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Stereoselective synthesis of a novel carbamoyl oxybiotin

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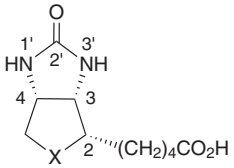
Abstract—Utilizing an L-serine derived enantiopure aminobutenolide as a chiral template, an efficient synthesis of a doubly modified novel biotin analog has been achieved. In view of the renewed interest in understanding the various biological roles of biotin, the title analog could provide some as yet unreported structure–activity relationship information on this important vitamin.

(+)-Biotin (**1**), a water-soluble vitamin,[1] is an essential enzyme cofactor that plays a critical role in gluconeogenesis, fatty acid biosynthesis, and amino acid catabolism. Acting as a mobile carrier of an activated carboxyl group, biotin facilitates the carboxylation of appropriate substrates by the biotin dependent enzymes pyruvate carboxylase, acetyl CoA carboxylases 1 and 2, propionyl CoA carboxylase, and β-methyl crotonyl CoA carboxylase.[2] In recent studies, there has also been evidence suggesting the involvement of biotin in the regulation of gene expression.[3] Additionally, a recent report has suggested that biotin deficiency might enhance the resistance of cancer cells to various antineoplastic agents.[4] Furthermore, in rodent models, deficiency of biotin during pregnancy has proven to be teratogenic and also the cause of several neurologic diseases.[5]

From a structural viewpoint (Fig. 1), the heterobicyclic core of biotin is comprised of a cyclic urea fused to a tetrahydrothiophene ring, with a valeric acid substituent attached to the 2-position of the thiophane. The three contiguous chiral centers of natural (+)-biotin are arranged in an all *cis*-(2*S*,3*S*,4*R*) configuration. Biochemically, an important function of the valeric acid side chain is to act as a linker that attaches biotin covalently to its client enzymes, through amide bond formation between the carboxylic acid of the biotin side chain and the ε-amino group of an appropriately located lysine residue present in the enzyme.[2] On the other hand, the 1′-nitrogen (N-1′) on the ureido portion of biotin is directly involved in the carboxyl transfer reactions.[6] The interesting structural features and its critical biological role in the human system has rendered biotin an attractive target for continued chemical and biological research.[7] For example, in structural modification studies, oxybiotin (**2**), an oxygenated analog (synthetic) of biotin,[8] was found to retain the growth-stimulatory activity of natural biotin,[9] indicating that replacement of the sulfur atom with a smaller and more electronegative oxygen atom does not adversely effect the biological activity of biotin. Similarly, various structural modifications of the valeryl side chain, the thiophane core and the cyclic urea moiety have also provided important structure–activity relationship (SAR) information on the various functionalities as present in biotin.[10]



1: X = S; (+)-Biotin
2: X = O; Oxybiotin

Figure 1. Structures of biotin and oxybiotin.

In a study aimed at a hitherto unreported biotin structural modification, the present research reports the synthesis of a novel, doubly modified 'carbamoyl oxybiotin' **3**, wherein, simultaneous bioisosteric replacement of the sulfur (S) atom in the thiophane ring and the 3′-nitrogen (3′-NH) on the ureido ring with oxygen atoms have been achieved. The retrosynthetic strategy and approach for the desired biotin analog is shown below (Fig. 2).

Keywords: Biotin; Bioisosteric replacement; Structure–activity relationship; Stereoselective.
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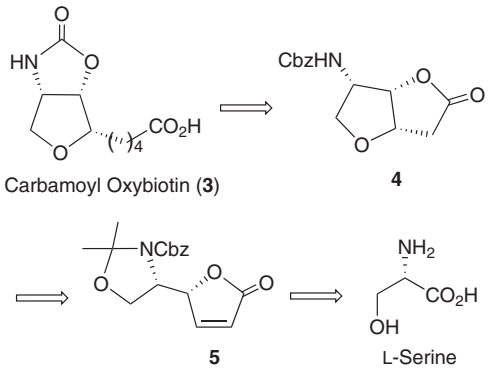
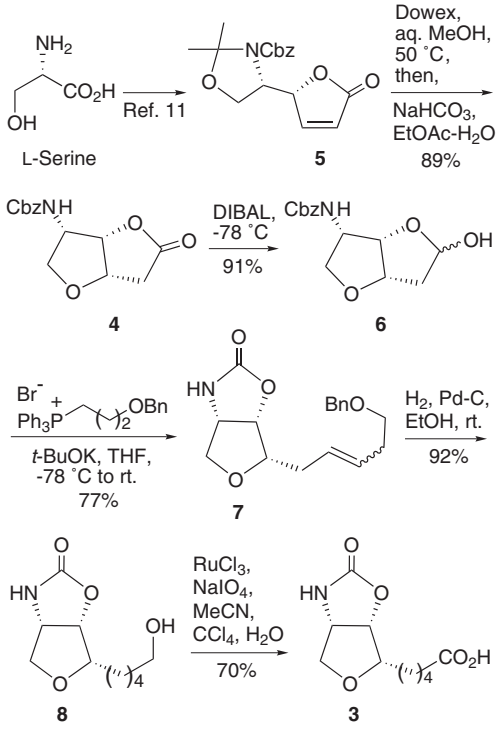


Figure 2. Retrosynthetic strategy and approach.

In recent studies from our group, we have reported an efficient route to enantiopure amino butenolides **5** and *ent*-**5**, starting from easily available L- or D-serine, respectively.[11,12] It has also been shown that, under appropriate conditions, hydrolysis of the acetonide linkage of **5** leads to the stereoselective formation of the *cis*-fused bicyclic lactone **4** in good yield.[12] Taking advantage of the above observation, the present study has been designed to utilize the butenolide **5** as a key chiral template toward construction of the required bicyclic core of the target oxybiotin analog **3**.

Accordingly, following a slight modification of our earlier reported procedure,[12] deprotection of the *N*,*O*-acetonide of **5** and basic workup of the reaction mixture resulted in the bicyclic lactone **4** (Scheme 1) in high yield. Partial reduction of the lactone to the corresponding lactol **6** and subsequent reaction with an appropriate 3-carbon alkyl donor Wittig reagent resulted in the formation of the *E*- and *Z*-mixture of olefins **7**. As expected,[12] during this reaction process, the C_3-secondary oxyanion, generated by the opening of the lactol, also underwent spontaneous intramolecular addition to the carbonyl carbon of the favorably placed *N*-Cbz group, resulting in concomitant formation of the desired bicyclic carbamoyl oxybiotin structural core. Toward completion of the synthesis, in a one-pot reaction, catalytic hydrogenation of **7** resulted in saturation of the olefinic moiety and simultaneous cleavage of the benzylic ether linkage to generate the free primary alcohol **8**. Finally, oxidation of the primary hydroxy group under standard reaction conditions culminated in the target oxybiotin derivative **3**.[13]



Scheme 1.

Although the key role of biotin in several key enzymatic reactions is a relatively well understood process, the recent findings suggesting potential involvement of biotin in the regulation of gene expression[3] has created renewed interest in this important vitamin. By modifying two hydrogen bond donor–acceptor functionalities of the biotin core, the present synthesis of a novel biotin analog has created an opportunity toward further investigating the role of the above functionalities in the bioactivity of biotin and possible utilization of the described analog as a potential tool in future biochemical studies. The synthetic route can also be easily extended toward further modifications at the C-2 position of the molecule, leading to various uniquely modified biotin analogs for future structure–activity relationship investigations.

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References and notes

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13. White solid; mp 146–148 °C; $[\alpha]_D^{25}$ 68.1 (*c* 1.55, MeOH); IR (Teflon) 3249, 1749, 1714, 1699 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 1.49–1.55 (m, 2H), 1.65–1.77 (m, 4H), 2.34 (t, $J = 7.4$ Hz, 2H), 3.53–3.61 (m, 2H), 3.86 (d, $J = 10.3$ Hz, 1H), 4.40 (dd, $J = 4.0$ and 7.5 Hz, 1H), 5.03 (dd, $J = 3.6$ and 7.5 Hz, 1H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 25.0, 25.6, 28.0, 33.8, 57.7, 73.3, 81.5, 83.0, 160.7, 176.5; HRMS (ES+) calcd for $C_{10}H_{15}NO_5Na$ *m/z* $(M+Na)^+$, 252.0848; found, 252.0823; Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.63; H, 6.78; N, 6.0.