231–233 °C; IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.22 (s, 2 H), 4.86 (s, 2 H), 5.17 (s, 4 H), 5.27 (s, 2 H), 6.62 (dd, J = 5.3, 3.2 Hz, 2 H), 6.76 (dd J = 5.3, 3.2 Hz, 2 H), 6.81 (dd, J = 5.3, 3.2 Hz, 2 H), 6.83 (dd, J = 5.3, 3.2 Hz, 2 H), 6.88 (dd, J = 5.3, 3.2 Hz, 2 H), 6.94 (dd, J = 5.3, 3.2 Hz, 2 H), 7.16 (dd, J = 5.3, 3.2 Hz, 2 H), 7.19 (dd, J = 5.3, 3.2 Hz, 2 H), 7.23 (dd, J = 5.3, 3.2 Hz, 2 H), 7.27 (s, 2 H)8 7.28 (s, 2 H), 7.28 (dd, J = 5.3, 3.2 Hz, 2 H), 7.37 (s, 2 H), 7.55 (dd, J = 6.3, 3.2 Hz, 2 H), 7.88 (dd, J = 6.3, 3.2 Hz, 2 H), 8.34 (s, 2 H); m/e (relative intensity) 208 (anthraquinone, 100), 180 (12.3), 152 (44.2), 126 (25.2), 44 (10.9); FAB mass spectrum, m/e (relative intensity) 915 (M + 1, 6.9), 914 (M^+, 8.0), 707 (21.8), 528 (3.7), 307 (23.5), 154 (100); high-resolution mass spectrum calcd for $C_{70}H_{42}O_2$ 914.3185, obsd 914.3140.

The crude diketone (778 mg) was reduced with 4 equiv of lithium aluminum hydride as in the preparation of **12**. Crude diol (889 mg) was reserved for the next step. A small amount of the product was chromatographed to give pure diol: mp 237–239 °C; ^1H NMR ($CDCl_3$) δ 2.04 (br s, 2 H, exchanges with D_2O), 2.19 (br s, 2 H), 4.33 (s, 2 H), 4.99 (s, 2 H), 5.09 (s, 2 H), 5.17 (s, 2 H), 5.21 (s, 2 H), 6.72–6.97 (m, 10 H), 7.09–7.24 (m, 16 H), 7.29 (s, 2 H), 7.36–7.44 (m, 2 H), 7.64–7.75 (m, 2 H); FAB mass spectrum, m/e (relative intensity) 919 (M + 1, 38.0), 918 (M^+, 40.0), 883 (5.6), 707 (98.9), 677 (18.5), 621 (63.0), 531 (72.5), 154 (100); high-resolution mass spectrum calcd for $C_{70}H_{46}O_2$ 918.3498, obsd 918.3470.

The crude diol (889 mg) was dehydrated following the same procedure as for the dehydration of **12**. Flash chromatography of the crude hydrocarbon (800 mg) on silica gel with 0–50% methylene chloride–hexane as eluent gave the desired pure noniptycene **13**[10] (431 mg, 0.488 mmol, 75% overall from **8**): mp 240 °C dec; ^1H NMR ($CDCl_3$) δ 5.07 (br s, 2 H), 5.12 (s, 2 H), 5.17 (s, 2 H), 5.31 (s, 2 H), 6.67 (dd, J = 5.4, 3.2 Hz, 2 H), 6.75–6.84 (m, 8 H), 6.88 dd, J = 5.4, 3.2 Hz, 2 H), 7.09 (dd, J = 5.3, 3.2 Hz, 2 H), 7.20 (s, 2 H), 7.25 (s, 2 H), 7.31 (s, 2 H), 7.33 (dd, J = 6.4, 3.2 Hz, 2 H), 7.08–7.35 (m, 6 H), 7.72 (s, 2 H) 7.85 (dd, J = 6.4, 3.2 Hz, 2 H), 8.11 (s, 2 H); UV (cyclohexane) λ_{max} (ε) 374 (6300), 355 (9400), 338 (8200), 296 (60 400), 265 (139 900), 226 (228 800); FAB mass spectrum, m/e (relative intensity) 883 (M + 1, 70.6), 882 (M^+, 66.8), 806 (6.75), 706 (10.1), 626 (13.1), 587 (30.0), 526 (17.8), 154 (100); high-resolution mass spectrum calcd for $C_{70}H_{42}$ 882.3286, obsd 882.3272.

Undecaiptycene 14. The pure noniptycene **13** (210 mg, 0.238 mmol) was treated with benzenediazonium 2-carboxylate hydrochloride as in the improved procedure for converting **8** to **9** (vide supra) to give 336 mg of crude **14**. Flash chromatography on silica gel with 0–40% methylene chloride in hexane as the eluent gave 217 mg (0.226 mmol, 95%) of pure **14**[11] as a white solid: mp >460 °C; ^1H NMR ($CDCl_3$) δ 5.02 (s, 2 H), 5.06 (s, 2 H), 5.12 (s, 2 H), 5.15 (s, 2 H), 5.17 (s, 2 H), 6.72 (dd, J = 5.3, 3.1 Hz, 2 H), 6.75–6.80 (m, 10 H), 6.84 (dd, J = 5.3, 3.2 Hz, 2 H), 7.08 (dd, J = 5.3, 3.2 Hz, 2 H), 7.11–7.24 (m, 12 H), 7.14 (s, 2 H), 7.19 (s, 2 H), 7.21 (s, 2 H), 7.24 (s, 2 H); FAB mass spectrum, m/e (relative intensity) 960 (M + 1, 87.3), 959 (M^+, 87.0), 307 (18.6), 154 (100), 137 (93.7); UV (cyclohexane) λ_{max} (ε) 298 (34 040), 227 (218 000), 211 (145 000); high-resolution mass spectrum calcd for $C_{76}H_{46}$ 958.3598, obsd 958.3588.[12]

Acknowledgment. We are indebted to the National Science Foundation (Grant CHE 87-12118) and the National Aeronautics and Space Administration (Grant NAG-3-670) for financial support of this research.

(10) 5,18:9,14[1′,2′:1″,2″]-dibenzeno-7,16[2‴,3‴]-(5‴,14‴[1⁗,2⁗]-benzeno-5‴,14‴-dihydropentaceno)-5,7,9,14,16,18-hexahydroheptacene.

(11) 5,18:9,14[1′,2′:1″,2″]-dibenzeno-7,16[2‴,3‴]-(5‴,14⁗:7‴,12⁗-[1⁗,2⁗:1⁗⁗,2⁗⁗]-dibenzeno-5‴,7‴,12‴,14‴-tetrahydropentaceno)-5,7,9,14,16,18-hexahydroheptacene.

(12) Most complex iptycenes tenaciously cling to recrystallization or chromatographic solvents, making it exceedingly difficult to obtain satisfactory elemental analyses (see, for example, footnote 15 in ref 4). Therefore we have used throughout this paper the somewhat less desirable purity criterion of high-resolution mass spectra.

A Method for the Synthesis of Angular Iptycenes

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Dienes **9** and **13** are useful starting points for the synthesis of angular iptycenes. Cycloaddition of *trans*-1,2-dichloroethylene to **9** gives chloropentiptycene **12** (two steps, 68%); similarly, **13** gives previously unknown angular pentiptycene **3** (two steps, 79%). Cycloaddition of cyclohexene to **13** gave pentiptycene **16** (two steps), which could also be prepared in one step from the lithio derivative of **9** and 1,2-dibromobenzene. Cycloaddition of 1,4-epoxynaphthalene to **13** gave pentiptycene **20** (three steps, 64%), and dichloropentiptycene **22** was similarly prepared. The structure of **20** was proven by addition of benzyne to give the known heptiptycene **8**. Thus cycloaddition of various dienophiles to dienes **9** and/or **13** provides a general route to angular iptycenes.

Triptycene **1** is the first member of a large class of compounds called iptycenes,[1,2] derived by the fusion of 9,10-anthradiyl-type[3] moieties to the arene rings of **1** or themselves. Thus pentiptycenes **2** and **3** (five separated arene planes) can be regarded as derived by fusing a 9,10-anthradiyl moiety, to a b or an a bond of **1**. It is convenient to use the terms linear and angular to describe the fusions in **2** and **3**, respectively, analogous to the descriptors used for acenes such as anthracene (linear) and phenanthrene (angular).

Most of the iptycenes synthesized to date are of the linear type.[1,2,4] Exceptions are the angular pentiptycene **5** synthesized in low yield from the 1,3-benzadiyne

(1) Hart, H.; Shamouilian, S.; Takehira, Y. *J. Org. Chem.* **1981**, *46*, 4427–4432.

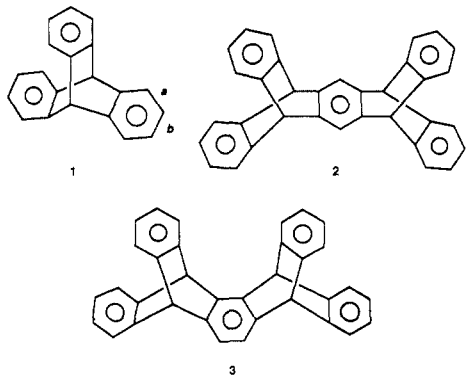
(2) Hart, H.; Bashir-Hashemi, A.; Luo, J.; Meador, M. A. *Tetrahedron* **1986**, *42*, 1641–1654.

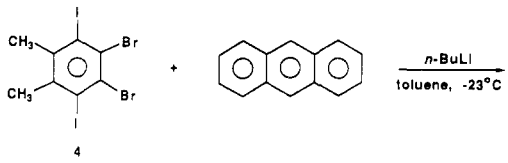
(3) The fused groups may be 9,10-anthradiyl itself, or analogues such as 5,12-naphthacenyl, etc.

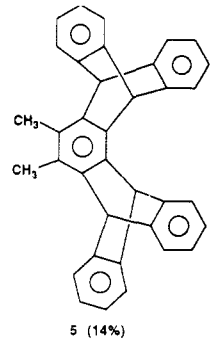
(4) Hart, H.; Raju, N.; Meador, M. A.; Ward, D. L. *J. Org. Chem.* **1983**, *48*, 4357–4360. Bashir-Hashemi, A.; Hart, H.; Ward, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 6675–6679. Luo, J.; Hart, H. *J. Org. Chem.* **1987**, *52*, 3631–3636.

(5) Huebner, C. F.; Puckett, R. T.; Brzechfta, M.; Schwartz, S. L. *Tetrahedron Lett.* **1970**, 359–362. Huebner, C. F. U.S. Patent 3 641 179, February 8, 1972.

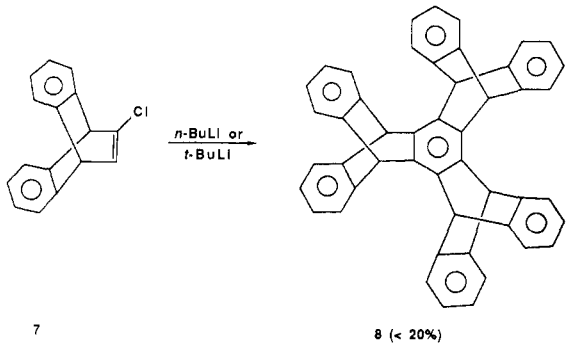
0022-3263/89/1954-2615$01.50/0







equivalent **4** and the heptiptycene **8** prepared by "trimerization" of **7**. Although each of these methods has potential for generalization, they have limitations beyond the obvious one of low yield. For example, the 1,3-benzadiyne analogue of **4** lacking the methyl groups is not readily prepared. The "trimerization" route may have greater potential,[6] but in its current form gives only a product in which all three anthradiyl moieties are identical.

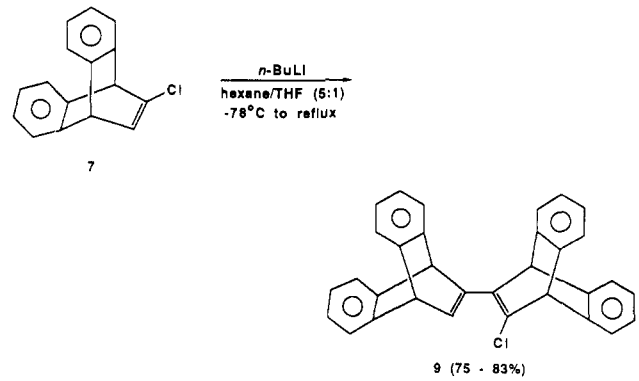


We wish to describe here a useful, high yield method for synthesizing angular iptycenes by the Diels–Alder reaction.

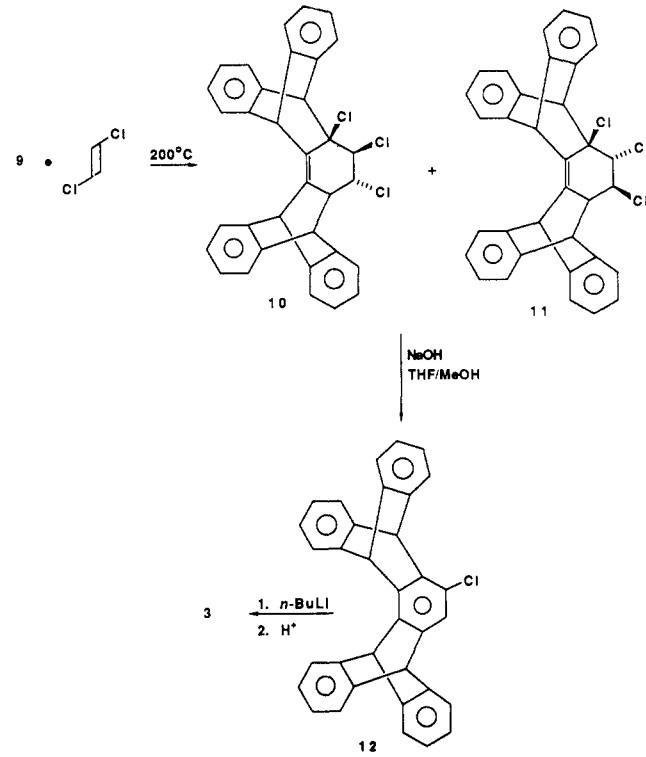
Results and Discussion

In connection with a mechanistic study of the "trimerization" of **7** to **8**, a procedure for the "dimerization" of **7** to **9** in good yield was developed.[6] Diene **9** and its dehalogenated analogue **13** proved to be useful precursors for angular iptycenes.

Heating a suspension of **9**[6] with excess *trans*-1,2-dichloroethene in a sealed tube (195–200 °C, 36 h) afforded



a mixture of adducts, presumably **10** and **11**. These were not separated or purified but were dehydrohalogenated directly with base to give the chloropentiptycene **12** in 68% overall yield from **9**.



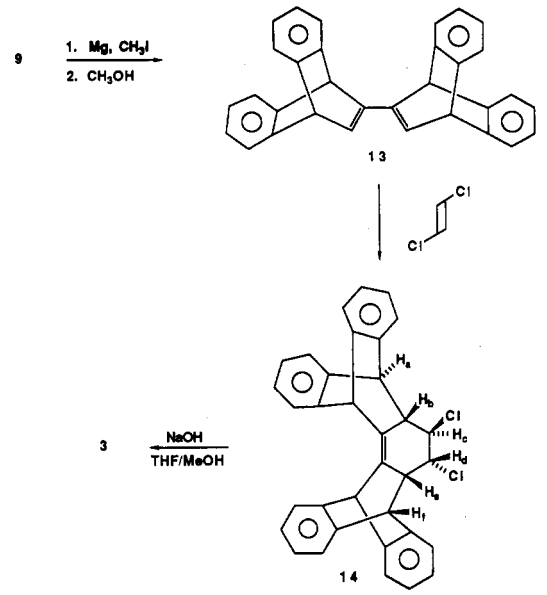
The structure of **12** was evident from its spectra. The ^{1}H NMR spectrum showed four one-proton singlets for the bridgehead protons (at δ 5.28, 5.83, 5.91, and 5.96), a one-proton singlet at δ 7.03 for the aromatic proton adjacent to the chlorine, and multiplets for the 16 remaining aromatic protons. The ^{13}C NMR spectrum of **12** showed four signals (at δ 50.02, 50.63, 50.83, and 53.94) for the bridgehead carbons. When **12** was converted to **3** by metal–halogen exchange followed by an aqueous quench,[7] the peaks due to the aliphatic protons were reduced to two singlets (at δ 5.31 and 5.94), and the carbon spectrum was similarly simplified (only two bridgehead carbon signals, at δ 50.51 and 54.59) as required by the C_{2h} symmetry of **3**.

An alternate synthesis of **3** was accomplished by reversing the above reaction sequence, i.e., by first removing the halogen from diene **9** and then adding dichloroethene

(6) Shahlai, K.; Hart, H. *J. Am. Chem. Soc.* **1988**, *110*, 7136–7140.

(7) Several attempts to generate an aryne from **12** by removing the proton adjacent to the chlorine with butyllithium either alone or with potassium *tert*-butoxide at various temperatures resulted, instead, in metal–halogen exchange.

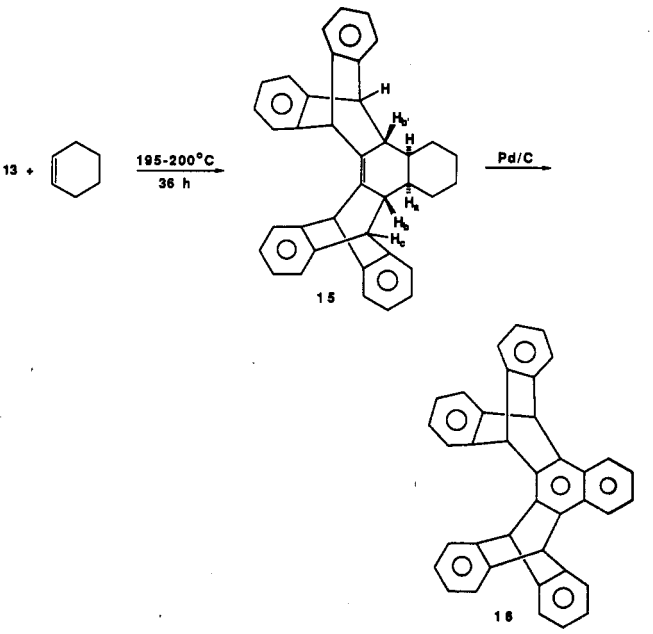
and dehydrohalogenating the adduct. This methodology



has the important consequence of providing the useful butadiene derivative **13**. Treatment of **9** with magnesium (using methyl iodide to initiate reaction) gave the Grignard reagent of **9**, which was quenched with methanol, resulting in a 91% yield of **13**, mp 323–324 °C.[8] Heating diene **13** with *trans*-1,2-dichloroethene (190–195 °C, 24 h) gave adduct **14**, mp 267–268 °C, in 91% yield.[9] Dehydrohalogenation of **14** gave **3** (87%), which was identical with a sample of **3** prepared from **12**.

Pentiptycene **3** can be regarded as having 9,10-anthradiyl moieties fused to the a and c bonds of a benzene ring. We next extended this methodology to the synthesis of iptycenes with 9,10-anthradiyl moieties fused to the a and c bonds of naphthalene and anthracene.

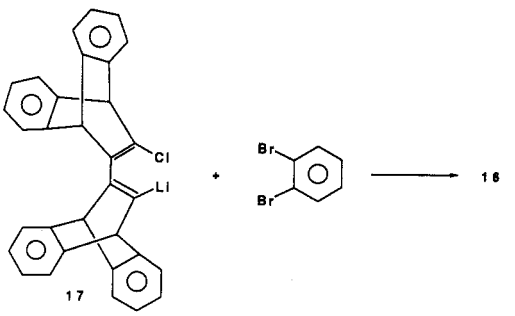
The naphthalene analogue of **3** was obtained as follows. A suspension of diene **13** in cyclohexene was heated at 195–200 °C in a sealed tube for 36 h to give adduct **15** in 91% yield. The stereochemistry of **15** was not unequivocally established, but it appeared to be a single isomer and is probably that as drawn (consistent with **14** and **18**).



Thus the bridgehead protons appeared as a singlet at δ 5.35 and a doublet at δ 4.18 (J = 2.3 Hz), coupled to allylic protons H_b at δ 1.88 on the cyclohexene ring. The ^{13}C NMR spectrum showed six peaks for the sp^3 carbons, as required by the symmetry of **15**.

Dehydrogenation of **15** to **16** was extraordinarily difficult and was accomplished in only 27% yield after 6 days of reflux with 10% Pd/C in mesitylene. However, **15** was converted quantitatively to **16** by dichlorodicyanoquinone (DDQ) in refluxing 1,1,2,2-tetrachloroethane. The product, mp 448–450 °C, had singlets at δ 6.17 and 6.21 for the bridgehead protons. The ^{13}C NMR spectrum of **16** had peaks at δ 50.17 and 51.25 for the two sets of sp^3 carbons; all the remaining peaks corresponded to aromatic carbons.

A one-step synthesis of **16** was also attempted. Treatment of **17**[10] with 1,2-dibromobenzene gave **16** but in only 17% yield. The reaction presumably involves metal–halogen exchange, generation of benzyne, and capture of the latter by **17**, followed by cyclization and loss of lithium chloride.[6]



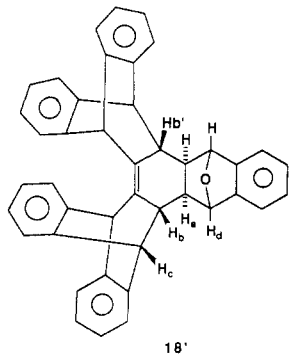
The anthracene analogue **20** was prepared as shown in Scheme I. Heating diene **13** with 1,4-epoxynaphthalene in refluxing xylene for 8 h gave a single cycloadduct **18** in 95% yield. Although not established unequivocally, the stereochemistry of **18** is probably as shown in **18′**.

Consistent with this stereochemistry, J_{ad} is essentially zero, and J_{bc} is small as a consequence of the near orthogonality of these proton pairs, whereas the anti relationship between H_a and H_b leads to a substantial J_{ab} (7.7 Hz). The upfield chemical shift of H_a (δ 0.97) is due to

(8) Use of *n*-butyllithium in place of magnesium to convert **9** to **13** was also possible, but required 2.2 equiv of BuLi due to competitive removal of the vinyl proton. The yield was only 63%, and the reaction presumably proceeds via the 1,4-dilithio diene. Ashe, A. J.; Drone, F. *Organometallics* **1985**, *4*, 1478–1480. Schleyer, P. v. R.; Kos, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 7928–7929.

(9) Although the dehydrohalogenation of **14** to **3** confirms the gross structure of **14**, its stereochemistry and NMR assignment required additional experimentation to establish. Irradiation at δ 2.31 (H_b) caused the following changes: the dd at δ 2.67 became a d, J = 6.8 Hz, the dt at δ 2.83 became a dd, J = 7.9, 2.0 Hz, and the d at δ 4.62 became a singlet. Irradiation at δ 2.67 (H_c) caused the following changes: the ddd at δ 2.31 became a m, the dd at δ 4.52 collapsed to a doublet, J = 7.9 Hz still split a little bit (J = 2.8 Hz) by coupling with H_c. Irradiation at δ 2.83 (H_e) caused the following changes: the ddd at δ 2.31 became a dd, J = 10.7, 2.0 Hz, the dd at δ 4.52 became a d, J = 6.8 Hz, and the d at δ 4.57 became a singlet. These data allowed the assignments to be made, and the spectrum could be reproduced by computer simulation. The small values of J_{ab} and J_{ef} are due to the near orthogonality of these protons. The small but observable coupling between H_b and H_e is not uncommon for cis-2,5 protons in a cyclohexene. The rather high field chemical shift of H_c vis-a-vis H_d (δ 2.67 and 4.52, respectively) is due to diamagnetic shielding by the benzene rings, and that of H_b vis-a-vis H_e (δ 2.31 and 2.84, respectively) is due to the anisotropy of the cis-chlorine. As a double check on these assignments, **9**-*d* was prepared (vinyl deuterium) by quenching **17**[6] with CH_3OD. Treatment of **9**-*d* with Mg, CH_3I followed by CH_3OH gave **13**-*d* with one of the vinyl protons replaced by deuterium (peak at δ 7.10 reduced in area to 1 H). Treatment of **13**-*d* with *trans*-1,2-dichloroethylene then gave **14**-*d* in which the peaks at δ 2.28–2.33 and δ 2.81–2.86 were reduced in area to 0.5 H each, all other peaks remaining the same in area.

(10) Compound **17** is the immediate precursor of **9** in its synthesis from **7**.[6]



18'

shielding by the "outer" aryl ring. The observed long-range couplings ($J_{ab'}$ = 2.3 Hz, $J_{bb'}$ = 1.8 Hz) are also consistent with this rigid geometry.

Dehydration of **18** with sulfuric acid in acetic anhydride (room temperature, 10 min) gave **19** in 73% yield. The ^{1}H NMR spectrum of **19** showed a broad singlet at δ 3.16 for the methine protons in the cyclohexene ring, a similarly broadened singlet at δ 5.14 for the adjacent bridgehead protons, and a sharp singlet at δ 5.46 for the remaining bridgehead protons.

Dehydrogenation of **19** with DDQ in refluxing benzene (12 h) gave the desired anthracene **20** in 92% yield. Solutions of **20** in methylene chloride were greenish yellow and strongly fluorescent. The ^{1}H NMR spectrum showed singlets at δ 6.25 and 6.36 for the bridgehead protons, a singlet at δ 8.84 for protons of the central anthracene ring, and appropriate peaks for the remaining aromatic protons. The ^{13}C NMR spectrum showed peaks at δ 50.64 and 51.57 for the bridgehead carbons and 13 aromatic carbon peaks as required by the C_{2h} symmetry. The structure of **20** was confirmed chemically by its reaction with benzyne to give **8**.

Finally, to illustrate the generality of this method, the dichloro analogue **22** was prepared (66% overall yield) from diene **13** and dichloronaphthalene endoxide **21**.[11] Pentiptycene **22** was obtained as a bluish-yellow solid, mp 380–382 °C. Its ^{1}H NMR spectrum showed bridgehead singlets at δ 6.29 and 6.40 and aromatic singlets at δ 7.39 and 9.26 (terminal and central anthracene rings, respectively), as well as appropriate multiplets for the remaining aromatic protons. The chlorines in **22** might serve as sites for the elaboration of the terminal ring of the anthracene moiety.

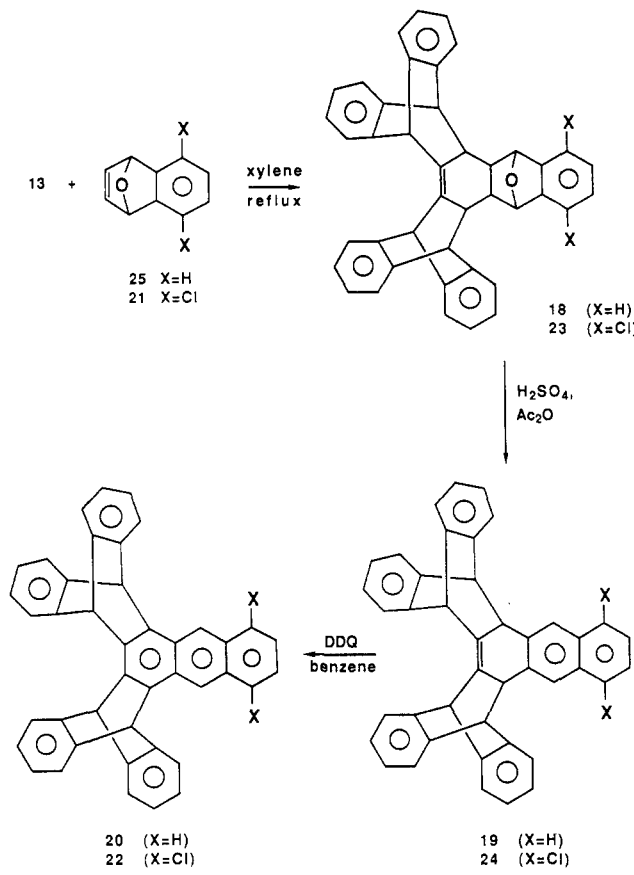
In summary, we describe here the synthesis of diene **13** and show how, through Diels–Alder cycloadditions, it and its chloro analogue **9** can be converted to angular iptycenes such as **3**, **16**, and **20**. The reaction of other dienophiles with these dienes promises to be useful in synthesizing more complex angular iptycenes.

Experimental Section

6-Chloro-5,8,13,14-tetrahydro-5,14:8,13-di-*o*-benzenopentaphene (12). A suspension of 1.77 g (4 mmol) of 3-chloro-1,4,1′,4′-tetrahydro-1,4:1′,4′-di-*o*-benzeno-2,2′-binaphthyl (**9**)[6] in 30 mL of *trans*-1,2-dichloroethylene in a sealed tube was heated at 190–195 °C for 36 h. After being cooled to 0 °C the tube was opened, and excess solvent was removed (rotavap). The residue (presumably a mixture of **10** and **11**) was added to 125 mL of THF/methanol (4:1) that contained 0.4 g (10 mmol) of sodium hydroxide. The mixture was heated at reflux for 48 h. The solvent was removed (rotavap); the residue was taken up in methylene chloride, washed with water, saturated sodium chloride, and dried

(11) Prepared together with the 5,6-dichloro isomer from 1,2,4-trichlorobenzene, butyllithium, and furan; see the Experimental Section for details.

Scheme I



($MgSO_4$). Evaporation of the solvent and chromatography of the residue (silica gel, 1:4 methylene chloride/hexane) gave 1.27 g (68%) of **12** as a white solid: mp 358–359 °C; ^{1}H NMR ($CDCl_3$) δ 5.28 (s, 1 H), 5.83 (s, 1 H), 5.91 (s, 1 H), 5.96 (s, 1 H), 6.94 (m, 8 H), 7.03 (s, 1 H), 7.29 (m, 2 H), 7.36 (m, 2 H), 7.42 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 50.02, 50.63, 50.83, 53.94, 121.11, 123.96, 124.08, 124.45, 125.84, 138.13, 139.31, 141.54, 144.13, 144.78, 144.89, 145.13; mass spectrum, *m/e* (relative intensity) 467 (6), 466 (M + 2$^+$, 43), 464 (M$^+$, 67), 429 (49), 138 (78), 111 (100), 82 (96), 77 (70). Anal. Calcd for $C_{34}H_{21}Cl$: C, 87.82; H, 4.56. Found: C, 87.91; H, 4.53.

5,8,13,14-Tetrahydro-5,14:8,13-di-*o*-benzenopentaphene (3) from 12. To a solution of **12** (930 mg, 2 mmol) in 30 mL of anhydrous THF under argon at room temperature was added dropwise 1.8 mL (2.2 eq) of 2.5 M *n*-butyllithium in hexane, and the mixture was heated at reflux for 4 h. Excess BuLi was destroyed by adding 1 mL of methanol. Solvent removal (rotavap) and chromatography of the residue on silica gel (hexanes/methylene chloride, 4:1) gave 487 mg (57%) of **3** as a white solid: mp 315–316 °C; ^{1}H NMR ($CDCl_3$) δ 5.31 (s, 2 H), 5.94 (s, 2 H), 6.94 (m, 10 H), 7.30 (m, 4 H), 7.42 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 50.51, 54.59, 120.43, 124.05, 125.71, 139.62, 142.57, 145.43, 146.01; mass spectrum, *m/e* (relative intensity) 431 (22), 430 (M$^+$, 100), 252 (49), 178 (20). Anal. Calcd for $C_{34}H_{22}$: C, 94.85; H, 5.15. Found: C, 94.89; H, 5.12.

1,4,1′,4′-Tetrahydro-1,4:1′,4′-di-*o*-benzeno-2,2′-binaphthyl (13). A mixture of **9** (4.40 g, 10 mmol), magnesium turnings (0.24 g, 10 mg-atom), and methyl iodide (0.1–0.3 mL) in anhydrous THF (100 mL) was heated at reflux under argon for 12–24 h, during which time the solution turned brownish-yellow. The mixture was quenched with methanol (5 mL). Evaporation of the solvent left a white solid, which was taken up in methylene chloride, washed with 5% hydrochloric acid, water, and saturated sodium chloride solution, and dried ($MgSO_4$). Evaporation of the solvent gave a yellow-white solid, which was triturated with ether to give 3.7 g (91%) of **13** as a white solid: mp 323–324 °C; ^{1}H NMR ($CDCl_3$) δ 5.13–5.16 (m, 4 H, bridgehead protons), 6.88 (m, 8 H), 7.10 (dd, 2 H, J = 6.0, 1.5 Hz, vinyl protons coupled to the adjacent and allylic bridgehead protons, respectively), 7.21 (m, 8 H); ^{13}C

NMR ($CDCl_3$) δ 51.31, 52.60, 123.12, 123.78, 124.90, 125.10, 131.04, 145.80; mass spectrum, *m/e* (relative intensity) 407 (6), 406 (M^+, 24), 228 (34), 203 (26), 202 (19), 191 (12), 178 (100). Anal. Calcd for $C_{32}H_{22}$: C, 94.54; H, 5.45. Found: C, 94.41; H, 5.48.

Preparation of 3 from 13. A suspension of **13** (1.63 g, 4 mmol) in 30 mL of *trans*-1,2-dichloroethene was heated in a sealed tube at 190–195 °C for 24 h. After being cooled to 0 °C, the tube was opened, and excess solvent was evaporated. Chromatography of the residue on silica gel using 5:1 hexanes/methylene chloride gave 1.84 g (91%) of a single isomer of 6,7-dichloro-5,6,7,8,13,14-hexahydro-5,14:8,13-di-*o*-benzenopentaphene (**14**) as an off-white solid: mp 267–268 °C; ^1H NMR ($CDCl_3$) δ 2.28–2.33 (ddd, J_{bc} = 10.7, J_{ab} = 2.3, J_{be} = 1.6 Hz, H_b), 2.64–2.71 (dd, J_{bc} = 10.7, J_{cd} = 6.8 Hz, H_c), 2.81–2.86 (dt, J_{de} = 7.9, J_{ef} = 2.0, J_{be} = 1.6 Hz, H_e), 4.50–4.54 (dd, J_{de} = 7.9, J_{cd} = 6.8 Hz, H_d), 4.56–4.57 (d, J_{ef} = 2.0 Hz, H_f), 4.62 (d, J_{ab} = 2.3 Hz, H_a), 5.31 (s, 1 H), 5.35 (s, 1 H), 7.03 (m, 8 H), 7.29 (m, 8 H); for experiments designed to elucidate the stereochemistry of **14** and assign its ^1H NMR spectrum see ref 9; ^{13}C NMR ($CDCl_3$) δ 45.62, 47.59, 48.56, 48.86, 49.11, 49.32, 66.63, 69.89, 122.80, 123.14, 123.57, 124.27, 124.50, 126.10, 126.19, 126.64, 126.86, 127.36, 128.15, 130.34, 131.16, 139.25, 141.54, 142.03, 142.34, 142.96, 143.16, 144.68; mass spectrum, *m/e* (relative intensity) 502 (M^+, 5), 467 (4), 431 (19), 289 (8), 253 (13), 178 (100). Anal. Calcd for $C_{34}H_{24}Cl_2$: C, 81.11; H, 4.80. Found: C, 80.94; H, 4.77.

A solution containing 0.4 g of sodium hydroxide and 1.52 g (3 mmol) of **14** in 250 mL of 4:1 THF/methanol was heated at reflux for 36 h. The solvent was removed (rotavap), and the residue was dissolved in methylene chloride, washed with water and saturated sodium chloride solution, and dried ($MgSO_4$). Evaporation of the solvent and chromatography of the residue (silica gel, 1:3 methylene chloride/hexanes) gave 1.15 g (87%) of **3**, identical with a sample prepared from **12**.

5,6,7,8,13,14,1′,2′,3′,4′-Decahydro-5,14:8,13-di-*o*-benzeno-6,7-benzopentaphene (15). A suspension of **13** (1.63 g, 4 mmol) in 30 mL of cyclohexene was heated at 195–200 °C in a sealed tube for 36 h. The tube was cooled to 0 °C and opened, and excess cyclohexene was removed (rotavap). Chromatography of the residue (silica gel, 4:1 hexanes/methylene chloride) gave 1.78 g (91%) of **15** as a white solid: mp 295–296 °C; ^1H NMR ($CDCl_3$) δ 0.46–0.50 (m, 2 H_a), 1.32 (br d, 2 H), 1.53 (br s, 6 H), 1.84–1.88 (dt, J_{ab} = 8.1, J_{bc} = 2.3, $J_{bb'}$ = 1.7 Hz, 2 H_b), 4.18–4.19 (d, J_{bc} = 2.3 Hz, 2 H_c), 5.35 (s, 2 H), 6.93–7.38 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ 23.75, 28.12, 40.41, 47.02, 49.05, 49.58, 123.33, 123.96, 124.83, 125.75, 126.58, 132.30, 141.25, 142.50, 142.83, 145.41; mass spectrum, *m/e* (relative intensity) 488 (1), 310 (8), 178 (100). Anal. Calcd for $C_{38}H_{32}$: C, 93.40; H, 6.60. Found: C, 93.49; H, 6.69.

5,8,13,14-Tetrahydro-5,14:8,13-di-*o*-benzeno-6,7-benzopentaphene (16). A mixture of **15** (490 mg, 1 mmol) and 200 mg of 10% palladium on charcoal in 50 mL of mesitylene was heated at reflux for 6 days. The mixture was cooled to 50 °C and filtered to remove the catalyst. Evaporation of the solvent and chromatography of the residue gave 128 mg (27%) of **16** as a white solid, mp 448–450 °C.

Alternatively, a solution of **15** (490 mg, 1 mmol) and DDQ (1.8 g, excess) in 1,1,2,2-tetrachloroethane (50 mL) was heated at reflux for 4 h. The mixture was chromatographed, with 3:1 hexanes/methylene chloride as the eluent. Evaporation of the solvent gave 480 mg (98%) of **16**, mp as above. For **16**: ^1H NMR ($CDCl_3$) δ 6.17 (s, 2 H), 6.21 (s, 2 H), 6.88–6.99 (m, 8 H), 7.38–7.50 (m, 10 H), 8.29 (dd, 2 H); ^{13}C NMR ($CDCl_3$) δ 50.17, 51.25, 123.42, 123.94, 124.11, 125.52, 125.58, 127.26, 139.36, 139.58, 146.07, 146.47. Anal. Calcd for $C_{38}H_{24}$: C, 94.96; H, 5.03. Found: C, 94.85; H, 5.11.

Alternate Synthesis of 16. The coupling product **17** was prepared in situ from 2.4 g (10 mmol) of **7** by the standard procedure,[6] except that instead of an aqueous quench, 1,2-dibromobenzene (2.4 g, 10 mmol) was added dropwise to refluxing **17**. When addition was complete, the mixture was heated under reflux for an additional 30 min. The solvent was removed (rotavap), the residue was taken up in methylene chloride, washed with water and saturated sodium chloride solution, and dried ($MgSO_4$). Evaporation of the solvent and chromatography of the residue on silica gel with 3:1 hexanes/methylene chloride as eluent, and subsequent recrystallization from acetone gave 410 mg (17%) of **16**, identical (melting point, spectra) with that prepared from **15**.

5,6,11,11a,11b,12,17,17a,17b,18-Decahydro-12,17-epoxy-5,18:6,11-di-*o*-benzenotrinaphthylene (18). A solution of **13** (1.02 g, 2.5 mmol) and 1,4-epoxynaphthalene (**25**) (0.36 g, 2.5 mmol) in 125 mL of xylenes was heated at reflux for 8 h, after which the solvent was removed (rotavap). Chromatography of the residue (silica gel, 2:1 hexanes/methylene chloride) gave 1.3 g (95%) of **18** as a white solid: mp 369–370 °C; ^1H NMR ($CDCl_3$) δ 0.95–0.99 (dd, J_{ab} = 7.7, $J_{ab'}$ = 2.3 Hz, H_a), 2.28–2.33 (dt, J_{ab} = 7.7, J_{bc} = 2.2, $J_{bb'}$ = 1.8 Hz, H_b), 4.39–4.40 (d, J_{bc} = 2.2 Hz, H_c), 5.28 (s, H_d), 5.30 (s, 2 H), 6.95 (m, 4 H), 7.08 (m, 6 H), 7.17 (m, 6 H), 7.31 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 46.10, 48.63, 49.54, 83.43, 119.14, 123.17, 124.01, 124.10, 125.80, 126.48, 126.87, 127.08, 131.05, 141.27, 142.29, 142.54, 144.23, 145.98; mass spectrum, *m/e* (relative intensity) 550 (5), 445 (1), 431 (2), 253 (5), 178 (100), 118 (46). Anal. Calcd for $C_{42}H_{30}O$: C, 91.60; H, 5.49. Found: C, 91.31; H, 5.63.

5,6,11,11a,17b,18-Hexahydro-5,18:6,11-di-*o*-benzenotrinaphthylene (19). To a solution of **18** (0.56 g, 1 mmol) in 15 mL of acetic anhydride was added slowly 2 mL of concentrated sulfuric acid. The solution was stirred for 10 min and then poured onto ice water. The organic product was extracted with ether. The ether extract was washed (3×) with 10% sodium hydroxide, water, saturated sodium chloride solution and dried ($MgSO_4$). Evaporation of the solvent and chromatography of the residue (silica gel, 4:1 hexanes/methylene chloride) gave 0.39 g (73%) of **19** as a white solid: mp >400 °C dec; ^1H NMR ($CDCl_3$) δ 3.15 (s, 2 H), 5.14 (s, 2 H), 5.46 (s, 2 H), 6.85 (m, 4 H), 7.12 (m, 6 H), 7.39 (m, 8 H), 7.48 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 46.30, 46.68, 48.88, 122.63, 123.02, 124.23, 125.71, 125.99, 126.58, 127.92, 131.08, 132.00, 138.97, 140.85, 142.44, 144.47; mass spectrum, *m/e* (relative intensity) 533 (8), 532 (29), 355 (24), 354 (100), 353 (50), 179 (8), 178 (15), 86 (24), 84 (44); high-resolution mass spectrum: calcd for $C_{42}H_{28}$ 532.6914, found 532.6882.

5,6,11,18-Tetrahydro-5,18:6,11-di-*o*-benzenotrinaphthylene (20). A solution of **19** (0.54 g, 1 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.23 g, 1 mmol) in 50 mL of benzene was heated at reflux under argon for 12 h. Evaporation of the solvent and chromatography of the solid residue on silica gel (3:1 hexanes/methylene chloride) gave 0.50 g (92%) of **20** as a yellow solid: mp 470–472 °C dec; ^1H NMR ($CDCl_3$) δ 6.25 (s, 2 H), 6.36 (s, 2 H), 6.94 (m, 8 H), 7.39 (dd, 2 H), 7.48 (m, 8 H), 8.03 (dd, 2 H), 8.84 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 50.64, 51.57, 121.70, 123.95, 124.12, 126.58, 127.69, 128.81, 129.20, 131.69, 146.26, 146.70; mass spectrum, *m/e* (relative intensity) 531 (30), 530 (100), 352 (36), 256 (7); high-resolution mass spectrum calcd for $C_{42}H_{26}$ 530.6755, found 530.6735.

Synthesis of 8 from 20. A mixture of **20** (0.531 g, 1 mmol), benzenediazoniumcarboxylate hydrochloride (0.8 g), and propylene oxide (1 mL) in 25 mL of 1,2-dichloroethane was heated at reflux for 12 h. Removal of the solvent and chromatography of the residue on silica gel (4:1 hexanes/methylene chloride) gave 158 mg (26%) of **8**, identical (NMR) with an authentic sample.[1,5]

5,8-Dichloronaphthalene 1,4-Endoxide (21). To a solution of 1,2,4-trichlorobenzene (9.1 g, 0.05 mol) and furan (34 g, 0.5 mol) in anhydrous THF (100 mL) under argon at −78 °C was added dropwise 22 mL (1.1 equiv) of 2.5 M *n*-BuLi in hexanes. After addition was complete, the mixture was allowed to warm to room temperature and then was heated at reflux for 30 min. Solvent and excess furan were removed (rotavap), and the dark oily residue was taken up in ether, washed with water and saturated sodium chloride solution, and dried ($MgSO_4$). Evaporation of the ether and chromatography of the remaining oil on silica gel with 6:1 hexanes/methylene chloride as eluent gave 3.27 g (30.7%) of **21** and 4.08 g (38.3%) of its 5,6-dichloro isomer. For the 5,6-dichloro isomer of **21**: mp 72–73 °C; ^1H NMR ($CDCl_3$) δ 5.72 (m, 1 H, *J* = 1 Hz), 5.85 (br s, 1 H), 7.04–7.08 (m, 4 H); mass spectrum, *m/e* (relative intensity) 216 (1), 214 (5), 212 (8), 188 (22), 186 (39), 151 (33), 149 (100), 113 (21), 63 (23). Anal. Calcd for $C_{10}H_6Cl_2O$: C, 56.37; H, 2.83. Found: C, 56.19; H, 2.72. For **21**: ^1H NMR ($CDCl_3$) δ 5.86–5.87 (t, *J* = 1 Hz, 2 H), 6.82 (s, 2 H), 7.06–7.07 (t, *J* = 1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 82.38, 125.21, 127.85, 143.17, 149.77; mass spectrum, *m/e* (relative intensity) 214 (2), 212 (4), 188 (20), 186 (39), 151 (33), 149 (100), 113 (24), 105 (43), 63 (27). Anal. Calcd for $C_{10}H_6Cl_2O$: C, 56.37; H, 2.83. Found: C, 56.44; H, 2.75.[12]

13,16-Dichloro-5,6,11,18-tetrahydro-5,18:6,11-di-*o*-benzenotrinaphthylene (22). Diene **13** (2.5 mmol) and endoxide **21** (2.5 mmol) were allowed to react in the same manner as in the preparation of **18** to give 1.42 g (91%) of cycloadduct **23** as a white solid: mp 360-361 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (dd, 2 H), 2.31 (br d, 2 H), 4.40 (d, 2 H), 5.29 (s, 2 H), 5.49 (s, 2 H), 6.90 (s, 2 H), 6.98 (m, 4 H) 7.09 (m, 4 H), 7.21 (m, 4 H), 7.32 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 45.61; 48.55, 49.29, 83.06, 123.15, 124.11, 124.46, 126.14, 126.19, 126.57, 126.95, 129.00, 131.13, 141.04, 142.39, 143.95, 145.49; mass spectrum, *m/e* (relative intensity) 620 (0.3), 618 (0.9), 431 (3), 186 (10), 178 (100), 86 (16), 84 (26). Anal. Calcd for $C_{42}H_{28}Cl_2O$: C, 81.42; H, 4.55. Found: C, 81.44; H, 4.53.

Adduct **23** (0.62 g, 1 mmol) was dehydrated in the same manner as **18** to give 0.46 g (76%) of **24** as a pale yellow solid: mp 340-342 °C; ^{1}H NMR ($CDCl_3$) δ 3.21 (s, 2 H), 5.20 (s, 2 H), 5.47 (s, 2 H), 6.89 (m, 4 H), 7.15 (m, 8 H), 7.36 (s, 2 H), 7.45 (m, 4 H), 8.27 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 46.6 (2 peaks overlapped), 49.0, 120.5, 123.3, 124.1, 124.7, 126.0, 126.1, 126.4, 126.9, 127.0, 130.4, 131.3, 140.9, 141.4, 142.6, 142.8, 144.3, 146.0; mass spectrum, *m/e* (relative intensity) 603 (2), 602 (6), 601 (6), 600 (18), 598 (15), 422 (20), 179 (27), 178 (100); high-resolution mass spectrum calcd for $C_{42}H_{26}Cl_2$ 601.5817, found 601.5695.

Dehydrogenation of **24** (0.60 g, 1 mmol) with DDQ in 75 mL of benzene was accomplished as for **19** to give 0.57 g (95%) of **22** as a bluish-yellow solid: mp 380-382 °C; ^{1}H NMR ($CDCl_3$) δ 6.29 (s, 2 H), 6.40 (s 2 H), 6.97 (m, 8 H), 7.39 (s, 2 H), 7.51 (m, 4 H), 7.53 (m, 4 H), 9.26 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 50.72, 51.64, 120.00, 124.06, 124.32, 125.03, 125.72, 127.05, 129.20, 131.66, 140.63, 141.49, 145.95, 146.33; mass spectrum, *m/e* (relative intensity) 602 (3), 601 (10), 600 (40), 598 (48), 422 (16), 420 (26), 264 (18), 262 (14), 178 (46), 44 (100). Anal. Calcd for $C_{42}H_{24}Cl_2$: C, 84.14; H, 4.03. Found: C, 84.22; H, 4.11.

(12) The two isomers were readily distinguished by the fact that the two bridgehead protons in **21** were identical (δ 5.86-5.87) whereas in the 5,6-isomer they were different (δ 5.72, 5.85). Also, the aryl protons in **21** appeared as a sharp singlet (δ 6.82). Finally, the ^{13}C NMR spectrum of **21** showed only five peaks, as required for the C_s symmetry.

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Synthesis of New Aromatic Retinoid Analogues by Low-Valent Titanium Induced Reductive Elimination

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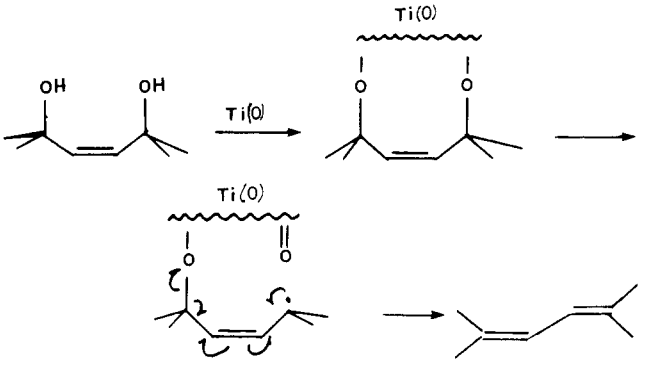
The low-valent titanium reductive elimination reaction, already applied to the stereospecific synthesis of vitamin A and 13-*cis*-retinol, was used to prepare several retinoic acid analogues in the all-trans configuration or in the 13-cis configuration. This highly stereospecific trans-diene formation allowed an improved synthesis of the title compounds without any purification of the intermediates before the final stage.

all-trans-Retinoic acid and its 13-cis isomer are used for the treatment of dermatological diseases such as acne and have been evaluated[1-6] for their possible beneficial effects in several cancerous conditions.[7-9] Unfortunately, their severe biological side effects (hypervitaminosis A syndrome, etc.) render their extensive clinical use difficult.

In an effort to obviate these drawbacks, many new analogues have been prepared.[10-12] Among these new molecules, aromatic analogues were shown to be interesting targets. However, a very small number contains a chroman unit.[11,12] With the hope of finding a less toxic retinoid we have synthesized some new chroman analogues with the low-valent titanium reductive elimination.

Low-valent titanium reductive elimination first used by Walborsky[13] to prepare 1,3-dienes from 2-ene-1,4-diols was



(1) Mayer, H.; Bollag, W.; Hanni, R.; Ruegg, R. *Experientia* **1978**, *34*, 1105.
(2) Dawson, M. I.; Hobbs, P. D.; Chan, R. L.; Chao, W. R.; Fung, V. A. *J. Med. Chem.* **1981**, *24*, 583.
(3) Dawson, M. I.; Hobbs, P. D.; Chan, R. L. S.; Chao, W. R. *J. Med. Chem.* **1981**, *24*, 1214.
(4) Pawson, B. A.; Ehmann, C. W.; Itri, L. M.; Sherman, M. I. *J. Med. Chem.* **1982**, *25*, 1269.
(5) Lowe, N. J. *J. Am. Acad. Dermatology* **1986**, *15*, 766.
(6) Cunliffe, W. J. *Biochem. Soc. Trans.* **1986**, *14*, 943.
(7) Lotan, R.; Neumann, G.; Lotan, D. *Cancer Res.* **1980**, *40*, 1097.
(8) Newton, D. L.; Henderson, W. R.; Sporn, M. B. *Cancer Res.* **1980**, *40*, 3413.
(9) Dawson, M. I.; Hobbs, P. D.; Kuhlman, K.; Fung, V. A.; Helmes, C. T.; Chao, W. R. *J. Med. Chem.* **1980**, *23*, 1013.
(10) Loeliger, P.; Bollag, W.; Mayer, H. *Eur. J. Med. Chem.* **1980**, *15*, 9.
(11) Dawson, M. I.; Hobbs, P. D.; Derdzinski, K.; Chan, R. L. S.; Gruber, J.; Chao, W.; Smith, S.; Thies, R. W.; Schiff, L. *J. Med. Chem.* **1984**, *27*, 1516.
(12) Wangh, K. M.; Berlin, K. D.; Fod, W. T.; Holt, E. M.; Carrol, J. P.; Schomber, P. R.; Thompson, M. D.; Schiff, L. J. *J. Med. Chem.* **1985**, *28*, 116.

0022-3263/89/1954-2620$01.50/0