13 (53% based on the amount of **11** initially present) and a 24% isolated yield of **14** (31% based on **11** initially present) were obtained. There was also achieved a 60% recovery of the *E,E* isomer, **12**. In a separate experiment **12** was resubjected to the same conditions with benzaldehyde. After 86 h there could be isolated 11% of the *trans*-pyrone **15** and 3% of the *cis*-pyrone **14**.

Compound **13** reacted with *m*-chloroperoxybenzoic acid to afford a 60% yield of the silyoxy ketone **16**. The formation of a single Rubottom product, **16**,[10] is also consistent with the all-cis formulation of **13**.

In summary the zinc chloride–THF catalyst system would appear to have exhibited all of the characteristics to be expected of the pericyclic (type a) model. The required intermediate type, **3**, is produced in a stereospecific reaction. No acyclic intermediates are observed. Strict suprafaciality, in addition to the diene, is apparently followed. The selective endo orientation of the diene has been rationalized.[2] Finally, the *trans,cis*-diene **11** reacts much faster than the *trans,trans*-diene **12** and gives a radically different stereochemical result.

In the BF_3·OEt_2 catalyzed reaction of **7** (Scheme III) with benzaldehyde (in methylene chloride at −78 °C), quenching after 5 min afforded a 48% yield of an 8:1 mixture of **17**:**9** and a 46% yield of a 2:1 mixture of *threo*-**20**:*erythro*-**21**. The stereochemistry of the separated acyclic compounds was deduced by their very clean conversion to **17** and 9 respectively, upon treatment with trifluoracetic acid. When the reaction time was extended to 45 min, the yields and ratios of the products changed only slightly (**17**:**9** = 9:1, 46% combined; **20**:**21** = 1.5:1, 44% combined). These data serve to establish that the dihydropyrones **17** and **9** are not arising from the same species (presumably **18** and **19**) that, on quenching, are giving rise to **20** and **21**. This is clear, since the initial (ca. 5 min) pyrone formation is not perceptibly augmented by ca. a 10-fold increase in reaction time nor are the amounts of acyclic products diminished. In another experiment a 1.5:1 mixture of alcohols **20**:**21** was resubjected to the reaction conditions. Following quenching at partial conversion (30 min) a 28% yield of a 4:1 ratio of **17**:**9** was produced. A 67% recovery of a 1:1.2 ratio of **20**:**21** was realized. Thus, the acyclic alcohols **20** and **21**, which arise from quenching, do suffer cyclization *but at a rate still much too slow to account for the initial, substantial formation of dihydropyrone*. The prequenching versions of **20** and **21** (presumably **18** and **19**) cyclize even more slowly, if at all. Furthermore, the pre-*trans*-alcohol **20** is closing more rapidly than the pre-cis-alcohol **21**.

The most concise interpretation of these findings is that in the BF_3·OEt_2 system a threo-selective path c (see above) pertains, leading to the siloxonium arrays **22** and **23**. These partition in different ways. Threo-**22** suffers more cyclization (leading to **17**) relative to silyl transfer (leading to **18** and thence to **20**), whereas **23** undergoes more silyl transfer (leading to **19** and thence to **21**) relative to cyclization (leading to **9**).

In summary the zinc chloride method operates through essentially a pericyclic model, whose topology is governed by *endo* additivity.[2] The BF_3·OEt_2 process operates through a threo-selective aldol-like array (cf. **6**).[11]

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Registry No. **7**, 82093-19-4; **8a**, 83399-57-9; **8b**, 83399-58-0; **8c**, 83399-59-1; **9**, 83378-98-7; **11**, 83399-60-4; **12**, 83416-30-2; **13**, 83399-61-5; **14**, 83399-62-6; **15**, 83399-63-7; **16**, 83399-64-8; **17**, 83379-03-7; **20**, 83399-65-9; **21**, 83399-66-0; benzaldehyde, 100-52-7; *m*-chloroperoxybenzoic acid, 937-14-4.

Supplementary Material Available: Listing of IR, NMR, and mass spectral data for all new compounds (2 pages). Ordering information is given on any current masthead page.

(10) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319.

(11) Interestingly, modest threo selectivity has also been observed in the Lewis acid catalyzed aldol condensations of (*Z*)-*O*-silyl ketene acetals derived from ethyl propionate: Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Ibid.* **1979**, 4029. It is recognized that compound **7** is a vinylogous ketene acetal.

Synthesis of *d*-Biotin from L-Cystine via Intramolecular [3 + 2] Cycloaddition

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The recent revival of interest in the synthesis of biotin[1,2] is due to an increased awareness of the importance of this vitamin in human nutrition and therapy[3] as well as in animal health.[4] Biochemically, biotin functions as an indispensable coenzyme in numerous naturally occurring carboxylation reactions that are part of important physiological processes such as gluconeogenesis and fatty acids synthesis.[5] In our present approach to the synthesis of *d*-biotin (**1**), we planned to effect in a single step the formation of the thiophane ring and the simultaneous creation of two out of three chiral centers with proper absolute stereochemistry by a nitrone to thioenol ether thermal intramolecular cycloaddition[6,7] of **5** to give **6** (Scheme I). The latter would then be converted to deoxybiotin (**2**) and finally to biotin via known microbiological oxidation.[8]

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(2) For earlier biotin syntheses see: (a) Harris, S. A.; Wolf, D. E.; Mozingo, R.; Folkers, K. *Science* (*Washington*, D. C.) **1943**, *97*, 447. (b) Harris, S. A.; Wolf, D. E.; Mozingo, R.; Anderson, R. C.; Arth, G. E.; Easton, N. R.; Heyl, D.; Wilson, A. N.; Folkers, K. *J. Am. Chem. Soc.***1944**, *66*, 1756. (c) Harris, S. A.; Wolf, D. E.; Mozingo, R.; Arth, G. E.; Anderson, R. C.; Easton, N. R.; Folker, K. *Ibid.* **1945**, *67*, 2096. (d) Schnider, O.; Bourquin, J.-P.; Grüssner, A. *Helv. Chim. Acta* **1945**, *28*, 510, 517, 528. (e) Baker, B. R.; Querry, M. V.; McEwen, W. L.; Bernstein, S.; Safir, S. R.; Dorfman, L.; Subbarow, Y. *J. Org. Chem.* **1947**, *12*, 186. (f) Goldberg, M. W.; Sternbach, L. H. U.S. Patent, 2 489 232, 2 489 235, 2 489 238, 1949. (g) Sternbach, L. H. *Compr. Biochem.* **1963**, *11*, 66.

(3) (a) McCormick, D. B. *Nutr. Rev.* **1975**, *33*, 97. (b) Bonjour, J. P. *Int. J. Vitam. Nutr. Res.* **1977**, *47*, 107.

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(5) Cravey, M. J. Kohn, H. *J. Am. Chem. Soc.* **1980**, *102*, 3928 and references cited therein.

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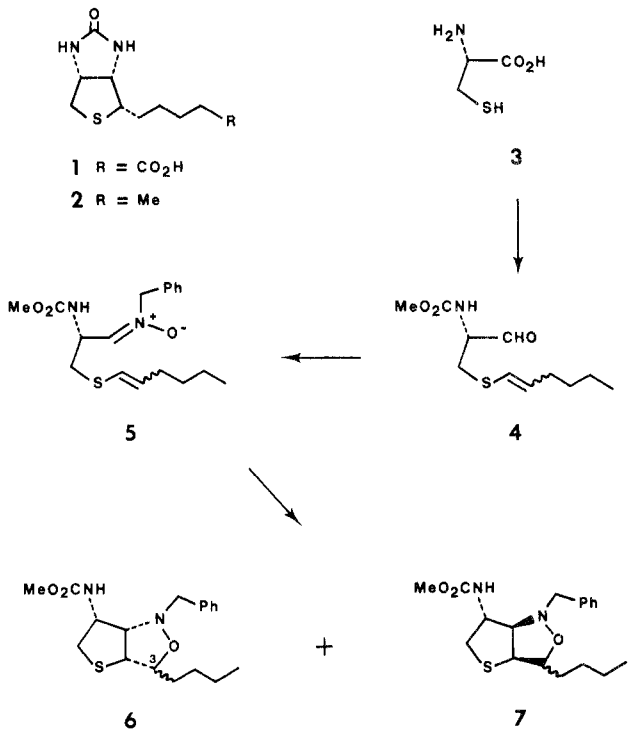
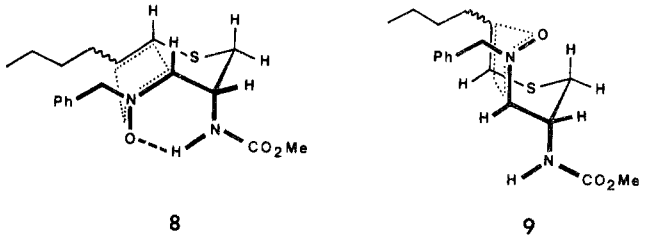
Scheme I



The intermediate **5**, easily prepared from L-cysteine (**3**)[9] underwent spontaneous cyclization at room temperature to give in high yield a mixture of the desired all-cis cycloadduct **6** and the diastereomer **7**, in the disappointing ratio of 1.9:1.[10,11]

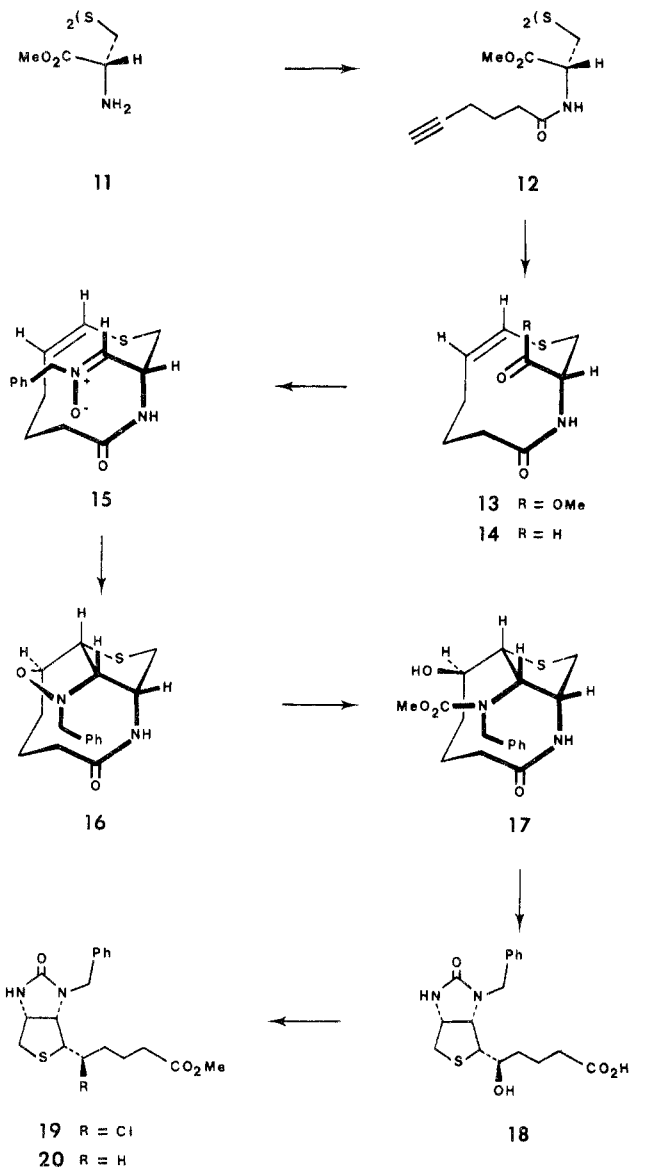
A careful inspection of Dreiding models of the possible transition states of the cyclization of **5** seems to favor the two conformations **8** and **9** of the (*Z*) nitrone configuration as the source of the



observed products **6** and **7**, respectively. Furthermore, the transition-state **8**, leading to the desired all-cis product **6**, should be of even lower energy than **9** due to stabilizing effects of the indicated hydrogen bonding. This may account for the observed product ratio, favoring **6**.

An obvious conclusion from the above transition-state analysis was that the desired specificity in the cycloaddition step could be achieved by using a modified precursor that would cyclize exclusively through a transition-state conformation corresponding to **8**. This led us to the design of the ten-membered ring intermediate **15** (Scheme II) containing the (*Z*)-thioenol ether double bond, which was prepared in the following manner. L-Cystine dimethyl ester (**11**) was acylated at the nitrogen with 5-hexynoyl chloride[12] to give **12** (pyridine/CH_2Cl_2, 0 °C, 90% yield), which

Scheme II



was then treated with zinc dust in acetic acid. Under these conditions, the disulfide bond of **12** is cleaved, and if the reaction is carried out in the presence of air, cyclization takes place simultaneously to produce a 9:1 mixture of the *Z*-olefinic product **13**[13] (65% yield) and the corresponding *E* isomer. After chromatographic separation, the desired isomer **13** was reduced with diisobutylaluminum hydride to **14** (toluene, −78 °C, 95% yield),[14] which in turn was treated with benzylhydroxylamine hydrochloride[15,16] (CH_2Cl_2, 72% yield) to give nitrone **15**[17] as an amorphous powder.

On refluxing in toluene, **15** underwent cycloaddition in the anticipated fashion with the exclusive formation of the tricyclic

(9) L-Cysteine was shown to be the biogenetic precursor of *d*-biotin: Lezius, A.; Ringelmann, E.; Lynen, F. *Biochem. Z.* **1963**, *336*, 510. Two syntheses of biotin from L-cysteine have been accomplished.[1d,k,2b]

(10) Isoxazolidines **6** and **7** are both a mixture of epimers at C-3, since the starting **5** was a mixture of geometrical isomers. If the cycloaddition is carried out by using pure (*Z*)- or (*E*)-**5**, the products **6** and **7** are formed as single epimers but in the same 1.9:1 ratio.

(11) Intramolecular cycloaddition of the nitrile oxides corresponding to **5** gave a 1:1 mixture of the isoxazolines corresponding to **6** and **7**.

(12) Prepared from the corresponding carboxylic acid and oxalyl chloride. See: (a) Eglinton, G.; Whiting, M. C. *J. Chem. Soc.* **1953**, 3052. (b) Ferrier, R. J.; Tedder, J. M. *J. Chem. Soc.* **1957**, 1435.

(13) **13**: mp 160–161 °C; $[\alpha]^{25}_D$ −144.8° (*c* 0.2, MeOH); NMR ($CDCl_3$) δ 2.02 (1 H, dd, J_1 = 11.6 Hz, J_2 = 14.0 Hz), 3.18 (1 H, dd, J_1 = 5.0 Hz, J_2 = 14.0 Hz), 3.73 (3 H, s), 4.99 (1 H, m), 5.67 (1 H, br s), 5.94 (1 H, dt, J_1 = 3.5 Hz, J_2 = 9.0 Hz), 6.17 (1 H, d, J = 9.0 Hz). The structure of **13** and the *Z* geometry of the double bond were also independently confirmed by X-ray crystal structure analysis.

(14) The reaction mixture was quenched at −78 °C with a 4:1 mixture of THF/2n HCl after its completion to avoid racemization of the product.

(15) (a) Feuer, H.; Vincent, B. F., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 3771. (b) Feuer, H.; Vincent, B. F., Jr.; Barlett, R. S. *J. Org. Chem.* **1965**, *30*, 2877.

(16) The formation of **15** by using the corresponding free base always took place with extensive racemization of the substrate.

(17) **15**: $[\alpha]^{25}_D$ = −241.9° (*c* 0.2, $CHCl_3$); NMR ($CDCl_3$) δ 4.85 (2 H, s), 5.02 (1 H, m), 5.96 (1 H, dt, J_1 = 4.4 Hz, J_2 = 9.2 Hz), 6.22 (1H, d, J = 9.2 Hz), 6.81 (1 H, d, J = 7.2 Hz), 6.87 (1 H, br d, J = 10.0 Hz), 7.41 (5 H, br s).

intermediate **16**[18] (63% yield), the structure of which was confirmed by a complete three-dimensional single-crystal X-ray analysis. A major problem that we had to deal with was a partial racemization during this cyclization step. Eventually we found that traces of acids in the reaction medium were catalyzing the loss of optical activity, which could be completely prevented by addition of small amounts of barium or calcium oxide.[19]

Cleavage of the isoxazolidine ring (Zn dust, $AcOH/H_2O$, 70 °C) and acylation of the free amine ($ClCO_2Me$, $THF/2nNa_2CO_3$, 0 °C) gave the bicyclic intermediate **17** (65% yield from **16**), which on treatment with barium hydroxide in refluxing aqueous dioxane underwent hydrolysis of the lactam moiety and concomitant cyclization to the imidazolidinone **18** (87% yield). Left to be solved at this point was the elimination of the superfluous hydroxy group in the side chain without affecting the vicinal chiral center. This was effected as follows. Thionyl chloride treatment in ether and subsequent quenching with methanol gave the chloro ester **19** (68% yield). X-ray single-crystal analysis of this product revealed that the hydroxy group was replaced with retention of configuration. Dechlorination to **20** was effected with excess of sodium borohydride in dimethylformamide (80 °C, 76% yield). Finally, treatment of **20** with aqueous hydrobromic acid[19] gave *d*-biotin (**1**; 85% yield), which was isolated and characterized as the corresponding methyl ester:[20] mp 165-166 °C; $[\alpha]^{25}_D$ +80.5° (*c* 0.3, MeOH). Its spectroscopic data were identical with those of *d*-biotin methyl ester prepared from the natural product.

Acknowledgment. We thank the staff of the Physical Chemistry Department of Hoffmann-La Roche Inc. for the determination of physical and analytical data, particularly Dr. J. F. Blount, who carried out the X-ray structure determinations.

(18) **16**: mp 129-130 °C; $[\alpha]^{25}_D$ = +78.3° (*c* 0.5, $CHCl_3$); NMR ($CDCl_3$) δ 4.00 (1 H, d, *J* = 8.2 Hz), 4.28 (1 H, d, *J* = 8.2 Hz), 4.50 (1 H, br s), 6.10 (1 H, br s), 7.33 (5 h, br m).

(19) The determination of the optical purity of **16** was carried out by converting it to **17**, forming the corresponding ester with (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid and analyzing the NMR spectrum and HPLC trace of the product. See: Dale, J. A.; Cull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(20) Hofmann, K.; Melville, D. B.; DuVigneau, V. *J. Biol. Chem.* **1941**, *141*, 207.

Methoxy Group Conformations of Phenyl Methyl Ethers in Solution

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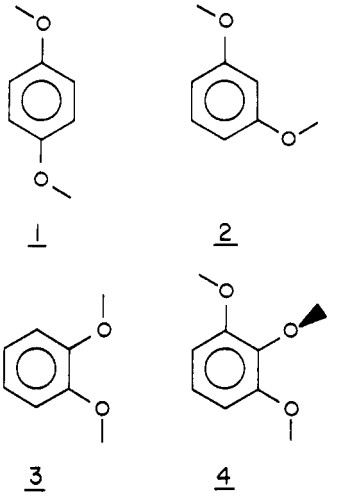
In a previous investigation, Anderson and co-workers[1] have reported the conformations of a group of methoxy-substituted benzenes in the gas phase through use of photoelectron spectroscopy and ab initio STO-3G calculations. The preferred conformations of methoxybenzene and *p*- and *m*-dimethoxybenzene (**1**, **2**) were reported to be planar. In contrast, *o*-dimethoxybenzene (**3**) in the gas phase was found to have one methoxy group predominantly in the nonplanar conformation with the O-CH_3 bond perpendicular to the plane of the aromatic ring. Principally on the basis of partition coefficient measurements, the authors concluded that also in solution *o*-dimethoxybenzenes had one of their methoxy groups in the nonplanar conformation. In a following publication, these results were used to explain some



1 2 3 4

crucial aspects of the pharmacological activity of methoxy-substituted hallucinogenic amphetamines.[2]

In the present communication, we report on the conformational analysis of methoxy groups in the same methoxy-substituted benzenes in solution by using a ^{13}C NMR method previously developed in this laboratory.[3] Our results show significant disagreement with the previously published conclusions.[1,2] The present study was carried out on the three dimethoxybenzenes (**1-3**). 1,2,3-trimethoxybenzene (**4**), a compound that was expected to have its 2-OCH_3 group in the out-of-plane conformation, was also included as a reference. The method we used relies on the observation that out-of-plane methoxy groups have abnormally high ^{13}C chemical shifts and unusually long T_1 values.

In planar arylmethoxy groups, the π orbitals of the aromatic ring tend to overlap with the lone-pair electron orbitals of the methoxy oxygen, leading to a delocalization of the nonbonding oxygen electrons and a strengthening of the Ar-O bond. This also results in increased electron density at the ring carbons ortho and para to the methoxy group. In the out-of-plane conformation the conjugation of the nonbonding oxygen electrons with the π bond of the ring is interrupted. Earlier studies[4,5] have shown that arylmethoxy groups that are believed to exist in the planar conformation have ^{13}C chemical shifts very similar to that of unsubstituted anisole (δ 55.1[6]). On the other hand, methoxy groups that are expected to exist predominantly in the out-of-plane conformation have chemical shifts 5-7 ppm downfield from that of anisole and not very different from those of aliphatic methoxy groups. Although the origin of the deshielding effect in the out-of-plane methoxy groups is not immediately evident, this observation is very consistent.[6]

Except for the 2-OCH_3 group in **4** all methoxy carbons had nearly equivalent and "normal" chemical shifts ($\delta_{^{13}C} \simeq 55$) characteristic of planar arylmethoxy groups. On the other hand, the ^{13}C resonance for the out-of-plane 2-OCH_3 (**4**) was shifted to lower fields ($\delta_{^{13}C}$ 60.8, Table I). The evidence for a predominantly all-planar *o*-dimethoxybenzene obtained from the OCH_3 ^{13}C value (55.8 ppm) is congruent with the observed chemical shift for the C_4 aromatic carbon ($\delta_{^{13}C}$ 120.9) in this molecule. If the methoxy groups in **3** are in the planar conformation, the para aromatic carbons should experience the full mesomeric shielding effect produced by the unshared oxygen electrons of the methoxy group similar to that experienced by C_4 in unsubstituted anisole. Since the effect of a *m*-methoxy group on an aromatic carbon is negligible, these two molecules would be expected to have similar

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