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Cyclododecatetraene Tetraepoxide: Highly Diastereofacial Epoxidation of *all*-(*Z*)-1,4,7,10-Cyclododecatetraene and Selective Synthesis of Bridged Bis-oxocanes

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Abstract: Epoxidation of *all*-(*Z*)-1,4,7,10-cyclododecatetraene has been investigated with use of *m*-CPBA and dimethyldioxirane in anhydrous solvent. The diastereoselectivity of multiple epoxidation steps is complete affording only *exo*,*exo*,*exo*,*endo*-1,4,7,10-tetraepoxide. To understand this result, the step-by-step epoxidation reaction was investigated and each step was found to be highly regio- and stereoselective. Finally, a Lewis acid-catalyzed ethanolysis or treatment with HBr/KBr of the tetraepoxide gave rearranged diepoxy-oxabicyclo[5.5.1]tridecane (bridged bis-oxocanes) in which eight stereocenters were controlled.

Since the epoxy functionality may be stereoselectively transformed through ring opening into a large number of highly functionalized products, epoxidation reactions, especially direct epoxidation of olefins, are among the most useful oxidation reactions in organic synthesis.[1] In many examples, this reaction proceeds selectively because the attack of the epoxidant prefers one of the π-faces of the olefinic substrate.[2] For this purpose, peracids[3] and, more recently, dioxiranes[4] have been used extensively as effective and mild epoxidants and were largely studied from a theoretical point of view.[5] To explain the origin of the diastereoselectivity observed, several factors such as steric,[6] H-bonding, and dipole−dipole interactions[7] were proposed. In this context, the directing propensity of allylic substituents is well documented but only relatively few examples are known for which there are no directing groups close to the reactive double bond. Among natural products bearing an epoxy moiety, epoxyeicosatrienoic acids (EETs) and leukotoxins (LTXs) have garnered increasing attention.[8] These metabolites are generated from the cytochrome P450 branch of the eicosanoid cascade and are derived from arachidonic acid and linoleic acid, respectively. They have been recognized to induce several important physiological effects such as stimulating the release of numerous hormones, biogenic amines, and other cellular mediators as well as regulation gene transcription.[9] In addition, we have recently described the synthesis of *all*-(*Z*)-cyclododecatetraene **1** (CDT),[10] which exhibits a poly-1,4-diene moiety identical with the one present in arachidonic acid. To broaden the synthetic use of **1** and to design a system suitable for describing a biomimetic route to polyfurans, we planned to prepare the polyepoxide of **1**, which we thought could undergo Lewis acid mediated rearrangement. Moreover, its crown conformation[11] could favor an *exo*-face selectivity in any electrophilic addition on the CDT (Figure 1). Described herein are a stereoselective synthesis and a reactivity study of a tetraepoxide of CDT **1**.

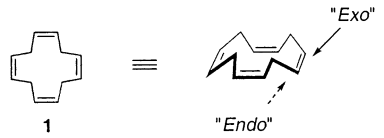
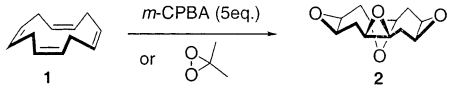


FIGURE 1.

Two different oxidants were used for the 4-fold epoxidation of CDT **1**. While the common epoxidation with *m*-chloroperbenzoic acid gave, after aqueous workup, a single diastereoisomer **2** in 75% yield, the more recently developed milder method with use of a solution of dimethyldioxirane (DMDO) in acetone afforded also **2** in 98% yield. Among the eight possibilities, only one tetraepoxide diastereoisomer was formed by using either epoxidant, indicating that each epoxidation step was highly selective (Scheme 1).

SCHEME 1



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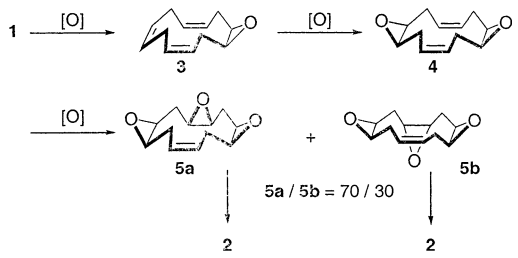
The ^{1}H NMR (500 MHz, $CDCl_3$) spectrum and COSY or NOESY NMR experiments did not unequivocally determine the structure of **2**. Additional information was given by the ^{13}C NMR spectrum which exhibited only 6 peaks (4 CH and 2 CH_2), indicating that the tetraepoxide could only present the *exo,exo,exo,endo* or *endo,endo,endo,exo* structures. Referring to the polyepoxidation reaction of cyclonona-1,4,7-triene[12] or triquinacene[13] in which a high *exo*-face selectivity was observed, we attributed the *tris-exo,endo* structure to **2**. Finally, the stereochemistry of this product was unambiguously assigned by X-ray crystallographic analysis.[14] The structure of **2** clearly demonstrates the *exo*-face selectivity; nevertheless, the absence of the tetrakis-*exo*-, bis-*endo*-, and tris-*endo*-isomers prompted us to examine the selectivity of each epoxidation step.

By using equimolar amounts of the reagent, monoepoxide **3** was isolated in fair yield (43%) along with diepoxide **4** (27%) and starting material **1** (10%). Both **3** and **4** were separated by flash chromatography and were obtained as single isomers. The ^{1}H NMR (500 MHz, $CDCl_3$) spectrum and COSY or NOESY NMR experiments did not firmly establish the structure of the diepoxide **4**; X-ray crystallographic analysis of a suitable crystal of diepoxide **4** obtained by crystallization in acetonitrile was required.[15] The second epoxidation reaction occurred in an *exo* fashion yielding the two epoxide functions in a 1,6-relationship. Moreover, it is interesting to note that the C-2 symmetric diepoxide **4** exhibits in the solid state a perfect columnar structure with a central channel of approximately 3 Å in diameter. With 3.0 equiv of *m*-CPBA, two triepoxides **5a** and **5b** were isolated in 52% and 22% yield, respectively, along with diepoxide **4** and tetraepoxide **2** (Scheme 2).

SCHEME 2. Sequential Epoxidation of CDT 1



These two triepoxides obtained in 70/30 mixture were separated by flash chromatography. The *exo,exo,exo*-structure of the major diastereoisomer **5a**, which was determined from X-ray crystallographic analysis, indicated one more time the predominance of the *exo* pathway.[16] The structure of minor triepoxide **5b** in which the third epoxidation step occurs in the *endo* position was determined by comparison of their NOESY spectra and presented the *exo,exo,endo*-arrangement. Finally, the fourth epoxidation step was found to be completely selective because only one tetraepoxide has been obtained. Starting from the triepoxide **5a**, the epoxidation occurred on the *endo*-face while the *exo*-face was attacked on diastereoisomer **5b**. This result clearly shows that the first two steps of the polyepoxidation of CDT **1** occur exclusively at the sterically less hindered convex side of the substrate molecule, whereas the two other epoxidation steps introduce one epoxy group on the concave side of the CDT framework.

As the ring opening of epoxides is an important synthetic strategy for the preparation of valuable building blocks, many nucleophiles, with the majority of these being heteroatom-based, have been employed successfully in these reactions and recently numerous chiral versions have been proposed from *meso* epoxides.[1c,17] We were intrigued by the possibility of performing, from CDT tetraepoxide **2**, controlled tandem ring opening-oxacyclization reactions with diverse acidic conditions as reported in the biomimetic synthesis of fused polycyclic ethers.[12,18] Since the multiple coordination sites available to Lewis acids might result in several pathways in these ring-opening reactions, we evaluated a series of reagents promoting the formation of a carbon−heteroatom bond. Theoretically, tetraepoxide **2** could suffer, after ring opening, oxacyclization via a 5-*exo* or 6-*endo* mode leading from the *endo*-epoxy function (the most accessible) to a tetrahydrofuran or a tetrahydropyran system, respectively. Nevertheless, the short distance between the oxygen atom of the *endo*-epoxide and carbon atoms 7 and 8[19] would rather lead to 7-*exo* or 8-*endo* pathways.

Upon screening several Lewis acids and reaction conditions, we found that the HBr/KBr couple promotes ring opening. It converted **2** to bromo-fused bis-oxocan **6** (27% isolated yield) and a more complex structure **7** (25% isolated yield). The ^{1}H NMR (500 MHz, $CDCl_3$) spectrum and COSY or NOESY NMR experiments did not allow us to firmly establish the structure of the bridged oxabicyclic compound **6**. Finally, the regioselectivity of the oxacyclization reaction and the relative stereochemistry of these products were unambiguously assigned by X-ray crystallographic analysis.[20] Partial structure assignments for **7** were based on NMR experiments and confirmed by X-ray diffraction.[21]

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(14) Colorless crystals of **2** ($C_{12}H_{16}O_4$) were grown from a solution of **2** in a 1/1 mixture of $CHCl_3$/acetone. Data collection was conducted at 298 K on a monoclinic crystal; a = 8.868(1) Å, b = 14.723(1) Å, c = 4.7658(4) Å; β = 120.423(6)°; v = 536.56(8) Å^3; space group Cm; z = 4; R = 0.053; wR = 0.063 ($w = 1/[\sigma^2(F_o^2) + 0.08F_o^2]$); Gof = 1.546; $\Delta\rho^+$ = 0.34 e•Å^{-3}; $\Delta\rho^-$ = −0.43 e•Å^{-3}.

(15) Colorless crystals of **4** ($C_{12}H_{16}O_2$) were grown from a solution of **4** in acetonitrile. Data collection was conducted at 298 K on a monoclinic crystal; a = 16.674(2) Å, b = 4.6225(3) Å, c = 27.491(4) Å, β = 95.610(4)°; v = 2108.7(4) Å^3; space group: C_2/c; z = 8; R = 0.041; wR = 0.04 ($w = 1/[\sigma^2(F_o^2) + 10.03F_o^2]$); Gof = 1.023; $\Delta\rho^+$ = 0.11 e•Å^{-3}; $\Delta\rho^-$ = −0.10 e•Å^{-3}.

(16) Colorless crystals of **5a** ($C_{12}H_{16}O_3$) were grown from a solution of **5a** in a 4/1 mixture of cyclohexane/ethanol. Data collection was conducted at 298 K on a monoclinic crystal; a = 8.800(9) Å, b = 7.7787(4) Å, c = 8.8535(4) Å, β = 117.685(3)°; v = 541.8(4) Å^3; space group $P2_1$; z = 2; R = 0.044; wR = 0.05 ($w = 1/[\sigma^2(F_o^2) + 0.03F_o^2]$); Gof = 1.0; $\Delta\rho^+$ = 0.14 e•Å^{-3}; $\Delta\rho^-$ = −0.12 e•Å^{-3}.

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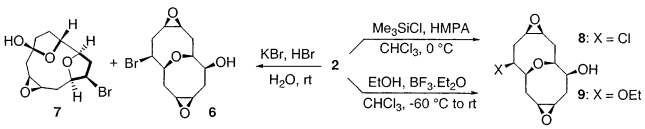
(19) X-ray structure: 3.775 Å. B3LYP/6.31G optimized geometry: 3.363 Å.

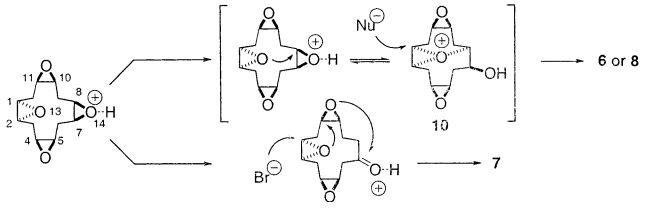
SCHEME 3



We also explored the reaction of tetraepoxide **2** with trimethylsilyl chloride in the presence of a catalytic amount of HMPA[22] at 0 °C, which promoted the ring-opening reaction with low conversion rate (ca 35%) to give oxabicyclo[5.5.1]tridecanol **8** in 29% isolated yield as the sole product after aqueous workup (Scheme 3). Similarly, reaction of tetraepoxide **2** with ethanol in the presence of $BF_3{\cdot}Et_2O$ in chloroform at −60 °C provided, in 49% isolated yield, oxabicyclo[5.5.1]tridecanol **9 (**the structure of which was assigned by comparison with the NMR spectra of **6** and by COSY and NOESY NMR experiments) along with an unidentified isomer. The structural and stereochemical assignments of **8** and **9** were based on careful comparison of their spectra with the ^1H and ^{13}C NMR spectra of oxabicyclo[5.5.1]tridecanol **6**.

To explain the regioselectivities observed for the formation of products **6**, **8**, and **9**, the electrophilic activation of one epoxide moiety in **2** (Scheme 4) induces intramolecular addition of a second epoxide moiety to form an epoxonium ion intermediate **10**. The attack of an external nucleophile (alkoxide, chloride, or bromide ions) finally terminates the ring-forming reaction. As seen on the resulting structures **6** and **7**, the oxygen atom of the epoxide in 7,8 appears to have the most basic character while the carbon atoms of the epoxide (position 1,2) are the most electrophilic. Two factors could be evoked: First, due to the short distance between oxygen atom 13 and carbon atoms 7 and 8, a partial overlapping of the lone pairs of oxygen atom 13 with the antibonding orbital σ^* of the C7−O14 (or C8−O14) bond would increase the Lewis base character of the oxygen atom 14.

SCHEME 4. Postulated Mechanism for the Formation of 6, 7, and 8



On the other hand, the sterically less hindered carbons are those on which the nucleophile could attack on the *exo*-face. Finally, the regioselectivity observed might be due in part to the difference in stability between two ions resulting from the opening of **10** and leading to bridged oxabicyclo[5.5.1] or to oxabicyclo[6.4.1] compounds. The polycyclic hemiketal **7** certainly resulted via a cascade in which, first, occurred a pinacolic transposition followed by two 1,5-oxacyclization reactions (Scheme 4).

In conclusion, the CDT is selectively epoxidized due to its crown conformation, giving only one tetraepoxide **2**. Each step of this preparation was also found to be selective. The unique structure of **2** was then exploited in an acidic cascade rearrangement. Our results represent the first 8-*exo*-selective oxacyclization approach to the synthesis of bridged bis-oxocane compounds in which eight stereocenters are controlled. The *endo*-epoxy function appears to play an essential role in the preference for the regioselective oxacyclization reactions: first, by exploiting the basic character of the oxygen atom of the opposite epoxy function and second because of its sterically less hindered electrophilic character. Further studies on the scope of this methodology and applications to efficient syntheses of the heterocycle natural products are underway.

Experimental Section

(*exo,exo,exo,endo*)-1,2:4,5:7,8:10,11-Tetraepoxy-cyclododecane (2). Procedure A: To a dichloromethane solution (50 mL) containing the *all-Z*-cyclododeca-1,4,7,10-tetraene (96 mg, 0.59 mmol) at 0 °C was added *m*-CPBA (1.18 g, 6.84 mmol) at once. The reaction was monitored by TLC. After 3 days, 30 mL of water was added to the reaction mixture. The aqueous layer was extracted with chloroform (3 × 30 mL). The organic layers were combined, washed with aqueous 2% NaOH, saturated aqueous NH_4Cl, and brine, and dried over $MgSO_4$. The solvents were removed in a vacuum. The tetraepoxide was obtained as a white solid (100 mg, 75% yield) by crystallization with ether (25 mL). **Procedure B:** DMDO in acetone was prepared following the procedure described in the literature by Murray.[23] To a dichloromethane solution (50 mL) containing the *all-Z*-cyclododeca-1,4,7,10-tetraene (96 mg, 0.59 mmol) at 0 °C was added 17.0 mL (2.62 mmol) of a 0.154 M solution of dimethyldioxirane in acetone, at room temperature. The reaction was monitored by TLC. After 2 days, the solvents were removed in a vacuum and 130 mg of the tetraepoxide was obtained as a white solid in 98% yield. Mp 253 °C. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.45; H, 7.08. ^1H NMR (500 MHz, $CDCl_3$): δ 3.28−3.33 (m, 2H), 3.19 (d, ^3J = 10.6 Hz, 2H), 3.14 (d, ^3J = 7.4 Hz, 2H), 2.45 (d, ^3J = 14.1 Hz, 2H), 2.39 (dd, ^3J = 15.1, 3.1 Hz, 2H), 1.15−1.27 (m, 2H), 1.15−1.27 (m, 2H), 1.04−1.11 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.0, 54.7, 54.4, 53.6, 26.2, 25.6. MS (70 eV): *m*/*z* 224 (M, 2), 166 (1), 147 (3), 145 (10), 133 (4), 131 (3), 119 (5), 117 (14), 107 (19), 105 (18), 95 (28), 93 (26), 91 (61), 41 (100), 81 (42), 79 (100), 77 (68), 69 (21), 67 (74), 65 (42), 57 (19), 55 (49), 53 (27), 43 (23), 41 (57).

(*exo*)-1,2-Epoxy-cyclododeca-4,7,10-triene (3) and (*exo, exo*)-1,2:7,8-Diepoxy-cyclododeca-4,10-diene (4). Procedure A was followed with *all-Z*-cyclododeca-1,4,7,10-tetraene (105 mg, 0.65 mmol) and *m*-CPBA (0.65 mmol). The crude product was purified by flash chromatography on silica gel (petroleum ether/ether 9/1 then 8/2). The monoepoxide **3** was obtained in 43% yield (50 mg) as a white solid. Mp 48 °C. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.52; H, 8.97. ^1H NMR (300 MHz, $CDCl_3$): δ 5.26−5.51 (m, 6H), 3.28 (ddd, ^3J = 13.9, 10.6, 10.3 Hz, 2H), 2.97−3.02 (m, 2H), 2.42−2.47 (m, 4H), 2.34 (d, ^3J = 13.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.4, 127.8, 122.4, 57.3, 26.6, 26.3. MS (70 eV): *m*/*z* 176 (M, 3), 158 (2), 147 (31), 143 (8), 133 (8), 130 (10), 129 (10), 119 (10), 117 (22), 115

(20) Colorless crystals of **6** ($C_{12}H_{17}BrO_4$) were grown from a solution of **6** in acetonitrile. Data collection was conducted at 298 K on a monoclinic crystal; a = 8.3022(5) Å, b = 16.291 (1) Å, c = 9.2001(8) Å; β = 94.427(6)°; v = 1240.6(2) Å^3; space group $P2_1$; z = 2; R = 0.048; wR = 0.073 ($w = 1/[\sigma^2(F_o^2) + 0.03F_o^2]$); Gof = 2.03; $\Delta\rho^+$ = 0.58 e·Å^{-3}; $\Delta\rho^-$ = −0.66 e·Å^{-3}.

(21) Colorless crystals of **7** ($C_{12}H_{17}BrO_4$) were grown from a solution of **7** in chloroform. Data collection was conducted at 298 K on a monoclinic crystal; a = 12.3951(6) Å, b = 7.9735(5) Å, c = 12.6196(8) Å, β = 101.416(4)°; v = 1222.5(1) Å^3; space group $P2_1/c$; z = 4; R = 0.042; wR = 0.058 ($w = 1/[\sigma^2(F_o^2) + 0.03F_o^2]$); Gof = 1.801; $\Delta\rho^+$ = 0.52 e·Å^{-3}; $\Delta\rho^-$ = −0.73 e·Å^{-3}.

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(12), 105 (20), 104 (15), 93 (21), 91 (100), 79 (86), 77 (74), 67 (27), 53(16), 51(24).

The diepoxide **4** was obtained in 27% yield (31 mg) as a white solid. Mp 145 °C. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.18; H, 8.27. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.37−5.47 (m, 4H), 3.04 (d, ^3J = 9.3 Hz, 4H), 2.47 (d, ^3J = 14.6 Hz, 4H), 2.16−2.27 (m, 4H).^{13}C NMR (75 MHz, $CDCl_3$): δ 125.4, 56.8, 26.9. MS (70 eV): *m*/*z* 192 (M, 13), 174 (2), 131 (10), 117 (16), 107 (13), 105 (18), 96 (27), 95 (39), 91 (59), 81 (45), 79 (100), 77 (72), 67 (74), 55 (28), 53 (35), 51 (27), 50 (28), 41 (50).

(*exo*,*exo*,*exo*)-1,2:4,5:7,8-Triepoxy-cyclododec-10-ene (5a) and (*exo*,*endo*,*exo*)-1,2:4,5:7,8-Triepoxy-cyclododec-10-ene (5b). Procedure A was followed with *all-Z*-cyclododeca-1,4,7,10-tetraene (105 mg, 0.65 mmol) and *m*-CPBA (1.95 mmol). The crude product was purified by flash chromatography on silica gel (petroleum ether/ether 5/5 then 3/7). The triepoxides **5a** and **5b** were obtained in respectively 52% and 22% yield. **5a:** white solid (70 mg); mp 151 °C. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.98; H, 7.52. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.44−5.51 (m, 2H), 3.11−3.17 (m, 4H), 2.94 (d, ^3J = 15.3 Hz, 2H), 2.34−2.39 (m, 2H), 2.03−2.13 (m, 2H), 1.16−1.35 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 125.2, 56.5, 54.6, 54.4, 27.0, 25.7. MS (70 eV): *m*/*z* 208 (M, 1), 190 (2), 145 (3), 135 (3), 133 (5), 117 (15), 109 (7), 107 (18), 105 (21), 95 (33), 91 (74), 83 (19), 81 (63), 79 (100), 77 (67), 67 (72), 65 (38), 57 (20), 55 (48).

5b: white solid (29 mg); mp 215 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.47−5.51 (m, 2H), 3.21 (ddd, ^3J = 12.1, 10.8, 2.4 Hz, 2H), 3.11−3.14 (m, 4H), 2.49 (d, ^3J = 15.6 Hz, 2H), 2.34 (dt, ^3J = 14.1, 2.4 Hz, 2H), 1.98−2.20 (m, 2H), 1.10−1.20 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 124.6, 56.8, 55.7, 53.8, 27.2, 26.1.

(1*R,2*R**,4*S**,5*R**,7*R**,8*R**,10*S**,11*R**)-4,5:10,11-Diepoxy-8-bromo-13-oxabicyclo[5.5.1]tridecan-2-ol (6) and (1*S**,3*S**,4*R**,6*R**,7*R**,9*R**,10*R**)-3,4-Epoxy-7-bromo-13,14-dioxatricyclo[8.2.2.1^{6,9}]tetradecan-1-ol (7).** To tetraepoxide **2** (85 mg, 0.38 mmol) and KBr (207 mg, 1.8 mmol) was added an aqueous solution of HBr (5%, 6 mL). The reaction mixture was stirred at room temperature and the reaction was monitored by TLC (PE/EtOAc 4/6). The mixture was hydrolyzed with saturated aqueous $NaHCO_3$ (pH 5). The aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with saturated aqueous NaCl, and dried over $MgSO_4$, then the solvent was removed in a vacuum. The crude product was purified by flash chromatography on silica gel (PE/EtOAc 4/6 then 2/8) leading to compound **6** as a white solid in 27% yield (30 mg). Compound **7** was obtained as a mixture with another unidentified product. Recrystallization from $CHCl_3$ afforded **7** as a white solid in 25% yield (29 mg).

(1*R,2*R**,4*S**,5*R**,7*R**,8*R**,10*S**,11*R**)-4,5:10,11-Diepoxy-8-bromo-13-oxabicyclo[5.5.1]tridecan-2-ol (6):** mp 219 °C. Anal. Calcd for $C_{12}H_{17}BrO_4$: C, 47.23; H, 5.61. Found: C, 46.98; H, 5.47. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.32 (ddd, ^3J = 10.7, 4.6, 3.6 Hz, 1H), 3.96 (m, 1H), 3.53 (dd, ^3J = 10.7, 3.3 Hz, 1H), 3.45 (dd, ^3J = 11.1, 2.7 Hz, 1H), 3.08−3.13 (m, 2H), 2.82−2.87 (m, 3H), 2.66 (ddd, ^3J = 12.4, 4.7, 4.2 Hz, 1H), 2.34 (dd, ^3J = 14.1, 5.9, 1H), 2.26 (dd, ^3J = 13.9, 5.9, 1H), 2.18 (m, 1H), 1.76−1.86 (m, 2H), 1.64−1.69 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 83.9, 82.1, 71.5, 54.9, 54.3, 53.6, 52.8, 51.7, 37.9, 36.7, 35.6, 32.4. MS (70 eV): *m*/*z* 288 (M − 18, 25), 286 (M − 18, 25), 207 (8), 189 (8), 149 (11), 123 (17), 119 (15), 105 (22), 95 (44), 91 (31), 81 (100), 77 (36), 67 (87), 55 (74), 53 (37), 41 (49).

(1*S,3*S**,4*R**,6*R**,7*R**,9*R**,10*R**)-3,4-Epoxy-7-bromo-13,14-dioxatricyclo[8.2.2.16,9]tetradecan-1-ol (7):** mp 181 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20−4.50 (m, 1H); 4.05 (br d, ^3J = 8.1 Hz, 1H), 3.96 (dd, ^3J = 9.1, 7.6 Hz, 1H), 3.81 (dd, ^3J = 9.3, 6.8 Hz, 1H), 3.72 (m, 1H), 3.11 (br s, 1H), 2.99 (m, 1H), 2.67−2.80 (m, 1H), 2.46−2.60 (m, 2H), 2.18−2.40 (m, 2H), 1.52−1.90 (m, 4H), 1.64−1.69 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 106.9, 81.7, 80.0, 79.2, 57.2, 54.8, 44.9, 39.6, 36.8, 34.3, 31.2, 28.6.

(1*R,2*R**,4*S**,5*R**,7*R**,8*R**,10*S**,11*R**)-4,5:10,11-Diepoxy-8-chloro-13-oxabicyclo[5.5.1]tridecan-2-ol (8).** To tetraepoxide (30 mg, 0.13 mmol) in $CHCl_3$ (5 mL), at 0 °C, was added chlorotrimethylsilane (16 μL, 0.13 mmol) and HMPA (2 μL, 0.013 mmol). The reaction mixture was stirred at room temperature and monitored by TLC (EtOAc). After 20 h, a low conversion was observed (35%). The mixture was hydrolyzed with saturated aqueous KF·$KHPO_4$. The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The organic layers were combined, washed with saturated aqueous NaCl, and dried over $MgSO_4$, then the solvent was removed in a vacuum. The crude product was purified by flash chromatography on silica gel (EtOAc). Pure alcohol **8** was obtained as an oil (10 mg). Yield: 29%. Anal. Calcd for $C_{12}H_{16}ClO_4$: C, 55.28; H, 6.57. Found: C, 55.81; H, 6.82. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (ddd, ^3J = 10.8, 4.7, 3.5 Hz, 1H), 3.96−3.98 (m, 1H), 3.65 (dd, ^3J = 10.8, 3.2 Hz, 1H), 3.43 (dd, ^3J = 11.2, 2.8 Hz, 1H), 3.07−3.14 (m, 2H), 2.83−2.88 (m, 2H), 2.76 (ddd, ^3J = 12.7, 4.7, 4.1 Hz, 1H), 2.66 (ddd, ^3J = 12.4, 4.5, 4.4 Hz, 1H), 2.34 (dd, ^3J = 14.1, 6.0 Hz, 1H), 2.29 (dd, ^3J = 14.1, 5.9 Hz, 1H), 2.04 (m, 1H), 1.85 (ddd, ^3J = 14.1, 5.3, 3.2 Hz, 1H), 1.78 (ddd, ^3J = 14.1, 5.4, 2.8 Hz, 1H), 1.64−1.69 (m, 1H).

(1*R,2*R**,4*S**,5*R**,7*R**,8*R**,10*S**,11*R**)-4,5:10,11-Diepoxy-8-ethoxy-13-oxabicyclo[5.5.1]tridecan-2-ol (9).** Tetraepoxide (63 mg, 0.29 mmol) in $CHCl_3$ (15 mL) was cooled at −60 °C, then 71 μL of 48% BF_3−Et_2O dropwise and EtOH (13.4 mg, 0.29 mmol) were added. The reaction mixture was stirred at room temperature and monitored by TLC. After 5 h, the mixture was hydrolyzed with aqueous 0.01 M $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The organic layers were combined, washed with saturated aqueous NaCl, and dried over $MgSO_4$ and the solvent was removed in a vacuum. The crude product was purified by flash chromatography on silica gel (EtOAc). Pure alcohol **9** was obtained in 49% (36 mg) yield as oil. Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 61.95; H, 8.35. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90−3.94 (m, 1H), 3.63−3.72 (m, 2H), 3.46 (m, 1H), 3.41 (dd, ^3J = 11.1, 3.4 Hz, 1H), 3.35 (dd, ^3J = 11.1, 2.7 Hz, 1H), 3.06−3.11 (m, 2H), 2.80−2.86 (m, 2H), 2.63 (2ddd, ^3J = 12.2, 4.3, 4.2, 2H), 2.30 (dd, ^3J = 14.3, 5.9, 1H), 2.27 (dd, ^3J = 14.0, 6.0, 1H), 1.73−1.83 (m, 3H), 1.66−1.70 (m, 1H), 1.21 (t, ^3J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 84.4, 83.9, 78.1, 71.3, 66.1, 55.1, 55.0, 53.1, 52.9, 35.8, 32.5, 32.4, 32.0, 15.9. MS (70 eV): *m*/*z* 270 (0.2), 253 (1), 223 (2), 207 (10), 165 (4), 163 (4), 141 (11), 125 (19), 123 (27), 114 (23), 113 (17), 112 (16), 111 (23), 107 (19), 101 (43), 95 (53), 83 (53), 81 (67), 79 (39), 73 (37), 71 (39), 67 (61), 57 (100), 55 (73), 41 (48).

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Supporting Information Available: Crystallographic information for compounds **4**, **5a**, **6**, and **7** (Ortep structures and CIF files); ^{1}H and ^{13}C NMR spectra for **1**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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