JOC*Note*

Short Synthesis of Enantiopure C_2-Symmetric 1,2:4,5-Diepoxypentane and "*Pseudo*"-C_2-Symmetric 3-Azido-1,2:4,5-diepoxypentane from Arabitol

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Abstract: On the basis of our previously described selective protection of arabitol as its 1,2:4,5-bis-pentylidene acetal **5**, we report a straightforward synthesis of the novel "*pseudo*"-C_2-symmetric 3-azido-1,2:4,5-diepoxypentane building block **4** in 6 steps from arabitol. Using a similar synthetic route, an improved synthesis of the C_2-symmetrical 1,2:4,5-bis-epoxypentane building block **1** is described, also in 6 steps from arabitol. Both enantiomers of **1** and **4** are accessible, and all reactions involved are easily amenable for large-scale synthesis.

Small symmetric bifunctional building blocks are useful starting materials in synthetic organic chemistry, especially when available in both enantiomeric forms. Due to their versatile reactivity, symmetric bis-epoxides are frequently used as starting materials or intermediates in bidirectional synthesis[1−3] and also in traditional organic synthesis.[2a,4] Very few enantiopure symmetric bis-epoxides are commercially available, and the development of efficient methods for the large-scale synthesis of small, symmetric bis-epoxides in both enantiomeric forms from cheap, commercially available starting materials is of interest.

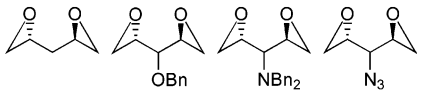

FIGURE 1. C_2-Symmetric and "*pseudo*"-C_2-symmetric 1,4-bis-epoxides.

Given the abundance of the 1,3-diol motif in natural products, 1,4-bis-epoxides such as **1**[2,4] and **2**[3] (Figure 1) have been extensively used as starting materials. Rychnovsky reported the synthesis of **1** in 3 synthetic steps from 2,4-pentanedione based on an enantioselective reduction using Noyori's asymmetric hydrogenation catalyst, which after recrystallization of an intermediate gave **1** (>97% ee) in 21% overall yield.[2a,5] An alternative route based on D-ribonic acid γ-lactone as a starting material for the synthesis of (*R*,*R*)-**1** was developed by Ley in 8 steps with a 21% overall yield,[4a] and subsequently improved by Jung, who obtained an overall yield of 30%.[2b] Both methods are frequently used and Jung reported that they gave similar results in terms of efficiency when employed on lab scale,[2b] although Rychnovksy claimed that partial racemization was observed in the route from the ribonic acid lactone.[2a] In addition, the D-ribonic acid γ-lactone method is confined to the (*R*,*R*) enantiomer of **1** as the starting material is only available in one enantiomeric form. Nakata recently communicated the synthesis of **1** starting from arabitol, for which both enantiomers are available at similar cost, in 6 steps in 28% overall yield.[4c] The synthesis of **2** also starts from arabitol, and has been described by Schreiber[3a] (3 steps, 45% yield) and Dreyer[3c] (2 steps, 30% yield). The corresponding 3-*O*-*tert*-butyldimethylsilyl silyl ether is also available through similar methodology (3 steps, 57%).[3b] The synthesis of both enantiomers of **3** has been reported from L-serine methyl ester, and required 8 steps for (2*R*,4*R*)-**3** and 11 steps for (2*S*,4*S*)-**3**.[6]

We have recently described a practical large-scale protection reaction of arabitol to its "*pseudo*"-C_2-symmetric 1,2:4,5-bis-pentylidene acetal (see below).[7] On the basis of this work, we wish to report here the preparation of the novel N-containing 1,4-bis-epoxide building block **4**. It would be a useful alternative for **3**, for which the use in its synthesis of alkyllithium reagents at very low temperature is a handicap for practical large-scale preparation. The azido group was recently singled out by Sharpless as a very useful functional group in "click-

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(1) (a) Holland, J. M.; Lewis, M.; Nelson, A. *J. Org. Chem.* **2003**, *68*, 747−753. (b) Gravier-Pelletier, C.; Andriuzzi, O.; Le Merrer, Y. *Tetrahedron Lett.* **2002**, *43*, 245−248. (c) Star, A.; Goldberg, I.; Fuchs, B. *Eur. J. Org. Chem.* **2001**, 729−734. (d) Mukai, C.; Kasamatsu, E.; Ohyama, T.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 737−744. (e) Morimoto, Y.; Iwai, T.; Kinoshita, T. *J. Am. Chem. Soc.* **1999**, *121*, 6792−6797. (f) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801−1802. (g) Brånalt, J.; Kvarnström, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1996**, *61*, 3611−3615. (h) Nugiel, D. A.; Jacobs, K.; Cornelius, L.; Chang, C.-H.; Jadhav, P. K.; Holler, E. R.; Klabe, R. M.; Bacheler, L. T.; Cordova, B.; Garber, S.; Reid, C.; Logue, K. A.; Gorey-Feret, L. J.; Lam, G. N.; Erickson-Viitanen, S.; Seitz, S. P. *J. Med. Chem.* **1997**, *40*, 1465−1474. (i) Wagner, H.; Koert, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1873−1875. (j) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369−9371. (k) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1991**, *56*, 1386−1393. (l) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 4718−4720. (m) Hatakeyama, S.; Sakurai, K.; Saijo, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 1333−1336. (n) Tzuzuki, K.; Nakajima, Y.; Watanabe, T.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1978**, *11*, 989−992.

(2) (a) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161−5169. (b) Jung, M. E.; Kretschik, O. *J. Org. Chem.* **1998**, *63*, 2975−2981. (c) Smith, A. B., III; Pitram, S. M. *Org. Lett.* **1999**, *1*, 2001−2004. (d) Van de Weghe, P.; Aoun, D.; Boiteau, J.-G.; Eustache, J. *Org. Lett.* **2002**, *4*, 4105−4108.

(3) (a) Schreiber, S. L.; Sammakia, T.; Uehling, D. E. *J. Org. Chem.* **1989**, *54*, 15−16. (b) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583−5601. (c) Dreyer, G. B.; Boehm, J. C.; Chenera, B.; DesJarlais, R. L.; Hassell, A. M.; Meek, T. D.; Tomaszek, T. A., Jr. *Biochemistry* **1993**, *32*, 937−947.

(4) (a) Ley, S. V.; Anthony, N. J.; Armstrong, A.; Brasca, M. G.; Clarke, T.; Culshaw, D.; Greck, C.; Grice, P.; Jones, A. B.; Lygo, B.; Madin, A.; Sheppard, R. N.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1989**, *45*, 7161−7194. (b) Zhou, S.-Z.; Anné, S.; Vandewalle, M. *Tetrahedron Lett.* **1996**, *37*, 7637−7640. (c) Terauchi, T.; Terauchi, T.; Sato, I.; Tsukada, T.; Kanoh, N.; Nakata, M. *Tetrahedron Lett.* **2000**, *41*, 2649−2653.

(5) Rychnovsky, S. D.; Griesgraber, G.; Powers, J. P. *Org. Synth.* **2000**, *77*, 1−11.

(6) Concellón, J. M.; Riego, E.; Rodríguez-Solla, H.; Plutín, A. M. *J. Org. Chem.* **2001**, *66*, 8661−8665.

(7) Linclau, B.; Boydell, A. J.; Clarke, P. J.; Horan, R.; Jacquet, C. *J. Org. Chem.* **2003**, *68*, 1821−1826.

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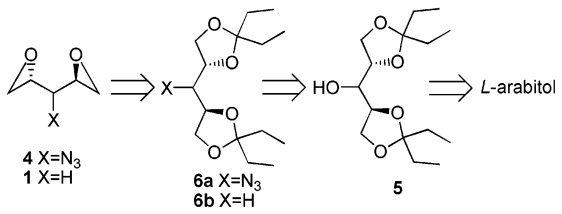
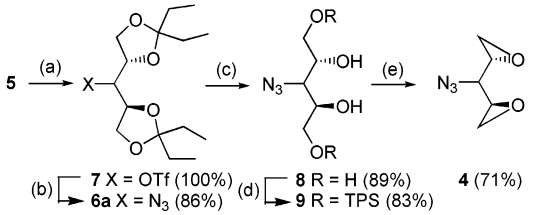
SCHEME 1. Retrosynthetic Analysis for the Synthesis of the Bis-epoxides



SCHEME 2. Synthesis of 4[a]



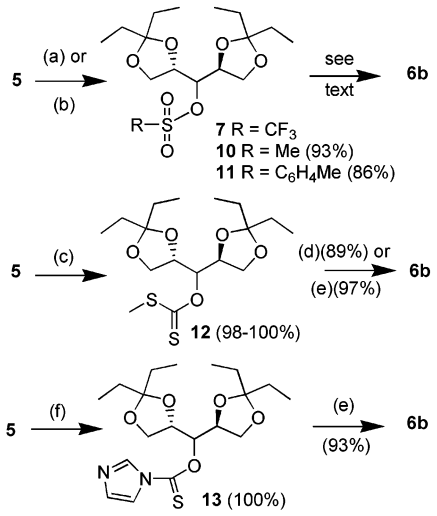
[a] Conditions and reagents: (a) Tf_2O, pyridine, 0 °C, 2.5 h. (b) NaN_3, DMF, rt, 3 h; $Br_2/H_2O/CH_2Cl_2$, 10 min, rt. (c) CSA, MeOH, reflux, 2.5 h. (d) TPSCl, pyridine, rt, 16 h. (e) NaH, Et_2O, rt, 16 h.

chemistry".[8] We also wish to report an improved preparation of **1**, based on the aforementioned arabitol protection reaction. Though strategically analogous, our synthetic methodology differs significantly from Nakata's work,[4c] with a main improvement being the use of tin-free conditions for the reduction of the arabitol 3-OH group.

The synthesis of the 1,4-bis-epoxides fits in a common retrosynthetic analysis (Scheme 1), with the "*pseudo*"-C_2-symmetric alcohol **5** as the central intermediate. The bis-acetal **5** can be prepared in one step from arabitol in excellent yield, although it is the thermodynamically less stable regioisomer. We have reported a kinetic protection of arabitol (80% yield, 74% on large scale),[7] including a scavenger workup to easily remove the minor 2,3:4,5-bis-pentylidene acetal byproduct. Maleczka has communicated a yield of 90% for this transformation.[9] In Nakata's synthesis of **1**,[4c] arabitol was protected as the 1,2:4,5-bis-acetonide, but no exact yield was given. The central hydroxyl group in **5** is subsequently transformed to **6** by functional group transformations**.** Finally, the protected diol units in **6** are converted into epoxide groups.

The synthesis of 1,4-bis-epoxide **4** is shown in Scheme 2. Conversion of **5** into triflate **7** under standard conditions proceeded in quantitative yield. The triflate **7** was relatively unstable, and could only be stored at −25 °C for up to 2 weeks. Nucleophilic substitution with azide led to **6a**, but was accompanied by a small amount of elimination byproduct (mixture of two diastereoisomers, not shown). As azide **6** and the alkene byproducts had identical R_f values, no efforts were undertaken regarding their separation by chromatography. Instead, a "chemical cleanup" was successfully employed in which the crude material was treated with a Br_2/water mixture, which, after workup, yielded the desired **6a** as a pure compound. Deprotection of the alcohol groups was followed by selective conversion of the primary alcohol groups to the corresponding 2,4,6-triisopropylbenzenesulfonates (TPS), leading to **9**. Finally, intramolecular sulfonate displacement led to the formation of the desired bis-epoxide **4** in good yield.

SCHEME 3.[10] **Deoxygenation Attempts**[a]



[a] Conditions and reagents: (a) MsCl, Et_3N, DCM, rt, 16 h. (b) TsCl, DABCO, DCM, rt, 16 h. (c) NaH, CS_2, THF, rt, 20 h.; MeI, rt, 6 h. (d) Bu_3SnH, AIBN, toluene, reflux, 4 h. (e) Et_3SiH, Bz_2O_2, reflux, 2 h. (f) Im_2CS, 1,2-dichloroethane, reflux, 6 h.

The synthesis of **1** from **5** requires reduction of the central hydroxyl group. We first investigated nucleophilic displacement of sulfonates with hydride reagents (Scheme 3). Treatment of the tosylate **11** with $LiAlH_4$ led to the formation of **5** as the only product in 47% yield (rt) or 52% yield (reflux, THF), indicating attack on sulfur. Attempted reduction of the mesylate **10** with $LiEt_3BH$ only returned starting material. When the triflate **7** was reacted with $LiEt_3BH$, a mixture of the desired **6b** and **5** was always obtained (ratio **6b**:**5** 1:1.5 (rt); 1:2.6 (−10 °C); complete conversion). With higher temperatures (40 °C), only **5** and elimination products were obtained

With the sulfonate displacement attempts being unsuccessful, we turned to radical deoxygenation reactions. Reacting the xanthate **12** under standard Barton−McCombie deoxygenation conditions with stoichiometric tributyl tin hydride,[11] analogous as in Nakata's synthesis of **1**,[4c] accomplished the reduction in excellent yield. Prompted not only by the toxicity of the alkyltin chemicals but also because of the rather difficult workup process on large scale, we decided to investigate other radical deoxygenation conditions.[12] We were delighted to find that reduction of the xanthate **12** with Et_3SiH/benzoyl peroxide[12b] proceeded in even better yield compared to tin hydride conditions. However, we found on some occasions that the synthesis of the xanthate **12** on large scale was difficult to drive to completion, and required additional amounts of NaH. To avoid such complications, we switched to the synthesis of the imi-

(8) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599. (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.

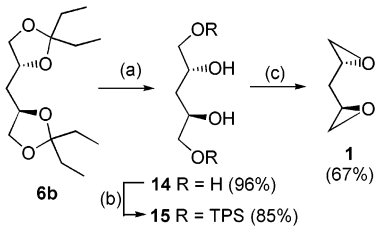
(9) Maleczka, R. E., Jr.; Terrell, L. R.; Geng, F.; Ward, J. S., III *Org. Lett.* **2002**, *4*, 2841−2844.

(10) For some of the experiments, the corresponding enantiomers were used. For reasons of clarity, this is not reflected in the text and the schemes.

(11) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

(12) (a) Review: Studer, A.; Amrein, S. *Synthesis* **2002**, 835−849. (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1991**, *32*, 7187−7190.

SCHEME 4.[10] Completion of the Synthesis of 1



[a] Conditions and reagents: (a) 0.5 M H_2SO_4, EtOH, reflux, 4 h. (b) TPSCl, pyridine, rt, 16 h. (c) NaH, THF, 1 h.

dazolyl thiocarbonyl group as a xanthate alternative, since no prior alcohol deprotonation was now required.[11] In the event, the imidazolyl thiocarbonyl derivative **13** was easily prepared in quantitative yield, and reduction under identical Et_3SiH/Bz_2O_2 conditions led to **6b** in equally good yield.

With the reduction accomplished, the subsequent synthesis to **1** was very straightforward (Scheme 4). Deprotection of **6b** led to the C_2-symmetric tetrol **14**, a known precursor for **1**.[2b,4a,c] Following Jung's synthesis,[2b] the bis-sulfonate **15** was prepared according to a slightly modified literature procedure.[13] Subsequently, bis-cyclization with NaH in THF as described gave the desired C_2-symmetric bis-epoxide **1** in 67% yield.

In summary, we have achieved the synthesis of the novel 1,2:4,5-diepoxy-3-azidopentane building block **4** from 1,2:4,5-bis-pentylidene protected arabitol **5** in 5 steps (45% overall yield). From **5**, the known 1,2:4,5-diepoxypentane building block **1** was synthesized in 5 steps (51% overall yield). All steps involved are experimentally straightforward and easily accomplished on multigram scale.

Experimental Section[14]

(2*S*,4*S*)-Di-*O*-(3,3-pentylidene)-3-*O*-trifluoromethylsulfonylarabitol (7). To a solution of pyridine (6.5 mL, 80.6 mmol) in CH_2Cl_2 (24 mL) at −40 °C was added triflic anhydride (11.6 mL, 69.1 mmol) with stirring for 10 min. A solution of **5** (16.60 g, 57.6 mmol) in CH_2Cl_2 (80 mL) was added dropwise via cannula over 5 min. The reaction mixture was then warmed to room temperature, recooled, and stirred for 2.5 h at 0 °C. The reaction mixture was then filtered through Celite washing with cold CH_2Cl_2 (50 mL), and evaporated to give an orange oil. Purification by chromatography (hexane/EtOAc 90:10) yielded a yellow oil (24.20 g, 100%). $[\alpha]_D$ −13.6 (*c* 1.64, $CHCl_3$, 25 °C); IR 2976 (m), 2944 (m), 2886 (m), 1414 (s), 1208 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.89 (1H, m), 4.28 (1H, dt, J = 7.4, 6.5 Hz), 4.22−4.12 (3H, m), 3.90 (1H, m), 3.83 (1H, dd, J = 8.7, 7.4 Hz), 1.71−1.60 (8H, m), 0.95−0.87 (12H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 118.4 (C, q, J = 319 Hz), 114.3 (C), 114.1 (C), 86.4 (CH), 74.7 (CH), 74.2 (CH), 66.1 (CH_2), 66.0 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 28.3 (CH_2), 8.2 (CH_3), 8.0 (CH_3), 7.9 (CH_3), 7.8 (CH_3) ppm; ^{19}F NMR (282 MHz, $CDCl_3$, C_6F_6) δ 87.6 ppm; EIMS, *m*/*z* (%) 391 ($(M - C_2H_5)^+$, 34), 305 (100); HRMS (EI) calcd for $C_{14}H_{22}O_7F_3S$ $(M - C_2H_5)^+$ 391. 1038, found 391.1046.

(2*R*,4*R*)-Di-*O*-(3,3-pentylidene)-3-deoxy-3-azidoarabitol (6a). To a solution of **7** (3.31 g, 7.87 mmol) in DMF (20 mL) was added NaN_3 (1.02 g, 15.7 mmol) with stirring for 3 h at room temperature. The reaction mixture was added to a mixture of bromine/water (0.3 mL of Br_2 in 30 mL of H_2O) and CH_2Cl_2 (40 mL) and stirred for 10 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated. Purification by chromatography (hexane/EtOAc 90:10) yielded a colorless oil (2.122 g, 86%). $[\alpha]_D$ −9.1 (*c* 1.44, $CHCl_3$, 25 °C); IR 2974 (m), 2941 (m), 2883 (m), 2112 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (1H, dt, J = 7.5, 6.5 Hz), 4.11 (1H, t, J = 5.8 Hz), 4.09 (1H, t, J = 6.0 Hz), 3.99 (1H, m), 3.86 (1H, dd, J = 8.0, 7.0 Hz), 3.83 (1H, t, J = 8.0 Hz), 3.40 (1H, dd, J = 7.3, 6.3 Hz), 1.73−1.57 (8H, m), 0.94−0.85 (12H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.8 (C), 113.3 (C), 77.3 (CH), 75.5 (CH), 67.7 (CH_2), 67.3 (CH_2), 65.2 (CH), 29.6 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 8.10 (2 × CH_3), 8.06 (CH_3), 8.04 (CH_3) ppm; CIMS, *m*/*z* (%) 286 ($(M - N_2)^+$, 100), 256 (23); HRMS (EI) calcd for $C_{13}H_{22}N_3O_4$ $(M - Et)^+$ 284.1610, found 284.1608. Anal. Calcd for $C_{15}H_{27}O_4N_3$: C, 57.49; H, 8.68; N, 13.40. Found: C, 57.34; H, 8.86; N, 13.19.

(2*R*,4*R*)-3-Azido-1,2,4,5-pentanetetrol (8). A stirred solution of **6a** (2.54 g, 8.10 mmol) and camphorsulfonic acid (CSA) (282 mg, 1.21 mmol) in MeOH (25 mL) was heated under reflux for 2.5 h. The mixture was then allowed to cool to room temperature. $NaHCO_3$ was then added until the solution was neutral, and the mixture was dried over Na_2SO_4 and filtered. The solids were collected and stirred with MeOH (30 mL) for 30 min and then filtered. The filtrates were then combined and concentrated in vacuo to give a pale yellow oil. Purification by chromatography (DCM/MeOH 80:20) yielded a viscous pale yellow oil (1.282 g, 89%). $[\alpha]_D$ +4.4 (*c* 0.59, MeOH, 25 °C); IR 3385 (br s), 2941 (w), 2887 (w), 2111 (s) cm^{-1}; ^1H NMR (400 MHz, d^6-acetone) δ 4.51 (1H, d, J = 5.5 Hz), 4.36 (1H, d, J = 5.5 Hz), 4.20−4.16 (2H, m), 4.08 (1H, m), 3.94 (1H, m), 3.80 (1H, dt, J = 11.5, 4.5 Hz), 3.72−3.61 (3H, m), 3.47 (1H, dd, J = 7.5, 2.5 Hz); ^{13}C NMR (100 MHz, d^6-acetone) δ 72.1 (CH), 71.1 (CH), 63.47 (CH), 63.44 (CH_2), 63.38 (CH_2) ppm; EIMS, *m*/*z* (%) 178 ($(M + H)^+$ 2), 61 (100); HRMS (ES^+) calcd for $C_{10}H_{22}N_6O_8Na$ $(2M + Na)^+$ 377.1391, found 377.1385.

(2*R*,4*R*)-3-Azido-2,4-dihydroxypentane-1,5-diyl Bis-(2,4,6-triisopropyl-1-benzenesulfonate) (9). To a solution of **8** (1.40 g, 7.90 mmol) in pyridine (20 mL) at 5 °C was added 2,4,6-triisopropylbenzenesulfonyl chloride (5.26 g, 17.4 mmol) with stirring at room temperature for 18 h. Pyridine was removed on a high-vacuum rotary evaporator to give a dark orange residue. Purification by chromatography (hexane/acetone 80:20) yielded a colorless solid (4.648 g, 83%). Mp 117−118 °C (acetone/hexane); $[\alpha]_D$ +1.9 (*c* 1.03, $CHCl_3$, 25 °C); IR 3511 (br m), 2961 (s), 2931 (m), 2871 (m), 2107 (s), 1178 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (2H, s), 7.21 (2H, s), 4.37−4.34 (2H, m), 4.25−4.05 (8H, m), 3.43 (1H, dd, J = 7.8, 2.3 Hz), 3.18 (1H, d, J = 5.7 Hz), 2.98−2.88 (3H, m), 1.28 (12H, d, J = 7.0 Hz), 1.27 (24H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3 (C), 154.2 (C), 150.99 (2 × C), 150.96 (2 × C), 128.7 (C), 128.6 (C), 123.97 (2 × CH), 123.94 (2 × CH), 70.2 (CH), 69.6 (CH), 69.3 (CH_2), 68.9 (CH_2), 61.9 (CH), 34.3 (2 × CH), 29.72 (2 × CH), 29.68 (2 × CH), 24.7 (8 × CH_3), 23.5 (4 × CH_3) ppm; ES^+, *m*/*z* (%) 732 ($(M + Na)^+$, 100); HRMS (ES^+) calcd for $C_{35}H_{55}N_3O_8S_2Na$ $(M + Na)^+$ 732.3323, found 732.3329. Anal. Calcd for $C_{35}H_{55}O_8N_3S_2$: C, 59.21; H, 7.81; N, 5.92. Found: C, 59.37; H, 8.03; N, 5.91.

(2*R*,4*R*)-3-Azido-1,2:4,5-diepoxypentane (4). Sodium hydride (2.26 g, 56.3 mmol, 60% suspension) was washed with dry hexane (3 × 20 mL) and added to a stirred solution of **9** (4.00 g, 5.63 mmol) in Et_2O (50 mL). The mixture was stirred at room temperature for 16 h and filtered over anhydrous $MgSO_4$ (2-cm pad, washed with Et_2O (50 mL)). The solids were stirred with Et_2O (100 mL) and filtered again. The filtrate was concentrated to a volume of ∼20 mL on a rotary evaporator. Purification by chromatography (hexane/acetone 80:20) was followed by distillation, using a short vigreux column (102 °C, 16 mmHg), and yielded a colorless oil (565 mg, 71%). $[\alpha]_D$ +52.5 (*c* 0.65, $CHCl_3$, 25 °C); IR 3067 (w), 3002 (m), 2106 (s), 1254 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.22−3.15 (3H, m), 2.90−2.88 (2H, m) 2.82 (1H, dd, J = 5.0, 2.5 Hz), 2.77 (1H, dd, J = 5.0, 2.0 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.8 (CH), 51.7 (CH), 50.6 (CH), 44.9 (CH_2), 44.4 (CH_2) ppm; CIMS, *m*/*z* (%) 159.3 ($(M + NH_4)^+$, 30), 114.3 (100); HRMS (EI) calcd for $C_5H_7N_3O_2$ $(M)^+$ 141.0538, found 141.0536.

(13) Attwood, S. V.; Barrett, A. G. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1315−1322.

(14) For general conditions: see Supporting Information.

(2*R*,4*R*)-Di-*O*-(3,3-pentylidene)-3-*O*[(methylthio)thiocarbonyl]arabitol (*ent*-12). To a solution of *ent*-**5** (12.03 g, 41.7 mmol) in THF (150 mL) and CS_2 (32.0 mL, 0.53 mol) at 0 °C was added NaH (2.0 g of a 60% dispersion in mineral oil, 50 mmol) and the reaction was stirred for 1 h at 0 °C. After being stirred overnight at room temperature, the reaction was cooled to 0 °C and MeI (3.3 mL, 54.21 mmol) was added. The reaction was warmed to room temperature and stirred for 6 h, then quenched by the slow addition of saturated aqueous NH_4Cl (200 mL) followed by diethyl ether (200 mL). The aqueous phase was extracted with diethyl ether (2 × 200 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification by chromatography (hexane/ethyl acetate 9:1) yielded a yellow oil (15.47 g, 98%). $[\alpha]_D$ +56.1 (*c* 0.53, $CHCl_3$, 20 °C); IR 2973 (s), 2940 (s), 2882 (m), 1463 (m), 1357 (w), 1209 (s), 1077 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.14 (1H, dd, J = 5.8, 2.8 Hz), 4.45−4.38 (2H, m), 4.11 (1H, dd, J = 8.8, 6.3 Hz), 4.03 (1H, dd, J = 8.3, 6.8 Hz), 4.00 (1H, dd, J = 8.8, 6.3 Hz), 3.70 (1H, t, J = 8.0 Hz), 2.60 (3H, s), 1.71−1.57 (8H, m), 0.95−0.87 (12H, m) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.2 (C), 113.3 (C), 113.2 (C), 79.4 (CH), 75.6 (CH), 75.4 (CH), 66.4 (CH_2), 65.6 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 28.95 (CH_2), 19.3 (CH_3), 8.09 (2 × CH_3), 8.05 (2 × CH_3) ppm; CIMS *m*/*z* (%) 349 ((M − Et)$^+$, 36), 293 (100), 263 (46), 241 (66); HRMS (ES$^+$) calcd for $C_{17}H_{30}O_5S_2Na$ (M + Na)$^+$ 401.1427, found 401.1426. Data for **12**: $[\alpha]_D$ −56.1 (*c* 0.60, $CHCl_3$, 20 °C); ^1H and ^{13}C NMR, CIMS and IR data correspond to those for *ent*-**12**; HRMS (ES$^+$) calcd for $C_{17}H_{30}O_5S_2Na$ (M + Na)$^+$ 401.14269, found 401.14267.

(2*R*,4*R*)-1,2:4,5-Di-*O*-(3,3-pentylidene)-3-*O*-[(*N*-imidazolyl)-thiocarbonyl]arabitol (*ent*-13). To a solution of *ent*-**5** (2.0 g, 6.94 mmol) in dry 1,2-dichloroethane (25 mL) was added *N*,*N*′-thiocarbonyldi-imidazole (2.16 g, 12.14 mmol) and the mixture was stirred for 6 h at reflux. The resultant orange/brown solution was concentrated in vacuo and purified by chromatography (hexane/EtOAc 85:15) to give a yellow oil (2.76 g, 100%). $[\alpha]_D$ +40.8 (*c* 0.90, $CHCl_3$, 23 °C); IR 3127 (w), 2973 (s), 2940 (s), 2882 (s), 1532 (m), 1464 (s), 1390 (s), 1080 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, s), 7.64 (1H, m), 7.06 (1H, m), 6.04 (1H, dd, J = 5.0, 3.5 Hz), 4.48−4.41 (2H, m), 4.15 (1H, dd, J = 8.8, 6.5 Hz), 4.10 (1H, dd, J = 8.7, 6.6 Hz), 4.04 (1H, dd, J = 8.8, 6.8 Hz), 3.74 (1H, t, J = 8.2 Hz), 1.69−1.45 (8H, m), 0.895 (3H, t, J = 7.4 Hz), 0.888 (3H, t, J = 7.5 Hz), 0.882 (3H, t, J = 7.5 Hz), 0.77 (3H, t, J = 7.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5 (C), 137.1 (CH), 131.1 (CH), 118.0 (CH), 113.5 (C), 113.4 (C), 80.1 (CH), 75.6 (CH), 75.1 (CH), 66.1 (CH_2), 65.5 (CH_2), 29.4 (2 × CH_2), 28.6 (2 × CH_2), 8.2 (CH_3), 8.1 (CH_3), 8.0 (CH_3), 7.7 (CH_3) ppm; CIMS *m*/*z* (%) 421.3 ((M + Na)$^+$, 12), 399.2 (100); HRMS (ES$^+$) calcd for $C_{19}H_{30}N_2O_5S$ (M + H)$^+$ 399.1948, found 399.1949.

(2*S*,4*S*)-Di-*O*-(3,3-pentylidene)-3-deoxyarabitol (*ent*-6b). (A) Tin hydride reduction of *ent*-12: AIBN (0.4 g, 2.5 mmol) and **11** (23.25 g, 61.42 mmol) were dissolved in degassed toluene (350 mL). Bu_3SnH (18.50 mL, 67.56 mmol) was added and the reaction was refluxed for 4 h. The reaction was allowed to cool, and concentrated in vacuo. Purification by chromatography (hexane/EtOAc 9:1) yielded *ent*-**6b** as a colorless oil (14.92 g, 89%). $[\alpha]_D$ +10.0 (*c* 0.46, $CHCl_3$, 20 °C); IR 2973 (s), 2941 (s), 2881 (s), 1173 (s), 1078 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (2H, ddd, J = 12.3, 7.7, 6.3 Hz), 4.11 (2H, dd, J = 7.8, 6.0 Hz), 3.52 (2H, t, J = 7.8 Hz), 1.81 (2H, t, J = 6.4 Hz), 1.67−1.58 (8H, m), 0.894 (6H, t, J = 7.4 Hz), 0.891 (6H, t, J = 7.4 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.6 (2 × C), 74.0 (2 × CH), 70.5 (2 × CH_2), 37.7 (CH_2), 29.9 (2 × CH_2), 29.7 (2 × CH_2), 8.2 (2 × CH_3), 8.0 (2 × CH_3) ppm; CIMS, *m*/*z* (%) 273 ((M + H)$^+$, 30), 243 (22), 157 (100). Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.43; H, 10.23. Data for **6b**: $[\alpha]_D$ −11.5 (*c* 0.60, $CHCl_3$, 20 °C). Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 66.20; H, 10.08. ^1H and ^{13}C NMR, CIMS, and IR data all correspond to that for *ent*-**6b**.

(B) Silane reduction of *ent*-12: To ***ent*-12** (2.0 g, 5.28 mmol) was added Et_3SiH (40 mL, 0.25 mol) and the reaction was brought to reflux. Benzoyl peroxide (0.26 g, 1.1 mmol) was added and the reaction refluxed for 2 h, with a similar quantity added after 30, 60, and 90 min. The solvent was then removed in vacuo and the crude material purified by chromatography (hexane/EtOAc 95:5). A second purification by chromatography was required, which yielded *ent*-**6b** as a colorless oil (1.39 g, 97%).

(C) Reduction of *ent*-13: As above for *ent*-**12**. *ent*-**13** (2.0 g, 5.02 mmol), Et_3SiH (38 mL, 0.24 mol), Bz_2O_2 (0.24 g, 1.0 mmol). Yield 1.27 g (93%).

(2*S*,4*S*)-Pentane-1,2,4,5-tetraol (*ent*-14). To a stirred solution of *ent*-**6b** (10.65 g, 39.11 mmol) in ethanol (50 mL) was added aqueous 0.5 M H_2SO_4 (50 mL) and the reaction was stirred at reflux for 4 h. The reaction was quenched by addition of powdered $BaCO_3$ until neutral. After stirring at reflux for another 10 min the reaction mixture was cooled and filtered. The residue was stirred again with hot methanol, filtered, and washed with methanol. The filtrate was concentrated in vacuo to give a white solid. This was purified by chromatography (CH_2Cl_2/MeOH 7:3) to give a white solid (5.092 g, 96%). Mp 104−106 °C (EtOH/hexane) [lit.[13] mp 106−107 °C]; $[\alpha]_D$ −47.7 (*c* 0.5, EtOH, 20 °C) [lit.[13] $[\alpha]_D$ −46.0 (*c* 1.03, EtOH, 22 °C)]; the ^1H and ^{13}C NMR spectra corresponded to the literature values.[13] Data for **14**: mp 105−107 °C; $[\alpha]_D$ +47.2 (*c* 0.4, EtOH, 20 °C); the ^1H and ^{13}C NMR correspond to those of *ent*-**14**.

(2*S*,4*S*)-2,4-Dihydroxypentane-1,5-diyl Bis-(2,4,6-triisopropyl-1-benzenesulfonate) (*ent*-15). To a stirred solution of *ent*-**14** (2.5 g, 18.36 mmol) in dry pyridine (22 mL) at 0 °C was added 2,4,6-tri-isopropyl benzenesulfonyl chloride (12.24 g, 40.41 mmol). The reaction was stirred overnight at room temperature and the solvent removed under high vacuum rotary evaporation. The resulting pale yellow solid was purified by chromatography (hexane/acetone 75:25) to give a white solid. Recrystallization (CH_2Cl_2/hexane) gave a fluffy white solid (10.43 g, 85%). Mp 154−156 °C (CH_2Cl_2/hexane) [lit.[13] mp 154−155 °C (CH_2Cl_2/light petroleum)]; $[\alpha]_D$ −7.5 (*c* 0.6, EtOH, 20 °C) [lit.[13] $[\alpha]_D$ −8.8 (*c* 0.2, EtOH, 22 °C)]; the ^1H and ^{13}C NMR spectra corresponded to the literature values.[13] Data for **15**: mp 153−154 °C (CH_2Cl_2/hexane); $[\alpha]_D$ +7.7 (*c* 0.4, EtOH, 22 °C); the ^1H and ^{13}C NMR correspond to those of *ent*-**15**.

(2*S*,4*S*)-1,2:4,5-Diepoxypentane (*ent*-1). To a stirred solution of *ent*-**15** (14.51 g, 21.7 mmol) in dry THF (600 mL) was added NaH (9.5 g, 60% dispersion in mineral oil, washed with pentane, 0.24 mol) and the reaction was stirred vigorously for 1 h. The reaction was then filtered through $MgSO_4$ and washed with pentane, and the solvent was removed by fractional distillation yielding a yellow slurry. Purification by chromatography (diethyl ether/pentane 4:1) and subsequent concentration by distillation gave a colorless oil that was purified by Kugelrohr distillation (90 °C, 18 mmHg) to yield a colorless oil (1.46 g, 67%). $[\alpha]_D$ −56.5 (*c* 0.6, $CHCl_3$, 20 °C) [lit.[2a] $[\alpha]_D$ −55.5 (*c* 0.92, $CHCl_3$)]; the ^1H and ^{13}C NMR spectra corresponded to the literature values. Data for **1**: $[\alpha]_D$ +55.9 (*c* 0.6, $CHCl_3$, 20 °C) [lit.[2a] $[\alpha]_D$ +57.6 (*c* 2.2, $CHCl_3$)]; the ^1H and ^{13}C NMR spectra corresponded to the literature values.[2a]

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all novel compounds. Experimental procedures and characterization for compounds **10** and ***ent*-11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The United Kingdom Database Service. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.