Acknowledgment. This work was supported by the Yamada Science Foundation. We are grateful to Daicel Chemical Industries, Ltd., for the determination of the enantiomeric excess of phosphine–borane **8**.

Supplementary Material Available: Melting points, spectroscopic (IR and ^{1}H NMR) data, and elemental analyses for phosphine boranes **1**,**3**–**8**, and **10** (5 pages). Ordering information is given on any current masthead page.

Diastereotopic Selectivity at Prochiral Carbon Centers: Functionalization of Differentiated Hydroxymethyl Groups Provides Access to Either Stereoisomeric Configuration

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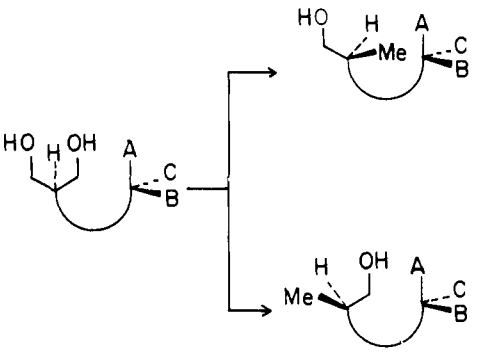
Synthetic methods that create new stereocenters with a high level of control are central to organic synthesis. Procedures that provide access to either stereoisomeric configuration can give rise to added flexibility. Recently, we described a reaction that proceeded with diastereotopic selectivity at a prochiral carbon center on route to a synthesis of talaromycin B[1] (Scheme I). Subsequently, a procedure was developed that resulted in the reversal of diastereotopic selectivity and provided the stereocontrol required for the synthesis of talaromycin A.[2b] Herein, we report on an alternative method for the generation of either stereoisomeric configuration at a prochiral carbon center. In Scheme I a generalized system is depicted that represents a compound equipped with diastereotopic hydroxymethyl groups. Reaction processes that engage one of these groups selectively and nondestructively can be parlayed into the desired objective through suitable functionalization procedures.[3] In this study we have employed the spiroketalization reaction to illustrate this strategy for stereocontrol. This method, in conjunction with other features of the spiroketalization reaction, has been applied to a synthesis of (±)-invictolide (**1**) the fire ant queen recognition pheromone of *Selonopsis invicta*[4,5] and to a nonracemic synthesis of the C_1–C_9 fragment **18** of the calcium ionophore ionomycin.[6,7]

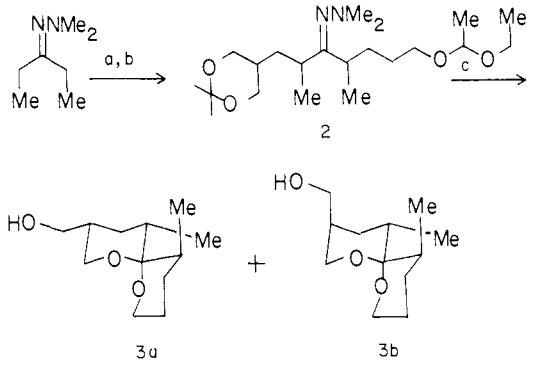
The acyclic spiroketal precursor **2** has been prepared as a complex mixture of diastereomers[8] by two consecutive alkylations of the dimethylhydrazone of 3-pentanone.[9] Treatment of **2** with 4 equiv of camphorsulfonic acid in 10:1 methylene chloride–methanol at room temperature for 24 h resulted in the thermodynamically controlled formation of a mixture of two major spiroketals in a 6:1 ratio (88% yield). The major diastereomer **3a** is equipped with three equatorial substituents, whereas the minor component **3b** contains an axial hydroxymethyl substituent. A trace amount of a third component (ca. 1%) was shown to contain the same spiroketal skeleton with an equatorial hydroxymethyl group and two axial methyl substituents. We did not observe any spiroketal isomer derived from the *syn*-1,3-dimethyl stereoisomer of **2** throughout the course of the reaction. Spiroketalization of this diastereomer would result in a syn-pentane interaction and was expected to be disfavored.[12] Presumably, prior equilibration through enolization is required for spiroketalization to occur. Each component gave rise to the same thermodynamic ratio of spiroketals upon resubjection to the equilibrating reaction conditions. The 6:1 equilibrium ratio of equatorial and axial hydroxymethyl-substituted spiroketals represents a pseudo *A* value of ca. 1.1 for this group at the 3-position of the tetrahydropyran ring system (Scheme II).

Two independent processes are operating in the conversion of **2** into **3**. Equilibration at the carbon bearing the hydroxymethyl

Scheme I



Scheme II[a]



[a] (a) 1.3 equiv of LDA, THF, 0 °C, 15 h, then $Br(CH_2)_3OEE$, −78 °C, 2 h, 95%; (b) 1.3 equiv of LDA, THF, 0 °C, 20 h, then 2,2-dimethyl-5-iodomethyl-1,3-dioxane, −78 °C, 2 h (2 exists as a complex mixture of diastereomers), 91%; (c) 4 equiv of CSA, CH_2Cl_2–methanol (10:1), room temperature, 24 h (6:1 mixture of diasteromers), 88%.

(1) (a) Schreiber, S. L.; Sommer, T. J. *Tetrahedron Lett.* **1983**, *24*, 4781. (b) Kozikowski, A. P.; Scripko, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 353. (c) Kocienski, P.; Yeates, C. *J. Chem. Soc., Chem. Commun.* **1984**, 151. (d) Kay, I. T.; Bartholomew, D. *Tetrahedron Lett.* **1984**, *25*, 2035.

(2) (a) Smith, A. B.; Thompson, A. S. *J. Org. Chem.* **1984**, *49*, 1469. (b) Schreiber, S. L.; Sommer, T. J.; Satake, K. *Tetrahedron Lett.* **1985**, *26*, 17. (c) Midland, M. M.; Gabriel, J. *J. Org. Chem.* **1985**, *50*, 1143.

(3) For the functionalization of enantiotopic hydroxymethyl groups, see: Fukuyama, T.; Wang, C.-L. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 261.

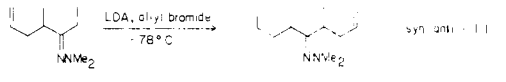
(4) Isolation and synthesis: (a) Rocca, J. R.; Tumlinson, J. H.; Lofgren, C. S.; Glancey, B. M. *Tetrahedron Lett.* **1983**, *24*, 1893. Synthesis: (b) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738.

(5) For other spiroketal-based strategies for the synthesis of nonspiroketal products, see: (a) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303, 1312, and ref 13. (b) Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon Press: New York, 1983; Vol. 1, Chapter 8. (c) Deslongchamps, P.; Sauve, G.; Schwartz, D. A.; Ruest, L. *Can. J. Chem.* **1984**, *62*, 2929. Spirolactone: (d) see ref 4b and 13.

(6) Toeplitz, B. K.; Cohen, A. I.; Funke, P. T.; Parker, W. L.; Gougoutas, J. Z. *J. Am. Chem. Soc.* **1979**, *101*, 3344.

(7) (a) Evans, D A. *Aldrichimica Acta* **1982**, *15*, 23. (b) Wuts, P. G. M.; D'Costa, R.; Butler, W. *J. Org. Chem.* **1984**, *49*, 2582.

(8) In addition to *E*/*Z* hydrazone stereoisomers, the three stereocenters in **2** were prepared without stereocontrol, e.g.,

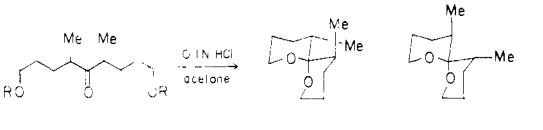


(9) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3.

(10) Lynn, D. G.; Phillips, N. J.; Hutton, W. C.; Shabonowitz, J.; Fennell, D. I.; Cole, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 7319.

(11) Evans, D. A.; Sacks, C. E.; Kelschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789.

(12) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.



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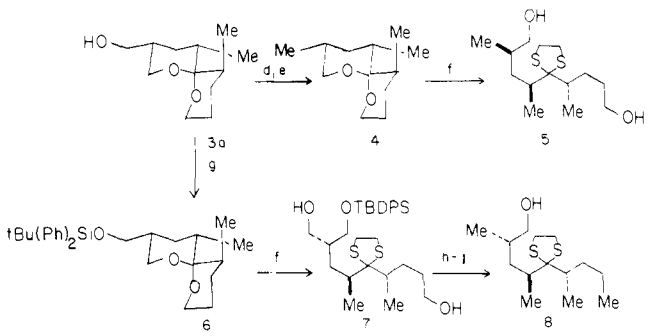
Scheme III[a]



[a] (d) 1.3 equiv of *p*-TsCl, py, CH_2Cl_2, room temperature, 48 h, 95%; (e) 2 equiv of $LiEt_3BH$, THF, room temperature 2 h, 93%; (f) 100 equiv of $BF_3{\cdot}OEt_2$ $HSCH_2CH_2SH$, −40 °C, 2 h, (**4** → **5**, 94%; **6** → **7**, 91%); (g) 2 equiv of *t*-$BuPh_2SiCl$, 4 equiv of imidazole, DMF, room temperature, 30 min, 92%; (h) 2.6 equiv of *p*-TsCl, py, CH_2Cl_2, room temperature, 48 h, 88%; (i) 4 equiv of $LiEt_3BH$, THF, room temperature, 2 h, 90%; (j) 6 equiv of *n*-Bu_4NF, THF, room temperature, 2 h, 91%.

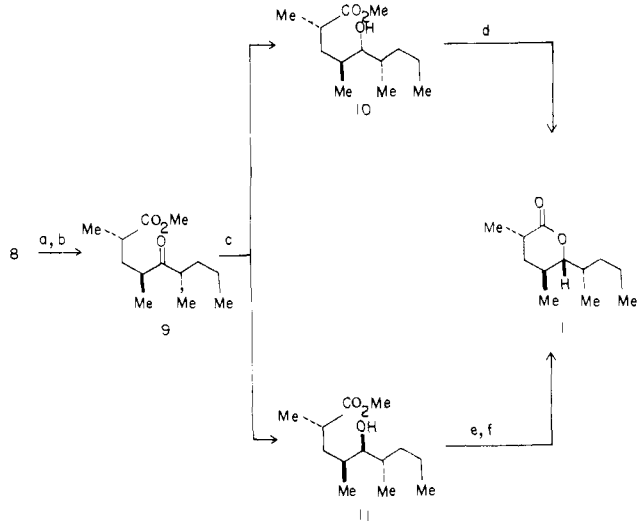
group occurs by ring opening of the spiroketal and reclosure with the alternate hydroxymethyl group. Stereocontrol in this manner was suggested by Lynn's studies of the equilibration of talaromycin A and B.[10] The acid-catalyzed equilibration of carbon centers α and α' to the spiroketal carbon was employed by Evans and co-workers in their synthesis of calcimycin[11] and has been examined in detail by the Deslongchamps group.[12] The Deslongchamps study provided the expectation that near complete *anti*-1,3-dimethyl stereocontrol could be obtained, as was observed. In the Hoye synthesis of invictolide, the *anti*-1,3-dimethyl stereochemistry was obtained by a related spirolactonization reaction.[13] In this work, it would appear that the direct equilibration α and α' to the spirolactone could not be achieved, although this problem could be corrected through a recycling maneuver. The advantage of the spiroketal system for problems of this type is associated with this equilibration through transiently formed enol ether intermediates.

Tosylation and reduction of **3a** afforded the trimethylated spiroketal **4** that could be ring opened to the acyclic derivative **5** without complications arising from epimerization by employment of the conditions of Ireland and Daub.[14] For the synthesis of invictolide, the opposite stereochemistry must be obtained at the carbon bearing the hydroxymethyl group of spiroketal **3**. This can be achieved by silylation of the hydroxyl (to afford **6**) prior to the despiroketalization reaction. Bistosylation of the resultant diol **7**, reduction with lithium triethylborohydride, and desilylation afforded the alcohol **8**, which contains the proper stereochemistry for the invictolide synthesis (Scheme III).

To complete the synthesis, the problem of stereoselective lactone construction was addressed. Corey–Schmidt oxidation,[15] esterification, and hydrolysis of the dithiolane afforded keto ester **9**. Reduction of the ketone with sodium borohydride provided a near 1:1 mixture of separable (HPLC) carbinol diastereomers. At this stage we could not make an assignment of stereochemistry at the carbinol site and felt we had little hope for significantly improving upon the stereoselectivity of the reduction. However, the ability to separate these diastereomers provided a simple solution to both of these problems.

The less mobile diastereomer lactonized directly to provide invictolide **1** upon treatment with catalytic trifluoroacetic acid in benzene and is thus assigned the structure **10**. The more mobile diastereomer **11** provided an isomer of invictolide upon similar treatment. However, mesylation and saponification of **11** with excess base produced an inverted hydroxyl carboxylate that lactonized to afford invictolide **1** upon acidification. In this manner,

Scheme IV[a]



[a] (a) 4 equiv of PDC, DMF, room temperature, 20 h, then CH_2N_2, Et_2O, 86%; (b) $HgCl_2$, $CaCO_3$, CH_3CN–H_2O (4:1), room temperature, 3 h, 88%; (c) 2 equiv of $NaBH_4$, MeOH, room temperature, 5 min (**10**/**11** ≈ 1:1), 95%; (d) catalytic CF_3CO_2H, benzene, room temperature, 2 h, 96%; (e) 20 equiv of MsCl, py, Et_2O–CH_2Cl_2 (4:1), 0 °C, 10 h, 87%; (f) 100 equiv of NaOH, MeOH–H_2O (2:1), room temperature, 10 min, then HCl, 1 h, 96%.

both reduction products **10** and **11** could be stereospecifically converted to invictolide.[16]

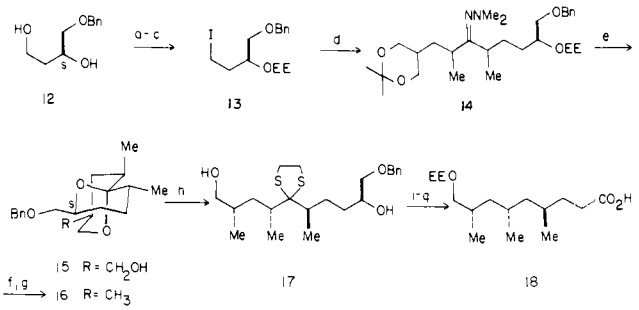
A simple modification of the spiroketalization protocol can be employed to control the absolute stereochemistry of the resultant products. A suitably placed substituent along the spiroketal precursor serves as a device for the promotion of remote internal asymmetric induction. This is illustrated in the context of a synthesis of the C_1–C_9 fragment of ionomycin **18**, wherein the absolute stereochemistry of each carbon bearing a methyl group can be controlled in a single operation.

The *S* alcohol **12**[17] was converted to the alkylating agent **13** and alkylated with a lithiated hydrazone to afford the acyclic spiroketal precursor **14** as a mixture of diastereomers. The thermodynamically controlled spiroketalization of this material produced a 8:1:0.1 mixture of three spiroketals, in analogy to the cyclization of **2** → **3**.[18] The major spiroketal **15** results from participation of the *S* alcohol in the ketalization so as to place the (benzyloxy)methyl substituent in an equatorial orientation. The large *A* value expected of an alkyl group at this position (note 1,3-relationship to the spiro-carbon) ensures a high degree of stereocontrol in the reaction. The 1,4- and 1,6-asymmetric induction proceeds via the Evans–Deslongchamps equilibration and the 1,8-asymmetric induction is obtained through the diastereotopic selectivity (8:1) in the ketalization. The structure of ionomycin dictates that, in this instance, the free hydroxymethyl group should be converted to the methyl substituent. Subsequent despiroketalization of the trimethylated spiroketal **16** produced the dithiolane **17**, which could be converted to the ionomycin fragment **18**, by employment of the indicated conditions (Scheme V).[19] In

(13) See: ref 5b. Hoye, T. R.; Peck, D. R.; Trumper, P. K. *J. Am. Chem. Soc.* **1981**, *103*, 5618.
(14) Ireland, R. E.; Daub, J. P. *Tetrahedron Lett.* **1982**, *23*, 3471.
(15) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(16) Comparison spectra were kindly provided by Dr. J. H. Tumlinson.[4a]
(17) $[\alpha]^{22}_D$ −7.68° (*c* 3.67, MeOH) [lit. $[\alpha]^{23}_D$ −7.56° (*c* 3.65, MeOH)]: (a) Tokano, S.; Kasahara, C.; Ogasawara, K. *Chem. Lett.* **1983**, 175. (b) Katsuki, T.; Lee, A.; Ma, P.; Martin, V.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373.
(18) The axial hydroxymethyl isomer (15% yield) and the bis(axial methyl) isomer (ca. 1% yield) of **15** could be separated at this stage (HPLC). However, to facilitate material throughput these compounds were carried through as a mixture on larger scale operations until after the despiroketalization, where the easily separated acyclic diols **17** were purified by flash chromatography.
(19) An alternative four-step procedure (Ra-Ni, EtOH; $NaIO_4$, MeOH; EVE; PDC, DMF) resulted in the formation of 15–20% of methyl epimers at the desulfurization step.[20] The indicated conditions (scheme V) completely avoided this problem.
(20) Koreeda, M.; Brown, L. *J. Org. Chem.* **1983**, *48*, 2122.

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.

Acknowledgment. This investigation was supported by the NIH and NSF (Presidential Young Investigator Award) to whom we are grateful. We thank the Dreyfus Foundation (Dreyfus Teacher–Scholar Grant), A. P. Sloan Foundation, Chicago Community Trust/Searle Scholars Program, and Pfizer, Inc., for additional support.

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

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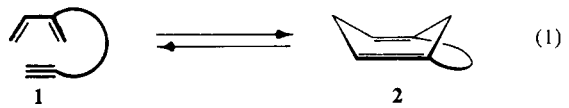
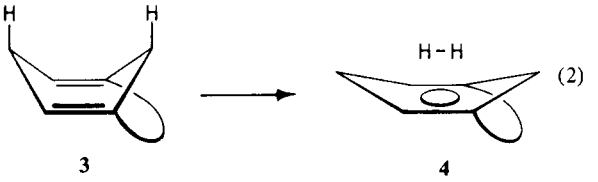
Received December 28, 1984

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)

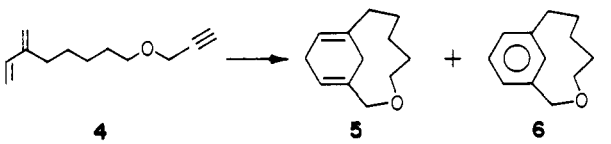
1,4-cyclohexadienes. The distortion imposed by the bridge constrains the 1,4-cyclohexadiene fragment to a boat conformation. The inherent reactivity of the ring system affords an opportunity for novel reaction manifolds not available to less strained species and a potential synthetic entry into topologically 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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