.0 (m, 1H, H_1); 2.95 (m, 1H, H_2); 4.24 (m, 1H, H_4); ^{13}C NMR (50.3 MHz, $CDCl_3$): −5.6, −4.7, 18.3, 25.6, 27.8, 34.5, 41.1, 44.2, 46.1, 75.2, 81.4, 171.4, 205.4.

Synthesis of (1*S*,2*S*,4*R*)-4-Acetoxy-5-oxocyclohexane-1,2-dicarboxylic Acid Di-*tert*-butyl Ester 18. To a solution of ketone **15** (51 mg, 0.16 mmol, 1 mol equiv) and pyridine (65 μL, 0.8 mmol, 5 mol equiv) in dry CH_2Cl_2 (1 mL) were added Ac_2O (270 μL, 2.4 mmol, 15 mol equiv) and a catalytic amount of DMAP. The solution was stirred at room temperature for

(23) This compound was prepared starting from a batch of **4** with 60% ee.

ca. 1 h. After reaction completion, the organic phase was washed first with saturated $NaHCO_3$ and then with H_2O, dried with Na_2SO_4, and evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel (hexane/AcOEt 8:2) to yield 49 mg of pure **18** (86%) as a white solid. Microanalysis: Found, C 60.73%, H 7.85%; $C_{18}H_{28}O_7$ requires C 60.66%, H 7.92%. ^{1}H NMR (200 MHz, $CDCl_3$): 1.5 (s, 18H, $COOC(CH_3)_3$); 1.75−2.15 (m, 2H, H_{6ax}, H_{3ax}); 2.2 (s, 3H, $OOCCH_3$); 2.45−2.6 (m, 2H, H_{6eq}, H_{3eq}); 2.7−3.2 (m, 2H, H_1, H_2); 5.25 (dd, 2H, H_4); ^{13}C NMR (50.3 MHz, $CDCl_3$): 20.5, 27.8, 33.4, 41.1, 43.7, 46.0, 74.3, 81.6, 170.9, 171.0, 200.7.

General Procedure for the Reduction of Ketones 15−18. To a solution (or a suspension, if no AcOH is present) of $Na(OAc)_3BH$ (117 mg, 0.55 mmol,5 mol equiv) in anhydrous CH_3CN (400 μL) at the indicated temperature was added a solution of ketone (40 mg, 0.11, 1 mol equiv) in anhydrous solvent (800μL). After the reaction mixture was stirred for the indicated time at the indicated temperature (Table 3), it was quenched by addition of 0.5 N aqueous sodium potassium tartrate with vigorous stirring for 30 min. The mixture was then diluted with AcOEt and washed with saturated $NaHCO_3$. The aqueous layer was back extracted several times with AcOEt, and the combined organic layers were dried with Na_2SO_4 and evaporated under reduced pressure. The crude was purified by flash chromatography on silica gel to yield the pure product.

3: $[\alpha]^{20}_D$: +64.6 (c = 0.7, EtOH);[23] Microanalysis: Found, C 60.97%, H 9.03%; $C_{16}H_{28}O_6$ requires C 60.74%, H 8.92%. ^{1}H NMR (200 MHz, $CDCl_3$): 1.45 (s, 18H, $COOC(CH_3)_3$); 1.25−1.55 (m, 2H, H_{3ax}, H_{6ax}); 2.2−2.35 (m, 2H, H_{3eq}, H_{6eq}); 2.5−2.6 (m, 2H, H_1, H_2); 3.4−3.55 (m, 2H, H_4, H_5); ^{13}C NMR (50.3 MHz,$CDCl_3$): 27.3; 34.3; 44.1; 74.0; 80.8.

19: $[\alpha]^{20}_D$: −11.3 (c = 1.8, EtOH);[23] Microanalysis: Found, C 68.01%, H 8.37%; $C_{23}H_{34}O_6$ requires C 67.96%, H 8.43%. ^{1}H NMR (400 MHz, $CDCl_3$): 1.2−1.4 (m, 2H, H_{3ax},H_{6ax}); 1.45 (m, 18H, $COOC(CH_3)_3$); 2.25−2.5 (m, 2H, H_{3eq}, H_{6eq}); 2.5−2.6 (m, 2H, H_1, H_2); 3.25 (m, 1H, H_4); 3.55 (m, 1H, H_5); 4.48 (d, 1H, $CH_2C_6H_5$, J_{gem} = 11.4 Hz); 4.75 (d, 1H, $CH_2C_6H_5$, J_{gem} = 11.4 Hz); 7.35 (s, 5H, C_6H_5). ^{13}C NMR (75.5 MHz, $CDCl_3$): 11.1; 27.9; 31.2; 33.8; 44.0; 44.3; 71.3; 72.5; 80.7; 80.8; 81.8; 127.8; 127.9; 128.7; 138.1; 172.7.

20: ^{1}H NMR (200 MHz, $CDCl_3$): 0.1 (s, 6H, $(CH_3)_2C(CH_3)_3$-Si); 0.9 (s, 9H, $(CH_3)_2C(CH_3)_3Si$); 1.45 (s, 18H, $COOC(CH_3)_3$); 2.05−2.15 (m, 2H, H_{3ax}, H_{6ax}); 2.24−2.35 (m, 2H, H_{3eq}, H_{6eq}); 2.42 (bs, 1H, OH); 2.55−2.64 (m, 2H, H_1, H_2); 3.34−3.5 (m, 2H, H_4, H_5).

21: $[\alpha]^{20}_D$: −27.5 (c = 1.02, $CHCl_3$);[23] Microanalysis: Found, C 60.08%, H 8.28%; $C_{18}H_{30}O_7$ requires C 60.32%, H 8.44%. ^{1}H NMR (200 MHz, $CDCl_3$): 1.2−1.6 (m, 2H, H_{3ax}, H_{6ax}); 1.45 (s, 18H, $COOC(CH_3)_3$); 2.1 (s, 3H, $OCOCH_3$); 2.2−2.4 (m, 2H, H_{3eq}, H_{6eq}); 2.33−2.55 (m, 2H, H_1, H_2); 3.65 (m, 1H, H_5); 4.65 (m, 1H, H_4); ^{13}C NMR (75.4 MHz, $CDCl_3$): 21.1, 27.9, 31.7, 34.8, 43.9, 44.1, 71.6, 76.4, 80.9, 171.0, 172.3.

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