Studies on the Synthesis of Vitamin B_{12}. 1. Introduction and Model Studies

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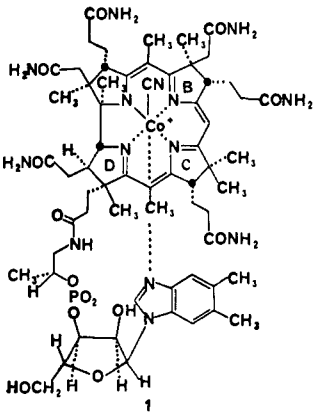
Abstract: A strategy for the total synthesis of vitamin B_{12} is presented which is supported by a number of carefully selected model studies.

Subsequent to its isolation in 1948[1] and x-ray crystallographic characterization in 1955,[2] vitamin B_{12} (**1**) has been the target of intensive and fruitful synthetic investigations.[3] These monumental achievements have been accompanied by and, indeed, inspired notable advances in our understanding of the art and science of organic chemistry.



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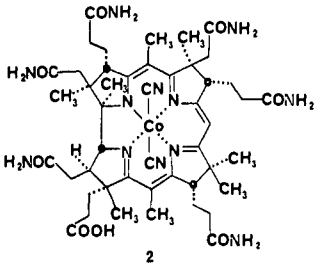

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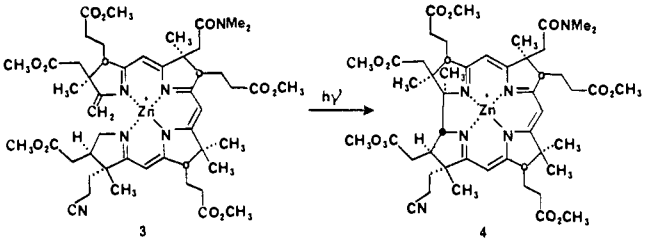
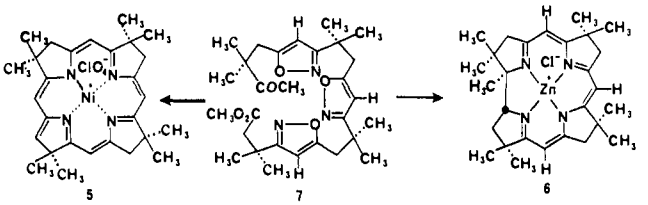
In contemplating the total synthesis of this complex and fascinating substance, it should be noted that a closely related natural product, cobyric acid (**2**), has been transformed previously[4] into the vitamin itself. A further simplification in our synthetic planning rests on the brilliant observation by the Eschenmoser group[3] that certain metal salts (such as zinc or cadmium) of the A/D-seco corrin complex (**3**) undergo a remarkably stereoselective photochemically induced ($\pi \rightarrow \sigma$)-valence isomerization to the natural A/D-trans series (**4**).



3 **4**

In evaluating possible approaches to cobyric acid or its A/D-seco precursor (**3**), it is apparent that a number of interacting considerations must be taken into account, of which we regard at least three as fundamental. First, a reliable method for construction of the macrocyclic ligand itself must be developed. Completion of the synthesis of octamethylcorphin (**5**)[5] and octamethylcorrin (**6**)[6] from triisoxazole (**7**) would appear to satisfy this criterion. Second, regardless of the chemistry utilized to satisfy this initial consideration, it must be compatible with the various functional groups which adorn the periphery of the ligand. Finally, the methodology developed must be capable of dealing with the nine chiral centers present

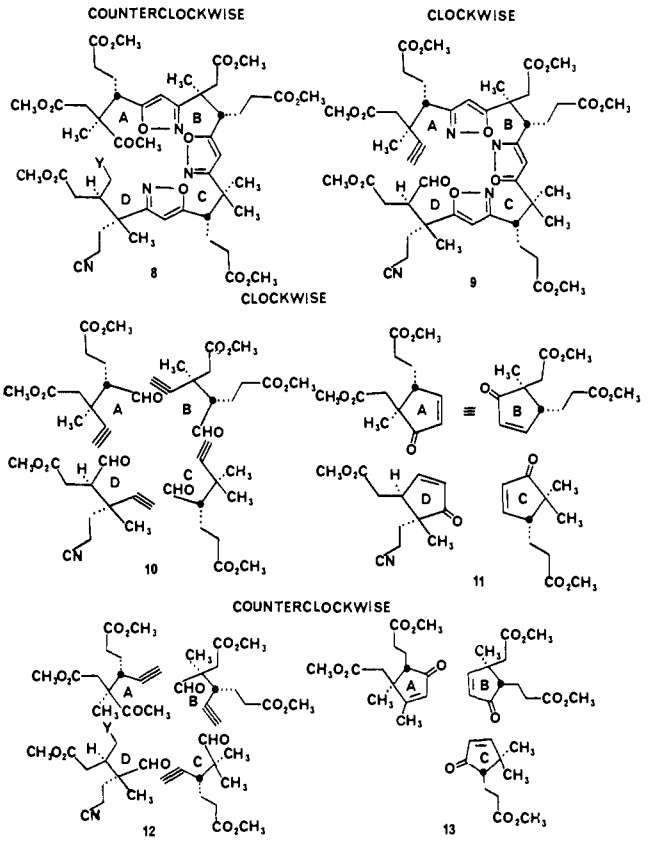


5 **7** **6**

in the molecule. It is the purpose of this and the following paper to present a synthetic plan and experimental support thereof which we believe to be capable of satisfying each of these criteria.

Our previous studies[5,6] demonstrated that, in principle, all of the essential features of the A/D-seco corrin complex (**3**) can be incorporated into either of two triisoxazole nuclei (**8** or **9**) which for the sake of convenience we shall refer to as the "counterclockwise approach" or the "clockwise approach" (see Scheme I). Each of these substances, in turn, can be assembled

Scheme I

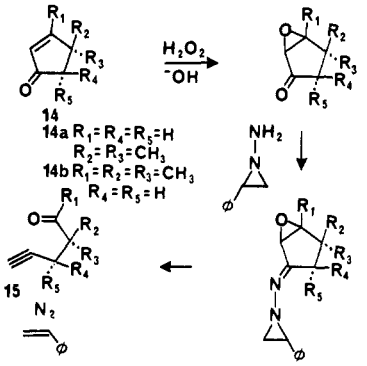


8 **9** **10** **11** **12** **13**

from four *relatively* simple subunits **10A–D** or **12A–D**. It is instructive to note that in the case of the clockwise approach (**10**) the A and B subunits are, in fact, identical. Furthermore,

although the C and D units are different and nontrivial, it should be noted that there are some singularly striking structural *and* stereochemical similarities between all four subunits. With the sole exception of the D ring in the counterclockwise precursors (**12A–D**), the same structural and stereochemical similarities are evident.

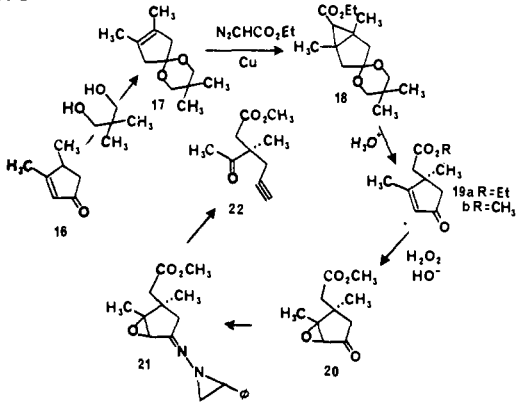
The aforementioned similarities between the vital seco corrin precursors **10A–D** and **12A–C** suggested to us the possibility of employing a common synthetic method, and, indeed, one reaction—the Eschenmoser fragmentation[7] of an appropriately substituted cyclopentenone (cf. **14** → **15**)—appeared ideally



suited for this crucial role. Therefore, for the clockwise approach we may redefine our synthetic targets as cyclopentenones **11A–D** and for the counterclockwise approach **13A–C**. When we had demonstrated to our satisfaction that simple cyclopentenones such as **14a** and **14b** readily undergo the fragmentation sequence, we turned our attention to somewhat more elaborate cases which were designed to ascertain what deleterious effects, if any, the presence of appropriately incorporated acetate or propionate side chains might have on the chemistry to be utilized in the synthesis of triisoxazoles **8** or **9**.

Ketalization of the readily prepared[8] cyclopentenone **16** was accompanied by acid-catalyzed double bond migration as we had hoped for (Scheme II). Cyclopropanation of this inter-

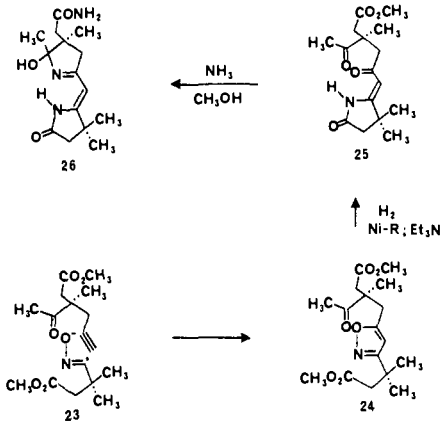
Scheme II



mediate (**17**) with ethyl diazoacetate and copper-bronze provide **18** as a mixture of epimers which were not separated but directly cleaved by trans-dioxonolation with acetone and *p*-toluenesulfonic acid. Trans-esterification of the resultant ethyl ester **19a** with sodium methoxide/methanol provided methyl ester **19b**. The overall yield[9] for this sequence was about 50%. Exposure of enone **19b** to alkaline hydrogen peroxide produced epoxide **20** as a mixture of diastereomers which, without purification, was converted to hydrazone **21**. Pyrolysis of **21** at 150 °C provided ynone **22** in about 60% overall yield.

Cycloaddition of nitrile oxide **23**, generated in situ from the corresponding nitro compound, with ynone **22** proceeded satisfactorily as did hydrogenolysis of the resultant isoxazole (**24**)

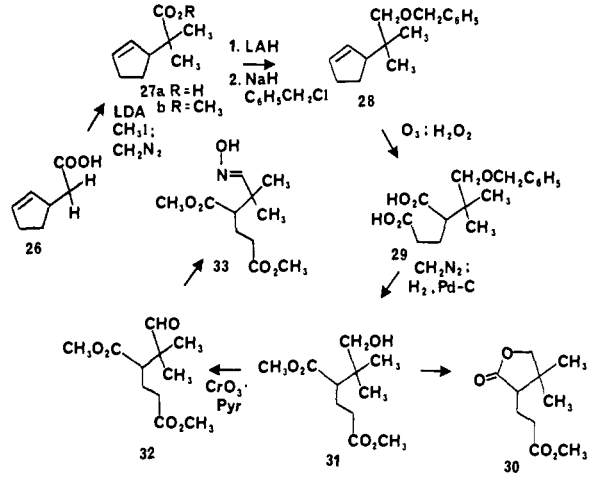
Scheme III



to the vinylogous imide **25** (Scheme III). Conversion of the latter intermediate to "semicorrin" **26** was accomplished by treatment with ammonia in methanol at room temperature. The additional observation that the methyl ester is also converted to the corresponding amide under these conditions was somewhat of a surprise in view of the fact that an even less hindered ester (**37**) remains unaffected. However, this result may be rationalized as a consequence of neighboring group participation involving the carbinolamine derived from addition of ammonia across the carbonyl group of the methyl ketone.

A rather different route was selected to study the effect of a propionate side chain (see Scheme IV). Stepwise alkylation

Scheme IV

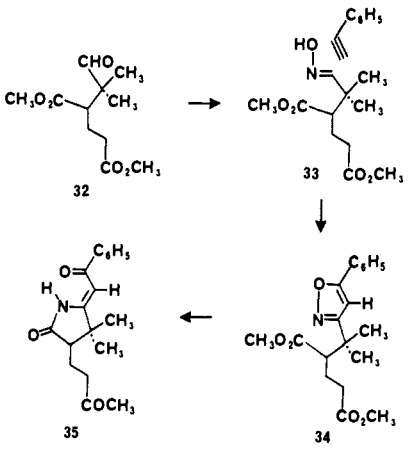


of 2-cyclopenten-1-acetic acid (**26**) with methyl iodide and lithium diisopropylamide (LDA) as the base[10] proceeded very smoothly as did esterification of the resultant acid (**27a**) with diazomethane. Reduction of ester **27b** with lithium aluminum hydride and protection of the alcohol as the benzyl ether (**28**) also proceeded in high yield. Oxidative cleavage of the double bond was accomplished by treatment with ozone in methanol at −78 °C followed by an alkaline hydrogen peroxide workup. In addition to the desired diacid (**29**), about 15% of the product was lactone **30**. Therefore, it is apparent that at some stage during this reaction sequence partial oxidative cleavage of the benzyl ether had occurred. The crude diacid **29** was esterified with diazomethane and the protecting group removed by hydrogenolysis to provide pure diester **31**. Not surprisingly, this substance was very labile and rapidly cyclized to the same lactone (**30**) obtained above when exposed to a trace of acid. Nevertheless, by working carefully **31** could be oxidized in high yield to aldehyde **32** from which oxime **33** was readily prepared.

Since intermediate **33** contains many of the same features

found in the actual ring C of cobyric acid, two model studies were undertaken in order to accumulate spectral data for subsequent investigations. In the first of these, aldoxime **33** was converted in situ to the corresponding nitrile oxide by treatment with *N*-bromosuccinimide and triethylamine in DMF[11] in the presence of phenylacetylene (Scheme V). Hydrogenolysis of

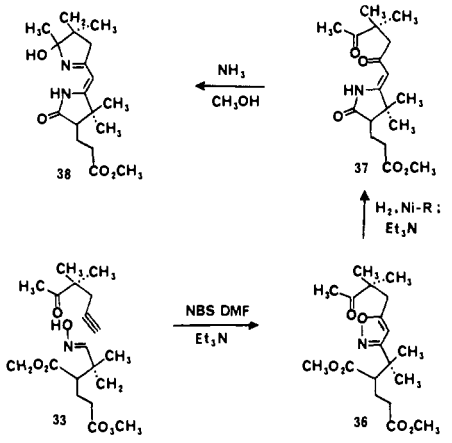
Scheme V



the isoxazole (**34**) obtained in this manner and subsequent ring closure provided vinylogous imide **35**.

In a similar fashion aldoxime **33** was transformed into isoxazole **36** and thereafter vinylogous imide **37** (Scheme VI).

Scheme VI



Incorporation of the second nitrogen was executed as described previously (**25** → **26**) providing "semicorrin" **38**. Based on the success of these experiments, it is apparent that the various required side chains are completely compatible with the methodology outlined above and encouraged us to continue on the work described in the following paper.[12]

Experimental Section[13]

Cyclopentene Ketal 17. 3,4-Dimethoxycyclopentenone[8] (220 g, 2.0 mol), 2,2-dimethyl-1,3-propanediol (312 g, 3.0 mol), and tosic acid (0.2 g) were heated to reflux in 1500 ml of toluene with azeotropic removal of water for 18 h at which time the reaction was stopped due to darkening of the solution, even though only 85% of the theoretical amount of water had been collected. Upon cooling to 5 °C most of the sparingly soluble excess glycol precipitated and was removed by filtration. The filtrate was washed with 3 × 350-ml portions of 0.5 N $NaHCO_3$ and the toluene solution distilled through a 12-in. Vigreaux column at atmospheric pressure until the bulk of the toluene had been removed. Fractional distillation of the residue through a 12-in. column packed with glass helices gave unreacted enone (74.8 g), bp 63–65 °C (2.5 mm), and ketal **7** (214 g), bp 80–83 °C (1.0 mm): yield 78% (based on recovered cyclopentenone); ir (film) 1470 (m), 1330 (m), 1245 (m), 1205 (m), and 1110 (s) cm^{-1}; ^1H NMR (CCl_4) δ 0.9 (s, 6 H), 1.6 (m, 6 H), 2.5 (m, 4 H); 3.44 (s, 4 H); mass spectrum *m/e* 196.

Ketal Ester 18. A mixture of ketal **17** (83.8 g, 0.48 mol) and finely divided copper–bronze (6.1 g, 9.6 mmol) was heated to 95 °C under N_2. To this hot mixture was added ethyl diazoacetate (82 g, 0.72 mol) dropwise at such a rate that N_2 evolution could be controlled (~5 h). The reaction was initiated by the addition of 15–20 drops of ethyl diazoacetate and waiting (15–30 min) for the first signs of N_2 evolution before proceeding with further additions. After the addition was complete, heating was continued for an additional 0.5 h. The dark colored solution was cooled to room temperature and the copper removed by filtration through Celite. Removal of the solvent and fractional distillation through a short Vigreaux column gave a forerun consisting of starting ketal, diethyl fumarate, and diethyl maleate followed by ketal ester **18** (94.2 g, 70%), bp 110–120 °C (0.2 mm), as a light-yellow oil which solidified on standing. An analytical sample was obtained by recrystallization from ethanol–water to give white crystals (mp 63–64 °C): ir (KBr) 2960 (m), 2760 (m), 1725 (s), 1255 (s), and 1090 (s) cm^{-1}; ^1H NMR (CCl_4) δ 0.9 (s, 6 H), 1.22 (t, J = 7 Hz, 3 H), 1.26 (s, 6 H), 1.75–2.5 (four br singlets, 5 H), 3.25 (br s, 2 H), 3.4 (br s, 2 H), 4.0 (q, J = 7 Hz, 2 H); mass spectrum *m/e* 282.

Enone 19a. Ketal ester **18** (90.6 g, 0.32 mol) was dissolved in 1500 ml of acetone, treated with tosic acid (9.0 g), and heated to reflux for 24 h. After cooling to room temperature the solution was allowed to stand for 48 h, and then the acetone was removed under reduced pressure and the residue poured into 1 N $NaHCO_3$. This mixture was extracted with 5 × 100-ml portions of CH_2Cl_2 and the combined organic layers backwashed with 1 N $NaHCO_3$, brine, and dried over $MgSO_4$. Removal of the solvents and distillation yielded 59.8 g (95%) of pure enone **19a**: bp 92–95 °C (0.25 mm); ir (film) 1730 (vs), 1690 (vs), 1620 (s), 1240 cm^{-1}; ^1H NMR (CCl_4) δ 1.22 (t, J = 7 Hz, 3 H), 1.32 (s, 3 H), 2.03 (d, J = 14 Hz, 1 H), 2.06 (d, $J \simeq$ 1 Hz, 3 H), 2.48 (s, 2 H), 2.56 (d, J = 14 Hz, 1 H), 4.05 (q, J = 7 Hz, 2 H), 5.72 (q, $J \simeq$ 1 Hz, 1 H); mass spectrum *m/e* 196.

Enone 19b. Ethyl ester **19a** (59 g, 0.31 mol) was dissolved in 200 ml of dry CH_3OH and added to a solution of 300 ml of CH_3OH in which 0.7 g of Na had been dissolved. The solution was refluxed for 8 h, cooled to room temperature, and the bulk of the CH_3OH removed under reduced pressure. The residue was added to dilute HCl and extracted with 3 × 100 ml of CH_2Cl_2. The combined extracts were washed with H_2O, brine, and dried over $MgSO_4$. Removal of the solvent and distillation gave methyl ester **19b** (48.5 g, 86%): bp 92–95 °C (0.25 mm); ir (film) 1730 (vs), 1695 (vs), 1620 cm^{-1}; ^1H NMR (CCl_4) δ 1.30 (s, 3 H), 2.03 (d, J = 16 Hz, 1 H), 2.04 (d, $J \simeq$ 1 Hz, 3 H), 2.48 (s, 2 H), 2.65 (d, J = 16 Hz, 1 H), 3.64 (s, 3 H), 5.83 (q, $J \simeq$ 1 Hz, 1 H); mass spectrum calcd for 196.1099, found 196.1103. A 2,4-DNP derivative was recrystallized from EtOH–$CHCl_3$, mp 133–135 °C dec.

Ynone 22. Epoxyketone **20** (570 mg, 2.89 mmol) and *N*-amino phenylaziridinium acetate (617 mg, 3.18 mmol), prepared according to the Eschenmoser procedure,[7] were dissolved in 15 ml of CH_2Cl_2 at 0 °C and stirred for 1 h. The solution was extracted with 8% $NaHCO_3$ (3 × 10 ml) and the organic layer dried over $MgSO_4$ and then concentrated to provide 900 mg (102%) of crude hydrazone **21** which was used in the next step without purification.

The crude hydrazone (500 mg, 1.61 mmol) was placed in the Kugelrohr apparatus and heated to 150 °C at 1.5 mm. Ynone **22** (181 mg, 62%) collected as essentially pure compound in the first bulb. An analytical sample was prepared by preparative layer chromatography (silica, $CHCl_3$:EtOAc 4:1): ir (film) 3190, 1735, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (s, 3 H), 2.75 (s, 1 H), 2.68 (s, 1 H), 2.52 (d, 2 H, J = 2.5 Hz), 2.20 (s, 3 H), 2.08 (t, 1 H, J = 2.5 Hz), 1.31 (s, 3 H); mass spectrum calcd for 182.0943, found 182.0946. A 2,4-DNP derivative melted at 82–85 °C.

Isoxazole 24. A solution of the nitro ester (580 mg, 3.3 mmol) in 0.5 ml of Et_3N and 12.8 ml of dry benzene was added over 56 h to acetylene **22** (1.49 g, 8.2 mmol) and phenyl isocyanate (790 mg, 6.7 mmol) in 1.3 ml of benzene. The solution was then stirred for 30 h at room temperature. The solution was then filtered, evaporated, and distilled in a Kugelrohr apparatus [155 °C (0.1 mm)]. The residue was pure isoxazole **24** (749 mg, 66%) as a viscous oil which was homogeneous by TLC: ir (film) 1740, 1725, 1650, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.40 (s, 6 H), 2.17 (s, 3 H), 2.55 (s, 2 H), 2.59 (s, 2 H), 3.01 (s, 2 H), 3.57 (s, 3 H), 3.61 (s, 3 H), 5.84 (s, 1 H); mass spectrum calcd for 339.1681, found 339.1681.

Vinylogous Imide 25. A solution of isoxazole **24** (250 mg, 0.74 mmol) and W-2 Raney nickel (2.5 g) in 10 ml of CH_3OH was stirred

under H_2 until the theoretical amount of H_2 was consumed. The solution was filtered and treated with 0.2 ml of Et_3N for 12 h. Evaporation of the solvents and preparative layer chromatography (alumina, $CHCl_3$) gave **24** (129 mg, 57%) as a clear oil: ir (film) 3300, 1755, 1710, 1660, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 6 H), 1.31 (s, 3 H), 2.20 (s, 3 H), 2.29 (s, 2 H), 2.60 (d, J = 4 Hz, 2 H), 2.86 (d, J = 5 Hz, 2 H), 3.59 (s, 3 H), 6.27 (s, 1 H); mass spectrum calcd for 309.1574, found 309.1598.

Semicorrin 26. A solution of vinylogous imide **25** (102 mg, 0.33 mmol) in 3 ml of CH_3OH was added to 6 ml of CH_3OH saturated with NH_3. The stoppered solution was allowed to stand for 56 h at room temperature. Evaporation of the solvent and preparative layer chromatography (alumina, $CHCl_3$) gave semicorrin **26** as a clear oil: ir ($CHCl_3$) 3415, 3200, 1700, 1650, 1570 cm^{-1}; ^{1}NMR ($CDCl_3$) δ 1.20 (s, 3 H), 1.30 (s, 6 H), 1.34 (s, 3 H), 2.28 (s, 2 H), 2.31 (s, 2 H), 2.62 (s, 2 H), 4.83 (s, 1 H), 6.02 (b, 4 H); mass spectrum calcd for 275.1633, found 275.1654.

Cyclopentene 27a. Diisopropylamine (22 g, 2.2 mol) was dissolved in 750 ml of THF in a 3-l., three-necked flask fitted with mechanical stirrer, thermometer, and N_2 bubbler. The solution was cooled to −5 °C, and *n*-BuLi (942 ml, 2.2 mol, hexane, 2.34 M) was added dropwise at such a rate that the temperature was maintained below 5 °C. After addition was complete, stirring was continued for 0.5 h at 0 °C and then 0.5 h at room temperature. The solution was then cooled to 0 °C and 2-cyclopenten-1-acetic acid (126 g, 1 mol) was added slowly maintaining the temperature below 5 °C. The solution was allowed to stir for 0.25 h at 0 °C after addition and then warm to room temperature and stirred 1 h. The solution was cooled again to 0 °C and CH_3I (213 g, 1.5 mol) added to the heterogeneous solution. The mixture was stirred at 0 °C for 1 h and then at room temperature for 6 h. The viscous solution was poured into 1.5 l. of water, the layers were separated, and the aqueous layer extracted with ether (3 × 250 ml). The combined organic layers were washed with water (200 ml), brine (3 × 100 ml), and dried over Na_2SO_4. Removal of the solvent and distillation yielded 135.8 g (97%) of a pale-yellow oil [bp 134–136 °C, (20 mm)]. This material is a mixture of diastereomers of monomethylated acid along with small amounts of unalkylated and dialkylated acid. This crude mixture was then subjected to the same procedure as just described to incorporate the second methyl group. The quantities were THF (750 ml), *i*-Pr_2NH (222 g, 2.2 mol), *n*-BuLi (942 ml, 2.2 mol), mixture of acids (133.1 g, 0.95 mol), and CH_3I (142 g, 1.0 mol). In this manner 135 g (92.5%) of **27a** was obtained, bp 110–12 °C (1.6 mm), which solidified upon standing (mp 25–27 °C): ir (film) 1695 cm^{-1}; ^1H NMR δ 1.13 (s, 3 H), 1.18 (s, 3 H), 1.40–2.50 (m, 4 H) 2.85–3.28 (m, 1 H), 5.50–5.93 (m, 2 H), 12.15 (s, 1 H); mass spectrum calcd for 154.0994, found 154.0988.

Ester 27b. The acid **27a** was treated with diazomethane in the usual way to provide ester **27b** (98%): bp 54–56 °C (2.5 mm); ir (film) 1730, 1365, 1385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.15 (s, 3 H), 1.90 (m, 4 H), 3.05 (m, 1 H), 3.67 (s, 3 H), 5.70 (m, 2 H).

Benzyl Ether 28. Ester **27b** was reduced with $LiAlH_4$ in ether in the usual way to provide the corresponding alcohol (100%): bp 92–94 °C (15 mm); ir (film) 3380, 3065, 1370, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (s, 6 H), 1.4–2.9 (m, 7 H), 3.39 (s, 2 H), 5.77 (m, 2 H). This alcohol (28 g, 0.20 mol) was added rapidly to a suspension of NaH (9.6 g, 0.40 mol) in THF (400 ml) followed by benzyl chloride (38 g, 0.30 mol). The mixutre was refluxed for 12 h then cooled and added cautiously to water (500 ml). The layers were separated, and the aqueous layer was extracted with ether (3 × 100 ml). The combined organic extracts were washed with H_2O (50 ml), brine (3 × 100 ml), and dried over K_2CO_3. Concentration and distillation of the residue yielded 44.2 g (96%) of **28**: bp 84–86 °C (0.04 mm); ^{H}NMR ($CDCl_3$) δ 0.86 (s, 3 H), 1.72 (m, 2 H), 2.22 (m, 2 H), 2.78 (m, 1 H), 3.18 (s, 2 H), 4.47 (s, 2 H), 5.69 (m, 2 H), 7.30 (s, 5 H); mass spectrum calcd for 230.1671, found 230.1667.

Diester 31. Olefin **28** (8.6 g, 37 mmol) was dissolved in 200 ml of CH_3OH and placed in a gas washing bottle. One equivalent of ozone was passed through this solution at −78 °C. The solution was then purged with N_2 and the cold mixture poured into an aqueous solution of NaOH (4.43 g, 111 mmol in 75 ml) and stirred for 2 h at room temperature. The methanol was removed under reduced pressure and the basic aqueous solution extracted with ether (3 × 25 ml). These extracts contained 1.7 g (7.2 mmol) of unreacted **28**. The aqueous layer was treated with 30% H_2O_2 (37 mmol) and warmed to 45 °C for 2 h. Pd (10%) on charcoal was added to destroy excess peroxide, and the solution was saturated with Na_2SO_4, acidified, and extracted with ether (3 × 100 ml) to yield 8.3 g of crude product which esterified with excess diazomethane in the usual fashion. Column chromatography (Al_2O_3 III, 50 g per g of product, 7:3 ether:hexane) yielded methyl benzoate, the benzyl ether of **31**, then lactone **30**. Benzyl ether of **31**: ir (CCl_4) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 1.0 (s, 3 H), 1.6–2.6 (m, 5 H), 3.20 (m, AB, 2 H), 3.64 (s, 3 H), 3.59 (s, 3 H), 4.46 (s, 2 H), 7.30 (s, 5 H); mass spectrum *m/e* 322. Lactone **30**: ir (film) 1780, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (s, 3 H), 1.15 (s, 3 H), 1.5–2.80 (m, 5 H), 3.53 (s, 3 H), 3.87 (s, 2 H); mass spectrum *m/e* 200. The benzyl ether of **31** (322 mg, 0.01 mol) was dissolved in EtOH (15 ml) and 100 mg of 10% Pd/C suspended in the solution. After hydrogenolysis at 50 psi for 12 h, the catalyst was filtered off, washed with EtOH, and the combined extracts evaporated to yield 230 mg (98%) of the desired alcohol **31**. This substance proved to be very labile being readily converted to lactone **30** and was used directly in the next step: ir (film) 3500, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (s, 3 H), 0.95 (s, 3 H), 1.6–2.6 (m, 5 H), 3.37 (s, 2 H), 3.71 (s, 6 H).

Aldehyde 32 and Oxime 33. Alcohol **31** (266 mg, 1.15 mmol) was oxidized with the CrO_3- (690 mg, 6.9 mmol) pyridine (1.09 g, 13.8 mmol) complex in 20 ml of CH_2Cl_2. The reaction mixture was filtered through neutral alumina, washed with dilute acid, and concentrated to yield 243 mg (92%) of aldehyde **32**: ir (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 3 H), 1.13 (s, 3 H), 1.6–2.8 (m, 5 H), 3.68 (s, 6 H), 9.27 (s, 1 H). Aldehyde **32** (400 mg, 1.74 mmol), NH_2OH·HCl (180 mg, 2.62 mmol), and pyridine (7 ml) were stirred for 6 h at room temperature. The solution was diluted with ether (15 ml), washed with 6 N HCl (2 × 5 ml), H_2O (5 ml), and dried over $MgSO_4$. Concentration yielded 557 mg of pure oxime (87%): ir (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (s, 6 H), 1.7–2.7 (m, 5 H), 3.67 (s, 3 H), 3.72 (s, 3 H), 7.41 (s, 1 H), 8.43 (bs, 1 H); mass spectrum *m/e* 245.

Isoxazole 34. Aldoxime **33** (480 mg, 1.96 mmol) was dissolved in 4 ml of dry DMF and cooled to 0 °C under N_2. *N*-Bromosuccinimide (524 mg, 2.94 mmol) in 3.5 ml of DMF was added dropwise by syringe to the magnetically stirred solution while maintaining the temperature between 0–5 °C. The mixture was stirred for 1 h at this temperature, and then a solution of triethylamine (297 mg, 2.94 mmol) and phenylacetylene (1.0 g, 9.8 mmol) was added dropwise, again at 0–5 °C. The solution was stirred at room temperature for 12 h, then poured into H_2O (20 ml), extracted with ether (3 × 20 ml), dried over $CaCl_2$, and concentrated to yield 557 mg (87%) of crude isoxazole. An analytical sample was obtained by column chromatography (silica, 9:1 hexane:ether): ir (CCl_4) 1735, 1615, 1595, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 1.48 (s, 3 H), 1.8–2.5 (m, 4 H), 2.8 (m, 1 H), 3.60 (s, 3 H), 3.67 (s, 3 H), 6.50 (s, 1 H), 7.50 (m, 5 H). This material was used directly in the reduction step.

Vinylogous Imide 35. The procedure was the same as for compound **25**. The product was purified by preparative layer chromatography (silica, 7:3 $CHCl_3$:EtOAc, R_f = 0.7): ir (CH_2Cl_2) 1765, 1663, 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (s, 3 H), 1.38 (s, 3 H), 1.7–2.8 (m, 5 H), 3.66 (s, 3 H), 6.14 (s, 1 H), 7.4 (m, 3 H), 7.95 (m, 2 H); mass spectrum calcd for 315.1470, found 315.1460.

Isoxazole 36. A solution of *N*-bromosuccinimide (1.45 g, 8.1 mmol) in 11.5 ml of dry DMF was added dropwise at 0 °C to oxime **33** (1.32 g, 5.4 mmol) in 13 ml of DMF and the mixture stirred for 1 h at room temperature. 3,3-Dimethyl-5-pentyn-2-one (3.42 g, 27.6 mmol) in triethylamine (0.82 g, 8.1 mmol) was then added dropwise at 0 °C. The solution was stirred for 6 h at room temperature and then poured into H_2O and extracted with ether. After removal of the ether the mixture was distilled in the Kugelrohr apparatus [100 °C (0.2 mm)] to separate volatile starting material from the desired product. The residue was chromatographed (alumina, activity III, benzene) to give pure isoxazole **36** (1.12 g, 57%) as an oil: ir (film) 1740, 1710, 1600 cm^{-1}; ^{1}N NMR ($CDCl_3$) 1.19 (S, 6 H), 1.29 (s, 3 H), 1.33 (s, 3 H), 1.54–2.73 (m, 5 H), 2.10 (s, 3 H), 2.87 (s, 2 H), 3.57 (s, 6 H), 5.79 (s, 1 H); mass spectrum calcd for 367.1994, found 367.1976.

Vinylogous Imide 37. The procedure was the same as for compound **25**. The product was purified by preparative layer chromatography (alumina, $CHCl_3$) providing a 78% yield of **37** as a clear colorless oil: ir (film), 3300, 1740, 1705, 1660, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (s, 3 H), 1.19 (s, 6 H), 1.29 (s, 3 H), 1.51–2.82 (m, 5 H), 2.17 (s, 3 H), 2.72 (s, 2 H), 3.64 (s, 3 H), 5.29 (s, 1 H); mass spectrum calcd for 337.1888, found 337.1883.

Semicorrin 38. A solution of vinylogous imide **37** (133 mg, 0.39 mmol) in 4 ml of CH_3OH was added to 8 ml of CH_3OH saturated with NH_3. The stoppered solution was allowed to stand at room temperature for 56 h. Removal of the solvent and preparative layer

chromatography (alumina, $CHCl_3$) gave semicorrin **38** as a clear colorless oil: ir ($CHCl_3$) 3300, 1730, 1650, 1590, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (s, 3 H), 1.09 (s, 3 H), 1.15 (s, 3 H), 1.29 (s, 3 H), 1.37 (s, 3 H), 1.59–2.78 (m, 5 H), 2.50 (s, 2 H), 3.64 (s, 3 H), 4.88 (s, 1 H), 5.11 (b, 2 H); mass spectrum ($-H_2O$) calcd for 318.1942, found 318.1930.

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Studies on the Synthesis of Vitamin B_{12}. 2. Synthesis of the "Southern" Half

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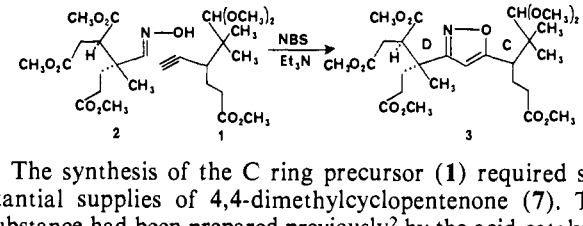
Abstract: The synthesis of racemic precursors of the C and D rings (**1** and **2**) of cobyric acid is presented together with their combination into a latent form (**3**) of the "southern" half of the vitamin.

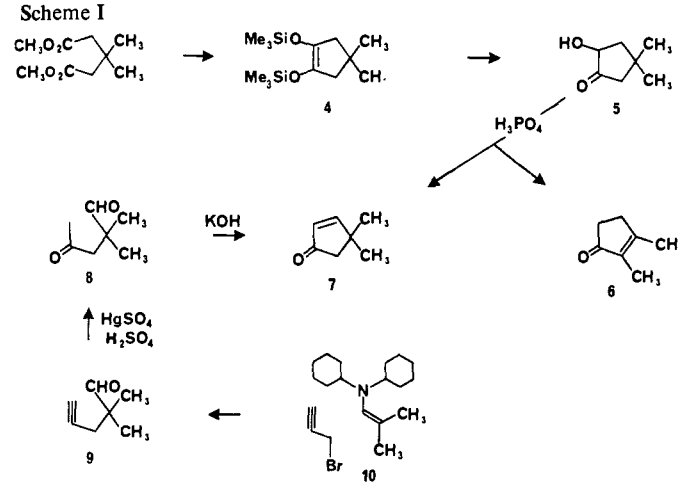
In the preceding paper[1] the close structural and stereochemical features of the "counterclockwise" precursors to the A, B, and C rings of cobyric acid were noted, and a general method of approach for their synthesis was presented together with some informative model studies. In this paper we describe the synthesis of the *racemic* forms of the C and "anomolous" D rings (**1** and **2**) and their combination into a latent form (**3**) of the "southern" half of the vitamin.



2 1 3

The synthesis of the C ring precursor (**1**) required substantial supplies of 4,4-dimethylcyclopentenone (**7**). This substance had been prepared previously[2] by the acid-catalyzed dehydration of acyloin **5** which, in turn, can be obtained directly from 3,3-dimethylglutarate or, alternatively, through the intermediacy of bis(trimethylsilyloxy)cyclopentene **4**.[3] Unfortunately, as shown more recently[4] and confirmed by others,[5] the dehydration of **5** to **7** is accompanied by substantial amounts of the rearranged cyclopentenone **6** which prompted us to investigate an alternate method (see Scheme I). Alkylation of the *N,N*-dicyclohexylenamine (**10**) of isobutyraldehyde with propargyl bromide gave aldehyde **9** as described previously.[6] The usual mercuric ion catalyzed hydration of the terminal acetylene provided ketoaldehyde **8** which suffered

Scheme I



intramolecular aldol condensation when exposed to base. The overall yield for this sequence was reproducibly in the 50–60% range and allowed us to build up a substantial supply of pure enone **7**.

Attempts to alkylate **7** directly with methyl acrylate or acrylonitrile were uniformly unsuccessful. However, treatment of **7** with ethyl formate and base provided the activated α-formyl derivative **11** in high yield. Although this substance could be alkylated with methyl acrylate to provide **13** directly, it proved to be more expeditious to alkylate first with acrylo-