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A Short and Efficient Enantiomeric Synthesis of Antitumor Fused Tetrahydrofurans

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A short and efficient enantiomeric synthesis of fused tetrahydrofuran derivatives is reported. The methodology is based on a regio- and stereoselective double *exo*-cyclization of enantiomeric bis-epoxy-diols. The six stereocenters of the bis-epoxy diols were introduced by the application of Katsuki–Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation reactions. In vitro cytotoxicities on HL60 human promyelocytic leukemia cells were determined for the bicyclic products. Active products showed exceptionally steep dose–response curves and DNA laddering.
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Introduction

The Developmental Therapeutics Program of the US National Cancer Institute (NCI) operates an anticancer screening program for the discovery of synthetic compounds or natural products that show selective growth inhibition or cell-killing of human tumor cell lines.[1] Figure 1 shows three compounds included in the NCI public database that have been tested against a panel of 60 human tumor cell lines. The feature common to these products is the presence of a molecular scaffold of 3,7-disubstituted dioxabicyclo[3.3.0]octane. The fused tetrahydrofuran (fTHF) skeleton is also present in the marine natural products kumausallene[2] and bromoallene.[3]

The screening results prompted further studies on **NSC695222**, the most active of this series with a modest antitumor activity towards all the cell lines. Diverse stereoisomers of said compound were prepared as intermediates during the synthesis of racemic kumausallene,[4] although there is no data available on their biological activity.

Within our program directed at the asymmetric total synthesis of novel antitumor compounds[5] and bioactive substances of marine origin,[6] these synthetically challenging ring systems have attracted our interest and we have sought to develop new methodologies for their enantiomerically pure synthesis.

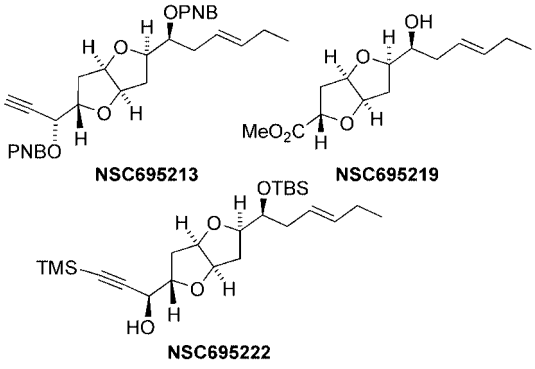

Figure 1. Fused tetrahydrofurans studied at the NCI.

In this study, a series of stereoisomeric derivatives of fTHFs substituted with diverse protecting groups either at the primary or secondary hydroxy groups were synthesized by means of a short and highly efficient synthetic methodology.[7] Unprotected derivatives were also prepared to investigate the influence of substituents on the antitumor activity of fTHFs.

Results and Discussion

As depicted in the retrosynthetic analysis outlined in Scheme 1, the fTHFs were envisioned through a regio- and stereoselective double *exo*-cyclization of the appropriate bis-epoxy alcohol, in which all its six stereocenters could be controlled by Katsuki–Sharpless asymmetric epoxidation (KSAE)[8] and Sharpless asymmetric dihydroxylation

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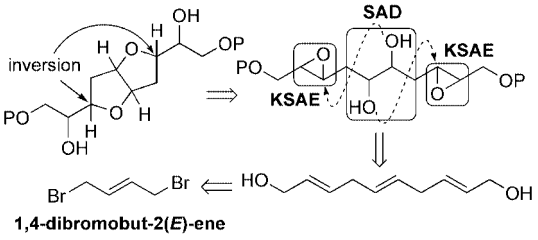
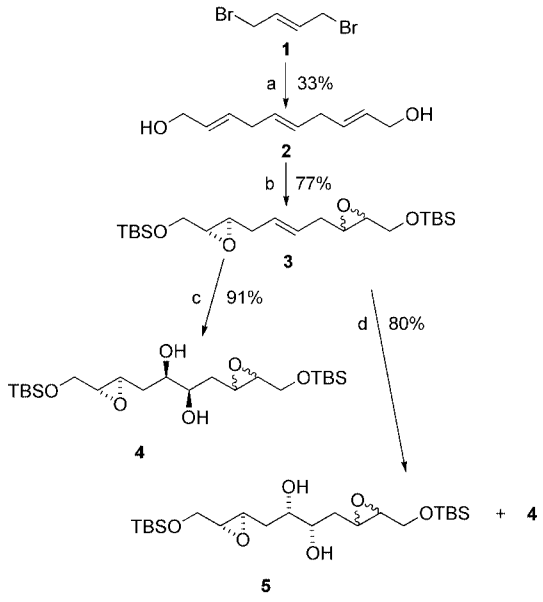
(SAD)[9] reactions of the appropriate bis-allylic alcohol. Two major advantages derive from this strategy: First, the synthesis of the fTHF stereoisomers can be modulated by simply changing the chiral auxiliary in the KSAE and SAD steps; secondly, the application of two consecutive enantioselective reactions ensures high enantiomeric purity of the final products. These linear precursors could be obtained by a simultaneous two-directional synthetic strategy to avoid the use of tedious protecting-group manipulation chemistry.[10] Hence, the necessary bis-allylic alcohol could be obtained from commercially available (*E*)-1,4-dibromobut-2-ene.



Scheme 1. Retrosynthetic analysis.

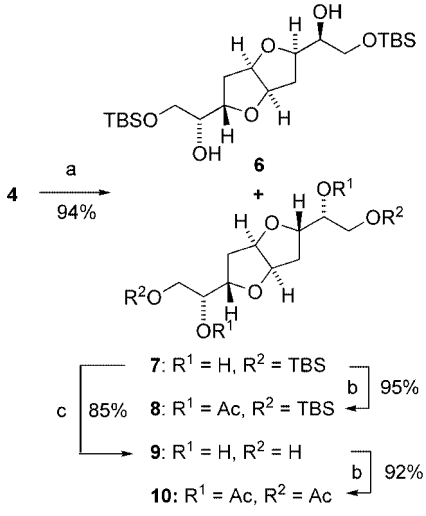
As shown in Scheme 2, the synthesis of the linear precursors of the fTHF derivatives started from (*E*)-1,4-dibromobut-2-ene (**1**). In order to build the carbon framework, **1** was homologated in both directions by a double coupling reaction under mild conditions with propargyl alcohol. Further reduction of the resulting bis-propargylic alcohol with $LiAlH_4$ afforded the corresponding bis-allylic alcohol **2**. It should be emphasized that this is the first report of the synthesis of bis-allylic alcohol **2** with an (*E*,*E*,*E*) configuration. Compound **2** was submitted to a semi-stoichiometric double KSAE reaction (25 mol-%)[11] using diisopropyl (*S*,*S*)-(–)-tartrate as the chiral auxiliary. The reaction led to the expected mixture of two diastereomeric bis-epoxy alcohols.[12] In this process four stereocenters were introduced in a single step. Subsequent in situ protection of the primary hydroxy groups as *tert*-butyldimethylsilyl (TBS) ethers provided a diastereomeric mixture of bis-epoxides (*R*,*R*,*R*,*R*)-**3** and (*R*,*R*,*S*,*S*)-**3** in a 2.1:1 ratio, respectively. The semi-stoichiometric KSAE reaction allows the primary alcohols to be protected in situ as silyl ethers to afford a less polar derivative which was easily purified and further manipulated.

The next step was the introduction of the last two stereocenters. These stereocenters are involved in the formation of the tetrahydrofuran ring fusion. Therefore, the mixture of bis-epoxy (*E*)-alkenes **3** was transformed into the corresponding bis-epoxy diols **4** and **5** by treatment with AD-mix-β and AD-mix-α, respectively. The SAD reaction of bis-epoxy (*E*)-alkenes **3** with AD-mix-β led to a mixture of the two diastereoisomeric diols (*R*,*R*,*R*,*R*,*R*,*R*)-**4** and (*R*,*R*,*R*,*R*,*S*,*S*)-**4** in a 2.1:1 ratio, respectively. However, the SAD step with AD-mix-α afforded an inseparable and indistinguishable mixture (vide infra) of three diastereoisomeric diols: (*R*,*R*,*R*,*R*,*R*,*R*)-**4**, (*R*,*R*,*S*,*S*,*R*,*R*)-**5**, and (*R*,*R*,*S*,*S*,*S*,*S*)-**5**.



Scheme 2. Synthesis of linear precursors of fTHFs. Reagents and contitions: a) i. Propargyl alcohol, K_2CO_3, TBAC, CuI, DMF; ii. $LiAlH_4$, THF; b) (*S*,*S*)-(–)-DIPT, Ti(*i*PrO)$_4$, *t*BuOOH, CH_2Cl_2, –20 °C; ii. TBSCl, imidazole, CH_2Cl_2, room temperature; c) AD-mix-β, $CH_3SO_2NH_2$, *t*BuOH/H_2O (1:1), 0 °C; d) AD-mix-α, $CH_3SO_2NH_2$, *t*BuOH/H_2O (1:1), 0 °C. TBAC = tetra-*n*-butylammonium chloride; DIPT = diisopropyl tartrate; TBSCl = *tert*-butyldimethylsilyl chloride.

With the necessary precursors in hand, we proceeded to perform the regio- and stereoselective double *exo*-cyclization with CSA in CH_2Cl_2 at room temperature. The results of the reactions of precursors **4** and **5** are shown in Scheme 3 and Scheme 4, respectively.



Scheme 3. Synthesis of fused tetrahydrofurans derived from **4**. Reagents and conditions: a) CSA, CH_2Cl_2, (*dr* **6**:**7**, 1:2.1); b) Ac_2O, DMAP, CH_2Cl_2; c) Dowex 50Wx8, MeOH. CSA = camphorsulfonic acid; DMAP = 4-(dimethylamino)pyridine.

The mixture of diastereoisomeric diols (*R*,*R*,*R*,*R*,*R*,*R*)-**4** and (*R*,*R*,*R*,*R*,*S*,*S*)-**4** afforded the mixture of fTHFs **6** and

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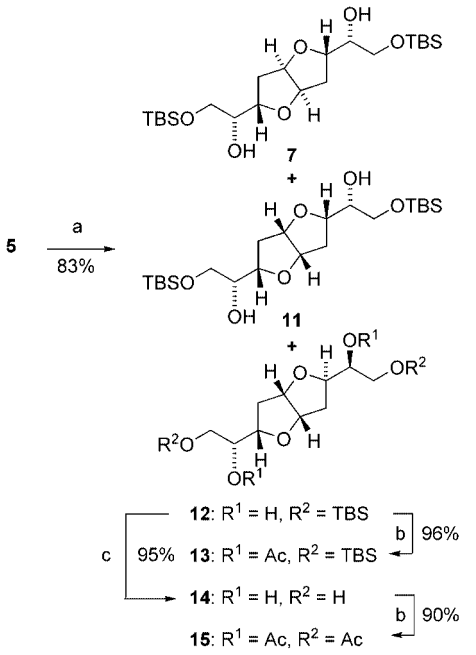

Scheme 4. Synthesis of fused tetrahydrofurans derived from **5**. Reagents and conditons: a) CSA, CH_2Cl_2, (*dr* **7**:**11**:**12**, 1:3:1.9); b) Ac_2O, DMAP, CH_2Cl_2; c) Dowex 50Wx8, MeOH.

7 in excellent yields and in a 1:2.1 ratio, respectively (Scheme 3). This time, both fTHFs were easily separated on a silica gel chromatographic column. These compounds can be easily distinguished since fTHF **7** possesses C_2 symmetry and gives NMR spectra with half the signals of **6**. The results suggest that compound **6** should originate from the minor product of the KSAE reaction of (*R*,*R*,*S*,*S*)-bis-epoxy (*E*)-alkene **3**, while **7** is derived from the major diastereoisomer (*R*,*R*,*R*,*R*)-bis-epoxy (*E*)-alkene **3**.

The mixture resulting from the SAD reaction with AD-mix-α was submitted to the aforementioned double *exo*-cyclization conditions. Compounds **7**, **11** and **12** were obtained in excellent yields and in a 1:3:1.9 ratio, respectively (Scheme 4). Thus, compound **7** is derived from diol (*R*,*R*,*R*,*R*,*R*,*R*)-**4**, which was obtained in a minor proportion in the SAD reaction of the bis-epoxy (*E*)-alkene (*R*,*R*,*R*,*R*)-**3**, as a consequence of a mismatch process. On the other hand, fTHF **11** originates from diol (*R*,*R*,*S*,*S*,*R*,*R*)-**5** and diol (*R*,*R*,*S*,*S*,*S*,*S*)-**5** gives fTHF **12**, which is the enantiomer of compound **6**.

In order to study the effect of functional groups on antitumor activity, a series of modifications were performed on compounds **7** and **12**. Thus, the secondary alcohols of compounds **7** and **12** were acetylated to provide the acetate derivatives **8** and **13**, respectively, in excellent yields. In addition, cleavage of the silyl groups of compounds **7** and **12** afforded the unprotected fTHFs **9** and **14**, which were treated with acetic anhydride to obtain the peracetylated derivatives **10** and **15**, respectively.

We screened bicyclic compounds **6**–**15** for growth inhibition and cytotoxicity against the human promyelocytic leukemia cell line HL60 using the SRB assay of the National Cancer Institute (NCI)[13] with slight modifications.[14] By using this method, for each drug a dose–response curve was generated and three levels of effect can be calculated, where possible. The effect is defined as the percentage of growth (PG), where 50% growth inhibition (GI_{50}), total growth inhibition (TGI), and 50% cell-killing (LC_{50}) represent the concentrations at which PG is +50, 0, and –50, respectively. A PG value of 0 corresponds to the amount of cells present at the start of drug exposure, while negative PG values denote net cell-kill. The sensitivities are listed in Table 1.

Table 1. Preliminary in vitro screening against human solid tumor cells.

Compound	CLOGP[a]	GI_{50}[b] [μM]	TGI[b] [μM]	LC_{50}[b] [μM]
6	3.271	13 (±1.4)	21 (±2.2)	31 (±2.8)
7	3.271	15 (±7.2)	25 (±10.3)	46 (±16.3)
8	4.977	41 (±9.8)	>100	>100
9	–3.502	>100	>100	>100
10	–0.003	>100	>100	>100
11	3.271	14 (±7.6)[c]	>100	>100
12	3.271	15 (±7.3)	25 (±9.2)	44 (±16.5)
13	4.977	35 (±19.5)	94 (±13.6)	>100
14	–3.502	>100	>100	>100
15	–0.003	>100	>100	>100

[a] See ref.[15] [b] Values are the means of at least three experiments; the standard deviations are given in parentheses. [c] The compound crystallizes in the culture medium at drug concentrations higher than 20 μM.

In addition, the lipophilicity of the compounds, expressed as CLOGP, was evaluated by in silico calculations based on their chemical structures.[15] CLOGP values were calculated to correlate lipophilicity with antitumor activity and are shown in Table 1.

From the obtained dose–response parameters we observe that those compounds bearing TBS protecting groups showed significant antileukemic activity whereas the compounds lacking such a functionality were found to be inactive. The CLOGP values show large differences in lipophilicity between silicon-bearing and non-silicon-bearing derivatives which may account for the observed activity profile. These results are consistent with our prior observation of the role of the TBS group in the enhancement of cytotoxic activity in human tumor cells.[5a] It is exceptional to find examples of silicon-containing anticancer drugs in the literature. However, cisplatin[16] and camptothecin[17] analogs containing silicon have been reported to give better activity profiles than their respective parent drugs.

Hence, lipophilicity is an important condition for the activity of fTHFs although it is not sufficient. The results also indicate that free secondary hydroxy groups are necessary for a better cytotoxic profile (**7** vs. **8** and **12** vs. **13**). In addition, antileukemic activity seems not to be influenced by the stereochemistry of the molecule.

As shown in Figure 2, exceptionally steep dose–response curves were found for compounds **6**, **7**, and **12**. These compounds prompted not only total growth arrest (cytostasis) but also considerable cell-kill, as indicated by the negative PG values at drug concentrations higher than 20 μM.

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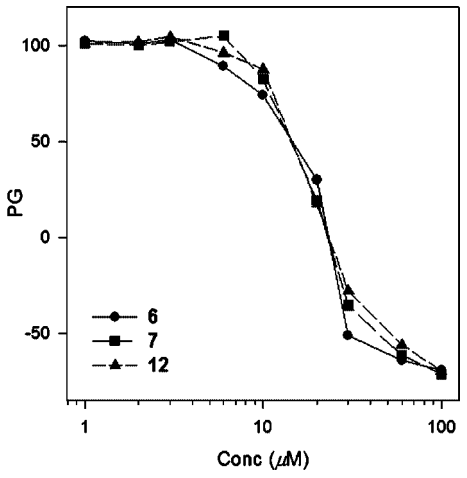

Figure 2. Representative dose–response curves against HL60 cells after 48 h exposure to fused tetrahydrofurans **6**, **7**, and **12**.

At present, the mechanism of action of these compounds remains unclear. However, morphological changes that resemble those of apoptosis were observed under the microscope in cells treated with active compounds (results not shown). The importance of apoptosis in many diseases, including cancer, has led to the use of various compounds that may inhibit or trigger this fundamental cellular process.[18] In this context, leukemic cells, including HL60, may act as useful models for studying the induction of apoptosis by antitumor agents.[19] Apoptosis is characterized by changes in the nucleus including chromatin condensation, fragmentation, and the laddering of chromosomal DNA mediated in part by nucleases. Nuclear DNA is first cut at A/T-rich sites in nuclear scaffold regions to form variably large (50–300 kb) fragments. These fragments are subsequently cut at internucleosomal spacer regions to form small, similar-sized (≈180 bp) pieces in a process known as DNA laddering.

To confirm that cell-death induced by fTHFs was apoptosis, we analyzed DNA fragmentation. Figure 3 shows the results of electrophoretic analysis of DNA extracted from the cells exposed to compounds **7** and **12** at 20 and 60 μM for 24 h. Treatment with the lower dose of **7** and **12** showed a typical DNA ladder. At the higher dose cell-kill was too large to allow isolation of DNA. Consistent with the results shown in Figure 2, **7** induced DNA fragmentation as much as **12** did.

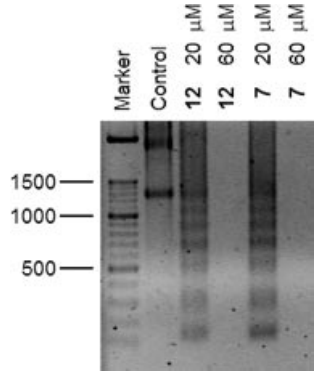

Figure 3. Agarose gel electrophoresis of DNA following treatment of HL60 cells with compounds **7** and **12**. HL60 cells (1×10^6 cells/mL) were exposed to compounds **7** and **12** (20 and 60 μM) or DMSO vehicle. After 24 h, genomic DNA was subjected to agarose gel electrophoresis.

Conclusion

Lipophilicity can be used at least in part to explain the antitumor activity exerted by the NCI compounds shown in Figure 1. The CLOGP values for the fTHFs **NSC695213**, **NSC695219**, and **NSC695222** are –1.011, 0.992, and 5.542, respectively. The most lipophilic compound gave the best activity profile of the three fTHFs. Moreover, the new synthetic derivatives reported herein, **6**, **7** and **12**, were more potent and were able to induce net cell-kill as indicated by the experimental TGI and LC_{50} values. We hypothesized that this latter observation is due to the presence of two free hydroxy groups in **6**, **7**, and **12**, whilst **NSC695222** only has one free hydroxy group. A defined structure–activity relationship in terms of the stereochemistry of the fTHFs could not be obtained from the growth inhibition parameters. Ongoing studies should shed some light on the structural requirements for activity, which in turn will allow us to design new derivatives with a better activity profile.

In summary, we have synthesized enantiomerically pure 3,7-disubstituted dioxabicyclo[3.3.0]octane ring systems in five chemical steps by a simultaneous two-directional synthetic strategy. The method opens the way to the fast and efficient synthesis of other enantiomeric series providing the proper stereoisomer of the tartrate is employed in the KSAE step. Although the results are preliminary, we found that the synthetic derivatives bearing TBS protecting groups induced considerable cytotoxicity in HL60 human leukemia cells and were more potent than previously reported analogs. These synthetic analogs were able to induce apoptosis.

Experimental Section

General Remarks: ^{1}H NMR spectra were recorded at 400 and 300 MHz and ^{13}C NMR spectra were recorded at 100 and 75 MHz; chemical shifts are reported relative to internal Me_4Si. Optical rotations were determined for solutions in chloroform or methanol. IR spectra were recorded with a Bruker IFS 55 spectrometer. Elemental analyses were obtained using an EA 1108 CHNS-O FISONS instruments. Column chromatography was performed on silica gel (60 Å and 0.2–0.5 mm). Compounds were visualized on TLC plates by means of UV light, 2.5% phosphomolybdic acid in ethanol or vanillin with acetic and sulfuric acid in ethanol with heating. All solvents were purified by standard techniques.[20] Reactions requiring anhydrous conditions were performed under nitrogen. Anhydrous $MgSO_4$ was used to dry solutions.

(2*E*,5*E*,8*E*)-2,5,8-Decatriene-1,10-diol (2): K_2CO_3 (3.88 g, 28.05 mmol), tetrabutylammonium chloride (520 mg, 1.87 mmol) and copper(I) iodide (178 mg, 0.93 mmol) were added sequentially to a stirred solution of propargyl alcohol (1.4 mL, 23.37 mmol) in dry DMF (37 mL) under argon and at room temperature. After

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10 min, (*E*)-1,4-dibromobut-2-ene (2.0 g, 9.35 mmol) was added. The reaction mixture was stirred for 24 h. Then, Et_2O (40 mL) was added and the mixture was filtered through a pad of Celite. The resulting solution was washed with brine (40 mL) and extracted with Et_2O (3 × 20 mL). The combined organic phases were dried with $MgSO_4$ and concentrated. The obtained crude was purified by flash chromatography to yield (*E*)-deca-5-en-2,8-diyne-1,10-diol (978 mg, 65% yield) as a white solid. M.p. 86–88 °C. ^{1}H NMR ($CDCl_3$): δ = 1.70 (br. s, 2 H), 2.99 (s, 4 H), 4.29 (s, 4 H), 5.69 (t, J = 2.6 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.4 (CH_2), 51.1 (CH_2), 80.2 (C), 83.0 (C), 125.6 (CH) ppm. IR (film): $\tilde{\nu}$ = 3133, 2893, 2359, 1030, 970, 697 cm^{-1}. $C_{10}H_{12}O_2$ (164.20): calcd. C 71.39, H 9.59; found C 71.35, H 10.09.

(*E*)-Deca-5-en-2,8-diyne-1,10-diol (927 mg, 5.64 mmol) was slowly added to a suspension of $LiAlH_4$ (576 mg, 16.93 mmol) in dry THF (56 mL) at 0 °C. The reaction was warmed to room temperature and then heated at 50 °C for 5 h. The reaction mixture was cooled to 0 °C and quenched with sequential addition of water (0.95 mL), an aqueous NaOH solution (15% w/v, 0.95 mL), and water (2.85 mL) and then stirred for 1 h. Et_2O (30 mL) and $MgSO_4$ were added to the resulting mixture with additional stirring for 15 min. The suspension was filtered through a pad of Celite and washed with Et_2O (3 × 30 mL). The resulting solution was concentrated and the obtained crude was purified by flash chromatography to yield bis-allylic alcohol **2** (470 mg, 50% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 2.71 (s, 4 H), 4.05 (s, 4 H), 5.35 (m, 2 H), 5.63 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.7 (CH_2), 63.5 (CH_2), 129.0 (CH), 129.7 (CH), 131.1 (CH) ppm. IR (film): $\tilde{\nu}$ = 3421, 2925, 2859, 1541, 973 cm^{-1}. MS: *m*/*z* (%) = 149 [M – 19]$^+$ (6), 119 (15), 91 (56), 79 (100), 67 (78), 55 (26). $C_{10}H_{16}O_2$ (168.23): calcd. C 73.15, H 7.37; found C 73.23, H 7.24.

(2*R*,3*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-3-[(*E*)-4-{(2*R*,3*R* and 2*S*,3*S*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]oxiran-2-yl}but-2-enyl]oxirane (3): Crushed, activated 4-Å molecular sieves were added under argon to stirred CH_2Cl_2 (12 mL). The flask was cooled to –20 °C and Ti(O*i*Pr)$_4$ (0.86 mL, 2.90 mmol), (*S*,*S*)-(–)-DIPT (0.92 mL, 4.34 mmol), and bis-allylic alcohol **2** (975 mg, 5.8 mmol) in CH_2Cl_2 (2 mL) were added sequentially with stirring. The mixture was stirred at said temperature for 20 min, and TBHP (3.8 mL, 3.2 M in isooctane, 12.2 mmol) was added slowly. After the addition was complete, the reaction was maintained at this temperature with stirring for 12 h. After this time triethanolamine (0.6 mL, 4.35 mmol) was added and the reaction was vigorously stirred for 2 h. The alcohol protection was performed in the same vessel by adding imidazole (1.97 g, 29 mmol) followed by *tert*-butyl(chloro) dimethylsilane (4.37 g, 29 mmol). The reaction was warmed to room temperature and was then filtered through a pad of Celite. The obtained crude was purified by flash chromatography to yield **3** (1.908 g, 77% overall yield) as an oil. ^{1}H NMR ($CDCl_3$): δ = 0.07 (s, 6 H), 0.08 (s, 6 H), 0.90 (s, 18 H), 2.31 (dd, J = 4.9, 4.9 Hz, 4 H), 2.88 (m, 4 H), 3.67 (dd, J = 12.0, 4.6 Hz, 2 H), 3.80 (dd, J = 12.0, 3.3 Hz, 2 H), 5.57 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.5 (CH_3), 18.3 (C), 25.8 (CH_3), 34.7 (CH_2), 55.2 (CH), 58.1 (CH), 63.4 (CH_2), 127.6 (CH) ppm. IR (film): $\tilde{\nu}$ = 2930, 2858, 1472, 1255, 1112, 838 cm^{-1}. $C_{22}H_{44}O_4Si_2$ (428.75): calcd. C 61.63, H 10.34; found C 61.77, H 10.37.

(2*R*,3*R*)-1,4-Bis{(2*R*,3*R*)-3-[(*tert*-butyldimethylsilyloxy)methyl]oxiran-2-yl}butane-2,3-diol and (2*R*,3*R*)-1-{(2*R*,3*R*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]oxiran-2-yl}-4-{(2*S*,3*S*)-3-[(*tert*-butyldimethylsilyloxy)methyl]oxiran-2-yl}butane-2,3-diol (4): The bis-epoxy alkene **3** (1.908 g, 4.45 mmol) was added to a mixture of *t*BuOH (23 mL), H_2O (23 mL), AD-mix-β (6.23 g, 1.4 g/mmol of 3) and methanesulfonyl amide (508 mg, 5.34 mmol) at 0 °C. The solution was stirred for 12 h at 0 °C. After addition of a saturated Na_2SO_3 solution (50 mL) the mixture was extracted with EtOAc. The extracts were dried, and the solvent was removed. Flash chromatography on silica gel yielded **4** (1.87 g, 91% yield) as an oil. ^{1}H NMR ($CDCl_3$): δ = 0.07 (s, 12 H), 0.89 (s, 18 H), 1.61 (m, 2 H), 2.01 (m, 2 H), 2.70 (m, 2 H), 2.95 (m, 2 H), 3.07 (m, 2 H), 3.66–3.85 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.5 (CH_3), 18.3 (C), 25.8 (CH_3), 35.2 (CH_2), 53.8 (CH), 58.6 (CH), 63.3 (CH_2), 71.5 (CH) ppm. IR (film): $\tilde{\nu}$ = 3444, 2930, 2858, 1472, 1256, 1114, 838 cm^{-1}. $C_{22}H_{46}O_6Si_2$ (462.77): calcd. C 57.10, H 10.02; found C 57.15, H 10.22.

(2*S*,3*S*)-1,4-Bis{(2*R*,3*R*)-3-[(*tert*-butyldimethylsilyloxy)methyl]oxiran-2-yl}butane-2,3-diol and (2*S*,3*S*)-1-{(2*R*,3*R*)-3-[(*tert*-Butyldimethylsilyloxy)methyl]oxiran-2-yl}-4-{(2*S*,3*S*)-3-[(*tert*-butyldimethylsilyloxy)methyl]oxiran-2-yl}butane-2,3-diol (5): The aforementioned procedure to obtain **4** was applied to **3** (170 mg, 0.40 mmol), but AD-mix-α was used instead of AD-mix-β to yield **5** (146 mg, 80% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 0.07 (s, 12 H), 0.89 (s, 18 H), 1.62 (m, 2 H), 2.00 (m, 2 H), 2.70 (m, 2 H), 2.98 (m, 2 H), 3.07 (m, 2 H), 3.64–3.85 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.4 (CH_3), 18.3 (C), 25.8 (CH_3), 35.2 (CH_2), 35.3 (CH_2), 53.8 (CH), 58.5 (CH), 58.6 (CH), 58.7 (CH), 63.2 (CH_2), 63.3 (CH_2), 71.5 (CH), 72.4 (CH) ppm. IR (film): $\tilde{\nu}$ = 3444, 2930, 2858, 1541, 1257, 839 cm^{-1}. $C_{22}H_{46}O_6Si_2$ (462.77): calcd. C 57.10, H 10.02; found C 57.35, H 9.94.

(2*R*,3a*R*,5*S*,6a*R*)-2-{(*S*)-[2-(*tert*-Butyldimethylsilyloxy)-1-hydroxyethyl]}-5-{(*R*)-[2-(*tert*-butyldimethylsilyloxy)-1-hydroxyethyl]}-hexahydrofuro[3,2-*b*]furan (6) and (2*S*,3a*R*,5*S*,6a*R*)-2,5-Bis{(*R*)-[2-(*tert*-butyldimethylsilyloxy)-1-hydroxyethyl]}hexahydrofuro[3,2-*b*]furan (7): A substoichiometric amount of CSA (3 mg, 0.014 mmol) was added to a stirred solution of bis-epoxy alcohol **4** (33 mg, 0.071 mmol) in dry CH_2Cl_2 (7 mL) under argon at room temperature. The reaction mixture was stirred for 2 h, after which time TLC showed complete conversion. Work up was started by addition of a saturated $NaHCO_3$ solution (10 mL), followed by extraction with CH_2Cl_2 (3 × 5 mL). The combined organic phase was dried with $MgSO_4$. After filtration, the solvent was evaporated and the crude was purified by flash chromatography column to afford compounds **6** (9.9 mg, 30%) and **7** (21.1 mg, 64%) with an overall yield of 94%.

Compound 6: Colorless oil. $[\alpha]_D^{25}$ = +4.7 (c = 1.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.07 (s, 12 H), 0,89 (s, 18 H), 1.88 (m, 1 H), 1.99 (ddd, J = 13.8, 7.7, 2.8 Hz, 1 H), 2.16 (dd, J = 13.5, 5.8 Hz, 1 H), 2.27 (ddd, J = 14.0, 7.1, 7.1 Hz, 1 H), 2.47 (d, J = 3.8 Hz, 1 H), 2.56 (d, J = 3.8 Hz, 1 H), 3.72–3.58 (m, 6 H), 3.83 (dd, J = 13.1, 7.4 Hz, 1 H), 4.05 (m, 1 H), 4.47 (dd, J = 4.5, 4.5 Hz, 1 H), 4.69 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.4 (CH_3), 18.2 (C), 25.8 (CH_3), 35.0 (CH_2), 35.5 (CH_2), 64.2 (CH_2), 64.3 (CH_2), 73.0 (CH), 73.1 (CH), 78.1 (CH), 80.0 (CH), 83.8 (CH), 84.2 (CH) ppm. IR (film): $\tilde{\nu}$ = 3462, 2930, 2858, 1472, 1255, 1121, 837 cm^{-1}. $C_{22}H_{46}O_6Si_2$ (462.77): calcd. C 57.10, H 10.02; found C 57.13, H 9.90.

Compound 7: Colorless oil. $[\alpha]_D^{25}$ = +2.2 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.08 (s, 12 H), 0.90 (s, 18 H), 1.95 (m, 2 H), 2.15 (dd, J = 13.4, 5.4 Hz, 2 H), 2.43 (d, J = 3.8 Hz, 2 H), 3.71–3.58 (m, 6 H), 4.01 (m, 2 H), 4.70 (d, J = 3.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.4 (CH_3), 18.3 (C), 25.8 (CH_3), 36.6 (CH_2), 64.2 (CH_2), 73.2 (CH), 79.8 (CH), 84.1 (CH) ppm. IR (film): $\tilde{\nu}$ = 3446, 2930, 2858, 1472, 1255, 1121, 836 cm^{-1}. $C_{22}H_{46}O_6Si_2$ (462.77): calcd. C 57.10, H 10.02; found C 57.21, H 10.05.

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(2*S*,3a*R*,5*S*,6a*R*)-2,5-Bis{(*R*)-[1-acetoxy-2-(*tert*-butyldimethylsilyloxy)ethyl]}hexahydrofuro[3,2-*b*]furan (8): DMAP (22 mg, 0.18 mmol) and acetic anhydride (17 μL, 0.18 mmol) were added to a solution of diol **7** (34 mg, 0.073 mmol) in dry CH_2Cl_2 (3 mL) under argon at room temperature. The reaction was stirred for 2 h. After this time, TLC showed that the starting material had disappeared. The reaction mixture was washed with brine and extracted with CH_2Cl_2 (3×3 mL). The organic phases were combined, dried, and concentrated. The obtained crude was purified by silica gel column chromatography to yield diacetate **8** (38 mg, 95% yield) as an oil. $[a]_D^{25}$ = +4.8 (*c* = 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.04 (s, 12 H), 0.87 (s, 18 H), 1.95 (m, 2 H), 2.06 (s, 6 H), 2.15 (dd, *J* = 13.5, 5.8 Hz, 2 H), 3.68 (dd, *J* = 11.1, 5.6 Hz, 2 H), 3.76 (dd, *J* = 11.0, 4.3 Hz, 2 H), 4.21 (ddd, *J* = 10.4, 5.5, 5.5 Hz, 2 H), 4.63 (d, *J* = 4.0 Hz, 2 H), 4.98 (ddd, *J* = 5.2, 5.2, 5.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.7 (CH_3), 18.0 (C), 20.9 (CH_3), 25.5 (CH_3), 36.3 (CH_2), 61.8 (CH_2), 74.8 (CH), 78.1 (CH), 83.4 (CH), 170.1 (C) ppm. IR (film): $\tilde{\nu}$ = 2930, 2858, 1748, 1472, 1235, 1127, 837 cm^{-1}. $C_{26}H_{50}O_8Si_2$ (546.84): calcd. C 57.11, H 9.22; found C 57.15, H 9.44.

(2*S*,3a*R*,5*S*,6a*R*)-2,5-Bis[(*R*)-1,2-dihydroxyethyl]hexahydrofuro[3,2-*b*]-furan (9): Dowex 50Wx8 (35 mg, 50% w/w) was added to a stirred solution of diol **7** (70 mg, 0.151 mmol) in MeOH (7 mL, 0.02 M) at room temperature. The reaction mixture was vigorously stirred for 15 h until TLC showed complete conversion. After filtration, the solution was concentrated to yield tetraol **9** (30 mg, 85% yield) as a white solid. M.p. 137–140 °C. $[a]_D^{25}$ = –2.4 (*c* = 1.6, CH_3OH). ^{1}H NMR (CD_3OD): δ = 1.98 (m, 2 H), 2.11 (dd, *J* = 13.4, 5.6 Hz, 2 H), 3.51 (dd, *J* = 11.0, 6.3 Hz, 2 H), 3.60–3.68 (m, 4 H), 4.08 (ddd, *J* = 10.7, 5.4, 5.4 Hz, 2 H), 4.74 (d, *J* = 4.3 Hz, 2 H) ppm. ^{13}C NMR (CD_3OD): δ = 35.7 (CH_2), 63.4 (CH_2), 73.4 (CH), 80.2 (CH), 84.0 (CH) ppm. IR (film): $\tilde{\nu}$ = 3348, 2936, 2858, 1541, 1038 cm^{-1}. $C_{10}H_{18}O_6$ (234.25): calcd. C 51.27, H 7.75; found C 51.29, H 7.57.

(2*S*,3a*R*,5*S*,6a*R*)-2,5-Bis[(*R*)-1,2-diacetoxyethyl]hexahydrofuro[3,2-*b*]-furan (10): The aforementioned procedure to obtain **8** from **7** was applied to **9** on a 22 mg (0.094 mmol) scale, but using twice the amount of acetic anhydride and DMAP and by heating the mixture to 40 °C to yield tetraacetate **10** (35 mg, 92% yield) as a colorless oil. $[a]_D^{25}$ = +30.1 (*c* = 1.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.88 (m, 2 H), 2.04 (s, 6 H), 2.07 (s, 6 H), 2.18 (dd, *J* = 13.6, 5.8 Hz, 2 H), 4.06 (dd, *J* = 12.1, 6.4 Hz, 2 H), 4.16 (m, 2 H), 4.36 (dd, *J* = 12.1, 3.0 Hz, 2 H), 4.63 (d, *J* = 4.1 Hz, 2 H), 5.08 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.7 (CH_3), 20.9 (CH_3), 36.8 (CH_2), 62.9 (CH_2), 72.4 (CH), 78.2 (CH), 84.1 (CH), 170.1 (C), 170.6 (C) ppm. IR (film): $\tilde{\nu}$ = 2955, 1745, 1438, 1372, 1224, 1061 cm^{-1}. MS: *m*/*z* (%) = 359 [M – Ac]$^+$ (1), 342 [M – AcOH]$^+$ (2), 299 (5), 257 (35), 197 (48), 137 (100). HRMS (EI): calcd. for $C_{16}H_{22}O_8$ [M – AcOH]$^+$: 342.1315; found 342.1311.

(2*S*,3a*S*,5*S*,6a*S*)-2,5-Bis{(*R*)-[2-(*tert*-butyldimethylsilyloxy)-1-hydroxyethyl]}hexahydrofuro[3,2-*b*]furan (11) and (2*R*,3a*S*,5*S*,6a*S*)-2-{(*S*)-[2-(*tert*-Butyldimethylsilyloxy)-1-hydroxyethyl]}-5-{(*R*)-[2-(*tert*-butyldimethylsilyloxy)-1-hydroxyethyl]}hexahydrofuro[3,2-*b*]furan (12): The aforementioned cyclization process to obtain **6** and **7** was applied to bis-epoxy alcohol **5** on a 137 mg (0.296 mmol) scale to yield **7** (21 mg, 14% yield), **11** (57 mg, 42% yield), and **12** (32 mg, 27% yield) with an overall yield of 83%.

Compound 11: A white solid. M.p. 51–52 °C. $[a]_D^{25}$ = –10.8 (*c* = 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.06 (s, 12 H), 0.88 (s, 18 H), 2.17 (m, 4 H), 3.03 (s, 2 H), 3.61 (d, *J* = 5.8 Hz, 4 H), 3.81 (dd, *J* = 10.1, 5.1 Hz, 2 H), 4.08 (m, 2 H), 4.43 (d, *J* = 4.7 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.5 (CH_3), 18.2 (C), 25.8 (CH_3), 32.9 (CH_2), 64.2 (CH_2), 72.7 (CH), 81.3 (CH), 84.5 (CH) ppm. IR (film): $\tilde{\nu}$ = 3445, 2929, 2858, 1472, 1255, 1118, 837 cm^{-1}. MS: *m*/*z* (%) = 463 [M + H]$^+$ (0.12), 405 [M – *t*Bu]$^+$ (28), 287 (4), 229 (13), 111 (14), 75 (100). $C_{22}H_{46}O_6Si_2$ (462.77): calcd. C 57.10, H 10.02; found C 57.17, H 9.99. HRMS (EI): calcd. for $C_{22}H_{47}O_6Si_2$ [M + H]$^+$: 463.2911; found 463.2906.

Compound 12: A colorless oil. $[a]_D^{25}$ = –5.3 (*c* = 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.07 (s, 12 H), 0,89 (s, 18 H), 1.88 (m, 1 H), 1.99 (ddd, *J* = 13.8, 7.7, 2.8 Hz, 1 H), 2.16 (dd, *J* = 13.5, 5.8 Hz, 1 H), 2.27 (ddd, *J* = 14.0, 7.1, 7.1 Hz, 1 H), 2.47 (d, *J* = 3.8 Hz, 1 H), 2.56 (d, *J* = 3.8 Hz, 1 H), 3.72–3.58 (m, 6 H), 3.83 (dd, *J* = 13.1, 7.4 Hz, 1 H), 4.05 (m, 1 H), 4.47 (dd, *J* = 5.0 Hz, 1 H), 4.69 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.4 (CH_3), 18.2 (C), 25.8 (CH_3), 35.0 (CH_2), 35.5 (CH_2), 64.2 (CH_2), 64.3 (CH_2), 73.0 (CH), 73.1 (CH), 78.1 (CH), 80.0 (CH), 83.8 (CH), 84.2 (CH) ppm. IR (film): $\tilde{\nu}$ = 3462, 2930, 2858, 1472, 1255, 1121, 837 cm^{-1}. $C_{22}H_{46}O_6Si_2$ (462.77): calcd. C 57.10, H 10.02; found C 57.13, H 9.90.

(2*R*,3a*S*,5*S*,6a*S*)-2-{(*S*)-[1-Acetoxy-2-(*tert*-butyldimethylsilyloxy)-ethyl]}-5-{(*R*)-[1-acetoxy-2-(*tert*-butyldimethylsilyloxy)ethyl]}-hexahydrofuro[3,2-*b*]furan (13): The aforementioned procedure to obtain **8** from **7** was applied to **12** on a 34 mg (0.073 mmol) scale to yield diacetate **13** (38 mg, 96% yield) as a colorless oil. $[a]_D^{25}$ = –12.5 (*c* = 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 0.04 (s, 12 H), 0.87 (s, 18 H), 1.87 (m, 2 H), 2.06 (s, 6 H), 2.12 (m, 1 H), 2.24 (m, 1 H), 3.65–3.80 (m, 4 H), 4.00 (m, 1 H), 4.19 (m, 1 H), 4.43 (dd, *J* = 4.6, 4.6 Hz, 1 H), 4,67 (m, 1 H), 5.03 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.4 (CH_3), 18.0 (C), 25.5 (CH_3), 34.9 (CH_2), 35.4 (CH_2), 61.6 (CH_2), 62.0 (CH_2), 74.5 (CH), 76.3 (CH), 78.0 (CH), 83.4 (CH), 83.7 (CH), 170.1 (C) ppm. IR (film): $\tilde{\nu}$ = 2931, 2858, 1748, 1472, 1235, 1126, 837 cm^{-1}. $C_{26}H_{50}O_8Si_2$ (546.84): calcd. C 57.11, H 9.22; found C 57.16, H 9.17.

(2*R*,3a*S*,5*S*,6a*S*)-2-[(*S*)-1,2-Dihydroxyethyl]-5-[(*R*)-1,2-dihydroxyethyl]hexahydrofuro[3,2-*b*]furan (14): The aforementioned procedure to obtain tetraol **9** from diol **7** was applied to diol **12** on a 70 mg (0.151 mmol) scale to yield tetraol **14** (33 mg, 95% yield) as a colorless oil. $[a]_D^{25}$ = –7.8 (*c* = 2.3, CH_3OH). ^{1}H NMR (CD_3OD): δ = 1.78–1.97 (m, 2 H), 2.08 (dd, *J* = 13.2, 5.1 Hz, 1 H), 2.26 (m, 1 H), 3.43–3.53 (m, 2 H), 3.56–3.68 (m, 4 H), 3.80 (m, 1 H), 4.09 (ddd, *J* = 10.0, 5.0, 5.0 Hz, 1 H), 4.48 (dd, *J* = 4.6, 4.6 Hz, 1 H), 4.71 (m, 1 H) ppm. ^{13}C NMR (CD_3OD): δ = 33.9 (CH_2), 35.2 (CH_2), 63.2 (CH_2), 63.3 (CH_2), 72.9 (CH), 73.2 (CH), 78.2 (CH), 79.8 (CH), 81.0 (CH), 83.5 (CH), 84.0 (CH) ppm. IR (film): $\tilde{\nu}$ = 3365, 2935, 2858, 1059 cm^{-1}. $C_{10}H_{18}O_6$ (234.25): calcd. C 51.27, H 7.75; found C 51.26, H 8.83. MS: *m*/*z* (%) = 235 [M + H]$^+$ (2), 199 (1), 173 (100), 137 (37), 95 (42), 81 (94). HRMS (EI): calcd. for $C_{10}H_{19}O_6$ [M + H]$^+$: 235.1182; found 235.1172.

(2*R*,3a*S*,5*S*,6a*S*)-2-[(*S*)-1,2-Diacetoxyethyl]-5-[(*R*)-1,2-diacetoxyethyl]hexahydrofuro[3,2-*b*]furan (15): The aforementioned procedure to obtain tetraacetate **10** from tetraol **9** was applied to tetraol **14** on a 31 mg (0.132 mmol) scale to yield tetraacetate **15** (46 mg, 90% yield) as a colorless oil. $[a]_D^{25}$ = –15.7 (*c* = 2.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.72–1.95 (m, 2 H), 2.03 (s, 3 H), 2.04 (s, 3 H), 2.06 (s, 6 H), 2.18 (dd, *J* = 13.7, 5.6 Hz, 1 H), 2.20–2.29 (m, 1 H), 3.97–4.20 (m, 4 H), 4.36 (dd, *J* = 12.1, 3.1 Hz, 1 H), 4.43 (dd, *J* = 12.2, 2.9 Hz, 1 H), 4.47 (dd, *J* = 4.4, 4.4 Hz, 1 H), 4.66 (m, 1 H), 5.10 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.5 (CH_3), 20.5 (CH_3), 20.7 (CH_3), 20.7 (CH_3), 35.4 (CH_2), 35.8 (CH_2), 62.4 (CH_2), 62.7 (CH_2), 72.1 (CH), 72.1 (CH), 76.3 (CH), 78.0 (CH), 83.6 (CH), 84.1 (CH), 169.8 (C), 169.9 (C), 170.4 (C), 170.4 (C) ppm. IR (film): $\tilde{\nu}$ = 2953, 1744, 1372, 1223, 1049. MS: *m*/*z* (%) = 342 [M – AcOH]$^+$ (1), 282 (2), 257 (34), 197 (66), 137 (100).

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HRMS (EI): calcd. for $C_{16}H_{22}O_8$ [M – AcOH]$^+$: 342.1315; found 342.1318.

Biological Tests

Chemicals and Reagents: All starting materials were commercially available research-grade chemicals and were used without further purification. RPMI 1640 medium was purchased from Flow Laboratories (Irvine, UK), fetal calf serum (FCS) was from Gibco (Grand Island, NY), trichloroacetic acid (TCA), glutamine, and gentamicin were from Merck (Darmstadt, Germany), and dimethyl sulfoxide (DMSO) and sulforhodamine B (SRB) were from Sigma (St Louis, MO).

Cells, Culture and Plating: The human promyelocytic leukemia cell line HL60 was used in this study. Cells were maintained in 25 cm^2 culture flasks in RPMI 1640 supplemented with 5% heat-inactivated fetal calf serum and 2 mM L-glutamine in a 37 °C 5% CO_2, 95% humidified air incubator. Exponentially growing cells were resuspended in an antibiotic-containing medium (100 units penicillin G and 0.1 mg of streptomycin per mL). Single-cell suspensions displaying >97% viability by Trypan blue dye exclusion were subsequently counted. After counting, dilutions were made to give the appropriate cell densities for inoculation onto 96-well microtiter plates. Cells were inoculated in a volume of 100 μL per well at densities of 10000 cells per well, based on their doubling times.

Chemosensitivity Testing: Chemosensititvity tests were performed by using the SRB assay of the NCI[13] with slight modifications.[14] Pure compounds were initially dissolved in DMSO at 400 times the desired final maximum test concentration. Control cells were exposed to an equivalent concentration of DMSO (negative control). Each agent was tested in triplicate at different dilutions in the range of 1–100 μM. Drug treatment was started on day 1 after plating. Drug incubation times of 48 h were used, after which time cells were precipitated with ice-cold 80% (w/v) trichloroacetic acid (50 μL) and fixed for 60 min at 4 °C. Then the SRB assay was performed. The optical density (OD) of each well was measured at 490 nm using BioTek's ELx800NB Absorbance Microplate Reader. Values were corrected for background OD using wells containing only the medium. The percentage growth (PG) was calculated with respect to untreated control cells (C) at each of the drug concentration levels based on the difference in OD at the start (T_0) and end of drug exposure (T), according to NCI formulae. Briefly, if T is greater than or equal to T_0 the calculation is $100 \times [(T - T_0)/(C - T_0)]$. If T is less than T_0, denoting cell-killing, the calculation is $100 \times [(T - T_0)/(T_0)]$. From these calculations a PG value of 0 corresponds to the amount of cells present at the start of drug exposure, while negative PG values denote net cell-kill.

DNA Isolation and Agarose Gel Electrophoresis: Single-cell suspensions of 10×10^6 cells in the culture medium (10 mL) were exposed for 24 h to compounds **7** and **12** at 20 or 60 μM, or to DMSO vehicle (30 μL). After said time cells were centrifuged at 1200 rpm for 15 min. Genomic DNA was subsequently extracted by using the QIAmp DNA Mini Kit (QIAGEN Inc., Valencia, CA) to afford a 200 μL DNA solution. An aliquot (20 μL) per sample was electrophoretically separated on a 0.8% agarose gel and then stained with a solution of ethidium bromide. The gels were analyzed with a GS-700 Imaging Densitometer (BioRad Laboratories, Hercules, California).

Supporting Information (for details see the footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **6**–**15**, and COSY and NOE spectra of compounds **11** and **13**.

Acknowledgments

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