Hsueh T'ung Pao, **21**, 512, 509 (1976)]. Their route to harringtonine is similar in concept, although different starting materials and some different intermediates were used to elaborate the acyl moiety.

(9) B. J. Clarke and R. P. Hildebrand, *J. Inst. Brew., London*, **73**, 60 (1967).
(10) F. Adickes and G. Andresen, *Justus Liebigs Ann. Chem.*, **555**, 41 (1944).
(11) The presence of hemiketal **5** in the hydrolysis product, although not isolated in a pure form, is thus strongly supported by the subsequent formation of **6**.
(12) K. L. Mikolajczak, R. G. Powell, and C. R. Smith, Jr., *J. Med. Chem.*, **18**, 63 (1975).
(13) W. M. Rathke and A. Lindert, *J. Org. Chem.*, **35**, 3966 (1970).
(14) NMR and LC are the only analytical tools (of those we have used) that are applicable to these diastereomeric compounds. Of these, only NMR is effective for differentiating between the two isomers. Data obtained by melting point (or boiling point), IR, UV, and MS analyses would, of course, be identical for both isomers. Our NMR data for the mixture of diastereomers (**10a, 10b**) are identical with NMR data obtained on an equivalent mixture of harringtonine and epiharringtonine resulting from a totally different synthesis (T. R. Kelly, R. W. McNutt, Jr., M. Montury, N. P. Tosches, K. L. Mikolajczak, C. R. Smith, Jr., and D. Weisleder, *J. Org. Chem.*, accepted for publication). In the cited work, the two diastereomers were resolved by LC, and each isomer's NMR spectrum was determined individually. These data were then also compared with the spectrum of our **10a, 10b** mixture, and no discrepancies were observed.
(15) The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.
(16) The active natural esters and most synthetic esters of cephalotaxine have never been obtained in crystalline form by us [see ref 12 above, and K. L. Mikolajczak, C. R, Smith, Jr., and D. Weisleder, *J. Med. Chem.*, **20**, 328 (1977), reference 14] or by other workers [see a reference cited in ref 8 above, S. Asada, *Yakugaku Zasshi*, **93**, 916 (1973), and H. Furukawa, M. Itoigawa, M. Haruna, Y. Jinno, K. Ito, and S.-T. Lu, *ibid.*, **96**, 1373 (1976)].
(17) Liquid esters **3, 4**, and **6** were subjected to GC–MS analysis, whereas the solid esters **8, 9**, and **10** were analyzed by the probe technique.
(18) An appropriate purity determination could not be made with **4** because it exists partially in the enol form and it also tends to decarbonylate during GLC or distillation.
(19) Composed of 1.184 g of NaOH and 6.800 g of KH_2PO_4 in 1 L of solution.
(20) Actually, this signal is an AB quartet with the two outside peaks of much lower intensity than the inner ones and hence hidden under other signals in this area.
(21) The authors thank L. W. Tjarks and D. Weisleder for NMR analyses and R. D. Plattner, G. F. Spencer, and W. K. Rohwedder for mass spectral data.

Synthesis of Betalains

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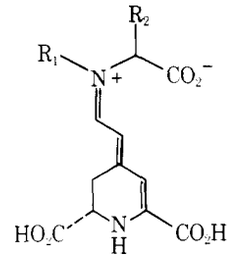
N-Benzylnorteloidinone (**10**) prepared by Robinson–Schöpf synthesis was converted to the ortho ester **18** with methyl orthoformate. Catalytic debenzylation of **18** followed by addition of allylmagnesium bromide gave carbinol **20**, which was transformed to the *O*-benzoylhydroxylamine **21** with benzoyl peroxide. Acetylation of the tertiary carbinol was followed by hydrolysis of the ortho ester to the diol **27**. Consecutive oxidations of the diol to the α-diketone **30** with dimethyl sulfide–*N*-chlorosuccinimide and of the olefin to the aldehyde with ozone gave the diketo aldehyde **31**. Treatment of **31** with lead tetraacetate in methanol–benzene afforded a dimethyl ester which, upon chromatography over silica gel, lost both acetic and benzoic acid to give dimethyl betalamate, characterized by a crystalline semicarbazone of unknown stereochemistry. Conversion of **32** to indicaxanthin (**4**) and betanidin (**5**) was accomplished using known procedures.

Betalains are water-soluble, nitrogenous plant pigments commonly found in species of the order *Centrospermae*.[2] The general structure **1** is derived from an amino acid and the aldehyde **2**, which was named betalamic acid. Betanin **3**, the most extensively studied member of the red-violet betacyanins, was found to be the characteristic pigment of the red beet, *Beta vulgaris*. Indicaxanthin (**4**) belongs to the betaxanthins and causes the yellow color of the fruit of the cactus *Opuntia ficus-indica*. All naturally occurring betacyanins are derived from either betanidin (**5**) or its C-15 epimer isobetanidin (**6**) and differ only in the sugar moiety and/or in the carboxylic acid attached to the sugar by an ester linkage. The structure of betanin was elucidated by Dreiding and coworkers,[3] and the relationship between the betacyanins and betaxanthins was established firmly by chemical interconversion[3f] of betanidin (**5**) and indicaxanthin (**4**).[4] Although betalamic acid (**2**) had been suspected of being an intermediate in these conversions, it was not until 1971 that it was isolated.[5,6] Condensation with L-proline and with synthetic cyclodopa gave indicaxanthin (**4**) and betanidin (**5**), respectively. Betalamic acid (**2**) was later isolated also from fly agaric (*Amanita muscaria*) along with muscaflavin (**7**).[7,8] Betanidin (**5**) proved to be a sensitive compound, and, especially in alkaline medium, it is oxidized easily to the much more stable neobetanidin (**8**).[3] Due to this instability, synthetic efforts have been directed toward more stable derivatives of both betanidin as well as the dihydroindole and dihydropyridine portions of the molecule. Three syntheses of the so-called cyclodopa moiety **9**, all starting from 3,4-dihydroxyphenylalanine, have been described,[9-11] and stable derivatives of this intermediate are now known.

The first total synthesis of betalamic acid (**2**) and betanidin (**5**) was reported by Hermann and Dreiding.[12] A new Horner–Emmons reagent was used to create the unsaturated aldehyde side chain, starting with 4-oxo 2,6-*cis*-piperidinedi-



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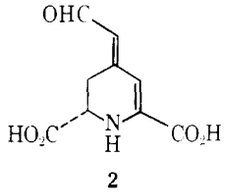

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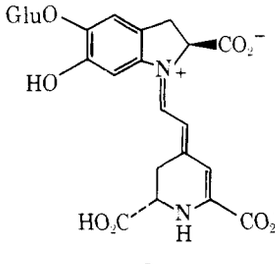

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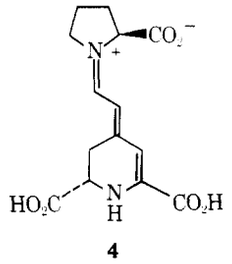

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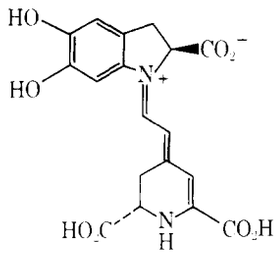

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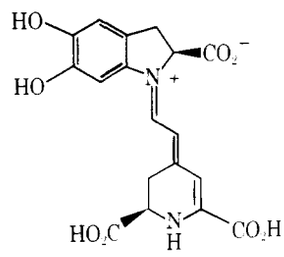

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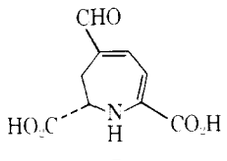

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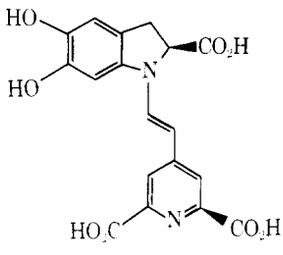

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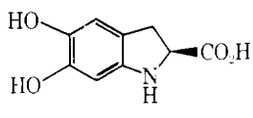
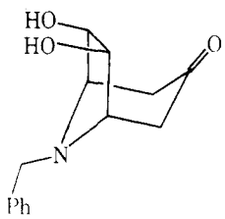


9

carboxylic acid dimethyl ester. The second cyclic double bond was introduced by Pfitzner–Moffat oxidation.

The known instability of betalamic acid (**2**) to oxidizing agents led us to consider synthetic schemes in which unwanted aromatizations could be avoided until the final product had been reached. For the same reason it was decided to introduce the second olefinic bond by an elimination, rather than an oxidation reaction. In this paper we describe a synthesis in detail[13] in which the hydropyridine framework used in the first synthesis[12] has been replaced by a tropane template.

Benzylnorteloidinone (**10**)[14] was synthesized by Robin-



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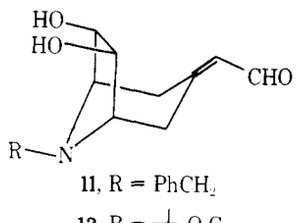
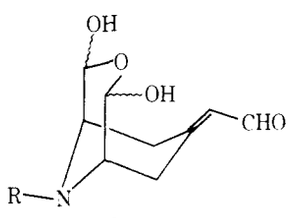


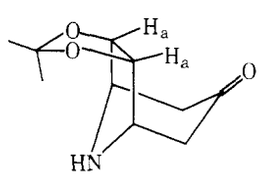
11, R = $PhCH_2$

12, R = $+O_2C$



13, R = $PhCH_2$

14, R = $+O_2C$



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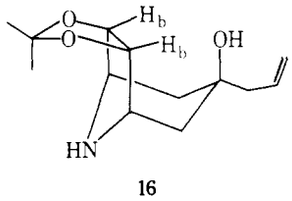

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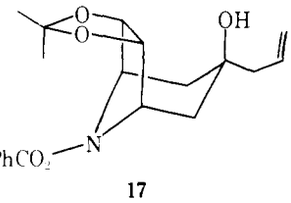
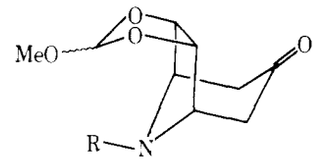


17

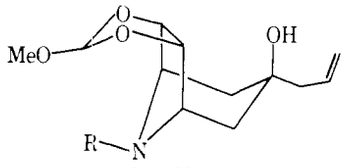
son–Schöpf condensation, following a procedure developed for the synthesis of teloidinone.[15] Our initial plan called for the preparation of intermediates **11** or **12**, and these were prepared by standard procedures.[16] Oxidation of the vicinal diols did proceed to the bishemiacetals **13** and **14**, but efforts to convert these to the corresponding dicarboxylic acids failed. Since the unsaturated aldehyde function seemed to interfere with the latter oxidations, it was replaced by a homoallylic alcohol. Treatment of ketone **15**, prepared by hydrogenolysis of *N*-benzylnorteloidinone acetonide, with allylmagnesium bromide afforded carbinol **16**, whose H_b protons appeared substantially downfield from the H_a protons in precursor **15**. This tentative assignment of configuration was later confirmed by chemical evidence. To introduce both a protective group for the basic nitrogen atom and a functionality capable of being converted to an imine, the secondary amine **16** was treated with benzoyl peroxide[17] in a mixture of benzene and ether at 50 °C containing suspended potassium carbonate. At this point we unfortunately observed that selective hydrolysis of the acetonide in **17** proved impossible, and a more labile cis diol protecting group was needed.

The trifluoroacetate of *N*-benzylnorteloidinone (**10**), when heated with trimethyl orthoformate and a catalytic amount of trifluoroacetic acid, afforded a mixture of epimeric orthoesters **18** in a ratio of approximately 10:1. This mixture was hydrogenolyzed in the presence of oxalic acid, and crystallization afforded a pure epimer **19** with unknown configuration. Addition of either allylmagnesium chloride in tetrahydrofuran or allylmagnesium bromide in ether furnished the expected carbinol **20**. Its configuration was assigned in analogy with that of **16**. Benzoylhydroxylamine **21** was prepared from amine **20** with benzoyl peroxide, this time in dimethylformamide at room temperature. The proton nuclear magnetic resonance spectrum of **21** was complex, but it could be rationalized by assuming the presence of two invertomers in a ratio of 3:1. Such high inversion barriers have been observed for other amines bearing a heteroatom on nitrogen.[18] Partial hydrolysis of the orthoester **21** afforded the monoformate **22**, and in the course of efforts to prepare an enediol the latter was oxidized with Collins' reagent. Acetylation of the resulting ketone **23** did not give the anticipated enol acetate, but instead a substance whose spectral properties were more consistent with those of the hemiketal acetate **24**, thus confirming the configuration of the Grignard adduct **20**. From these observations it became clear that oxidative cleavage of the two carbon bridge within these substituted tropanes will only be successful after the tertiary carbinol has been protected. Acetylation was chosen, and esterification of **21** was effected using 4-dimethylaminopyridine as the catalyst.[19] Hydrolysis of the orthoester **25** with aqueous oxalic acid did not affect the tertiary acetate and gave monoformate **26**, which was oxidized to the ketone **28** with pyridinium chlorochromate.[20] Surprisingly, saponification of formate **28** with aqueous bicarbonate in methanol, a method that served to hydrolyze formate **26** to the diol **27**, cleaved the benzoate. Selective hydrolysis was, however, possible using the nonnucleophilic cosolvents *tert*-butyl alcohol or dioxane. The resulting acyloin **29** was readily oxidized to the diketone **30** with pyridinium chlorochromate. Further evidence for an unusual electronic interaction between the nitrogen atom and the carbonyls on the two carbon bridge was provided by the visible absorption spectrum of the purple diketone **30**, which displayed an unusually long wavelength maximum at 496 nm.[21] It was subsequently found that diketone **30** could be obtained more directly from the cis diol **27** by oxidation with dimethyl sulfide–*N*-chlorosuccinimide.[22] Diketone **30** was stable to periodic acid in methanol, even in the presence of sodium cyanide, which could have induced cyanohydrin formation.

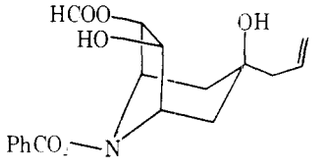
At this point, we decided to first cleave the side chain double bond and to scissor the tropane ring in the last stages of the synthesis. Ozonolysis of **30** afforded the desired aldehyde, which decomposed on attempted purification by chromatography but survived crystallization. Incidentally, the di-



18. R = $PhCH_2$
19. R = H



20. R = H
21. R = $PhCO_2$



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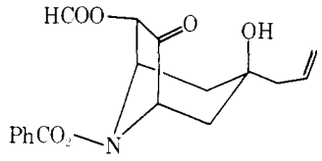

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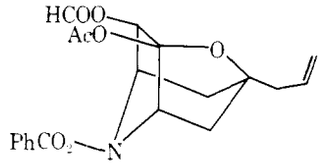

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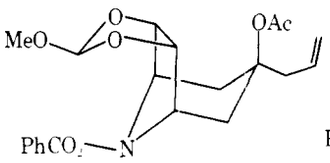

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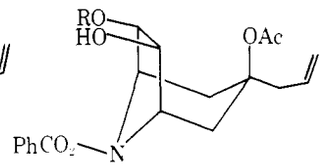
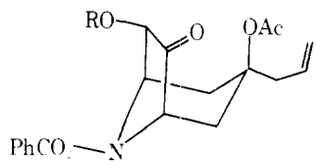
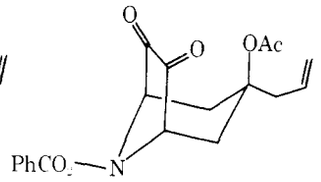


26. R = HCO
27. R = H



28. R = HCO
29. R = H



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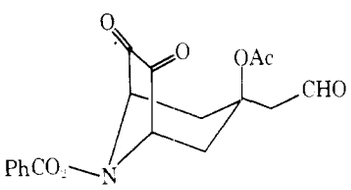

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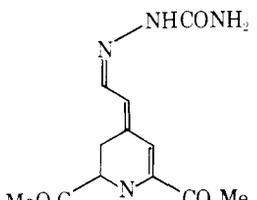

32

methyl sulfide employed to reduce intermediate peroxides after ozonization did not affect the hydroxylamine function and emphasized the usefulness of this highly selective method.[23] Diketone **31** consumed lead tetraacetate rapidly in a mixture of benzene–methanol,[24] and chromatography on silica gel produced an orange-colored product whose NMR spectrum was consistent with the presence of a mixture of *E* and *Z* isomers of dimethyl betalamate.[7] This mixture of diastereomers was converted to the semicarbazones, and after chromatography one isomer crystallized from ethanol. The identity of this substance **32** was ascertained by matching its ultraviolet, infrared, and proton nuclear magnetic resonance spectra with the published spectra of natural material.[12,26] Furthermore, a direct comparison (mixture melting point and chromatographic behavior) of our material with that obtained in the first synthesis confirmed its identity.[25] The conversion of **32** to betanidin (**5**) and indicaxanthin (**4**) is well documented in the literature.[3,4,12]

Experimental Section

The following spectrometers were used: IR, Perkin-Elmer Models 247, 237B, or 567; NMR, Varian T60 (60 MHz) or Perkin-Elmer R-22 (90 MHz), and tetramethylsilane was used as an internal standard; MS, Hitachi Perkin-Elmer RMU-6E at 70 eV; UV and vis, Perkin-Elmer 202 or Cary 14. All melting points were determined on a Reichert Hot-stage microscope and are corrected. Adsorbents used for chromatography were either aluminum oxide or silica gel (70–230 mesh), purchased from Brinkmann Instruments, Inc. Analytical thin-layer silica gel plates were purchased from Brinkmann Instruments, Inc., silica gel 60 F-254. Preparative layer chromatography was performed on either 0.5, 1.0, or 2.0 mm silica gel plates purchased from Analtech, Inc. Elemental analyses were performed by Robertson Laboratories, Florham Park, N.J.

***N*-Benzylnorteloidinone (10).** The procedure of Sheehan and Bloom[15] for the preparation of teloidinone was adapted. A solution of *meso*-tartaric dialdehyde was prepared by heating 26.0 g (0.16 mol) of *cis*-3,4-dihydroxy-2,5-dimethyltetrahydrofuran[15] in 100 mL of 1 N HCl (aqueous) on a steam bath for 20 min, cooling, neutralizing with $NaHCO_3$ (saturated), and adding the mixture to a buffer solution (pH 5) prepared from 495 g of citric acid monohydrate and 2.0 L of 2 N NaOH containing 22.8 g (0.16 mol) of benzylamine hydrochloride. A suspension of 50 g of 1,3-acetonedicarboxylic acid was neutralized with $NaHCO_3$ (saturated), and this solution was added to the buffer. The reaction mixture was stirred for 50 h under argon, during which time it evolved CO_2 and turned dark brown. After saturation with NaCl and addition of NaOH to pH 11, thorough extraction with ether and evaporation to dryness afforded a dark oil, to which was added 200 mL of acetone and 60 mL of 2 N HCl. The hydrochloride salt which crystallized was filtered, washed with acetone and ether, and dried to afford 20.6 g (45%) of **10** HCl as plates, mp 243–245 °C dec. The free base was obtained by extraction from aqueous base and crystallization (CH_2Cl_2–Et_2O): mp 84–85 °C; IR ($CHCl_3$) 3400, 2930, 1705, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.20 (d, 2, J = 16 Hz), 2.65 (dd, 2, J = 16 and 5 Hz), 3.35 (broad d, 2, J = 5 Hz), 3.90 (two s, 6), 7.30 (s, 5). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

Norteloidinone Acetonide (15). *N*-Benzylnorteloidinone hydrochloride (**10**; 5.45 g, 19.2 mmol) was dissolved in 300 mL of 33% aqueous methanol and hydrogenated in the presence of 300 mg of 5% palladium on carbon for 1.5 h at room temperature and 1 atm. After filtration of the catalyst, the filtrate was concentrated to dryness and the residue was suspended in 500 mL of acetone containing ca. 1 mL of concentrated sulfuric acid and heated at reflux for 24 h. Evaporation of most of the acetone and addition of 300 mL of ether precipitated a salt which was filtered, neutralized with aqueous base, and extracted thoroughly with methylene chloride. The residue from evaporation of solvent was sublimed in a Kugelrohr apparatus (140 °C/0.1 mm) to afford the crystalline acetonide (3.11 g, 81% from **10**): mp 107–108 °C; IR ($CHCl_3$) 3250, 2950, 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (s, 3), 1.48 (s, 3), 2.0–3.0 (m, 5), 3.55 (m, 2), 4.50 (s, 2). Anal. ($C_{10}H_{15}NO_3$) C, H, N.

Grignard Adduct 16. An ethereal solution of allylmagnesium bromide (100 mL of an approximately 0.5 M solution) was cooled to 0 °C, and 2.5 g of **15** in 100 mL of anhydrous ether was added dropwise with vigorous stirring. After 2 h, the mixture was poured into cold NH_4Cl (aqueous). Extraction for basic material gave 2.60 g of crude product, which by TLC and NMR analyses appeared to be composed of a major adduct, starting material, and a minor adduct. The pure adduct was obtained by crystallization (Et_2O–hexane) to afford 1.87 g (62%) of **16**: mp 133–134 °C; IR ($CHCl_3$) 3200, 2950, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (s, 3), 1.48 (s, 3), 1.8 (m, 4), 1.9–3.0 (m, 2), 2.13 (d, 2, J = 7 Hz), 3.23 (broad t, 2), 4.97 (s, 2), 5.0–6.2 (m, 3). Anal. ($C_{13}H_{21}NO_3$) C, H, N.

Benzoylhydroxylamine 17. A mixture of 2.39 g (10 mmol) of the Grignard adduct **16**, 2.2 g of benzoyl peroxide, and excess anhydrous potassium carbonate was heated at 45 °C in a benzene–ether solvent mixture for 2 days, whereupon it was cooled, filtered, and rapidly chromatographed on silica gel. The crude product was crystallized from ether–hexane to afford 2.83 g (80%) of **17**: mp 101–102 °C; IR ($CHCl_3$) 3550, 2970, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.3 (s, 6), 1.5–2.5 (m, 7), 3.95 and 4.15 (two m in a ratio of ca. 2:1, total 2), 4.9–6.1 (m, 3), 5.23 (s, 2), 7.2–7.6 (m, 3), 7.8–8.1 (m, 2). Anal. ($C_{20}H_{25}NO_5$) C, H, N.

N-Benzylnorteloidinone Methyl Orthoformate (18). The trifluoroacetate of N-benzylnorteloidinone (7.56 g, 21 mmol) was suspended in 300 mL of dichloromethane, and 10 drops of trifluoroacetic acid, 5 mL of dimethylformamide, and 5 mL of trimethyl orthoformate were added. After heating at reflux for 5 h, the solution was concentrated to a small volume, poured into cold aqueous bicarbonate, and extracted with ether. The residue was crystallized from Et_2O–hexane to give 5.75 g (95%) of a mixture of epimeric **18**, mp 110–150 °C. An NMR spectrum showed the composition to be approximately 10:1: NMR ($CDCl_3$) δ 2.20 (broad d, 2, J = 16 Hz), 2.71 (dd, 2, J = 16 and 5 Hz), 3.29 (s) and 3.43 (s) (3, in a ratio of ca. 10:1), 3.63 (broad d, 2), 4.00 (s, 2), 4.26 (s) and 4.46 (s) (2, in a ratio of ca. 1:10), 5.70 (s) and 5.97 (s) (1, in a ratio of ca. 1:10), 7.40 (broad s, 5). Recrystallization of this mixture from CH_2Cl_2–hexane afforded the major epimer: mp 101 °C; IR ($CHCl_3$) 3050, 2950, 2850, 1710, 1600 cm^{-1}. Anal. ($C_{16}H_{19}NO_4$) C, H, N.

Norteloidinone Methyl Orthoformate (19). A solution of 12.45 g (43 mmol) of **18** and 4.00 g of trifluoroacetic acid in 700 mL of methanol was hydrogenated in the presence of 1.5 g of 5% palladium on carbon for 1 h. Solid K_2CO_3 (anhydrous) was added with stirring. Filtration, concentration, and aqueous workup afforded 8.25 g (97%) of crystalline product. An analytical sample was recrystallized from CH_2Cl_2–Et_2O: mp 106–108 °C; IR ($CHCl_3$) 3500, 2950, 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.1–3.0 (m, 5), 3.30 (s, 3), 3.67 (m, 2), 4.66 (s, 2), 5.80 (s, 1). Anal. ($C_9H_{13}NO_4$) C, H, N.

Grignard Adduct 20. To an ice-cooled solution of allylmagnesium chloride (60 mL of a 2.2 M solution in THF) was added 6.94 g of **19** in 100 mL of THF under an argon atmosphere. After 30 min at 0 °C, 100 mL of anhydrous ether was added and the mixture was poured into cold aqueous NH_4Cl and thoroughly extracted with CH_2Cl_2. Recrystallization of the waxy residue from CH_2Cl_2–hexane and chromatography of the mother liquor on 40 g of silica gel afforded 5.97 g (71%) of **20**. An analytical sample had mp 137 °C: IR ($CHCl_3$) 3570, 2950, 1640, 840 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.0 (m, 4), 2.13 (d, 2, J = 7 Hz), 2.0–3.0 (broad, 2, exchange with D_2O), 3.30 (s, 3), 3.32 (broad s, 2), 5.10 (s, 2), 4.9–6.3 (broad, 3), 5.76 (s, 1). Anal. ($C_{12}H_{19}NO_4$) C, H, N.

***O*-Benzoylhydroxylamine 21.** In a flask wrapped in aluminum foil was stirred 3.045 g (12.5 mmol) of **20**, 3.04 g (12.5 mmol) of benzoyl peroxide, 3 g of anhydrous K_2CO_3, and 30 mL of DMF from a freshly opened bottle. After 30 h, anhydrous ether was added and the mixture was filtered and concentrated. The residue was filtered through 50 g of silica gel with 10% EtOAc–CH_2Cl_2, affording 3.8 g (85%) of **21**: mp 108 °C; IR ($CHCl_3$) 3570, 2950, 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.6–2.6 (m, 7), 3.28 and 3.33 (s, 3), 4.11 (broad t, 2), 5.15 and 5.45 (s, 2), 5.85 and 6.05 (s, 1), 5.0–6.4 (broad m, 3), 7.3–7.8 (m, 3), 7.9–8.2 (m, 2). Anal. ($C_{19}H_{23}NO_6$) C, H, N.

Acyloin Formate 23. A mixture of 230 mg of orthoester **21** in 10 mL of acetone and 10 mL of 5% aqueous oxalic acid was stirred for 15 min. Extraction with methylene chloride afforded 225 mg of an oil which was not further purified, but oxidized directly by adding it in 15 mL of dry methylene chloride to a solution of Collins' reagent (prepared in situ from 500 mg of CrO_3 and 800 μL of dry pyridine in 7 mL of dry CH_2Cl_2). After stirring for 30 min, the reaction was worked up in the usual manner and chromatographed on a 2 mm silica gel plate to yield 100 mg (50%) of **23** as an oil: IR (film) 3400, 2950, 1780 (sh), 1750 (sh), 1720 cm^{-1}; NMR ($CDCl_3$) δ 1.0–2.6 (m, 7), 3.5–4.5 (m, 2), 4.8–6.2 (m, 4), 7.1–8.3 (m, 6). Anal. ($C_{18}H_{19}NO_6$) C, H, N.

Hemiketal Acetate 24. In 10 mL of methylene chloride was dissolved 100 mg of ketone **23**, 1 mL of freshly distilled acetic anhydride, and 2 drops of trifluoroacetic acid. After heating at reflux for 1 h, the product, which was stable to chromatography and to treatment with aqueous methanolic bicarbonate, was purified by preparative TLC to afford 38 mg of an oil: NMR ($CDCl_3$) δ 1.6–2.8 (m, 9), 4.0–4.8 (m, 2), 4.9–6.1 (m, 4), 7.3–7.7 (m, 3), 7.9–8.2 (m, 2), 8.20 (s, 1). Anal. ($C_{20}H_{21}NO_7$) C, H, N.

Tertiary Acetates 25, 26, and 27. The tertiary alcohol **21** (9.50 g) was treated with 8 mL of acetic anhydride, 10 mL of triethylamine, and 1.5 g of 4-dimethylaminopyridine in 100 mL of anhydrous ether for 5 days at reflux. Workup with ice-cold aqueous $NaHCO_3$ followed by elution of the crude product through a short silica gel column with $CHCl_3$ afforded 10.6 g (100%) of **25** as a colorless oil, homogeneous by TLC. This oil was dissolved in 100 mL of acetone and stirred for 30 min with 5% aqueous oxalic acid (20 mL). If desired, this could be worked up to afford the monoformate **26**: mp 159–160 °C (CH_2Cl_2; crystallized with a molecule of solvent); IR ($CHCl_3$) 3570, 3420, 2960, 1730, 1640, 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (s, 3), 2.1–3.2 (m, 7), 4.05 (m, 2), 4.6–6.2 (m, 5), 7.3–7.6 (m, 3), 7.7–8.2 (m, 2), 8.20 (s, 1). Anal. ($C_{20}H_{23}NO_7$) C, H, N.

Alternatively, the reaction mixture could be treated with solid potassium carbonate and stirred for 1 h to yield, after workup and recrystallization from CH_2Cl_2–hexane, 7.65 g of **27** (81% based on **21**): mp 171–175 °C; IR ($CHCl_3$) 3400, 2950, 1730, 1640 cm^{-1}; NMR ($CDCl_3$; two invertomers were observed) after D_2O exchange, δ 2.00 and 2.03 (s, 3), 2.1–3.0 (m, 6), 3.8 and 4.0 (m, 2), 4.43 and 4.72 (s, 2), 4.8–6.2 (m, 3), 7.3–8.3 (m, 5). Anal. ($C_{19}H_{23}NO_6$) C, H, N.

Acyloin Formate 28. To a suspension of 6.0 g of pyridinium chlorochromate and an approximately equal weight of dry Celite in 100 mL of anhydrous methylene chloride was added 5.88 g of alcohol **26**, and the mixture was stirred for 24 h. Filtration and evaporation of solvent afforded a dark residue which was applied to a short column of silica gel and eluted with 10% EtOAc–hexane to afford 5.05 g (87%) of crystalline **28**: mp 139–140 °C; IR ($CHCl_3$) 3450, 3070, 2970, 2930, 1770, 1730 cm^{-1}; NMR ($CDCl_3$) δ 2.0 (s, 3), 2.1–3.3 (m, 6), 3.8 (m, 1), 4.2 (m, 1), 4.9–6.0 (m, 3), 5.73 (s, 1), 7.2–8.1 (m, 5), 8.13 (s, 1). Anal. ($C_{20}H_{21}NO_7$) C, H, N.

Acyloin 29. A mixture of 5.05 g of **28**, 50 mL of *tert*-butyl alcohol, 50 mL of THF, 20 mL of dioxane, and 50 mL of 5% aqueous $NaHCO_3$ was stirred at room temperature for 6 days, concentrated to approximately 50 mL, and extracted with methylene chloride. The residue from evaporation of solvent was crystallized (Et_2O–hexane) to afford 4.1 g (87%) of **29**: mp 134–135 °C; IR ($CHCl_3$) 3350, 1770, 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.9 (s, 3), 2.2–3.3 (m, 7, 1 exchanges with D_2O), 3.8 (m, 1), 4.2 (m, 1), 4.6 (s, 1), 4.9–6.1 (m, 3), 7.3–8.1 (m, 5). Anal. ($C_{19}H_{21}NO_6$) C, H, N.

Diketone 30. To a solution of 7.05 g (53 mmol) of N-chlorosuccinimide in 300 mL of dry toluene was added 5.0 mL (68 mmol) of dimethyl sulfide at 0 °C, and the mixture was stirred at this temperature for 30 min. After cooling to −40 °C, 7.65 g (21.2 mmol) of **27** in a minimum volume of methylene chloride was added and stirred for 1.5 h at −40 to −35 °C. Excess triethylamine (5 mL) was added, and the mixture was allowed to warm to room temperature. An equal volume of ether was added (300 mL), the mixture was washed with water several times and concentrated, and the residue was crystallized from ethanol to afford 4.78 g (75%) of pure diketone: mp 146 °C; vis ($CHCl_3$) 496 nm (ε 45); IR ($CHCl_3$) 3000, 1790, 1777, 1745, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.80 (s, 3), 2.2–3.2 (m, 6), 4.19 (broad t, 2), 4.8–6.1 (m, 3), 7.1–7.9 (m, 5). Anal. ($C_{19}H_{19}NO_6$) C, H, N.

Aldehyde 31. The diketone **31** (620 mg) in 37 mL of 30:7 EtOAc–MeOH was treated with ozone at −78 °C. Excess ozone was blown off with argon at −78 °C, 2 mL of dimethyl sulfide was added, and the solution was allowed to warm slowly to 0 °C over a period of 2.5 h. After 3 additional hours at room temperature, the solution was concentrated, and the residue was dissolved in 100 mL of 1:1 Et_2O–benzene and washed with water, 1 N HCl, and 5% $NaHCO_3$ to afford a quantitative recovery of crude product. Recrystallization from CH_2Cl_2–Et_2O gave 420 mg (68%) of pure aldehyde **31**: mp 134 °C; vis ($CHCl_3$) 497 nm (ε 25); IR ($CHCl_3$) 3000, 2830, 2730, 1785, 1775, 1750, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.85 (s, 3), 2.67 (broad d, 2, J = 16 Hz), 3.00 (broad d, 2, J = 16 Hz), 3.19 (d, 2, J = 1 Hz), 4.25 (broad t, 2), 7.4–8.0 (m, 5), 9.65 (t, 1, J = 1 Hz). Anal. ($C_{18}H_{17}NO_7$) C, H, N.

Betalamic Acid Dimethyl Ester Semicarbazone (32). A solution of 400 mg of **31** in 28 mL of 1:1 benzene–methanol was stirred at 0 °C under argon, and 920 mg of lead tetraacetate (containing 10% acetic acid) was added. After stirring for 45 min at 0 °C, a few drops of ethylene glycol were added, followed by ice water. The aqueous mixture was extracted with ethyl acetate, which was washed with brine and then stirred for 2 h with an aqueous solution of 276 mg of semicarbazide hydrochloride and 300 mg of sodium acetate. The ethyl acetate layer was separated, dried (Na_2SO_4), and concentrated. Rapid chromatography of the residue through silica gel furnished 108 mg (33%) of the product as an oil. Crystallization from EtOH–H_2O afforded an analytical sample: mp 183–188 °C; IR (KBr) 3460, 3360, 2950, 1680, 1580, 1470, 1430, 1270 cm^{-1}; the NMR (Me_2SO-d_6) spectrum matched that given in ref 26; UV (EtOH) λ_{max} 375 nm (ε 33 700), 265 (10 500); MS *m/e* (relative intensity) 296 (M^+, 30), 279 (9), 253 (14), 237 (46), 220 (30), 194 (35), 177 (100). Anal. Calcd for $C_{12}H_{16}N_4O_5$: C, 48.64; H, 5.44; N, 18.91. Found: C, 48.34; H, 5.47; N, 17.60.

Dreiding's synthetic sample recrystallized from EtOH–H_2O: mp 185–192 °C; R_f (15% MeOH–EtOAc) 0.48. Our sample recrystallized from EtOH–H_2O: mp 183–188 °C; R_f (15% MeOH–EtOAc) 0.51. A mixture melting point was not depressed.

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Registry No.—**10**, 63322-00-9; **10** HCl, 67858-62-2; **10** F_3CCO_2H, 67891-06-9; **15**, 67858-63-3; **16**, 67858-64-4; **17**, 67858-65-5; **18** (isomer 1), 67919-54-4; **18** (isomer 2), 67919-55-5; **19**, 63321-93-7; **20**, 63321-94-8; **21**, 63321-95-9; **22**, 67858-66-6; **23**, 67858-67-7; **24**, 67858-68-8; **25**, 67858-69-9; **26**, 67919-56-6; **27**, 63321-97-1; **28**, 67858-70-2; **29**,

67858-71-3; **30**, 63321-98-2; **31**, 63321-99-3; **32**, 67919-57-7; *meso*-tartaric dialdehyde, 58066-70-9; *cis*-3,4-dihydroxy-2,5-dimethyltetrahydrofuran, 67858-72-4; benzylamine hydrochloride, 3287-99-8; 1,3-acetonedicarboxylic acid, 542-05-2; allyl bromide, 106-95-6; allyl chloride, 107-05-1.

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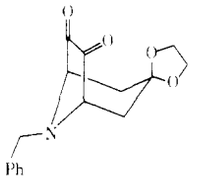

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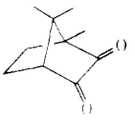

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Synthesis of Vitamin A and Related Compounds via a π-Allylpalladium Complex

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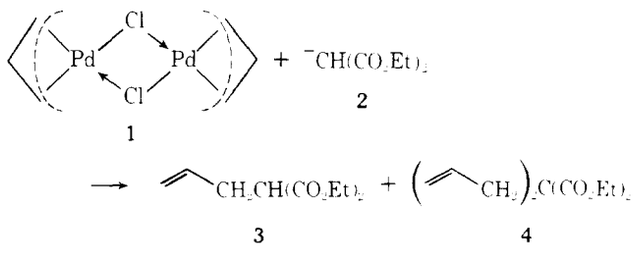
Reaction of the anion derived from 3-methyl-1-(phenylsulfonyl)-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)penta-2,4-diene (**8a**), in dimethylformamide and in the presence of triphenylphosphine, with the π-allyl complex **9** prepared from prenyl acetate (**6**) and palladium(II) chloride gave 1-acetoxy-3,7-dimethyl-5-(phenylsulfonyl)-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)nona-2,6,8,-triene (**10a**) in 52% yield. Treatment of **10a** with sodium ethoxide in boiling ethanol produced a stereoisomeric mixture of vitamin A (**11a**), which contained a preponderance of the all-trans isomer, in 81% yield. The reaction of **9** with some related polyisoprenoid sulfones, followed by elimination of benzenesulfinic acid, is also described. The stereostructure of **9** was established by X-ray crystallography.

Although the application of transition metal complexes in the synthesis of organic substances has burgeoned during the past decade,[1] use of these complexes in the construction of intricate natural products has emerged only recently. In this context the efforts by Corey and his collaborators using π-allylnickel complexes[2] and by Trost and his associates using π-allylpalladium complexes[3] are preeminent. Some recent, notable achievements in this area are exemplified by a facile synthesis of the alkaloid cephalotaxinone by Semmelhack[4] using a nickel complex, an elegant prostaglandin synthesis by Holton[5] using a palladium complex, and an intriguing steroid synthesis by Vollhardt[6] employing a cobalt complex. In this paper we describe a novel synthesis of vitamin A (**11a**),[7] and some related polyisoprenoids, using the crystalline π-allylpalladium complex **9**.

It is well established[8] that π-olefinpalladium and π-allylpalladium complexes are highly susceptible to attack by nucleophiles, a reaction which forms the basis of the Wacker process[9] for producing acetaldehyde from ethylene and water in the presence of palladium(II) chloride. Extension of this reaction to include carbanions was first demonstrated by Tsuji, who in 1965 reported[10] that complex **1** reacted with malonate anion in a mixture of ethanol and dimethyl sulfoxide at room temperature to give esters **3** and **4** (Scheme I).

The synthetic potential of Tsuji's reaction remained unrecognized until the recent, excellent studies by Trost and his collaborators.[3] These workers (and ourselves) have found that Tsuji's original experiment is not of general applicability in organic synthesis since it fails, or gives only very poor yields of products, when alkyl-substituted π-allylpalladium complexes that do not bear electron-withdrawing groups are used.

Scheme I



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