Acknowledgment. We thank Nancy Arnold Perkinson of Lederle Laboratories for the chemical ionization mass spectrum and Professor Christopher Walsh of Massachusetts Institute of Technology for kindly supplying a reference sample of synthetic FO.[12]

Registry No. 3, 37333-48-5.

(12) Wallace T. Ashton, Ronald D. Brown, Frederick Jacobson, and Christopher Walsh, *J. Am. Chem. Soc.*, **101**, 4419 (1979).

Total Synthesis of Milbemycin β_3

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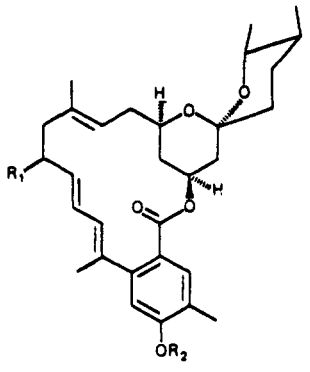
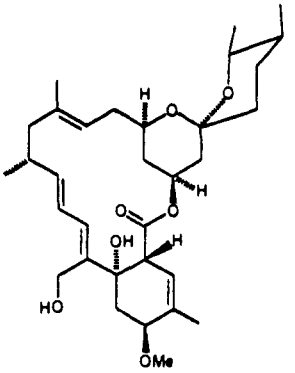
Milbemycin β_3 (**1a**), the simplest member of a family of some 13 architecturally novel macrolide antibiotics structurally related to the avermectins,[2] was first isolated in 1975 by Mishima et al.[3,4] from *Streptomyces* B-41-146. Subsequent screening demonstrated that this antibiotic complex possessed remarkably potent pesticidal activity[4] against a host of agricultural pests, including aphids, laval forms of insects of the order *Lepidopera*, mites, rice leaf beetles, and tent caterpillars, with little or no associated phytotoxicity.[4]



1



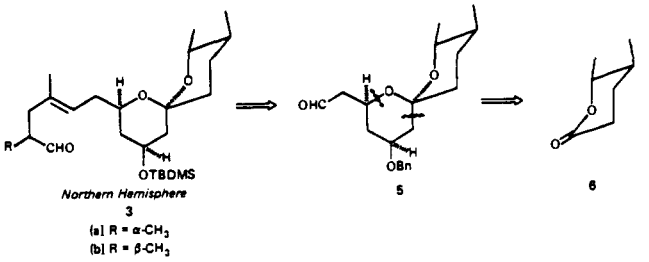
2

(a) R_1 = α-CH_3; R_2 = H
(b) R_1 = β-CH_3; R_2 = H
(c) R_1 = α-CH_3; R_2 = CH_3
(d) R_1 = β-CH_3; R_2 = CH_3

The structures of the milbemycins, initially assigned on the basis of detailed spectroscopic analysis, were secured through aegis of a single-crystal X-ray analysis of milbemycin β_1 (**2**).[3] Central to the derived structures are the spiroketal functionality, the 16-membered macrolide ring, and the conjugated diene system.

In this communication we announce preparation of milbemycin β_3 (**1a**), *the first member of the milbemycin–avermectin class to yield to total synthesis.* We note in advance that our strategy is short (longest linear sequence, 16 steps), convergent, and highly stereocontrolled.[5,6]

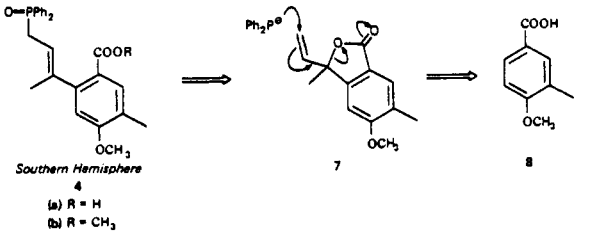
At the onset, we set as an overall goal the development of a common synthetic strategy that would yield members of both the milbemycin and avermectin families as well as possible structural analogues of biological interest. From the retrosynthetic perspective we initially divided milbemycin β_3 at the diene and ester linkage to generate the spiroketal northern hemisphere (**3a**) and



Northern Hemisphere
3
(a) R = α-CH_3
(b) R = β-CH_3

5

6



Southern Hemisphere
4
(a) R = H
(b) R = CH_3

7

8

an aromatic southern hemisphere (**4**). Union of the two was envisioned to take place via a Horner–Wittig coupling[7] followed by macrocyclic lactonization.[8] Further simplification of the northern hemisphere lead to aldehyde **5**, which in turn could be derived from lactone **6**.[9] The aromatic southern hemisphere, on the other hand, was envisioned to arise via a novel S_N2' displacement employing lithium diphenylphosphide[10] on lactone **7**, the latter prepared from 3-methyl-*p*-anisic acid (**8**).[11]

The success of this scenario rested on our ability to construct aldehyde **5** in a stereocontrolled manner. Here we planned to take advantage of the anomeric effect.[12] In particular, under equil-

(1) Camille and Henry Dreyfus Teacher Scholar, 1978–1983; National Institutes of Health (National Cancer Institute) Career Development Awardee, 1980–1985.

(2) Albers-Schönberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Lusi, A.; Mrozik, H.; Smith, J. L.; Tolman, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4216. Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1981**, *103*, 4221.

(3) Mishima, H.; Kurabayashi, M.; Tamura, C. *Tetrahedron Lett.* **1975**, 711.

(4) Takiguchi, Y.; Mishima, H.; Okuda, M.; Terao, M.; Aoki, A.; Fukuda, R. *J. Antibiot.* **1980**, *33*, 1120.

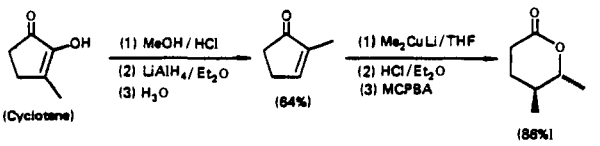
(5) A preliminary account of this work, in which completion of the first total synthesis of milbemycin β_3 was disclosed, was presented at the 183rd National Meeting of the American Chemical Society, Las Vegas, NV, March 1982, ORGN 16.

(6) To the best of our knowledge there exists only two other reports directed at construction of the basic carbocyclic ring of the milbemycin; see: Attwood, S. V.; Barrett, A. G.; Florent, J.-C. *J. Chem. Soc. Chem. Commun.* **1981**, 556. Williams, D. R.; Barner, B. A.; Phillips, J. G.; Nishitani, K., 183rd National Meeting of the American Chemical Society, Las Vegas, NV, March 1982, ORGN 15.

(7) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61. For the use of allylic phosphine oxide stabilized anions see: Lythgoe, B.; Moran, T. A.; Nambudiry, M. E. N.; Ruston, S.; Tideswell, J.; Wright, P. W. *Tetrahedron Lett.* **1975**, 3863.

(8) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49. Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

(9) Lactone **6** has been prepared in both racemic and chiral form, the latter from (−)-citronellol. The racemic approach beginning with cyclotene is illustrated below. For other approaches to lactone **6** see: Dev, S.; Rai, C. *J. Ind. Chem. Soc.* **1957**, *34*, 266. Honkanen, E.; Moisio, T.; Karvonen, P.; Virtanen, A. I. *Acta Chem. Scand.* **1968**, *22*, 2041.



(Cyclotene)
(64%)
(86%)

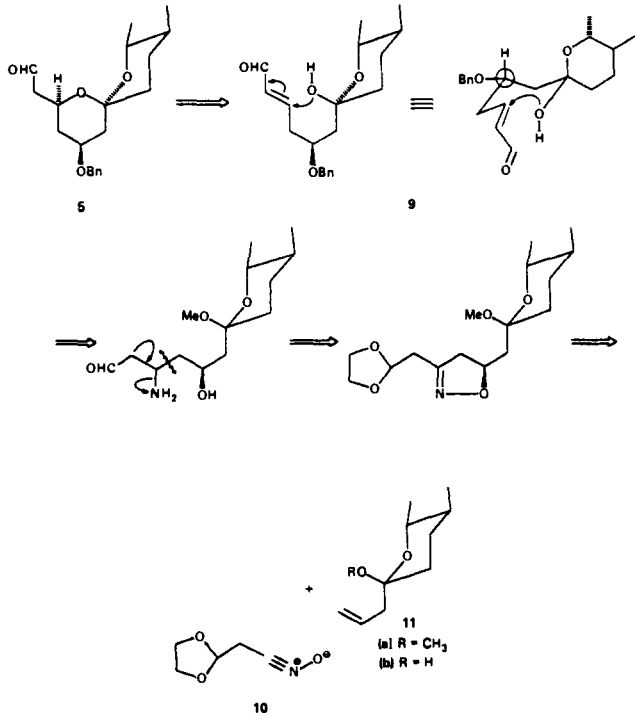
(10) Mann, F. G.; Tong, B. P.; Wystrach, V. P. *J. Chem. Soc.* **1963**, 1155. Mann, F. G.; Pragnell, M. J. *J. Chem. Soc.* **1965**, 4120. Ireland, R. E.; Welch, S. C. *J. Am. Chem. Soc.* **1970**, *92*, 7232.

(11) Schall, C. *Chem. Ber.* **1879**, *12*, 816. Also see: Quelet, R. *Bull Soc. Chim. Fr.* **1940**, *7*, 205.

(12) For a discussion on the utility of the oxygen anomeric effect in the construction of architecturally complex natural products see: Kishi, Y. *Lect. Heterocycl. Chem.* **1980**, *5*, S95.

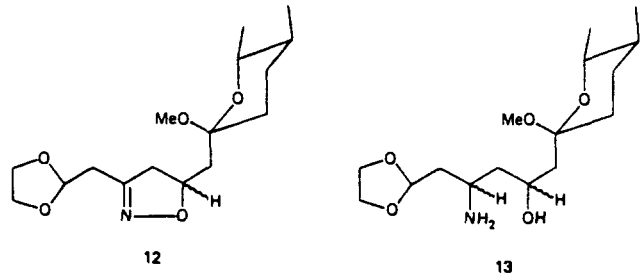
0002-7863/82/1504-4015$01.25/0

ibrating conditions the spiroketal oxygens could be anticipated to assume axial configurations with respect to the conspecific rings. We further conjectured that closure of an appropriately designed α,β-unsaturated aldehyde (e.g., **9**) via Michael addition would



place the acetaldehyde group in the proper equatorial position. Refinement of this plan suggested that aldehyde **9**, at least as a reactive intermediate, might be constructed via 1,3-dipolar addition[13] of nitrile oxide **10** to ketal **11a**, followed by reduction and elmination of the resultant β-amino group.

We initiated the synthesis by treatment of lactone **6** with allyl Grignard [0.95 equiv/−78 °C/THF] to yield an unstable hemiketal (**11b**),[14a] which without purification was promptly converted in 71% yield[15] to a single mixed methyl ketal (**11a**)[14,16] [3 equiv of $CH(OMe)_3$/catalyst $CeCl_3 \cdot 7H_2O$/room temperature, 18 h].[17] Ketal **11a** in turn was treated with 1.5 equiv of nitrile oxide **10** derived from the ethylene ketal of 3-nitropropanal[18] (MeNCO/Et_3N/benzene/at reflux, 24 h)[19] to give in 68% a 2:1 mixture of isoxazoline **12**.[14a] Without separation, reduction ($LiAlH_4$/ether)[20] led in high yield (ca. 90%)[15] to aminol **13**[14a] (four components by 250-MHz ^1H HMR), which as a mixture was treated consecutively with KH (15 equiv/0 °C), benzyl iodide (1 equiv/0 °C), methyl iodide (excess/25 °C), and then aqueous TsOH (25 °C). To our delight flash chromatography [hexane–ethyl acetate] yielded a *single crystalline* aldehyde (**5**)[14] [mp 56.5–58.5 °C (from hexane)] in 20–25% yield based on **13**.[21] Stereochemical assignment of **5** rests on direct spectral comparison of the derived diol with an authentic sample prepared from natural milbemycin β_1.[22]



With the structure and stereochemistry of aldehyde **5** secure, we turned to introduction of the six-carbon unit required to complete construction of the northern hemisphere. In this regard, aldehyde **5** was treated with isopropenyl Grignard (ether/−78 °C) and the resulting alkoxide acylated with propionyl chloride to afford in 71% yield a 2:1 mixture of propionates **14b** and **14a**,[14a] which could be readily separated by flash chromatography [hexane–ether (15:1)]. Subsequent application of the highly stereoselective Ireland–Claisen rearrangement[23a] [KN$(Me_3Si)_2$/TMSCl/−78 → 25 °C] to each proprionate (**14a** and **14b**) generated epimerically distinct acids **15a**[14a] and **15b**[14a] in 54–57% yield.[23b-d]

Well aware that the relative configurations of **15a** and **15b** could not easily be established until spectral comparisons were made between synthetic and natural milbemycin β_3, we carried both

(13) For a review of 1,3-dipolar cycloadditions see: Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565.

(14) (a) The structure assigned to each new compound was in accord with its infrared and 60- and/or 250-MHz NMR spectra as well as appropriate parent ion identification by high-resolution mass spectrometry. (b) In addition, analytical samples of new compounds, obtained by recrystallization or chromatography (LC or TLC) gave satisfactory C and H combustion analysis within 0.4%. (c) IR and 250-MHz NMR spectral data of representative intermediates are recorded here. **17b**: IR ($CHCl_3$) 2975 (br), 1705 (s), 1325 (s), 1270 (s) cm^{-1}; NMR n$CDCl_3$) δ 1.84 (d, J = 8 Hz, 3 H), 2.14 (s, 3 H), 3.25 (dd, J = 7.5, 14.8 Hz, 2 H), 3.75 (s, 6 H), 5.35 (m, 1 H), 6.29 (s, 1 H), 7.45 (m, 6 H), 7.63 (s, 1 H), 7.78 (m, 4 H). **5**: IR (CCl_4) 2923 (s), 1723 (s), 1095 (s) cm^{-1}; NMR ($CDCl_3$) δ 0.81 (d, J = 7 Hz, 3 H), 1.13 (d, J = 6 Hz, 3 H), 1.73–1.00 (m, 7 H), 2.20–2.00 (m, 2 H), 2.54–2.40 (m, 1 H), 2.72–2.57 (m, 1 H), 3.34–3.19 (m, 1 H), 4.03–3.87 (m, 1 H), 4.16–4.03 (m, **1** H), 4.55 (s, 2 H), 7.33–7.24 (m, 5 H), 9.83 (t, J = 2 Hz, 1 H). **3a**: IR (CCl_4) 2938 (s), 1725 (s), 1071 (br), 835 (m) cm^{-1}; NMR ($CDCl_3$) δ 0.00 (s, 6 H), 0.76 (d, J = 7 Hz, 3 H), 0.82 (s, 9 H), 1.00 (d, J = 7 Hz, 3 H), 1.04 (d, J = 6 Hz, 3 H), 1.58 (s, 3 H), 1.64–0.71 (m, 8 H), 2.00–1.64 (m, 3 H), 2.23–2.01 (m, 1 H), 2.54–2.31 (m, 2 H), 3.20–3.09 (m, 1 H), 3.48–3.34 (m, 1 H), 4.08–3.89 (m, 1 H), 5.24 (t, J = 7 Hz, 1 H), 9.58 (d, 2 J = Hz, 1 H).

(15) All yields recorded here are based upon isolated material that was >97% pure.

(16) Structural assignment of **11a** was based on the oxygen anomeric effect see ref 12.

(17) For utilization of $CeCl_3$ as a catalyst in ketalization protocols, see: Luche, J.-L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976.

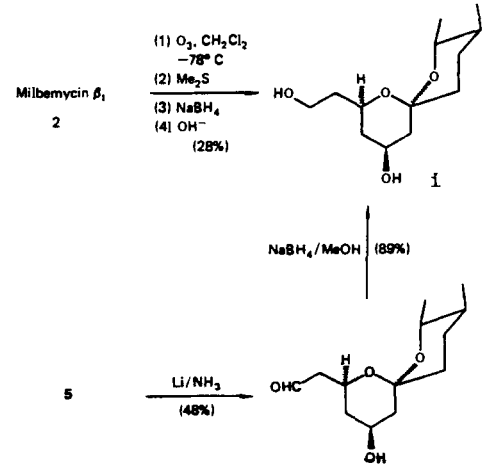
(18) Ketal **12** was prepared in 55% yield from 3-bromopropanal ethylene ketal [Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122] via treatment with $NaNO_2$ in Me_2SO (room temperature, 3 h).

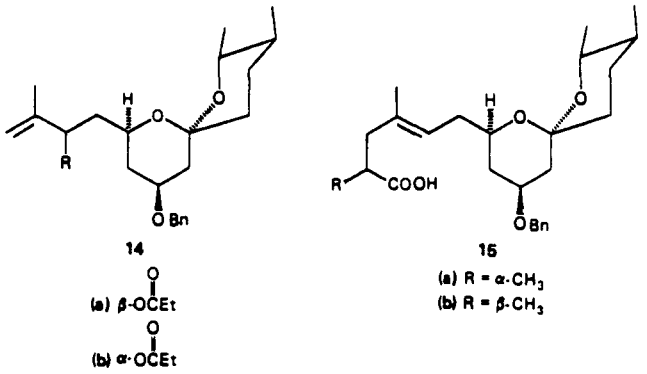
(19) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

(20) It was found to be imperative that this reduction be carried out with a homogeneous etheral solution of $LiAlH_4$. The latter was prepared by Soxhlet extraction of $LiAlH_4$ powder with ether.

(21) Assuming that the Michael addition proceeds to afford only the isomer possessing the more favorable equatorial acetaldehyde substituent, we need only consider the stereochemical consequences of the carbon bearing the benzyl ether to explain formation of a single product in this sequence of transformations. [It should be noted that the benzyl ether center is set in the initial dipolar addition.] In the case of unsaturated **9**, where in the benzyl ether occupies an equatorial position, ring closure to afford aldehyde **8** proceeds smoothly. Alternatively, in the epimer of **9** a serious 1,3-diaxial interaction may prevent this isomer from attaining the necessary transition-state conformation to permit facile cyclization. In this case competitive elimination of benzyl alcohol and subsequent decomposition may intervene. Support for this scenario derives from observation of an, as yet, uncharacterized polyunsaturated product.

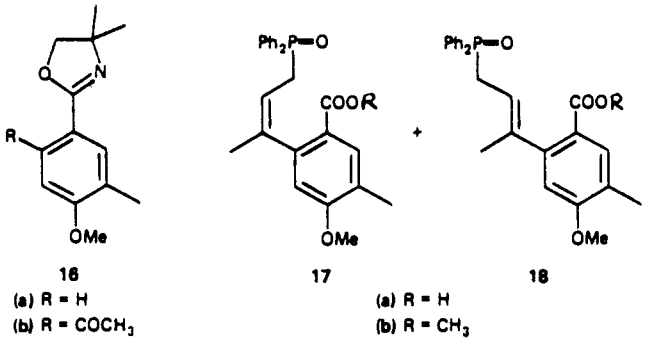
(22) Degradation of milbemycin β_1 (**2**) and chemical correlation with synthetic aldehyde **5** via diol i is outlined below. Comparisons were made on both diol i and the corresponding diacetate.

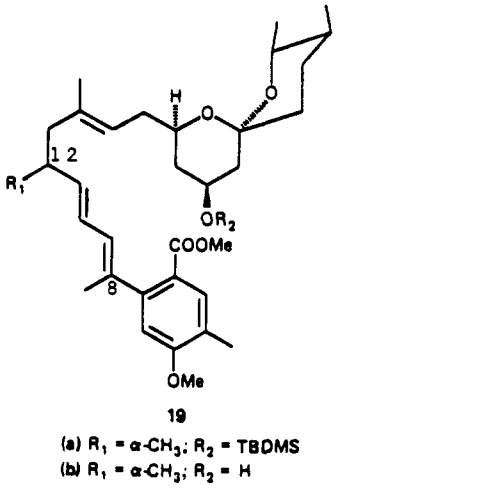




isomers through the remainder of the synthesis. Toward this end, epimeric acids **15a** and **15b** were converted to aldehyde **3a**[14] and **3b**,[14] respectively [(a) Li/liq NH_3, (b) excess TBDMSCl/DMF/imidazole/catalytic amount of DMAP, (c) $LiAlH_4$/ether, and (d) Collins oxidation;[24] overall yield 59%].

With northern hemispheres corresponding to milbemycin and epimilbemycin in hand, we turned to the construction of the southern hemisphere (**4**). Toward this end 3-methyl-*p*-anisic acid[11] was intially converted to oxazoline **16a**[14] [(a) $SOCl_2$, 96%; (b)





2-amino-2-methyl-1-propanol/CH_2Cl_2, 95%; (c) $SOCl_2$, 95%][25] followed by metalation[26] with *s*-BuLi (ether/0 °C, 4 h) and inverse addition to acetic anhydride (3 equiv, ether, −78 °C) to yield methyl ketone **16b**[14a] in 45–50% yield as the *sole* regioisomer. Subsequent condensation with vinyl Grignard followed by acid hydrolysis (3 M H_2SO_4/THF/25 °C, 12 h) gave lactone **7**[14] in 84% yield. Treatment of the latter with lithium diphenylphosphide[10] (THF/−22 → 25 °C, 3 h) led to a mixture of phosphines, which was not isolated but exposed to air [or O_2/$CHCl_3$, 18 h] to yield a 3:1 mixture of isomeric phosphine oxides (**17a**[14a] and **18a**,[14a] respectively), which could be readily separated by flash chromatography [hexane–ethyl acetate–acetic acid (20:10:1), R_f 0.19 and 0.14].[27] Fortunately for our purposes the ratio of *Z* and *E* isomers could be converted in 85–90% yield to a more favorable 1:1 by treatment with strong base (KOH/ethylene glycol/140 °C, 12 h). Finally, exposure to ethereal diazomethane in each case afforded methyl esters **17b**[14a] and **18b**.[14]

The stage was now set for construction of the macrolide ring. Aldehyde **3a** was added to the anion of **18b** (1.5 equiv) generated at −78 °C in THF with sodium hexamethyldisilamide. The resultant diene, **19a**[14a] isolated in 85–95% yield, was shown by high-field (250 MHz) ^1H NMR to be a 7:1 mixture of the trans and cis isomers at C(10,11). Significantly, the methyl group at C(12) had not undergone epimerization. The silyl group was then removed [$(n\text{-Bu})_4NF$/THF/25 °C, 4 h][28] and the resulting alcohol ester (**19b**)[18] treated with potassium hydride (THF/room temperature, 4 h) to yield milbemycin β_3 methyl ether (**1c**)[14a] in 76% yield from **18a**. Similarly, aldehyde **3b** was converted to epimilbemycin β_3 methyl ether (**1d**)[14a] in 79% yield based on **3b**.

Completion of the total synthesis of milbemycin β_3 now required only demethylation of the aryl methyl ether. To this end, treatment of **1c** with excess NaSEt (DMF at reflux, 1 h) according to the method of Feutrill and Mirrington[29] afforded milbemycin β_3 (**1a**) in 86% yield after purification by preparative TLC [hexane–ether (3:1); white solid, mp 153–156 °C (from hexane)]. That indeed (±)-milbemycin β_3 was in hand derived from careful comparison of the ^1H and ^{13}C NMR spectral data with that of authentic milbemycin β_3 kindly provided by Dr. Yo Takiguchi.[30] Similarly, demethylation of **1d** provided epimilbemycin β_3 (**1b**).

In summation, the total synthesis of both (±)-milbemycin and its epimer (±)-epimilbemycin β_3 has been achieved via a convergent approach (longest linear sequence, 16 steps). Studies to improve the overall strategy, in particular the yield of aldehyde **4**, as well as possible communication of the inherent chirality of **4** to the C(12) secondary methyl substituent via increasing the selectivity of the isopropenyl Grignard addition process are currently under active investigation in our laboratory.

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (Institute

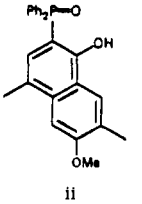
(23) (a) Interestingly no rearrangement was observed on deployment of the original Ireland–Claisen conditions (i.e., LDA/THF, followed by trapping with TBDMSCl in HMPA). Presumably, as postulated by Ireland in the chlorothricolide synthesis, lithium coordinates with neighboring oxygen atoms in highly oxygenated systems in such a manner as to prevent approach of the amide base to the propionate side chain; see: Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041 and references cited therein. (b) The stereoselectivity in each case (i.e., **14a** and **14b**) appeared to be >6:1. (c) Assignment of propionate stereochemistry was based on the assumption that $KN(Me_3Si)_2$ yields the *E* enolate: Professor R. E. Ireland, private communication. (d) **Note Added in Proof**: Since acceptance of this manuscript, we have successfully converted the major propionate **14b** to **15a** in 78% yield employing the conditions (a) LDA/DME/−78 °C, (b) HMPA/−78 °C, (c) TMSCl/−78 °C, (d) *t*-BuOH/−78 °C, and (e) −78–25 °C; the stereoselectivity of this transformation was ca. 3:1.

(24) Collins, J. C.; Hess, W. W., Frank, F. J. *Tetrahedron Lett.* **1968**, 3363.

(25) Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787.

(26) Gschwend, H. W.; Hamdan, A. *J. Org. Chem.* **1975**, *40*, 2008.

(27) Assignment of the *Z* and *E* olefinic configurations of **17b** and **18b** was based on both spectroscopic and chemical data. In particular irradiation of the olefinic methyl protons in **17b** resulted in a 27% NQE enhancement of the corresponding vinyl hydrogen. No enhancement was observed upon similar irradiation of **18b**. In addition, treatment of **17b** with NaH (THF, 25 °C led via intramolecular cyclization to afford naphthol ii, while **18b** did not react.



ii

(28) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(29) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327. *Aust. J. Chem.* **1972**, *25*, 1719.

(30) We are grateful to Dr. Yo Takiguchi, Group Director of the Fermentation Research Laboratories, Sankyo & Company, Ltd., Tokyo, Japan, for providing the ^1H and ^{13}C NMR spectra of milbemycin β_3 as well as a generous sample of milbemycin β_1 utilized in our degradation studies.

of General Medical Sciences) through Grant GM-29028 and by Merck Sharp and Dohme. In addition, we thank S. T. Bella of the Rockefeller University for the microanalyses and Drs. G. Furst and T. Terwilliger of the University of Pennsylvania Spectroscopic Service Centers for aid in recovering and interpretating the high-field NMR and mass spectra, respectively.

Registry No. (±)-**1a**, 82079-52-5; (±)-**1b**, 82079-53-6; (±)-**1c**, 82045-35-0; (±)-**1d**, 82079-54-7; (±)-**3a**, 82045-36-1; (±)-**3b**, 82109-85-1; **4a**, 82045-37-2; **4b**, 82045-38-3; (±)-**5**, 82045-39-4; (±)-**6**, 82045-40-7; (±)-**7**, 82045-41-8; **8**, 6880-04-2; (±)-**9**, 82045-42-9; **10**, 82045-43-0; (±)-**11a**, 82045-44-1; (±)-**11b**, 82045-45-2; (±)-**12**, isomer 1, 82045-46-3; (±)-**12**, isomer 2, 82045-47-4; (±)-**13**, isomer 1, 82045-48-5; (±)-**13**, isomer 2, 82079-55-8; (±)-**13**, isomer 3, 82079-56-9; (±)-**13**, isomer 4, 82079-57-0; (±)-**14a**, 82045-49-6; (±)-**14b**, 82079-58-1; (±)-**15a**, 82109-86-2; (±)-**15b**, 82045-50-9; **16a**, 82045-51-0; **16b**, 82045-52-1; **17a**, 82045-53-2; **17b**, 82045-54-3; (±)-*E*-**19a**, 82045-55-4; (±)-*Z*-**19a**, 82079-59-2; (±)-**19b**, 82045-56-5; 2-amino-2-methyl-1-propanol, 124-68-5.

Stereoselective Generation of *Z* Secondary Thioamide Dianion: Application to Diastereoselective Aldol Condensations and Thio Claisen Rearrangements

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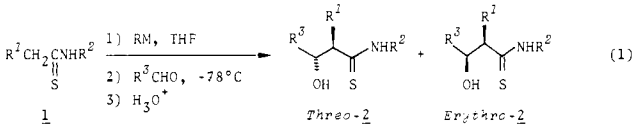
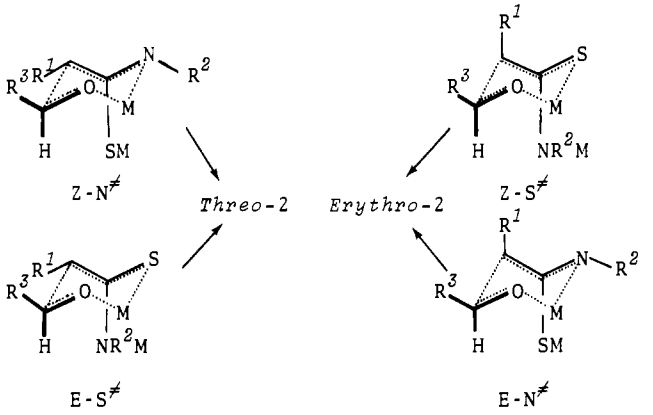
Aldol (β-hydroxycarbonyl) units are a characteristic structural element of numerous macrolide[1] and polyether antibiotics. This led to recent development of new synthetic methods that allow the diastereoselective generation of aldols.[2] Most of them utilize the enolate monoanions of a ketone, an ester, or their equivalents. The aldol condensation with dianions of carboxylic acid or its equivalent has been very scarcely studied probably owing to the low diastereoselectivity as observed for carboxylic acid[3] and secondary amide dianions[4] and considerable scarcity of dianions[5] as well as their mechanistic complexity (vide infra).[6] Generally the diastereoselectivity of an aldol is well correlated to the geometric purity of enolate (*E* or *Z*) and to the six-membered chairlike transition state ordering the substituent of the aldehyde in an equatorial position (see eq 1).[7,8] In addition to these, we have



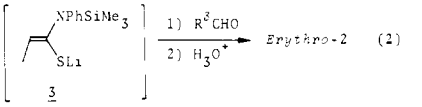
(1)

Scheme I



to consider another factor in the cases of enolate dianion, i.e., the selectivity for the coordination of the aldehyde oxygen to two kinds of metals, as exemplified with secondary thioamide dianion in Scheme I.

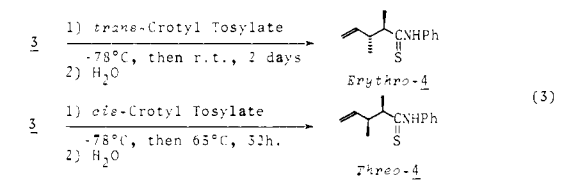
Nothing is known about the stereochemistry of dianions,[4] and first the stereochemistry of secondary thioamide dianions is examined as follows (eq 2): the lithium enolate of *N*-(trimethylsilyl)-*N*-phenylthiopropionamide (**3**),[9] generated either by treatment with 2 equiv of *n*-BuLi (0 °C, 1 h in THF) followed by N-alkylation with 1 equiv of trimethylsilyl chloride (0 °C, 1 h, condition A) or by sequential treatment with 1 equiv of *n*-BuLi (0 °C, 1 h in THF), 1 equiv of trimethylsilyl chloride (0 °C, 1 h, selective N-silylation[9b]), and 1 equiv of *n*-BuLi (−78 °C, 1 h) (condition B), was treated with isobutyraldehyde (−78 °C, 1 min) to provide *erythro*-**2** ($R^1 = CH_3$, $R^2 = C_6H_5$, $R^3 = (CH_3)_2CH$) selectively [*erythro*-**2**/*threo*-**2** = 94:6 in 97% yield (condition A); 92:8 in 99% yield (condition B)] (see eq 2). These parallel results



(2)

suggest that the secondary thioamide dianion possesses the *Z* configuration (condition A), provided that no isomerization takes place during the N-silylation of the secondary thioamide dianion,[10] because it has been already established that the enolate generated from *tert*-thioamide[11] (condition B) possesses the *Z* configuration and provides erythro aldols selectively.

So that further insight into the structure of dianion, especially its geometric purity, could be gained, **3** was treated with *trans*- and *cis*-crotyl tosylates and subjected to the thio Claisen rearrangement conditions (trans, room temperature, 40 h; cis, THF reflux 32 h). From *trans*- and *cis*-crotyl tosylates were obtained *erythro*- and *threo*-*N*-phenyl-2,3-dimethylthio-4-pentenoylamides (**4**) in 51% and 50% yields, respectively (eq 3).[12] This stereo-



(3)

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