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 1950s1 erythromycins have captured the interest of biologists, synthetic chemists, and clinicians alike. Physicians have long valued the antibacterial properties2 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 Rosenbrook4 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 Masamune7c and Evans7a each disclosed a convergent synthesis of...
6-deoxyerythronolide B, relying on double diastereoselective aldol reactions to assemble the polypropionate backbone. By contrast, Dansishefsky\(^7^b\) 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 thiazolidinethiones chiral auxiliaries.\(^8\) The ease of removal and facile functional group interconversion of N-acethylthiazolidinethiones 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 aldhyde with \(\text{i-Bu}_2\text{AlH}\).\(^7^b\) 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 \(N\)-acethylthiazolidinethione to an aldehyde.

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 \(i\)-PrNEt. 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 TIPSO\(_2\)F gave the requisite silyl ether in 96% yield. Reduction of the thioimide with \(\text{i-Bu}_2\text{AIH}\) 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 \(\text{i-Bu}_2\text{AIH}\) 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\(_2\)NEt) 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 \(\text{i-Bu}_2\text{AIH}\) reduction of imide \(11\) provided the aldehyde \(12\), and a subsequent Still–Gennari\(^11\) modified Horner–Wadsworth–Emmons reaction delivered the Z-enolate. Treatment of the enolate 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-


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 pseudoephedrine 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
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 oxidation14 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-acylthiazolidine provided aldehyde 24 in 98% yield.

The final aldol reaction employed excess enolate under the Evans syn protocol (1.0 equiv of TiCl4, 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 stereo-centers of 6-deoxyerythronolide B.

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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.