14). Accordingly, cyclocondensation of **11** with **6** was carried out with zinc chloride in tetrahydrofuran. There were obtained two cis isomers in a combined yield of 72%. *The major product (43%, mp 188–187 °C) is the cis "Cram"[9] system* ***12***.[10] There was also obtained (29%) another *cis*-dihydro-γ-pyrone, which is presumably[11] the "anti-Cram" isomer **13**.

When the reaction was carried out in methylene chloride with BF_3·OEt_2 catalysis, a 2:1 mixture of trans-[12]: cis-**12** compounds was obtained. The stereochemistry of the major trans compound (see structure **15**) must be left unassigned vis-ā-vis the Cram–anti-Cram diastereofacial issue.[9,13]

Thus, erythro (cis) specificity has been achieved in reaction of the complex **11** with **6** under the conditions of method B. We note that intrinsic diastereofacial[13,14] selection in addition reactions to **11** was never solved per se, even in the landmark Masamune synthesis.[2] The device of double stereodifferentiation[15,16] using a chiral (boron) enolate[17] was necessary to override the absence of inherent diastereofacial selectivity. The solution offered here lacks, for the moment, the element of auxiliary chiral guidance for the control of the diastereofacial problem available in the Masamune[17] and Evans[16] regimens.

Ozonolysis of **12** under the usual conditions[1b] gave the formate acid **14a**, best characterized as its methyl ester **14b**.[17,18] These structures embrace the chirality of carbons 1–9 of 6a-deoxyerythronolide.

The formation of cis products[19] corresponds, in cycloaddition terms, to an endo orientation of the R″ group of the aldehyde relative to the diene. It can be argued that this mode arises from the propensity of L^+ to complex with the basic aldehydo oxygen, anti to the R″ group (cf. **16**).[20] For steric or other reasons, the L^+ ensemble takes up the exo orientation in the pericyclic process. This would lead to *cis*-pyrone. In the case of aldehyde **2e**, a chelative bonding between L^+ and the two oxygen sites may result,[21] at least to some extent, in a syn-type of complex (cf. **17**). Exo addition of **17** would lead to trans product **8e**.

In the following paper mechanistic evidence regarding these reactions is gathered.

Acknowledgment. We acknowledge generous support from the American Cancer Society (Postdoctoral Fellowship to E.R.L., Grant No. PF-2020). The research was also supported by PHS Grant HL 25848. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale Unversity, which was supported by the NSF Chemistry Division Grant CHE 7916210.

Registry No. 2a, 66-25-1; **2b**, 100-52-7; **2c**, 33530-47-1; **2d**, 18328-11-5; **2e**, 60656-87-3; **6**, 82093-19-4; **7a**, 83378-97-6; **7b**, 83378-98-7; **7c**, 83378-99-8; **7d**, 83379-00-4; **7e**, 83379-01-5; **8a**, 83379-02-6; **8b**, 83379-03-7; **8c**, 80160-77-6; **8d**, 83379-04-8; **8e**, 83379-05-9; **9**, 80226-06-8; **10**, 83379-06-0; **11**, 83434-82-6; **12**, 83379-07-1; **13**, 83434-83-7; **14a**, 83379-08-2; **14b**, 83379-09-3; **15**, 83434-84-8; BF_3·Et_2O, 109-63-7; $ZnCl_2$, 7646-85-7.

Supplementary Material Available: Listing of IR, NMR, and mass spectra data for all new compounds (3 pages). Ordering information is given on any current masthead page.

(8) An 8:1 mixture of the Cram and anti-Cram adducts.
(9) Cram, D. J.; Abd. Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828; Cram, D. J. Kopecky, K. R. *Ibid.* **1959**, *81*, 2748.
(10) We thank Dr. Richard D. Adams of the Department of Chemistry, Yale University, for carrying out the single-crystal X-ray structure determination, the full details of which will be published elsewhere.
(11) Epimerism at the C-4 (erythronolide numbering) stereocenter of **12** arising from epimerization of the α center in the aldehyde **11** prior to reaction with **6** could, in theory, lead to two diastereomeric Cram cis adducts. However, on quenching of the reaction at partial conversion only stereochemically homogeneous **11** was recovered, indicating **11** retains its stereochemical integrity under the reaction conditions, and we, therefore, infer **13** to be the result of anti-Cram addition to **11**.
(12) A single diastereomer.
(13) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; John, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.
(14) For another related breakdown in inherent diastereofacial selectivity in reactions of a closely related aldehyde see: Lu, L.-D. L. *Tetrahedron Lett.* **1982**, *23*, 1867.
(15) Heatcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076.
(16) Cf.: Evans, D. A.; Bartoli, J. *Tetrahedron Lett.* **1982**, 807.
(17) Masamune, S.; Choy, W., Kerdesky, A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.
(18) The alcohol corresponding to formate acid **14a** was reported by Masamune.[2a] Several attempts on our part to retrieve this alcohol by cleavage of this formate ester led to a mixture of products. Professor Masamune has described to us the instability of this compound to acidic and basic reagents. Our structural and stereochemical formulations of these compounds rest securely on the crystallographic determination of compound **12**[10] and full spectral characterization of both **14a** and **b**.
(19) Satisfactory IR, NMR, and mass spectra were obtained for all new compounds. The data are available in detail in the supplementary material.
(20) Studies of the protonation of aldehydes in superacid media show preferential, if not exclusive, anti orientation of the alkyl residue with respect to the carbonyl-associated proton (Brookhart, M.; Levy, G. C.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1735. Olah, G. H.; O'Brien, D. H.; Calin, M. *Ibid.* **1967**, *89*, 3582). The larger steric demand of the $ZnCl_2$·solvent catalyst used in this study would presumably increase this preference for anti orientation.
(21) Protonation of α-chloro-substituted aldehydes in superacid media shows a divergence from the preferred anti orientation.[20] The syn-protonated aldehyde is presumably stabilized by intramolecular hydrogen bonding between the α-choro substituent and the carbonyl-associated proton (Thil, L.; Riehl, J. J.; Rimmelin, P.; Sommer, J. M. *J. Chem. Soc., Chem. Commun.* **1970**, 591).

Mechanistic Variations in the Lewis Acid Catalyzed Cyclocondensation of Siloxydienes with Aldehydes

Eric R. Larson and Samuel Danishefsky*

Department of Chemistry, Yale University
New Haven, Connecticut 06511

Received June 21, 1982

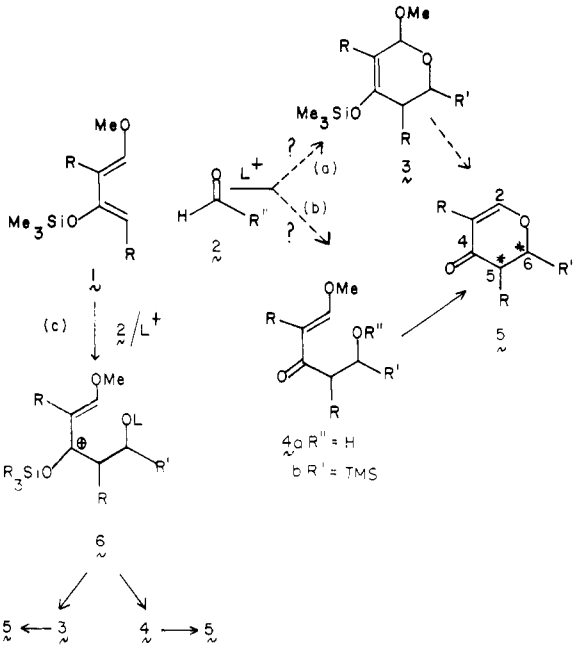
The Lewis acid (L^+) mediated cyclocondensation of siloxydienes (**1**, Scheme I) with aldehydes (**2**) has been described both as to scope and pertinence.[1] With the particular diene, R = Me, (hereafter called diene **7**) a change in the 5–6 stereochemical relationship was achieved by manipulating the catalytic system.[2] In this communication we relate an investigation into the mechanisms of these processes.

Two limiting formulations are advanced for the cyclocondensation process. In the "pericyclic" model (a) cycloadduct **3** is directly produced. Its vinylogous ortho ester sytem suffers unraveling (by L^+) to afford **5**. It is the intent of the pericyclic model to formulate the process in the familiar framework of the classical all-carbon Diels–Alder process. In so doing it is well to take note that the precise issues of mechanistic nuance of that venerable "reference" process, not to mention the Lewis acid mediated variation,[3] await full elucidation.

(1) (a) Danishefsky, S.; Kerwin, J. F.; Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358. (b) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin, J. F.; Jr. *Ibid.* **1982**, *104*, 360. (c) Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.* in press. (d) Danishefsky, S.; Kobayashi, S.; Kerwin, J. F., Jr. *Ibid.* **1982**, *47*, 1981.
(2) Danishefsky, S.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.* **1982**, *104*.

0002-7863/82/1504-6458$01.25/0

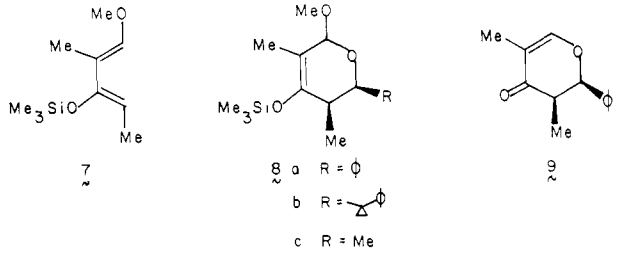
Scheme I



Alternatively, formulation in terms of a Mukaiyama silyl ether aldol-like process[4,5] leads to intermediates **4a** and or **4b**. The central element of this proposition (b) is that formation of the C–C and C–O bonds of the cyclocondensation process are discrete in an experimentally ascertainable way.

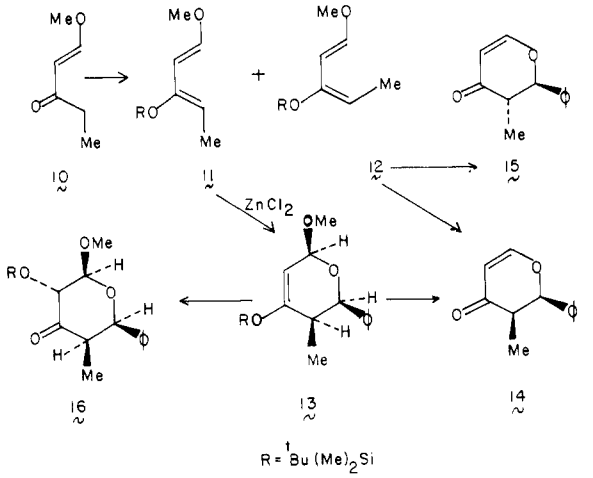
Between these limiting proposals is a formulation (c) wherein early C–C formations leads to the array **6**.[6] This sort of possibility is experimentally discernible from that contemplated in (a) *when the array* **6** *need not necessarily suffer cyclization to* **3**. In terms of stereochemical outcome it seems likely that the pericyclic conceptualization predicts an overall *endo* additivity, leading to the cis (or erythro) version of **5**.[2] It seems reasonable to suppose that process c would most likely reflect whatever kinetic selectivities are built into the Mukaiyama aldol-like model (b).

Reaction of benzaldehyde with diene **7** in THF with zinc

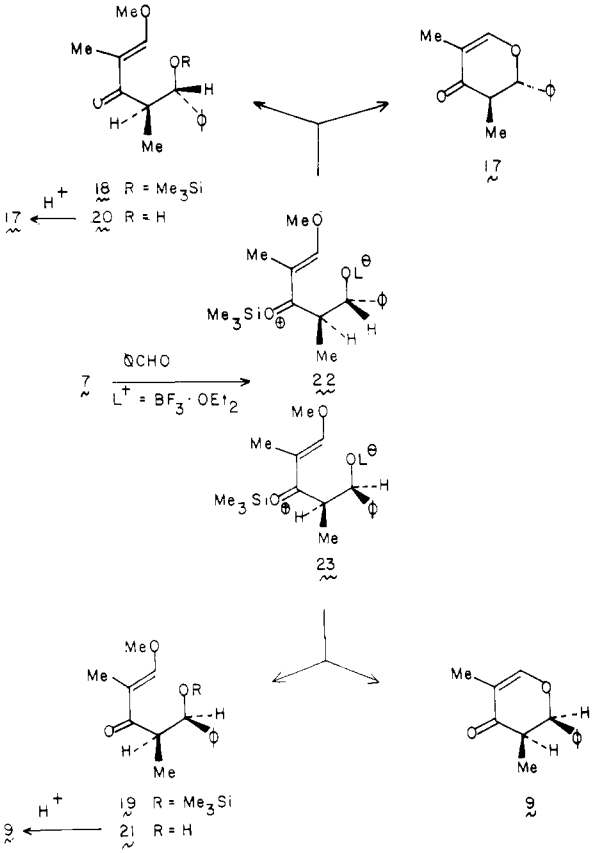


chloride catalysis, workup under anhydrous conditions, and rapid chromatography on silica gel allowed for the isolation, in 41% yield, of compound **8a**, whose stereochemical homogeneity is supported by both ^{13}C and ^{1}H measurements. *This is the first example of the isolation of a simple type* **3** *intermediate from the cyclocondensation process.* The cis stereochemistry at the 5- and 6-positions was corroborated by the smooth conversion of **8a** → **9** upon brief treatment with trifluoracetic acid. In a similar way the intermediacy of the homogeneous dihydropyrans **8b** and **c**, prior to acidic workup, could be detected by NMR analysis.

Scheme II



Scheme III



More discriminating mechanistic information was available from dienes **11** and **12**, which were prepared[8] as shown from the known ketone **10** (Scheme II).[9] Unfortunately, we were unable to separate the components of the mixture formed this way. However, when a 4:1 mixture of **11**:**12** was subjected to the action of benzaldehyde in the presence of zinc chloride as above, after 36 h only the *E*,*Z* isomer, **11**, reacted. A 42% isolated yield of

(3) For a recent review, see: Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.

(4) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011; *J. Am. Chem. Soc.* **1974**, *96*, 7503. These authors generally use titanium tetrachloride catalysis, although boron trifluoride has high efficacy for this procedure.

(5) Cf.: Larson, E. R.; Danishefsky, S. *Tetrahedron Lett.* **1982**, 1975.

(6) Analogous zwitterionic intermediates have been implicated as participants in the Lewis acid catalyzed carbocyclic Diels–Alder process. See: Thompson, H. W.; Melillo, D. G. *J. Am. Chem. Soc.* **1970**, *92*, 3218.

(7) Satisfactory IR, NMR, and mass spectra were obtained for all new compounds. The data are available in detail in the supplementary material.

(8) **10**: (0.2 M, Et_2O), Me_2 *t*-$BuSiO_3SCF_3$ (1.05 equiv), Et_3N (1.2 equiv), −5 °C, 1 h. Procedure of Emde (Emde, H.; et al. *Synthesis* **1982**, 2. The stereochemical assignments of **11** and **12** are based on the ^{13}C NMR chemical shifts of the C-2 resonances (δ 104.5, 99.1, respectively, determined by correlations of the ^{13}C NMR and ^{1}H NMR spectra by single-proton off-resonance decoupling experiments on isolated **12** and a 4:1 mixture of **11**:**12**). The suitability of this method for the determination of trisubstituted silyl enol ether stereochemistry has been demonstrated: Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

(9) Hills, P. R.; McQuillin, F. J. *J. Chem. Soc.* **1953**, 4060.

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]

Acknowledgment. We acknowledge generous support from the American Cancer Society (Postdoctoral Fellowship to E.R.L, Grant No. PF-2020). The research was also supported by PHS Grant HL 25848. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by the NSF Chemistry Division Grant CHE 7916210.

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

Enrico G. Baggiolini,* Hsi Lin Lee, Giacomo Pizzolato, and Milan R. Uskoković

Chemical Research Department, Hoffmann-La Roche Inc. Nutley, New Jersey 07110

Received August 20, 1982

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]

(1) (a) Bory, S.; Luche, M. J.; Moreau, B.; Lavielle, S.; Marquet, A. *Tetrahedron Lett.* **1975**, 827. (b) Ohrui, H.; Emoto, S. *Ibid.* **1975**, 2765. (c) Zav'yalov, S. I.; Rodionova, N. A.; Zheleznaya, L. L.; Bolestova, G. I.; Filippov, V. V.; Parnes, Z. N.; Kursanov, D. N. *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1975**, *24*, 1533. (d) Confalone, P. N.; Pizzolato, G.; Baggiolini, E. G.; Lollar, D., Uskoković, M. R. *J. Am. Chem. Soc.* **1975**, *97*, 5936. (e) Confalone, P. N.; Pizzolato, G.; Uskoković, M. R. *Helv. Chim. Acta* **1976**, *59*, 1005. (f) Confalone, P. N.; Pizzolato, G.; Uskoković, M. R. *J. Org. Chem.* **1977**, *42*, 135, 1630. (g) Marx, M.; Marti, Z.; Reisdorff, J.; Sandmeier, R.; Clark, S. *J. Am. Chem. Soc.* **1977**, *99*, 6754. (h) Confalone, P. N.; Pizzolato, G.; Baggiolini, E. G.; Lollar, D.; Uskoković, M. R. *Ibid.* **1977**, *99*, 7020. (i) Ogawa, T.; Kawano, T.; Matsui, M. *Carbohyd. Res.* **1977**, *57*, C31. (j) Lavielle, S.; Bory, S.; Moreau, B.; Luche, M. J.; Marquet, A. *J. Am. Chem. Soc.* **1978**, *100*, 1558. (k) Confalone, P. N.; Lollar, E. D.; Pizzolato, G.; Uskoković, M. R. *Ibid.* **1978**, *100*, 6291. (l) Vasilevskis, J.; Gualtieri, J. A.; Hutchings, S. D.; West, R. C.; Scott, J. W.; Parrish, D. R.; Bizzarro, F. T.; Field, G. F. *Ibid.* **1978**, *100*, 7423. (m) Ohrui, H.; Sueda, N.; Emoto, S. *Agric. Biol. Chem.* (Tokyo) **1978**, *42*, 865. (n) Confalone, P. N.; Pizzolato, G.; Lollar-Confalone, D.; Uskoković, M. R. *J. Am. Chem. Soc.* **1980**, *102*, 1954. (o) Fliri, A.; Hohenlohe-Oehringen, K. *Chem. Ber* **1980**, *113*, 607. (p) Rossy, Ph.; Vogel, F. G. M.; Hoffmann, W.; Paust, J.; Nürrenbach, A. *Tetrahedron Lett.* **1981**, *22*, 3493. (q) Whitney, R. A. *Can. J. Chem.* **1981**, *59*, 2650.

(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.

(4) (a) Anderson, J. O.; Warnick, R. E. *Poultry Sci.* **1970**, *49*, 569. (b) Blair, R.; Whitehead, C. *Feedstuffs* **1976**, *48*, 30.

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

(6) Alternate synthetic approaches to biotin based on intramolecular dipolar cycloadditions have been reported.[1k,n,g]

(7) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396 and leading references therein.

(8) Ogino, S.; Fujimoto, S.; Aoki, Y. *Agric. Biol. Chem.* **1974**, *38*, 275, 707.

0002-7863/82/1504-6460$01.25/0