A Facile and Convenient Synthesis of (±)-Biotin via $MgCl_2/Et_3N$-Mediated C–C Coupling and Mitsunobu Reaction

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Abstract: A synthesis of (±)-biotin is described starting from simple starting materials viz. cyclohexanone and amino malonic acid ester. The key steps involved are $MgCl_2/Et_3N$ coupling of amino malonic acid ester derivative and acid chloride, Mitsunobu reaction, ozonolysis, Staudinger reduction, novel urea formation, and subsequent dibenzylation. This approach is economical and involves high-yielding steps and simple reaction conditions.

Key words: biotin, ozonolysis, Appel reaction, Mitsunobu reaction, Staudinger reduction

Biotin is the water-soluble vitamin H that was isolated by Kogl et al. in 1936 from egg yolk and later on from pig liver and milk concentrate.[1] It is present as a key constituent of animal and human tissues. The structure of vitamin H was elucidated in 1942, and the presence of bicyclic framework was confirmed by the first total synthesis in 1945.[2] (+)-Biotin acts as a cofactor in CO_2 fixation, decarboxylation, and transcarboxylation in some key physiological processes, that is, gluconeogenesis and fatty acid synthesis. It also has significant importance in human nutrition and plays a key role in animal-growth promotion. Biotin deficiency is found in humans and birds, and animals are treated by providing biotin as a feed additive especially in poultry and swine. In addition, biotin is used in pharmaceutical formulations as an additive, and its avidin complex is used in the area of drug delivery, immunoassay, isolation, and localization.[3]

Given the fundamental and commercial importance of vitamin H in the poultry (biochemistry and pharmaceutical formulations) interest in this molecule was revived. As a result, numerous efforts have been directed by synthetic community to develop new and efficient approaches for biotin.[4,5] Although several elegant syntheses have been reported in the literature, many of them possess drawbacks like tedious reaction conditions and use of expensive catalysts and reagents, with low overall yields. Biotin is manufactured and supplied on an industrial scale by using Hoffmann La Roche's method from fumaric acid. Although a variety of methods are known for the synthesis of biotin, there still exists a need to develop an efficient and practical strategy which involves simple starting materials, inexpensive reagents, and high-yielding steps.

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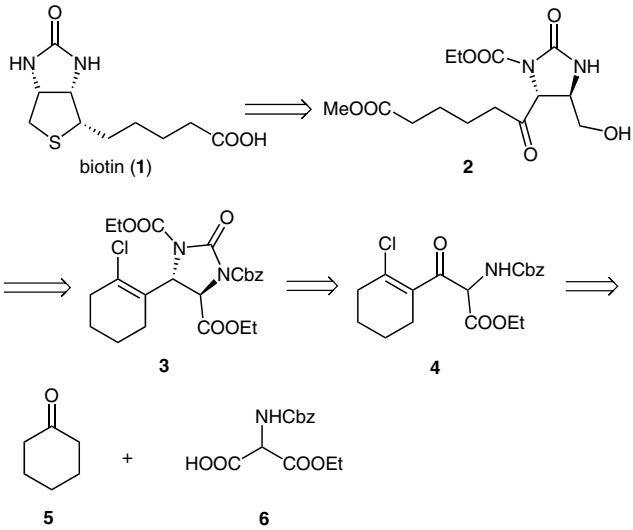
Our longstanding interest in the synthesis of biologically important molecule led us to explore a practical route for biotin. Earlier we have reported the syntheses of D-(+)-biotin involving features of acyliminium chemistry, stereoselective amido alkylation, intramolecular radical cyclization, and Sharpless asymmetric dihydroxylation as the key steps.[6] Considering key requirements and needful objectives in mind, this communication describes our efforts towards a facile and convenient strategy for the total synthesis of biotin (**1**), which involves notable features like $MgCl_2/Et_3N$-mediated C–C coupling reaction, Mitsunobu inversion, ozonolysis, Staudinger reduction, novel urea formation, and subsequent dibenzylation as the key organic reactions.

It was envisaged that biotin (**1**) can be synthesized from ketone **2** which could be derived from crucial intermediate **3** using proper chemical transformations. Intermediate **3** would be simply obtained from β-keto ester **4**, which in turn can be easily prepared from cyclohexanone and amino malonic acid ester derivative (Scheme 1).



Scheme 1 Retrosynthetic analysis for biotin (**1**)

Accordingly, the synthesis of biotin (**1**) commenced with coupling of the acid **6** and acid choride **8** (which was readily prepared from cyclohexanone as shown in Scheme 2)[7] in the presence of $MgCl_2$ and Et_3N and furnished β-keto ester **4** in 65% yield.[8] The chemoselective reduction of β-keto ester **4**[9] was carried out using $NaBH_4$ in MeOH to

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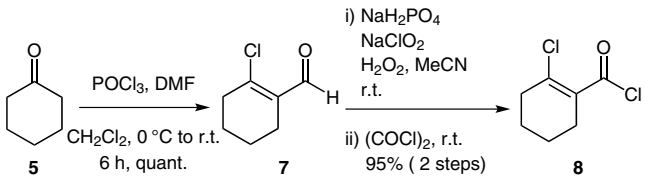
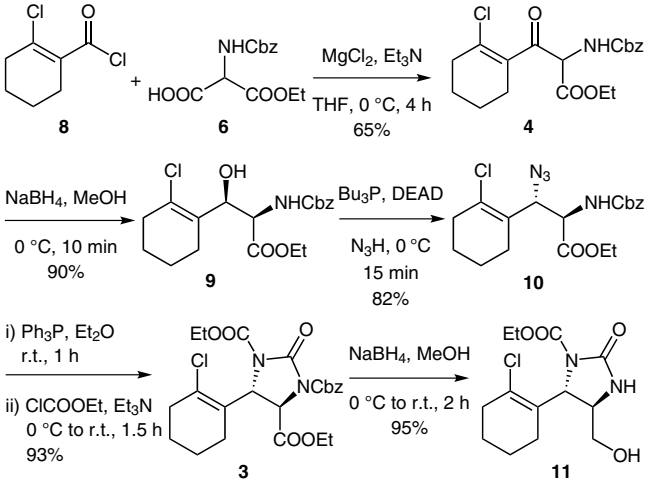
afford β-hydroxy ester **9** in 90% yield as a mixture of diastereomers in the ratio of 9:1.



Scheme 2 Synthesis of acid chloride **8**

The stereochemistry of the major isomer of **9** was expected to be *syn* based on literature reports,[10] and it was further established by carrying out acetonide protection of hydroxy amine **9** using 2,2-dimethoxypropane in acetone in the presence of a catalytic amount of $BF_3 \cdot OEt_2$[11] and was confirmed by ^1H NMR spectroscopy (coupling constant, J = 6.84 Hz), which clearly established its stereochemistry



Scheme 3 Synthesis of alcohol **11**

to be *cis* and was in accordance with the data of similar compounds reported in the literature.[10,12]

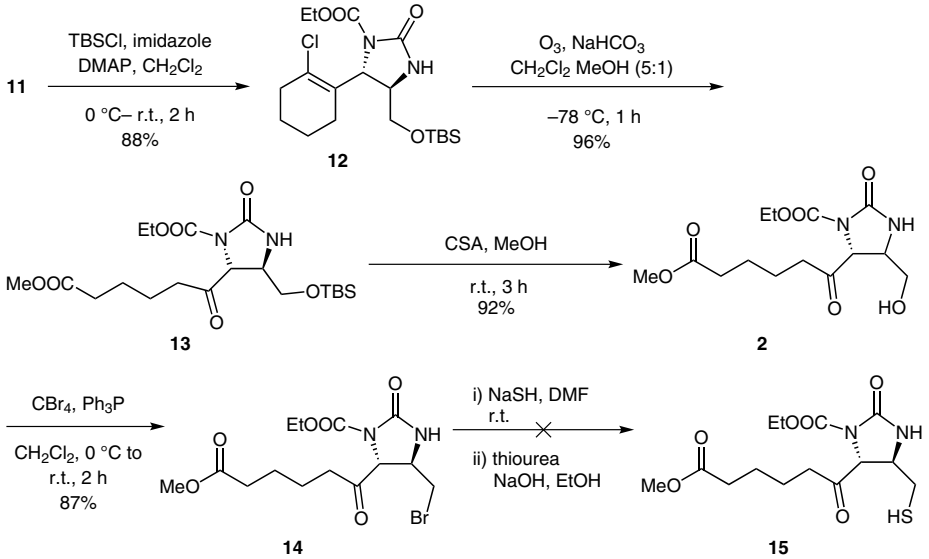
Next task was the introduction of second nitrogen atom, which was done by treating **9** under optimized Mitsunobu reaction conditions, involving Bu_3P, N_3H, and DEAD in toluene, to give azide **10** in 82% yield.[13] The azide **10** was subjected to Staudinger reaction conditions[14] using Ph_3P in Et_2O to afford an amine, which without further purification was subjected to chemical masking with ethyl chloroformate and Et_3N as the base to obtain cyclic urea **3**[15] as the sole product in excellent yield. After successfully forming the urea ring, the task remaining for biotin (**1**) synthesis was the construction of the tetrahydrothiophene ring and unmasking of the valeric acid side chain. Further, urea **3** was reduced with $NaBH_4$ in MeOH to furnish alcohol **11** in 95% yield (Scheme 3). It is interesting to note that two reactions occur in one pot viz. reduction of the ester to an alcohol group and removal of the *N*-Cbz group.

The resultant alcohol **11** was subjected to ozonolysis using O_3 and $NaHCO_3$ in CH_2Cl_2–MeOH, but unfortunately did not furnish the desired product.

However, when the hydroxy group was protected as its TBS ether **12**, using TBSCl, imidazole, and catalytic DMAP, it underwent smooth ozonolysis to afford ketone **13** in 96% yield. The TBS deprotection of ketone **13** was carried out with CSA and MeOH to afford alcohol **2** in 92% yield.[16] As per structural demand for biotin (**1**) motif, further plan was to introduce a sulfur atom by converting hydroxy group into a good leaving group.

Attempts to convert alcohol **2** into its mesylate and tosylate derivatives under standard conditions met with failure. So the alcohol **2** was subjected to Appel reaction conditions using Ph_3P and CBr_4 to furnish bromide **14** in 87% yield.[17]

Although the bromide **14** appeared to be an ideal substrate for thiol substitution, various conditions were utilized to



Scheme 4 Synthetic attempt towards thiol **15**

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introduce the sulfur functionality such as NaSH/DMF, thiourea/NaOH/EtOH, KSAc/DMF, etc., proved to be ineffective (Scheme 4). Notably, the reactions failed to provide the desired thiol **15**. These observations forced us to slightly modify our strategy for biotin (**1**).

It was decided to protect the NH group of urea **12** as its *N*-benzyl ether. Accordingly, the urea **12** was treated with benzyl bromide and NaH as the base, and, interestingly, the formation of dibenzyl urea **16**[18] was observed in excellent yield. It is interesting to note that this transformation involves unusual decaboxylation followed by protection of the NH functionality of urea as its bisbenzyl derivative.[19] The dibenzyl urea **16** thus obtained was subjected to ozonolysis to provide ester **17** in good yield. The TBS deprotection of ester **17** was carried out in MeOH using CSA to afford alcohol **18** in 92% yield.

Next task was to introduce the thiol group. Accordingly, alcohol **18** was converted into tosylate **19** using tosyl choride, Et_3N, and catalytic DMAP to furnish tosylate **19**. Tosylate **19** was then subjected to nucleophilic displacement using potassium thioacetate in DMF–THF to afford thioacetate **20** in 90% yield.[20] The conversion of thioacetate **20** into biotin (**1**) has been recently reported by us (Scheme 5).[6a]

In conclusion, we have demonstrated a novel and efficient total synthesis of (±)-biotin (**1**) using cyclohexanone and amino malonic acid ester derivative as commercially readily available inexpensive starting materials. The noteworthy features of this synthesis are the $MgCl_2/Et_3N$-mediated coupling, Mitsunobu reaction, ozonolysis, and Staudinger reduction as the key synthetic protocols. The synthesis of biotin has been accomplished in 13 purification steps with 13.68% overall yield. This method could be of great value in terms of its simplicity in the construction of urea, the tetrahydrothiophene ring, and also elaboration of the pentanoic acid side chain of the biotin skeleton. Investigation of the enzymatic and catalytic asymmetric reduction procedures to accomplish the asymmetric total synthesis of (+)-biotin is currently under way, and the results will be reported in due course.

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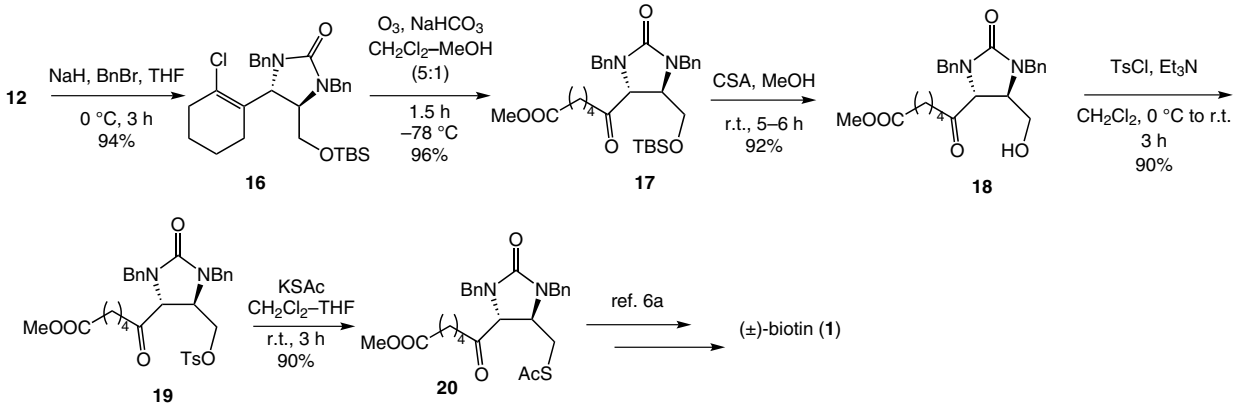

Scheme 5 Synthesis of (±)-biotin (**1**)

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(9) **Data for Compound 4**
R_f = 0.6 (PE–EtOAc = 70:30). ^{1}H NMR (200 MHz, $CDCl_3$ + CCl_4): δ = 7.40–7.26 (m, 5 H), 5.99 (d, *J* = 7.7 Hz, 1 H), 5.66 (d, *J* = 7.8 Hz, 1 H), 5.12 (s, 2 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 2.59–2.21 (m, 4 H), 1.83–1.52 (m, 4 H), 1.28 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$ + CCl_4): δ = 195.2, 165.9, 155.3, 134.5, 133.2, 128.5, 128.0, 127.8, 67.1, 62.6, 62.3, 34.0, 28.2, 23.0, 21.2, 14.0. IR ($CHCl_3$): ν_{max} = 2937, 2866, 1728, 1716, 1699, 1653, 1502, 1330 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{19}H_{22}ClNO_5Na$: 402.1079 [M + Na]$^+$; found: 402.1074.

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(15) **Data for Compound 3**
R_f = 0.7 (PE–EtOAc = 75:25). ^{1}H NMR (400MHz, $CDCl_3$ + CCl_4): δ = 7.43–7.28 (m, 5 H), 5.39–5.23 (m, 3 H), 4.40–4.14 (m, 5 H), 2.48–2.36 (m, 2 H), 1.98 (br s, 2 H), 2.06–1.91 (m, 2 H), 1.79–1.60 (m, 4 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ = 168.5, 150.9, 150.5, 147.3, 134.7, 131.6, 129.4, 128.5, 128.4, 127.9, 68.8, 63.2, 62.4, 57.9, 55.4, 33.9, 24.1, 23.3, 21.7, 14.2, 14.0. IR ($CHCl_3$): ν_{max} = 2983, 2938, 1817, 1750, 1728, 1661, 1370, 1024 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{23}H_{27}ClN_2O_7Na$: 510.1399 [M + Na]$^+$; found: 501.1400.

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(18) **Data for Compound 16**
R_f = 0.5 (PE–EtOAc = 60:40); mp 87–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$ + CCl_4): δ = 7.34–7.21 (m, 10 H), 4.59 (d, *J* = 6.0 Hz, 1 H), 4.52 (d, *J* = 14.7 Hz, 1 H), 4.12–3.97 (m, 1 H), 4.10–4.00 (m, 2 H), 3.52–3.45 (m, 1 H), 3.14–3.07 (m, 1 H), 2.22 (t, *J* = 6.2 Hz, 2 H), 1.77–1.68 (m, 1 H), 1.58–1.49 (m, 3 H), 1.42–1.33 (m, 1 H), 1.20 (dd, *J* = 6.4, 13.3 Hz, 1 H), 0.84 (s, 9 H), –0.01 (s, 3 H), –0.03 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ = 160.3, 137.3, 131.1, 130.1, 128.8, 128.4, 128.3, 127.3, 127.2, 62.5, 57.6, 56.5, 46.8, 46.1, 34.2, 25.8, 23.6, 21.6, 18.2., –5.4, –5.5. IR ($CHCl_3$): ν_{max} = 3030, 2930, 1698, 1657, 1448, 1357, 1119 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{30}H_{41}ClN_2O_2SiNa$: 547.2518 [M + Na]$^+$; found: 547.2523.

(19) The urea **16** is the same intermediate which we recently reported in enantiopure form, by following an entirely different strategy for the synthesis of D-(+)-biotin.[6a] Based on this, the stereochemistry of other major compounds have been deduced and depicted.

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