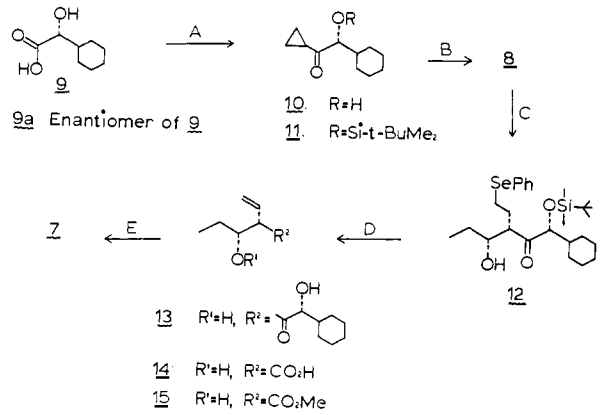
Scheme III



[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)$_2$BOTf (2-C_3H_7)$_2$NEt (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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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.

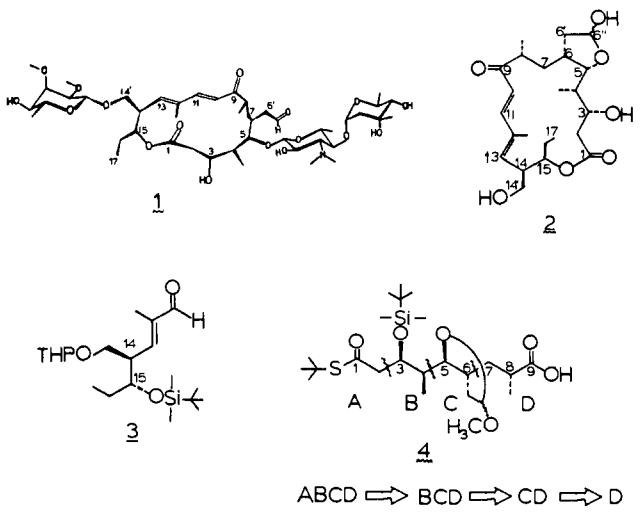
(6) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.*, preceding communication in this issue. For the definition of syn and anti, see footnote 3 of this reference.

(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.

0002-7863/82/1504-5523$01.25/0

Scheme I



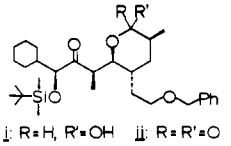
developed for the construction of this unit,[6] the aldol approach to the synthesis of **2** now becomes feasible[10] and indeed has been realized. A retrosynthetic analysis of **2** similar to those applied earlier[7-9] dissects the 16-membered ring into three fragments: the left-hand [C(11)–C(17)] (**3**), [C(10)], and the right-hand [C(1)–C(9)] (**4**); this last fragment is further split into four subunits in the manner ABCD → BCD → CD → C.[11] The synthesis of **4** documented below features the asymmetric aldol reaction and asymmetric hydroboration. The synthesis of **3** is described in the preceding communication. The coupling of **3** and **4** and lactonization of the resulting seco acid derivative complete the *stereoselective* synthesis of tylonolide.

Preparation of Subunit CD [C(5)–C(9) in 4] (Scheme II). The synthesis begins with 4-benzyloxybutyric acid (**5**), readily available from γ-butyrolactone.[12] Treatment of **5** with 2.2 equiv of lithium diisopropylamide in tetrahydrofuran (THF) containing 1.1 equiv of hexamethylphosphoramide and then with methallyl chloride provides in 82% yield the monoalkylated product **6**.[13] Compound **6** is in turn reduced to the alcohol **7** with lithium aluminum hydride (98%) and then oxidized to the corresponding aldehyde **8** with chromic anhydride (Collins–Ratcliffe) (87%). Attempts to resolve **6** or **7** were unsuccessful, but the *S* enantiomer, which is of no avail in this synthesis, is most conveniently removed in the ensuing step.[14a]

Preparation of Subunit BCD [C(3)–C(9) in 4)] (Scheme II). The construction of this subunit involves the creation of three chiral centers [C(4), C(5), and C(8)], which has been achieved with an excellent overall stereoselection of >25:1. Also, the stereochemistry assigned to each product in the sequence of reactions below stands on sound ground, as **8b** is converted to the homo Prelog–Djerassi[7a,8a] lactonic acid derivative **9**, which has been prepared earlier in racemic form.[11] Thus, aldol reaction of **8** with 1.7 equiv of the *S*-boron enolate reagent **10**[15] with R = *n*-butyl proceeds with the dominating diastereofacial selectivity[16] inherent in the reagent,[17] converting **8a** to *only* **11** and **8b** (the *R* enantiomer of **8**) to *only* **12** in a combined yield of 80%.[14b] The products **11** and **12** are separated through flash chromatography, and subsequently the hydroxyl group of **12** (76% isolated yield on the basis of **8b**) is triethylsilylated[18] to afford **13** (100%), which is ready for the next reaction, hydroboration. While treatment with 9-borabicyclo[3.3.1]nonane (9-BBN) in THF followed by oxidative workup with *m*-chloroperoxybenzoic acid[14c] leads to the formation of a 2:1 mixture of the expected primary hydroxy compounds **14** and **15** (90%), the use of the chiral reagents purified (–)-bis(isopinocamphenyl)borane[19] and its (+) isomer results in the mutually exclusive formation of **14** and **15**, respectively (90% in both cases). This remarkably high stereoselectivity (>50:1) was not expected for the reaction of the methallyl system with these reagents.[20,21] Compound **13** behaves in a unique manner, and apparently the chirality existing in **13** hardly influences the overall steric course of the reaction.[17] Propitiation continues. After selective deprotection of the C(5)-hydroxyl group of **14** (this numbering corresponds to that of **2**), the resulting dihydroxyl compound **16** is oxidized with Fetizon's reagent (Ag_2CO_3 on Celite)[22] to give *directly* the lactone **17** in 70% yield. However, because of the somewhat capricious behavior of this reagent in our hands, the preparative scale (5–10 g) conversion of **14** to **17** was carried out stepwise: Collins–Ratcliffe oxidation of **14**, conversion of the resulting aldehyde into the corresponding lactol by deblocking the C(5)-hydroxyl group with aqueous acetic acid–THF, and finally further oxidation provide **17** in overall 67% yield. Removal of the chiral auxiliary used in the aldol reaction proceeds in the standard fashion[15] to afford the carboxylic acid **18**, mp 143–144 °C, which through methylation, debenzylation, and silylation with *tert*-butyldiphenylsilyl chloride, is converted to **9** (overall 85%), identical with the corresponding known racemate[11] except for optical rotation. This establishes the stereochemistry of **17**, which is used in the subsequent step.

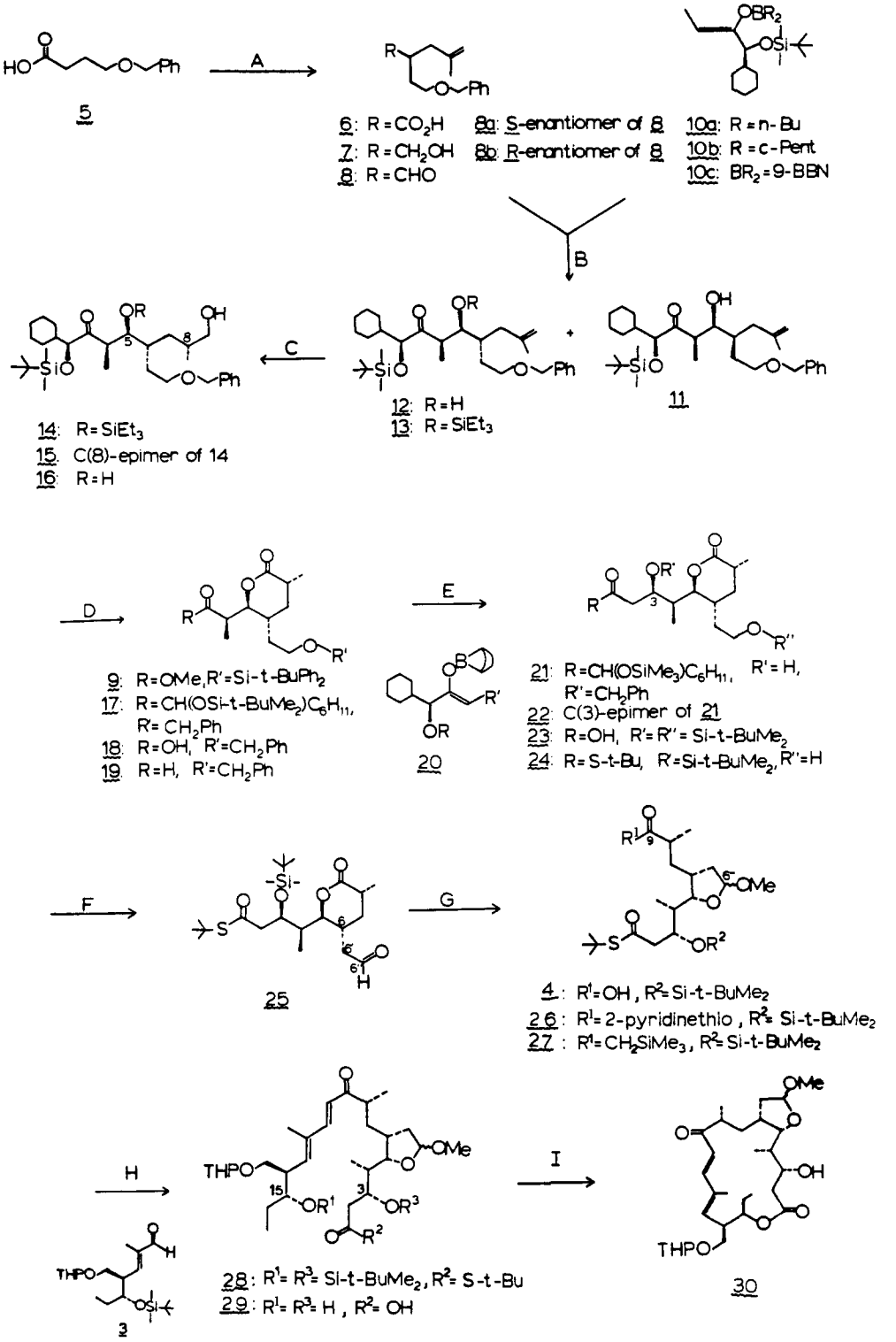
Preparation of 4 (Scheme II). This last stage of the sequence leading to **4** involves a stereoselective addition of an acetate unit to the aldehyde **19**, which is prepared from **17** in 73% overall yield through a sequence of three steps: desilylation, borane–ammonia reduction,[23] and sodium *m*-periodate oxidation. This two-carbon

(9) Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612.
(10) Another approach to this problem is the use of an available monosaccharide from the "chiral pool" (see: Hanessian, S. *Acc. Chem. Res.* **1979**, *12*, 159. Fraser-Reid, B. *Ibid.* **1975**, *8*, 192), as has been demonstrated by two groups: (a) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Tetrahedron Lett.* **1981**, *22*, 3997. (b) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2027. (c) Nicolaou, K. C.; Seitz, S. P. Pavia, M. R. *Ibid.* **1982**, *104*, 2030.
(11) The synthesis of the right-hand fragment equivalent to **4** has been accomplished in racemic form: Lu, L. D.-L. *Tetrahedron Lett.* **1982**, *23*, 1867.
(12) (a) Sudo, R.; Kaneda, A.; Itoh, N. *J. Org. Chem.* **1967**, *32*, 1844. (b) Lee, V. J., private communications.
(13) Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M., Jr. *J. Org. Chem.* **1972**, *37*, 451.
(14) For comments on this reaction, see the supplementary material; "a" of "14a" indicates section a of this attachment.
(15) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.
(16) When an achiral substrate approaches a chiral reagent (e.g., enolate) from either its *re* or *si* face, the substrate, in principle, exhibits a varying degree of preference for one face over the other, because the two faces are diastereotopic. The degree of this preference normally shown in the product ratio is defined as diastereofacial selectivity. The same definition applies to a chiral substrate approaching an achiral reagent.
(17) For the interaction between a chiral reagent and a chiral substrate, see: (a) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076. (b) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557.
(18) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
(19) Brown, H. C.; Yoon, N. M. *Isr. J. Chem.* **1976/1977**, *15*, 12.
(20) The highest ee for the methallyl system is approximately 30%: (a) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547. (b) Zweifel, G.; Ayyangar, N. R.; Munekata, T.; Brown, H. C. *J. Am. Chem. Soc.* **1964**, *86*, 1076.
(21) Compound **15**, the C(8) epimer of **14**, was converted into the lactol



i and lactone ii. The original plan was to equilibrate a mixture of **17** and ii or of the lactol mixture to **17** or the epimer of i, as the two latter compounds are more stable stereoisomers. However, this equilibration met with meager success. Thus, the stereoselective hydroboration turned out to be all the more important. Compare: (a) Grieco, P. A.; Ohfune, Y.; Yokoyama, Y.; Owens, W. *J. Am. Chem. Soc.* **1979**, *101*, 4749. (b) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Ibid.* **1981**, *103*, 1224. (c) Evans, D. A.; Bartroli, J. *Tetrahedron Lett.* **1982**, *23*, 807. Also see ref 10b.
(22) (a) Fetizon, M.; Golfier, M.; Louis, J.-M. *Tetrahedron* **1975**, *31*, 171. (b) Morgans, D. J., Jr. *Tetrahedron Lett.* **1981**, *22*, 3721. (c) Still, W. C.; Shaw, K. R. *Ibid.* **1981**, *22*, 3725.
(23) Andrews, G. C.; Crawford, T. C. *Tetrahedron Lett.* **1980**, *21*, 693.

Scheme II[a]



[a] Key: (A) $(2\text{-}C_3H_7)_2NLi$, HMPA, $CH_2{=}C(CH_3)CH_2Cl$ (THF/hexane), 0 °C → room temperature, 1.5 h; 6 → 7, $LiAlH_4$ (THF), 0 °C → room temperature, 45 min; 7 → 8, $CrO_3{\cdot}2C_5H_5N$ (CH_2Cl_2), 0 °C, 15 min; (B) 10a (CH_2Cl_2), room temperature, 17 h; 12 → 13, $(Et)_3SiOTf$, 2,6-lutidine (CH_2Cl_2), −10 °C → 0 °C, 20 min; (C) (−)-$(IPC)_2BH$ (THF), room temperature, 30 min; MCPBA (THF), 0 °C, 1 h; 14 → 16, 70% aq HOAc-THF (2:1 v/v), 55 °C, 3 h; (D) 16 → 17, Ag_2CO_3-Celite (C_6H_6), reflux, 45 min; 14 → 17, $CrO_3{\cdot}2C_5H_5N$ (CH_2Cl_2), room temperature, 20 min; 70% aq HOAc-THF (2:1 v/v), 55 °C, 8 h; $CrO_3{\cdot}2C_5H_5N$ (CH_2Cl_2), room temperature, 25 min; 17 → 18, concentrated HF-CH_3CN (1:20 v/v), room temperature, 4 h; $NaIO_4$ ($MeOH/H_2O$), room temperature, 2.5 h; 17 → 19, concentrated HF-CH_3CN (1:20 v/v), room temperature 4 h; $BH_3{\cdot}NH_3$ (Et_2O), 0 °C, 1 h; $NaIO_4$ ($MeOH/H_2O$), room temperature, 40 min; (E) 20 [R = Me_3Si; R' = H] (CH_2Cl_2), 0 °C, 45 min; 21 → 23, $(n\text{-}Bu)_4NF$ (THF), 0 °C, 15 min; $NaIO_4$ ($MeOH/H_2O$), room temperature, 2 h; H_2, 5% Pd/C (aq EtOH), room temperature, 1.5 h; t-$BuMe_2SiCl$, $C_3H_4N_2$ (THF), room temperature, 1.5 h; t-$BuMe_2SiCl$, $C_3H_4N_2$ (DMF), 45-50 °C, 9 h; $(C_2H_5)_3N$(MeOH), room temperature, 1 h; 23 → 24, $ClCO_2Et$, C_5H_5N (THF), 0 °C, 2 h; TlS-t-Bu, t-BuSH (THF), room temperature, 24 h; 70% aq HOAc-THF (1:1 v/v), 50 °C, 7.3 h; (F) $CrO_3{\cdot}2C_5H_5N$ (CH_2Cl_2), room temperature, 15 min; (G) 70% aq HOAc-THF (1:1 v/v), 50 °C, 20 h; $HC(OMe)_3$, MeOH, p-TsOH·H_2O (THF), room temperature, 2 h; (H) 4 → 26, $(2\text{-}SC_5H_4N)_2$, Ph_3P (C_6H_6), room temperature, 2.5 h; 26 → 27, $LiCu(Me_3SiCH_2)_2$ (Et_2O), −78 °C, 15 min; 27 → 28, n-BuLi, $(Me_3Si)_2NH$ (THF), −78 °C, 1 h; (I) 28 → 29, $(CF_3CO_2)_2Hg$, Na_2HPO_4 (CH_2Cl_2), room temperature, 1 h; HF/C_5H_5N (THF), room temperature, 40 h; 29 → 30, $(PhO)_2POCl$, Et_3N (THF), 0 °C, 30 min; DMAP (C_6H_6), 80 °C, 18 h; 30 → 2, 70% AcOH, 85 °C 1 h.

extension is indeed a fundamental process in the synthesis of acetate-derived natural products for which general methodologies have been sought, e.g., aldol reaction[14d] and the epoxidation–reductive ring cleavage sequence.[24] After extensive reactions including reagent **20** with R′ = SMe, SPh, SeMe, Se-*c*-C_6H_{11}, and SePh,[14d] we find that the aldehyde **19** behaves in a manner totally unexpected from model experiments. Therefore, we conclude at this time that the following aldol reaction of **19** serves as the best solution, in terms of yield, stereoselectivity, and operational simplicity, all considered. Thus, with the chiral boron enolate **20** (R = trimethylsilyl, instead of *tert*-butyldimethylsilyl; R′ = H) in our standard boron-mediated aldol reaction with 9-BBN(OTf),[15] **19** provides a 4:1 mixture of aldol products **21** and **22** in 88% yield. The stereochemical assignments to these compounds are based on spectral comparison with similar racemic aldol products obtained earlier.[11] While both the substrate **19** and reagent **20** exhibit small but apparently "matched"[8b] diastereofacial selectivities,[14e] thus bringing about the above modest ratio, this selectivity certainly falls short of the standards originally set for this project. Further efforts to enhance this ratio continue.

Compound **21** is subjected to the following functional group transformations: (1) removal of the chiral auxiliary (100%),[15] (2) catalytic hydrogenolysis [5% Pd/C in aqueous ethanol (100%)], (3) stepwise silylation [*t*-$BuMe_2SiCl$[14f]], (4) hydrolysis of the silyl ester (80%) to give **23**, (5) conversion (78%) into the thioester ($ClCO_2Et$, TlS-*t*-Bu); (6) selective hydrolysis of the primary silyl ether to provide **24** (87%) $[\alpha]^{23}_D = +74.4°$ (*c* 1.35, $CHCl_3$), $[\alpha]^{25}_D = +78.3°$ (*c* 0.47, $CHCl_3$). Comparison of **24** with material derived from tylonolide[14g] establishes the identity of these compounds.

Conversion of **24** into **4** involves an intriguing ring "switching". Collins–Ratcliffe oxidation of **24** proceeds smoothly to provide the corresponding aldehyde (**25**), which upon treatment with 70% aqueous acetic acid and THF (1:1) at 50 °C, forms exclusively a γ-lactol, liberating the C(9) carboxylic acid. Subsequent methylation of the lactol with trimethyl orthoformate and methanol in THF containing *p*-toluenesulfonic acid completes the synthesis of **4** (84%, 3 steps), which is an approximately 3:2 mixture of two compounds epimeric at the C(6″) position. The synthetic material is identical with that obtained from natural **2** except for a slight difference in the epimeric ratio.[14g] This varying ratio is of no consequence to the remaining sequence of the tylonolide synthesis that follows.

Synthesis of 2 from 4. This last sequence leading to **2** patterns after that adopted in the synthesis of narbonolide.[9] Thus, treatment with 2,2′-dipyridyl disulfide (1.5 equiv) and triphenylphosphine (1.5 equiv)[14h] converts **4** to its 2-pyridine thioester **26** (75%), which is in turn reacted in ether with lithium bis-[(trimethylsilyl)methyl]cuprate to provide the α-(trimethylsilyl)methyl ketone **27** (80%).[9] The corresponding anion generated with lithium hexamethyldisilazide in tetrahydrofuran at −78 °C is highly nucleophilic and undergoes a Peterson condensation with the left-hand fragment **3** to give rise to a seco acid derivative (**28**) in 60% yield. The base-sensitive C(3) silyloxyl group remains virtually intact. So that the phosphoric acid mixed anhydride procedure[9] for lactonization could be used, the thioester of **28** is hydrolyzed with mercuric trifluoroacetate followed by aqueous $NaHCO_3$ (100%),[25] and then the C(3) and C(15) *tert*-butyldimethylsilyl groups are removed with pyridine hydrofluoride[26] to give **29** (83%). Treatment of **29** (0.1 mM) in 1 mL of tetrahydrofuran with triethylamine (0.1 mM) and diphenyl phosphorochloridate (0.1 mM) at 0 °C produces the mixed anhydride, which after dilution with 40 mL of benzene, is added over a period of 8 h to 60 mL of warm (80 °C) benzene containing 4-(dimethylamino)pyridine (0.6 mM). The solution is refluxed for 10 h and then worked up in the usual manner. The yield of **30** is 32%.[14h] Regeneration of the C(6″) and C(14′) hydroxyl groups from **30** (70% aqueous AcOH) (100%) completes the synthesis of tylonolide (**2**), the intact and unmodified aglycone of tylosin.[27]

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Supplementary Material Available: Listing of optical rotations and spectral data and additional comments on several reactions (11 pages). Ordering information is given on any current masthead page.

(24) (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.

(25) Masamune, S. *Aldrichimica* **1978**, *11*, 23.

(26) (a) Trost, B. M.; Caldwell, C. G. *Tetrahedron Lett.* **1981**, *22*, 4999. (b) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011.

(27) Antibiotic M-4365 G_2 (Kinumaki, A.; et al. *J. Antibiot.* **1977**, *30*, 443) is converted to its intact aglycone, which has been shown to be 14′-deoxytylonolide by synthesis (see ref 14i).

Aldol Strategy: Coordination of the Lithium Cation with an Alkoxy Substituent

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Lithium and magnesium enolates used in aldol reactions, in contrast to boron enolates, exhibit distinctive propensities for coordination with oxygenated functional groups present in either the enolate itself or the reacting aldehyde.[1] This rather general observation is also encountered in many other reactions, including those involving organolithium and Grignard reagents. The profound stereochemical consequences resulting from this coordination have beenm delineated by Cram's cyclic (coordination) model,[2] and its validity has been amply demonstrated in the literature.[3] Although until quite recently only a modest stereoselectivity (apparently) due to this effect had been attained in the aldol reaction,[4] we observed that the lithium enolate derived from **1** (Scheme I) reacted with aldehyde **2** to provide **3** with a 17:1 diastereoselectivity.[5] This result has led us to search for the factors necessary to achieve this high and synthetically significant selection. This communication discloses new findings encountered in this pursuit, which culminates in a remarkably simplified synthesis of the ansa chain of the antibiotic rifamycin S, as described in the last of this series.[6]

(1) Masamune, S. In "Organic Synthesis Today and Tomorrow"; Trost, B. M., Hutchinson, C. R., Eds.; Pergamon Press: New York, 1981; pp 199–215.

(2) (a) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Cram, D. J.; Kopecky, K. R. *Ibid.* **1959**, *81*, 2748. (c) Cram, D. J.; Wilson, D. R. *Ibid*, **1963**, *85*, 1245.

(3) For instance, see: (a) Morrison, J. D.; Mosher, H. S. In "Asymmetric Organic Reactions"; American Chemical Society; Washington, D.C., 1976; Chapt 3. (b) Boyd, D. R.; McKervey, M. A. *Q. Rev. Chem. Soc.* **1968**, *22*, 95. (c) Inch, T. D. *Synthesis* **1970**, *2*, 466. For recent dramatic examples, see: (d) Still, W. C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, *21*, 1031. (e) Still, W. C.; Schneider, J. A. *Ibid.* **1980**, *21*, 1035.

(4) Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118.

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

0002-7863/82/1504-5526$01.25/0