Chemical Society, for support of this research. Acknowledgment is due to the Johnson-Matthey Precious Metal Loan Program for donations of palladium chloride and to the National Science Foundation (CHE-8905465) for partial funding of the purchase of the 300-MHz NMR spectrometer used in this research. W.A.D. thanks the Alexander von Humboldt Foundation for a Research Fellowship (1990–91) during which time portions of this manuscript were prepared.

Ipso Nitration of *p*-*tert*-Butylcalix[4]arenes

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Received July 8, 1991

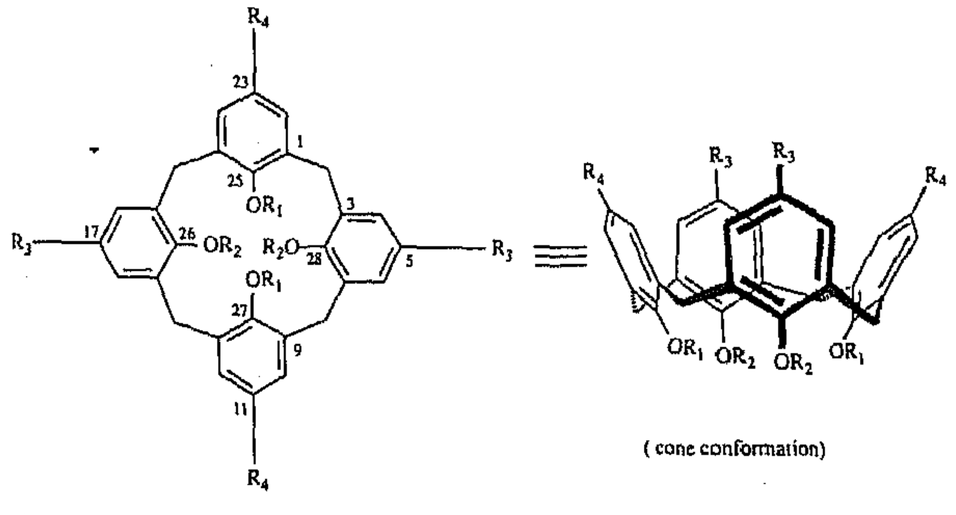
Functionalized calixarenes represent an important class of compounds that can complex cations and neutral molecules.[1,2] Calix[4]arenes can easily be functionalized both at the phenolic OH groups (lower rim) and, after (partial) removal of *tert*-butyl groups, at the para positions of the phenol rings (upper rim). Several methods have been reported for the (selective) introduction of nitro groups at the upper rim viz. direct nitration of free para positions[3,4] and replacement of *p*-sulfonate moieties.[5] Calix[4]arenes having one or two nitro groups at the upper rim have also been prepared by a stepwise synthesis.[6,7] In this paper we describe the (selective) introduction of one or more nitro groups by direct replacement of (a) *tert*-butyl group(s) via an ipso aromatic nitration.[8] After reduction these compounds are important starting materials for molecular receptors based on calixarenes.

Results and Discussion

Reaction of conformationally flexible 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene (**1**) with an excess (20 equiv) of 100% HNO_3 in a 1:1 mixture of dichloromethane and acetic acid for 2 h gave upon crystallization of the crude reaction mixture from ethanol the tetra-ipso-nitrated calix[4]arene **2** in 75% yield. According to the ^1H NMR spectrum, **2** exists as a 93:7 mixture of the partial cone and cone conformation with for the former characteristic absorptions for the methylene bridge protons at δ 4.11 and 3.45 (AB q) and 3.84 (s) and the typical singlet of one of the methoxy groups at δ 3.05. Shinkai et al.[9] described **2** as a complex mixture of conformational isomers (not further assigned) upon methylation of *p*-tetranitrocalix[4]arene. We have also reacted the other tetraalkylated calix[4]arenes **3**, **5**, and **7** (all in the cone conformation)[10] to give the tetranitrocalix[4]arenes **4**, **6**, and **8** (cone conformation) in yields of 67%, 76%, and 37%, respectively. Ipso nitration of the parent calix[4]arene **9** under the above-mentioned conditions failed probably due to the low solubility of the substrate.

Subsequently we studied the behavior of the *diametrically* dialkylated calix[4]arenes **10** and **12**. Treatment of **10** and **12** with about 5 equiv of 100% HNO_3 for only 5–10 min afforded selectively the 11,23-dinitrocalix[4]arenes **11** and **13** in 46% and 24% yield, respectively. Comparison of the NMR data of **11** and **13** with those of the starting compounds **10** and **12** and of the tetranitro compound **14** (vide infra) indicated that the ipso nitration had taken place exclusively at the para position of the phenolic units. Very characteristic in the ^1H NMR spectra is for instance the absorption of the OH group that shifts downfield from δ 7.91 (**10**) and δ 7.22 (**12**) to δ 9.50 and δ 8.99 in the "4-nitrophenol" derivatives **11** and **13**, respectively; in the corresponding tetranitro compound **14** the

Chart I

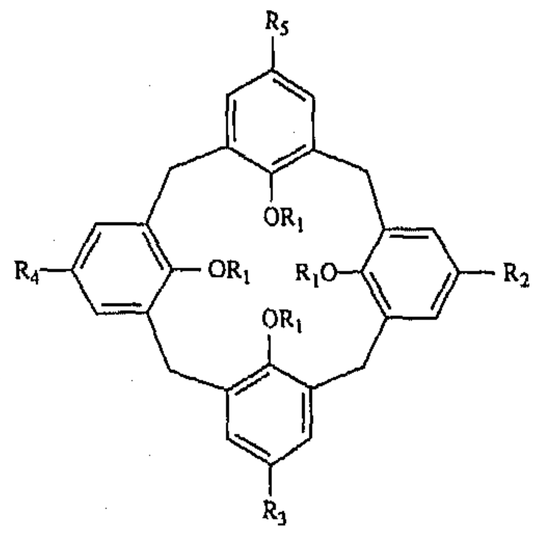


1 $R_1=R_2=Me$ $R_3=R_4=t\text{-}Bu$
2 $R_1=R_2=Me$ $R_3=R_4=NO_2$
3 $R_1=R_2=Pr$ $R_3=R_4=t\text{-}Bu$
4 $R_1=R_2=Pr$ $R_3=R_4=NO_2$
5 $R_1=R_2=CH_2CH_2OEt$ $R_3=R_4=t\text{-}Bu$
6 $R_1=R_2=CH_2CH_2OEt$ $R_3=R_4=NO_2$
7 $R_1=R_2=CH_2C(O)OEt$ $R_3=R_4=t\text{-}Bu$
8 $R_1=R_2=CH_2C(O)OEt$ $R_3=R_4=NO_2$
9 $R_1=R_2=H$ $R_3=R_4=t\text{-}Bu$

10 $R_1=H$, $R_2=Pr$ $R_3=R_4=t\text{-}Bu$
11 $R_1=H$, $R_2=Pr$, $R_3=t\text{-}Bu$, $R_4=NO_2$
12 $R_1=H$, $R_2=CH_2C(O)OEt$ $R_3=R_4=t\text{-}Bu$
13 $R_1=H$, $R_2=CH_2C(O)OEt$, $R_3=t\text{-}Bu$, $R_4=NO_2$
14 $R_1=H$, $R_2=Pr$, $R_3=R_4=NO_2$
15 $R_1=H$, $R_2=CH_2C(O)OEt$, $R_3=R_4=NO_2$

20 $R_1=H$, $R_2=Me$, $R_3=t\text{-}Bu$, $R_4=H$
21 $R_1=R_2=H$, $R_3=t\text{-}Bu$, $R_4=H$
22 $R_1=R_2=CH_2CH_2OEt$, $R_3=t\text{-}Bu$, $R_4=H$
23 $R_1=R_2=CH_2CH_2OEt$, $R_3=NO_2$, $R_4=H$

Chart II



16 $R_1=Pr$, $R_2=R_3=t\text{-}Bu$, $R_4=R_5=NO_2$
17 $R_1=Pr$, $R_2=R_4=t\text{-}Bu$, $R_3=R_5=NO_2$
18 $R_1=Pr$, $R_2=t\text{-}Bu$, $R_3=R_4=R_5=NO_2$
19 $R_1=CH_2CH_2OEt$, $R_2=R_3=R_4=t\text{-}Bu$, $R_5=NO_2$

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(10) The tetrapropoxycalix[4]arene **3** could be obtained exclusively in the cone conformation in 66% yield by reaction of calix[4]arene **9** with 1-iodopropane in NaH/DMF at 75 °C for 18 h. Using somewhat other reaction conditions, Shinkai et al.[11] found a mixture of cone and partial cone conformations of which the latter is the major isomer. For a general study in which the possible factors are discussed that determine the ultimate conformation of tetra-O-alkylated calix[4]arenes, see ref 12.
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0022-3263/92/1957-1313$03.00/0

OH is located at δ 8.85. Previously,[4] we have demonstrated that the para positions of phenol rings are much more reactive than those of alkoxybenzene rings as was for instance illustrated in the selective de-*tert*-butylation. Tetra-ipso-nitration of **10** could be achieved by treatment with excess of 100% HNO_3 for 1 h to give compound **14** in a yield of 64%.[13]

In the cases of **10** and **12** two nitro groups could be selectively introduced at the upper rim (vide supra) due to the two pairs of different functional groups (OR vs OH) of the lower rim. However, by slightly modifying the nitration conditions it appeared even possible to partly ipso nitrate the upper rim of tetra-O-alkylated calix[4]arenes. Firstly, reaction of tetrapropoxycalix[4]arene **3** with 50 equiv of 65% HNO_3 in a 17:1 mixture of dichloromethane and acetic acid for 2 d afforded, after trituration of the crude reaction mixture with methanol, a mixture of the 17,23-dinitro- (**16**), 11,23-dinitro- (**17**), and 11,17,23-trinitrocalix[4]arene (**18**), in a ratio of 3:2.2:1 in a total yield of 64% (Chart II). Analytically pure samples of these compounds could be obtained after preparative TLC. The two dinitrocalix[4]arenes were distinguished on account of their ^{1}H NMR spectra. The spectrum of the proximally substituted compound **16** exhibits four signals for the aromatic hydrogen atoms at δ 7.72 and 7.63 [d, ArC-(NO_2)CH] and δ 6.73 and 6.63 (d) and in addition three AB systems for the methylene bridge hydrogens at δ 4.47 and 3.26 (4 H, J = 13.1 Hz) and δ 4.52, 4.41 and 3.31, 3.17 (J = 12.9 and 13.0 Hz). The ^{1}H NMR spectrum of the diametrically substituted compound **17** shows a symmetrical structure with only two signals for the aromatic hydrogen atoms at δ 7.17 and 6.97 and one AB system at δ 4.45 and 3.18 (J = 13.5 Hz). Nitration of **3** using about 200 equiv of 65% HNO_3 for 2.5 d gave exclusively the *tri*nitrocalix[4]arene **18** in 58% yield. Secondly, treatment of tetrakis(ethoxyethoxy)calix[4]arene **5** with 50 equiv of 65% HNO_3 for 18 h gave the *mono*nitrocalix[4]arene **19** in 73% yield. We have also treated tetrakis((ethoxycarbonyl)methoxy)calix[4]arene (**7**) with 65% HNO_3. However, under this condition a calix[4]arene in which selectively one ester moiety had been hydrolyzed was identified, probably due to the presence of water in the 65% HNO_3. Prolonged reaction times gave rise to a very complicated reaction mixture in which no ipso nitrated compound could be detected. Böhmer et al.[14] reported the formation of the same monoacid triester upon treatment of **5** with trifluoroacetic acid.

Finally, we have investigated the nitration of 5,17-di-*tert*-butyl-25,26,27,28-tetrakis(ethoxyethoxy)calix[4]arene (**22**) in which in principle both a normal electrophilic aromatic substitution and an ipso nitration are possible. Compound **22** was prepared by demethylation of 5,17-di-*tert*-butyl-26,28-dimethoxycalix[4]arene (**20**)[15] with boron tribromide in dichloromethane to give calix[4]arene **21** in 94% yield which was subsequently treated with 5 equiv of bromoethyl ethyl ether in NaH/DMF for 6 h at 80 °C to afford **22** exclusively in the cone conformation in 89% yield. Treatment of **22** with 50 equiv of 65% HNO_3 in a 17:1 mixture of dichloromethane and acetic acid for 16 h at room temperature afforded the ipso nitrated 5,17-dinitrocalix[4]arene **23** in 78% yield. In the ^{1}H NMR spectrum of **23** the original *tert*-butyl signals are absent; the presence of two nitro groups is indicated by the low field position of four aromatic hydrogen atoms at δ 7.66. Apparently the ipso nitration is much faster than the classical nitration. This is precedented in the ipso nitration of 2,4,6-tri-*tert*-butylaniline[16] which has been explained in addition to steric reasons by the activation of the concerning *tert*-butyl group by the electron-releasing amino group.[17]

Although the replacement of a *tert*-butyl group by a nitro group has frequently been described in the literature,[8] generally the yields are mostly modest. Only in activated compounds are better yields obtained. The presence of electron-donating groups at the lower rim (OH, OR) makes calix[4]arenes excellent substrates for ipso nitration which has been demonstrated for the first time in this paper. In conclusion we can state that by carefully selecting the reaction conditions the ipso nitration of (partly) O-alkylated *p-tert*-butylcalix[4]arenes represents a fast and useful method for the preparation of mono-, two isomeric di-, tri-, and tetranitrocalix[4]arenes in only one step.

Experimental Section

Melting points are uncorrected. ^{1}H *and* ^{13}C NMR *spectra were recorded in* $CDCl_3$ *with* Me_4Si *as an internal standard. Positive ion fast atom bombardment (FAB) mass spectra were obtained with* *m*-nitrobenzyl alcohol *as a matrix. The calix[4]arenes* **1**,[20] **5**,[21] **7**,[14] **9**,[22] **10**,[23] **12**,[24] *and* **20**[4] *were prepared according to literature procedures.* CH_2Cl_2 *was distilled from* CaH_2 *and stored over molecular sieves. Petroleum ether refers to the fraction with bp 40–60 °C. Silica gel (particle size 0.040–0.063 mm, 230–240 mesh) was obtained from Merck. All commercially available chemicals were obtained from Janssen.*

In the workup procedures the organic layers were dried with $MgSO_4$ *whereupon the solvent was removed under reduced pressure. The presence of* CH_2Cl_2 *in the analytical samples was confirmed by* ^{1}H NMR *spectroscopy.*

General Procedure for the Preparation of the Tetranitrocalix[4]arenes 2, 4, 6, and 8. To a solution of calix[4]arenes **1**, **3**, **5**, and **7** (3.00 mmol) in a mixture of CH_2Cl_2 (30 mL) and glacial acetic acid (30 mL) was added 100% HNO_3 (10 mL, ~240 mmol) at 0 °C. The reaction mixture was stirred at room temperature until the black purple color had discharged and was subsequently poured into water (200 mL). The water layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with water (2 × 30 mL). Recrystallization of the

(13) Under these conditions **12** gave rise to a very complicated reaction mixture from which the tetranitro compound **15** could not be isolated.

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(15) This way was chosen because selective de-*tert*-butylation[4] of 5,11,17,23-tetra-*tert*-butyl-26,28-bis(ethoxyethoxy)-25,27-dihydroxycalix[4]arene with 2 equiv of $AlCl_3$ in toluene at room temperature could only be achieved in moderate yield.

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(18) A somewhat related reaction has recently been described by Biali et al.[19] who treated a partly dehydroxylated *p-tert*-butylcalix[4]arene with NO_2BF_4. In this case the *tert*-butyl groups of the two phenol rings are removed under the conditions used, whereupon a fast oxidation gives a diquinone calix[4]arene.

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(24) Collins, E. M.; McKervey, M. A.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 372.

(25) For reasons of simplicity and in order to reduce space in this paper the Gutsche convention[26] is followed using 25,26,27,28-tetrahydroxycalix[4]arene instead of the official Chemical Abstracts 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-25,26,27,28-tetrol.

(26) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782.

crude reaction products gave the pure compounds.

25,26,27,28-Tetramethoxy-5,11,17,23-tetranitrocalix[4]arene (2):[9] reaction time 2 h; yield 75% (partial cone/cone 93/7); mp >300 °C (EtOH); ^{1}H NMR (partial cone) δ 8.24, 8.14 (s, 2 H, ArH), 7.87, 7.28 (d, 2 H, J = 2.7 Hz, ArH), 4.11 and 3.45 (AB q, 4 H, J = 14.0 Hz, ArCH_2Ar), 3.92 (s, 3 H, OCH_3), 3.84 (s, 10 H, 2 OCH_3, ArCH_2Ar), 3.05 (s, 3 H, OCH_3).

5,11,17,23-Tetranitro-25,26,27,28-tetrapropoxycalix[4]arene (4): reaction time 2 h; yield 67%; mp >300 °C (CH_2Cl_2/MeOH); ^{1}H NMR δ 7.58 (s, 8 H, ArH), 4.53 and 3.41 (AB q, 8 H, J = 14.1 Hz, ArCH_2Ar), 3.96 (t, 8 H, J = 7.4 Hz, ArOCH_2), 1.02 (t, 12 H, J = 7.4 Hz, CH_3); ^{13}C NMR δ 161.6 (ArC-O), 142.6 (s, ArC-NO_2), 123.8 (d, ArC-H), 77.6 (t, ArOCH_2), 30.9 (t, ArCH_2Ar); FAB mass spectrum, m/e 773.1 [$(M + H)^+$, calcd 773.3]. Anal. Calcd for $C_{40}H_{44}N_4O_{12}$·0.66CH_2Cl_2: C, 58.89; H, 5.51; N, 6.76. Found: C, 58.44; H, 5.90; N, 6.68.

25,26,27,28-Tetrakis(ethoxyethoxy)-5,11,17,23-tetranitrocalix[4]arene (6): reaction time 1 h; yield 76%; mp 174–176 °C (MeOH); ^{1}H NMR δ 7.59 (s, 8 H, ArH), 4.68 and 3.37 (AB q, 8 H, J = 14.1 Hz, ArCH_2Ar), 4.24 (t, 8 H, J = 4.6 Hz, ArOCH_2), 3.78 (t, 8 H, J = 4.6 Hz, ArOCH_2CH_2), 3.50 (q, 8 H, J = 7.0 Hz, OCH_2CH_3), 1.17 (t, 12 H, J = 7.0 Hz, OCH_2CH_3); ^{13}C NMR δ 161.5 (s, ArC-O), 142.7 (s, ArC-NO_2), 123.7 (d, ArC-H), 74.2 (t, ArOCH_2), 69.3, 66.3 (t, OCH_2), 30.8 (t, ArCH_2Ar); mass spectrum, m/e 892.337 (M^+, calcd 892.337). Anal. Calcd for $C_{44}H_{52}N_4O_{16}$: C, 59.18; H, 5.87; N, 6.27. Found: C, 58.99; H, 6.18; N, 6.23.

2,2′,2″,2‴-[[5,11,17,23-Tetranitrocalix[4]arene-25,26,27,28-tetrayl]tetrakis(oxy)]tetrakis(acetic acid), tetraethyl ester (8): reaction time 40 min; yield 37%; mp 218–221 °C (CH_2Cl_2/petroleum ether); ^{1}H NMR δ 7.61 (s, 8 H, all ArH), 5.06 and 3.49 (AB q, 8 H, J = 14.2 Hz, ArCH_2Ar), 4.78 (s, 8 H, Ar-OCH_2), 4.24 (q, 8 H, J = 7.1 Hz, OCH_2CH_3), 1.31 (t, 12 H, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR δ 168.7 (s, C=O), 160.6 (s, Ar 25,26,27,28-C), 143.2 (s, Ar 5,11,17,23-C), 124.1 (d, all ArC-H), 71.4 (t, ArOCH_2), 61.1 (t, OCH_2), 31.4 (t, ArCH_2Ar), 14.0 (q, CH_3); mass spectrum, m/e 948.259 (M^+, calcd 948.255). Anal. Calcd for $C_{44}H_{44}N_4O_{20}$·H_2O: C, 59.66; H, 4.80; N, 5.79. Found: C, 59.53; H, 4.53; N, 5.93. Karl-Fischer calcd for 1 H_2O 1.86, found 1.84.

General Procedure for the Nitration of the Diametrically Dialkylated Calix[4]arenes 10 and 12. Formation of 11, 13, and 14. To a solution of calix[4]arenes 10 and 12 (3.5 mmol) in a mixture of CH_2Cl_2 (25 mL) and glacial acetic acid (25 mL) was added 100% HNO_3 [1.5 mL, 36 mmol (formation of 11, 13) or 15 mL, 360 mmol (formation of 14)] at −10 °C, whereupon the reaction mixture was stirred at room temperature. The workup was identical to that of the calix[4]arenes 2, 4, 6, and 8 (vide supra).

5,17-Bis(1,1-dimethylethyl)-25,27-dihydroxy-11,23-dinitro-26,28-dipropoxycalix[4]arene (11): reaction time 10 min; yield 46%; mp >300 °C (CH_2Cl_2/petroleum ether); ^{1}H NMR δ 9.50 (s, 2 H, OH), 8.04 [s, 4 H, ArC(NO_2)CH], 6.97 (s, 4 H, ArH), 4.29 and 3.48 (AB q, 8 H, J = 13.2 Hz, ArCH_2Ar), 4.00 (t, 4 H, J = 6.4 Hz, OCH_2), 1.07 [s, 18 H, $C(CH_3)_3$]; ^{13}C NMR δ 159.5 (s, Ar 25,27-C), 149.4, 148.4 (s, Ar 5,17,26,28-C), 139.6 (s, Ar 11,23-C), 126.1, 124.2 (d, Ar 4,6,10,12,16,18,22,24-C), 78.5 (t, ArOCH_2), 34.1 [s, $C(CH_3)_3$], 31.4 (t, ArCH_2Ar), 31.0 [q, $C(CH_3)_3$]; mass spectrum, m/e 710.353 (M^+, calcd 710.357). Anal. Calcd for $C_{42}H_{50}N_2O_8$·0.5H_2O: C, 70.07; H, 7.14; N, 3.89. Found: C, 69.86; H, 7.05; N, 3.93. Karl-Fischer calcd for 0.5 H_2O 1.25, found 1.22.

2,2′-[[5,17-Bis(1,1-dimethylethyl)-25,27-dihydroxy-11,23-dinitrocalix[4]arene-26,28-diyl]bis(oxy)]bis(acetic acid), diethyl ester (13): reaction time 5 min; yield 24%; mp 198–200 °C ($CHCl_3$/petroleum ether); ^{1}H NMR δ 8.99 (s, 2 H, OH), 7.99 [s, 4 H, ArC(NO_2)CH], 7.03 (s, 4 H, ArH), 4.80 (s, 4 H, OCH_2CO_2), 4.49 and 3.49 (AB q, 8 H, J = 13.3 Hz, ArCH_2Ar), 4.36 (q, 4 H, J = 7.2 Hz, OCH_2), 1.37 (t, 6 H, J = 7.2 Hz, CH_3), 1.12 [s, 18 H, $C(CH_3)_3$]; ^{13}C NMR δ 169.1 (s, C=O), 158.7 (s, Ar 25,27-C), 150.2, 148.9 (s, Ar 5,17,26,28-C), 139.9 (s, Ar 11,23-C), 126.4, 124.3 (d, Ar 4,6,10,12,16,18,22,24-C), 71.9 (t, ArOCH_2), 61.5 (t, OCH_2), 34.3 [s, $C(CH_3)_3$], 31.5 (t, ArCH_2Ar), 31.0 [q, $C(CH_3)_3$], 14.0 (q, CH_3); mass spectrum, m/e 798.337 (M^+, calcd 798.336). Anal. Calcd for $C_{44}H_{50}N_2O_{12}$: C, 66.15; H, 6.31; N, 3.51. Found: C, 65.90; H, 6.34; N, 3.27.

25,27-Dihydroxy-5,11,17,23-tetranitro-26,28-dipropoxycalix[4]arene (14): reaction time 1 h; yield 64%; mp >300 °C (CH_2Cl_2/petroleum ether); ^{1}H NMR δ 8.85 (s, 2 H, OH), 8.16 (s, 4 H, Ar 10,12,22,24-H), 7.86 (s, 4 H, Ar 4,6,16,18-H), 4.35 and 3.66 (AB q, 8 H, J = 13.6 Hz, ArCH_2Ar), 4.10 (t, 4 H, J = 6.2 Hz, ArOCH_2), 1.34 (t, 6 H, J = 7.4 Hz, CH_2CH_3); ^{13}C NMR δ 158.8, 156.6 (s, Ar 25,26,27,28-C), 144.2, 140.0 (s, Ar 5,11,17,23-C), 125.4 (d, all ArC-H), 79.4 (t, ArOCH_2), 31.1 (t, ArCH_2Ar), 23.2 (t, OCH_2CH_2), 10.5 (q, CH_2CH_3); mass spectrum, m/e 688.203 (M^+, calcd 688.202). Anal. Calcd for $C_{34}H_{32}N_4O_{12}$·0.66CH_2Cl_2: C, 55.90; H, 4.51; N, 7.52. Found: C, 56.13; H, 4.61; N, 7.66.

General Procedure for the Nitration of Calix[4]arenes 3, 5, and 22. Formation of 16, 17, 18, 19, and 23. To a solution of calix[4]arenes 3, 5, and 22 (0.75 mmol) in a mixture of CH_2Cl_2 (25 mL) and glacial acetic acid (1.5 mL) was added 65% HNO_3 (2.5 mL) at room temperature. The reaction was monitored with TLC. The workup was identical to that of the calix[4]arenes 2, 4, 6, and 8 (vide supra). Nitration of 3 for 2 d afforded a crude mixture which upon trituration with methanol gave a mixture of 16, 17, and 18 in a ratio of 3:2.2:1, respectively, in a total yield of 64%. Analytically pure samples were obtained after preparative TLC (SiO_2, CH_2Cl_2).

5,11-Bis(1,1-dimethylethyl)-17,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (16): mp 259–261 °C (CH_2Cl_2/MeOH); ^{1}H NMR δ 7.72, 7.63 (d, 2 H, J = 2.7 Hz, Ar 16,18,22,24-H), 6.73, 6.63 (d, 2 H, J = 2.3 Hz, Ar 4,6,10,12-H), 4.52, 4.47, 4.41 and 3.31, 3.26, 3.17 (3 AB q, together 8 H, J = 12.9, 13.1, and 13.0 Hz, ArCH_2Ar), 4.15–3.75 (m, 8 H, OCH_2), 1.01 [s, 18 H, $C(CH_3)_3$]; ^{13}C NMR δ 161.8, 153.5, 145.2, 142.3 (s, Ar 5,11,17,23,25,26,27,28-C), 77.3, 76.9 (t, OCH_2), 33.6 [s, $C(CH_3)_3$], 31.0 [q, $C(CH_3)_3$], 31.0, 30.9 (t, ArCH_2Ar); FAB mass spectrum, m/e 794.6 (M^+, calcd 794.4). Anal. Calcd for $C_{48}H_{62}N_2O_8$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.39; H, 8.04; N, 3.33.

5,17-Bis(1,1-dimethylethyl)-11,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (17): mp 277–280 °C dec (CH_2Cl_2/MeOH); ^{1}H NMR δ 7.17 [s, 4 H, ArC(NO_2)CH], 6.97 (s, 4 H, Ar H), 4.45 and 3.18 (AB q, 8 H, J = 13.5 Hz, ArCH_2Ar), 3.74 (t, 8 H, J = 6.7 Hz, ArOCH_2), 1.39 [s, 18 H, $C(CH_3)_3$]; ^{13}C NMR δ 160.1, 154.5, 145.9, 142.4 (s, Ar 5,11,17,23,25,26,27,28-C), 77.1, 77.0 (t, OCH_2), 34.1 [s, $C(CH_3)_3$], 31.4 [q, $C(CH_3)_3$], 31.1 (t, ArCH_2Ar); FAB mass spectrum, m/e 795.7 [$(M + H)^+$, calcd 795.4]. Anal. Calcd for $C_{48}H_{62}N_2O_8$·0.25CH_2Cl_2: C, 71.00; H, 7.72; N, 3.43. Found: C, 70.88; H, 7.36; N, 3.15.

5-(1,1-Dimethylethyl)-11,17,23-trinitro-25,26,27,28-tetrapropoxycalix[4]arene (18): mp 287–290 °C dec (MeOH); ^{1}H NMR δ 7.74 (s, 2 H, Ar 16,18-H), 7.52, 7.46 (d, 4 H, J = 2.7 Hz, Ar 10,12,22,24-H), 6.75 (s, 2 H, Ar 4,6-H), 4.53, 4.47 and 3.36, 3.28 (2 AB q, 8 H, J = 13.9 and 13.6 Hz, ArCH_2Ar), 4.1–3.8 (m, 8 H, OCH_2), 2.05–1.85 (m, 8 H, OCH_2CH_2), 1.1–0.9 [m, 21 H, CH_3 and $C(CH_3)_3$]; ^{13}C NMR δ 161.8, 161.3 (s, Ar 25,26,27-C), 153.7 (s, Ar 28-C), 146.1, 142.6, 142.4 (s, Ar 5,11,17,23-C), 77.2, 77.0 (t, Ar-OCH_2), 33.7 [s, $C(CH_3)_3$], 31.0 [q, $C(CH_3)_3$], 31.1, 30.9 (t, ArCH_2Ar); FAB mass spectrum, m/e 783.6 (M^+, calcd 783.4). Anal. Calcd for $C_{44}H_{53}N_3O_{10}$: C, 67.41; H, 6.81; N, 5.36. Found: C, 67.72; H, 7.06; N, 5.31.

Compound 18 could also be obtained in 58% yield upon nitration of 3 with 65% HNO_3 (10 mL) for 2.5 d.

5,11,17-Tris(1,1-dimethylethyl)-25,26,27,28-tetrakis(ethoxyethoxy)-23-nitrocalix[4]arene (19): reaction time 18 h; purification with column chromatography (SiO_2, CH_2Cl_2); yield 73%; mp 124–126 °C (MeOH); ^{1}H NMR δ 7.20 [s, 2 H, ArC(NO_2)CH], 7.02, 6.99 (d, 2 H, J = 2.3 Hz, ArH), 6.17 (s, 2 H, ArH), 4.45, 4.45 and 3.07, 3.03 (2 AB q, 8 H, J = 13.0 and 13.2 Hz, ArCH_2Ar), 1.25 [s, 18 H, $C(CH_3)_3$], 0.56 [s, 9 H, $C(CH_3)_3$]; ^{13}C NMR δ 160.2, 154.4, 152.0, 145.4, 144.6, 142.5 (s, Ar 5,11,17,23,25,26,27,28-C), 30.8 (t, ArCH_2Ar); FAB mass spectrum, m/e 925.7 (M^+, calcd 925.6). Anal. Calcd for $C_{56}H_{70}NO_{10}$: C, 72.26; H, 8.70; N, 1.53. Found: C, 72.49; H, 8.56; N, 1.33.

25,26,27,28-Tetrakis(ethoxyethoxy)-5,17-dinitrocalix[4]arene (23): reaction time 16 h; purification with column chromatography (SiO_2, CH_2Cl_2–EtOAc, 95:5); yield 78%; mp 152–154 °C (MeOH); ^{1}H NMR δ 7.66 [s, 4 H, ArC(NO_2)CH], 6.55 (br s, 6 H, ArH), 4.58 and 3.26 (AB q, 8 H, J = 13.7 Hz, ArCH_2Ar), 4.30 [t, 4 H, J = 5.0 Hz, Ar(NO_2)OCH_2], 4.07 (t, 4 H, J = 5.1 Hz, ArOCH_2); ^{13}C NMR δ 162.4 (s, Ar 26,28-C), 155.4 (s, Ar 25,27-C), 142.3 (s, Ar 5,17-C), 128.4, 123.5, 123.0 (d, Ar 4,6,10,11,12,16,18,22,23,24-C), 30.7 (t, ArCH_2Ar); FAB mass spectrum, m/e 803.7 [$(M + H)^+$, calcd 803.4]. Anal. Calcd for $C_{44}H_{54}N_2O_{12}$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.67; H, 7.11; N, 3.37.

5,17-Bis(1,1-dimethylethyl)-25,26,27,28-tetrahydroxycalix[4]arene (21). To a solution of boron tribromide (7.0 g, 28 mmol) in CH_2Cl_2 (10 mL) was added a solution of 5,17-bis(1,1-dimethylethyl)1-25,27-dihydroxy-26,28-dimethoxycalix[4]arene[4] (4.0 g, 7.0 mmol) in CH_2Cl_2 (250 mL) for 1 h at −78 °C. After being stirred for 20 h at room temperature, the reaction mixture was quenched by addition of MeOH (50 mL) in order to destroy the excess of boron tribromide. After removal of the solvent the residue was taken up in CH_2Cl_2 (250 mL) and subsequently washed with a concentrated $NaHCO_3$ solution (2 × 50 mL) and with brine (1 × 100 mL). The crude reaction product was recrystallized from CH_2Cl_2/hexane to give pure **21** as a white solid: yield 94%; mp >300 °C; ^{1}H NMR δ 10.28 (s, 4 H, OH), 7.08 (s, 4 H, Ar 4,6,16,18-H), 7.04 (d, 4 H, J = 3.0 Hz, Ar 10,12,22,24-H), 6.75–6.65 (m, 2 H, Ar 11,23-H), 4.26 and 3.56 (br s, 8 H, $ArCH_2Ar$), 1.27 [s, 18 H, $C(CH_3)_3$]; FAB mass spectrum, m/e 537.0 (M^+, calcd 537.3). Anal. Calcd for $C_{36}H_{40}O_4 \cdot CH_2Cl_2$: C, 71.49; H, 6.81. Found: C, 71.76; H, 6.72.

5,17-Bis(1,1-dimethylethyl)-25,26,27,28-tetrakis(ethoxyethoxy)calix[4]arene (22). To a suspension of sodium hydride (80% in oil, 0.7 g, 23.3 mmol; freed from protective mineral oil by 2 hexane washings) in dry DMF (100 mL) was added **21** (2.14 g, 3.9 mmol). After the mixture was stirred for 20 min 2-bromoethyl ethyl ether (4.0 g, 26.1 mmol) was added, and the solution was heated at 80 °C for 5 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 (200 mL), and the resulting solution was washed with 1 N HCl (2 × 50 mL) and brine (50 mL). The crude reaction product was recrystallized from MeOH to give pure **22** as a white solid: yield 89%; mp 188 °C; ^{1}H NMR δ 7.00 (s, 4 H, Ar 4,6,16,18-H), 6.28 (m, 2 H, Ar 11,23-H), 6.16 (d, 4 H, J = 7.5 Hz, Ar 10,12,22,24-H), 4.46 and 3.10 (AB q, 8 H, J = 13.3 Hz, $ArCH_2Ar$), 4.21 [t, 4 H, J = 6.6 Hz, Ar(p-H)-OCH_2], 3.96 [t, 4 H, J = 5.2 Hz, Ar(p-t-Bu)-OCH_2], 1.31 [s, 18 H, $C(CH_3)_3$]; ^{13}C NMR δ 155.3, 154.8 (s, Ar 25,26,27,28-C), 144.5 (s, Ar 5,17-C), 127.4, 125.5, 122.3 (d, all ArC-H), 34.0 [s, $C(CH_3)_3$], 31.7 [q, $C(CH_3)_3$], 31.1 (t, $ArCH_2Ar$); FAB mass spectrum, m/e 825.4 (M^+, calcd 825.5). Anal. Calcd for $C_{52}H_{72}O_8$: C, 75.69; H, 8.79. Found: C, 75.85; H, 8.75.

Acknowledgment. We thank T. W. Stevens for recording the mass spectra and A. M. Montanaro-Christenhusz for performing the elemental analyses.

Registry No. **1**, 105880-81-7; **2**, 121935-18-0; **3**, 126372-90-5; **4**, 137571-04-1; **5**, 137571-05-2; **6**, 137571-06-3; **7**, 121702-03-2; **8**, 137594-00-4; **9**, 60705-62-6; **10**, 137693-26-6; **11**, 137571-07-4; **12**, 97600-49-2; **13**, 137571-08-5; **14**, 137571-09-6; **15**, 137594-01-5; **16**, 137571-10-9; **17**, 137571-11-0; **18**, 137571-12-1; **19**, 137571-13-2; **20**, 137571-14-3; **21**, 137571-15-4; **22**, 137571-16-5; **23**, 137571-17-6; 2-bromoethyl ethyl ether, 592-55-2.

A Nitrone-Based Approach to the Enantioselective Total Synthesis of (−)-Anisomycin

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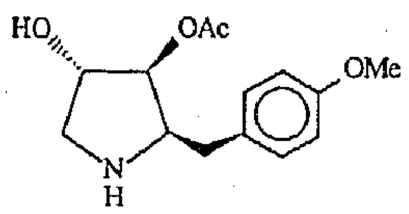
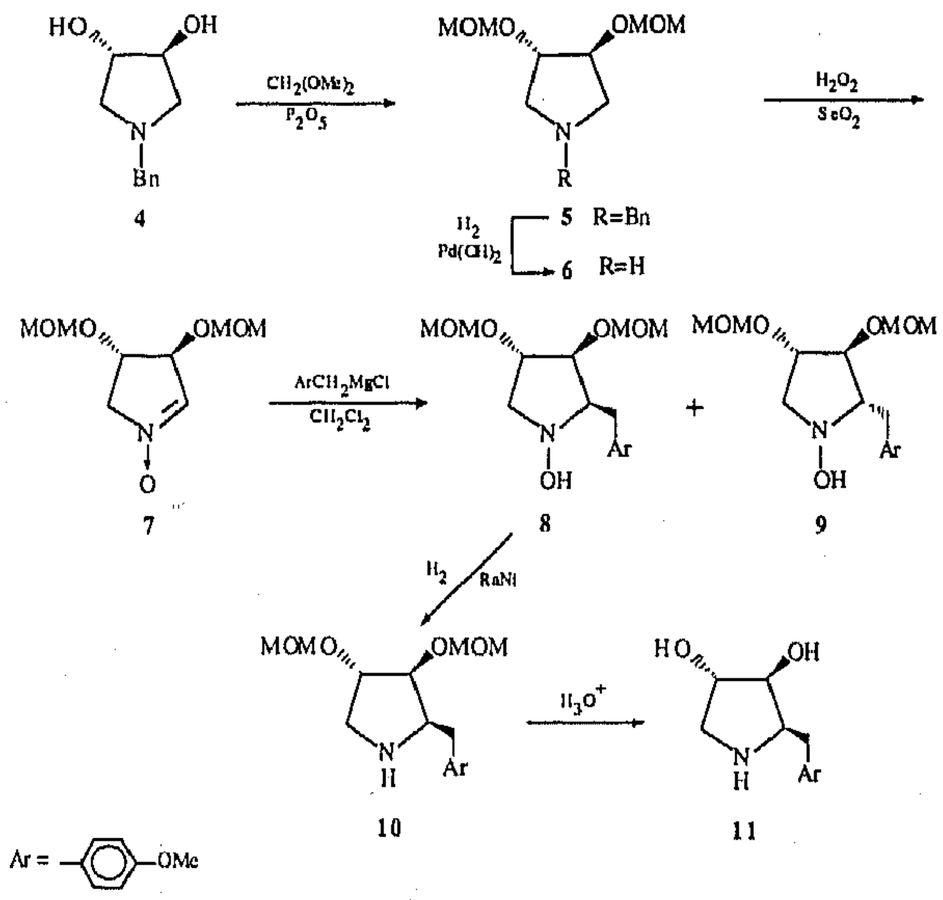
Received June 28, 1991

The antibiotic (−)-anisomycin **1** is a fermentation product of various species of streptomyces[1] which exhibits strong and selective activity against pathogenic protozoa and fungi.[2]



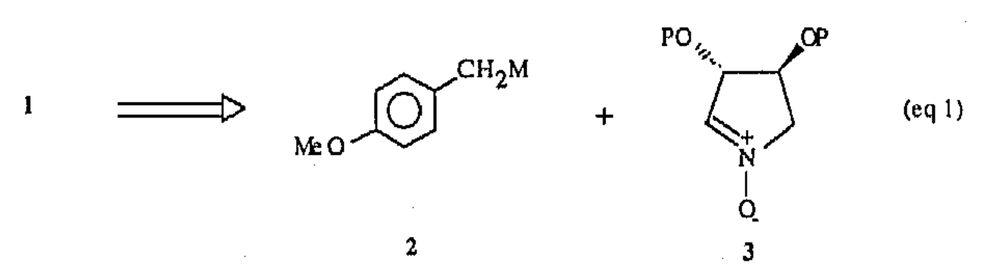
1

Scheme I



It has been shown to act as an inhibitor of protein synthesis,[3] and it finds wide use in the treatment of trichomonas vaginitis and amebic dysentery. Its absolute configuration was definitively established in 1968 by chemical correlation with L-tyrosine.[4] Several chiral syntheses of (−)-anisomycin have appeared in literature for the most part employing naturally occurring starting materials such as carbohydrates,[5] amino acids,[6] and L-tartaric acid or its esters.[7]

Both enantiomers of **1** can be prepared starting from (*R*)- and (*S*)-epichlorohydrin using the method of Takano.[8] Our retrosynthetic analysis[9] as depicted in eq 1 shows that



(eq 1)

by means of a carbon–carbon disconnection two synthons **2** and **3** could be envisaged. The reagent for **2** can be trivially found in the Grignard reagent 4-methoxybenzylmagnesium chloride, less obvious is the substrate corresponding to structure **3**. An electrophilic carbon in the position α to a nitrogen atom can be generated via iminium derivatives,[10] by a carbonyl group (e.g., amide),[11]

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