trans,anti,trans-Tetra(spirotetrahydrofuranyl)cyclohexane-1,2-dione. Stereocontrolled Synthesis and Definition of Its Susceptibility to Photoisomerization

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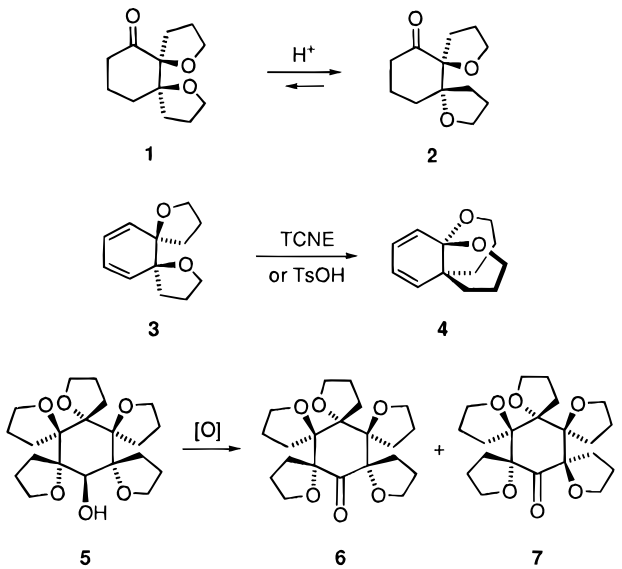
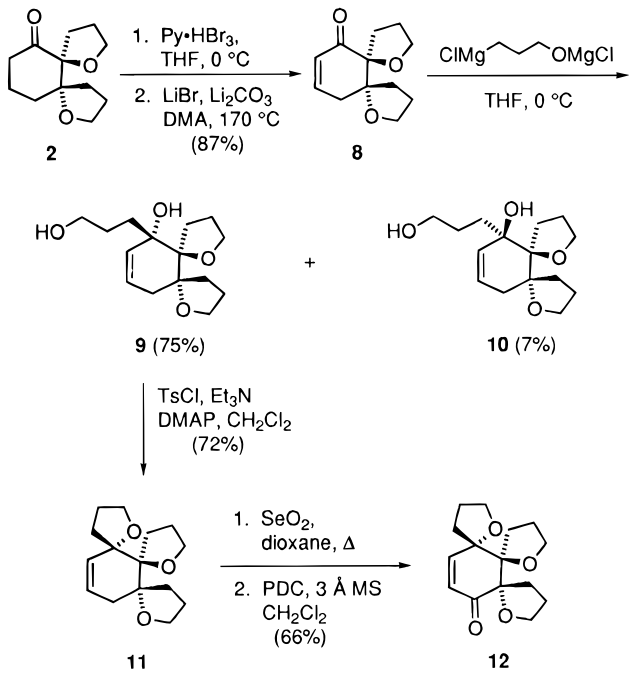
The title α-diketone (**18**) has been synthesized in stereocontrolled fashion. The ability to introduce the four contiguous spirocyclic ether oxygens in extended trans fashion rests on the ability of the Normant reagent ($ClMgCH_2CH_2CH_2OMgCl$) to engage in chelation control during 1,2-addition to an α-oxy substituted cyclohexanone. The successful pathway is dependent on the ability of osmium tetraoxide to add (slowly) across the double bond of the cyclohexene precursor. The highly substituted 1,2-cyclohexanedione is quite sensitive to light and rearranges by means of an interesting photoisomerization process to a laterally fused pyran system. A likely mechanistic pathway for this intramolecular isomerization is presented.

In the early developmental phases of our quest for belted spirocyclic tetrahydrofurans,[1] a structural reorganization was encountered in precursors substituted with only two adjacent heterocyclic rings. Notable examples include the ready acid-catalyzed equilibration of *cis*-**1** with *trans*-**2**[2] and the isomerization of **3** to propelladiene **4** in the presence of tetracyanoethylene (TCNE)[3] or *p*-toluenesulfonic acid.[4] More recently, the loss of stereochemical integrity associated with the mild oxidation (periodinane, Swern, perruthenate, and PDC) of the pentaspirocyclohexanol **5** has been noted.[5]



These unprecedented transformations reveal the frangibility of carbon−oxygen bonds when these are arranged in any of a number of spirocyclic combinations. Their thoughtful deployment could usefully expand synthetic technology while simultaneously providing enrichment at the associated mechanistic level. It is in this context that we describe herein our observation of yet another fascinating rearrangement associated with this class of compounds. This finding is preceded by details of the strategy involved in stereocontrolled construction of the requisite polyspirocyclic α-diketone.

Scheme 1



Results

Introduction of a double bond into readily available **2**[1] was best accomplished by conversion to the α-bromo ketone with pyridinium hydrobromide perbromide and dehydrobromination with lithium carbonate and lithium bromide in hot *N*,*N*-dimethylacetamide (DMA)[6] (Scheme 1). The bromination step occurs readily to give a mixture of two diastereomers in quantitative yield. During the

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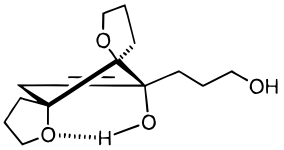
dehydrobromination, it is imperative that the lithium bromide be absolutely dry and that excessive temperatures not be used to remove the solvent after the reaction is completed. Best results were realized when the DMA was evaporatively distilled in vacuo below 50−55 °C. Under these conditions, **8** was obtained in 87% overall yield.

The need to introduce a third spirotetrahydrofuran ring stereoselectively now had to be addressed. It was at this point that we became aware of the fact that the Normant reagent[7] is especially well suited to ensuring nucleophilic attack with high syn selectivity.[8] When the addition was performed in THF at 0 °C, enone **8** was transformed into a mixture of **9** (75%), **10** (7%), and a 1,4-addition product (5%). Cyclohexanols in which the hydroxyl substituent is projected axially are recognized often to be less polar than their equatorial counterparts.[9] This is regarded to be a reflection of the inability of the sterically more crowded axial OH to bind as tightly to the adsorbent. Since **9** is more rapidly eluted from silica gel than **10** and is expected to exhibit the ground state conformation depicted in **A**, equatorial attack on **8** was tentatively



A

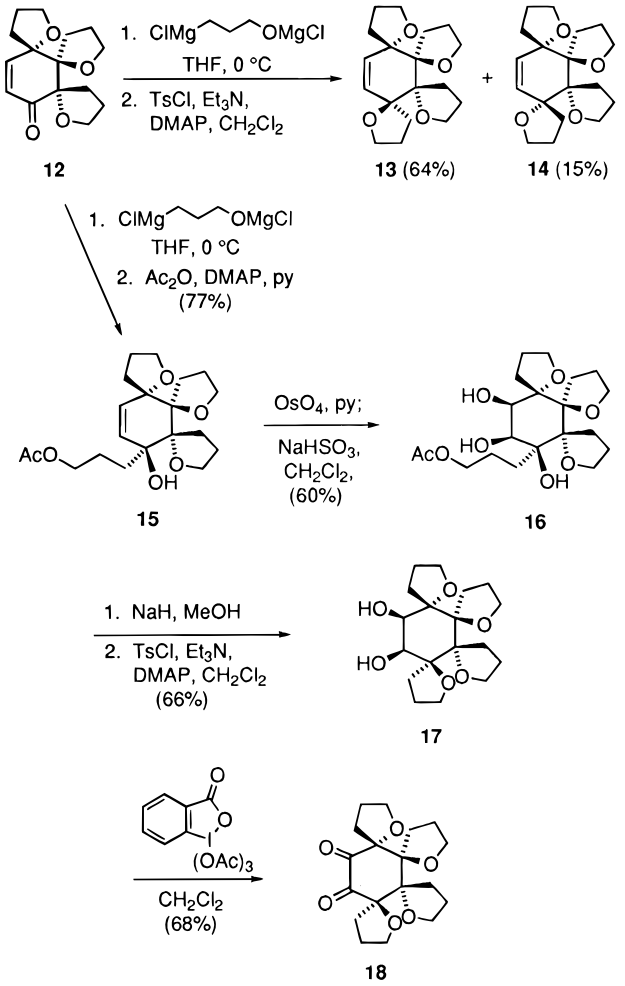
formulated as the predominant reaction trajectory. This conclusion conforms to the chelation-controlled selectivity with which Grignard reagents add to α-alkoxycyclohexanones[10] and is substantiated below.

Although the polar diols **9** and **10** could be separated by medium-pressure liquid chromatography (MPLC) on silica gel, it proved more convenient to isolate **11** by effecting ring closure on the mixture. When this protocol was followed, the trispiro ether was isolated in 72% overall yield following separation of the minor diastereomer.

Allylic oxidation of **11** with selenium dioxide in anhydrous dioxane provided the intermediate alcohols after a reflux period of 36 h. Direct exposure of the resulting product mixture to pyridinium dichromate and powdered 3 Å molecular sieves gave **12** (66%). On exposure of **12** to the Normant reagent, the normal reaction course was again followed. The extent to which syn facial selectivity had operated was determined by direct cyclization of the resulting diol mixture to the tetraspirocyclohexenes **13** and **14** (Scheme 2). That the all-anti isomer predominated by a factor in excess of 4:1 was evident from the C_2-symmetric nature of **13**. Thus, in contrast to **14**, which exhibits the full complement of 18 carbon signals in its ^{13}C NMR spectrum, **13** is characterized by only nine peaks.

Attempts to dihydroxylate or epoxidize **13** were soon discovered to be problematical, most likely due to the considerable steric shielding about the double bond. Recourse to dimethyldioxirane did indeed lead to the

Scheme 2



consumption of **13**, but degradative attack at the tetrahydrofuranyl sites appeared to be operative. For this reason, hydroxyl-associated dihydroxylation was pursued. To this end, acetate **15** was prepared to enhance solubility and facilitate purification. The catalytic osmylation of **15** continued to prove sluggish, requiring well in excess of 1 week to proceed to completion. The reaction time can be reduced to 3 days by using > 1.0 equiv of OsO_4 and by minimizing the quantity of pyridine so as to maximize reagent concentration. Since the acetoxy triol **16** that is liberated upon hydrolysis with sodium bisulfite is rather water-soluble, repeated extraction with CH_2Cl_2 was necessary to ensure its maximum recovery (60%).

The hydrolysis of **16** proved to be straightforward, providing an intermediate tetraol which underwent cyclization to **17** (66%) following monotosylation. When recorded at room temperature, the ^1H and ^{13}C NMR spectra of **16** and **17** exhibit very broad peaks due to conformational interconversions that are relatively slow on the NMR time scale. Consequently, these spectra were rerecorded in toluene-d_8 at ca. 375 K in order to achieve enhanced resolution and permit confirmation of the structural assignments.

From among the variety of oxidants examined to effect the conversion of **17** to **18**, the Dess−Martin periodinane[11] emerged as the most satisfactory. In the presence of 6 equiv of this reagent, the consumption of starting diol was complete within 12 h. The bright yellow

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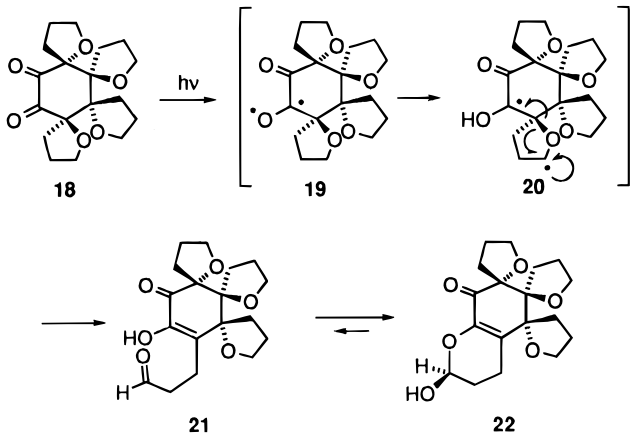
Scheme 3



α-diketone was readily purified by flash chromatography on a short column of silica gel and proved to be reasonably stable when stored at 0 °C under nitrogen *in the absence of laboratory light*. The nine carbon signals observed for **18** reflect the return to a C_2-symmetric molecule.

At the experimental level, the routine handling of **18** was noted to be accompanied by loss of its characteristic yellow hue. This process, which was accelerated during attempts at recrystallization or, more generally, at somewhat elevated temperatures, culminated in the acquisition of a white solid. The spectral properties of this substance proved to be of little diagnostic structural value because they obviously reflected the presence of two or more stereoisomers and/or tautomers in equilibrium. Ultimately, colorless crystals well suited to X-ray crystallographic analysis were grown and unequivocal corroboration of the keto lactol structure **22** was in hand. The hydroxyl substituent of **22** occupies a quasi-axial orientation, which may be attributed to an anomeric effect. When crystals of **22** are dissolved in C_6D_6 and the ^{1}H NMR spectrum immediately recorded, the complex spectrum is originally recorded is again observed. Presently, it is possible to attribute this behavior to ring−chain tautomerism involving the aldehyde **21** (Scheme 3). Quite evidently, slow crystallization of this equilibrating mixture from ethyl acetate results in exclusive deposition of the cyclized keto lactol.

Discussion

Six distinctively different *photoinduced isomerization* processes have previously been identified for aliphatic α-diketones, none of which has a parallel in the present study. The earliest synthetically useful discovery appears to have been made by Urry and co-workers somewhat more than three decades ago.[12] In their systems, irradiation was seen to promote intramolecular γ-hydrogen transfer with exclusive formation of 2-hydroxycyclobutanones. The regioselectivity of these processes is remarkable in that no 1-acylcyclobutanols result despite the fact that pseudo six-membered cyclic transition states would likely be involved along both reaction trajectories. The inoperability of the latter pathway may stem from the kinetic and/or thermodynamic preference for incorporating the trigonal carbonyl carbon as a structural component of the pseudo ring. Burkoth and Ullman have shown, however, that the second option can be made operative if the alternative reaction site is benzylic.[13,14] Hydrogen abstraction does not occur if a highly strained product would be formed. Instead, rearrangement occurs via a rebonding scheme similar to that commonly observed for cross-conjugated dienones.

When a double bond is properly positioned relative to one of the carbonyls, oxetane formation via the Paterno−Büchi reaction operates to the exclusion of type II elimination, photoenolization, or α-cleavage.[15] The two latter processes have been previously documented.[16,17]

The sixth type of photorearrangement operates in bridged cyclohexenediones. Upon photoexcitation, 1,3-acyl migration is induced with the formation of unsaturated cyclobutanediones.[18−21] Continued irradiation leads to expulsion of 2 equiv of carbon monoxide and formation of the 1,3-diene.[22]

The 1,2-cyclohexanedione **18** represents, to our knowledge, the first α-diketone to be substituted at C_α with a heteroatom. The fact that this compound exhibits an unusual facility for photoactivation perhaps accounts for its relatively low triplet energy (biacetyl = 56 kcal/mol).[23] The photoreactivity exhibited by **18** following excitation (see **19**) consists of γ-hydrogen abstraction to produce the carbon-centered radical **20**, which is stabilized by an α-oxygen atom.[24] Fragmentation of **20** leads to aldehyde **21**, whose subsequent cyclization affords **22**. This reasonable mechanistic pathway is very likely accompanied by release of a modicum of nonbonded steric compression, as the fourth spirotetrahydrofuran ring is transformed into a laterally fused pyran subunit.

The salient features of our results are (a) the remarkable ease with which **18** experiences photoisomerization under ordinary laboratory conditions, (b) the discovery of an intramolecular photorearrangement not previously observed with a cyclic α-diketone, and (c) the inertness of **21** (as its diketo tautomer) toward further photochemically-induced change. Finally, we note that a variety of options are available for general adaptation of this chemistry to the construction of multiple chiral ensembles. One of these involves the reliable control of

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facial selectivity during the capping of carbonyl groups as spirotetrahydrofurans. Major progress in this regard has been realized by methodology described in the following paper.

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at the indicated field strengths. High-resolution mass spectra were measured at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All reactions were carried out under a nitrogen atmosphere, and the ensuing separations were effected either with Merck Lobar columns (Lichroprep Si-60) fitted to a Fluid Metering INC pump (MPLC) or on Merck silica gel HF_{254} (flash chromatography). The organic extracts were dried over anhydrous magnesium sulfate or sodium sulfate. Solvents were reagent grade and in many cases dried prior to use.

(5*R,6*S**)-1,7-Dioxadispiro[4.0.4.4]tetradec-12-en-11-one (8).** A cold (0 °C), magnetically stirred solution of pyridinium hydrobromide perbromide (2.71 g, 8.85 mmol) in anhydrous THF (35 mL) was treated dropwise with a solution of **2** (1.77 g, 8.36 mmol) in THF (10 mL). The reaction mixture was allowed to warm to rt and after 15 min was diluted with ether and washed consecutively with 10% sodium thiosulfate solution, water, and brine. After drying and solvent evaporation, the resulting pale yellow oily α-bromo ketone mixture (2.44 g, 100%) was directly dehydrobrominated. If desired, separation and purification can be achieved by MPLC on silica gel (elution with 40% ether in petroleum ether). The major diastereomer was isolated as a colorless oil with the following spectral properties: IR (film, cm^{-1}) 2980, 1740, 1450, 1290, 1060, 920; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (dd, J = 11.6, 6.7 Hz, 1 H), 3.82 (m, 2 H), 3.71 (m, 1 H), 3.63 (m, 1 H), 2.63 (m, 1 H), 2.32−2.10 (m, 4 H), 1.94−1.56 (series of m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.4, 92.2, 88.7, 69.1, 68.2, 53.5, 34.0, 33.4, 32.8, 26.2, 25.9, 25.8; MS m/z (M^+) calcd 290.0340, obsd 290.0335.

To a solution of the α-bromo ketone mixture (1.74 g, 6.02 mmol) in N,N-dimethylacetamide (35 mL) were added dry lithium carbonate (1.44 g, 19.0 mmol) and lithium bromide (1.41 g, 16.3 mmol). The reaction mixture was heated at 170 °C for 1.5 h, cooled to 25 °C, and subjected to Kugelrohr distillation (30−40 °C, 0.1 Torr) in order to remove the majority of the solvent. The residue was taken up in ether and filtered through a small pad of Celite. The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel (elution with 40% ether in petroleum ether) to give 1.09 g (87%) of **8** as a colorless oil; IR (film, cm^{-1}) 2990, 1690, 1380, 1220, 1090, 1060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (m, 1 H), 5.91 (m, 1 H), 4.04 (m, 1 H), 3.90−3.65 (m, 3 H), 2.57 (m, 1 H), 2.48−2.26 (m, 2 H), 2.13 (m, 1 H), 2.05−1.66 (series of m, 5 H), 1.54 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.8, 146.7, 128.1, 91.8, 86.1, 69.9, 69.2, 39.7, 32.3, 29.4, 26.3, 25.6; MS m/z (M^+) calcd 208.1099, obsd 208.1105.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.97; H, 7.88.

(5*R,6*R**,11*S**)-11-Hydroxy-1,7-dioxadispiro[4.0.4.4]-tetradec-12-ene-11-propanol (9) and (5*R**,6*R**,11*R**)-11-Hydroxy-1,7-dioxadispiro[4.0.4.4]tetradec-12-ene-11-propanol (10).** A cold (0 °C) solution of **8** (1.12 g, 5.38 mmol) in anhydrous THF (50 mL) was treated dropwise via syringe with a solution of the Normant reagent derived from 1-chloro-3-propanol (15.0 mL of 0.54 N, 8.08 mmol). The reaction mixture was allowed to warm to rt over 15 min and then quenched by the addition of saturated NH_4Cl solution. The separated aqueous phase was extracted with ether, and the combined organic solutions were dried, filtered, and concentrated to leave a pale yellow oil, which was purified by MPLC on silica gel (elution with 5% methanol in CH_2Cl_2). There were obtained 1.01 g (75%) of **9**, 89 mg (7%) of **10**, and 61 mg (5%) of a 1,4-addition product.

For **9**: colorless oil; IR (film, cm^{-1}) 3460, 2970, 1050; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (m, 1 H), 5.69 (m, 1 H), 4.38 (br s, 1 H), 3.91 (m, 4 H), 3.68 (m, 1 H), 3.60 (m, 1 H), 2.92 (br s, 1 H), 2.36 (m, 2 H), 2.20−1.42 (series of m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 130.1, 125.0, 88.4, 87.0, 74.3, 70.1, 67.9, 63.5, 34.9, 33.5, 31.5, 27.3, 26.9, 26.3, 25.6; MS m/z (M^+) calcd 268.1674, obsd 268.1675.

For **10**: colorless oil; IR (film, cm^{-1}) 3450, 2980, 1050; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (m, 2 H), 3.92 (m, 2 H), 3.81 (m, 1 H), 3.63 (m, 2 H), 2.52 (br s, 1 H), 2.32−1.50 (series of m, 14 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 129.8, 127.0, 89.7, 86.4, 75.8, 70.0, 67.4, 63.6, 37.4, 33.6, 32.8, 27.7, 27.6, 26.8, 26.4; MS m/z (M^+) calcd 268.1674, obsd 268.1679.

(5*R,6*S**,11*S**)-1,7,12-Trioxatrispiro[4.0.4.0.4.3]octadec-16-ene (11). A. Ring Closure of 9.** To a solution of **9** (163 mg, 0.61 mmol) in CH_2Cl_2 (4 mL) was added triethylamine (1 mL) followed by *p*-toluenesulfonyl chloride (139 mg, 0.73 mmol) and 4-(dimethylamino)pyridine (4 mg). The reaction mixture was stirred at 25 °C for 8 h, diluted with ether, washed sequentially with 1 N HCl and brine, dried, and evaporated. Purification of the residue by MPLC on silica gel (elution with 30% ether in petroleum ether) gave 110 mg (72%) of **11** as a colorless crystalline solid: mp 80−81 °C; IR (film, cm^{-1}) 3000, 2880, 1090, 1050; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (m, 1 H), 5.39 (m, 1 H), 3.91−3.52 (m, 6 H), 2.54 (m, 1 H), 2.25−1.74 (series of m, 11 H), 1.53 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.2, 123.2, 89.1, 87.7, 86.9, 69.7, 67.8, 38.6, 33.4, 32.1, 30.1, 27.6, 27.4, 26.8 (1 C not observed); MS m/z (M^+) calcd 250.1569, obsd 250.1569.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.02; H, 8.99.

B. Direct Conversion from 8. A 200 mg (0.96 mmol) sample of **8** in cold (0 °C), anhydrous THF (5 mL) was treated with the Normant reagent (3.43 mL of 0.42 N, 1.44 mmol) according to the predescribed conditions. After 15 min at rt, the same workup provided a pale yellow oil, 163 mg of which was cyclized by reaction with *p*-toluenesulfonyl chloride (139 mg, 0.73 mmol), triethylamine (1 mL), and DMAP (4 mg) in CH_2Cl_2 (4 mL). The resulting solution was stirred at 25 °C for 8 h, diluted with ether, washed with 1 N HCl and brine, dried, and evaporated. Purification of the residue by MPLC as before furnished 110 mg (72%) of colorless crystalline **11**.

(5*R,6*S**,11*R**)-1,7,12-Trioxatrispiro[4.0.4.0.4.3]octadec-17-en-16-one (12).** A mixture of **11** (350 mg, 1.40 mmol) and selenium dioxide (466 mg, 4.20 mmol) in dioxane (17 mL) was heated at reflux for 36 h, cooled, filtered through Celite, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and to this solution were added pyridinium dichromate (526 mg, 1.40 mmol) and finely powdered 3 Å molecular sieves (526 mg). This mixture was stirred at 25 °C for 30 min, diluted with ether, and filtered through Celite. The filtrate was concentrated to give an orange oil, which was purified by MPLC on silica gel (elution with 30% ether in petroleum ether). There was isolated 137 mg of **12** accompanied by 154 mg of recovered **11**. The yield based on unreacted **11** was 66%.

For **12**: colorless solid, mp 76−77 °C; IR (film, cm^{-1}) 3000, 2900, 1690, 1450, 1110, 1060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (d, J = 10.3 Hz, 1 H), 5.77 (d, J = 10.3 Hz, 1 H), 4.10 (dt, J = 4.6, 2.3 Hz, 1 H), 3.84 (m, 2 H), 3.72 (m, 3 H), 2.61 (dt, J = 12.4, 8.5 Hz, 1 H), 2.28 (m, 1 H), 2.06 (m, 1 H), 2.04−1.76 (m, 7 H), 1.62 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 201.2, 153.8, 124.6, 92.2, 89.9, 86.8, 70.5, 69.1, 68.6, 33.9, 31.8, 30.7, 27.5, 27.1, 25.8; MS m/z (M^+) calcd 264.1361, obsd 264.1363.

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.03; H, 7.67.

(5*R,6*S**,11*S**,16*R**)-1,7,12,17-Tetraoxatetraspiro-[4.0.4.0.4.0.4.2]docos-21-ene (13) and (5*R**,6*R**,11*R**,16*S**)-1,7,12,17-Tetraoxatetraspiro[4.0.4.0.4.0.4.2]docos-21-ene (14).** To a solution of **12** (182 mg, 0.69 mmol) in anhydrous THF (8 mL) cooled to 0 °C was added a solution of the Normant reagent (1.85 mL of 0.41 N, 0.76 mmol). The reaction mixture was allowed to warm to rt during 20 min and then quenched with saturated NH_4Cl solution. The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried and concentrated at 1 Torr for 24 h. The pale yellow oil thus obtained (224 mg, quantitative)

was dissolved in CH_2Cl_2 (7 mL) and treated with triethylamine (0.241 mL, 1.73 mmol) followed by methanesulfonyl chloride (60 μL, 0.76 mmol). After overnight stirring at rt, the reaction mixture was diluted with ether, washed sequentially with 1 N HCl and saturated $NaHCO_3$ solution, dried, and concentrated. MPLC purification of the residue on silica gel (elution with 30% ether in petroleum ether) gave 135 mg (64%) of **13** and 32 mg (15%) of **14**.

For **13**: colorless solid: mp 71−72 °C; IR (film, cm^{-1}) 2980, 2870, 1460, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (s, 2 H), 3.89 (m, 2 H), 3.82 (m, 2 H), 3.65 (m, 4 H), 2.58 (dt, J = 12.1, 9.3 Hz, 2 H), 2.24 (d, J = 8.0 Hz, 2 H), 2.05−1.79 (series of m, 10 H), 1.57 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 130.8, 90.3, 87.4, 68.9, 67.8, 34.0, 31.3, 28.0, 27.4; MS m/z (M^+) calcd 306.1831, obsd 306.1817.

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.64; H, 8.58.

For **14**: colorless solid: mp 67−69 °C; IR (film, cm^{-1}) 2980, 2880, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 5.53 (d, J = 10.2 Hz, 1 H), 5.35 (d, J = 10.2 Hz, 1 H), 3.99 (dt, J = 7.7, 1.6 Hz, 1 H), 3.83 (m, 5 H), 3.62 (m, 2 H), 2.56 (m, 2 H), 2.40 (m, 1 H), 2.19−1.77 (series of m, 10 H), 1.65 (m, 1 H), 1.52 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 134.0, 128.6, 91.0, 89.3, 87.4, 85.8, 69.3, 68.6, 68.5, 67.7, 34.5, 33.1, 31.6, 31.4, 27.94, 27.85, 27.4, 25.7; MS m/z (M^+) calcd 306.1831, obsd 306.1839.

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.51; H, 8.63.

(5*R,6*S**,11*S**,16*R**)-16-Hydroxy-1,7,12-trioxatrispiro-[4.0.4.0.4.3]octadec-17-ene-16-propanol 16^3-Acetate (15).** A cold (0 °C), magnetically stirred solution of **12** (220 mg, 0.84 mmol) in anhydrous THF (10 mL) was treated with a solution of the Normant reagent (1.95 mL of 0.46 N, 0.92 mmol), allowed to warm to rt during 20 min, and quenched with saturated NH_4Cl solution. The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were dried, filtered, and concentrated. The resulting pale yellow oil (268 mg, quantitative) was directly acetylated.

The unpurified diol (266 mg, 0.825 mmol) was taken up in dry pyridine (5 mL) and treated with acetic anhydride (154 μL, 1.65 mmol) and DMAP (3 mg). The reaction mixture was stirred at 25 °C for 3 h, diluted with CH_2Cl_2 (100 mL), and washed with 0.5 N HCl (2×) and brine. After being dried and concentrated, the residue was subjected to MPLC on silica gel. Elution with 50% ethyl acetate in petroleum ether furnished 231 mg (77% overall) of **15** as a colorless oil: IR (film, cm^{-1}) 3500, 2990, 2890, 1735, 1240, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (d, J = 10.4 Hz, 1 H), 5.57 (d, J = 10.4 Hz, 1 H), 4.05 (m, 4 H), 3.93 (m, 4 H), 3.20 (br s, 1 H), 2.25 (m, 1 H), 2.11 (m, 3 H), 2.00 (s, 3 H), 2.00−1.85 (m, 8 H), 1.85−1.65 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.1, 130.8, 128.8, 93.8, 91.9, 90.1, 85.1, 70.1, 69.6, 69.0, 65.2, 34.5, 32.5, 29.8, 29.2, 27.4, 27.3, 25.5, 22.4, 20.9; MS m/z (M^+) calcd 366.2042, obsd 366.2053.

Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.52; H, 8.17.

(5*R,6*S**,11*S**,16*R**,17*R**,18*S**)-16-(3-Hydroxypropyl)-1,7,12-trioxatrispiro[4.0.4.0.4.3]octadecane-16,17,18-triol 16^3-Acetate (16).** A solution of **15** (182 mg, 0.50 mmol) in pyridine (2 mL) was treated with osmium tetraoxide (189 mg, 0.75 mmol) in one portion and stirred at rt for 3 days. The pyridine was removed in vacuo, the residue was dissolved in CH_2Cl_2 (5 mL), and saturated sodium bisulfite solution (5 mL) was added. The resulting heterogeneous mixture was stirred very rapidly for 2 h and the separated aqueous phase was extracted six times with CH_2Cl_2. The combined organic layers were dried and concentrated to leave a brown oil, which was subjected to MPLC on silica gel. Elution with 5% methanol in CH_2Cl_2 afforded **16** (65 mg, 60%) as a powdery white solid, mp 117−118 °C; IR ($CHCl_3$, cm^{-1}) 3580, 2990, 1722, 1240, 1050; ^1H NMR (250 MHz, toluene-d_8, 350 K) δ 4.06 (t, J = 6.7 Hz, 2 H), 3.94 (br s, 1 H), 3.81 (dt, J = 7.8, 4.2 Hz, 1 H), 3.72−3.52 (m, 6 H), 2.94 (br s, 1 H), 2.52 (br s, 1 H), 2.47 (br s, 1 H), 2.45−1.57 (series of m, 17 H), 1.47 (m, 2 H); ^{13}C NMR (62.5 MHz, toluene-d_8, 350 K) ppm 170.2, 93.3, 92.5, 90.1, 77.4, 73.3, 73.1, 68.9, 68.8, 68.4, 65.5, 31.7, 31.5, 30.4, 28.1, 28.0, 24.2, 20.5 (2 signals not resolved); MS m/z (M^+) calcd 400.2097, obsd 400.2084.

Anal. Calcd for $C_{20}H_{32}O_8$: C, 59.98; H, 8.05. Found: C, 60.01; H, 8.22.

(5*R,6*S**,11*S**,16*R**,21*R**,22*S**)-1,7,12,17-Tetraoxatetraspiro[4.0.4.0.4.0.4.2]docosane-21,22-diol (17).** A solution of **16** (135 mg, 0.339 mmol) in methanol (4 mL) was treated with sodium hydride (5 mg), stirred at 25 °C for 2 h, and freed of solvent in vacuo. The residue was dissolved in CH_2Cl_2, washed with water and brine, dried, and concentrated to leave 117 mg (97%) of the tetrol as a white solid, mp 81−82 °C; IR ($CHCl_3$, cm^{-1}) 3430, 2980, 1050; ^1H NMR (250 MHz, toluene-d_8, 375 K) δ 3.85 (d, J = 3.6 Hz, 1 H), 3.78 (dt, J = 7.7, 4.4 Hz, 1 H), 3.72−3.50 (m, 6 H), 3.41 (d, J = 11.8 Hz, 1 H), 3.38 (d, J = 11.8 Hz, 1 H), 2.40−2.22 (series of m, 4 H), 2.20−1.61 (series of m, 14 H), 1.50 (m, 2 H); ^{13}C NMR (62.5 MHz, toluene-d_8, 350 K) ppm 93.6, 92.6, 90.6, 77.4, 74.0, 73.4, 68.8, 68.7, 68.4, 63.8, 32.1, 31.6, 30.5, 28.40 (2 C), 28.36, 28.0, 27.8; FAB MS m/z ($M^+ + 1$) calcd 359.21, obsd 359.18 (100%).

This solid was dissolved in dry CH_2Cl_2 (6 mL), cooled to 0 °C, and treated in turn with *p*-toluenesulfonyl chloride (69 mg, 0.36 mmol), DMAP (2 mg), and triethylamine (182 μL, 1.30 mmol). The resulting solution was allowed to warm to ambient temperature and was stirred overnight before being diluted with CH_2Cl_2, washed with 0.5 N HCl, dried, and freed of solvent. The residue was purified by MPLC on silica gel (elution with 5% methanol in CH_2Cl_2) to give 82 mg (71%) of **17** as a white solid: mp 115−116 °C; IR ($CHCl_3$, cm^{-1}) 3470, 2980, 1050; ^1H NMR (250 MHz, toluene-d_8, 375 K) δ 3.77 (m, 1 H), 3.68 (m, 1 H), 3.59 (m, 5 H), 3.45 (m, 2 H), 3.38 (s, 1 H), 2.50-2.15 (m, 6 H), 2.10 (m, 2 H), 2.02 (m, 1 H), 1.93−1.50 (series of m, 5 H), 1.67−1.43 (m, 2 H), 1.10 (br m, 1 H); ^{13}C NMR (62.5 MHz, toluene-d_8, 375 K) ppm 91.9, 91.0, 76.5, 73.8, 68.4, 68.1, 67.9, 67.7, 67.3, 31.8, 31.0, 30.7, 29.1, 29.0, 28.7, 27.52, 27.45 (one signal not resolved); MS m/z (M^+) calcd 340.1906, obsd 340.1902.

Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.36; H, 8.16.

(5*R,6*S**,11*S**,16*R**)-1,7,12,17-Tetraoxatetraspiro-[4.0.4.0.4.0.4.2]docosane-21,22-dione (18).** To a solution of **17** (31 mg, 0.091 mmol) in CH_2Cl_2 (2 mL) was added the Dess−Martin periodinane (200 mg, 0.547 mmol) in one portion, and the resulting solution was stirred at ambient temperature overnight. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (elution with 40% ethyl acetate in petroleum ether). There was obtained 26 mg (88%) of **18** as bright yellow crystals, mp 132−135 °C; IR (CCl_4, cm^{-1}) 2990, 1728, 1440, 1088, 1060; ^1H NMR (300 MHz, C_6D_6) δ 3.94 (m, 2 H), 3.78 (m, 2 H), 3.62 (m, 2 H), 3.44 (m, 2 H), 2.40 (m, 2 H), 2.27−1.98 (series of m, 6 H), 1.74 (m, 2 H), 1.53 (m, 2 H), 1.34 (m, 4 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 204.0, 95.0, 88.7, 69.6, 68.6, 30.9, 29.6, 28.5, 25.1; MS m/z (M^+) calcd 336.1573, obsd 336.1567.

(5*R,6*S**,11*R**)-17-Hydroxy-18-oxo-1,7,12-trioxatrispiro-[4.0.4.0. 4.3]octadec-16-ene-16-propionaldehyde (21) and (2*R**,5*S**,6*R**,7*S**)- 4',4',4'",5',5",5'"-Hexahydro-2-hydroxytrispiro[chroman-5,2'(3'*H*): 6,2"(3"*H*):7(8*H*),2'",3'"*H*)-trisfuran]-8-one (22).** When samples of **18** were allowed to sit on the benchtop or repeated recrystallizations were undertaken, the bright yellow hue of the α-diketone faded to colorless. Slow crystallization of this material from ethyl acetate−hexane afforded colorless crystals of mp 141−143 °C: IR (KBr, cm^{-1}) 3428, 2952, 1676, 1624, 1252, 1104, 1052, 990; ^1H NMR (300 MHz, C_6D_6) δ 9.40 (s), 5.52 (m), 4.28−4.20 (m), 3.90−3.56 (series of m), 2.78−2.30 (m), 2.29−2.08 (m), 1.91−1.22 (series of m); ^{13}C NMR (75 MHz, C_6D_6) ppm 196.2, 196.0, 140.2, 137.0, 136.6, 98.9, 91.8, 91.7, 91.4, 91.2, 90.4, 90.3, 88.3, 87.9, 70.6, 69.7, 69.6, 68.9, 68.6, 34.5, 34.4, 34.3, 32.4, 32.2, 31.8, 31.5, 28.5, 27.70, 27.67, 26.7, 26.4, 26.0, 25.8, 17.5, 16.6; MS m/z (M^+) calcd 336.1573, obsd 336.1577.

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27, H, 7.19. Found: C, 64.29; H, 7.31.

This compound was subjected to X-ray crystallographic analysis.[25]

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(25) The authors have deposited the atomic coordinates for the X-ray structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Supporting Information Available: Crystallographically determined molecular structure of 22 (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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