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Formal Synthesis of 6-Deoxyerythronolide B

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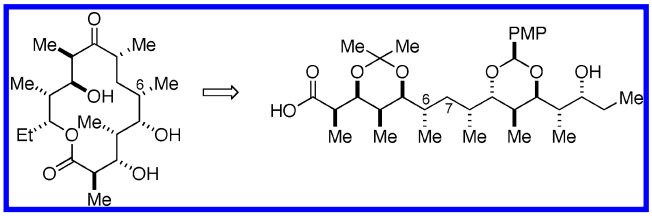
ABSTRACT



The enantioselective synthesis of the carbon skeleton of 6-deoxyerythronolide B has been achieved in 23 linear steps from propionaldehyde. The synthesis relies on an iterative approach employing an asymmetric acyl-thiazolidinethione propionate aldol reaction to establish eight of nine stereogenic centers. The remaining stereogenic center at C6 was set through a Myers alkylation employing a complex alkyl iodide.

Since their discovery in the 1950s[1] erythromycins have captured the interest of biologists, synthetic chemists, and clinicians alike. Physicians have long valued the antibacterial properties[2] of the family while the synthetic community has been intrigued by challenges inherent in the strict polypropionate backbone. Biologists, meanwhile, have focused on the biosynthesis of the various members of the family, and have successfully elucidated the complete biosynthetic pathway.[3] The first isolable (nonenzyme bound) intermediate in the biosynthesis of the erythromycins is 6-deoxyerythronolide B, which was first isolated in 1967 by Martin and Rosenbrook[4] from a blocked mutant of *Streptomyces erythreus*.[5] Three different multidomain enzymes, the deoxyerythronolide B synthases, have been shown to be responsible for assembling 6 units of methylmalonyl CoA and one unit of propionyl CoA in an iterative fashion. As the three enzymes involved contain 31 distinct domains, nature performs the synthesis of 6-deoxyerythronolide B in 31 sequential biosynthetic "steps".[6] 6-Deoxyerythronolide B has been the subject of substantial synthetic interest, with three total syntheses having been previously reported.[7] Masamune[7c] and Evans[7a] each disclosed a convergent synthesis of

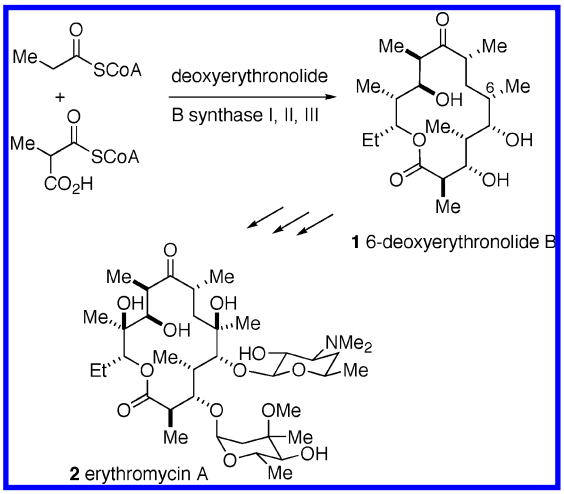


Figure 1. Biosynthesis of erythromycins.

(1) 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.
(2) Nakayama, I. In *Macrolide Antibiotics. Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984; p 261.
(3) (a) Cortes, J.; Haydock, S. F.; Roberts, G. A.; Bevitt, D. J.; Leadlay, P. F. *Nature* **1990**, *348*, 176. (b) Donadio, S.; Staver, M. J.; McAlpine, J. B.; Swanson, S. J.; Katz, L. *Science* **1991**, *252*, 675. (c) Malpartida, F.; Hopwood, D. A. *Nature* **1984**, *309*, 462.
(4) Martin, J. R.; Rosenbrook, W. *Biochemistry* **1967**, *6*, 435.
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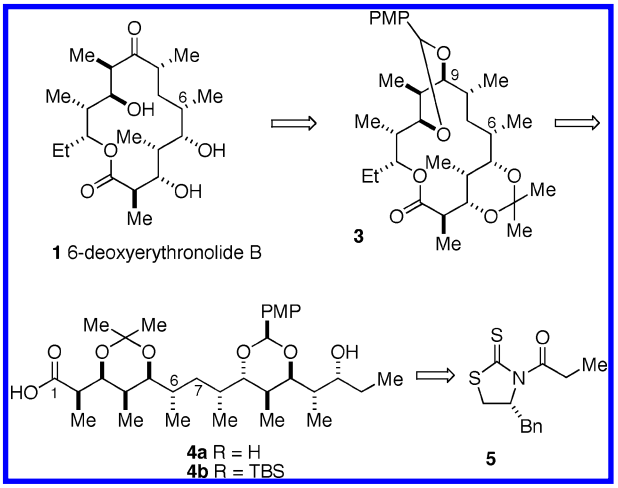
Scheme 1



6-deoxyerythronolide B, relying on double diastereoselective aldol reactions to assemble the polypropionate backbone. By contrast, Danishefsky[7b] employed a linear approach to 6-deoxyerythronolide B based on the Lewis acid-catalyzed diene aldehyde condensation to complete the synthesis in 44 linear steps.

Recent reports from our laboratory have described a diastereoselective propionate aldol reaction based on the use of thiazolidinethione chiral auxiliaries.[8] The ease of removal and facile functional group interconversion of *N*-acylthiazolidinethiones render this aldol reaction particularly well-suited for an iterative process for polypropionate synthesis.[9] The advantages of thiazolidinethiones in asymmetric aldol reactions are (1) the use of inexpensive commercial $TiCl_4$ as the Lewis acid, (2) both syn aldol diastereomers of the aldol adduct can be accessed from a single antipode of the auxiliary simply by changing the amount and type of base used, and (3) the thiazolidinethione can be reductively cleaved to the aldehyde with *i*-Bu_2AlH.[7,10] Thus, the *N*-propionylthiazolidinethione allows for a three-step iterative aldol sequence: (1) diastereoselective aldol addition, (2) protection of the aldol hydroxyl, and (3) reduction of the *N*-acylthiazolidinethione to an aldehyde.

Inspired by the iterative biosynthesis of 6-deoxyerythronolide B, and intrigued by the possibilty of performing a synthesis of the natural product using a strictly linear, iterative approach, we set out to test the applicability of thiazolidinethione aldol reactions in the context of a synthesis of 6-deoxyerythronolide B.

The accumulated knowledge of the three previous syntheses[7] provided a wealth of information concerning the unique challenge of performing the macrolactonization of the 6-deoexyerythronolide B backbone and suggested that the Evans seco-acid **4a** would be an ideal substrate to target for a successful synthesis.[7a] Careful examination of seco-acid **4a** revealed that all the stereogenic centers could be directly established through syn aldol reactions with the possible exception of C6. Two potential approaches were envisioned to establish the requisite stereocenter at C6: a stereoselective hydrogenation or a Myers diastereoselective alkylation. It was anticipated that both approaches could be investigated through a common intermediate **11**, available from three propionate aldol iterations beginning with propionaldehyde.

The synthesis of the tetrapropionate **11** commenced with a non-Evans syn aldol reaction between the *N*-propionylthiazolidinethione **5** and propionaldehyde. The chlorotitanium enolate of **5** was formed by addition of 1.05 equiv of $TiCl_4$, followed by 1.1 equiv of *i*-Pr_2NEt. Subsequent addition of propionaldehyde gave alcohol **6** in 91% yield (>20:1 dr). The reaction was readily scalable, providing reproducible results (both yield and diastereoselectivity) on scales ranging from 1 mmol to over 100 mmol of propionate **5**. Exposure of alcohol **6** to TIPSOTf gave the requisite silyl ether in 96% yield. Reduction of the thioimide with *i*-Bu_2AlH provided aldehyde **7** in 98% yield. The second aldol iteration required the opposite sense of asymmetric induction in the aldol addition. Thus, aldol reaction of imide **5** with aldehyde **7** was performed by enolization with 1.0 equiv of $TiCl_4$, 1.0 equiv of (−)-sparteine, and 1.0 equiv of NMP to provide Evans syn aldol adduct **8** in 96% yield with excellent (>20:1 dr) diastereoselectivity. Alcohol **8** was silylated by the action of TBSOTf in 95% yield, whereupon reduction of the imide with *i*-Bu_2AlH provided aldehyde **9** in 93% yield. The third iteration of the aldol sequence was performed by buffering the chlorotitanium enolate of thioimide **5** (2.5 equiv of *i*-Pr_2NEt) during the reaction with aldehyde **9** to avoid loss or migration of the C11 silyl ether. The non-Evans syn aldol adduct **10** was obtained in 98% yield with excellent selectivity (>20:1 dr). Protection of alcohol **10** as its TES ether provided the silyl ether **11** in 96% yield.

To examine the diastereoselective hydrogenation to establish the C6 stereocenter, imide **11** was converted to lactone **13**. A *i*-Bu_2AlH reduction of imide **11** provided the aldehyde **12**, and a subsequent Still−Gennari[11] modified Horner−Wadsworth−Emmons reaction delivered the *Z*-enoate. Treatment of the enoate with *p*-TsOH in methanol removed the silyl ethers and effected concomitant lactonization to provide the unsaturated lactone **13**. Catalytic hydrogenation of **13** proceeded smoothly to provide the desired saturated lactone as a single isomer **14** (structural proof provided by single-crystal X-ray analysis). Interestingly, attempted hydrogena-

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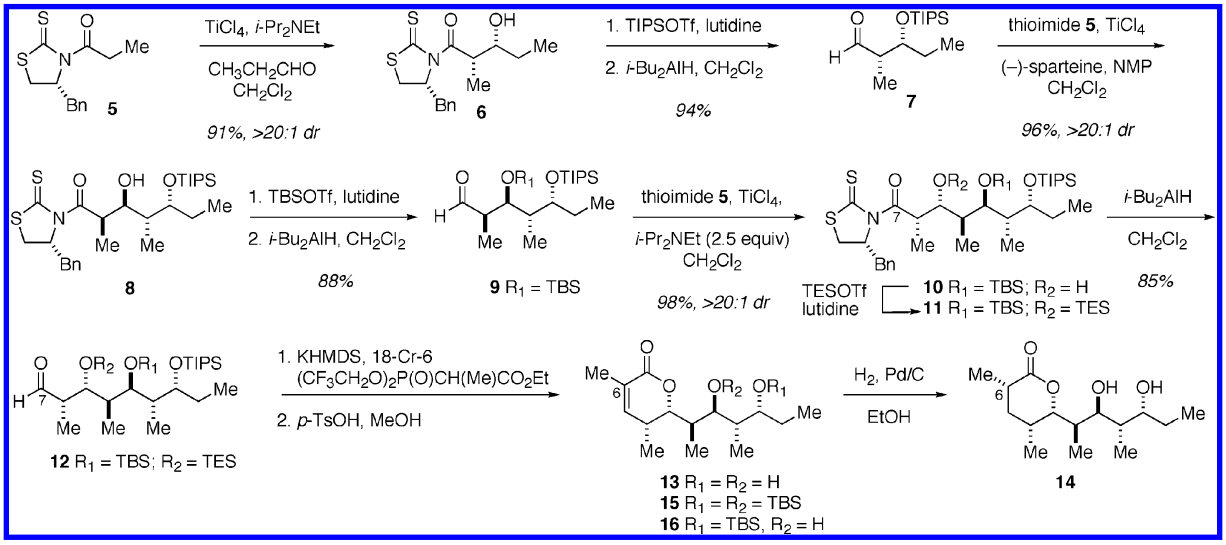
Scheme 2

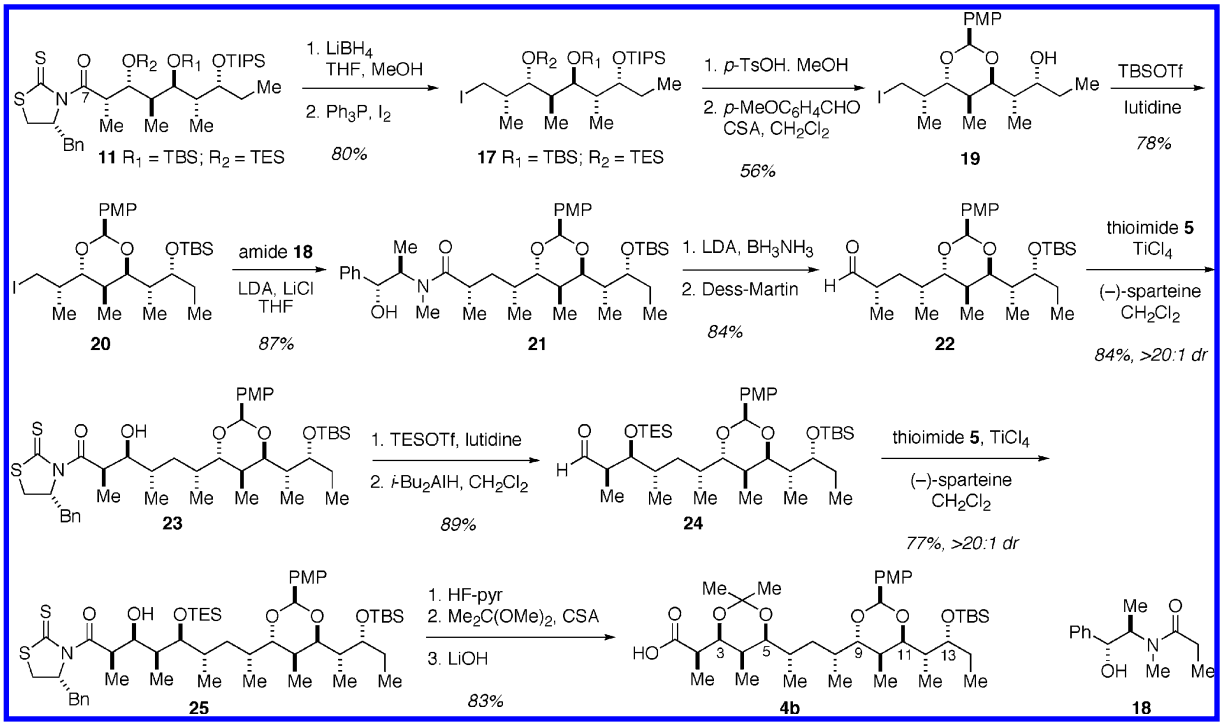


tion on intermediates with the hydroxyl groups protected, for example **15** or **16** and similar variants, led to very poor conversion, and/or poor selectivity. Due to the protecting group difficulties inherent in the hydrogenation approach to set the C6 stereocenter, we turned our attention to establishing the C6 stereocenter via a Myers alkylation (Scheme 3).[12]

N-Acylthiazolidinethione **11** was reductively converted to the primary alcohol in 94% yield. After routine conversion to iodide **17** (85% yield), a Myers alkylation was attempted with pseudephedrine propionate **18** (Scheme 3). Unfortunately, no reaction occurred, even after extended reaction times and at elevated temperatures. In an attempt to improve the reactivity of the iodide, the C9 and C11 silyl ethers were replaced with a sterically less demanding cyclic acetal protecting group, and to allow intersection with Evans seco-acid **4a**, a TBS group was used to protect the C13 hydroxyl.

After substantial experimentation, it was determined that the most effective route to the required C9−C11 cyclic acetal was to fully deprotect iodide **17** (*p*-TsOH, MeOH) to obtain the corresponding triol as a white powder (97% yield) followed by formation of the cyclic PMP acetal as a mixture of all four possible six-membered acetals. The desired *S*

Scheme 3



acetal of the C9−C11 regioisomer **19** could be easily separated from the mixture, and after equilibration of the undesired isomers, a 56% yield of acetal **19** was obtained after 3 recycles.

Installation of the requisite TBS group proceeded in 78% yield providing iodide **20**. Myers alkylation of amide **18** with iodide **20** proceeded in 87% yield to provide amide **21** (>98:2 dr). Removal of the chiral auxiliary in the presence of the acetal was accomplished with lithium amido trihydroborate in 98% yield.[12,13] Dess−Martin oxidation[14] of the resulting primary alcohol provided aldehyde **22** in 86% yield.

The stage was now set for the remaining two iterations of the aldol reaction sequence. An Evans syn mediated protocol employing excess enolate delivered the desired aldol adduct **23** in 84% yield (>20:1 dr). Alcohol **23** was masked as the TES ether in 91% yield and reduction of the *N*-acylthiazolidinethione provided aldehyde **24** in 98% yield.

The final aldol reaction employed excess enolate under the Evans syn protocol (1.0 equiv of $TiCl_4$, 1.0 equiv of (−)-sparteine, 1.0 equiv of NMP) and gave alcohol **25** in 77% yield. Completion of the formal synthesis of 6-deoxyerythronolide B required only protecting group manipulation and hydrolysis of the auxiliary. Selective deprotection of the TES ether proceeded in 99% yield by exposure of imide **25** to HF−pyridine buffered with pyridine. The resulting C3−C5 diol was converted to the acetonide under acidic conditions in 85% yield. Hydrolysis of the auxiliary by treatment with LiOH provided the acid **4b** in 99% yield constituting a formal synthesis of 6-deoxyerythronolide B. Spectral data for synthetic **4b** matched the literature values in all respects.[9a]

In conclusion, a formal synthesis of 6-deoxyerythronolide B has been achieved in 23 steps and 7.5% overall yield, thus validating the utility of *N*-acylthiazolidinethiones in an iterative approach to polypropionates. Aldol additions of thiazolidinethione **5** served to establish 10 of the 11 stereocenters of 6-deoxyerythronolide B.

Acknowledgment. Financial support of this work by the National Institute of General Medical Sciences (GM38904) is acknowledged with thanks.

Supporting Information Available: Experimental details and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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