ORGANIC LETTERS

2000
Vol. 2, No. 20
3139−3141

Efficient Synthesis of the D-Ring Fragment of Cobyric Acid

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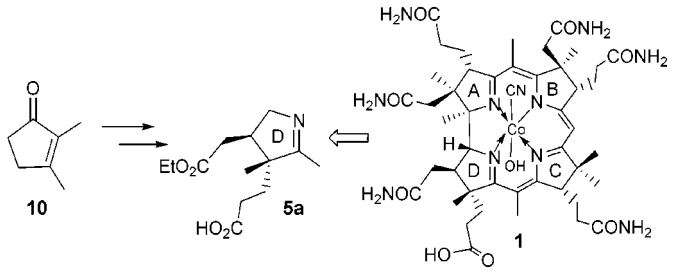
Received July 17, 2000

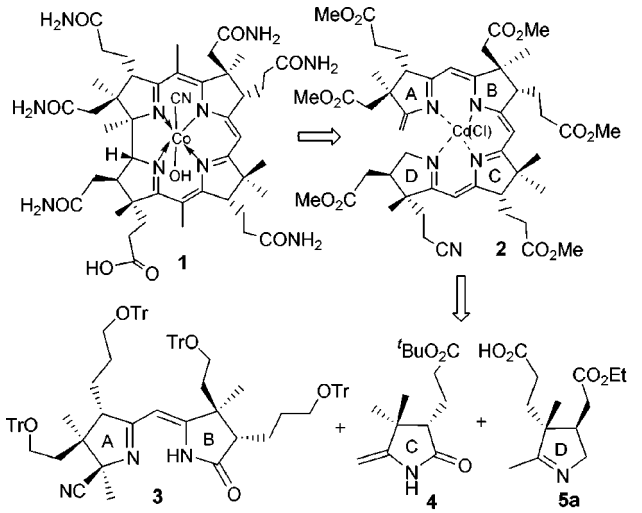
ABSTRACT



The synthesis of a highly functionalized 4,5-dihydro-3*H*-pyrrol, namely, the D-ring fragment 5a of cobyric acid (1), is described in this letter. A very efficient assembly to 5a involves CBS-reduction of 10, a [2,3] Wittig−Still rearrangement, and a stereoselective Michael addition to a nitro olefin.

The first two total syntheses of cobyric acid (**1**) and the discovery of the Woodward−Hoffmann rules were the result of the brilliant and extensive studies by Woodward and Eschenmoser.[1] No further synthesis has been achieved since, but there are promising approaches by Stevens and Jacobi.[2] Previously we described the first total synthesis of a northern A−B-semicorrin **3**[3] and an efficient assembly to the C-ring fragment **4**.[4] As a continuation of our efforts directed toward the total synthesis of cobyric acid (**1**), we now wish to report an efficient and stereoselective synthesis of the D-ring fragment **5a** (Scheme 1).

Scheme 1



The substitution patterns of the ring fragments significantly differ from each other, except the ring fragments of A−B-

(1) (a) Woodward, R. B. *Pure Appl. Chem.* **1968**, *17*, 519. (b) Woodward, R. B. *Pure Appl. Chem.* **1971**, *25*, 283. (c) Woodward, R. B. *Pure Appl. Chem.* **1973**, *33*, 145. (d) Eschenmoser, A.; Winter, C. E *Science* **1977**, *196*, 1410−1420.

(2) (a) Stevens, R. V.; Beaulieu, N.; Chan, W. H.; Daniewski, A. R.; Takeda, T.; Waldner, A.; Williard, P. G.; Zutter, U. *J. Am. Chem. Soc.* **1986**, *108*, 1039−1049 and references therein. (b) Jacobi, P. A.; Brielmann, H. L.; Hauck, S. I. *J. Org. Chem.* **1996**, *61*, 5013−5023. (c) Jacobi, P. A.; Liu, H. *Org. Lett.* **1999**, *1*, 341. (d) Jacobi, P. A.; Liu, H. *J. Org. Chem.* **1999**, *64*, 1778.

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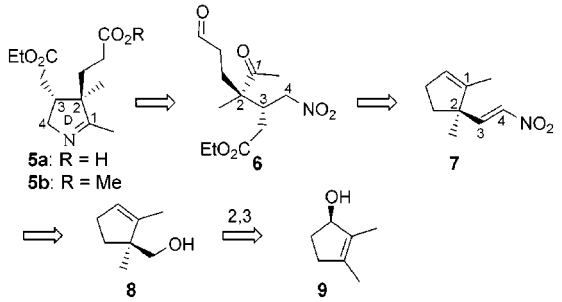
10.1021/ol006337n CCC: $19.00
Published on Web 09/09/2000

semicorrin **3**, which are accessible from the same intermediate.[3] In the C-ring fragment **4** the acetate side chain is replaced by a methyl group. The D-ring fragment **5a** differs from the other rings not only by its lower oxidation state but also by its substitution pattern; **5a** contains a quaternary stereogenic center, bearing a propionate and a methyl group vicinal to a tertiary stereogenic center with an acetate side chain. Further, it should be pointed out that the two side chains of **5a** have to be differentiable for a selective introduction of the nucleotide moiety at this position to transform cobyric acid (**1**) into vitamin B_{12}.[5]

It was our intention to synthesize fragments **3**, **4**, and **5a** by different strategies for each ring. The synthesis of the D-ring fragment **5a** relies upon a CBS reduction as the source of chirality. A sigmatropic rearrangement is used to establish the crucial quaternary center and a Michael addition of an ester enolate to nitro olefin **7** serves to create the tertiary center (Scheme 2).

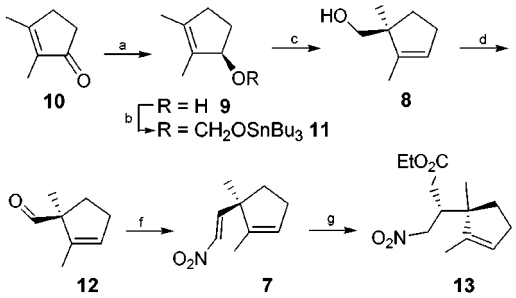
Scheme 2



Enantioselective reduction[6,7] of commercially available 2,3-dimethyl-2-cyclopentenone (**10**) gave the corresponding allylic alcohol **9** with 96% ee (determined by HPLC analysis), which was in turn converted to the stannyl methyl ether **11**.[8] Tin−lithium exchange and [2,3] Wittig−Still sigmatropic rearrangement[9] furnished the homoallylic alcohol **8** along with 10% of the [1,2] Wittig rearranged product. Parikh−Doering[10] oxidation of **8** provided the corresponding aldehyde **12**. Henry reaction with nitromethane under phase transfer conditions,[11] followed by dehydration, gave nitro olefin **7**. Michael addition of the lithium enolate of ethyl acetate to **7** at −100 °C furnished **13** in good yield (Scheme 3).

The diastereomeric ratio obtained in this reaction is 86:14. The selectivity can be explained by the shielding effect

Scheme 3[a]



[a] Reagents and conditions: (a) (*S*)-CBS *B*-butyloxazaborolidine catalyst, 0.6 equiv BH_3·THF, THF, −80 °C, 6 days, 97%; (b) KH, ICH_2SnBu_3, THF, 99%; (c) *n*-BuLi, THF, −78 °C, 55%; (d) SO_3·Py, DMSO, NEt_3, CH_2Cl_2; (e) 0.025M NaOH, CH_3NO_2, CTACl; (f) NEt_3, MsCl, ethyl acetate; (56% over three steps); (g) ethyl acetate, LiHMDS, HMPA, THF, −100 °C, 65%.

of the methyl group at C(5), which directs the attack of the enolate preferentially to the opposite side (Figure 1). The

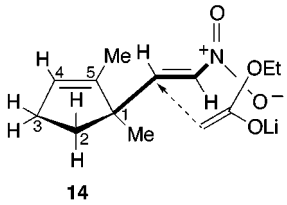


Figure 1.

configuration at the newly created stereogenic center was confirmed at the stage of nitrone **19** (Figure 2).

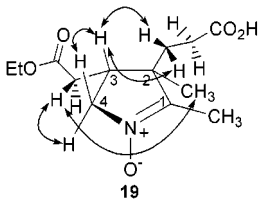


Figure 2.

When the Michael addition of the enolate to the nitro olefin **7** was performed at higher temperatures (−78 °C) or the lithium enolate of *tert*-butyl acetate was reacted with **7** at −100 °C, dimer **14** was isolated as the main product. The formation of **14** can be explained by a Michael addition of the enolate to **7**, followed by the attack of the resulting anion to another molecule of nitro olefin **7**. Subsequent elimination of the enolate in a retro-Michael fashion leads then to **14** (Scheme 4). The diastereomeric ratio of the reaction is again 86:14.

(5) Friedrich, W.; Gross, G.; Bernhauer, K.; Zeller, P. *Helv. Chim. Acta* **1960**, *43*, 704. (b) Friedrich, W. *2. Europäisches Symposium über Vitamin B_{12} u. Intrinsic Factor 2.-5. August 1961*; Enke Verlag: Stuttgart, Germany, 1962; pp 8ff.
(6) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
(7) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
(8) Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151. Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.
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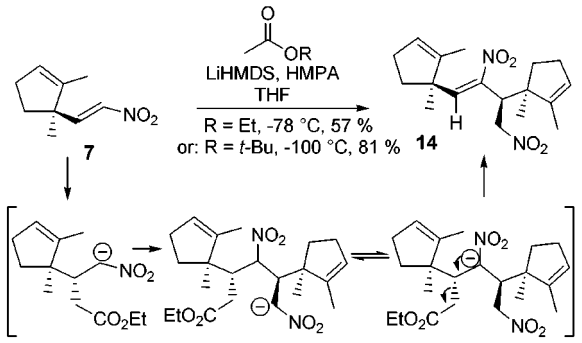
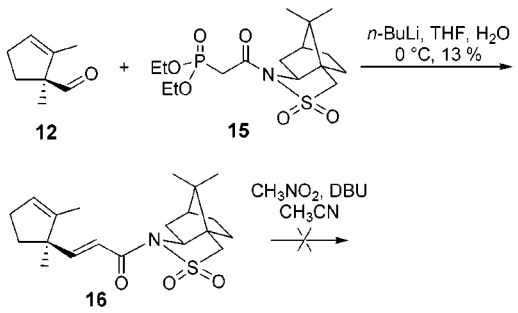
(10) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(11) Ballini, R.; Bosica, G. *J. Org. Chem.* **1997**, *62*, 425.

Scheme 4



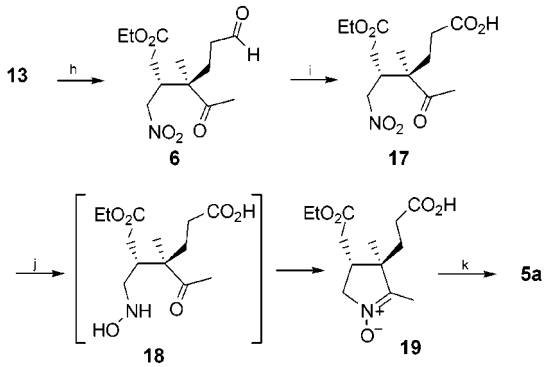
A slightly different route to Michael adduct **13** has been investigated. Thus, aldehyde **12** was reacted with (1*R*)-sultamphosphonate **15** in a Horner−Wadsworth−Emmons reaction[12,13] to give enone **16** in only 13% yield. Further, Michael addition of nitromethane to enone **16** failed under standard conditions. Assuming that the steric demands for these reactions are very high, no further efforts were put into this alternative route (Scheme 5).

Scheme 5



Having successfully achieved the Michael addition to **7**, the endocyclic olefinic linkage of **13** was oxidatively cleaved to give aldehyde **6**, which was subsequently converted to the acid **17** by Pinnick oxidation. The completion of the synthesis of **5a** required a reduction of the nitro group and condensation of the amine with the methyl ketone. Upon reduction of **17** with ammonium formate and Pd/C, hydroxylamine **18** was formed which spontaneously cyclized to give nitrone **19**. Further reduction was accomplished with $TiCl_3$[14] to give the desired cyclic imine **5a** (Scheme 6). The two

Scheme 6[a]



[a] Reagents and conditions: (h) O_3, PPh_3, −78 °C, 87%; (i) $NaClO_2$, 2,3-dimethylbutene, *t*-BuOH, KH_2PO_4, 74%; (j) $HCO_2^-NH_4^+$, Pd/C, 87%; (k) $TiCl_3$, THF, water, NaOAc, rt, 65%.

diastereomers of **5a** could be separated by chiral HPLC. As a result of aggregation effects of **5a** the peaks of the NMR spectrum were very broad. For this reason **5a** was treated with diazomethane to give methyl ester **5b**, which gave sharp, well-defined peaks in the ^{1}H NMR spectrum.

The relative stereochemistry of the two chiral centers of **19** was proved by the nuclear Overhauser effects shown in Figure 2.

The ^{1}H NMR data of **5a** and **5b** are compatible with those reported by the Eschenmoser group.[15] Divergences are only due to different functional groups at the side chains (CO_2H or CO_2Me instead of CN and CO_2Et instead of CO_2Me).

In summary, we have developed a new stereoselective synthesis of substituted 4,5-dihydro-3*H*-pyrrols. The D-ring fragment **5a** is available from 2,3-dimethyl-2-cyclopentenone **10** in 11 steps and 7% overall yield. In contrast, Eschenmoser's synthesis of ring D required 22 steps, including an optical resolution of enantiomeres.[16] Now **5a** can be used in a sulfide contraction with the C-ring fragment **4** or an A−B−C fragment. Having all ring fragments (**3**, **4**, and **5a**) in hand, we are now confident of completing the total synthesis of cobyric acid (**1**).

Acknowledgment. We thank Professor A. Eschenmoser for providing us with unpublished data, Dr. H. P. Kählig for NMR experiments, and S. Schneider for HPLC analysis.

Supporting Information Available: Experimental procedures, full characterization, and NMR spectra for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006337N

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