On Five- vs Six-membered Diacetal Formation from Threitol and the Intermediacy of Unusually Stable Protonated Species[1]

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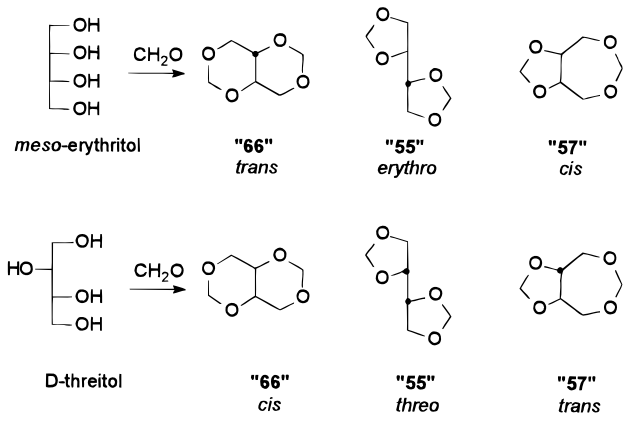
The long known, but hitherto poorly understood, thermodynamically controlled diacetalation of *rac*-threitol with alkylaldehydes provided bicyclic, *cis*-tetraoxadecalin (TOD) ("**66**") and bi(dioxolanyl) (BDO) ("**55**") products, shown to be formed in acid-concentration and temperature-dependent ratio. The configurational and conformational isomeric diacetals obtained in four such reactions of substituted aldehydes (RCHO, R = CH_3, CH_2Cl, CH_2Br, CO_2CH_3) with *rac*-threitol were isolated and characterized. A variable acid-concentration analysis of the equilibrium mixture of products in one such case (R = CH_2Br) was performed and provided equilibrium constants and, hence, free-energy differences among these products and their relatively stable protonated intermediates. The latter were rationalized by the unusually high proton-affinity calculated for the *cis*-TOD ("**66**") form.

Introduction

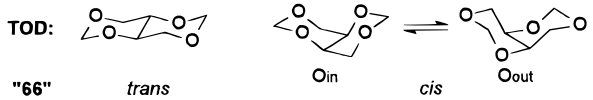
The condensation of a 1,2,3,4-tetrahydroxybutane with formaldehyde under acid catalysis can take place in 1,2;3,4-, 1,3;2,4-, or 1,4;2,3-fashion to give bicyclic diacetals "**55**", "**66**", or "**57**", respectively, which are formed in a stereospecific manner (Scheme 1). The most significant and ubiquitous ones are the "**66**" type compounds, namely, the *trans*- and *cis*-1,3,5,7-tetraoxadecalin (TOD)[6] system (Scheme 2), formed from erythritol or threitol, respectively.[2−6] The conformationally stable form of the *trans* isomer is a configurationally fixed double-chair, while the *cis* isomer can exist in two possible diastereoisomeric chair-chair forms, Oinside ($\mathbf{O_{in}}$) and Ooutside ($\mathbf{O_{out}}$). These can interconvert by conformational ring inversion ($\mathbf{O_{in}} \rightleftharpoons \mathbf{O_{out}}$) (Scheme 2), but bias can be introduced by substitution in the 2,6 positions. Thus, two 2,6-diequatorially substituted $\mathbf{O_{in}}$ and $\mathbf{O_{out}}$ may undergo conformational interconversion only by chemical (acid-catalyzed) isomerization. It was shown that $\mathbf{O_{in}}$ is energetically preferred in the parent molecule and in simply substituted derivatives,[2,6] but purposeful substitution in the 4,8 or 9,10 positions may alter this order of stability.[3−5]

These systems have been studied most in the carbohydrate field,[4,6e,7] where they occur most often. A number of significant contributions have also been made toward the understanding of the stereochemical and conformational features of these, mainly "**66**" diacetals, substituted in the 4(8) or 9(10) positions.[3−6] However, while the erythritol diacetal formation and isomerism had been well investigated,[2,4,7] in particular by Burden and Stoddart,[4] there was no detailed documentation on the isomerism of threitol diacetals. Generally, the reaction

Scheme 1. Stereospecific Reaction Products of Erythritol and *rac*-Threitol with Formaldehyde



Scheme 2. Diastereomeric 1,3,5,7-tetraoxadecalin (TOD) System



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(1) (a) New Supramolecular Host Systems. 12. Part 11: Star, A.; Goldberg, I.; Lemcoff, N. G.; Fuchs, B. *Eur. J. Org. Chem.* **1999**, 2033. (b) We use consistently the 1,3,5,7-tetraoxadecalin nomenclature. Other possible names are *cis*- or *trans*-2,4,7,9-tetraoxabicyclo[4.4.0]decane, 1,3:2,4-di-*O*-methylenethreitol, or (cf. CA) (4a*R*)-(4ar,8ac)-tetrahydro-[1,3]dioxino[5,4-*d*]-1,3-dioxin. Also, due to a minor but basic omission of the CIP rules, one can assign unequivocally configurations to chiral *cis*-decalin systems, only by 9,10-helicity designation, e.g., molecule **3c** is (2*R*,6*R*,9*R*;9,10-*M*)-2,6- bis(bromomethyl)-*cis*-1,3,5,7-tetraoxadecalin.

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(3) (a) Jensen, R. B.; Buchardt, O.; Jørgensen, S. E.; Nielsen, J. U. R.; Schroll, G.; Altona, C. *Acta Chem. Scand. B* **1975** *29B*, 373. (b) Nørskov, L.; Jensen, R. B.; Schroll, G. *Acta Chem. Scand. B* **1983** *37B*, 133 and previous parts in this series.

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(5) Santos, A. G.; Hoffman, R. W. *Tetrahedron: Asymmetry* **1995**, *6*, 2767.

(6) (a) Senderowitz, H.; Linden, A.; Golender, L.; Abramson, S.; Fuchs, B. *Tetrahedron* **1994**, *50*, 9691. (b) Senderowitz, H.; Golender, L.; Fuchs, B. *Tetrahedron* **1994**, *50*, 9707. (c) Abramson, S.; Ashkenazi, E.; Goldberg, I.; Greenwald, M.; Jatzke, H.; Vardi, M.; Weinman, S.; Fuchs, B. *J. Chem. Soc., Chem. Commun.* **1994**, 1611. (d) Frische, K.; Greenwald, M.; Ashkenazi, E.; Lemcoff, N. G.; Abramson, S.; Golender, L.; Fuchs, B. *Tetrahedron Lett.* **1995**, *36*, 9193. (e) Jatzke, H.; Frische, K.; Greenwald, M.; Golender, L.; Fuchs, B. *Tetrahedron* **1997**, *53*, 4821. (f) Grabarnik, M.; Goldberg, I.; Fuchs, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3123. (g) Linden, A.; Beckhaus, H.-D.; Verevkin, S. P.; Rüchardt, Chr.; Ganguly, B.; Fuchs, B. *J. Org. Chem.* **1998**, *63*, 8205.

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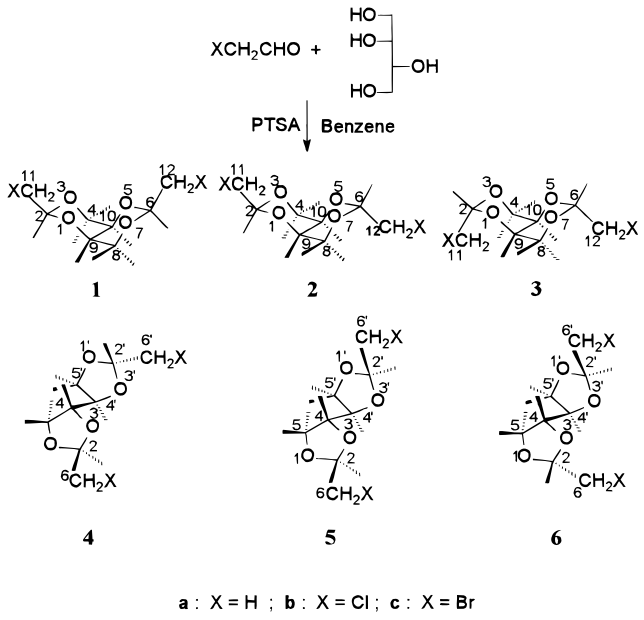
Scheme 3. Acetalation Reaction Products of D-Threitol with Substituted Acetaldehydes



with substituted aldehydes had been commonly taken to be selective, in yielding only 2,6-diequatorially substituted "**66**" acetals in their *cis*-$\mathbf{O_{in}}$ forms, based on the behavior of aromatic aldehydes.

We have been dealing with such systems in connection with our probes of new types of host systems based, inter alia, on *cis*-1,3,5,7-TOD "core" units.[6] The problem we have encountered in the course of these studies was the lack of information concerning the preparative details of this, apparently simple, acetalation reaction in particular with aliphatic aldehydes and the considerable confusion surrounding the conditions for obtaining exclusively or selectively any of the bicyclic isomeric products. In this paper we deal with this problem, analyzing the formation, structure, conformation, and thermodynamic parameters of the isomeric 2,6- disubstituted diacetals of threitol.

Results and Discussion

Condensation of *rac*-threitol with substituted acetaldehydes (XCH_2CHO, X = H, Cl, Br) (Scheme 3), provided the 2,6-disubstituted-*cis*-TOD products, with the 2(eq), 6(eq)-derivative (**1**) as the main ones, accompanied by minute amounts of the new 2(eq),6(ax)-derivatives (**2**) (Scheme 3). In addition to those, there were variable amounts (around 30%) of five-membered ring products (**4**−**6**). Careful workup made possible separation and isolation of all these products and their reliable characterization by NMR spectroscopy.

The NMR spectral data of the TOD ("**66**") products are presented in Tables 1 and 2. The chemical shifts and coupling constants in the $CH-CH_2$ group of the six-membered ring in **1** (Table 1) are well defined (only $J_{4(8)eq,10(9)}$ is mostly undinstinct and seen as signal broadening) and in excellent agreement with literature data and our previous investigations.[3−6] NOE experiments on H2(6) vs H4ax (8ax) and H9 (H10) supports the described structure in these molecules.

Contrary to **1**, the ^{1}H NMR spectra of the new 2(eq), 6(ax)-disubstituted-TOD compounds (**2**) exhibit two sets of signals. The first set, consisting of H2, H4ax, H4eq and H10, is similar (in both chemical shifts and coupling constants) to that observed in the ^{1}H NMR spectra of the symmetrical diequatorial system (**1**) in this work, as well as in previous ones (vide supra). The second set, consisting of H6, H8ax, H8eq, and H9, is different from the first one and unprecedented in previously reported TOD systems. Assignment of chemical shift was unequivocal on the basis of NOE experiments and analysis of the chemical shifts and coupling constants: irradiation of H2 enhanced the H4ax and H9 signals, whereas irradiation of H6 enhanced H8β and that of H12 enhanced H8α. The angular H9 proton is shifted downfield (as compared with H9(10) in **1** and H(10) in **2**) and coupled with H8α, $J_{9,8\alpha}$ growing up to 5.9 Hz (as compared to 1.2 Hz in **1**). H8α was first concluded to be H8ax, and H8β is H8eq, but the overall behavior was subsequently taken to stem from a fluctuational behavior in the C6−O7−C8 moiety within that ring.

The coupling constants in the second set, e.g., $J_{8\alpha,9}$ 5.8 Hz and $J_{8\beta,9}$ 1.7 Hz, reflect the fact that the dihedral angle H9−C9−C8−H8α becomes smaller (∼30°) and H9−C9−C8−H8β wider (∼100°) as compared with the diequatorial system (**1**). These changes in coupling constants fit a twist-boat conformation of the second ring in **2**, which, following the above-described NOE results, exists within a chair/chair-chair/twist-boat conformational equilibrium **2** ⇌ **7** (Scheme 4).

These structures are supported by ^{13}C NMR spectra, the details of which are presented in the Table 2. Assignment of ^{13}C signals was carried out using DEPT for all compounds and C−H correlation for **2b**.

Our conclusions about the structures of and the conformational equilibrium between **2** and **7** are well sustained by molecular mechanics calculations of **1**−**3a** (X = H), carried out using the MM3 force field,[8] which had been parametrized for the *anomeric effect* in O−C−O systems and which we have reparametrized (MM3-GE)[6b] for the *gauche effect* in O−C−C−O containing systems. This modified MM3(92)[8c] force field has been successfully used in the meantime on several similar systems.[5,6c−g] As evident, all our isomers contain both these types of dioxa (O−C−O and O−C−C−O) units and have to be treated accordingly. Relative stabilities of the lowest conformations of **1**−**3a** are presented in Table 3.

These results lend strength to the conclusion that, at the reaction temperature (80° C) used, the unsymmetrical diastereomer **2a**, inferred by the NMR spectrum in solution, is actually an equilibrium mixture of two stable conformers of similar energy, **2a** and **7a** (Scheme 4). The calculated data are in good agreement with the energy differences calculated for the naked *cis*-TOD system,[9] in which the chair/twist-boat form is about 5 kcal/mol higher

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(8) (a) MM3 is available from QCPE (latest public version); the official distributors are Technical Utilization Corporation, Inc., 235 Glen Village Court, Powell, OH 43065, and Tripos Associates, 1699 S. Hanley Road, St. Louis, MO 63144. (b) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H.; *J. Am. Chem. Soc.* **1989**, *111*, 8551 and subsequent articles, in particular that on alcohols and ethers: (c) Allinger, N. L.; Rahman, M.; Lii, J.-H. *J. Am. Chem. Soc.* **1990**, *112*, 8293, subsequently updated in MM3(92) for the *anomeric effect* by P. Aped. (d) MM3-GE[6b] is a reparametrized version for the *gauche effect* in O−C−C−O-containing systems.

Table 1. ^{1}H NMR Spectral Data ($CDCl_3$/TMS, 25 °C) of 2(eq),6(eq)-bis(XCH_2)-*cis*-TOD (X = H, Cl, Br) (1a−c) and 2(eq),6(ax)-bis(XCH_2)-*cis*-TOD (X = H, Cl, Br) (2a−c) (δ, ppm; J,[a] Hz)

	1a	1b	1c	2a	2b	2c
H_2	4.78 (q)	4.80 (d^2)	4.83 (d^2)	4.74 (q)	4.79 (d^2)	4.79 (d^2)
H_{4eq}	4.10 (d)	4.23 (d)	4.23 (d)	4.09 (d^2)	4.21 (d^2)	4.22 (d^2)
H_{4ax}	3.89 (d^2)	3.94 (d^2)	3.93 (d^2)	3.85 (d^2)	3.90 (d^2)	3.89 (d^2)
H_9	3.61 (m)	3.70 (m)	3.67 (m)	3.92 (d^3)	4.12 (d^3)	4.11 (d^3)
H_{11}	1.41 (d)	3.60 (d)	3.44 (d)	1.41 (d)	3.58 (d)	3.42 (d)
H_6				5.39 (q)	5.30 (d^2)	5.30 (d^2)
H_{8ax}				4.17 (d^2)	4.26 (d^2)	4.26 (d^2)
H_{8eq}				3.85 (d^2)	3.93 (d^2)	3.92 (dd)
H_{10}				3.72 (m)	3.79 (d^3)	3.78 (d^3)
H_{12}				1.38 (d)	3.63 (d^2)(a)	3.47 (d^2)(a)
					3.56 (d^2)(b)	3.44 (d^2)(b)
	$J_{2,11} = 5.1$	$J_{2,11} = 5.1$	$J_{2,11a} = 5.0$	$J_{2,11} = 5.1$	$J_{2,11a} = 4.8$	$J_{2,11a} = 4.8$
	$J_{4eq,4ax} = 12.5$	$J_{4eq,4ax} = 12.5$	$J_{2,11b} = 5.0$	$J_{4eq,4ax} = 13.0$	$J_{2,11b} = 4.8$	$J_{2,11b} = 4.8$
	$J_{4ax,10} = 1.3$	$J_{4ax,10} = 1.3$	$J_{4eq,4ax} = 12.6$	$J_{4eq,10} = 1.2$	$J_{4eq,4ax} = 12.9$	$J_{4eq,4ax} = 12.7$
	$J_{4eq,10} < 1$	$J_{4eq,10} < 1$	$J_{4ax,10} = 1.2$	$J_{4ax,10} = 1.0$	$J_{4eq,10} = 1.2$	$J_{4eq,10} = 1.3$
				$J_{9,8ax} = 4.9$	$J_{4ax,10} = 1.7$	$J_{4ax,10} = 1.6$
				$J_{9,8eq} = 1.5$	$J_{9,8ax} = 5.8$	$J_{9,8ax} = 5.9$
				$J_{9,10} \sim 1.5$	$J_{9,8eq} = 1.7$	$J_{9,8eq} = 1.7$
				$J_{6,12} = 5.3$	$J_{9,10} = 1.7$	$J_{9,10} = 1.7$
				$J_{8ax,8eq} = 12.2$	$J_{6,12a} = 5.2$	$J_{6,12a} = 5.0$
					$J_{6,12b} = 4.1$	$J_{6,12b} = 4.0$
					$J_{8ax,8eq} = 12.3$	$J_{8ax,8eq} = 12.3$
					$J_{12a,12b} = 11.4$	$J_{12a,12b} = 11.2$

[a] Multiplicity: d = doublet (d^2 = dd, d^3 = ddd), t = triplet, q = quadruplet, m = multiplet.

Table 2. ^{13}C NMR Spectral Data ($CDCl_3$/TMS, 25 °C) of 2,6-Disubstituted-TOD (1a−c, 2a−c) (δ, ppm)

	1a	1b	1c	2a	2b	2c
C2	98.9	100.1	100.1	98.4	99.6	99.2
C4	69.4	69.4	69.5	69.7	69.5	69.6
C9	69.6	69.4	69.5	70.9	71.3	71.3
C11	21.0	43.8	30.9	19.0	43.6	31.0
C6				94.0	95.3	94.7
C8				65.8	67.0	67.0
C10				62.2	63.3	63.3
C12				20.9	43.9	31.5

Scheme 4. Two Double-Chair (2) and Chair/Twist-Boat (7) Forms of 2*S*,6*R*-Disubstituted-*cis*-TOD

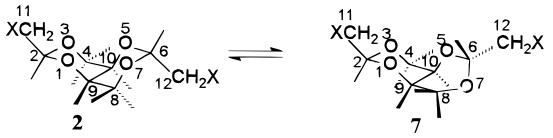

Table 3. Calculated (MM3-GE) Relative Free Energy Differences of 2,6- Dimethyl-TOD (1−3a) in Their Lowest Minima Conformations (kcal/mol)

conformation[a]	ΔG^{353} rel
2(eq),6(eq)-dimethyl-*cis*-TOD (Oinside) (**1a**)	0.0
2(eq),6-dimethyl-1,3-*c*−5,7-*tb*-*cis*-TOD (Oinside) (**7a**)	4.4
2(eq),6(ax)-dimethyl-*cis*-TOD (**2a**) (Oinside)	5.1
2(eq),6(eq)-dimethyl-*cis*-TOD (Ooutside)	5.4
2(eq),6-dimethyl-1,3-*c*-(Ooutside)−5,7-*tb*-*cis*-TOD	7.7
2(ax),6(ax)-dimethyl-*cis*-TOD (Oinside) (**3a**)	11.1
2(ax),6(eq)-dimethyl-*cis*-TOD (Ooutside)	13.2
2(ax),6(ax)-dimethyl-*cis*-TOD (Ooutside)	22.1

[a] c = chair; *tb* = twist-boat.

than the chair/chair, with a ca. 10 kcal/mol barrier between them. Moreover, there is good agreement of the calculated free energy difference between the diastereomers **1a** and **2a**/**7a** with the experimental ratio of these diastereomeric products (ca. 1000:1). Interestingly, the high-energy 2(ax),6(ax)-*cis*-TOD-Oinside diastereomer **3a** could conformationally invert into the 2(eq),6(eq)-*cis*-TOD-Ooutside one, which is of similar free energy as conformers **2a** and **7a**, but was not found among the reaction products. We will address this issue later.

Turning to the diastereomeric 2,2′-disubstituted-4,4′-bi(1,3-dioxolanyl) (BDO) (**4**−**6**) products (Scheme 3) isolated from the reactions of threitol with the mentioned substituted aldehydes, they could be well characterized by their NMR spectra, the data of which are presented in Tables 4 and 5. It merits recalling at this point that a related issue, 1,3-dioxolane vs 1,3-dioxane formation in acetalation of glycerol, has been receiving continuing attention.[10]

The ^{1}H NMR spectra (Table 4) of each and all "*cis*,*trans*" compounds (**5**) are practically superimposed spectra of the symmetrical "*cis*,*cis*" (**6**) and "*trans*,*trans*" (**4**) diastereomers, except the H4 and H4′ signals, which are close but changed places. This was established by irradiation of the low field "ddd"-signal. The configurational assignments within the 4,4′-BDO systems were supported by NOE experiments on compound **5c**, namely, irradiation of the low-field H2 signal, enhanced those of H5*cis* and H4′, and that of the high-field H2′ signal, enhanced H5′*trans* and H4′. These findings are in very good agreement with the available[10d,e] detailed NMR data of *cis*- and *trans*-2-methyl-4-XCH_2-1,3-dioxolanes.

Notably, in all cases the isomers of **4**, **5**, and **6** occur in statistic ratio, i.e., 1:2:1 and are not substituent dependent, which means that no significant free energy differences of those isomers should be anticipated. This was nicely confirmed by MM3-GE[9] calculations, the results of which are presented in Table 6.

Our interest in the intimate behavior of substituted TOD systems and the peculiar phenomena we encountered in the first stages of this investigation compelled us to probe the reaction mechanism and optimization conditions of the described double acetalation process. We chose the reaction of *rac*-threitol with bromoacetaldehyde as a model for this purpose, 2,6-bis(bromomethyl)-TOD (**1c**) having been designed as a useful starting material in our past[6f] and present investigations.

The yields of crude product in this reaction were, as a rule, nearly quantitative, and of the products (**1c**, **2c**, **4c**, **5c**, **6c**), **1c** could be crystallized from methanol in pure form and the rest was resolved when needed, by column

(9) Golender, L.; Senderowitz, H.; Fuchs, B. *J. Mol. Struct. THEOCHEM* **1996**, *370*, 221.

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Table 4. ^{1}H NMR Spectral Data ($CDCl_3$/TMS, 25 °C) of 2,2′-bis(XCH_2)-4,4′-BDO (X = H, Cl, Br) (4a−c, 5a−c, 6a−c) (δ, ppm; J,[a] Hz)[b]

	4a	4b	4c	5a	5b	5c	6a	6b	6c
H_2	5.16 (q)	5.30 (d^2)	5.28 (d^2)	5.18 (q)	5.33 (d^2)	5.32 (d^2)	5.03 (q)	5.17 (d^2)	5.15 (d^2)
H_4	4.10 (m)	4.27 (m)	4.26 (m)	4.17 (d^3)	4.33 (d^3)	4.35 (d^3)	4.19 (m)	4.32 (m)	4.34 (m)
H_{5t}	4.10 (m)	4.21 (d^2)	4.22 (d^2)	4.11 (d^2)	4.21 (d^2)	4.22 (d^2)	3.90 (m)	4.02 (d^2)	4.03 (d^2)
H_{5c}	3.74 (d^2)	3.92 (d^2)	3.92 (d^2)	3.67 (d^2)	3.90 (d^2)	3.91 (d^3)	3.90 (m)	3.97 (bd^2)	3.96 (d^2)
H_6	1.36 (d)	3.54, 3.56 (d^2,d^2)	3.44, 3.38 (d^2,d^2)	1.36 (d)	3.54, 3.56 (d^2,d^2)	3.38, 3.42 (2d^2)	1.40 (d)	3.59, 3.61 (d^2,d^2)	3.43, 3.46 (d^2,d^2)
$H_{2'}$				5.04 (q)	5.20 (d^2)	5.19 (d^2)			
$H_{4'}$				4.12 (d^3)	4.25 (d^3)	4.23 (d^3)			
$H_{5't}$				3.90 (d^2)	4.05 (d^2)	4.04 (d^2)			
$H_{5'c}$				3.79 (d^2)	3.95 (d^2)	3.96 (d^2)			
$H_{6'}$				1.40 (d)	3.59 (d^2_a) 3.56 (d^2_b)	3.47, 3.44 (2d^2)			
J	$J_{2,6}$ = 4.8	$J_{2,6a}$ = 3.7 $J_{2,6b}$ = 3.7 $J_{5t,4}$ = 6.3 $J_{5c,5t}$ = 7.7 $J_{5c,4}$ = 6.0 $J_{6a,6b}$ = 11.8	$J_{2,6a}$ = 3.7 $J_{2,6b}$ = 3.7 $J_{5t,4}$ = 7.7 $J_{5c,5t}$ = 7.7 $J_{5c,4}$ = 6.2 $J_{6a,6b}$ = 11.2	$J_{2,6}$ = 4.8 $J_{4,5t}$ = 6.8 $J_{4,5c}$ = 7.0 $J_{4,4'}$ = 6.0 $J_{5c,5t}$ = 8.1 $J_{2',6'}$ = 4.8 $J_{4',5't}$ = 7.4 $J_{4',5'c}$ = 5.4 $J_{5't,5'c}$ = 8.2	$J_{2,6a}$ = 3.8 $J_{2,6b}$ = 3.8 $J_{4,5t}$ = 6.7 $J_{4,5c}$ = 6.5 $J_{4,4'}$ = 4.3 $J_{5c,5t}$ = 8.3 $J_{6a,6b}$ = 11.8 $J_{2',6'a}$ = 3.9 $J_{2',6'b}$ = 3.9 $J_{4',5't}$ = 7.0 $J_{4',5'c}$ = 6.5 $J_{5't,5'c}$ = 8.3 $J_{6'a,6'b}$ = 11.8	$J_{2,6a}$ = 3.9 $J_{2,6b}$ = 3.9 $J_{4,5t}$ = 6.8 $J_{4,5c}$ = 6.6 $J_{4,4'}$ = 4.2 $J_{5c,5t}$ = 8.2 $J_{6a,6b}$ = 11.1 $J_{2',6'a}$ = 4.0 $J_{2',6'b}$ = 4.0 $J_{4',5't}$ = 7.0 $J_{4',5'c}$ = 6.7 $J_{5't,5'c}$ = 8.3 $J_{6'a,6'b}$ = 11.2	$J_{2,6}$ = 4.8	$J_{2,6a}$ = 3.8 $J_{2,6b}$ = 3.8 $J_{5c,4}$ = 5.6 $J_{5c,5t}$ = 8.5 $J_{6a,6b}$ = 11.8	$J_{2,6a}$ = 3.8 $J_{2,6b}$ = 3.8 $J_{5c,4}$ = 5.0 $J_{5t,4}$ = 6.9 $J_{5c,5t}$ = 8.5 $J_{6a,6b}$ = 11.2

[a] Multiplicity: d = doublet (d^2 = dd, d^3 = ddd), t = triplet, q = quadruplet, m = multiplet, b = broad. [b] *cis* and *trans* designations (including subscripts) refer to the central 4,4′ bond.

Table 5. ^{13}C NMR Spectral Data ($CDCl_3$/TMS, 25 °C) of 2,2′-bis(XCH_2)-4,4′-BDO (X = H, Cl, Br) (4a−c, 5a−c, 6a−c) (δ, ppm)

	4a	4b	4c	5a	5b	5c	6a	6b	6c
C_2	102.2	103.0	102.6	102.2	103.3	102.7	102.2	102.6	102.4
C_4	75.8	76.2	76.3	76.1	76.5	76.6	76.3	76.1	76.3
C_5	66.6	67.0	67.1	66.4	67.0	66.9	66.0	66.4	66.5
C_6	19.8	44.5	32.4	19.8	44.5	32.4	19.5	43.8	31.7
$C_{2'}$				102.2	103.1	102.6			
$C_{4'}$				76.3	75.9	75.8			
$C_{5'}$				66.1	66.4	66.4			
$C_{6'}$				19.5	43.9	31.7			

Table 6. Calculated (MM3-GE) Relative Free Energy Differences of 2,2′-Dimethyl-4,4′-bi(dioxolanyl) (4−6a) in Their Lowest Minima Conformations (kcal/mol)

diastereomer	conformation	ΔG^{353}rel
trans,trans-**4a**	H4−C4−C4′-H4′ *anti*	0.8
	C5−C4−C4′-C5′ *anti*	0.7
	O3−C4−C4′-O3′ *anti*	1.4
cis,trans-**5a**	H4−C4−C4′-H4′ *anti*	0.0
	C5−C4−C4′-C5′ *anti*	0.4
	O3−C4−C4′-O3′ *anti*	0.7
cis,cis-**6a**	H4−C4−C4′-H4′ *anti*	0.2
	C5−C4−C4′-C5′ *anti*	1.1
	O3−C4−C4′-O3′ *anti*	0.9

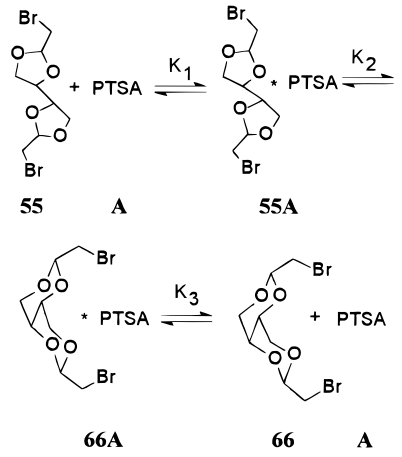
Table 7. Yields of 1c in Various Reaction Conditions (Scheme 3)

no.	temp, °C	[PTSA]/[threitol]	time, h	yield, %
1	80[a]	157	16	70
2	80[a]	7	16	60
3	80[a]	116	2	65
4	80[a]	19	2	25
5	80[a]	9	5	60
6	110[b]	9	12	55

[a] In refluxing benzene; [b] In refluxing toluene.

chromatography. The yields of **1c** in some such experiments are presented in Table 7, showing that they depend on the reaction temperature, on the concentration of PTSA, and on the reaction time. These results were taken as an indication that **4c**−**6c** are produced under "kinetic control" (Table 7, no. 1), after which an equilibration process between **4c**−**6c** and **1c** sets in, depending on temperature and concentration of acid (PTSA). We proceeded probing the mechanism of the reaction depicted in Scheme 5. As shown above, isomers **4c**, **5c**, and **6c** were calculated to have nearly the same free energies, and were obtained in statistical ratio. This justified using

Scheme 5. Thermodynamically Controlled Acid Promoted Reaction Modes of Threitol with 2-Bromoacetaldehyde



the entire mixture of diastereomers as **55** alongside the TOD product (**1c**), henceforth **66**, to probe the acid (**A**)-promoted equilibrium.

Thus, the following expressions could be set up, defining the equilibrium constants for the three equilibria (eqs 1, 2, and 3) and, since we are measuring de facto overall concentrations **[66]**+**[66A]** and **[55]**+**[55A]** (eqs 4 and 5), the observed equilibrium constants (K_{obs}) can be expressed as in eq 6, where **[A]** is a function of substrate concentration (**[S]**) and starting concentration of PTSA **[A]**^{o} and can be expressed by eq 7. Hence, we performed a number of reactions, varying the concentrations of substrate (**1c** or **4c**−**6c**) and PTSA. The reactions were monitored by GC and/or NMR, and the results are presented in Table 8. A plot of the resulting K_{obs} vs the initial acid concentrations (**[A]**^{o}) was made (Figure 1), and the three equilibrium constants (K_1, K_2, K_3) were optimized in a nonlinear regression procedure, based on eqs 6 and 7 and the experimental data.

$$K_1 = \frac{\mathbf{[55A]}}{\mathbf{[55][A]}} \qquad (1)$$

Table 8. K_{obs} in the Equilibria between 2(eq),6(eq)-bis(bromomethyl)-*cis*-Tod (1c) and All Isomers of 2,2′-bis(bromomethyl)-4,4′-BDO (4−6c) (Scheme 5)

no.	start. mater.	$[S] \times 10^3$	$[A]^0 \times 10^3$	$[S]/[A]^0 \times 10^2$	time, h	K_{obs}
1	**1c**[a]	19.1	8.4	228	160	1.63
2	**1c**[a]	18.4	18.6	100	50	1.82
3	**1c**[a]	19.4	34.6	56	30	2.14
4	**1c**[b]	22.3	5.1	437	100	1.72
5	**1c**[b]	10.7	35.0	31	50	2.03
6	**1c**[b]	6.2	44.0	14	50	2.25
7	**4−6c**[a]	10.4	9.4	111	50	1.56
8	**4−6c**[a]	25.0	37.4	67	30	2.17
9	**4−6c**[a]	1.7	150	1.13	2	2.48
10	**4−6c**[a]	1.7	350	0.49	1	3.00
11	**4−6c**[a]	1.7	530	0.32	1	3.06
12	**4−6c**[a]	1.7	1340	0.13	1	3.09

[a] By GC. [b] By NMR.

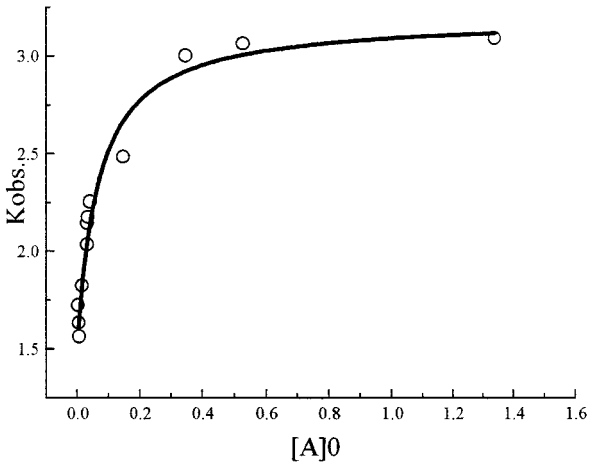


Figure 1. Experimental and calculated dependence of K_{obs} on initial concentration of PTSA, in the equilibrium between 2(eq),6(eq)-bis(bromomethyl)-*cis*-tetraoxadecalin (**1c**) and 2,2′-bis(bromomethyl)-4,4′-bi(dioxolanyl) (**4c**−**6c**) in boiling benzene.

$$K_2 = \frac{[\mathbf{66A}]}{[\mathbf{55A}]} \tag{2}$$

$$K_3 = \frac{[\mathbf{66A}]}{[\mathbf{66}][\mathbf{A}]} \tag{3}$$

$$[\mathbf{S}] = [\mathbf{55}] + [\mathbf{66}] + [\mathbf{55A}] = [\mathbf{66A}] \tag{4}$$

$$[\mathbf{A}]^\circ = [\mathbf{A}] + [\mathbf{55A}] + [\mathbf{66A}] \tag{5}$$

$$K_{obs} = \frac{[\mathbf{66}] + [\mathbf{66A}]}{[\mathbf{55}] + [\mathbf{55A}]} = \frac{K_1K_2*\left(\frac{1}{K_3} + [\mathbf{A}]\right)}{1 + K_1[\mathbf{A}]} \tag{6}$$

$$[\mathbf{A}] = -0.5\left(\frac{K_1K_2 + K_3}{K_1K_3(1 + K_2)} + [\mathbf{S}] - [\mathbf{A}]^\circ\right) + \sqrt{0.25\left(\frac{K_1K_2 + K_3}{K_1K_3(1 + K_2)} + [\mathbf{S}] - [\mathbf{A}]^\circ\right)^2 + \frac{K_1K_2 + K_3}{K_1K_3(1 + K_2)}*[\mathbf{A}]^\circ} \tag{7}$$

In the optimization process, different starting parameters were used in the interval from 0 to 10^6, and the calculated results ($K_1 = 15 \pm 4$; $K_2 = 3.2 \pm 0.1$; $K_3 = 32 \pm 9$ l/mol) correspond to a unique global minimum. The suggested model appears, therefore, to be correct, and the equilibrium constants can be safely used for the calculation of thermodynamic parameters. A free energy diagram for the set of three equilibria is presented in Figure 2, in which the species involved appear in the stability order (kcal/mol): **66A** (0.0), **55A** (0.8), **66** (2.5), and **55** (2.7).

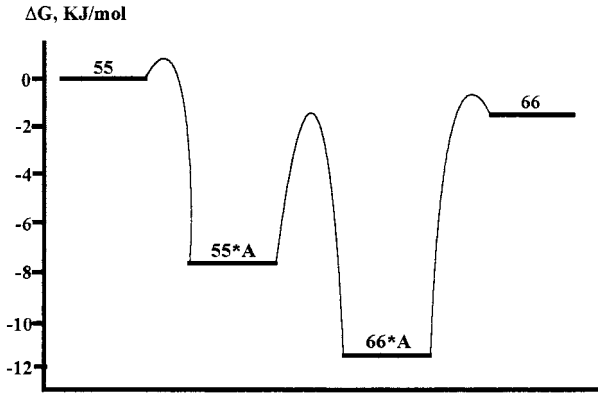


Figure 2. The free energy diagram of the equilibrium between 2(eq),6(eq)-bis(bromomethyl)-*cis*-tetraoxadecalin (**1c**) and 2,2′-bis(bromomethyl)-4,4′-bi(dioxolanyl) (**4c**−**6c**) in boiling benzene in the presence of PTSA.

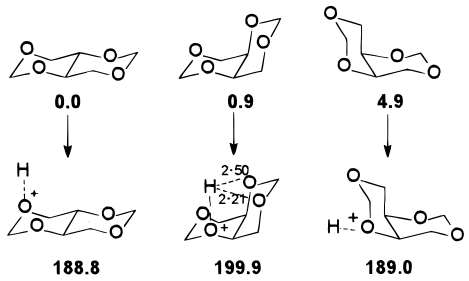
Making the reasonable assumption that the rearrangement step itself (**66A** ⇌ **55A**) has a lower rate constant, i.e., a higher barrier (without going into the nature of this process) associated with it, than the flanking two and that the Curtin−Hammett principle does not apply, we may conclude that the equilibrium between **66** (= **1c**) and **55** (= **4c**−**6c**) depends on the free energy difference between **66A** and **55A.** Increasing the PTSA concentration caused not only reduction of the time to reach equilibrium (i.e., increase of the reaction rate), but also growth of the **66A** mole fraction and, consequently, K_{obs} (Table 8). On the other hand, raising the temperature caused a decrease in the yield of **1c** (no. 6 in Table 7). This relative increase in the population of **55A** can be easily rationalized in terms of its enhanced entropy on two accounts: its (rotationally) flexible molecular frame and its being a mixture of at least three (**4c**, **5c**, and **6c**) diastereomers.

Notably, the equilibrium between **1c** and **4c**−**6c** depends on the kind of acid used: all other things being equal, K_{obs} for PTSA, Dowex, and TFA were about 2.8, 0.72, and 0.71, respectively. Thus, the association energy depends not only on the "acidity", but also on the structure of the proton carrier (e.g., large steric interference by Dowex); be that as it may, the highest association energy was achieved by *cis*-TOD-(Oinside) with PTSA.

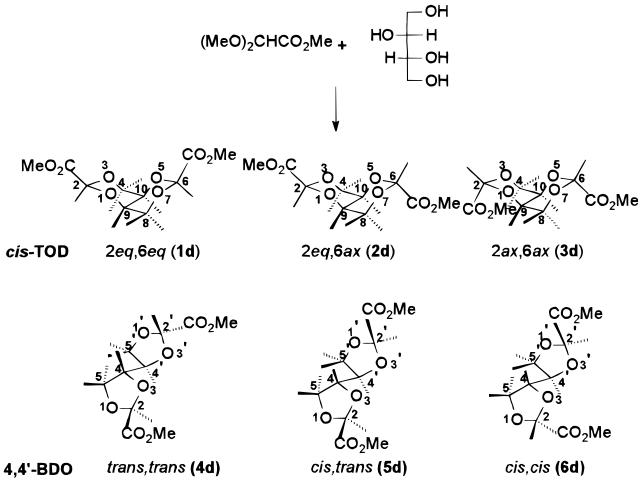
Theoretical support to this mechanistic picture can be found in the results of a computational ab initio study we have recently reported, in which, among the three possible TOD diastereomers (Scheme 6),[6g] *cis*-TOD-Oinside exhibits the highest proton affinity, way outside the range of O−C−O *anomeric* systems, which are known to be relatively weak bases,[11a] but similar to the stronger gauche O−C−C−O bases.[11b] This is due, in large measure, to the strong intramolecular hydrogen bonds within the cavity of *cis*-TOD-Oinside (Scheme 6). The fact that the 2(eq),6(eq)-disubstituted-*cis*-TOD-Ooutside species (i.e., the ring-inverted form of 2(ax),6(ax)-*cis*-TOD-Oinside) is practically absent in the reaction product, despite its calculated energy being similar to that of **2** and **7**

(11) (a) Ganguly, B.; Fuchs, B. *J. Org. Chem.* **1997**, *62*, 8892. (b) Ganguly, B.; Fuchs, B. *J. Org. Chem.*, in press.

Scheme 6. Relative Energies and Proton Affinities (in kcal/mol) of *trans*- and *cis*-TOD-Oinside and -Ooutside, Taken from Ref 6g (calculated using Gaussian 94 at the MP2/6-31+G* level)



Scheme 7. Acetalation Reaction Products of D-Threitol with Methyl Glyoxylate



(Table 3), is evidently due its much lower protonation energy. It should be mentioned that a similar calculation of the BDO system has not yet been performed, due to the CPU exigency of the job.

It is at this point that we see fit to present the findings that actually triggered the above-reported investigation and which stemmed from our keen interest in TOD systems with functionalized substituents, as cores for novel macromolecular systems. These are the results of the condensation of *rac*-threitol with methyl glyoxylate (MeO_2CCHO) (Scheme 7), viz., all three isomers of bis-(methoxycarbonyl)-1,3,5,7-*cis*-TOD, which were individually isolated, viz., 2(eq),6(eq) (**1d**), 2(eq),6(ax) (**2d**) and (the only existing case of) 2(ax),6(ax) (**3d**) in 20%, 15%, and 2% yield, respectively, along with the 2,2′-bis-(methoxycarbonyl)-4,4′-BDO isomers: **4d, 5d**, and **6d**, which were obtained in 25% yield and 1:2:1 ratio (as evaluated by NMR of the mixture) and could not be separated. The detailed NMR data (strengthened by NOE and DEPT studies) are given in Table 9 and are illuminating, due to the presence of the hitherto unavailable 2(ax),6(ax) form (**3d**). Both the ^1H and ^{13}C NMR spectra of the 2(eq),6(ax)-isomer (**2d**), exhibit two sets of signals, as before (vide supra). The first set in each spectrum is similar to that observed in the spectrum of the symmetrical diequatorial system (**1d**), while the second set resembles that of 2(ax),6(ax)-bis(methoxycarbonyl)-1,3,5,7-*cis*-TOD (**3d**). The fact that axially 2(6)-substituted species (**2d, 3d**) are relatively well populated in this case is clearly due to the methoxycarbonyl substituent. The latter's relative propensity to assume axial conformation (which explains why no ring inverted *tb* species are seen in this case) is due to its intrinsical low conformational energy (1.2 kcal/mol)[12] (its periodicity number is 6) and to a possible *anomeric effect*.[6e] This is now being looked into.

Conclusion

We have unraveled the thermodynamic features of the diacetalation reaction of threitol with alkylaldehydes and the details of the dependence of the ratios of the bicyclic *cis*-tetraoxadecalin (TOD) ("**66**") and bi(dioxolanyl) (BDO) ("**55**") products, on acid-concentration and temperature. The isomeric diacetals obtained in four such reactions of substituted aldehydes (RCHO, R = CH_3, CH_2Cl, CH_2Br, CO_2CH_3) with *rac*-threitol were isolated and characterized configurationally and conformationally. A variable acid-concentration analysis of the equilibrium mixture of products in one such case (R = CH_2Br) was performed and provided equilibrium constants and, hence, free-energy differences among these products and their unprecedented stable protonated intermediates. The latter were rationalized by the unusually high proton-affinity calculated for the *cis*-TOD ("**66**") form (which can be extrapolated to further *threo*-tetraol diacetals). Attempts to ferret out (mass spectrometrically) these and similar stable protonated species are in course.

Experimental Section

General. Melting points were recorded on a capillary melting point apparatus and are uncorrected. The NMR spectra were obtained on 200, 360, and 500 MHz NMR spectrometers. All ^1H chemical shifts are in ppm and δ-values are relative to TMS as internal standard. ^{13}C chemical shifts are reported in ppm relative to $CDCl_3$ (center of triplet δ 77.0) Mass spectra (DEI-MS, DCI-MS, and FAB) were recorded on an Autospec 250 mass-spectrometer. Commercial solvents and reagents were used without purification. Chromatographic separations were performed on a silica gel 60 column, eluting with gradient petroleum ether:ethyl acetate (9:1 to 1:1). Nonlinear regression optimizations were performed using Origin 4.0. While we deal with racemic mixtures throughout, the designation is made throughout on D-threitol products.[1b] Elemental analyses were not performed, since we deal with isomeric mixtures. Mass spectral (EI) analyses were performed in each case, and the molecular ions were observed only for the methyl-substituted TOD and BDO products; otherwise the fragment $M^+ - CH_2X$ was the first and most abundant one. The ^1H and ^{13}C NMR spectra were the diagnostic tool (see text) and are given in detail in Tables 1, 2, 4, 5, and 9.

Acetalation of *rac*-Threitol with Acetaldehyde. To a mixture of *rac*-threitol (1.2 g, 10 mmol) and Dowex-H^+ (2.6 g) in dichloromethane (200 mL) was added 1.5 mL (27 mmol) of acetaldehyde, and the mixture was refluxed with separation of water in a Dean−Stark adapter. The organic solution was filtered and evaporated. The crude product (1.6 g, yield 92%) was separated by column chromatography. The first three fractions eluted were the three 2,2′-dimethyl-4,4′-bi(1,3-dioxolanyl) isomers in the order: **6a, 4a**, and **5a**. The fourth fraction consisted of a minute quantity of the 2(eq),6(ax) isomer (2*S*,6*R*,9*R*;9,10-*M*)-dimethyl-1,3,5,7-*cis*-tetraoxadecalin (**2a**), and the last fraction was the 2(eq),6(eq) isomer (2*S*,6*S*,9*R*;9,-10-*M*)-dimethyl-1,3,5,7-*cis*-tetraoxadecalin (**1a**) (1.5 g, 87%).

Acetalation of *rac*-Threitol with 2-Chloroacetaldehyde. To a solution of PTSA (0.33 g, 1.7 mmol) in water (20 mL) was added chloroacetaldehyde dimethylacetal (5.7 mL, 50 mmol), and the reaction mixture was stirred at 60−65° C

(12) Eliel, E. L.; Willen, S. *Stereochemistry of Carbon Compounds*; Wiley: New York, 1994; p 696.

Table 9. ^{1}H and ^{13}C NMR Spectral Data ($CDCl_3$/TMS, 25 °C) of 2(eq),6(eq)- Bis(methoxycarbonyl) *cis*-Tod (1d), 2(eq),6(ax)-bis(methoxycarbonyl)-*cis*-Tod (2d), and 2(ax),6(ax)-Bis(methoxycarbonyl)-*cis*-Tod (3d) (δ, ppm; J,[a] Hz)

^{1}H NMR

	H_2	H_{4eq}	H_{4ax}	H_9	OCH_3	H_6	H_{8ax}	H_{8eq}	H_{10}	OCH_3
1d	5.11 (s)	4.41 (bd)	3.93 (d^2)	3.81 (bs)	3.85 (s)					
		$J_{4eq,4ax} = 12.8$; $J_{4ax,10} = 1.3$								
2d	5.11 (s)	4.34 (d^2)	3.96 (d^2)	3.83 (s)	3.85 (s)	5.48 (bs)	4.22 (d^2)	4.12 (d^2)	4.15 (bs)	3.82 (s)
			$J_{4eq,4ax} = 12.9$, $J_{4eq,10} = 1.0$, $J_{4ax,10} = 1.9$, $J_{9,8ax} = 2.1$, $J_{9,8eq} = 1.4$, $J_{8ax,8eq} = 13.0$							
3d	5.50 (s)	4.16 (d^2)	4.07 (d^2)	4.18 (bs)	3.83 (s)					
		$J_{4eq,4ax} = 13.1$; $J_{4ax,10} = 1.4$								

^{13}C NMR

	C_2	C_4	C_9	OCH_3	C=O	C_6	C_8	C_{10}	OCH_3	C=O
1d	95.9	69.5	69.9	52.9	165.3					
2d	95.9	69.8	70.2	53.0	165.5	92.3	64.5	63.7	52.4	168.1
3d	92.4	64.7	64.1	52.5	168.1					

[a] Multiplicity: d = doublet (d^2 = dd, d^3 = ddd), t = triplet, q = quadruplet, m = multiplet, b = broad.

for 5 h, until the solution became clear, indicating full acetal hydrolysis (by NMR). This aqueous solution was continuously extracted with dichloromethane for 48 h, and the chloroacetaldehyde solution was continuously transferred to a mixture of *rac*-threitol (3 g, 24 mmol) and Dowex-H^+ (5 g) in boiling dichloromethane (250 mL). The resulting solution was filtered and evaporated. The crude product (5.3 g, yield 91%) was crystallized from ethyl acetate, to give the 2(eq),6(eq) (2*S*,6*S*,9*R*;9,10-*M*)-bis(chloromethyl)-1,3,5,7-*cis*-tetraoxadecalin (**1b**) (3.4 g, 58%). Evaporation of the mother liquor gave an oil, which was separated by column chromatography. The first three products were the 2,2′-bis(chloromethyl)-4,4′-bi(1,3-dioxolanyl) isomers, in the order: **4b, 6b**, and **5b**. The fourth fraction consisted of a minute quantity of the 2(eq),6(ax) (2*S*,6*R*,9*R*;9,10-*M*)-bis(chloromethyl)-1,3,5,7-*cis*-tetraoxadecalin (**2b**) and the last product of additional **1b**.

Acetalation of *rac*-Threitol with 2-Bromoacetaldehyde. To a solution of PTSA (4.85 g, 25 mmol) in water (25 mL) was added bromoacetaldehyde dimethylacetal (5 mL, 41 mmol), and the reaction mixture was stirred at 60−65° C for 4 h, until the solution became clear, indicating full acetal hydrolysis (by NMR). *rac*-Threitol (2 g, 15.9 mmol) was added, along with 150 mL of benzene. The mixture was refluxed overnight under Ar, using a Dean−Stark adapter. After cooling, the organic solution was washed with 10% aqueous sodium carbonate (20 mL), dried with calcium chloride, and evaporated. The crude product (5.1 g, 97%) was crystallized from methanol, to give **1c** (2.1 g, 40%). Evaporation of the mother liquor provided an oil, which was separated by column chromatography. The first three fractions were the 2,2′-bis-(bromomethyl)-4,4′-bi(1,3-dioxolanyl) isomers, in the order: **4c**, **6c**, and **5c**. The fourth fraction consisted of a minute quantity of 2(eq),6(ax)-bis(chloromethyl)-1,3,5,7-*cis*-tetraoxadecalin (**2c**) and the last fraction was additional **1c**.

Acetalation of *rac*-Threitol with Methyl Glyoxylate. To a solution of PTSA (0.25 g, 1.3 mmol) and dimethoxyacetic acid methyl ester (methyl glyoxylate dimethyl acetal) (1.24 g, 9.3 mmol) in water (5 mL) was added *rac*-threitol (0.4 g, 3.28 mmol) followed by 40 mL of benzene. The mixture was refluxed overnight under Ar, using a Dean−Stark adapter. The benzene overlayer was decanted, and the residual viscous oil was dissolved in methanol (40 mL). The resulting solution was concentrated and taken up in chloroform. This solution was washed with water and aq K_2CO_3, dried on $MgSO_4$, filtered, and evaporated. The residue was separated by column chromatography, to give first three fractions (the NMR spectra are assembled in Table 9):

(2*S*,6*S*,9*R*;9,10-*M*)-Bis(methoxycarbonyl)-1,3,5,7-*cis*-TOD (2(eq),6(eq)) (**1d**) (175 mg, 20%). mp: 136.5−137.5 °C (from EtAc). TLC: $R_f = 0.28$ (EtAc, silica gel). EI-MS (70 eV): *m*/*z* (%) 261 ([M − H]$^+$, ∼1), 203 (100); 115 (19). FAB-MS (70 eV): *m*/*z* (%) 263 ([MH]$^+$, 100), 203 (91). Anal. Calcd for $C_{10}H_{14}O_8$ (262.22): C, 45.81; H, 5.38. Found: C, 45.98; H, 5.49.

(2*S*,6*R*,9*R*;9,10-*M*)-Bis(methoxycarbonyl)-1,3,5,7-cis-TOD (**2d**) (2(eq),6(ax)) (130 mg, 15%). TLC: $R_f = 0.56$ (EtAc, silica gel). EI-MS (70 eV): *m*/*z* (%) 203 (100), 115 (47). FAB-MS (70 eV): *m*/*z* (%) 263 ([MH]$^+$, 66), 203 (100).

(2*R*,6*R*,9*R*;9,10-*M*)-Bis(methoxycarbonyl)-1,3,5,7-cis-TOD (**3d**) (2(ax),6(ax)) (2 mg, 2%). TLC: $R_f = 0.73$ (E.A, silica gel). EI-MS (70 eV): *m*/*z* (%) 203 (100), 115 (40).

The following fraction (220 mg, 25%) was a mixture of the 2,2′-bis(methoxycarbonyl)-4,4′-bi(dioxolanyl) isomers: **4d, 5d**, and **6d**, in 1:2:1 ratio (from the NMR spectrum of the mixture).

Equilibrium Studies. A solution of PTSA in benzene was refluxed for 2 h, using a Dean−Stark adapter under Ar, after which, was added a mixture of substrate (**1c** or **4c**−**6c**) with biphenyl (as an inert GC internal standard) in mole ratio 1:1. Samples were taken through an immersed capillary tube using positive Ar pressure, washed with 10% aqueous sodium carbonate, and examined by GC or, after evaporation of benzene, by ^{1}H NMR in $CDCl_3$. Every experiment was finished when the ratio between **1c** and **4c**−**6c** remained unchanged. Chromatographic analysis were run on a Varian 3400 instrument with TCD on Megabor DB5 column (15 m × 0.53 mm, He carrier gas flow 30 mL/min, column temperature from 60 to 200° C with gradient 15 deg/min). The retention times of biphenyl, **4c**−**6c** and **1c** were 4.7, 8.1, and 8.4 min, respectively.

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