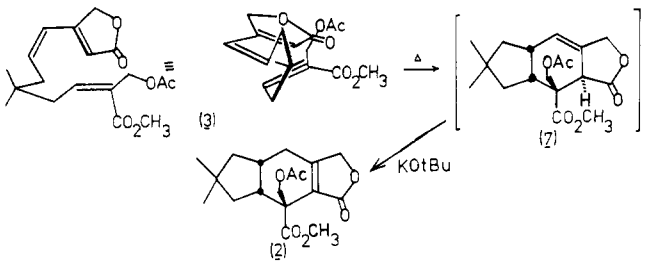
the stabilized ylide **5** (2 equiv) (obtained from the corresponding (bromomethyl)butenolide[9] as shown) in methanol/CH_2Cl_2 (1:4) at reflux (3.5 h) afforded **3** and the related trans-isomer **6** (5:1) in 65% yield.[10]

Thermolysis of **3** was conducted at ~230 °C (sealed tube in toluene) for 32 h. Treatment of the crude product with KO-*t*-Bu/ether and workup afforded cleanly a single cycloadduct, the cis-conjugated lactone **2**, in 80% yield. This substance was shown to be identical with an authentic sample of lactone **2** by 400-MHz NMR and all other criteria.[1] No evidence of the formation of any other isomeric cycloadducts was observed.[11] In this instance, at elevated temperatures, partial conjugation of the primary cycloadduct **7** occurred as was observed in the cyclization of the related (*Z*,*E*,*Z*)-triene (eq 3).



(3)

It was also confirmed that the cyclization of **3** proceeds significantly more slowly than for the related *Z*,*E*,*Z* isomer, as would be anticipated on steric grounds. We have measured the relative rates of cyclization of the (*Z*,*Z*,*Z*)- and (*Z*,*E*,*Z*)-trienes at 205 °C, and the latter is more reactive by a factor of ~42 ($t_{1/2}$ 76.6 h vs. $t_{1/2}$ 1.81 h) as expected. On this basis, we estimate the difference in activation energy ($\Delta\Delta G^{\ddagger}$) to be about 3.5 kcal/mol at 205 °C.[12,13] This difference, while significant, appears smaller than one might have anticipated by analogy to conceivable bimolecular reactions.

These results, for the highly functionalized and somewhat deactivated (*Z*)-diene system **3** *substantially extend the scope of these cyclizations and suggests that the approach will likely prove a general one.* Furthermore, these results serve to point out in striking fashion several significant generalizations regarding the use of (*Z*)-dienes: (1) transition-state selection is primarily governed by diene geometry; (2) dienophile orientation is independent of dienophile geometry; (3) the dienophile orientation has no great effect on the overall activation energy; (4) 1,5 sigmatropic hydrogen shifts and other isomerizations apparently do not present a limitation even in highly substituted systems.

Thus, the completely stereoselective cycloaddition (**3** → **2**) provides the basis for further experiments to exploit this general approach to cis-fused polycyclic ring systems for the synthesis of natural products.

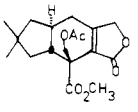
Acknowledgment. This investigation was supported by a research grant, GM-29290, from the Institute for General Medical Sciences of the National Institutes of Health, to whom we are extremely grateful. We also thank the NSF for a grant in support of the acquisition of the Bruker WH-400 400 MHz NMR spectrometer.

Registry No. 2, 81600-71-7; **3**, 81554-04-3; **4**, 75887-41-1; **5**, 81554-05-4; **6**, 75887-44-4; (bromomethyl)butenolide, 61934-55-2.

(9) Martin, R.; Chapleo, C. B.; Svanholt, K. L.; Dreiding, A. S. *Helv. Chim. Acta* **1976**, *59*, 2724.

(10) House, H. O.; Jones, V. K.; Frank, G. *J. Org. Chem.* **1964**, *29*, 3327.

(11) Separation of the isomeric dienes is tedious, and so for preparative purposes cyclization can be conducted on the 5:1 mixture of (*Z*,*Z*,*Z*)- and (*Z*,*E*,*Z*)-trienes, which affords, after treatment with *t*-BuOK, a readily separable mixture of **2** and **6** (~11:1). It should be pointed out that, in this case, the practical limit on stereoselectivity resides in geometric selectivity observed in the *production* of the (*Z*)-diene. Methodology for the construction of (*Z*)-dienes with high geometric specificity is under investigation in our laboratories.



i

(12) Measured by NMR (400 MHz) by repetitive integration of diagnostic peaks in the olefin region of compounds **2** and **3**. The values for half-lives were derived from least-squares treatment of the data points for 3 or more half-lives. The reactions showed good first-order kinetics (within experimental error), and values for the half-lives are the average results of duplicate determinations.

(13) The observed differences for our system may be rather structure dependent, due in part to the relative rigidity of the diene system, although the fact that the C-2 diene substituent is tied back in a ring and the diene is carbonyl conjugated would appear to result in decreased rather than increased reactivity. Activation parameters are certainly structure dependent as shown by the cyclization of the system studied by Fuchs at 110 °C.[6]

Biosynthesis of Sulfur Compounds. Elucidation of the Stereochemistry of the Conversion of [3-(Methylthio)propyl]glucosinolate into Allylglucosinolate (Sinigrin)

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The mustard oil glucoside allylglucosinolate (sinigrin) (**1**) is a common constituent of plants of the mustard family (*Cruciferae*).[1] The biosynthesis of **1** in horseradish (*Armoracia lapathifolia* Gilib.) has been shown[2,3] to proceed from homomethionine (**2**) via [3-(methylthio)propyl]glucosinolate (**3**) (Scheme I). [3-(Methylsulfinyl)propyl]glucosinolate (**4**) was also found to be a highly efficient precursor of allylglucosinolate. The transformation of **3** into **1** is an unusual biochemical reaction for which at least three possible mechanisms can be envisioned (Scheme II). One mechanism would proceed by the β-elimination of methanethiol (path a). A more likely mechanism (path b) could involve the conversion of **3** into a sulfonium salt followed by β-elimination of an alkyl methyl sulfide. Finally, a third mechanism (path c) could proceed via the pericyclic elimination of methanesulfenic acid from the sulfoxide **4**. This last pathway would be of particular interest since there are no established examples of enzyme-catalyzed pericyclic reactions, with the possible exception of chorismate mutase.[4] In principle, a distinction between the pericyclic reaction pathway (c) and the two alternatives might be achieved by elucidation of the stereochemistry of the elimination process. The pericyclic route must proceed by a syn-elimination mechanism, while paths a and b could follow either a syn or anti geometry, with anti geometry being more likely.[5] We now report the results of experiments that rule out a pericyclic elimination process in the biosynthesis of allylglucosinolate.

The elucidation of the stereochemistry of the elimination reaction was accomplished in two stages by precursor incorporation experiments with chirally labeled forms of homomethionine. The first stage utilized DL-[4(*RS*)-, 4(*R*)-, and 4(*S*)-^{3}H]homomethionine. The synthesis of these labeled amino acids was accomplished as outlined in Scheme III. Benzyloxybenzaldehyde, prepared in 56% yield by DCC/Me_2SO oxidation[6,7] of benzyl-

(1) (a) Kjaer, A. *Fortschr. Chem. Org. Naturst.* **1960**, *18*, 122. (b) Ettlinger, M. G.; Kjaer, A., in *Recent Adv. Phytochem.* **1968**, *1*, 58.

(2) Matsuo, M.; Yamazaki, M. *Chem. Pharm. Bull.* **1968**, *16*, 1034.

(3) Chisholm, M. D.; Matsuo, M. *Phytochem.* **1972**, *11*, 203.

(4) Andrews, P. R.; Cain, E. N.; Rizzardo, E.; Smith, G. D. *Biochemistry* **1977**, *16*, 4848.

(5) Hanson, K. R.; Rose, I. A. *Acc. Chem. Res.* **1975**, *8*, 1.

(6) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1963**, *85*, 3027.

(7) Attempts to achieve this oxidation with the Collins reagent or PCC were unsuccessful.

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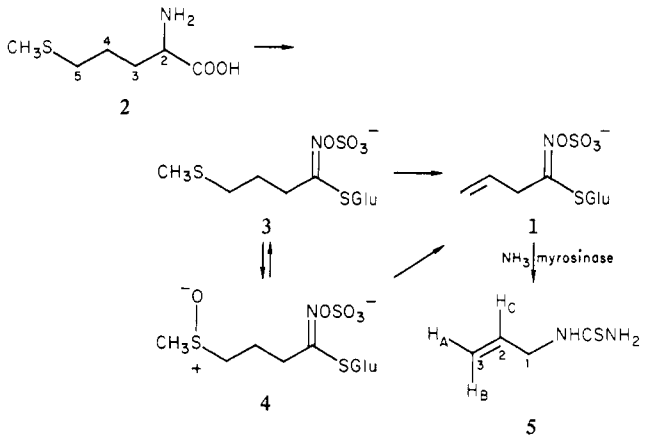
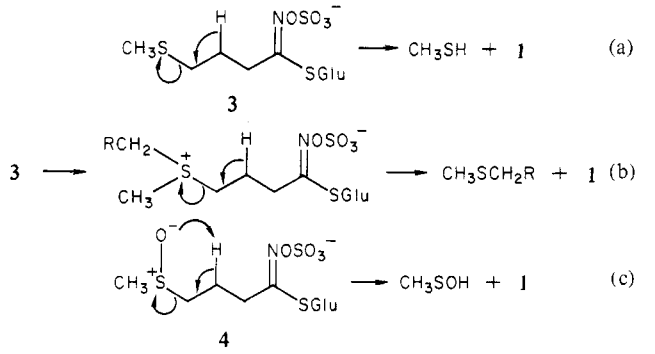
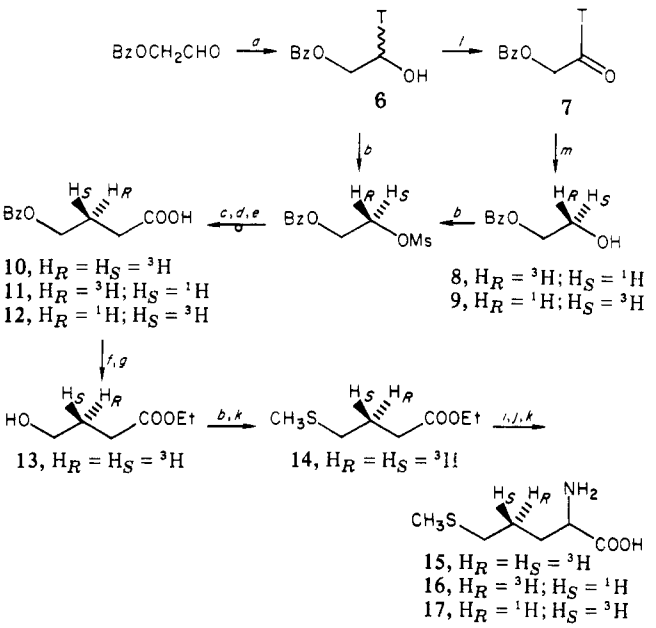
Scheme I



Scheme II



Scheme III



[a] [^{3}H]-KBH_4. [b] MsCl, Et_3N. [c] $NaCH(CO_2Et)_2$. [d] KOH. [e] H^+, Δ. [f] EtOH, H^+. [g] H_2, Pd/C. [h] CH_3SH, HO^-, Adogen$^+Cl^-$. [i] Red-Al, C_4H_9NO. [j] KCN, $(NH_4)_2CO_3$. [k] $Ba(OH)_2$. [l] Me_2SO, DCC. [m] 9-BBN, (−)- or (+)-α-pinene.

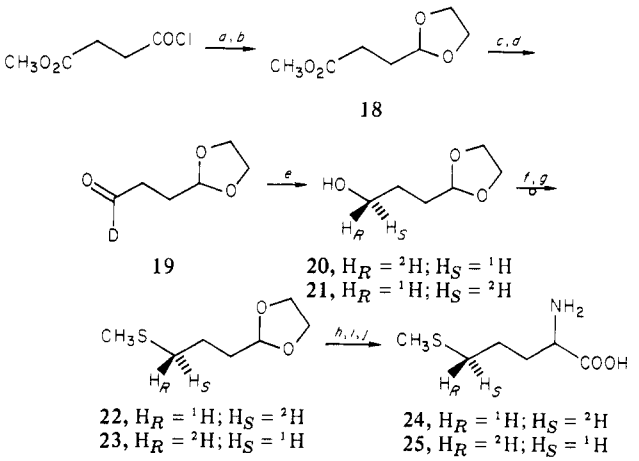
oxyethanol,[8] was reduced with tritiated potassium borohydride to yield [1(*RS*)-^{3}H]benzyloxyethanol (**6**). Mesylation of **6** followed by a malonic ester synthesis yielded [3(*RS*)-^{3}H]-4-benzyloxybutanoic acid (**10**) (75%). Esterification of **10** with subsequent catalytic debenzylation then gave ethyl [3(*RS*)-^{3}*H*]-4-hydroxybutanoate (**13**) (65%). Mesylation of **13** and reaction with methanethiol under phase-transfer conditions[9] cleanly produced ethyl [3(*RS*)-^{3}H]-4-(methylthio)butanoate (**14**) (81%). Finally, **14** was reduced to the corresponding aldehyde with Red-al and morpholine[10] and DL-[4(*RS*)-^{3}H]homomethionine (**15**) obtained by Bücherer synthesis (21%). DL-[4(*R*)- and 4(*S*)-^{3}H]-homomethionine (**16**, **17**) were prepared by a variation of the same reaction sequence. [*formyl*-^{3}H]Benzyloxybenzaldehyde (**7**) was reduced with the adduct of 9-borabicyclononane (9-BBN) and (−)- or (+)-α-pinene[11] to give [1(*R*)- and 1(S)-^{3}H]benzyloxyethanol (**8**, **9**), respectively. The stereochemistry assigned to **8** and **9** derives from literature precedents.[11-14] Mesylation of **8** and **9** followed by a malonic ester synthesis yielded [3(*R*)- and 3(*S*)-^{3}H]-4-benzyloxybutanoic acid (**11**, **12**). The stereochemistry assigned to **11** and **12** is based upon the assumption that the malonate alkylation proceeds with inversion of configuration.[15] The chirally tritiated acids **11** and **12** were then transformed into DL-[4(*R*)- and 4(*S*)-^{3}H]homomethionine (**16**, **17**) by the methods already outlined.

The three forms of tritiated homomethionine prepared according to Scheme III were each mixed with DL-[2-^{14}C]homomethionine[16] and the three doubly labeled precursors administered to freshly cut leaves of *Armoracia lapathifolia*. After 24 h, the leaves were

Table I. Incorporation of Labeled Homomethionine into Allylglucosinolate

expt no.	precursor (^{3}H/^{14}C)	% incorpn	allyl-thiourea (^{3}H/^{14}C)	% ^{3}H retention
1	[4(*RS*)-^{3}H,2-^{14}C]-**2** (10.8)	12.5	6.18	57.2
2	[4(*R*)-^{3}H,2-^{14}C]-**2** (4.93)	2.73	4.70	95.3
3	[4(*S*)-^{3}H,2-^{14}C]-**2** (2.46)	9.67	0.62	25.3
4	[5(*R*)-^{2}H_1,2-^{14}C]-**2**	7.1		
5	[5(*S*)-^{2}H_1,2-^{14}C]-**2**	2.2		

Scheme IV



[a] H_2, Pd/C. [b] $HOCH_2CH_2OH$, *p*-TsOH. [c] $LiAlD_4$. [d] $C_5H_5NH^+CrO_3Cl^-$. [e] 9-BBN, (−)- or (+)-α-pinene. [f] MsCl, Et_3N. [g] CH_3SH, HO^-, Adogen$^+Cl^-$. [h] H_3O^+. [i] KCN, $(NH_4)_2CO_3$. [j] $Ba(OH)_2$.

(8) Butler, C. L.; Renfrew, A. G.; Clapp, M. *J. Am. Chem. Soc.* **1938**, *60*, 1472.

(9) Herriott, A. W.; Picker, D. *Synthesis* **1975**, 447.

(10) Kanazawa, R.; Tokoroyama, T. *Synthesis* **1976**, 527.

(11) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 5211.

(12) Parry, R. J. *J. Chem. Soc., Chem. Commun.* **1978**, 294.

(13) Parry, R. J.; Trainor, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 5243.

(14) Aberhart, D. J.; Lin, H.-J.; Weiller, B. H. *J. Am. Chem. Soc.* **1981**, *103*, 6750.

(15) Because of the operation of the sequence rule, the configurational designations remain unchanged even though the reactions proceed with inversion of configuration.

(16) The labeled amino acid was synthesized in 8% overall yield by treatment of 1-chloro-3-(methylthio)propane with [^{14}C]potassium cyanide in DMF followed by hydrolysis of the labeled nitrile, esterification of the resulting acid, reduction[10] of the ester to [1-^{14}C]-3-(methylthio)butanal, and Bücherer amino acid synthesis.

Table II. Chemical Shift Data for Samples of [3-$^2H_1$]Allylthiourea in the Presence of Eu(fod)$_3$

precursor	resonance positions of allylthiourea, ppm H_A	H_B	D_A	D_B	rel intens of D_A and D_B
24	5.33	5.57	5.36	5.57	$D_A:D_B \simeq 1:4$
25	5.39	5.62	5.38	5.60	$D_A:D_B \simeq 5:1$

harvested and homogenized, and the homogenate was incubated at 37 °C for 12 h. Radioinactive allyl isothiocyanate was then added as carrier and labeled allyl isothiocyanate recovered by steam distillation. Treatment of the allyl isothiocyanate with ammonia produced crystalline allylthiourea (**5**, Scheme I) that was recrystallized to constant specific activity and constant ratio. The results of the three incorporation experiments are summarized in Table I (experiment numbers 1–3). The data clearly show that homomethionine is transformed into allylglucosinolate with the stereospecific removal of the 4 *pro-S* hydrogen atom.[17]

The second stage of the stereochemical analysis required determination of the spatial orientation of the 5 *pro-R* and 5 *pro-S* hydrogen atoms of homomethionine at C-3 of **5**. This determination was achieved by means of precursor incorporation experiments with DL-[5(*S*)- and 5(*R*)-$^2H_1$]homomethionine. The synthesis of these chirally deuterated forms of the amino acid is summarized in Scheme IV. 3-Carbomethoxypropionyl chloride[18] was converted to the acetal ester **18** by using methods previously devised in our laboratories.[19] **18** was reduced with lithium aluminum deuteride and the resulting dideutero alcohol oxidized with PCC to give the deuterated aldehyde **19**. Reduction of **19** with the adduct derived from 9-borabicyclononane and (−)- or (+)-α-pinene[11] yielded the [1(*R*)- and 1(*S*)-$^2H_1$] alcohols **20** and **21** (43%). The stereochemistry assigned to **20** and **21** follows from literature precedents.[11-14] Alcohols **20** and **21** were mesylated and the mesyl groups displaced with sodium methylthiolate (81%). If it is assumed that the displacement proceeds with inversion of configuration, then the alcohols **20** and **21** should produce the chiral thioethers **22** and **23**, respectively. Finally, **22** and **23** were converted to DL-[5(*S*)- and 5(*R*)-$^2H_1$]homomethionine (**24**, **25**) by removal of the acetal functions and Bücherer synthesis (37%).

The two chirally deuterated forms of homomethionine were each mixed with DL-[2-^{14}C]-**2** and the doubly labeled precursors administered to *A. lapathifolia* in the usual way. Workup after 24 h yielded radioactive allylthiourea in each case (Table I, experiment numbers 4, 5). Location of the deuterium label in each of the two samples of allylthiourea was accomplished by ^{2}H NMR. The ^{1}H NMR spectrum of unlabeled allylthiourea at 90 mHz in $CDCl_3$ exhibits a multiplet at δ ca. 5.9 assignable to H_C, while H_A and H_B overlap to form a multiplet at δ ca. 5.3. Addition of Eu(fod)$_3$ resolves the multiplet at δ 5.3 into two doublets whose coupling constants (J_{AC} = 9.3 Hz, J_{BC} = 17.3 Hz) show that H_B has shifted downfield relative to H_A. The deuterium labeling pattern of the two samples of allylthiourea isolated in experiments 4 and 5 was elucidated by comparing the 400-mHz ^{1}H NMR spectrum of each sample in the presence of Eu(fod)$_3$ with the corresponding 61.4-mHz ^{2}H NMR spectrum. The results of this comparison are shown in Table II. It can be seen that [5(*S*)-$^2H_1$]homomethionine (**24**) yielded allylthiourea with most of the deuterium label present at the chemical shift position of H_B. Conversely, [5(*R*)-$^2H_1$]homomethionine (**25**) gave allylthiourea with the higher level of deuterium enrichment at the chemical shift position of H_A.[20] From these observations and the data in Table I, one can conclude that the conversion of [3-(methylthio)propyl]glucosinolate (**3**) into allylglucosinolate (**1**) proceeds by an anti elimination process. The possibility of a pericyclic elimination via the sulfoxide **4** is therefore rule out.[21]

Acknowledgment. We are pleased to thank the National Science Foundation (Grant CHE 8004112) and the Robert A. Welch Foundation (Grant C-729) for support of this research, and the Nuclear Magnetic Resonance Laboratory at the University of South Carolina for the ^{2}H NMR spectra.

Registry No. [1-^{14}C]-**1**, 81624-87-5; [4(*RS*)-^3H,2-^{14}C]-**2**, 81624-88-6; [4(*R*)-^3H,2-^{14}C]-**2**, 81655-15-4; [4(*S*)-^3H,2-^{14}C]-**2**, 81655-16-5; [5(*R*)-^2H,2-^{14}C]-**2**, 81624-89-7; [5(*S*)-^2H,2-^{14}C]-**2**, 81624-90-0; DL[2-^{14}C]-**2**, 15995-78-5; [1-^{14}C]-**3**, 81624-91-1; (*R*)-**4**, 27303-31-7; [^{3}H-^{14}C]-**5**, 81624-92-2; (±)-**6**, 81624-93-3; **7**, 81624-94-4; (*R*)-**8**, 81655-17-6; (*S*)-**9**, 81655-18-7; **10**, 81624-95-5; (*R*)-**11**, 81643-40-5; (*S*)-**12**, 81624-96-6; **13**, 81624-97-7; **14**, 81624-98-8; **14** aldehyde, 81624-99-9; DL-**15**, 81625-00-5; (*R*)-DL-**16**, 81625-01-6; (*S*)-DL-**17**, 81625-02-7; **18**, 81625-03-8; **19**, 81625-04-9; (*R*)-**20**, 81625-05-0; (*S*)-**21**, 81625-06-1; (*S*)-**22**, 81625-07-2; (*R*)-**23**, 81625-08-3; (*S*)-DL-**24**, 81625-09-4; (*R*)-DL-**25**, 81625-10-7; (*Z*)-[3-$^2H_1$–a^{14}C]-**5**, 81625-11-8; (*E*)-[3-$^2H_1$-^{14}C]-**5**, 81625-12-9; 1-chloro-3-(methylthio)propane, 13012-59-4; [1-^{14}C]-3-(methylthio)-propanenitrile, 81625-13-0; [1-^{14}C]-3-(methylthio)propanoic acid, 81625-14-1; phenyl isocyanate, 103-71-9; [7-^3H,4-^{14}C]-1-phenyl-4-thio-5-allylbiuret, 81625-15-2; benzyloxyacetaldehyde, 60656-87-3.

(17) The degree of tritium retention in experiments 1–3 is slightly higher than that expected on the basis of experimental error. In order to ascertain if this slight excess might be due to a radiochemical contaminant, the allylthiourea obtained in experiment 3 was derivatized with phenylisocyanate to give 1-phenyl-4-thio-5-allylbiuret. After chromatography and recrystallization the tritium to carbon-14 ratio of the biuret was the same as that of the allylthiourea. The presence of a radiochemical impurity therefore seems unlikely.

(18) Riegel, B.; Lilienfeld, W. M. *J. Am. Chem. Soc.* **1945**, *67*, 1273.

(19) Parry, R. J.; Kunitani, M. G.; Viele, O., III *J. Chem. Soc., Chem. Commun.* **1975**, 321.

(20) The presence of deuterium at both the H_A and H_B positions of the two allylthiourea samples is expected since the optical purity of the (+)- and (−)-α-pinene used in the 9-BBN reductions is ca. 80%.

(21) An anti elimination proceeding via sulfoxide **4** remains a viable possibility.

Total Synthesis of the First Molecular Möbius Strip

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Received February 19, 1982

Chemical topology, as defined by Wasserman in 1961,[1] deals with certain kinds of novel isomerism that may occur upon formation of macrocyclic rings.[2] As first discussed by Wasserman[1] and later by Schill,[3] one may conceive of classes of molecules, including knotted rings and linked rings (catenanes), with interesting topological properties. In addition, a favorite subject of topology for mathematicians and chemists alike involves the properties of the Möbius strip, the one-sided, one-edged "isomer" of a cylinder with a single 180° twist about its long axis. In principle, it should be possible to prepare such structures by total synthesis. These interesting speculations have captured the imaginations of many chemists; however, of the structures mentioned above, only syntheses of catenanes have actually been demonstrated to date.[1,3,4] In this communication, we report an efficient total synthesis of the first molecular Möbius strip (**2**)[5] and its cylindrical isomer (**3**) via high-dilution cyclization of the tris(tetrahydroxymethylethylene) (THYME) diol ditosylate (**1**) (Scheme I).

(1) (a) Frisch, H. L.; Wasserman, E. *J. Am. Chem. Soc.* **1961**, *83*, 3789–3795. (b) Wasserman, E. *Sci. Am.* **1962**, *207*, 94–100.

(2) Mathematically, chemical topology deals with geometrical properties of molecules that remain invariant upon continuous deformation in three-dimensional space.

(3) Schill, G. "Catenanes, Rotaxanes, and Knots"; Academic Press: New York, 1971.

(4) (a) Ben-Efrain, D. A.; Batich, C.; Wasserman, E. *J. Am. Chem. Soc.* **1970**, *92*, 2133–2135. (b) Wolovsky, R. *Ibid.* **1970**, *92*, 2132–2133.

(5) The structure of macrotetracyclic polyether **2** may be considered as a graph possessing three four-sided figures. The surface defined by these figures is a Möbius strip. Though only a single enantiomer is shown, compound **2** formed in this manner is racemic.

0002-7863/82/1504-3219$01.25/0