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A highly stereocontrolled total synthesis of (+)-biotin from L-cysteine

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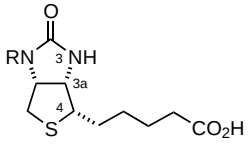
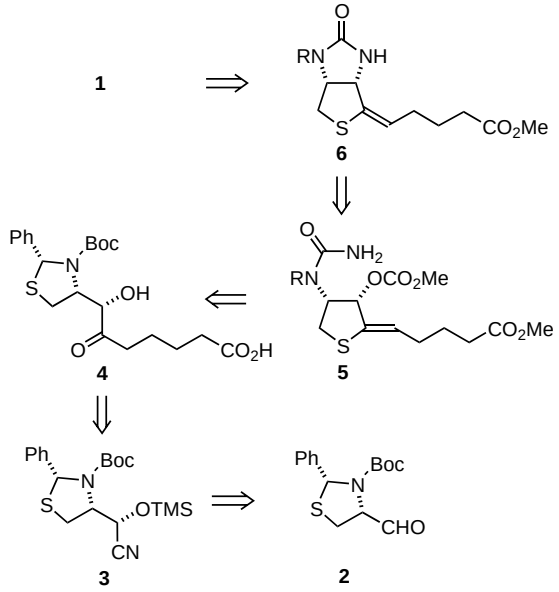
Abstract—(+)-Biotin was synthesized in 11 steps and in 25% overall yield from readily accessible L-cysteine through a Lewis base-catalyzed highly diastereoselective cyanosilylation of (2*R*,4*R*)-*N*-Boc-2-phenylthiazolidine-4-carbaldehyde **2** and a ring closure of a *cis*-allylic carbonate **5b** utilizing a palladium-catalyzed intramolecular allylic amination. © 2002 Published by Elsevier Science Ltd.

(+)-Biotin (**1**) has received considerable attention due to the significant biological properties for human nutrition and animal health.[1] The industrial production of **1** (ca. 40 t/year) has been relying on a total synthetic method due to the lack of an efficient fermentation method.[2] Since the first total synthesis of (+)-biotin was accomplished about 50 years ago,[3,4] a number of synthetic routes have been devised.[2] Among them, synthesis utilizing L-cysteine as a starting material[5] is one of the steadiest approaches to **1** because of its inherent structural features having required heteroatoms (nitrogen and sulfur atoms) and a stereogenic center corresponding to the (+)-biotin ring skeleton. However, there are few approaches based on this strategy that overcome such drawbacks as need for multi-steps, expensive or hazardous reagents and quite low temperature.[6] A more efficient synthetic method utilizing the L-cysteine skeleton is thus still in much demand. We report herein a practical synthesis of **1** from L-cysteine based on a novel strategy involving a highly diastereoselective cyanosilylation and a palladium-catalyzed intramolecular allylic amination.



(+)-Biotin (**1**)

In retrosynthetic analysis (Scheme 1), an intramolecular allylic amination of a carbonate **5** would set the stage for the final cyclization required in the preparation of the *cis*-fused bicyclic ring skeleton of **1**. Since the palladium-catalyzed allylation takes place with retention of the configuration,[7] a *cis* isomer **5** is expected to be required for the ring closure. Compound **5** may be derived from a ketoacid **4** through esterification, *O*-methoxycarbonylation, removal of the Boc and the



Scheme 1.

Keywords: vitamines; amino nitriles; Grignard reactions/reagents; allylation; palladium and compounds.

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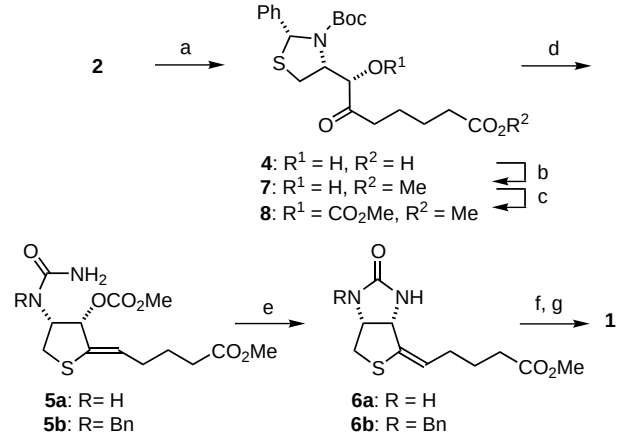
benzylidene groups, dehydrative cyclization and a ureido formation. The carboxybutyl chain of **1** was envisaged to arise from the reaction of an *O*-TMS-cyanohydrin **3** with a di-Grignard reagent prepared from 1,4-dibromobutane followed by reacting with carbon dioxide. An *anti*-selective cyanosilylation of an α-amino aldehyde **2** is required to ensure the *cis* configuration of **5**.

Compound **2** was prepared from L-cysteine in four steps and in 80% yield by modification of the reported procedure,[5c,8] employing sulfur trioxide pyridine as an alternative oxidant.[9]

The synthesis of the *anti*-*O*-TMS-cyanohydrin **3** was initially tested in the presence of a Lewis acid. However, all attempts using popular Lewis acids such as zinc iodide failed accompanied by a considerable decomposition of the reactant **2** and/or the product **3**. Mukaiyama and co-workers have reported a high-yielding Lewis base-catalyzed cyanosilylation of aldehydes.[10] We applied the procedure to the cyanosilylation of **2** (Table 1).[11] Upon treatment of **2** with trimethylsilyl cyanide (TMSCN) (1.1 equiv.) in the presence of Et_3N (10 mol%) at −10°C in CH_2Cl_2, the reaction rapidly took place to afford the desired *O*-TMS-cyanohydrin **3** in 96% yield albeit in a poor selectivity (*anti*/*syn*= 72:28) (Table 1, entry 1). Since a hypervalent silicate formed from TMSCN and Et_3N has been assumed to be an active species in the cyanosilylation and the stereochemical outcome might be accounted for by the Felkin–Ahn model, a more sterically demanding Lewis base should improve the diastereoselectivity. As expected, when *i*-Pr_2NEt in place of Et_3N was employed as the Lewis base, the diastereoselectivity was remarkably elevated (*anti*/*syn*=89:11, 97%) (Table 1, entry 2). Further screening of the bulky Lewis bases resulted in a finding that tri-*n*-butylphosphine can effect the cyanosilylation with an excellent diastereoselectivity and in high yield (*anti*/*syn*=92:8, 96%) (Table 1, entry 5). To the best of our knowledge, this represents the first example of a Lewis base-catalyzed highly diastereoselective cyanosilylation.[12]

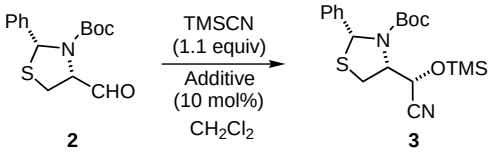
The carboxybutyl chain of **1** was installed by the reaction of the in situ generated *O*-TMS-cyanohydrin **3** with di-Grignard reagent[5a,13] derived from 1,4-dibromobutane and subsequent treatment with carbon dioxide (Scheme 2). While the yield was poor in THF (20%), the use of ether considerably improved the reaction to give a ketoacid **4**[14] in 61% yield based on **2**. Much safer solvent system of *n*-butyl ether and toluene (1:2) was found to give **4** in 79% yield.

The ketoacid **4** was esterified and purified by crystallization to give enantiomerically and diastereomerically pure ketoester **7**[15] in 73% yield. The hydroxyl group of **7** was then protected as a methyl carbonate, which, in a later step, functioned as an activating group for the ring closure. Treatment of **8** with acetyl chloride in the presence of methanol effected the successive transfor-



Scheme 2. (a) (i) TMSCN, *n*-Bu_3P, −10°C, CH_2Cl_2, (ii) $BrMg(CH_2)_4MgBr$, *n*-Bu_2O, toluene, −3 to −25°C, (iii) CO_2, (iv) aq. citric acid, 79%; (b) Me_2SO_4, K_2CO_3, 25°C, DMF, 73%; (c) $ClCO_2Me$, Et_3N, DMAP, 0°C, THF, quant.; (d) for **5a**: (i) AcCl, MeOH, toluene, 0°C, (ii) KOCN, H_2O, 25°C, 86%; for **5b**: (i) AcCl, MeOH, toluene 0°C, (ii) PhCHO, $NaBH_3CN$, THF, H_2O, 5°C, (iii) KOCN, H_2O, 25°C, 82%; (e) for **6a**: $Pd(OAc)_2$, $NaHCO_3$, $P(OEt)_3$, THF, H_2O, 38°C, 30%; for **6b**: $Pd(OAc)_2$, $NaHCO_3$, $P(OEt)_3$, DMF, *n*-Bu_4NCl, 100°C, 77%; (f) H_2, $Pd(OH)_2/C$, 25°C, AcOEt; (g) aq. HBr, reflux, 85% (two steps).

Table 1. A Lewis base-catalyzed cyanosilylation of **2**[a]



Entry	Additive	*T* (°C)	*t* (h)	*anti*/*syn*[b]	Yield (%)[b]
1	Et_3N	−10	0.5	72:28	96
2	*i*-Pr_2NEt	−10	0.5	89:11	97
3	*n*-Bu_3N	−10	0.5	77:23	92
4	*t*-Bu_3P	25	19	88:12	84
5	*n*-Bu_3P	−10	0.5	92:8	96

[a] The reactions were conducted on 1 mmol scale.
[b] Determined by HPLC analysis of the crude reaction mixture after desilylation with aqueous citric acid.

mations involving removal of the Boc and benzylidene groups, cyclization to the tetrahydrothiophene ring and dehydration. The resulting crude amine hydrochloride was treated with potassium cyanate to furnish a *cis*-allylic carbonate **5a** in 86% yield based on **8**.

With the *cis*-allylic carbonate **5a** in hand, we attempted the palladium-catalyzed ring closure of **5a**. Treatment of **5a** with $Pd(OAc)_2$ in the presence of $P(OEt)_3$ and $NaHCO_3$ in aqueous THF[16] afforded the desired cyclized product **6a** albeit in a poor yield (30%). As De Clercq and co-workers have pointed out an importance of an *N*-benzyl group for the thermal cyclization of an ene carbamoyl azide at C-3 and C-3a position of the (+)-biotin ring skeleton,[5c] an *N*-benzyl derivative **5b** was tested in place of **5a**. The compound **5b**[17] was readily prepared from **8** in 82% yield by a slight modification of the reaction sequence involving a reductive alkylation with benzaldehyde. The compound **5b** was subjected to the same reaction conditions as those for the cyclization of **5a**, expectedly affording **6b** in good yield (60%). The structure of **6b** was assigned by comparison of the IR, ^1H NMR and MS spectra with those described in the literature.[5c] The reaction under solid–liquid phase transfer conditions using a catalytic amount of tetrabutylammonium chloride in DMF[18] was found to be extremely effective to provide **6b** in a much improved yield (77%). Following the reported procedure,[5c] the compound **6b** was converted to (+)-biotin (**1**) in 85% yield through hydrogenation and subsequent deprotection with aqueous HBr.[19]

In conclusion, (+)-biotin was synthesized in 11 steps and in 25% overall yield from readily accessible L-cysteine. The high overall yield, short steps, simple operation and use of readily accessible reagents would permit not only the practical large-scale preparation of (+)-biotin but also the synthesis of (+)-biotin derivatives having promising biological properties.

Acknowledgements

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References

1. (a) Mistry, P. S.; Dakshinamurti, K. *Vitam. Horm.* **1964**, *22*, 1; (b) Coggeshall, C. J.; Heggers, P. J.; Robson, C. M.; Baker, H. *Ann. N.Y. Acad. Sci.* **1985**, *447*, 389; (c) Maebashi, M.; Makino, Y.; Furukawa, Y.; Ohinata, K.; Kimura, S.; Sato, T. *J. Clin. Biochem. Nutr.* **1993**, *14*, 211.
2. De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755.
3. (a) Goldberg, M. W.; Sternbach, L. H. US Patent 2,489,232, Nov. 22, 1949; *Chem. Abstr.* **1951**, *45*, 184b; (b) Goldberg, M. W.; Sternbach, L. H. US Patent 2,489,235, Nov. 22, 1949; *Chem. Abstr.* **1951**, *45*, 186a; (c) Gerecke, M.; Zimmermann, J.-P.; Ashwanden, W. *Helv. Chim. Acta* **1970**, *53*, 991.
4. For recent improvements in the Goldberg–Sternbach synthesis,[2] see: (a) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2000**, *41*, 5099; (b) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2001**, *42*, 429; (c) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2002**, *43*, 1039.
5. (a) Poetsch, E.; Casutt, M. *Chimia* **1987**, *41*, 148; (b) Fujisawa, T.; Nagai, M.; Koike, Y.; Shimizu, M. *J. Org. Chem.* **1994**, *59*, 5865; (c) Deroose, F. D.; De Clercq, P. J. *J. Org. Chem.* **1995**, *60*, 321; (d) Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H.; Poetsch, E.; Casutt, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2391; (e) Chaven, S. P.; Tejwani, B.; Ravindranathan, T. *J. Org. Chem.* **2001**, *66*, 6197.
6. The number of steps, expensive or hazardous reagents and quite low temperature required for the known synthesis of (+)-biotin starting from L-cysteine: Poetsch approach:[5a] 9 steps, BnNCO; Fujisawa approach:[5b] 12 steps, CH_2N_2, DIBALH, 1-pentyne, BnNCO, KH, CsOH, −78°C; De Clercq approach:[5c] 12 steps, CH_2N_2, $NaBH_3CN$, NaN_3, −60°C; Speckamp approach:[5d] 13 steps, BnNCO, DIBALH, $MeO_2C(CH_2)_3C(O)CH_2Cl$, $(TMS)CH_2CO_2Et$, TBAF, TMSOTf, DBU, −78°C; Ravindranathan approach:[5e] 12 steps, DIBALH, TBSCl, DBU, TBSOTf, $Ph_3P{=}CHCH{=}CHCO_2Me$, −78°C.
7. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173.
8. Gonzalez, A.; Lavilla, R.; Piniella, J. F.; Alvarez-Larena, A. *Tetrahedron* **1995**, *51*, 3015.
9. (a) Doering, W. V. E.; Parikh, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 5505; (b) Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 1921.
10. Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 537.
11. The *O*-TMS cyanohydrin **3** was desilylated quantitatively by the treatment with aqueous citric acid and was allowed to measure the yield and the diastereomeric ratio by HPLC (Nucleosil 5C18, $CH_3CN/H_2O = 50{:}50$, 40°C, 0.8 mL/min, 254 nm, *anti*: 8.1 min, *syn*: 9.4 min). The structure of the cyanohydrin was confirmed by X-ray crystallographic analysis.
12. A highly diastereoselective cyanosilylation of an (*S*)-*N*-protected phenylalaninal using chiral Lewis-acid-base catalyst, see: Manickam, G.; Nogami, H.; Kanai, M.; Groger, H.; Shibasaki, M. *Synlett* **2001**, 617.
13. Silverman, G. S.; Rakita, P. E. *Handbook of Grignard Reagent*; Marcel Dekker: New York, Basel, Hong Kong, 1996; pp. 497–526.
14. **Compound 4**: mp 101–103°C; IR (Nujol) $\nu = 3470$, 2976, 1702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (2H, d, $J = 6.6$ Hz), 7.30–7.40 (3H, m), 6.07 (1H, s), 4.73 (1H, d), 4.42–4.51 (1H, m), 3.23 (1H, dd, $J = 12$, 5.1 Hz), 3.02 (1H, dd, $J = 12$, 6.6 Hz), 2.57 (2H, br), 2.34 (2H, brt, $J = 7.0$ Hz), 1.51–1.80 (4H, m), 1.33 (9H, s); SIMS m/z 424 (M^++1). The structure of **4** was confirmed by X-ray crystallographic analysis.
15. The optical purity (>99% ee) of **7** was determined by HPLC (CHIRALPAK AD, EtOH/*n*-hexane = 5:95, 40°C, 0.5 mL/min, 254 nm, **7**: 35.9 min, the antipode of **7**: 25.2 min).
16. Seki, M.; Kondo, K.; Kuroda, T.; Yamanaka, T.; Iwasaki, T. *Synlett* **1995**, 609.
17. **Compound 5b**: mp 105–108°C; IR (KBr) 3432, 1754, 1728, 1656, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.44–7.21 (m, 5H), 5.90 (t, $J = 7.2$ Hz, 1H), 5.63 (d, $J = 3.9$ Hz, 1H), 5.16–

5.10 (m, 1H), 4.71 (d, $J=18$ Hz, 1H), 4.63 (brs, 1H), 4.61 (d, $J=18$ Hz, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.33 (dd, $J=10$, 11 Hz, 1H), 3.01 (dd, $J=6.9$, 10 Hz, 1H), 2.30 (t, $J=7.5$ Hz, 2H), 2.04–1.99 (m, 2H), 1.78–1.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 174.2 (s), 159.6 (s), 155.1 (s), 137.5 (s), 135.6 (s), 129.5 (d), 128.0 (d), 126.0 (d), 125.9 (d), 81.2 (d), 58.0 (d), 55.1 (q), 51.9 (q), 48.9 (t), 33.8 (t), 30.5 (t), 30.0 (t), 24.1 (t); SIMS m/z 423 (M^++1). The structure of **5b** was confirmed by X-ray crystallographic analysis.

18. Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.
19. Starting from 121 g of L-cysteine, every step was conducted at several gram quantities and 3.1 g of the final product (**1**) was obtained.