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Efficient Desymmetrization of "*Pseudo*"-C_2-Symmetric Substrates: Illustration in the Synthesis of a Disubstituted Butenolide from Arabitol

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A short synthesis of the homochiral disubstituted butenolide **1** is described in four steps from arabitol. The key steps are the selective kinetic protection of arabitol and the cyclization of **11** to form the butenolide ring. This last transformation represents a rare example of a fully stereoselective cyclitive desymmetrization process of a "*pseudo*"-C_2-symmetric substrate.

Butenolides [2(5*H*)-furanones] are substructures found in many natural products. The wide range of biological activities displayed by these natural products include the following: cytotoxic, antitumor, antimalarial, immunosuppressive, antiviral, antibacterial, and antifungal activity.[1,2] The important biological role of butenolides is further underlined by the synthesis, including synthesis on solid support, of unnatural butenolide-containing products.[3] Because of their intrinsic reactivity, butenolides are versatile building blocks for the synthesis of a wide variety of biologically active compounds,[4] and they are also used as advanced intermediates in the synthesis of complex natural products.[5] Consequently, the development of methodologies to access butenolides has received much attention and continues to be an active research field.[2−6]

As part of a research program in developing efficient desymmetrization methodologies, we became interested in the synthesis of homochiral butenolides starting from carbohydrates.[7] The selected target **1** (Scheme 1) contains chiral centers both in the ring and the β-substituent. Very few butenolides with this substitution pattern have been reported,[7c] but **1** is an interesting synthetic building block with good opportunities for subsequent diastereoselective

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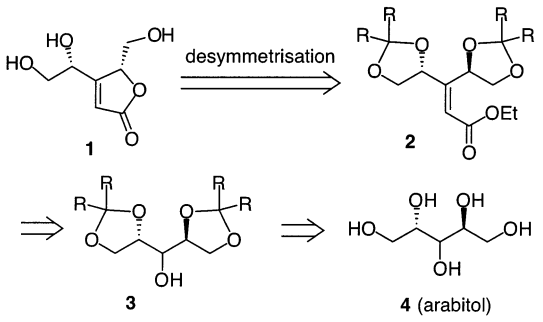
SCHEME 1. Retrosynthetic Analysis



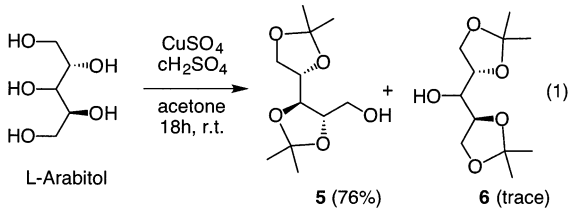
transformations, and is a valuable precursor for the synthesis of nucleoside and carbohydrate derivatives.

As can be seen from the retrosynthetic analysis (Scheme 1), the synthesis of **1** is designed to exploit the symmetrical nature of the starting material, arabitol **4**, and of the intermediate products. The first key step is the regioselective protection of arabitol (**4** → **3**), which, surprisingly, was not described at the outset of this work. The second key step in the proposed synthesis is an efficient desymmetrization of the ester **2** to form the butenolide ring system.[8] We have identified **2** as a novel subclass (see below) of "*pseudo*"-C_2-symmetric[9] substrates, and the described desymmetrization methodology should be applicable to other systems as well and hence be of general interest.[10] Unlike most carbohydrate-based starting materials, arabitol is commercially available in both enantiomeric forms at similar cost.

In this paper, we disclose our results for the arabitol protection and subsequent butenolide synthesis. Using the butenolide synthesis as an example, we introduce a novel subclass of "*pseudo*"-C_2-symmetric substrates and show that for this subclass, desymmetrization with complete diastereoselectivity is possible.

Results and Discussion

As can be seen from the retrosynthetic analysis, the first aim was the regioselective protection of arabitol as the 1,2:4,5-bis-acetal product **5**. Unfortunately, literature reports revealed that the protection of arabitol as its bis-acetonide under typical conditions results in the formation of the undesired 2,3:4,5-di-*O*-isopropylidene arabitol **5** (eq 1).[11] The isomer **5** contains an internal trans-disubstituted acetonide, which is more stable than a terminal acetonide.[11b,12]



Although the desired bis-protected arabitol **6** is accessible in four steps from mannose,[13] it was decided to investigate the direct protection of arabitol in more detail. Since it is known that primary alcohols react faster in an acetonide formation reaction,[12a] kinetic protection protocols were investigated. We based our first experiments on literature procedures for selective terminal acetonide formation of substrates containing a terminal triol moiety.[14] Gratifyingly, it was found that reaction of arabitol with acetone/2,2-dimethoxypropane and 50 mol % of camphor sulfonic acid (CSA) at room temperature led to the desired 1,2:4,5-di-*O*-isopropylidene product **6** in 58% yield, with 9% of the undesired regioisomer **5**. The reaction could easily be monitored by visual disappearance of arabitol, which has a low solubility in the reaction mixture. The NMR of the reaction mixture was remarkably clean, with **5** and **6** present as the two major compounds and a small amount of mono-acetonide species. The mixture of the 1,2:4,5-di-*O*-isopropylidene and 2,3:4,5-di-*O*-isopropylidene regioisomers could be separated by careful column chromatography,[15] with the mono-acetonide derivatives being easily removed during the same separation process.

Although useful quantities of **6** could be obtained by using this procedure, the separation of **5** and **6** was time-consuming and prohibited further up-scaling. In addition, an improvement regarding yield was also desirable.

Further optimization has led us to use 3,3-dimethoxypentane leading to the di-*O*-isopentylidene acetal **7** (Table 1) with refluxing tetrahydrofuran (THF) as solvent and using very short reaction times. The formation of iso-

(7) Examples: (a) Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 2773−2775. (b) de March, P.; Figueredo, M.; Font, J.; Raya, J. *Tetrahedron Lett.* **1999**, *40*, 2205−2208. (c) Mulzer, J.; Pietschmann, C.; Schöllhorn, B.; Buschmann, J.; Luger, P. *Liebigs Ann.* **1995**, 1433−1439. (d) Mann, J.; Partlett, N. K.; Thomas, A. *J. Chem. Res. (S)* **1987**, 369. (e) Vekemans, J. A. J. M.; Franken, G. A. M.; Chittenden, G. J. F.; Godefroi, E. F. *Tetrahedron Lett.* **1987**, *28*, 2299−2300. (f) Chen, S.-Y.; Joullié, M. M. *J. Org. Chem.* **1984**, *49*, 2168−2174. (g) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988−2006. See also refs 2g,h and 3a.

(8) Butenolides have been synthesized from symmetric, achiral ketones: Lattmann, E.; Hoffmann, H. M. R. *Synthesis* **1996**, 155−163.

(9) The term "*pseudo*"-C_2-*symmetric* refers to molecules that would be C_2-symmetric if they did not contain a central chirotopic, nonstereogenic carbon center ((a) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17. (b) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563−566). See also further in the text and ref 22.

(10) During the course of this work, an example of a similar symmetry-breaking tactic was published: Hale, K. J.; Hummersone, M. G.; Bhatia, G. S. *Org. Lett.* **2000**, *2*, 2189−2192.

(11) (a) Bukhari, M. A.; Foster, A. B.; Lehmann, J.; Webber, J. M.; Westwood, J. H. *J. Chem. Soc.* **1963**, 2291−2295. (b) Nakagawa, T.; Tokuoka, H.; Shinoto, K.; Yoshimura, J.; Sato, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2150−2154. (c) After our initial studies in the area, the protection of arabitol in DMF as solvent (12 h, rt) was reported to yield the 1,2:4,5-bis-acetonide, although no detailed experimental was given (Terauchi, T.; Terauchi, T.; Sato, I.; Tsukada, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2000**, *41*, 2649−2653.

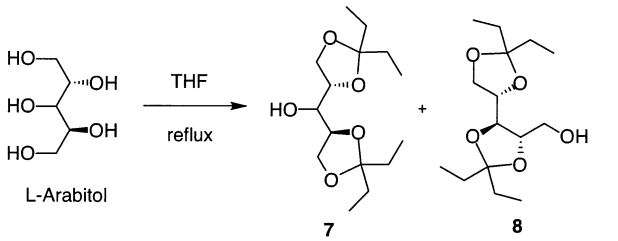
(12) (a) Grindley, T. B.; Wickramage, C. *Carbohydr. Res.* **1987**, *167*, 105−121. (b) Clode, D. M. *Chem. Rev.* **1979**, *79*, 491−513.

(13) Francisco, C. G.; León, E. I.; Martin, A.; Moreno, P.; Rodriguez, M. S.; Suárez, E. *J. Org. Chem.* **2001**, *66*, 6967−6976. D-Mannose is reported to yield *ent*-**6**.

(14) Examples: (a) Kilonda, A.; Compernolle, F.; Peeters, K.; Joly, G. J.; Toppet, S.; Hoornaert, G. J. *Tetrahedron* **2000**, *56*, 1005−1012. (b) Kölln, O.; Redlich, H. *Synthesis* **1996**, 963−969. (c) Kölln, O.; Redlich, H. *Synthesis* **1996**, 826−832.

(15) Identification of the isomers by ^{1}H NMR was very straightforward: the secondary hydroxyl group of the desired isomer **5** appeared as a doublet at 2.30 ppm, while the primary alcohol proton of the thermodynamic isomer **6** appeared as a doublet of doublets at 2.34 ppm. In addition, the observed ^{13}C NMR chemical shift values for the isopropylidene acetal− and methyl carbons correlated well with the general chemical shift regions reported for five-membered acetonides: Buchanan, J. G.; Chacón-Fuertes, M. E.; Edgar, A. R.; Moorhouse, S. J.; Rawson, D. I.; Wightman, R. H. *Tetrahedron Lett.* **1980**, *21*, 1793−1796. Buchanan, J. G.; Edgar, A. R.; Rawson, D. I.; Shahidi, P.; Wightman, R. H. *Carbohydr. Res.* **1982**, *100*, 75−86.

TABLE 1. Optimization of the Arabitol Protection Reaction



entry	time (min)	CSA (mol %)	dimethoxypentane (equiv)	yield of **7** (%)[a]	yield of **8** (%)[a]
1	5	4[b]	2.2	69	9
2	240	4[b]	2.2	13	50
3	5	10	2.2	71	10
4	5	35	2.2	37	31
5	5	10	4.4	66	6
6	5	30	4.4	80	12

[a] Isolated yields. [b] *p*-Toluenesulfonic acid was used.

pentylidene acetals should increase selectivity for 1,3-dioxolane over 1,3-dioxane isomers under the kinetic conditions employed. The high temperature was found necessary because of the low solubility of arabitol in the reaction mixture, which resulted in long reaction times and low yields. A summary of the optimization process is listed in Table 1. A good yield and isomer ratio was obtained after only 5 min. The use of long reaction times, resulting in thermodynamic reaction conditions, yielded **8** as the major isomer (entry 2 vs 1). Increasing the amount of acid catalyst to 35 mol % also promoted the isomerization to **8** (entry 4 vs 3). However, when employing 4.4 equiv of 3,3-dimethoxypentane, we found that a high catalyst loading was required for optimum results (30 mol %, entry 6 vs 5). Under those conditions, an isolated yield for **7** of 80% was obtained, with 12% of **8** isolated as well.

Having obtained an improved yield for the desired "*pseudo*"-C_2-symmetric bis-acetal **7**, we next aimed to improve the isolation procedure, although chromatographic separation turned out to be somewhat easier for **7** and **8** than for the mixture of **5** and **6**. Since the undesired **8** contains a more reactive primary alcohol group compared to the sterically hindered secondary alcohol in **7**, we decided to investigate a scavenger approach. In the event, the crude reaction mixture containing **7**, **8**, and monoprotected arabitol species was reacted with succinic anhydride (Scheme 2). The unreacted product **7** was easily separated from the reaction product **9** and similar products that were formed from monoprotected arabitol species, by a basic aqueous extraction, obviating the need for chromatographic separation. The arabitol protection reaction was successfully carried out on 10 g scale by using the anhydride scavenging workup.[16] However, when working on large scale we found that there were still trace amounts of impurities present in the product that was isolated after the basic extraction procedure. These impurities were very easily removed by column chromatography. Nevertheless, the whole process including the necessary chromatography can be carried out in less than 1 day.

(16) The protection of arabitol as its bis-pentylidene acetal has been communicated very recently: Maleczka, R. E., Jr.; Terrell, L. R.; Geng, F.; Ward, J. S., III *Org. Lett.* **2002**, *4*, 2841−2844.

Having achieved a practical large-scale synthesis of the desired bis-protected arabitol **7**, we proceeded with the synthesis of the butenolide **1** (Scheme 3). Parikh−Doering oxidation[17] of **7** gave the C_2-symmetrical ketone **10** in 99% yield without any detectable trace of epimerization to the meso-isomer (^{1}H and ^{13}C NMR). The increase in molecular symmetry resulted in a significant simplification of both the ^{1}H and ^{13}C NMR spectra, which confirmed that both acetonide groups in the bis-protected arabitol were situated at the terminal positions.

Reaction of **10** with (ethoxycarbonylmethylene)triphenylphosphorane[18] led to the desired unsaturated ester **11** in excellent yield without epimerization. Because the double bond of **11** is nonstereogenic,[19,20] the formation of *E*/*Z* diastereoisomers is not possible. However, the double bond does not coincide with a symmetry plane or inversion axis, which leads us to assign the double bond as being chirotopic.[19,21] In addition, the central double bond does not coincide with a C_2-axis either, which allows us to classify alkenes such as **11** into an interesting subclass of "*pseudo*"-C_2-symmetric compounds,[22] which to the best of our knowledge has not yet been identified as such. The symmetry of **11** is comparable to that of arabitol, which contains a nonstereogenic and chirotopic carbon center.[9] The variation in having a "*pseudo*"-C_2-symmetric center or a "*pseudo*"-C_2-symmetric double bond (axis)[20] will prove crucial for the efficiency of the following cyclization step.

Treatment of **11** with CSA in methanol leads to diol deprotection, followed by cyclization. The resulting butenolide **1** was isolated in 95% yield. The observed multiplicities of the alcohol protons in the ^{1}H NMR spectrum, one doublet and two triplets, suggested that the cyclization proceeded as expected. In addition, a D_2O-exchange experiment clearly indicated the presence of two primary alcohols, with both CH_2 groups appearing as a set of doublets of doublets, and one secondary alcohol (see Supporting Information). The cyclization of **11** results in a differentiation of the diastereotopic diol chains and in the double bond becoming stereogenic, which formally allows us to characterize the reaction as a desymmetrization[23] step. The desymmetrization reaction features some interesting stereochemical aspects. Whereas terminus differentiation through monocyclization of "*pseudo*"-C_2-symmetric compounds that possess a nonstereogenic, chirotopic carbon atom typically led to a mixture of diastereomers,[9,24] there is the possibility that the corresponding process for compounds that possess a nonstereogenic, chirotopic double bond yields a single diaste-

(17) Parikh, J. R.; Doering, W von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(18) Vidyasagar Reddy, G.; Sreevani, V.; Iyengar, D. S. *Tetrahedron Lett.* **2001**, *42*, 531−532.

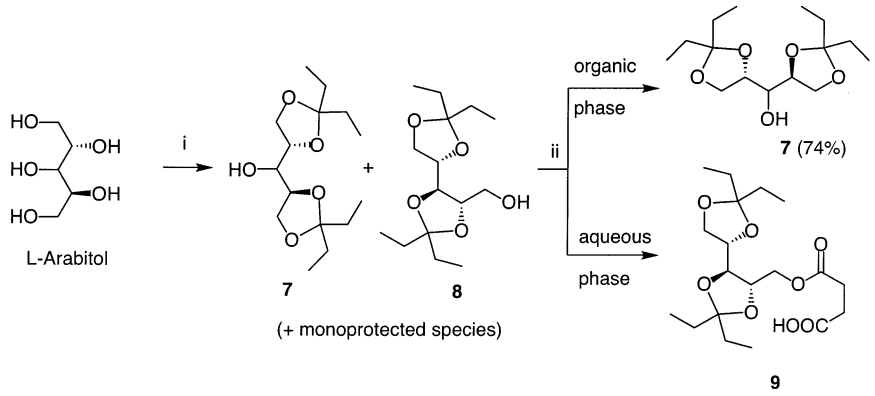
(19) Permutation of two ligands of the double bond does not lead to a stereoisomer. For a clear discussion about stereogenicity/chirotopicity, see: (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Chapters 3 and 5, pp 53 and 123. (b) Helmchen, G. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, Germany, 1995: Vol. E21a, Chapter 1, pp 17−21.

(20) Both a single carbon and an olefinic double bond (axis) can be stereogenic elements. See ref 19a, pp 52−53 and 1208, and ref 19b, pp 11−13.

(21) Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319−3328.

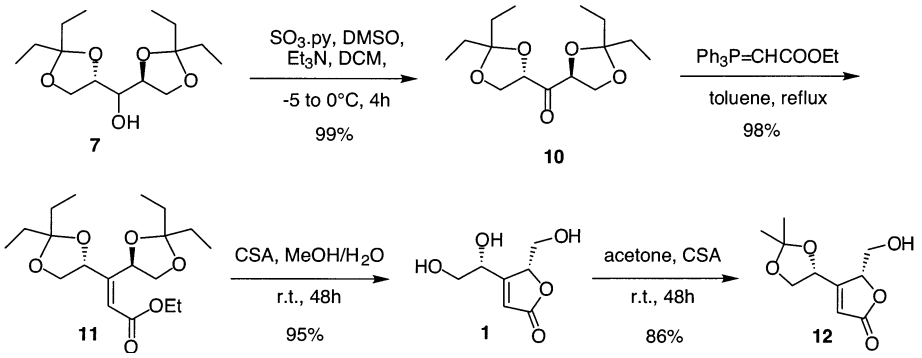
(22) Following Schreiber's description of "*pseudo*"-C_2-*symmetry* (ref 9), **11** would be C_2-symmetric if it did not contain a central chirotopic, nonstereogenic double bond (axis).

SCHEME 2. Separation of the Bis-acetal Regioisomers 7 and 8, Using a Scavenging Approach[a]



[a] Conditions and reagents: (i) 3,3-dimethoxypentane, CSA, THF, reflux, 5 min; aq NaOH. (ii) succinic anhydride, Et_3N, DCM; basic aqueous extraction.

SCHEME 3. Synthesis of the Butenolide



reoisomer only. As after desymmetrization the double bond becomes stereogenic, there is the possible formation of *E*/*Z* isomers. The diastereotopic group selection in the terminus differentiation process is now determined by the difference in product stability of the possible *E*/*Z* isomers. For small ring sizes, the product with the *E*-configuration is not formed, resulting in complete selectivity. Hence, no tedious diastereomer separation is required, which should make such cyclization processes useful for general synthetic applications.[10]

Protection of the diol moiety of **1** was achieved by subsequent acetonide formation. The presence of the residual primary alcohol of **12** could be observed in the ^{1}H NMR and the IR showed the characteristic absorption (1744 cm^{-1}) for a butenolide carbonyl group. The protection of the diol moiety effectively differentiates both primary alcohol groups, adding to the synthetic utility of the building block.

In conclusion, we have synthesized an enantiopure disubstituted butenolide using an efficient desymmetrization process of a "*pseudo*"-C_2-symmetric substrate. A practical kinetic protection protocol for arabitol leading to the 1,2:4,5-bis-isopentylidene acetal is described. In addition, we were able to identify a novel subclass of "*pseudo*"-C_2-symmetric substrates, based on a full stereochemical description of **11** according to the chirotopicity/stereogenicity concept.

(23) Desymmetrization of a compound that contains a "*pseudo*"-C_2-symmetric center is characterized by terminus differentiation, and by the transition of the nonstereogenic, chirotopic center to a stereogenic, chirotopic center. However, the term "desymmetrization" could rightly be questioned in this context. Desymmetrization formally indicates a removal of a symmetry element. Since a "*pseudo*"-C_2-symmetric molecule does not possess any symmetry elements, there can strictly speaking be no desymmetrization process. Nevertheless, there is common agreement in the synthetic organic community to use the term "*desymmetrization of "pseudo"-C2-symmetric compounds*" (refs 9 and 24).

Experimental Section

Arabitol was obtained from commercial sources, and used without further purification. Reaction solvents were dried immediately before use as follows: acetone was distilled from $ZnCl_2$, THF was distilled from Na/benzophenone, Et_3N and CH_2Cl_2 were distilled from CaH_2, and toluene was distilled from Na. DMSO was distilled from CaH_2 and stored over molecular sieves. Glassware was flame dried immediately prior to use. All reactions were carried out under an atmosphere of nitrogen. Solvents for chromatography were HPLC-grade. Column chromatography was performed on 230−400 mesh silica gel. Reactions were monitored by TLC (Merck) with detection by UV-light or through alkaline $KMnO_4$ oxidation.

1,2:4,5-Di-*O*-isopropylidene-L-arabitol (6) and 2,3:4,5-Di-*O*-isopropylidene-L-arabitol (5). To a stirred suspension of L-arabitol (1.0 g, 6.6 mmol) in acetone (48 mL) and 2,2-dimethoxypropane (12 mL, 0.1 mol) at room temperature was added CSA (0.77 g, 3.3 mmol). The reaction was stopped after 10 min by rapidly adding saturated aqueous $NaHCO_3$ (50 mL). After the solution was stirred for 30 min, acetone was removed in vacuo. The aqueous solution was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4. After the solvent was removed in vacuo, the crude product was purified by column chromatography (hexane/ethyl acetate 7:3). The silica gel was treated with eluent containing 0.1% Et_3N before use. This yielded a colorless oil (1.1 g, 66%) that was further purified

by preparative HPLC (hexane/ethyl acetate 65:35). This yielded **6** (889 mg, 58%) and **5** (131 mg, 9%) as colorless oils.

Data for **6**: $[\alpha]_D$ +3.9 (*c* 0.94, $CHCl_3$, 27 °C), lit.[13a] $[\alpha]_D$ −14.3 (*c* 0.21, $CHCl_3$) (for *ent*-**6**); CIMS, *m*/*z* (%) 233 ($(M + H)^+$, 40), 217 (40), 101 (100); HRMS (CI) calcd for $C_{10}H_{17}O_5$ $(M - CH_3)^{+\bullet}$ 217.1076, found 217.1077. The IR and ^1H and ^{13}C NMR spectra corresponded to the reported data.[13a]

Data for **5**: $[\alpha]_D$ +1.2 (*c* 1.21, $CHCl_3$, 26 °C), lit.[11a] $[\alpha]_D$ ca. +1 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (1H, dd, $J = 8.5$, 6.0 Hz), 4.10−3.97 (3H, m), 3.85−3.73 (2H, m), 3.72 (1H, t, $J = 8.3$ Hz), 2.34 (1H, dd, $J = 8.5$, 4.3 Hz), 1.44 (3H, s), 1.41 (3H, s), 1.40 (3H, s), 1.36 (3H, s) ppm; CIMS, *m*/*z* (%) 233 ($(M + H)^+$, 42), 217 (36), 101 (100); HRMS (CI) calcd for $C_{11}H_{21}O_5$ $(M + H)^+$ 233.1389, found 233.1387. The IR and ^{13}C NMR spectra corresponded to the reported data.[5f,25]

(2*S*,4*S*)-1,2:4,5-Di-*O*-(3,3-pentylidene)arabitol (7) and (2*S*,3*R*,4*S*)-2,3:4,5-Di-*O*-(3,3-pentylidene)arabitol (8). To a refluxing suspension of L-arabitol (0.51 g, 3.35 mmol) in 3,3-dimethoxypentane (1.96 g, 14.8 mmol) and THF (5 mL) was added CSA (0.23 g, 0.99 mmol) and the reaction was stirred at reflux for 5 min. Triethylamine (1 mL) was added to the refluxing reaction, and the mixture was concentrated in vacuo and loaded directly onto a silica gel column (hexane/ethyl acetate 8:2). This yielded a colorless oil that was further purified by preparative HPLC (hexane/acetone 95:5) to give **7** (0.76 g, 80%) and **8** (0.155 g, 12%) as colorless oils.

Data for **7**: $[\alpha]_D$ −5.8 (*c* 0.9, $CHCl_3$, 20 °C); IR 3477 (m), 2973 (s), 2941 (s), 2883 (s), 1082 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (1H, m), 4.14 (1H, dd, $J = 7.8$, 5.8 Hz), 4.08 (1H, dd, $J = 8.0$, 6.5 Hz), 3.98 (1H, m), 3.93 (1H, app. t, $J = 7.3$ Hz), 3.86 (1H, app. t, $J = 8.0$ Hz), 3.46 (1H, dt, $J = 7.5$, 5.3 Hz), 2.39 (1H, d, $J = 5.5$ Hz), 2.4−1.56 (8H, m), 0.94−0.86 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.30, 112.92, 76.82, 76.47, 72.99, 67.87, 66.55, 29.54, 29.52, 29.05, 28.96, 8.19, 8.17, 8.04 ppm; CIMS, *m*/*z* (%) 289 ($(M + H)^+$, 38), 259 (25), 203 (100); HRMS (EI) calcd for $C_{13}H_{23}O_5$ $(M - CH_2CH_3)^+$ 259.1546, found 259.15484. Anal. Calcd for $C_{15}H_{28}O_5$: C, 62.47; H, 9.79. Found: C, 62.36; H, 9.49.

Data for **8**: $[\alpha]_D$ −7.1 (*c* 0.9, $CHCl_3$, 20 °C); IR 3493 (m), 2973 (s), 2941 (s), 2882 (s), 1085 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (1H, dd, $J = 8.3$, 6.3 Hz), 4.05−3.99 (2H, m), 3.91 (1H, dd, $J = 8.3$, 6.3 Hz), 3.85−3.74 (2H, m), 3.65 (1H, t, $J = 8.4$ Hz), 2.46 (1H, dd, $J = 8.5$, 4.5 Hz), 1.70−1.59 (8H, m), 0.92−0.86 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.86, 113.10, 81.40, 79.75, 76.95, 68.74, 62.88, 30.39, 30.27, 29.50, 28.81, 8.15, 8.00, 7.91; CIMS, *m*/*z* (%) 289 ($(M + H)^+$, 44), 259 (86), 203 (100); HRMS (EI) calcd for $C_{13}H_{23}O_5$ $(M - CH_2CH_3)^+$ 259.1546, found 259.1541. Anal. Calcd for $C_{15}H_{28}O_5$: C, 62.47; H, 9.79. Found: C, 62.37; H, 9.76.

(2*S*,4*S*)-1,2:4,5-Di-*O*-(3,3-pentylidene)arabitol (7) (including scavenging workup). A refluxing suspension of L-arabitol (10.0 g, 65.72 mmol) and 3,3-dimethoxypentane[26] (38.25 g, 0.29 mol) in THF (100 mL) was stirred for 15 min. CSA (4.58 g, 19.72 mmol) was added and the reaction was stirred at reflux for 5 min. The reaction was quenched by addition of NaOH (aq, 2 M, 20 mL) at reflux. Diethyl ether (50 mL) and water (10 mL) were added and the layers separated. The aqueous solution was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give a colorless oil. The crude product was dissolved in CH_2Cl_2 (200 mL) and Et_3N (10 mL) was added. The mixture was heated to reflux and succinic anhydride (1.71 g, 17.09 mmol) was added. The reaction was stirred at reflux until the presence of **2** was undetectable by TLC (approximately 1 h), and then quenched with $NaHCO_3$ (aq, 5%, 100 mL) at reflux temperature. After cooling, the layers were separated and the aqueous solution extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting product was finally purified by column chromatography (column diameter 8 cm, with 13 cm silica gel; eluted with hexane/ethyl acetate 85:15). After collection of a 900-mL prefraction 13 × 100 mL fractions were collected and concentrated to yield pure **7** as a pale yellow oil (14.09 g, 74%).

(2*S*,4*S*)-1,2:4,5-Bis(3,3-pentylidenedioxy)-3-pentanone (10). A suspension of SO_3·pyridine (0.85 g, 5.4 mmol) in CH_2Cl_2 (3.5 mL) was dissolved in DMSO (8.5 mL) and Et_3N (0.9 mL, 6.5 mmol). This solution was immediately added dropwise to a stirred solution of **7** (0.5 g, 1.7 mmol) in CH_2Cl_2 (12 mL) and DMSO (25 mL) at −5 °C, and the reaction mixture was stirred at 0 °C for 6 h. The reaction mixture was poured into a solution of saturated aqueous NH_4Cl:water:Et_2O:pentane (1:1:1:1, 100 mL), and the aqueous phase was extracted with an Et_2O:pentane mixture (1:1, 3 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4. After the solvent was removed in vacuo the obtained pale yellow oil was purified by column chromatography (hexane/ethyl acetate 9:1) to yield a colorless oil (483 mg, 99%).

$[\alpha]_D$ −71.6 (*c* 0.42, $CHCl_3$, 27 °C); IR 2969 (s), 2945 (s), 2884 (s), 1739 (s), 1469 (s), 1086 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.79 (2H, t, $J = 7.3$ Hz), 4.28 (2H, t, $J = 8.3$ Hz), 3.94 (2H, dd, $J = 8.3$, 7.1 Hz), 1.72−1.62 (8H, m), 0.91 (12H, dd, $J = 15.3$, 7.5 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 114.8, 78.7, 66.2, 29.1, 28.2, 8.1, 7.9 ppm; EIMS, *m*/*z* (%) 257 ($(M - CH_2CH_3)^+$, 4), 57 (100); HRMS (ES+) calcd for $C_{15}H_{26}O_5Na$ $(M + Na)^+$ 309.1674, found 309.1672.

Ethyl-3,3-bis[(4*R*)-2,2-diethyl-1,3-dioxolan-4-yl] Propenoate (11). (Ethoxycarbonylmethylene)triphenylphosphorane (5.7 g, 16.2 mmol) was added to a solution of **10** (2.32 g, 8.1 mmol) in toluene (25 mL) and the resulting mixture was stirred at reflux temperature for 1 h. The reaction mixture was allowed to cool and the solvent was evaporated in vacuo. The resulting mixture was purified by column chromatography (hexane/ethyl acetate 85:15), which yielded **11** as a colorless oil (2.83 g, 98%).

$[\alpha]_D$ −116.7 (*c* 1.10, $CHCl_3$, 28 °C); IR 2969 (s), 2941 (s), 2879 (s), 1715 (s), 1649 (s), 1465 (s), 1148 (s), 883 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (1H, t, $J = 1.7$ Hz), 5.59 (1H, td, $J = 7.5$, 1.8 Hz), 5.00 (1H, ddd, $J = 8.0$, 6.5, 1.5 Hz), 4.49 (1H, t, $J = 8.3$ Hz), 4.34 (1H, dd, $J = 7.8$, 6.8 Hz), 4.14 (2H, m), 3.53 (1H, t, $J = 7.8$ Hz), 3.37 (1H, t, $J = 8.0$ Hz), 1.75−1.61 (8H, m), 1.28 (3H, t, $J = 7.0$ Hz), 0.97−0.85 (12H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 157.5, 114.9, 113.2, 112.9, 74.6, 74.3, 69.6, 69.1, 60.2, 29.5, 29.0, 28.9, 26.6, 14.2, 8.4, 8.3, 8.2, 8.1 ppm; CIMS, *m*/*z* (%) 357 ($(M + H)^+$, 10), 327 (16), 271 (100); HRMS (ES+) calcd for $C_{19}H_{32}O_6Na$ $(M + Na)^+$ 379.2092, found 379.2091.

(5*S*)-4-[(1*R*)-1,2-(Dihydroxy)ethyl]-5-hydroxymethylfuran-2-(5*H*)-one (1). To a solution of **11** (366 mg, 1.0 mmol) in methanol (5 mL) and H_2O (0.1 mL) was added CSA (37 mg, 0.16 mmol). The mixture was stirred at room temperature for 48 h. Solid $NaHCO_3$ (40 mg) was added, and the reaction was stirred for 15 min. The suspension was directly loaded onto a silica gel column (CH_2Cl_2/methanol 95:5). Elution with a 8:2 mixture of the same solvent yielded **1** as a colorless oil (165 mg, 95%).

$[\alpha]_D$ +25.8 (*c* 0.88, CH_3OH, 26 °C); IR 3363 (s, br), 2938 (m), 2883 (m), 1732 (m), 1640 (m), 1058 (m) cm^{-1}; ^1H NMR (400 MHz, d_6-acetone) δ 6.04 (1H, t, $J = 1.7$ Hz), 5.16 (1H, td, $J = 3.6$, 1.8 Hz), 4.73 (1H, d, $J = 5.1$ Hz), 4.70 (1H, ddd, $J = 10.5$, 5.2, 1.6 Hz), 4.23 (1H, t, $J = 6.2$ Hz), 4.21 (1H, t, $J = 6.0$ Hz), 3.97 (1H, ddd, $J = 12.2$, 6.5, 3.7 Hz), 3.90 (1H, ddd, $J = 12.2$, 6.5, 3.7 Hz), 3.79 (1H, dt, $J = 11.1$, 5.6 Hz), 3.74 (1H, ddd,

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(26) Napolitano, E.; Fiaschi, R.; Mastrorilli, E. *Synthesis* **1986**, 122−125. The preparation was slightly modified: CSA was used instead of *p*-TsOH, and 5 equiv of methanol was used instead of 15 equiv. We found that it was important to purify the 3,3-dimethoxypentane by fractional distillation (bp 125 °C, atmospheric pressure) before use in the protection reaction.

J = 11.1, 6.1, 5.1 Hz) ppm; ^{13}C NMR (100 MHz, d_6-acetone) δ 173.1, 173.0, 117.7, 84.4, 70.6, 66.5, 62.3 ppm; ES, m/z (%) 371.1 $(2M + Na)^+$, 197.1 $(M + Na)^+$, 175.1 $(M + H)^+$; HRMS (CI) calcd for $C_7H_{11}O_5$ $(M + H)^+$ 175.0607, found 175.0608.

(5*S*)-4-[(1*R*)-1,2-(Isopropylidenedioxy)ethyl]-5-hydroxymethyl-furan-2-(5*H*)-one (12). To a stirred solution of **1** (87 mg, 0.5 mmol) in acetone (5 mL) was added CSA (30 mg) and the mixture was stirred for 48 h. A 5% solution of $NaHCO_3$ (15 mL) was added followed by extraction with DCM (4 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered and the solvent removed in vacuo. The residue was purified by column chromatography (hexane/acetone 6:4), which yielded **12** as a colorless oil (75 mg, 86%).

$[\alpha]_D$ −85.0 (*c* 0.81, $CHCl_3$, 26 °C); IR 3437 (br m), 2988 (w), 2931 (w), 1744 (s), 1640 (w), 1370 (m), 1062 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (1H, m), 5.05 (1H, td, J = 4.0, 1.8 Hz), 5.01 (1H, td, J = 6.9, 1.2 Hz), 4.28 (1H, dd, J = 8.3, 7.2 Hz), 4.04 (1H, ddd, J = 12.3, 6.3, 4.0 Hz), 3.96−3.90 (2H, m), 2.18 (1H, t, J = 6.8 Hz), 1.49 (3H, s), 1.43 (3H, s) ppm; ^{13}C NMR (100 MHz, d_6-$CDCl_3$) δ 171.8, 166.9, 118.0, 110.8, 83.0, 72.0, 67.8, 61.6, 26.2, 25.0 ppm; CIMS, m/z 214 (M^+, 100); HRMS (CI) calcd for $C_{10}H_{15}O_5$ $(M + H)^+$ 215.0920, found 215.0919.

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of all compounds, including D_2O-exchange experiments for **1**, **5**, **6**, **7**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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