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Synthesis of 6-Deoxyerythronolide B. Implementation of a General Strategy for the Synthesis of Macrolide Antibiotics

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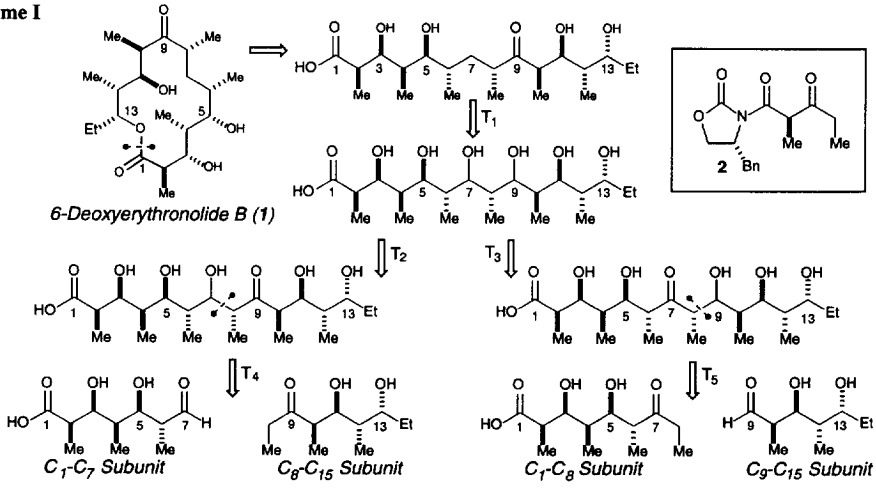
Abstract: The synthesis of 6-deoxyerythronolide B (**1**) has been completed using the β-ketoimide dipropionyl building block **2** in the synthesis of the C_1-C_7 and C_8-C_{15} subunits. A convergent double stereodifferentiating Mukaiyama aldol coupling reaction, a biomimetic deoxygenation, and a high-yield macrocyclization were employed in an 18-step synthesis of this natural product. Copyright © 1996 Elsevier Science Ltd

6-Deoxyerythronolide B (**1**) is the first isolable biosynthetic precursor to erythromycins A and B, antibiotics best known for their potency against Gram-positive bacteria and mycoplasma.[1] Isolated from *Saccharopolyspora erythraea*,[2] these antibiotics are biosynthesized by an iterative acylation-reduction sequence resulting in the linear incorporation of individual propionyl fragments into the evolving seco-acid.[3] Recent methodology developed in this laboratory has addressed the assemblage of polypropionate structures from dipropionyl building blocks such as **2** (Scheme I), rendering the laboratory-based strategy more convergent than the linear biosynthetic assembly sequence.[4] In our synthesis of **1**, described in this Letter, we have further extended the biomimetic analogy by employing a C_7-oxygenated precursor to the hypothetical 6-deoxyerythronolide B seco-acid (Transform 1). In turn, this intermediate may be readily constructed through either of the illustrated convergent aldol fragment coupling processes (Transforms 4 and 5). Since macrocyclization necessitates the hydroxyl oxidation state at C_9,[5] either aldol adduct could serve as a precursor to the C_7-oxygenated array. The ensuing discussion describes our successful implementation of this synthesis plan.

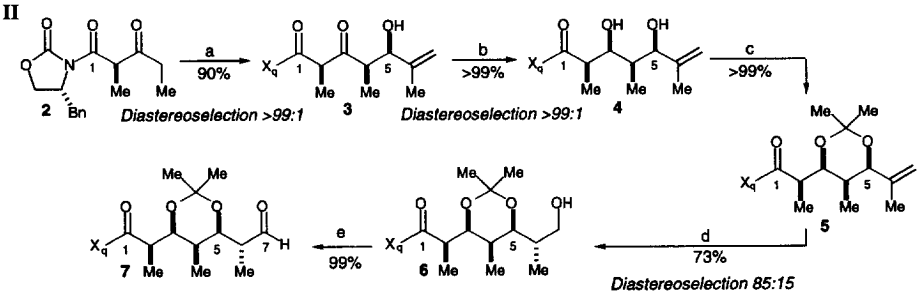
Scheme I



Both aldol assemblage strategies illustrated in Scheme I (Transforms 4 and 5) were investigated during the course of this project. Based on strong precedent, the aldol bond construction represented by Transform 5 was initially examined. Unfortunately, this process failed to deliver the desired *syn* 6,8-Me↔Me stereochemical relationship in the aldol adduct.[6] However, preliminary studies on Mukaiyama aldol coupling reactions suggested a possible solution to the bond construction represented by Transform 4.[7,8] A discussion of this successful approach to the target structure follows.

β-Ketoimide **2** provided an ideal entry to the stereochemical motif found in the C_1-C_7 subunit (Scheme II). $TiCl_4$-mediated addition of **2** to methacrolein afforded the *syn* aldol adduct **3** in 90% yield and >99:1 diastereoselection.[4a,9] Following quantitative *syn* reduction of the C_3-ketone (>99:1 selectivity) by $Zn(BH_4)_2$,[10] protection of the diol as the acetonide afforded olefin **5** in >99% yield. Hydroboration of this olefin with 9-BBN proceeded with 85:15 diastereoselection to yield 73% of the desired *anti* product **6**.[11] Swern oxidation completed the synthesis of this fragment in 65% overall yield for the five-step sequence.

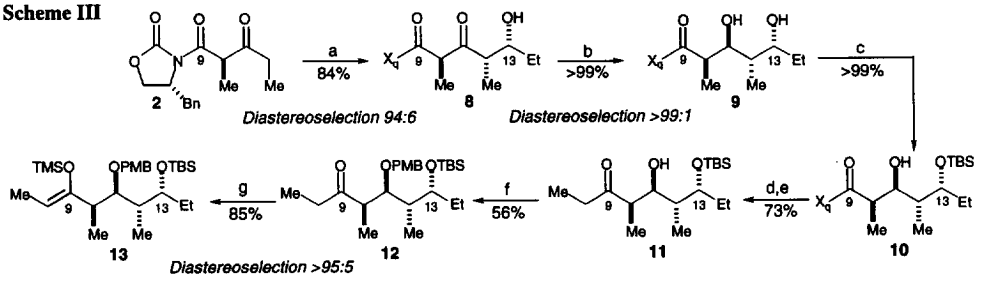
Scheme II



a) $TiCl_4$, *i*-Pr_2NEt, methacrolein, 0 °C, CH_2Cl_2. b) $Zn(BH_4)_2$, -78 °C, CH_2Cl_2. c) $Me_2C(OMe)_2$, CSA, 25 °C, CH_2Cl_2. d) 9-BBN, THF, 0 to 25 °C. e) $(COCl)_2$, DMSO, Et_3N, -78 °C, CH_2Cl_2.

The synthesis of the C_9-C_{15} fragment (Scheme III) began with the $Sn(OTf)_2$-mediated aldol reaction of β-ketoimide **2** with propionaldehyde, affording a 94:6 ratio of diastereomers from which the desired *syn* adduct **8** could be crystallized in 84% yield.[4a] Reduction of **8** with $Na(OAc)_3BH$[12] provided in >99:1 selectivity the *anti* reduction product **9**,[4a] which was immediately monosilylated with TBS-OTf to selectively protect the C_{13} alcohol in quantitative yield. Following a series of standard transformations, ethyl ketone **12** was obtained. Formation of the (*Z*) silyl enol ether **13** (as a >95:5 ratio of olefin isomers) was achieved in 85% yield by selective deprotonation with lithium 1,1,3,3-tetramethyl-1,3-diphenyldisilazide and silylation of the derived lithium enolate with TMS-OTf in the presence of 2,6-lutidine.[13]

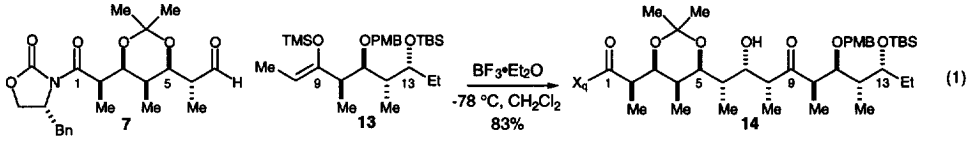
Scheme III



a) $Sn(OTf)_2$, Et_3N, propionaldehyde, -78 °C, CH_2Cl_2. b) $Na(OAc)_3BH$, 25 °C, AcOH. c) TBS-OTf, 2,6-lutidine, 0 °C, CH_2Cl_2. d) $AlMe_3$, (MeO)MeNH•HCl, 0 °C, CH_2Cl_2. e) EtMgBr, 0 to 25 °C, Et_2O. f) $Cl_3CC(NH)O(p\text{-}OMe)Bn$, TfOH, 25 °C, CH_2Cl_2. g) *n*-BuLi, $(PhMe_2Si)_2NH$, TMS-OTf, 2,6-lutidine, -78 to 25°C, THF.

With aldehyde **7** and silyl enol ether **13** in hand, the critical Mukaiyama aldol fragment coupling was attempted. Treatment of one equivalent each of **7** and **13** with BF_3•Et_2O (10 equiv, CH_2Cl_2, 1.5 h, -78 °C) afforded a single aldol adduct with the desired sense of induction at both newly formed stereocenters in 83% yield (eq 1). Through the intermediacy of an open transition state, the enolsilane directed formation of the α-

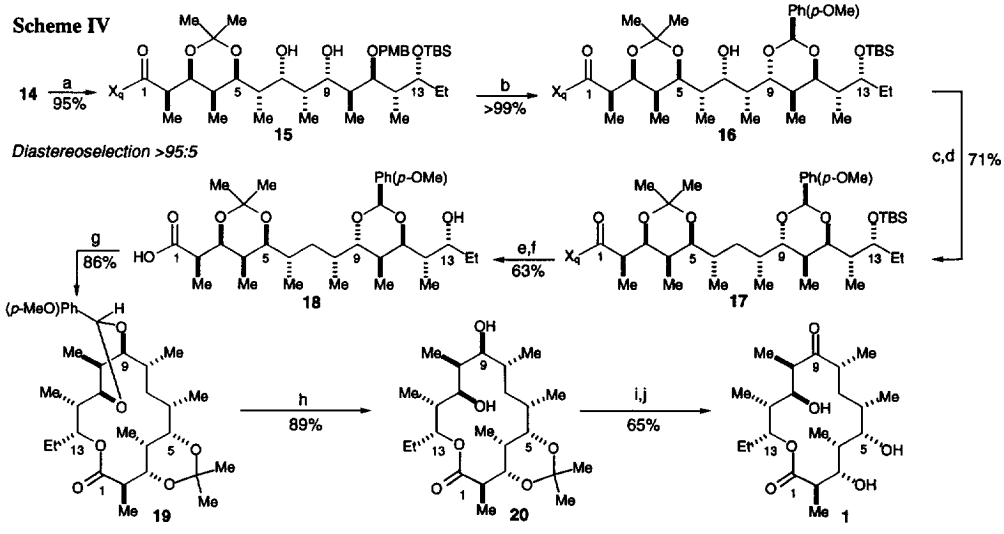
methyl stereogenic center, establishing the *anti* 8,10-Me↔Me relationship across the incipient carbonyl. It is presumed that simultaneous 1,2 (Felkin) induction from the aldehyde established the configuration at the β-stereocenter (C_7). Subsequent studies have examined n depth the elements of stereoinduction in these types of Mukaiyama aldol bond constructions.[8]



Chelate-controlled reduction by $Zn(BH_4)_2$ afforded diol **15** in 95% yield as a single isomer, establishing the C_9-hydroxyl in the desired (*S*) configuration (Scheme IV).[14] Following anhydrous DDQ oxidation, the resultant benzylidene acetal **16** was isolated in >99% yield as a single acetal isomer, thereby differentiating the C_7 and C_9 alcohols and constraining the C_9 and C_{11} hydroxyls as a prerequisite for macrocyclization.[14,15]

With the successful installation of all the requisite stereocenters, it remained to deoxygenate the C_7 position, macrocyclize, and oxidize the C_9 position. Conversion of **16** to the C_7-methyl xanthate (84% yield) set the stage for a Barton radical deoxygenation which was achieved in 84% yield.[16] In preparation for macrocyclization, initial conversion to the carboxylic acid (LiOOH, 72% yield) was required to inhibit elimination in the subsequent TBAF deprotection step. This latter transformation was effected in 88% yield, providing seco-acid **18**. Macrocyclization under modified Yamaguchi conditions afforded **19** in 86% yield.[17] This material was submitted to hydrogenolysis of the benzylidene acetal with Pearlman's catalyst (20% $Pd(OH)_2/C$) in isopropanol to yield 89% of diol **20**. Finally, selective oxidation of the C_9-hydroxyl by PCC[5,18] (76% yield) and treatment with HCl/THF[19] (85% yield) afforded 6-deoxyerythronolide B (**1**). This material proved identical in all respects with authentic samples of the natural product.

Scheme IV



a) $Zn(BH_4)_2$, 0 °C, CH_2Cl_2. b) DDQ, 25 °C, CH_2Cl_2. c) NaH, CS_2, MeI, 0 to 25 °C, THF. d) *n*-Bu_3SnH, AIBN, 110 °C. e) LiOOH, 0 °C, THF. f) TBAF, 65 °C, THF. g) 2,4,6-$Cl_3C_6H_2COCl$, *i*-Pr_2NEt, DMAP, 25 °C, benzene. h) 20% $Pd(OH)_2/C$, 25 °C, *i*-PrOH. i) PCC, 25 °C, CH_2Cl_2. j) 1M HCl, 25 °C, THF.

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References and Notes

1) Nakayama, I. In *Macrolide Antibiotics. Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: Orlando FL, 1984; pp 261-298.

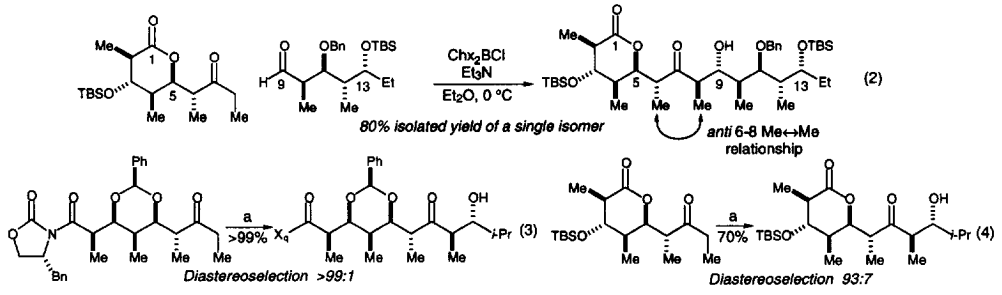
2) McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. *Antibiot. Chemother.* **1952**, *2*, 281-283.

3) (a) Cortes, J.; Haydock, S. F.; Roberts, G. A.; Bevitt, D. J.; Leadlay, P. F. *Nature* **1990**, *348*, 176-178. (b) Donadio, S.; Staver, M. J.; McAlpine, J. B.; Swanson, S. J.; Katz, L. *Science* **1991**, *252*, 675-679. (c) Malpartida, F.; Hopwood, D. A. *Nature* **1984**, *309*, 462-464.

4) (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866-868. (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127-2142.

5) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem Soc.* **1981**, *103*, 1568-1571.

6) Initial evaluation of this hypothetical array of 12 stereocenters focused on the desired *syn* 6,8-Me↔Me relationship about a C_7 carbonyl. A preponderance of data had documented the formation of this array in double stereodifferentiating reactions of both (*Z*) and (*E*) metal enolates. See: (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073-9074. (b) Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1996**, *37*, 1957-1960. However, when this coupling was attempted (eq 2), the *anti* 6,8-Me↔Me relationship was obtained with high diastereoselection. Apparently the discrepancies between our coupling partners configured for future macrocyclization and those of the idealized systems prohibited the establishment of the desired stereochemistry. Further investigation identified a correlation between cyclic protecting groups at C_5 and this reversal of enolate facial bias (eq 3, 4).



a) Chx_2BCl, Et_3N, *i*-PrCHO, 0 °C, Et_2O.

7) These preliminary studies employed $TiCl_4$ as the catalyst. Evans, D. A.; Dart, M. J. Unpublished Results.

8) Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L.; Kim, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 9598-9599.

9) Ng, H. P. Ph.D. Thesis, Harvard University, Aug. 1993.

10) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338-344.

11) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487-2489.

12) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578.

13) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526-5528.

14) Woodward, R. B. *et al. J. Am. Chem. Soc.* **1981**, *103*, 3213-3215.

15) (a) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613-4628. (b) Yonemitsu, O. *J. Synth. Org. Chem., Jpn.* **1994**, *52*, 74-83.

16) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. I* **1975**, 1574-1585. (b) Barton, D. H. R.; Dorchak, J.; Jaszberenyi, J. Cs. *Tetrahedron* **1992**, *48*, 7435-7446.

17) (a) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367-6370. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7-9. (c) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.

18) Corey, E. J.; Melvin, L. S. *Tetrahedron Lett.* **1975**, 929-932.

19) Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620-4622.

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