Diastereoface Discrimination in the Addition of Acetylide to a Chiral Aldehyde, Leading to a Synthesis of (+)-Deoxybiotin in Enantiomerically Pure Form Starting from L-Cysteine

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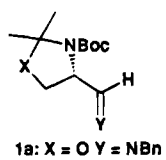
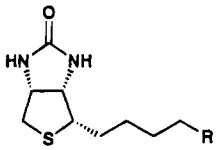
Summary: Complete diastereofacial discrimination was observed upon addition of the chlorozinc acetylide derived from 1-hexyne to a chiral aldehyde prepared from L-cysteine. The addition product was used in a short synthesis of (+)-deoxybiotin, a precursor of (+)-biotin, which was produced in enantiomerically pure form in 12 steps, starting from L-cysteine.

Since its isolation from liver in 1941,[1] biotin, or vitamin H, has received considerable attention as a synthetic target[2] due to its application to human and animal therapy and the study of biosynthetic pathways.[3] A number of synthetic routes have been reported that employ racemic substances and optical resolution at an appropriate stage. However, there are few approaches involving highly stereocontrolled processes. This is



1a: X = O Y = NBn
1b: X = S, Y = NBn
1c: X = O, Y = O
1d: X = S, Y = O



8: R = Me, (+)-deoxybiotin
9: R = CO_2H, (+)-biotin

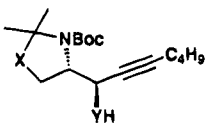
surprising given the simple, *all-cis* structure of biotin. We have been interested in diastereofacial discrimination in the addition of organometallics to carbonyl and imino compounds and have disclosed several tools for stereocontrol.[4] Herein we report a new route to (+)-deoxybiotin (**8**), a precursor of (+)-biotin **9**, using the highly diastereoselective addition of acetylide to chiral aldehyde **1d**, derived from L-cysteine.

Table 1. Addition of the Acetylide Prepared from 1-Hexyne to 1[a]

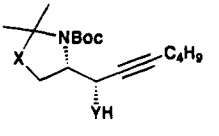
entry	substrate 1	Met	additive	solvent	time (h)	yield[c] (%)	*syn*-**2**: *anti*-**2**[d]
1	**1a**	Li	none[b]	THF	15	44	>99:<1
2	**1a**	Li	HMPA	THF	15	40	>99:<1
3	**1a**	ZnBr	none	Et_2O	15	81	>99:<1
4	**1a**	Cu	none	THF	15	26	>99:<1
5	**1a**	Cu	BF_3·Et_2O	THF–Et_2O	14	45	>99:<1
6	**1b**	Li	none[b]	THF	15	36[e]	>99:<1
7	**1b**	Li	BF_3·Et_2O	THF	4	59[e]	>99:<1
8	**1c**	ZnBr	none	Et_2O	15	95	95:5
9	**1c**	Li	HMPA	THF	20	85	14:86
10	**1d**	Li	none[b]	THF	14	88	40:60
11	**1d**	Li	HMPA	THF	12	71	17:83
12	**1d**	ZnBr	none	Et_2O	21	48	95:5
13	**1d**	ZnCl	none	Et_2O	10	86	>99:<1

[a] The reaction was carried out with 1.20–1.45 equiv of *n*-BuLi and 1.30–1.61 equiv of 1-hexyne at −78 °C. The bromozinc, chlorozinc, and copper(I) acetylides were prepared from the lithium acetylide via transmetalation with $ZnBr_2$, $ZnCl_2$, and CuI, respectively. [b] 3.0 equiv of *n*-BuLi and 3.5 equiv of 1-hexyne was used. [c] Isolated yields. [d] Determined by ^1H, ^{13}C NMR, and/or HPLC. [e] The product was obtained as imidazolidone **4'**.

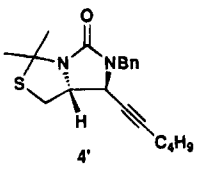
The addition of the acetylide derived from 1-hexyne to imines **1a** and **b** or to aldehydes **1c**[5] and **d** was examined. Chiral aldehyde **1d** was prepared in four steps, in 72% overall yield, from L-cysteine hydrochloride via protection of the sulfur and nitrogen atoms followed by esterification[6] and reduction of the ester moiety with diisobutylaluminum hydride. The imines **1a** and **b** were prepared from the corresponding aldehydes (**1c** and **d**) and benzylamine by dehydration. First, in order to obtain *anti*-1,2-diamine **2** (Y = NBn), which possesses the correct



anti-**2**



syn-**2**



4'

stereochemistry for the construction of the imidazolidone ring of deoxybiotin, imines **1a** and **b** were subject to the addition reaction. Representative results are shown in Table 1. The addition of the acetylide to the chiral imine **1a** afforded only *syn*-**2a**, regardless of the acetylide metal,

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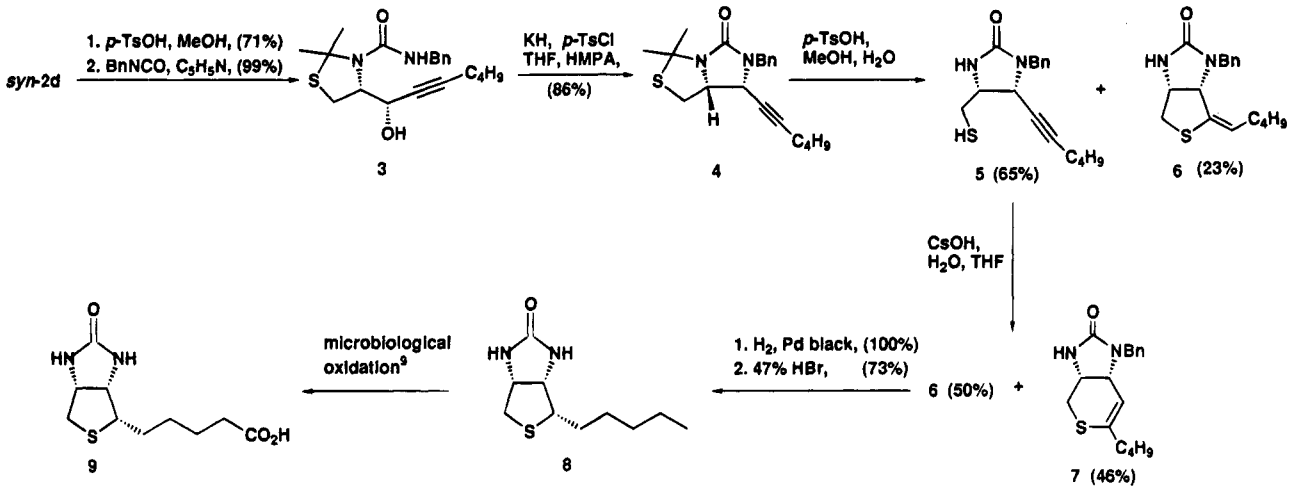
Scheme 1



under both chelation and nonchelation conditions (entries 1–5). Addition to the imine **1b**, derived from L-cysteine, showed a similar trend. Imidazolidone **4'**, a cyclization product from *syn*-**2b**, was obtained as the sole product when the reaction was carried out in the presence or absence of boron trifluoride etherate (entries 6 and 7). Unfortunately, reaction of the lithium acetylide in the presence of HMPA and that of the halozinc acetylides, did not afford the desired addition product, but resulted in the formation of a complex mixture or the recovery of the starting material, respectively. Thus, switchover of the diastereofacial selectivity that would lead to the formation of the desired *anti*-**2a** or **-b** was not observed by using imines **1a** or **b**, despite attempts with both chelation and nonchelation conditions. Therefore, we turned our attention to the inversion of the chiral center by an S_N2 type displacement of the hydroxyl functionality by a nitrogen nucleophile. For this purpose a stereodivergent synthesis of *syn*-amino alcohol **2c** or **-d** was needed, and the addition to the aldehyde **1c** and **-d** was examined. The addition of the bromozinc acetylide to chiral aldehyde **1c** gave the desired *syn*-**2c** with good diastereofacial selectivity (entry 8), whereas the switchover of the diastereoselectivity was observed by using the lithium acetylide in the presence of HMPA (entry 9). This is analogous to the reported case of (trimethylsilyl)-acetylide,[5] in which the *syn* and the *anti* addition products were obtained from the bromozinc and the lithium acetylides–HMPA, respectively. As to the addition to aldehyde **1d**, which is more suitable as a chiral synthon of biotin due to the sulfur moiety, the lithium acetylide in THF gave *anti*-**2d** as a major isomer. The same reaction, conducted in the presence of 1 equiv of HMPA, increased the proportion of *anti* isomer to 17:83 (entry 11), whereas the desired amino alcohol *syn*-**2d** was obtained as a major product but in moderate yield by using bromozinc acetylide (entry 12). The chlorozinc acetylide gave *syn*-**2d** as the sole product in good yield (entry 13). Under the conditions used in the present study, no epimerization was observed, and the cases where the adducts were obtained in low yields involved the recovery of the starting material. The high selectivity obtained in the present system is explicable in terms of a chelation-control model, in which the metal is chelated by the aldehyde and carbamate oxygens.

The transformation of the propargylic alcohol *syn*-**2d** thus obtained to (+)-deoxybiotin was rather straightforward and involved cyclization of the thiol functionality to the triple bond (Scheme 1). Chemoselective deprotection of the *tert*-butoxycarbonyl group with 1 equiv of *p*-toluenesulfonic acid in methanol at 35 °C for 11 h gave the Boc-free intermediate in 71% yield, which upon treatment with 1 equiv of benzyl isocyanate in pyridine at 0 °C, followed by room temperature conditions for 12 h, gave urea **3** in 99% yield. Cyclization of the urea to imidazolidone **4** was not trivial and depended on chemoselective displacement at the nitrogen atom. Selective cyclization to the imidazolidone was accomplished under carefully controlled conditions by combining 5 equiv of potassium hydride and 1.2 equiv of *p*-toluenesulfonyl chloride in the presence of 30 equiv of hexamethylphosphoramide in THF at 0 °C, followed by 10 min at room temperature and resulted in **4** in 86% yield. Deprotection of the acetonide with 1 equiv of *p*-toluenesulfonic acid in methanol–water at 40 °C for 15 h furnished a 23% yield of the cyclized compound (*E*)-**6**, along with thiol **5** in 65% yield. The use of oxygen-free methanol and water proved to be essential for reproducible results. Cyclization of the thiol **5** presented a regiochemical problem, *i.e.*, formation of the desired 5-membered product **6** or 6-membered isomer **7**. Under acidic conditions (*p*-toluenesulfonic acid or trifluoroacetic acid), the reaction gave the 5-membered product **6** selectively, but in only 37% or 14% yield, respectively. After a series of conditions were screened, cyclization under the influence of 2 equiv of cesium hydroxide in water–THF (10:1) at 40 °C for 10 h was found to afford the desired 5-membered cyclization product **6**[7] in 50% yield and the 6-membered isomer **7** in 46% yield, respectively. This kind of product distribution was also observed when the reaction was carried out using other bases, such as barium hydroxide and lithium hydroxide. The vinyl sulfide **6** was hydrogenated under 10 atm of hydrogen in the presence of palladium-black catalyst in 2-propanol–water (6:1) at 40 °C for 8 h to give *N*-benzylated deoxybiotin in quantitative yield in a stereospecific manner. Debenzylation was carried out with 47% aqueous HBr at reflux for 2 h to give (+)-deoxybiotin (**8**) in 73% yield,[8] which showed $[\alpha]^{23}_D$ +85.70 (lit.[2p] $[\alpha]^{25}_D$ +85.36). The conversion of (+)-

(7) The following spectral properties were obtained for **6**: $[\alpha]^{23}_D$ +142.0 (*c* 0.1, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (t, J = 6.93 Hz, 3H), 1.26–1.36 (m, 4H), 2.05–2.14 (m, 2H), 2.98–3.03 (m, 1H), 3.12–3.24 (m, 1H), 3.96 (d, J = 15.50 Hz, 1H), 4.31–4.38 (m, 1H), 4.42 (d, J = 7.59 Hz, 1H), 4.90 (d, J = 15.50 Hz, 1H), 5.47 (t, J = 7.26 Hz, 1H), 7.23–7.37 (m, 5H); IR (neat) 3000, 2900, 2400, 1710, 1680, 1480, 1450, 1280, 1260, 720 cm^{-1}.

(8) The spectral properties obtained for (+)-deoxybiotin (**8**) were identical with those reported.[2p]

deoxybiotin to (+)-biotin is a known microbiological oxidation process.[9]

Thus, we have developed a stereodivergent addition of acetylide to a chiral aldehyde derived from L-cysteine and have applied it to a short approach to (+)-deoxybiotin in a stereoselective manner. Several approaches to (+)-biotin hitherto reported employ inexpensive chiral substrates such as amino acids, sugars, and so on as starting materials. Among them, L-cysteine, in particular, possesses potential as a chiral building block, since it contains thiol and amino moieties of the correct stereochemistry. From this standpoint, L-cysteine has been one of the most useful starting materials for (+)-biotin.[2i,o,p,q,s] Many of the reported procedures, however, provide low yield and low stereo- and regioselectivity. The present method has several advantages. The starting aldehyde is readily available and of good stability at ambient temperature. The *all-cis* stereochemistry of the substituents was established by stereospecific chelation-controlled addition to the aldehyde and hydrogenation of double bonds. Other functional group manipulations proceeded well to give enantiomerically pure (+)-deoxybiotin in 15% overall yield in 12 steps starting from L-cysteine hydrochloride.

Supplementary Material Available: Experimental procedures and product characterization data (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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