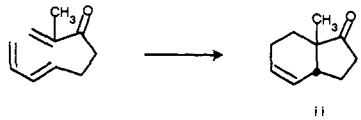
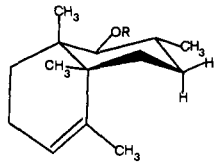


ii

Shiratori, Y. Kato, H. Ihara, and K. Fukomoto, *J. Org. Chem.*, **42**, 2672 (1977).
(13) J. A. Marshall and A. R. Hochstetler, *J. Am. Chem. Soc.*, **91**, 648 (1969).
(14) Control of the trans geometry is often lacking in eudesmane synthesis owing to the very small energy difference between cis and trans in this series.[15] The only really successful control of trans ring geometry is seen in routes involving Birch reduction.[5]
(15) A. Ross, P. A. Smith, and J. L. Coke, *J. Org. Chem.*, **26**, 2096 (1961).
(16) IR (film) 3330 cm^{-1}; NMR ($CDCl_3$) δ 6.38 (1 H, dd, J = 10 Hz, J = 17.5 Hz), 5.5 (1 H, t, J = 8 Hz), 4.7–5.25 (4 H, m), 3.65 (1 H, m), 1.95–2.22 (4 H, m), 1.5–1.8 (9 H, m).
(17) IR (KBr) 3250 cm^{-1}; NMR ($CDCl_3$) δ 5.3 (1 H, br s), 4.14 (1 H, m), 1.57 (3 H, s), 1.14–2.45 (12 H, m), 0.80 (3 H, s).
(18) IR (film) 3360 cm^{-1}; NMR ($CDCl_3$) δ 5.32 (1 H, br s), 3.59 (1 H, m), 1.60 (3 H, s), 1.70–2.05 (12 H, m), 0.82 (3 H, s).
(19) Compound **6** could not be isolated in pure form; however, its presence was inferred by the angular methyl at δ 0.91 and –CH–O at 3.80 in the NMR spectrum of mixtures.
(20) IR (film) 1720 cm^{-1}; NMR ($CDCl_3$) δ 5.40 (1 H, br s), 1.85–2.70 (8 H, m), 1.1–2.7 (6 H, m), 1.10 (3 H, s).
(21) G. H. Posner, G. L. Loomis, and H. S. Sawaya, *Tetrahedron Lett.*, 1373 (1975).
(22) Synthetic 1 possessed IR, NMR, and mass spectra identical with those of the natural material.[2]
(23) The X-ray structure of a cis-fused terpenoid iii related to **7** has been reported: G. Saucy, R. E. Ireland, J. Bordner, and R. E. Dickerson, *J. Org. Chem.*, **36**, 1195 (1971). The proximity (3.49 Å) of the vinylic methyl to C-7 can be clearly seen in the stereopair (Figure 1) in that paper, even though the A ring exists as a half-chair in the crystal structure, while the Diels–Alder transition state is a boat. Flipping from a boat to a half-chair greatly relieves the nonbonded interaction in question (3.5 Å vs. 3.0 Å in models).



iii (R=*p*-BROMOBENZOATE)

(24) Indirect evidence for transition states **7** and **8** is available from consideration of two points. First, the ratios of equatorial to axial alcohols **3c/3b** and **3f/3e** are 1.4:1 and 1.6:1, respectively. These ratios are about what are expected (based on known *A* values) for a transition state in which ring B is chair-like. Second, the lack of any detectable axial cis-fused alcohol is consistent with transition state **7** in which such an axial substituent would produce even more severe nonbonded interactions.

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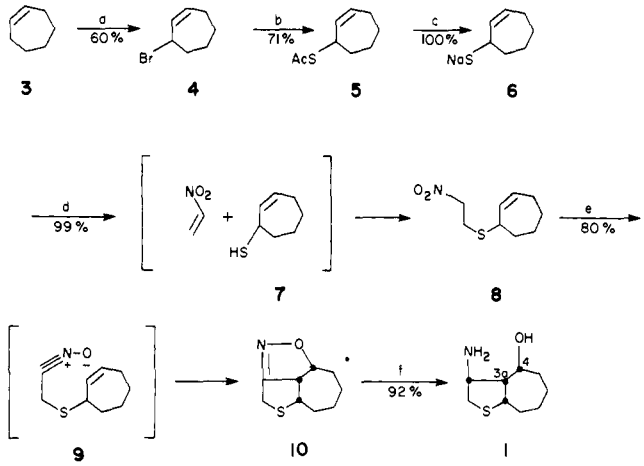
Use of Intramolecular [3 + 2] Cycloaddition Reactions in the Synthesis of Natural Products. A Stereospecific Synthesis of (±)-Biotin from Cycloheptene

Sir:

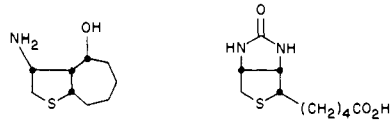
Reactions generally classified as 1,3-dipolar cycloadditions have been extensively employed in the synthesis of a diverse array of heterocyclic compounds.[1] However, this reaction mode has been alloted a more limited role in the preparation of natural products.[2] This is surprising since the cycloadditions are not only ring-forming reactions but also proceed with a high degree of stereoselectivity.[3]

We have utilized an intramolecular [3 + 2] cycloaddition reaction of an olefinic nitrile oxide in the stereospecific synthesis of the key amino alcohol **1**, which was converted in five subsequent steps to (±)-biotin (**2**).[4]

Scheme I



[a] a: NBS, AIBN, CCl_4, reflux, 1.5 h. b: AcSH, CH_3CN, Et_3N, 0 °C, 3 h. c: NaOEt/EtOH, reflux, 15 min. d: $NO_2CH_2CH_2OAc$, EtOH, 0 °C, 3 h. e: PhNCO, PhH, Et_3N (cat.), 25 °C, 24 h. f: $LiAlH_4$, Et_2O, reflux, 4 h.



1 2

Allylic bromination of cycloheptene **3** with NBS[5] and subsequent treatment of the 3-bromo product **4**[6] with thiolacetic acid yielded the desired thiol ester **5**, bp 64–65 °C (0.25 mm) (Scheme I), serving to introduce the requisite sulfur atom at an early stage. The mercaptide **6**, generated in situ with ethanolic sodium ethoxide, was treated with 1 equiv of 1-nitro-2-acetoxyethane,[7] a process which presumably generated nitroethylene and the mercaptan **7**. These intermediates then underwent a Michael reaction to afford the nitro olefin **8** (IR 1640 (C=C), 1555, 1378 cm^{-1} (NO_2); *m/e* 201 (M^+) in virtually quantitative yield. Treatment of this nitro compound with phenyl isocyanate led directly to the novel tricyclic adduct **10** (IR 1717 cm^{-1} (C=N), *m/e* 183 (M^+)) obtained stereospecifically in high yield as a colorless oil. This result implicates the intermediacy of an intramolecular [3 + 2] cycloaddition of the nitrile oxide **9**. Although only two of the three ultimate stereocenters of biotin were created in this step, the third was stereospecifically introduced in the desired cis configuration by $LiAlH_4$. This reagent not only cleaved the N–O bond of the tricyclic adduct **10** but also reduced the imino functionality. Hydride delivery occurred from the less hindered convex side[8] of the cup-shaped structure and led directly to the desired amino alcohol **1** (IR 3400 (OH), 3200–3350 cm^{-1} (NH_2)), characterized as its crystalline hydrochloride (IR 3100 cm^{-1} (NH_3^+); *m/e* 187 (M^+), mp 192–193 °C). This straightforward sequence of reactions allowed the preparation of pure **1** in an overall yield of 73% based on the thiol ester **5**.

Further elaboration of **1** in the direction of biotin required scission of the C(3a)–C(4) bond with insertion of a nitrogen atom attached to C(3a), as well as an elevation of C(4) to the oxidation state of an acid. To this end, the amino alcohol **1** was converted to the ketone **12** (IR 1703 cm^{-1} (ketone), mp 102–103 °C) via the intermediate urethane alcohol **11** (IR 3510 (OH), 3330 cm^{-1} (NH), mp 109–110 °C) (Scheme II). At this point, the ruinous possibility of an epimerization at C(3a) to the thermodynamically more stable trans fused 5,7 system had to be ruled out. Treatment of our pure all cis ketone with sodium acetate in refluxing ethanol quantitatively converted it to the trans isomer **12a**, verifying our structural assignment.[9] Treatment of the ketone **12** with hydroxylamine

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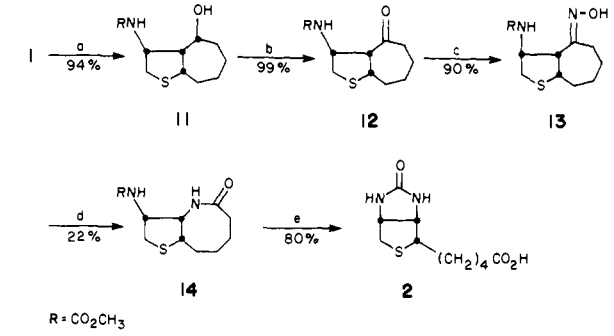
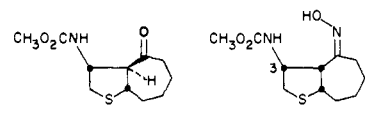
Scheme II

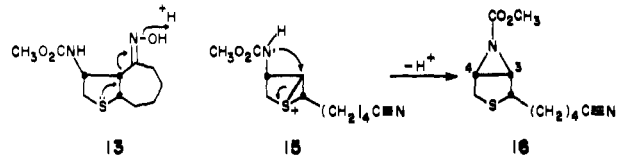


[a] a: CH_3OH, CH_3OCOCl, 10% $NaHCO_3$, 25 °C, 0.5 h. b: Me_2SO/Ac_2O (3:2), 25 °C, 18 h. c: EtOH/Py (25:1), NH_2OH·HCl, reflux, 0.5 h. d: PPA, 100 °C, 15 min. e: $Ba(OH)_2$, H_2O, reflux, 20 h, $COCl_2$, 0 °C.



led directly to the anti oxime **13** (NMR δ 7.51 (br s, 1 H, OH), 5.70 (br d, 1 H, NH), 4.55 (br m, 1 H, C*H*NH)) with only a trace amount of the undesired syn oxime **13a.** The marked predominance of the desired anti oxime **13** is presumably a result of the undesirable steric interaction with the proximate carbomethoxyamino group attached to C(3) rendering **13a** much less stable. A Beckmann rearrangement of the anti oxime **13** yielded the all-cis 5,8 bicyclic lactam **14** (IR 1686 (urethane), 1652 cm^{-1} (lactam); *m/e* 258 (M^+), mp 242-243 °C), which was easily converted to (±)-biotin (**2**) by basic hydrolysis and phosgene (Scheme II).

A competing and quite facile Beckmann fragmentation of the anti oxime **13** to yield the 3,5-aziridine system **16** (NMR δ 5.2 (m, 1 H), 4.3 (m, 1 H), 4.1 (s, 3 H); *m/e* 240 (M^+)) accounted for the difficulty[10] in the key Beckmann step d (Scheme II), which constitutes the only low-yield reaction in this synthesis. A plausible mechanism is shown. Initiation of the undesired fragmentation is sparked by the sulfur lone pair leading to the transient episulfonium cation **15.** This reactive



intermediate is internally quenched by the nitrogen atom attached to C(4) thus accounting for the expulsion of the oximino carbon with 100% retention at C(3).

In summary, we have demonstrated the utility of an intramolecular [3 + 2] cycloaddition of the reactive nitrile oxide **9** to generate directly the tricyclic adduct **10.** This latter intermediate was then transformed into the target structure of biotin (**2**), taking full advantage of the stereospecificity of the key ring-forming cycloaddition.[11]

Acknowledgment. We express our gratitude to the staff of the Physical Chemistry Department of Hoffmann-La Roche for their determination of spectral and analytical data. A special note of thanks is given to Dr. J. Blount who carried out two X-ray structure determinations.

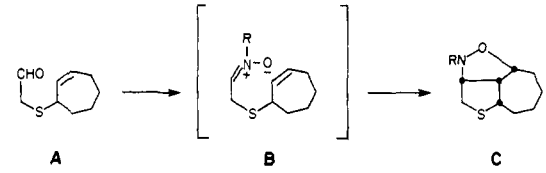
References and Notes

(1) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 5656, 633 (1963); **7**, 321-328 (1968). R. Huisgen, *Helv. Chim. Acta*, **50**, 2421-2439 (1967). R. Huisgen, *J. Org. Chem.*, **33**, 2291-2297 (1968). J. Hammer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964).

(2) For a recent elegant application of a nitrone cycloaddition to the synthesis of *dl*-lucidulline, see W. Oppolzer and M. Petrzilka, *J. Am. Chem. Soc.*, **98**, 6722-6723 (1967). Another notable exception is the brilliant approach to vitamin B_{12} whose cornerstone is a nitrile oxide/acetylene cycloaddition; cf. R. V. Stevens, J. M. Fitzpatrick P. B. Germeraad, B. L. Harrison, and R. Lapalme, *J. Am. Chem. Soc.*, **98**, 6313-6317 (1976); R. V. Stevens, R. E. Cherpeck, B. L. Harrison, J. Lai, and R. Lapalme, *ibid.*, **98**, 6317-6321 (1976); J. W. Cornforth (reported by P. B. D. de la Mare), *Nature*, **195**, 441 (1962). See also A. Vasella, *Helv. Chim. Acta*, **60**, 426-446 (1977); J. J. Tufariello and J. P. Tette, *J. Org. Chem.*, **40**, 3866-3869 (1975); J. E. Baldwin, C. Hoskins, and L. Kruse, *J. Chem., Soc., Chem. Commun.*, 795-796 (1976); J. J. Tufariello and G. B. Mullen, *J. Am. Chem. Soc.*, **100**, 3638-3639 (1978). For three recent review articles of intramolecular [3 + 2] cycloaddition reactions, see D. S. Black, R. F. Crozier, and V. C. Davis, *Synthesis*, **7**, 205 (1975); A. Padwa, *Angew. Chem. Int. Ed. Engl.*, **15**, 123 (1976); W. Oppolizer, *ibid.*, **16**, 10 (1977).

(3) N. A. LeBel, M. E. Post, and J. J. Whang, *J. Am. Chem. Soc.*, **86**, 3759 (1964); N. A. LeBel and J. J. Whang, *ibid.*, **81**, 6334 (1959); N. A. LeBel, *Trans. N.Y. Acad. Sci.*, **27**, 858 (1965); W. Oppolzer and K. Keller, *Tetrahedron Lett.*, 1117, 4313 (1970); F. J. Vinick, I. E. Fengler, and H. W. Gschwend, *J. Org. Chem.*, **42**, 2936-2937 (1977).

(4) A second route involves the conversion of A → C via the nitrone B. Details



of the synthesis of A and the transformation of C into the amino alcohol 1 will be presented in the full paper.

(5) L. F. Hatch and G. Bachmann, *Ber.*, **97**, 132-139 (1964).

(6) This intermediate and all others reported in this communication have the expected spectral and analytical properties. Details will be presented in the full paper which is to follow.

(7) Tindall, *Ind. Eng. Chem.*, **33**, 65 (1941).

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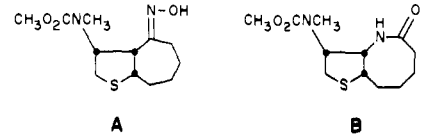
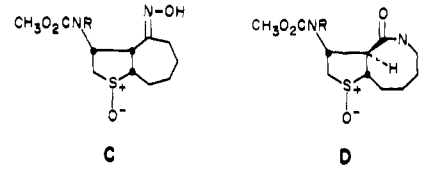
(9) In fact, this entire sequence had previously been carried out in a model series leading ultimately to the *N*-methyl-5,8-lactam B. In this series, an X-ray structure was determined on the analogous oxime A and completely



corroborated our assignments, hitherto made on theoretical grounds only. Hence, most of the postulated structures in the real series are based on firm analogy to the model study.

(10) In support of this mechanism, which implicates anchimeric initiation of the reaction by sulfur, the oximino sulfoxide C was prepared. This compound was found not to undergo fragmentation but rather elected still another abnormal Beckmann pathway leading to the epimerized lactam D



whose structure was shown to be as indicated by an X-ray determination. Details of this interesting result and other efforts aimed at avoiding fragmentation will be presented in the full paper.

(11) Recent developments have enforced the importance of *d*-biotin in the maintenance of health in not only animals but also in man; cf. J. P. Bonjour, *Int. J. Vitam. Nutr. Res.*, **47**, 107-118 (1977). This has sparked a renewed interest in novel syntheses of biotin and several have been recently reported: S. Bory, M. J. Luche, B. Moreau, S. Lavielle, and A. Marquet Cercoa, *Tetrahedron Lett.*, 827 (1975); H. Kuzuhara, H. Ohrui, and S. Emoto, *Ibid.*, 1185 (1975); H. Ohrui and S. Emoto, *Ibid., 2765 (1975); S. I. Zav'yalov et al., Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **24**, 1533 (1975); P. N. Confalone, G. Pizzolato, E. G. Baggiolini, D. Lollar, and M. R. Uskoković, *J. Am. Chem. Soc.*, **97**, 5936 (1975); P. N. Confalone, G. Pizzolato, and M. R. Uskoković, *Helv. Chim. Acta*, **59**, 1005 (1976); P. N. Confalone, G. Pizzolato, and M. R. Uskoković, *J. Org. Chem.*, **42**, 135-139, 1630-1633, (1977); G. F. Field, Abstracts, the 172nd National Meeting of the American Chemical Society, San Francisco, Calif., 1976; P. N. Confalone, G. Pizzolato, E. G. Baggiolini, D. Lollar, and M. R. Uskoković, *J. Am. Chem. Soc.*, **99**, 7029, (1977); M. Marx, F. Martl, J. Reisdorff, R. Sandmeier, and S. Clark, *Ibid.*, **99**, 6754-6765 (1977).

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