High-Pressure Diels–Alder Reactions of 1-Oxa[4.4.4]propella-5,7-diene Proceed with Framework Isomerization

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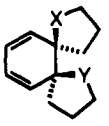
The title compound is shown to be unreactive to Diels–Alder cycloaddition under high pressure conditions. However, by virtue of acid catalysis (spontaneous or purposeful), the propelladiene experiences rearrangement to a diene isomer which, although thermodynamically less favored, is reactive toward several classical dienophiles. Extensive use has been made of 2-D NMR and X-ray crystallography in product characterization. The distributions of the adduct pairs show that the oxido atom does not exert a consistent oriental dominance on π-facial selectivity. The heats of formation of the isomeric dienes, estimated by molecular mechanics calculations, are consistent with the experimental inability to isolate and characterize the rearrangement product.

The recent availability of dispiro[4.0.4.4]tetradeca-11,-13-dienes substituted with one or two heteroatoms as in **1** and **2** has brought to light several interesting properties of these systems. Regardless of the level of incorporation of oxygen or sulfur at X and Y or of their relative



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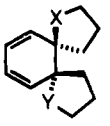

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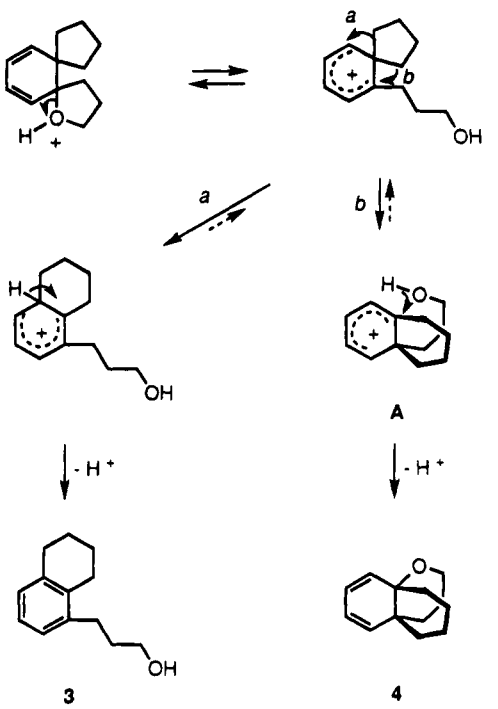
stereochemical disposition, a sensitivity to structural rearrangement is observed. In the specific case of acid catalysis,[3] an interplay between steric and electronic factors has been put forward as the controller of competing aromatization and conversion to a [4.4.4]propelladiene such as **4** (Scheme 1). Exposure of the monooxa derivative to 8 mol % of *p*-toluenesulfonic acid at 25 °C gives rise to a 1:2 mixture of **3** and **4**.[3] Tetracyanoethylene is also capable of promoting this isomerization, a 1:3.5 ratio of the same two products being formed after 20 h in $CDCl_3$.[4] Polar charge-transfer intermediates have been implicated in the latter reactions.

Dienes **1** and **2** (as well as **4**) are also recognized to be quite unreactive toward dienophiles.[5] The one exception is *N*-methyltriazolinedione (MTAD), which cycloadds with high levels of facial selectivity in most cases. The exclusive formation of **6** from **5** and of **9** from **4** is illustrative (Scheme 2). When lesser reactive 2π reagents such as *N*-phenylmaleimide (NPM) are involved, high-pressure conditions are required to induce **5** to react and a tertiary amine must be present to curtail acid-catalyzed rearrangement. The 13:1 distribution of **7** and **8** denotes that respectable stereocontrol persists, although in the direction opposite to that preferred by MTAD!

The fate of **4** under similar conditions is not to enter

Scheme 1



into observable cycloaddition. However, omission of the buffer culminates in successful Diels–Alder chemistry.

Herein, we demonstrate that the reactive diene is actually not **4**, but an isomer thereof. These findings reveal the mechanistic considerations outlined in Scheme 1 to be incomplete.

Results

Reaction of **4** with 1,4-naphthoquinone (NQ) took place slowly in CH_2Cl_2 solution under 200 000 psi of pressure during 14 days. Chromatography on silica gel afforded the adducts **10** and **11** in isolated yields of 16 and 11%, respectively. In their ^{13}C NMR spectra, both products exhibit carbon atoms adjacent to oxygen which were of the methine (85.7 and 82.1 ppm) and methylene type (61.7 and 62.2 ppm). Structures related to **6–9** could

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(1) Procter and Gamble Graduate Fellow, 1993.

(2) Author to whom inquiries should be addressed regarding the X-ray crystallographic analyses.

(3) Branan, B. M.; Paquette, L. A. *J. Am. Chem. Soc.* **1994**, *116*, 7658.

(4) Paquette, L. A.; Branan, B. M. *Heterocycles* **1995**, *40*, 101.

(5) Branan, B. M. Ph.D. Thesis, The Ohio State University, 1994.

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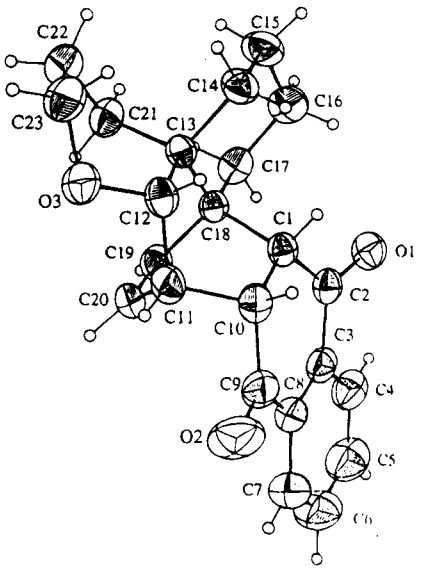
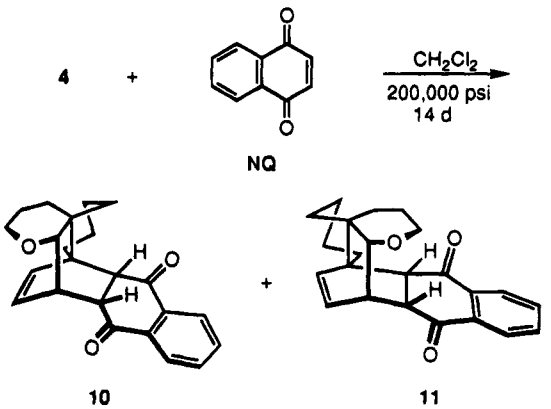
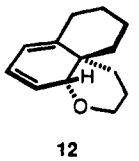


Figure 1. Computer-generated perspective drawing of **10** as determined by X-ray crystallography.

consequently be dismissed immediately. Since the 300 MHz ^{1}H NMR spectrum of **10** did not prove amenable to first-order analysis because of many overlapping signals, its structural features were established by X-ray crystallographic analysis.[15] As seen in Figure 1, the dienophile has actually been captured by the isomeric diene **12** with



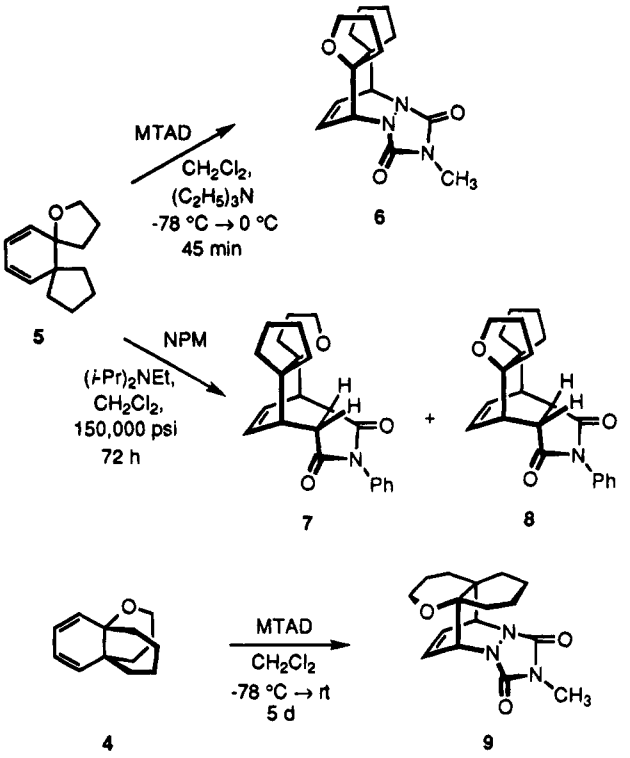
endo selectivity and from that direction anti to the ethereal oxygen. In the solid, state, the tetrahydropyranyl ring in **10** exists in a twist-boat geometry while its fused cyclohexane part structure adopts an approximate chair-like arrangement. The very close similarity of the spectral features of **10** and **11** (see the Experimental Section) allowed the latter to be confidently assigned as the syn isomer.



12

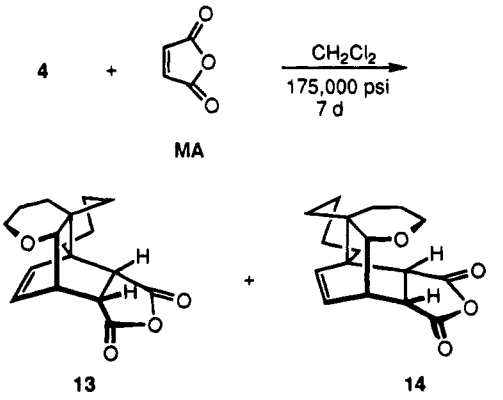
Maleic anhydride (MA) proved to be somewhat more reactive in the present setting. When pressurized with **4** (in CH_2Cl_2) to 175 000 psi, reaction was complete in 7 days. Uniquely in this example did the presence of a catalytic quantity of tertiary amine (viz., Hünig's base)

Scheme 2



have no obvious impact on the progress of reaction.[6] Two cycloadducts were again formed. Following their separation, the major isomer **14** (34%) was found to predominate by a factor of approximately 2 over **13** (19%). Consequently, orientational dominance by the ether oxygen does not follow a consistent pattern.

^{13}C-DEPT, H/C-COSY, and INEPT experiments performed on **14** made possible a mapping of its entire carbon connectivity. However, selective NOE studies did not prove definitive of relative stereochemistry. For this reason, recourse was again made to X-ray crystal-



lography.[15] By this means, **14** was demonstrated to be the syn isomer (Figure 2) and the general topology of its two pendant rings were seen to closely mirror those found in **10**. The most significant difference resides in the direction in which the cyclohexane chair is projected. In the anti adduct, this subunit resides in the vicinity of the dienophile. When syn stereochemistry prevails, the cyclohexane ring lies much closer to the bicyclo[2.2.2]-octene double bond. Not unexpectedly, therefore, the

(6) Evidently, sufficient acid is liberated by the MA under these conditions to overwhelm the minor proportion of (*i*-Pr)$_2$NEt present.

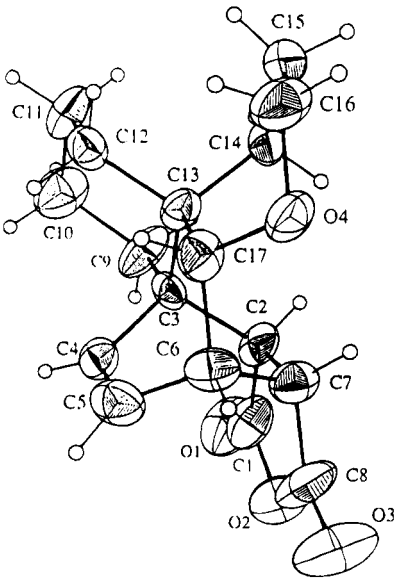
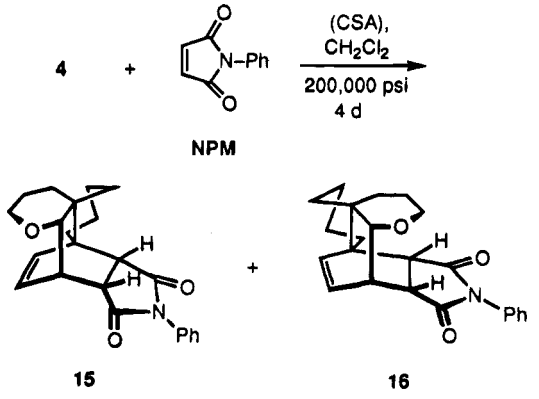


Figure 2. Computer-generated perspective drawing of **14** as determined by X-ray crystallography.

NOE interaction between H-4 and H-9 in **14** (see X-ray numbering) is of a magnitude (4%) indicative of their spatial proximity. That **13** was the π-facial isomer of **14** was again clearly evident on the basis of its close spectral similarities.

N-Phenylmalemide (NPM) exhibits no tendency to react with **4** at 200 000 psi when Hünig's base is present. If a small crystal of camphorsulfonic acid is added instead, smooth reaction occurs in the course of 4 days to provide a near-equal mixture of **15** (23%) and **16** (29%).

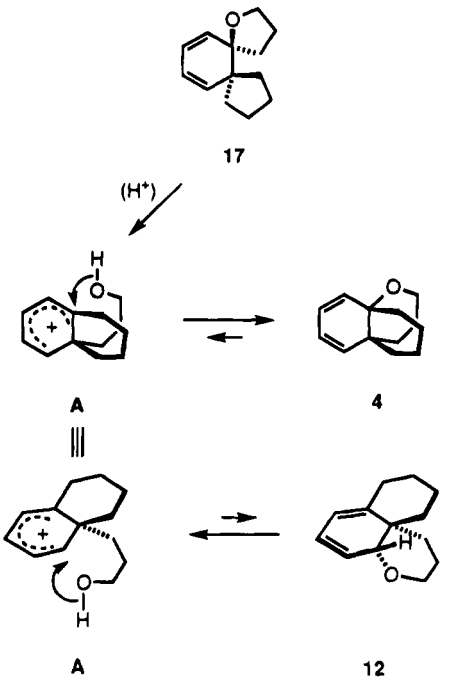


As before, a large battery of 2-D NMR experiments was applied to **15** and **16** in order to map out their connectivities and confirm their overall structural features. Identification of **16** as the syn isomer rests on the NOE interactions observed between the methine proton adjacent to oxygen and the nearby olefinic (1.5%) and bridgehead (13%) protons. In **15**, the same methine proton interacts only with the bridgehead proton (9%).

Discussion

[4.4.4]- and [4.4.3]propelladienes related to **4** have been extensively investigated and shown to undergo π-facially selective cycloadditions to triazolinediones.[7] Their limited reactivity as 4π reaction partners, although not widely touted, is anticipated as a consequence of the neopentyl nature of the terminal diene carbon atoms. The inference is that an approaching dienophile finds it difficult to position itself within bonding distance to these centers, even when an endo alignment has been adopted. The success achieved with MTAD and its congeners may stem from a skirting of the classical Diels–Alder pathway in favor of a reaction channel involving aziridinium imide intermediates.[8-11]

Scheme 3



The existing propellane literature is notably lacking of examples where structural rearrangement precedes capture of a dienophile. This may be ascribed to the prior absence of compounds possessing heteroatoms directly linked to the central ring-conjoining carbons. This is not the case with **4**, which clearly experiences unimolecular acid-catalyzed rearrangement to **12** in advance of cycloaddition (Scheme 3). The most expedient way to accomplish this isomerization involves initial C–O bond heterolysis to produce cation **A**, which recloses by intramolecular nucleophilic attack at the alternative terminus of the pentadienyl system as shown. It will be recalled (see Scheme 1) that intermediate **A** also likely serves as a direct precursor to **4** when **17** is treated with a catalytic quantity of *p*-toluenesulfonic acid.

While the greater reactivity of **12** as a Diels–Alder diene can be readily appreciated on simple steric grounds, our singular inability to observe **12** following acid treatment of either **17**[3] or **4** is of added mechanistic significance. A principal consideration is the relative facility with which **4** interconverts with **12**. This equilibrium must favor **4** since the concentration gradient of **12** never becomes sufficiently large to be detected spectroscopically or chromatographically. The irreversible consumption of **12** in a [4 + 2] cycloaddition does, however, reveal its capability for being produced via cyclization of **A**. For

(7) (a) Ginsburg, D. *Acc. Chem. Res.* **1974**, *7*, 286. (b) Ginsburg, D. *Propellanes. Structure and Reactions*; Verlag Chemie: Weinheim, 1975. (c) Ginsburg, D. *Tetrahedron* **1983**, *39*, 2095. (d) Gleiter, R.; Ginsburg, D. *Pure Appl. Chem.* **1979**, *51*, 1301.

(8) Seymour, C. A.; Greene, F. D. *J. Am. Chem. Soc.* **1980**, *102*, 6384.
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didactic reasons, the equilibrium arrows in Scheme 3 have been drawn to reflect this thermodynamic bias.

MM2 calculations (MODEL version KS 2.99)[12] performed on **4** and **12** show the heat of formation of the latter to exceed that of the propellane by 3.1–4.0 kcal/mol.[13,14] Although this difference may reside within the error bounds of such calculations, the data are suggestive as to why the presence of **12** is not observed in the absence of a kinetic trap. The high-pressure Diels–Alder additions described herein serve as a convenient forum for its detection.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at the indicated field strengths. High resolution mass spectra were recorded at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All reactions were carried out under a nitrogen atmosphere and the ensuing separations were effected under flash chromatography conditions on Merck silica gel HG_{254}. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases dried before use.

Cycloaddition of 1,4-Naphthoquinone to 4. Diene **4** (103 mg, 0.541 mmol), 1,4-naphthoquinone (94 mg, 0.595 mmol), and dry CH_2Cl_2 (2 mL) were placed in a high-pressure reaction tube and subjected to 200 000 psi for 14 d. At this point, TLC analysis revealed that quantities of **4** and NQ still remained. After solvent evaporation, the residue was chromatographed on silica gel (elution with 10% ethyl acetate in hexanes) to afford in order of elution recovered **4** (40 mg), 1,4-naphthoquinone (55 mg), **11** (21 mg, 11%), and **10** (30 mg, 16%).

For **10**: colorless crystals, mp 197–198 °C (from ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 7.90–7.84 (m, 1 H), 7.81–7.76 (m, 1 H), 7.67–7.59 (m, 2 H), 5.90–5.85 (m, 1 H), 5.62 (dd, J = 8.1, 0.9 Hz, 1 H), 3.86–3.74 (m, 2 H), 3.27–3.14 (m, 4 H), 2.16–2.03 (m, 1 H), 1.90–1.72 (m, 3 H), 1.71–1.56 (m, 3 H), 1.55–1.38 (m, 3 H), 1.37–1.23 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 198.5, 198.0, 138.8, 138.5, 136.3, 134.1, 133.4, 128.4, 126.2, 126.0, 85.7, 61.7, 48.6, 46.9, 46.5, 43.3, 42.3, 30.0, 26.6, 20.9, 20.1, 19.4, 19.2; MS m/z (M^+) calcd 348.1725, obsd 348.1732. Anal. Calcd for $C_{23}H_{24}O_3$: C, 79.28; H, 6.94. Found: C, 79.02; H, 6.99.

For **11**: white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90–7.86 (m, 1 H), 7.82–7.78 (m, 1 H), 7.66–7.59 (m, 2 H), 5.89–5.83 (m, 2 H), 4.00 (td, J = 11.2, 3.0 Hz, 1 H), 3.78 (dd, J = 8.7, 2.0 Hz, 1 H), 3.38–3.29 (m, 2 H), 3.09–3.05 (m, 1 H), 2.73 (d, J = 3.3 Hz, 1 H), 1.96–1.69 (m, 4 H), 1.59–1.38 (m, 6 H), 1.37–1.23 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 199.2, 198.2, 138.6, 138.4, 136.2, 133.9, 133.3, 128.1, 126.1 (2 C), 82.1, 62.2, 51.3, 46.7, 44.6, 43.5, 37.6, 34.2, 28.5, 23.2, 21.0, 18.2, 17.5; MS m/z (M^+) calcd 348.1725, obsd 348.1728.

Cycloaddition of Maleic Anhydride to 4. A solution of **4** (101 mg, 0.532 mmol), maleic anhydride (57 mg, 0.585 mmol), and diisopropylethylamine (9.4 mg, 0.07 mmol) in CH_2Cl_2 (3 mL) was subjected to a pressure of 175 000 psi for 7 days. Solvent evaporation left a solid which was chromatographed on silica gel (elution with 20% ethyl acetate in hexanes) to give 53 mg (34%) of **14** and 30 mg (19%) of **13**.

For **13**: white solid; ^1H NMR (300 MHz, $CDCl_3$) δ 6.19–6.15 (m, 1 H), 6.00 (d, J = 7.5 Hz, 1 H), 3.82 (td, J = 11.3, 3.0 Hz, 1 H), 3.64 (d, J = 8.9 Hz, 1 H), 3.25–3.21 (m, 2 H), 3.15 (td, J = 10.0, 3.0 Hz, 1 H), 2.94 (d, J = 2.0 Hz, 1 H), 2.40–2.34 (m, 1 H), 1.93–1.55 (m, 8 H), 1.54–1.42 (m, 1 H), 1.31–1.10 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 172.1, 171.6, 138.8, 128.3, 84.4, 61.9, 44.6, 42.6, 41.1, 41.0, 37.9, 29.9, 24.8, 20.6, 20.0, 18.9, 18.7; MS m/z (M^+) calcd 288.1362, obsd 288.1346.

For **14**: colorless crystals, mp 137.5–138.5 °C (from ether); ^1H NMR (300 MHz, $CDCl_3$) δ 6.24–6.14 (m, 2 H), 3.93 (td, J = 11.3, 3.6 Hz, 1 H), 3.59 (dd, J = 8.7, 2.8 Hz, 1 H), 3.33–3.24 (m, 1 H), 3.22–3.18 (m, 1 H), 3.11 (d, J = 8.7 Hz, 1 H), 2.75 (d, J = 3.2 Hz, 1 H), 2.43–2.37 (m, 1 H), 1.92–1.82 (m, 2 H), 1.81–1.42 (series of m, 6 H), 1.27–1.15 (m, 2 H), 1.09–0.99 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 173.4, 172.3, 139.2, 127.3, 80.9, 62.2, 46.7, 44.2, 39.4, 38.8, 36.9, 33.4, 27.3, 22.4, 20.9, 17.8, 17.4; MS m/z (M^+) calcd 288.1362, obsd 288.1364. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.64; H, 7.00.

Cycloaddition of *N*-Phenylmaleimide to 4. Diene **4** (51 mg, 0.269 mmol), *N*-phenylmaleimide (51 mg, 0.296 mmol), a single small crystal of camphorsulfonic acid, and CH_2Cl_2 (2 mL) were combined and subjected to 200 000 psi for 4 days. Solvent evaporation and silica gel chromatography (elution with 20% ethyl acetate in hexanes) afforded 29 mg (29%) of **16** followed closely by 23 mg (23%) of **15**.

For **15**: colorless crystals, mp 201–203 °C (from 40% ethyl acetate in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.31 (m, 3 H), 7.18–7.14 (m, 2 H), 6.16 (dd, J = 8.2, 6.1 Hz, 1 H), 5.98 (d, J = 7.9 Hz, 1 H), 3.84 (td, J = 11.2, 2.9 Hz, 1 H), 3.54 (d, J = 8.2 Hz, 1 H), 3.32–3.30 (m, 1 H), 3.28–3.18 (m, 1 H), 3.02–2.98 (m, 2 H), 2.55–2.51 (m, 1 H), 1.91–1.44 (series of m, 9 H), 1.35–1.23 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 177.2, 177.1, 138.4, 131.9, 129.0, 128.5, 127.5, 126.5, 85.2, 62.0, 44.8, 41.9, 41.5, 40.0, 38.6, 29.9, 25.0, 20.8, 20.2, 19.0, 18.0; MS m/z (M^+) calcd 363.1834, obsd 363.1842. Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93. Found: C, 75.81; H, 6.68.

For **16**: colorless crystals, mp 195 °C dec (from 40% ethyl acetate in hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.31 (m, 3 H), 7.21–7.14 (m, 2 H), 6.22–6.12 (m, 2 H), 3.96 (td, J = 11.3, 3.4 Hz, 1 H), 3.49 (dd, J = 8.0, 2.7 Hz, 1 H), 3.35–3.24 (m, 2 H), 3.01 (d, J = 8.0 Hz, 1 H), 2.79 (d, J = 3.2 Hz, 1 H), 2.56–2.49 (m, 1 H), 1.94–1.87 (m, 2 H), 1.85–1.68 (m, 2H), 1.63-1.23 (series of m, 6 H), 1.14–1.04 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 178.4, 177.8, 138.5, 132.1, 129.0, 128.4, 126.8, 126.5, 81.6, 62.2, 45.6, 44.7, 39.2, 38.6, 37.3, 33.7, 27.8, 22.6, 21.1, 18.0, 17.3; MS m/z (M^+) calcd 363.1834, obsd 363.1839.

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(13) For a relevant review, consult Lipkowitz, K. B.; Peterson, M. A. *Chem. Rev.* **1993**, *93*, 2463.

(14) A multiconformer search within the Grid Search function initially generated >980 conformers of **4** and >520 conformers for **12**. Subsequent MM2 minimization gave rise to two local minima in each example. The MMX function was then used to optimize these minima in order to ensure discovery of the global energy minimum. The respective energy values were derived by both restricted Hartree–Fock (RHF) and unrestricted Hartree–Fock (UHF) methods. The π-systems of both isomers were *not* restricted to planarity for any of the calculations. The following energy data were produced:

	ΔH_f	Strain Energy	Total Energy
4 (RHF)	-29.08	14.51	24.57
4 (UHF)	16.60	13.69	23.75
12 (RHF)	-25.08	16.59	26.02
12 (UHF)	19.71	15.61	25.04

(15) The authors have deposited the atomic coordinates for the X-ray structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.