Synthesis and Molecular Structure of (Z)-[6]Paracycloph-3-enes

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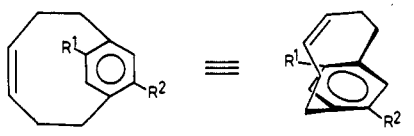
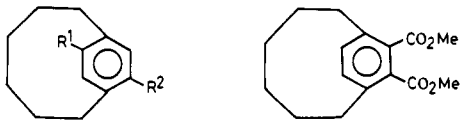
Abstract: (*Z*)-[6]Paracycloph-3-ene (**1a**) and its ester derivatives **1b** and **1c**, the smallest bridged [*n*]paracyclophanes having a double bond in the bridge, have been synthesized successfully by utilizing the thermal valence isomerization of the corresponding Dewar benzene isomers **5a–c**. Examination of the spectroscopic data, especially that of **1a**, has provided qualitative but important information concerning the conformation of the bridge and the deformation of the benzene ring and the bridge double bond. Namely, the upfield shift in the ^{1}H NMR spectra of the vinyl protons and the aromatic protons located on the same side with the bridge double bond and the downfield shift in the ^{13}C NMR spectra of the aromatic carbons on the same side with the double bond indicate that the double bond is located closely over the aromatic ring. Moreover, the vinyl–allylic and benzyl–allylic coupling constants in the ^{1}H NMR spectra suggest that the plane of the double bond tilts toward the opposite direction against the benzene plane. The large olefinic vicinal coupling constant (^3J(H(3)–H(4)) = 12.2 Hz) and low wavenumber C=C stretching band in the IR spectrum of **1a** suggest that the bond angle of the double bond (C(3)–C(4)–C(5)) is remarkably expanded (128°) and the bond length of the double bond is coniderably stretched, respectively. The remarkable bathochromic shift in the long wavelength region of the electronic spectra of **1a–c** relative to the corresponding [6]paracyclophanes **2a–c** indicates that the out-of-plane bending of the benzene ring of **1a–c** is greater than that of **2a–c**. The rate of mutual isomerization between the conformational isomers, *anti*-**1b** and *syn*-**1b**, which corresponds to the inversion of the bridge of this system, has been determined from which the barrier for the inversion has been estimated to be 24.6 kcal/mol. More precise information about the structure of this system has been elucidated by the single crystal X-ray analysis of the diester **1c**. The crystal structure of **1c** has the conformation which is in accord with that deduced from ^{1}H NMR coupling constants; the dihedral angle between planes C(2A)–C(3A)–C(3B′)–C(2B′) and C(8)–C(9)–C(8′)–C(9′) is 17.7°, and the nonbonded distance between two π-systems is 3.04 (2) (C(3A′)–C(8)) or 3.03 (1) (C(3B)–C(9)) Å. The bending angle of the para carbon out of the base plane of the benzene ring (C(8)–C(9)–C(8′)–C(9′)) is 20.5° and that of the benzyl carbon from the plane of C(7)–C(8)–C(9) is 24.1°. The total bending angle (44.6°) represents the most highly deformed benzene ring so far isolated. The bond angles of the bridge double bond are considerably widened from the normal; C(2A)–C(3A)–C(3B′) = 130 (2)°, C(2B)–C(3B)–C(3A′) = 132 (1)°. Moreover, the bond length of the double bond is remarkably longer than the normal one: C(3A)–C(3B′) = 1.37 (2) Å. This represents one of the longest unconjugated C=C double bond hitherto known. Thus it has been clarified that the bridge double bond of this system is expanded and stretched by the inherently planar benzene ring which is in turn bent by the short rigid bridge having a double bond in the center.

Considerable interest has been focused on the chemistry of small bridged [*n*]paracyclophanes,[1] in view of the unusual spectroscopic, conformational, and chemical properties due to deformation and strain in the aromatic ring and the bridging chain. Of the [*n*]-paracyclophanes that have been isolated, [6]paracyclophanes such as **2a–d** have the smallest bridge.[2] The parent hydrocarbon **2a**



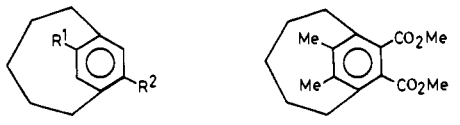
1a $R^1=R^2=H$
1b $R^1=H$, $R^2=CO_2Me$ or $R^1=CO_2Me$, $R^2=H$
1c $R^1=R^2=CO_2Me$



2a $R^1=R^2=H$
2b $R^1=H$, $R^2=CO_2Me$
2b′ $R^1=H$, $R^2=CO_2H$
2c $R^1=R^2=CO_2Me$

2d

was synthesized for the first time by Jones et al.[2a] albeit in low yield and then by Bickelhaupt[2b] and by us[2c] in more efficient manners. Recently, Tochtermann and we have elucidated independently the molecular structure of this system by the X-ray crystallographic analysis of the crystalline derivatives **2b′**,[2c] **2c**,[2e] and **2d**[2d]; the out-of-plane bending angles (α) of the para carbons are 19.4–20.5°, those (β) of the benzyl carbons are 18.7–20.2°, and the sum of them ($\alpha + \beta$) amounts to 39.2–39.6°. Moreover, Tochtermann and we have clarified the remarkable reactivities of **2a** and **2d** toward isomerization and addition reactions which are associated with the severe deformation of the benzene ring.[2c,d] As for the next smaller homologue, [5]paracyclophane, Bickelhaupt and we have succeeded in spectroscopic characterization of the parent hydrocarbon **3a**[3a] as well as the ester derivatives **3b**,[3b]



3a $R^1=R^2=H$
3b $R^1=H$, $R^2=CO_2Me$
3c $R^1=R^2=CO_2Me$

3d

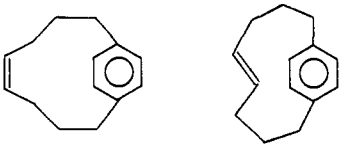
* Department of Applied Fine Chemistry.
‡ Department of Applied Chemistry.

(1) For a recent review: Keehn, P. M.; Rosenfeld, S. M. *Cyclophanes*; Academic Press: New York, 1983.
(2) (a) Cane, V. V.; Wolf, A. D.; Jones, M., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 2643. (b) Kammula, S. L.; Iroff, L. D.; Jones, M., Jr.; van Straten, J. W.; de Wolf, W. H.; Bickelhaupt, F. *Ibid.* **1977**, *99*, 5815. (c) Tobe, Y.; Ueda, K.; Kakiuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. *Tetrahedron Symposia-in-Print* **1986**, *42*, 1851. (d) Liebe, J.; Wolff, C.; Krieger, C.; Weiss, J.; Tochtermann, W. *Chem. Ber.* **1985**, *118*, 4144. (e) Tobe, Y.; Nakayama, A.; Kakiuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. *J. Org. Chem.*, submitted for publication.

0002-7863/87/1509-1136$01.50/0

3c,[3d] and **3d**[3c] as unstable but still aromatic intermediates (by the ring current criterion in the ^{1}H NMR spectra). However, these have so far eluded isolation because of lability.

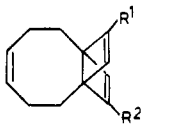
In this connection, we turned our attention to (*Z*)-[6]paracycloph-3-ene system such as **1a**, which, because of the length of its bridge, must be allotted a place between [6]- and [5]paracyclophanes with regard to the out-of-plane deformation of the benzene ring. Namely, since the bridge of **1a** consists of six carbon atoms and has one cis double bond at the center of the bridge, the length of the $-CH_2-CH=CH-CH_2-$ bridge linking the benzyl carbons would be longer than the corresponding trimethylene bridge of **3a** but shorter than the tetramethylene bridge of **2a**. Thus **1a** would have the most highly strained benzene ring hitherto isolated. Moreover, while [8]paracycloph-4-enes **4E**[4] and **4Z**[4c] and their derivatives have been reported, **1a** represents the



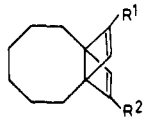
4Z 4E

smallest bridged [*n*]paracyclophane having a double bond in the bridge. Accordingly, some interesting, unusual properties with respect to the double bond in the bridge are expected. For example, in view of the remarkably expanded bond angles and lengths of the bridge of the [6]paracyclophanes **2b'**,[2c] **2c**,[2e] and **2d**,[2d] it is reasonable to expect an unusual deformation in the bond angles and lengths of the bridge double bond of **1a** because of greater tension in the conjoined benzene ring. The present paper reports the synthesis and conformational properties of (*Z*)-[6]paracycloph-3-ene (**1a**) and its 8-methoxycarbonyl derivative **1b** and 8,11-dimethoxycarbonyl derivative **1c** and an X-ray crystal structure study of **1c**.[5]

Synthesis of (*Z*)-[6]Paracycloph-3-enes via Dewar Benzene Valence Isomers. For the synthesis of (*Z*)-[6]paracycloph-3-enes (**1a–c**), we took advantage of the thermal valence isomerization[2b,c] of the Dewar benzene valence isomers, [6.2.2]propellatrienes (**5a–c**) (Schemes I–III).



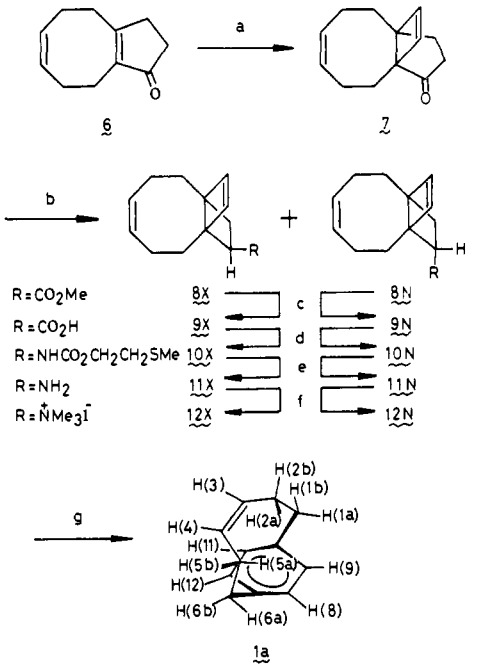
5a $R^1=R^2=H$
5b $R^1=H, R^2=CO_2Me$
5c $R^1=R^2=CO_2Me$



17b $R^1=H, R^2=CO_2Me$
17c $R^1=R^2=CO_2Me$

Firstly, the synthesis of the parent hydrocarbon **1a** was undertaken as shown in Scheme I. By our photocycloaddition–ring contraction protocol[2c] the bicyclic enone **6**[6] was converted to *exo*- and *endo*-[6.2.2]propelladienecarboxylates **8X** and **8N** in a ratio of 3:1 in 43% overall yield via the propellanone **7**. Since oxidative decarboxylation with lead tetraacetate of the carboxylic acid **9X**

Scheme I



1a

[a](i) 1,2-dichloroethylene, hν; (ii) $LiAlH_4$, Et_2O; (iii) Na, NH_3; (iv) CrO_3, Pyr, CH_2Cl_2. [b](i) HCO_2Et, NaOEt, Et_2O; (ii) TsN_3, Et_3N, CH_2Cl_2; (iii) hν, MeOH. [c]*aqueous* KOH. [d]$(PhO)_2PON_3$, $HOCH_2CH_2SMe$, C_6H_6. [e](i) Me_2SO_4; (ii) NaOH, MeOH. [f]MeI, $KHCO_3$, MeOH. [g](i) Ag_2O, H_2O; (ii) 120 °C, 0.1 torr.

or **9N** derived from **8X** or **8N**, which was the successful method for the short and efficient preparation of [6]paracyclophane **2a**,[2c] did not provide any desirable products, **1a** was synthesized through the following several steps.[7] Reaction of **9X** or **9N** with diphenylphosphoryl azide[8] and the subsequent treatment with 2-methylmercaptoethanol afforded the carbamate **10X** or **10N** in 78 or 51% yield. Alkaline hydrolysis[9] of the sulfonium salt of **10X** or **10N** furnished the amine **11X** or **11N** (66 or 87% yield), which was converted to the quaternary ammonium salt **12X** (81%, mp 147–150 °C) or **12N** (84%, mp 161–163 °C). After conversion into the corresponding hydroxide and the subsequent pyrolysis (120 °C, 0.1 torr), **1a** was obtained as a colorless waxy solid (mp 29–33 °C) in 44% yield from **12X** (or 8% yield from **12N**). Although the Dewar benzene isomer **5a** was not detected at all, it is reasonable to assume that **1a** was formed by thermal isomerization of **5a** during pyrolysis (Scheme I).

In order to clarify the conformational behavior of the present system, the mono ester **1b** was synthesized. The Dewar benzene isomer **5b** was prepared from **8X** or **8N** by phenylselenenylation[10] to give the *endo*-selenide **13N** mainly (85–88% yield, 13N:13X = 10:1) and the subsequent oxidative elimination[10] (54%). The isomerization of **5b** took place readily to afford the cyclophane **1b** as a 1:1 mixture of two conformational isomers, *anti*-**1b** and *syn*-**1b** (Scheme II). The isomerization rate of **5b** to **1b** (k(40 °C) = 1.11×10^{-4}, k(50 °C) = 3.52×10^{-4}, k(60 °C) = 1.01×10^{-3} s^{-1}, E_a = 23.9 kcal/mol, log A = 12.8, in hexane) determined by UV spectroscopy is 4.1 times faster at 50 °C than that of the corresponding Dewar benzene isomer **17b** of the [6]paracyclophane **2b**.[2c] The conformers, *anti*-**1b** and *syn*-**1b**, were separated by silica gel chromatography, and the structural assignment was made on the basis of the following NMR data: In

(3) (a) Jenneskens, L. W.; de Kanter, F. J. J.; Kraakman, P. A.; Turkenburg, L. A. M.; Koolhaas, W. E.; de Wolf, W. H.; Bickelhaupt, F.; Tobe, Y.; Kakiuchi, K.; Odaira, Y. *J. Am. Chem. Soc.* **1985**, *107*, 3716. (b) Tobe, Y.; Kaneda, T.; Kakiuchi, K.; Odaira, Y. *Chem. Lett.* **1985**, 1301. (c) Kostermans, G. B. M.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1986**, *27*, 1095. (d) Tobe, Y.; Nakayama, A.; Kakiuchi, K.; Odaira, Y., unpublished results.

(4) (a) Cram, D. J.; Montgomery, C. S.; Knox, G. R. *J. Am. Chem. Soc.* **1966**, *88*, 515. (b) Cope, A. C.; Pawson, B. A. *Ibid.* **1968**, *90*, 636. (c) Tsuji, T.; Shibata, T.; Hienuki, Y.; Nishida, S. *Ibid.* **1978**, *100*, 1806. (d) Noble, K.-L.; Hopf, H.; Ernst, L. *Chem. Ber.* **1984**, *117*, 474.

(5) Preliminary results of this work have already been reported; Tobe, Y.; Ueda, K.; Kakiuchi, K.; Odaira, Y. *Angew. Chem.* **1986**, *98*, 364; *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 369. Tobe, Y.; Kaneda, T.; Kakiuchi, K.; Odaira, Y. *Chem. Lett.* **1986**, 1217.

(6) Mehta, G.; Rao, K. S. *Tetrahedron Lett.* **1984**, *25*, 1839.

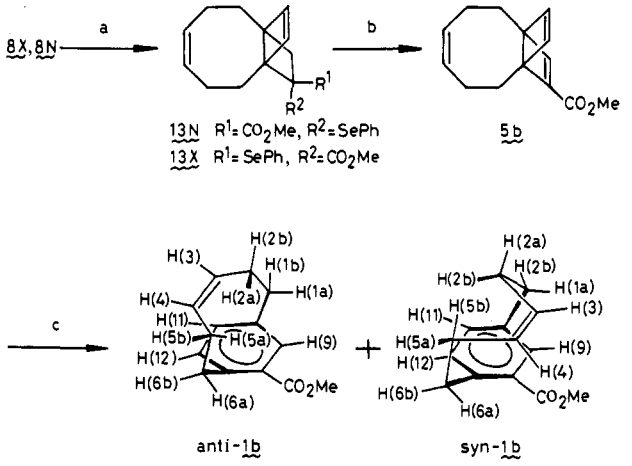
(7) For a similar transformation: Tsuji, T.; Nishida, S. *Tetrahedron Lett.* **1983**, *24*, 3361.

(8) Ninomiya, K.; Shioiri, T.; Yamada, S. *Chem. Pharm. Bull.* 1974, *22*, 1398.

(9) Kunz, H. *Chem. Ber.* **1976**, *109*, 3639.

(10) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* 1973, *95*, 6137. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

Scheme II



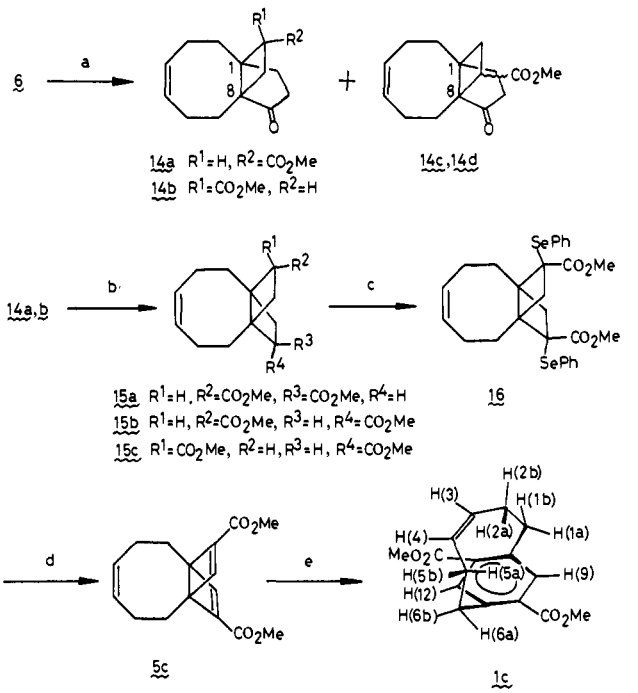
[a] LDA, Ph_2Se_2, THF. [b] H_2O_2, pyr, CH_2Cl_2. [c] 60 °C, 12 h.

the ^1H NMR spectra, the aromatic proton H(9) of *syn*-**1b** which is on the same side of the molecule with the bridge double bond appears at higher field than that of *anti*-**1b** ($\Delta\delta$ = 0.24) which is opposite to the double bond due to the shielding effect of the double bond. Similarly, the syn protons H(11) and H(12) of *anti*-**1b** are observed at higher field than the anti protons of *syn*-**1b** ($\Delta\delta$ = 0.15–0.21). Moreover, in the ^{13}C NMR spectra, the aromatic carbon C(8) of *syn*-**1b** appears at lower field than that of *anti*-**1b** ($\Delta\delta$ = 3.2) due to p-orbital compression effect[11] between the closely located aromatic and vinyl carbons.

Finally, for the purpose of the X-ray structure determination of the present system, the diester **1c** was prepared. Photocycloaddition of the enone **6** with methyl acrylate gave the four isomers of cycloadducts in 58% combined yield: *exo*-head-to-tail-**14a**, *endo*-head-to-tail-**14b**, and head-to-head adducts, **14c** and **14d**, (stereochemistry undetermined) in a ratio of ca. 4:3:1:7. The head-to-tail/head-to-head regiochemical assignment was done on the basis of the difference between the ^{13}C NMR chemical shifts of the central quaternary carbons (C(1) and C(8)); $\Delta\delta$ for the head-to-tail isomers, **14a** and **14b**, are 2.0 and 1.7, whereas those for the head-to-head isomers **14c** and **14d** are 12.7 and 12.9, respectively. The exo/endo stereochemistry of **14a** and **14b** was determined based on the configuration of the corresponding ring contraction products **15a–c** derived from them; *exo*-**14a** gave the *exo,exo*-diester **15a** and *exo,endo*-**15b** in a ratio of 5:1 (20% combined yield), whereas *endo*-**14b** gave **15b** and *endo,endo*-**15c** in a ratio of 2:1 (21% yield). The stereochemistry of the diesters **15a–c** was in turn elucidated on the basis of the symmetry in the ^{13}C NMR spectra and the general tendency that the exo esters are formed predominantly in the ring contraction of [*n*.3.2]-propellanones.[2c,12] Phenylselenenylation[10] of either of **15a–c** afforded the crystalline bisselenide **16** in 21–30% yield whose oxidation[10] yielded the Dewar benzene isomer **5c** in 54% yield as colorless crystals (mp 70–74 °C). Thermal valence isomerization of **5c** took place smoothly to give **1c** as pale yellow crystals (mp 59–61 °C) in 74% yield after purification (Scheme III). The isomerization rate of **5c** (k(30.0 °C) = 3.89 × 10^{-6}, k(35.0 °C) = 8.44 × 10^{-6}, k(40.0 °C) = 1.54 × 10^{-5} s^{-1}, E_a = 25.9 kcal/mol, log A = 13.3, in hexane) is 7.9 times faster at 40 °C than that of the corresponding Dewar benzene isomer **17c** of the [6]paracyclophane **2c**,[2e] while it is 0.14 times that of the mono ester **5b**.

Spectral and Conformational Properties of (*Z*)-[6]Paracycloph-3-enes. Besides providing unambiguous evidence for the structure assignment of **1a–c**, the spectral properties of those afford qualitative but important information about the structural feature of this system.

Scheme III



[a] Methyl acrylate, hν. [b] (i) HCO_2Me, NaOMe, Et_2O; (ii) TsN_3, Et_3N, CH_2Cl_2; (iii) hν, MeOH. [c] LDA, Ph_2Se_2, THF. [d] H_2O_2, pyr, CH_2Cl_2. [e] 50 °C, 4 days.

Table I. ^1H NMR Chemical Shifts of Aromatic Protons of Paracyclophanes **1a–c** and **2a–c**[a]

compd	syn proton[b]	anti proton[c]	proton of **2a–c**[d]
1a	7.07 (H(11), H(12))	7.20 (H(8), H(9))	**2a**, 7.22
anti-**1b**[e]	7.13 (H(11))	7.93 (H(9))	**2b**, 7.92
	7.19 (H(12))		
syn-**1b**[e]	7.69 (H(9))	7.34 (H(11), H(12))	7.36
1c[e]	7.71 (H(12))	7.98 (H(9))	**2c**, 7.91

[a] δ in ppm. Taken in $CDCl_3$ unless otherwise noted. [b] Aromatic proton located on the same side of the bridge double bond. [c] Aromatic proton located on the opposite side of the bridge double bond. [d] Chemical shift of the aromatic proton of **2a–c** corresponding to the anti proton of **1a–c**. [e] Taken in CD_2Cl_2.

Table II. ^{13}C NMR Chemical Shifts of Aromatic Carbons of Paracyclophanes **1a–c** and **2a–c**[a]

compd	syn carbon[b]	anti carbon[c]	carbon of **2a–c**[d]
1a	136.0 (C(11), C(12))	132.1 or 132.0	**2a**, 131.8
anti-**1b**	139.0 (C(11))	133.0 (C(8))	**2b**, 131.9
	137.6 (C(12))	134.7 (C(9))	134.4
syn-**1b**	136.4, 136.2	134.6 (C(11))	134.3
	(C(8), C(9))	133.7 (C(12))	133.7
1c	138.8 (C(11))	135.9 (C(9))	**2c**, 136.5
	138.0 (C(12))	135.2 (C(8))	133.6

[a] δ in ppm. Taken in $CDCl_3$. [b] Aromatic carbon located on the same side of the bridge double bond. [c] Aromatic carbon located on the opposite side of the bridge double bond. [d] Chemical shift of the aromatic carbon of **2a–c** corresponding to the anti carbon of **1a–c**.

In the ^1H NMR spectra of **1a–c**, two kinds of aromatic protons are observed irrespective to the temperature; those on the same side (syn protons) and those on the opposite side of the bridge (anti protons) (Table I). Syn protons exhibit upfield shift by 0.13–0.27 ppm relative to the anti protons because of the shielding effect of the bridge double bond. Similarly, the vinyl protons of **1a–c** appear at higher field ($\Delta\delta$ = ca. 1.0) compared with the propellanes such as **8X**, **8N**, **15a–c**, and Dewar benzene isomers, **5b** and **5c**, due to the shielding of the aromatic ring. In analogy, in the ^{13}C NMR spectra, remarkable downfield shift of the carbons

(11) Sato, T.; Takemura, T. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1195. Takemura, T.; Sato, T. *Can. J. Chem.* **1976**, *54*, 3412.
(12) Sakai, Y.; Toyotani, S.; Ohtani, M.; Matsumoto, M.; Tobe, Y.; Odaira, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1474.

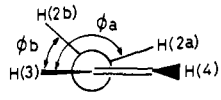
Table III. Vicinal Coupling Constants and Calculated Dihedral Angles between Benzyl and Allylic Protons

protons	J, Hz 1a	anti-1b	syn-1b	1c	dihedral angle,[a] deg
H(1a)–H(2a)	3.5	3.6	3.1	3.5	64
H(1a)–H(2b)	3.5	3.6	12.0	3.5	64
H(1b)–H(2a)	12.0	12.1	4.2[b]	12.3	18
H(1b)–H(2b)	3.0	2.9	3.1[b]	3.4	68
H(6a)–H(5a)	3.5	3.6	12.1	3.6	64
H(6a)–H(5b)	3.5	3.6	3.4	3.6	64
H(6b)–H(5a)	12.0	12.1	3.5	12.1	18
H(6b)–H(5b)	3.0	3.1	3.5	2.8	68

[a] Calculated dihedral angle of **1a** according to the equation of Karplus (ref 15). [b] Assignment of these constants is exchangeable.

on the same side of the bridge was observed compared to those on the opposite side (Table II). This is attributed to the p-orbital compression effect[11] on the syn aromatic carbons due to the vinyl carbons of the bridge double bond. The above upfield or downfield shift in the ^1H and ^{13}C NMR spectra indicates that the bridge double bond is located closely over the aromatic ring in nearly parallel alignment with the latter. The chemical shift of the anti located protons are almost the same as those of the corresponding [6]paracyclophanes (**2a–c**) as shown in Table I. Consequently, it is deduced that aromaticity of the benzene ring of this system is still intact from the ring current criterion.

The vinyl protons of **1a** were analyzed as XX′ part of an AA′BB′XX′ system by simulation from which the coupling constants were determined as follows: ^3J(H(3)–H(4)) = 12.2, ^3J(H(3)–H(2a)) = 11.6, ^3J(H(3)–H(2b)) = 4.5, ^4J(H(3)–H(5a)) = −0.5, ^4J(H(3)–H(5)) = −1.2 Hz. By using the semiempirical equations derived by Garbish[13] for the dependence of vinyl–allylic coupling constants on the dihedral angle, the angles, ϕ_a and ϕ_b,



are estimated to be 167 ± 13° and 50 ± 4°, respectively. This indicates that the atoms H(2a), C(2), C(3), C(4), C(5), and H(5a) form an almost flat plane. As a result, the allylic protons, H(2a) and H(5a), which show an upfield shift of 0.8–1.0 ppm relative to H(2b) and H(5b), are immersed into the shielding cone of the aromatic ring. Moreover, it is worth noting that the olefinic coupling constant ^3J(H(3)–H(4)) is significantly large (12.2 Hz). On the basis of the empirical relationship afforded by Cooper and Manatt,[14] which closely corresponds to the dependence predicted by Karplus,[15] a large bond angle of 128° for the vinyl carbon (C(2)–C(3)–C(4)) is estimated.

The benzyl protons of **1a–c** appear as two sharp ddd signals, and the allylic protons collapse into two ddd patterns when the vinyl protons are decoupled by double irradiation. The coupling constants between these protons are determined from which the corresponding dihedral angles are calculated for **1a** according to the equation of Karplus[15] (Table III). On the basis of these calculated dihedral angles as well as those for the vinyl and allylic hydrogens described above, molecular model examination indicates that the plane of the bridge double bond (C(2)–C(3)–C(4)–C(5)) tilts slightly toward the opposite direction against the base plane of the benzene ring (C(8)–C(9)–C(11)–C(12)). While the corresponding coupling constants of **1b** and **1c** are similar to those of **1a**, small deviation from the latter is observed as can be seen from Table III. This difference is attributed to unsymmetrical structure of the bridge of *anti*-**1b**, *syn*-**1b**, and **1c** due to the steric repulsion between the ester group and the neighboring benzyl hydrogen.

In addition to the bond angle deformation of the bridge double bond predicted from the olefinic coupling constant of **1a**, elongation

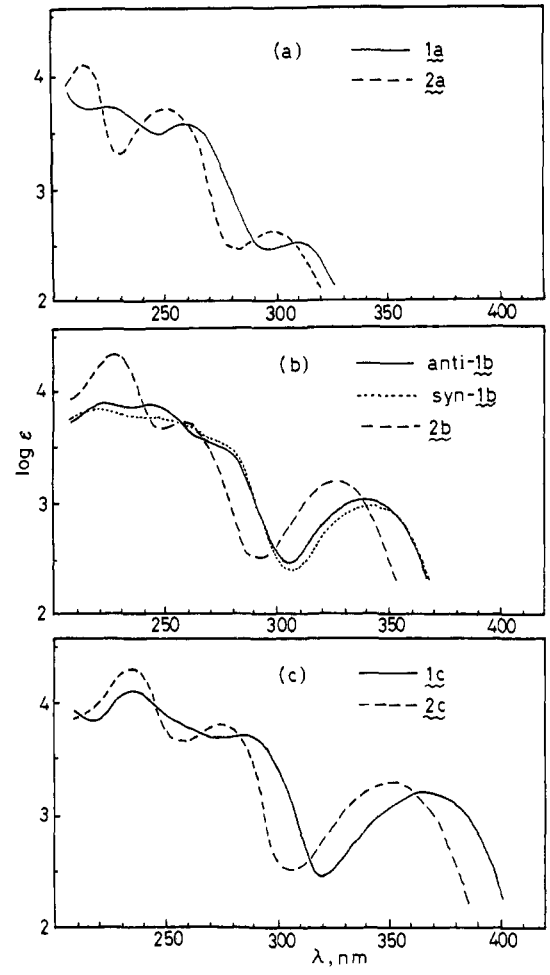


Figure 1. Electronic spectra of paracyclophanes (a) **1a** and **2a**, (b) *anti*-**1b**, *syn*-**1b**, and **2b**, and (c) **1c** and **2c** in hexane.

Table IV. Absorption Maxima in Electronic Spectra of Paracyclophanes **1a–c**, **2a–c**, and **3a–c**

substituent	λ_{max},[a] nm 2a-c	1a-c	3a-c
a, $R^1 = R^2 =$ H	299[b]	310[c]	330[d]
b, R^1 = H, $R^2 = CO_2Me$	327[b]	342[c]	360[e]
c, $R^1 = R^2 = CO_2Me$	350[f]	366[c]	388[g]

[a] Taken in hexane. [b] Reference 2c. [c] This work. [d] Reference 3a. [e] Reference 3b. [f] Reference 2e. [g] Reference 3d.

of the bond distance of the double bond (C(3)–C(4)) of this system is indicated by the IR stretching band. Namely, **1a** exhibits the double bond stretching band at the very low wavenumber of 1530 cm^{-1}.[16] Taking into account the planarity of the double bond as indicated from both ^1H NMR (vide supra) and the X-ray analysis of **1c** (vide infra), this absorption band suggests that the bridge double bond is considerably stretched from the normal bond length.[17]

(13) Garbisch, E. W. *J. Am. Chem. Soc.* **1964**, *86*, 5561.
(14) Cooper, M. A.; Manatt, S. L. *Org. Magn. Reson.* **1970**, *2*, 511.
(15) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.

(16) The corresponding $\nu_{C=C}$ bands of the ester derivatives, **1b** and **1c**, are not clear, since they overlap with the aromatic absorption band near 1530 cm^{-1}. While the ester derivatives of [6]paracyclophanes **2b** and **2c** exhibit absorptions at this region, the hydrocarbon **2a** do not.

Table V. Kinetic Data for Isomerization between *anti*-**1b** and *syn*-**1b**[a]

temp, °C	10^6k_1, s^{-1} (syn → anti)	10^6k_{-1}, s^{-1} (anti → syn)	K[b]	$\Delta H^{\ddagger}$[c] kcal/mol	$\Delta S^{\ddagger}$[c] cal/deg mol
25.0	5.58 ± 0.12	5.64 ± 0.07	0.97 ± 0.01	24.9 (24.6)	0.6 (0.2)
38.0	29.1 ± 0.2	30.1 ± 0.6	0.96 ± 0.03		
50.0	153 ± 6	155 ± 7	0.97 ± 0.02		

[a] 2×10^{-3} M in methanol. [b] Observed equilibrium ratio of *syn*-**1b**/*anti*-**1b**. [c] Values for *syn*-**1b** → *anti*-**1b**. Those for *anti*-**1b** → *syn*-**1b** are given in parentheses.

Concerning the out-of-plane deformation of the benzene ring, the electronic spectra of **1a–c** provide important information.[18] As shown in Figure 1 and Table IV, **1a–c** exhibit ca. 10–15-nm bathochromic shift in the longest wavelength absorption relative to the corresponding [6]paracyclophanes **2a–c**. Moreover, the wavelength of the absorption maxima of **1a–c** lies in the center of those of **2a–c** and the corresponding [5]paracyclophanes **3a–c** regardless of the substituent. Consequently, it is deduced that the out-of-plane bending of the benzene ring of (*Z*)-[6]paracycloph-3-ene system is greater than that of the [6]paracyclophanes and that the former must be allotted a place between the [6]- and [5]paracyclophanes with regard to the out-of-plane deformation as expected at the outset. Though the contribution of the π–π interaction between the bridge double bond and the benzene ring to the above bathochromic shift cannot be ruled out at present in view of relatively short nonbonded distance between the two π-systems (ca. 3 Å by X-ray analysis), we feel it is unimportant on the basis of the similarity in the spectra of **1a–c** and **2a–c** in the long wavelength region as shown in Figure 1.

The NMR spectra of **1a** was temperature-independent (up to 150 °C), indicating that the conformational inversion of the bridge of this system is very slow on the NMR time scale. Accordingly, in order to clarify the dynamic behavior of the bridge, the mutual anti⇄syn isomerization rate between the mono esters, *anti*-**1b** and *syn*-**1b**, which corresponds to the conformational inversion of the bridge, was determined. The rate constants determined by measurement of the change in methanol by HPLC are summarized in Table V. At temperature examined, the equilibrium constants (K) between *anti*-**1b** and *syn*-**1b** are nearly unity. The barrier for the inversion of the bridge obtained from the above data ($\Delta G^{\ddagger}$(anti→syn, 25 °C) = $\Delta G^{\ddagger}$(syn→anti, 25 °C) = 24.6 kcal/mol) is considerably higher than those of [6]paracyclophanes ($\Delta G^{\ddagger}$ = 13.3–14.0 kcal/mol),[2c,19,20] [5]paracyclophanes ($\Delta G^{\ddagger}$ = 14.3–14.4 kcal/mol),[3a,c] and [8]paracycloph-4-enes ($\Delta G^{\ddagger}$ = ca. 13–14 kcal/mol).[4c]

X-ray Crystal Structure Determination of 8,11-Bis(methoxycarbonyl)-(*Z*)-[6]paracycloph-3-ene. In order to obtain more precise information about the deformation imposed on both the benzene ring and the bridging chain, a single crystal X-ray analysis of the diester **1c** was undertaken. The molecular structure of **1c** is shown in Figure 2, and the bond angles and distances are found in Supplementary Material.[21] Since the crystal structure is disordered due to the crystallographic C_2 symmetry, the structure of the bridge is of limited accuracy. In accord with the deduction made on the basis of the ^{1}H NMR spectra of **1a**, **1c** has the conformation in which the bridge double bond tilts slightly toward the opposite direction against the benzene ring with a dihedral angle between planes C(2A)–C(3A)–C(3B′)–C(2B′) and C-(8)–C(9)–C(8′)–C(9′) of 17.7°. The nonbonded distance between the two π-systems is relatively short: C(3A′)–C(8) is 3.04 (2) Å, and C(3B)–C(9) is 3.03 (1) Å.

Table VI. Out-of-Plane Bending Angles of Paracyclophanes **1c**, **2b′**, **2c**, and **2d**

compd	bending angle, deg α	β	$\alpha + \beta$	ref
3-Carboxy[7]paracyclophane	16.8	6.8	23.6	22
2b′	20.5	18.7	39.2	2c
2c	19.4	20.2	39.6	2e
2d	19.5	19.9	39.4	2d
1c	20.5	24.1	44.6	this work

One of the most important features of the structure of **1c** is, of course, the out-of-plane deformation of the benzene ring. As expected from the bathochromic shift of the electronic spectra of **1a–c** relative to **2a–c**, the benzene ring of **1c** is bent to a greater extent than that of [6]paracyclophanes; the angle (α) of the bending of the para carbon (C(7)) out of the base plane of the benzene ring (C(8), C(9), C(8′), C(9′)) is 20.5° and that (β) of the benzyl carbon (C(1)) from the plane of C(7)–C(8)–C(9) is 24.1°. Comparison of these values of **1c** with those of **2b′**, **2c**, and **2d** shows that while the out-of-plane deformation of the para carbons of **1c** is only slightly larger than those of the latter, that of the benzyl carbons of **1c** is significantly greater than those of the latter as summarized in Table VI. This indicates that further folding of the para carbons in such a highly bent benzene ring is energetically less favorable than that of the benzyl carbons. This tendency is compatible with that observed for the difference between the bent angles of [7]- and [6]paracyclophanes[2c,d,22] as well as the molecular mechanics calculations by Allinger et al.[18] Anyway, the above results demonstrate that **1c** has the most highly deformed benzene ring ($\alpha + \beta$ = 44.6°) so far known.

Another significant feature of the structure of **1c** is the deformation imposed on the bridge double bond, which is in agreement with the expectation based on the ^{1}H NMR and IR spectra of **1a**. The bridge double bond is almost planar with a small twisting around C=C bond axis; the dihedral angle between planes C(2A)–C(3A)–C(3B′) and C(2B′)–C(3B′)–C(3A) is 2.2°. On the other hand, the bond angles of the double bond are considerably widened from the normal angle of sp^2 carbon; the angle C(2A)–C(3A)–C(3B′) is 130 (2)°, and C(2B)–C(3B)–C(3A′) is 132 (1)°. Moreover, the bond length of the double bond is remarkably longer than the normal one; C(3A)–C(3B′) is 1.37 (2) Å. Even taking into account the limited accuracy in the structure of the bridge, this represents one of the longest unconjugated C=C double bond hitherto known.[17]

Finally, it is noteworthy that the bond angle of the benzyl carbons connecting the two strained π-systems, i.e., the benzene ring and the —CH_2—CH=CH—CH_2— unit of the bridge, is extremely small; the angle C(2A)–C(1)–C(7′) is 103.7 (8)° and C(2B)–C(1)–C(7′) is 103.9 (7)°. This remarkably deformed structure of the bridge of **1c** has similarity with the calculated (MM2) structure of cyclooct-1-en-5-yne[23] in which the —CH_2—CH=CH—CH_2— bridge is connected by the —CH_2—C≡C—CH_2— unit. Namely, in this ene–yne system, the double bond unit is expanded by the inherently linear acetylene group which is in turn bent by the short rigid bridge. On the other hand, in the case of the (*Z*)-[6]paracycloph-3-ene system, the bridge double bond is expanded and stretched by the inherently planar

(17) Although it has been reported that some sterically crowded alkenes exhibit very low wavenumber stretching bands in the Raman spectra, these might be attributed to not only significant bond length elongation but also large twisting of the double bond. See, for example: Krebs, A.; Kaletta, B.; Kickel, W.-V.; Rüger, W.; Tikwe, L. *Tetrahedron Symposia-in-Print* **1986**, *42*, 1693.

(18) Allinger, N. L.; Sprague, J. T.; Liljefors, T. *J. Am. Chem. Soc.* **1974**, *96*, 5100.

(19) van Straten, J. W. Thesis, Frie University, Amsterdam, 1978.

(20) Günther, H.; Schmitt, P.; Fischer, H.; Tochtermann, W.; Liebe, J.; Wolff, C. *Helv. Chim. Acta* **1985**, *68*, 801.

(21) For the discussion of the X-ray structure of **1c**, the numbering of atoms *in* Figure 2 is used.

(22) Allinger, N. L.; Walter, T. J.; Newton, M. G. *J. Am. Chem. Soc.* **1974**, *96*, 4588.

(23) Leupin, W.; Wirz, J. *Helv. Chim. Acta* **1978**, *61*, 1663.

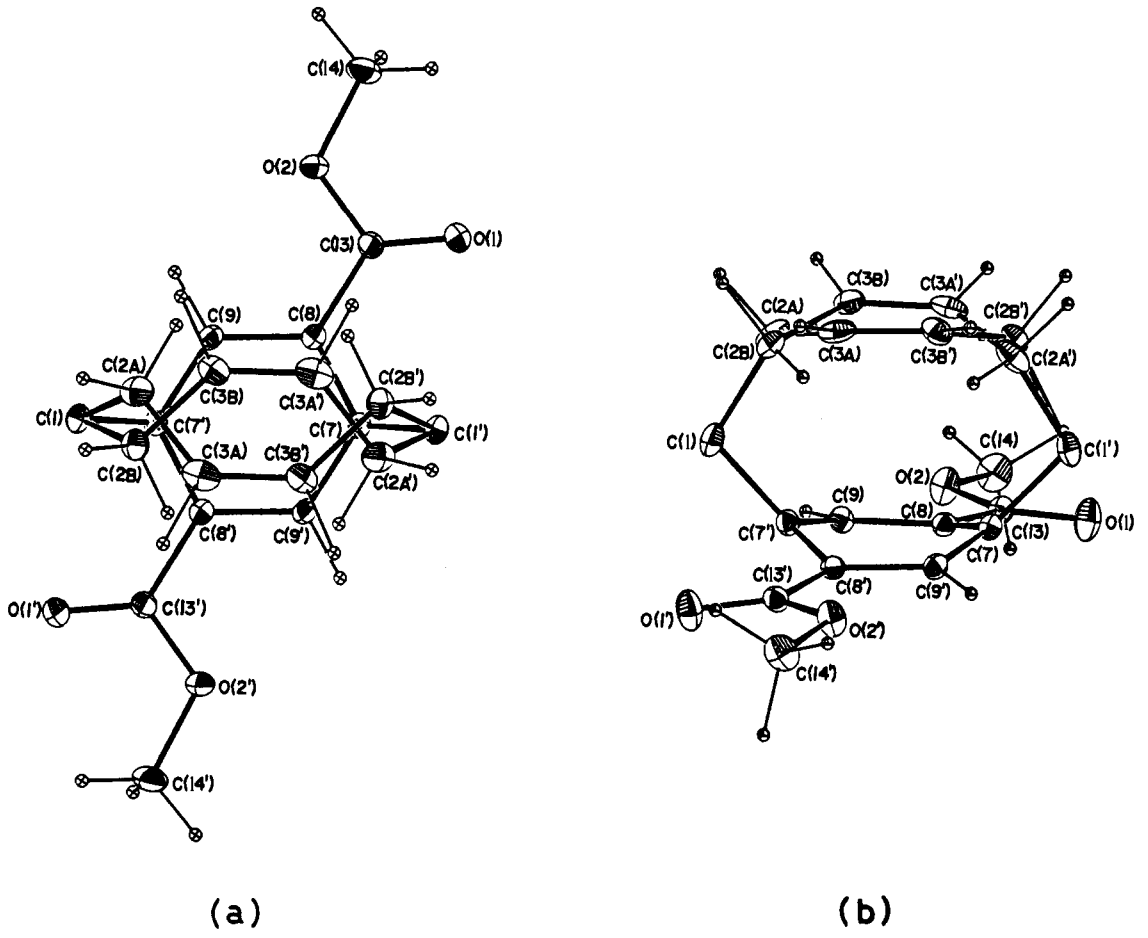


Figure 2. Molecular structure of 8,11-(dimethoxycarbonyl)-(*Z*)-[6]paracycloph-3-ene (**1c**): (a) top view, (b) side view.

benzene ring which is in turn bent by the short rigid bridge. Thus it has been clarified that the present system has not only the most highly bent benzene ring but also one of the most highly strained double bonds. Further research, especially that on the reactivities of these molecules, is being undertaken in our laboratories and will be reported in due course.

Experimental Section

[6.3.2]Propella-4,12-dien-9-one (7). A solution of the enone 6[6] (7.14 g, 44.1 mmol) in 250 mL of *trans*-1,2-dichloroethylene was irradiated in a Pyrex vessel with a 500-W high-pressure mercury lamp under nitrogen for 14 h. Evaporation of the excess olefin gave 13.1 g of the cycloadducts (three isomers detected by GLC) [IR 1730 cm^{-1}]. A solution of the above cycloadducts in 490 mL of dry ether was added dropwise to a suspension of 960 mg (25.3 mmol) of $LiAlH_4$ in 130 mL of ether. The mixture was stirred at room temperature for 1 h before careful addition of water followed by 1 N HCl. The organic layer was separated, and the aqueous layer was extracted with ether. The combined extract was washed with $NaHCO_3$ solution and water and dried over anhydrous magnesium sulfate ($MgSO_4$). The solvent was removed in vacuo to afford 13.1 g of a mixture of alcohols [IR 3350 cm^{-1}]. To a solution of the above alcohols in 130 mL of ether and 560 mL of freshly distilled liquid ammonia was added sodium (5.0 g, 217 mmol) cut in small pieces at −78 °C. The mixture was stirred at that temperature for 2 h, and then an excess of ammonium chloride was added. The ammonia was allowed to evaporate, and the residue was diluted with water. The organic layer was separated, and the aqueous layer was extracted with ether. The combined extract was washed with water and dried. Solvent evaporation gave 9.6 g of the crude dechlorinated alcohol [IR 3350 cm^{-1}] as a light brown oil. A solution of this alcohol in 60 mL of CH_2Cl_2 was added dropwise to a solution of 30.4 g (304 mmol) of chromium trioxide and 48.1 g (608 mmol) of pyridine in 760 mL of the same solvent. After having been stirred for 1 h, the mixture was filtered, and the filtrate was washed successively with 1 N NaOH, 1 N HCl, $NaHCO_3$, and water and then dried. Evaporation of the solvent followed by chromatography on silica gel with ether/petroleum ether = 1:19 eluent afforded 4.45 g (54% yield from **6**) of the propellanone **7** as a colorless oil: IR 3000, 1720, 740 cm^{-1}; MS, *m/e* (rel intensity) 188 (M^+, 27), 134 (84), 91 (100); ^1H NMR δ 1.4–2.5 (m, 11 H), 2.80 (ddd, *J* = 17, 10, 10 Hz, 1 H), 5.4–5.8 (m, 2 H), 5.98 (d, *J* = 2 Hz, 1 H), 6.1, (d, *J* = 2 Hz, 1 H); semicarbazone mp 197–200 °C. Anal. Calcd for $C_{14}H_{19}ON_3$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.36; H, 7.78; N, 17.07.

***exo*- and *endo*-9-[6.2.2]Propella-4,11-dienecarboxylates 8X and 8N.** To a suspension of 1.14 g (23.6 mmol) of 50% sodium hydride in mineral oil and 0.21 mL of ethanol in 71 mL of anhydrous ether was added a mixture of the propellanone **7** (4.45 g, 23.6 mmol) and ethyl formate (2.62 g, 35.4 mmol), and the mixture was stirred at room temperature for 2 h. Water was added, and the organic layer was separated and extracted with 1 N NaOH. The aqueous extract was combined with the original aqueous phase, washed with ether, acidified with 1 N HCl, and extracted with ether. The ether extract was washed with water and dried. Removal of the solvent in vacuo gave 4.85 g of the hydroxymethylene derivative as yellow solid [IR (KBr) 3600–2300, 1680, 1620, 1550 cm^{-1}]. To a solution of the above product and 4.52 g (44.8 mmol) of triethylamine in 22 mL of CH_2Cl_2 cooled in a ice–salt bath was added dropwise 4.62 g (23.5 mmol), of tosyl azide. The solution was warmed up to room temperature and was stirred for 2 h. A solution of KOH (1.50 g, 26.9 mmol) in 20 mL of water was added, and the mixture was stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with KOH and water and dried. Evaporation of the solvent afforded the diazo ketone [IR 2070, 1650 cm^{-1}] which was dissolved in 280 mL of methanol and was irradiated with a high-pressure mercury lamp for 14 h. The solvent was evaporated, and the residue was chromatographed on silica gel with ether/petroleum ether = 3:97 eluent to yield *endo*-**8N** (0.80 g), a mixture of **8X** and **8N** (0.42 g), and *exo*-**8X** (2.55 g) (total yield 73% from **7**; **8X**:**8N** = 3:1).

8X: IR 3000, 1730, 1190, 730 cm^{-1}; MS, *m/e* (rel intensity) 218 (M^+, 44), 159 (55), 105 (100); ^1H NMR δ 1.2–2.4 (m, 10 H), 2.77 (dd, *J* = 9, 7 Hz, 1 H), 3.55 (s, 3 H), 5.58 (br t, 2 H), 5.99 (d, *J* = 2 Hz, 1 H), 6.22 (d, *J* = 2 Hz, 1 H). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.98; H, 8.57.

8N: IR 3000, 1725, 1160, 750, 730 cm^{-1}; MS, *m/e* (rel intensity) 218 (M^+, 27), 159 (60), 105 (100); ^1H NMR δ 1.2–2.4 (m, 10 H), 2.64 (dd, *J* = 8, 6 Hz, 1 H), 3.60 (s, 3 H), 5.56 (quintet, *J* = 4 Hz, 2 H), 6.22 (s, 2 H). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.18; H, 8.61.

***exo*- and *endo*-9-[6.2.2]Propella-4,11-dienecarboxylic Acids 9X and 9N.** A solution of 2.55 g (11.7 mmol) of **8X** in 40 mL of 2% aqueous KOH was stirred with heating at 60 °C for 2 days. The aqueous solution was washed with ether, acidified with concentrated HCl, and extracted with ether. The extract was washed with water, dried, and evaporated to give 2.19 g (92%) of the acid **9X** which was recrystallized from petroleum ether. Similar reaction of 0.801 g (3.67 mmol) of **8N** for 6 days afforded 0.736 g (82%) of **9N**.

9X: mp 96–97 °C; IR (KBr) 3200–2300, 1680 cm^{-1}; MS, *m/e* (rel intensity) 204 (M^+, <1), 150 (39), 105 (100), 91 (42); ^1H NMR δ 1.4–2.4 (m, 10 H), 2.86 (dd, J = 9, 7 Hz, 1 H), 5.58 (m, 2 H), 6.11 (d, J = 2 Hz, 1 H), 6.26 (d, J = 2 Hz, 1 H), 11.74 (br s, 1 H). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.51; H, 8.09.

9N: mp 119–120 °C; IR (KBr) 3400–2300, 1690 cm^{-1}; MS, *m/e* (rel intensity) 204 (M^+, <1), 150 (47), 105 (100), 91 (44); ^1H NMR δ 1.4–2.4 (m, 10 H), 2.72 (dd, J = 8, 6 Hz, 1 H), 5.58 (m, 2 H), 6.27 (br s, 2 H), 12.03 (br s, 1 H). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.46; H, 8.01.

***exo*- and *endo*-9-Amino[6.2.2]propella-4,11-dienes 11X and 11N.** A solution of **9X** (1.03 g, 5.05 mmol), 1.53 g (5.55 mmol) of diphenylphosphoryl azide,[24] and 560 mg (5.55 mmol) of triethylamine in 16 mL of benzene was heated at 60 °C for 1 h. After having been cooled to room temperature, 4.65 g (5.05 mmol) of 2-methylmercaptoethanol[25] was added, and the solution was heated again at 60 °C for 8 h. The solvent was evaporated in vacuo, and the residue was dissolved in ethyl acetate. The solution was washed with 1 N HCl, water, $NaHCO_3$, and brine and dried. Removal of the solvent followed by chromatography on silica gel with ether/petroleum ether = 1:9 eluent afforded 1.04 g (78%) of the carbamate **10X** as a colorless oil: IR 3300, 1700, 770, 730 cm^{-1}; MS, *m/e* (rel intensity) 293 (M^+, <1), 75 (100); ^1H NMR δ 1.4–2.4 (m, 10 H), 2.10 (s, 3 H), 2.58 (t, J = 7 Hz, 2 H), 3.8–4.2 (m, 1 H), 4.09 (t, J = 7 Hz, 2 H), 4.56 (br d, 1 H), 5.61 (m, 2 H), 6.13 (d, J = 2 Hz, 1 H), 6.36 (d, J = 2 Hz, 1 H). Similarly, by using 640 mg (3.14 mmol) of *endo*-**9N** was obtained 471 mg (51%) of the endo carbamate **10N** as colorless solid which was recrystallized from ether/petroleum ether: mp 74–75 °C; IR (KBr) 3300, 1700, 1510, 740 cm^{-1}; MS, *m/e* (rel intensity) 293 (M, <1), 75 (100); ^1H NMR ($CDCl_3$) δ 1.2–2.4 (m, 10 H), 2.14 (s, 3 H), 2.70 (t, J = 7 Hz, 2 H), 3.83 (br d, 1 H), 4.22 (t, J = 7 Hz, 2 H), 4.90 (br d, 1 H), 5.64 (m, 2 H), 6.21 (d, J = 2 Hz, 1 H), 6.28 (d, J = 2 Hz, 1 H). Anal. Calcd for $C_{16}H_{23}O_2NS$: C, 65.49; H, 7.90; N, 4.77. Found: C, 65.60; H, 8.02; N, 4.82.

A mixture of 147 mg (0.50 mmol) of *exo*-**10X** and 68 mg (0.54 mmol) of dimethyl sulfate was heated at 60 °C with stirring for 4 h. After having been cooled to room temperature, the mixture was diluted with 13 mL of methanol, and then 0.5 mL of 1 N NaOH was added. The solution was stirred for 15 min before 1 mL of 1 N HCl was added. The methanol was evaporated, and the residue was extracted with ether. The ether layer was extracted with 1 N HCl, and the aqueous extract was made alkaline by 1 N NaOH and extracted with ether. The organic layer was washed with water and dried. The solvent was removed in vacuo to give the exo amine **11X** (57 mg, 66%) as a slightly brown oil: IR 3300 (br) 1570, 760, 730 cm^{-1}; MS, *m/e* (rel intensity) 175 (M^+, 71), 120 (100), 91 (100); ^1H NMR δ 1.0–1.7 (m, 2 H), 1.7–2.5 (m, 10 H), 3.06 (dd, J = 9, 5 Hz, 1 H), 5.56 (m, 2 H), 6.10 (d, J = 2 Hz, 1 H), 6.34 (d, J = 2 Hz, 1 H). In a similr manner, 433 mg (1.48 mmol) of the endo carbamate **10N** afforded the endo amine **11N** (224 mg, 87%) as a colorless oil: IR 3300 (br), 1580, 735 cm^{-1}; MS, *m/e* (rel intensity) 175 (M^+, 40), 120 (89), 91 (100); ^1H NMR δ 0.8–2.6 (m, 12 H), 3.01 (dd, J = 9, 5 Hz, 1 H), 5.58 (m, 2 H), 6.13 (d, J = 2 Hz, 1 H), 6.18 (d, J = 2 Hz, 1 H).

(*Z*)-[6]Paracycloph-3-ene (1a). A mixture of *exo*-**11X** (100 mg, 0.57 mmol), iodomethane (1.30 g, 9.20 mmol), and $KHCO_3$ (570 mg, 5.70 mmol) in 12 mL of methanol was stirred at room temperture for 27 h. The solvent and the excess iodomethane were removed in vacuo, and the solid residue was washed with $CHCl_3$. The mixture was filtered, and the filtrate was evaporated to yield 146 mg (81%) of the ammonium salt **12X** as a white solid: mp 147–150 °C; IR (KBr) 780, 730 cm^{-1}. Anal. Calcd for $C_{15}H_{24}NI$: C, 52.18; H, 7.01; N, 4.06. Found: C, 51.61; H, 6.92; N, 3.84. Similarly, 340 mg (84%) of the endo ammonium salt **12N** was obtained from 204 mg (1.17 mmol) of *endo*-**11N**: mp 161–163 °C; IR (KBr) 745 cm^{-1}. Anal. Calcd for $C_{15}H_{24}NI$: C, 51.18; H, 7.01; N, 4.06. Found: C, 51.61; H, 6.95; N, 3.87.

A mixture of 150 mg (0.435 mmol) of **12X** and 101 mg (0.435 mmol) of silver oxide in 1.5 mL of water was stirred at room temperature for 15 h. The mixture was filtered, and the filter was washed with methanol. The methanol and water of the filtrate was evarpoated to give the ammonium hydroxide as a brown oil which was transferred into a distillation flask. Distillation under reduced pressure (0.1 torr) at ca. 120 °C (bath temperature) afforded a distillate which was being cooled with dry ice during distillation. The distillate was diluted with pentane and washed with 0.5 N HCl, 1 N $NaHCO_3$, and water and then dried. Evaporation of the solvent followed by flash chromatography with pentane as the eluent gave 29 mg (44%) of the cyclophane **1a** as a waxy solid: mp 29–33 °C; IR 3050, 1572, 1530, 1441, 1165, 974, 926, 899, 798, 739, 709, 696, 601 cm^{-1}; MS, *m/e* (rel intensity) 158 (M^+, 10), 104 (100); ^1H NMR (360 MHz, $CDCl_3$) δ 1.01 (m, 2 H, H(2a), H(5a)), 1.08 (m, 2 H, H(2b), H(5b)), 2.26 (ddd, ^2J = 12.0, ^3J = 12.0, ^3J = 3.5 Hz, 2 H, H(1b), H(6b)), 2.79 (ddd, ^2J = 12.0, ^3J = 3.5, ^3J = 3.5 Hz, 2 H, H(1a), H(6a)), 4.68 (XX′ of AA′BB′XX′, ^3J = 12.2, ^3J = 11.6, ^3J = 4.5, ^4J = −0.5, ^4J = −1.2 Hz, 2 H, H(3), H(4)), 7.07 (dd, ^4J = 1.0, ^5J = 0.9 Hz, 2 H, H(11), H(12)), 7.20 (dd, ^4J = 1.0, ^5J = 0.9 Hz, 2 H, H(8), H(9)); ^{13}C NMR δ 142.9 (s, C(7), C(10)), 136.0 (d, C(11), C(12)), 132.1, 132.0 (d, C(3), C(4), and C(8), C(9)), 35.8 (t, C(1), C(6)), 34.2 (C(2), C(5)); UV (hexane) λ_{max} (ϵ) 310 (340), 260 (3900), 227 (5400) nm. Anal. Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 90.73; H, 8.95.

8-(Methoxycarbonyl)-(*Z*)-[6]paracycloph-3-enes *anti*-(1b) and *syn*-(1b). To a solution of LDA prepared from 121 mg (1.20 mmol) of diisopropylamine and 1.2 mL of 1 N butyllithium in 4 mL of THF was added 218 mg (1.99 mmol) of the exo ester **8X** in 1 mL of THF at −78 °C. The solution was stirred for 15 min, and then a solution of diphenyl diselenide (374 mg, 1.20 mmol) and hexamethylphosphoramide (215 mg, 1.20 mmol) in 1 mL of THF was added dropwise to this solution. The solution was stirred at that temperature for 45 min and warmed up to room temperature, and then 1 N HCl was added. The organic layer was separated, and the aqueous layer was extracted with ether. The combined extract was washed with $NaHCO_3$ and water and dried. The solvent was removed in vacuo, and the residue was chromatographed on silica gel with ether/petroleum ether = 1:19 eluent to yield 29 mg (8%) of the exo selenide **13X** and 288 mg (77%) of the endo selenide **13N**. Similar results were obtained by using the endo ester **8N**.

13X: IR 3000, 1720, 1250, 1120, 730, 680 cm^{-1}; ^1H NMR δ 1.0–2.4 (m, 9 H), 2.82 (d, J = 12 Hz, 1 H), 3.48 (s, 3 H), 5.5–5.8 (m, 2 H), 6.12 (d, J = 2 Hz, 1 H), 6.30 (d, J = 2 Hz, 1 H), 7.0–7.5 (m, 5 H).

13N: IR 3000, 1720, 1250, 1100, 725, 675 cm^{-1}; ^1H NMR δ 1.0–2.3 (m, 9 H), 2.43 (d, J = 13 Hz, 1 H), 3.49 (s, 3 H), 5.5–5.8 (m, 2 H), 6.00 (d, J = 2 Hz, 1 H), 6.31 (d, J = 2 Hz, 1 H), 7.1–7.6 (m, 5 H).

To a solution of 3.00 g (8.04 mmol) of the endo selenide **13N** and 1.27 g (16.1 mmol) of pyridine in 30 mL of CH_2Cl_2 was added 5.6 mL of 15% H_2O_2. The mixture was stirred vigorously for 1 h, and then 1 N $NaHCO_3$ was added. The organic layer was separated, washed with 1 N HCl, $NaHCO_3$, and water, and dried. Evaporation of the solvent followed by flash chromatography with ether/petroleum ether = 3:97 eluent furnished the Dewar benzene isomer **5b** as a colorless oil which gradually isomerized to the cyclophane **1b** on standing at room temperature: IR 3000, 1710, 1590, 1540, 1295, 1250, 1230, 775, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8–2.2 (m, 8 H), 3.71 (s, 3 H), 5.5–5.8 (m, 2 H), 6.45 (d, J = 2 Hz, 1 H), 6.61 (d, J = 2 Hz, 1 H), 7.22 (s, 1 H): ^{13}C NMR δ 163.5 (s), 156.0 (d), 146.3 (s), 145.0 (d), 143.9 (d), 132.2 (d), 131.5 (d), 67.6 (s), 66.5 (s), 51.4 (q), 30.3 (t), 28.9 (t), 22.5 (t), 22.3 (t).

A solution of **5b** (942 mg, 4.36 mmol) in 150 mL of methanol was heated at 60 °C under nitrogen for 12 h. The solvent was evaporated, and the residue was chromatographed on silica gel with ether/petroleum ether = 3:97 eluent to give 177 mg (19%) of *anti*-**1b**, 253 mg (27%) of a mixture of *anti*-**1b** and *syn*-**1b**, and 215 mg (23%) of *syn*-**1b**.

***anti*-1b + *syn*-1b**: MS, *m/e* (rel intensity) 216 (M^+, 16), 162 (100), 147 (15). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.35; H, 7.86.

***anti*-1b**: IR 1710, 1255, 1195, 1070, 785, 745, 705, 685 cm^{-1}; ^1H NMR (360 MHz, CD_2Cl_2) δ 0.82–0.95 (m, 2 H, H(2a), H(5a)), 1.89–2.00 (m, 2 H, H(2b), H(5b)), 2.28 (ddd, ^2J = 12.1, ^3J = 12.1, ^3J = 2.9 Hz, 1 H, H(1b)), 2.33 (ddd, ^2J = 12.1, ^3J = 12.1, ^3J = 3.1 Hz, 1 H, H(6b)), 2.90 (ddd, ^2J = 12.1, ^3J = 3.6, ^3J = 3.6 Hz, 1 H, H(1a)), 3.76 (ddd, ^2J = 12.1, ^3J = 3.6, ^3J = 3.6 Hz, 1 H, H(6a)), 3.89 (s, 3 H, Me), 4.69–4.81 (m, 2 H, H(3), H(4)), 7.13 (B of ABX, $^3J_{AB}$ = 7.7, $^5J_{BX}$ = 0 Hz, 1 H, H(11)), 7.19 (A of ABX, $^3J_{AB}$ = 7.7, $^4J_{AX}$ = 1.6 Hz, 1 H, H(12)), 7.93 (X of ABX, $^4J_{AX}$ = 1.6, $^5J_{BX}$ = 0 Hz, 1 H, H(9)); ^{13}C NMR δ 167.4 (s, C=O), 145.2 (s, C(7)), 142.5 (s, C(10)), 139.0, 137.6 (d, C(11), C(12)), 134.7 (d, C(9)), 133.0 (s, C(8)), 132.5, 131.4 (d, C(3), C(4)), 51.8 (q, Me), 36.6, 35.7, 34.2, 33.1 (t, C(1), C(2), C(5), C(6)); UV (EtOH) λ_{max} (ϵ) 344 (1080), 275 (3300), 245 (7400), 224 (7400) nm.

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syn-**1b**: IR 1710, 1250, 1190, 1070, 785, 755, 705, 685 cm^{-1}; ^1H NMR (360 MHz, CD_2Cl_2) δ 1.10–1.21 (m, 2 H, H(2b), H(5b)), 1.86–1.97 (m, 2 H, H(2a), H(5a)), 2.36 (ddd, ^2J = 12.0, ^3J = 12.0, ^3J = 3.1 Hz, 1 H, H(1a)), 2.79 (ddd, ^2J = 12.0, ^3J = 4.2, ^3J = 3.1 Hz, 1 H, H(1b)), 2.92 (ddd, ^2J = 12.1, ^3J = 3.5, ^3J = 3.5 Hz, 1 H, H(6b)), 3.26 (ddd, ^2J = 12.1, ^3J = 12.1, ^3J = 3.4 Hz, 1 H, H(6a)), 3.88 (s, Me), 4.62–4.78 (m, 2 H, H(3), H(4)), 7.34 (s, 2 H, H(11), H(12)), 7.69 (br s, 1 H, H(9)); ^{13}C NMR δ 167.7 (s, C=O), 148.5 (s, C(7)), 143.2 (s, C(10)), 136.4 (d, C(9)), 136.2 (s, C(8)), 134.6, 133.7 (d, C(11), C(12)), 131.6, 131.4 (d, C(3), C(4)), 51.8 (q, Me), 36.0, 34.7 (2C), 34.0 (t, C(1), C(2), C(5), C(6)); UV (EtOH) λ_{max} (ϵ) 345 (920), 278 (3500), 255 (5500), 232 (6400) nm.

12-(Methoxycarbonyl)[6.3.2]propell-4-en-9-one (14a and 14b) and 13-(Methoxycarbonyl)[6.3.2]propell-4-en-9-ones (14c and 14d). A solution of the enone **6** (1.0 g, 6.17 mmol) and methyl acrylate (5.31 g, 61.7 mmol) in 15 mL of ether was irradiated with a high-pressure mercury lamp through a Pyrex filter under nitrogen for 10 h. During irradiation each 2.5 mL of methyl acrylate was added 3 times. The contents of the reaction tube was transferred with acetone, and the solvent was removed in vacuo. The viscous residue was extracted with ether six or seven times, and the solvent of the extract was evaporated. Recrystallization of the residue from ether gave one of the head-to-head isomer **14d** (384 mg, 25%), and the mother liquor was chromatographed on silica gel with ether/petroleum ether = 13:87 eluent to give *exo*-head-to-tail-**14a** (259 mg, 17%), *endo*-head-to-tail-**14b** (177 mg, 12%), and a head-to-head isomer **14c** (59 mg, 4%).

14a: IR 1730, 1720, 1190, 1020 cm^{-1}; MS, *m/e* (rel intensity) 248 (M^+, 21), 216 (71), 162 (62), 134 (100), 133 (72), 91 (87); ^1H NMR δ 1.6–2.8 (m, 14 H), 3.03 (dd, J = 9, 9 Hz, 1 H), 3.65 (s, 3 H), 5.3–5.7 (m, 2 H); ^{13}C NMR δ 219.9 (s), 173.2 (s), 132.3 (d), 130.1 (d), 53.3 (s), 51.3 (s + q), 44.8 (d), 37.1 (t), 36.8 (t), 31.3 (t), 30.3 (t), 25.1 (t), 28.7 (2C, t). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.21; H, 8.27.

14b: IR 1730, 1720, 1180, 950 cm^{-1}; MS, *m/e* (rel intensity) 248 (M^+, 15), 162 (55), 134 (100), 133 (65), 91 (60); ^1H NMR δ 1.6–2.7 (m, 14 H), 2.78 (dd, J = 9, 9 Hz, 1 H), 3.68 (s, 3 H), 5.4–5.7 (m, 2 H); ^{13}C NMR δ 221.8 (s), 173.5 (s), 132.0 (d), 130.4 (d), 53.9 (s), 52.2 (s), 51.3 (q), 44.7 (d), 36.1 (t), 33.0 (t), 32.9 (t), 31.1 (t), 28.7 (t), 23.5 (t), 22.7 (t). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.18; H, 8.32.

14c: IR 1730, 1720, 1200, 950 cm^{-1}; MS, *m/e* (rel intensity) 248 (M^+, 18), 162 (100), 91 (62); ^1H NMR δ 1.5–2.7 (m, 14 H), 2.81 (dd, J = 18, 8 Hz, 1 H), 3.56 (s, 3 H), 5.4–5.7 (m, 2 H), ^{13}C NMR δ 220.6 (s), 172.3 (s), 131.0 (2C, d), 59.1 (s), 51.5 (q), 46.4 (s), 41.9 (d), 37.6 (t), 36.7 (t), 34.2 (t), 33.2 (t), 31.6 (t), 23.3 (t), 23.1 (t); semicarbazone mp 203–206 °C. Anal. Calcd for $C_{16}H_{23}O_3N_3$: C, 62.93; H, 7.59; N, 13.76. Found: C, 62.77; H, 7.55; N, 13.76.

14d: mp 108–110 °C; IR (KBr) 1730, 1720, 1195, 960 cm^{-1}; MS, *m/e* (rel intensity) 248 (M^+, 10), 201 (70), 162 (100), 134 (60), 91 (78); ^1H NMR ($CDCl_3$) δ 1.6–3.0 (m, 15 H), 3.67 (s, 3 H), 5.3–5.6 (m, 2 H); ^{13}C NMR δ 219.2 (s), 172.3 (s), 132.1 (d), 130.7 (d), 58.5 (s), 51.5 (q), 45.6 (s), 40.5 (d), 37.1 (t), 36.9 (t), 34.4 (t), 30.6 (t), 26.4 (t), 23.6 (t), 23.5 (t). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.63; H, 8.12.

9,11-Bis(methoxycarbonyl)[6.2.2]propell-4-enes (15a, 15b, and 15c). To a suspension of 484 mg of 60% sodium hydride in mineral oil and 0.042 mL of methanol in 36 mL of ether was added dropwise a mixture of 3.0 g (12.1 mmol) of the keto ester **14a** and 1.09 g (18.2 mmol) of methyl formate in 20 mL of the same solvent. The mixture was heated at reflux temperature for 2 h. Workup as described for the preparation of **8X** and **8N** afforded 3.75 g of the hydroxymethylene derivative as a pale yellow solid [IR (KBr) 3600–2300, 1730, 1690, 1555, 1200 cm^{-1}]. The diazo transfer and the subsequent photo-Wolff rearrangement was carried out as described for **8X** and **8N**. Chromatography on silica gel with ether/petroleum ether = 1:19 eluent afforded 110 mg (3% from **14a**) of the exo,endo diester **15b** and with ether/petroleum ether = 1:9 549 mg (16% from **14a**) of the exo,exo isomer **15a**. In a similar manner, ring contraction of 1.67 g (6.73 mmol) of **14b** gave 273 mg (21% from **14b**) of a mixture of *exo,endo*-**15b** and the endo,endo isomer **15c** (**15b**:**15c** = 2:1 by ^{13}C NMR).

15a: mp 92–93 °C (from petroleum ether); IR (KBr) 1720, 1330, 1190, 1040, 930, 750 cm^{-1}; MS, *m/e* (rel intensity) 278 (M^+, 2), 105 (100); ^1H NMR ($CDCl_3$) δ 1.7–2.4 (m, 10 H), 2.50 (dd, J = 12, 8 Hz, 2 H), 3.27 (dd, J = 12, 8 Hz, 2 H), 3.68 (s, 6 H), 5.7–5.9 (m, 2 H); ^{13}C NMR δ 173.4 (s), 131.4 (d), 51.2 (q), 50.1 (s), 42.8 (d), 38.5 (t), 28.7 (t), 22.6 (t). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.85; H, 7.98.

15b + 15c (2:1): IR 1725, 1175, 1020, 910, 740 cm^{-1}; MS, *m/e* (rel intensity) 278 (M^+, <1), 105 (100); ^1H NMR δ 1.3–2.3 (m, ca. 12 H), 2.70 (dd, J = 12, 8 Hz, ca. 1 H), 3.3–3.9 (m, ca. 1 H), 3.62, 3.64 (2 s, 6 H), 5.5–5.8 (m, 2 H); ^{13}C NMR for **15b** δ 174.4 (s), 173.9 (s), 131.4 (2C, d), 51.4 (s), 52.2 (s), 51.5 (2C, q), 46.8 (d), 45.7 (d), 35.0 (2C, t), 33.0 (t), 32.8 (t), 22.4 (t), 22.0 (t); for **15c** δ 173.7 (s), 131.4 (d), 51.5 (q), 51.3 (s), 41.3 (d), 39.1 (t), 2.92 (t), 22.4 (t). Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.52; H, 8.03.

8,11-Bis(methylcarbonyl)-(*Z*)-[6]paracycloph-3-ene (1c). Phenylselenenylation of **15a** (227 mg, 0.817 mmol) with 4 equiv of LDA and diphenyl diselenide as described for the preparation of **13X** and **13N** afforded after silica gel chromatography (ether/petroleum ether = 1:9 eluent) 144 mg (30%) of the bisselenide **16** as a white solid which was recrystallized from CH_2Cl_2/petroleum ether: mp 145–146 °C; IR (KBr) 1720, 1255, 1100, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7–2.9 (m, 8 H), 2.36 (d, J = 16 Hz, 2 H), 2.76 (d, J = 16 Hz, 2 H), 3.56 (s, 6 H), 5.8–5.9 (m, 2 H), 7.2–7.6 (m, 10 H). Anal. Calcd for $C_{28}H_{30}O_4Se_2$: C, 57.15; H, 5.14. Found: C, 56.86; H, 5.12. Similar reaction of **15b + 15c** (183 mg, 0.658 mmol) with 2.5 equiv of LDA and diphenyl diselenide yielded **16** (82 mg, 21%) and a monoselenide (stereochemistry undetermined; 38 mg, 13%) as a white solid: mp 107–108 °C (from CH_2Cl_2/petroleum ether); IR (KBr) 1720, 1260, 1210, 1090, 1050, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–2.5 (m, 12 H), 2.79 (d, J = 15 Hz, 1 H), 3.61 (s, 3 H), 3.66 (s, 3 H), 5.6–5.9 (m, 2 H), 7.2–7.6 (m, 5 H). Anal. Calcd for $C_{22}H_{26}O_4Se$: C, 60.97; H, 6.05. Found: C, 60.73; H, 6.03. Phenylselenenylation of this mono selenide with 1.5 equiv of the reagents gave **16** in 39% yield.

Oxidative elimination of 109 mg (0.185 mmol) of **16** as described for **5b** yielded after flash chromatography (ether/petroleum) ether = 3:7 eluent) 27 mg (54%) of the Dewar benzene isomer **5c** as a colorless solid: mp 70–74 °C; IR (KBr) 1710, 1590, 1300, 1010, 785, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.9–2.3 (m, 8 H), 3.70 (s, 6 H), 5.62 (m, 2 H), 7.27 (s, 2 H); ^{13}C NMR δ 162.9 (s), 154.9 (d), 145.3 (s), 131.7 (d), 65.5 (s), 51.6 (q), 28.7 (t), 22.4 (t). A solution of 73 mg (0.266 mmol) of **5c** in 70 mL of degassed hexane was heated at 50 °C for 4 days. The solvent was removed in vacuo, and the subsequent flash chromatography furnished 54 mg (74%) of the cyclophane **1c** as a yellow viscous oil which solidified on standing in a refrigerator. Recrystallization from hexane afforded pale yellow columns: mp 59–61 °C; IR (KBr) 2997, 1723, 1575, 1528, 1258, 1175, 1115, 1090, 994, 913, 779, 769, 737, 707, 675, 645 cm^{-1}; MS, *m/e* (rel intensity) 274 (M^+, 13), 220 (39), 205 (100); ^1H NMR (360 MHz, CD_2Cl_2) δ 0.98 (m, 2 H, H(2a), H(5a)), 1.94 (m, 2 H, H(2b), H(5b)), 2.34 (ddd, ^2J = 12.1, ^3J = 12.1, ^3J = 2.8 Hz, 1 H, H(6b)), 2.86 (ddd, ^2J = 12.3, ^3J = 3.5, ^3J = 3.5 Hz, 1 H, H(1a)), 3.25 (ddd, ^2J = 12.3, ^3J = 12.3, ^3J = 3.4 Hz, 1 H, H(1b)), 3.79 (ddd, ^2J = 12.1, ^3J = 3.6, ^3J = 3.6 Hz, 1 H, H(6a)), 3.89, 3.91 (2 s, 6 H, Me), 4.72 (m, 2 H, H(3), H(4)), 7.71 (s, 1 H, H(12)), 7.98 (s, 1 H, H(9)); ^{13}C NMR δ 167.0, 166.7 (s, C=O), 147.5, 144.9 (s, C(7), C(10)), 138.8 (s, C(11)), 138.0 (d, C(12)), 135.9 (d, C(9)), 135.2 (s, C(8)), 132.2, 131.0 (d, C(3), C(4)), 52.2 (2C, q, Me), 36.8, 34.7 (2C), 33.2 (t, C(1), C(2), C(5), C(6)); UV (hexane) λ_{max} (ϵ) 366 (1500), 284 (5500), 233 (13 000) nm. Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.88; H, 6.66.

Kinetic Measurements. Rate of Valence Isomerization of Dewar Benzene Isomers 5b and 5c. The isomerization rates of **5b** and **5c** in hexane (5×10^{-4} and 4×10^{-4} M, respectively) were determined by UV spectroscopy[2c] measuring the absorption of **1b** and **1c** at 342 and 366 nm, respectively.

Isomerization between *anti*-1b and *syn*-1b. A solution of *anti*-**1b** or *syn*-**1b** in methanol (3×10^{-3} M) was set in a constant temperature bath, and aliquots were analyzed by HPLC at appropriate intervals. The rate constants were calculated by using the usual expression for a reversible first-order reaction.[26] The results are summarized in Table V.

X-ray Crystallographic Analysis of 1c. Crystal data of **1c**: $C_{16}H_{18}O_4$, M_r 274.3, monoclinic, space group $C2/c$, a = 19.304 (2) Å, b = 6.616 (1) Å, c = 12.175 (1) Å, β = 112.95 (1)°, U = 1431.9 (2) Å^3, D_x = 1.272 g cm^{-3}, Z = 4. Diffraction intensities were measured on a Rigaku four-circle diffractometer by using nickel-filtered Cu Kα radiation. A total of 1073 reflections was collected up to 2θ = 120°, among which 956 were observed reflections. The crystal structure was solved by the direct method (MULTAN-78)[27] and refined by the full-matrix least-squares (X-RAY SYSTEM)[28] to the R index of 0.089. Because of the crystallographic C_2 symmetry, the bridging carbons of **1c** molecule (C(2), C(3)) were refined as the disordered structures with equivalent population. The non-hydrogen atoms were refined anisotropically, and hydrogen atoms

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(28) Stewart, J. M. "XRAY76"; Report TR-466, 1976; University of Maryland, MD.

except those bonding to C(1) were refined isotropically. The fractional atomic parameters and the interatomic bond distances and angles are given in the Supplementary Material.

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Supplementary Material Available: Listing of the bond distances, bond angles, fractional atomic coordinates, and anisotropic thermal parameters for non-hydrogen atoms (3 pages). Ordering information is given on any current masthead page.

Structure of Brevetoxin A as Constructed from NMR and MS Data

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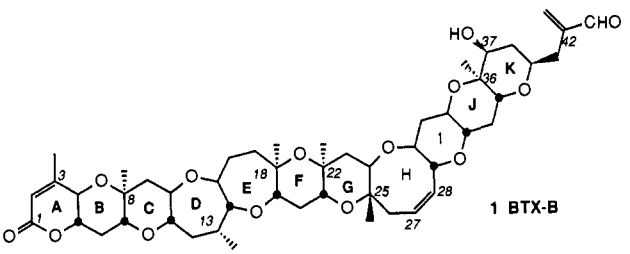
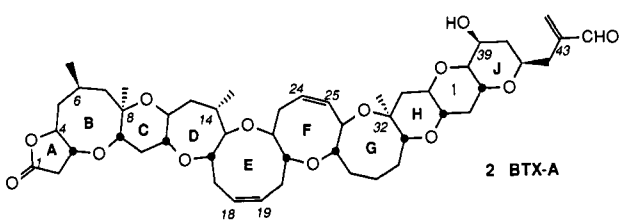
Abstract: Brevetoxins (BTX) exemplified by BTX-B $C_{50}H_{70}O_{14}$ (**1**) are neurotoxins produced by *Gymnodinium breve*. The blooms of these dinoflagellates known as red tide have led to massive fish kills, mollusk poisoning, etc. along the Florida coast and the Gulf of Mexico. Up to date, a total of five BTX's with the same skeleton have been found. The skeleton is an unprecedented array of trans-linked 6/6/6/7/7/6/6/8/6/6/6-membered rings, one δ-lactone and ten ether rings, leading to a stiff ladderlike linear structure. The structure of BTX-A $C_{49}H_{70}O_{13}$ (2), recently determined by X-ray crystallography, has an even more unique oxacarbocyclic skeleton made up of 5/8/6/7/9/8/8/6/6/6-membered rings. An independent study based solely on spectroscopic data, namely NMR and MS has led to the same structure except for an error in the configuration of one methyl group (at C-6). It was possible to construct the entire skeleton of BTX-A from the NMR data and MS of two derivatives. Two general fragmentation patterns in the MS of brevetoxin derivatives were recognized, and it was these patterns, assisted by NMR data, which enabled one to reconstruct the structure of brevetoxin A in a logical manner.

The red tide dinoflagellate *Gymnodinium breve* (*Ptychodiscus brevis* Davis) is responsible for massive fish kills and food poisoning occurring in the Gulf of Mexico and along the coast of Florida.[1] The brevetoxins, the causative agents of the poisoning, have attracted considerable interest since 1968;[2] they are lipid soluble neurotoxins which block the neuromuscular action.[3]

The full structure of the first member of these toxins, brevetoxin B ($C_{50}H_{70}O_{14}$) (BTX-B) (1), elucidated in 1981,[4] was of unprecedented nature. Namely, it consists of 11 oxygen-containing trans fused 6/6/6/7/7/6/6/8/6/6/6 rings condensed in a ladder shape, 30 Å long, 6 Å wide, and 6 Å high, the only flexible portion in the polyether skeleton being the site of the two seven-membered rings. The structures of five more toxins in this series have since been elucidated, i.e., BTX-C,[5] GB-3,[6] GB-5,[7] and GB-6.[7,8] Recently[9] the structure of a new member of the brevetoxins BTX-A (GB-1 toxin) ($C_{49}H_{70}O_{13}$), which had remained unknown because of its poor crystallinity, was finally elucidated by X-ray crystallography as **2**, another extraordinary structure consisting of trans fused 5/8/6/7/9/8/8/6/6/6 lactone–ether rings. The different ring structure of BTX-A makes it more flexible than BTX-B, hence reducing its crystallinity and lead to broadened ^1H NMR signals. In the following we present results of our independent structural studies on brevetoxin-A (BTX-A), which after proposals of a transitional working structure,[10-12] arrived



1 BTX-B



2 BTX-A

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