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Synthesis of (–)-Caronaldehyde from (+)-3-Carene

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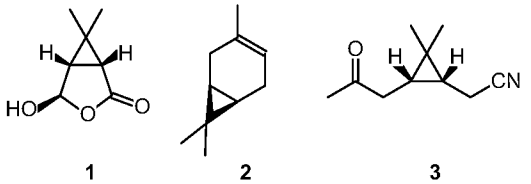
The preparation of (–)-caronaldehyde from monoterpene hydrocarbon (+)-3-carene is described.

The optically active furanoid type heterocyclic compound caronaldehyde **1** is known to be an intermediate compound in pyrethroid syntheses[1,2] as well as an effective chiral agent for the resolution of racemic alcohols.[3–6] We now describe a new synthetic route to this compound from the (+)-3-carene molecule **2** using 3,4-*seco*-carene derivative **3**[7] as intermediate. The synthetic pathway developed is shown in Scheme 1.

When treated with bromine in an alkaline methanolic



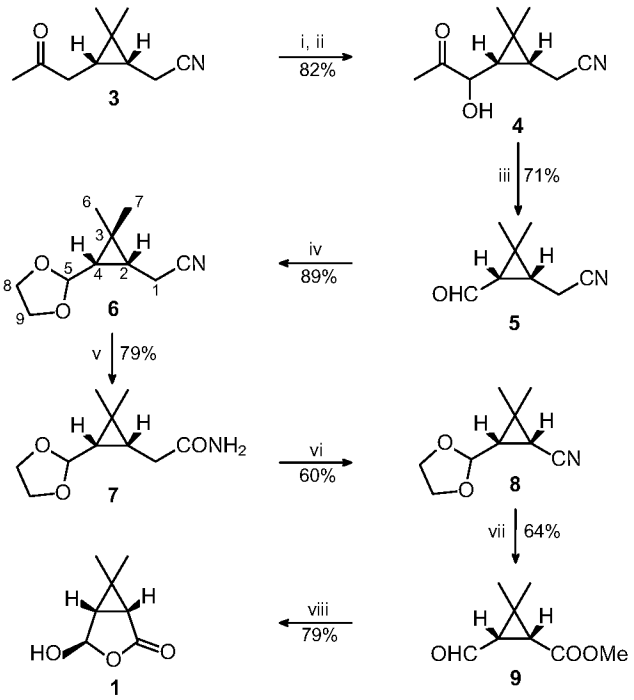
1 **2** **3**

solution, oxonitrile **3** is transformed to the corresponding α-hydroxy ketone **4**.[8] Although this reaction is very fast and allowed us to perform a double-stage reaction sequence (bromination at the α-position of the carbonyl function followed by nucleophilic substitution of the bromine atom) as a single-stage process, yields were not good.† To improve the yield of the desired compound **4**, we have broken the process down into two reactions. The bromo derivative is quite an unstable compound so the best yield of hydroxy derivative **4** was achieved when the process was carried out as a one-pot synthesis without isolation and purification of the bromide. In the first stage, oxo derivative **3** was brominated with bromine in a methylene dichloride solution at 10–15 °C. The resulting bromo derivative was then subjected to an alkali at −15–10 °C to give hydroxy derivative **4** in 82% overall yield. The preparation of aldehyde **5** from hydroxy ketone **4** was described earlier.[8]

p-Toluenesulfonic acid, being the most commonly used acidic catalyst for the introduction of the dioxolane protecting group, was unsuitable for the reaction of aldehyde **5** because of the low yield of the desired compound due to the formation of a large number of by-products. The use of pyridinium hydrochloride in boiling benzene makes it possible to obtain dioxolane derivative **6**‡ as the main product, the yield being dependent on the quantity of catalyst used. An equimolar amount of catalyst resulted in cyclopropane ring

† Although the yield of the crude hydroxynitrile was about 85%, the pure compound can be isolated only in 45% yield.

‡ (1*R*,3*S*)-2,2-Dimethyl-3-(1,3-dioxolan-2-yl)cyclopropane acetonitrile **6**, after sublimation of the crude product in vacuum: $[\alpha]_{578}^{23}$ +50.4° ($c = 2.74$ in $CHCl_3$). IR ($CHCl_3$) ν/cm^{-1} 2250 (CN), 1200–1070 (–O–C–O–). ^{1}H NMR ($CDCl_3$–CCl_4, 1:1 v/v) δ 2.20 (dd, $J = 17$ and 9 Hz, 1H, 1-Ha), 2.50 (dd, $J = 17$ and 5 Hz, 1H, 1-Hb), 0.96 (m, 1H, 2-H), 0.78 (dd, $J = 8$ and 8 Hz, 1H, 4-H), 4.46 (d, $J = 8$ Hz, 1H, 5-H), 1.05 (s, 3H, 6-H_3 or 7-H_3), 1.07 (s, 3H, 6-H_3 or 7-H_3), 3.80 (m, 4H, 8-H_2 and 9-H_2). ^{13}C NMR ($CDCl_3$–CCl_4, 1:1 v/v) δ 118.60 (C≡N), 13.43 (C-1), 22.46 (C-2), 18.61 (C-3), 28.07 (C-4), 103.35 (C-5), 14.40 (C-6), 28.00 (C-7), 64.41 and 64.50 (C-8 and C-9).



Scheme 1 The numbering scheme of the C atoms is given only for the NMR interpretation and does not coincide with the numbering of the system according to IUPAC nomenclature rules. *Reagents and conditions*: i, Br_2/CH_2Cl_2, 10 °C, 15 min; ii, KOH–H_2O, acetone, −15 °C, 15 min; iii, $NaIO_4$, acetone (ref. 8); iv, $HOCH_2CH_2OH$/Py·HCl–benzene, reflux, 3 h; v, KOH–Bu^tOH, reflux, 10 min; vi, Br_2–KOH–H_2O/$[Et_3NCH_2Ph]Cl$–CH_2Cl_2, 0 °C, 1 h; reflux, 2 h; vii, HCl–MeOH, room temp., 2 h; viii, KOH–H_2O–THF, 0 °C, 5 min.

cleavage, and 0.1% of catalyst led to the formation of a significant amount of *trans*-isomer (up to 50%) at the cyclopropane moiety; 0.01% of Py·HCl gave the best results (89% yield). As shown earlier,[9] hydrolysis of cyclopropylacetonitrile derivatives with a boiling suspension of potassium hydroxide in *tert*-butyl alcohol is the most suitable method for converting the nitriles to the corresponding amides. The hydrolysis of nitrile **6** gave amide **7**§ in 79% yield. Transformation of the amide to nitrile **8**¶ in 60% yield was carried out using a two-phase variant of the hypobromite oxidation at room temperature for 1 h, and then under reflux for 2 h.[10]

Hydrolysis of nitrile **8** with a saturated methanolic solution of dry HCl for 2 h afforded compound **9*** in 64% yield, whose NMR spectra were identical to those described earlier in ref. 11. An increase in reaction time to more than 2 h decreased the yield of the product significantly due to accumulation of the *trans*-isomer. Alkaline hydrolysis of ester **9** proceeds much more rapidly as compared to the corresponding *trans*-isomer; this may result from the intramolecular participation of the aldehyde group. Different rates of hydrolysis of the isomers enables selective hydrolysis of the *cis*-isomer **9** (5 min at 0 °C) and reduces the isolation procedure for the desired caronaldehyde **1**. Thus, hydrolysis of **9** (2.5 g) for 5 min at 0 °C gave 2.0 g of the crude product containing no less than 90% (^{1}H NMR) of caronaldehyde **1** (yield 79%). Two-fold crystallisation of the crude product from diethyl ether–pentane gave an analytical sample of caronaldehyde **1** with m.p. 114–115 °C, $[\alpha]_{578}^{22}$ −104° ($c = 1.73$ in $CHCl_3$) [ref. 12: m.p. 114.5–115.5 °C, $[\alpha]_D^{28}$ +99.41° ($c = 0.9$ in EtOH)] whose NMR spectra were identical to those published in ref. 12.

See ref. 8 for general experimental details. The chemical shifts in the NMR spectra were calculated relative to the solvent signal ($CDCl_3$) used as internal standard: δ_H 7.24 ppm and δ_C 76.90 ppm.

Satisfactory microanalyses for all new compounds were obtained: C ±0.47, H ±0.38, N ±0.43.

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§ (1*R*,3*S*)-2,2-Dimethyl-3-(1,3-dioxolan-2-yl)cyclopropane acetamide **7**: m.p. 71.5–73 °C (Et_2O–EtOAc); $[\alpha]_{578}^{22}$ −46.42° ($c = 1.45$ in $CHCl_3$). IR ($CHCl_3$): ν/cm^{-1} 3540 and 3410 (NH_2), 1670 (C=O), 1580 (H–N), 1150–1040 (–O–C–O–). ^{1}H NMR ($CDCl_3$–CCl_4, 1:1 v/v): δ 2.12 (dd, $J = 15$ and 9 Hz, 1H, 1-Ha), 2.23 (dd, $J = 15$ and 6 Hz, 1H, 1-Hb), 0.96 (m, 1H, 2-H), 0.73 (dd, $J = 8$ and 8 Hz, 1H, 4-H), 4.52 (d, $J = 8$ Hz, 1H, 5-H), 1.04 (s, 3H, 6-H_3 or 7-H_3), 1.00 (s, 3H, 7-H_3 or 6-H_3), 3.80 (m, 4H, 8-H_2 and 9-H_2), 6.4 (br.s, 2H, NH_2). ^{13}C NMR ($CDCl_3$–CCl_4, 1:1 v/v): δ 174.85 ($CONH_2$), 32.32 (C-1), 23.98 (C-2), 18.16 (C-3), 28.07 (C-4), 103.33 (C-5), 15.11 (C-6), 28.43 (C-7), 64.42 and 64.69 (C-8 and C-9).

¶ (1*R*,3*S*)-2,2-Dimethyl-3-(1,3-dioxolan-2-yl)cyclopropane carbonitrile **8**, after sublimation of the crude product in vacuum: $[\alpha]_{578}^{24}$ +11.6° ($c = 2.92$ in $CHCl_3$). IR ($CHCl_3$): ν/cm^{-1} 2250 (CN), 1170–1030 (–O–C–O–). ^{1}H NMR ($CDCl_3$–CCl_4, 1:1 v/v): δ 4.58 (d, $J = 8$ Hz, 1H, 5-H), 1.14 (s, 3H, 6-H_3 or 7-H_3), 1.25 (s, 3H, 6-H_3 or 7-H_3), 3.80 (m, 4H, 8-H_2 and 9-H_2). ^{13}C NMR ($CDCl_3$–CCl_4, 1:1 v/v): δ 117.10 (C-1), 13.51 (C-2), 22.76 (C-3), 31.42 (C-4), 102.30 (C-5), 16.74 (C-6), 26.31 (C-7), 64.42 and 64.69 (C-8 and C-9).

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