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Ips0 Nitration of *p*-*tert*-Butylcalix[4]arenes

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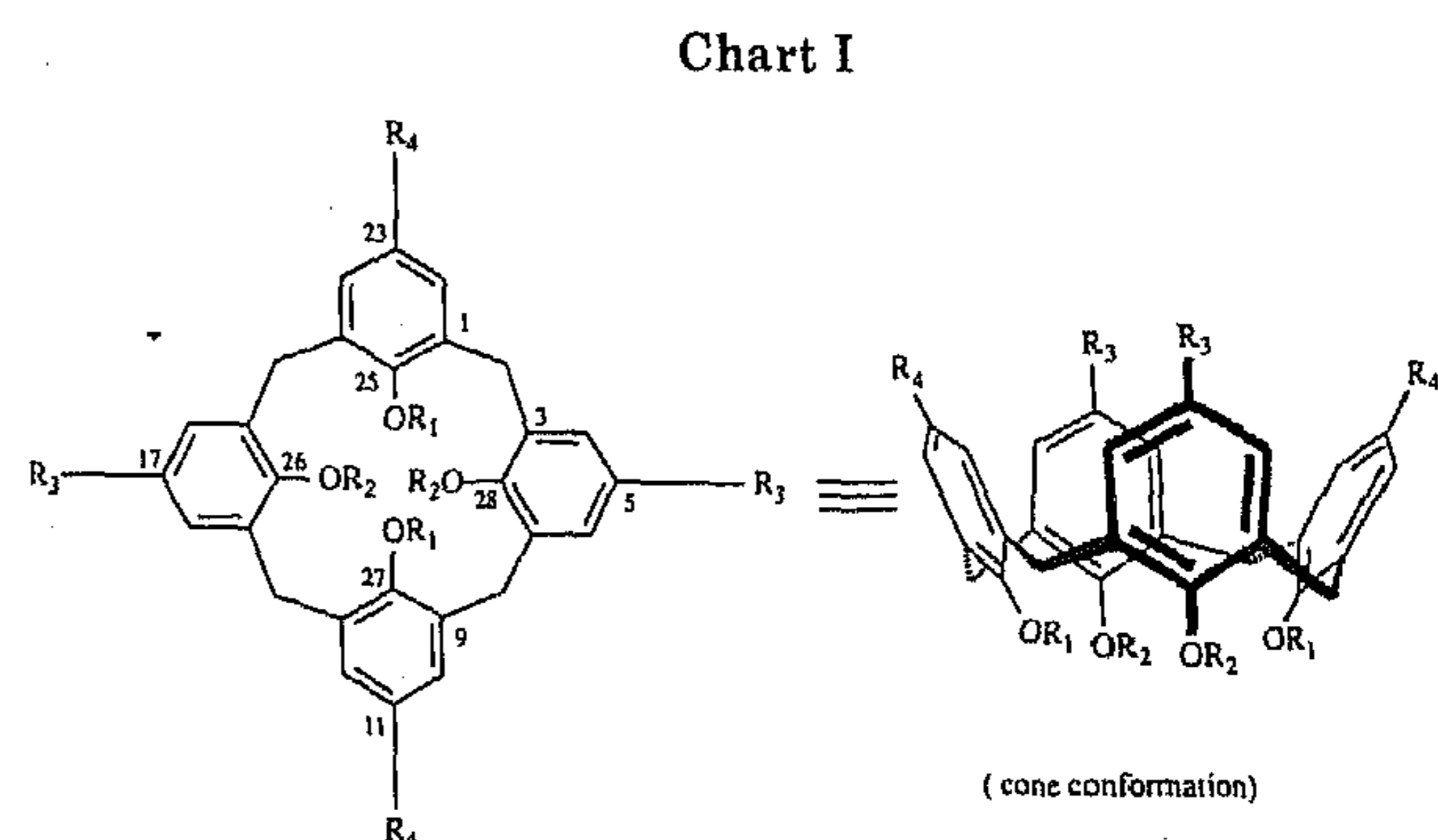
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Functionalized calixarenes represent an important class of compounds that can complex cations and neutral molecules.^{1,2} Calix[4]arenes can easily be functionalized both at the phenolic OH groups (lower rim) and, after (partial) removal of *tert*-butyl 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.

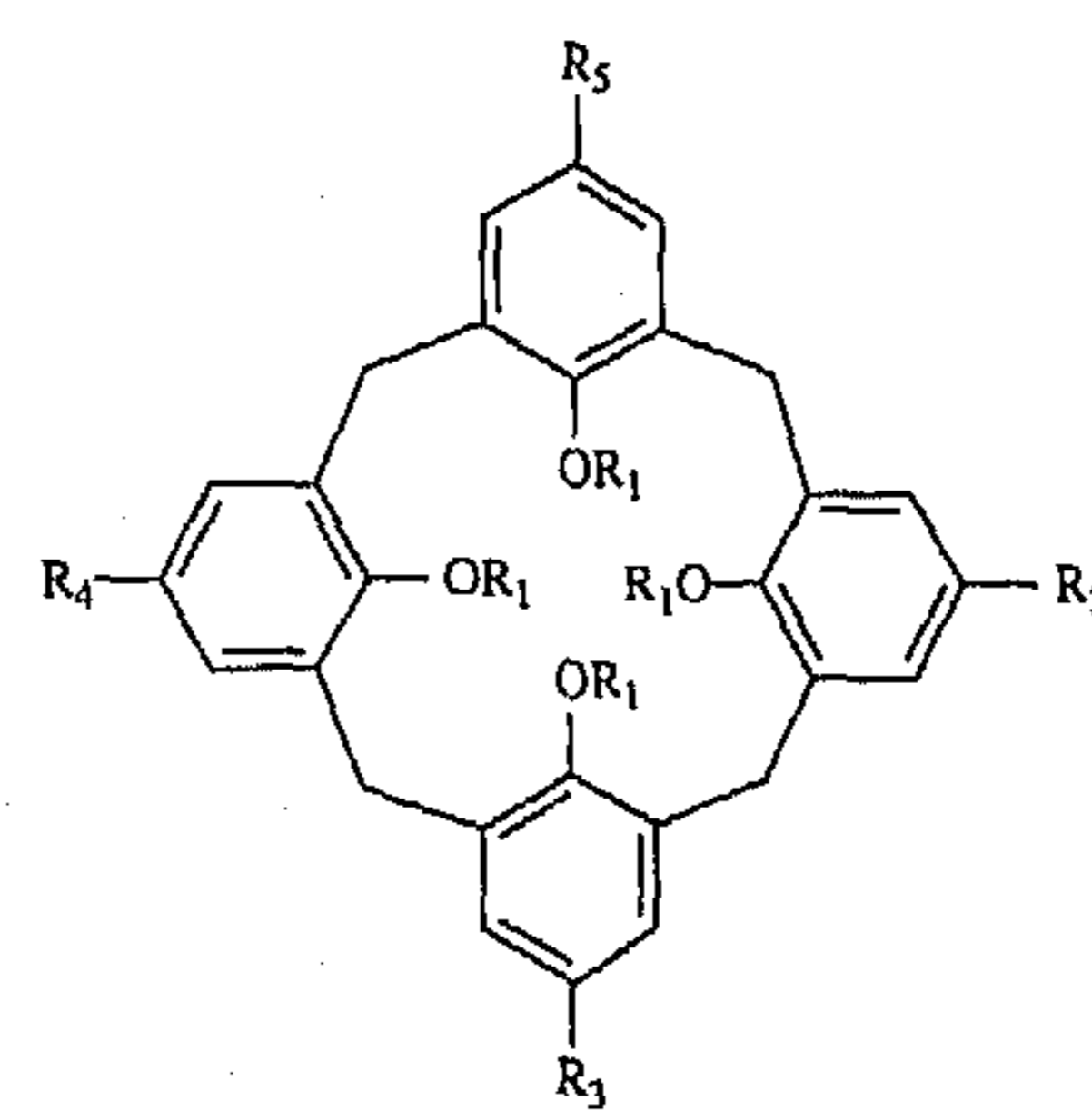
Results and Discussion

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% HNO₃ 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*-tetra-nitrocalix[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,



- | | | | | | |
|----|-----------------------------------------------------------------------------------------|-----------------------------------------------|----|----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| 1 | R ₁ =R ₂ =Me | R ₃ =R ₄ = <i>t</i> -Bu | 2 | R ₁ =R ₂ =Me | R ₃ =R ₄ =NO ₂ |
| 3 | R ₁ =R ₂ =Pr | R ₃ =R ₄ = <i>t</i> -Bu | 4 | R ₁ =R ₂ =Pr | R ₃ =R ₄ =NO ₂ |
| 5 | R ₁ =R ₂ =CH ₂ CH ₂ OEt | R ₃ =R ₄ = <i>t</i> -Bu | 6 | R ₁ =R ₂ =CH ₂ CH ₂ OEt | R ₃ =R ₄ =NO ₂ |
| 7 | R ₁ =R ₂ =CH ₂ C(O)OEt | R ₃ =R ₄ = <i>t</i> -Bu | 8 | R ₁ =R ₂ =CH ₂ C(O)OEt | R ₃ =R ₄ =NO ₂ |
| 9 | R ₁ =R ₂ =H | R ₃ =R ₄ = <i>t</i> -Bu | | | |
| 10 | R ₁ =H, R ₂ =Pr | R ₃ =R ₄ = <i>t</i> -Bu | 11 | R ₁ =H, R ₂ =Pr, R ₃ = <i>t</i> -Bu, R ₄ =NO ₂ | |
| 12 | R ₁ =H, R ₂ =CH ₂ C(O)OEt | R ₃ =R ₄ = <i>t</i> -Bu | 13 | R ₁ =H, R ₂ =CH ₂ C(O)OEt, R ₃ = <i>t</i> -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 ₂ C(O)OEt, R ₃ =R ₄ =NO ₂ | |
| 20 | R ₁ =H, R ₂ =Me, R ₃ = <i>t</i> -Bu, R ₄ =H | | 22 | R ₁ =R ₂ =CH ₂ CH ₂ OEt, R ₃ = <i>t</i> -Bu, R ₄ =H | |
| 21 | R ₁ =R ₂ =H, R ₃ = <i>t</i> -Bu, R ₄ =H | | 23 | R ₁ =R ₂ =CH ₂ CH ₂ OEt, R ₃ =NO ₂ , R ₄ =H | |

Chart II



- | | |
|----|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| 16 | R ₁ =Pr, R ₂ =R ₃ = <i>t</i> -Bu, R ₄ =R ₅ =NO ₂ |
| 17 | R ₁ =Pr, R ₂ =R ₄ = <i>t</i> -Bu, R ₃ =R ₅ =NO ₂ |
| 18 | R ₁ =Pr, R ₂ = <i>t</i> -Bu, R ₃ =R ₄ =R ₅ =NO ₂ |
| 19 | R ₁ =CH ₂ CH ₂ OEt, R ₂ =R ₃ =R ₄ = <i>t</i> -Bu, R ₅ =NO ₂ |

and 8 (cone conformation) in yields of 67%, 76%, and 37%, respectively. Ips0 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% HNO₃ 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

(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.

(11) (a) Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Chem. Lett.* 1989, 1747. (b) Iwamoto, K.; Fujimoto, K.; Matsuda, T.; Shinkai, S. *Tetrahedron Lett.* 1990, 31, 7169.

(12) Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Timmerman, P.; Verboom, W.; Harkema, S.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron Lett.* 1991, 32, 2675.

(1) Gutsche, C. D. *Calixarenes, monographs in supramolecular chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1989; Vol 1.

(2) Vicens, J.; Böhmer, V., Eds. *Calixarenes, a versatile class of macrocyclic compounds*; Kluwer: Dordrecht, 1991.

(3) No, K.; Noh, Y. *Bull. Korean Chem. Soc.* 1986, 7, 314.

(4) Van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* 1990, 55, 5639.

(5) Shinkai, S.; Araki, K.; Tsubaki, T.; Arimura, T.; Manabe, O. *J. Chem. Soc., Perkin Trans. 1* 1987, 2297.

(6) De Mendoza, J.; Nieto, P. M.; Prados, P.; Sánchez, C. *Tetrahedron* 1990, 46, 671.

(7) Böhmer, V.; Schade, E.; Vogt, W. *Makromol. Chem., Rapid Commun.* 1984, 5, 221 and unpublished results mentioned in the chapter of Böhmer and Vicens in ref 2.

(8) Moodie, R. B.; Schofield, K. *Acc. Chem. Res.* 1976, 9, 287.

(9) Shinkai, S.; Arimura, T.; Araki, K.; Kawabata, H.; Satoh, H.; Tsubaki, T.; Manabe, O.; Sunamoto, J. *J. Chem. Soc., Perkin Trans. 1* 1989, 2039.

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% HNO₃ 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% HNO₃ 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 ¹H 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-(NO₂)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 ¹H 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% HNO₃ for 2.5 d gave exclusively the trinitrocalix[4]arene **18** in 58% yield. Secondly, treatment of tetrakis(ethoxyethoxy)calix[4]arene **5** with 50 equiv of 65% HNO₃ for 18 h gave the mononitrocalix[4]arene **19** in 73% yield. We have also treated tetrakis((ethoxycarbonyl)methoxy)calix[4]arene (**7**) with 65% HNO₃. 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% HNO₃. 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% HNO₃ 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 ¹H 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 preceded in the ipso nitration of 2,4,6-tri-*tert*-butylaniline¹⁶ 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. ¹H and ¹³C NMR spectra were recorded in CDCl₃ with Me₄Si 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. CH₂Cl₂ was distilled from CaH₂ 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 MgSO₄ whereupon the solvent was removed under reduced pressure. The presence of CH₂Cl₂ in the analytical samples was confirmed by ¹H 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 CH₂Cl₂ (30 mL) and glacial acetic acid (30 mL) was added 100% HNO₃ (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 CH₂Cl₂ (2 × 50 mL). The combined organic layers were washed with water (2 × 30 mL). Recrystallization of the

(16) (a) Burgers, J.; van Hartingsveldt, W.; van Keulen, J.; Verkade, P. E.; Visser, H.; Wepster, B. M. *Recl. Trav. Chim. Pays-Bas* 1956, 75, 1327. (b) Burgers, J.; Hoefnagel, M. A.; Verkade, P. E.; Visser, H.; Wepster, B. M. *Ibid.* 1958, 77, 491.

(17) Watari, W. *Bull. Chem. Soc. Jpn.* 1964, 37, 204.

(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 NO₂BF₄. 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.

(19) Grynszpan, F.; Dinoor, N.; Biali, S. E. *Tetrahedron Lett.* 1991, 32, 1909.

(20) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. *J. Tetrahedron* 1983, 39, 409.

(21) Chang, S.-K.; Cho, I. *J. Chem. Soc., Perkin Trans. 1* 1986, 211.

(22) Gutsche, C. D.; Iqbal, M.; Stewart, D. *J. Org. Chem.* 1986, 51, 742.

(23) (a) Iwamoto, K.; Yanagi, A.; Araki, K.; Shinkai, S. *Chem. Lett.* 1991, 473. (b) Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* 1991, 47, 4325.

(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 convention²⁶ 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}]octacosane-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.

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

(14) Böhmer, V.; Vogt, W.; Harris, S. J.; Leonard, R. G.; Collins, E. M.; Deasy, M.; McKervey, M. A.; Owens, M. *J. Chem. Soc., Perkin Trans. 1* 1990, 431.

(15) This way was chosen because selective de-*tert*-butylation⁴ of 5,11,17,23-tetra-*tert*-butyl-26,28-bis(ethoxyethoxy)-25,27-dihydroxycalix[4]arene with 2 equiv of AlCl₃ in toluene at room temperature could only be achieved in moderate yield.

crude reaction products gave the pure compounds.

25,26,27,28-Tetramethoxy-5,11,17,23-tetranitrocalix[4]arene (2):¹¹ reaction time 2 h; yield 75% (partial cone/cone 93/7); mp >300 °C (EtOH); ¹H 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, ArCH₂Ar), 3.92 (s, 3 H, OCH₃), 3.84 (s, 10 H, 2 OCH₃, ArCH₂Ar), 3.05 (s, 3 H, OCH₃).

5,11,17,23-Tetranitro-25,26,27,28-tetrapropoxycalix[4]arene (4): reaction time 2 h; yield 67%; mp >300 °C (CH₂Cl₂/MeOH); ¹H NMR δ 7.58 (s, 8 H, ArH), 4.53 and 3.41 (AB q, 8 H, *J* = 14.1 Hz, ArCH₂Ar), 3.96 (t, 8 H, *J* = 7.4 Hz, ArOCH₂), 1.02 (t, 12 H, *J* = 7.4 Hz, CH₃); ¹³C NMR δ 161.6 (ArC-O), 142.6 (s, ArC-NO₂), 123.8 (d, ArC-H), 77.6 (t, ArOCH₂), 30.9 (t, ArCH₂Ar); FAB mass spectrum, *m/e* 773.1 [(M + H)⁺, calcd 773.3]. Anal. Calcd for C₄₀H₄₄N₄O₁₂·0.66CH₂Cl₂: 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); ¹H NMR δ 7.59 (s, 8 H, ArH), 4.68 and 3.37 (AB q, 8 H, *J* = 14.1 Hz, ArCH₂Ar), 4.24 (t, 8 H, *J* = 4.6 Hz, ArOCH₂), 3.78 (t, 8 H, *J* = 4.6 Hz, ArOCH₂CH₂), 3.50 (q, 8 H, *J* = 7.0 Hz, OCH₂CH₃), 1.17 (t, 12 H, *J* = 7.0 Hz, OCH₂CH₃); ¹³C NMR δ 161.5 (s, ArC-O), 142.7 (s, ArC-NO₂), 123.7 (d, ArC-H), 74.2 (t, ArOCH₂), 69.3, 66.3 (t, OCH₂), 30.8 (t, ArCH₂Ar); mass spectrum, *m/e* 892.337 (M⁺, calcd 892.337). Anal. Calcd for C₄₄H₅₂N₄O₁₀: 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 (CH₂Cl₂/petroleum ether); ¹H NMR δ 7.61 (s, 8 H, all ArH), 5.06 and 3.49 (AB q, 8 H, *J* = 14.2 Hz, ArCH₂Ar), 4.78 (s, 8 H, ArOCH₂), 4.24 (q, 8 H, *J* = 7.1 Hz, OCH₂CH₃), 1.31 (t, 12 H, *J* = 7.1 Hz, OCH₂CH₃); ¹³C 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, ArOCH₂), 61.1 (t, OCH₂), 31.4 (t, ArCH₂Ar), 14.0 (q, CH₃); mass spectrum, *m/e* 948.259 (M⁺, calcd 948.255). Anal. Calcd for C₄₄H₄₄N₄O₂₀·H₂O: C, 59.66; H, 4.80; N, 5.79. Found: C, 59.53; H, 4.53; N, 5.93. Karl-Fischer calcd for 1 H₂O 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 CH₂Cl₂ (25 mL) and glacial acetic acid (25 mL) was added 100% HNO₃ [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 (CH₂Cl₂/petroleum ether); ¹H NMR δ 9.50 (s, 2 H, OH), 8.04 [s, 4 H, ArC(NO₂)CH], 6.97 (s, 4 H, ArH), 4.29 and 3.48 (AB q, 8 H, *J* = 13.2 Hz, ArCH₂Ar), 4.00 (t, 4 H, *J* = 6.4 Hz, OCH₂), 1.07 [s, 18 H, C(CH₃)₃]; ¹³C 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, ArOCH₂), 34.1 [s, C(CH₃)₃], 31.4 (t, ArCH₂Ar), 31.0 [q, C(CH₃)₃]; mass spectrum, *m/e* 710.353 (M⁺, calcd 710.357). Anal. Calcd for C₄₂H₅₀N₂O₈·0.5H₂O: 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 H₂O 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 (CH₂Cl₂/petroleum ether); ¹H NMR δ 8.99 (s, 2 H, OH), 7.99 [s, 4 H, ArC(NO₂)CH], 7.03 (s, 4 H, ArH), 4.80 (s, 4 H, OCH₂CO₂), 4.49 and 3.49 (AB q, 8 H, *J* = 13.3 Hz, ArCH₂Ar), 4.36 (q, 4 H, *J* = 7.2 Hz, OCH₂), 1.37 (t, 6 H, *J* = 7.2 Hz, CH₃), 1.12 [s, 18 H, C(CH₃)₃]; ¹³C 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, ArOCH₂), 61.5 (t, OCH₂), 34.3 [s, C(CH₃)₃], 31.5 (t, ArCH₂Ar), 31.0 [q, C(CH₃)₃], 14.0 (q, CH₃); mass spectrum, *m/e* 798.337 (M⁺, calcd 798.336). Anal. Calcd for C₄₄H₅₀N₂O₁₂: 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 (CH₂Cl₂/petroleum ether); ¹H 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, ArCH₂Ar), 4.10 (t, 4 H, *J* = 6.2 Hz, ArOCH₂), 1.34 (t, 6 H, *J* = 7.4 Hz, CH₂CH₃); ¹³C 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, ArOCH₂), 31.1 (t, ArCH₂Ar), 23.2 (t, OCH₂CH₂), 10.5 (q, CH₂CH₃); mass spectrum, *m/e* 688.203 (M⁺, calcd 688.202). Anal. Calcd for C₃₄H₃₂N₄O₁₂·0.66CH₂Cl₂: 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 CH₂Cl₂ (25 mL) and glacial acetic acid (1.5 mL) was added 65% HNO₃ (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 (SiO₂, CH₂Cl₂).

5,11-Bis(1,1-dimethylethyl)-17,23-dinitro-25,26,27,28-tetrapropoxycalix[4]arene (16): mp 259–261 °C (CH₂Cl₂/MeOH); ¹H 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, ArCH₂Ar), 4.15–3.75 (m, 8 H, OCH₂), 1.01 [s, 18 H, C(CH₃)₃]; ¹³C 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, OCH₂), 33.6 [s, C(CH₃)₃], 31.0 [q, C(CH₃)₃], 31.0, 30.9 (t, ArCH₂Ar); FAB mass spectrum, *m/e* 794.6 (M⁺, calcd 794.4). Anal. Calcd for C₄₈H₆₂N₂O₈: 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 (CH₂Cl₂/MeOH); ¹H NMR δ 7.17 [s, 4 H, ArC(NO₂)CH], 6.97 (s, 4 H, Ar H), 4.45 and 3.18 (AB q, 8 H, *J* = 13.5 Hz, ArCH₂Ar), 3.74 (t, 8 H, *J* = 6.7 Hz, ArOCH₂), 1.39 [s, 18 H, C(CH₃)₃]; ¹³C 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, OCH₂), 34.1 [s, C(CH₃)₃], 31.4 [q, C(CH₃)₃], 31.1 (t, ArCH₂Ar); FAB mass spectrum, *m/e* 795.7 [(M + H)⁺, calcd 795.4]. Anal. Calcd for C₄₈H₆₂N₂O₈·0.25CH₂Cl₂: 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); ¹H 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, ArCH₂Ar), 4.1–3.8 (m, 8 H, OCH₂), 2.05–1.85 (m, 8 H, OCH₂CH₂), 1.1–0.9 [m, 21 H, CH₃ and C(CH₃)₃]; ¹³C 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, ArOCH₂), 33.7 [s, C(CH₃)₃], 31.0 [q, C(CH₃)₃], 31.1, 30.9 (t, ArCH₂Ar); FAB mass spectrum, *m/e* 783.6 (M⁺, calcd 783.4). Anal. Calcd for C₄₄H₅₃N₃O₁₀: 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% HNO₃ (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 (SiO₂, CH₂Cl₂); yield 73%; mp 124–126 °C (MeOH); ¹H NMR δ 7.20 [s, 2 H, ArC(NO₂)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, ArCH₂Ar), 1.25 [s, 18 H, C(CH₃)₃], 0.56 [s, 9 H, C(CH₃)₃]; ¹³C 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, ArCH₂Ar); FAB mass spectrum, *m/e* 925.7 (M⁺, calcd 925.6). Anal. Calcd for C₆₆H₇₀N₁O₁₀: 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 (SiO₂, CH₂Cl₂-EtOAc, 95:5); yield 78%; mp 152–154 °C (MeOH); ¹H NMR δ 7.66 [s, 4 H, ArC(NO₂)CH], 6.55 (br s, 6 H, ArH), 4.58 and 3.26 (AB q, 8 H, *J* = 13.7 Hz, ArCH₂Ar), 4.30 [t, 4 H, *J* = 5.0 Hz, Ar(NO₂)OCH₂], 4.07 (t, 4 H, *J* = 5.1 Hz, ArOCH₂); ¹³C 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, ArCH₂Ar); FAB mass spectrum, *m/e* 803.7 [(M + H)⁺, calcd 803.4]. Anal. Calcd for C₄₄H₅₄N₂O₁₂: 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-tetrahydrocalix[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]arene⁴ (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 $>300^\circ\text{C}$; $^1\text{H NMR}$ 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, $\text{C}(\text{CH}_3)_3$]; FAB mass spectrum, m/e 537.0 (M^+ , calcd 537.3). Anal. Calcd for $\text{C}_{36}\text{H}_{40}\text{O}_4 \cdot \text{CH}_2\text{Cl}_2$: 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 ; $^1\text{H NMR}$ 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, $\text{Ar}(p\text{-H})\text{-OCH}_2$], 3.96 [t, 4 H, $J = 5.2$ Hz, $\text{Ar}(p\text{-t-Bu})\text{-OCH}_2$], 1.31 [s, 18 H, $\text{C}(\text{CH}_3)_3$]; $^{13}\text{C NMR}$ 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, $\text{C}(\text{CH}_3)_3$], 31.7 [q, $\text{C}(\text{CH}_3)_3$], 31.1 (t, ArCH_2Ar); FAB mass spectrum, m/e 825.4 (M^+ , calcd 825.5). Anal. Calcd for $\text{C}_{52}\text{H}_{72}\text{O}_8$: C, 75.69; H, 8.79. Found: C, 75.85; H, 8.75.

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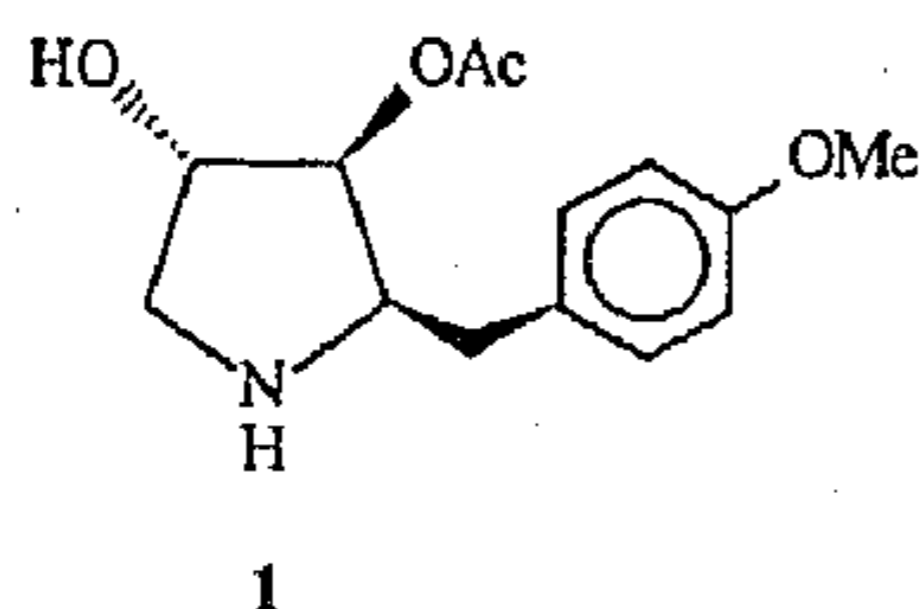
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A Nitrene-Based Approach to the Enantioselective Total Synthesis of (-)-Anisomycin

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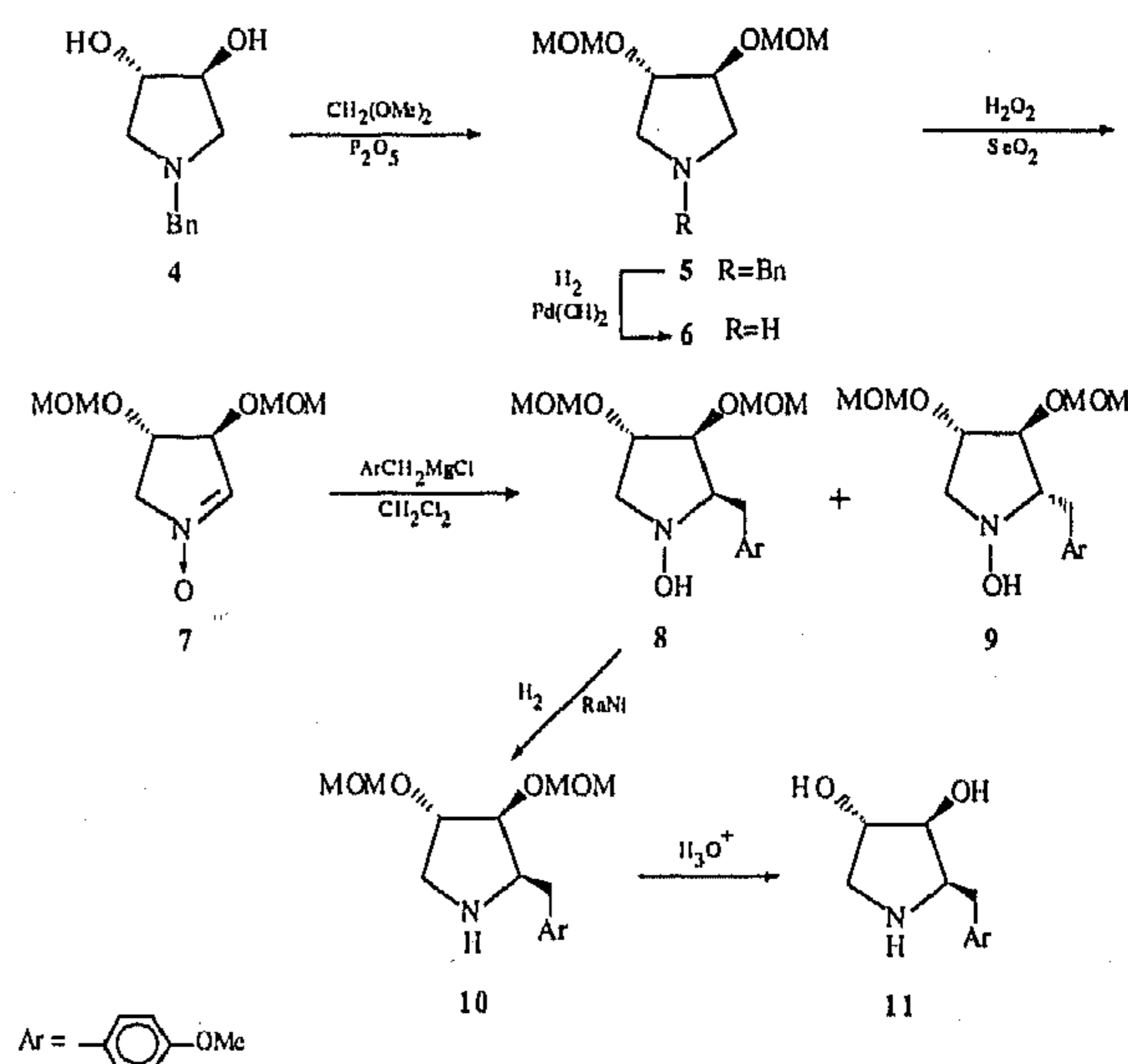
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The antibiotic (-)-anisomycin 1 is a fermentation product of various species of streptomyces¹ which exhibits strong and selective activity against pathogenic protozoa and fungi.²



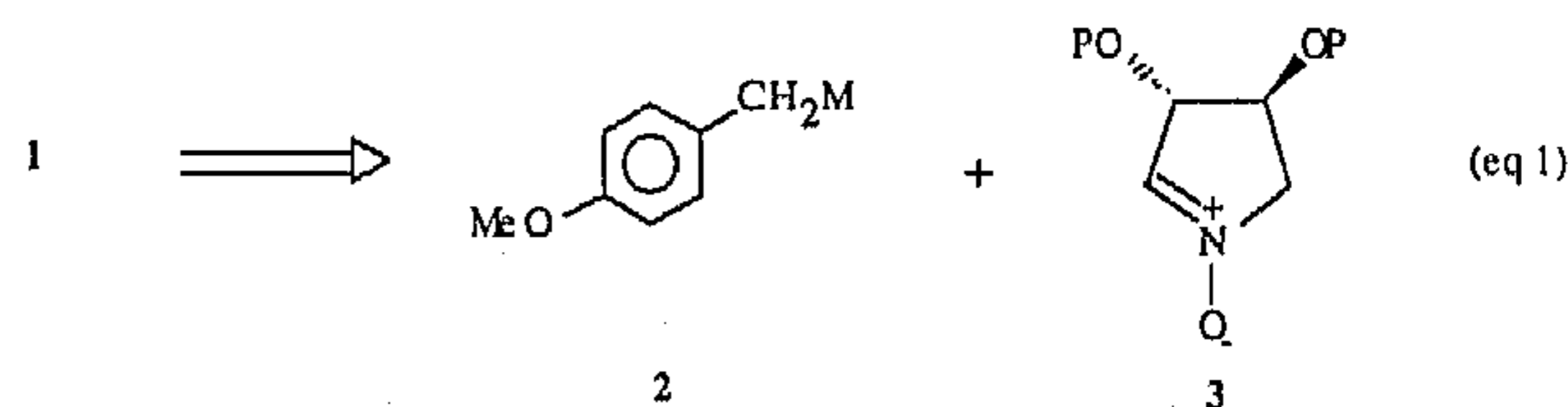
(1) Sobin, B. A.; Tanner, F. W. *J. Am. Chem. Soc.* 1954, 76, 4053.

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 analysis⁹ as depicted in eq 1 shows that



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

(2) Jimenez, A.; Vazquez, D. In *Antibiotics*; Hahn, F. E., Ed.; Springer Verlag: Berlin, 1979.

(3) Grollman, A. P. *J. Biol. Chem.* 1967, 242, 3226.

(4) Wong, C. M. *Can. J. Chem.* 1968, 46, 1101.

(5) (a) Verheyden, J. P. H.; Richardson, A. C.; Bhatt, R. S.; Grant, D. B.; Fitch, W. L.; Moffatt, J. G. *Pure Appl. Chem.* 1978, 50, 1363. (b) Buchanan, J. G.; McLean, K. A.; Wightman, R. H.; Paulsen, H. *J. Chem. Soc. Perkin Trans. I* 1985, 1463. (c) Baer, H. H.; Zamkane, M. *J. Org. Chem.* 1988, 53, 4786.

(6) (a) Meyers, A. I.; Dupre, B. *Heterocycles* 1987, 25, 113. (b) Shono, T.; Kise, N. *Chem. Lett.* 1987, 697. (c) Jegham, S.; Das, B. C. *Tetrahedron Lett.* 1989, 29, 4419.

(7) (a) Wong, C. M.; Buccini, J.; Chang, I.; Te Raa, J.; Schwenk, K. *Can. J. Chem.* 1969, 47, 2421. (b) Felner, I.; Schenker, K. *Helv. Chim. Acta* 1970, 53, 754. (c) Iida, A. I.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* 1986, 51, 1069.

(8) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *Heterocycles* 1989, 29, 1861.

(9) For an authoritative presentation of this strategy, see: (a) Warren, S. *Organic Synthesis: The Disconnection Approach*; Wiley: New York, 1982. (b) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: Oxford, 1983. (c) Corey, E. J.; Cheng, X. M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989.