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Stereoselective Synthesis of Skipped Polyols by Substrate-Directed Asymmetric Induction

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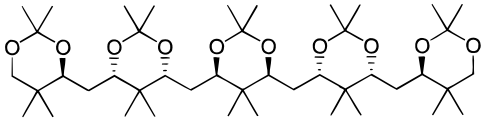
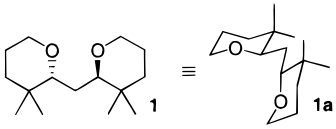
ABSTRACT



A series of C_2- or σ-symmetric oligo-1,3-dioxanylmethanes, 2–5, have been prepared using a bidirectional approach. In bidirectional syntheses of *meso* compounds, only substrate-based asymmetric induction could be applied. 1,3-Asymmetric induction in Mukaiyama-aldol additions, 1,5-asymmetric induction in enol–borinate aldol reactions, and 1,3-*anti*-selective reduction of aldols turned out to be reliable tools in the preparation of compounds 3–5.

In the context of conformation design,[1] we are interested in small flexible molecules which populate a single preferred conformation. For instance, for compound **1**, conformation **1a** (Scheme 1) has been estimated to be populated to >95%.[2]

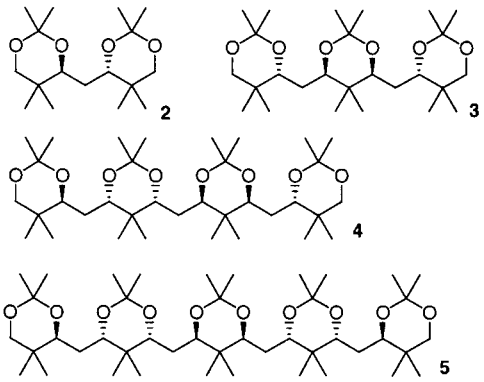
Scheme 1. Preferred Conformation of a Ditetrahydropyranylmethane



The key structural element is the *gem*-dimethyl group, which causes any other diamond lattice type conformaton than **1a** to be destabilized by two *syn*-pentane interactions.

The marked conformational preference in **1** should allow the combination of several such modules with one another to reach larger molecular entities, which should maintain conformational flexibility on one side and the preference to populate a single conformation, i.e., to adopt a distinct shape, on the other side.[3] In initiating such a study, synthetic accessibility is a key issue. For this reason we turned our attention to the related oligo-1,3-dioxanylmethanes **2**−**5** (Scheme 2).

Scheme 2. Target Molecules



By studying the conformational preferences of such a series of compounds, we could explore the limits of a

(1) (a) Hoffmann, R. W. *Angew. Chem.* **1992**, *104*, 1147−1157; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124−1134. (b) Göttlich, R.; Kahrs, B. C.; Krüger, J.; Hoffmann, R. W. *J. Chem. Soc., Chem. Commun.* **1997**, 247−251. (c) Hoffmann, R. W.; Stahl, M.; Schopfer, U.; Frenking, G. *Chem. Eur. J.* **1998**, *4*, 559−566.

(2) Hoffmann, R. W.; Kahrs, B. C.; Schiffer, J.; Fleischhauer, J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2407−2414.

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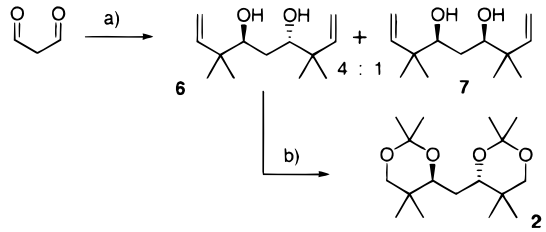
conformation design along those lines. The limits are dictated by a loss in entropy which goes along with adopting a single conformation at every rotatable bond. If an overall conformational preference is to be maintained, the loss of entropy has to be overcompensated by an enthalpy penalty for adopting any undesired conformation. We were confident that the enthalpy penalty inherent in system **1** or **2** would endow compounds **3**−**5** with high conformational preferences. In this paper we report on the synthetic aspects of this project. These are tantamount to the synthesis of 1,3,5, ... *n*-polyhydroxylated alkane chains of a defined configuration. The synthesis of the C_2-symmetric compound **2** is straightforward (see Scheme 3).

Scheme 3. Bidirectional Synthesis of a Bis-dioxanylmethane



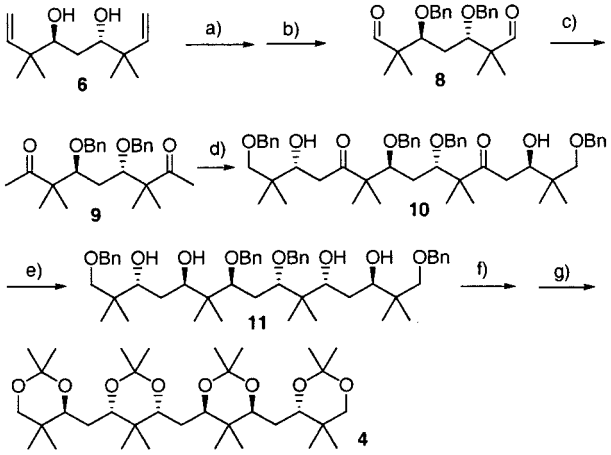
a) Me_2C=CH-CH_2Br, NaI, $SnCl_2$, 4d 0-25°C, DMF, crystallize **6**, 25 %, b) i: O_3, -78°C, CH_3OH, $NaBH_4 \rightarrow$ 0°C; ii: $Me_2C(OMe)_2$, TsOH, acetone, 2d 25°C, 75 %. For characteristic data of **2**, see footnote 12.

Reaction of malonaldehyde with prenyl bromide, sodium iodide, and tin dichloride led to a 4:1 mixture of **6** and **7**, from which *anti*-diol **6** could be crystallized in 25% yield.[2] Ozonolysis and reduction gave a tetraol, which was immediately converted to the racemic bis-acetonide **2**. Because of the C_2-symmetry of the molecule, the protons of the methylene bridge show a higher order coupling pattern. The coupling constants of interest here (J = 10.4 and 1.7 Hz, toluene) were derived by simulation of the coupling pattern. The coupling constants indicate a high conformational preference for adopting a conformation analogous to that of **1a**.

These results encouraged us to continue with the synthesis of the other members, **3**−**5**, of this group. These are symmetrical molecules of either C_2- or σ-symmetry. This suggests the use of bidirectional synthetic strategies.[4] As *meso* compounds with σ-symmetry are targeted, symmetry-related stereogenic centers of opposite absolute configuration have to be created in a bidirectional approach. This prohibits the application of reagent or auxiliary control of stereoselectivity. We found ourselves thus restricted to the use of substrate-directed asymmetric induction, an art which has been used less and less since the days of R. B. Woodward, a master of this genre.

For the synthesis of the "tetramer" **4**, diol **6** was again the starting point (cf. Scheme 4). The diol was protected as the

Scheme 4. Bidirectional Synthesis of the Tetrakis-acetonide **4**



a) NaH, BnBr,$Bu_4N^+I^-$, 15h 0 to 25°C, THF, 71 %; b) i: O_3, -78°C, CH_2Cl_2 , ii: PPh_3 to 0°C, 85 %; c) i: MeMgCl, 5 min -20°C, THF; ii: $(COCl)_2$, DMSO, NEt_3, -78°C, 86%; d) $^cHex_2BCl$, Et_3N, 3h 0°C, Et_2O; then $BnOCH_2C(CH_3)_2CHO$, 3d -90°C, 65 % (4:1 *anti,anti* : *anti,syn*); e) $Me_4N^+(AcO)_3BH^-$, 24h 0 to 25°C, acetone, 80 % (4:1 *anti,anti* : *anti,syn*); f) H_2, $Pd(OH)_2$/C, 1d 25°C, THF, 80 %; g) CH_2=C(Me)OMe, TsOH, 15h 25°C, DMF, 65 %. For characteristic data of **4**, see footnote 12.

dibenzyl ether and converted to dialdehyde **8**. The later was converted to diketone **9** by addition of methyl Grignard, followed by Swern oxidation.

At this stage a boron-mediated aldol addition could be realized[5,6] to give aldol **10**. The product was obtained as a 4:1 *anti,anti:anti,syn* mixture corresponding to a 90% level of 1,5-asymmetric induction. The desired stereoisomer could easily be identified from the ^{13}C NMR spectrum by virtue of its symmetry. The standard[7] *anti*-selective reduction of the aldol moiety with tetramethylammonium triacetoxyborohydride proceeded uneventfully to give tetraol **11**. Hydrogenolytic debenzylation liberated an octaol which was converted to the desired (racemic) tetrakis-acetonide **4** by treatment with 2-methoxypropene and acid.

For *meso* compounds **3** and **5**, a different core molecule, **12**, is needed to start the bidirectional synthesis. The diastereomeric mixture of *syn*- and *anti*-diols **12** is available by allylation of dimethylmalonaldehyde. Separation of the diastereomers was not possible at this stage, but was possible after conversion to monobenzyl ethers **13** (Scheme 5). Rather than discarding the undesired stereoisomer **13b**, it may be converted to **13a** by oxidation to ketone **15** followed by stereoselective reduction.[8] The desired **13a** was then con-

(3) Cf. the design of conformationally preorganized glycoside mimetics: Wei, A.; Haudrechy, A.; Audin, A.; Jun, H.-S.; Haudrechy-Bretel, N.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 2160−2169.

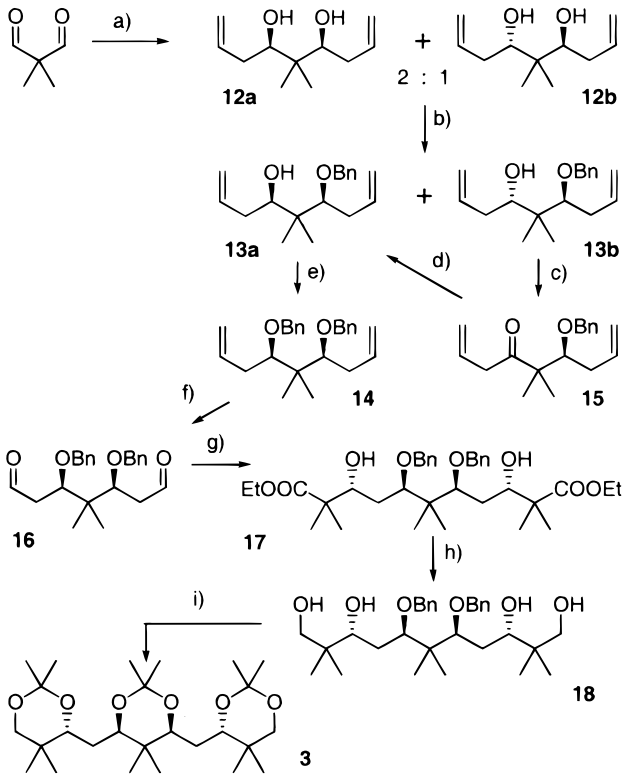
(4) (a) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17. (b) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167−2213.

(5) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588.

(6) Evans, D. A.; Coleman, P. J.; Coté, B. *J. Org. Chem.* **1997**, *62*, 788−789.

(7) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

Scheme 5. Bidirectional Synthesis of the Tris-acetonide **3**

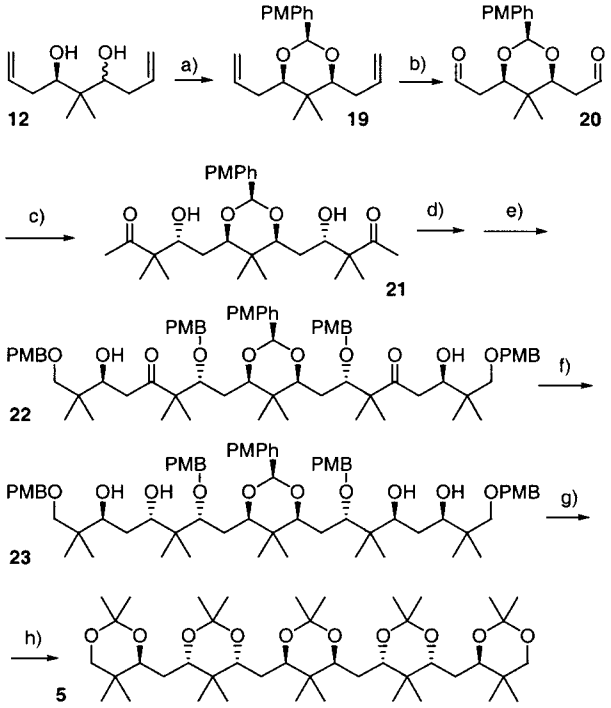


a) CH_2=CH-CH_2Cl, $SnCl_2$, NaI, 6d, 25°C, DMF, 69 %; b) NaH, BnBr, $Bu_4N^+I^-$, 15 h 0-25°C THF/DMF, 57 % **12a**, 28 % **12b**; c) Dess-Martin periodinane, pyridine, 2h 0°C, CH_2Cl_2, 95 %; d) $LiAlH_4$, 18 h -120 to -60 °C, Et_2O/THF, 82%; e) $BnOC(NH)CCl_3$, CF_3SO_3H, 15h 25°C Et_2O, 92 %; f) i: O_3, CH_2Cl_2, -78°C, ii:Ph_3P -78 to 0°C, 88%; g) Me_2C=C(OEt)OTMS, BF_3•OEt_2, 20h -90°C, CH_2Cl_2, 77 %; h) DIBAH, 20h -78°C, CH_2Cl_2, 69%; i) i: H_2, $Pd(OH)_2$, THF; ii: CH_2=C(Me)OMe, TsOH, 4h 25°C, DMF, 80 %. For characteristic data of **3**, see footnote 12.

verted to the symmetrical dibenzyl ether **14**. Ozonolysis of **14** led to dialdehyde **16**, the starting point for further stereoselective elaboration of the molecular skeleton. A $TiCl_4$-mediated chelation-controlled addition of prenyltrimethylsilane to **16** could not be realized, presumably due to the coordination of $TiCl_4$ to the two benzyloxy groups. We then turned to a C−C bond-forming reaction, which does not rely upon chelation control, the 1,3-*anti*-selective Mukaiyama aldol addition using activation by BF_3•OEt_2.[9] We were pleased that this reaction also worked well with silylketene acetals, furnishing in the end diester **17** as a 6:1 diastereomer mixture. The major (symmetrical) product **17** is recognized to be an *anti*-diol derivative according to its ^{13}C NMR shift positons.[10] The diastereomer mixture of **17** was reduced to tetraol **18**, which was obtained diastereomerically pure after chromatography. Debenzylation and acetonization furnished eventually the desired tris-acetonide **3**.

The use of the benzyl ether protection in **16** was chosen in order to follow the precedent set by Evans in the 1,3-*anti*-selective Mukaiyama aldol addition.[9] This required the somewhat lengthy route via monobenzyl ethers **13**. When addressing the synthesis of the larger target **5**, we looked for a more efficient opening of the synthesis (Scheme 6).

Scheme 6. Bidirectional Synthesis of the Pentakis-acetonide **5**



PMPh = p-MeO-C_6H_4-; PMB = p-MeO-$C_6H_4CH_2$-
a) p-MeO-C_6H_4-$CH(OEt)_2$, camphorsulfonic acid, 2h 40°C, CH_2Cl_2, 67 %; b) i: O_3, -78°C, CH_2Cl_2, ii: Ph_3P, to 0°C, 92 %; c) Me_2C=C(Me)OTMS, BF_3•OEt_2, 12h -78°C, CH_2Cl_2, 63 %; d) p-$MeOC_6H_4CH_2OC(NH)CCl_3$, CF_3SO_3H, 2h -20°C, CH_2Cl_2, 69 %; e) $^cHex_2BCl$, NEt_3, 3h 0°C, then $PMBOCH_2C(CH_3)_2CHO$ 5d -90°C, Et_2O, 72 %; f) Me_4N^+ $(AcO)_3BH^-$, 1d, 0°C, acetone, 96 %; g) H_2, $Pd(OH)_2$/C, 4d 25°C, MeOH, 90 %; h) CH_2=C(Me)OMe, TsOH, 18h 25°C, DMF, 52 %; For characteristic data of **5**, see footnote 12.

To this end, we converted the mixture of diols **12** into a mixture of the *p*-methoxybenzylidene acetals, from which σ-symmetric acetal **19** could be readily obtained in 67% yield. Its conversion to dialdehyde **20** was straightforward. The critical point was whether the Mukaiyama aldol addition to give **21** would tolerate the *p*-methoxybenzylidene acetal and whether high asymmetric induction could be reached with this functionality. To our delight, the aldol addition proceeded smoothly when activated by BF_3•OEt_2 and the diastereoselectivity was satisfactory (6:1). The major (symmetrical) diastereomer was obtained pure by chromatography and assigned[10] to have the *anti* configuration.

(8) Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron* **1990**, *46*, 3469−3488.
(9) (a) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537−8540. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.
(10) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3980−3992.

The next chain extension made use of the Paterson/Evans 1,5-asymmetric induction:[5,6] The newly generated hydroxyl functions were first protected as PMB ethers. Conversion of the diketone to the bis-enolborinate was followed by reaction with the appropriate aldehyde to furnish in one step the doubly extended aldol **22** with 5:1 diastereoselectivity. The configuration of the major (symmetrical) diastereomer could be shown to be 1,5-*anti* by the arguments given in the next paragraph. The further elaboration relied on the 1,3-*anti*-selective reduction[7] to give tetraol **23**. Because of the poor solubility of **21** in acetonitrile, a slower reduction in acetone was adopted. The *p*-methoxybenzyl- and -benzylidene groups were removed simultaneously by hydrogenolysis. The resulting decaol could readily be converted to the desired penta-acetonide **5**.

The ^{13}C NMR spectra of **5** showed the presence of only *syn*-acetonides.[11] The reduction of aldol **22** to tetraol **23** should have given an *anti*-1,3-diol.[7] These two statements taken together prove that the aldol addition of **21** to give **22** had generated a 1,5-*anti* arrangement of the oxygen functionalities.

The syntheses described here show that stereodefined skipped polyols can be obtained using solely substrate-based asymmetric induction. The 1,3-asymmetric induction in the Mukaiyama aldol reaction, the 1,5-asymmetric induction in the Paterson/Evans enol borinate aldol addition, and the 1,3-induction in the triacetoxyborohydride reduction of aldols turned out to be reliable tools. Conformational analysis by advanced NMR techniques of the compounds obtained is now in progress and the results will be reported in due course.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (Graduierten-Kolleg "Metallorganische Chemie"), the Volkswagenstiftung, and the Fonds der Chemischen Industrie for support of this study. We thank Dr. B. C. Kahrs for initial experiments toward the synthesis of compounds **2** and **3**.

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(11) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945−948. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7100 The Rychnovsky/Evans rules hold also for 5,5-disubstituted 1,3-dioxanes, see: Pihlaja, K.; Kivimäki, M.; Ari-Matti, M.; Nurmi, T. *J. Org. Chem.* **1982**, *47*, 4688−4692.

(12) Bis[(4*R**)-2,2,5,5-tetramethyl-1,3-dioxan-4-yl]methane (**2**): R_f = 0.35 (20% *tert*-butyl methyl ether in pentane). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.67 (s, 6H), 0.93 (s, 6H), 1.27 (m, 2H), 1.34 (s, 6H), 1.35 (s, 6H), 3.24 (d, J = 11.3 Hz, 2H), 3.50 (d, J = 11.3 Hz, 2H), 3.58 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.0 (2C), 18.8 (2C), 21.6 (2C), 28.7 (2C), 30.0 (2C), 32.4, 72.0 (2C), 72.1 (2C), 98.4 (2C). Anal. Calcd for $C_{17}H_{32}O_4$: C, 67.96; H, 10.74. Found: C, 67.91; H, 10.96. (4*R**,6*S**)-2,2,5,5-Tetramethyl-4-[(4*R**)-2,2,5,5-tetramethyl-1,3-dioxan-4-ylmethyl]-6-[(4*S**)-2,2,5,5-tetramethyl-1,3-dioxan-4-ylmethyl]-1,3-dioxane (**3**): R_f = 0.17 (10% *tert*-butyl methyl ether in pentane). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.70 (s, 9H), 0.81 (s, 3H), 0.99 (s, 6H), 1.34 (ddd, J = 13.6, 9.6, 2.4 Hz, 2H), 1.35 (m, 9H), 1.38 (s, 9H), 1.39 (m, 2H), 3.27 (d, J = 11.3 Hz, 2H), 3.59 (d, J = 11.3 Hz, 2H), 3.62 (dd, J = 9.6, 2.4 Hz, 2H), 3.68 (dd, J = 9.6, 2.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.0, 18.2 (2C), 19.0 (2C), 19.5, 20.5, 21.7 (2C), 28.7 (2C), 29.7 (2C), 30.3, 32.6 (2C), 35.1, 72.4 (2C), 72.6 (2C), 73.3 (2C), 98.2, 98.5 (2C). HRMS (FAB): $C_{26}H_{48}O_6$ requires for ($[M + H]^+$) 457.3529, found 456.3531. (4*R**,6*S**)-2,2,5,5-Tetramethyl-4-[(4*R**)-2,2,5,5-tetramethyl-1,3-dioxan-4-ylmethyl]-6-{(4*S**,6*R**)-2,2,5,5-tetramethyl-6-[(4*R**)-2,2,5,5-tetramethyl-1,3-dioxan-4-ylmethyl]}-1,3-dioxan-4-ylmethyl-1,3-dioxane (**4**): R_f = 0.21 (10% *tert*-butyl methyl ether in pentane). ^1H NMR (500 MHz, C_6D_6): δ = 0.54 (s, 6H), 0.67 (s, 6H), 0.98 (s, 6H), 1.09 (s, 6H), 1.41 (s, 6H), 1.50 (m, 4H), 1.52 (s, 6H), 1.54 (m, 2H), 1.55 (s, 6H), 1.56 (s, 6H), 3.25 (d, J = 11.3 Hz, 2H), 3.51 (d, J = 11.3 Hz, 2H), 3.87 (dd, J = 9.3, 2.8 Hz, 2H), 3.91 (m, 4H). ^{13}C NMR (100 MHz, C_6D_6): δ = 18.2 (2C), 18.4 (2C), 19.2 (2C), 20.5 (2C), 21.5 (2C), 21.7 (2C), 29.4 (2C), 29.5 (2C), 30.1, 30.7 (2C), 32.7 (2C), 35.3 (2C), 72.3 (2C), 73.9 (2C), 74.0 (2C), 74.4 (2C), 74.5 (2C), 98.5 (2C), 98.7 (2C). HRMS (FAB): $C_{35}H_{64}O_8$ requires for ($[M + Na]^+$) 635.4601, found 635.4474. (4*S**,6*R**)-2,2,5,5-Tetramethyl-4-{(4*S**,6*R**)-2,2,5,5-tetramethyl-6-[(4*R**)-2,2,5,5-tetramethyl-1,3-dioxan-4-ylmethyl]-1,3-dioxan-4-ylmethyl-6-(4*R**,6*S**)-2,2,5,5-tetramethyl-6-[(4*S**)-2,2,5,5-tetramethyl-1,3-dioxan-4-ylmethyl]}-1,3-dioxan-4-ylmethyl-1,3-dioxane (**5**): R_f = 0.54 (10% *tert*-butyl methyl ether in pentane). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.65 (s, 6H), 0.75 (s, 6H), 0.77 (s, 6H), 0.78 (s, 3H), 0.81 (s, 6H), 1.15 (s, 3H), 1.15 (s, 3H), 1.16 (s, 6H), 1.17 (s, 6H), 1.21 (s, 6H), 1.22 (s, 6H), 1.49 (m, 4H), 1.51 (m, 4H), 2.96 (d, J = 8.5 Hz, 2H), 3.10 (d, J = 8.5 Hz, 2H), 3.51 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.4 (2C), 18.5 (2C), 18.8, 20.1 (2C), 20.3 (2C), 21.1, 24.5 (2C), 24.6 (2C), 24.7, 24.8 (2C), 26.0 (2C), 28.1 (2C), 28.3 (2C), 28.4, 37.6 (2C), 40.0 (2C), 40.8, 66.6 (2C), 69.8 (2C), 70.1 (2C), 70.2 (2C), 70.4 (2C), 99.5 (2C), 99.8 (2C), 99.9. HRMS (FAB): $C_{44}H_{80}O_{10}$ requires 768.5752, found 768.5414.