1730, 1620, 1240; ^{1}H NMR δ 3.71 (3 H, s), 3.77 (2 H, s), 4.39 (2 H, d, J = 5.7 Hz), 5.12 (2 H, s), 5.18 (1 H, br s), 6.07 (1 H, br s), 7.28 (10 H, m); mass spectrum, m/e (relative intensity) 149 (39), 91 (65), 71 (35), 43 (100); calcd for $C_{21}H_{22}N_3O_5$ (chemical ionization, M + 1), 396.1559; found, 396.1604.

2-(2-Phenylvinyl)-4-isobutyl-5-((carbomethoxy)amino)oxazole (49c): 85%; mp 134–136 °C; R_f (1:1 Et_2O/Skelly solve); IR (CH_2Cl_2) cm^{-1} 3690, 3405, 3025, 2860, 1810, 1750, 1660; ^{1}H NMR δ 0.94 (6 H, d, J = 6.6 Hz), 2.05 (1 H, m), 2.30 (2 H, d, J = 7.2 Hz), 3.79 (3 H, s), 6.25 (1 H, br s), 6.83 (1 H, d, J = 16.5 Hz), 7.25–7.51 (5 H, m); mass spectrum, m/e (relative intensity) 300 (53, M$^+$), 268 (50), 225 (32), 197 (65), 129 (100), 103 (55); calcd for $C_{17}H_{20}N_2O_3$, 300.1448; found, 300.1461.

2-[1(S)-(Carbobenzyloxyamino)-3-methylbutyl]-4-benzyl-5-(trimethylacetamido)oxazole: 41%; R_f (20% EtOAc/Skelly Solve) 0.13; IR (CCl_4, cm^{-1}) 3440, 3310, 1730, 1710, 1660; NMR δ 0.94 (6 H, d, J = 6 Hz), 1.23 (9 H, s), 1.69 (3 H, s), 3.79 (2 H, s), 5.09 (2 H, s), 6.69 (1 H, br s), 7.23 (5 H, s), 7.28 (5 H, s); mass spectrum, m/e (relative intensity) 477 (7, M$^+$), 285 (12), 91 (97), 57 (100); calcd for $C_{28}H_{35}N_3O_4$, 477.2628; found, 477.2609.

2-Methyl-4-benzyl-5-acetamidooxazole (54) via 2-Methyl-4-benzyl-5-(trifluoroacetamido)oxazole with Sodium Hydride. To oxazole **53** (33.0 mg, 0.1162 mmol) in THF (0.3 mL) was added sodium hydride (12 mg, 0.2300 mmol 56% dispersion) at 0 °C. After hydrogen evolution was complete (~15 min) the reaction mixture was transferred via cannula to acetyl chloride (41 μL, 0.581 mmol) in THF (0.1 mL) at 0 °C. Washing with THF (2 × 75 μL) brought the substrate concentration to about 0.2 M. Stirring was continued for 2 h with gradual warming to room temperature at which point the reaction was quenched with saturated $NaHCO_3$ (1.5 mL) and stirred overnight. Following aqueous workup and column chromatography (80% EtOAc/CH_2Cl_2), 13.3 mg (50%) of a pale yellow solid was obtained, identical with a sample prepared via the corresponding amide nitrile.

Acknowledgment. Financial support provided by grants from the National Institutes of Health (GM 28128), Merck Sharp and Dohme, and the American Cancer Society (JFRA No. 37 to B.H.L.) is greatefully acknowledged. We also appreciate the expert technical assistance of Johnson Loh and the mass spectral data obtained under the direction of Drs. P. Boshoff and H. Webb. Our thanks go to Professor Curt Anderson for overseeing the undergraduate laboratories where a number of starting materials used in this work were prepared and to the NSF for a departmental instrumentation grant (CHE-80-18438) which assisted in the purchase of the NT 300-MHz NMR Spectrometer.

Registry No. (*S*)-**5** (R = CH_2Ph), 87783-58-2; (*S*)-**5** (R = $CH_2CH=CH_2$), 87783-59-3; (*S*)-**5** (R = H), 7376-90-1; (*S*)-**6** (R = H), 87783-60-6; (*S*)-**6** (R = CH_2Ph), 87783-61-7; **7**, 69753-67-9; **8** (R = CH_2Ph), 87783-62-8; **8** (R = $CH_2CH=CH_2$), 87783-63-9; **8** (R = H), 87784-06-3; **9**, 87783-64-0; **10**, 87783-65-1; **11**, 87783-66-2; **12** (R = $CH_2CH(CH_3)_2$), 87783-67-3; **12** (R = CH_2Ph), 24748-46-7; **13** (R = CH_2Ph), 87783-68-4; **13** (R = H), 87783-69-5; **14**, 87783-70-8; **15** (R = $CH_2CH(CH_3)_2$; R′ = CH_3), 87783-71-9; **15** (R = R′ = CH_2Ph), 87783-72-0; **16**, 27395-05-7; **17** (R = $CH_2CH(CH_3)_2$; R′ = $COCH_3$), 87783-73-1; **17** (R = $CH_2CH(CH_3)_2$; R′ = $COCHCl_2$), 87783-74-2; **17** (R = CH_2Ph; R′ = $COCH_3$), 87783-75-3; **18** (R = CH_2Ph), 87783-76-4; **18** (R = H), 87783-77-5; **19**, 87783-78-6; **20**, 87783-79-7; **21** (R = $CH_2CH(CH_3)_2$; R′ = CH_3), 87783-80-0; **21** (R = $CH_2CH(CH_3)_2$; R′ = CH_3), 87783-81-1; **21** (R = R′ = CH_2Ph), 87783-82-2; **22**, 87783-83-3; (*S*)-**24** (R = CH=CHPh; R′ = $CH_2CH=CH_2$), 87783-84-4; (*S*)-**24** (R = CH_3; R′ = H), 28529-34-2; **26** (R = CH_2Ph), 87783-85-5; **23** (R = CH_3; R′ = CH_2Ph; R″ = CH_3), 87783-86-6; **27** (R = CH=CHPh; R′ = $CH_2CH=CH_2$; R″ = *p*-$CH_3OC_6H_4$), 87783-87-7; **27** (R = CH_3; R′ = H; R″ = Ph), 87783-88-8; **27** (R = CH_3; R′ = CH_2Ph; R″ = Ph), 87783-89-9; **28**, 87783-90-2; **31**, 87783-91-3; **32**, 87783-92-4; **38a**, 87783-93-5; **40a**, 87783-94-6; **42**, 87783-95-7; **43**, 87783-96-8; (L,L)-**45**, 87783-97-9; (L,D)-**45**, 87783-98-0; (*S*)-**46**, 87783-99-1; **48b**, 87784-00-7; **49a**, 87784-01-8; **49c**, 87784-02-9; **50**, 87784-03-0; **51**, 87784-04-1; (L)-**52**, 87784-05-2; **53**, 87784-06-3; *t*-BuCOCl, 3282-30-2; CH_3COCl, 75-36-5; CH_3COBr, 506-96-7; *p*-$CH_3OC_6H_4COCl$, 100-07-2; PhCOCl, 98-88-4; PhCOBr, 618-32-6; $Cl_2CHCOCl$, 79-36-7; *p*-$AcOC_6H_4CH_2COCl$, 65448-20-6; TFAA, 407-25-0; 2-methyl-4-benzyl-5-[*N*-(((*p*-benzoxyphenyl)carbonyl)methyl)acetamido]oxazole, 87784-07-4; 2-methyl-4-benzyl-5-(*N*-(*p*-benzoxyphenylethyl)acetamido)oxazole, 87784-08-5; 2-(2-phenylvinyl)-5-[*N*-(*p*-benzoxyphenyl)methylcarbonyl]oxazole, 87784-09-6; 2-methyl-4-benzyl-5-oxazolone, 5469-44-3; α-isobutyl-α-aminoacetonitrile hydrochloride, 72177-82-3; α-benzyl-α-(acetylamino)acetonitrile, 24748-46-7; L-carbobenzyloxyglycylphenylalanine, 87784-10-9; L-*N*-cinnamoylleucine methyl ester, 87784-11-0; benzaldehyde, 100-52-7; L-phenylalanine, 63-91-2; benzylamine, 100-46-9; acetylglycine, 543-24-8.

Camphorae: Chiral Intermediates for the Enantiospecific Total Synthesis of Steroids. 1[1]

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Contribution from the Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024. *Received January 31, 1983*

Abstract: An enantiospecific approach to the total synthesis of cortisone and related steroids from readily available levorotatory borneol is presented.

It is not unjust to state that steroids are probably the single most intensely scrutinized class of natural products in the history of organic chemistry and that the science as a whole has been enriched by these studies. Nowhere is this more true than in the area of synthesis where many notable achievements have been forged out over the past 4 decades.[2] Many new strategies and methodological advances continue to be made in this area. As important as most of these advances have been, one crucial issue is often ignored and that is the question of stereochemistry—in the *absolute* sense. Since the biological activity of steroids is restricted to one enantiomer, a major problem has been the development of a practical method for the production of useful steroid intermediates in chirally pure form. A number of ingenious solutions to this important problem are now beginning to emerge. For example, the development and employment of remarkably efficient asymmetric induction reactions can be considered a major advance in this area.[3,4] Such methodology is clearly more ex-

(1) A portion of this research has been communicated previously: Stevens, R. V.; Gaeta, F. C. A. *J. Am. Chem. Soc.* **1977**, *99*, 6105.

(2) Three comprehensive monographs dealing with the total synthesis of steroids have appeared: (a) Bucourt, R. *MTP Int. Rev. Scie.: Org. Chem., Ser. One* **1976**, *8*. (b) Blickenstaff, R. T.; Ghosh, A. C.; Wolf, G. C. "Total Synthesis of Steroids"; Academic Press: New York, 1974; (c) Akhrem, A. A.; Titov, Y. A. "Total Steroid Synthesis"; Plenum Press: New York, 1970.

(3) (a) Cohen, N. *Acc. Chem. Res.* **1976**, *9*, 412. (b) Danishefsky, S.; Cain, P. *J. Am. Chem. Soc.* **1976**, *98*, 4975. (c) *Ibid.* **1975**, *97*, 5282. (d) Daniewski, A. R. *J. Org. Chem.* **1975**, *40*, 3135. (e) Nagasawa, K.; Takahashi, H.; Hiroi, K.; Yamada, S. *Yakugaku Zasshi* **1975**, *95*, 33. (f) Nagasawa, K.; Hiroi, K.; Yamada, S. *Ibid.* **1975**, *95*, 46. (g) Daniewski, A. R.; Kocor, M. *J. Org. Chem.* **1975**, *40*, 3136. (h) Hajos, Z. G.; Parrish, D. R. *Ibid.* **1974**, *39*, 1615. (i) Cohen, N.; Banner, B. L.; Blount, J. F.; Tsai, M.; Saucy, G. *Ibid.* **1973**, *38*, 2229, and references cited therein. (j) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496.

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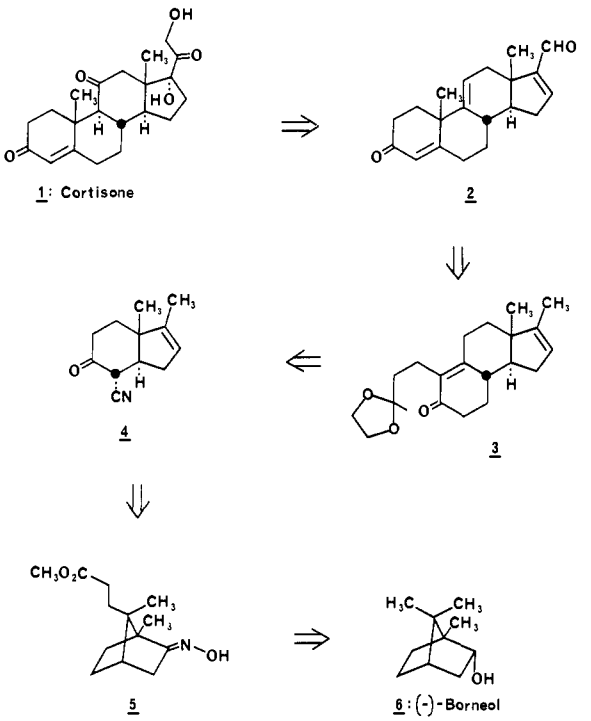
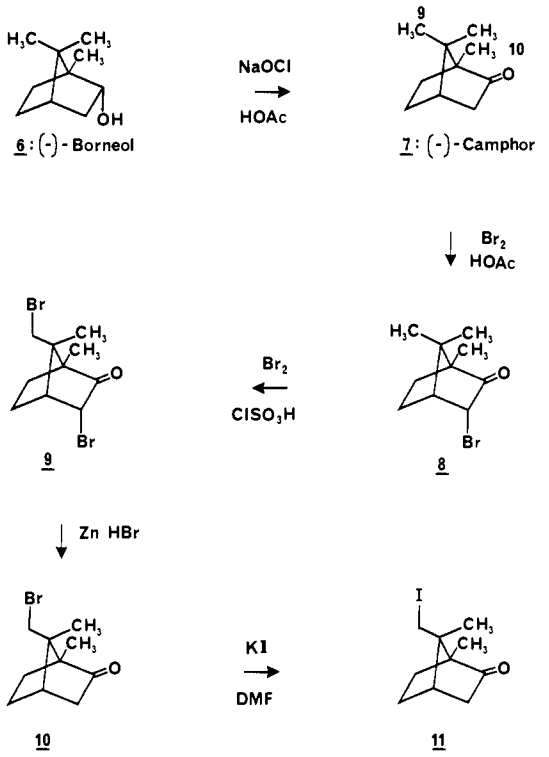
Scheme I



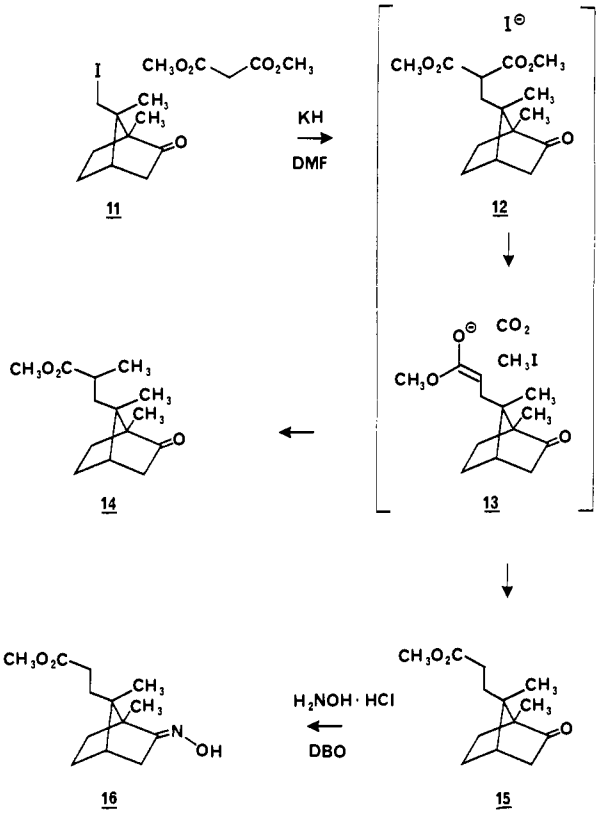
peditious than classical resolution by derivatization.[4] The employment of enzymes to achieve enantiospecific transformations is also gaining popularity.[5] In connection with our studies on the total synthesis of vitamin B-12[6] it occurred to us that we might also be able to take advantage of the topology and natural chirality of camphor to effect an enantiospecific total synthesis of various steroids without resorting to the techniques cited above. For example, in contemplating the synthesis of certain corticosteroids, e.g., cortisone (**1**), via the classic Woodward intermediate **2**,[7] one might be able to employ levorotatory camphor as a commercially available starting material for the synthesis of the obligatory trans-fused hydrindenone **4**. The retrosynthetic analysis is outlined in Scheme I, although it should be noted that this scheme was actually arrived at by prosynthetic logic.

Both enantiomers of camphor are available commercially. Unfortunately, the obligatory levorotatory isomer (**7**) is rather expensive. Accordingly, an alternate source of this substance had to be secured. Happily, relatively inexpensive levorotatory borneol (**6**) lies only an oxidation step away, but for large-scale production of **7** we required an inexpensive and convenient method for achieving this transformation. Ultimately, such a procedure was developed by employing concentrated aqueous solutions of sodium hypochlorite.[8] With a secure supply of **7** in hand we proceeded to functionalize the C-9 methyl group by a remarkable series of reactions (see Scheme II) reported first in 1893 by Kipping and Pope[9] and subsequently studied extensively.[10] It should be noted that this sequence of reactions (**7–10**) *proceeds with complete retention of chirality* and that certain improvements in yield and ease of isolation were made (see Experimental Section). With

Scheme II



Scheme III



bromide **10** in hand we undertook a study of its displacement with various carbon necleophiles hoping to effect a two-carbon homologation to afford **15**. These experiments failed to provide significant displacement—a reflection no doubt of the neopentyl nature of this halide. Accordingly, bromide **10** was converted to the more reactive iodide (**11**) in 95% yield by heating with potassium iodide in dimethylformamide to 100 °C for 4 h. These conditions were superior to those recorded previously.[11]

(4) The concept of "chiral economy" has been discussed: Fischli, A. *Chimia* **1976**, *30*, 4.

(5) For one particularly cogent example of this technique in steroid chemistry, see: Mosbach, K.; Larsson, P. *Biotechnol. Bioeng.* **1970**, *12*, 19.

(6) Stevens, R. V.; Chang, J. H.; Lapalme, R.; Schow, S.; Schlageter, M. G.; Shapiro, R.; Weller, H. N. *J. Am. Chem. Soc.* **1983**, preceding paper in this issue.

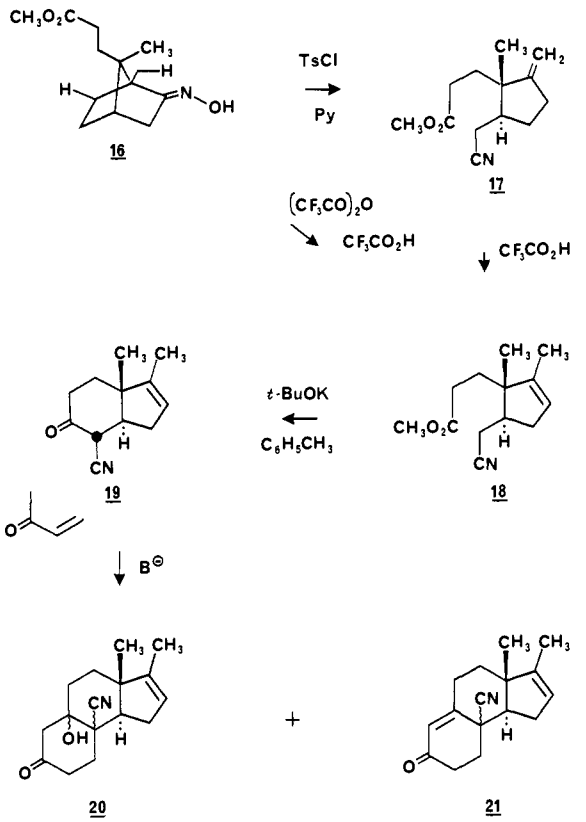
(7) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 1423.

(8) Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, *45*, 203. Stevens, R. V.; Chapman, K. T.; Stubbs, C. A.; Tam, W. W.; Albizati, K. *Tetrahedron Lett.* **1982**, 4647.

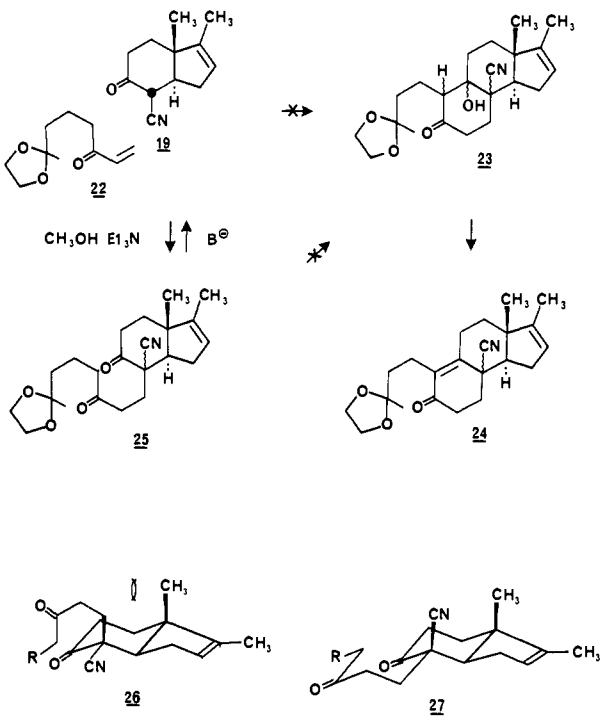
(9) Kipping, F. S.; Pope, W. J. *J. Chem. Soc.* **1893**, *63*, 549, 577, 593.

(10) See the preceding paper[6] for references.

Scheme IV



Scheme V



The displacement of 9-iodocamphor with the anion of dimethyl malonate was intensely investigated.[12] When 10 equiv of the sodium salt of dimethyl malonate was heated to reflux with iodide **11** in dimethylformamide (see Scheme III), the desired keto ester **15** was obtained in 40% yield. Analysis of the reaction mixture revealed the presence of two major impurities, mainly diester **12** and the methylated product **14**. The formation of these byproducts suggested that under these conditions the initially formed diester **12** suffers decarbomethoxylation from the iodide released in its formation to afford the ester enolate **13** and methyl iodide. Protonation or methylation of this anion accounts for the major and minor products of the reaction, **15** and **14**, respectively. However, this mechanism does not account for the multitude of other byproducts produced. Careful scrutiny of these reaction conditions revealed a serious flaw. The sodium salt of dimethyl malonate was prepared by dropwise addition of the diester to sodium hydride in dimethylformamide during which a substantial rise in temperature was noted. However, it is now known that even at room temperature bases such as sodium or potassium hydroxide and calcium hydride induce decomposition of dimethylformamide to carbon monoxide and dimethylamine.[13] Furthermore, it has been reported that sodium hydride reacts with this solvent to generate cyanide.[14] No doubt the presence of these additional nucleophiles accounts for the modest yield of keto ester **15** observed. Accordingly, we substituted potassium carbonate for sodium hydride and were pleased to observe a substantial increase in yield (73%), but impurities still plagued the isolation and purification of **15**. In order to maximize purity we felt that it was essential that no base stronger than malonate anion be present in the dimethyl malonate. To achieve this goal, excess malonate was added dropwise to an ethereal solution of potassium hydride, precipitating its salt out of solution. The ether was then removed and replaced with dimethylformamide and allowed to react with iodide **11** under the prescribed conditions. In this fashion a 76% yield of readily purified keto ester **15** was obtained, and the reaction proved to be very reproducible. Oximation of the latter intermediate could be accomplished in pyridine at 50 °C for 48 h or better yet with 1,4-diazabicyclooctane in methanol at room temperature. Thus, our first goal, the selective and efficient functionalization of levorotatory borneol, was accomplished in an overall yield of 22%.

Next, we focused our attention on the conversion of **16** to the *trans*-hydrindane **19** (see Scheme IV). The Beckman fragmentation of camphor itself is well-known[15] and treatment with *p*-toluenesulfonyl chloride in pyridine induced this fragmentation to afford **17** and **18** in a 2/3 ratio. Although **17** might prove to be a useful intermediate one day for the synthesis of 17-keto steroids, its isolation in the present study was undesirable and we discovered that it could be converted *without rearrangement* (see later) to the endo isomer **18** by exposure to trifluoroacetic acid in methylene chloride. The latter observation prompted us to employ these conditions in the fragmentation itself, and indeed, under these conditions **16** led exclusively to **18** in high yield. The conversion of cyano ester **18** to bicycle **19** proved more difficult than we had anticipated. Various bases were examined to effect this hybrid of the Thorpe-Zeigler and Dieckmann condensations with little success until we discovered that addition of **18** to a suspension of potassium *tert*-butoxide in toluene immediately precipitated out the potassium salt of **19**, which upon acidification afforded **19** in 85% yield. A coupling constant of 14 Hz between the protons at C-8 and C-14 (steroid numbering) is consistent only with an equatorial nitrile as shown. Thus, the second goal of this investigation was met in 15% overall yield from borneol. The last phase of this program required annulation of the B ring (or the A and B rings) and at an appropriate stage removal of the nitrile group. This proved to be much more difficult than we had hoped or anticipated. Mostly starting material was recovered when **19** was treated with methyl vinyl ketone and sodium ethoxide in benzene. Two other products were produced in less than 10% yield and these proved to be **20** and **21** of undefined stereochemistry. This approach was abandoned when it was discovered the gentle heating of **20** in the presence of sodium ethoxide led to extensive

(11) (a) Eck, C. R.; Mills, R. W.; Money, T. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1938. (b) Corey, E. J.; Ohna, M.; Chow, S. W.; Scherrer, R. A. *J. Am. Chem. Soc.* **1959**, *81*, 6305.

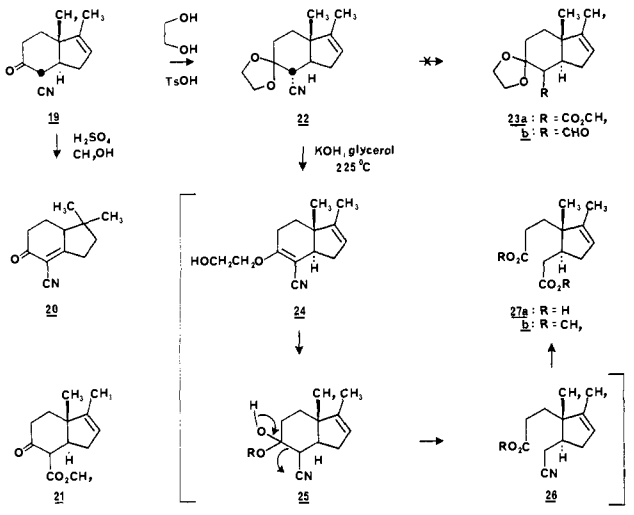
(12) These experiments were carried out in collaboration with Dr. M. Schlageter.[6]

(13) Julliard, J. *Pure Appl. Chem.* **1977**, *49*, 885.

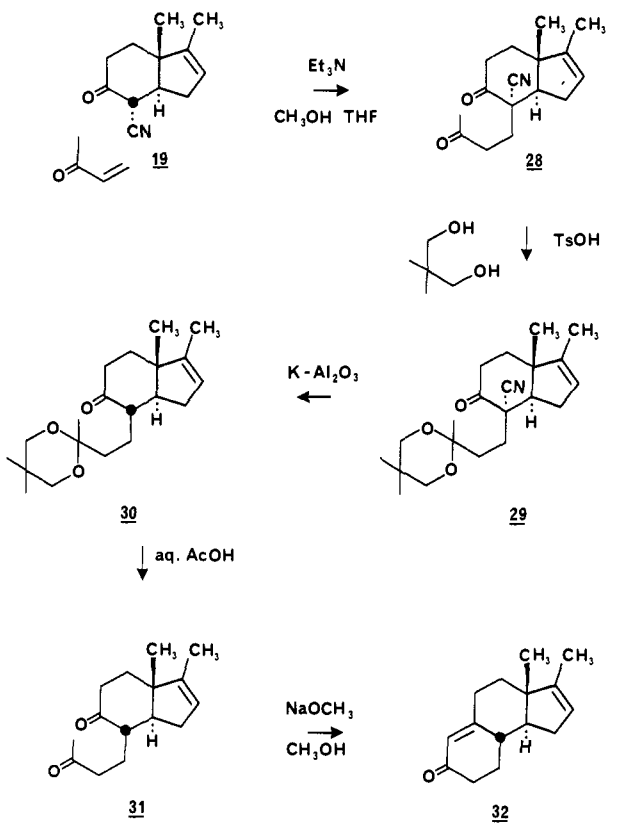
(14) Trisler, J. C.; Freasier, B. F.; Wu, S. *Tetrahedron Lett.* **1972**, 669.

(15) (a) Battersby, A. R.; Laing, D. G.; Ramage, R. *J. Chem. Soc.* **1972**, 669. (b) Buchmann, E. R.; Sargent, H. *J. Org. Chem.* **1942**, *7*, 140.

Scheme VI



Scheme VII



decomposition rather than to **21**. The same result was obtained when a large excess of methyl vinyl ketone was employed in the **19** to **20** and/or **21** transformation.

Next we turned our attention to employing enone **22**[16] as the annulating agent. When **19** was reacted with this enone (see Scheme V), mostly starting material was recovered. However, as with methyl vinyl ketone, two minor products were also obtained. Tricyclic enone **24** was isolated in 5% yield together with a small amount of another material, presumably ketol **23**. The assignment of configuration at C-8 in **24** (and in the case of **23** at C-9) was not made at this point, but the cyano group is probably α (see later). Our inability to effect either annulation in anything approaching a reasonable yield was contrary to the general efficacy of this reaction with other stabilized ketone enolates.[17] Accordingly, we undertook a stepwise approach to ascertain where the difficulty lies. Clearly it was not in the Michael-addition step because reaction of **19** with **22** in 2:1 tetrahydrofuran–methanol afforded diketone **25** in 91% yield. However, when the latter intermediate was exposed to various bases, only **19** was recovered. Neither of the aldol products **2o** or **24** could be detected. The fact that this retro-Michael reaction occurred so readily vis-à-vis the desired aldol condensation suggested that the problem resided in the stereochemistry at C-8. If the conjugate addition **22** to **25** led to the stereoisomer **26**, then a severe 1,3-diaxial interaction is established between the methyl group at C-18 and the large ketoketal side chain at C-8. This interaction is immediately removed via the retro-Michael reaction, which is what is observed. Similar observations in closely related systems have been reported.[18]

Several attempts were made to convert the nitrile to another functional group in the hope that that might alter the stereochemical course of the Michael addition. The results were disappointing but informative. Thus, standard methods for the alcoholysis of **19** to the corresponding ester **21** (see Scheme VI) such as the Pinner reaction[19] gave either starting material or very complex mixtures depending upon the conditions employed. The use of *p*-toluenesulfonic acid[20] and methanol afforded a mixture of the ketal and corresponding enol enther without affecting the nitrile. When a methanolic solution of concentrated sulfuric acid was employed, **19** rearranged cleanly to **20**. In order to circumvent these difficulties we next turned our attention to base-catalyzed hydrolysis procedures. In an attempt to prevent a retro–Dieckmann–Thorpe–Ziegler reaction, the ketone was first protected as its ethylene ketal (**22**). We were therefore very surprised to observe that when the latter substance was exposed to base under forcing conditions followed by treatment with diazomethane, only diester **27b** was formed. In retrospect, this result can be rationalized by the sequence **22**–**26** or an equivalent thereof. Next, we turned our attention to the selective reduction of **22** to the corresponding aldehyde (**23b**). It has been noted[21] that conformational inversions between the various puckered conformations of *unhindered* dioxolane rings occur readily; consequently, no spin–spin coupling is observed between the four protons in their ^{1}H NMR spectra. However, these protons appear as a complex multiplet in ketal **22**, suggesting that they are in a very congested environment. This was confirmed in several unsuccessful attempts to reduce **22** with *i*-Bu_2AlH, $LiAl(OEt)_2H_2$, or even $LiAlH_4$ itself. Thus, it became painfully clear that some alternate method would have to be unearthed for dealing with the nitrile group in hydrindane **19** if this substance was ever to be deployed as an intermediate in steroid synthesis. Happily, a satisfactory solution to this problem now revealed itself.

As noted previously, conjugate addition of **19** with enone **22** proceeds readily and in high yield. The problem lies in effecting the subsequent aldol condensation without reversing the conjugate addition step. Thus, removal of the menacing cyano group *after* conjugate addition offered itself as a potential solution to the problem. Indeed, treatment of **19** with methyl vinyl ketone in methanol–tetrahydrofuran with a trace of triethylamine provided dione **28** in essentially quantitative yield (see Scheme VII). Now we were in a position to take advantage of the highly congested environment about the cyano ketone that had plagued our earlier studies. Thus, treatment of dione **28** with 2,2-dimethylpropane-1,3-diol under carefully defined conditions afforded the desired monoprotected ketone **29** in good yield. Methods for the reductive decyanation of *alkyl* cyanides to alkanes are well-known. However, to our knowledge no such reaction has been reported for β-cyano ketones. Recently, it was reported[22] that aliphatic nitriles undergo fragmentation in the presence of a potassium

(16) Stevens, R. V.; Lee, A. J. *J. Chem. Soc., Chem. Commun.* **1982**, 102.
(17) For an excellent review of this subject, cf.: Jung, M. E. *Tetrahedron* **1976**, *32*, 3, and references cited therein.
(18) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, *38*, 3244.
(19) cf.: Zillberman, E. N. *Russ. Chem. Rev. (Engl. Transl.)* **1962**, *31*, 615.
(20) James, F. L.; Bryan, W. H. *J. Org. Chem.* **1958**, *23*, 1225.
(21) Caspi, E.; Zajac, H.; Wittstruck, T. A. *J. Org. Chem.* **1964**, *29*, 640.
(22) Savola, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1980**, *45*, 3227.

dispersion on neutral activity I alumina. Nitrile **29** gave a complex mixture under these conditions. However, it was found that reasonably good results could be obtained by heating the alumina to 155 °C for 12 h in vacuo prior to the preparation of the potassium dispersion. The best results were obtained by being careful to exclude oxygen and by quenching the reaction mixture instantaneously (see Experimental Section). It is instructive to compare the ^{1}H NMR signals for the ketal protons in **29** and **30**. In **30** the ketal side chain occupies an equatorial position wherein it is free to rotate. Accordingly, no splitting between the methylene protons is expected[21] (or observed). However, when this side chain occupies an axial position as in **29**, the steric constraints imposed by the C-18 methyl group restrict this conformational freedom and the methylene protons split into a doublet of doublets. Deprotection of **30** in aqueous acetic acid provided the dione **31** in 92% yield. Finally, the aldol condensation to **32** was effected with sodium methoxide in benzene to afford a mixture of **32** and the corresponding ketol, which was dehydrated with methanesulfonyl chloride and triethylamine in benzene.

Experimental Section

^{1}H NMR spectra were measured at 200 MHz on a Bruker WP-200 spectrometer. ^{13}C NMR spectra were measured at 22.5 MHz on a Jeol FX 90Q spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Infrared spectra were recorded on a Beckman 4210 infrared spectrophotometer and were calibrated with the 1601-cm^{-1} absorption of polystyrene. Mass spectra were recorded on an AEI-M59 mass spectrometer. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are corrected.

All solvents were purified before use: ethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, benzene, and toluene were distilled from sodium benzophenone ketyl, dichloromethane and diisopropylamine were distilled from calcium hydride, and methanol was distilled from magnesium metal. Dimethylformamide was percolated through 3-Å molecular sieves. Trifluoroacetic acid and trifluoroacetic anhyrdide were distilled from phosphorous pentoxide.

Medium-pressure liquid chromatography was performed with Altex equipment using E. Merck silica gel (particle size 0.040–0.063 mm). High-performance liquid chromatography was performed on a Waters Associates Prep LC/System 500. All chromatography solvents were distilled prior to use.

(−)-Camphor (7). (−)-Borneol (**6**) (502 g, 3.26 mol) was dissolved in glacial acetic acid (1.5 L) in a 5-L three-neck round-bottomed flask fitted with a mechanical sitrring apparatus and thermometer. Aqueous NaOCl solution (2 L of a 2 M solution, 4 mol) was added dropwise over 2.5 h. The mixture was cooled in an ice bath as necessary to keep the internal temperature in the range of 15–25 °C. The mixture was stirred for 1 h after completion of addition, at which time a positive starch–potassium iodide test was obtained. Saturated aqueous $NaHSO_3$ solution (200 mL) was added until the color changed from yellow to white and the starch–potassium iodide test was negative. The mixture was then poured over an ice–brine mixture (10 L), and the resulting white solid was collected on a Büchner funnel and washed with saturated aqueous sodium carbonate solution until foaming was no longer evident. The solid product was pressed as dry as possible and dissolved in petroleum ether (2 L, bp 20–60 °C), and the aqueous and organic layers were separated. The aqueous layer was extracted twice with petroleum ether and then discarded. The organic layers were combined and dried over anhydrous calcium chloride. The mixture was concentrated by rotary evaporation ultil most of the petroleum ether was removed and the white slurry remained. The remainder of the petroleum ether was then removed by high-vacuum rotary evaporation with the condenser cooled to −78 °C to prevent sublimation of camphor, leaving 475 g (95.8%) of (−)-camphor as a free flowing white powder: mp 175.5–176.5 °C; $[\alpha]^{20}_D$ −38.1° (CH_3OH); IR, identical with Sadtler spectra no. 15264, 1750 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$), identical with Sadtler spectrum no. 30; ^{13}C NMR ($CDCl_3$), identical with Sadtler spectrum no. 4635, δ 196.8 (C=O).

(−)-3-Bromocamphor (8). A solution of camphor (1000 g, 6.58 mol) in acetic acid (2.5 L) in a 5-L three-neck round-bottomed flask was warmed to 85 °C and maintained at that temperature by using a temperature controller (see Figure 1). A mixture of Br_2 (400 mL) and acetic acid (400 mL) was added slowly over a period of about 8 h; the addition rate was adjusted to avoid the deep red color of excess bromine in the reaction mixture as much as possible. Bromine and/or camphor that sublimed into the reflux condenser between the reaction vessel and the addition funnel were melted by warming with steam or hot water periodically. Hydrogen bromide gas was carried away into an aspirator

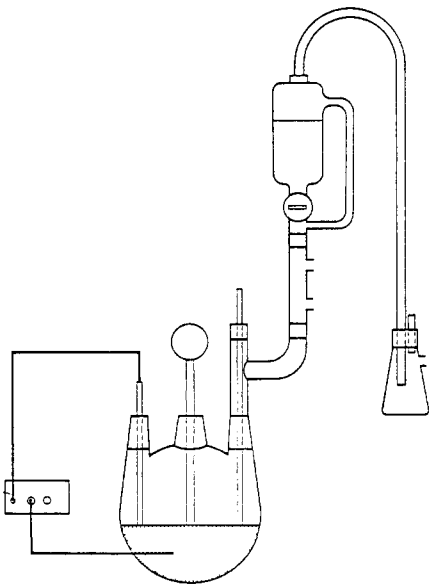


Figure 1.

(nalgene, not metal!) as shown in the diagram. The mixture was then stirred overnight at 85 °C and cooled, and a piece of glass tubing extending to the bottom of the flask was connected to one neck of the flask; a gas inlet was connected to another neck. A Büchner funnel was filled with ice and placed atop a 4-L filter flask on the floor next to the hood. The reaction mixture was slowly siphoned onto the ice (using pressure to start the siphon) where the product precipitated and the mother liquors were drawn into the flask. The crude product was washed with water and dried thoroughly in the air and then recrystallized from 1 L of 95% ethanol to yield 1000 g (65.8%) of (−)-3-bromocamphor: mp 75–78 °C; $[\alpha]^{20}_D$ −132° (CH_3OH); IR, identical with Sadtler spectra no. 15478, 1769 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$), identical with Sadtler spectrum no. 6760, δ 4.62 (d, J = 4.5 Hz); ^{13}C NMR ($CDCl_3$), identical with Sadtler spectrum no. 5803, δ 201.4 (C=O), 53.9 (C–Br).

(−)-9-Iodocamphor (11). In a 500-mL three-neck round-bottomed flask, fitted with an N_2 inlet, a magnetic stirring bar, a condenser, and an addition funnel were placed 83.0 g (0.5 mol) of dry pulverized KI in 300 mL of dimethylformamide. The reaction temperature was brought to 100–110 °C and a clear yellow solution resulted. To the reaction was rapidly added a solution of (−)-9-bromocamphor (**10**) (23.1 g, 0.1 mol) in 25 mL of dimethylformamide. The reaction became cloudy instantly and a precipitate resulted shortly (KBr). Heating was continued for 4 h, after which time the reaction was cooled to room temperature and poured into a separatory funnel containing 150 mL of H_2O. The remaining solid was dissolved with additional water and added to the funnel. The mixture was extracted 3 times with 100 mL of 30–60 petroleum ether. The organic layers were combined and concentrated on a steam bath to about 50 mL and allowed to cool. Colorless needles were obtained. Two crops were collected to afford 25.3 g (91%) of (−)-9-iodocamphor: mp 62–63 °C; $[\alpha]^{29}_D$ −139° (*c* 0.878, $CHCl_3$); IR (CCl_4) 1750 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 3.2–3.6 (q, 2 H), 2.3–2.5 (m, 2 H), 1.3–2.0 (m, 5 H), 1.0 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 2174, 57.6, 50.4, 43.1, 42.8, 29.4, 26.4, 18.0, 15.5, 9.4.

(−)-Keto ester 15. To 200 g (5.00 mol) of KH (previously freed of oil) in a 5-L round-bottomed flask was added 3 lb of absolute ether under an Ar atmosphere. With efficient mechanical stirring, freshly distilled dimethyl malonate (750 g, 5.68 mol) in 1 lb of absolute ether was added slowly via a syringe pump. After the addition was complete, the resulting suspension was heated to reflux for 2 h, and then approximately 2 L of ether was distilled off and 1 L of dimethylformamide (previously percolated through 3-Å molecular sieves) added. The temperature was slowly raised to remove the remaining ether. Another 3 L of dimethylformamide was added and 165 g (0.593 mol) of (−)-9-iodocamphor (**11**) introduced. The temperature was set to 120 °C and stirring continued for 40 h. At this point dry potassium iodide (50 g, 0.3 mol) was added and the temperature of the reaction vessel carefully raised to 140 °C. After a total of 64 h the suspension was cooled in ice and 70 mL of water added. By use of ahigh-vacuum rotorevaporator, most of the dimethylformamide and dimethyl malonate was removed at room temperature. The brownish residue was taken up in 3 L of water and with vigorous stirring carefully acidified to Ph 3 by using concentrated hydrochloric acid. The suspension obtained was continuously extracted with 30–60 petroleum ether for 2 days. The extract was

washed once with brine and dried over Na_2SO_4. The solvent was removed via rotary evaporation and the brownish residue was tken up in a small mount of 30–60 petroleum ether and filtered through a column of basic alumina (~250 g). After evaporation of the solvent 115.4 g of a light yellow oil was obtained. Distillation under high vacuum yielded 101 g (76%) of almost colorless (–)-keto ester: bp 90–92 °C/0.003 mm; $[\alpha]^{25}_D$ –69.2° (*c* 1.0, $CHCl_3$); IR (film) 1735–1750 cm^{-1} (carbonyls of ester and ketone); ^1H NMR ($CDCl_3$) δ 3.7 (s, 3 H, CCH_3), 2.15–2.55 (m, 4 H), 1.65–1.95 (m, 4 H), 1.30–1.55 (m, 3 H), 0.94 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR δ 218.3, 174.1, 58.6, 51.6, 48.9, 42.8, 40.0, 29.7, 28.8, 27.2, 26.6, 16.6, 9.3; mass spectrum calculated for $C_{13}H_{20}O_3$ = 224.1413, found = 224.1418.

(+)-Oxime Ester 16. Into a 250-mL round-bottomed flask containing an efficient stirring bar was added (–)-keto ester **15** (8.0 g, 35.7 mmol), hydroxylamine hydrochloride (12.5 g, 178 mmol), diazobicyclooctane (4.4 g, 39.3 mmol), and CH_3OH (80 mL). The reaction mixture was stirred at room temperature for 53 h. The CH_3OH was removed via rotary evaporation and the residue taken up in 150 mL of H_2O. This solution was acidified to pH 4 with concentrated HCl and extracted 3 times with 50-mL portions of ether. The ethereal layers were combined, dried over $MgSO_4$, and then removed by rotary evaporation to yield 7.4 g (86.7%) of (–)-oxime ester **16**. The crystalline oxime ester was pure enough to use in the next step. Alternatively, it may be recrystallized from ether: mp 90–91 °C; $[\alpha]^{24}_D$ +18.5° (*c* 1, $CHCl_3$); IR (CCl_4) 3440 (OH), 1720 (C=O), 1680 (C=N), 920 cm^{-1} (N–O); ^1H NMR ($CDCl_3$) δ 5.35 (br, 1 H, OH), 4.71 (s, 3 H, OCH_3), 1.15–2.6 (m, 11 H), 1.05 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.4, 169.5, 52.8, 51.6, 50.6, 40.7, 32.8, 32.5, 29.7, 27.1, 26.9, 16.2, 11.1; mass spectrum calculated for $C_{13}H_{21}O_3N$ = 239.1522, found = 239.1528.

(–)-Cyano Ester 18. Into an oven-dried three-neck round-bottomed flask (magnetic stirring bar, N_2 inlet) was placed 10.0 g (41.84 mmol) of oxime ester **16** and 10 mL of CH_2Cl_2. The resulting solution was cooled to 0 °C and 10 mL (70.3 mmol) of trifluoroacetic anhydride was added dropwise via syringe. The reaction vessel was then allowed to slowly attain room temperature and after a total of 4 h, 10 mL (41.67 mmol) of trifluoroacetic acid was added and stirring was continued for 24 h. All volatiles were removed in vacuo and the residual oil taken up in 100 mL of ether and extracted with brine (3 × 25 mL) and saturated K_2HCO_3 (5 × 25 mL). The aqueous layer was back-extracted with ether and the combined organic extracts dried (Na_2SO_4). The ether was removed in vacuo to furnish a yellow oil which was distilled under high vacuum to yield 3.44 g (80%) of a colorless oil: bp 88–90 °C/0.003 mm; $[\alpha]^{24}_D$ –36.2° (*c* 1, $CHCl_3$); IR (film) 3034 (C=C–H), 2240 (C≡N), 1730 (C=O), 1650 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 5.30–5.35 (br, 1 H, C=C–H), 3.68 (s, 3 H, OCH_3), 1.95–2.65 (m, 7 H), 1.70–1.85 (m, 2 H), 1.55–1.62 (m, 3 H, C=C–CH_3), 0.90 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 174.0, 145.1, 123.5, 119.5, 51.6, 50.1, 40.9, 35.9, 32.1, 29.6, 19.2, 18.5, 12.7; mass spectrum calculated for $C_{13}H_{19}O_2N$ = 221.1412, found = 221.1421.

(+)-Hydrindan 19. Into an oven-dried 500-mL three-neck round-bottomed flask fitted with efficient stirring bar and condenser eith N_2 inlet was placed *tert*-butanol (5.2 mL, 55 mmol), toluene (150 mL), and potassium (1.95 g, 50 g-atoms). this mixture was heated to 70 °C for 12 h. Then an additional 150 mL of toluene was added and the reaction mixture was allowed to reattain 70 °C. (–)-Cyano ester **18** (4.65 g, 21.0 mmol) in 5 mL of toluene was added in one portion to the reaction mixture. A precipitate immediately formed. After 30 min the reaction mixture was allowed to cool. It was then poured into a separatory funnel containing 400 mL of 2.5% HCl. Ether was added and the organic layer was collected. The aqueous phase was extracted twice more with ether and then discarded. The combined organics were dried over Na_2SO_4 and removed via rotary evaporation. The yellow solid was dissolved in a minimum amount of 60%g EtOAc–hexane and filtered through a small column of Florisil. Removal of the solvent yielded 3.38 g (85%) of (+)-hydrindan **19**. The slightly yellow crystals were pure enough for the next reaction. Alternatively, they may be recrystallized from ether: mp 130–131 °C; $[\alpha]^{29}_D$ +44.3° (*c* 0.658, $CHCl_3$); IR (CCl_4) 3040 (HC=C), 2250 (C≡N), 1730 (C=O); ^1H NMR δ 5.4 (m, 1 H, vinyl H), 3.6 (d, 1 H, J = 14 Hz), 1.8–2.7 (m, 7 H), 1.7 (br s, 3 H, vinyl CH_3), 1.0 (s, 3 H, CH_3); ^{13}C NMR δ 199.7, 148.6, 123.4, 115.8, 51.3, 45.9, 44.1, 36.7, 33.0, 31.8, 1.0, 12.4; mass spectrum calculated for $C_{12}H_{15}ON$ = 189.1154, found = 189.1151.

Dione 25. Into an oven dried 25-mL three-neck round-bottomed flask (magnetic stirring bar, nitrogen atmosphere) was placed (+)-**19** (0.40 g, 2.12 mmol), enone **22** (0.40 g, 2.18 mmol), a 2:1 solution of tetrahydrofuran–methanol (12 mL), and 10 drops of triethylamine. The solution was stirred at room temperature for 48 h. Thin-layer chromatography revealed three compounds: enone (R_f = 0.40), CD bicycle (R_f = 0.50), and the desired product as the major material (R_f = 0.34). The solvent was removed via rotary evaporation, and the residue taken up in ether and washed with water and then brine. The organic phase was dried (Na_2SO_4) and removed under reduced pressure. The resulting crude product was subjected to medium-pressure liquid chromatography to furnish pure **25** in 91.2% yield (720 mg) as a solid: mp 102–103 °C; IR (Nujol mull) 3020 (shoulder, H–C=C), 2240 (CN), 1730 (C=O), 1710 (C=O), 1638 (C=C), 1160 (C–O–C), 1070 cm^{-1} (C–O–C); ^1H NMR ($CDCl_3$) δ 5.3–5.4 (m, 1 H, vinyl H), 3.95 (s, 4 H, O–CH_2–CH_2–O), 1.8–2.9 (m, 17 H), 1.6 (br s, 3 H, vinyl CH_3), 1.3 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 208.7, 205.8, 147.6, 122.7, 118.7, 109.8, 64.6, 54.5, 51.1, 46.1, 42.7, 38.2, 37.8, 33.8, 32.0, 30.1, 24.3, 18.2, 17.5, 12.0; mass spectrum calculated for $C_{22}H_{31}NO_4$ = 373.2254, found = 373.2255.

Ketal 22. Into an oven-dried 100-mL round-bottomed flask (sitrring bar, Dean-Stark apparatus, N_2 atmosphere) was placed (+)-**19** (1.0 g, 5.3 mmol), ethylene glycol (1.55 g, 25 mmol), toluenesulfonic acid (0.01 g), and benzene (25 mL). The mixture was heated to reflux for 22 h and then cooled. It was then poured into a separatory funnel containing 50 mL of saturated $NaHCO_3$ and 50 mL of ether. The mixture was shaken and the aqueous phase discarded. The organic phase was then washed with brine, dried (Na_2SO_4), and removed via rotary evaporation to furnish the ketal **22** (1.22 g, 99%) as a solid: mp 158.0–159.5 °C; IR (CCl_4) 3040 (HC=C), 2240 (CN), 1640 (C=C), 1450 (CH_3), 1160 (C–O–C), 1040 (C–O–C), 940 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 5.30–5.38 (m, 1 H, vinyl H), 3.98–4.30 (m, 4 H, O–CH_2–CH_2–O), 2.9–3.0 (d, 1 H, HC–CN, *J* = 12 Hz), 1.7–2.4 (m, 5 H), 1.65 (br s, 3 H, vinyl CH_3), 0.85 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 149.6, 122.8, 119.1, 108.9, 65.9, 65.8, 49.0, 45.8, 39.2, 32.0, 31.4, 30.9, 13.7, 12.5; mass spectrum calculated for $C_{14}H_{19}NO_2$ = 233.1416, found = 233.1397.

Diester 27b. Into a one-neck 100-mL round-bottomed flask (magnetic stirring bar) was placed the (+)-ketal **22** (0.1 g, 0.43 mmol), KOH (1.2 g, 21.5 mmol), glycerol (50 mL), and ethanol (10 mL). Placed on top of the reaction vessel was a Soxhlet extractor filled with ethanol. The mixture was heated to 225 °C. The presence of ethanol vapor throughout the reaction vessel prevented the sublimation of the material in the glycerol solution. This reaction was heated for 12 h and then allowed to cool. The reaction mixture was diluted with a 3-fold excess of water and acidified to pH 3 with concentrated HCl. This solution was extracted with ether, and the ethereal layer was dried (Na_2SO_4) and removed under reduced pressure to yield 0.05 g (51.5%) of the diacid, as an oil. The diacid was taken up in ether and cooled to 0 °C. It was treated with an excess of CH_2N_2 and allowed to stir for 0.25 h. All volatiles were removed in vacuo to furnish the diester **27b** in quantitative yield as an oil: IR (film) 3200/3600 (water), 3015 (H–C=C), 1720–1740 (C=O), 1440 (CH_3), 1370 (CH_3), 1140–1300 cm^{-1} (C–O–C, ester); ^1H NMR ($CDCl_3$) δ 5.28–5.35 (m, 1 H, vinyl H), 3.69 (s, 3 H, CH_3 of ester), 3.67 (s, 3 H, CH_3 of ester), 1.7–2.5 (m, 9 H), 1.6 (br s, 3 H, vinyl CH_3), 0.85 (s, 3 H, CH_3); ^{13}C NMR (C_6D_6) δ 173.6, 173.1, 145.5, 124.3, 51.0, 50.1, 40.8, 36.2, 35.4, 32.2, 30.0, 29.9, 19.5, 12.7.

Dione 28. Into an oven dried 500 mL three-neck round-bottomed flask (magnetic stirring bar, N_2 atmosphere) was placed (+)-**19** (2.0 g, 10.6 mmol), tetrahydrofuran (200 mL), methanol (80 mL), triethylamine (10 drops), and methyl vinyl ketone (2.0 mL, 24.5 mmol). After 1i h a second addition of methyl vinyl ketone (2.0 mL, 24.5 mmol) was made. A third addition of methyl vinyl ketone (2.0 mL, 24.5 mmol) was made after 24 h. After a total of 36 h all volatiles were removed via rotary evaporation. The residue was taken up in ether, washed with water and then brine, and dried over Na_2SO_4. The ether was removed under reduced pressure to yield 2.73 g (99%) of dione **28** as an oil. The crude product was pure enough to be taken onto the next step. Some dione **28** was recovered in the next step by chromatography. This recovered material was solid and was used to obtain the spectral data presented here: mp 56.5–57.5 °C; $[\alpha]^{25}_D$ 161.6° (*c* = 0.05, $CHCl_3$); IR (CCl_4) 3420 (HC=C), 2230 (CN), 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 5.4 (m, 1 H, vinyl H), 2.5–3.0 (m, 4 H, CH_2C=O), 2.05–2.16 (t, 2 H, CH_2), 1.8–1.95 (m, 2 H), 1.6 (br s, 3 H, vinyl CH_3), 1.09 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 206.5, 205.7, 147.7, 122.7, 118.7, 54.7, 51.1, 46.2, 38.8, 33.9, 32.5, 30.1, 30.0, 17.4, 12.0; mass spectrum calculated for $C_{16}H_{21}O_2N$ = 259.1573, found = 259.1585.

Ketal 29. Into an oven-dried 500-mL three-neck round-bottomed flask (magnetic stirring bar, N_2 atmosphere, condenser) was placed **28** (2.46 g, 9.5 mmol), 2,2-dimethyl-1,3-propanediol (9.88 g, 95 mmol), $MgSO_4$ (11.4 g, 95 mmol), benzene (150 mL), and toluenesulfonic acid (0.1 g). The reaction mixture was heated to reflux for 16 h, cooled, and filtered, and the solid residue was washed several times with ether. The combined organics were washed with water and then brine and dried (Na_2SO_4), and the ether–benzene was removed under reduced pressure to afford a mixture of starting material and desired product along with a small amount of unknown high-R_f material. This mixture was subjected to medium-pressure liquid chromatography using 15% EtOAc–hexane as the solvent. A total of 0.17 g of starting material was recovered (which

at this point is crystalline). Also furnished was 2.31 g (75.5% based on recovered starting material) of **29** as a viscous oil: $[\alpha]^{25}_D$ 115.6° (*c* 0.1, $CHCl_3$); IR (film) 3220 (HC≡C), 2220 (CN), 1712 (C=O), 1640 (C=C), 1450 (CH_3), 1360–1380 [C-(CH_3)$_2$], 1070–1120 cm^{-1} (C–O–C); ^1H NMR ($CDCl_3$) δ 5.4 (m, 1 H, vinyl H), 3.35–3.65 (dd, 4 H, O–CH_2–CH_2–O), 2.6–2.75 (t, 2 H, CH_2), 2.25–2.41 (m, 3 H), 1.85–2.15 (m, 6 H), 1.6–1.73 (br s, 3 H, vinyl CH_3), 1.4 (s, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.0 (s, 3 H, CH_3), 0.9 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 205.5, 147.6, 122.8, 119.0, 98.2, 70.4, 54.3, 51.4, 46.3, 33.9, 32.5, 30.9, 30.6, 29.8; 23.0, 22.4, 20.2, 17.4, 12.0; ^{13}C NMR (C_6D_6) δ 204.6, 147.4, 122.9, 119.1, 98.4, 70.4, 54.2, 51.6, 46.2, 34.7, 33.7, 32.3, 31.3, 30.7, 29.7, 29.6, 23.0, 22.3, 20.1, 17.4; 11.8; mass spectrum calculated for $C_{21}H_{31}O_3N$–CH_3 = 330.2070, found = 330.2071.

Keto Ketal 30. Into an oven-dried 250-mL three-neck round-bottomed flask (stirring bar, Ar-vacuum inlet) was placed 11.7 g of neutral alumina (activity greater than 1 according to Boeckman). The alumina was then heated to 180 °C for 12 h under vacuum (to remove any remaining water). An argon atmosphere was introduced and potassium chunks (1.9 g, 0.05 g-atom) were carefully added with rapid stirring. Once a fine black snd resulted, the reaction temperature was lowered to room temperature and tetrahydrofuran (125 mL) introduced. Next, the **29** (1.3 g, 3.77 mmol) was dissolved in tetrahydrofuran (5 mL) and added in one portion, via syringe, to the reaction mixture. After 1 h the reaction mixture ws allowed to settle and then rapidly decanted into a coarse sintered glass funnel connected to a filtration flask under vacuum (the filtration flask contained 200 mL of a rapidly stirring ice-cold 20% NH_4Cl solution). Ether was added to the residue in the reaction vessel, the mixture was stirred and allowed to settle. This solution was also decanted rapidly through the sintered glass funnel into the filtration flask. This process was repeated twice. (Note: to quench the K–Al_2O_3 add hexane and slowly add ethanol until the yellow color persists; then add water.) The solution in the filtration flask was then placed in a separatory funnel, and ether and water were added until two distinct phases became apparent. The organic phase was collected and the aqueous phase was twice extracted with ether. The combined organic phases were washed with brine and dried (Na_2SO_4) and the solvent was removed via rotary evaporation. The resulting oil was subjected to medium-pressure liquid chromatography using 10% EtOAc–hexane as the solvent (the desired product has an R_f = 0.5 with 20% EtOAc–hexane). The pure (+)-keto ketal **30** was obtained in 51.7% yield (620 mg) as a viscous oil: $[\alpha]^{25}_D$ +48.8° (*c* 0.05, $CHCl_3$); IR (film) 3030 (H–C=C), 1708 (C=O), 1638 (C=C), 1450 (CH_3), 1370–1390 [C-(CH_3)$_2$], 1090–1110 cm^{-1} (C–O–C); ^1H NMR ($CDCl_3$) δ 5.3–5.4 (m, 1 H, vinyl H) 3.5 (s, 4 H, O–CH_2–CH_2–O), 2.35–2.55 (m, 3 H), 1.5–2.3 (m, 1 OH), 1.35 (s, 3 H, CH_3), 1.2–1.45 (t, 2 H), 1.0 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 0.90 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 212.3, 149.k, 123.6, 99.2, 70.4, 53.7, 49.5, 46.5, 38.0, 34.1, 33.9, 31.8, 29.9, 22.7, 21.7, 21.4, 14.8, 12.5; mass spectrum calculated for $C_{20}H_{32}O_3$ = 320.2353, found = 320.2330.

(+)-Dione 31. Into a 50-mL one-neck round-bottomed flask was placed the **30** (0.595 g, 1.86 mmol) and 90% aqueous acetic acid (20 mL). The reaction was stirred for 2 h, poured into a separatory funnel containing 30 mL of water, and extracted 3 times with ether. The combined ethereal layers were washed with saturated $NaHCO_3$ until neutralized and then with brine. The organic layer was dried (Na_2SO_4) and removed via rotary evaporation to furnish 400 mg (91.9%) of pure (+)-dione **31** as an oil: $[\alpha]^{25}_D$ +29.11 (*c* = 0.0615, $CHCl_3$); IR (film) 3040 (HC=C), 1695–1720 (C=O), 1660 (C=C), 1440 cm^{-1} (CH_3); ^1H NMR ($CDCl_3$) δ 5.3–5.4 (m, 1 H, vinyl H), 2.4–2.8 (m, 6 H), 2.2 (s, 3 H, CH_3–C=O), 1.7–2.2 (m, 6 H), 1.65 (br s, 3 H, vinyl methyl), 1.0 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 212.5, 208.7, 149.5, 123.5, 53.7, 48.7, 46.4, 41.4, 38.0, 33.8, 31.6, 29.8, 21.7, 14.7, 12.5; mass spectrum calculated for $C_{15}H_{22}O_2$ = 234.1621, found = 234.1620.

(+)-BCD Tricycle 32. Into an oven-dried 25-mL round-bottomed flask (magnetic stirring bar, N_2 atmosphere) was placed (+)-dione **31** (0.37 g, 1.58 mmol), benzene (10 mL), and a previously made 0.1 M $NaOCH_3$–CH_3OH solution (0.5 mL). The reaction mixture was allowed to stir for 15 h, after which time thin-layer chromatography (40% EtOAc–hexane) revealed a UV-active product (R_f = 0.41), a second product (R_f = 0.3), and the absence of starting material (R_f = 0.36). All volatiles were removed by rotary evaporation and the residue taken up in ether. The ethereal solution was washed with water and then brine, dried (Na_2SO_4), and finally removed under reduced pressure. The mixture ws subjected to medium-pressure liquid chromatography (10% EtOAc–hexane), which yielded the ketol (0.1 g, 27%) as a solid and the desired (+)-BCD tricycle **32** (0.21 g, 62%) as an oil. Ketol: mp 171–173 °C; IR (Nujol mull) 3390 (OH), 3020 (H–C=C), 1700 (C=O), 1630 (C=C), 1120 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 5.2–5.4 (m, 1 H, vinyl H), 2.3–2.5 (m, 4 H), 1.3–2.0 (m, 13 H), 0.8 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 211.3, 151.7, 123.7, 75.8, 56.3, 50.0, 47.9, 42.1, 42.0, 37.2, 31.5, 30.9, 26.3, 15.2, 13.5, mass spectrum calculated for $C_{15}H_{22}O_2$ = 234.1621, found = 234.1642. BCD tricycle **32**: $[\alpha]^{35}_D$ +11.58° (*c* 0.01, $CHCl_3$); IR (film) 3040 (H–C=C), 1675 (C=O), 1620 (C=C), 1450 (CH_2), 970 (C=C), 800 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 5.83–5.88 (m, 1 H, enone H), 5.27–5.35 (m, 1 H, vinyl H), 1.7–2.75 (m, 9 H), 1.65 (br s, 3 H, vinyl CH_3), 1.4–1.6 (m, 3 H), 0.92 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 199.5, 166.7, 150.2, 125.4, 122.8, 55.6, 46.4, 37.3, 37.0, 34.0, 31.4, 31.0, 27.7, 14.4, 12.4; mass spectrum calculated for $C_{15}H_{20}O$ = 216.1515, found = 216.1510.

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Registry No. 6, 464-45-9; **7**, 464-48-2; **8**, 64474-54-0; **10**, 64474-56-2; **11**, 64474-57-3; **15**, 64421-34-7; **16**, 64421-35-8; **18**, 64421-37-0; **19**, 64478-24-6; **22** (enone), 51297-42-8; **22** (ketal), 87803-76-7; **25**, 87803-77-8; **27a**, 87803-78-9; **27b**, 87803-79-0; **28**, 87803-80-3; **29**, 87803-81-4; **30**, 87803-82-5; **31**, 87803-83-6; **32**, 87803-84-7; ethylene glycol, 107-21-1; dimethyl malonate, 108-59-8; 2,2-dimethyl-1,3-propanediol, 126-30-7; methyl vinyl ketone, 78-94-4.

Studies on the Synthesis of Vitamin B-12. 3

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Abstract: An enantiospecific approach to the synthesis of four precursors to vitamin B-12 from dextrorotatory and levorotatory camphor is described.

Previous accounts from this laboratory[1] have dealth with the design and development of a different strategy for the synthesis of cobyric acid (**1**) (Scheme I) and related corrinoid natural products. These studies established the feasibility of incorporating all of the essential features of this substance into a triisoxazole scaffold (e.g., **3**) that can serve as a latent synthon for the crucial secocorrin intermediate **2**. The triisoxazole **3** could, in turn, be assembled from four precursors (**4A–D**) via nitrile oxide cycloaddition technology. During the course of these previous studies the fundamental issue of stereochemistry, especially absolute stereochemistry, was largely ignored. In this paper and those that will follow[2] we address this fundamental problem.

(1) cf.: Stevens, R. V.; Lapalme, R.; Fitzpatrick, J. M.; Germeraad, P. B.; Harrison, B. L. *J. Am. Chem. Soc.* **1976**, *98*, 6313. Stevens, R. V.; Cherpeck, R. E.; Harrison, B. L.; Lai, J.; Lapalme, R. *Ibid.* **1976**, *98*, 6317. Stevens, R. V. *Tetrahedron* **1976**, *32*, 1599. Stevens, R. V. "Vitamin B-12. Proceedings of the Third European Symposium on Vitamin B-12 and Intrinsic Factors", Zagalak, B.; Friedrich, W., Ed.; W. de Gryter: Berlin, 1979, and references cited therein.

(2) Stevens, R. V.; Beaulieu, N.; Chan, W. H.; Takeda, T.; Waldner, A.; Zutter, U.; Daniewski, A. R., unpublished results.

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