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Proline-catalyzed stereoselective synthesis of natural and unnatural nocardiolactone

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ABSTRACT

A concise diastereo and enantioselective synthesis of natural and unnatural nocardiolactone is accomplished by proline-catalyzed crossed-aldol reaction as the key step.

1. Introduction

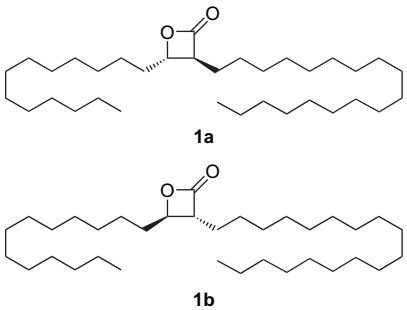
Disubstituted *trans*-β-lactones are considered to be pivotal structural motif for many natural and unnatural molecules such as ebelactones, lipstatin, panclicins, tetrahydrolipstatin, 1233A, belactosins, and nocardiolactone.[1] These molecules display significant biological activity such as antibiotic and antiobesity.[1c,d] Additionally, the simplified disubstituted *trans*-β-lactones potentially act as inhibitors of several enzymes including proteases,[2] HMG Co-A synthase,[3] and esterase.[4] Nocardiolactone **1a**, a trans-disposed disubstituted β-lactone was isolated by Mikami et al. from pathogenic *Nocardia strains* and found to exhibit narrow spectrum activity against Gram-positive bacteria, *Bacillus subtilis* ATCC 6633[5] (Fig. 1). Nocardiolactone **1a** has been synthesized for the first time through an enantioselective route based on Crimmins aldolization followed by DBU-mediated lactonization thereby establishing the absolute configuration of the *trans*-β-lactone as *S*,*S*.[6]

Recently, impressive organocatalytic routes have been developed for the disubstituted *cis*-β-lactones in high enantiopurity.[7] The *cis*-β-lactones were also epimerized to thermodynamically favored *trans*-β-lactones under strong basic conditions.[8]

2. Results and discussion

Our continuing interest in the development of enantioselective synthetic routes[9] for the disubstituted *trans*-β-lactones prompted us to apply *S*-proline-catalyzed crossed-aldol reaction to install the two stereocenters of the *trans*-β-lactone in a highly diastereo and enantioselective manner. Our approach toward the synthesis of nocardiolactone **1a** is shown in Scheme 1.

We have initiated *S*-proline (10 mol %) catalyzed crossed-aldol reaction between eicosanal **2** and glyceraldehyde acetonide **3**, which in turn was prepared from D-mannitol. After considerable experimentation, the reaction was carried out with 10 mol % of *S*-proline and 1 equiv of **2** and 2 equiv of **3** in dry DMF at ambient



1a

1b

Figure 1.

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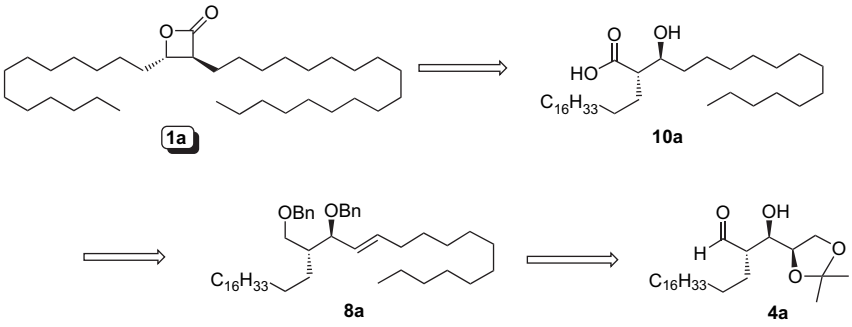


Scheme 1.

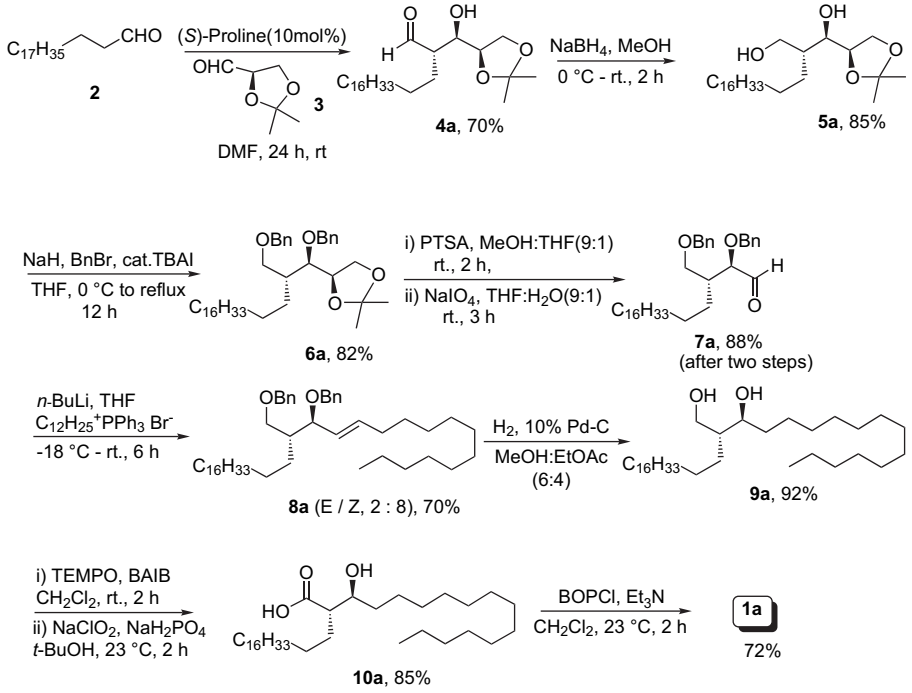
temperature stirring for 24 h, which lead to the *anti*-aldol product **4a** in 70% isolated yield (dr=9:1).[10] Interestingly, we were also able to show that by changing (*S*)- to (*R*)-proline (10 mol %), under otherwise identical conditions, the aldol product **4b** was received in slightly less yields with same diastereoselectivity. The result indicates that there is a negligible matched or mismatched effect on the outcome diastereoselectivity of product **4a** and **4b**. Furthermore, the reagent plays a decisive role on the *anti*-aldol diastereoselectivity, which is also consistent with similar proline-catalyzed reactions.[11]

The subsequent reduction of **4a** using $NaBH_4$/MeOH resulted to the 1,3-diol **5a** in 85% yield. The 1,3-hydroxyl groups were protected as its benzyl ethers using NaH/BnBr in the presence of catalytic amount of TBAI. The acetonide was deprotected with PTSA/(MeOH:THF) (9:1) to give 1,2-diol, followed by oxidative cleavage of the corresponding 1,2-diol using sodium metaperiodate in THF/H_2O (9:1) resulting in aldehyde **7a** in 88% yield. This aldehyde was subjected to Wittig reaction using $C_{12}H_{25}^{+}PPh_3Br^{-}$ and *n*-BuLi in THF to give the olefin (*E*/*Z*, 2:8) **8a** in 70% yield. Hydrogenation of **8a** with 10% Pd–C/H_2 in MeOH/EtOAc (6:4) gave the corresponding 1,3-diol **9a** in 92% yield.

The TEMPO catalyzed chemoselective oxidation[12a] of **9a** with bis(acetoxy)iodobenzene (BAIB) in CH_2Cl_2 followed by further oxidation of the resulting aldehyde employing perchlorite/dihydrogen orthophosphate furnished the β-hydroxy acid[12b] **10a** in 85% yield. The β-hydroxy acid **10a** was lactonized to bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) and Et_3N as base lead to the title compound **1a** in 72% yield (Scheme 2). The spectral and analytical data of **1a** were in full agreement with the reported data ($[\alpha]_D^{25}$ −12.6 (*c* .01, $CHCl_3$); lit.[5] $[\alpha]_D^{25}$ −12.7 (*c* 2.5, $CHCl_3$)).[5] The unnatural nocardiolactone **1b** was synthesized starting from **4b** following the same reaction sequence of **1a**. The optical rotation of **1b** found to be similar in magnitude but opposite in sign to that of **1a**.

3. Conclusion

In conclusion, we have developed the organocatalytic route for the total synthesis of natural and unnatural nocardiolactone molecules. To the best of our knowledge this is the first catalytic route to nocardiolactone **1a**. Significantly, the chirality of the β-lactone moiety was installed with inexpensive naturally occurring amino-acid such as L-proline. Application of this novel methodology to synthesize various disubstituted *trans*-β-lactones in order to study their activity profiles is under progress.



Scheme 2.