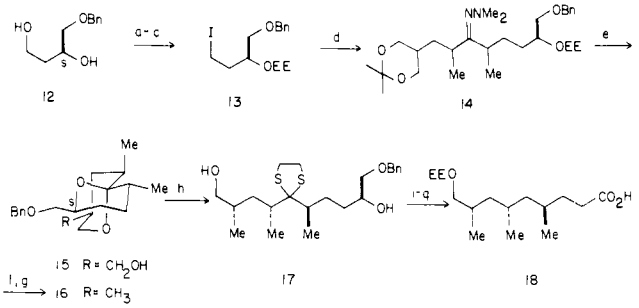
Scheme V[a]



[a] (a) 1 equiv of *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, 20 h, 78%; (b) CH_2=CHOEt, ppts, 100%; (c) NaI, acetone, 83%; (d) metalated DMH prepared as before, THF, −78 °C, 91%; (e) 4 equiv of CSA, 10:1 CH_2Cl_2–MeOH, 2 days, then CF_3SO_3H, CH_2Cl_2, MeOH, −60 °C, 2 h, 80%; (f) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, 95%; (g) $LiBEt_3H$, THF, 10 h, 93%; (h) $HSCH_2CH_2SH$, $BF_3 \cdot OEt_2$, −40 °C, 24 h, 92%; (i) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 95%; (j) $CaCO_3$, $HgCl_2$, 4:1 CH_3CN–H_2O, 90%; (k) $NaBH_4$, MeOH, 95%; (l) MsCl, pyridine, 4:1 Et_2O–CH_2Cl_2, 98%; (m) LAH, Et_2O, 0 °C, 2 days, 95%; (n) Pd/C, H_2, EtOAc, 100%; (o) $NaIO_4$, 1:1 THF–H_2O, 95%, (p) CH_2=CHOEt, ppts, 100%; (q) PDC, DMF, 81%.

this manner the *S* alcohol serves its final role as a carboxyl surrogate and provides a means of selectively adjusting the oxidation level of the C_1 terminus of the ionomycin fragment **18**.

In summary, the spiroketalization reaction with diastereotopic hydroxymethyl groups provides access to products with complementary stereochemistry. Other reaction processes that proceed with diastereotopic selectivity at prochiral carbon centers have been developed and will be the subject of future reports.

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Novel Synthesis of Metacyclophanes. Thermal- and DDQ-Induced Aromatization of Bridgehead Dienes

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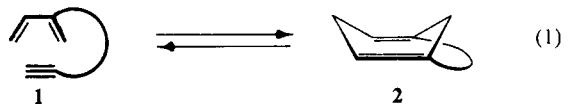
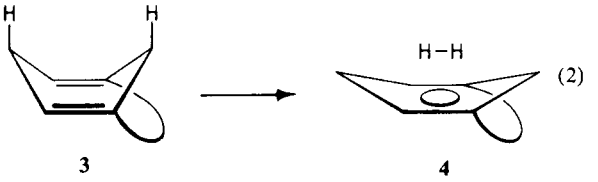
We have recently reported a general synthesis of bridgehead dienes utilizing a type II intramolecular Diels–Alder cycloaddition (eq 1).[1] The resulting bridgehead dienes **2** are 1,5-bridged



(1)

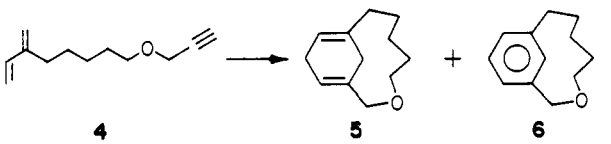
1,4-cyclohexadienes. The distortion imposed by the bridge constrains the 1,4-cyclohexadiene fragment to a boat conformation. The inherent reactivity of the ring system affords an opportunity for novel reaction manifolds not available to less strained species and a potential synthetic entry into topologically interesting molecules. A particularly intriguing possibility, illustrated in eq 2, involves dehydrogenation of the bridgehead diene to a metacyclophane.[2] Realization of this aromatization reaction would



(2)

offer a new entry into this interesting class of molecules that would complement existing methods.[3] The present paper reports the successful synthesis of metacyclophanes by dehydrogenation of bridgehead dienes and X-ray structural data for a derivative prepared by this method, a [6]metacyclophane.

Evidence for thermal dehydrogenation of bridgehead dienes was obtained by a careful analysis of the products of thermolysis (xylene, 260 °C, 2.8 h) from the intramolecular Diels–Alder cycloaddition of dienyne ether **4**.[4] A GC mass spectrum of the thermolysate indicated that in addition to cycloadduct **5** (*m/e* 178), a smaller quantity of an aromatic side product (*m/e* 176) was also produced. In a subsequent investigation, it was learned that



thermolysis of bridgehead diene **5** (sealed tube, benzene, 259.5 °C) resulted in smooth dehydrogenation to metacyclophane **6** in quantative yield ($t_{1/2}$ = 10 h).

In addition to thermal dehydrogenation, bridgehead dienes may also be aromatized by treatment with DDQ. Thus, bridgehead diene **5** and 1.1 equiv of DDQ in toluene (25 °C, 6 h) affords the [7]metacyclophane **6** in 81% isolated yield. Since the bridgehead precursors are prepared by Diels–Alder chemistry, additional functionality is readily incorporated on the ring. For example, bridgehead diene ester **7**, prepared by cycloaddition of the corresponding acyclic dienyne ester, was converted to [7]metacyclophane **8** in 64% isolated yield upon treatment with DDQ in toluene at reflux for 1 h. The methyl ester derivatives of these metacyclophanes have proven to be extremely valuable since they are crystalline compounds suitable for X-ray analysis.[5]

Extension of this methodology to the preparation of [6]metacyclophanes has also been accomplished. For example, the [6]metacyclophane **10** is isolated in 28% yield upon treatment of diene

(1) Shea, K. J.; Burke, L. D. *J. Org. Chem.* **1985**, *50*, 725. (b) Shea, K. J.; Burke, L. D., manuscript in preparation.

(2) An aromatization pathway to small [*n*]paracyclophanes has recently been reported by Gassman and co-workers: Gassman, P. G.; Bailey, T. F.; Hoye, R. C. *J. Org. Chem.* **1980**, *45*, 2923.

(3) The chemistry of [*n*]metacyclophanes has been reviewed: Greenberg, A.; Liebman, J. F. "Strained Organic Molecules"; Academic Press: New York, 1978. More recent synthetic entries into [*n*]metacyclophanes can be found in: (a) Hirano, S.; Hara, H.; Hiyama, T.; Fujita, S.; Nozaki, H. *Tetrahedron* **1975**, *31*, 2219. (b) Turkenburg, L. A. M.; Blok, P. M. L.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1981**, 3317. (c) Turkenburg, L. A. M.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1983**, 1817. (d) Turkenburg, L. A. M.; van Straten, J. W.; de Wolf, W. H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1980**, *102*, 3256.

(4) All new compounds gave spectroscopic properties consistent with the assigned structures. The spectroscopic data for the metacyclophanes is included as supplemental information.

(5) The X-ray crystal structure for the [7]metacyclophane **8** will be published in the full acount of this work.

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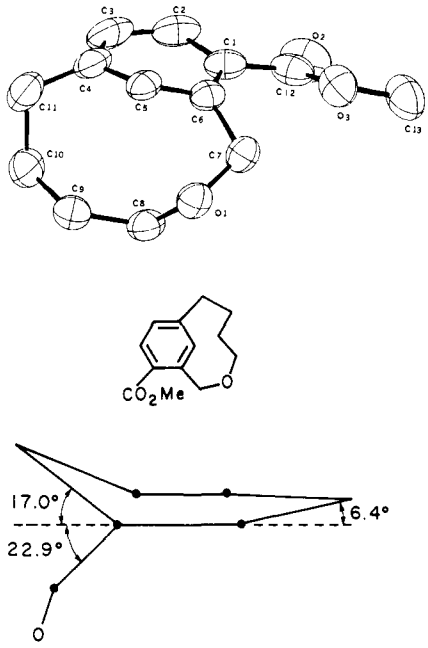

Figure 1. ORTEP drawing of [6]metacyclophane **10** showing the atomic numbering scheme.

9 with DDQ in toluene, while the thermal aromatization (280 °C, 8 h) gives the ester **10** in 50% isolated yield. The methyl ester is a crystalline solid, mp 61.5–62.5 °C. Slow evaporation from CH_2Cl_2/pentane afforded crystals suitable for X-ray analysis. Figure 1 shows an ORTEP drawing of the structure of **10**.[6] Noteworthy is the absence of C(5) substituents in this derivative, common to the two small ring metacyclophane derivatives for which structural data are now available.[7]

Key structural features of this compound are the nonplanarity of the benzene ring which exists in an unsymmetrical boat conformation with bow (C(4)–C(5)–C(6)) and stern (C(1)–C(2)–C(3)) deformations of 17.0° and 6.4°, respectively. Although the sum of these distoritons (23.4°) is significant, it is smaller than that found in the [6]paracyclophane (39°)[8] and the recently reported [5]metacyclophane (38.3°).[7a] Since the six-atom bridge cannot be coplanar with the aromatic ring, there is substantial distortion at the benzylic carbons. This distortion is observed in the angles of 22.9° and 20.1° formed by bond vectors C(7)–C(6) and C(11)–C(4) to the aromatic plane defined by atoms C(1)–C(6)–C(3)–C(4) (Figure 1).

The distortions at the benzylic positions also manifest themselves in the bond angles, of which representative values include C(3)–C(4)–C(11) = 126.1° and C(5)–C(4)–C(11) = 113.2°. Rather severe distortions are found in the six-atom bridge. Although the bond angles at the two benzylic carbons (C(4)–C(11)–C(10) = 108.0°, C(6)–C(7)–O(1) = 109.7°) are near normal, the valence angles at C(9) and C(10) (C(8)–C(9)–C(10) = 120.6° and C(9)–C(10)–C(11) = 119.2°) are significantly expanded.

The thermal extrusion of hydrogen from bridgehead dienes may occur by one of several plausible mechanisms. In addition to a stepwise free radical loss of hydrogen, the enforced boat conformation of the bridgehead diene **2** predisposes the molecule for a 4+2 cycloreversion. Indeed, monitoring the aromatization of diene **7** in benzene over several half-lives revealed that the reaction exhibits clean first-order kinetics. The solution-phase rate constants for aromatization over a 40 °C temperature range (260–300 °C) allowed calculation of the Arrhenius activation energy parameters, ΔE_a^* 40.0 ± 0.6 kcal/mol and $\Delta S^*_{280} = -6.9 \pm 0.9$ eu for the reaction. These values are to be compared with data for aromatization of 1,4-cyclohexadiene, ΔE_a^* 43.8 kcal/mol and $\Delta S^*_{280} = -10.8$ eu.[9] The similarity of activation energy parameters for the two reactions and the failure to intercept radical chain processes argues for a concerted thermal extrusion of hydrogen from bridgehead diene **2** (eq 2).

Acknowledgment. We are grateful to the National Science Foundation for financial support of this work.

Supplementary Material Available: Spectroscopic data for metacyclophanes **6**, **8**, and **10** and tables of positional parameters, anisotropic temperature factors, bond angles, and interatomic distances for metacyclophane **10** (6 pages). Ordering information is given on any current masthead page.

(6) Crystal data for [6]metacyclophane **10**: $C_{13}H_{16}O_3$, triclinic, space group $P\bar{1}$, $a = 6.743$ (4) Å, $b = 12.221$ (6) Å, $c = 7.605$ (4) Å, $\alpha = 91.27$ (4)°, $\beta = 109.91$ (4)°, $\gamma = 100.27$ (4)°, $V = 576.8$ (5) Å^3, $Z = 2$. Intensity measurements were made on a Syntex $P2_1$ diffractometer, Mo Kα radiation $\lambda = 0.71073$ Å, graphite monochromator. Intensities of 2662 reflections with $2\theta \leq 55°$ were measured; of these 1982 had intensities $I > 3\sigma(I)$. The structure was solved by direct methods (MULTAN 80) and refined by full-matrix least-squares calculations to $R = 0.067$. $R_w = 0.093$ (anisotropic thermal parameters for carbon and oxygen, hydrogen in calculated positions). Tables of positional parameters, anisotropic temperature factors, bond angles, and interatomic distances are included as supplemental information.

(7) (a) X-ray structure of a [9]metacyclophane: Effenberger, F.; Schönwalder, K.-H.; Stezowski, J. J. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 871. (b) X-ray structure of a [5]metacyclophane: Jenneskens, L. W.; Klamer, J. C.; de Boer, H. J. R.; de Wolf, W. H.; Bickelhaupt, F.; Stam, C. H., *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 238.

(8) (a) Tobe, Y.; Kakiuchi, K.; Odaira, T.; Hosaki, Y.; Kasai, N. *J. Am. Chem. Soc.* **1983**, *105*, 1376. (b) Krieger, C.; Liebe, W.; Tochtermann, W. *Tetrahedron Lett.* **1983**, *24*, 707.

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The Uncatalyzed Claisen Rearrangement of Chorismate to Prephenate Prefers a Transition State of Chairlike Geometry

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Direct comparison of the transition-state structure of an enzymic reaction with that of the analogous uncatalyzed reaction is usually impossible. First, many enzyme-catalyzed reactions do not proceed at measurable rates in the absence of the catalyst. Second, the chemical participation of active-site amino acids in the enzymic reaction makes the choice of appropriate reaction conditions for the uncatalyzed reaction arbitrary at best. For the Claisen rearrangement of chorismate to prephenate catalyzed by the enzyme chorismate mutase,[1] however, the comparison is easier. There is no evidence for chemical participation by the enzyme, and although the reaction rate is more than a million times faster at the active site than free in solution,[2] the uncatalyzed rearrangement is still a facile process.[3] Here, we address the question of whether this enzyme accelerates the *un*catalyzed pathway that has the lower free energy of activation. Having recently demonstrated[4] that the enzymic reaction proceeds via a transition state of chairlike geometry (Figure 1), we now report the stereochemical course of the nonenzymic rearrangement.

The stereochemical course of several Claisen rearrangements and of the related Cope and oxy-Cope rearrangements has been determined. While in sterically unhindered cases a chairlike transition state can be favored by as much as 6 kcal/mol,[5] geometric constraints can shift the relative energies of the chair and boat transition states so that reaction proceeds partially or com-

(1) Haslam, E. "The Shikimate Pathway"; Wiley: New York, 1974.

(2) Andrews, P. R.; Smith, G. D.; Young, I. G. *Biochemistry* **1973**, *12*, 3492.

(3) The half-life of chorismate in neutral aqueous solution is approximately 25 min at 60 °C.

(4) Sogo, S. G.; Widlanski, T. S.; Hoare, J. H.; Grimshaw, C. E.; Berchtold, G. A.; Knowles, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 2701.

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