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Synthesis of 4-Membered Carbasugars by Way of Stereoselective SmI_2-Mediated Aldehyde–Alkene Cyclization

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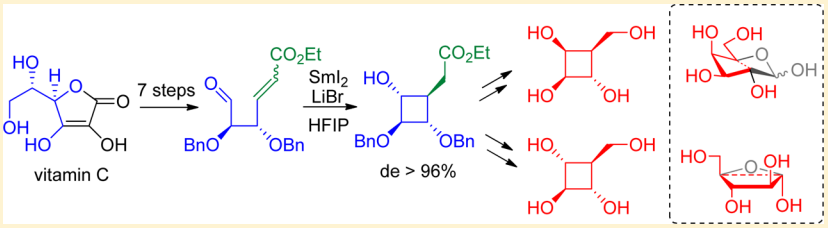
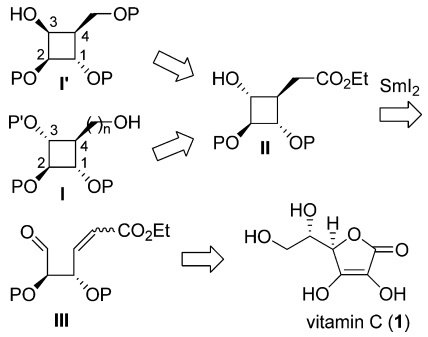
Supporting Information



ABSTRACT: A stereodivergent synthesis of the first examples of 4-membered carbasugars has been achieved from vitamin C by way of an efficient intramolecular SmI_2-mediated aldehyde–alkene coupling. In this key step, cylobutanes with four contiguous asymmetric centers are generated with a high level of stereocontrol.

Carbohydrates mimetics are structurally altered analogues of carbohydrate designed to simulate the shape and most functionalities of the natural substrates in the ground state or in the transition state with the goal of discovering drug candidates or useful biological probes.[1] The most common structural modification performed is the replacement of the endocyclic and/or the glycosidic oxygen atom by a heteroatom or by a carbon atom. Carbasugars, named "pseudosugars" in the pioneering article of McCasland et al.,[2] are one of the most important class of glycomimetics.[3] In these analogues of furanoses or pyranoses, the ring oxygen is replaced by a methylene group (branched-chain cyclitols). Carbasugars are attractive in the context of drug discovery because of their stability toward endogenous degradative enzymes as well as their interesting biological properties mainly as antibiotics and as glycosidase inhibitors.[3,4] For example, acarbose (Glucobay)[5] and voglibose (Basen)[6] are now clinically useful therapeutic agents to control diabetes. If not surprisingly most carbocyclic sugar mimetics are carbafuranoses or carbapyranoses, few examples of seven-,[7] eight-,[8] and even nine-membered[9] carbasugars have been reported recently in the literature. Beyond the synthetic challenges, the main motivation for the synthesis of such medium-ring carbasugars is the access to a diversity of conformations other than the traditional chair boat of six-membered rings. The original distributions of hydroxyl groups thus obtained in addition to the fine-tuning of the hydrophobic–hydrophilic balance are thought to be of likely significance for receptor recognition purposes. In contrast, to our knowledge, no example of 4-membered carbasugars has been reported in the literature to date. These compounds are attractive as they offer opposite and complementary structural features compared to the corresponding medium-ring analogues including conformational rigidity and molecular simplicity. On the basis of these considerations and in conjunction with our continuing studies on original glycomimetics,[10] we have synthesized the first members of a new class of 4-membered carbasugars, "carbaoxetanoses" from vitamin C (**1**).[11] Our retrosynthetic analysis takes advantage of the chirality of **1**, which provides two stereogenic centers (C1 and C2) of the final compounds and secures the stereocontrol of the key reductive coupling reaction from γ,δ-unsaturated aldehydes **III** (Scheme 1). This pivotal step based on an intramolecular SmI_2-mediated carbonyl–alkene coupling[12] was expected to provide cyclobutanols **II** with the four contiguous stereogenic centers of the target molecules of type **I** with predictable stereocontrol. The absolute configuration of the resulting alcohol at C3 may be directly inverted to provide

Scheme 1. Retrosynthetic Analysis



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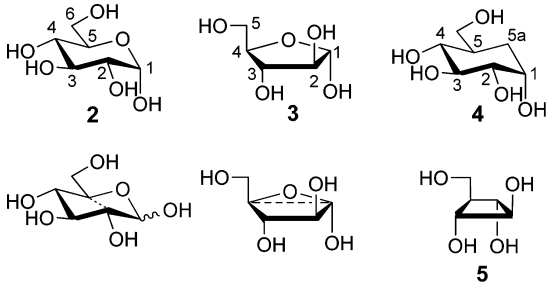
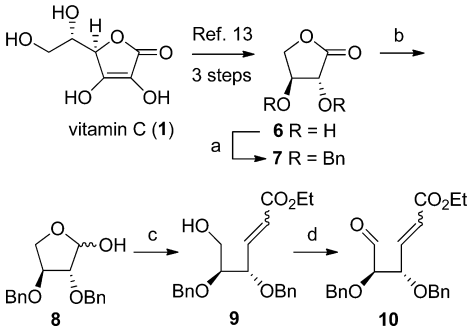
access to further members of carbaoxetanoses of type **I′**. 4-Membered carbasugars of type **I** and **I′** may be seen as simplified structural analogues of hexopyranoses in the D-gluco and D-galacto series, respectively lacking the endocyclic oxygen and the anomeric carbon. They may be seen also as analogues of pentofuranoses in the D-arabino (type **I**) or D-lyxo (type **I′**) series lacking the endocyclic oxygen (Scheme 2).

Scheme 2. α-D-Glucopyranose (2), α-D-Arabinofuranose (3), and Their Corresponding Carbasugar Analogues 5a-Carba-α-D-glucopyranose (4)[3] and Carbaoxetanose 5 (this study)



The synthesis began with the *O*-benzylation of γ-lactone **6** obtained in three steps from vitamin C according to a procedure reported by Eschenmoser et al. (Scheme 3).[13]

Scheme 3[a]

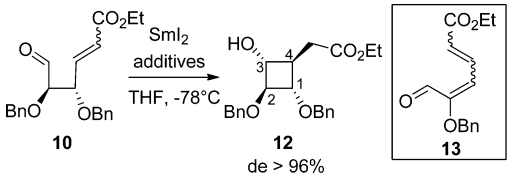


[a]Reagents and conditions: (a) BnBr (5 equiv), $CaSO_4$ (5 equiv), Ag_2O (4 equiv), CH_3CN, rt, 48 h, 79%; (b) DIBAL-H (1.9 equiv), THF, −78 °C, 2.5 h, 85%; (c) **11** (1.2 equiv), $PhCO_2H$ (0.03 equiv), CH_2Cl_2, reflux, 97% (*Z*/*E*, 1:2); (d) $(ClCO)_2$ (2.2 equiv), DMSO (4.6 equiv), NEt_3 (5.5 equiv), CH_2Cl_2, −78 to −20 °C, 79% [(**Z**/**E**)-**10**)], 79% [(**Z**)-**10**)], 74% [(**E**)-**10**)].

Reduction of 2,3-di-*O*-benzyl-L-threonolactone (**7**)[14] using DIBAL-H provided the corresponding lactol **8**, which was readily converted to the α,β-unsaturated esters **9** obtained as a separable 1:2 mixture of *Z*- and *E*-isomers by treatment with ethyl(triphenylphosphoranylidene)acetate (**11**) in the presence of catalytic amount of benzoic acid.[15]

Swern oxidation performed on the mixture of alcohols **9**, or on the corresponding pure (*E*)- or (*Z*)-stereoisomers, afforded the desired γ,δ-unsaturated aldehydes **10** in good yields. The key SmI_2-mediated 4-*exo*-*trig* radical cyclization was first evaluated from the pure alkene (*E*)-**10**. In a first attempt, treatment of (*E*)-**10** with SmI_2 at −78 °C in the presence of HMPA did not lead to the formation of the expected cyclobutanol ring (Table 1, entry 1).[16] The only identified product was the conjugated aldehyde **13** resulting from the

Table 1. SmI_2-Mediated 4-*exo*-*trig* Radical Cyclization of 10[a]



entry	**10** (*Z*/*E*)	SmI_2 (equiv)	additives (equiv)	time (min)	**12**[b] (yield %)
1	0/1	3	HMPA (6.8)	120	–
2[c]	0/1	3	HMPA (6.8)	960	15
3[d]	0/1	3	MeOH (3)	960	14
4	0/1	3	MeOH (3)	150	28
5	0/1	3	MeOH (22)	135	21
6	0/1	3	MeOH (3)	10	42
7	1/0	3	MeOH (3)	10	35
8	1/2	4	H_2O/LiBr (8/12)	5	48
9	1/2	4	HFIP/LiBr (8/12)	5	67
10[e]	1/2	4	HFIP/LiBr (8/12)	19[e]	57

[a]Reaction performed with 0.3 mmol of **10**. [b]Isolated yield. [c]−78 °C to rt. [d]0 °C to rt. [e]Reaction performed with 1.2 mmol of **10**.

elimination of a benzyloxy group. The formation of this side-product, which is favored by conjugation, further highlights that γ,δ-unsaturated aldehyde **10** is a challenging substrate for 4-*exo*-*trig* radical cyclization reactions. Small amount of the desired cyclized product **12** (~15%) could nevertheless be obtained by increasing the reaction time and temperature (entry 2) or using MeOH[17] as a proton source (entry 3). Cyclization of **10** was found to proceed with complete *anti* selectivity,[12a] affording the desired cyclobutanol **12** as a single diastereoisomer with the desired stereochemistry. The absolute configuration of the two new stereogenic centers were unambiguously determined by 2D COSY and NOESY NMR experiments. In particular, the definite NOE effects between H-1 and H-3, and between H-2 and H-4 were crucial to establish the *R*-configuration at C-3 and C-4 (see Supporting Information). In the presence of MeOH, the yield of the cyclization process could be tripled to 42% by shortening the reaction time to 10 min (entries 3−6). Addition of more equivalents of MeOH (entry 5) did not improve the efficiency of the coupling reaction. It is noteworthy that the coupling process performed from the TBDMS protected analogues of **10** led only to partial recovery of starting material. We then evaluated the impact of the double bond configuration on the cyclization outcome. Pleasingly, treatment of alkene (*Z*)-**10** under our first optimized reaction conditions led to the desired cyclobutanol **12** in high diastereoselectivity and in similar yield than from the corresponding *E*-stereoisomer (entries 6−7). The SmI_2-mediated radical coupling reaction was then performed directly from the *E*/*Z* mixture of **10**, leading to a more efficient synthetic sequence and better overall yields, by avoiding the separation of diastereoisomers. Further optimization was performed with a combination of SmI_2 and LiBr/proton source additives[18] by analogy with the reaction conditions reported recently for the cross-coupling of nitrones with β-silyl acrylates (entries 8−10).[19] Similar to the results obtained by Py et al.[19] for this cross-coupling, the optimum reaction conditions were obtained with the use of hexafluoroisopropanol (HFIP) as a proton source, with **12** being isolated in 57−67% yield (entries

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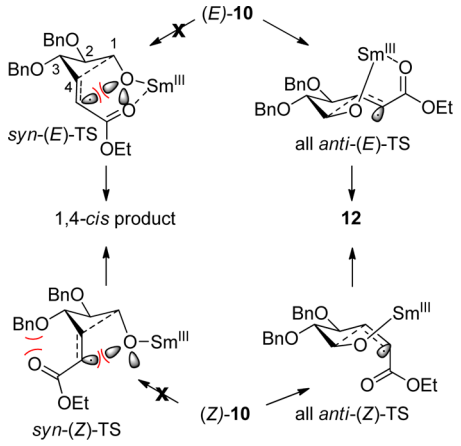
9 and 10). The optimum reaction time was found to be related to the amount of substrate used with one minute for ca. 0.06 mmol of **10** as a rule of thumb (entries 9 and 10).

The complete *anti* selectivity observed for the 4-*exo*-*trig* cyclization of aldehyde **10** can be rationalized considering the four possible transition state structures depicted in Scheme 4.[12a] From *E*- or *Z*-alkene substrates **10**, *syn*-(*E*)-TS or *syn*-(*Z*)-

Scheme 4. Possible Transition States for the Intramolecular SmI_2-Mediated Aldehyde–Alkene Coupling

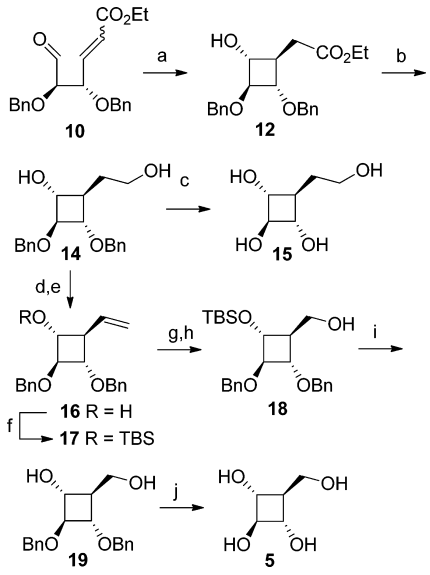


TS leading to the 1,4-*cis* product are disfavored mainly by electrostatic repulsion between the O1 oxygen lone pairs and the developing electron density in α to the ester group. The all *anti*-(*E*)-TS and all *anti*-(*Z*)-TS leading to the all-*trans* product **12** are electronically and sterically favored since the above-mentioned electrostatic interactions as well as the steric hindrance between vicinal substituents are minimized.

Having in hand the key intermediate **12**, we first prepared 4-membered carbasugar **15** with a hydroxyethyl group at C4 as its synthesis required only two steps. Reduction of ester **12** with LAH followed by catalytic hydrogenolysis of the benzyl protecting groups provided tetrol **15** (Scheme 5). Synthesis of **5** that may be seen as a structurally simplified analogue of D-glucopyranose or α-D-arabinofuranose required the dehomologation of the side chain in **14** by one methylene unit. As a prelude to the dihydroxylation–dehomologation sequence, alkene **16** was synthesized from alcohol **14** via Grieco elimination.[20] Treatment of alcohol **14** with *o*-nitrophenylselenocyanate and tributylphosphine provided a selenide derivative. This intermediate was directly oxidized with Davis oxaziridine[20b] to give the corresponding selenoxide in which a Cope-type elimination took place to afford the desired to afford the desired alkene **16**.

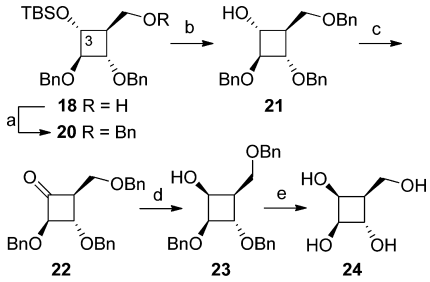
Protection of the secondary alcohol as a TBS ether to provide compound **17** in 77% yield from **14** was found to be necessary for effective olefin cleavage. Olefin **17** was treated under Lemieux–Johnson oxidative cleavage conditions to give the primary alcohol **18** in 82% yield after reduction with $NaBH_4$. The deprotected carbaoxetanose **5** was finally obtained in quantitative yield after removal of the TBS group in **18** using TBAF followed by hydrogenolysis of the benzyl protecting groups. Access to other members of carbaoxetanoses as simplified mimetics of D-galactopyranose or D-lyxofuranose was easily achieved by inversion of configuration at C3 (Scheme 6). Benzylation of the primary hydroxyl group in **18** followed by treatment of the resulting product **20** with TBAF

Scheme 5[a]



[a]Reagents and conditions: (a) SmI_2 (4 equiv), LiBr (12 equiv), HFIP (8 equiv), THF, −78 °C, 5 min, 67%; (b) LAH (1.5 equiv), THF, rt, 2.5 h, 68%; (c) Pd/C 10%, HCO_2H, H_2, EtOH, rt, 16 h, quant.; (d) *o*-$NO_2PhSeCN$ (2.2 equiv), *n*-Bu_3P (2.2 equiv), THF, 35 min; (e) Davis oxaziridine (1.2 equiv), CH_2Cl_2, 0 °C, 40 min, 84% in two steps; (f) TBSCl (1.5 equiv), DMAP (0.5 equiv), NEt_3 (2 equiv), CH_2Cl_2, rt, 14 h, 77%; (g) OsO_4 (0.04 equiv), $NaIO_4$ (1.9 equiv), THF/H_2O (4:1), rt, 5 h; (h) $NaBH_4$ (1.2 equiv), MeOH, rt, 15 min, 82% in two steps; (i) TBAF (5 equiv), THF, rt, 4 h, quant.; (j) Pd/C 10%, HCO_2H, H_2, EtOH, rt, 16 h, quant.

Scheme 6[a]



[a]Reagents and conditions: (a) NaH (1.3 equiv), BnBr (1.2 equiv), THF, rt, 18 h, 49% (73% based on recovered starting material); (b) TBAF (5 equiv), THF, rt, 3 h, 97%; (c) DMP (1.6 equiv), CH_2Cl_2, rt, 92%; (d) L-selectride (1.1 equiv), THF, −78 °C, 1 h, 67%; (e) Pd/C 10%, HCO_2H, H_2, EtOH, rt, 20 h, quant.

afforded the key alcohol intermediate **21**. Oxidation of **21** with Dess–Martin periodinane reagent provided the corresponding ketone **22**, which was reduced with L-selectride. This diastereoselective process gave the desired alcohol **23** in 62% yield from the corresponding C3 epimer **21**. Deprotection of **23** by hydrogenolysis under acidic conditions afforded cyclobutanic pseudogalactose **24**.

In conclusion, we have reported the stereodivergent synthesis of the first members of a new class of carbasugars by way of an efficient intramolecular SmI_2-mediated aldehyde–alkene coupling using a combination of LiBr/HFIP additives. In this key step, despite the high density of functional groups, cyclobutanes with four contiguous asymmetric centers are generated with a high level of stereocontrol in reproducible yields. Beyond the

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synthesis of carbaoxetanoses and analogues, this process may find application in the stereocontrolled synthesis of functionalized cyclobutanes.

EXPERIMENTAL SECTION

(3*R*,4*S*)-3,4-Bis(benzyloxy)dihydrofuran-2(3*H*)-one (7). To lactone **6** (12.89 mmol, 1 equiv) in dry CH_3CN (73 mL) were added BnBr (7.7 mL, 64.5 mmol, 5 equiv) and $CaSO_4$ (8.77 g, 64.5 mmol, 5 equiv). The solution was stirred for 5 min, and the flask was covered with aluminum foil. Ag_2O (5.97 g, 25.8 mmol, 2 equiv) was added in 3 portions over 5 min. The solution was stirred for 12 h, at which point a second portion of Ag_2O (5.97 g, 25.78 mmol, 2 equiv) was added. The resulting mixture was stirred for 36 h. The reaction mixture was then filtered through a pad of Celite, and the resulting filter cake was washed with CH_3CN (3 × 30 mL). The solution was concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:9 to 1:3) to afford the desired lactone **7** (3.04 g, 79%) as a colorless oil. Spectroscopic data are in accordance with literature data.[14]

(3*R*,4*S*)-3,4-Bis(benzyloxy)tetrahydrofuran-2-ol (8). DIBAL-H (1 M in hexane, 9 mL, 9.0 mmol, 1.9 equiv) was added to a solution of lactone **7** (1.37 g, 4.59 mmol, 1 equiv) in THF (7 mL) cooled to −78 °C. The solution was stirred at −78 °C for 2.5 h. MeOH (0.69 mL) was slowly added, and the reaction mixture was warmed up to rt. After 5 min, saturated aqueous sodium potassium tartrate (6 mL) was added. The solution was stirred overnight. The organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:3 to 1:2) to afford the desired lactol **8** (1.18 g, 85%) as a colorless oil: TLC R_f 0.19 (silica gel, EtOAc/petroleum ether, 1:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.24 (m, 10H), 5.44 (dd, J = 8.5, 4.2 Hz, 0.4H, α isomer), 5.33 (d, J = 9.9 Hz, 0.6H, β isomer), 4.66−4.60 (m, 2H), 4.56−4.47 (m, 2H), 4.22−4.05 (m, 2.6H), 4.01−3.94 (m, 1H), 3.84−3.78 (m, 0.4H, α isomer), 3.69 (d, J = 8.6 Hz, 0.4H, α isomer), 3.29 (d, J = 10.1 Hz, 0.6H, β isomer). Spectroscopic data are in accordance with literature data of its enantiomer.[21]

(4*S*,5*S*,*E*)-Ethyl 4,5-bis(benzyloxy)-6-hydroxyhex-2-enoate ((*E*)-9) and (4*S*,5*S*,*Z*)-Ethyl 4,5-bis(benzyloxy)-6-hydroxyhex-2-enoate ((*Z*)-9). To a solution of lactol **8** (1.85 g, 6.17 mmol, 1 equiv) in CH_2Cl_2 (31 mL), was added (ethoxycarbonylmethylene)-triphenylphosphorane **11** (2.58 g, 7.40 mmol, 1.2 equiv) followed by benzoic acid (23 mg, 1.85 mmol, 0.03 equiv). The mixture was refluxed for 15 h. After cooling, the solution was concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:3 to 1:1) to afford the desired alcohol **9** (2.22 g, 97%, Z/E (1:2)) as a colorless oil. **(*E*)-9**: TLC R_f 0.38 (silica gel, EtOAc/petroleum ether, 1:2); $[\alpha]_D^{20}$ = +7 (c 1.1, $CHCl_3$); IR (film) 3417, 2873, 1715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.24 (m, 10H), 6.95 (dd, J = 15.9, 5.9 Hz, 1H), 6.11 (dd, J = 15.9, 1.3 Hz, 1H), 4.72 (d, J = 11.7 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.63 (d, J = 11.7 Hz, 1H), 4.42 (d, J = 11.7 Hz, 1H), 4.27−4.18 (m, 3H), 3.73 (dd, J = 10.9, 3.8 Hz, 1H), 3.68−3.53 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 144.2, 138.1, 137.7, 128.6, 128.1, 128.0, 123.8, 80.7, 78.6, 73.5, 71.9, 62.0, 60.7, 14.4; HRMS (ESI) m/z 393.166 ([M + Na]$^+$, calcd. for $C_{22}H_{26}O_5Na$ 393.167).

(*Z*)-9. Data: TLC R_f 0.43 (silica gel, EtOAc/petroleum ether, 1:2); $[\alpha]_D^{20}$ = +16 (c 1.0, $CHCl_3$); IR (film) 3463, 2870, 1715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.17 (m, 10H), 6.22 (dd, J = 11.7, 9.1 Hz, 1H), 5.92 (d, J = 11.7 Hz, 1H), 5.27 (dd, J = 9.0, 4.0 Hz, 1H), 4.68 (d, J = 11.7 Hz, 1H), 4.58 (d, J = 11.6 Hz, 1H), 4.56 (d, J = 11.7 Hz, 1H), 4.39 (d, J = 11.7 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.75−3.68 (m, 3H), 2.45−2.17 (br s, 1H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 146.8, 138.4, 138.0, 128.5, 128.4, 128.10, 128.07, 127.9, 127.8, 123.2, 80.9, 75.6, 73.2, 71.9, 62.1, 60.6, 14.2; HRMS (ESI) m/z 393.167 ([M + Na]$^+$, calcd. for $C_{22}H_{26}O_5Na$ 393.167).

(4*S*,5*R*,*E*)-Ethyl 4,5-bis(benzyloxy)-6-oxohex-2-enoate ((*E*)-10) and (4*S*,5*R*,*Z*)-Ethyl 4,5-bis(benzyloxy)-6-oxohex-2-enoate ((*Z*)-10). A solution of DMSO (0.60 mL, 8.50 mmol, 4.6 equiv) in CH_2Cl_2 (4.6 mL) was slowly added to a solution of oxalyl chloride (0.35 mL, 4.07 mmol, 2.2 equiv) in CH_2Cl_2 (8.8 mL) cooled to −78 °C. The solution was stirred for 30 min. A solution of alcohol **9** (685 mg, 1.85 mmol, 1 equiv) in CH_2Cl_2 (8.8 mL) was slowly added. The solution was stirred for 1 h. A solution of NEt_3 (1.4 mL, 10.16 mmol, 5.5 equiv) in CH_2Cl_2 (8.8 mL) was slowly added, and the solution was stirred for 1.25 h. The reaction mixture was warmed up to −20 °C. Water (58 mL) was added, and the product was extracted with CH_2Cl_2 (3×). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:7 to 1:2) to afford the desired aldehyde **10** (554 mg, 79%, Z/E (1:2)) as a pale yellow oil.

(*E*)-10. Data: TLC R_f 0.59 (silica gel, EtOAc/petroleum ether, 1:2); $[\alpha]_D^{20}$ = +61 (c 1.0, $CHCl_3$); IR (film) 1717 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, J = 1.0 Hz, 1H), 7.40−7.20 (m, 10H), 6.95 (dd, J = 15.7, 7.2 Hz, 1H), 6.09 (dd, J = 15.9, 1.0 Hz, 1H), 4.80−4.55 (m, 4H), 4.35 (m, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.83 (dd, J = 3.9, 1.1 Hz, 1H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 165.7, 143.1, 137.0, 136.7, 128.7, 128.6, 128.44, 128.41, 128.22, 128.16, 124.5, 84.0, 77.9, 73.7, 72.0, 60.8, 14.4; HRMS (ESI) m/z 391.151 ([M + Na]$^+$, calcd. for $C_{22}H_{24}O_5Na$ 391.152).

(*Z*)-10. Data: TLC R_f 0.41 (silica gel, EtOAc/petroleum ether, 1:2); $[\alpha]_D^{20}$ = +89 (c 1.0, $CHCl_3$); IR (film) 1732, 1714 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (d, J = 1.0 Hz, 1H), 7.35−7.16 (m, 10H), 6.31 (dd, J = 11.7, 8.1 Hz, 1H), 5.86 (dd, J = 11.7, 1.5 Hz, 1H), 5.41 (ddd, J = 8.1, 3.6, 1.4 Hz, 1H), 4.72 (d, J = 12.1 Hz, 1H), 4.57−4.48 (m, 2H), 4.34 (d, J = 11.9 Hz, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.99 (dd, J = 3.6, 1.1 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 165.6, 146.8, 137.4, 137.1, 128.53, 128.48, 128.4, 128.23, 128.21, 128.0, 122.8, 85.3, 75.1, 73.8, 72.2, 60.7, 14.3; HRMS (ESI) m/z 391.151 ([M + Na]$^+$, calcd. for $C_{22}H_{24}O_5Na$ 391.152).

Ethyl 2-((1*R*,2*S*,3*S*,4*R*)-2,3-bis(benzyloxy)-4-hydroxycyclobutyl)acetate (12). SmI_2 (0.1 M in THF, 12.5 mL, 1.25 mmol, 4 equiv) was added to LiBr (325 mg, 3.74 mmol, 12 equiv) in a flask covered with aluminum foil. The solution was stirred for 20 min and then cooled to −78 °C. HFIP (0.26 mL, 2.50 mmol, 8 equiv) followed by a solution of aldehyde **10** (115 mg, 0.31 mmol, 1 equiv) in degassed THF (10.6 mL) were added. The solution was stirred for 5 min, and HCl 1 N (15.5 mL) was added. The solution was then stirred at rt for 30 min. The product was extracted with CH_2Cl_2 (3×). The combined organic layer was washed with saturated aqueous $NaHSO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:5 to 1:1) to afford the desired cyclobutane **12** (78 mg, 67%) as a yellow oil: TLC R_f 0.34 (silica gel, EtOAc/petroleum ether, 1:2); $[\alpha]_D^{20}$ = −32 (c 1.0, $CHCl_3$); IR (film) 3444, 1731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.17 (m, 10H), 4.62 (d, J = 11.7 Hz, 1H), 4.57−4.47 (m, 2H), 4.42 (d, J = 11.9 Hz, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.81 (t, J = 5.8 Hz, 1H), 3.51 (t, J = 6.6 Hz, 1H), 3.32 (m, 1H), 3.17 (br s, 1H), 2.65 (dd, J = 16.7, 4.7 Hz, 1H), 2.65 (dd, J = 16.7, 10.7 Hz, 1H), 1.93 (m, 1H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 138.2, 138.1, 128.6, 128.5, 128.0, 127.9, 127.8, 85.1, 76.9, 72.3, 71.63, 71.56, 61.1, 40.2, 36.7, 14.3; HRMS (ESI) m/z 393.167 ([M + Na]$^+$, calcd. for $C_{22}H_{26}O_5Na$ 393.167).

(1*R*,2*S*,3*S*,4*R*)-2,3-Bis(benzyloxy)-4-(2-hydroxyethyl)cyclobutanol (14). LAH (13 mg, 0.33 mmol, 1.5 equiv) was added to a solution of ester **12** (82 mg, 0.22 mmol, 1 equiv) in THF (1.2 mL) cooled at 0 °C. The solution was stirred at rt for 2.5 h. After cooling at 0 °C, H_2O (0.01 mL) followed by aqueous 10% NaOH (0.02 mL) and H_2O (0.03 mL) were added. The solution was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:1 to 4:1) to afford the desired diol **14** (50 mg, 68%) as a white solid: TLC R_f 0.16 (silica gel, EtOAc/petroleum ether, 2:1); $[\alpha]_D^{20}$ = −9 (c 1.0, $CHCl_3$); IR (film) 3379 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.25 (m, 10H), 4.67−4.57 (m, 3H), 4.53 (d, J = 11.7 Hz, 1H), 3.78 (t, J = 5.9

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Hz, 1H), 3.71 (m, 1H), 3.61 (m, 1H), 3.42 (t, J = 6.5 Hz, 1H), 3.36 (m, 1H), 2.96−2.75 (br s, 2H), 1.79 (m, 1H), 1.73−1.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 138.0, 128.6, 128.5, 128.03, 127.95, 127.9, 85.8, 76.9, 72.4, 71.71, 71.66, 62.0, 42.7, 34.6; HRMS (ESI) m/z 351.155 ([M + Na]$^+$, calcd. for $C_{20}H_{24}O_4Na$ 351.157).

General Method A for Debenzylation. Pd/C 10% (10% weight) and HCO_2H (2 drops) were added to a solution of cyclobutane derivatives in EtOH (0.083 M). The solution was placed under H_2 atmosphere and stirred until disappearance of the starting material (16 h). The solution was filtered through Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography.

(1*R*,2*r*,3*S*,4*s*)-4-(2-Hydroxyethyl)cyclobutane-1,2,3-triol (15). According to general method A, **14** (250 mg, 0.76 mmol) afforded the tetrol **15** (112 mg, quant.) as a colorless oil: TLC R_f 0.19 (silica gel MeOH/CH_2Cl_2, 2:8); IR (neat) 3274, 1050, 1024 cm^{-1}; ^{1}H NMR (300 MHz, MeOD) δ 3.65 (t, J = 6.9 Hz, 2H), 3.55 (t, J = 6.3 Hz, 1H), 3.17 (dd, J = 7.8, 6.2 Hz, 2H), 1.79 (q, J = 7.1 Hz, 2H), 1.47 (m, 1H); ^{13}C NMR (75 MHz, MeOD) δ 81.7, 73.8, 61.5, 44.0, 36.0; HRMS (ESI) m/z 171.065 ([M + Na]$^+$, calcd. for $C_6H_{12}O_4Na$ 171.063).

(1*R*,2*S*,3*S*,4*R*)-2,3-Bis(benzyloxy)-4-vinylcyclobutanol (16). To a solution of diol **14** (200 mg, 0.61 mmol, 1 equiv) in THF (20 mL) were added 2-nitrophenyl selenocyanate (304 mg, 1.34 mmol, 2.2 equiv) in one portion followed by tributylphosphine (0.33 mL, 1.34 mmol, 2.2 equiv) dropwise. The solution was stirred at rt for 35 min. Water was added, and the product was extracted with Et_2O (3×). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. A solution of the crude selenyl derivative in CH_2Cl_2 (8 mL) was added to a solution of Davis oxaziridine[20b] (191 mg, 0.73 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) cooled to 0 °C. The solution was stirred at 0 °C for 40 min. Saturated aqueous Na_2CO_3 (6 mL) was added, and the solution was stirred at rt for 1 h. The product was extracted with CH_2Cl_2 (3×). The combined organic layer was washed with saturated aqueous $NaHSO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:7 to 1:3) to afford the desired vinylcyclobutanol **16** (160 mg, 84%) as a yellow oil: TLC R_f 0.49 (silica gel, EtOAc/petroleum ether, 1:2); $[\alpha]_D^{20}$ = +14 (c 1.0, $CHCl_3$); IR (film) 3392, 2871, 1087 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.16 (m, 10H), 5.80 (ddd, J = 17.3, 10.1, 7.4 Hz, 1H), 5.09 (d, J = 17.0 Hz, 1H), 5.01 (d, J = 10.2 Hz, 1H), 4.59 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 12.0 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 11.9 Hz, 1H), 3.73 (t, J = 5.9 Hz, 1H), 3.50 (m, 1H), 3.42 (m, 1H), 2.25 (q, J = 7.7 Hz, 1H), 2.19−2.10 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 138.0, 137.0, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 116.2, 85.4, 76.9, 71.83, 71.81, 71.4, 48.3; HRMS (ESI) m/z 333.145 ([M + Na]$^+$, calcd. for $C_{20}H_{22}O_3Na$ 333.146).

((1*R*,2*R*,3*S*,4*S*)-2,3-Bis(benzyloxy)-4-vinylcyclobutoxy)(*tert*-butyl)dimethylsilane (17). To a solution of **16** (99 mg, 0.32 mmol, 1 equiv) in CH_2Cl_2 (0.61 mL) cooled to 0 °C were added TBSCl (72 mg, 0.48 mmol, 1.5 equiv), DMAP (20 mg, 0.16 mmol, 0.5 equiv) and NEt_3 (0.09 mL, 0.64 mmol, 2 equiv). The solution was stirred at rt for 14 h. Water was added, and the product was extracted with CH_2Cl_2 (3×). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 3:97) to afford the desired cyclobutane **17** (105 mg, 77%) as a yellow oil: TLC R_f 0.42 (silica gel, EtOAc/petroleum ether, 1:19); $[\alpha]_D^{20}$ = +6.5 (c 1.0, $CHCl_3$); IR (film) 2928, 2857, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.22 (m, 10H), 5.87 (ddd, J = 17.2, 10.1, 8.3 Hz, 1H), 5.14 (d, J = 17.2 Hz, 1H), 5.07 (d, J = 10.1 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 11.7 Hz, 1H), 4.57 (d, J = 11.9 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 3.83 (t, J = 5.9 Hz, 1H), 3.62 (t, J = 6.5 Hz, 1H), 3.49 (t, J = 6.3 Hz, 1H), 2.33 (q, J = 7.6 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.31, 138.26, 137.8, 128.5, 127.9, 127.7, 116.2, 85.5, 77.4, 72.4, 71.6, 71.3, 49.0, 25.9, 18.0, −4.0, −4.6. HRMS (ESI) m/z 447.236 ([M + Na]$^+$, calcd. for $C_{26}H_{36}O_3SiNa$ 447.233).

((1*S*,2*S*,3*R*,4*R*)-2,3-Bis(benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)cyclobutyl)methanol (18). To a solution of **17** (99 mg, 0.23 mmol, 1 equiv) in a mixture of THF/H_2O (4:1, 0.7 mL) were added OsO_4 (2.5 wt % in *t*BuOH, 0.09 mL, 0.009 mmol, 0.04 equiv) and $NaIO_4$ (94 mg, 0.44 mmol, 1.9 equiv). The solution was stirred at rt for 5 h. Saturated aqueous $Na_2S_2O_3$ was added, and the product was extracted with EtOAc (3×). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in MeOH, and the solution was cooled to 0 °C. $NaBH_4$ (11 mg, 0.29 mmol, 1.2 equiv) was added, and the solution was stirred at rt for 15 min. Acetone (0.5 mL) was added. The solution was stirred 5 min and then concentrated under reduced pressure. The residue was dissolved in EtOAc and H_2O, and the product was extracted with EtOAc (4×). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 3:97) to afford the desired alcohol **18** (82 mg, 82%) as a colorless oil: TLC R_f 0.18 (silica gel, EtOAc/petroleum ether, 1:5); $[\alpha]_D^{20}$ = +0.1 (c 1.0, $CHCl_3$); IR (film) 3454, 2929, 2857 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.25 (m, 10H), 4.64 (d, J = 11.6 Hz, 1H), 4.58 (d, J = 12.7 Hz, 1H), 4.56 (s, 2H), 3.84 (t, J = 5.8 Hz, 1H), 3.76 (dd, J = 11.1, 4.5 Hz, 1H), 3.72−3.64 (m, 2H), 3.50 (m, 1H), 1.91 (m, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 138.3, 128.6, 128.5, 127.94, 127.87, 127.8, 127.7, 85.9, 74.8, 71.7, 71.6, 68.2, 62.0, 47.0, 25.9, 18.1, −4.4, −4.6; HRMS (ESI) m/z 451.230 ([M + Na]$^+$, calcd. for $C_{25}H_{36}O_4SiNa$ 451.228).

(1*R*,2*S*,3*S*,4*R*)-2,3-Bis(benzyloxy)-4-(hydroxymethyl)cyclobutanol (19). TBAF (1 M in THF, 3.1 mL, 3.1 mmol, 5 equiv) was added to a solution of **18** (264 mg, 0.62 mmol, 1 equiv) in THF (1 mL). The solution was stirred at rt for 4 h. Saturated aqueous NH_4Cl was added, and the product was extracted with EtOAc (3×). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (MeOH/CH_2Cl_2, 3:97 to 5:95) to afford the desired diol **19** (197 mg, quant.) as a colorless oil: TLC R_f 0.49 (silica gel, MeOH/CH_2Cl_2, 10:90); $[\alpha]_D^{20}$ = +21 (c 1.0, MeOH); IR (neat) 3369, 2930, 2871 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.35 (m, 10H), 4.65 (d, J = 11.9 Hz, 1H), 4.58 (d, J = 11.9 Hz, 1H), 4.56 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 11.7 Hz, 1H), 3.80 (t, J = 5.7 Hz, 1H), 3.73 (dd, J = 11.1, 5.0 Hz, 1H), 3.65−3.55 (m, 2H), 3.45 (m, 1H), 2.68−2.56 (br s, 1H), 2.18−2.07 (br s, 1H), 1.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 138.2, 128.63, 128.58, 128.1, 128.01, 127.98, 127.94, 85.8, 74.2, 71.79, 71.77, 69.3, 62.4, 46.5; HRMS (ESI) m/z 337.143 ([M + Na]$^+$, calcd. for $C_{19}H_{22}O_4Na$ 337.141).

(1*R*,2*r*,3*S*,4*s*)-4-(Hydroxymethyl)cyclobutane-1,2,3-triol (5). According to general method A, **19** (80 mg, 0.25 mmol) afforded the tetrol **5** (33 mg, quant.) as a colorless oil: TLC R_f 0.28 (silica gel, $CH_3CN/H_2O/NH_4OH$, 5:1:1); IR (film) 3237, 1068 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 3.80−3.71 (m, 3H), 3.50−3.42 (m, 2H), 1.76 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 79.1, 68.1, 60.2, 46.2; HRMS (ESI) m/z 157.048 ([M + Na]$^+$, calcd. for $C_5H_{10}O_4Na$ 157.047).

((1*R*,2*R*,3*S*,4*S*)-2,3-Bis(benzyloxy)-4-((benzyloxy)methyl)cyclobutoxy)(*tert*-butyl)dimethylsilane (20). NaH (17 mg, 0.41 mmol, 1.3 equiv) was added to a solution of **18** (136 mg, 0.32 mmol, 1 equiv) in THF (1.7 mL) cooled at 0 °C. The solution was stirred at rt for 30 min. BnBr (45 μL, 0.38 mmol, 1.2 equiv) was then added. The solution was stirred at rt for 18 h. Water was added, and the product was extracted with CH_2Cl_2 (3×). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 3:97 to 15:85) to afford the desired cyclobutane **20** (80 mg, 49%) as a colorless oil: TLC R_f 0.51 (silica gel, EtOAc/petroleum ether, 1:9); IR (film) 2929, 2856, 1096 cm^{-1}; $[\alpha]_D^{20}$ = +2 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.23 (m, 15H), 4.64 (d, J = 11.7 Hz, 1H), 4.58 (d, J = 11.7 Hz, 1H), 4.57 (d, J = 12.1 Hz, 1H), 4.54−4.46 (m, 3H), 3.84 (t, J = 5.7 Hz, 1H), 3.73 (m, 1H), 3.60−3.47 (m, 3H), 1.97 (m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 138.5, 138.4, 128.5, 127.89, 127.86, 127.81, 127.7, 86.0, 75.1, 73.2, 71.6, 71.5, 68.9, 68.4,

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45.3, 25.9, 18.1, −4.4, −4.6; HRMS (ESI) m/z 541.274 ([M + Na]$^+$, calcd. for $C_{32}H_{42}O_4SiNa$ 541.274).

(1*R*,2*S*,3*S*,4*R*)-2,3-Bis(benzyloxy)-4-((benzyloxy)methyl)-cyclobutanol (21). TBAF (1 M in THF, 1.1 mL, 1.10 mmol, 5 equiv) was added to a solution of **20** (113 mg, 0.22 mmol, 1 equiv) in THF (0.4 mL). The solution was stirred at rt for 3 h. Saturated aqueous NH_4Cl was added, and the product was extracted with EtOAc (3×). The combined organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 3:97 to 15:85) to afford the desired cyclobutanol **21** (85 mg, 97%) as a colorless oil: TLC R_f 0.29 (silica gel, EtOAc/petroleum ether, 1:2); IR (film) 3406, 2861, 1051 cm^{-1}; $[\alpha]_D^{20}$ = −3 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.25 (m, 15H), 4.67 (d, J = 11.9 Hz, 1H), 4.61 (d, J = 11.9 Hz, 1H), 4.56 (s, 2H), 4.52 (s, 2H), 3.83 (t, J = 5.9 Hz, 1H), 3.65 (m, 1H), 3.61−3.47 (m, 3H), 2.41−2.26 (br s, 1H), 2.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.55, 128.50, 128.46, 128.1, 127.9, 127.7, 85.7, 74.6, 73.2, 71.7, 71.6, 69.5, 69.3, 44.8; HRMS (ESI) m/z 427.191 ([M + Na]$^+$, calcd. for $C_{26}H_{28}O_4Na$ 427.188).

(2*R*,3*S*,4*S*)-2,3-Bis(benzyloxy)-4-((benzyloxy)methyl)cyclobutanone (22). Dess−Martin periodinane (0.3 M in CH_2Cl_2, 0.5 mL, 0.15 mmol, 1.6 equiv) was added to a solution of alcohol **21** (37.5 mg, 0.093 mmol, 1 equiv) in CH_2Cl_2 (0.35 mL) cooled at 0 °C. The solution was stirred at rt for 1 h. Saturated aqueous $Na_2S_2O_3$ was added, and the product was extracted with CH_2Cl_2 (3×). The combined organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:7 to 1:5) to afford the desired cyclobutanone **22** (34.5 mg, 92%) as a colorless oil: TLC R_f 0.62 (silica gel, EtOAc/petroleum ether, 1:2); IR (film) 2862, 1786, 1116 cm^{-1}; $[\alpha]_D^{20}$ = +33 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 7.31−7.01 (m, 15H), 4.69 (d, J = 11.9 Hz, 1H), 4.58 (m, 1H), 4.54 (d, J = 11.6 Hz, 1H), 4.49 (d, J = 12.2 Hz, 1H), 4.44 (d, J = 12.2 Hz, 1H), 4.31 (m, 1H), 4.18 (s, 2H), 3.35 (d, J = 2.0 Hz, 1H), 3.33 (d, J = 0.7 Hz, 1H), 2.84 (m, 1H); ^{13}C NMR (75 MHz, C_6D_6) δ 203.2, 138.6, 138.5, 138.0, 128.63, 128.61, 128.2, 127.9, 127.8, 91.3, 74.4, 73.2, 72.4, 72.2, 65.8, 58.2; HRMS (ESI) m/z 425.174 ([M + Na]$^+$, calcd. for $C_{26}H_{26}O_4Na$ 425.172).

(1*S*,2*S*,3*S*,4*R*)-2,3-Bis(benzyloxy)-4-((benzyloxy)methyl)-cyclobutanol (23). L-Selectride (1 M in THF, 0.18 mL, 0.18 mmol, 1.1 equiv) was added to a solution of ketone **22** (66 mg, 0.16 mmol, 1 equiv) in THF (0.66 mL) cooled to −78 °C. The solution was stirred for 1 h. Water (0.01 mL) was added, and the solution was warmed up to 0 °C. Aqueous 35% H_2O_2 (0.02 mL) was added, and the solution was diluted in EtOAc. The organic layer was washed with saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:5 to 1:2) to afford the desired cyclobutanol **23** (44 mg, 67%) as a colorless oil: TLC R_f 0.34 (silica gel, EtOAc/petroleum ether, 1:2); IR (film) 3455, 2863, 1100 cm^{-1}; $[\alpha]_D^{20}$ = +9 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.24 (m, 15H), 4.57 (s, 2H), 4.54−4.46 (m, 4H), 4.31 (m, 1H), 4.04 (dd, J = 8.2, 6.2 Hz, 1H), 3.87 (m, 1H), 3,73 (dd, J = 9.7, 7.4 Hz, 1H), 3.63 (dd, J = 9.7, 5.5 Hz, 1H), 2.40 (d, J = 4.1 Hz, 1H), 2.19 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 138.3, 137.8, 128.7, 128.5, 128.21, 128.18, 127.9, 127.85, 127.80, 127.76, 81.3, 78.1, 73.3, 72.0, 71.9, 67.4, 64.7, 41.6; HRMS (ESI) m/z 427.187 ([M + Na]$^+$, calcd. for $C_{26}H_{28}O_4Na$ 427.188).

(1*S*,2*R*,3*S*,4*S*)-4-(Hydroxymethyl)cyclobutane-1,2,3-triol (24). General method A was used, and **23** (44 mg, 0.11 mmol) afforded the tetrol **24** (14.5 mg, quant.) as a white solid: TLC R_f 0.26 (silica gel, $CH_3CN/H_2O/NH_4OH$, 5:1:1); IR (neat) 3207, 1051 cm^{-1}; $[\alpha]_D^{20}$ = −42 (c 0.5, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 4.32 (m, 1H), 3.99−3.87 (m, 2H), 3.87−3.71 (m, 2H), 2.04 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 74.8, 72.0, 64.8, 58.0, 43.0; HRMS (ESI) m/z 157.047 ([M + Na]$^+$, calcd. for $C_5H_{10}O_4Na$ 157.047).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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