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Synthesis of the C-ring fragment of cobyric acid

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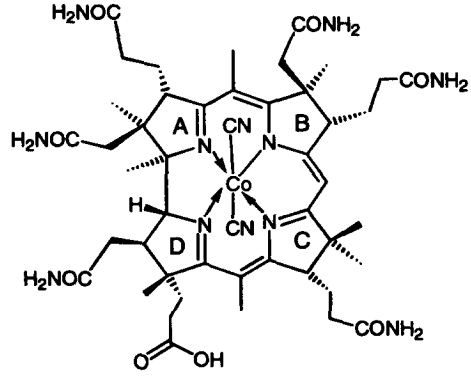
Abstract

An efficient stereocontrolled synthesis of the C-ring fragment of cobyric acid **1** is described. The key step is an auxiliary controlled conjugate addition of vinyl cuprate to (5*S*)-menthyloxy-2[5*H*]-furanone **3**.

Keywords: vitamin B_{12} synthesis; conjugate addition; vinyl cuprate; auxiliary control.

Aiming at a novel synthesis of cobyric acid (**1**)[1,2] we recently described a stereocontrolled access to the semicorrin, the AB-segment of **1**.[3] In continuation of this work we now report an efficient synthesis of the C-ring fragment **2a** which differs from the Woodward–Eschenmoser intermediate **2b** only with respect to the ester group (*t*-Bu instead of Me). The synthetic methodology, however, is totally different from the one applied by Woodward and Eschenmoser for **2b**[1] and by ourselves for the AB-segment.[3]



Cobyric Acid (1)

(5*S*)-Menthyloxy-2[5*H*]-furanone **3**, which is readily available from furan,[4] was used in a 1,4-addition of vinyl cuprate (Scheme 1), which proceeded with >95% *ds* from the less hindered face due to the shielding effect of the bulky menthyloxy substituent.[5] The relative stereochemistry of **4** was confirmed

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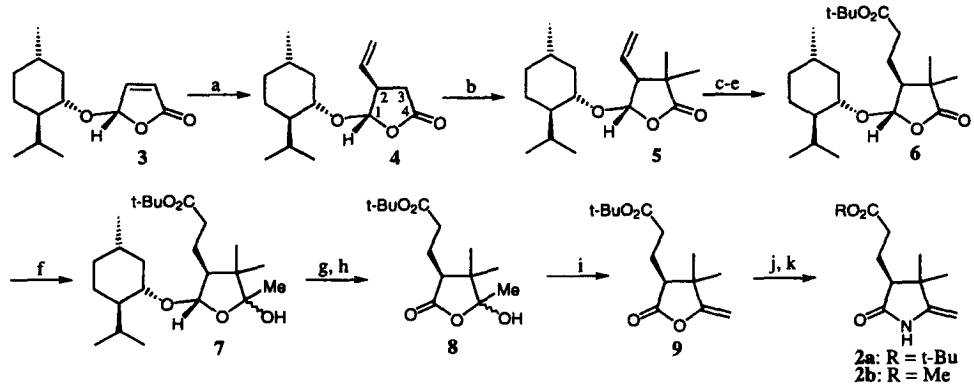
by the small coupling constant of H1 and H2 (J=2.8 Hz) which clearly indicates an *anti* arrangement of these two vicinal hydrogens. This result is in accord with thiol and amine additions to **3**.[6] The geminal dimethyl group in **5** was introduced by double alkylation of the enolate with methyl iodide. Ozonolytic oxidation of the vinyl substituent followed by a Wittig reaction with (*t*-butoxycarbonylmethylene)-triphenylphosphorane and subsequent hydrogenation of the newly formed double bond led to the desired propionate **6**. Addition of methyllithium furnished the hemiketal **7**. Acid catalyzed cleavage of menthyloxy acetal followed by oxidation with PDC delivered lactone ketal **8**.[5] To introduce the nitrogen, **8** was converted to enol lactone **9** which was treated with ammonia in ethanol to give the enol lactam **2a**.[3,5] This building block, which is thus available from **7** in 11 steps (overall yield 27%), can now be used for condensation via a sulfide contraction with AB-thioamide.



Scheme 1. Reagents and conditions: (a) vinyl MgCl, CuI, TMSCl, THF, −78°C, then TBAF, THF, 5 min, rt, 65%; (b) LiHMDS, MeI, THF, −78°C, 92%; (c) O_3, PPh_3, THF, −78°C; (d) $Ph_3PCHC(O)Ot$-Bu, MeOH, 0°C; (e) H_2, $Pd/CaCO_3$, ethyl acetate, rt, 96% for three steps; (f) MeLi, THF:toluene (1:3), −78°C, 65%; (g) *p*-TsOH cat., toluene, rt; (h) PDC, DMF, rt, 2 days, 80% for two steps; (i) MsCl, NEt*i*-Pr_2, CH_2Cl_2, 0°C, 99%; (j) NH_3, EtOH, CH_2Cl_2, 90%; (k) 110°C, 1 mbar, 100%

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5. **4**: ^{1}H NMR (400 MHz, $CDCl_3$)=5.73 (ddd, J=17.44 Hz, J=10.16 Hz, J=7.40 Hz, 1H), 5.33 (d, J=2.8, 1H), 5.13 (m, 2H), 3.44 (dt, J=10.67 Hz, J=4.14 Hz, 1H), 2.89 (m, 1H), 2.79 (dd, J=17.57 Hz, J=8.53 Hz, 1H), 2.30 (dd, J=17.32 Hz, J=4.77 Hz, 1H), 2.02 (m, 2H), 1.59 (m, 2H), 1.30 (m, 1H), 1.17 (m, 1H), 0.92 (ddd, J=12.67 Hz, J=3.39 Hz, 1H), 0.86 (d, J=7.03 Hz, 3H), 0.82 (d, J=7.03 Hz, 3H), 0.88–0.75 (m, 2H), 0.72 (d, J=7.03 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$,)=190.4, 135.3, 118.0, 104.8, 77.8, 48.1, 45.9, 40.3, 34.7, 33.8, 31.8, 25.8, 23.5, 22.6, 21.3, 16.0; MS (FI, 40°C): *m/z*=266.1 (M^+); IR(Si-pellet): 2956, 2944, 2924, 1792, $[\alpha]_D^{20}$=+150.5 (*c*=1, $CHCl_3$). **9**: ^{1}H NMR (400 MHz, $CDCl_3$)=4.67 (d, J=2.74 Hz,

1H), 4.34 (d, J=2.74 Hz, 1H), 2.75–2.62 (m, 1H), 2.57–2.42 (m, 2H), 1.83 (m, 2H), 1.47 (s, 9H), 1.34 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)=175.7, 172.6, 165.0, 86.7, 81.0, 49.7, 43.0, 33.0, 28.5, 25.8, 23.6, 20.8; HRMS (EI): *gem*: 254.1524±0.0013; calcd: 254.1518; IR(Si-pellet): 1803, 1728, 1671; $[\alpha]_D^{20}$=–20.2 (*c*=1.12, $CHCl_3$). **2a**: ^1H NMR (400 MHz, $CDCl_3$)=6.88 (s, br, 1H), 4.25 (d, J=1.9 Hz, 1H), 4.14 (d, J=1.9 Hz, 1H), 2.70 (m, J=16.5 Hz, J=9.0 Hz, J=5.5 Hz, 1H), 2.49 (m, J=16.5 Hz, J=9.2 Hz, J=9.0 Hz, 1H), 2.26 (dd, J=5.6 Hz, J=9.2 Hz, 1H), 1.84 (m, 2H), 1.47 (s, 9H), 1.30 (s, 3H), 1.17 (s, 3H); MS (FI, 30°C): *m/z*=253.3 (M^+). The ^1H NMR spectrum is largely analogous to that reported for compound **2b**.[1e]

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