# Notes

## A New Practical Synthesis of 5-Hydroxy-3,4-dihydrocarbostyril and 5-Hydroxycarbostyril

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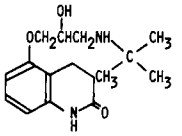
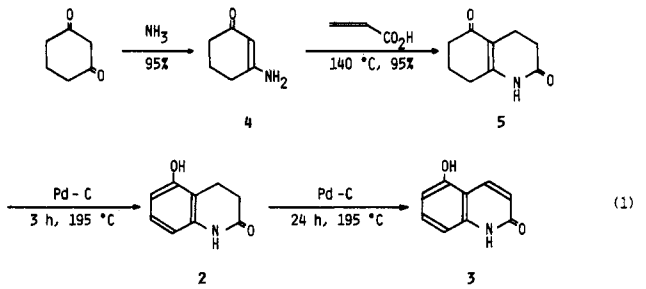
Although compound **1** has been known to show a strong



**1**

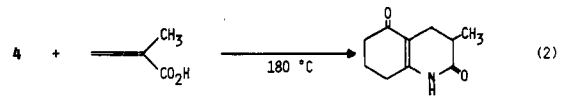
$\beta$-blocking activity,[1] a simple synthesis of the key intermediate, 5-hydroxy-3,4-dihydrocarbostyril (**2**) is lacking. The typical synthetic method hitherto known involves the reaction of 1,3-cyclohexanedione with acrylonitrile as the key step, though the yield is far from satisfactory.[2] We now describe a new and practical synthesis of **2** and 5-hydroxycarbostyril (**3**) from 3-amino-2-cyclohexenone (**4**), which is easily obtainable from 1,3-cyclohexanedione in a 95% yield.[3]

Thus, heating a mixture of **4** and acrylic acid for 3 h at 140 °C gave compound **5** in 95% yield. Dehydrogenation of **5** to **2** was accomplished by refluxing a mixture of **5** and 10% Pd–charcoal in decalin for 3 h. On the other hand, refluxing the same mixture for 24 h gave predominantly **3**. Isolation of **2** or **3** was easily achieved by recrystallization. Accordingly, both products **2** and **3** could be prepared in good yields through highly simple procedures (eq 1).



(1)

The use of methacrylic acid instead of acrylic acid gave a similar result, although the reaction required a higher temperature than that in the synthesis of **2**. Crotonic acid, cinnamic acid, and ethyl acrylate did not react with **4**.



**6**

(2)

### Experimental Section

**Synthesis of 5.** A mixture of **4**[3] (33.3 g, 0.30 mol) and acrylic acid (26.0 g, 0.36 mol) was heated at 140 °C for 3 h to afford **5**[2a] as a precipitate, which could be recrystallized from methanol: yield 95% (47.0 g); mp 194–195 °C; IR (KBr) 3200, 3100, 1685, 1625, 820 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 1.60–2.95 (m, 10 H), 9.90 (m, 1 H). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.15; H, 6.71; N, 8.44.

**Synthesis of 2 and 3.** A solution of **5** (1.65 g, 0.01 mol) in decalin (20 mL) containing 10% Pd–C (0.5 g) was refluxed for 3 h and extracted with methanol after it was cooled to room temperature. The extracts contained **2**, **3**, and **5** in the ratio of 8:1:1. Concentration of the methanolic solution gave **2** as a precipitate. When the product is contaminated by a small amount of **3** or **5**, the contaminants can be removed by TLC (silica gel, $CH_2Cl_2/CH_3OH$ 10:1). The yield of **2** was 74% (1.21 g). The spectroscopic data and melting point of **2** were identical with those reported in the literature;[4] NMR ($Me_2SO$-$d_6$) $\delta$ 2.23–3.16 (m, 4 H), 6.23–7.45 (m, 3 H), 9.95 (br s, 1 H).

Prolonged heating (24 h) of a mixture of **5** and 10% Pd–C in decalin predominantly yielded **3**, which could be purified by recrystallization from methanol. The IR spectrum and melting point of the product were identical with those of an authentic sample:[5] 1.30 g (81%); NMR ($Me_2SO$-$d_6$) $\delta$ 6.35 (d, $J$ = 10 Hz, 1 H), 6.63 (dd, $J$ = 7.5, 7.5 Hz, 2 H), 7.24 (dd, $J$ = 7.5, 7.5 Hz, 1 H), 8.10 (d, $J$ = 10 Hz, 1 H).

**Synthesis of 6.** A mixture of **4** (1.11 g, 0.01 mol) and methacrylic acid (1.3 g, 0.015 mol) was heated at 180 °C for 3 h. The isolation of the product **6** was carried out in a similar way to that of **2**: 1.28 g (72%); mp 197–198 °C; IR 3450, 3250, 1700, 1600, 1480, 1390, 1240, 1220, 1190 $cm^{-1}$; NMR ($Me_2SO$-$d_6$) $\delta$ 9.50 (br s, 1 H), 1.60–3.0 (m, 9 H), 1.33 (d, $J$ = 6 Hz, 3 H). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.80. Found: C, 66.96; H, 7.51; N, 7.77.

**Registry No. 2**, 30389-33-4; **3**, 31570-97-5; **4**, 5220-49-5; **5**, 5057-12-5; **6**, 77903-18-5; acrylic acid, 79-10-7; methacrylic acid, 79-41-4.

(1) Nakagawa, K.; Murakami, N.; Yoshizaki, S.; Tominaga, M.; Mori, H.; Yakuuchi, Y.; Shintani, S. *J. Med. Chem.* **1974**, *17*, 529.
(2) (a) Nazarov, I. N.; Zav'yalov, S. I. *Zh. Obshch. Khim.* **1954**, *24*, 469; *Chem. Abstr.* **1955**, *49*, 6142*h*. (b) Böhme, E. H. W.; Valenta, Z.; Wiesner, K. *Tetrahedron Lett.* **1965**, 2441.
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(4) Tamura, Y.; Terashima, M.; Higuchi, Y.; Ozaki, K. *Chem. Ind. (London)* **1970**, 1435.
(5) Fleming, W. C.; Pettit, G. R. *J. Org. Chem.* **1971**, *36*, 3490.

## Synthesis of (+)-Methyl Vouacapenate from Podocarpic Acid. An Improved Route

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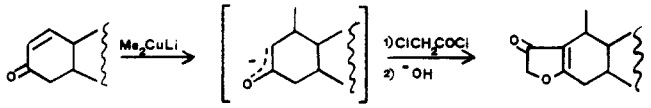
(+)-Methyl vouacapenate (**1**), an abundant constituent of South American hardwood, was isolated by King et al.[1] who also established its structure as a furanoid diterpene with the cassane skeleton. Later, Spencer et al.[2] completed

(1) F. E. King, D. H. Godson, and T. J. King, *J. Chem. Soc.*, 1117 (1955).

0022-3263/81/1946-3719$01.25/0 

Scheme I




the structure elucidation of the substance, assigning the stereochemistry at C-14, and also described the total synthesis of 1 both in racemic and enantiomerically pure form.

The structural features of (+)-methyl vouacapenate (1) seemed very appropriate to test the applicability of a new method for construction of the furan ring which we successfully developed during studies on the total syntheses of some pinguisane derivatives[3] and of pinguisone itself.[4]

As illustrated in Scheme I, an enolate anion, generated by conjugate addition of lithium dimethylcuprate to a cyclohexenone derivative, quenched with chloroacetyl chloride, followed by base-promoted ring closure, affords in one step a β-furanone system.

The intermediate of choice for the synthesis of (+)-methyl vouacapenate (1) was that used by Spencer et al.,[2] enone 2. Starting from commercially available podocarpic acid and following the procedure of Bell and Gravestock,[5] we synthesized enone 2 in an overall yield of 42%.

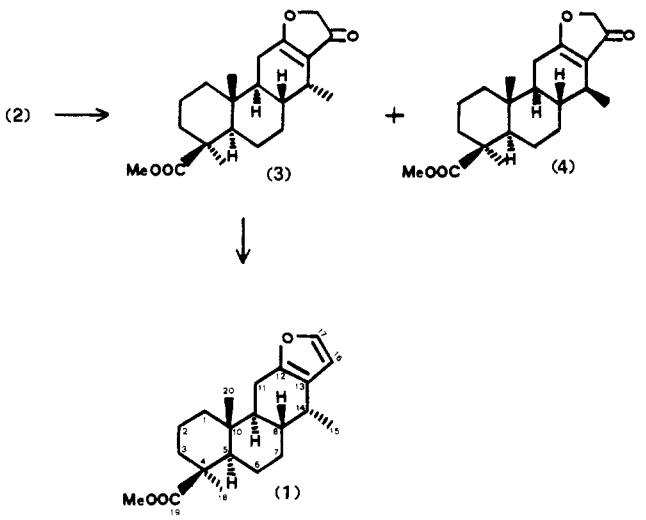
Treatment of enone 2 with 2 equiv of lithium dimethylcuprate at −25 °C resulted in the complete disappearance of the starting material after 1 h. Quenching of the enolate anion with a large excess of chloroacetyl chloride at room temperature followed by ether extraction from basic solution afforded a mixture of two diastereoisomeric β-furanones (3 and 4) in a total yield of 76%. They could be nicely separated as noncrystalline materials in a 1.5:1 ratio in favor of the less polar substance. If the same reaction was carried out at −40 °C, the ratio was raised to 2:1; lower temperatures did not allow the reaction to proceed at a significant rate.

Both compounds display very similar spectroscopic data which are in full agreement with the proposed structures. The most significant difference is in the $^1$H NMR spectra, in which the $C_{14}$-methyl group resonates at δ 0.92 for the less polar compound and at δ 1.22 for the more polar one. Structure 4, where the $C_{14}$-methyl group is β equatorial, can be assigned to the latter diastereoisomer, for which the deshielding effect of the β-furanone carbonyl group is stronger.

The stereoisomer useful for our synthetic purpose was therefore the kinetically favored, less polar compound 3. Smooth reduction of 3 with 9-BNN in THF[3,4] afforded the crystalline furan compound 1 in 80% yield, which, in all its spectroscopic and physical properties, was identical to natural (+)-methyl vouacapenate (1).

The synthesis illustrated in Scheme II undoubtedly presents advantages in brevity and yields in comparison with the previously reported ones.

Scheme II




## Experimental Section

$^1$H NMR spectra were recorded at 100 MHz with a Varian XL-100 instrument (tetramethylsilane as internal standard, $CDCl_3$ as solvent). IR spectra were registered on a Perkin-Elmer 257 spectrophotometer. Mass spectra were taken on a Varian Mat 112 spectrometer (DIS-71 EV acc. pot.). Podocarpic acid (ex rimu resin, pure) was purchased from Koch-Light Laboratories Ltd.

**Synthesis of β-Furanones 3 and 4.** In a 25-mL flask equipped with a dry argon inlet and kept at −25 °C with dry ice–acetone, 1.1 mL (1.7 mmol) of a 1.55 M ethereal solution of methyllithium was added to a stirred suspension of 162 mg (0.85 mmol) of CuI and 4 mL of anhydrous ether. After few minutes the solution became colorless and the formation of lithium dimethylcuprate was complete. Enone 2 (80 mg, 0.27 mmol) in 3 mL of anhydrous ether was then added. After 1 h, 0.22 mL (2.7 mmol) of freshly distilled chloroacetyl chloride was added, the cooling bath removed, and the reaction left to proceed for 1.5 h.

The reaction mixture was poured into a slurry of ammonia and crushed ice, stirred for 30 min, and then extracted several times with ether; the combined extracts were washed with dilute ammonia and water and then dried ($Na_2SO_4$). After evaporation at reduced pressure, 150 mg of a thick oil was obtained which was chromatographed on a Florisil column (8 g). By elution with low-boiling petroleum ether–ethyl acetate (95:5 v/v), 43 mg (46% yield) of pure 3 was obtained: oil; IR ($CHCl_3$) 1715, 1630 cm$^{-1}$; $^1$H NMR δ 4.45 (br s, 2 H, $H_{17}$), 3.65 (s, 3 H, $OCH_3$), 1.21 (s, 3 H, $H_{18}$), 0.92 (d, $J$ = 7 Hz, 3 H, $H_{15}$), 0.71 (s, 3 H, $H_{20}$); mass spectrum, $m/e$ 346 ($M^+$, 15%), 331 (23%), 271 (38%), 163 (23%), 161 (27%), 147 (42%), 124 (46%), 109 (100%). Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.83; H, 8.67. Found: C, 72.78; H, 8.63.

Further elution with low-boiling petroleum ether–ethyl acetate (90:10 v/v) afforded 28 mg (30% yield) of pure 4: oil; IR ($CHCl_3$) 1720, 1695, 1630 cm$^{-1}$; $^1$H NMR δ 4.44 (br s, 2 H, $H_{17}$), 3.64 (s, 3 H, $OCH_3$), 1.22 (d, 3 H, $J$ = 6 Hz, $H_{15}$), 1.22 (s, 3 H, $H_{18}$), 0.70 (s, 3 H, $H_{20}$); mass spectrum, $m/e$ 346 ($M^+$, 46%), 331 (42%), 271 (69%), 163 (38%), 161 (50%), 147 (77%), 124 (80%), 109 (100%). Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.83; H, 8.67. Found: C, 72.80; H, 8.64.

The above procedure was adopted when the reaction was carried out at −40 °C. It took 2 h for the complete disappearance of the starting material. From 80 mg (0.27 mmol) of enone 2, after the usual workup and purification by Florisil chromatography, 44 mg of pure 3 and 22 mg of pure 4 were obtained (total yield 70.6%).

**9-BBN Reduction of 3.** Compound 3 (21 mg, 0.06 mmol) was dissolved in 2 mL of anhydrous THF and placed in a flask equipped with a dry argon inlet and cooled in ice. To the stirred solution was added 8.3 mg (0.07 mmol) of 9-BBN. After 1 h at 0 °C and 3 h at room temperature, 320 μL of methanol was added and then the solvents were evaporated under reduced pressure. The residue was dissolved in $n$-pentane and 36 μL of ethanolamine was added. The precipitate was removed by filtration and washed several times with $n$-pentane. The filtrate and washings were combined and dried ($Na_2SO_4$), and the solvent was evaporated under reduced pressure. The oily residue (20 mg) was purified by column chromatography (2 g of silica gel, low-boiling petroleum ether–ethyl acetate, (98:2 v/v) to give 16 mg of pure 1 which was crystallized from methanol: mp 101–102 °C (lit. mp 103–104 °C,[1] 99.5–100.5 °C[2]); $[\alpha]^{20}_D$ +98° (c 5.5, $CCl_4$) [lit. $[\alpha]^{20}_D$ +101° (c 1.5, $CCl_4$),[1] $[\alpha]^{20}_D$ +96° (c 5.5, $CCl_4$) IR ($CCl_4$) 1720, 1640, 1580, 1500

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(3) S. Bernasconi, M. Ferrari, P. Gariboldi, G. Jommi, M. Sisti, and R. Destro, *J. Chem. Soc., Perkin Trans. 1*, in press.
(4) S. Bernasconi, P. Gariboldi, G. Jommi, S. Montanari, and M. Sisti, *J. Chem. Soc., Perkin Trans. 1*, in press.
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cm$^{-1}$; $^1$H NMR $\delta$ 7.20 (m, 1 $H_{17}$), 6.18 (d, 1 H, $J$ = 2 Hz, $H_{16}$), 3.66 (s, 3 H, $OCH_3$), 1.20 (s, 3 H, $H_{18}$), 0.97 (d, 3 H, $J$ = 7 Hz, $H_{15}$), 0.70 (s, 3 H, $H_{20}$); mass spectrum, $m/e$ 330 ($M^+$, 41%), 315 (5%), 271 (4%), 255 (11%), 221 (4%), 161 (14%) 108 (100%). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.36; H, 9.09. Found: C, 76.34; H, 9.07.

**Acknowledgment.** We thank CNR for financial support.

**Registry No.** 1, 4614-50-0; 2, 24402-16-2; 3, 78004-32-7; 4, 78085-85-5; chloroacetyl chloride, 79-04-9.

## Synthesis of Chlorinated and Brominated Biphenyl Oxides[1]

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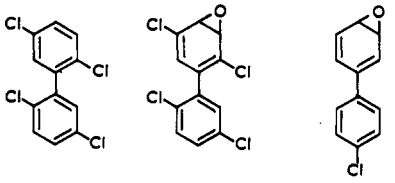
Vogel, Schubart, and Böll first reported the synthesis of the benzene oxide–oxepin valence tautomers in 1964.[2] Since then, a large number of arene oxides have been prepared and their chemistry has been studied.[2b,3,4] In recent years these substances have become of intense interest as potential intermediates in the metabolism of aromatic compounds. In fact, many of the adverse biological effects of aromatic compounds have been ascribed to the interaction of arene oxides with cell constituents. For this reason the synthesis of several chlorinated and brominated biphenyl oxides described here was undertaken, with the goal of studying their properties in relation to the toxic effects of polychlorinated and polybrominated biphenyls (PCB's, PBB's).[5] Several related compounds, including the 3- and 4-chlorobenzene oxides[4a] and biphenyl 2,3-oxide,[4b] have been prepared.

2,5,2′,5′-Tetrachlorobiphenyl (1) has been extensively

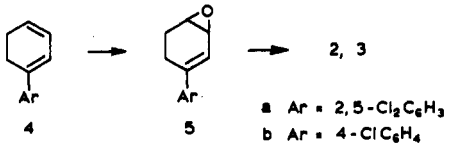


1 2 3

studied as a model for the biological effects of Arachlor mixtures,[6] and the arene oxide 2 has been implicated as an intermediate during its metabolic degradation.[6a] This compound was the primary goal of this study. We also prepared several analogues of 2 having chlorines replaced by bromines or hydrogens, as well as arene oxide 3, a possible metabolite of 4-chlorobiphenyl.[7] These compounds are the first PCB arene oxides to be prepared.

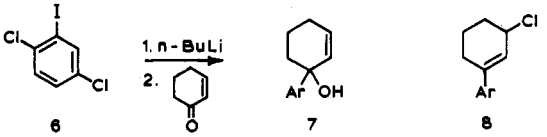
### Results and Discussion

The synthetic approach is outlined below. The principal problems appeared to be regiochemical control during introduction of double bonds in 4 and the chlorines in 2.



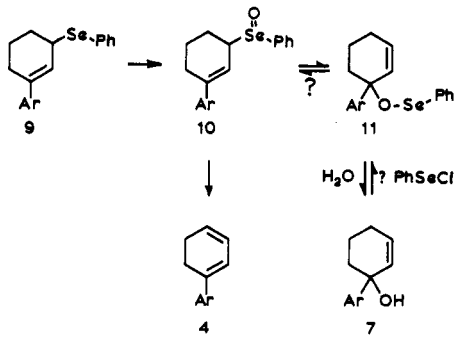

4 5

A suitable precursor for 4a was 7a, prepared by addition of the unstable 2,5-dichlorophenyllithium (6)[8] to cyclohexenone (throughout this paper the "a" series of compounds will refer to Ar = 2,5-dichlorophenyl, the "b" series to Ar = 4-chlorophenyl). However, neither direct dehydration of 7a with acid or phosphorus oxychloride or




6 7 8

dehydrohalogenation of the allylic chloride 8a under basic conditions could be carried out to give useful amounts of the diene 4a. Some success was achieved by converting 8a to the selenide 9a and oxidizing to the unstable selenoxide 10a. Although most allylic selenoxides give almost




9 10 11 4 7

exclusively products of [2,3] sigmatropic rearrangement,[9,10] several examples have been reported where syn elimination competes.[10,11] This is the case here also, although the major pathway was still rearrangement (60/40). The diene 4a was easily separated from the alcohol 7a, which could be recycled. Electron-withdrawing substituents have been

(1) Some of these results were published in preliminary form: Reich, H. J.; Reich, I. L.; Wollowitz, S. *J. Am. Chem. Soc.* **1978**, *100*, 5981.

(2) (a) Vogel, E.; Schubart, R.; Böll, W. A. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 510. (b) Vogel, E.; Günther, H. *Ibid.* **1967**, *6*, 385.

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(4) (a) Selander, H. G.; Jerina, D. M.; Piccolo, D. E.; Berchtold, G. A. *J. Am. Chem. Soc.* **1975**, *97*, 4428. (b) Serve, M. P.; Jerina, D. M. *J. Org. Chem.* **1978**, *43*, 2711. (c) Chao, H. S.-I.; Berchtold, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 898. (d) Jeffrey, A. M.; Yeh, H. J. C.; Jerina, D. M.; DeMarinis, R. M.; Foster, C. H.; Piccolo, D. E.; Berchtold, G. A. *Ibid.* **1974**, *96*, 6929. (e) Berchtold, G. A., private communication.

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