Synthesis of Triketide δ-Lactones

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Abstract: An efficient synthetic route was developed to prepare substituted δ-lactones 1 and 2 in enantiopure forms which are potentially useful for biosynthetic studies with genetically engineered modular polyketide synthase (PKS). The key step to prepare the target epimeric lactones involves the samarium(II) iodide-mediated Reformatsky reaction.

Key words: polyketide biosynthesis, lactones, samarium(II) iodide, aldol reaction, Reformatsky reaction

Modular polyketide synthases (PKSs) are giant multienzyme complexes to produce structurally diverse natural products by successive cycles of chain extension.1 ‘Non-natural’ natural products from the hybrid modular PKSs have attracted much attention in connection with natural product drug discovery and development by so-called ‘Combinatorial Biosynthesis’. Smaller hybrid PKS systems such as DEBS1 (DEBS = 6-deoxyerythronolide B synthase)+TE (thioesterase),2 or DEBS1–TE3 truncated versions of the erythromycin PKS, both of which containing the first two modules of 6-deoxyerythronolide B fused to the TE domain, have been extensively utilized in order to facilitate the detailed investigations on the biosynthesis of 6-deoxyerythronolide B. These hybrid PKSs are responsible for producing smaller lactones.4 In connection with the generation of hybrid PKSs derived from the pikromycin PKS system,5 we are interested in the following δ-lactones 1 and 2. The synthesis of these lactones would facilitate the identification and isolation of the lactones produced by hybrid PKSs. Herein, we wish to report a successful and practical synthetic route to prepare both enantiopure lactones 1 and 2 utilizing aldol and the Reformatsky reactions as key synthetic steps to secure the desired stereochemical relationships. Although both lactones has been reported to be isolated in connection with the study on the bimodular polyketide synthase based on domain or modular exchanges, they have not been chemically prepared yet.6

Synthesis of both lactones could be achieved by coupling between the fragments A and B shown in the retrosynthetic scheme (Scheme 1). The synthetic scheme for the aldehyde fragment (Scheme 2) is quite straightforward and involves boron enolate aldol reaction7 with the known propionate oxazolidinone 3 to produce the required two stereogenic centers. After protection of the OH group, reduction to remove the chiral auxiliary followed by the Swern oxidation gave the desired known aldehyde 7 in good yield overall.4f

Scheme 1

Scheme 2

Acetate aldol reaction was the next crucial step to establish the stereochemistry of the 3-hydroxyl group in the desired lactones. Acetate aldol condensations has been known to offer low diastereoselectivity with chiral enolates derived from α-acetyl oxazolidinones. The simple adaptation of boron enolate aldol strategy under the identical conditions described in Scheme 2 provided a mixture of products that was not easy to separate.

There have been several methods available in the literature to achieve the acetate aldol reaction efficiently such as Nagao’s chiral 1,3-thiazolidine-2-thione technology $^8$ and the method via titanium enolates. $^9$ Recently utilization of the Reformatsky reaction to resolve acetate aldol reactions has been reported. For example, the chromium Reformatsky reaction has been applied to produce stereogenic carbon centers $^{6a,10}$ We looked for milder and easier methods to generate the desired stereochemistry of the hydroxyl group. Samarium(II) iodide has been known as a very versatile reagent for numerous organic transformations. We were interested in the samarium(II) iodide-mediated asymmetric Reformatsky-type reaction $^{11}$ which was recently reported to be efficient. The synthetic scheme to prepare the desired lactones is shown in Scheme 3.

Bromoacetoxyazolidinone 9 was easily prepared from the commercially available (R)-oxazolidinone 8. The key Reformatsky reaction mediated by samarium(II) iodide was performed at −78 °C to give the desired condensation products in a highly diastereoselective fashion (25:1 based on isolated yields after separation) in favor of 10a. The stereochemistry of the major product 10a was predicted by the model proposed. $^{11}$ We found that this samarium(II) iodide-mediated Reformatsky reaction was efficient and easy to perform. Conversion of the condensation product 10a to the lactone has been carried out by hydrolysis to a free acid, which was subjected to acid-catalyzed lactonization without isolation to give the target lactone 2. The $^1$H NMR spectral data of the lactone 2 completely matched with those reported in the literature, obtained from the compound isolated from the culture with the mutant strain producing a hybrid PKS protein. $^{12}$

The epimeric lactone 1 could be more efficiently prepared starting from the enantiomeric (S)-oxazolidinone 11 as shown in Scheme 4.

Scheme 4

The chiral bromoacetoxyazolidinone 12, prepared under the same reaction condition described before, was subjected to the samarium(II) iodide-mediated Reformatsky reaction. In this case the diastereoselectivity of the two possible isomers 13a and 13b was low and an 1:1 ratio of the two diastereoisomers was observed presumably due to the mismatched pair relationship of the chiral enolate and the aldehyde used. This could be, however, used as an advantage since eventually we need to prepare both isomers. After separation, both isomers were successfully converted to the desired lactones 1 and 2. For comparison, we performed the same Reformatsky reaction with ethyl bromoacetate and a 6:1 ratio of the corresponding two isomers [compared to the 25:1 ratio (10a:10b) from the matched pair] was obtained; this is due to the intrinsic selectivity originating from the aldehyde. Therefore, the 1:1 ratio of the two diastereomers was not impressive, but it was the best selectivity attainable with the Evans’ auxiliary for the lactone 1.

In summary, we have successfully developed synthetic routes to the substituted δ-lactones. The samarium(II) iodide-mediated Reformatsky reaction was successfully
employed to establish the stereochemistry of the carbon center bearing the hydroxyl group for both epimers. This whole sequence could be used as an access to compounds derived from bimodular or trimodular PKSs.

1H NMR and 13C NMR spectra were recorded on a Bruker AM300 and Bruker AM400 spectrometers. The chemical shifts (δ) are reported in ppm downfield from TMS. IR spectra were recorded on a Jasco DIP-1000 digital polarimeter in solution in a 1 dm cell. MS and HRMS were obtained on a VG Autospec Ultima GC/MS system using direct insertion probe (DIP) and electron impact (EI, 70eV) methods. Compounds 9 and 12 were prepared based on a standard acylation procedure. The aldehyde 7 was synthesized according to the literature.

**Procedure**

CH$_2$I$_2$ (161 mg, 2.00 mmol) was added to a solution of (4R,3'S,4'R,5'R)-4-Benzyl-3-[5'-tert-butyldimethylsilyloxy]-3'-hydroxy-4'-methylheptanoyl-2-oxazolidinone 10a and (4R,3'R,4'R,5'R)-4-Benzyl-3-[5'-tert-butyldimethylsilyloxy]-3'-hydroxy-4'-methylheptanoyl-10b: Typical

To this solution was added a solution of (4R)-4-benzyl-3-(2'-bromocetyl)-2-oxazolidinone (9: 298 mg, 1.00 mmol) and (2R,3R)-3-(tert-butyldimethylsilyloxy)-2-methylpentan-1-ol (7: 242 mg, 1.05 mmol) in THF (3.0 mL) at 0 °C. After stirring for 1 h at −78 °C, the solution was warmed to r.t. and stirred for 2 h. The resulting greenish blue solution was cooled to 0 °C. To this solution was added a solution of (4R)-4-benzyl-3-(2'-bromocetyl)-2-oxazolidinone (9: 298 mg, 1.00 mmol) and (2R,3R)-3-(tert-butyldimethylsilyloxy)-2-methylpentan-1-ol (7: 242 mg, 1.05 mmol) in THF (3.0 mL) at −78 °C. After stirring for 1 h at −78 °C, the solution was warmed to r.t. and stirred for 2 h. The resulting greenish blue solution was cooled to 0 °C.

The resulting solution was neutralized with Et$_3$O (3 × 30 mL). The organic layer was washed with aq Na$_2$SO$_3$ and brine, dried (MgSO$_4$) and concentrated. The residue was purified by flash chromatography (hexane–EtOAc, 3:1) to give 10a (405 mg, 90%) and 10b (16 mg, 4%) as yellowish oils.

**MS (EI):** m/z (%) = 449 (M$^+$), 402, 392, 374, 334, 300, 252, 225, 215, 197, 178, 123, 99, 91, 71, 57(100).

**HRMS: m/z Calculated for C$_{24}$H$_{39}$NO$_5$Si: 449.2598. Found: 449.2591.**

**IR (film):** 1785 (C=O), 1698, 1387 cm$^{-1}$.

**HRMS: m/z Calculated for C$_{24}$H$_{39}$NO$_5$Si: 449.2598. Found: 449.2597.**

**IR (film):** 1785 (C=O), 1698, 1388 cm$^{-1}$.

**HRMS: m/z Calculated for C$_{24}$H$_{39}$NO$_5$Si: 449.2598. Found: 449.2608.**

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1 H, J = 13.9, 7.2, 7.0 Hz, CH2CH2), 1.02 (t, 3 H, J = 7.4 Hz, CH2CH3), 0.93 (d, 3 H, J = 7.2 Hz, CHCH3).

13C NMR (100 MHz, CDCl3): δ = 170.8, 79.6, 68.5, 36.8, 35.7, 24.9, 10.1, 10.0.

MS (EI): m/z (%) = 158 (M+), 141(100), 123, 111, 99, 82, 70, 58, 55.

HRMS: m/z Calcd for C8H14O3: 158.0943. Found: 158.0944.

[α]D 25.7 + 72.3 (c = 0.47, CHCl3).

IR (film): 3428, 1719 (C=O), 1240 cm⁻¹.

1H NMR (300 MHz, CDCl3): δ = 4.24 (ddd, 1 H, J = 10.6, 6.6, 4.3 Hz, H-4), 4.13 (m, 1 H, H-6), 2.87 [dd, 1 H, J = 18.3, 6.9 Hz, CHH(C=O)], 2.48 [dd, 1 H, J = 18.3, 10.5 Hz, CHH(C=O)], 1.84 (ddq, 1 H, J = 14.2, 7.1, 7.3 Hz, CH/CH3), 1.75 (br, 1 H, CHOH), 1.59 (ddq, 1 H, J = 14.0, 7.1, 7.0 Hz, CHH/CH3), 1.01 (t, 3 H, J = 7.4 Hz, CH2CH3), 0.95 (d, 3 H, J = 7.1 Hz, CHCH3).

13C NMR (100 MHz, CDCl3): δ = 170.4, 82.2, 67.1, 36.2, 35.3, 25.2, 9.92, 3.82.

MS (EI): m/z (%) = 158 (M+), 149, 141, 129, 116, 111, 100, 91, 86, 82, 77, 71, 65, 62, 58(100), 55, 49.


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References


