times in the range 10^{-14}–10^{-12} s ($k = 10^{12}$–10^{14} s^{-1}). Our results demonstrate (1) much fragmentation occurs with rate constants in the range 10^4–10^8 s^{-1}; (2) roughly equal amounts of fragmentation with rate constants greater and less than 10^8 s^{-1} occurs; (3) a wide range of rate constants exists for each fragmentation; (4) relatively slow fragmentation of the negative molecular ions occurs.

We can make no direct measurement of reaction rates larger than 10^8 s^{-1}. Reactions with such rates obviously occur (prompt reactions).

Our findings lead us to suggest that the fission fragment induced fragmentation processes involve many of the concepts embodied in the quasi-equilibrium theory of mass spectra, e.g., the formation of reactant ions with a wide range of energies, which results in a network of sequential and competing unimolecular reactions with variable and wide-ranging rate constants. This is contrary to the hypothesis of Hunt and co-workers.

Acknowledgment. This work was supported in part by the Division of Research Resources, National Institutes of Health.

Registry No. Chlorophyll a, 479-61-8.

Aldol Methodology: Synthesis of Versatile Intermediates. 3-Hydroxy-2-vinylcarbonyl Compounds

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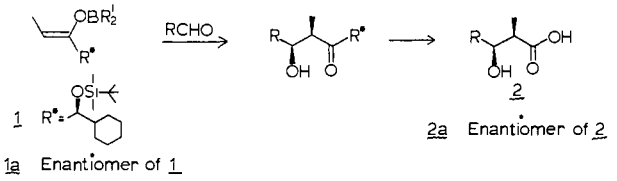
Reaction of an aldehyde with the chiral *Z*(*O*)-enolate **1** or **1a**,[1] followed by simple modification of the resulting aldol product, constitutes an enantioselective synthesis of a *syn*-3-hydroxy-2-methylcarboxylic acid (**2** or **2a**) (Scheme I),[2,3] a fundamental

Scheme I



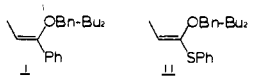
structural unit embedded in numerous natural products of propionate origin.[4] It has been demonstrated that such aldol reactions indeed play the major role in constructing the carbon framework of the complex metabolite 6-deoxyerythronolide B, which contains ten chiral centers.[5] While this achievement represents a major breakthrough in the development of the aldol methodology, further generalization of this approach demands solutions to several other problems. Two of them are the enantioselective synthesis of (1) *anti*-3-hydroxy-2-methyl carbonyl compounds (**3**) (for this introductory paragraph see the compounds in boxes in Scheme II) and, more importantly, (2) systems represented by compounds **4** and **5**, which correspond to the C(13)–C(19) fragment of amphotericin B (**6**)[6] and the C(11)–C(17) fragment of tylonolide (for the structure see the following two communications[7]), respectively. Note that both **4** and a synthetic precursor[8] of **5** carry two hydroxyl groups at the β and β' positions to a carbonyl group. These two problems now find a simultaneous solution: All of the compounds **3**–**5** are derived from the common intermediate **7** or **7a** (see the bold arrows in Scheme II), a compound accessible via a diastereoselective aldol reaction using the new chiral reagent **8** or **8a**. We outline herein the strategy for the construction of these unique structural units and then describe in the following communication[7] the synthesis of tylonolide, the aglycone of the 16-membered polyoxomacrolide antibiotic tylosin.[4]

Synthesis of Reagents 8 and 8a (Scheme III). Treatment of *R*-hexahydromandelic acid (**9**)[2a] with 3.5 equiv of cyclopropyllithium[9] in ether provides the cyclopropylketone **10**, which is in turn converted to its *tert*-butyldimethylsilyl derivative (**11**) (83% overall yield). Heating a benzene solution of **11** with 1 equiv of lithium benzeneselenolate in the presence of 12-crown-4 at 70 °C[10] opens the cyclopropane ring to yield the 3-benzeneseleno ketone **8** (91%). The use of *S*-hexahydromandelic acid (**9a**)[2] in this sequence leads naturally to the preparation of the enantiomer (**8a**) of **8**, and thus both the *S* and *R* isomers of the reagent are available.

Preparation of 7 and 7a (Scheme III). Generation of the dicyclopentylboron enolate from **8** and subsequent aldol condensation with 3.5 equiv of propanal is performed in the standard fashion[2,11] to provide the expected 2,3-syn product **12** in 97% yield (based on **8**) and with >100:1 diastereoselection. The high yield and selectivity observed in this reaction with **8** are general for a variety of achiral aldehydes (e.g., **7a**). After desilylation, elimination of the benzeneselenol group from **12** [ozonization at −78 °C followed by warming (50 °C) the resulting selenoxide in hexane containing pyridine[12]] proceeds well and affords **13** in 86% overall

†The work outlined in this and the following communications was presented by S.M. at the 24th Bachmann Memorial lecture at the University of Michigan on April 15 and 16, 1982, and also was outlined in September 1981 at several German universities, including the University of Cologne.

(1) The two boron enolates i and ii shown below are designated *Z* and *E*. Since very often we are concerned with the relative disposition of the OB-Bu_2 and methyl groups with respect to the double bond, it is preferred to assign the same descriptor to i and ii. We propose the use of *Z*(*O*), indicating that top priority is conferred on the element in the bracket in this special case.



(2) (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (b) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557. Also see: (c) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(3) Assignment of the *R* or *S* configuration to each chiral center unambiguously defines the relative stereochemistry of any pair of the chiral centers existing in a molecule. However, as erythro and threo used in conjunction with the Fischer projection formula have served to express *conveniently* the stereochemical relationship between the substituents attached to the adjacent carbon atoms of a saccharide molecule, it is expedient to have stereochemical descriptors associated with the zigzag formula that is now commonly used for the acyclic system. The use of "syn" and "anti" previously proposed[2b] to describe two (non-hydrogen) substituents on the same side and those on the opposite side of the plane defined by the zigzag main chain has the advantage of *instant recognition* of relative configuration. If there are more than two (non-hydrogen) substituents attached to a pair of carbon atoms, the substituent of the highest priority at each carbon atom is chosen to designate the relative stereochemistry. Thus, "syn" and "anti" is perhaps the simplest of any stereochemical description designed for the acyclic system where the main chain is clearly identified. This is indeed very often the case. These descriptors may be replaced by any of other pairs of words, "con and dis", "like and unlike", "same and opposite", etc., with the exception of erythro and threo. The recent usage of these latter words in aldol chemistry is confusing and conflicts with the convention adopted in carbohydrate chemistry. These two areas of chemistry are now closely related. Recently, S.M. has received preprints from Professors D. Seebach and V. Prelog and also from Professor F. A. Carey, both proposing new sets of descriptors through the extension of the Cahn–Ingold–Prelog system. We gratefully appreciate the information.

(4) For a review of the chemistry and biochemistry of macrolide antibiotics, see: Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585.

(5) Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.

(6) Ganis, P.; Avitabile, G.; Mechlinski, W.; Schaffner, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 4560. Mechlinski, W.; Schaffner, C. P.; Ganis, P.; Avitabile, G. *Tetrahedron Lett.* **1970**, 3873.

(7) Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.*, following communication in this issue.

(8) Such as compound **22**: see Scheme II.

(9) Seyferth, D.; Cohen, H. M. *J. Organomet. Chem.* **1963**, *1*, 15.

(10) Smith, A. B., III; Scarborough, R. M., Jr. *Tetrahedron Lett.* **1978**, 1649.

(11) Propanal, which is inexpensive, was used in excess. A 1:1 mixture of an aldehyde and the boron enolate normally leads to an approximately 80% yield of the aldol product.

(12) (a) Reich, H. J.; Renga, J. N.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. (b) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697.

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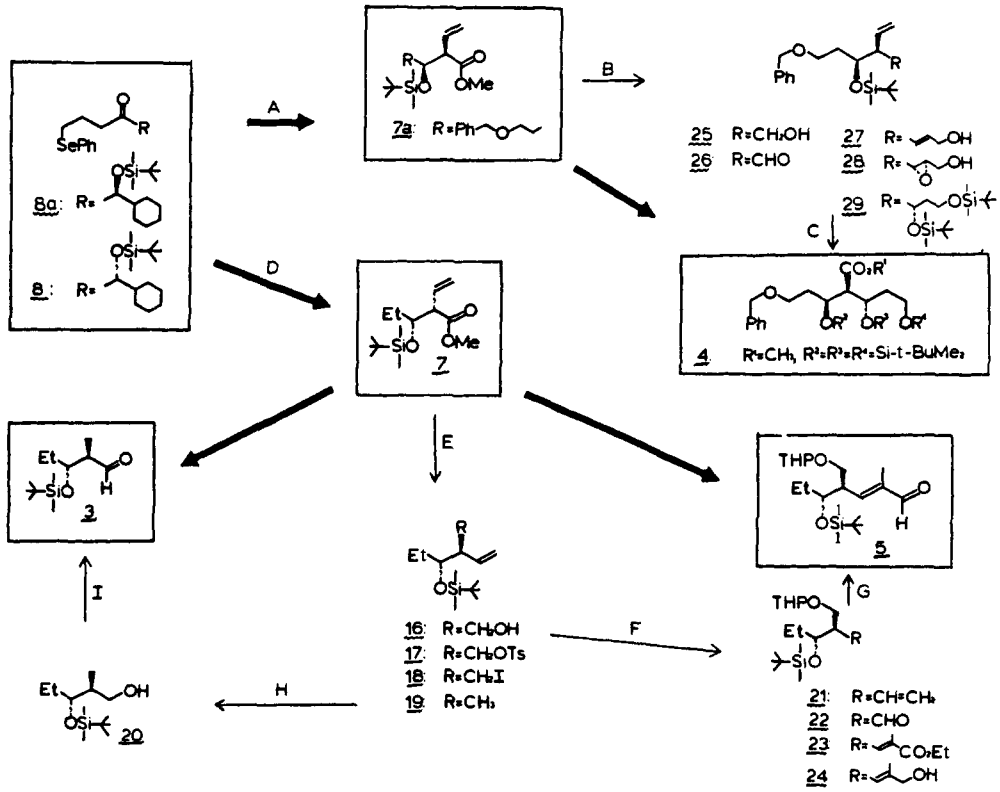
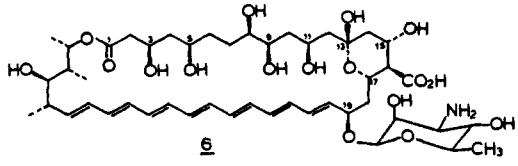
Scheme II





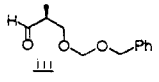
[a] Key: (A) $(c\text{-}C_5C_9)_2BOTf$, $(2\text{-}C_3H_7)_2NEt$ (CH_2Cl_2), −78 → 0 °C, 6 h; $PhCH_2O(CH_2)_2CHO$, 0 °C, 2 h; concentrated HF–CH_3CN (1:20 v/v), room temperature, 3 h; O_3 (CH_2Cl_2), −78 °C; C_5H_5N (hexane), 50 °C, 1 h; $NaIO_4$ (MeOH/H_2O), room temperature, 5 h; CH_2N_2 (Et_2O), 0 °C; *t*-$BuMe_2SiOTf$, 2,6-lutidine (CH_2Cl_2), 0 °C, 15 min; (B) Dibal (toluene), 0 °C, 20 min; 25 → 26, $CrO_3 2C_5H_5N$ (CH_2Cl_2), 0 °C, 15 min; 26 → 27, $Ph_3P{=}CHCO_2Et$ (C_6H_6), room temperature, 16 h, Dibal (hexane), 0 °C, 30 min; 27 → 28, $Ti(2\text{-}C_3H_7O)_4$, (−)-DET, *t*-BuOOH (CH_2Cl_2), −20 °C, 15 h; 28 → 29, Red-al (THF), 0 °C, 14 h; *t*-$BuMe_2SiOTf$, 2,6-lutidine (CH_2Cl_2), 0 °C, 20 min; (C) $KMnO_4$–$NaIO_4$ (*t*-BuOH/H_2O), room temperature, 20 h; CH_2N_2 (Et_2O), 0 °C; (D) see Scheme III; (E) Dibal (toluene), 0 °C, 1 h; 16 → 17, TsCl (C_5H_5N), 0 °C, 4 h; 17 → 18, NaI (acetone), reflux, 8 h; 18 → 19 $NaCNBH_3$ (HMPA), 70 °C, 8 h. (F) 16 → 21 Dihydropyran, PPTS (CH_2Cl_2), room temperature, 4 h; 21 → 22 ($MeOH/CH_2Cl_2$, 3:1), −78 °C; $(CH_3)_2S$, −78 °C → room temperature; 22 → 23, $Ph_3P{=}CMeCO_2Et$ (toluene), 100 °C, 12 h; 23 → 24, Dibal (toluene), 0 °C, 30 min; (G) 24 → 5, $CrO_3 \cdot 2C_5H_5N$ (CH_2Cl_2), room temperature, 20 min; (H) 19 → 20, O_3 (MeOH), −78 °C; $NaBH_4$, −78 °C → room temperature, 30 min; (I) $C_5H_5NHCrO_3Cl$ (CH_2Cl_2), room temperature, 1 h.

yield. Successive treatments of **13** with sodium *m*-periodate, diazomethane, and finally *tert*-butyldimethylsilyl triflate[13] provides the key intermediate **7** through intermediates **14** and **15**. In the same manner, this sequence of reactions starting with 3-benzyloxypropanal and the *S*-reagent **8a** provides **7a** with equal efficiency.

Conversion of 7 to 3 and 5 (Scheme II). Intermediates **7** and **7a** possess two different functional groups, an olefin and ester, both of which are subjected to further appropriate operations to achieve a specific aim in each case. Thus, diisobutylaluminum hydride (Dibal) reduction coverts **7** to the corresponding hydroxyl compound (**16**) (70%). Conversions of **16** into **3** and **5** are straightforward and consist of the following sequence of reactions: (1) for **3**, tosylation, sodium iodide treatment (85–95%, two steps), sodium cyanoborohydride reduction (81–84%), ozonolysis (reductive workup) (81%),[14] and finally PCC oxidation through the intermediates **17**–**20**; (2) for **5**, protection of the primary hydroxyl group (of **16**) as the tetrahydropyranyl ether (95%),[15] ozonolysis followed by dimethyl sulfide workup,[16] Wittig reaction with

(13) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

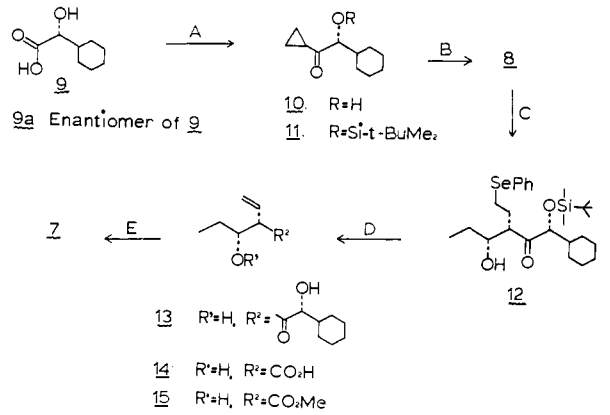
(14) We (Ma, P.; Masamune, S.) prepared **20** also from iii using lithium diethylcuprate [(a) Still, W. C.; Schneider, J. A. *Tetrahedron Lett.* **1980**, *21*, 1035]. Compound iii is available from *S*-3-hydroxyisobutyric acid through three steps [(b) Goodhue, C. T.; Schaeffer, J. R. *Biotechnol. Bioeng.* **1971**, *13*, 203. (c) Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505. (d) Choy, W.; Ma, P.; Masamune, S. *Tetrahedron Lett.* **1981**, *22*, 3555]. However, this cuprate method is not suitable for further chain extension.



iii

(15) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

Scheme III



[a] Key: (A) *c*-C_3H_5Li (Et_2O), −78 °C, 2 h, 0 °C 6 h; **10** → **11**, *t*-$BuMe_2SiCl$, imidazole, DMAP (THF), 70 °C, 12 h; (B) PhSeLi, 12-crown-4 (C_6H_6), reflux, 18 h; (C) (c-$C_5H_9)_2BOTf$ (2-$C_3H_7)_2NEt$ (CH_2Cl_2), −78 → 0 °C, 6 h; EtCHO, 0 °C, 2 h; (D) concentrated HF–CH_3CN (1:20 v/v), room temperature, 4 h; O_3 (CH_2Cl_2), −78 °C; C_5H_5N (hexane), 50 °C, 1 h; **13** → **14** $NaIO_4$ ($MeOH/H_2O$), room temperature, 5 h; **14** → **15** CH_2N_2 (Et_2O), 0 °C. (E) *t*-$BuMe_2SiOTf$, 2,6-lutidine (CH_2Cl_2), 0 °C, 15 min.

(ethoxycarbonyl)ethylidenetriphenylphosphorane (70%, 2 steps), Dibal reduction (77%), and finally Collins oxidation (94%) through the intermediates **21**–**24**. It is clearly recognized that the right-hand end of the main chain and the 2-substituent of the key intermediate **7** are interchanged in **3** as well as in **5**, for whose synthesis no practical enantioselective methodology using a chiral $E(O)$-enolate[1] reagent is currently available.

Conversion of 7a to 4 (Scheme II). The hydroxy compound obtained on Dibal reduction of **7a** is oxidized with Collins reagent to yield (without isomerization of the double bond or epimerization at the C(2) center of **25**) the corresponding aldehyde (**26**), which is reacted with (ethoxycarbonyl)methylenetriphenylphosphorane and then is reduced with Dibal (94%, 3 steps). The titanium-mediated asymmetric epoxidation[17] of the resulting allylic alcohol **27** leads to the formation of epoxide **28**, which, after reductive ring opening (Red-al[18]) and silylation (*tert*-butyldimethylsilyl triflate[13]) provides compound **29** (72%, three steps). Thereafter, a sequence of two standard reactions follows: Lemieux–Rudloff oxidation of the vinyl group and methylation complete the synthesis of **4**.

The use of the versatile intermediates **7** and **7a**, available in optically pure form, certainly add to the repertoire of the aldol reaction. The near-perfect stereocontrol at the 2,3-positions of aldol products as well as the construction of a methyl substituent of varying oxidation states are now possible. Finally, we would like to add that a precursor (**12**) (of **7**) with the benzeneselenoethyl group serving as a masked double bond may be, in some cases, even more versatile than **7** in that this seleno group itself rather than an olefin can be preserved during the multistep transformation of other functional groups in this precursor.[19]

Acknowledgment. We thank the National Institutes of Health (AI 15403) and Hoffmann-La Roche for financial support and also thank Dr. W. P. Jackson for the preparation of compounds **16**–**20**. T.K. is on leave from Mitsui Toatsu Chemical Inc., Japan, and D.S.G. is a National Cancer Institute Trainee (NCI, 2-T32-CA 09112). High-resolution mass spectra were provided by the facility, supported by National Institutes of Health (Grant RR 00317; the principal investigator Professor K. Biemann), from the Biotechnology Resources Branch, Division of Research Resources.

Registry No. 3, 82919-18-4; **4**, 82919-30-0; **5**, 82919-23-1; **7**, 82919-12-8; **7a**, 82919-24-2; **8**, 82919-06-0; **8a**, 82919-07-1; **9**, 53585-93-6; **9a**, 61475-31-8; **10**, 82919-05-9; **10a**, 82919-31-1; **11**, 82932-68-1; **11a**, 82932-70-5; **12**, 82919-08-2; **12a**, 82919-11-7; **12a** de(*tert*-butyldimethylsilyl), 82919-35-5; **13**, 82919-09-3; **13a**, 82919-32-2; **14**, 82919-10-6; **14a**, 82932-71-6; **15**, 82932-69-2; **15a**, 82919-33-3; **16**, 82919-13-9; **17**, 82919-14-0; **18**, 82919-15-1; **19**, 82919-16-2; **20**, 82919-17-3; **21**, 82919-19-5; **22**, 82919-20-8; **23**, 82919-21-9; **24**, 82919-22-0; **25**, 82919-25-3; **26**, 82919-26-4; **27**, 82919-27-5; **28**, 82919-28-6; **29**, 82919-29-7; **29** de(*tert*-butyldimethylsilyl), 82919-34-4; *t*-$BuMe_2SiCl$, 18162-48-6; cyclopropyllithium, 3002-94-6; lithium benzeneselenoate, 52251-58-8; propanal, 123-38-6; *tert*-butyldimethylsilyl triflate, 69739-34-0; 3-(benzyloxy)propanal, 19790-60-4; (ethoxycarbonyl)ethylidenetriphenylphosphorane, 5717-37-3; (ethoxycarbonyl)methylenetriphenylphosphorane, 1099-45-2; (*E*)-5-[(*tert*-butyldimethylsilyl)oxy]-7-phenoxy-4-vinyl-2-heptenoate, 82919-36-6.

Supplementary Material Available: Listing of spectral data (6 pages). Ordering information is given on any current masthead page.

(16) (a) Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273. (b) Woodward, R. B.; et al. *J. Am. Chem. Soc.* **1981**, *103*, 3210, 3213, 3215.

(17) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *Ibid.* **1981**, *103*, 464. (c) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *Ibid.* **1981**, *103*, 6237.

(18) (a) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378. (b) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109.

(19) The specific rotations $[\alpha]_D$ (°C, concentration) in $CHCl_3$ of compounds prepared in this work are as follows: **7** (26, 1.93), −9.9°; **7a** (27, 1.4), −2.1°; **8a** (26, 2.16), +36.5°; **11** (21, 1.49), +65.1°; **12** (27, 1.04), −25.4°; **25** (24, 1.1), −7.4°; **28** (25, 1.24), +7.3°; **29** (26, 1.14), −18.3°. Also see supplementary material for those of the intermediates not numbered.

Synthesis of Tylonolide, the Aglycone of Tylosin

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Received May 20, 1982

The antibiotic tylosin (**1**)[1] represents the well-known family of 16-membered polyoxomacrolide antibiotics.[2] Degradative studies on **1**[3] and the efficient preparation of tylonolide hemiacetal (**2**) (the intact aglycone of **1**) from **1**,[4] as well as the recent crystallographic analysis of protylonolide,[5] establish the stereostructure of **1** and **2** as shown in Scheme I. The structure of **2** reveals that it incorporates the unique C(13)–C(15) unit with an *anti*-14-hydroxymethyl-15-acyloxy stereochemistry (see **3**),[6] a structural and stereochemical feature *absent* in the macrolides selected earlier as our synthetic targets, e.g., methymycin[7] 6-deoxyerythronolide B[8] and narbonolide.[9] With the methodology

(1) For the isolation of **1** from fermentation broths of *Streptomyces fradiae*, see: (a) Hamill, R. L.; Haney, M. E., Jr.; Stamper, M.; Wiley, P. F. *Antibiot. Chemother. (Washington, D.C.)* **1961**, *11*, 328. (b) McGuire, J. M.; Boniece, W. S.; Higgins, C. E.; Hoehn, M. M.; Stark, W. M.; Westhead, J.; Wolfe, R. N. *Ibid.* **1961**, *11*, 320.

(2) For a review on the chemistry and biochemistry of macrolide antibiotics, see: Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585.

(3) (a) Morin, R. B.; Gorman, M. *Tetrahedron Lett.* **1964**, 2339. (b) Morin, R. B.; Gorman, M.; Hamill, R. L.; Demarco, P. V. *Ibid.* **1970**, 4737.

(4) Masamune, S.; Hayase, Y.; Chan, W. K.; Sobczak, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 7874.

(5) Ōmura, S.; Matsubara, H.; Nakagawa, A. *J. Antibiot.* **1980**, *33*, 915. An X-ray analysis of acumycin has also been reported: Clardy, J.; Finer-Moore, J.; Weiler, L.; Wiley, D. C. *Tetrahedron, Suppl.* **1981**, *37*, 91.

(6) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.*, preceding communication in this issue. For the definition of syn and anti, see footnote 3 of this reference.

(7) (a) Masamune, S.; Kim, C. U.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. (b) Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *Ibid.* **1975**, *97*, 3513.

(8) (a) Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568. (b) Masamune, S. In "Organic Synthesis Today and Tomorrow"; Trost, B. M., Hutchinson, C. R., Eds.; Pergamon Press: New York, 1981; pp 197–215. (c) Hirama, M.; Masamune, S. In "Medium- and Large-Sized Ring Natural Products"; Oishi, T., Ed.; Japan Chemical Society: Tokyo, 1981; pp 219–242.

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