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Synthesis of (+)-2,3-PinDione, a versatile chiral 1,2-diketone

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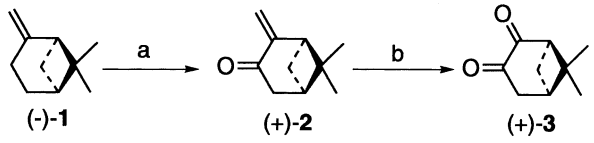
Abstract—The preparation of a 1,2-diketone derived from (−)-β-pinene, i.e. (+)-2,3-PinDione, is reported. The latter is shown to be a useful substrate for the Hinzberg-type syntheses of chiral quinoxaline ((−)-6,7-dimethyl-PinQuinox) and pyrazine ((+)-2,3-diphenylPinazine) derivatives as well as in the preparation of the bis-hydrazone ((+)-*N*′,*N*′-diphenyl-2,3-Pinazone).

We already reported the synthesis of a (−)-β-pinene derived 2-phenylpyridine analog by the so-called Krönhke condensation method and used it in the preparation of optically-pure helical metallo-spiralenes.[1a] We now report on the preparation of a 1,2-diketone derived from (−)-β-pinene, i.e. (+)-6,6-dimethylbicyclo[3.1.1]-heptane-2,3-dione **3** (Scheme 1), a versatile reagent that can be advantageously used for the synthesis of new chiral ligands for the synthesis of new bis-manganospiralenes.[1b]

Although diketone **3** has been identified as one of the numerous products of the tropospheric oxidation of α- and/or β-pinene,[2a] its large-scale synthesis has never been fully described. According to Tius and Kannanyara,[2b] **3** is obtainable by the ozonolysis (−78°C with CH_2Cl_2/pyridine, 1/1) of the α-hydroxymethylene ketone derived from (+)-nopinone, and further reduction of the intermediary ozonide by dimethyl sulfide. Unfortunately, full experimental and analytical data related to **3** were never reported.



Scheme 1. *Reagents and conditions*: (a) SeO_2, CCl_4, 16% yield, see Ref. 3; (b) O_3, CH_2Cl_2/MeOH (1/1), −78°C and $S(Me)_2$, −78°C to rt, 3 days, 70% yield.

To efficiently prepare **3**, we chose an alternative and shorter pathway than that proposed by Tius and Kannanyara, as shown below in Scheme 1. The oxidation of (−)-β-pinene **1** ($[\alpha]_D = -21$) with SeO_2 allowed us to obtain (+)-pinocarvone **2** ($[\alpha]_D = +46$).[3] Compound **3** was obtained from the careful ozonolysis[4] of **2** (5 g, 33.3 mmol) in a mixture of CH_2Cl_2/MeOH (1/1, 70 ml) at −78°C by bubbling dioxygen enriched in O_3 through a 20 cm long and coiled punctured Teflon tubing (5 mm inner diameter) over 4 h and subsequent treatment of the ozonide with an excess of dimethyl sulfide (70 ml). After 3 days at room temperature, the solution was stripped of solvents under reduced pressure. The remaining oil was extracted with ether, the organic phase washed with water, treated with an aqueous ferrous sulfate solution and a saturated solution of Na_2CO_3. Kugelrohr distillations afforded pure **3**[5] as a bright yellow solid in 70% yield (3.5 g, 23 mmol, mp 94°C). Other attempts to prepare **3** by different approaches were unsuccessful: catalytic oxidative cleavage of the C=C bond of **2** (catalytic amounts of OsO_4, Me_3NO, pyridine, $NaIO_4$, *t*-BuOH–H_2O),[6] as well as α-oxidation of (+)-nopinone by inorganic oxidizers such as SeO_2[7] proved to be inefficient in producing **3** in high yields.

In absolute ethanol, the UV-visible spectrum of α-diketone **3** displays two absorption bands at $\lambda_{max.} = 420$ nm ($\varepsilon = 20$ mol^{-1} dm^3 cm^{-1}) and $\lambda_{max.} = 273$ nm ($\varepsilon = 130$ mol^{-1} dm^3 cm^{-1}), which correspond to the n–π* transition of the –C(O)–C(O)– system and to the absorption of a single carbonyl, respectively.[8] In *n*-hexane the band at the highest wavelength undergoes a red shift and appears as an overlay of at least three discrete absorption bands at $\lambda_{max.} = 455$ ($\varepsilon = 18$ mol^{-1} dm^3 cm^{-1}), 451 ($\varepsilon = 15$ mol^{-1} dm^3 cm^{-1}) and 427 ($\varepsilon = 23$ mol^{-1} dm^3

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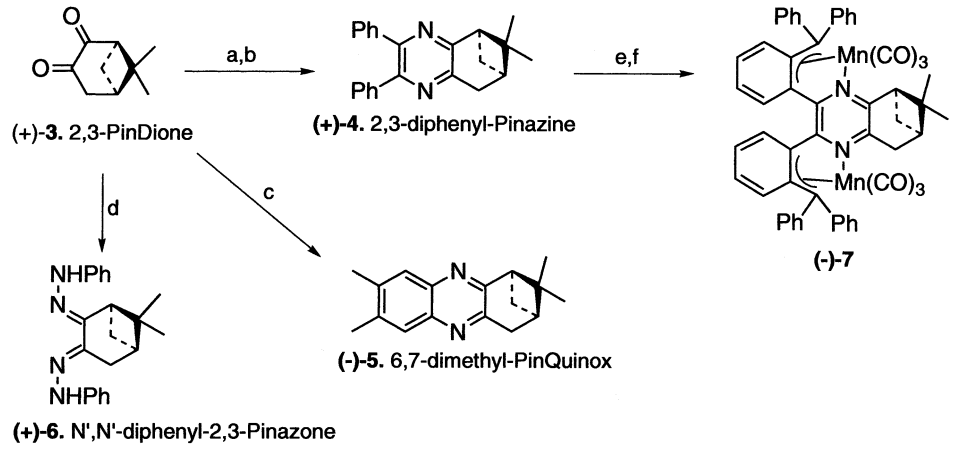

Scheme 2. *Reagents and conditions*: (a) *meso*-1,2-diphenylethylenediamine,[9] toluene, reflux 7 h under argon; (b) nickel peroxide, distilled benzene, reflux 7 days under argon, 50% yield; (c) 4,5-dimethyl-1,2-phenylene-diamine, EtOH, reflux 1 h, 85% yield; (d) phenylhydrazine, EtOH, 79% yield; (e) excess $(PhCH_2)Mn(CO)_5$, toluene/heptane (1:1), reflux 24 h; (f) excess N_2CPh_2, toluene, reflux 1 h, 7% yield in **7** (calculated versus **4**).

cm^{-1}) nm. In *n*-hexane, the band at the lowest wavelength undergoes a two-fold decrease of its extinction coefficient, which might be symptomatic of a decrease of the proportions of the enol form related to **3**. According to the correlation established by Leonard and Mader,[8a] and by Cerfontain and Verheijdt,[8f] between the energy of the n–π* transition and the intercarbonyl dihedral angle, these spectroscopic data suggest that the two carbonyl groups in **3** are nearly coplanar and in a *cis* relationship.

We investigated different aspects of the reactivity of **3**. First, **3** (2.9 g, 19 mmol) was condensed with *meso*-1,2-diphenylethylenediamine[9] (4.9 g, 23 mmol) in refluxing toluene with a Dean–Starck apparatus under argon over 7 h to afford, after evaporation of toluene, the resulting dihydropyrazine. The latter was directly converted to the corresponding pyrazine by oxidation with nickel peroxide in dry refluxing benzene. After extraction with ether, a chromatographic purification on silica gel with hexane/CH_2Cl_2 (80/20) as eluent afforded **4**[10] as a light-brown oil (3.2 g, 9.8 mmol, 50% yield). The condensation of **3** (0.3 g, 2 mmol) with 4,5-dimethyl-1,2-phenylene-diamine (0.27 g, 2 mmol) in absolute ethanol (20 ml) under reflux (1 h) led to **5**. A flash chromatographic purification on silica gel with CH_2Cl_2 gave pure **5**[11] as a white solid (0.42 g, 1.7 mmol, 85% yield, mp 110°C). Synthon **3** (0.3 g, 2 mmol) reacted readily with phenylhydrazine (0.9 g, 8.3 mmol) in refluxing absolute ethanol (12 ml) over one night. The residue remaining after evaporation of the solvent under reduced pressure was purified on silica gel and eluted with hexane/CH_2Cl_2 (60/40) to give **6**[12] as an orange solid (0.56 g, 1.5 mmol, 79% yield, mp 157°C) (Scheme 2).

In contrast with the camphorquinone-derived analogs,[13] ligands **4** and **5** are less sterically hindered. The chemistry of these chiral reagents is currently under investigation. Worthy of note, in a preliminary attempt, we succeeded in doubly manganating ligand **4** by an overnight reaction with $(PhCH_2)Mn(CO)_5$.[1] The resulting crude mixture was reacted immediately with excess amounts of N_2CPh_2 to yield a new bright red chiral bis-manganospiralene **7** ($[\alpha]_D = -665$). The spectroscopic properties and analytical data[14] of the latter suggest structural similarities with the first achiral bis-spiralene synthesized by the same method, structurally characterized and reported by us recently.[1b]

For commodity, **3** can be referred to as (+)-2,3-PinDione; **4** as (+)-2,3-diphenyl-Pinazine; **5** as (−)-6,7-dimethyl-PinQuinox; **6** as (+)-*N*′,*N*′-diphenyl-2,3-Pinazone.

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5. **3**: (+)-(1*S*,5*S*)-6,6-Dimethylbicyclo[3.1.1]heptane-2,3-dione. $[\alpha]_D = +173$ (CH_2Cl_2, 20°C, $c = 0.12$ g/100 ml). IR: (KBr) ν(CO) 1740, 1719 cm^{-1}. Anal. calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.97; H, 8.08%. HRMS (EI) calcd for $C_9H_{12}O_2$: m/z 152.0837; found (%): m/z 152.0831 (61.8). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.99 (t, 1H, $^3J = 5.9$ Hz), 2.90 (m, 1H), 2.82 (t, 1H, $^3J = 3.3$ Hz), 2.69 (m, 1H), 2.44 (m, 1H), 1.68 (d, 1H, $^2J = 11.5$ Hz), 1.46 (s, 3H), 0.93 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 197.0, 195.7, 56.6, 42.4, 41.4, 38.2, 28.0, 26.4, 22.2.
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10. **4**: (+)-(1*S*,5*S*)-2,3-(2′,3′-Diphenyl-1′,4′-diazabenzo)-6,6-dimethylbicyclo[3.1.1]heptane. $[\alpha]_D = +22$ (CH_2Cl_2, 20°C, $c = 0.33$ g/100 ml calculated based on the 1:1 *n*-hexane solvate of **4**). Anal. calcd for $C_{23}H_{22}N_2 \cdot n$-hexane: C, 84.44; H, 8.73; N, 6.78. Found: C, 84.51; H, 8.43; N, 6.72%. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.43 (m, 4H), 7.28 (m, 6H), 3.20 (d, 2H, $^3J = 2.9$ Hz), 3.15 (t, 1H, $^3J = 5.7$ Hz), 2.85 (m, 1H), 2.48 (m, 1H), 1.48 (s, 3H), 1.46 (d, 1H, $^2J = 10.0$ Hz), 0.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 159.4, 150.4, 149.6, 147.9, 139.3, 139.2, 129.9, 129.8, 128.3, 128.2, 128.1, 128.0, 48.9, 40.1, 40.0, 34.8, 31.1, 26.1, 21.6. HRMS (EI) calcd for $C_{23}H_{22}N_2$: m/z 326.1782; found (%): m/z 326.1787 (100).
11. **5**: (−)-(1*S*,5*S*)-2,3-(3′,4′-Dimethyl-1′,6′-diazanaphtho)-6,6-dimethylbicyclo[3.1.1]heptane. $[\alpha]_D = -1.7$ (CH_2Cl_2, 20°C, $c = 2.02$ g/100 ml). Anal. calcd for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.86; H, 8.12; N, 11.18%. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.70 (s, 1H), 7.69 (s, 1H), 3.23 (d, 2H, $^3J = 2.9$ Hz), 3.14 (t, 1H, $^3J = 5.7$ Hz), 2.85 (m, 1H), 2.48 (m, 1H), 2.42 (s, 6H), 1.46 (s, 3H), 1.42 (d, 1H, $^2J = 10.3$ Hz), 0.67 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 160.9, 153.1, 140.6, 139.0, 138.9, 138.6, 127.9, 127.7, 50.2, 40.3, 39.8, 35.6, 31.0, 26.1, 21.5, 20.3, 20.2.
12. **6**: (+)-(1*S*,5*S*)-(6,6-Dimethylbicyclo[3.1.1]heptane-2,3-dione)bisphenylhydrazone. $[\alpha]_D = +191$ (CH_2Cl_2, 20°C, $c = 0.27$ g/100 ml). Anal. calcd for $C_{21}H_{24}N_4$: C, 75.87; H, 7.28; N, 16.85. Found: C, 75.50; H, 7.28; N, 17.52%. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.48 (s, 1H), 7.40 (t, 2H, $^3J = 7.9$ Hz), 7.28 (t, 2H, $^3J = 7.9$ Hz), 7.17 (d, 2H, $^3J = 8.5$ Hz), 7.13 (d, 2H, $^3J = 8.7$ Hz), 6.99 (t, 1H, $^3J = 7.4$ Hz), 6.84 (t, 1H, $^3J = 7.2$ Hz), 2.80 (t, 1H, $^3J = 5.8$ Hz), 2.68 (m, 1H), 2.65 (d, 2H, $^3J = 3.4$ Hz), 2.28 (m, 1H), 1.39 (s, 3H), 1.36 (d, 1H, $^2J = 10.2$ Hz), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 145.2, 143.9, 141.7, 139.4, 129.7, 129.4, 121.3, 119.8, 113.3, 112.8, 50.0, 40.9, 37.8, 31.3, 29.3, 25.9, 21.4. HRMS (EI) calcd for $C_{21}H_{24}N_4$: 332.2001; found (%): 332.2001 (100).
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14. **7**: $[\alpha]_D = -665$ (CH_2Cl_2, 20°C, $c = 0.28$ g/100 ml). IR: (*n*-hexane) ν(CO) 2004, 1936, 1916 cm^{-1}. Anal. calcd for $C_{55}H_{40}N_2O_6Mn_2$: C, 70.67; H, 4.31; N, 3.00. Found: C, 70.80; H, 4.65; N, 2.94%. ^1H NMR ($CDCl_3$, 500 MHz, 303 K) δ (ppm) 7.66 (m, 4H), 7.53 (d, 1H, $^3J = 8.5$ Hz), 7.40 (m, 5H), 7.29 (m, 4H), 7.12 (m, 4H), 6.99 (m, 7H), 6.76 (m, 3H), 2.73 (t, 1H, $^3J = 5.5$ Hz), 2.63 (dd, 1H, $^2J = 18.4$ Hz, $^3J = 3.3$ Hz), 2.46 (m, 1H), 2.25 (d, 1H, $^2J = 19.9$ Hz), 2.17 (m, 1H), 1.31 (s, 3H), 0.21 (d, 1H, $^2J = 10.5$ Hz), −0.05 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, 283 K) δ (ppm) 230.7, 230.0, 221.2, 221.1, 218.8, 218.6, 162.5, 152.9, 147.9, 147.8, 147.5, 147.3, 141.8, 141.7, 136.0, 135.0, 134.0 (2C), 133.1, 132.6, 132.5, 131.6, 131.5, 131.2, 129.6, 129.2, 128.8 (2C), 127.2, 127.1, 126.4, 126.3, 125.8, 125.2, 125.1, 124.8, 124.5, 124.4, 114.6, 113.7, 92.1, 86.9, 75.7, 44.9, 40.9, 38.5, 29.9, 25.8, 22.9. MS (FAB+) m/z 935 $(MH)^+$, 850 $(M-3CO)^+$, 766 $(M-6CO)^+$.