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Registry No. (±)-**1**, 112420-42-5; (±)-**2**, 111901-54-3; (±)-**3**, 123286-19-1; (±)-**5a**, 118798-10-0; (±)-**5b**, 118798-18-8; (±)-**6a** (isomer 1), 128442-06-8; (±)-**6a** (isomer 2), 128442-07-9; **6b**, 128321-73-3; **6d**, 128321-74-4; (±)-**7**, 128442-08-0; (±)-**8a**, 128359-18-2; (±)-**9a**, 128359-19-3; (±)-**9b**, 128359-20-6; (±)-**9c**, 128359-21-7; (±)-**10**, 128359-22-8; (±)-**11**, 128442-09-1; **12**, 128321-69-7; **12** diol, 128359-23-9; **14**, 128321-70-0; **15a**, 128321-75-5; **15b**, 128442-10-4; (±)-**16**, 114375-41-6; **17**, 128359-24-0; (±)-**18**, 128442-11-5; (±)-**25**, 128442-12-6; (±)-**26**, 128359-25-1; **27**, 128359-26-2.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **6b,d**, **8a,b**, **9a–c**, **10**, **12–14**, **15a,b**, **16–18**, **23**, **24a,b**, **26**, and **27** (62 pages). Ordering information is given on any current masthead page.

Selective Functionalization of Calix[4]arenes at the Upper Rim

Jan-Dirk van Loon,[†] Arturo Arduini,[§] Laura Coppi,[§] Willem Verboom,[†] Andrea Pochini,[§] Rocco Ungaro,*[,§] Sybolt Harkema,[‡] and David N. Reinhoudt*[,†]

Laboratories of Organic Chemistry and Chemical Physics, University of Twente, 7500 AE Enschede, The Netherlands, and the Institute of Organic Chemistry, University of Parma, 43100 Parma, Italy

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Methods are described for the selective diametrical functionalization of calix[4]arenes at the upper rim, either by the selective removal of the *p-tert*-butyl groups and subsequent substitution at the free phenol rings or by selective reactions at the phenol rings of dialkoxycalix[4]arenes without the *tert*-butyl groups. This includes selective mercuration and the synthesis of 5,17-di-*tert*-butyl-26,28-dimethoxy-11,23-diphenylcalix[4]arene (**13**), of which the crystal structure is described. The first synthesis of macrocyclic diquinones derived from calix[4]arenes (calix[4]diquinones) is described.

The interest in calix[4]arene chemistry is rapidly increasing because its derivatives can form inclusion complexes with cations or with neutral molecules.[1] The parent *p-tert*-butylcalix[4]arene (**1**)[2] contains two interesting substructures. At the lower rim[1] four hydroxyl groups are present in very close proximity; these can be used for cation binding[3] and transport.[4] The upper rim contains a hydrophobic cavity that is potentially able to complex neutral substrates. The introduction of ester, keto, or amide groups at the lower rim of **1** fixes this macrocycle in a cone conformation, giving *sodium*-selective cation ligands.[5] We have recently bridged the lower rim of *p-tert*-butylcalix[4]arene (**1**) for the synthesis of a new class of *potassium*-selective cation receptors, the calixspherands and the calixcrowns.[6] The calixspherands are able to form *kinetically* stable complexes with Na^+, K^+, and Rb^+.

Surprisingly, only a limited number of complexes are described with hydrophobic organic substrates complexed in the *upper rim* cavity. Except for some complexes in the solid state,[7] and the complexes in water based on hydrophobic or electrostatic forces,[8] only several amines are known to form a complex in the upper rim cavity in solution.[9] The reason is the lack of appropriate functionalization at the upper rim.

The cavity of the upper rim can be modified by introducing substituents at the para positions of the phenol rings of calix[4]arene (**2**). Gutsche et al. have described modification via a Claisen rearrangement[10] and via an intermediate *p*-quinone methide.[11] Shinkai et al. succeeded in sulfonation and nitration,[12] and we have performed the chloromethylation.[13] However, these methods only give access to *tetra*substituted calix[4]arenes with four identical substituents at the para positions of the phenol rings. In principle it would be desirable to have individual control of the para substitution of the four aromatic rings, but except for one example by Gutsche and Lin,[14] until now the only method to obtain nonsymmetrically substituted calix[4]arenes are the stepwise routes developed by Böhmer et al.[15] Therefore we are currently investigating

[†] Laboratory of Organic Chemistry, University of Twente.
[‡] Laboratory of Chemical Physics, University of Twente.
[§] University of Parma.

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the selective functionalization of calix[4]arenes at the upper rim. Our objective was to discriminate between two diametrically located para positions out of the four, thus being able to introduce two pairs of different substituents at the upper rim.

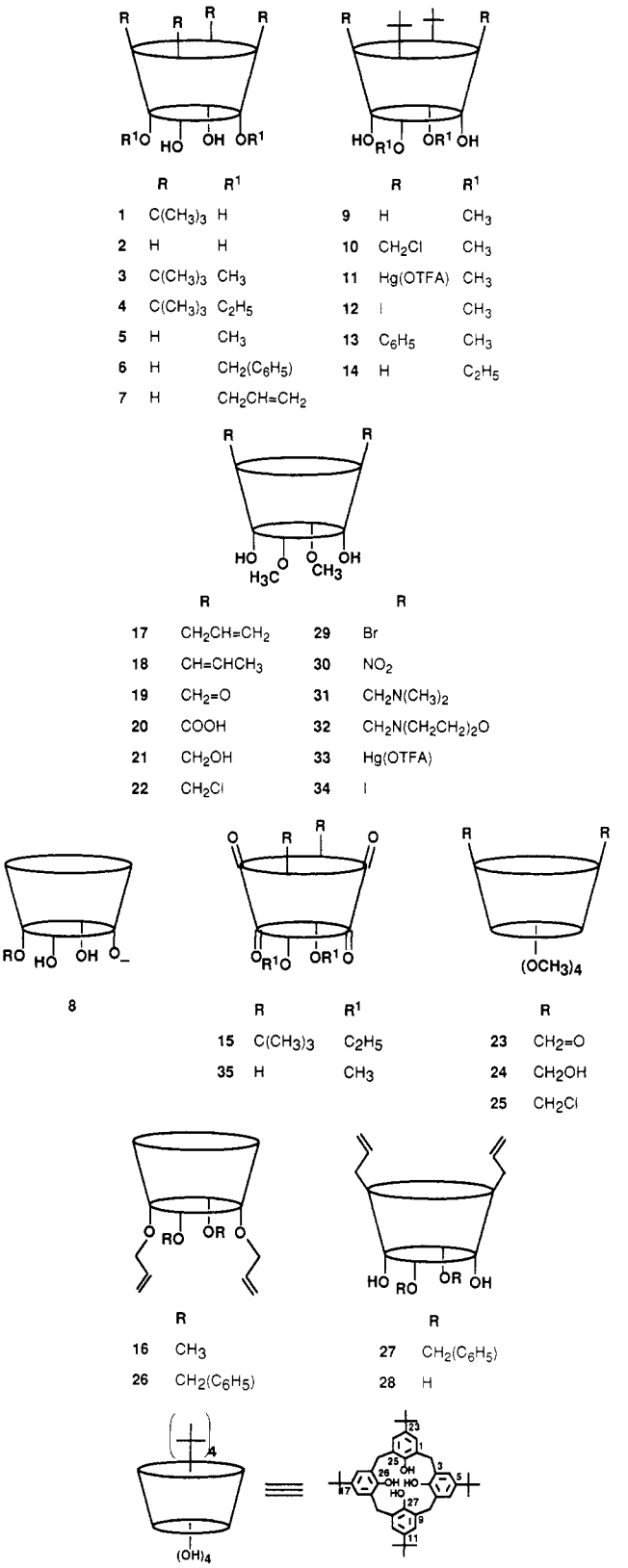
The methodologies are based on transformation of selectively dialkylated calix[4]arenes, either by selective removal of two of the four *p-tert*-butyl groups, followed by reactions at the resulting free para positions of the phenol rings, or by selective reactions on dialkoxycalix[4]arenes without the *p-tert*-butyl groups.

Results and Discussion[16]

Since it is not possible to discriminate directly between the four para positions of the phenol rings in calix[4]arene (**2**) we have first developed a method to introduce selectivity at the *lower* rim. In subsequent reactions this selectivity could be used to selectively introduce functional groups at the *upper* rim. When calix[4]arenes **1** and **2** were reacted with alkyl tosylates or alkyl bromides in the presence of 1 equiv of K_2CO_3 in refluxing CH_3CN, almost quantitative yields of the corresponding 26,28-dialkoxycalix[4]arenes **3**–**7** (Chart I) could be isolated.[17] Surprisingly, this reaction selectively leads to diametrically substituted calix[4]arenes in the cone conformation, as was indicated by the ^1H NMR spectra, showing a typical AB pattern for the methylene bridge protons (J = 13–14 Hz). This observation can be explained by the mechanism of substitution. The first step is the monoalkylation of calix[4]arene. Under the reaction conditions subsequently a proton is abstracted from the monoalkoxycalix[4]arene giving anion **8**. Since the negative charge at the oxygen atom opposite to the alkoxy group will be stabilized by two hydrogen bonds, thus keeping the calix[4]arene in the cone conformation, the second electrophile will react on this position. When more than 1 equiv of K_2CO_3 was used in the reaction with methyl tosylate, mixtures of mono-, di-, and trimethoxycalix[4]arenes were obtained. The diametrical dialkylation seems to be general.[18,19] The above observation might explain the fact that until now tetrasubstituted products were not isolated in a 1,2-alternate conformation.[20]

The first approach for the selective introduction of functional groups at the upper rim comprises the selective removal of two *p-tert*-butyl groups. We found that the reaction of tetra-*p-tert*-butyl-26,28-dimethoxycalix[4]arene (**3**) with 2 equiv of $AlCl_3$ in toluene at room temperature gave 5,17-di-*tert*-butyl-26,28-dimethoxycalix[4]arene (**9**) in 78% yield. These mild conditions allow the selective removal of the two *tert*-butyl groups from the phenolic nuclei, while the phenol ether rings do not react. Only a few examples of the selective Lewis acid catalyzed de-

Chart I



tert-butylation procedures have been reported in the literature.[21] The para positions of the phenol rings are now available for further substitution, while the remaining two para positions are protected. Reaction of **9** with chloromethyl *n*-octyl ether in the presence of $SnCl_4$ yielded 90%

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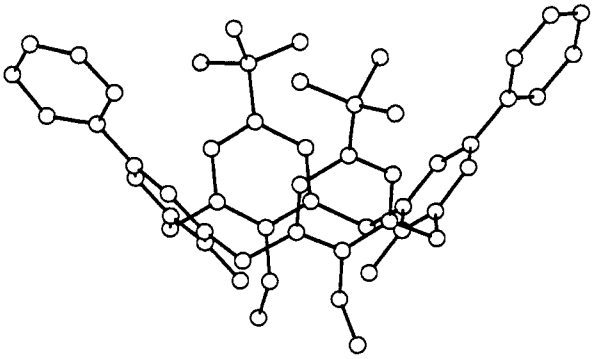

Figure 1. View of compound **13** (hydrogen atoms are omitted for clarity).

of the 5,17-di-*tert*-butyl-11,23-bis(chloromethyl)-26,28-dimethoxycalix[4]arene (**10**), a precursor for the quinone methide that allows the introduction of other functional groups.[22]

Another interesting reaction is the introduction of electrophilic centers at the upper rim. When **9** was reacted with $Hg(OTFA)_2$ a quantitative yield of the 11,23-di-*tert*-butyl-5,17-bis[(trifluoroacetoxy)mercury]-25,27-dimethoxycalix[4]arene (**11**) was obtained.[23] The dimercury compound **11** smoothly reacted with I_2 to give 5,17-di-*tert*-butyl-11,23-diiodo-26,28-dimethoxycalix[4]arene (**12**) in 80% yield.[24] The diiodo compound **12** is a very useful intermediate, because it can be converted to other calixarenes with various coupling reactions.[25] As an example we have carried out the synthesis of a calix[4]arene derivative with a larger rigid cavity. Irradiation of **12** in benzene at 254 nm[26] afforded 5,17-di-*tert*-butyl-26,28-dimethoxy-11,23-diphenylcalix[4]arene (**13**) in 58% yield. This represents a very facile route for the synthesis of *p*-phenylcalix[4]arenes, because until now they only could be prepared by stepwise routes and in very low yields.[27] The crystal structure of **13** is shown in Figure 1. From the figure the distorted cone conformation of the molecule is evident. The angles between the best plane fitted to the carbon atoms of the connecting methylene groups and the planes of the phenol groups are 48.6° and 47.7°, respectively. The angles between the methylene plane and the anisole rings are 66.0° and 67.5°. The two anisole moieties are more parallel (interplanar angle 46.4°) than the two phenol groups (angle 96.2°). The angles between the phenyl rings within the biphenyl moieties are 32.9° and 41.7°.

When 5,17-di-*tert*-butyl-26,28-diethoxycalix[4]arene (**14**) was reacted with $Tl(NO_3)_3 \cdot 3H_2O$,[28] the two phenol rings were oxidized to quinones giving **15** in 70% yield. It proved that the oxidizing agent had an important influence on the yield. The use of Jones reagent was uneffective, and Fremy's salt[29] in the presence of a quaternary ammonium salt only gave 35% yield. In solution compound **15** exhibits a rigid cone conformation; the ^1H NMR shows one singlet at 6.31 ppm for the protons of the quinone rings. To the best of our knowledge the formation of **15** represents the first example of a calix[4]diquinone. Calixquinones are an interesting class of compounds, because they may be used as new redox systems on electrodes or as models for memory and switching elements.[30] Very recently Taniguchi et al. reported the synthesis and crystal structure of a tetraquinone derived from calix[4]arene (**2**),[31] which shows a partial cone structure for this compound. One advantage of compound **15** is its *rigid cone* conformation, which creates a cavity suitable for the study of donor–acceptor inclusion complexes.

It could also be useful not to have the *p*-*tert*-butyl groups on the upper rim of the calix[4]arene, which partly occupy the cavity. Therefore we developed a second approach comprising the selective functionalization of the completely de-*tert*-butylated calix[4]arene (**2**).

One method to obtain such well-defined difunctionalized calix[4]arenes is the Claisen rearrangement route.[10] Reaction of 26,28-dimethoxycalix[4]arene (**5**) with allyl bromide in THF afforded 25,27-dimethoxy-26,28-bis(2-propenyloxy)calix[4]arene (**16**) in 91% yield. The ^1H NMR spectrum of **16** is very complex, which is probably due to a mixture of conformers. Claisen rearrangement of **16** in refluxing *N*,*N*-dimethylaniline afforded only 26,28-dimethoxy-11,23-di-2-propenylcalix[4]arene (**17**) in 99% yield. This calixarene shows the AB pattern of a cone conformation in the ^1H NMR spectrum. Subsequent isomerization of the double bond with KOtBu gave 26,28-dimethoxy-11,23-di-1-propenylcalix[4]arene (**18**) in 99% yield. This product consists of a mixture of isomers having cis and trans double bonds. As a consequence the ^1H NMR spectrum shows four sharp singlets for the OH protons, probably resulting from cis–cis (1 OH), cis–trans (2 OH), and trans–trans (1 OH) products. Ozonolysis of **18** in $CHCl_3$ afforded 25,27-dimethoxycalix[4]arene-5,17-dicarboxaldehyde (**19**) in 96% yield. It proved to be important to control the amount of ozone added, because otherwise overoxidation occurred. Diformylcalix[4]arene **19** is a useful compound because it can be converted to many other functionalized calix[4]arenes. As an example **19** could be oxidized with $NaClO_2$ to 25,27-dimethoxycalix[4]arene-5,17-dicarboxylic acid (**20**) in 75% yield. Reduction of **19** with diborane gave 11,23-bis(hydroxymethyl)-26,28-dimethoxycalix[4]arene (**21**) in 93% yield. The use of diborane in this reaction proved to be essential, because even with $NaBH_4$ partly overreduction occurred to *p*-methylcalix[4]arenes, most likely via a quinone methide intermediate. Compound **21** could be converted to the chloromethyl derivative **22** with $SOCl_2$ in 95% yield. This product is not very stable in solution, probably due to the facile formation of quinone methides. All attempts to prepare **22** by direct chloromethylation reactions resulted in the formation of tars. The 5,17-bis(chloromethyl)-25,26,27,28-tetramethoxycalix[4]arene (**25**), which could be prepared from **19** by methylation of the hydroxyl functions (giving **23**), followed by reduction of the aldehyde moieties to give **24** and subsequently a reaction with $SOCl_2$, is a more stable compound and could be purified by column chromatography. The bis(chloromethyl) compound **25** is a good starting compound for upper rim bridged calix[4]arenes.[32]

(22) The chloromethylation is a good alternative for the Mannich reaction, which we described previously,[16] because the latter reaction always gave mixtures of mono and disubstituted products, which were difficult to separate.

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Using the Claisen rearrangement 26,28-bis(benzyloxy)-11,23-di-2-propenylcalix[4]arene (**27**) was prepared from 26,28-bis(benzyloxy)calix[4]arene (**6**) via **26** in a 37% overall yield. The yield is low because debenzylation already occurred under the strenuous reaction conditions; from the reaction mixture, 5,17-di-2-propenylcalix[4]arene (**28**) was isolated in 7% yield. The latter product could also be prepared in quantitative yield by Claisen rearrangement of 26,28-bis(2-propenyloxy)calix[4]arene (**7**).

Selective functionalization of 26,28-dimethoxycalix[4]arene (**5**) could also be accomplished by selective electrophilic substitution at the para positions of the phenol rings, because these are much more reactive than the two anisole rings.[33] When **5** was reacted with 2 equiv of bromine, 11,23-dibromo-26,28-dimethoxycalix[4]arene (**29**) was isolated in 82% yield. Nitration of **5** with 2 equiv of acetyl nitrate in CH_2Cl_2 at room temperature afforded 26,28-dimethoxy-11,23-dinitrocalix[4]arene (**30**) in 57% yield. From this compound the crystal structure was solved to prove that substitution takes place exclusively at the para positions of the phenol moieties.[16] Although direct chloromethylation of **5** resulted in the formation of tars, a good alternative was found in the Mannich reaction. Reaction of **5** with CH_2O/Me_2NH in refluxing dioxane afforded 26,28-dimethoxy-11,23-bis((dimethylamino)methyl)calix[4]arene (**31**) in 91% yield. Treatment of **31** with ethyl chloroformate in $CHCl_3$,[34] resulted in the formation of the bis(chloromethyl) derivative **22** in 85% yield. Reaction of **5** with 4-(butoxymethyl)morpholine[35] gave the bis(morpholinylmethyl) derivative **32** in 74% yield. Furthermore, selective mercuration of **5** afforded 11,23-bis[(trifluoroacetoxy)mercury]-26,28-dimethoxycalix[4]arene (**33**) in 92% yield, which could be converted to the diiodo compound **34** in 70% yield. The calix[4]diquinone **35** could be obtained from 26,28-dimethoxycalix[4]arene (**5**) by selective oxidation of the phenols with $Tl(NO_3)_3 \cdot 3H_2O$ in 75% yield.[28] The ^1H NMR spectrum indicates that the calix[4]diquinone **35** is a mobile structure in solution.[36]

We can conclude that selectively diametrically disubstituted calix[4]arenes at the upper rim can be prepared in good yields using different methods, and we are currently studying the introduction of various functional groups at the upper rim of the calix[4]arene moiety.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) with Me_4Si as an internal standard. FAB-mass spectra were recorded, using *m*-nitrobenzyl alcohol as a matrix. All chemicals were reagent grade and used without further purification. Compounds **1**,[37] **2**,[14] **3**,[6] and **4**[6] were prepared according to the literature. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone ketyl, while acetonitrile was distilled and kept over molecular sieves (3 Å). Petroleum ether refers to the fraction boiling at 40–60 °C. All reactions were carried out in a nitrogen atmosphere. Chromatographic separations were performed on silica gel 60 (SiO_2, E. Merck, particle size 0.040–0.063 mm, 230–240 mesh) whereas preparative TLC was performed on 60 F254 (Al_2O_3) preparative plates (E. Merck, thickness 1.5 mm).

26,28-Dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (5). A suspension of calix[4]arene (**2**) (30.0 g, 70.7 mmol), potassium carbonate (anhydrous, 10.7 g, 77.4 mmol), and methyl tosylate (26.3 g, 141.4 mmol) was refluxed in CH_3CN (500 mL) for 24 h. After evaporation of the solvent, the mixture was taken up in CH_2Cl_2 (500 mL) and washed with 1 N HCl (2 × 50 mL) and brine (50 mL). The organic layer was dried with $MgSO_4$, and the solvent was evaporated to afford **5** as a pure white solid: yield 30.8 g (97%); mp >300 °C dec ($CHCl_3$/MeOH); ^1H NMR δ 7.67 (s, 2 H, OH), 7.15–6.5 (m, 12 H, ArH), 4.31 and 3.39 (AB q, 8 H, J = 13.2 Hz, $ArCH_2Ar$), 3.97 (s, 6 H, OCH_3); ^{13}C NMR δ 153.2, 153.0 (s, Ar 25,26,27,28-C), 132.9, 128.1 (s, Ar 1,3,7,9,13,15,19,21-C), 129.0, 128.4 (d, Ar 4,6,10,12,16,18,22,24-C), 125.2 (d, 5,17-C), 119.1 (d, Ar 11,23-C), 63.6 (q, OCH_3), 31.1 (t, 2,8,14,20-C); mass spectrum, *m/e* 452.200 (M^+, calcd 452.199). Anal. Calcd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.24. Found: C, 79.68; H, 6.35.

26,28-Bis(phenylmethoxy)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (6). A suspension of calix[4]arene (**2**) (3.0 g, 7.1 mmol), K_2CO_3 (1.12 g, 8.1 mmol), and benzyl bromide (2.48 g, 14.2 mmol) in CH_3CN (100 mL) was refluxed for 12 h. After evaporation of the solvent the mixture was taken up in $CHCl_3$ (100 mL) and washed with 1 N HCl (2 × 25 mL) and brine (25 mL). The organic layer was dried with $MgSO_4$ and evaporated to yield pure **6** as a white solid: yield 4.12 g (96%); mp 220–223 °C ($CHCl_3$/MeOH); ^1H NMR δ 7.74 (s, 2 H, OH), 7.7–6.5 (m, 22 H, ArH), 5.05 (s, 4 H, OCH_2Ph), 4.32 and 3.32 (AB q, 8 H, J = 13.2 Hz, $ArCH_2Ar$); ^{13}C NMR δ 78.4 (t, OCH_2Ph); mass spectrum, *m/e* 604.265 (M^+, calcd 604.261). Anal. Calcd for $C_{42}H_{36}O_4 \cdot 0.5MeOH$: C, 82.23; H, 6.17. Found: C, 82.12; H, 5.86.

26,28-Bis(2-propenyloxy)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (7). A suspension of calix[4]arene (**2**) (5.0 g, 11.8 mmol), K_2CO_3 (anhydrous, 1.79 g, 13.0 mmol), and allyl bromide (2.92 g, 24.1 mmol) was refluxed in CH_3CN (100 mL) for 15 h. After evaporation of the solvent, the mixture was taken up in CH_2Cl_2 (100 mL) and washed with 1 N HCl (2 × 25 mL) and brine (25 mL). The organic layer was dried with $MgSO_4$ and evaporated to afford **7** as a white solid: yield 5.89 g (99%); mp 187.5–188.0 °C ($CHCl_3$/MeOH); ^1H NMR δ 7.90 (s, 2 H, OH), 7.1–6.0 (m, 14 H, ArH, $CH_2CH{=}CH_2$), 5.9–5.2 (m, 4 H, $CH{=}CH_2$), 4.55 (m, 4 H, $CH_2CH{=}CH_2$), 4.33 and 3.37 (AB q, 8 H, J = 13.0 Hz, $ArCH_2Ar$); ^{13}C NMR δ 153.2, 151.7 (s, Ar 25,26,27,28-C), 133.4, 128.0 (s, Ar 1,3,7,9,13,15,19,21-C), 132.7 (d, $CH{=}CH_2$), 128.9, 128.4 (d, Ar 4,6,10,12,16,18,22,24-C), 125.4, 119.0 (d, 5,11,17,23-C), 117.9 (t, $CH{=}CH_2$), 76.8 (t, $CH_2CH{=}CH_2$), 31.4 (t, $ArCH_2Ar$); mass spectrum, *m/e* 504.232 (M^+, calcd 504.230). Anal. Calcd for $C_{34}H_{32}O_4$: C, 80.95; H, 6.35. Found: C, 81.02; H, 6.51.

5,17-Bis(1,1-dimethylethyl)-26,28-dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (9). To a suspension of $AlCl_3$ (2.5 g, 18.7 mmol) in anhydrous toluene (500 mL) was added 26,28-dimethoxycalix[4]arene (**3**) (6.1 g, 9.0 mmol), and the mixture was stirred at room temperature. The reaction was followed by the disappearance of the NMR signal at 1.3 ppm. For this purpose aliquots (3 mL) were taken, which were treated with 10% HCl. The organic layer was washed with H_2O, and the solvent was evaporated in vacuo. The yellowish product was triturated with hexane (3 × 1 mL) and dried in vacuo. When the reaction was complete (in 5 h), the reaction was quenched with 10% HCl (300 mL). The organic layer was washed with water and dried with $CaCl_2$. The solvent was evaporated, and the residue was triturated twice with hexane (10 mL) to give **9** as a pure white solid: yield 3.96 g (78%); mp 271–273 °C (hexane); ^1H NMR δ 7.3 (s, 2 H, OH), 7.08 (d, 4 H, J = 6.95 Hz, ArH), 6.76 (s, 4 H, ArH), 6.75–6.60 (m, 2 H, ArH), 4.28 and 3.36 (AB q, 8 H, J = 13.2 Hz, $ArCH_2Ar$), 3.94 (s, 6 H, OCH_3), 0.96 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR δ 152.9, 151.5, 147.2 (s, Ar 5,17,25,26,27,28-C), 132.2, 128.7 (s, Ar 1,3,7,9,13,15,19,21-C), 128.3, 125.7 (d, Ar 4,6,10,12,16,18,22,24-C), 119.2 (d, Ar 11,23-C), 63.5 (q, OCH_3), 34.0 (s, $C(CH_3)_3$), 31.5 (t, 2,8,14,20-C), 31.2 (q, $C(CH_3)_3$); mass spectrum, *m/e* (%) 564 (100), 549 (48). Anal. Calcd for $C_{38}H_{44}O_4$: C, 80.81; H, 7.85. Found: C, 80.65; H, 7.84.

11,23-Bis(chloromethyl)-5,17-bis(1,1-dimethylethyl)-26,28-dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (10). To a solution of compound **9** (1.0 g, 1.77 mmol) and chloromethyl *n*-octyl ether (0.69 mL, 3.5 mmol) in $CHCl_3$ (200 mL, dried on mol sieves 3 Å) was added $SnCl_4$ (1.0 mL, 8.5 mmol) at −40 °C. The mixture was allowed to warm up to room temper-

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ature, and it was stirred until all starting material had disappeared (TLC, SiO_2, hexane–CH_2Cl_2, 1:1). The organic layer was washed with water (2 × 25 mL), dried with $MgSO_4$, and evaporated. The crude product was triturated with hexane (2 × 2 mL) and dried in vacuo to afford **10** as a white solid that became pink in a few hours at room temperature. Therefore it could not be recrystallized: yield 1.05 g (90%); mp 170 °C dec; ^1H NMR δ 7.6 (s, 2 H, OH), 7.18, 6.83 (s, 8 H, ArH), 4.60 (s, 4 H, CH_2Cl), 4.32 and 3.34 (AB q, 8 H, J = 13.0 Hz, $ArCH_2Ar$), 3.95 (s, 6 H, OCH_3), 0.95 (s, 18 H, $C(CH_3)_3$); mass spectrum, m/e (%) 660 (5), 626 (7), 590 (13), 225 (100). Anal. Calcd for $C_{40}H_{46}Cl_2O_4$: Cl, 10.71. Found: Cl, 10.79 (argentometric).

[μ-[11,23-Bis(1,1-dimethylethyl)-26,28-dihydroxy-25,27-dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-5,17-diyl]]bis(trifluoroacetato-*O*)dimercury (11). A mixture of compound **9** (1.0 g, 1.77 mmol) and mercury trifluoroacetate (1.52 g, 3.55 mmol) in $CHCl_3$ (90 mL) was stirred at room temperature for 14 h. The homogeneous solution was evaporated to yield a pure white solid: yield 2.09 g (99%); mp 248–250 °C (CH_3CN); ^1H NMR δ 7.85 (br s, 2 H, OH), 7.04, 6.62 (s, 8 H, ArH), 4.26 and 3.37 (AB q, 8 H, J = 13.2 Hz, $ArCH_2Ar$), 3.95 (s, 6 H, OCH_3), 1.01 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR δ 154.8, 151.3, 147.9 (s, Ar 5,17,25,26,27,28-C), 135.4, 129.7 (s, Ar 1,3,7,9,11,13,15,19,21,23-C), 131.5, 126.0 (d, Ar 4,6,10,12,16,18,22,24-C), 63.6 (q, OCH_3), 34.9 (s, $C(CH_3)_3$), 31.5 (t, 2,8,14,20-C), 31.3 (q, $C(CH_3)_3$); mass spectrum (FAB), m/e 1189 [$(M + H)^+$]. Anal. Calcd for $C_{42}H_{42}F_6Hg_2O_8$: C, 42.39; H, 3.55. Found: C, 42.10; H, 3.50.

5,17-Bis(1,1-dimethylethyl)-11,23-diiodo-26,28-dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (12). A solution of compound **11** (1.0 g, 0.84 mmol) and I_2 (0.50 g, 1.96 mmol) in CH_3CN (50 mL) was stirred at room temperature for 1 h. Excess I_2 was removed by adding $Na_2S_2O_5$ (15% in H_2O, 10 mL). CH_2Cl_2 (50 mL) was added to the mixture, and the organic layer was washed with water (2 × 25 mL), dried with $MgSO_4$, and evaporated to give a white solid: yield 0.55 g (80%); mp >330 °C (CH_3CN); ^1H NMR δ 7.6 (s, 2 H, OH), 7.37, 6.83 (s, 8 H, ArH), 4.23 and 3.30 (AB q, 8 H, J = 13.2 Hz, $ArCH_2Ar$), 3.93 (s, 6 H, OCH_3), 1.05 (s, 18 H, $C(CH_3)_3$); mass spectrum, m/e (%) 689 (M^+ – HI, 33), 562 (38), 393 (40), 57 (100). Anal. Calcd for $C_{38}H_{42}I_2O_4$: C, 55.89; H, 5.18; I, 31.08. Found: C, 56.21; H, 5.09; I, 31.25 (argentometric).

5,17-Bis(1,1-dimethylethyl)-26,28-dimethoxy-11,23-diphenylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (13). A solution of compound **12** (0.04 g, 0.05 mmol) in benzene (80 mL) was irradiated at 254 nm with a low-pressure Hg lamp under a nitrogen atmosphere until all starting material had disappeared (TLC, SiO_2, CH_2Cl_2). To the resulting violet solution was added 10% $Na_2S_2O_5$ (20 mL), and the mixture was stirred for 10 min. The organic layer was dried with $MgSO_4$ and evaporated to afford a yellow solid, which was purified by column chromatography (SiO_2, CH_2Cl_2): yield 0.02 g (58%); mp 270–272 °C ($CHCl_3$); ^1H NMR δ 7.5–6.9 (m, 18 H, ArH), 4.36 and 3.44 (AB q, 8 H, J = 13.1 Hz, $ArCH_2Ar$), 3.98 (s, 6 H, OCH_3), 0.97 (s, 18 H, $C(CH_3)_3$); mass spectrum, m/e (%) 716 (100), 701 (15), 358 (20), 57 (50). Anal. Calcd for $C_{50}H_{52}O_4$: C, 83.76; H, 7.31. Found: C, 83.80; H, 7.28.

5,17-Bis(1,1-dimethylethyl)-26,28-diethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (14) was prepared analogously to compound **9**: yield 80%; mp 263–265 °C (hexane); ^1H NMR δ 8.1 (s, 2 H, OH), 7.04 (d, 4 H, J = 7.8 Hz, ArH), 6.91 (s, 4 H, ArH), 6.7–6.4 (m, 2 H, ArH), 4.34 and 3.35 (AB q, 8 H, J = 12.9 Hz, $ArCH_2Ar$), 4.11 (q, 4 H, J = 7.0 Hz, OCH_2CH_3), 1.66 (t, 6 H, OCH_2CH_3), 1.08 (s, 18 H, $C(CH_3)_3$); ^{13}C NMR δ 152.8, 147.1 (s, Ar 25,26,27,28-C), 133.0, 128.9 (s, Ar 1,3,5,7,9,13,15,17,19,21-C), 128.2, 125.6, 119.4 (d, Ar 4,6,10,11,12,16,18,22,23,24-C), 71.9 (t, OCH_2CH_3), 34.2 (s, $C(CH_3)_3$), 31.8 (t, 2,8,14,20-C), 31.2 (q, $C(CH_3)_3$), 15.3 (q, OCH_2CH_3); mass spectrum, m/e (%) 592 (30), 536 (19), 253 (57), 119 (100). Anal. Calcd for $C_{40}H_{48}O_4$: C, 81.04; H, 8.16. Found: C, 81.19; H, 8.21.

11,23-Bis(1,1-dimethylethyl)-25,27-diethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,6,9,11,13(27),15,18,21,23-decaene-5,17,26,28-tetrone (15). To a solution of $Tl(NO_3)_3{\cdot}3H_2O$ (3.0 g, 6.8 mmol) in dry MeOH (120 mL) and dry EtOH (360 mL) was added a solution of compound **14** (1.0 g, 1.7 mmol) in $CHCl_3$ (100 mL). The mixture was stirred for 1 h and quenched with H_2O (50 mL), and then 10% HCl was added dropwise until complete dissolution of the precipitate. After addition of $CHCl_3$ (100 mL) the organic layer was separated, dried with Na_2SO_4, and evaporated. The resulting yellow solid was triturated with cold CH_3CN (5 mL and 2 × 2 mL) to afford **15**: yield 0.74 g (70%); mp 258–260 °C dec (CH_3CN); ^1H NMR δ 7.19 (s, 4 H, ArH), 6.31 (s, 4 H, C=CHC=O), 3.82 and 3.31 (AB q, 8 H, J = 13.5 Hz, $ArCH_2Ar$), 3.44 (q, 4 H, OCH_2CH_3), 1.35 (s, 18 H, $C(CH_3)_3$), 1.03 (t, 6 H, OCH_2CH_3); ^{13}C NMR δ 188.0, 186.1 (s, 5,17,26,28-C), 153.4 (s, 25,27-C), 147.7, 146.9, 132.0 (s, 1,3,7,9,11,13,15,19,21,23-C), 132.9, 127.9 (d, 4,6,10,12,16,18,22,24-C), 67.5 (t, OCH_2CH_3), 34.3 (s, $C(CH_3)_3$), 32.4 (t, $ArCH_2Ar$), 31.5 (q, $C(CH_3)_3$), 14.7 (q, OCH_2CH_3); mass spectrum, m/e (%) 621 (38), 281 (19), 57 (100); IR (KBr) 1665 cm^{-1} (C=O). Anal. Calcd for $C_{40}H_{44}O_6$: C, 77.39; H, 7.14. Found: 77.44; H, 7.08.

25,27-Dimethoxy-26,28-bis(2-propenyloxy)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (16). Sodium hydride (80% in oil, 2.72 g, 90.7 mmol) was freed from protective mineral oil by two hexane washings, and it was suspended in dry THF (200 mL). To the suspension was added compound **5** (20.0 g, 44.2 mmol) in portions at 0 °C. After stirring for 30 min allyl bromide (16.0 g, 132 mmol) was added, and the solution was refluxed for 15 h. Excess NaH was destroyed by addition of water (caution!), and then the solvent was evaporated. The residue was taken up in CH_2Cl_2 (250 mL), and the resulting solution was washed with 1 N HCl (50 mL) and brine (25 mL). The organic layer was dried with $MgSO_4$ and evaporated to afford **16** as a white solid: yield 21.4 g (91%); mp 157–158 °C ($CHCl_3$/MeOH); ^1H NMR δ 7.4–6.3 (m, 12 H, ArH), 6.3–4.8 (m, 6 H, $CH_2CH{=}CH_2$), 4.5–2.8 (m, 18 H, $CH_2CH{=}CH_2$, OCH_3, $ArCH_2Ar$); mass spectrum, m/e 532.255 (M^+, calcd 532.261). Anal. Calcd for $C_{36}H_{36}O_4$: C, 81.17; H, 6.81. Found: C, 81.13; H, 6.78.

26,28-Dimethoxy-11,23-di-2-propenylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (17). A solution of compound **16** (20.0 g, 37.6 mmol) in *N*,*N*-dimethylaniline (50 mL) was refluxed for 2 h. The cooled reaction mixture was poured into a 1:1 mixture of concentrated HCl/ice (600 mL). The precipitate was taken up in CH_2Cl_2 (500 mL) and washed with 6 N HCl (3 × 50 mL), water (50 mL), and brine (50 mL). The organic layer was dried with $MgSO_4$ and evaporated to afford a gray solid which was further purified by column chromatography (SiO_2, CH_2Cl_2): yield 19.8 g (99%); mp 265 °C dec ($CHCl_3$/MeOH); ^1H NMR δ 7.67 (s, 2 H, OH), 6.87 (s, 4 H, ArH), 6.9–6.7 (m, 6 H, ArH), 6.1–5.8 (m, 2 H, $CH_2CH{=}CH_2$), 5.15–4.95 (m, 4 H, $CH_2CH{=}CH_2$), 4.28 and 3.36 (AB q, 8 H, J = 13.0 Hz, $ArCH_2Ar$), 3.97 (s, 6 H, OCH_3), 3.26 (d, 4 H, J = 6.5 Hz, $CH_2CH{=}CH_2$); ^{13}C NMR δ 153.2, 151.2 (s, Ar 25,26,27,28-C), 138.2 (d, $CH_2CH{=}CH_2$), 133.0 (s, Ar 3,7,15,19- or 1,9,13,21-C), 130.3 (s, Ar 11,23-C), 128.9, 128.5 (d, Ar 4,6,10,12,16,18,22,24-C), 128.0 (s, Ar 3,7,15,19- or 1,9,13,21-C), 125.3 (d, Ar 5,17-C), 115.2 (t, $CH{=}CH_2$), 63.6 (q, OCH_3), 39.4 (t, $CH_2CH{=}CH_2$), 31.2 (t, 2,8,14,20-C); mass spectrum, m/e 532.263 (M^+, calcd 532.261). Anal. Calcd for $C_{36}H_{36}O_4$: C, 81.17; H, 6.81. Found: C, 81.56; H, 6.73.

26,28-Dimethoxy-11,23-di-1-propenylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (18). A mixture of compound **17** (2.0 g, 3.76 mmol) and KOtBu (1.9 g, 16.9 mmol) in THF (50 mL) was refluxed for 15 h. The color of the reaction mixture changed from yellow to orange/red. After addition of a saturated NH_4Cl solution (50 mL) the THF was evaporated, and the residue was taken up in $CHCl_3$ (400 mL). The organic layer was washed with brine (50 mL), dried with $MgSO_4$, and evaporated to afford a white solid, which consists of a mixture of isomers with cis and trans double bonds: yield 1.98 g (99%); mp >300 °C dec ($CHCl_3$/MeOH); ^1H NMR δ 7.81, 7.72, 7.70, 7.60 (s, 2 H, OH), 7.06, 7.04 (s, 4 H, ArH), 6.95–6.65 (m, 6 H, ArH), 6.4–6.2 (m, 2 H, $CH{=}CHCH_3$), 6.2–5.9 and 5.75–5.55 (m, 2 H, $CH{=}CHCH_3$), 4.30 and 3.38, 4.28 and 3.38, 4.27 and 3.38 (AB q, 8 H, J = 13.0 Hz, $ArCH_2Ar$), 3.98, 3.97, 3.96 (s, 6 H, OMe), 1.93 and 1.85 (dd, 6 H, J = 6.0 and 1.5 Hz, $CHCH_3$); mass spectrum, m/e 532.265 (M^+, calcd 532.261). Anal. Calcd for $C_{36}H_{36}O_4$: C,

81.17; H, 6.81. Found: C, 81.01; H, 6.87.

26,28-Dihydroxy-25,27-dimethoxypentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene-5,17-dicarboxaldehyde (19). Through a solution of compound **18** (0.5 g, 0.94 mmol) in $CHCl_3$ (50 mL) was bubbled ozone (2 equiv) for 30 min at −15 °C. To the mixture was added a solution of $Na_2S_2O_5$ (0.75 g) in H_2O (30 mL), and the solution was stirred for 15 min. Brine (50 mL) was added, and the water layer was extracted with $CHCl_3$ (2 × 50 mL). The combined organic layers were dried and evaporated to afford a pure white solid: yield 0.46 g (96%);[38] mp >315 °C ($CHCl_3$/EtOAc); ^{1}H NMR δ 9.81 (s, 2 H, CH=O), 8.66 (s, 2 H, OH), 7.65 (s, 4 H, ArH), 7.1–6.7 (m, 6 H, ArH), 4.32 and 3.52 (AB q, 8 H, J = 13.4 Hz, $ArCH_2Ar$), 4.02 (s, 6 H, OCH_3); ^{13}C NMR δ 190.8 (d, CH=O); IR (KBr) 1685 (C=O) cm^{-1}; mass spectrum, m/e 508.193 (M$^+$, calcd 508.189). Anal. Calcd for $C_{32}H_{28}O_6$·0.6EtOAc: C, 73.59; H, 5.89. Found: C, 73.32; H, 5.64.

26,28-Dihydroxy-25,27-dimethoxypentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene-5,17-dicarboxylic Acid (20). To a solution of compound **19** (0.87 g, 1.71 mmol) in CH_2Cl_2 (35 mL) and acetone (20 mL) was added dropwise a solution of $NaClO_2$ (0.80 g, 8.8 mmol) and NH_2SO_3H (1.1 g, 11.3 mmol) in H_2O (5 mL). After 2 h the organic solvents were evaporated. To the residue was added EtOAc (400 mL), and the resulting cloudy solution was washed with 1 N HCl (25 mL) and brine (25 mL). After drying with $MgSO_4$ and evaporation of the solvent, the residue was triturated with MeOH (3 × 3 mL) to yield 0.69 g (75%) of **20**, which showed 1 spot on TLC (SiO_2, EtOAc–MeOH, 95:5). The compound is poorly soluble in a number of organic solvents, but it dissolves readily in basic MeOH and H_2O: mp >300 °C (MeOH); ^{1}H NMR (CD_3OD) δ 8.04 (s, 4 H, ArH), 7.3–6.8 (m, 6 H, ArH), 4.51 and 3.60 (AB q, 8 H, J = 13.2 Hz, $ArCH_2Ar$), 4.18 (s, 6 H, OCH_3); IR (KBr) 1690 cm^{-1} (C=O); mass spectrum, m/e (%) 540 (80), 522 (70), 57 (100). No satisfactory elemental analysis could be obtained.

11,23-Bis(hydroxymethyl)-26,28-dimethoxypentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene-25,27-diol (21). To a solution of compound **19** (0.49 g, 0.96 mmol) in THF (20 mL) was added a solution of B_2H_6 (1 M in THF, 2 mL, 2 mmol) at −40 °C. The mixture was stirred at −40 °C for 2 h and subsequently at room temperature for 1 h. Water was added dropwise (caution!), and after evaporation of the solvent the mixture was taken up in $CHCl_3$ (50 mL), and the resulting solution was washed with a saturated NH_4Cl solution (50 mL). The organic layer was dried with $MgSO_4$ and evaporated to afford a white solid: yield 0.46 g (93%); mp >320 °C ($CHCl_3$/MeOH); ^{1}H NMR δ 7.81 (s, 2 H, OH), 7.08 (s, 4 H, ArH), 7.0–6.6 (m, 6 H, ArH), 4.55 (d, 4 H, J = 4.9 Hz, CH_2OH), 4.32 and 3.40 (AB q, 8 H, J = 13.2 Hz, $ArCH_2Ar$), 3.99 (s, 6 H, OMe), 1.4 (br t, 2 H, CH_2OH); mass spectrum, m/e 494.215 (M$^+$ − H_2O, calcd 494.209). Anal. Calcd for $C_{32}H_{32}O_6$·0.4$CHCl_3$: C, 69.45; H, 5.83. Found: C, 69.35; H, 5.74.

11,23-Bis(chloromethyl)-26,28-dimethoxypentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene-25,27-diol (22). A mixture of compound **21** (0.46 g, 0.9 mmol) and $SOCl_2$ (0.25 g, 2.1 mmol) in $CHCl_3$ (50 mL) was stirred for 30 min at room temperature. Evaporation of the solvent yielded a pure white solid, which appeared to be unstable in solution and on silica. Therefore it could not be recrystallized: yield 0.47 g (95%); mp >300 °C dec; ^{1}H NMR δ 7.88 (s, 2 H, OH), 7.10 (s, 4 H, ArH), 7.0–6.6 (m, 6 H, ArH), 4.52 (s, 4 H, CH_2Cl), 4.28 and 3.39 (AB q, 8 H, J = 13.2 Hz, $ArCH_2Ar$), 3.98 (s, 6 H, OMe); mass spectrum, m/e 548.162 (M$^+$, calcd 548.152). Anal. Calcd for $C_{32}H_{30}Cl_2O_4$·0.2 $CHCl_3$: C, 67.45; H, 5.30. Found: C, 67.56; H, 5.27.

25,26,27,28-Tetramethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-5,17-dicarboxaldehyde (23). A mixture of compound **19** (1.71 g, 3.36 mmol), K_2CO_3 (1.7 g, 12.4 mmol), and MeI (1.7 g, 12.1 mmol) in CH_3CN (100 mL) was refluxed for 5 h. After filtration the solvent was evaporated, and the mixture was taken up in $CHCl_3$ (100 mL). The organic layer was washed with 1 N HCl (25 mL) and brine (25 mL), dried with $MgSO_4$, and evaporated to afford a white foam, which was pure enough for synthetic purposes: yield 1.79 g (99%). An analytically pure sample was obtained by flash chromatography (SiO_2, CH_2Cl_2–EtOAc, 95:5): mp 80–82 °C (CH_2Cl_2/EtOAc); ^{1}H NMR δ 9.8 and 9.5 (br s, 2 H, CH=O), 8.0–6.2 (m, 10 H, ArH), 4.5–2.6 (m, 20 H, OCH_3, $ArCH_2Ar$); IR (KBr) 1691 (C=O) cm^{-1}; mass spectrum, m/e 536.222 (M$^+$, calcd 536.220). Anal. Calcd for $C_{34}H_{32}O_6$·0.5EtOAc: C, 74.46; H, 6.25. Found: C, 74.87; H, 6.16.

25,26,27,28-Tetramethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-5,17-dimethanol (24). To a solution of compound **23** (1.0 g, 1.86 mmol) in THF (50 mL) was added dropwise a solution of B_2H_6 (1 M in THF, 3 mL, 3 mmol) at −40 °C. After stirring for 1 h at −40 °C and 3 h at room temperature, the excess B_2H_6 was destroyed with water, and the solvent was evaporated. The mixture was taken up in $CHCl_3$ (100 mL), and the solution was washed with water (25 mL) and brine (25 mL). The organic layer was dried with $MgSO_4$ and evaporated to give pure **24** as a white foam in 98% (0.99 g) yield. An analytically pure sample was obtained by flash chromatography (SiO_2, CH_2Cl_2–EtOAc, 2:1): mp 68–70 °C (CH_2Cl_2); ^{1}H NMR δ 7.4–6.1 (m, 10 H, ArH), 4.5–2.7 (m, 24 H, OMe, $ArCH_2Ar$, $ArCH_2O$); mass spectrum, m/e 540.253 (M$^+$, calcd 540.251). Anal. Calcd for $C_{34}H_{36}O_6$·0.5CH_2Cl_2: C, 71.06; H, 6.40. Found: C, 71.31; H, 6.51.

5,17-Bis(chloromethyl)-25,26,27,28-tetramethoxy-pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7-(28),9,11,13(27),15,17,19(26),21,23-dodecaene (25). A mixture of compound **24** (0.46 g, 0.85 mmol) and $SOCl_2$ (0.3 g, 2.6 mmol) in $CHCl_3$ (20 mL) was stirred for 0.5 h. Evaporation of the solvent yielded a white foam, which was pure enough for synthetic purposes: yield 0.45 g (92%). An analytically pure sample was obtained by flash chromatography (SiO_2, CH_2Cl_2–petroleum ether, 4:1); mp 202–203 °C (CH_2Cl_2); ^{1}H NMR δ 7.1–6.4 (m, 10 H, ArH), 4.3 (br s, 4 H, CH_2Cl), 4.5–2.8 (m, 20 H, OMe, $ArCH_2Ar$); mass spectrum, m/e 576.181 (M$^+$, calcd 576.183). Anal. Calcd for $C_{34}H_{34}Cl_2O_4$·0.25CH_2Cl_2: C, 68.70; H, 5.81. Found: 68.43; H, 6.02.

25,27-Bis(phenylmethoxy)-26,28-bis(2-propenyloxy)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13-(27),15,17,19(26),21,23-dodecaene (26). To a solution of compound **6** (1.5 g, 2.48 mmol) in THF (100 mL) was added NaH (80% in oil, 0.26 g, 8.68 mmol) at 0 °C. After the solution was stirred for 30 min, allyl bromide (1.20 g, 9.92 mmol) was added, and the mixture was refluxed for 12 h. Excess NaH was destroyed with water (caution!), after evaporation of the solvent the mixture was taken up in $CHCl_3$ (100 mL), and the organic layer was washed with brine (25 mL) and dried with $MgSO_4$. Evaporation of the solvent afforded an oil: yield 1.56 g (92%); ^{1}H NMR δ 7.6–4.2 (m, 36 H, ArH, CH_2Ph, $CH_2CH=CH_2$), 4.3–2.8 (m, 8 H, $ArCH_2Ar$); mass spectrum, m/e 684.322 (M$^+$, calcd 684.324). Anal. Calcd for $C_{48}H_{44}O_4$: C, 84.18; H, 6.48. Found: C, 84.04; H, 6.54.

26,28-Bis(phenylmethoxy)-11,23-di-2-propenyl-pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7-(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (27). A solution of compound **26** (0.94 g, 1.4 mmol) in *N*,*N*-dimethylaniline (30 mL) was refluxed for 2 h. The solution was poured into a mixture of concentrated HCl/ice, 1:1 (200 mL), to form a precipitate, which was taken up in CH_2Cl_2 (100 mL). After washing the organic layer with 6 N HCl (3 × 25 mL) and brine (25 mL), it was dried with $MgSO_4$ and evaporated to afford a crude product, which was further purified by flash chromatography (SiO_2, CH_2Cl_2–petroleum ether, 3:5) to afford pure **27**: yield 0.38 g (40%); mp 75–76 °C ($CHCl_3$/MeOH); ^{1}H NMR δ 7.61 (s, 2 H, OH), 7.7–6.7 (m, 16 H, ArH), 6.85 (s, 4 H, ArH), 6.2–5.7 (m, 2 H, $CH_2CH=CH_2$), 5.2–4.9 (m, 4 H, $CH=CH_2$), 5.04 (s, 4 H, CH_2Ph), 4.28 and 3.28 (AB q, 8 H, J = 13.2 Hz, $ArCH_2Ar$), 3.24 (d, 4 H, J = 6.5 Hz, $CH_2CH=CH_2$); ^{13}C NMR δ 78.3 (t, OCH_2Ph), 39.4 (t, $CH_2CH=CH_2$), 31.5 (t, $ArCH_2Ar$); mass spectrum, m/e 684.328 (M$^+$, calcd 684.324). Anal. Calcd for $C_{48}H_{44}O_4$·MeOH: C, 82.09; H, 6.75. Found: C, 82.35; H, 6.36.

5,17-Di-2-propenylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,26,27,28-tetrol (28). A solution of compound **7** (5.92 g, 11.7 mmol) in *N*,*N*-dimethylaniline (50 mL) was refluxed for 2 h. The

(38) If more than 2 equiv of ozone are used, overoxidation occurs, leading to a mixture of products. The desired product can be isolated by column chromatography (SiO_2, CH_2Cl_2–EtOAc, 95:5), but often up to 50% of material is lost due to decomposition on the column.

solution was poured into a mixture of concentrated HCl/ice, 1:1 (400 mL), to form a precipitate, which was taken up in CH_2Cl_2 (150 mL). The organic layer was washed with 6 N HCl (3 × 50 mL) and brine (25 mL), dried with $MgSO_4$, and evaporated to afford **28** as a white solid, which turned yellowish upon standing in the light: yield 5.86 g (99%); mp 85–87.5 °C ($CHCl_3$/MeOH); ^1H NMR δ 10.2 (s, 4 H, OH), 7.2–6.5 (m, 10 H, ArH), 6.3–5.5 (m, 2 H, CH_2CH=CH_2), 5.1–4.9 (m, 4 H, CH_2CH=CH_2), 4.5–3.3 (br s, 8 H, $ArCH_2Ar$), 3.17 (d, 4 H, J = 7.0 Hz, CH_2CH=CH_2); ^{13}C NMR δ 149.0, 147.1 (s, Ar 25,26,27,28-C), 137.5 (d, CH_2CH=CH_2), 133.6, 128.4, 128.2 (s, Ar 1,3,7,9,13,15,17,19,21-C), 129.0 (d, Ar 4,6,10,12,16,18,22,24-C), 122.2 (d, Ar 11,23-C), 115.6 (t, CH_2CH=CH_2), 39.4 (t, CH_2CH=CH_2), 31.9 (t, $ArCH_2Ar$); mass spectrum, m/e 504.227 (M^+, calcd 504.230). Anal. Calcd for $C_{34}H_{32}O_4$·MeOH: C, 78.33; H, 6.76. Found: C, 78.73; H, 6.37.

11,23-Dibromo-26,28-dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (29). To a solution of compound **5** (1.0 g, 2.21 mmol) in $CHCl_3$ (45 mL) was added dropwise a solution of Br_2 (0.71 g, 4.42 mmol) in $CHCl_3$ (45 mL) during 2 h at 0 °C. After being stirred for 2 h at room temperature the precipitate formed was filtered off and washed with cold $CHCl_3$ to give pure **29**: yield 1.11 g (82%); mp >300 °C ($CHCl_3$); ^1H NMR δ 7.87 (s, 2 H, OH), 7.21 (s, 4 H, ArH), 7.1–6.7 (m, 6 H, ArH), 4.27 and 3.37 (AB q, 8 H, J = 13.0 Hz, $ArCH_2Ar$), 3.97 (s, 6 H, OCH_3); mass spectrum, m/e 608.012 (M^+, calcd 608.020). Anal. Calcd for $C_{30}H_{28}Br_2O_4$: C, 59.04; H, 4.29. Found: C, 58.64; H, 4.23.

26,28-Dimethoxy-11,23-dinitropentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (30). A mixture of compound **5** (1.0 g, 2.21 mmol), acetic acid (1 mL), and HNO_3 (65%, 0.35 mL, 4.8 mmol) in CH_2Cl_2 (100 mL) was vigorously stirred for 12 h at room temperature. After addition of CH_2Cl_2 (150 mL) to dissolve the precipitate formed, the solution was washed with a concentrated $NaHCO_3$ solution (2 × 50 mL). The organic layer was dried with $MgSO_4$ and evaporated to afford a yellow solid, which was further purified by flash chromatography (SiO_2; CH_2Cl_2–petroleum ether, 4:1) to give a white solid: yield 0.68 g (57%); mp >300 °C (CH_2Cl_2); ^1H NMR δ 8.87 (s, 2 H, OH), 8.06 (s, 4 H, ArH), 7.1–6.6 (m, 6 H, ArH), 4.31 and 3.52 (AB q, 8 H, J = 13.4 Hz, $ArCH_2Ar$); ^{13}C NMR δ 159.3 (s, Ar 25,27-C), 152.9 (s, Ar 26,28-C), 139.9 (s, Ar 11,23-C), 131.4, 128.2 (s, Ar 1,3,7,9,13,15,19,21-C), 129.7, 124.6 (d, Ar 4,6,10,12,16,18,22,24-C), 125.9 (d, Ar 5,17-C), 64.0 (q, OCH_3), 31.0 (t, $ArCH_2Ar$); mass spectrum, m/e 542.168 (M^+, calcd 542.169). Anal. Calcd for $C_{30}H_{26}N_2O_8$·0.75CH_2Cl_2: C, 60.92; H, 4.57; N, 4.62. Found: C, 61.31; H, 4.63; N, 4.38.

11,23-Bis[(dimethylamino)methyl]-26,28-dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (31). A mixture of compound **5** (0.5 g, 1.1 mmol), dimethylamine (40%, 2.5 g, 22 mmol), and formaline (37%, 1.8 g, 22 mmol) in dioxane (45 mL) was refluxed for 66 h. After evaporation of the solvent the mixture was taken up in $CHCl_3$ (150 mL), and the resulting solution was washed with water (2 × 25 mL) and brine (25 mL). The organic layer was dried with $MgSO_4$ and evaporated to yield a white solid, which was pure enough for synthetic purposes: yield 0.57 g (91%); mp >300 °C dec (EtOAc); ^1H NMR δ 7.69 (s, 2 H, OH), 6.99 (s, 4 H, ArH), 7.0–6.6 (m, 6 H, ArH), 4.30 and 3.38 (AB q, 8 H, J = 13.0 Hz, $ArCH_2Ar$), 3.98 (s, 6 H, OMe), 3.30 (s, 4 H, CH_2NMe_2), 2.22 (s, 12 H, NMe_2); ^{13}C NMR δ 64.0 (t, CH_2NMe_2), 45.3 (q, NMe_2); mass spectrum, m/e 566.314 (M^+, calcd 566.314). Anal. Calcd for $C_{36}H_{42}N_2O_4$·0.5EtOAc: C, 74.73; H, 7.59; N, 4.59. Found: C, 74.84; H, 7.50; N, 4.50.

26,28-Dimethoxy-11,23-bis(4-morpholinylmethyl)pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (32). A suspension of compound **5** (2.0 g, 4.4 mmol) in 4-(butoxymethyl)morpholine[35] (15 mL) was heated at 130 °C for 2 days. The mixture was poured into water (200 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried with $MgSO_4$. Evaporation of the solvent yielded a light brown solid, which was further purified by flash chromatography [Al_2O_3 neutral(II–III), CH_2Cl_2] to afford pure **32**: yield 2.12 g (74%); mp >300 °C dec (EtOAc); ^1H NMR δ 7.77 (s, 2 H, OH), 7.00 (s, 4 H, ArH), 7.0–6.6 (m, 6 H, ArH), 4.30 and 3.38 (AB q, 8 H, J = 13.1 Hz, $ArCH_2Ar$), 3.98 (s, 6 H, OMe), 3.8–3.6 (m, 4 H, OCH_2), 3.36 (s, 4 H, $ArCH_2N$), 2.6–2.4 (m, 4 H, NCH_2); ^{13}C NMR δ 67.0 (t, OCH_2), 63.1 (t, $ArCH_2N$), 53.6 (t, NCH_2); mass spectrum, m/e 650.339 (M^+, calcd 650.336). Anal. Calcd for $C_{40}H_{46}N_2O_6$·0.5EtOAc: C, 72.60; H, 7.25; N, 4.03. Found: C, 72.76; H, 6.87; N, 3.80.

[μ-[26,28-Dihydroxy-25,27-dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-5,17-diyl]]bis(trifluoroacetato-*O*)dimercury (33). A mixture of compound **5** (1.0 g, 2.21 mmol) and mercury trifluoroacetate (1.92 g, 4.5 mmol) in $CHCl_3$ (70 mL) was stirred overnight to afford a heterogeneous mixture. Evaporation of the solvent gave a white solid: yield 2.19 g (92%); mp >270 °C dec ($CHCl_3$); ^1H NMR δ 8.0 (s, 2 H, OH), 7.2–6.7 (m, 10 H, ArH), 4.22 and 3.42 (AB q, 8 H, J = 13.1 Hz, $ArCH_2Ar$), 3.84 (s, 6 H, OCH_3); mass spectrum (FAB), m/e 1080 (M^+). Anal. Calcd for $C_{34}H_{26}F_6Hg_2O_8$: C, 37.89; H, 2.41. Found: C, 37.93; H, 2.47.

11,23-Diiodo-26,28-dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-25,27-diol (34). A solution of compound **33** (1.08 g, 1.0 mmol) and I_2 (0.56 g, 2.2 mmol) in CH_3CN (100 mL) was stirred at room temperature for 1 h. Excess I_2 was removed by adding $Na_2S_2O_5$ (15% in H_2O, 30 mL). CH_2Cl_2 (100 mL) and brine (50 mL) were added to the mixture, and the organic layer was washed with water (2 × 50 mL), dried with $MgSO_4$, and evaporated to give a pale yellow solid: yield 0.49 g (70%); mp >300 °C dec (CH_3CN/CH_2Cl_2); ^1H NMR δ 7.8 (s, 2 H, OH), 7.37 (s, 4 H, ArH), 7.5–6.9 (m, 6 H, ArH), 4.22 and 3.31 (AB q, 8 H, J = 13.0 Hz, $ArCH_2Ar$), 3.94 (s, 6 H, OCH_3); mass spectrum, m/e (%) 703 (19), 577 (9), (9), 450 (15), 142 (100). Anal. Calcd for $C_{30}H_{26}I_2O_4$: C, 51.15; H, 3.72; I, 36.03. Found: C, 51.09; H, 3.75; I, 36.10.

25,27-Dimethoxypentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,6,9,11,13(27),15,18,21,23-decaene-5,17,26,28-tetrone (35). To a solution of $Tl(NO_3)_3$·3H_2O (5.0 g, 11.3 mmol) in a mixture of dry MeOH (120 mL) and dry EtOH (360 mL) was added a solution of compound **5** (1.0 g, 2.21 mmol) in $CHCl_3$ (100 mL). The mixture was stirred for 15 min and quenched with H_2O (50 mL), and then 10% HCl was added dropwise until complete dissolution of the precipitate. After addition of $CHCl_3$ (100 mL), the organic layer was separated, dried with Na_2SO_4, and evaporated. Purification by preparative chromatography (SiO_2, $CHCl_3$) gave pure **35**: yield 0.80 g (75%); mp 242–245 °C dec (CH_3CN); ^1H NMR δ 7.2 (m, 4 H, ArH), 6.9 (m, 2 H, ArH), 6.29 (s, 4 H, C=C*H*C=O), 3.70 (br s, 4 H, $ArCH_2Ar$), 3.38 (br s, 4 H, $ArCH_2Ar$), 3.12 (s, 6 H, OCH_3); ^{13}C NMR δ 167.9, 165.7 (s, 5,17,26,28-C), 157.5 (s, Ar 25,27-C), 147.5 (s, 1,3,7,9,13,15,19,21-C), 132.3, 131.1, 124.2 (d, 4,6,10,12,16,18,22,24-C), 59.1 (q, OCH_3), 31.5 (t, $ArCH_2Ar$); IR (KBr) 1685 cm^{-1} (C=O); mass spectrum, m/e (%) 480 (26), 449 (100). Anal. Calcd for $C_{30}H_{24}O_6$: C, 74.99; H, 5.03. Found: C, 75.08; H, 5.07.

X-ray Crystallography of Compound 13. The crystal structure of **13** was determined by X-ray diffraction. Crystal data: $C_{50}H_{52}O_4$, monoclinic, space group $P2_1/c$; a = 19.988 (4) Å, b = 10.795 (2) Å, c = 22.515 (11) Å, β = 115.57 (2)°; V = 4382 (3) Å^3; Z = 4; d_{calc} = 1.30 g cm^{-3}, μ = 0.84 cm^{-1}. Reflections were measured in the $\omega/2\theta$ scan mode, using graphite monochromated Mo Kα radiation [scan width (ω) 1.00 + 0.34 tan θ]. The structure was solved by direct methods and refined with full-matrix least-squares methods. A total of 3251 reflections with $F_o^2 > 3\sigma(F_o^2)$ was used in the refinement. The number of parameters refined was 488 [scale factor, extinction parameter, positional parameters and anisotropic thermal parameters for the non-hydrogen atoms]. Hydrogen atoms were put in calculated positions and were treated as riding atoms in the refinements. The positions of the phenolic hydrogens could not be calculated. Attempts to locate these atoms in a difference Fourier synthesis failed, so these hydrogen atoms were not included in the refinement. In the final difference Fourier syntheses the largest peaks were between the molecules, presumably caused by disordered molecules. The final R factors were R = 7.0%, R_w = 6.9%. All calculations were done with SDP.[39]

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(39) Structure Determination Package; B. A. Frenz and Associates Inc., College Station, TX, and Enraf-Nonius, Delft, 1983.

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Supplementary Material Available: Tables of positional and thermal parameters and bond distances and angles (8 pages). Ordering information is given on any current masthead page.

The *N*-Acyl-α-cyano-1-azadienes. Remarkably Reactive Heterodienes in the Diels–Alder Reaction[1]

Min Teng and Frank W. Fowler*

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794

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A method for the prepartion of the *N*-acyl-α-cyano-1-azadienes has been developed and their Diels–Alder reactions have been studied. The intramolecular Diels–Alder reaction of these dienes with unactivated dienophiles occurs readily with a high preference for the exo (anti) reaction pathway. The *N*-acyl-α-cyano-1-azadienes are relatively stable allowing for their isolation and an investigation of their intermolecular Diels–Alder reactions. The azadiene **6** reacted with a range of dienophiles such as, ethyl vinyl ether, styrene, 1-hexene, and methyl acrylate. The reaction of **6** with *cis*- and *trans*-1-phenylpropene gave different products which was not consistent with a two-step reaction involving a common intermediate. The reactivity, regiochemistry, and stereochemistry of these reactions is interpreted in terms of a concerted mechanism with a transition state possessing a high degree of diradical character.

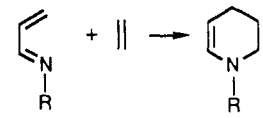
Introduction

A six-membered ring containing a nitrogen atom is a common structural feature in compounds of interest to synthetic chemists. Because of the efficiency of the Diels–Alder reaction for the preparation of six-membered rings with control of stereochemistry, much effort has been devoted to the development of aza analogues of this reaction for the preparation of nitrogen heterocycles.[2] The 1-azadienes are particularly attractive substrates for the hetero Diels–Alder reaction because, in addition to the normal advantages of the Diels–Alder reaction, they produce synthetically useful endocyclic enamine derivatives.

There are two problems that must be addressed in the development of 1-azadienes as reactants in the Diels–Alder reaction: (1) The reaction is less thermodynamically favorable than the all carbon dienes.[3] (2) The conditions necessary to induce the Diels–Alder reaction result in decomposition of the relatively sensitive endocyclic enamine functionality.[4]

There have been various creative solutions to overcome these difficulties for the development of a synthetically useful Diels–Alder reaction of 1-azadienes.[2] An early approach is the use of the *o*-quinone methide imine ring system.[5] Although restricted to the synthesis of quinoline derivatives, this reaction has been successfully incorporated into a scheme for the total synthesis of gephyrotoxin.[6] Other approaches to this problem have used activating substituents on the imine bond of these azadienes. These include the use of both electron-donating[7] or electron-withdrawing groups[8] on the nitrogen and electron-withdrawing groups on the carbon atom of the imine.[9] Among these approaches, the *N*-sulfonyl-1-azadienes have shown promise as reactive dienes in the Diels–Alder reaction.[8a]

Scheme I



We have previously observed that *N*-acyl-1-azadienes, generated as transient intermediates from *O*-acylhydroxamic acid derivatives under flash vacuum thermolysis conditions, will participate in the intramolecular version of the Diels–Alder reaction.[10] The utility of this approach was demonstrated by an efficient total synthesis of (−)-deoxynupharidine.[11]

(1) For a preliminary account of this work, see: Teng, M.; Fowler, F. W. *Tetrahedron Lett.* **1989**, *30*, 2481.

(2) *Hetero Diels-Alder Methodology in Organic Synthesis*; Boger, D. L., Weinreb, S. M., Eds.; Academic Press: San Diego, 1987.

(3) The primary reason that Diels–Alder reactions of 1-azadienes are less thermodynamically favorable than the all carbon dienes is because of the relative weakness of the carbon–nitrogen single bond in the product. The σ-bond strengths for ethane and methylamine are 85.8 and 84.8 kcal/mol, respectively,[3l] whereas the π-bond strengths for ethylene and methylene imine have been calculated to be 59.4 and 74.3 kcal/mol, respectively. (Shaw, R. In *The Chemistry of Double Bonded Functional Groups*; Patai, S., Ed.; Wiley, New York, 1977; p 131.)

(4) Six-membered endocyclic enamine derivatives without substituents on the double bond are notoriously unstable. For example, attempts to prepare the simple *N*-methyl-Δ^2-piperidine usually result in formation of the dimer. (a) Martinez, S. J.; Joule, J. A. *Tetrahedron* **1978**, *34*, 3027. (b) Beeken, P.; Fowler, F. W. *J. Org. Chem.* **1980**, *45*, 1336.

(5) Burgess, E. M.;; McCullagh, L. *J. Am. Chem. Soc.* **1966**, *88*, 1580. With this example the problem of the thermodynamics of the reaction and the instability of the product are solved by the enamine double bond being part of an aromatic ring.

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