Stereocontrolled Synthesis of a Nonracemic Vitamin B_{12} A−B-Semicorrin

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Received January 6, 1997[⊗]

Abstract: The first synthesis of a vitamin B_{12} A−B-semicorrin **44** is described. Both A and B rings were prepared from the same precursor, enamide **40**, which is obtained by a sequence of sigmatropic rearrangements and a biomimetic oxylactonization. The coupling has been achieved via Eschenmoser sulfide contraction. A−B-semicorrin **44** allows a new approach toward vitamin B_{12} and other uroporphinoids.

Vitamin B_{12} (**1**) belongs to the family of the uroporphinoid cofactors, the so-called "pigments of life",[1,2] which includes such vital substances as chlorophyll *a* (**4**), used by plants in photosynthesis, and heme (**7**), the red blood pigment which is essential for oxygen transport. Other members of this family are siroheme (**6**), which has been discovered in sulfite and nitrite reductases of bacteria and plants, and the nickel-containing factor F 430 (**5**), the prosthetic group for the coenzyme M reductase of primitive methanogenic bacteria (Figure 2).[3]

The cobalamins (**1**), methylcobalamin (**2**), and coenzyme B_{12} (**3**) (Figure 1) contain a reduced tetrapyrrole, the *corrin* macrocycle, which is less symmetric than porphyrin and characterized by the direct junction of rings A and D. The ligand is decorated with methyl, acetamide, and propionamide substituents. This creates the situation in which nine of the 10 sp^3 carbons are stereogenic centers, with three of them being quaternary.

After the brilliant and extensive studies by R. B. Woodward and A. Eschenmoser, culminating in the first two total syntheses[4] of **1** and in the discovery of the Woodward−Hoffmann rules,[5] no further synthesis has been achieved, despite promising approaches by Stevens and Jacobi.[6] In this paper, we wish to disclose our own work in this area, which led to the first synthesis of a northern (A−B) vitamin B_{12} semicorrin.

Results and Discussion

Strategy and Retrosynthetic Analysis. The A−B Strategy. It is known from the work of Bernauer et al.[7] that cobyric acid (**8**), a corrinoid natural product and biosynthetic intermediate

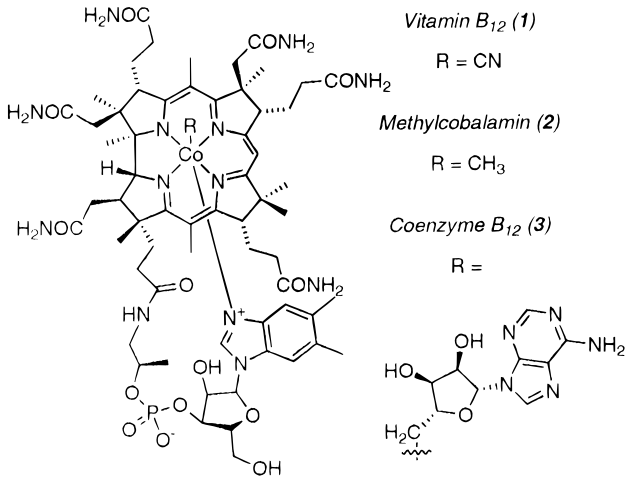

Figure 1. Vitamin B_{12} and its coenzymatic forms.

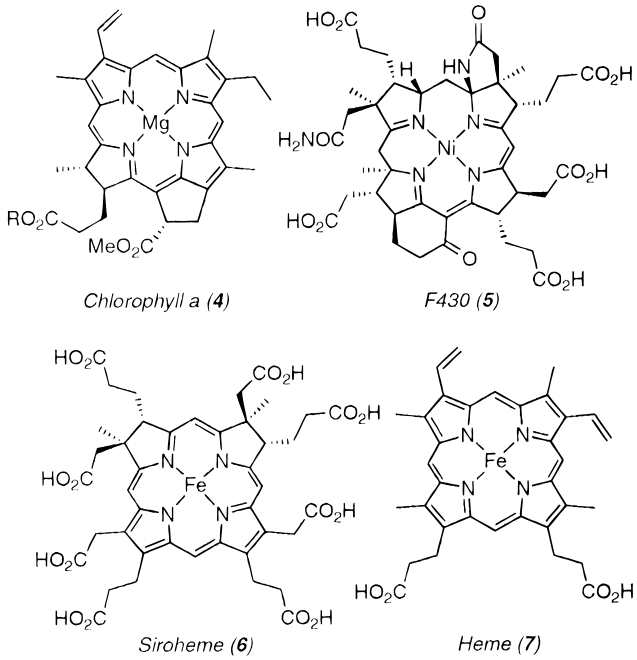

Figure 2. Uroporphinoid cofactors: "the pigments of life".

of **1**, can be transformed into the vitamin. In view of the structural similarities of the A−B part in **1**, **6**, and **5**, we use a convergent and flexible A−B + C−D strategy, which could

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[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1997.

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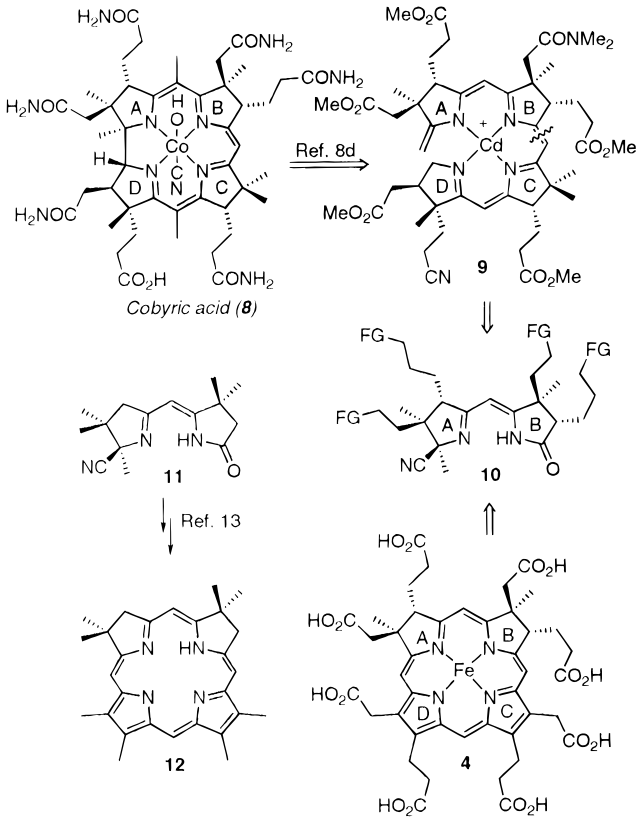
S0002-7863(97)00051-6 CCC: $14.00

Scheme 1



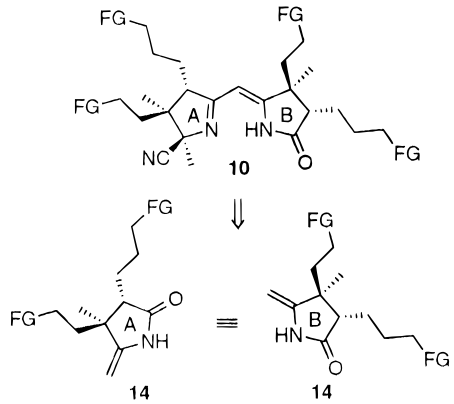
give access to all of these compounds by only varying the C−D portion. Furthermore, Eschenmoser's photoinduced A−D-secocorrin cyclization[4d,8] is perfectly suited to solve the "zero-linkage problem", i.e. the direct junction of rings A and D in **1**. This leads to the A−D-secocorrin **9** as a precursor. Further bond disconnection between rings B and C gives A−B-semicorrin **10**. Interestingly semicorrin **11** has been used to synthesize model isobacteriochlorin **12**.[9] Analogously, **10** could be used in a synthesis of **6**, besides the synthesis of **9** and **8** (Scheme 1).

Retrosynthetic Analysis of 10. Both rings, A and B, contain a quaternary stereogenic center, bearing an acetate and a methyl group vicinal to a tertiary stereogenic center with a propionate side chain. They should therefore be accessible from the *same* intermediate, namely enamide **14**. This reduces the synthesis of semicorrin **10** to a synthesis of enamide **14** and its dimerization (Scheme 2).

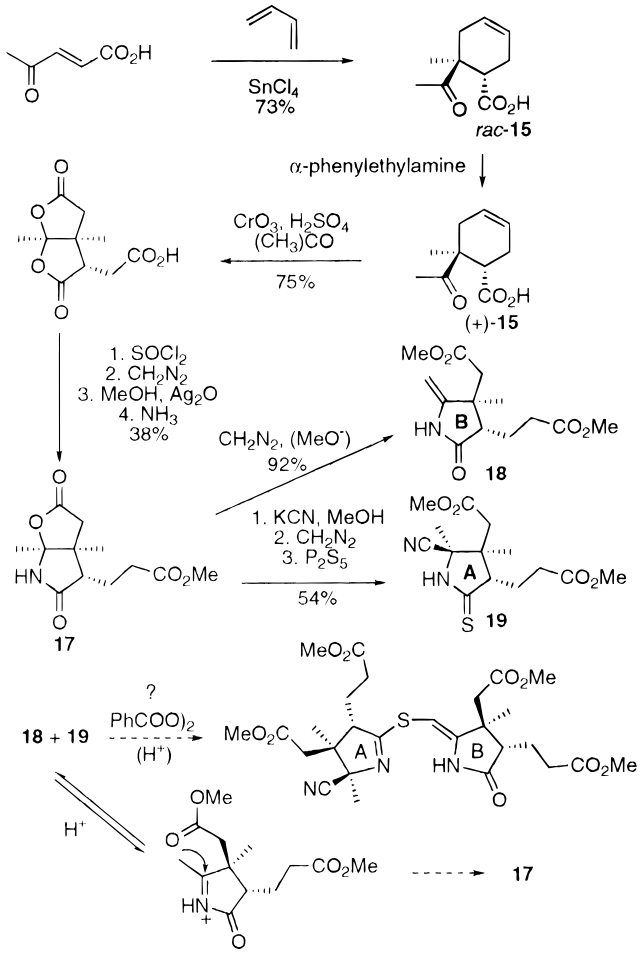
Interestingly, such an approach could have also been realized *via* Eschenmoser's synthesis of the ring fragments A and B as outlined in Scheme 3.[4d]

Although this has never been attempted, the A and B rings could in principle be connected by means of a sulfide contraction between enamide **18** and thioamide **19** (*vide infra*). However, under the acidic conditions which are required in the oxidative precoupling to the sulfide, it is likely that the methyl ester in **18** exerts a neighbouring group effect and recyclizes to lactone

Scheme 2



Scheme 3. Eschenmoser's Synthesis of Ring A and B Fragments



17 via an acyl iminium intermediate. Moreover, the Eschenmoser approach has three additional drawbacks: (a) it includes optical resolution on the stage of carboxylic acid *rac*-**15**, which implies a considerable loss of material; (b) the two stereogenic centers in **18** and **19** are configurationally not independent, as they are generated by the initiating Diels−Alder reaction; (c) the side chains in **18** and **19** are not easily variable with respect to chain length and functionalization.

Therefore, we decided to use a different approach to ring A and B fragments which is based on lactic acid as the source of chirality and utilizes sigmatropic rearrangements to establish the crucial tertiary and quaternary stereogenic centers (Scheme 4). In this way, the sequence is more flexible, predictable with respect to absolute configurations and optical purity, and does

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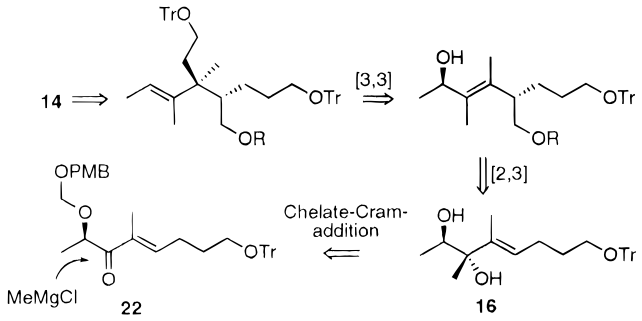
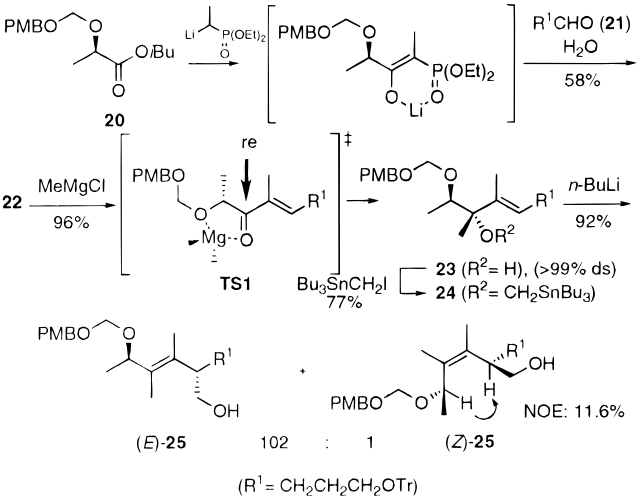
Scheme 4



Scheme 5

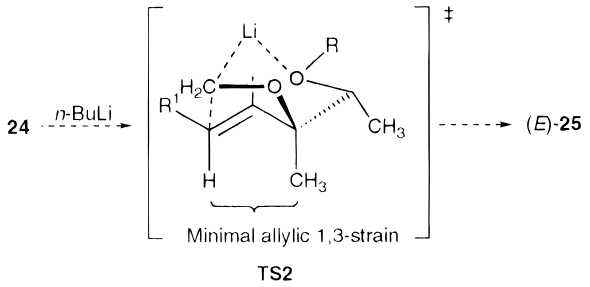


not require optical resolution. It also overcomes the problem of reactive side chain functionalities, as they are introduced as protected alcohols. Hence, enamide **14** could be prepared from allyl diol **16** *via* [3,3]-Claisen rearrangement for the construction of the quaternary center and a [2,3]-Wittig rearrangement for the tertiary center. Allyl diol **16** in turn could be elaborated from enone **22**.

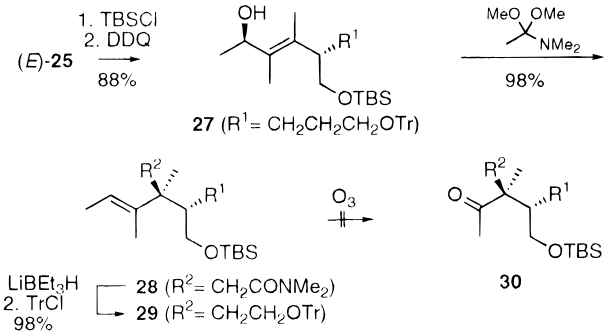
Synthesis. For the synthesis of enone **22**, we used a novel one-pot three-component synthesis of α,*β*-unsaturated ketones which has been developed in our laboratories.[10] Thus, treatment of the known lactic ester derivative **20**[11] with diethyl 1-(lithioethyl)phosphonate and then with water and aldehyde **21** (from 1,4-butanediol *via* monotritylation and Swern oxidation, see Supporting Information) gave enone **22** in 58% yield, as a single diastereomer (^{1}H and ^{13}C NMR). Presumably, this new Corey−Kwiatkowski[12] Horner−Wadsworth−Emmons tandem reaction, which creates two carbon−carbon bonds in one operation, proceeds *via* a *β*-keto phosphonate carbanion. Treatment of enone **22** with methyl magnesium chloride at low temperature gave exclusively the *anti*-allylic alcohol **23** (from NOEDS of an acetonide) in high yield. The high selectivity can be interpreted in terms of the chelate Cram model (**TS1**) (Scheme 5).[13]

Quite obviously, this connective assemblage of alcohol **23** from simple components (α-hydroxy ester + aldehyde + Grignard reagent) allows the formation of a wide variety of

Scheme 6



Scheme 7



functionalized analogues of **23** and, hence, semicorrin **10**. As semicorrins have found widespread applications as chiral catalysts,[14] this is of interest also beyond the synthesis of **1**.

We have shown that tetrasubstituted homoallylic alcohols can be formed (*E*)-stereoselectively *via* [2,3]-Wittig−Still sigmatropic rearrangement[15] from trisubstituted allylic alcohols.[13c] Thus, alcohol **23** was converted to the stannylmethyl ether **24** on treatment with potassium hydride and tri-*n*-butyl (iodomethyl)stannane.[16] Tin−lithium exchange of stannylmethyl ether **24** with *n*-butyllithium and subsequent [2,3]-Wittig−Still rearrangement at low temperature furnished the tetrasubstituted homoallylic alcohol (*E*)-**25** *with an E/Z ratio > 100:1*. The double-bond configuration was assigned by NOEDS measurement on the minor isomer (*Z*)-**25**. The stereochemical outcome of this reaction can be explaned with transition state **TS2**, where allylic 1,3-strain interactions are minimized (Scheme 6). A related transition state has recently been proposed by Kallmerten in the synthesis of trisubstituted olefins.[17]

Alcohol (*E*)-**25** was converted to **27**,[18] which underwent a highly effective and stereoselective Eschenmoser Claisen rearrangement[19] under mild conditions, to give the *γ*,*δ*-unsaturated amide **28** as a single diastereomer.[20] The stereochemical outcome of this reaction can be interpreted in terms of a chairlike transition state **TS3** (Scheme 8), in which allylic 1,3-strain interactions are minimized.[17a] Interestingly this reaction was originally designed by Eschenmoser for the creation of exactly the same quaternary stereogenic center in an intended vitamin B_{12} synthesis but was not used in the final synthesis. To our disappointment neither amide **28** nor ether **29** could be oxidized to the desired ketone **30**, presumably a result from the sterical

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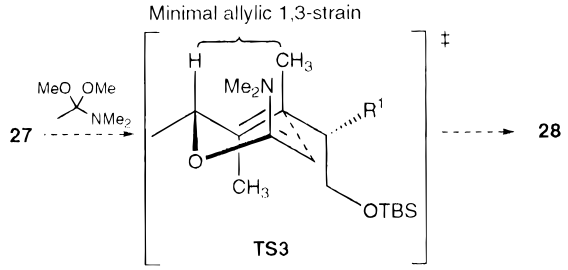
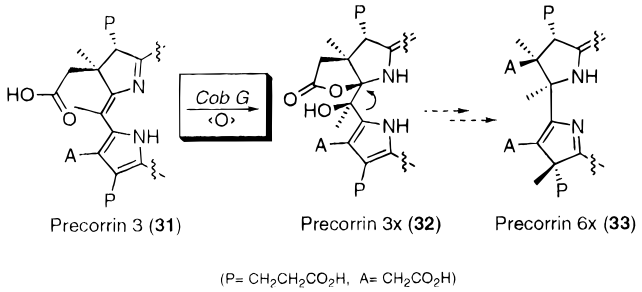
(20) Assigned from NOEDS measurements.

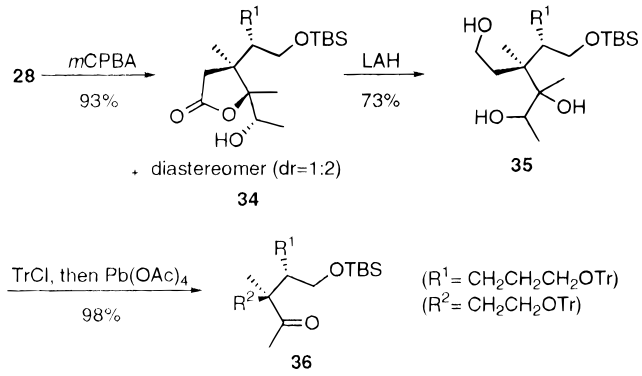
Scheme 8



Scheme 9



Scheme 10

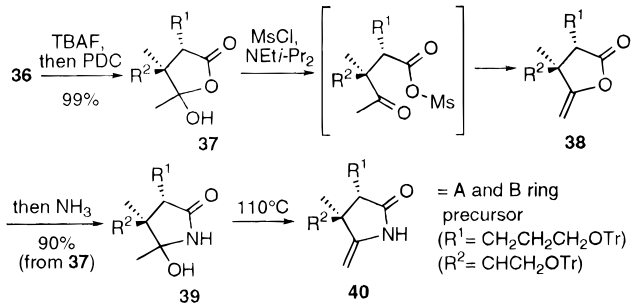


shielding of the adjacent quaternary center. A new route had to be found (Scheme 7).

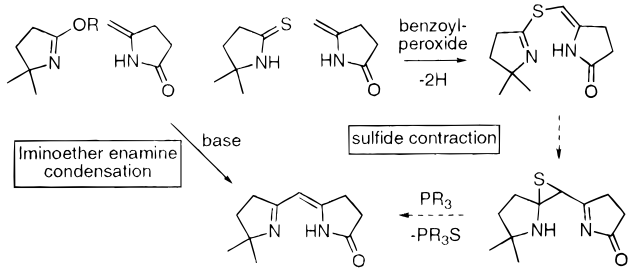
On considering the biosynthesis of vitamin B_{12},[21] we noticed that nature has to solve a similar problem (Scheme 9). The crucial ring contraction step, from precorrin-3A (**31**) to precorrin-6A (**33**) is initiated by an oxygenase (*CobG*) converting **31** into precorrin-3B (=3×) (**32**), which chemically represents an olefin oxy-lactonization. This gave us the idea to mimic the *CobG* step by converting amide **28** to the corresponding hydroxy lactone *via* an epoxidation reaction.[22]

Indeed, treatment of amide **28** with *m*-chloroperbenzoic acid furnished hydroxy lactone **34** as a mixture of diastereomers (2:1, structural assignment by NOEDS of the isolated isomers) in high yield (Scheme 10). Reduction (LAH), tritylation of the primary alcohol function of the resulting triol (**35**),[23] and in situ glycol cleavage with $Pb(OAc)_4$ gave ketone **36** in 72% overall

Scheme 11



Scheme 12



yield from lactone **34**. The absolute and relative configurations of the stereogenic centers in **36** were determined by single-crystal X-ray diffraction (Figure 3, Supporting Information).

After deprotection (TBAF) and in situ oxidation (PDC) of ketone **36**, keto acid **37** was obtained (Scheme 11). To introduce nitrogen, **37** was dehydrated to the corresponding enol lactone.[24] This is usually achieved under harsh conditions (for example, H_2SO_4, Ac_2O, HOAc).[25] Much to our surprise, we found this transformation to proceed quite readily on treating acid **37** with MsCl and Hünig's base. *At 0 °C enol lactone **38** is quantitatively formed within minutes*. The reaction presumably proceeds *via* the mixed anhydride.

From **38**, enamide **40** was then prepared with ammonia[26] and by dehydrating the intermediate keto amide **39** in vacuo. Amide **40**, which is both the precursor for rings A and B, is sensitive to moisture and is rehydrolyzed to **39**. Therefore it was not isolated and used directly for the next steps.

Dimerization of Enamide 40 *via* Sulfide Contraction. The sulfide contraction was originally developed by Eschenmoser during the synthesis of vitamin B_{12}[27,4a] because the more obvious imino ether enamine condensation, which proved to be very successful in model studies, failed with vitamin B_{12} intermediates (Scheme 12). In principle, both reactions represent aza analogous Claisen condensations, the sulfide contraction being an intramolecular version.

For the synthesis of ring A precursor **42**, the exocyclic double bond in enamide **40** was first protected as cyano lactam,[26,28] which was in situ treated with Lawesson's reagent,[26] to furnish thio lactam **42** in 88% yield from keto amide **39** (Scheme 13). Thio lactam **42** was produced as a mixture of diastereomers (6:1, NMR) in favor of the (2*R*)-isomer, which was confirmed by NOEDS of the final product. According to the protocol developed by Eschenmoser et al.,[27] treatment of a mixture of enamide **40** and thio lactam **42** with benzoyl peroxide gave the stable sulfide **43** which was isolated in 56% yield. This reaction is presumably initiated by the formation of disufide $(\mathbf{42})_2$, which

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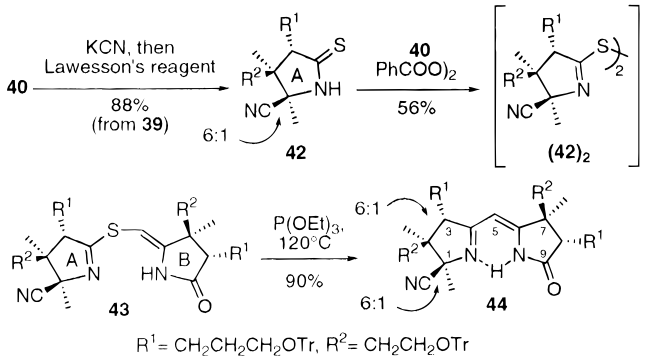
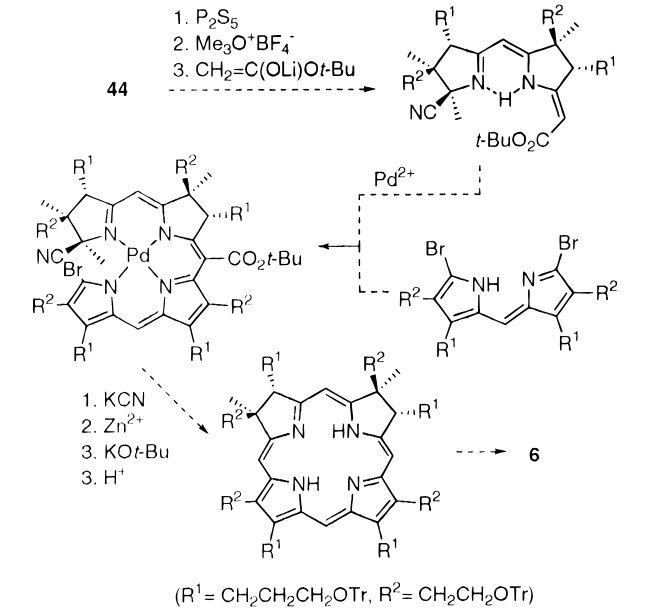
Scheme 13



Scheme 14



is cleaved by a nucleophilic attack from enamide **40**. Thereby thiolactam **42** is regenerated and can be oxidized with benzoyl peroxide again. On being heated in benzene (sealed tube, 120 °C, 70 h), **43** was converted into A−B-semicorrin **44** in 90% yield, as a mixture of four diastereomers (ca. 36:6:6:1, NMR and HPLC analysis), probably arising from an epimerization (6:1) at C-3, during the sulfide contraction.[4d] Diastereomerically pure **44** was obtained in 67% yield after HPLC separation. The structural assignment of A−B-semicorrin **44** is based on high-field NMR (600 MHz ROESY, NOESY, COSY 90, $^{13}C-^{1}H$-COSY), IR and MS spectroscopy, and combustion analysis. An obvious synthesis of siroheme from **44** is suggested in Scheme 14, which is based on the Eschenmoser synthesis of model isobachteriochlorin **12**.[9]

Conclusion. In this paper, we describe the first synthesis of a vitamin B_{12} A−B-semicorrin (**44**). By *starting from (R)-isobutyl lactate, this synthesis requires only 16 isolated intermediates. The total yield is 7%.* Key steps are a sequence of sigmatropic rearrangements, including a [2,3]-Wittig−Still rearrangement for the construction of the tertiary stereogenic centers and a [3,3]-Claisen−Eschenmoser rearrangement for the quaternary centers. Furthermore, we made use of a biomimetic oxylactonization process. The sulfide contraction was used for the final coupling reaction between a B ring enamide (**40**) and an A ring thio lactam (**42**), which has been prepared in a one-pot procedure from a ring A enamide. The tandem Corey−Kwiatkowski/Horner−Wadsworth−Emmons reaction,[10] a new and highly diastereoselective synthesis of tetrasubstituted olefins,[13c] and a novel, very mild procedure for the enol lactonization of keto acids have been developed during this investigation. The oxidation of the side chains to carboxylates has been reported.[6b]

With substantial quantities of **44** at hand, we feel in a good position to complete total syntheses of siroheme (**6**), cobyric acid (**8**), and finally vitamin B_{12} (**1**).

Experimental Section

(2*R*,3*S*,4*E*)-2-(((4-Methoxybenzyl)oxy)methoxy)-3,4-dimethyl-8-(trityloxy)oct-4-en-3-ol (23). A cooled (−78 °C) solution of 9.30 g (16.47 mmol) of enone **22** in 50 mL of dry THF under argon was treated with 10 mL (30.00 mmol) of methyl magnesium chloride (3 M in THF). After 30 min, 3 mL of saturated aqueous NH_4Cl were added and the mixture was warmed to room temperature (rt), dried ($MgSO_4$), filtered, and concentrated. Column chromatography (10:1 hexane/EtOAc) gave 9.23 g (96%) of allylic alcohol **23** as a clear oil: $[\alpha]^{20}_D = -17.7°$ (*c* 1.15, $CHCl_3$); IR (thin film) 3567, 1491, 1449 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.97 (d, $J = 6.3$, 3H), 1.30 (s, 3H), 1.53 (d, $J = 1.0$, 3H), 1.70 (m, 2H), 2.13 (m, 2H), 3.05 (t, $J = 6.5$, 2H), 3.72 (q, $J = 6.3$, 1H), 3.80 (s, 3H), 4.54 (d, $J = 11.4$, 1H), 4.59 (d, $J = 11.4$, 1H), 4.75 (d, $J = 7.1$, 1H), 4.82 (d, $J = 7.1$, 1H), 5.55 (dt, $J = 1.0$, 7.2, 1H), 6.88 (m, 2H), 7.17−7.21 (m, 11H), 7.38−7.46 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.02, 14.27, 24.36, 25.55, 29.86, 55.16, 63.04, 69.35, 77.36, 86.24, 93.26, 113.80, 123.80, 126.73, 127.61, 128.59, 129.40, 129.66, 137.06, 144.37, 159.22; EIMS *m/z* 330 (1), 243 (100), 121 (45). Anal. Calcd for $C_{38}H_{44}O_5$: C, 78.54; H, 7.64. Found: C, 78.50; H, 7.74.

(2*R*,3*S*,4*E*)-2-(((4-Methoxybenzyl)oxy)methoxy)-3,4-dimethyl-3-(tri-*n*-butylstannyl)methoxy-8-(trityloxy)oct-4-ene (24). Potassium hydride (1.51 g, 37.69 mmol, prewashed three times with 8 mL of dry pentane), vigorously stirred in a separate flask with 20 mL of dry THF, was transferred through a transfer needle to an ice cold solution of the alcohol **23** (8.74 g, 15.06 mmol) in 80 mL of dry THF. of Dry DMPU (7.8 mL), and after 20 min, (iodomethyl)tri-*n*-butyltin (16.22 g, 37.69 mmol) in 30 mL of dry THF were added. After 6 h at rt, the mixture was cooled to 0 °C and carefully treated under argon with water and ice. The organic layer was washed with water, and the combined aqueous layers were extracted with hexane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (40:1 hexane/EtOAc) afforded 10.23 g (77%) of ether **24**: $[\alpha]^{20}_D = -5.8°$ (*c* 3.54, $CHCl_3$); IR (thin film) 2954, 1491, 1449 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.80−0.92 (m, 15H), 1.13 (d, $J = 6.3$, 3H), 1.17 (s, 3H), 1.29 (mc, 6H), 1.43−1.53 (m, 6H), 1.55 (s, 3H), 1.70 (mc, 2H), 2.11−2.20 (m, 2H), 3.06 (d, $J = 9.5$, 1H), 3.08 (t, $J = 6.5$, 2H), 3.36 (d, $J = 9.5$, 1H), 3.68 (q, $J = 6.3$, 1H), 3.77 (s, 3H), 4.40 (d, $J = 11.4$, 1H), 4.49 (d, $J = 11.4$, 1H), 4.53 (d, $J = 7.2$, 1H), 4.62 (d, $J = 7.2$, 1H), 5.38 (t, $J = 6.2$, 1H), 6.81−6.87 (m, 2H), 7.13−7.31 (m, 11H), 7.41−7.46 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −6.28, 8.79, 12.39, 13.73, 14.44, 15.17, 25.19, 27.33, 29.16, 30.05, 50.35, 55.21, 63.31, 68.79, 76.14, 83.16, 86.30, 93.40, 113.76, 126.79, 127.66, 128.65, 129.33, 130.16, 136.76, 144.42, 159.08; EIMS *m/z* 827 ($[M - Bu]^+$, 3), 689 (1), 371 (6), 291 (12), 243 (100), 121 (32). Anal. Calcd for $C_{51}H_{72}O_5Sn$: C, 69.31; H, 8.21. Found: C, 69.38; H, 8.18.

(2*S*,3*E*,5*R*)- and (2*R*,3*Z*,5*R*)-5-(((4-Methoxybenzyl)oxy)methoxy)-3,4-dimethyl-2-(3-(trityloxy)propyl)hex-3-en-1-ol (25). A cold (−95 °C) solution of 9.94 g (11.27 mmol) of ether **24** in 70 mL of dry THF was treated with 21.2 mL of *n*-BuLi (1.6 M in hexane, 33.85 mmol). After 2 h, the mixture was warmed to −50 °C and treated with 5 mL of saturated aqueous NH_4Cl and 100 mL of diethyl ether. The mixture was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (5:1 hexane/EtOAc) afforded 6.20 g (10.43 mmol, 92%) of olefin (*E*)-**25** and 61 mg (0.10 mmol, 0.9%) of (*Z*)-**25**, both as clear oils. Data for (*E*)-**25**: $[\alpha]^{20}_D = +70.5°$ (*c* 0.20, $CHCl_3$); IR (thin film) 3455, 1613, 1449 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.21 (d, $J = 6.5$, 3H), 1.23−1.53 (m, 4H), 1.55 (s, 6H), 2.83 (mc, 1H), 3.02 (mc, 2H), 3.46 (mc, 2H), 3.64 (s, 1H), 3.74 (s, 3H), 4.45 (d, $J = 12.1$, 1H), 4.49 (d, $J = 6.7$, 1H), 4.60 (d, $J = 6.7$, 1H), 4.61 (d, $J = 12.1$, 1H), 4.83 (q, $J = 6.5$, 1H), 6.80−6.86 (m, 2H), 7.16−7.29 (m, 11H), 7.39−7.43 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 11.23, 11.52, 19.16, 25.05, 27.65, 44.12, 55.07, 63.32, 64.67, 68.77, 69.95, 86.20, 91.00, 113.64, 126.70, 127.58, 128.52, 129.31, 130.04, 130.68, 133.32,

144.25, 159.02; EIMS *m/z* 594 (M^+, <0.1), 243 (100), 121 (87). Anal. Calcd for $C_{39}H_{46}O_5$: C, 78.76; H, 7.79. Found: C, 78.50; H, 7.86. Data for (*Z*)-**25**: $[\alpha]^{20}_D = +45.6°$ (*c* 1.00, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.31 (d, $J = 6.5$, 3H), 1.20−1.75 (m, 4H), 1.61 (d, $J = 0.9$, 3H), 1.72 (d, $J = 0.9$, 3H), 2.90−3.19 (mc, 3H), 3.50 (mc, 2H), 3.78 (s, 3H), 4.54 (d, $J = 11.7$, 1H), 4.60 (d, $J = 6.8$, 1H), 4.65 (d, $J = 6.8$, 1H), 4.68 (d, $J = 11.7$, 1H), 4.95 (q, $J = 6.5$, 1H), 6.85−6.91 (m, 2H), 7.22−7.37 (m, 11H), 7.44−7.52 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.82, 20.1125.91, 27.90, 43.46, 55.12, 63.73, 64.64, 68.68, 69.24, 86.26, 90.87, 113.66, 126.75, 127.63128.62, 129.18, 130.19, 131.44, 134.06, 144.39, 158.97. Anal. Calcd for $C_{39}H_{46}O_5$: C, 78.76; H, 7.79. Found: C, 78.61; H, 7.94.

[3*S*,3(1*S*),4*E*]-3-[1-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-(trityloxy)butyl]-3,4-dimethylhex-4-enoic acid Dimethyl Amide (28). A solution of allyl alcohol **26** (4.38 g, 7.84 mmol) in 200 mL of toluene was treated at 110 °C with 7.67 mL (6.97 g, 47.04 mmol) of dimethylacetamide dimethyl acetal (90%) in 10 mL of toluene. During the following 4 h, a mild argon stream was introduced into the solution through a glass capillary to remove methanol. The solution was concentrated and purified by silica gel chromatography (3:1 hexane/EtOAc) to give 4.82 g (98%) of amide **28** as clear, viscous oil: $[\alpha]^{20}_D = -2.2°$ (*c* 1.00, $CHCl_3$); IR (thin film) 1647, 1449 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.87 (s, 9H), 1.16 (s, 3H), 1.50 (mc, 2H), 1.56 (mc, 1H), 1.58 (s, 3H), 1.62 (d, $J = 5.5$, 3H), 1.92 (mc, 1H), 2.40 (d, $J = 12.3$, 1H), 2.52 (d, $J = 12.3$, 1H), 2.87 (s, 3H), 2.92 (s, 3H), 3.08 (mc, 2H), 3.50 (mc, 2H), 5.28 (q, $J = 5.5$, 1H), 7.16−7.34 (m, 9H), 7.39−7.60 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −5.75, −5.66, 13.23, 13.70, 18.06, 19.78, 23.84, 25.82, 29.45, 35.30, 37.87, 39.31, 45.37, 46.67, 62.92, 63.75, 86.16, 118.52, 126.70, 127.58, 128.59, 139.59, 144.43, 171.60; EIMS *m/z* 627 (M^+, 1), 570 (12), 368 (20), 243 (100). Anal. Calcd for $C_{40}H_{57}O_3NSi$: C, 76.51; H, 9.15; N, 2.23. Found: C, 76.44; H, 9.11; N, 2.22.

[4*S*,4(1*S*),5*S*,5(1*R*)]- and [4*S*,4(1*S*),5*R*,5(1*S*)]-4-[1-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-(trityloxy)butyl]-5-(1-hydroxyethyl)-4,5-dimethyldihydrofuran-2-one (34a,b). Amide **28** (4.52 g, 7.19 mmol) and 3.37 g (23.73 mmol) of Na_2HPO_4 in 80 mL of CH_2Cl_2 were treated with 5.86 g (23.73 mmol) of *m*-CPBA in portions. After 4 h, the mixture was washed twice with saturated aqueous $NaHCO_3$ and with water. The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (10:1 hexane/EtOAc) afforded 2.74 g of a major diastereomer which crystallizes from hexane and 1.37 g of a minor diastereomer as amorphous solid. The total yield of both diastereomers (dr: 2:1) is 4.11 g (93%). Data for the major diastereomer lactone (**34a**): mp 124 °C (hexane); $[\alpha]^{20}_D = -17.7°$ (*c* 1.31, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 1.03 (s, 3H), 1.22 (d, $J = 6.3$, 3H), 1.32 (mc, 1H), 1.33 (s, 3H), 1.55 (mc, 1H), 1.80 (mc, 2H), 2.13 (d, $J = 17.3$, 1H), 2.58 (d, $J = 17.3$, 1H), 2.99−3.11 (m, 2H), 3.22 (s, 1H), 3.62 (mc, 2H), 3.96 (q, $J = 6.3$, 1H), 7.16−7.31 (m, 9H), 7.37−7.42 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −5.78, 15.13, 15.26, 17.99, 18.14, 18.98, 25.80, 28.64, 42.90, 43.09, 48.11, 62.75, 63.28, 65.71, 67.13, 86.32, 91.95, 126.82, 127.65, 128.46, 144.02, 174.88. Anal. Calcd for $C_{38}H_{52}O_5Si$: C, 73.98; H, 8.50. Found: C, 73.42; H, 8.64. Data for the minor diastereomer lactone (**34b**): ^1H NMR (250 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 1.15 (s, 3H), 1.21 (d, $J = 6.3$, 3H), 1.24 (s, 3H), 1.42−1.48 (mc, 3H), 1.76−1.83 (m, 1H), 2.20 (d, $J = 17.1$, 1H), 2.41 (d, $J = 17.1$, 1H), 3.07 (mc, 2H), 3.67 (m, 1H), 3.84 (mc, 2H), 4.03 (mc, 1H), 7.16−7.30 (m, 9H), 7.36−7.41 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −5.57, 14.61, 17.56, 18.00, 18.36, 25.31, 25.71, 28.46, 44.52, 45.91, 48.46, 62.32, 63.87, 67.72, 86.45, 91.33, 126.90, 127.69, 128.49, 143.99, 174.47. Data for a mixture of both diastereomers: IR (KBr pellet) 1774, 1756 cm^{-1}; EIMS *m/z* 616 (M^+, <0.1), 243 (100).

(3*S*,4*S*]-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-methyl-7-(trityloxy)-3-(2-(trityloxy)ethyl)heptan-2-one (36). Triol **35** (2.40 g, 3.87 mmol) as a mixture of diastereomers was dissolved in 40 mL of pyridine, and a catalytic amount of DMAP and 4.30 g (15.49 mmol) of Ph_3CCl were added. After 2 d at rt, a small amount of water and 40 mL of ethanol were added. The mixture was concentrated, treated with 25 mL of hexane, and filtered, and the residue was washed with hexane. This hexane solution was dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in 60 mL of CH_2Cl_2 and treated with 1.72 g (3.87 mmol) of $Pb(OAc)_4$. After 5 min, 2 g of solid Na_2CO_3 was added and the mixture was stirred for 30 min, filtered, and concentrated. Purification by silica gel chromatography (10:1 hexane/EtOAc) gave 3.10 g (98%) of ketone **36** as crystals: mp 93−95 °C (THF); $[\alpha]^{20}_D = -6.9°$ (*c* 0.77, $CHCl_3$); IR (KBr pellet) 2928, 1702 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.88 (mc, 14H), 1.00−2.00 (m, 5H), 2.00 (s, 3H), 2.82−3.18 (m, 4H), 3.36−3.56 (m, 2H), 7.12−7.68 (m, 30H); ^{13}C NMR (63 MHz, $CDCl_3$) δ −5.77, 15.31, 18.25, 23.36, 25.87, 26.61, 29.25, 37.12, 47.22, 51.79, 60.00, 63.22, 63.66, 86.36, 86.98, 126.86, 127.71, 128.57, 128.62, 144.08, 144.35, 212.80; EIMS *m/z* 573 (M^+ − Tr, 0.1), 243 (100). Anal. Calcd for $C_{55}H_{64}O_4Si$: C, 80.84; H, 7.89. Found: C, 80.62; H, 7.85.

Crystal Structure Determination of 36. Crystals of **36**, grown from THF, are monoclinic, space group $P2_1$ with $a = 9.3738(8)$ Å, $b = 13.007(2)$ Å, $c = 21.668(3)$ Å, $\beta = 100.856(8)°$, $V = 2595(1)$ Å^2, $Z = 2$, and $\rho_{calc} = 1.138$ g/cm^3 at rt. A colorless, transparent crystal of dimensions $0.09 \times 0.32 \times 0.37$ mm^3 was measured on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Cu Kα radiation. A total of 5255 reflections, corresponding to hemisphere of reciprocal space, were collected up to $2\theta = 110°$. A total of 5113 reflections with $I > 0$ were used. Three standard reflections, remeasured every 5500 s, decreased 3% during data collection. The data were rescaled with respect to the standards. An empirical absorption correction based on ψ-scan gave a relative transmission factor from 0.86 to 1.00. The structure was determined by direct methods using program SHELXS. A difference Fourier synthesis revealed a completely disordered THF molecule per asymmetric unit. H atoms were placed at calculated positions and were not refined. The non-H atoms were refined with anisotropic thermal parameters on *F* values using weighting scheme $w(F) = 4F^2/\{\sigma^2(F^2) + (0.03F^2)^2\}$. Refinement converged at $R(F) = 0.064$, $wR(F) = 0.073$, $S = 2.44$. The final difference density was less than 0.44 e/Å^3. A refinement including the Flack *x*-parameter gave $x = -0.03(5)$ and confirmed the absolute configuration of the structure (see Figure 3, Supporting Information).

(3*S*,4*S*)-4-Methyl-5-methylene-4-(2-(trityloxy)ethyl)-3-(3-(trityloxy)propyl)dihydrofuran-2-one (38) and (3*S*,4*S*)-5-Hydroxy-4,5-dimethyl-4-(2-(trityloxy)ethyl)-3-(3-(trityloxy)propyl)pyrrolidin-2-one (39). To a cold (0 °C) solution of 2.37 g (3.30 mmol) of acid **37** in 60 mL of CH_2Cl_2 was added 4.51 mL (3.40 g, 26.43 mmol) of *i*-Pr_2NEt and 1.03 mL (1.52 g, 13.20 mmol) of MsCl. After 2−3 min the mixture was filtered through silica gel. The product crystallizes very readily from many common solvents (e.g., from diethyl ether/hexane). Enol lactone **38** (2.30 g (>99%)) as fine white crystals can be obtained. Usually the residue from the above filtration was used for the next step without purification, by dissolving in 65 mL of THF and 40 mL of ethanol and adding this solution to liquid ammonia (700 mL). After 36 h nearly the entire ammonia has evaporated. The residue was concentrated and chromatographed (1:1 hexane/EtOAc) to yield 2.15 g (91%) of keto amide **39** as a solid. (*Note*: This material is not stable on storage.) Enol lactone **38**: mp 133−135 °C; $[\alpha]^{20}_D = -16.0°$ (*c* 0.75, $CHCl_3$); IR (KBr pellet) 1799, 1669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.46−1.60 (m, 3H), 1.79−1.94 (m, 3H), 2.47 (dd, $J = 7.7$ and 6.3, 1H), 2.99−3.08 (m, 2H), 3.20 (mc, 2H), 4.06 (d, $J = 2.9$, 1H), 4.56 (d, $J = 2.9$, 1H), 7.18−7.30 (m, 18H), 7.36−7.43 (m, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.13, 27.84, 38.50, 44.65, 44.66, 47.43, 59.91, 63.29, 86.39, 86.90, 87.18, 126.72, 126.84, 127.58, 127.66, 128.47, 128.57, 143.85, 144.27, 163.03, 175.58. Anal. Calcd for $C_{49}H_{46}O_4$: C, 84.21; H, 6.63. Found: C, 84.06; H, 6.86. Keto amide **39**: $[\alpha]^{20}_D = +11.5°$ (*c* 0.60, $CHCl_3$); IR (KBr pellet) 3387, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.76 (s, 3H), 1.25 (s, 3H), 1.20−1.40 (m, 1H), 1.50−1.70 (m, 2H), 1.73−1.81 (m, 1H), 1.85−2.10 (m, 2H), 2.41 (mc, 1H), 2.99−3.10 (m, 2H), 3.19−3.38 (m, 2H), 3.84 (s, 1H), 5.71 (s, 1H), 7.21−7.33 (m, 18H), 7.34−7.44 (m, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.13, 22.96, 23.55, 48.12, 48.33, 60.34, 63.15, 86.29, 88.04, 88.62, 126.78, 126.90, 127.65, 127.73, 128.51, 128.63, 144.34, 144.37, 178.76. Anal. Calcd for $C_{49}H_{49}NO_4$: C, 82.21; H, 6.90; N, 1.96. Found: C, 81.21; H,6.95; N, 1.88.

(3*S*,4*S*)-4-Methyl-5-methylene-4-(2-(trityloxy)ethyl)-3-(3-(trityloxy)propyl)pyrrolidin-2-one (40), (2*R*,3*S*,4*S*)-2,3-Dimethyl-5-oxo-3-(2-(trityloxy)ethyl)-4-(3-(trityloxy)propyl)pyrrolidine-2-carboni-

trile, and (2*R*,3*S*,4*S*)-2,3-Dimethyl-5-thioxo-3-(2-(trityloxy)ethyl)-4-(3-(trityloxy)propyl)pyrrolidine-2-carbonitrile (42). Keto amide **39** (1933 mg, 2.70 mmol) was melted at 1 mbar and 110 °C and kept under these conditions for 1 h. Spectroscopically pure enamide **40** (1884 mg, >99%) was thus obtained. (*Note*: This amide is moisture sensitive and gives keto amide **39** on storage.) The above enamide (**40**) (796 mg, 1.14 mmol) was dissolved in 8 mL of THF and treated with a mixture of KCN (222 mg, 3.42 mmol) and $KHCO_3$ (342 mg, 3.42 mmol) and dissolved in 8 mL of water and 16 mL of isopropanol. After being stirred at 55 °C for 24 h, the mixture was poured into CH_2Cl_2 and brine. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give 827 mg (>99%) of cyano lactam **41**. This was dissolved in 10 mL of dry THF and treated with Lawesson's reagent (593 mg, 1.60 mmol). After 45 min at 60 °C, the mixture was poured into diethyl ether and saturated aqueous $NaHCO_3$; the aqueous layer was extracted with diethyl ether, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (5:1 hexane/EtOAc) afforded 744 mg (88%) of thio lactam **42** as a solid. Enamide **40**: IR (KBr pellet) 1709, 1677, 1654 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.40−1.70 (m, 3H), 1.75−1.97 (m, 3H), 2.30 (mc, 1H), 2.90−3.10 (m, 2H), 3.17 (mc, 2H), 3.89 (d, J = 1.9, 1H), 4.15 (d, J = 1.9, 1H), 7.15−7.35 (m, 18H), 7.35−7.47 (m, 12H), 7.52 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.88, 23.51, 28.35, 39.68, 44.06, 48.67, 60.21, 63.58, 84.00, 86.23, 86.93, 126.72, 126.84, 127.58, 127.66, 128.47, 128.57, 143.85, 144.27, 162.51, 177.91. Cyano lactam **41** [(2*R*:2*S*) = 6:1 mixture of diastereomers]: $[\alpha]^{20}_D = -10.7°$ (*c* 1.20, $CHCl_3$); IR (KBr pellet) 1709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (s, 3H), 1.25−1.38 (m, 1H), 1.31 (s, 3H), 1.66 (mc, 1H), 1.92−1.97 (m, 1H), 2.08 (mc, 1H), 2.19 (mc, 1H), 2.30 (dd, J = 3.5, 9.3, 1H), 3.04 (mc, 2H), 3,14 (mc, 1H), 6.06 (s, 1H), 7.17−7.36 (m, 18H), 7.41−7.45 (m, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.09, 21.24, 21.70, 28.62, 37.43, 48.45, 51.55, 59.15, 59.84, 63.23, 86.46, 87.50, 120.17, 126.89, 127.09, 127.75, 127.89, 128.58, 128.68, 143,76, 144,36, 176.91. Anal. Calcd for $C_{50}H_{48}N_2O_3$: C, 82.84; H, 6.67, N, 3.86. Found: C, 82.34; H, 7.03; N, 3.52. Thio lactam **42** [(2*R*:2*S*) = 6:1 mixture of diastereomers]: $[\alpha]^{20}_D = +3.4°$ (*c* 0.85, $CHCl_3$); IR (KBr pellet) 1596 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.59 (s, 3H), 1.25 (s, 3H), 1.24−1.41 (m, 1H), 1.57−190 (m, 3H), 2.01−2.33 (m, 2H), 2.40−2.50 (m, 1H), 2.93−3.12 (m, 4H), 7.09−7.29 (m, 18H), 7.30−7.45 (m, 12H), 8.28 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.35, 20.41, 23.45, 29.25, 36.74, 51.06, 59.58, 61.07, 63.06, 64.01, 86.41, 87.47, 126.81, 127.02, 127.67, 127.83, 128.46, 128.57, 143.54, 144.25. Anal. Calcd for $C_{50}H_{48}N_2O_2S$: C, 81.05; H, 6.53; N, 3.78. Found: C, 81.22; H, 6.43; N, 3.51.

[2*R*,3*S*,4*S*,5(2*Z*,3*S*,4*S*)]-2,3-Dimethyl-5-[(3-methyl-5-oxo-3-(2-(trityloxy)ethyl)-4-(3-(trityloxy)propyl)pyrrolidin-2-ylidene)methanesulfonyl]-3-(2-(trityloxy)ethyl)-4-(3-(trityloxy)propyl)-3,4-dihydro-2*H*-pyrrole-2-carbonitrile (43). A solution of thio lactam **42** (1740 mg, 1.00 mmol) in 5 mL of dry benzene was added to freshly prepared enamide **40** (1047 mg, 1.50 mmol). At 0 °C benzoyl peroxide (415 mg, 1.20 mmol) was added. The mixture was stirred in the dark and under argon for 24 h and poured into a mixture of diethyl ether and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (linear gradient of 10−20% EtOAc/hexane) afforded 804 mg (56%) of sulfide **43** as a solid. $[\alpha]^{20}_D = +4.8°$ (*c* 1.05, $CHCl_3$); IR (KBr pellet) 1716, 1646, 1566 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.64 (s, 3H), 1.09 (s, 3H), 1.21 (s, 3H), 1.22−1.55 (m, 6H), 1.76−1.95 (m, 5H), 2.13 (mc, 1H), 2.40 (mc, 1H), 2.70 (dd, J = 4.5 and 8.4, 1H), 2.95−3.11 (m, 5H), 3.12−3.28 (m, 3H), 5,14 (s, 1H), 7.04 (s, 1H), 7.13−7.34 (m, 36H), 7.36−7.48 (m, 24H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 15.03, 22.14, 22.93, 23.04, 23.24, 28.14, 29.34, 31.34, 37.82, 39.12, 45.29, 48.37, 51.61, 59.99, 60.35, 62.87, 63.36, 73.00, 83.65, 86.11, 86.36, 86.93, 87.04, 119.69, 126.61, 126.78, 127.47, 127.59, 128.37, 128.42, 128.45, 143.68, 143.76, 143.99, 144.14, 152.02, 176.88, 178.40. Anal. Calcd for $C_{99}H_{93}N_3O_5S$: C, 82.75; H, 6.52; N, 2.92. Found: C, 82.49; H, 6.89; N, 2.67.

[2*R*,3*S*,4*S*,5(2*Z*,3*S*,4*S*)]-2,3-Dimethyl-5-[(3-methyl-5-oxo-3-(2-(trityloxy)ethyl)-4-(3-(trityloxy)propyl)pyrrolidin-2-ylidene)methyl]-3-(2-(trityloxy)ethyl)-4-(3-(trityloxy)propyl)-3,4-dihydro-2*H*-pyrrole-2-carbonitrile (44). A solution of 200 mg (139 μmol) of sulfide **43** and triethyl phosphite (0.148 mL, 142 mg, 850 μmol) in 2 mL of dry benzene was degassed and heated to 120 °C for 72 h in a sealed tube. The mixture was concentrated and chromatographed on aluminium oxide (activity III−IV, linear gradient of 10−20% EtOAc/hexane) to give 177 mg (90%) of A−B-semicorrin **44** as a mixture of diastereoisomers (ca. 36:6:6:1). Diastereomerically pure material was obtained by HPLC (Nuc 50−10, 10:1:2 hexane/MeOAc/diethyl ether, +20% hexane, 10 mL/min). The pure A−B-semicorrin **44** (130 mg, 67%) was thus obtained as an amorphous solid: $[\alpha]^{20}_D = +17.3°$ (*c* 0.26, $CHCl_3$); IR (KBr pellet) 1738, 1638, 1545 cm^{-1}; ^1H NMR (600 MHz, with ROESY, NOESY, COSY 90, $^{13}C-^1H$-COSY, C_6D_6) δ 0.34 (s, 3H, C_2-*Me*), 0.87 (s, 3H, C_7-*Me*), 1.18 (s, 3H, C_1-*Me*), 1.18 (mc, 1H, $C_{3'}$-H_a), 1.34 (mc, 2H, $C_{3''}$-H_a, $C_{8'}$-H_a), 1.54 (mc, 2H, $C_{3'}$-H_b, $C_{8'}$-H_b), 1.67 (mc, 2H, $C_{8''}$-H_a, $C_{3''}$-H_b), 1.78 (mc, 2H, $C_{7'}$-H_2), 2.00 (mc, 1H, $C_{2'}$-H_a), 2.25 (mc, 1H, $C_{8''}$-H_b), 2.34 (mc, 1H, $C_{2'}$-H_b), 2.51 (dd, J = 5.8 and 8.5, 1H, C_8-*H*), 2.61 (dd, J = 4.1 and 7.9, 1H, C_3-*H*), 3.02 (mc, 1H, $C_{3'''}$-H_a), 3.10−3.28 (m, 6H, $C_{2''}$-H_a, $C_{3'''}$-H_b, $C_{7''}$-H_2, $C_{8'''}$-H_2), 3.34 (mc, 1H, $C_{2''}$-H_b), 5.05 (s, 1H, C_5-*H*), 7.00−7.20 (m, 36H, Ar-*H*), 7.48−7.60 (m, 24H, Ar-*H*), 11.24 (s, br, 1H, N-*H*); ^{13}C NMR (63 MHz, C_6D_6) δ 14.28 (C_2-*Me*), 22.65 (C_1-*Me*), 23.60 ($C_{3'}$), 23.82 ($C_{8'}$), 23.91 (C_7-*Me*), 29.05 ($C_{8''}$), 30.60 ($C_{3''}$), 38.44 ($C_{2'}$), 39.47 ($C_{7'}$), 45.50 (C_2), 47.60 (C_8), 50.69 (C_7), 59.44 (C_3), 60.48 ($C_{7''}$), 60.93 ($C_{2''}$), 63.57 ($C_{3'''}$), 64.18 ($C_{8'''}$), 72.94 (C_1), 86.91, 87.04, 87.67, 87.71, 87.87 (C_5), 120.61 (C_1-*CN*), 126.85, 126.99, 127.03, 127.10, 127.71, 127.81, 127.86, 128.48, 128.58, 128.68, 144.31, 144.61, 144.82, 145.03, 162.95 (C_6), 177.69 (C_4), 178.36 (C_9); FDMS *m/z* 1403 (M^+, 15), 1377 (M^+ − CN, 100), 1134 (M^+ − Tr − CN, 15), 243 (96); [+]-FAB (*m*-nitrobenzyl alcohol, CsI, xenon) *m/z* 1537 (M^+ + Cs, 0.3), 243 (100). Anal. Calcd for $C_{99}H_{93}N_3O_5 \cdot 4H_2O$: C, 80.51; H, 6.89; N, 2.85. Found: C, 80.62; H, 7.20; N, 2.61.

Acknowledgment. This work is taken from the Ph.D. Thesis of B.L., Johann Wolfgang Goethe-Universität, 1997. The crystallography was performed by J.W.B. Financial support by the Deutsche Forschungsgemeinschaft and Schering AG, Berlin, is gratefully acknowledged. We thank Professor Eschenmoser and Professor Montforts for helpful discussions and for providing us with unpublished experimental details. B.L. thanks the City of Berlin for a *NaFöG* stipendium. We thank Dr. G. Zimmermann (NMR), Dr. A. Schäfer (NMR), Dr. G. Dürner (HPLC), M. Christoph (analyses), and J. del Corte for technical assistance. Mass spectra were obtained from the Max-Planck-Institut für Polymerforschung, Mainz, and from the Institut für Organische Chemie der FU, Berlin. Dedicated to Professor E. Winterfeldt on the occasion of his 65th birthday.

Supporting Information Available: Preparation and analytical data of compounds **20**, **21**, **22**, **26**, **27**, **29**, **35**, and **37** and crystal data of ketone **36** (31 pages). See any current masthead page for ordering and internet access instructions.

JA9700515