A New Preparation of 1,3,3-Trimethylbicyclo[2.2.2]octan-2,6-dione, a Never Isolated Intermediate in a Total Synthesis of (+)-Norpatchoulenol. Formal Total Synthesis of (±)-Iso-Norpatchoulenol

by **Angela La Bella**, **Francesca Leonelli**, **Ilse De Salve**, **Luisa M. Migneco**, and **Rinaldo Marini Bettolo***

Dipartimento di Chimica and Istituto di Chimica Biomolecolare del CNR, Sezione di Roma,
Università degli Studi di Roma 'La Sapienza', Piazzale Aldo Moro 5, P.O. Box 34 Roma 62, I-00185 Rome
(phone: +39 0649913615; fax. +39 0649913750; e-mail: rinaldo.marinibettolo@uniroma1.it)

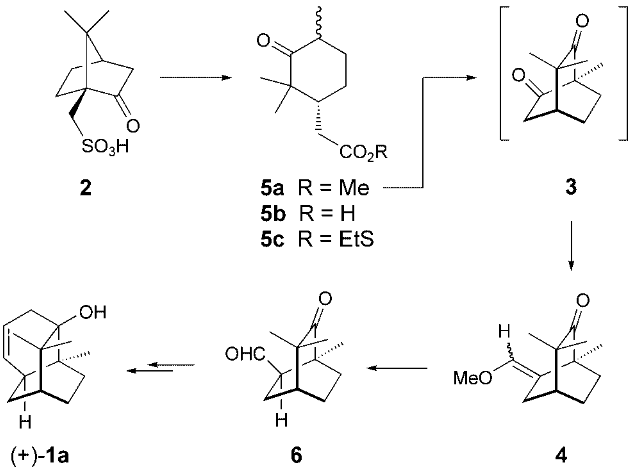
A new preparation and the isolation and spectroscopic characterization of 1,3,3-trimethylbicyclo[2.2.2]octan-2,6-dione (**3**), a so far elusive key intermediate in the *Liu–Ralitsch* total synthesis of (+)-norpatchoulenol ((+)-**1a**), is described. The preparation of **3** constitutes also a formal total synthesis of (±)-iso-norpatchoulenol ((±)-**1b**), since **3** is correlated to an intermediate in the *Monti* and co-workers synthesis of (±)-**1b**.

Introduction. – (+)-Norpatchoulenol (=1*R*,4a*S*,6*R*,8a*S*)-4a,5,6,7,8,8a-hexahydro-8a,9,9-trimethyl-1,6-methanonaphthalen-1(2*H*)-ol; (+)-**1a**) is a minor component of *patchouli* oil, obtained by steam distillation of *Pogostemon patchouli* leaves, and is one of the major determinants of the *patchouli* scent [1]. Several authors have reported syntheses of **1a** [2]. *Liu* and *Ralitsch* described the total synthesis of (+)-**1a** from (+)-camphor-10-sulphonic acid (*Scheme 1*) (**2**) [2h]. Trapping of the 1,3-diketone intermediate **3** with a *Wittig* reagent to give **4** was a key feature of their approach. Thereby, the authors successfully managed to overcome the problem of the preparation of **4**, since '*under no conditions applied could the desired product* (**3**) *be obtained*' by direct cyclization of **5a**, while, starting from **5b** or **5c**, the diketone **3** was obtained in very low yield. Compound **4** was then converted to (+)-**1a** *via* **6**. The latter compound is also an intermediate in the synthesis of (±)-iso-norpatchoulenol **1b**, described in 1996 by *Monti* and co-workers (see *Scheme 2*) [3]. Thus, intermediate **3** is related to both **1a** and **1b** *via* compound **6**. However, compound **3** had originally been obtained much earlier, though not isolated, by *Curtin* and *Fraser* during their studies on the reactivity of 2,6,6-trimethylcyclohexa-2,4-dien-1-one towards a series of dienophiles [4].

In the frame of a project directed to the synthesis of *patchouli-alcohol*-like fragrances, whose bicyclo[2.2.2]octane system we intend to construct by the intramolecular aldol condensation of 3-oxocyclohexaneacetaldehydes [5], a methodology not yet extended to the synthesis of this class of compounds, we prepared the '*apparently unstable*' 1,3-diketone **3**. Owing to the importance of **3** as a synthetic intermediate (or reaction product), we wish to describe hereafter its preparation, isolation, and spectroscopic characterization.

Results and Discussion. – The starting material for this study was the known 6-hydroxybicyclo[2.2.2]octan-2-one **7** [6a], available in three steps from the cyclohexanone **8** [7] according to *Scheme 2*. Compound **7** was obtained as an *endo*/*exo* 85:15

Scheme 1. Liu–Ralitsch *Synthesis of (+)-Norpatchoulenol* (**1a**) via *1,3,3-Trimethyl-bicyclo[2.2.2]octan-2,6-dione* (**3**)



mixture, *endo*-**7** being the major component. In principle, both epimers, *endo*- and *exo*-**7**^{1}), were potential intermediates for further work. However, for practical reasons, the synthesis was carried on with only *endo*-**7**. The latter was protected as tetrahydropyranyl (THP) ether by standard methods to give **9**, which was then converted to the *gem*-dimethylated compound **10** by reaction with *t*-BuOK and MeI. THP Deprotection of **10** in mildly acidic medium gave the *endo*-hydroxy ketone **11**^{2}) as the only product.

The *endo*-configuration of the HO–C(6) group of **11** was attributed by comparing the H–C(6) and C(6) NMR chemical shifts of **11** with those of *endo*- and *exo*-**7**. The corresponding values for *endo*-**7**, *exo*-**7**, and **11** were, for H–C(6), δ 3.85, 3.75, and 3.85, respectively, and those for C(6), 73.8, 69.8, and 74.6. Thus, epimerization at C(6) was excluded during the formation of **9** and **11**.

Pyridinium dichromate (PDC) oxidation^3) of **11** in CH_2Cl_2 finally gave **3**. The direct conversion of **10** to **3** could be also achieved with the *Jones* reagent. Interestingly, the so-far elusive **3** turned out to be a stable compound, and could be fully characterized. Its structure was further confirmed by *Wittig* reaction to **4** with (methoxymethyl)triphenylphosphonium chloride, the same reagent used by *Liu* and *Ralitsch* for their one-pot transformation of **5a** into **4** [2h]. The isomeric product due to the attack of the *Wittig* reagent at the more-hindered C=O group was not observed.

Conclusions. – In view of the syntheses of *Liu* and *Ralitsch* [2h], and *Monti* and coworkers [3], the preparation of **3** (and **4**) constitutes formal total syntheses of both norpatchoulenol ((±)-**1a**) and iso-norpatchchoulenol ((±)-**1b**). Moreover, by correlating *endo*-**7** [6a] with **1a** [2h] and **1b** [3], the 3-oxo-cyclohexaneacetaldehyde intra-

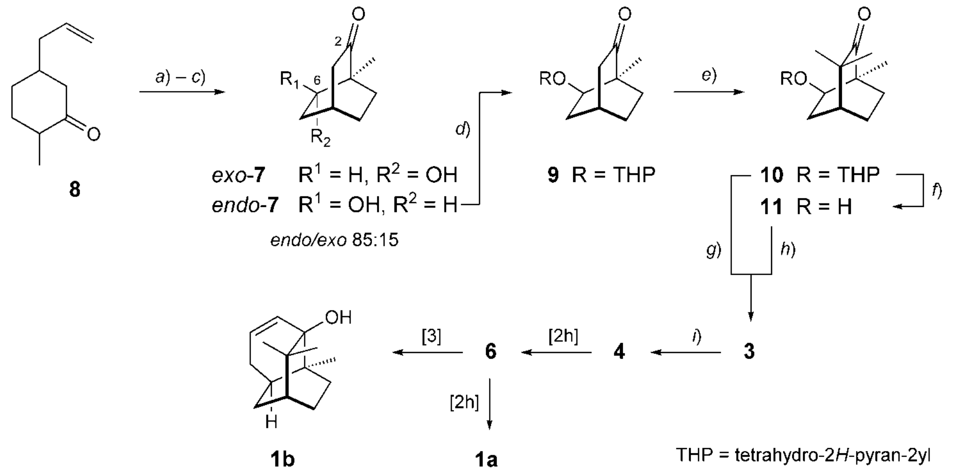
---

^{1}) For a preparation of (–)-*endo*-**7** and (–)-*exo*-**7**, see [6a] and [6b], resp.

^{2}) As for **3**, *Curtin* and *Fraser* [4] also reported of **11**. However, they did not isolate it.

^{3}) For oxidations of a 6-hydroxybicyclo[2.2.2]octan-2-one to a bicyclo[2.2.2]octan-2,6-dione, see [6a][8].

Scheme 2. *Preparation of the Elusive Intermediate* **3**, *and Formal Total Syntheses of Norpatchoulenol* (**1a**) *and Iso-Norpatchoulenol* (**1b**)



a) C_6H_6, TsOH, ethylene glycol, reflux; 86%. *b*) OsO_4, THF, pyridine, $NaIO_4$, H_2O, r.t.; 65%. *c*) THF/2N HCl 2 : 1, reflux; 86%. *d*) 3,4-dihydro-2*H*-pyran, CH_2Cl_2, TsOH, r.t.; 96%. *e*) *t*-BuOK, THF, MeI, r.t.; 70%. *f*) THF/1N HCl 4 : 1, r.t.; 73%. *g*) *Jones* reagent, acetone; 80%. *h*) pyridinium dichromate (PDC), CH_2Cl_2; 89%. *i*) $Ph_3P{=}C(H)OMe$, THF, 0°; 86%.

molecular aldol condensation is extended to the synthesis of *patchouli-alcohol*-like fragrances, showing the complementarity of this methodology to others adopted to date to this end.

Financial support by the Università degli Studi di Roma 'La Sapienza' (Ateneo 60%) and the *Ministero dell'Istruzione, Università e Ricerca* (COFIN 2000: 'Sintesi di Sostanze di Comunicazione Chirali', and COFIN 2002: 'Aromi e Fragranze') is gratefully acknowledged.

Experimental Part

General. All solns. were evaporated to dryness under vacuum. All solvents were of anal. or HPLC grade. Compound **8** was prepared from commercial 2-methylanisole (*Aldrich*) according to [7]. The purity of all compounds was evaluated by HPLC analysis: *Shimadzu LC-10AD* with RID detector; *250/4 Nucleosil 100-5* column (*Macherey-Nagel*), at a flow of 0.8 ml/min; t_R in min. TLC: *Merck* silica gel *60* F_{254}. M.p.: *Mettler FP-61* apparatus, uncorrected. IR Spectra: *Shimadzu 470* and *Perkin-Elmer 298* spectrophotometers; in cm^{-1}. ^1H- and ^{13}C-NMR: *Bruker AC-300P* (300.13 and 75.48 MHz, resp.), and *Varian Gemini-200* (200 and 50 MHz, resp.); δ in ppm rel. to internal Me_4Si (=0 ppm), *J* in Hz. GC/MS: *HP5890* GC (*OV1* capillary column, 12 m × 0.2 mm), *HP5970* MSD; in *m/z* (rel. %).

Data of endo-**7** (=*1*S*,4*R*,6*R*)-6-Hydroxy-1-methylbicyclo[2.2.2]octan-2-one*) [6a]. HPLC (hexane/AcOEt 70 : 30): t_R 14.30 (100%). M.p. 124.4–126.4° (hexane/Et_2O 70 : 30). IR (CCl_4): 1727. ^1H-NMR ($CDCl_3$): 3.86–3.83 (*m*, 1 H); 2.54–2.01 (5 H); 1.72–1.31 (5 H); 1.00 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 215.9; 73.8; 48.7; 44.0; 36.7; 28.1; 27.7; 25.1; 16.7.

Data of exo-**7** [6a]. HPLC (hexane/AcOEt 70 : 30): t_R 11.77 (100%). M.p. 104.6–106.6° (hexane). IR (CCl_4): 1724. ^1H-NMR ($CDCl_3$): 3.85–3.64 (*m*, 1 H); 2.53–1.15 (10 H); 0.98 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 216.5; 69.8; 49.3; 43.6; 37.3; 27.2; 25.0; 23.2; 16.0.

1-Methyl-6-[(tetrahydro-2H-pyran-2-yl)oxy]bicyclo[2.2.2]octan-2-one (**9**). To a stirred soln. of *endo*-**7** (710 mg, 4.6 mmol) in CH_2Cl_2 (11 ml), cooled to 0° under Ar, were added portionwise 3,4-dihydro-2*H*-pyran (1 ml, 11 mmol) and a cat. amount of TsOH. The mixture was allowed to warm to r.t. When TLC (hexanes/Et_2O 30:70) showed the disappearance of the starting material, a sat. $NaHCO_3$ soln. (2 ml) was added under stirring. The two phases were separated, and the org. layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by CC (SiO_2; hexanes/Et_2O 75:25) to afford **9** (1 g; 96%) as a diastereoisomeric mixture. Colouless oil. HPLC (hexane/AcOEt 90:10): t_R 11.60 min (100%). IR (CCl_4): 1725. ^{1}H-NMR ($CDCl_3$): 4.74–4.45 (*m*, 1 H), 3.90–3.62 (*m*, 2 H), 3.50–3.33 (*m*, 1 H), 2.35–0.90 (18 H). EI-MS: 238 (0.4, M^+), 154 (62), 93 (43), 85 (100), 67 (20).

1,3,3-Trimethyl-6-[(tetrahydro-2H-pyran-2-yl)oxy]bicyclo[2.2.2]octan-2-one (**10**). To a stirred soln. of **9** (475 mg, 2 mmol) in THF (7 ml) was added under Ar a suspension of *t*-BuOK (449 mg, 4 mmol) in THF (5 ml). MeI (0.6 ml, 10 mmol) was then added dropwise. When TLC (hexanes/Et_2O 70:30) showed the disappearance of the starting material, the mixture was neutralized with 0.5N HCl, washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by CC (SiO_2; hexanes/Et_2O 90:10) to afford **10** (372 mg; 70%) as a diastereoisomeric mixture. Colorless oil. HPLC (hexane/AcOEt 90:10): t_R 6.92 min (98%). IR (CCl_4): 1720. ^{1}H-NMR ($CDCl_3$): 4.80–4.49 (*m*, 1 H); 3.91–3.61 (*m*, 2 H); 3.52–3.39 (*m*, 1 H); 2.13–1.35 (13 H); 1.17–0.87 (9 H). EI-MS: 266 (0.1, M^+), 182 (45), 137 (14), 95 (11), 85 (100), 67 (12).

6-Hydroxy-1,3,3-trimethylbicyclo[2.2.2]octan-2-one (**11**). Compound **10** (230 mg, 0.9 mmol) was dissolved in THF/1N HCl 4:1 (10 ml). This soln. was stirred at r.t., until TLC analysis (hexanes/Et_2O 60:40) showed the disappearance of the starting material (after *ca.* 72 h). The mixture was then neutralized with a sat. $NaHCO_3$ soln. and diluted with Et_2O. After separation of the layers, the aq. phase was thoroughly extracted with Et_2O, the combined org. extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The resulting residue was purified by CC (SiO_2; hexanes/Et_2O 85:15) to afford **11** (120 mg; 73%). M.p. 84.5–86.5° (hexane/Et_2O 70:30). IR (CCl_4): 1720. ^{1}H-NMR ($CDCl_3$): 3.92–3.79 (*m*, 1 H); 2.20–1.37 (9 H); 1.13 (*s*, 3 H); 1.09 (*s*, 3 H); 0.98 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 220.2; 74.6; 48.7; 45.5; 38.7; 34.4; 28.0; 24.3; 23.2; 22.3; 16.9. HPLC (hexane/AcOEt 70:30): t_R 7.40 min (100%). EI-MS: 182 (2, M^+), 95 (100), 94 (35), 88 (64), 79 (15), 69 (12), 67 (12).

1,3,3-Trimethylbicyclo[2.2.2]octane-2,6-dione (**3**). *Method 1:* To a stirred soln. of **11** (80 mg, 0.44 mmol) in CH_2Cl_2 (10 ml), pyridinium dichromate (PDC; 330 mg, 0.88 mmol) was added. The mixture was stirred for 24 h at r.t. After filtration through *Florisil* and phase separation, the org. soln. was washed with a sat. aq. $CuSO_4$. soln. and brine, dried (Na_2SO_4), and evaporated. The residue was purified by CC (SiO_2; hexanes/Et_2O 75:25) to afford **3** (71 mg; 89%).

Method 2: To a stirred soln. of **10** (320 mg, 1.2 mmol) in anh. acetone (5 ml), cooled to 0°, was added dropwise 0.8 ml of *Jones* reagent (prepared by addition of CrO_3 (10 g, 0.1 mmol) at 0° to 96% H_2SO_4 (8.6 ml) and H_2O (14 ml), followed by dilution with additional H_2O (12 ml)). The mixture was then allowed to warm to r.t.. When TLC analysis (hexanes/Et_2O 70:30) showed the disappearance of the starting material, the mixture was treated with a 10% aq. $Na_2S_2O_5$ soln., and filtered (*Celite*). The org. soln. was evaporated, the residue was diluted with Et_2O, washed with sat. $NaHCO_3$ soln., H_2O, and brine, dried (Na_2SO_4), and evaporated. The resulting residue was purified by CC (SiO_2; hexanes/Et_2O 85:15) to afford **3** (173 mg; 80%).

Data of **3**. Colorless oil. HPLC (hexane/AcOEt 9:10): t_R 11.68 min (100%). IR (CCl_4): 1709. ^{1}H-NMR ($CDCl_3$): 2.66 (*A* of *ABMX*; $J_{AB} = 19.50$; $J_{AX} = J_{AM} = 3.02$; 1 H); 2.36 (*B* of *ABMX*; $J_{AB} = 19.50$; $J_{BX} = 2.93$; $J_{BM} = 0$; 1 H); 2.24–2.06 (*m*, 2 H); 1.90–1.69 (*m*, 3 H); 1.26 (*s*, 3 H); 1.06 (*s*, 3 H); 1.05 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 213.2; 208.6; 62.4; 46.0; 42.0; 38.4; 29.8; 24.4; 23.9; 22.2; 12.6. EI-MS: 180 (24, M^+), 165 (37), 110 (10), 109 (25), 108 (24), 95 (22), 81 (100), 69 (75).

6-(Methoxymethylidene)-1,3,3-trimethylbicyclo[2.2.2]octan-2-one (**4**). To a stirred soln. of (methoxymethyl)triphenylphosphonium chloride (1.3 g, 3.8 mmol) in THF (7.5 ml) was added *t*-BuOK (284 mg, 2.5 mmol) at 0°C under Ar atmosphere. A reddish color indicated ylide formation. After 1 h, a soln. of **3** (100 mg, 0.54 mmol) in THF (2 ml) was added dropwise to the *Wittig* reagent. The mixture was stirred until TLC (hexanes/Et_2O 80:20) showed the disappearance of the starting material (after *ca.* 2 h). The mixture was warmed to r.t., quenched with H_2O, and thoroughly extracted with Et_2O. The combined org. extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by CC (SiO_2; hexanes/Et_2O 90:10) to afford **4** (97 mg; 86%). Colorless oil. HPLC (hexane/AcOEt 90:10): $t_R = 4.77$ and 5.17 (100%); (*E*)/(*Z*) 96:4. IR (CCl_4): 1718. ^{1}H-NMR ($CDCl_3$): 5.84–5.76 (*m*, 1 H); 3.57 (*s*, 3 H); 2.67–2.58 (*m*, 1 H); 2.27–2.15 (*m*, 1 H); 2.00–1.51 (*m*, 5 H); 1.12 (*s*, 3 H); 1.01 (*s*, 3 H); 1.00 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$): 218.7; 141.8; 115.5; 59.6; 46.0; 45.5; 38.1; 31.9; 27.5; 24.2; 24.1; 22.9; 16.4. EI-MS: 208 (27, M^+), 180 (43), 165 (17), 137 (100), 123 (22), 105 (37), 77 (19).

REFERENCES

[1] P. Teisseire, P. Maupetit, B. Corbier, *Recherches* **1974**, *19*, 8.

[2] a) P. Teisseire, P. Pesnelle, B. Corbier, M. Plattier, P. Maupetit, *Recherches* **1974**, *19*, 69;b) L. Bang, G. Ourisson, P. Teisseire, *Tetrahedron Lett.* **1975**, 2211; c) W. Oppolzer, R. L. Snowden, *Tetrahedron Lett.* **1978**, 3505; d) M. Bertrand, P. Teisseire, G. Pélerin, *Tetrahedron Lett.* **1980**, 2051; e) M. Bertrand, P. Teisseire, G. Pélerin, *Nouv. J. Chim.* **1983**, *7*, 61; f) H. Niwa, T. Hasegawa, N. Ban, K. Yamada, *Tetrahedron Lett.* **1984**, 2797; g) H. Niwa, T. Hasegawa, N. Ban, K. Yamada, *Tetrahedron* **1987**, *43*, 825; h) H.-J. Liu, M. Ralitsch, *J. Chem. Soc., Chem. Commun*. **1990**, 997; i) K. P. Kaliappan, G. S. R. Subba Rao, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1385; l) D. Spitzner, K. Oesterreich, *Eur. J. Org. Chem.* **2001**, 1883.

[3] H. Monti, P. Charles, G. Léandri, *Synth. Commun.* **1996**, *26*(22), 4123.

[4] D. Y. Curtin, R. R. Fraser, *J. Am. Chem. Soc*. **1959**, *81*, 662.

[5] a) B. De Santis, A. L. Iamiceli, R. Marini Bettolo, L. M. Migneco, R. Scarpelli, G. Cerichelli, G. Fabrizi, D. Lamba, *Helv. Chim. Acta* **1998**, *81*, 2375, and refers. cit. therein; L. M. Migneco, F. Leonelli, R. Marini Bettolo, *ARKIVOC* **2004**, *7*, 253.

[6] a) K. Mori, E. Nagano, *Biocatalysis* **1990**, *3*, 25; b) K. Mori, Y. Matsushima, *Synthesis* **1993**, 406; c) I. Sarvary, Y. Wan, T. Frejd, *J. Chem. Soc., Perkin Trans. 1* **2002**, 645; d) S. Di Stefano, F. Leonelli, B. Garofalo, L. Mandolini, R. Marini Bettolo, L. M. Migneco, *Org. Lett.* **2002**, *4*, 2783.

[7] A. Yanagisawa, S. Habaue, K. Yasue, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 6130.

[8] a) R. W. Guthrie, A. Philipp, Z. Valenta, K. Wiesner, *Tetrahedron Lett*. **1965**, 2945; b) K. Mori, Y. Nakahara, M. Matsui, *Tetrahedron* **1972**, *28*, 3217; T. Kitahara, N. Miyake, M. Kido, K. Mori, *Tetrahedron: Asymmetry* **1990**, *1*, 775.

Received May 10, 2004