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Synthesis and Chemistry of 2,3-Dioxabicyclo[2.2.2]octane-5,6-diols

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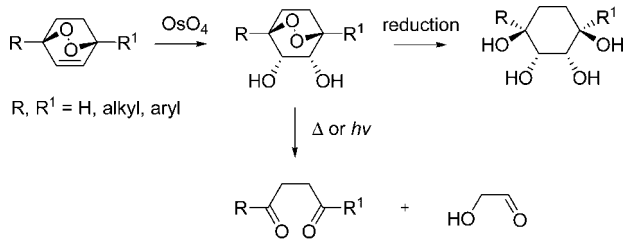

1,4-Disubstituted 2,3-dioxabicyclo[2.2.2]oct-5-enes were dihydroxylated with osmium tetroxide to yield diols *anti* to the peroxide linkage in a highly selective manner. Reduction of the peroxide bond furnished cyclohexane-1,2,3,4-tetraols with toxocarol relative stereochemistry in excellent yield. This new methodology was employed to synthesize the natural product (1*S*,2*R*,3*S*,4*R*,5*R*)-2-methyl-5-(propan-2-yl)cyclohexane-1,2,3,4-tetrol (**1**) in a short sequence from (*R*)-α-phellandrene. Moreover, during the study of the chemistry of 2,3-dioxabicyclo[2.2.2]octane-5,6-diols a hitherto unknown rearrangement was discovered which has wide applicability for the synthesis of 1,4-dicarbonyls, including optically enriched synthons. A broad range of mechanistic investigations applicable to this rearrangement are also reported.

Introduction

Cyclohexane-1,2,3,4-tetraols of the configuration in Figure 1 are relatively rare in nature except for the simple toxocarol-like compounds such as (+)-pinitol, conduritol A, and (−)-quebrachitol. Several more complex natural products exhibit this toxocarol configuration such as altersolarol A,[1] auxarthrol B,[2] **1**[3,4] and **2**,[5] and many yet to be synthesized. The toxocarol configuration also has appeared in several pharmacologically active compounds [6,7] and as structures in the synthetic routes to several natural products such as the otteliones[8] and zeylenone.[9]

Of the compounds that have been synthesized, the general approach has been to prepare them first by reduction of the peroxide linkage of an appropriate 2,3-dioxabicyclo[2.2.2]oct-5-ene **3**, followed by dihydroxylation of the alkene (Scheme 1).[10−14] In some cases, extra synthetic steps for protection and deprotection of the diol (from the reduced peroxide linkage) are employed to aid workup after dihydroxylation.[6,10,12−14]

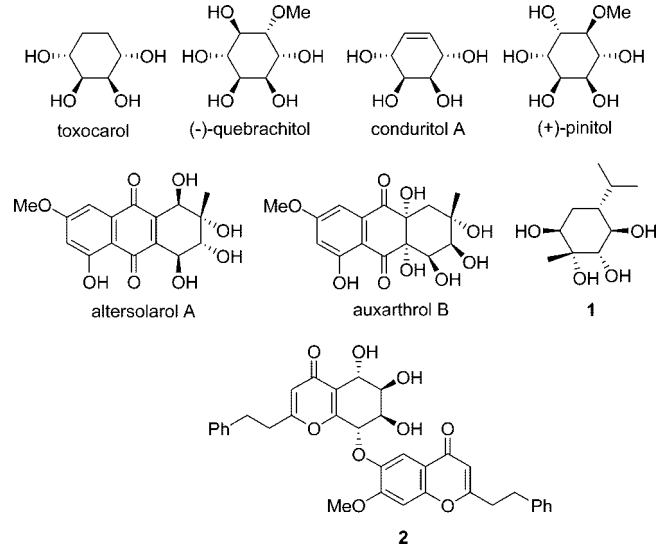

FIGURE 1. Natural products displaying the toxocarol relationship of hydroxyl groups.

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(1) Stoessl, A. *Can. J. Chem.* **1969**, *47*, 777–784.
(2) Alvi, K. A.; Rabenstein, J. *J. Ind. Microbiol. Biotechnol.* **2004**, *31*, 11–15.
(3) Jiang, H. X.; Gao, K. *Chin. Chem. Lett.* **2005**, *16*, 1217–1219.
(4) Jiang, H. X.; Li, Y.; Pan, J.; Gao, K. *Helv. Chim. Acta* **2006**, *89*, 558–566.
(5) Iwagoe, K.; Kakae, T.; Konishi, T.; Kiyosawa, S.; Fujiwara, Y.; Shimada, Y.; Miyahara, K.; Kawasaki, T. *Chem. Pharm. Bull.* **1989**, *37*, 124–128.

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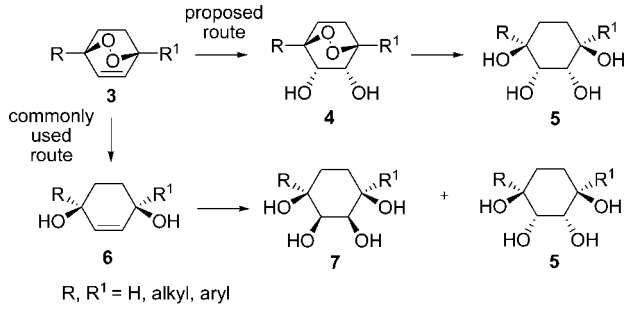
SCHEME 1



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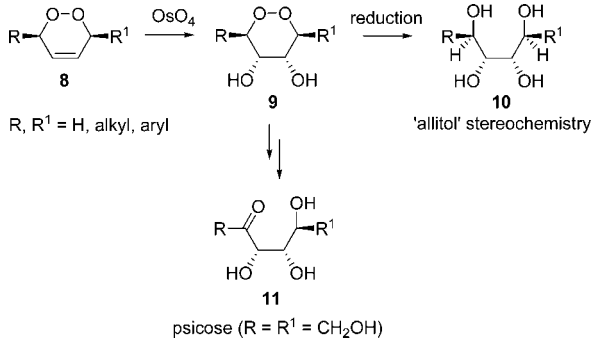
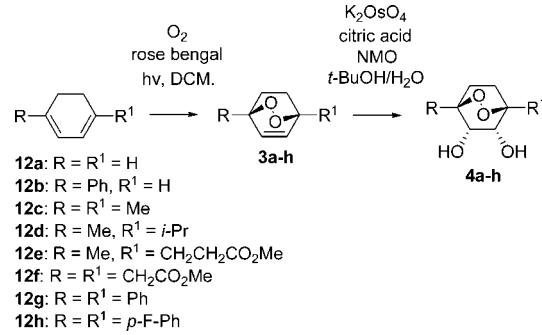


Alternatively, photooxygenation of 3,5-cyclohexadiene-1,2-diol and subsequent reduction of the peroxide linkage represents another route to the toxocarol configuration.[10,11]

We have recently published a method for the dihydroxylation of 1,2-dioxines **8** (Scheme 2) and their application to the synthesis of tetraols of "allitol" stereochemistry and sugars such as (±)-psicose **11** in excellent overall yields.[15]

With the above results in mind, we now examined an extension to this methodology for the ready construction of cyclohexane-1,2,3,4-tetraols **5**. Thus, we felt that the dihydroxylation of bicyclic systems **3** (to give **4**) followed by reduction of the peroxide bond would afford cyclohexane-1,2,3,4-tetraols **5** in a highly stereoselective manner (Scheme 1). We anticipated that dihydroxylation would occur *anti* to the peroxide bond because of the steric bulk and repulsive effect of the electronegative oxygen atoms on the approach of osmium tetroxide, a hypothesis found to be true (vide infra). Moreover, it was considered that variation of the substituents R and R^1 would have little effect on the facial selectivity of dihydroxylation as the groups have an identical steric presence on either face of the alkene. This method also would have the advantage of simple purification of the tetraol with no requirements for a protection−deprotection protocol, as highlighted previously.[6,10,12−14]

SCHEME 3



Furthermore, it has been found that facial selectivity of dihydroxylation for the previous common route is extremely dependent on the steric environment of the alkene with mixtures sometimes observed (Scheme 1).[6,7] High selectivity of dihydroxylation was observed for **6** (R and R^1 = H). In these cases, one of the hydroxyl groups will sit axial in the lowest-energy half-chair conformation, thus always yielding direct dihydroxylation "*trans*" to the hydroxyl groups, giving the stereochemistry of tetraol **5**. When R and $R^1 \neq$ H, we expect that both faces would be hindered similarly, and a mixture of tetraols **5** and **7** would be observed, a hypothesis which turned out to be true (vide infra). Our methodology should offer higher and in some instances alternate facial selectivity for dihydroxylation in an approach to cyclohexane-1,2,3,4-tetraols of toxocarol stereochemistry.

In addition to the use of 2,3-dioxabicyclo[2.2.2]octane-5,6-diols **4** for the synthesis of cyclohexane-1,2,3,4-tetraols **5**, the synthesis of a broad range of substituted compounds of type **4** also provided us with the opportunity to investigate an underexplored area of 2,3-dioxabicyclo[2.2.2]oct-5-ene chemistry. Thermal,[16−18] metal catalyzed,[19,20] and photo-induced electron-transfer-assisted[21,22] decomposition of bicyclic endoperoxides have been extensively studied; however, no such possible transformations have been investigated for 2,3-dioxabicyclo-[2.2.2]octane-5,6-diol substrates. Consequently, we report herein new studies on the thermal and photochemical decomposition of systems of type **4** for the ready construction of 1,4-dicarbonyl derivatives.

Results and Discussion

Dihydroxylation of 1,4-Disubstituted 2,3-Dioxabicyclo-[2.2.2]oct-5-enes. A broad range of 2,3-dioxabicyclo[2.2.2]oct-5-enes (**3a**−**f**) were synthesized by standard methods, featuring a range of H, alkyl, and aryl substituents (Scheme 3 and Table 1).

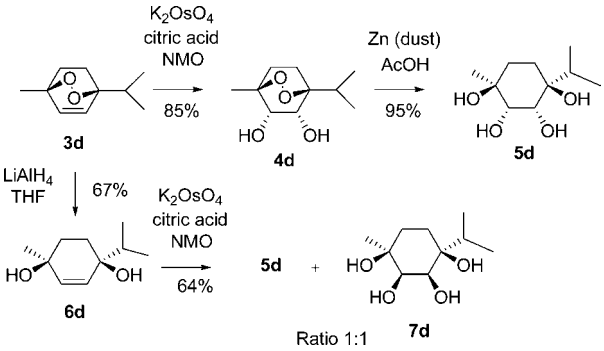
Treatment of compounds **3a**−**h** under conditions previously identified as suitable for dihydroxylation of 1,2-dioxines[15] gave diols **4b**−**h** in moderate to high yields as single diastereomers; however, the reaction of **3a** resulted in a complex mixture of unidentified products (Table 1). Yields of the diols **4a**−**h** varied considerably because of their susceptibility to rearrangement

(6) Kelebekli, L.; Kara, Y.; Balci, M. *Carbohydr. Res.* **2005**, *340*, 1940–1948.
(7) Mehta, G.; Ramesh, S. S. *Tetrahedron Lett.* **2001**, *42*, 1987–1990.
(8) Araki, H.; Inoue, M.; Suzuki, T.; Yamori, T.; Kohno, M.; Watanabe, K.; Abe, H.; Katoh, T. *Chem.—Eur. J.* **2007**, *13*, 9866–9881.
(9) Liu, A.; Liu, Z. Z.; Zou, Z. M.; Chen, S. Z.; Xu, L. Z.; Yang, S. L. *Chin. Chem. Lett.* **2004**, *15*, 1433–1436.
(10) Carless, H. A. J.; Busia, K. *Tetrahedron Lett.* **1990**, *31*, 1617–1620.
(11) Carless, H. A. J.; Billinge, J. R.; Oak, O. Z. *Tetrahedron Lett.* **1989**, *30*, 3113–3116.
(12) Gültekin, M. S.; Çelik, M.; Turkut, E.; Tanyeli, C.; Balci, M. *Tetrahedron: Asymmetry* **2004**, *15*, 453–456.
(13) Gültekin, M. S.; Salamci, E.; Balci, M. *Carbohydr. Res.* **2003**, *338*, 1615–1619.
(14) Salamci, E.; Seçen, H.; Sütbeyaz, Y.; Balci, M. *J. Org. Chem.* **1997**, *62*, 2453–2457.
(15) Robinson, T. V.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2006**, *71*, 7236–7244.
(16) Coughlin, D. J.; Salomon, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 2761–2763.
(17) Moore, C. G. *J. Chem. Soc.* **1951**, 234–235.
(18) Zand, R.; Mesrobian, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 6523–6524.
(19) Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1982**, *104*, 2024–2025.
(20) Suzuki, M.; Ohtake, H.; Kameya, Y.; Hamanaka, N.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 5292–5302.
(21) Akaba, R.; Kiyota, Y.; Nishimoto, S.; Kamata, M. *Proc.—Electrochem. Soc.* **2004**, *10*, 201–204.
(22) Kamata, M.; Kaneko, J.; Hagiwara, J.; Akaba, R. *Tetrahedron Lett.* **2004**, *45*, 7423–7428.

TABLE 1. Osmium-Catalyzed Dihydroxylation of 2,3-Dioxabicyclo[2.2.2]oct-5-enes 3a−h

entry	cyclohexadiene	**3** (% yield)	**4** (% yield)
1	**12a**	54	0
2	**12b**	27	63
3	**12c**	70	66
4	**12d**	95	85
5	**12e**	65	83
6	**12f**	89	55
7	**12g**	73	75
8	**12h**	51	68

SCHEME 4



to 1,4-dicarbonyl compounds and acetaldehyde, vide infra. 1,4-Dicarbonyls made up the bulk of the remaining isolable products.

The anticipated orientation of the diols **4a−h** formed was *anti*, with respect to the peroxide linkage, in all cases. This was confirmed through two-dimensional (2D) NMR spectroscopy and by obtaining crystal structures of diol **4h** and tetraol **5d**. No evidence for the formation of the *syn* product was observed in any example.

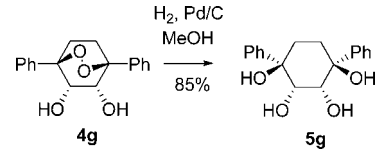
Synthesis of Tetraols with Toxocarol Relative Configuration. To directly compare the two synthetic routes to cyclohexane-1,2,3,4-tetraols outlined in Scheme 1, we chose the easily synthesized ascaridole **3d** as a model system (Scheme 4).

Given that dihydroxylation of **3d** is completely facially selective, we expected to obtain tetraol **5d** in good yield after reduction of the peroxide linkage of **4d**. Tetraol **5d** was obtained in 95% isolated yield, which is in complete contrast to the alternative method of peroxide reduction followed by dihydroxylation (Scheme 4). The workup of the dihydroxylation of **6d** resulted in a poorly combined overall yield of 64% because of the difficulty in separating the water soluble tetraols from the aqueous phase with no facial selectivity. Tetraols **5d** and **7d** were isolated as a 1:1 mixture inseparable by column chromatography. This demonstrates clearly that our approach to tetraols of type **5** is superior in both yield and ease of workup.

In order to demonstrate the synthetic scope, we next examined tetraol formation from aryl substituted diol **4g**, which was obtained from endoperoxide **3g** in 73% yield (Table 1, entry 7), and subsequently reduced to give tetraol **5g** in 85% yield (Scheme 5). Consequently, both alkyl and aryl substituents can be tolerated in the 1,4-positions.

Interestingly, attempted reduction of **4f** with 5% Pd/C and hydrogen in methanol resulted in the formation of bicyclic diol **16** in 35% yield with no observation of tetraol **5f** (Scheme 6). This rearrangement was due solely to the 5% Pd/C because the same major product was observed in the same yield when the reaction was repeated in the absence of hydrogen. While the mechanism for the transformation of **4f** into **16** is unclear,

SCHEME 5



we can draw on the observation that palladium(0) can induce fragmentation in a free radical manner of the peroxide linkage.[23] Thus, we propose that homolytic cleavage of **4f** followed by β scission and intramolecular H atom abstraction affords dicarbonyl **13**. Simple intramolecular cyclization affords hemiacetals **14** and **15**. Further cyclization of **15** leads to the observed hemiacetal **16**. Coordination of Pd appears to be assisted by the proximal methyl ester groups, giving facile rearrangement in preference to reduction, as Pd-induced reduction of **4d** and **4g** proceeded as expected. Reduction of the peroxide linkage of **4f** also was attempted using Zn in acetic acid. No evidence for the formation of diol **5f** was found presumably because of ester hydrolysis and decomposition to diketone **29f** (Scheme 9).

Dihydroxylation of Heavily Substituted 2,3-Dioxabicyclo-[2.2.2]oct-5-enes. In order to investigate a highly sterically hindered system, peroxide **17** was used as a model system for dihydroxylation and reduction (Scheme 7). Tetraol **19** is also a known compound, resulting from ring opening and dihydroxylation of peroxide **17**.[24] In complete contrast to the *anti* dihydroxylation observed for our other 1,4-disubsituted 2,3-dioxabicyclo[2.2.2]oct-5-enes, dihydroxylation of **17** proceeded in a *syn* fashion to afford diol **18**, which is most likely because of the sterically restricted environment of the steroid framework. Hydrogenation of **18** afforded the all *cis* tetrol **19** in excellent yield with physical data matching that previously reported. [24]

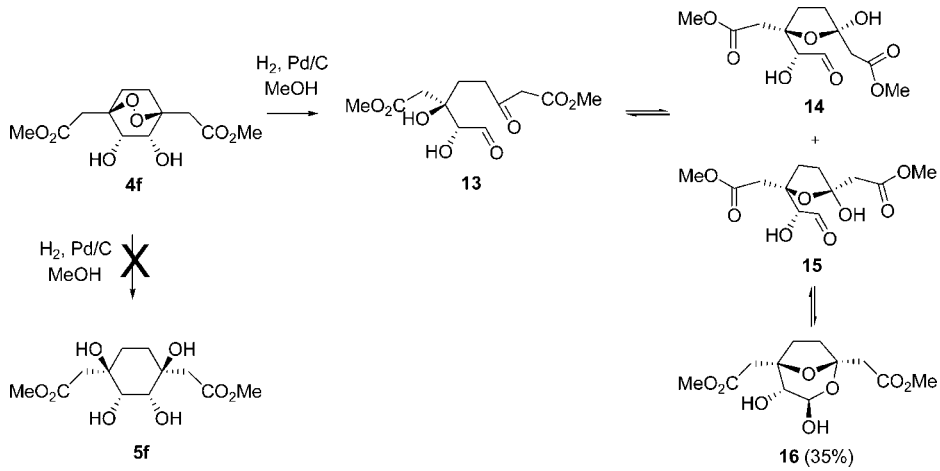
Synthesis of Natural Product 1. Terpenoid **1** has been reported recently to have been isolated from *Eupatorium fortunei*, which has been used for a long time as a Chinese medicine for the treatment of dropsical swelling, chills, and fever, and as a diuretic and antipyretic.[25] In order to evaluate the dihydroxylation of compounds of type **3** in the case where R and R^1 = H and to investigate the synthesis of reported natural product **1**, we chose to look at the dihydroxylation of 2,3-dioxabicyclo[2.2.2]oct-5-enes derived from α-phellandrene (**20**).[26,27] Peroxides **21** and **22** were synthesized in 65% overall yield from optically pure α-phellandrene (**20**) in a similar ratio (2:1) as reported in the literature[26] and were easily separable. Dihydroxylation of **21** gave two peroxide isomers (**23** and **24**) with the *syn* isomer being favored, while dihydroxylation of **22** gave only the *anti* diol (**25**) along with a significant amount of ketone **26** as the only other isolable product (Scheme 8).

The stereochemical outcome of the dihydroxylation of **21** and **22** is explained simply by the overriding steric bulk of the isopropyl group illustrated in Figure 2.

The formation of ketone **26** may have been initiated by trace metal catalysis. Numerous metals are known to induce the peroxide bond cleavage of cyclic endoperoxides, followed by

(23) Suzuki, M.; Oda, Y.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 4413–4416.
(24) Rodewald, W. J.; Boñcza-Tomaszewski, Z. *Pol. J. Chem.* **1979**, *53*, 1679–1682.
(25) Medicine, J. C. o. N. *A Dictionary of the Traditional Chinese Medicines*; People Hygene Publisher: Shanghai, 1977.
(26) Atkins, R.; Carless, H. A. J. *Tetrahedron Lett.* **1987**, *28*, 6093–6096.
(27) Turner, J. A.; Herz, W. *J. Org. Chem.* **1977**, *42*, 1895–1900.

SCHEME 6



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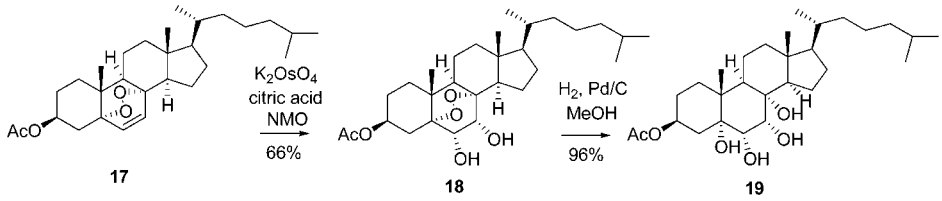

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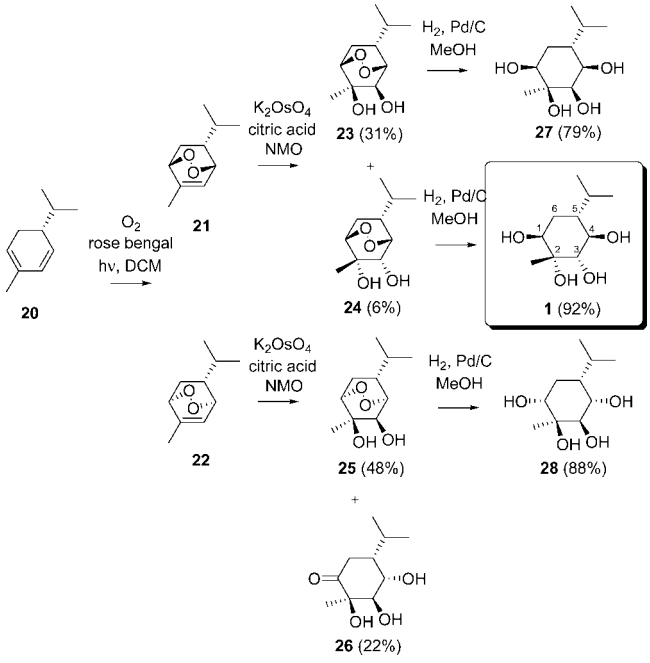

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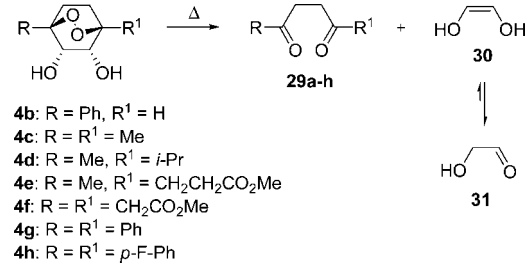


a 1,5-hydrogen atom abstraction to yield 4-hydroxy ketones of type **26**.[28,29] It is also possible that ketone byproduct, although not isolated, may be responsible for the relatively low yields of dihydroxylated compounds **23** and **24**.

The reduction of diols **23**, **24**, and **25** proceeded smoothly in excellent yields providing the reported natural product **1** along with related isomers **27** and **28**. The stereochemistry of the three tetraols was assigned by 2D NMR, and the structure of **28** was further confirmed by X-ray crystallography.

Figure 3displays the observed clear cross-peaks in the ROESY spectrum and confirms the stereochemistry of tetraol **1**.

Our synthesized tetraol **1**, however, did not match the data reported for this compound in the literature.[3,4] There were a

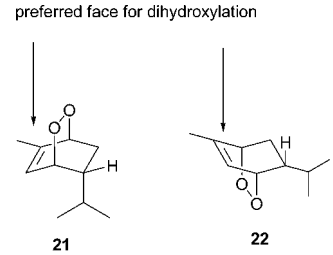


FIGURE 2. Illustration of the steric environment which directs the dihydroxylation of **21** and **22**.

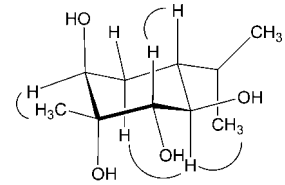


FIGURE 3. Through-space interactions of protons in tetraol **1**.

(28) Suzuki, M.; Ohtake, H.; Kameya, Y.; Hamanaka, N.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 5292–5302.

(29) Kamata, M.; Kudoh, T.; Kaneko, J.-i.; Kim, H.-S.; Wataya, Y. *Tetrahedron Lett.* **2002**, *43*, 617–620.

TABLE 2. Comparison of Reported ^{1}H and ^{13}C NMR Data for 1 and for Synthesised 1 and 27 in $CDCl_3$

carbon	**1** (lit.)		**1** (synthesized)		**27** (synthesized)	
	δ ^{1}H (*J*, Hz)	δ ^{13}C	δ ^{1}H (*J*, Hz)	δ ^{13}C	δ ^{1}H (*J*, Hz)	δ ^{13}C
1	3.77 (t, 2.4)	72.9	3.77 (brs)	73.3	3.70 (brs)	78.1
2		74.6		74.3		73.0
3	3.69 (d, 9.3)	76.7	3.50 (d, 9.6)	77.3	3.62 (brd, 7.2)	70.6
4	3.96 (dd, 11.4, 9.3)	68.9	3.53 (dd, 9.6, 9.6)	73.8	3.67 (brs)	74.3
5	1.97 (ddt, 11.7, 11.4, 3.0)	41.4	1.76 (m)	40.6	1.77 (m)	37.9
6	1.78 (m)	26.8	1.78 (m)	26.2	1.78 (m)	26.4
	1.70 (m)		1.56 (m)		1.41 (brt, 7.2)	
Me	1.39 (s)	23.9	1.39 (s)	23.7	1.18 (s)	22.8
*i*Pr	2.30 (m)	27.8	2.18 (dsept, 6.6, 1.8)	25.6	2.08 (brs)	25.5
*i*Pr	0.92 (d, 7.2)	20.9	0.95 (d, 6.6)	20.8	0.96 (d, 7.2)	20.9
*i*Pr	0.78 (d, 7.2)	14.9	0.86 (d, 6.6)	16.0	0.87 (d, 7.2)	16.9

number of noticeable differences between our tetraol **1** and that previously reported. The melting point we obtained for our tetraol **1** was 124−126 °C, whereas the compound reported in the literature was an oil. In addition, our tetraol **1** was virtually insoluble in chloroform and dichloromethane, which were the solvents used to obtain NMR spectra and optical rotation, respectively, for the reported literature compound. Therefore, obtaining an optical rotation in dichloromethane for comparison was not possible. The HRSIMS obtained for $[M + H]^+$ of **1** by Gao et al. was found as 205.0536[4] for a calculated mass peak of $C_{10}H_{21}O_4^+$ 205.1434, which actually should be 205.1440. This reported HRSIMS is outside the normal range for a match with the calculated mass, while our value for compound **1** was within the acceptable limits. The authors also report an IR resonance at 1705 cm^{-1} in the compound characterization data which contradicts the proposed structure. Once ^{1}H and ^{13}C NMR spectra of **1** and isomer **21** were recorded in deuterated chloroform, it was clear that the compound reported in the literature was neither tetraol **1** nor isomer **21** (Table 2). We were unable to obtain a good enough spectrum of **22** in deuterated chloroform for comparison because of extremely poor solubility. Consequently, we conclude that the reported tetraol **1** is not the compound isolated by Gao et al.

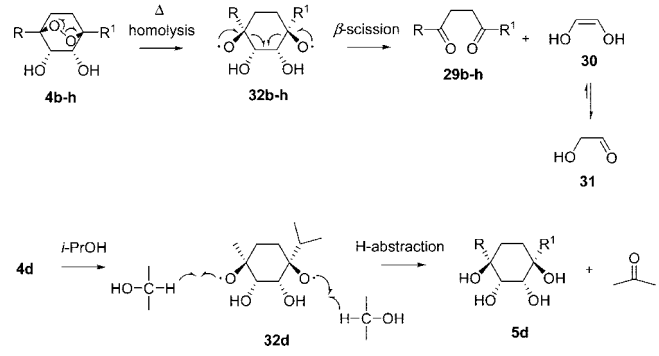
Facile Rearrangement of 2,3-Dioxabicyclo[2.2.2]octane-5,6-diols to 1,4-Dicarbonyls. As previously mentioned, the stability of diols of type **4** was found to be extremely variable during their formation and upon isolation (Table 1). Upon closer examination, we found that diols of type **4** will undergo an extremely clean thermal rearrangement to their 1,4-dicarbonyls **29** and glycoaldehyde (**31**) (Scheme 9), a rearrangement not previously reported in the literature. (Note: glycoaldehyde was detected as the dimeric and polymeric species by NMR.) We examined this rearrangement for a range of peroxide diols **4b**−**h** under a variety of conditions as summarized in Table 3. It was found that the thermally induced rearrangement of diols **4b**−**h** to dicarbonyls **29b**−**h** proceeds quantitatively in acetonitrile and can tolerate a broad range of substituents. Comparison of Table 3, entries 1−7 or 8−11, clearly indicates that the reaction rate increases with solvent polarity.

It has been reported previously that thermal decomposition of 2,3-dioxabicyclo[2.2.2]octane proceeds in a radical manner involving first the homolytic cleavage of the peroxide linkage followed by β scission.[30] This process affords a range of products via a polar transition state, with the rate-determining step being accelerated with increasing solvent polarity and H-bonding ability. Moreover, it has been demonstrated that β scission is the rate-determining step in the decomposition of alkoxy radicals, which are generated from homolytic cleavage of dialkylperoxides, and is accelerated again with increasing solvent polarity and H-bonding ability.[31] Therefore, mechanistically we propose that the rearrangement of 2,3-dioxabicyclo[2.2.2]octane-5,6-diols proceeds via the mechanism outlined in Scheme 10.

TABLE 3. Thermal Rearrangement of 2,3-Dioxabicyclo[2.2.2]octane-5,6-diols 4b−h to Dicarbonyls 29b−h

entry	diol	solvent/conditions	**29** (% conversion)
1	**4d**	methanol/reflux 0.5 h	100
2	**4d**	acetonitrile/reflux 2 h	100
3	**4d**	ethylacetate/reflux 5.5 h	100
4	**4d**	THF/reflux 16 h	100
5	**4d**	benzene/reflux 16 h	0
6	**4d**	DCM/reflux 24 h	0
7	**4d**	neat/4 °C 1 week	25
8	**4e**	acetonitrile/reflux 16 h	100
9	**4e**	THF/reflux 16 h	50
10	**4e**	DCM/reflux 16 h	0
11	**4e**	neat/4 °C 48 h	100
12	**4c**	acetonitrile/reflux 16 h	100
13	**4f**	acetonitrile/reflux 16 h	100
14	**4g**	acetonitrile/reflux 16 h	100
15	**4h**	acetonitrile/reflux 16 h	100

SCHEME 10



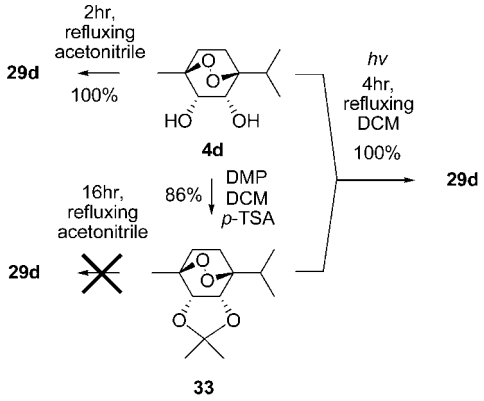
In further confirm that decomposition was a radical process, **4d** was heated in isopropanol, which is a solvent well-known to inhibit free radical processes by competition via radical abstraction of a hydrogen atom from isopropanol to give acetone.[19,20] Indeed, tetraol **5d** (Scheme 4) was now isolated in 30% yield, with the remainder of the yield being 1,4-diketone **29d**, confirming the free radical nature of these rearrangements.

Concern about the stability of the 2,3-dioxabicyclo[2.2.2]octane-5,6-diols **4b**−**h** led us to investigate protection of the diol moiety of **4d** as the acetonide, a technique which previously allowed stabilization of dihydroxylated 1,2-dioxines.[15] Furthermore, this would allow us to examine the importance of the "free" hydroxyl

(30) Coughlin, D. J.; Brown, R. S.; Salomon, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 1533–1539.

(31) Tsentalovich, Y. P.; Kulik, L. V.; Gritsan, N. P.; Yurkovskaya, A. V. *J. Phys. Chem. A* **1998**, *102*, 7975–7980.

SCHEME 11



groups on the outcome of the radical rearrangement. Acetonide **33** showed no signs of decomposition in refluxing acetonitrile over 16 h, whereas the unprotected diol **4d** showed complete conversion within 2 h (Scheme 11). Thus, under thermal conditions, the free hydroxyl groupings are vital for rearrangement to occur.

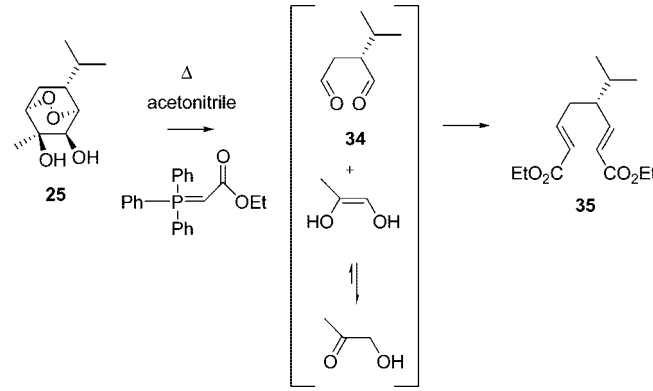
Interestingly, under photolytic conditions, both the protected (**33**) and unprotected (**4d**) diol underwent complete conversion to dicarbonyl **29d** in 4 h in refluxing dichloromethane, conditions under which **4d** is stable in the absence of light (compare with Table 3, entry 6). To the best of our knowledge, this is the first example of unassisted photolytic decomposition of 2,3-dioxabicyclo[2.2.2]octanes, although ascaridole **3d** has been decomposed in this fashion[32] along with many other acyclic peroxides and hydroperoxides.[33] The identical rates obtained for photolytic decomposition of **4d** and **33** and different rates for their thermal decomposition can be explained by the fact that photodissociation of the peroxide linkage initially affords an excited dialkoxy radical, which undergoes decomposition via β scission in an "early vibration" as opposed to thermal decomposition, which is reversible.[33]

Synthesis of Optically Pure 1,4-Dicarbonyl Compounds. Formation of 1,4-dicarbonyl compounds in this fashion opens the opportunity for the synthesis of dicarbonyls containing other stereochemical features such as chiral centers. As an example, photooxidation and dihydroxylation of **22** provided **25**. Heating of **25** in acetonitrile under reflux followed by in situ trapping of dialdehyde **34** with ethyl (triphenyl-λ^5-phosphanylidene) acetate afforded diester **35** in 90% yield (Scheme 12).

Diol Orientation with Respect to the Peroxide Bond and Its Influence on Radical Rearrangement. Given that we now have shown that *anti* diol **25** afforded dicarbonyl **34**, and that we also had the *syn* diastereomer **26** of α-phellandrene-derived diol **22** in hand, this provided us with a unique opportunity to examine the relationship of the peroxide bond to the diol on product outcome during thermolysis (Scheme 13). Thermal decomposition of **22** in acetonitrile under reflux resulted in the formation of a 1:1 mixture of anomers **38** and **39**, along with bicyclic hemiacetal **42**, with no dialdehyde **34** being formed. Anomers **38** and **39** were heated under reaction conditions and did not give rise to compound **42**. The formation of the mixture of anomers, **38** and **39**, and **42** is rationalized from intramolecular hydrogen atom abstraction of different chair conformations of diradical **36** (Scheme 13). These compounds

(32) Russell, K. E.; Tobolsky, A. V. *J. Am. Chem. Soc.* **1954**, *76*, 395–399.
(33) Calvert, J. G.; Pitts, J. N., Jr. *Photochemistry*; John Wiley and Sons, Inc: New York, 1966.

SCHEME 12



formed as opposed to dialdehyde **34** because of the orientation of the hydroxyl group and its proximity to the oxygen-centered radical, resulting from homolytic cleavage. Confirmation of the structures was made by examining the clear cross-peaks in the ROESY spectrum (see compounds **38**, **39**, and **42** in Scheme 13).

Conclusion

Herein, we have demonstrated an alternative route to cyclohexane-1,2,3,4-tetraols of toxocarol relative stereochemistry. The method has higher selectivity in cases where the parent 2,3-dioxabicyclo[2.2.2]oct-5-ene has functionality other than H at the bridgehead position. The alternative route also allows for a simplified workup, and the necessity in some literature procedures for a protection−deprotection protocol is removed. Our application of dihydroxylation of 2,3-dioxabicyclo[2.2.2]oct-5-enes to the synthesis of tetraols **1**, **27**, and **28** demonstrated that **1** was not the natural product isolated by Gao et al. nor was it the configuration of tetraols **27** or **28**. We also have touched on potential routes into stereochemically specific-substituted dicarbonyl compounds and presented a mechanistic explanation for the susceptibility of 2,3-dioxabicyclo[2.2.2]oct-5,6-diols to rearrange to 1,4-dicarbonyl compounds.

Experimental Section

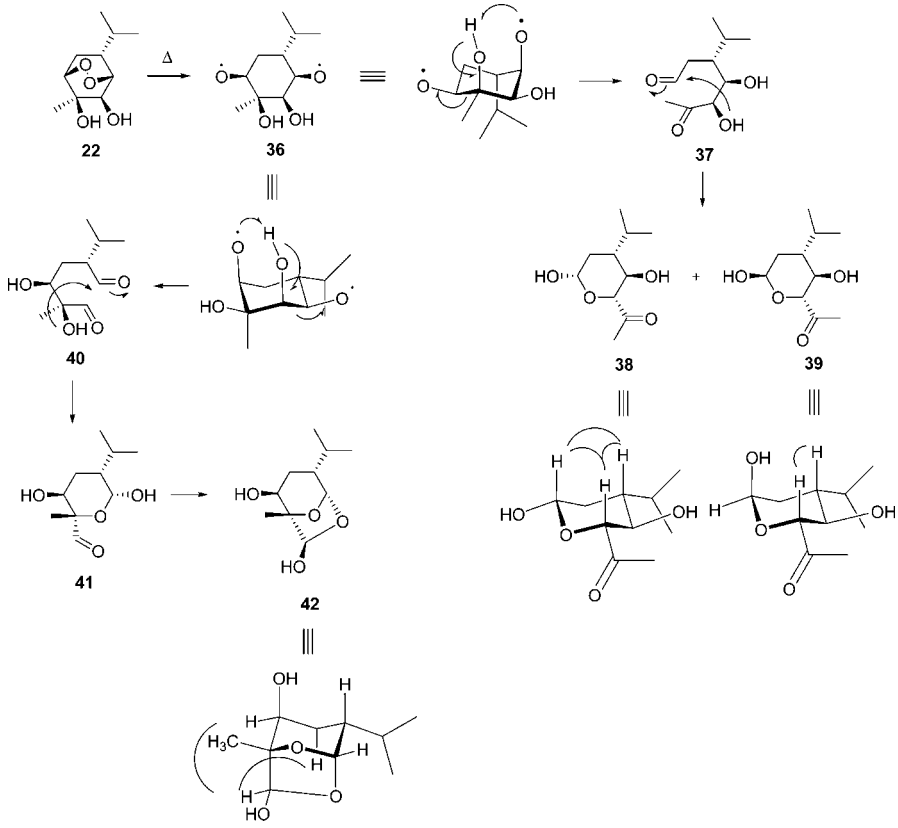
Compounds **3a**,[34] **3d**,[35] **12b**,[36] **12c**,[37] **12g**,[38] **12h**,[39] **21**,[27] and **22**[27] showed ^{1}H NMR spectra identical to the literature.

General Procedure for the Synthesis of Endoperoxides. A solution of the appropriate 1,3-diene (∼1 g) in CH_2Cl_2 (60 mL/g) was photolyzed with 3 × 500 W halogen lamps in the presence of Rose Bengal bis(triethylammonium) salt (100 mg) and oxygen until a reaction was determined by TLC. The reaction was performed in a flask fitted with an external cooling jacket. The solution was concentrated in vacuo, and the resulting residue was purified by flash chromatography.

(±)-(1*R*,4*S*)-1-Phenyl-2,3-dioxabicyclo[2.2.2]oct-5-ene (3b): yield 27%, colorless solid; mp 50−52 °C; R_f 0.48 (1:4 ethylacetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55−1.69 (m, 1H), 1.76−1.90 (m, 1H), 2.38−2.49, (m, 2H), 4.71−4.82 (m, 1H),

(34) Spivey, A. C.; Manas, C. G.; Mann, I. *Chem. Commun. (Cambridge, U.K.)* **2005**, 4426–4428.
(35) Fuchter, M. J.; Hoffman, B. M.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 724–729.
(36) Reich, H. J.; Wollowitz, S. *J. Am. Chem. Soc.* **1982**, *104*, 7051–7059.
(37) Brady, W. T.; Norton, S. J.; Ko, J. *Synthesis* **1985**, 704–705.
(38) Dale, J.; Kristiansen, P. O. *Acta Chem. Scand.* **1971**, *25*, 359–360.
(39) del Pilar Crespo, M.; Avery, T. D.; Hanssen, E.; Fox, E.; Robinson, T. V.; Valente, P.; Taylor, D. K.; Tilley, L. *Antimicrob. Agents Chemother.* **2008**, *52*, 98–109.

SCHEME 13



6.71−6.83 (m, 2H), 7.30−7.49 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.4, 27.9, 71.3, 78.0, 126.2, 128.5, 128.7, 132.9, 136.1, 140.0; IR (solid) 2932, 1493, 1447, 1016, 919, 695 cm^{-1}; MS *m*/*z* (+EI) 188 (M^+, 4), 115 (15), 105 (100), 77 (33); HRMS (+EI) (M + Na)$^+$ found 211.0723, (M + Na)$^+$ calcd for $C_{12}H_{12}O_2Na$, 211.0735.

1,4-Dimethyl-2,3-dioxabicyclo[2.2.2]oct-7-ene (3c): yield 70%, pale yellow oil; R_f 0.44 (1:4 ethylacetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 6H), 1.47−1.59 (m, 2H), 1.97−2.13 (m, 2H), 2.99 6.38 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 21.6, 30.0, 74.8, 136.0; IR (neat) 2932, 1452, 1380, 1052, 874, 699 cm^{-1}; HRMS (+EI) (M)$^+$ found 140.0839, (M)$^+$calcd for $C_8H_{12}O_2$, 140.0837.

(±)-Methyl-3-(4-methyl-2,3-dioxabicyclo[2.2.2]oct-7-en-1-yl)-propanoate (3e): yield 65%, colorless oil; R_f 0.29 (1:4 ethylacetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.44−1.57 (m, 2H), 1.97−2.17, (m, 4H), 2.39−2.57 (m, 2H), 3.69 (s, 3H), 6.42 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 21.3, 28.1, 28.2, 29.5, 30.2, 51.7, 74.8, 76.2, 133.8, 136.6, 173.5; IR (neat) 1737, 1637, 1438, 1378, 1197, 1172, 883 cm^{-1}; MS *m*/*z* (+EI) 211 (M^+, 4), 181 (100), 148 (38), 123 (60), 106 (46); HRMS (+EI) (M + Na)$^+$ found 235.0948, (M + Na)$^+$calcd for $C_{11}H_{16}O_4Na$, 235.0946.

Dimethyl 2,2′-[(1*R*,4*S*)-2,3-dioxabicyclo[2.2.2]oct-5-ene-1,4-diyl]diacetate (3f): yield 89%, colorless solid; mp 32−34 °C; R_f 0.50 (1:1 ethylacetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66−1.82 (m, 2H), 2.06−2.22 (m, 2H), 2.65 (d, 2H, J = 15.0 Hz), 2.73 (d, 2H, J = 15.0 Hz), 3.71 (s, 6H), 6.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 27.9, 39.5, 52.1, 75.7, 134.0, 169.4; IR (solid) 2955, 1725, 1436, 1295, 1151, 1006, 698 cm^{-1}; HRMS (+EI) (M + Na)$^+$ found 279.0853, (M+Na)$^+$calcd for $C_{12}H_{16}O_6Na$, 279.0853.

General Procedure for the Synthesis of *syn* Diols. To a solution of endoperoxide (3 mmol) and citric acid (6 mmol) in *tert*-butanol/H_2O (1:1) was added potassium osmate dihydrate (0.03mmol) followed by 4-methylmorpholine N-oxide (3 mmol). The reaction was stirred at 50 °C until TLC was determined. The *tert*-butanol was removed in vacuo, and the aqueous layer was extracted with ethyl acetate. The combined organics were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. The crude product was purified by flash chromatography.

(±)-(1*S*,4*S*,5*S*,6*R*)-1-Phenyl-2,3-dioxabicyclo[2.2.2]octane-5,6-diol (4b): yield 63%, colorless solid; R_f 0.14 (3:7 ethylacetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06−2.29 (m, 3H), 2.46−2.57 (m, 1H), 2.68, (br, 1OH), 3.13 (br, 1OH), 4.28 (m, 2H), 4.47 (dd, 1H, J = 7.5, 4.8 Hz), 7.30−7.50 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 18.9, 22.4, 65.2, 69.6, 75.0, 80.3, 126.0, 128.3, 128.6, 128.8. Compound was too unstable to obtain HRMS or melting point.

(1*R*,4*S*,5*S*,6*R*)-1,4-Dimethyl-2,3-dioxabicyclo[2.2.2]octane-5,6-diol (4c): yield 66%, white needles; mp 38−40 °C; R_f 0.3 (2:3 ethylacetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 6H), 1.72 (dd, 2H, J = 13.5, 5.4 Hz), 2.00 (dd, 2H, J = 13.2, 5.4 Hz), 2.99 (br, 2OH), 3.92 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 21.7, 24.5, 69.5, 77.5. IR (neat) 3415, 3266, 2934, 1453, 1370, 1062, 980, 864, 652 cm^{-1}; HRMS (+EI) (M − H)$^-$ found 173.0821, (M − H)$^-$calcd for $C_8H_{13}O_4$, 173.0819.

(±)-(1*R*,4*R*,5*S*,6*R*)-1-Isopropyl-4-methyl-2,3-dioxabicyclo[2.2.2]-octane-5,6-diol (4d): yield 85%, colorless oil; R_f 0.25 (3:7 ethylacetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, 3H, J = 6.9 Hz), 0.99 (d, 3H, J = 6.9 Hz), 1.17 (s, 3H), 1.66−1.74 (m, 1H), 1.80 (sept, 1H, J = 6.9 Hz), 1.85−2.05 (m, 3H), 3.00 (br s, 2OH), 3.91 (dd, 1H, J = 7.8, 1.5 Hz), 4.19 (dd, 1H, J = 7.8, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 16.6, 16.9, 20.9, 21.2, 24.6, 33.1, 67.0, 69.8, 76.8, 80.6; IR (neat) 3437, 1454, 1388, 1371, 1085, 1019 cm^{-1}; HRMS (+EI) (M + Na)$^+$ found 225.1102, (M + Na)$^+$calcd for $C_{10}H_{18}O_4Na$, 225.1103.

(±)-Methyl-3-[(1*S*,4*S*,5*R*,6*S*)-5,6-dihydroxy-4-methyl-2,3-dioxabicyclo [2.2.2]octan-1-yl]propanoate (4e): yield 83%, colorless oil; R_f 0.30 (1:1 ethylacetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.62−1.83 (m, 3H), 1.91−2.09, (m, 3H), 2.34−2.58 (m, 2H), 3.65 (br, 2OH), 3.70 (s, 3H), 3.88 (dd, 1H, J = 8.2, 1.5 Hz) 3.94 (dd, 1H, J = 8.2, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$)

21.4, 23.2, 24.3, 27.1, 29.4, 52.0, 66.4, 69.1, 77.7, 78.0, 175.1; IR (neat) 3468, 2936, 1731, 1441, 1105 cm^{-1}; MS *m*/*z* (+EI) 248 (M^+, 5), 230 (19), 178 (39), 167 (53), 133 (65), 118 (42), 65 (39), 48 (100). HRMS (+EI) $(M)^+$ found 246.1102, $(M)^+$calcd for $C_{11}H_{18}O_6$, 246.1103.

Dimethyl 2,2′-[(1R,4S,5R,6S)-5,6-dihydroxy-2,3-dioxabicyclo-[2.2.2]octane-1,4-diyl]diacetate (4f): yield 55%, white solid; mp 92−94 °C; R_f 0.45 (4:1 ethylacetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82−1.98 (m, 2H), 2.09−2.26 (m, 2H), 2.55 (d, 2H, J = 14.7 Hz), 2.59 (d, 2H, J = 14.7 Hz), 3.71 (s, 6H), 4.22 (s, 2H), 4.72 (br, 2OH); ^{13}C NMR (75 MHz, $CDCl_3$) 23.4, 40.3, 52.4, 68.0, 78.6, 170.6; IR (solid) 3394, 3251, 2957, 2938, 1729, 1440, 1348, 1299, 1212, 1172, 1090, 1014, 955, 714 cm^{-1}; MS *m*/*z* (+EI) 290 (M^+, <1), 193 (15), 183 (60), 151 (58), 145 (100), 91 (39), 85 (35); HRMS (+EI) $(M + Na)^+$ found 313.0901, $(M+Na)^+$calcd for $C_{12}H_{18}O_8Na$, 313.0899.

(1*R*,4*S*,5*R*,6*S*)-1,4-Diphenyl-2,3-dioxabicyclo[2.2.2]octane-5,6-diol (4g): yield 65%, white solid; mp 138−140 °C; R_f 0.48 (2:3 ethylacetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24−2.35 (m, 2H), 2.63−2.73 (m, 2H), 2.76 (br, 2OH), 4.47 (s, 2H), 7.35−7.46 (m, 6H), 7.51−7.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.7, 70.7, 81.1, 126.3, 128.8, 139.7, 199.0; IR (solid) 3366, 2943, 1497, 1447, 1100, 748, 695 cm^{-1}; MS *m*/*z* (+EI) 296 (M^+, <1), 238 (30), 133 (24), 105 (100), 77 (37); HRMS (+EI) $(M + Na)^+$ found 321.1109, $(M + Na)^+$calcd for $C_{18}H_{18}O_4Na$, 321.1103.

(1*R*,4*S*,5*R*,6*S*)-1,4-Bis(4-fluorophenyl)-2,3-dioxabicyclo[2.2.2]-octane-5,6-diol (4h): yield 68%, white solid; mp 120−122 °C; R_f 0.54 (2:3 ethylacetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26−2.34 (m, 2H), 2.55−2.71 (m, 2H), 2.72 (br, 2OH), 4.43 (s, 2H), 7.06−7.11 (m, 4H), 7.48−7.53 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): 24.7, 70.5, 80.8, 115.7 (d, J = 21.0 Hz), 128.2 (d, J = 8.3 Hz), 135.4, 163.0 (d, J = 246.4 Hz); IR (nujol) 3484, 3379, 1598, 1505, 1462, 1377, 1230, 1160, 1107, 1092, 1005, 957, 837, 814 cm^{-1}. Anal. Calcd for $C_{18}H_{16}F_2O_4$: C, 64.67; H, 4.82. Found: C, 64.66; H, 4.96.

(3*β*,5α,6α,7α,8α)-6,7-Dihydroxycholestan-3-yl acetate (18): yield 66%, white crystals; mp 174−176 °C (ethanol) R_f 0.70 (1:1 ethylacetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, 3H, J = 0.9 Hz), 0.87 (d, 3H, J = 0.9 Hz), 0.90 (d, 3H, J = 6.6 Hz), 0.91 (s, 3H), 1.03 (s, 3H), 1.04−1.96 (m, 24H), 2.0 (s, 3H), 2.13−2.30 (m, 1H), 2.92 (brs, 2OH), 3.76 (d, 1H, J = 7.8 Hz), 4.21 (d, 1H, J = 7.8 Hz), 4.76 (tt, 1H, J = 4.5, 11.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 12.6, 17.5, 18.6, 20.4, 21.2, 22.0, 22.5, 22.8, 23.7, 25.9, 27.9, 28.2, 33.4, 33.8, 35.4, 35.9, 36.0, 39.4, 39.8, 44.2, 51.8, 55.7, 56.5, 66.9, 68.9, 69.3, 82.7, 83.4, 170.1; IR (solid) 3476, 2930, 1726, 1366, 1244, 1115, 1058, 1029 cm^{-1}. Anal. Calcd for $C_{29}H_{48}O_6$: C, 70.70; H, 9.82. Found: C, 70.75; H, 9.79.

(1*R*,4*S*,5*R*,6*R*,7*R*)-5-Methyl-7-(propan-2-yl)-2,3-dioxabicyclo-[2.2.2]octane-5,6-diol (23): yield 31%, colorless oil; R_f 0.30 (2:3 ethylacetate/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.96 (d, 3H, J = 6.6 Hz), 0.97 (d, 3H, J = 6.6 Hz), 1.30−1.35 (m, 4H), 1.40 (ddsept, 1H, J = 10.8, 6.6, 0.6, Hz), 1.91 (dddd, 1H, J = 10.8, 10.2, 8.4, 2.4 Hz), 2.40 (dddd, 1H, J = 14.4, 10.2, 6.0 Hz), 3.45−3.52 (m, 3H), 3.92 (dd, 1H, J = 6.0, 2.4 Hz) 4.08 (dd, 1H, J = 2.4, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 20.3, 20.4, 23.0, 27.1, 30.8, 40.8, 68.0, 69.4, 78.7, 82.0; IR (neat) 3431, 2960, 1387, 1370, 1094, 963, 733 cm^{-1}; HRMS (+EI) $(M + H)^+$ found 203.1287, $(M + H)^+$calcd for $C_{10}H_{19}O_4$, 203.1283.

(1*R*,4*S*,5*S*,6*S*,7*R*)-5-Methyl-7-(propan-2-yl)-2,3-dioxabicyclo-[2.2.2]octane-5,6-diol (24): yield 6%, colorless oil; R_f 0.50 (2:3 ethylacetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 6.0 Hz), 0.97 (d, 3H, J = 6.0 Hz), 1.50 (s, 3H), 1.77−1.91 (m, 4H), 2.15−2.32 (m, 1H), 3.07 (s, 1OH), 3.20 (d, 1OH, J = 6.0 Hz), 3.88−3.95 (m, 2H), 4.23 (ddd, 1H, J = 2.4, 2.4, 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 20.4, 21.2, 24.8, 27.0, 31.1, 40.5, 67.3, 71.8, 75.1, 78.8; HRMS (+EI) $(M + H)^+$ found 203.1288, $(M + H)^+$calcd for $C_{10}H_{19}O_4$, 203.1285.

(1*S*,4*R*,5*R*,6*R*,7*R*)-5-Methyl-7-(propan-2-yl)-2,3-dioxabicyclo-[2.2.2]octane-5,6-diol (25): yield 48%, colorless oil; R_f 0.44 (2:3 ethylacetate/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 6.6 Hz), 0.98 (d, 3H, J = 6.6 Hz), 1.49 (s, 3H), 1.60 (ddddd, 1H, J = 10.8, 9.6, 7.8, 3.0, 2.4 Hz), 1.71 (ddd, 1H, J = 13.8, 7.8, 3.0, Hz), 1.80 (ddsept, 1H, J = 9.6, 6.6, 1.2 Hz), 2.27 (dddd, 1H, J = 13.8, 10.8, 3.0, 1.2 Hz), 2.52 (br, 1OH), 2.95 (br, 1OH), 3.89 (ddd, 1H, J = 3.0, 3.0, 3.0 Hz), 3.92 (d, 1H, J = 3.6 Hz) 4.00 (dd, 1H, J = 3.6, 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 20.0, 20.2, 25.4, 26.2, 29.6, 33.7, 68.4, 70.6, 76.9, 79.0; IR (neat) 3415, 2961, 1370, 1078, 980, 940, 735 cm^{-1}; HRMS (+EI) $(M + H)^+$ found 203.1283, $(M + H)^+$calcd for $C_{10}H_{19}O_4$, 203.1285.

(2*R*,3*R*,4*S*,5*R*)-2,3,4-Trihydroxy-2-methyl-5-(propan-2-yl)cyclohexanone methane (26): yield 22%, pale yellow solid; mp 72−74 °C; R_f 0.30 (1:1 ethylacetate/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.94 (d, 3H, J = 6.0 Hz), 1.01 (d, 3H, J = 6.0 Hz), 1.52 (s, 3H), 1.80 (m, 1H), 1.85 (m, 1H), 2.44 (dd, 1H, J = 13.2, 3.6 Hz), 2.70 (t, 1H, J = 13.2 Hz), 3.93 (d, 1H, J = 2.4 Hz), 4.27 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 20.6, 20.7, 24.1, 28.8, 36.1, 45.6, 69.3, 77.5, 79.4, 213.8.; IR (nujol) 3436, 1715, 1135, 1040, 948, 736 cm^{-1}; HRMS (+EI) $(M + H)^+$, found 203.1283, $(M + H)^+$calcd for $C_{10}H_{19}O_4$, 203.1283.

General Methods for Peroxide Reduction. Method A. To a stirred solution of endoperoxide (1 mmol) in methanol (5 mL) was added 10% w/w of 5% palladium on carbon, and the mixture was stirred under a hydrogen atmosphere until TLC was completed. The suspension was then filtered through kenite and washed with methanol, and the solvent was removed in vacuo to give crude tetraol. The crude product was purified by flash column chromatography or recrystallization.

Method B. To a stirred solution of endoperoxide (1 mmol) in acetic acid (5 mL) was added zinc dust (5 mmol), and the mixture was stirred for 24 h. The acetic acid was removed in vacuo, and the solids were triturated with THF to give crude tetraol. The crude product was purified by flash column chromatography or recrystallization.

(1*S*,2*R*,3*S*,4*R*,5*R*)-2-Methyl-5-(propan-2-yl)cyclohexane-1,2,3,4-tetrol (1): yield 92%, white solid; mp 124−126 °C (DCM); R_f 0.40 (1:9 methanol/ethylacetate); ^{1}H NMR (600 MHz, CD_3OD) δ 0.82 (d, 3H, J = 6.6 Hz), 0.92 (d, 3H, J = 6.6 Hz), 1.30 (s, 3H), 1.43−1.50 (m, 1H), 1.66−1.74 (m, 2H), 2.19 (dsept, 1H, J = 6.6, 1.8 Hz), 3.35 (d, 1H, J = 9.0 Hz), 3.46 (dd, 1H, J = 9.0, 9.0 Hz), 3.59 (brt, 1H); ^{13}C NMR (75 MHz, CD_3OD) 16.7, 21.9, 24.4, 27.1, 27.2, 42.7, 74.2, 75.5, 76.2, 78.6; IR (solid) 3374, 2954, 1363, 1225, 1031 cm^{-1}; HRMS (+EI) $(M-H)^-$ found 203.1289, $(M - H)^-$calcd for $C_{10}H_{19}O_4$, 203.1289.

(1*S*,2*S*,3*R*,4*S*)-1-Methyl-4-(propan-2-yl)cyclohexane-1,2,3,4-tetrol (5d): yield 95%, white solid; mp 122−124 °C (DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, 3H, J = 6.9 Hz), 0.93 (d, 3H, J = 6.9 Hz), 1.26 (s, 3H), 1.42−1.55 (m, 2H), 1.58−1.70 (m, 1H), 1.75−2.0 (m, 2H), 3.71−3.73 (m, 1H), 3.78 (d, 1H, J = 3.6 Hz), 4.88 (s, 4OH); ^{13}C NMR (75 MHz, CD_3OD) 16.6, 16.7, 21.9, 29.5, 34.1, 35.3, 74.3, 75.0, 76.2, 76.6; IR (solid) 3482, 3375, 2959, 1454, 1368, 1164, 1088, 989, 694 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.66; H, 9.65.

(1*R*,2*S*,3*R*,4*S*)-1,4-Diphenylcyclohexane-1,2,3,4-tetrol (5g): yield 85%, white solid; mp 162−164 °C (DCM); ^{1}H NMR (200 MHz, CD_3OD) δ 2.04−2.20 (m, 2H), 2.53−2.69 (m, 2H), 4.15 (s, 2H), 7.15−7.36 (m, 6H), 7.69−7.76 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD) 33.1, 76.3, 78.3, 127.9, 128.7, 146.7; IR (nujol) 3581, 3541, 3469, 3434, 1308, 1234, 787, 700 cm^{-1}; HRMS (+EI) $(M - H)^+$ found 299.1281, $(M - H)^+$calcd for $C_{18}H_{19}O_4$, 299.1283.

Dimethyl 2,2′-(3,4-dihydroxy-2,8-dioxabicyclo[3.2.1]octane-1,5-diyl)diacetate (16): yield 35%, colorless oil; R_f 0.40 (4:1 ethylacetate/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.60−1.68 (m, 1H), 1.69−1.75 (m, 2H), 1.84−1.90 (m, 1H), 2.57 (d, 1H, J = 16.2 Hz), 2.86 (d, 1H, J = 16.2 Hz), 2.88 (d, 1H, J = 16.2 Hz), 2.90 (d, 1H, J = 16.2 Hz), 3.71 (s, 3H), 3.72 (s, 3H), 4.06 (s, 1OH), 4.15 (s, 1H), 4.32 (d, 1OH, J = 9.6 Hz), 5.65 (d, 1H, J = 9.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 30.2, 31.7, 39.7, 40.0, 51.7, 67.0, 85.4, 95.6, 107.1, 169.5, 173.1; IR (solid) 3456, 2955, 1728, 1439, 1206,

1167, 1042 cm^{-1}; HRMS (+EI) $(M + Na)^+$ found 313.0887, $(M + Na)^+$calcd for $C_{12}H_{18}O_8Na$, 313.0899.

(3β,5α,6α,7α,8α)-5,6,7,8-Tetrahydroxycholestan-3-yl acetate (19): yield 96%, white crystals; mp 218−220 °C (ethanol) R_f 0.50 (1:1 ethylacetate/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (s, 3H), 0.85 (d, 3H, $J = 1.2$ Hz), 0.88 (d, 3H, $J = 1.2$ Hz), 0.92 (d, 3H, $J = 6.6$ Hz), 1.08 (s, 3H), 1.04−1.96 (m, 24H), 2.03 (s, 3H), 2.13−2.30 (m, 1H), 3.40 (brs, 4OH), 3.70 (d, 1H, $J = 7.8$ Hz), 4.04 (d, 1H, $J = 7.8$ Hz), 5.08−5.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 11.7, 18.8, 20.8, 21.4, 22.5, 22.8, 23.2, 23.3, 23.8, 26.7, 27.5, 28.0, 33.7, 35.7, 35.9, 38.0, 38.8, 39.1, 39.4, 42.5, 48.0, 56.0, 60.2, 69.0, 70.1, 70.3, 74.8, 78.2, 170.6; IR (solid) 3445, 3335, 3145, 2929, 1717, 1462, 1380, 1264, 1243, 1100, 1039, 992 cm^{-1}. Anal. Calcd for $C_{29}H_{50}O_6$: C, 70.41; H, 10.19. Found: C, 70.21; H, 10.16.

(1*S*,2*S*,3*R*,4*R*,5*R*)-2-Methyl-5-(propan-2-yl)cyclohexane-1,2,3,4-tetrol (27): yield 79%, white solid; mp 48−50 °C (DCM); R_f 0.26 (1:9 methanol/ethylacetate); ^1H NMR (600 MHz, $CDCl_3$) δ 0.87 (d, 3H, $J = 7.2$ Hz), 0.96 (d, 3H, $J = 7.2$ Hz), 1.18 (s, 3H), 1.41 (brt, 1H, $J = 12.6$, Hz), 1.77−1.81 (m, 2H), 2.08 (brs, 1H), 3.53 (br, 1OH), 3.62 (brd, 1H, $J = 7.2$ Hz), 3.67 (brs, 1H), 3.70 (brs, 1H), 4.16 (br, 1OH), 4.55 (br, 1OH), 4.65 (br, 1OH); ^{13}C NMR (75 MHz, $CDCl_3$) 16.9, 20.9, 22.8, 25.5, 26.4, 37.9, 70.6, 73.0, 74.3, 78.1; IR (solid) 3364, 2956, 1442, 1386, 1142, 1039, 930 cm^{-1}; HRMS (+EI) $(M + H)^+$ found 205.1440, $(M + H)^+$calcd for $C_{10}H_{21}O_4$, 205.1440.

(1*R*,2*S*,3*R*,4*S*,5*R*)-2-Methyl-5-(propan-2-yl)cyclohexane-1,2,3,4-tetrol (28): yield: 88%, white solid; mp 176−178 °C (ethylacetate); R_f 0.48 (1:9 methanol/ethylacetate); ^1H NMR (300 MHz, CD_3OD) δ 1.68 (d, 6H, $J = 6.6$ Hz), 1.90 (s, 3H), 1.93−2.17 (m, 2H), 2.24−2.46 (m, 2H), 4.08−4.21 (m, 1H), 4.29 (ddd, 1H, $J = 11.4$, 4.2, 4.2 Hz), 4.51−4.58 (m, 1H), 4.71 (s, 1OH), 4.93 (d, 1OH, $J = 4.5$ Hz), 5.14 (d, 1OH, $J = 2.7$ Hz), 5.31 (d, 1OH, $J = 4.2$ Hz); ^{13}C NMR (75 MHz, CD_3OD) 28.7, 30.5, 31.0, 37.1, 40.4, 51.4, 79.7, 81.9, 83.4, 87.4; IR (Solid) 3368, 2892, 1340, 1282, 1068, 1022, 973, 734, 693, 617 cm^{-1}; HRMS (+EI) $(M + H)^+$ found 409.2811, $(M + H)^+$calcd for $(C_{10}H_{20}O_4)_2H$ (dimer), 409.2801.

(3a*S*,4*S*,7*S*,7a*R*)-2,2,4-Trimethyl-7-(propan-2-yl)hexahydro-4,7-epidioxy-1,3-benzodioxole (33). To a stirred solution of **4d** (0.5 g, 2.5 mmol) in dry CH_2Cl_2 (25 mL) was added 2,2-dimethoxypropane (1.3 g, 12.4 mmol) followed by *p*-toluenesulfonic acid (10 mol %), and the solution was stirred under nitrogen overnight. The reaction mixture was washed with saturated $NaHCO_3$ (20 mL), dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo. The residue was purified by flash chromatography: yield 86%, colorless oil; R_f 0.69 (3:7 ethylacetate:hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, 3H, $J = 9.0$ Hz), 0.97 (d, 3H, $J = 9.0$ Hz), 1.17 (s, 3H), 1.37 (s, 3H), 1.50 (s, 3H), 1.58−1.80 (m, 1H), 1.90−2.05 (m, 3H), 4.10 (dd, 1H, $J = 7.8$, 1.5 Hz), 4.30 (dd, 1H, $J = 7.8$, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 17.1, 17.2, 19.6, 21.9, 23.9, 24.6, 26.4, 34.3, 74.5, 76.3, 77.1, 80.6, 110.2; IR (nujol) 1267, 1209, 1179, 1161, 1076, 1023, 874 cm[1]; (+EI) $(M + Na)^+$ found 265.1414, $(M+Na)^+$calcd for $C_{13}H_{22}O_4Na$, 265.1416.

General Methods for Thermal and Photochemical Decomposition of Endoperoxides. Thermal. A stirred solution of 2,3-dioxine (1 mmol) was boiled under reflux in various solvents (5 mL) until decomposition was determined by TLC. The crude products were purified by flash column chromatography.

Photochemical. A solution of 2,3-dioxine (1 mmol) in DCM (5 mL) was irradiated with a sun lamp under reflux until decomposition was determined by TLC. The crude products were purified by flash column chromatography.

Compounds **29b**,[40] **29c**,[41] **29d**,[42] **29e**,[43] **29f**,[44] **29g**,[45] and **29h**[45] showed ^1H NMR spectra identical to the literature.

Diethyl (2*E*,4*R*,6*E*)-4-(Propan-2-yl)octa-2,6-dienedioate (35). The dialdehyde decomposition product **34** was trapped by the addition of ethyl (triphenyl-λ^5-phosphanylidene) acetate (1 g, 2.9 mmol) to a solution of **25** (140 mg, 0.69 mmol) in acetonilrile (10 mL). The solution was boiled under reflux for 30 min. The resulting product was purified by flash chromatography: yield 90%, slightly yellow oil; R_f 0.25 (1:9 ethylacetate/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 3H, $J = 6.6$ Hz), 0.93 (d, 3H, $J = 6.6$ Hz), 1.28 (t, 3H, $J = 7.2$ Hz), 1.30 (t, 3H, $J = 7.2$ Hz), 1.74 (septd, 1H, $J = 6.6$, 1.2 Hz), 2.12−2.46 (m, 3H), 4.18 (q, 2H, $J = 7.2$ Hz), 4.19 (q, 2H, $J = 7.2$ Hz), 5.75−5.86 (m, 2H), 6.73−6.92 (m, 2H,); ^{13}C NMR (75 MHz, $CDCl_3$) 14.2, 18.6, 20.5, 31.1, 34.3, 47.9, 60.2, 60.3, 122.8, 122.9, 146.5, 149.4, 166.2; IR (neat) 2961, 1715, 1652, 1368, 1240, 1154, 1038, 984 cm^{-1}; HRMS (+EI) $(M)^+$ found 268.1681, $(M)^+$calcd for $C_{15}H_{24}O_4$, 268.1675.

2,3,7-Trideoxy-3-propan-2-yl-L-arabino-heptopyranos-6-ulose (38, 39): yield 65%, yellow oil; R_f 0.40 (1:1 ethylacetate/hexane). **38α**: ^1H NMR (600 MHz, $CDCl_3$) 0.82 (d, 3H, $J = 6.6$ Hz), 0.93 (d, 3H, $J = 6.6$ Hz), 1.44 (ddd, 1H, $J = 13.2$, 13.2, 3.0 Hz), 1.71 (dd, 1H, $J = 13.2$, 3.0 Hz), 1.98 (dddd, 1H, $J = 13.2$, 9.0, 3.0, 3.0 Hz), 2.21−2.28 (m, 1H), 2.27 (s, 3H), 3.53 (dd, 1H, $J = 9.0$, 9.0 Hz), 4.10 (d, 1H, $J = 9.0$ Hz), 5.42 (d, 1H, $J = 3.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 15.8, 20.3, 24.9, 27.1, 28.1, 39.6, 68.8, 76.4, 91.7, 212.9; IR (neat) 3415, 2958, 1709, 1357, 1244, 1068, 1016, 736 cm^{-1}; HRMS (+EI) $(M)^+$ found 202.1201, $(M)^+$calcd for $C_{10}H_{18}O_4$, 202.1205. **39β**: ^1H NMR (600 MHz, $CDCl_3$) 0.82 (d, 3H, $J = 7.2$ Hz), 0.93 (d, 3H, $J = 7.2$ Hz), 1.25 (ddd, 1H, $J = 13.8$, 12.6, 9.0 Hz), 1.59 (dddd, 1H, $J = 13.8$, 10.2, 3.6, 3.6 Hz), 1.86 (ddd, 1H, $J = 12.6$, 3.6, 1.2 Hz), 2.21−2.28 (m, 1H), 2.32 (s, 3H), 3.48 (dd, 1H, $J = 10.2$, 9.0 Hz), 3.62 (d, 1H, $J = 9.0$ Hz), 4.90 (dd, 1H, $J = 9.0$, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 15.9, 20.5, 25.1, 27.0, 30.7, 45.1, 68.0, 81.8, 96.7, 211.7.

(1*S*,2*S*,4*R*)-1-Methyl-4-(propan-2-yl)-6,8-dioxabicyclo[3.2.1]-octane-2,7-diol (42): yield 25%, white solid; mp 110−112 °C (hexane/DCM) R_f 0.20 (1:1 ethylacetate/hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, 3H, $J = 6.6$ Hz), 0.95 (d, 3H, $J = 6.6$ Hz), 1.38 (s, 3H), 1.41 (m, 1H), 1.46 (m, 1H), 1.50 (m, 1H), 1.85 (ddd, 1H, $J = 6.6$, 6.6, 3.6 Hz), 2.16 (brs, 1OH), 2.74 (brs, 1OH), 3.53 (s, 1H), 5.02 (s, 1H), 5.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 15.6, 19.8, 20.3, 28.7, 30.1, 41.1, 67.7, 84.5, 96.2, 103.9 cm^{-1}; HRMS (+EI) $(M - H)^-$ found 201.1132, $(M - H)^-$ calcd for $C_{10}H_{17}O_4$, 201.1132.

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Supporting Information Available: Experimental details for compounds **3g**, **3h**, **6d**, **12e**, and **12f**; ^{13}C NMR spectra for compounds **3b**, **3c**, **3e**, **3f**, **4b, 4c**, **4e−h**, **5d**, **5g**, **16**, **19**, **23−28**, **1**, **33**, **35**, **39**, and **42**; ^1H NMR spectra for compounds **3b**, **3c**, **3e**, **3f**, **4b−h**, **5d**, **5g**, **16**, **19**, **23−28**, **1**, **33**, **35**, **39**, and **42**; and crystallographic data for compounds **4h**, **5d**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(40) Cantrell, T. S.; Allen, A. C.; Ziffer, H. *J. Org. Chem.* **1989**, *54*, 140–145.

(41) Nikishin, G. I.; Troyanskii, E. I.; Lazareva, I. *Tetrahedron Lett.* **1984**, *25*, 4987–4978.

(42) Moreau, J. L.; Couffignal, R. *J. Organomet. Chem.* **1985**, *294*, 139–144.

(43) Zschiesche, R.; Hafner, T.; Reissig, H. U. *Liebigs Ann. Chem.* **1988**, 1169–1173.

(44) Hirai, K.; Ojima, I. *Tetrahedron Lett.* **1983**, *24*, 785–788.

(45) Huang, J. T.; Su, T. L.; Watanabe, K. A. *J. Org. Chem.* **1991**, *56*, 4811–4815.