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Total synthesis of D-(+)-biotin

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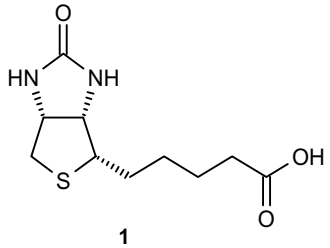
Abstract—A total synthesis of D-(+)-biotin is described starting from D-(+)-glucosamine using acyliminium chemistry.

D-(+)-biotin (vitamin H)[1a] **1** is a biocatalyst of reversible metabolic reactions involving carbon dioxide transport in organisms. As one of the B-complex group of vitamins, it is significant for human nutrition and animal health. In the pharmaceutical context it is used as an additive and as an avidin complex in the area of drug delivery, immunoassay, isolation and localization. Lack of efficient fermentation methods have drawn the attention of organic chemists towards the synthesis of biotin. Many synthetic approaches,[1a] such as diastereoisomeric or enzymatic resolutions,[1b,c] chiral pool methods involving carbohydrates,[2] cysteine,[3] L-aspartic acid,[4] as well as asymmetric syntheses have been described.



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To the best of our knowledge only one synthesis of D-(+)-biotin from glucosamine[2d] has been reported and all the syntheses from carbohydrates, including glucosamine, feature the construction of the ureido ring during the final stages of the synthesis. It has been reported[5] that reaction of 2-amino-2-deoxy pyranoses with arylisocyanates in aqueous $NaHCO_3$–dioxane at room temperature, gives 2-arylureido-2-deoxy sugars, which on subjecting to basic pH result in the formation of hydroxy imidazolidinones. Subsequent treatment with acid furnishes the *cis*-fused furanoid bicycles in high yields. Our ongoing interest in acyliminium chemistry[3e] led us to devise a strategy for cationic C–C bond formation in order to construct the ureido ring.

This communication describes our efforts to utilize acyliminium chemistry for the synthesis of D-(+)-biotin from glucosamine.

Following a literature procedure,[5] treatment of glucosamine hydrochloride **2** with benzyl isocyanate in aqueous $NaHCO_3$–dioxane at room temperature gave the desired 2-benzylureido-2-deoxy sugar, which in the presence of a catalytic quantity of pyridine in water at 55 °C furnished the *cis* furanoid bicycle **3** in 82% yield, in contrast to the hydroxy imidazolidinone described in the literature procedure. The product obtained was crystallized from methanol and its structure confirmed by single crystal X-ray analysis as shown in Figure 1. The terminal diol of **3** was protected as the acetonide using acetone and cat. *p*-TSA at room temperature and subsequent protection with BnBr and NaH in DMF gave the bicyclic intermediate **4** in excellent yield (86%) over two steps.

Although the intermediate **4** appeared to be an ideal substrate for carbon–carbon bond formation, various attempts using intermediate **4** and derivatives of intermediate **3** under a variety of Lewis acid mediated conditions, viz., $BF_3{\cdot}Et_2O$, $TiCl_4$, TMSOTf, $SnCl_4$, etc., proved to be ineffective. This prompted us to look for

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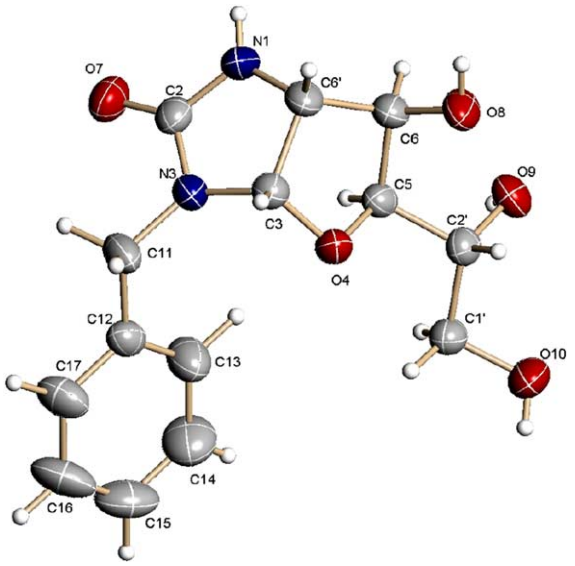


Figure 1. ORTEP representation of **3**.

other options to generate the acyliminium ion from **4**. As one option, it was anticipated that the formation of an exocyclic enol ether with the oxygen attached to the ureido ring as part of the enol ether/acetate would be suitable for carbon–carbon bond formation.

To validate this assumption, the acetonide in **4** was unmasked with cat. *p*-TSA in refluxing THF–H_2O (9:1) to furnish the diol **5** in excellent yield (98%). Diol **5** was cleaved to the aldehyde using $NaIO_4$ in acetone–water (9:1), which on further treatment with acetic anhydride, Et_3N and cat. DMAP in refluxing dichloroethane furnished the exocyclic enol acetate **6** in good yield (83%) over two steps (Scheme 1).

Gratifyingly, carbon–carbon bond formation via an acyliminium ion was effected by treating the enol acetate **6** with TMSCN and $BF_3{\cdot}Et_2O$ in DCM at −78 °C to room temperature for 15 min to furnish the cyano substituted intermediate **7** in good yield (62%). The structure of the product was confirmed by X-ray analysis[7] (Fig. 2).

Having formed the crucial carbon–carbon bond, the stage was now set to generate the correct stereochemistry at the C-5 and C-3 carbons of intermediate **7** in order to arrive at the biotin skeleton.

The intermediate **7** on reduction with $NaBH_4$ in methanol furnished a diol, as a mixture of products, formed by the reduction of the keto group and partial conversion of the cyano group to a methyl ester, both as diastereoisomeric mixtures in variable ratios. The problem of the formation of multiple products was addressed by subjecting the crude reaction mixture obtained on reduction with $NaBH_4$ to TMSCl in methanol[8] to furnish the required methyl ester **8** in excellent overall yield (93%) over the two steps (Scheme 2).

The diol **8** was cleaved using $NaIO_4$ in acetone–water (9:1) to furnish the aldehyde, which on subsequent treat-

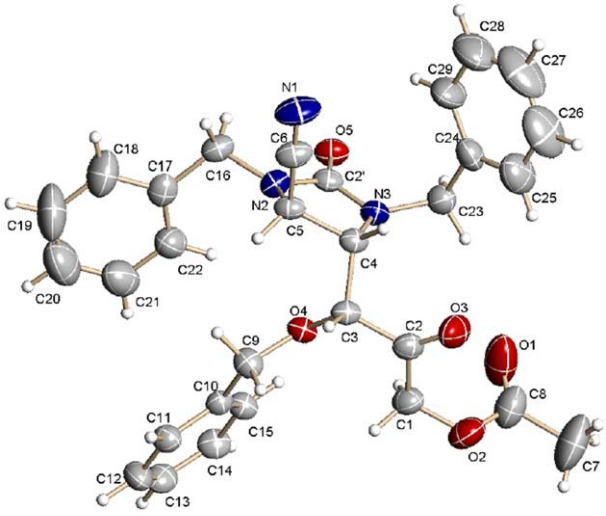
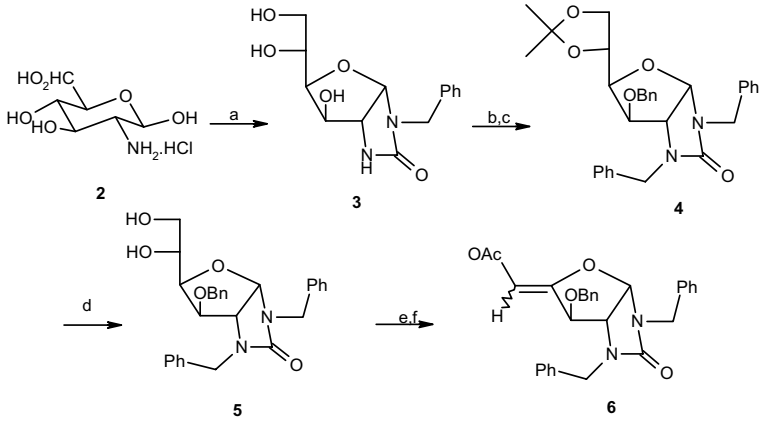
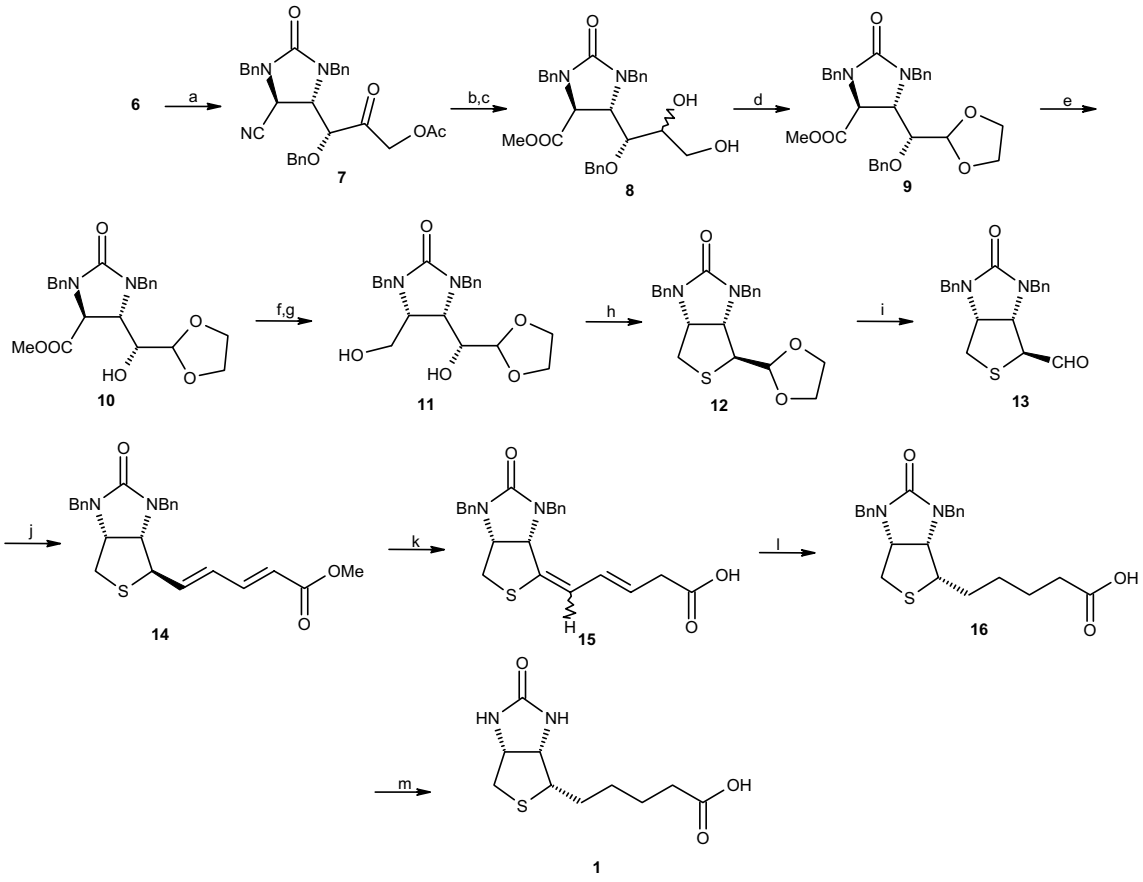


Figure 2. ORTEP representation of **7**.



Scheme 1. Reagents and conditions: (a) (i) BnNCO, aq $NaHCO_3$; (ii) pyridine (cat.), H_2O, 82%; (b) *p*-TSA (cat.), acetone, rt; (c) NaH, BnBr, DMF, 0 °C to rt, 6 h, 86% over two steps; (d) *p*-TSA (cat.), THF–H_2O (9:1), reflux, 6 h, 98%; (e) $NaIO_4$, acetone–H_2O (9:1), rt, 30 min; (f) Ac_2O, Et_3N, DMAP (cat.), dichloroethane, reflux, 4 h, 83%.



Scheme 2. Reagents and conditions: (a) TMSCN, $BF_3{\cdot}Et_2O$, DCM, −78 °C to rt, 15 min, 62%; (b) (i) $NaBH_4$, MeOH, 0 °C to rt, 4 h; (c) TMSCl, MeOH, 40 °C, 4 h, 93% over two steps; (d) (i) $NaIO_4$, acetone–water (9:1), rt, 30 min; (ii) ethylene glycol, *p*-TSA, C_6H_6, reflux, 6 h, 65% over two steps; (e) Pd–$CaCO_3$, MeOH, rt, 24 h, 95%; (f) DBU (cat.), toluene, reflux, 24 h; (g) $NaBH_4$, EtOH, reflux, 2 h, 86% over two steps; (h) (i) MsCl, Et_3N, DMAP (cat.), 0 °C to rt, 4 h, 74%; (ii) Na_2S, DMF, 100 °C, 2 h, 78%; (i) 6 N HCl, CH_3COOH, rt, 24 h, 82%; (j) $Ph_3P{=}CH{-}CH{=}CH{-}COOCH_3$, DCM, rt, 12 h, 89%; (k) 1 M NaOH, MeOH, 0 °C, 12 h, 97%; (l) 10%Pd–C/H_2 (3 atm), 8 h, 96%; (m) 48% HBr, reflux, 2 h, 80%.

ment with ethylene glycol and *p*-TSA gave the dioxalane derivative **9** in good yield (65%) over the two steps. Selective *O*-debenzylation of **9** was accomplished using Pd–$CaCO_3$ in methanol in excellent yield (95%) to give the hydroxy ester **10**.

Correction of the stereochemistry at C-4 of **10** was achieved by epimerization with cat. DBU in refluxing toluene, which also caused formation of a lactone which, being unstable to column chromatography was reduced with $NaBH_4$ in refluxing ethanol to give the diol **11** in very good yield (86%) over two steps.

Sulfur was introduced by transforming diol **11** into a dimesylate in 78% yield with mesyl chloride and subsequent treatment with Na_2S in DMF to give the tetrahydro-thieno imidazolidinone **12** in good yield (78%). The intermediate **12** was deprotected with 6 N HCl in acetic acid to furnish the aldehyde **13** in 82% yield. The stereochemistry at C-2 of intermediate **13** was corrected following our earlier synthesis.[3e] Wittig homologation of the aldehyde with (3-methoxycarbonyl-2-propenylidine) triphenylphosphorane in DCM furnished the unsaturated ester **14**, having the biotin framework, in 89% yield. Treatment with NaOH in MeOH caused deconjugation and concomitant hydrolysis in one step in almost quantitative yield. The resulting acid **15** on hydrogenation provided the saturated acid **16** in 96% yield (characterized as its methyl ester) having *cis* stereochemistry as required for biotin. Debenzylation of **16** afforded D-(+)-biotin **1** (80% yield, mp: 230 °C lit. mp: 232–233 °C), which was also characterized as its methyl ester. ^1H NMR and mass spectroscopy and optical rotation of the synthetic product in addition to comparison with authentic samples of D-(+)-biotin and its biotin methyl ester, confirmed the structure.

Conclusion

We have demonstrated that glucosamine can be efficiently converted to D-(+)-biotin following intermolecular C–C bond formation through acyliminium ion chemistry.

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acknowledged. We are thankful to Green Chem. Bangalore for a generous supply of D-glucosamine hydrochloride.

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6. Crystal data of compound **3**: $C_{14}H_{18}N_2O_5$ $M = 294.3$; space group Monoclinic, $P2(1)$, $a = 7.6332(12)$ Å, $b = 9.5764(15)$ Å, $c = 9.5875(15)$ Å, $\beta = 100.092(2)°$, $\alpha = 90°$ $\gamma = 90°$, $V = 689.99(19)$ Å3, $D_c = 2$, $1.417\,mg/m^3$ (Mo-Kα) $= 0.108\,mm^{-1}$, $T = 312$; crystal size $= 0.52 \times 0.47 \times 0.16$ mm; theta range for data collection = 2.16–26.99°, limiting indices $= 9 \leqslant h \leqslant 9$, $-12 \leqslant k \leqslant 12$, $-12 \leqslant l \leqslant 12$; reflections collected/unique 7590/2993 [$R_{(int)} = 0.0209$]; completeness to theta = 26.99, 99.8%, absorption correction = semi-empirical from equivalents; max. and min. transmission = 0.9829 and 0.9458, refinement method = full-matrix least-squares on $F2$; data/restraints/parameters 2993/1/245; Goodness-of-fit on $F2 = 1.097$, final R indices [$I > 2$sigma(I)] = $R1 = 0.0362$, $wR2 = 0.0932$, R indices (all data) = $R1 = 0.0366$, $wR2 = 0.0936$, absolute structure parameter = −0.1(8), largest diff. peak and hole = 0.185 and $-0.257\,e\,Å^{-3}$. Additional crystallographic details CCDC243900 (atomic co-ordinates and equivalent isotropic displacement coefficients) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
7. Crystal data of compound **7**: $C_{30}H_{29}N_3O_5$; $M = 511.56$, space group = 0 Monoclinic, $P2(1)$, $a = 12.1575(18)$ Å, $b = 7.5820(11)$ Å, $c = 15.312(2)$Å·. $\alpha = 90°$. $\beta = 92.297(2)°$, $\gamma = 90°$, $V = 1410.3(4)$ Å^3, $D_c = 2$, $1.205\,Mg/m^3$, (Mo-Kα) $= 0.083\,mm^{-1}$, $F(0\,0\,0) = 540$; crystal $= 0.75 \times 0.28 \times 0.16$ mm; theta range for data collection 1.68–26.00°, limiting $= -14 \leqslant h \leqslant 14$, $-9 \leqslant k \leqslant 9$, $-17 \leqslant l \leqslant 18$; reflections collected/unique 11003/5391 [$R_{(int)} = 0.0231$]; completeness to theta = 26.00, 99.6%, absorption correction semi-empirical from equivalents; max. and min. = 0.9869 and 0.9405, refinement method = full-matrix least-squares on $F2$; data/restraints/parameters 5391/1/344; goodness-of-fit on $F2 = 1.078$, final R indices [$I > 2$sigma(I)] $R1 = 0.0493$, $wR2 = 0.1179$; R indices (all data) = $R1 = 0.0598$, $wR2 = 0.1242$, absolute structure parameter = −1.1(11), Largest diff. peak and hole = 0.137 and $-0.110\,e\,Å^{-3}$. Additional crystallographic details CCDC243901 (atomic co-ordinates and equivalent isotropic displacement coefficients) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Experimental data: mp: 57–59 °C; $[\alpha]_D^{25} + 18.69$ (c 0.58, $CHCl_3$). δ_H ($CDCl_3$, 200 MHz): 2.12 (s, 3H), 3.83 (dd, $J = 5.48$, 2.74 Hz, 1H), 3.89 (d, $J = 5.5$ Hz, 1H), 4.00 (d, $J = 2.7$ Hz, 1H), 4.04 (d, $J = 14.8$ Hz, 1H), 4.08 (d, $J = 15.3$ Hz, 1H), 4.27 (d, $J = 17.7$ Hz, 1H), 4.39 (d, $J = 11.7$ Hz, 1H), 4.52 (d, $J = 17.2$ Hz, 1H), 4.56 (d, $J = 11.7$ Hz, 1H), 4.92 (d, $J = 15.3$ Hz, 1H), 4.97 (d, $J = 14.9$ Hz, 1H), 7.09–7.46 (m, 15H). δ_C ($CDCl_3$, 50 MHz): 20.1, 46.0, 46.7, 47.0, 57.0, 67.0, 73.7, 79.4, 115.0, 126.2–129.1, 134.9, 135.4, 135.6, 158.1, 169.9, 201.5. MS (ESI) m/z: 511.5 Anal. Calcd for $C_{30}H_{29}N_3O_5$: C 70.43, H 5.71, N 8.21. Found: C 70.70, H 5.59, N 8.17.
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