A Formal Catalytic Asymmetric Synthesis of (+)-Biotin with Modified Cinchona Alkaloids

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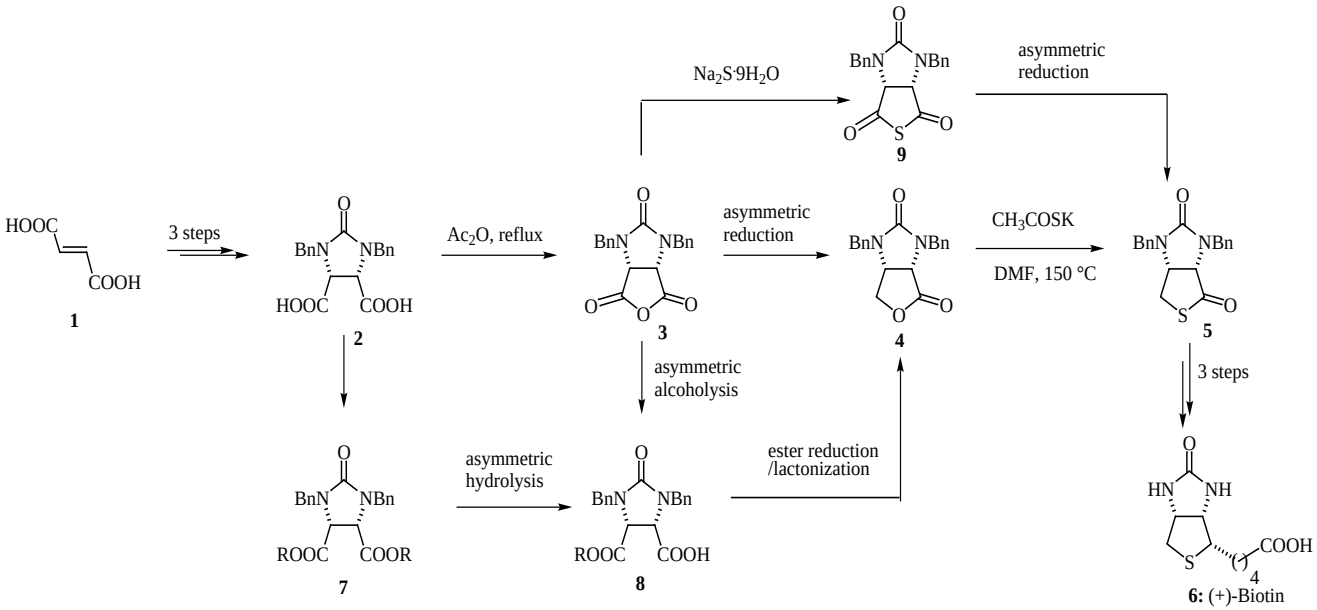
Abstract: A formal catalytic asymmetric synthesis of (+)-biotin was realized. The key steps involve a catalytic, highly enantioselective and quantitative desymmetrization of a meso cyclic anhydride followed by a one-pot chemoselective reduction to form the optically active lactone intermediate in the Goldberg–Sternbach (+)-biotin synthesis.

Key words: biotin, vitamin, cinchona alkaloids, asymmetric catalysis, enantioselective desymmetrization

The unusual structure, biological significance, and commercial importance of biotin (**6**) have made it a fascinating target for total synthesis both in academia and industry for more than fifty years.[1] The total synthesis of biotin has become a test case for evaluation of new strategies that are conceived upon emergence of new synthetic methods. Among numerous approaches reported to date, the first synthesis of biotin (**6**) described by Goldberg and Sternbach, after subsequent modifications, is still one of the best syntheses of biotin.[2–4] The unsurpassed efficiency and practicality of the Goldberg–Sternbach strategy (Scheme 1) results from its ability to take advantage of a readily available symmetric bifunctional starting material, fumaric acid (**1**), for the efficient construction of the bicyclic thiolactone intermediate **5**, and subsequently, to capitalize on the sterically well-differentiated two faces of the *cis*-fused bicyclic ring in **5** to realize the controlled creation of the third stereogenic center during the introduction of the side chain to give biotin (**6**).

The potential of the Goldberg–Sternbach approach has, however, not yet been fully realized due to the lack of an efficient method for the desymmetrization of meso intermediates such as acid **2**, anhydride **3**, or diester **7** to form optically active lactone **4** or thiolactone **5**. Highly efficient routes for the preparation of biotin (**6**) from either optically active **4** or **5** have been established.[5–10] Matsuki and Chen recently reported enantioselective reduction of anhydride **3** and thioanhydride **9** to the corresponding lactone **4** (90% ee)[11] and thiolactone **5** (98.5% ee),[12] respectively. In spite of their brevity and high enantiose-



Scheme 1

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lectivity, both approaches required the use of a large excess of Noyori's BINAL-H (Figure 1) (4.0 equiv for the conversion of **3** to **4**, and 3.0 equiv for the conversion of **9** to **5**) as the reducing agent.

The bulky size of and the presence of multiple polar and Lewis basic functionalities in meso intermediates **3** and **7** make the development of catalytic methods for their desymmetrization using either enzymes or chiral transition metal-complexes extremely difficult. For example, although Pig liver esterase (PLE)-catalyzed hydrolysis is known to be a general and efficient enzymatic method for the transformation of meso diesters to optically active hemiesters, it afforded only modest enantioselectivity (75% ee) in the hydrolysis of meso diester **7** to form hemiester **8**.[13] Sih devised an enzymatic resolution route to convert **2** to lactone **4** with high enantioselectivity (93% ee), but it involved an eight-step sequence.[14] Attempts to effect enantioselective ring-opening of anhydride **3** with a chiral Lewis acid promoter have also met with limited success. While Ti-TADDOLates-promoted (Figure 1) alcoholysis was highly enantioselective for a broad range of meso cyclic anhydrides, its application to the desymmetrization of **3** resulted in a low enantioselectivity (26% ee).[15] Ideally, desymmetrization of meso intermediates along the Goldberg–Sternbach route should be accomplished in high enantioselectivity and yield with a catalytic amount of a readily available chiral reagent. Here we present our efforts towards accomplishing such a goal.

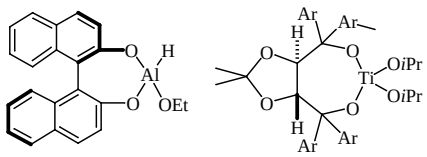


Figure 1 Structures of (*R*)-BINAL-H and Ti-TADDOLate

We recently discovered a general and highly enantioselective catalytic desymmetrization of meso and prochiral cyclic anhydrides catalyzed by commercially available mono and bis-cinchona alkaloid derivatives (Figure 2).[16] Particularly noteworthy is the effectiveness of this chiral Lewis base-catalyzed reaction with bulky as well as fuctionalized cyclic anhydrides, which suggests that it may be able to desymmetrize anhydride **3**. Following our previously reported conditions, we first examined the desymmetrization of anhydride **3** in diethyl ether with $(DHQD)_2AQN$ as the catalyst and methanol as the nucleophile. While $(DHQD)_2AQN$ was found to be a highly efficient and general catalyst for the desymmetrization of a wide variety of meso cyclic anhydrides such as *cis*-2,3-dimethylsuccinic anhydride (**10**), it catalyzed the desymmetrization of **3** to give hemiester **11a** in only 59% ee at room temperature (entry 1, Table).

After screening other modified mono and bis-cinchona alkaloids, we found that the catalyst structure-enantioselectivity profile with anhydride **3** as the substrate is substantially different from that with *cis*-2,3-dimethylsuccinic anhydride (**10**) as shown in the Table. However, we were pleased to find that DHQD-PHN, although slightly inferior to $(DHQD)_2AQN$ with simple cyclic anhydrides, is much more effective than $(DHQD)_2AQN$ for the desymmetrization of anhydride **3** to afford **11a** in 89% ee at room temperature (entry 7, Table). The ee was improved to 93% when the reaction was carried out at –40 °C. Moreover, the reaction proceeded cleanly allowing both the isolation of hemiester **11a** and the recovery of the catalyst in quantitative yield without chromatographic purification. Further reducing the reaction temperature to –60 °C resulted in a slight decrease of enantioselectivity (entry 11, Table). The absolute configuration of hemiester **11a** was determined to be 4*R* and 5*S*, which is consistent with our previously proposed stereochemical projection for modified cinchona alkaloid-catalyzed desymmetrization of cyclic anhydride.[16] The employment of DHQ-PHN led to the generation of **11b**, the antipode of **11a**, but surpris-

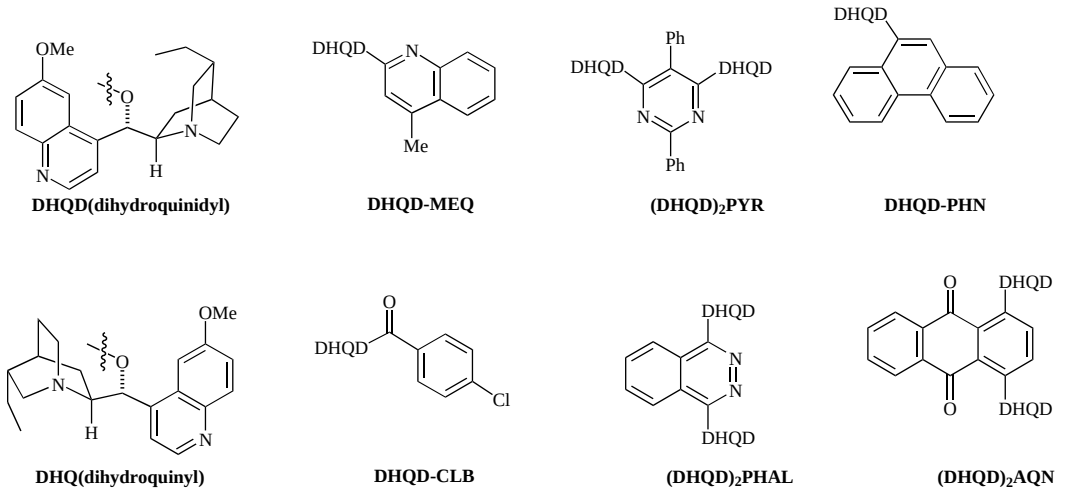
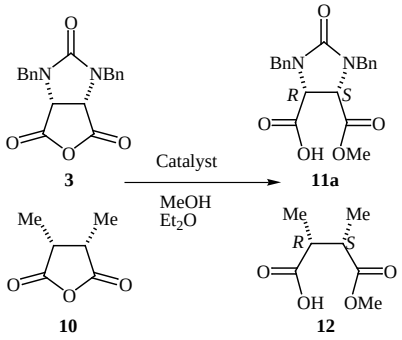


Figure 2 Catalysts used for asymmetric ring-opening of anhydrides **3** and **10**

Table Asymmetric Ring-Opening of Anhydrides **3** and **10** with Natural and Modified Cinchona Alkaloids



Entry	Catalyst (mol%)	T (°C)	ee (%) of **11a**	ee (%) of **12**[a]
1	$(DHQD)_2AQN$ (5)	25	59	93
2	$(DHQD)_2PHAL$ (5)	25	~0	62
3	$(DHQD)_2PYR$ (5)	25	46	72
4	quinidine (10)	25	53	70
5	DHQD-MEQ (10)	25	41	61
6	DHQD-CLB (10)	25	73	69
7	DHQD-PHN (10)	25	89	92
8	DHQD-PHN (20)	0	90	-
9	DHQD-PHN (20)	–20	91	-
10	DHQD-PHN (20)	–40	93	-
11	DHQD-PHN (20)	–60	88	-
12	DHQ-PHN (20)	–40	70[b]	-

[a] For the ee determination of **12**, see supporting information given in Ref.[16]

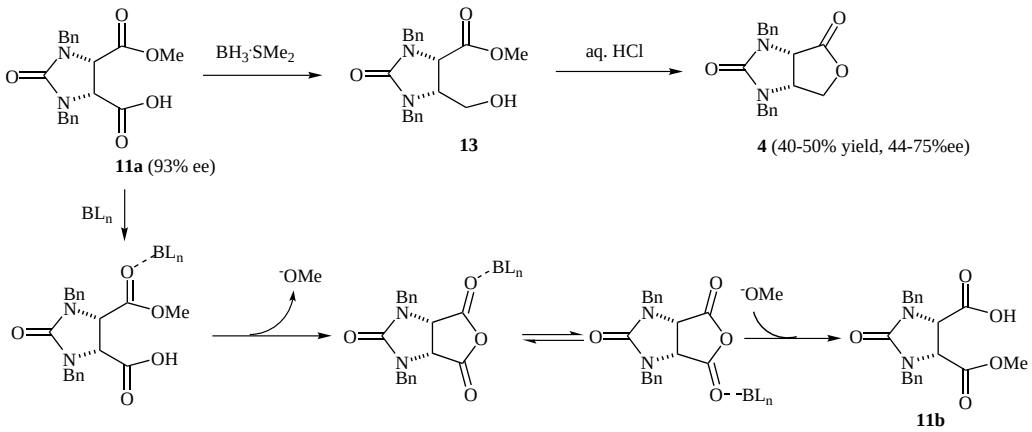
[b] Compound **11b**, the antipode of **11a**, is formed as the major enantiomer.

ingly, in significantly lower ee than that obtained with DHQD-PHN (entry 12 vs.10, Table).

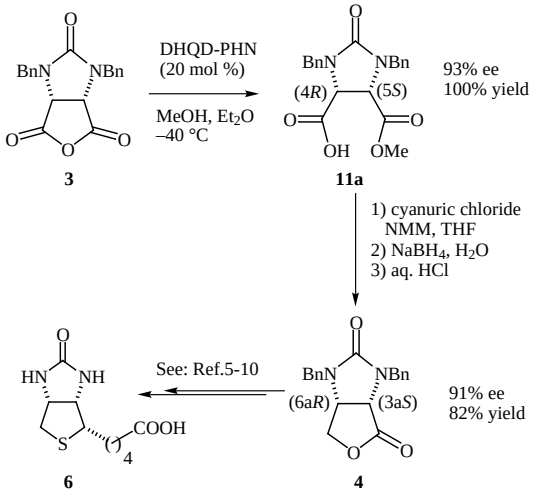
Having succeeded in establishing the first highly efficient catalytic desymmetrization of anhydride **3**, we next focused our attention on the development of an efficient conversion of hemiester **11a** to lactone **4**. A chemoselective reduction of the carboxylic acid group in hemiester **11a** would provide **13** as the precursor for the formation of lactone **4** to complete a formal catalytic asymmetric synthesis of (+)-biotin. Treatment of hemiester **11a** with BH_3SMe_2[17,18] followed by ring cyclization of **13** in the presence of aqueous HCl resulted in the formation of lactone **4** in 40–50% isolated yield (Scheme 2). We were especially disappointed to observe that the ee of lactone **4** was found to fluctuate in a range (44–75%) that was significantly lower than the ee (93%) of the starting hemiester **11a**.

This disparity between the enantiomeric excesses of hemiester **11a** and lactone **4** could be caused by a partial racemization of **11a** via a scrambling of the ester group mediated by a Lewis acidic boron species as shown in Scheme 2 (**11a** to **11b**). When the borane reduction was stopped at partial conversion, the ee of the recovered hemiester **11a** was found to decrease from 93% to 79%, thus confirming that optically active hemiester **11a** racemized during the borane reduction. Given that highly enantiomerically enriched **11a** was obtained from an amine-catalyzed reaction, we examined procedures involving reduction of carboxylic acids to alcohols under mildly basic conditions. A slight modification of a one-pot procedure reported by Falorni, utilizing cyanuric chloride, *N*-methylmorpholine and $NaBH_4$ as stoichiometric reagents,[19] generated lactone **4** from hemiester **11a** in 91% ee and 82% isolated yield, thereby completing a formal catalytic asymmetric synthesis of (+)-biotin (Scheme 3).[5–10]

In summary, we have developed a two-step sequence to accomplish a highly enantioselective conversion of meso



Scheme 2



Scheme 3

anhydride **3** to chiral lactone **4** in 82% overall yield. The absolute stereochemistry is controlled via a catalytic, highly enantioselective and quantitative desymmetrization of anhydride **3** using a catalytic amount of DHQD-PHN, a commercially available and fully recyclable modified cinchona alkaloid. With the new development described here, the elegant and practical approach outlined by Goldberg and Sternbach more than fifty years ago is realized in a catalytic asymmetric synthesis of biotin.

^{1}H and ^{13}C spectra were recorded on a Varian instrument (400 MHz and 100 MHz, respectively) and internally referenced to tetramethylsilane signal. Specific rotations were measured on a Jasco Digital Polarimeter. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on EM science silica gel 60 (SiO_2, 230–400 mesh). HPLC analyses were perfomed on a Hewlett-Packard 1100 series instrument equipped with a quaternary pump using OD (Daicel Chiralpak, 250 × 4.6 mm). UV variable wavelength detector was used to monitor at 254 nm or 280 nm. All reactions were conducted in oven or flame dried glassware under inert atmosphere of dry N_2. Et_2O and THF were distilled from sodium ketyl of benzophenone immediately before use. Toluene and MeOH were distilled from CaH_2 and stored over molecular sieves type 4 Å. *cis*-1,3-Dibenzyltetrahydro-2*H*-furo[3,4-*d*]imidazole-2,4,6-trione (**3**) was prepared according to the literature procedure.[10,20]

(4*R*,5*S*)-1,3-Dibenzyl-5-(methoxycarbonyl)-2-oxoimidazolidine-4-carboxylic Acid (11a)[21,22]

Anhyd MeOH (480 mg, 0.60 mL, 15 mmol) was added dropwise to a mixture of anhydride **3** (504 mg, 1.5 mmol) and DHQD-PHN (151 mg, 0.30 mmol, 20 mol%) in Et_2O (75 mL) at –40 °C. The resulting mixture was stirred for 28 h at –40 °C. The reaction mixture became clear and the anhydride was completely consumed as shown by TLC analysis. Aq HCl (1.0 N, 30 mL) was added to the mixture. The organic phase was collected and the aqueous layer was extracted with EtOAc (100 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated to give hemiester **11a** (550 mg, ~100%) as a solid. The ee of **11a** was determined to be 93% by HPLC analyses of a diastereomeric mixture of amide-esters prepared from **11a** and (*R*)-(+)-1-(1-napthyl)ethylamine according to the literature procedure (HPLC conditions: Daicel Chiralpak, OD, λ = 280 nm, 0.6 mL/min, hexane:propan-2-o, 4:1, t_{major} = 26.9 min, t_{minor} = 20.5 min);[23] $[\alpha]_D^{25}$ –7.3 (*c* = 1.56, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.59 (s, 3 H), 4.02–4.13 (m, 4 H), 4.97 (d, *J* =14.8 Hz, 1 H), 5.08 (d, *J* =14.8 Hz, 1 H), 7.18–7.39 (m, 10 H), 10.53 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.9, 47.0, 52.8, 57.0, 57.5, 128.1, 128.7, 128.8, 128.97, 129.01, 135.6, 160.0, 168.7, 171.4.

To recover the catalyst (DHQD-PHN), K_2CO_3 was added to the aqueous layer to adjust the pH value of the solution to 9–11. The resulting mixture was extracted with EtOAc (50 mL), and the organic layer was washed with brine, dried (Na_2SO_4) and concentrated to afford the catalyst in quantitative yield and in pure form as shown by ^{1}H NMR. The recovered catalyst was used for a new batch of reaction to give **11a** in the same ee and yield as described above.

(3a*S*,6a*R*)-1,3-Dibenzyltetrahydro-1*H*-furo[3,4-*d*]imidazole-2,4-dione (4)[11]

To a solution of cyanuric chloride (159 mg, 0.86 mmol) in THF (3 mL) at r.t. was added *N*-methylmorpholine (77 mg, 0.74 mmol). A white suspension was formed. A solution of the hemiester (210 mg, 0.57 mmol, 93% ee) in THF (2 mL) was added to this mixture. The resulting mixture was stirred for 3 h and then filtered. A solution of $NaBH_4$ (46 mg, 1.2 mmol) in H_2O (1 mL) was added dropwise to the filtrate at 0 °C. The resulting mixture was stirred for 6 min after which 2 N aq HCl (5 mL) was added to the mixture. The resulting mixture was stirred at r.t. for 3 h and then extracted with EtOAc (20 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (silica gel, EtOAc–hexane, 1:4) to give the desired chiral lactone as a white solid: 151 mg (82%). The ee of the lactone was determined to be 91% (HPLC conditions: Daicel Chiralpak OD, λ = 254 nm, hexane:propan-2-ol, 9:1, t_{major} = 37.7 min, t_{minor} = 32.1 min); $[\alpha]_D^{25}$ +56.4 (*c* = 1.12, $CHCl_3$) {Lit.[11] $[\alpha]_D^{25}$ +52.2 (*c* = 1.03, $CHCl_3$; 90% ee)}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.92 (d, *J* = 8.4 Hz, 1 H), 4.08–4.17 (m, 3 H), 4.31–4.39 (m, 2 H), 4.62 (d, *J* = 15.6 Hz, 1 H), 5.06 (d, *J* = 14.6 Hz, 1 H), 7.24–7.39 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.4, 47.1, 52.6, 54.6, 70.3, 128.0, 128.3, 128.4, 128.9, 129.0, 129.1, 136.1, 136.2, 158.4, 173.0.

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