Oxa Bowls: Studies Toward Hexaoxa-[6]-peristylane. Synthesis of a *Seco*-Derivative of Hexaoxa-[6]-peristylane

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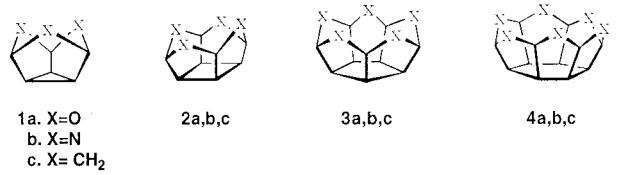
When the concept of equivalency of *all-cis*-[*n*]-formyl-[*n*]-cycloalkanes with [*n*]-oxa-[*n*]-peristylanes was followed, an approach to the "oxa bowl" hexaoxa-[6]-peristylane **4a** was delineated. This required an access to *all-cis*-cyclohexane-hexacarbaldehyde **5**, which could be subjected to a 6-fold intramolecular acetalization cascade. A readily available Diels−Alder adduct of cyclooctatetraene and maleic anhydride was chosen as the starting material and was elaborated to the *endo, endo*-tetraene **6** in which all the six aldehyde functionalities are present in a latent form with *cis* orientation in a locked cyclohexane ring. Although ozonolysis of **6** has so far led only to intractable products, the novelty and brevity of our approach have been demonstrated through the intramolecular acetalizations through ozonolysis in **7** and **15**, leading to oxa bowls **9** (*seco*-hexaoxaperistylane) and **16**, respectively. The formation of **9** and **16** requires the generation of five tetrahydrofuran and four oxacyclic rings, respectively, in a single-pot operation.

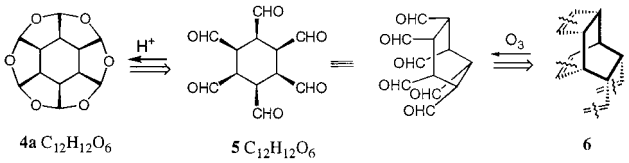
The design of new molecular entities with two chemically distinct surfaces and the probing of their structure and reactivity constitute an interesting area of organic chemistry research. In this context, we have conceived of [*n*]-hetero-[*n*]-peristylanes **1a,b**−**4a,b** (*n*-heterobowls) as a new class of molecular entities which are derived through the replacement of methylene groups by heteroatoms in the family of homologous polycyclic hydrocarbons known as peristylanes **1c**−**4c**. Besides having high C_{nv} symmetry, these heterobowls are composed of a hydrophobic base and a hydrophilic rim and are expected to exhibit many interesting properties such as selective avidity for metal ions. Among the carba-analogues, syntheses of [3]- (**1c**),[1a,b] [4]- (**2c**),[1c] and [5]-peristylanes (**3c**)[1d] have been accomplished over the years but the synthesis of [6]-peristylane **4c** has proved to be a difficult proposition and has remained unattained, perhaps due to the buildup of prohibitive strain as the six-membered bottom of the bowl tends to approach near planarity. Since the [*n*]-oxa-[*n*]-peristylanes, in general, have been found to be more stable than the carba-analogues,[2] we considered **4a** to be more amenable to successful synthetic pursuits than **4c**. After our successful syntheses of the parent tetraoxa-[4]-peristylane **2a**[3] and pentaoxa-[5]-peristylane **3a**,[4] following the basic concept of *all-cis*-[*n*]-formyl-[*n*]-cycloalkane equivalency with [*n*]-oxa-[*n*]-peristylane, it was decided to adopt the same protocol toward hexaoxa-[6]-peristylane **4a**.[5] Consequently, the synthetic strategy toward **4a** hinged on the recognition that it represents the cyclic acetal form of *all-cis*-1,2,3,4,5,6-cyclohexane-hexacarbaldehyde **5**, which is a compound, to our knowledge, not previously described in the literature. We envisioned accessing **5** or its equivalent from an *endo, endo*-7,8-disubstituted tricyclo[4.2.2.0^{2,5}]-deca-3,9-diene **6** through oxidative cleavage, Scheme 1. It was anticipated that **5** would undergo a 6-fold acetal-forming cascade cyclization to **4a**. An interesting feature of this conceptualization process was that the skeleton of the precursor *endo, endo*-7,8-disubstituted tricyclo-[4.2.2.0^{2,5}]deca-3,9-diene **6** could be readily accessed through the Diels−Alder reaction of cyclooctatetraene (COT) through its biCOT valence tautomer **7**.[6]

To test the validity of the retrosynthetic approach depicted in Scheme 1, a model study with the readily

Chart 1



Scheme 1



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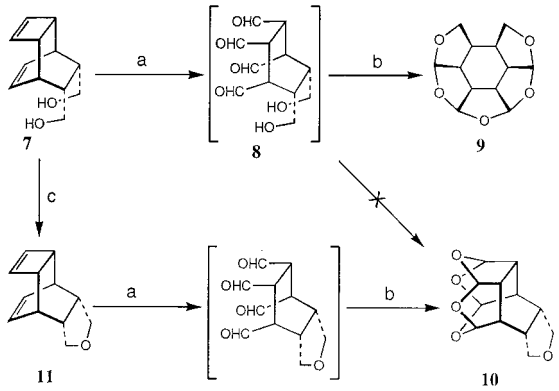
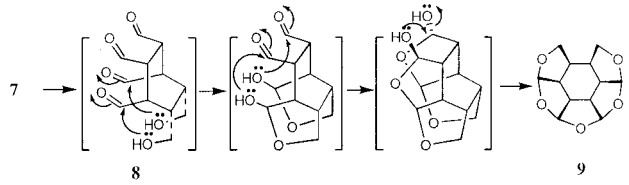
Scheme 2[a]



[a] Reagents and Conditions. (a) O_3, DCM; DMS, −78 °C; (b) Amberlyst-15, rt, 40% for **9** and 10% for **10**; (c) PTSA, C_6H_6, 90%.

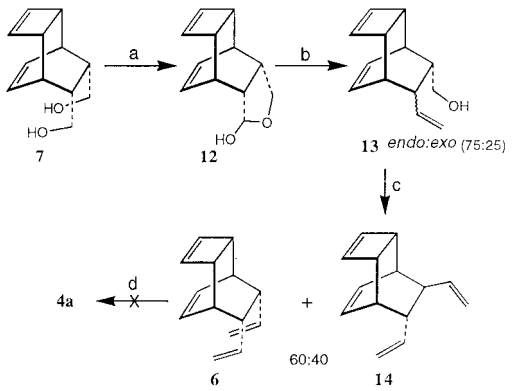
Scheme 3



accessible *endo, endo*-tricyclic diene-diol **7** was considered appropriate.[7] When diol **7** was subjected to ozonolysis and reductive workup, a single product was obtained in 40% yield. It was considered plausible that the intermediate tetra-aldehyde **8** under acid catalysis could lead to the formation of either hexacyclic acetal **9** or tetraoxa-cage compound **10**, Scheme 2. The NMR spectral features of the ozonolysis product were compatible with either **9** or **10**. To differentiate between the structures **9** and **10**, it was decided to carry out the ozonolysis of diene-ether **11**.[7] The tetracyclic ether **11** was obtained from diol **7** using *p*-TSA and was subjected to ozonolysis to yield a single product in poor yield (10%), Scheme 2. However, the ^{1}H and ^{13}C NMR spectra of the cyclic acetals derived from **7** and **11** showed significant differences in the chemical shift values. The structure of **10** was deduced through careful examination and comparison of its ^{1}H and ^{13}C NMR spectral data with that of **9**. The presence of shielded protons at δ 5.39 (2H) in the ^{1}H NMR spectrum and carbons at δ 101.6 (2C) in the ^{13}C NMR spectrum of **10** indicated the presence of a seven-membered ether ring (vide infra) and differentiated it from the structure of **9**.

With the formulation of **10** settled, the structure of C_s symmetry bearing *seco*-derivative of hexaoxa-[6]-peristylane **9** was secured from its characteristic ^{1}H NMR and six-line ^{13}C NMR spectra.[5] In the case of **9**, the two acetal carbon resonances are considerably deshielded at δ = 114.6 and 111.8. Remarkably, five tetrahydrofuran rings in hexacyclic acetal **9** are generated in a one-pot operation, through multiple intramolecular acetalizations in the intermediate **8** as shown in Scheme 3, with complete restructuring of the precursor **7**. Since this preliminary study with the diol **7** was fruitful in accessing a *seco*-derivative of hexaoxa-[6]-peristylane **9**, attention was turned toward the synthesis of parent hexaoxa-[6]-peristylane **4a**. For this purpose, *endo, endo*-7,8-divinyl

Scheme 4[a]



[a] Reagents and Conditions. (a) IBX, DMSO: Acetone, rt, 2 h, 93%; (b) CH_3PPh_3Br, NaO^{t}Am, THF, reflux, 1 h, 75%; (c) i, $(COCl)_2$, DMSO, Et_3N, DCM, −60 °C; ii, CH_3PPh_3Br, NaO^{t}Am, THF, rt, 30 min, 56%; (d) O_3, DCM; DMS, −78 °C.

tricyclo[4.2.2.0^{2,5}]deca-3,9-diene **6** had been identified as the equivalent of **5**, Scheme 1. Ozonolysis of **6** was expected to lead to a cyclohexane having six formyl functionalities in all cis arrangement, e.g., **5** or its equivalent which on a nucleophile-triggered intramolecular cascade cyclization would deliver **4a**, Scheme 1. To access **6**, a sequence starting from diene-diol **7** was pursued.[4]

The diene-diol **7** was oxidized with *o*-iodoxybenzoic acid (IBX)[8] to the *endo*-lactol **12** in 93% yield. Wittig olefination on **12** using methylenetriphenylphosphorane did not proceed stereoselectively and furnished a mixture of *endo*- and *exo*-vinyl carbinols **13** in a ratio of 75:25 (NMR) in 75% yield, Scheme 4. Attempts made to separate these diastereomers were not successful. Consequently, the mixture was subjected as such to Swern oxidation and the resulting aldehyde on Wittig olefination with methylenetriphenylphosphorane furnished the tricyclic divinyl-tetraene as a mixture of *endo,endo*-**6** and *endo,exo*-**14** isomers in a ratio of ∼60:40 (^{1}H and ^{13}C NMR spectra). Separation of **6** and **14** could not be achieved, and therefore, it was decided to proceed further with the mixture. It was hoped that the *endo,endo*-divinyl compound **6** in the mixture, on ozonolysis, would furnish the requisite precursor **5** of the hexaoxa-[6]-peristylane **4b**. However, ozonolysis of the mixture of epimers **6** and **14** followed by reductive workup did not furnish a characterizable product. It could not be ascertained whether hexaoxa-[6]-peristylane **4a** or its precursors were initially formed and decomposed in the reaction mixture or if the expected intermediate **5** underwent an aberrant reaction course.

The stereochemical difficulties encountered in the exclusive preparation of the *endo,endo*-divinyl compound **6** and its failure to deliver the targeted structure on ozonolysis compelled us to focus our attention on a suitable derivative of **9**, which could be transannularly cyclized through remote functionalization. In this context, the lactone **15**, derived from the COT−maleic anhydride adduct[6] through $NaBH_4$ reduction, was subjected to ozonolysis followed by reduction with dimethyl sulfide. The resulting product on exposure to Amberlyst-15 furnished a novel tetraoxa-cage compound **16** (34% yield) instead of the expected hexacyclic lactone **17**, Scheme 5.

(7) (a) Avram, M.; Sliam, E.; Nenitzescu, C. D. *Justus Liebigs Ann. Chem.* **1960**, *184*, 636. (b) Mehta, G.; Dutta, P. K.; Pandey, P. N. *Tetrahedron Lett.* **1975**, 445.

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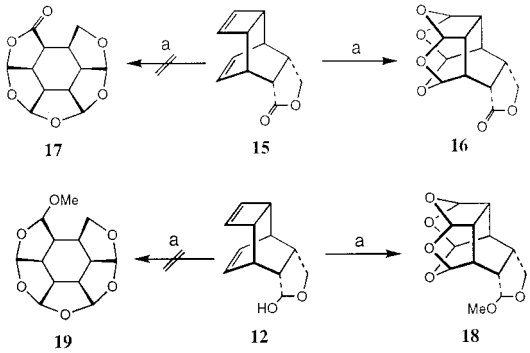
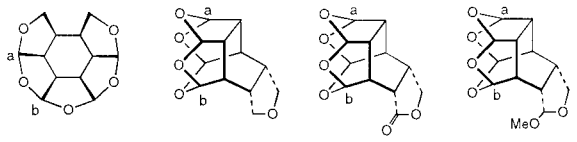
Scheme 5[a]



[a] Reagents and Conditions. (a) O_3, MeOH, −78 °C; DMS, −78 °C; Amberlyst-15, rt, 10 h, 34% (**16**) and 8% (**18**).

Chart 2



Ha	δ 5.99 (2H)	5.94, 5.92	5.86 (2H)	5.94 (2H)
Hb	δ 5.76 (2H)	5.39 (2H)	5.43, 5.08	5.45, 5.41
Ca	δ 114.6 (2C)	110.7 (2C)	111.0, 110.6	111.0, 110.8
Cb	δ 111.8 (2C)	101.6 (2C)	100.9, 100.6	101.5 (2C)

Though the IR, ^{1}H NMR, ^{13}C NMR, and MS spectral data of the ozonolysis product were compatible with either structure (**16** or **17**), an incisive analysis of the NMR spectral data indicated that there are subtle differences in the chemical shift values in the skeletal structures represented by **16** and **17**. In the case of **16** and its close sibling **10** (vide supra), the acetal carbon resonances in the seven-membered ring (Cb) were relatively shielded in the ^{13}C NMR spectrum compared to the carbon resonances of five-membered acetal carbons (Ca). The comparison of the ^{13}C NMR values of the acetal carbon atoms in **9** and **10** clearly indicates this trend, Chart 2. The same shielding effect was also observed for the corresponding protons in the ^{1}H NMR spectra, Scheme 6. The structure of **16** was unequivocally established through X-ray crystal structure determination. The ORTEP diagram of **16** is shown in Figure 1.

Intramolecular cascade cyclization was also attempted in lactol **12**, which was obtained from **7**. Ozonolysis of **12** and exposure of the reaction mixture to Amberlyst-15 led once again to the isolation of the tetraoxa cage **18**, instead of the expected hexacyclic methyl ether **19**, Scheme 5.[9] The structural formulation of **18** was arrived at by the incisive analysis of its ^{1}H and ^{13}C NMR spectra and comparison with other related compounds, Scheme 6.

Since we could not acquire the suitably functionalized precursor of hexaoxa-[6]-peristylane from any of the dienes (**15** and **12**), it was decided to revert to the hexacyclic acetal **9** available in one step from the diol **7**.

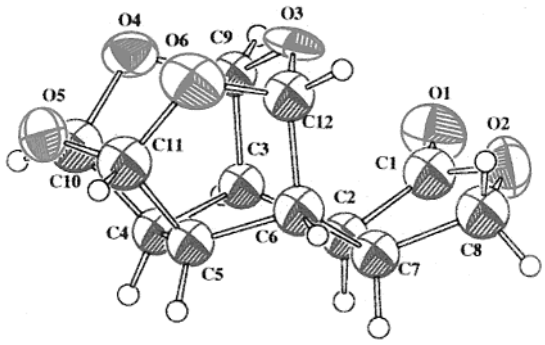
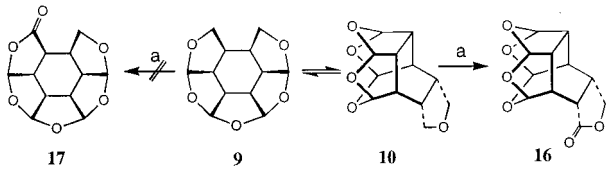


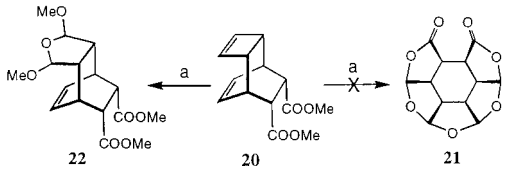
Figure 1. ORTEP diagram of **16**.

Scheme 6[a]



[a] Reagents and Conditions. (a) $RuCl_3 \cdot 3H_2O$, $NaIO_4$, CCl_4/CH_3CN/H_2O (2:1:3), reflux, 24 h, 9%.

Scheme 7[a]



[a] Reagents and Conditions. (a) O_3, DCM/MeOH (4:1), −78 °C; DMS, −78 °C; Amberlyst-15, rt, 68%.

Attempts were made to elaborate **9** to **4a**. Thus, *seco*-hexaoxa-[6]-peristylane **9** was subjected to RuO_4 oxidation[10] in the hope of obtaining the corresponding lactone **17** to further elaborate it to **4a**. But in practice, **9** furnished a mixture of compounds with poor material balance in which the previously obtained lactone **16** was the major product, Scheme 6. When **10** was independently subjected to RuO_4 oxidation, the lactone **16** was obtained. It follows that the hexacyclic acetal **9** is in equilibrium with **10** under the reaction conditions used, and Ru^{3+} oxidation leads to **16**. Because of the isolation of the undesired product **16** in poor yield, we sought for an alternate route to **4a**.

The diene-diester **20**[6] was subjected to ozonolysis with the hope of obtaining the symmetrical bis-lactone **21**. However, ozonolysis of **20** and acid exposure led to hemiacetal-diester **22** in 68% yield, instead of the expected symmetrical hexacyclic bis-lactone **21**, Scheme 7. It turns out that in **20**, only the well-exposed cyclobutene double bond undergoes the oxidative cleavage leaving the other double bond uncleaved and this may be attributed to the steric shielding of the bicyclo[2.2.2]octene double bond on both the faces by the diester group and the cyclobutene ring.

Finally, we attempted to make the diene-dialdehyde from acyloin **23a**,[11] which can be transformed directly to

(9) In our preliminary communications,[5] structure to the ozonolysis product of **12** was erroneously assigned as **19**. Careful reexamination of the spectral data has led to the reformulation of the product as **18**. This assignment is also supported by the X-ray crystal structure of the related compound **16**.

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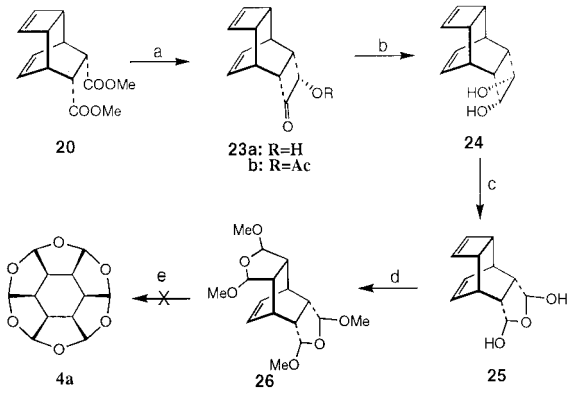
(11) Avram, M.; Dinulescu, I. G.; Chiraleu, F.; Nenitzescu, C. D. *Rev. Roum. Chim.* **1973**, *18*, 863.

Scheme 8[a]



[a] Reagents and Conditions. (a) i, Na, TMS−Cl, toluene, Ar, reflux, 12 h; ii, 1 N HCl, THF, reflux, 1 h; $CaCO_3$, rt, 1 h; iii, Ac_2O, Py, 0 °C−rt, 16 h, 77% from **20**; (b) $NaBH_4$, MeOH, 0 °C, 30 min, 73%; (c) $NaIO_4$, DCM/H_2O (7:2), rt, 2 h; (d) O_3, DCM/MeOH (1:1), −78 °C; DMS, −78 °C; Amberlyst-15, rt, 30% from **24**; (e) O_3, DCM, −78 °C; DMS, −78 °C; Amberlyst-15, rt, 10 h.

cyclohexanehexacarbaldehyde **5** or its equivalent. To access the *endo*-α-hydroxy ketone **23a**, the readily available diester **20** was subjected to acyloin condensation reaction[12] using Na−TMSCl milieu. The crude product was hydrolyzed to afford the acyloin **23a** which was characterized as its crystalline acetate **23b**, Scheme 8.

The acyloin **23a** on $NaBH_4$ reduction afforded the 1,2-diol **24** in 73% yield, Scheme 8.[11] Sodium metaperiodate cleavage[13] of the diol **24** gave the dialdehyde in its hydrate form **25**, which was then subjected to the next step as such. Ozonolysis of **25**, followed by reduction with dimethyl sulfide and treatment of the reaction mixture with Amberlyst-15 furnished the bis-hemiacetal **26** in 30%yield, Scheme 8. Many attempts were made toward further ozonation of **26** but without success. Once again the steric shielding of the bicyclo[2.2.2]octene double bond prevented further elaboration of **25** and **26**.

The failure of the various adaptations of our general approach (Scheme 1) toward **4a** indicates that hexaoxa-[6]-peristylane is a very difficult proposition, since the cyclohexane ring (base of the bowl) has to attain a near planar geometry. Initial MMX calculations on **4a** and **9** indicated that the base six-membered ring acquires a flattened "boatlike" shape. Higher order computational studies were also carried out on [6]-peristylane **4c** and hexaoxa-[6]-peristylane **4a**.[2] The C_{6v} symmetry structures are calculated to be higher order stationary points. A C_{3v} structure (where three oxygen atoms are pushed in) is calculated to be a minimum and is lower in energy by 6.8 kcal mol^{-1} (5.9 kcal mol^{-1}) for the parent system and 18.8 kcal mol^{-1} (16.5 kcal mol^{-1}) for the hexaoxa-[6]-peristylane at HF/6-31G* (B3LYP). In view of our attempts toward the synthesis of **4a** via the *seco*-derivative **9**, we also estimated the increase in strain in going from the *seco*-structure **9** to **4a**. Calculations indicate that there is no unusual strain increment in going from the *seco*-derivative to hexaoxa-[6]-peristylane **4a** which has C_{3v} symmetry. Consequently, from the computational studies at least, **4a** remains an attainable objective.

(12) (a) Miller, R. D.; Dolce, D. L.; Merritt, V. Y. *J. Org. Chem.* **1976**, *41*, 1221. (b) Bloomfield, J. J.; Owsley, D. C.; Nelke, J. M. *Org. React.* **1976**, *23*, 259.

(13) Taniguchi, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1997**, 1399.

In summary, the synthesis of a *seco*-derivative **9** of hexaoxa-[6]-peristylane from the readily available *endo,endo*-diol **7** derived from COT is reported in which as many as five tetrahydrofuran rings are formed in a single chemical operation through the intramolecular cascade acetalization process. Various adaptations of our general theme (Scheme 1) or maneuvers on **9** have so far not delivered hexaoxa-[6]-peristylane **4a**. However, several novel oxa cages **10**, **16**, and **18** have been obtained and their structures have been unambiguously established from spectral data and the single-crystal X-ray analysis of **16**.

Experimental Section

General. For a general write-up, see the accompanying paper.

Perhydro-2,3,4,5,6-pentaoxacyclopenta[*ij*]pentaleno-[2,1,6,5-*cdef*]*s*-indacene (9). Through a solution of diol **7** (100 mg, 0.521 mmol),[7] in dichloromethane at −78 °C, ozone was bubbled until a blue color appeared. Excess ozone was flushed off using nitrogen, and the ozonide was quenched with dimethyl sulfide (5 equiv) at −78 °C. The mixture was stirred with Amberlyst-15 at room temperature for 5 h. The resin was filtered off, and the residue was charged on a silica gel column. Elution with 70% EtOAc−hexane furnished the pentaoxa compound **9** (49 mg, 40%), which was recrystallized from dichloromethane−hexane: mp 194 °C; IR (KBr) 2912, 1236, 1053 cm^{-1}; ^1H NMR δ 5.99 (d, 2H, J = 5.5 Hz), 5.76 (d, 2H, J = 5 Hz), 4.38 (dd, 2H, J = 9, 6 Hz), 4.00 (dd, 2H, J = 9, 6.2 Hz), 2.99−2.50 (series of m, 6H); ^{13}C NMR δ 114.6 (CH), 111.8 (CH), 71.7 (CH_2), 40.6 (CH), 39.4 (CH), 35.1 (CH); MS m/z 239 ($M^+ + 1$). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.55; H, 5.90.

5,12,14,16,17-Pentaoxahexacyclo[9.5.1.0^{2,10}.0^{3,7}.0^{8,15}.0^{9,13}]-heptadecane (10). The tetracyclic ether **11**[7] (180 mg, 1.034 mmol) obtained from the diol **7** was subjected to ozonolysis, as described above for **9,** to afford **10** (22 mg, 10%), which after purification on a silica gel column, was crystallized from ethyl acetate−hexane: mp 185−195 °C dec; IR (KBr) 2980, 1109, 1041 cm^{-1}; ^1H NMR δ 5.94 (d, 1H, J = 2 Hz), 5.92 (d, 1H, J = 2 Hz), 5.39 (d, 2H, J = 4.5 Hz), 4.09 (t, 2H, J = 7 Hz), 3.63 (t, 2H, J = 3.6 Hz), 2.93−2.87 (m, 2H), 2.73−2.60 (m, 4H); ^{13}C NMR δ 110.7, 101.6, 70.8, 43.8, 43.6, 35.5; MS m/z 238 (M^+). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.55; H, 5.95.

4-Oxatetracyclo[5.4.2.0^{2,6}.0^{8,11}]trideca-9,12-dien-3-ol (12). A mixture of dimethyl sulfoxide (3 mL), acetone (12 mL), and *o*-iodoxybenzoic acid (1.75 g, 6.250 mmol) was stirred for 1 h, and the resulting solution was added to the diol **7**[7] (1 g, 5.208 mmol). After 1 h at room temperature, the reaction mixture was quenched with water (15 mL) and filtered. The filtrate was extracted with dichloromethane, washed with water, dried over sodium sulfate, and concentrated. Passage through a silica gel column and elution with 50% EtOAc−hexane furnished the lactol **12** (0.92 g, 93%), which was crystallized from dichloromethane−hexane: mp 62 °C; IR (KBr) 3393, 1020 cm^{-1}; ^1H NMR δ 5.94 (t, 2H, J = 7 Hz), 5.85 (s, 2H), 4.97 (s, 1H), 4.06 (t, 1H, J = 8.2 Hz), 3.61 (dd, 1H, J = 8.6, 3 Hz), 2.80−2.32 (series of m, 6H); ^{13}C NMR δ 137.8, 137.6, 129.2, 128.8, 107.6, 72.6, 51.5, 45.0, 44.9, 42.6, 39.2, 37.5; MS: m/z 173 (M^+ − OH). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.68; H, 7.45.

***endo*- and *exo*-8-Vinyltricyclo[4.2.2.0^{2,5}]deca-3,9-dien-7-ylmethanol (13).** To a suspension of methyltriphenylphosphonium bromide (2.3 g, 6.443 mmol) in dry THF (10 mL) was added freshly sublimed sodium *t*-amyloxide (450 mg, 4.091 mmol) in THF (3 mL), and the mixture was stirred for 5 min at room temperature. To the canary yellow ylide, the lactol **12** (0.5 g, 2.632 mmol) in THF (5 mL) was added, and the mixture was refluxed for 1 h, then cooled, and quenched with water (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined

organic layer was washed with water and brine and dried. The residue was charged on a silica gel column. Elution with 15% EtOAc−hexane furnished the vinyl-carbinol **13** (380 mg, 75%) as a mixture (75:25, NMR) of *endo, endo*- and *endo, exo*-isomers. Purification through a 10% $AgNO_3$-impregnated silica gel column (elution with 25% EtOAc−hexane) led to a poor separation of the isomers, and only the major *endo,endo*-isomer could be obtained in its pure form: IR (KBr) 3344, 1635, 1039 cm^{-1}; ^1H NMR δ 6.01−5.97 (m, 2H), 5.85 (s, 2H), 5.78−5.62 (m, 1H), 5.18−4.98 (m, 2H), 3.59−3.30 (m, 2H), 2.74 (s, 2H), 2.62−2.39 (m, 3H), 2.07−1.93 (m, 1H); ^{13}C NMR δ 141.3, 137.6(2C), 129.4, 129.3, 115.5, 64.9, 46.5, 45.9, 45.5, 45.2, 42.0, 37.6; MS *m*/*z* 187 ($M^+ - 1$).

***endo,endo*- and *endo,exo*-9,10-Divinyltricyclo[4.2.2.0^{2,5}]-deca-3,7-diene (6).** To oxalyl chloride (0.28 mL, 3.191 mmol) in dichloromethane (1 mL) was added dimethyl sulfoxide (0.58 mL, 7.979 mmol) in dichloromethane (1 mL) at −60 °C under N_2. After 15 min at −60 °C, the vinyl carbinol mixture **13** (300 mg, 1.596 mmol) in dichloromethane (3 mL) and triethylamine (1.8 mL, 12.766 mmol) was added and then warmed to 0 °C. The reaction was quenched by water (5 mL), extracted with dichloromethane, washed with brine, and dried. The crude material (234 mg) was subjected to the next step.

Wittig olefination of the crude aldehyde was carried out as described above for **13** at room temperature. After work up, the residue was charged on a silica gel column. Elution with pentane furnished the divinyl compound (160 mg, 56% from **13**) as a mixture (~60:40, ^1H and ^{13}C NMR). of *endo,endo*- and *endo,exo*- isomers **6** and **14**. This mixture could not be separated, but the NMR peaks could be picked up due to the major and minor compounds **6** and **14**. **6** (major): ^1H NMR δ 5.93 (t, 2H, $J = 4$ Hz), 5.78 (s, 2H), 5.65−5.47 (m, 2H), 4.91−4.77 (m, 4H), 2.68 (br. s, 2H), 2.47−2.39 (m, 4H); ^{13}C NMR δ 142.1, 137.7, 129.2, 113.5, 47.7, 45.7, 41.3 (from mixture). **14** (minor): ^1H NMR δ 6.02 (t, 2H, $J = 6$ Hz), 5.79 (s, 2H), 5.85−5.70 (m, 2H), 5.01−4.89 (m, 4H), 2.87 (t, 2H, $J = 4$ Hz), 1.96−1.88 (m, 4H); ^{13}C NMR δ 143.4, 140.4, 138.2, 137.1, 131.8, 127.6, 114.5, 112.7, 48.2, 47.8, 46.2, 41.0, 40.6, 40.5 (from mixture).

Ozonolysis of 6 and 14. Tetraenes **6** and **14** (100 mg, 0.543 mmol) in dichloromethane (25 mL) were subjected to ozonolysis at −78 °C, and the resulting ozonide was quenched with dimethyl sulfide. TLC profile of the reaction mixture was extremely complex, and no characterizable product could be isolated.

4-Oxatetracyclo[5.4.2.0^{2,6}.0^{8,11}]trideca-9,12-dien-3-one (15). To a solution of the COT−maleic anhydride adduct[6] (0.5 g, 2.475 mmol) in methanol at 0 °C was added $NaBH_4$ (282 mg, 7.426 mmol), and the mixture was stirred for 3 h. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed, dried, and concentrated. The residue was purified over silica gel. Elution with 30% EtOAc−hexane furnished the lactone **15** (0.32 g, 70%), which was crystallized from dichloromethane−hexane: mp 121 °C; IR (KBr) 3109, 1755, 1016 cm^{-1}; ^1H NMR δ 6.08−5.92 (m, 2H), 5.86 (s, 2H), 4.37 (t, 1H, $J = 8$ Hz), 3.96−3.88 (m, 1H), 3.07 (br. s, 1H), 2.75−2.66 (m, 5H); ^{13}C NMR δ 179.0, 138.0, 137.9, 130.4, 128.5, 72.2, 44.0, 43.9, 43.7, 38.6, 37.3, 37.2; MS *m*/*z* 189 ($M^+ + 1$), 143 ($M^+ - CO_2H$), 129 ($M^+ - CH_2CO_2H$). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.65; H, 6.46.

5,12,14,16,17-Pentaoxahexacyclo[9.5.1.0^{2,10}.0^{3,7}.0^{8,15}.0^{9,13}]-heptadecan-4-one (16). Through a solution of lactone **15** (73 mg, 0.388 mmol), in methanol at −78 °C, ozone was bubbled, and the ozonide was quenched with dimethyl sulfide. The reaction mixture was stirred overnight over Amberlyst-15. Filtration of the resin and purification through silica gel column chromatography (elution with 80% EtOAc−hexane) furnished **16** (33 mg, 34%), which was recrystallized from dichloromethane−hexane: mp > 260 °C dec: IR (KBr) 1747, 1186, 1113 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.86 (t, 2H, $J = 5$ Hz), 5.43 (d, 1H, $J = 4.8$ Hz), 5.08 (d, 1H, $J = 4.5$ Hz), 4.50 (t, 1H, $J = 9.4$ Hz), 4.32 (dd, 1H, $J = 9$, 4 Hz), 3.23−2.65 (series of m, 6H); ^{13}C NMR (DMSO-d_6) δ 177.9, 111.0, 110.6, 100.9, 100.6, 70.1, 44.3, 41.7, 41.5, 41.1, 34.5, 29.9; MS *m*/*z* 253 ($M^+ + 1$). Anal. Calcd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.83. Found: C, 57.18; H, 4.85.

4-Methoxy-5,12,14,16,17-pentaoxahexacyclo-[9.5.1.0^{2,10}.0^{3,7}.0^{8,15}.0^{9,13}] heptadecane (18). The lactol **12** (100 mg, 0.526 mmol) was subjected to ozonation, as described earlier, for **15** to furnish **18** (11 mg, 8%, unstable) as a colorless liquid, which was obtained after purification on a silica gel column, IR (neat) 2955, 1369, 1049 cm^{-1}; ^1H NMR δ 5.94 (d, 2H, $J = 4$ Hz), 5.45 (d, 1H, $J = 4$ Hz), 5.41(d, 1H, $J = 4$ Hz), 4.97 (d, 1H, $J = 2$ Hz), 4.21−4.12 (m, 1H), 3.92−3.86 (m, 1H), 3.37 (s, 3H), 2.85−2.54 (series of m, 6H); ^{13}C NMR δ 111.0, 110.8, 108.1, 101.5 (2C), 69.6 (CH_2), 55.0, 44.8, 43.2 (2C), 43.0, 42.8, 33.8; MS *m*/*z* 267 ($M^+ - 1$), 237 ($M^+ - OCH_3$).

Dimethyl 3,5-Dimethoxy-4-oxatricyclo[5.2.2.0^{2,6}]undec-8-ene-10,11-dicarboxylate (22). Diester **20**[6] (100 mg, 0.403 mmol) in dichloromethane/methanol (4:1) was ozonized at −78 °C, and the resulting ozonide was quenched with dimethyl sulfide (0.12 mL, 1.615 mmol). The reaction mixture was stirred over Amberlyst-15 at room temperature for 16 h. The resin was filtered, and purification over silica gel column (elution with 20% EtOAc−hexane) afforded **22** (90 mg, 68%), which was crystallized from dichloromethane−hexane: mp 126 °C; IR (KBr) 1743, 1726, 1176, 1093 cm^{-1}; ^1H NMR δ 6.34−6.31 (m, 2H), 4.67 (s, 2H), 3.59 (s, 6H), 3.35 (s, 6H), 3.13 (br. s, 2H), 3.02 (s, 2H), 2.56 (s, 2H); ^{13}C NMR δ 172.5, 131.2, 111.2, 55.1, 51.7, 50.6, 46.4, 35.3; MS *m*/*z* 326 (M^+), 295 ($M^+ -$ OMe), 147 ($M^+ -$ 2OMe, −2E). Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.79. Found: C, 58.85; H, 6.81.

4-Oxotetracyclo[4.4.2.0^{2,5}.0^{7,10}]dodeca-8,11-dien-3-yl Acetate (23b).[11] Into a 100 mL three-necked flask fitted with an addition funnel, a condenser with an argon gas inlet, and a septum was placed 2.8 g (0.12 mol) of sodium in 60 mL of dry toluene. The mixture was refluxed and stirred for 30 min to disperse the sodium. A mixture of 6 g (0.024 mol) of diester **20**[6] and 15 mL (13 g, 0.12 mol) of distilled trimethylsilyl chloride in 10 mL of toluene was added dropwise over 3 h at room temperature. The mixture was refluxed for 12 h and cooled, and the suspension was passed through a Celite pad. Solvent was removed, and the residue was subjected to the next step.

The above material in THF (20 mL) was refluxed with 1 N HCl (5 mL) for 1 h under N_2. The reaction mixture was cooled and quenched with $CaCO_3$. After 1 h, the solution was filtered and concentrated. The residue was extracted with ether, washed with saturated sodium bicarbonate, dried, and concentrated to give acyloin **23a** which was used as such in the next step.

A mixture of **23a** (4.7 g, crude), Ac_2O (20 mL), and pyridine (1 mL) was stirred at room temperature for 16 h under N_2. Water (20 mL) was added, and the aqueous layer was extracted repeatedly with ether. The organic layer was washed with saturated sodium bicarbonate and brine and dried over Na_2SO_4. The crude material was loaded on a silica gel column, and elution with 15% EtOAc−hexane furnished **23b** (4.3 g, 77%), which was crystallized from dichloromethane−hexane: mp 106 °C; IR (KBr) 1786, 1739, 1377 cm^{-1}; ^1H NMR δ 5.90−5.81 (m, 4H), 5.52 (dd, 1H, $J_1 = 8.8$ Hz, $J_2 = 3.0$ Hz), 3.27−3.20 (m, 1H), 2.95−2.63 (series of m, 5H), 2.07 (s, 3H); ^{13}C NMR δ 206.4, 169.4, 137.7, 137.2, 129.5, 127.6, 79.4, 57.4, 44.8, 43.0, 35.5, 34.5, 34.1, 20.3; MS *m*/*z* 187 ($M^+ - COCH_3$). Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13. Found: C, 73.30; H, 5.75.

Tetracyclo[4.4.2.0^{2,5}.0^{7,10}]dodeca-3,11-diene-8,9-diol (24).[11] Acyloin **23b** (1 g, 5.319 mmol) was reduced with $NaBH_4$ (200 mg, 5.263 mmol) in methanol(15 mL) at 0 °C under N_2. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification over silica gel furnished the tetracyclic 1,2-diol **24** (0.73 g, 73%) as a crystalline solid: mp 174−176 °C; IR (KBr) 3476, 3368, 1398, 1128 cm^{-1}; ^1H NMR δ 6.18 (dd, 2H, $J_1 = 4.3$ Hz, $J_2 = 3.5$ Hz), 5.80 (s, 2H), 4.41−4.37 (m, 2H), 2.72−2.60 (m, 6H), 2.26 (br. s, 2H, −O*H*); ^{13}C NMR δ 137.1, 130.6, 69.7, 45.0, 44.7, 34.6; MS *m*/*z* 190 (M^+). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.80; H, 7.45.

3,5,9,11-Tetramethoxy-4,10-dioxatetracyclo[5.5.2.0^{2,6}.0^{8,12}]-tetradec-13-ene (26). To the diol **24** (125 mg, 0.658 mmol) in CH_2Cl_2/H_2O (7:2), sodium metaperiodate (282 mg, 1.316 mmol) was added, and the reaction was stirred at room temperature for 2 h under N_2. The reaction mixture was diluted with dichloromethane, and the organic layer was washed with water and brine and dried over Na_2SO_4.

Ozone was bubbled through the above material in dichloromethane/methanol (20 mL, 1:1) at −78 °C, and the ozonide was quenched with dimethyl sulfide. The reaction mixture was stirred overnight over Amberlyst-15 at room temperature. After the filtration of the resin and concentration, the residue was loaded on a silica gel column. Elution with 50% EtOAc−hexane furnished **26** (60 mg, 30%, after two steps) as the major compound along with several minor products: mp 154−155 °C; IR (KBr) 2953, 1371, 1099 cm^{-1}; ^{1}H NMR δ 6.22 (t, 2H, J = 4 Hz), 4.63 (s, 4H), 3.32 (s, 12H), 2.97 (br. s, 2H), 2.54 (s, 4H); ^{13}C NMR δ 131.8 (2C), 111.0 (4C), 55.0 (4C), 50.7 (4C), 35.4 (2C); MS m/z 281 ($M^+ - OCH_3$). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.62; H, 7.76.

Crystal Data for 16. $C_{12}H_{12}O_6$, M = 252.22, colorless crystals, monoclinic, space group Pc, a = 6.2674(14) Å, b = 6.9759(11) Å, and c = 11.746(7) Å, β = 98.28(3)°, V = 508.2(3) Å^3, Z = 2, D_c = 1.648 Mg m^{-3}, T = 293(2) K, $F(000)$ = 264, μ (Mo Kα) = 0.134 mm^{-1}, crystal dimensions 0.60 × 0.68 × 0.40 mm^3. Data were collected on an Enraf-Nonius MACH-3 diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) by the ω-scan method in the range 2.92 ≤ θ ≤ 24.93°, 1075 unique reflections [R_{int} = 0.00], of which 889 had $F_o > 4\sigma(F_o)$, were used in all calculations. At final convergence, $R_1(I > 2\sigma(I))$ = 0.0763, wR_2 = 0.1767 for 103 parameters and 2 restraints, GOF = 1.078, $\Delta\rho_{max}$ = 0.294 e Å^{-3}, and $\Delta\rho_{min}$ = −0.331 e Å^{-3}. The data were reduced using XTAL (version 3.4), solved by direct methods, refined by full matrix least-squares on F^2 with oxygen atoms anisotropic and H atoms were placed in calculated positions and were allowed to ride on their parent atoms.[14]

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Supporting Information Available: Tables of X-ray crystal data, atomic coordinates, bond lengths, bond angles, and anisotropic thermal parameters for **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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