Synthetic Studies on d-Biotin, Part 9.1) An Improved Asymmetric Synthetic Route to d-Biotin via Hoffmann–Roche Lactone–Thiolactone Approach

Fen-Er Chen,*a Hui-Qing Jia,*a Xu-Xiang Chen,b Hui-Fang Dai,a Bin Xie,a Yun-Yan Kuang,a and Jian-Feng Zhaoa

a Department of Chemistry, Fudan University; Shanghai, 200433, People’s Republic of China; and b School of Pharmaceutical Engineering, Shenyang Pharmaceutical University; 110016, People’s Republic of China.

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An efficient and highly stereoselective total synthesis of d-biotin has been achieved starting from cis-1,3-dibenzyl-2-imidazolidone-4,5-dicarboxylic acid (2) with an overall yield of 33%. Polymer-supported oxazaborolidine-catalyzed asymmetric reduction of meso-cyclic imide 4 constitutes the key synthetic step in introducing stereogenic centers into the d-biotin molecule.

Key words: d-biotin; vitamin H; polymer-supported oxazaborolidine; asymmetric reduction; Wittig reaction; desymmetrization

The development of efficient processes for the total synthesis of d-biotin (1), continues to be an attractive goal in synthetic organic chemistry, because of its unique structural features, significant biological properties and commercial importance.2—8 Despite great advances9—21 in total synthesis over the past 55 years, large-scale preparation of this vitamin has been difficult mainly because of lack of an efficient and convenient procedure for the desymmetrization of dicarboxylic acid 2 to form (3aS,6aR)-lactone (6). Our recent strategy, using a polymer-supported oxazaborolidine catalyzed enantioselective reduction of meso-cyclic imide approach, allowed us to prepare (3aS,6R,6aR)-hydroxylactam 5 from 2 in high yield and excellent enantiomeric excess.23 However, this procedure is impractical for large-scale synthesis due to the use of expensive and toxic BF3·Me2S as the reducing agent which requires a lot of precautions, and lack of a stable polymer-supported chiral ligand.24 These obstacles prompted us, as part of our strategy to develop a new oxazaborolidine-catalyzed reducing system that can easily be employed and that gives high enantiomeric excess for a large-scale conversion of 4 into 5 as a precursor for the formation of 6, to complete the asymmetric synthesis of 1.

In the present paper, we describe an efficient and practical asymmetric total synthesis of 1 starting from commercially available dicarboxylic acid 2 through an improved enantioselective reduction of meso-cyclic imide 4 with the use of recoverable chiral polymer-supported oxazaborolidine as a catalyst.

Results and Discussion

The asymmetric synthesis of 1 is presented in Chart 1. The known meso-cyclic-1,2-dicarboxylic anhydride 3 was prepared in almost quantitative yield by heating 2 in xylene with a catalytic amount of Ac2O with azeotropic removal of H2O for 13 h. Treatment of 3 with benzylamine in toluene under reflux for 6 h afforded the meso-cyclic imide 4 in 90% yield.

Next, we embarked upon the development of an efficient and convenient strategy for the large-scale asymmetric borane reduction of 4 into (3aS,6R,6aR)-hydroxylactam 5 using a chiral polymer-supported oxazaborolidine derived from polymer-supported ligand 1025 (containing 0.39 mmol of di-aryprolinol function units/g of polymer by elemental analysis) with in situ generated borane from cheap and convenient hydriodic reagents and boron halide ethers. Thus, the meso-cyclic imide 4 was treated with 80% NaH and BF3·Et2O in the presence of 10 under reflux in anhydrous THF to afford 5 in 82% yield. The enantiomeric excess of 5 was measured to be >98% by HPLC analysis using a Chiralcel OD column (eluents: hexane/2-propanol, 6:4, 0.7 ml/min).

As pointed out in a number of studies,26—32 one of the major advantages of a polymer reagent is the ease with which it can be worked up and recycled. The polymer-supported ligand 10 could be conveniently recovered from the reaction mixture by simple filtration followed by washing with hot H2O, and EtOH after the reduction was completed. To demonstrate that the ligand 10 can be recycled a number of times, the enantioselective reduction of 4 was repeated fourteen times under the same reaction conditions. As shown in Table 1, the reached enantioselectivities remained around 98% ee, clearly illustrating the reusability of the polymer-supported ligand 10.

The reduction of 5 by NaBH4 in EtOH at 50 °C for 4 h and subsequent hydrolysis with 2N aq. H2SO4 at 80 °C for 1 h afforded the (3aS,6aR)-lactone 6 in 90% yield. Comparison of its specific optical rotation [α]D20 +57.3° (c=2.0, CHCl3) with the literature value [α]D20 +59.8° (c=2, CHCl3)23) for 6 implied an enantiomeric purity of 95.8%, which was then upgraded to 98.6% ee by recrystallization from EtOH. Treatment of 6 with potassium butylthioxanthogenate (n-BuSC(S)SK) in DMA at 125 °C for 6 h effected the thiolactonization to form the (3aS,6aR)-thiolactone 7 in 82% yield.

From a practical point of view, a one-step introduction of the carboxybutyl chain to 7 based on a Wittig reaction to form (Z)-configured unsaturated acid 8 seemed to be very attractive. Following the published conditions,34) Wittig olefination of 7 with the ylide, derived from 4-carboxybutyltriphenylphosphonium bromide (BrPhP(CH2)3CH2CH2CO2H)
provided the (Z)-configured unsaturated acid 8 with low yield (max. 40%). Attempts to treat 4-carboxybutyltriphenyl phosphonium bromide with freshly sublimed t-BuOK with 7 at reflux in anhydrous toluene failed completely. However, heating a toluene solution of these compounds at 135 °C in a sealed vessel for 7 h gave the desired 8 exclusively as a single (Z)-isomer in 81% yield. The (Z)-configuration of 8 was unequivocally ascertained by NOE experiments (Fig. 1). A 10.1% enhancement of the signal of H-C3a at δ=4.62 was observed on irradiation of the signal at δ=5.53, which belongs to the olefinic H-atom of the side chain.

Stereospecific hydrogenation of 8 was carried out under 4 atm of H2 in the presence of Pd(OH)2 over charcoal to give the N,N-dibenzyldibiotin 9 in 95% yield. Removal of the N-benzyl group was conducted with CH3SO3H–AcOH–H2O (1.5:1.5:1) under reflux for 10 h to afford d-biotin (1) in 80% yield.

Table 1. Recycling of the Chiral Polymer-Supported Ligand 10 in the Asymmetric Reduction of 4 in THF Under Reflux

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<th>ee (%)b</th>
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<td>14</td>
<td>80.5</td>
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Fig. 1. 1H-NMR Studies of NOE for Compound 8

Conclusion

We have developed a very efficient route for the highly stereoselective synthesis of d-biotin in a 33% overall yield starting from readily accessible cis-1,3-dibenzy-2-imidazolidine-4,5-dicarboxylic acid (2), via Hoffmann–Roche’s lactone–thiolactone approach. The short steps, high yield, simple work-up, and ready availability of the reagents should provide a practical means with which to obtain d-biotin.

Experimental

General Procedure

Melting points (mp) were measured using a WRS-1B digital melting point apparatus and are uncorrected. 1H-NMR was recorded on Bruker DMX500 (500 MHz) spectrometer. Chemical shifts (δ) are expressed in ppm with TMS as an internal standard. Optical rotations were measured on a WZZ-2S digital automatic polarimeter. IR spectra were measured using a Nicolet FT-IR 360 Spectrometer. Mass spectra (MS) were recorded on HP-5988 A mass spectrometer. THF was distilled from sodium benzo phenone ketyl and DMA was distilled from CaH2 before use. Routine monitoring of reaction was carried out using Merck 60 GF254 silica gel, glass-supported plates (TLC). Polymer-supported chiral ligand 10 was prepared according to a literature method.25)
toluene (280 ml) was heated under reflux for 5 h. The reaction mixture was cooled to r.t. and the precipitate was filtered, and dried to afford 4 as a white solid (68 g, 90%), mp 115—117°C (lit; mp 114—116°C). IR (KBr) νmax 3435, 1712, 1688, 1647 cm⁻¹; H-NMR (CDCl₃): δ 4.24, 2H, 4.27, 2.48, 4.71, 4.19 (4H, d, J = 15.8, 15.42 Hz), 4.54 (2H, s), 7.30—7.28 (15H, m); EI-MS m/z: 425 (28, M⁺), 334 (6), 237 (6), 132 (11), 91 (100).

(3aS,6aR)-1,3-Dibenzylyl-tetrahydro-4H-furo[3,4-d]imidazole-2(1H)-one (5) BiF₄·EtOAc (35.7 ml, 0.28 mol) was added dropwise over 2.5 h. Stirring was continued under reflux until the reaction mixture was heated to 80 °C and stirring for a further 1 h. After cooling to r.t., the mixture was filtered, and the polymer-supported ligand was washed with EtOAc (3×50 ml) and H₂O (3×40 ml). The organic layers were separated, and the aqueous layers were extracted with EtOAc (3×50 ml). The combined organic layers were washed successively with sat. aq. NaHCO₃ (3×30 ml), H₂O (3×40 ml), and sat. aq. NaCl (3×30 ml), and dried over Na₂SO₄. The solvent was evaporated under reduced pressure. The residue was purified by CC (silica gel, hexane/EtOAc 2: 1) to afford 5 as a white solid (21 g, 82%), mp 127—130°C, [α]D²⁵⁺ 69.1° (c = 0.1, CHCl₃) [lit.²] mp 128—131°C, [α]D²⁵⁺ 69.2° (c = 0.1, CHCl₃). IR (KBr) νmax 3315, 2930, 1703, 1451, 1229, 912, 858, 734, 676 cm⁻¹. H-NMR (DMSO-d₆) δ: 7.36—7.38 (15H, m), 4.11, 4.40, 5.03, 5.10 (4H, d, J = 14.9 Hz), 4.20, 4.93 (2H, 2d, J = 13.7 Hz), 2.58 (1H, dd, J = 1.7, 5.4 Hz), 7.12—7.41 (15H, m), EI-MS m/z: 427 (13, M⁺), 264 (21), 106 (6), 91 (100).

(3aS,6aR)-1,3-Dibenzylyl-tetrahydro-4H-furo[3,4-d]imidazole-2(1H)-dione (6) Compound (128.25 g, 0.30 mol) in anhydrous EtOH (460 ml) was added dropwise at 0—5°C to a stirred mixture of NaN₃ (22.7 g, 0.60 mol) and anhydrous EtOH (100 ml). After stirring at 50°C for 4 h, 2N H₂SO₄ (245 ml) was added dropwise to the reaction mixture. The reaction mixture was allowed to warm to 80°C and stirring for a further 1 h. After cooling to r.t., the mixture was extracted with EtOAc (4×80ml). The combined organic layers were washed successively with sat. aq. NaCl (3×35 ml) and H₂O (3×40 ml), and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to give the crude product, which was recrystallized from EtOH to afford 6 as a white solid (86.9 g, 90%), mp 118—120°C, [α]D²⁵⁺ 61.5° (c = 2, CHCl₃) [lit.²] mp 120—121°C, [α]D²⁵⁺ 61.6° (c = 2, CHCl₃). IR (KBr) νmax 1755—1792 cm⁻¹. H-NMR (CDCl₃) δ: 3.25 (1H, dd, J = 2.3, 12.8 Hz), 3.35 (1H, dd, J = 5.5, 12.8 Hz), 3.82 (1H, d, J = 8.0 Hz), 4.14 (1H, dd, J = 2.2, 12.8 Hz), 3.35 (1H, dd, J = 5.5, 12.8 Hz), 3.82 (1H, d, J = 8.0 Hz), 4.14 (1H, dd, J = 2.2, 5.4, 8.0 Hz), 4.43, 4.32, 4.46, 4.95 (4H, 4d, J = 7.2—7.37 (10H, m), EI-MS m/z: 322 (25, M⁺), 265 (58), 245 (78), 187 (62), 91 (100).

(3aS,6aR)-1,3-Dibenzylyl-tetrahydro-4H-thieno[3,4-d]imidazole-2(1H)-dione (7) Potassium butylxanthogenate (30.7 g, 0.15 mol) was added to a stirred solution of 6 (48.3 g, 0.15 mol) in DMA (125 ml) and the mixture was heated at 75°C for 3 h. After cooling to r.t., the mixture was filtered and evaporated under reduced pressure. The crude product was recrystallized from EtOAc to afford 7 as colourless crystals (41.6 g, 82%), mp 125—126°C, [α]D²⁵⁺ 90.8° (c = 1, CHCl₃) [lit.²] mp 125—128°C, [α]D²⁵⁺ 90.5° (c = 1, CHCl₃). IR (KBr) νmax 1705, 1695, 1424, 1225 cm⁻¹; H-NMR (CDCl₃) δ: 3.28 (1H, dd, J = 2.2, 12.8 Hz), 3.35 (1H, dd, J = 5.5, 12.8 Hz), 3.82 (1H, d, J = 8.0 Hz), 4.14 (1H, dd, J = 2.2, 5.4, 8.0 Hz), 4.35, 4.38, 4.67, 5.00 (4H, 4d, J = 15.2 Hz), 7.27—7.35 (10H, m); EI-MS m/z: 338 (5, M⁺), 310 (25), 277 (8), 264 (66), 91 (100).

(3aS,6aR,6bR)-1,3-Dibenzylyl-tetrahydro-1H-thieno[3,4-d]imidazole-2(1H)-one (8) t-BuOK (10.8 g, 90 mmol) was added to a suspension of 4-carboxybutyltriphenylphosphonium bromide (19.95 g, 45 mmol) in anhydrous toluene (100 ml) at 10°C and the reaction mixture was stirred for 4 h. After cooling to r.t., H₂O (150 ml) was added. The organic layer was separated and the aqueous layer was extracted with toluene (3×50 ml). The combined organic layers were washed successively with sat. aq. NaCl (3×40 ml) and H₂O (3×40 ml), dried over Na₂SO₄, and concentrated under reduced pressure to yield 8 as a white solid (7.13 g, 58%), mp 84—85°C, [α]D²⁵⁺ 236° (c = 1, 0.1 N NaOH) [lit.²] mp 84—85°C, [α]D²⁵⁺ 236.2° (c = 1, 0.1 N NaOH). IR (KBr) νmax 3432, 1725, 1662, 1485, 1452 cm⁻¹; H-NMR (CDCl₃) δ: 1.39—1.93 (4H, m, 2×CH₂), 2.00 (2H, t, J = 7.4 Hz), 2.81 (1H, dd, J = 5.5, 12.1 Hz), 2.95 (1H, d, J = 12.3 Hz), 4.16 (1H, m), 4.62 (1H, d, J = 7.9 Hz), 4.05, 4.34, 4.52, 4.97 (4H, 4d, J = 15.5, 16.8 Hz), 5.53 (1H, t, J = 7.8 Hz), 7.24—7.40 (10H, m); EI-MS m/z: 422 (6, M⁺), 311 (6), 289 (20), 238 (12), 106 (48), 91 (100).

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24) We noticed that the polymer-supported chiral sulfonamide was partially decomposed in the sixth cycle in the enantioselective reduction of 4 into 5. This made the work-up procedure very difficult to carry out and recycling of the polymer inefficient.


