The Asymmetric Synthesis of Erythromycin B

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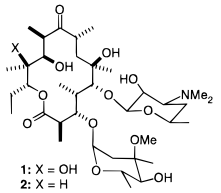
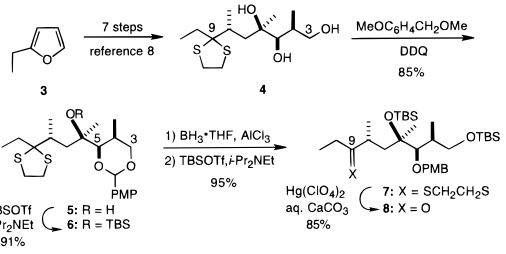
The macrolide antibiotics erythromycins A (**1**) and B (**2**), which owe their antibiotic activity to their ability to inhibit ribosomal-dependent protein biosynthesis,[3] have been the objects of numerous synthetic investigations.[4] However, despite these efforts and a variety of elegant investigations and approaches, there is but a single total synthesis of erythromycin A (**1**) by



Woodward[5] and a formal total synthesis of **1** reported subsequently by Oishi.[6] Tatsuta has since described an alternate glycosylation strategy for preparing **1** from naturally-derived 9(*S*)-dihydroerythronolide A.[7] We now report a concise and highly efficient route to the erythromycin antibiotics that has resulted in the first asymmetric synthesis of erythromycin B.

The point of embarkation for the total synthesis of erythromycin B (**2**) was the differential protection of the three hydroxyl groups of the known trihydroxy ketal **4**, which we had previously prepared in 32% overall yield and seven steps from 2-ethylfuran.[8] The criteria applied to selecting the specific hydroxyl protecting groups was crucial to the eventual success of the synthesis and hence merit brief discussion: Based upon

Scheme 1



previous work in our laboratory,[9] we surmised that protection of the C(6) alcohol had to remain in place until after macrolactonization of the seco-acid derivative at which time selective deprotection under basic or neutral conditions would be required; the dimethyl-*tert*-butylsilyl (TBS) group emerged as a reasonable choice. Formation of the 14-membered lactone is favored by incorporating the C(3) and C(5) hydroxyl groups in a cyclic array.[4] To minimize unnecessary manipulations, we decided that the protecting group for the C(5) alcohol should be easily modified for cyclization with a free C(3) hydroxyl function; consequently, the *p*-methoxybenzyl group (PMB) was selected.[10] Protection for the C(3) hydroxyl group had to be reasonably robust, but yet removable under mild conditions that left other protecting groups intact. The TBS group was then selected in anticipation that it could be selectively removed in the presence of the more hindered TBS group on the C(6) hydroxy group to enable chain extension at C(3). This analysis led to **7** as the initial goal of the synthesis.

Thus, a cyclic *p*-methoxybenzylidene acetal was first formed involving the primary and secondary alcohol groups at C(3) and C(5) of **4**, and the remaining tertiary hydroxyl group at C(6) was silylated to give **6** (Scheme 1).[11] Reductive cleavage of the acetal moiety in **6** with BH_3-THF in the presence of $AlCl_3$ effected the selective release of the less hindered primary hydroxyl group that was then reprotected to give **7** in 73% overall yield from **4**. It is noteworthy that hydride reduction of the acetal in the tertiary alcohol **5** proceeded in the opposite regiochemical sense to give a vicinal diol in which the C(3) *primary* hydroxyl group was protected as a *p*-methoxybenzyl ether. The altered mode of acetal cleavage in **5** presumably arises from preferential complexation of the Lewis acid with the tertiary alcohol at C(6) *prior* to coordination with and activation of the proximal oxygen at C(5), which is more hindered, whereas activation of the less hindered acetal oxygen is observed for **6**.

Deprotection of the thio ketal using mercury(II) perchlorate in the presence of calcium carbonate to give the ketone **8** then set the stage for the stereoselective aldol reaction that would complete construction of the C(3)−C(15) segment of the macrolide backbone. In the event, reaction of **8** with lithium hexamethyldisilazide generated an enolate that added to the aldehyde **9**[8] to give **10** with excellent *syn* and *anti* Felkin−Anh stereoselectivity (>40:1). A comparison of this and several related aldol reactions[4b,k,8,12] suggests that the diastereofacial selectivities in such processes may be affected by subtle differences in substitution on the enolate that are more than five atoms from the reacting center.[13]

With **10** in hand, it remained to add a propionate group to C(3) and incorporate the cyclic protecting groups between the

(1) On leave from Takeda Chemical Industries, Ltd.
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(3) *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984.
(4) For leading references and representative synthetic approaches, see: (a) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131. (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568. (c) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauvé, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2810, 2814, 2818. (d) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564, 1565. (e) Chamberlin, A. R.; Dezube, M.; Reich, S. H.; Sall, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6247. (f) Paterson, I.; Rawson, D. J. *Tetrahedron Lett.* **1989**, *30*, 7463. (g) Nakata, M.; Arai, M.; Tomooka, K.; Ohsawa, N.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618. (h) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7. (i) Myles, D. C.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 1636. (j) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613. (k) Sviridov, A. F.; Borodkin, V. S.; Ermolenko, M. S.; Yashunsky, D. V.; Kochetkov, N. K. *Tetrahedron* **1991**, *47*, 2291, 2317. (l) Mulzer, J.; Mareski, P. A.; Buschmann, J.; Luger, P. *Synthesis* **1992**, 215. (m) Stürmer, R.; Ritter, K.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 101. (n) Evans, D. A.; Kim, A. S. *Tetrahedron Lett.* **1997**, *38*, 53.
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(11) The structure assigned to each compound was in accord with its spectral (^1H and ^{13}C NMR, IR, MS) characteristics. Analytical samples of new compounds were obtained by distillation, recrystallization, flash chromatography, or preparative HPLC and gave satisfactory identification by high-resolution mass spectrometry. All yields are based on isolated, purified materials.
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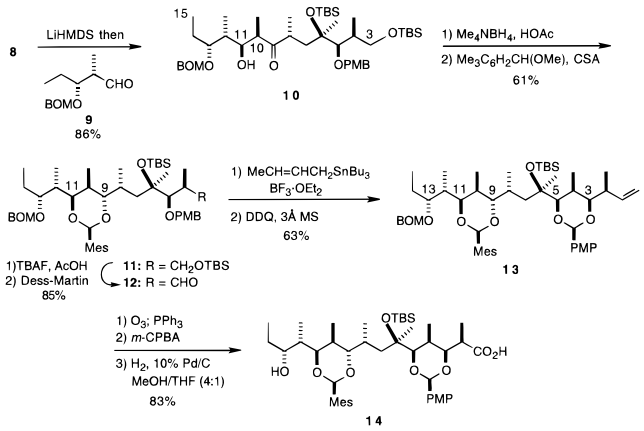
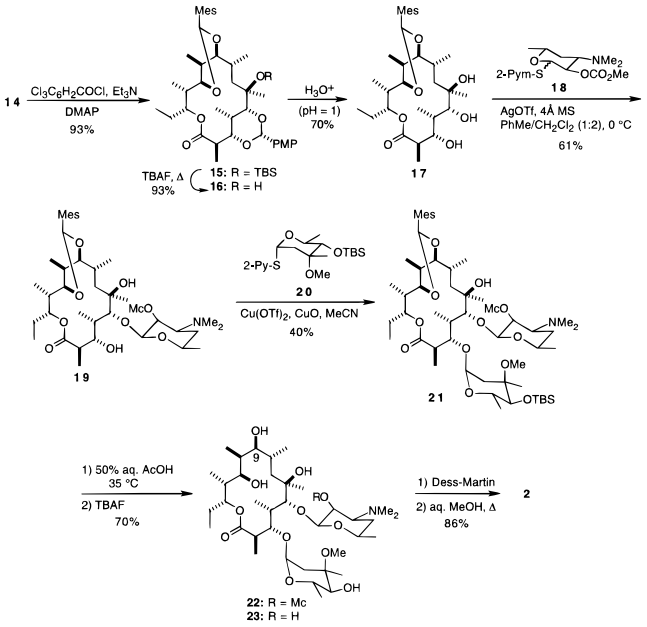
S0002-7863(96)03575-5 CCC: $14.00

Scheme 2



Scheme 3



C(3)−C(5) and C(9)−C(11) alcohol pairs to give a *seco*-acid derivative of erythromycin B that would undergo macrolactonization. Thus, reduction of the hydroxy ketone with $Me_4NBH(OAc)_3$ proceeded stereoselectively (9:1) to give an intermediate C(9)−C(11) *anti* diol[14] that was protected as a cyclic mesitylene acetal (Mes) to provide **11** (Scheme 2). Selective deprotection of the primary hydroxyl followed by oxidation with the Dess−Martin periodinane[15] then gave the aldehyde **12**. Reaction of **12** with tri-*n*-butylcrotylstannane in the presence of boron trifluoride etherate delivered a separable mixture (percent yield ratio of 69:6:12:6) of all four possible diastereomeric homoallylic alcohols in which the major, and desired, product was the *syn*-isomer arising from nucleophilic attack according to the Felkin−Anh model. The free hydroxyl group at C(3) of the major adduct was then incorporated into a *p*-methoxyphenyl (PMP) acetal by oxidative cyclization[10] to give **13**. Oxidative cleavage of the carbon−carbon double bond in **13** followed by removal of the C(13) hydroxyl protecting group by hydrogenolysis, the selectivity of which was critically dependent upon solvent, furnished the *seco*-acid derivative **14**.

Macrolactonization of the conformationally constrained *seco*-acid **14** according to the Yamaguchi protocol proceeded with high efficiency to give the erythronolide B derivative **15** (Scheme 3).[16] Deprotection of the C(6) tertiary hydroxyl group then proceeded smoothly to give **16**. On the other hand, selective removal of the *p*-methoxybenzylidene acetal from the hydroxyl groups at C(3) and C(5) proved somewhat troublesome. Hydrogenolysis was unselective, and under the best conditions identified thus far for hydrolytic removal of this protecting group, the desired triol **17** could be isolated in 70% yield (84% based upon recovered **16**). However, starting material **16** (17%) together with 9(*S*)-dihydroerythronolide (7%) were also recovered from the reaction.

It now remained to append the D-desosamine and L-cladinose residues to **17**. Thus, reaction of **17** with the pyrimidyl thioglycoside **18** in the presence of silver triflate according to a slight modification of the precedent set forth by Tatsuta[7] furnished **19** as a single isomer. Introducing a protected L-cladinose moiety onto **19** by the Woodward protocol,[5] in which lead(II) perchlorate was used to activate the glycosyl donor, failed in our hands, but we discovered that treating **19** with **20** in the presence of a mixture of copper(II) triflate and copper(II) oxide in acetonitrile provided **21** in 40% yield (65% based upon recovered **19**).[17]

Selective hydrolysis of the mesitylene acetal in **21** followed by fluoride-induced removal of the silyl protecting group on the L-cladinose moiety then gave the tetraol **22**. Oxidation of **22** with 1 equiv of the Dess−Martin periodinane reagent proceeded *exclusively* at the C(9) hydroxyl group; subsequent removal of the methyl carbonate moiety from the desosamine residue then delivered erythromycin B (**2**). The synthetic erythromycin B, which was thus obtained in only 30 chemical steps from commercially available 2-ethylfuran (**3**), was identical to a natural sample by comparison of TLC, ^{1}H and ^{13}C NMR, and HRMS. The unusual ability of the Dess−Martin reagent to selectively oxidize secondary alcohols, even in the presence of *unprotected* tertiary amines, based on slight variations in their steric environments, is virtually unprecedented and warrants further investigation.[18] In this context, we also discovered that 9(*S*)-dihydroerythromycin B (**23**) itself may be selectively oxidized to give **2** by using a stoichiometric amount of the Dess−Martin reagent. The scope of selective oxidations of sterically-differentiated secondary alcohols using the Dess−Martin reagent is currently being examined, and these results will be reported in due course.

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Supporting Information Available: Complete characterization (^{1}H and ^{13}C NMR and IR spectra and mass spectral data) for all new compounds (9 pages). See any current masthead page for ordering and Internet access instructions.

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(17) The corresponding β-anomer was also isolated in 10% yield (17% based upon recovered starting material).

(18) Oxidation of the *N*-oxide derivative of 9(*S*)-dihydroerythromycin with bromine in the presence of bis(tri-*n*-butyl)tin oxide was recently reported to proceed selectively at the C(9) hydroxyl group.[7]