67999-02-4; **11**, 67938-45-8; **12**, 67938-46-9; **13**, 67938-47-0; **13** benzoate, 67938-48-1; **14**, 167999-03-5; **15**, 67999-04-6; (+)-**17**, 10064-26-3; (±)-**17**, 64199-80-0; **18**, 67999-05-7; 3,12-dioxo-19-norabiet-9(11)-ene-5β,8β-carbolactone 3-ethylene ketal phenylselenyl derivative, 67938-49-2; 2-carboethoxycyclohexanone, 1655-07-8; ethyl vinyl ketone, 1629-58-9; acetaldehyde, 75-07-0; phenylselenyl chloride, 5707-04-0.

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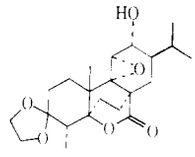

i

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# Synthesis of Harringtonine, a *Cephalotaxus* Antitumor Alkaloid[1]


Kenneth L. Mikolajczak* and Cecil R. Smith, Jr.

*Northern Regional Research Center, Federal Research, Science and Education Administration, U.S. Department of Agriculture, Peoria, Illinois 61604*


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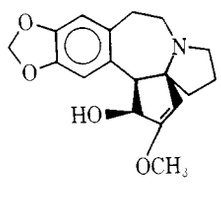
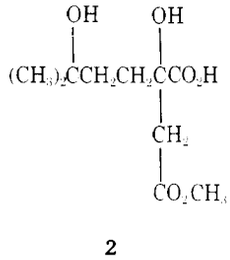
Harringtonine (**10a**), one of the antitumor alkaloid esters from *Cephalotaxus harringtonia*, has been synthesized from cephalotaxine (**1**) by an indirect approach involving a series of cyclic ketal and hemiketal intermediates. A Claisen condensation of $(CH_3)_2C{=}CHCH_2CO_2Et$ (**3**) with diethyl oxalate gives $(CH_3)_2C{=}CHCH(COCO_2Et)(CO_2Et)$ (**4**). This substituted oxalacetate affords methyl 2-methoxy-5,5-dimethyltetrahydro-2-furoate (**6**) on aqueous acid hydrolysis followed by reaction with HCl–MeOH. Cyclic ketal **6** is then converted by a series of transformations to cephalotaxyl 2-hydroxy-5,5-dimethyltetrahydro-2-furoate (**9**) as a mixture of two diastereomers. Treatment of this mixture with methyl bromoacetate and zinc via the Reformatsky procedure yields harringtonine (**10a**) and its acyl C-2 epimer, epiharringtonine (**10b**).


*Cephalotaxus harringtonia* plant material contains small amounts of a number of ester alkaloids which have shown significant activity in several experimental tumor systems in mice.[2,3] Prominent in this active alkaloid group are harringtonine and homoharringtonine. Harringtonine[4] is an ester composed of the alkaloid (−)-cephalotaxine (**1**) esterified with the 2*R* enantiomer of acid **2**, and homoharringtonine contains an additional methylene group in the acyl side chain.[4] More recently, clinical testing with mixtures of these two alkaloids has given promising results with leukemia patients in the People's Republic of China.[5] However, a scarcity of plant material has halted testing of these alkaloid esters in the United States at the preclinical stage.



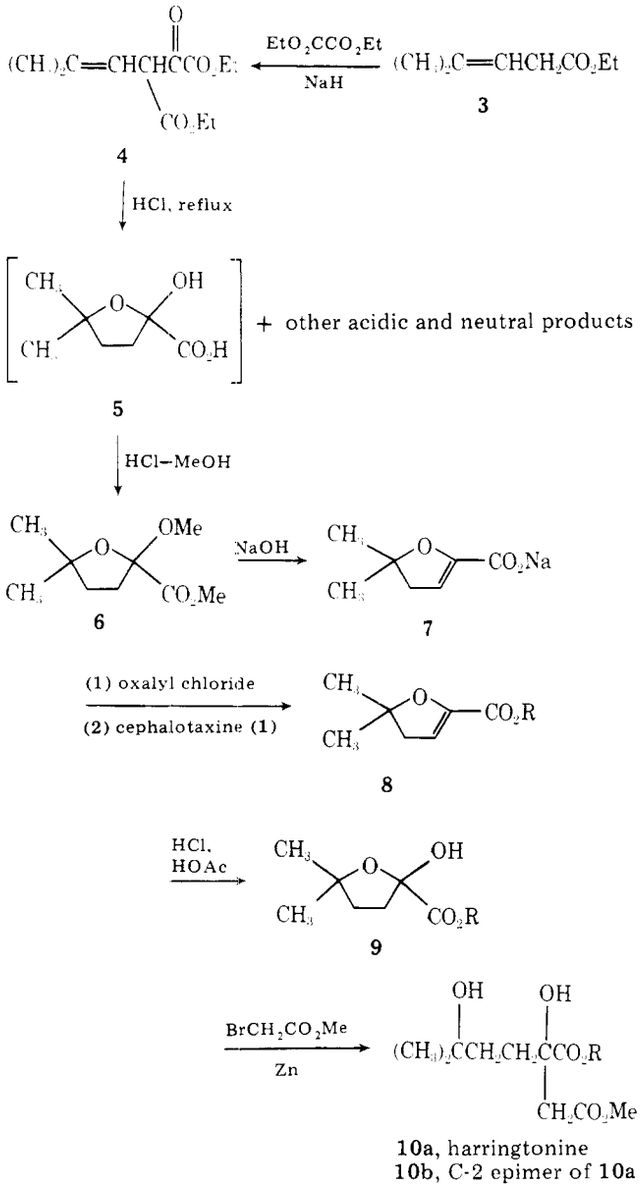
1



2

*Cephalotaxus* plant material usually contains appreciably more unesterified cephalotaxine (**1**) than its active esters. Since cephalotaxine has also been synthesized,[6] it is desirable to have an effective method of converting **1** to its active esters. All attempts to acylate **1** directly with fully elaborated acid moieties,[7] such as **2**, have failed due to (a) severe steric hindrance at the reaction site, (b) difficulties in unmasking hydroxyl functions and generating the carbomethoxymethylene side chain at the terminal stage, and (c) problems associated with instability of α-keto esters having a $-C(O-)CCC(=O)-C(=O)O-$ grouping. The sequence we employed[8] in synthesizing harringtonine, shown in Scheme I, deals with all of these problems in some degree by utilizing intermediates which cyclize readily to form ketals or hemiketals in a way reminiscent of common reducing sugars.

Scheme I




## Results and Discussion

Ester **3** (Scheme I) was prepared in three steps. Condensation of isobutyraldehyde with malonic acid[9] and concomitant decarboxylation give an $\alpha,\beta$-unsaturated acid which is isomerized to the corresponding $\beta,\gamma$-unsaturated acid with base; esterification with boron trifluoride in ethanol provides **3**. Although sodium ethoxide can be used in the Claisen condensation of **3** with diethyl oxalate[10] to give **4**, we obtained better yields with sodium hydride as the condensing agent. Esters **3** and **4** must not be permitted to remain in contact with aqueous acid because hydration of the double bond occurs readily at room temperature.[9]

When **4** was refluxed with aqueous HCl, a number of reaction processes occurred. After hydration of the double bond (a fast process), numerous reaction pathways, including hydrolysis of ester groupings, decarboxylation, lactonization, and ketal formation, are available and lead ultimately to a very complex mixture. Neutral constituents (probably $\gamma$- and $\delta$-lactones) were removed. The acidic components, without further purification, were treated with hydrochloric acid in methanol; separation of the products gave a 36% yield of cyclic ketal **6**.[11] Saponification of this ketal is accompanied by base-initiated $\beta$-elimination of the elements of methanol. Attempts to isolate the free acid derived from **6** were unsuccessful. However, by evaporating the saponification mixture to dryness, one obtains the sodium salt **7** which is suitable for direct conversion to the acid chloride with oxalyl chloride. Reaction of the acid chloride with cephalotaxine provides **8** in 73% yield.

Hydration of the double bond in the acyl moiety of **8** was effected with hydrochloric acid–acetic acid under mild conditions which are compatible with other functional groupings in the molecule. The generation of a new chiral center (C-2 of the acyl moiety) during hydration results in the formation of two diastereomers as evidenced by the NMR spectrum of **9**. The *gem*-dimethyl proton signal appears as two distinct sets of signals,[12] and the signals of the C-3 and C-4 protons of the cephalotaxine moiety are partially resolved into two sets of signals. The signals of all other protons in both isomers have the same chemical shifts. Crude **9** (88% yield) was nearly pure as shown by NMR even though only 57% of **9** was recovered by preparative TLC. This may indicate that decomposition of **9** occurs on silica gel. Because of the scarcity of material, crude **9** was used in the Reformatsky reaction.

Application of the Reformatsky reaction to hemiketal **9** is possible, perhaps due to an equilibrium between **9** and its open chain ketone form. A modified version of this reaction was employed[13] in which trimethyl borate is used to reduce the alkalinity of the reaction mixture. Even under these mild conditions, however, a considerable proportion of **9** is deacylated and thus reverts to unesterified **1**. This side reaction helps reduce the yield of harringtonine (**10a**) plus epiharringtonine (**10b**) to a level of 5–10% [based on cephalotaxine (**1**) used]; **1** can, of course, be recycled since it is stable and is relatively easy to recover and purify. Epiharringtonine (**10b**) is formed along with harringtonine (**10a**) because C-2 of the acyl group is generated in both configurations during the Reformatsky reaction. The NMR spectrum[14] of the mixture of **10a** and **10b** exhibits two sets of signals for the *gem*-dimethyl group of the acyl portion, and also for protons at the following positions on the cephalotaxine moiety: C-1, C-3, C-4, C-14, C-17, and methoxyl.

## Experimental Section

**General.** High-resolution mass spectral analyses were performed with a Nuclide 12-90G spectrometer[15] and low-resolution analyses with a DuPont CEC 21-492-1 spectrometer. Chemical ionization spectra were obtained with a Finnigan Model 4000 spectrometer using isobutane. NMR data were obtained on $CDCl_3$ solutions with Varian HA-100 and Bruker WH-90 Fourier transform spectrometers, and chemical shifts ($\delta$) are given in parts per million downfield from internal $Me_4Si$. Infrared spectra were determined on methylene chloride solutions with a Perkin-Elmer Model 137 spectrophotometer. Alkaloidal materials were subjected to TLC on Brinkmann precoated silica gel F-254 plates (0.25 mm for analytical analyses and 2.0 mm for preparative separations) with MeOH–$CHCl_3$ (from 1:9 to 1:2) or MeOH–$CH_2Cl_2$ (from 1:49 to 1:9). Nonalkaloid compounds were analyzed on the same type of plates, usually with ether–hexane solutions ranging from 1:9 to 1:2, but occasionally with MeOH–$CH_2Cl_2$ (1:99 or 1:49). Spots were visualized by one or more of the following methods: staining with iodine vapor, spraying with bromothymol blue solution, charring after spraying with 50% aqueous $H_2SO_4$, and by viewing the plates (containing a built-in phosphor) under UV light. When needed, anhydrous reagents, solvents, and solutions of reactants were prepared by drying at least 4 h over type 3A or 4A molecular sieves. Extracts of aqueous systems were routinely dried with anhydrous $MgSO_4$. All new compounds were liquids or amorphous solids,[16] and each gave IR, NMR, and mass spectra[17] consistent with its structure. Yield and purity values reported are based on a combination of NMR, IR, TLC, and GLC (where appropriate) data.[18]

(−)-Cephalotaxine used for these reactions was previously isolated in this laboratory from the natural source.

**Ethyl 4-Methyl-3-pentenoate (3).** Malonic acid (137 g) was dissolved in a mixture of 121 mL of redistilled isobutyraldehyde plus 105

mL of pyridine, and then 0.8 mL of piperidine was added.[9] A slow exothermic reaction began and bubbling was observed. The solution was heated to reflux temperature (gradually to control foaming) and then was refluxed for 4 h under a Dean-Stark trap. Residual aldehyde was distilled off, and the residue was poured into 6 N HCl and ice. This solution was extracted immediately with ethyl ether to yield 138 g of crude 4-methyl-2-pentenoic acid, which was then refluxed for 8 h with a solution of 530 g of KOH in 1 L of water. The isomerized acid that was recovered (by acidification and ether extraction) was treated with 300 mL of 12% $BF_3$ in absolute ethanol for 30 min at reflux. Recovery of 85% pure **3** was 136.9 g or 64% overall yield: IR 1730 (ester carbonyl) and 1770 $cm^{-1}$ (γ-lactone, a minor impurity); NMR δ 1.24 (t, 3 H, $J$ = 7 Hz, $CH_3CH_2O$–), 1.63 (s, 3 H, $CH_3C$=C–), 1.74 (d, 3 H, $J$ = 1.5 Hz, $CH_3C$=C–), 3.00 (broad d, 2 H, $J$ = 7 Hz, –$CH_2C$(=O)–), 4.10 (q, 2 H, $J$ = 7 Hz, $CH_3CH_2O$–), and 5.27 (t, 1 H, $J$ = 7 Hz, fine splitting by methyl protons, $J$ = 1.5 Hz, –C=CH–); GC–MS $m/e$ (relative intensity) 142 ($M^+$, 26), 97 (8), 69 (98), and 41 (100). Chemical ionization MS gave $MH^+$ $m/e$ 143 (100); $C_8H_{14}O_2$ requires $m/e$ 142.

**Ethyl 3-Carbethoxy-2-oxo-5-methyl-4-hexenoate (4).** A mineral oil suspension (42 g) of 55% NaH under a nitrogen atmosphere was washed free of mineral oil with anhydrous hexane, and 200 mL of anhydrous benzene was added. The mixture was cooled (ice–water bath) and stirred while 117 g of diethyl oxalate was added over a period of 5 min, and then 103 g of **3** was added dropwise. This reaction solution was stirred for 3 h while coming to room temperature and was then left overnight without stirring. Careful acidification of this mixture with dilute HCl (with cooling) to pH 4 followed by ether extraction produced 116.4 g (65%) of **4**:[18] IR 1740 $cm^{-1}$ (slight broadening); NMR δ 1.28 and 1.30 (two overlapping t, 6 H, $J$ = 7 Hz, $2CH_3CH_2$–O–), 1.70 and 1.78 [2d, 6 H, $J$ = 1 Hz, $(CH_3)_2C$=], 4.24 and 4.26 (two overlapping q, 4 H, $J$ = 7 Hz, $2CH_3CH_2$–O–), 4.72 (d, 1 H, $J$ = 9 Hz, –C(=O)CHC(=O)–), and 5.37 (d of quintets, 1 H, $J$ = 9 and 1 Hz, >C=CH–); GC–MS $m/e$ (relative intensity) 242 ($M^+$, 10), 169 (26), 141 (100), 103 (55), 95 (71), and 87 (88). Chemical ionization MS gave $MH^+$ $m/e$, 243 (60); $C_{12}H_{18}O_5$ requires $m/e$ 242.

**Methyl 2-Methoxy-5,5-dimethyltetrahydro-2-furoate (6).** After treating the crude substituted diethyl oxalacetate **4** (4.8 g) with refluxing 4 N HCl for 6 h, extraction of the aqueous mixture with ether provided 4.2 g of product. This product, in ether, was extracted with 5% aqueous $Na_2CO_3$ solution, and the extract was acidified and reextracted to give 2.2 g of a mixture of acidic constituents: IR 3560 (OH) and 1770 sh, 1760, 1730, and 1720 sh $cm^{-1}$ (carbonyl groups). Conversion of these acidic materials to methyl esters was achieved by refluxing for 4 h with 3% HCl in MeOH containing 20% benzene. During the reaction, the condensate was percolated through 4A-type molecular sieves during its return to the pot. Recovery of the esters by conventional techniques gave 2.1 g of a complex mixture as shown by TLC. This mixture was resolved into its components on a 3 × 40 cm silica gel column eluting with ether–hexane in the following manner: 100 mL of 1:9, 200 mL of 2:8, 200 mL of 3:7, and 200 mL of 4:6. The major component (**6**) was obtained in 36% recovery (pure by GLC): IR 1750 (ester carbonyl) and 1060 and 1075 $cm^{-1}$ (–C–O–C–); NMR δ 1.30 and 1.38 [2s, 3 H each, $(CH_3)_2C$–], 1.70–2.35 (overlapping m, 4 H, $-CH_2CH_2$–), and 3.25 and 3.75 (2s, 3 H each, $OCH_3$); GC–MS $m/e$ (relative intensity) 173 ($M^+ - CH_3$, 9), 157 (9), 141 (20), 129 (86), 97 (55), and 69 (100). Chemical ionization MS gave a major ion of $m/e$ 157 ($M^+ - OCH_3$, 100), but no $MH^+$ ion was observed; $C_9H_{16}O_4$ requires $m/e$ 188.

**Cephalotaxyl 5,5-Dimethyl-4,5-dihydro-2-furoate (8).** Saponification of **6** (0.38 g) with an equivalent amount of 0.1 N NaOH in $H_2O$–EtOH (4:1) was achieved by a 4-h reflux. The solution was evaporated to dryness, and the residue was thoroughly dried in a vacuum desiccator for 60 h. A slurry was made of the dried salt (**7**), 10 mL of ether, and 2 drops of pyridine, and the mixture was cooled in an ice–water bath with stirring. Oxalyl chloride (0.4 mL) was added, and after 30 min of stirring at 0 °C the solution was allowed to come to room temperature and was stirred overnight. Solvent and excess reagent were evaporated at room temperature in vacuo, and the acid chloride–NaCl mixture was slurried in methylene chloride. This slurry was then added to a cold (ice–water bath) solution of 0.45 g of cephalotaxine (**1**) and 1 mL of pyridine dissolved in 10 mL of methylene chloride. Stirring at 0 °C was continued for 2 h and then at room temperature overnight. The mixture was poured into pH 7.0 buffer[19] (50 mL) and extracted with methylene chloride to give 0.482 g (73% yield based on cephalotaxine used) of 98% pure **8**: IR 1730 (ester –C=O), 1640 and 1665 (trisubstituted olefins), 1120 and 1040 (vinyl ethers), and 942 $cm^{-1}$ (methylenedioxy); NMR δ 1.24 and 1.30 [2s, 3 H each, $(CH_3)_2C$–], 1.5–3.3 (overlapping m, ring $CH_2$'s of cephalotaxine moiety), 2.38 (d, 2 H, $J$ = 3 Hz, –$CH_2C$=), 3.68 (s, 3 H, cephalotaxyl $OCH_3$), 3.76 (d, 1 H, $J$ = 9 Hz, cephalotaxyl C-4 proton), 5.03 (s, 1 H, cephalotaxyl vinyl proton), 5.29 (t, 1 H, $J$ = 3 Hz, dihydrofuran ring vinyl), 5.79 (dd, 2 H, $J$ = 1 Hz, methylenedioxy), 5.91 (d, 1 H, $J$ = 9 Hz, cephalotaxyl C-3 proton), and 6.52 (s, 2 H, aromatic); MS $m/e$ (relative intensity) 439 ($M^+$, 40), 408 (7), 314 (16), 298 (100), 266 (26), and 150 (26). Found: $M^+$, $m/e$ 439.1994; $C_{25}H_{29}NO_6$ requires $m/e$ 439.1994.

**Cephalotaxyl 2-Hydroxy-5,5-dimethyltetrahydro-2-furoate (9).** Ester **8** (0.248 g) was dissolved in 10 mL of 1 N HCl–HOAc (1:3) and heated in a 50–55 °C water bath for 2 h. The solution was basified with 3 N $NH_4OH$ and extracted with methylene chloride to yield 0.221 g of crude hydrated product. Pure compound **9** (0.146 g, 57%) was obtained as a mixture of two diastereomers by preparative TLC using MeOH–$CHCl_3$ (1:3): IR 3675 (OH), 1750 (ester –C=O), 1665 (cephalotaxine trisubstituted double bond), 1040 (vinyl ether), and 940 $cm^{-1}$ (methylenedioxy); NMR δ 1.02 and 1.26 [2s, $(CH_3)_2C$– of one diastereomer], 1.16 and 1.28 [2s, $(CH_3)_2C$– of second diastereomer], 1.5–3.4 (overlapping m, ring $CH_2$'s), 3.65 (s, 3 H, $OCH_3$), 3.77 (d, 1 H, $J$ = 9 Hz, cephalotaxyl C-4 proton; additional overlapping signal from second diastereomer was also observed as fine splitting), 5.01 (brd s, 1 H, vinyl proton), 5.80 and 5.82 (2s, 2 H, methylenedioxy signals of both diastereomers), 5.86 (d, 1 H, $J$ = 9 Hz, cephalotaxyl C-3 proton; additional overlapping signal from second diastereomer was also observed as fine splitting), and 6.54 (brd s, 2 H, aromatic); MS $m/e$ (relative intensity) 457 ($M^+$, 12), 426 (3), 314 (6), 298 (100), 266 (12). Found: $M^+$, $m/e$ 457.2103; $C_{25}H_{31}NO_7$ requires $m/e$ 457.2100.

**Harringtonine (10a) and Epiharringtonine (10b).** Crude hemiketal **9** (0.020 g) was treated with methyl bromoacetate and zinc via a modified Reformatsky reaction as defined by Rathke and Lindert.[13] A tenfold excess of zinc and bromoacetate was used to compensate for the small sample, and methylene chloride was used to extract the products. Resolution of the mixture (0.021 g) by preparative TLC on a 0.25-mm silica gel plate yielded 2.2 mg (10%) of a mixture of harringtonine (**10a**) and epiharringtonine (**10b**). This mixture was filtered through 0.5 g of neutral alumina (Woelm, grade III) as a MeOH–$CHCl_3$ (1:9) solution, recovery 2.0 mg: IR spectrum was identical with that of authentic harringtonine; NMR[14] δ 1.15 and 1.17 [2s, 3 H each, $(CH_3)_2C$–], 2.09 (AB q, 2 H, $J$ = 18 Hz, $-CH_2CO_2CH_3$), 1.3–3.3 (overlapping m, $CH_2$'s), 3.58 and 3.69 (2s, 3 H each, $OCH_3$ and $-CO_2CH_3$), 3.78 (d, 1 H, $J$ = 10 Hz, cephalotaxyl C-4 proton), 5.07 (d, 1 H, $J$ = 0.8 Hz, vinyl), 5.86 (s, 2 H, $-OCH_2O$–), 6.00 (d, 1 H, $J$ = 10 Hz with fine splitting, cephalotaxyl C-3 proton), and 6.54 and 6.62 (2s, 1 H each, aromatic). Additional signals observed in the spectrum of the mixture of diastereomers are due to **10b**: δ 1.09 and 1.11 [2s, 3 H each, $(CH_3)_2C$–], 2.60 (apparent (d,[20] 2 H, $-CH_2CO_2CH_3$), 3.65 and 3.67 (2 s, 3 H each, $OCH_3$ and $-CO_2CH_3$), 3.77 (d, 1 H, $J$ = 10 Hz, cephalotaxyl C-4 proton), 5.03 (d, 1 H, $J$ = 1 Hz, vinyl), 5.86 (indistinct m overlapping **10a** s, $-O-CH_2O$–), 6.00 (complex signal, d, 1 H, $J$ = 10 Hz with fine splitting overlapping **10a** d, cephalotaxyl C-3 proton), and 6.62 (s, 2 H, aromatic); MS[21] $m/e$ (relative intensity) 531 ($M^+$, 10), 500 (3), 314 (7), 298 (100), 266 (14). Found: $M^+$, $m/e$ 531.2455; $C_{28}H_{37}NO_9$ requires $m/e$ 531.2468. This value is identical with that found for natural harringtonine.[2]

**Registry No.**—**1**, 24316-19-6; **3**, 2258-65-3; **4**, 67938-53-8; **6**, 67938-54-9; **7**, 67938-55-0; **8**, 62630-97-1; **9** (isomer 1), 67999-06-8; **9** (isomer 2), 67999-07-9; **10a**, 26833-85-2; **10b**, 67938-56-1; malonic acid, 141-82-2; isobutylaldehyde, 78-84-2; 4-methyl-2-pentenoic acid, 10321-71-8; 4-methyl-3-pentenoic acid, 504-85-8; diethyl oxalate, 95-92-1; methyl bromoacetate, 96-32-2.

## References and Notes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(7) Low-yielding indirect syntheses of harringtonine [Anonymous, *K'o Hsueh T'ung Pao*, **20**, 437 (1975)] and deoxyharringtonine, another antitumor ester alkaloid of *Cephalotaxus* [K. L. Mikolajczak, C. R. Smith, Jr., D. Weisleder, T. R. Kelly, J. C. McKenna, and P. A. Christenson, *Tetrahedron Lett.*, 283 (1974); S. Li and J. Dai, *Hua Hsueh Hsueh Pao*, **33**, 75 (1975)], have been reported.
(8) At an advanced stage of our work, we became aware of somewhat parallel work by investigators in the People's Republic of China [Anonymous, *K'o*

*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

George Büchi,* Hans Fliri, and Rafael Shapiro[1]

*Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139*

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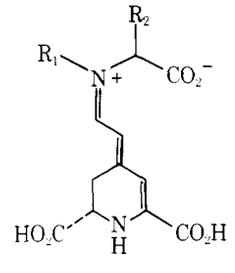
*N*-Benzylnorteloidinone (**10**) prepared by Robinson–Schöpf synthesis was converted to the ortho ester **18** with methyl orthoformate. Catalytic debenzylation of **18** followed by addition of allylmagnesium bromide gave carbinol **20**, which was transformed to the *O*-benzoylhydroxylamine **21** 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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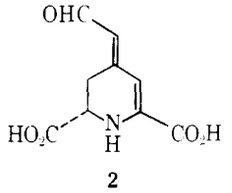


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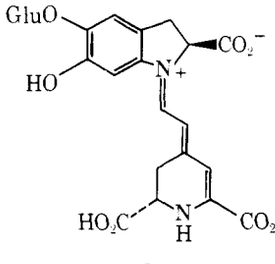


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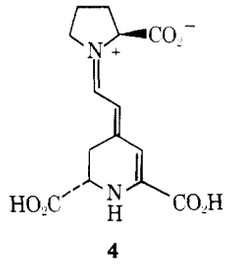


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