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Synthesis in fluorous phase: a convenient synthesis of isolongifolene epoxide and its rearrangement to ketone

K.S. Ravikumar, Jean-Pierre Bégué*, Danièle Bonnet-Delpon, Michèle Ourévitch

Laboratoire BIOCIS associé au CNRS, Centre d'Etudes Pharmaceutiques, Rue J.B. Clément, 92296 Châtenay-Malabry, France

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Dedicated to Professor Paul Tarrant on the occasion of his 85th birthday

Abstract

Aerobic epoxidation of isolongifolene **1** with pivalaldehyde/oxygen in perfluoro-2-butyltetrahydrofuran (FC-75) in the presence of $Mn(OAc)_3{\cdot}2H_2O$ as catalyst yielded isolongifolene-epoxide **3** in good yield. The rearrangement of isolongifolene-β-epoxide to ketone **4** was achieved. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Fluorous phase; Epoxidation; Terpenes; Aerobic oxidation; Manganese catalyst

1. Introduction

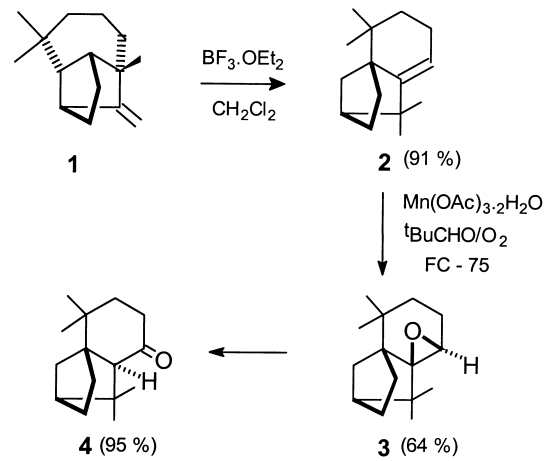
Longifolene **1** and its derivatives find a major role in fragrance industry. It is reported that the rearrangement of longifolene performed with $BF_3{\cdot}OEt_2$ affords isolongifolene **2** [1,2,3]. However, this reaction occurs with a high rate of racemization (ee 14%) [2]. We have observed that this racemization could be greatly limited if the reaction was performed in dichloromethane as solvent. Treatment of longifolene **1** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 35°C for 8 h afforded isolongifolene **2** in very good yield (91%) with an optical rotation ($[\alpha]_D = -66.6^\circ$). The highest optical rotation reported for isolongifolene **2** is ($[\alpha]_D = 82^\circ$) [3], when the reaction is performed in $AcOH/H_2SO_4$ medium, and after a several step purification [3].

Peracetic acid [4] and perbenzoic acid [1,3,5] oxidation of isolongifolene **2** generally led to a mixture of compounds such as epoxide, alcohol, ketone, and lactone, since the longifolene system is prone to undergo acid catalyzed rearrangement or overoxidation. Consequently, isolongifolene epoxide **3** was isolated in poor yields after a laborious separation protocol [3].

The use of the ''fluorous phase'' has been shown to present several advantages for oxidations in organic syntheses [6–12]. We have recently shown that the $Mn(OAc)_3{\cdot}2H_2O$ catalyzed aerobic oxidation of unfunctionalized olefins in a fluorous solvent afforded epoxides in very high yield [6]. These new neutral epoxidation conditions appeared to be well adapted to the acid sensitive isolongifolene system.

Isolongifolene **2** (1 equivalent) was allowed to react with oxygen/pivalaldehyde (3 equivalent) in perfluoro-2-butyltetrahydrofuran (FC-75) in the presence of $Mn(OAc)_3{\cdot}2H_2O$ (4 mol%) as catalyst and provided isolongifolene β-epoxide **3** (H-7: ^{1}H NMR $\delta = 3.15$, dd, $J = 2.2$, 2.9 Hz) as the only product in 64% yield (Scheme 1).

Treatment of longifolene **1** under the same aerobic oxidation conditions led only to recovered olefin **1**. These results



Scheme 1.

* Corresponding author. Tel.: 33-1-46-83-57-38; fax: 33-1-46-83-57-40.
E-mail address: jean-pierre.begue@cep.u-psud.fr (J.-P. Bégué).

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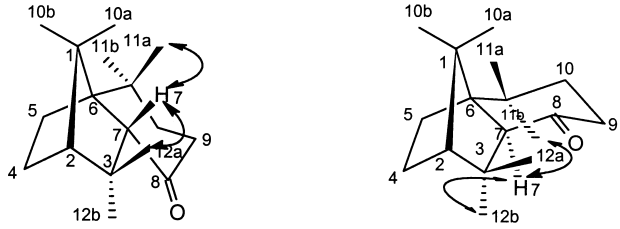

Fig. 1. nOe effects in ketones **4** and **5**.

confirm that our reagent system does not effect terminal double bonds, even 1,1 disubstituted ones, and that the reaction conditions are mild enough to avoid any rearrangement.

Surprisingly, we observed by NMR that the longifolene epoxide **3** rearranged slowly in a solution of $CDCl_3$, in the presence of tetramethylsilane, into the ketone **4** as the only product. From a preparative point of view, the isomerisation to ketone **4** was faster when performed in $CHCl_3$ with one equivalent of TMS. Isomerisation of this ketone **4** under basic conditions provided the ketone **5** [3].

Contradictory NMR data for ketones **4** and **5** have been clarified [13], and the configuration of these ketones has been determined without ambiguity with the complete assignment of ^1H and ^{13}C NMR spectrum and nOe experiments (Fig. 1). In ketone **4**, nOe effects were observed on Me-11a and Me-12a by irradiation of H-7, while in ketone **5** irradiation of H-7 was accompanied by nOe effects to Me-11b and Me-12b.

In conclusion, we have reported an improved method for the preparation of isolongifolene **2** and the clean preparation of pure isolongifolene-β-epoxide **3** in good yield. Finally the quantitative conversion of β-epoxide **3** into the ketone **4** was achieved under smooth conditions.

2. Experimental section

2.1. Isolongifolene 2

To a stirred solution of longifolene (20.4 g, 0.1 mol) in dry CH_2Cl_2 (20 ml), was added $BF_3{\cdot}OEt_2$ (0.5 ml) and the reaction was stirred for a further 8 h at 35°C. The crude product was poured into aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (2 × 25 ml), washed with brine and dried ($MgSO_4$). Removal of solvent followed by bulb-to-bulb distillation afforded isolongifolene **2** as a colourless oil (18.6 g, 91%). bp 82–83°C/0.4 mm (lit. 105–106°C/6 mm [2]) ; $[\alpha]_D = -66.6^\circ$ [($c = 3.56$, $CHCl_3$, lit. $[\alpha]_D = -74.8^\circ$ ($CHCl_3$)] [2]; IR (neat): ν 1363, 1378, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (s, 3 H), 0.94 (s, 3 H), 0.96 (s, 3 H), 1.05 (s, 3 H), 1.16–1.24 (m, 2 H), 1.32–1.52 (m, 3 H), 1.6–1.8 (m, 4 H), 1.88–2.0 (m, 2 H), 5.14 (t, $J = 3.3$ Hz, 1 H); ^{13}C NMR ($CDCl_3$): δ 22.9, 24.2, 24.9, 25.7, 26.6, 29.0, 31.2, 33.9, 36.8, 42.0, 46.7, 56.0, 110.67, 155.54.

2.2. Isolongifolene β-epoxide 3

To a stirred solution of isolongifolene (2.04 g, 10 mmol) in FC-75 (5 ml) and toluene (5 ml) at 25°C was added $Mn(OAc)_3{\cdot}2H_2O$ (0.11 g, 4 mol%). To this heterogeneous biphasic solution, pivalaldehyde (3.2 ml, 30 mmol) was added under an atmosphere of oxygen (bubbling throughout the experiment). The reaction was followed by GC. After complete disappearance of olefin, a solution of 5% aqueous $K_2CO_3$was added and the three phase system was stirred for an additional 15 min (25°C). The fluorous phase was removed by phase separation. The reaction mixture was extracted with ether (2 × 10 ml) and it was washed with brine and dried ($MgSO_4$). The solvent was evaporated and the residue was dissolved in pentane (5 ml) and filtered through a short silicagel column. Removal of solvent afforded isolongifolene-β-epoxide **3** as a colorless oil (1.4 *g*, 64%). $[\alpha]_D = -11.6^\circ$ ($c = 3.36$, $CHCl_3$); IR (neat) ν 1372, 1392, 1245, 922, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.81 (s, 6 H), 0.89 (s, 3 H), 1.0–1.3 (m, 5 H), 1.3–1.6 (m, 2 H), 1.60–1.90 (m, 4 H), 3.15 (dd, $J = 2.15$, 2.93 Hz, 1 H); ^{13}C NMR ($CDCl_3$) 20.8, 22.2, 24.5, 25.0, 25.3, 26.6, 27.2, 30.2, 32.9, 36.6, 39.3, 46.6, 52.3, 57.0, 72.6.

2.3. Ketone 4

A solution of isolongifolene epoxide **3** (200 mg) in $CHCl_3$ (3 ml) was kept at room temperature in the presence of TMS (100 mg) for 16 h. Evaporation of solvents provided the pure ketone **4** [3]. (196 mg, 98%); ^1H NMR ($CDCl_3$) δ 0.85 (s, 3 H, CH_3-11b), 0.9 (s, 3 H, CH_3-12a), 0.92 (m, 1 H, H-4b), 1.00 (s, 3 H, CH_3-11a), 1.02 (dd, $J_{1a\text{-}2} = 1.6$ Hz, $J_{1a\text{-}1b} = 9.7$ Hz, 1 H, H-1b), 1.19 (ddd, $J_{5a\text{-}5b} = 12.4$ Hz, $J_{5b\text{-}4a} = 3.7$ Hz, $J_{5b\text{-}4b} = 6.7$ Hz, 1 H, H-5b), 1.26 (s, 3 H, CH_3-12b), 1.29 (ddd, $J_{10b\text{-}9b} = 2.3$ Hz, $J_{10b\text{-}9a} = 6.5$ Hz, $J_{10b\text{-}10a} = 13.6$ Hz, 1 H, H-10b), 1.38 ($J_{1a\text{-}7} = J_{1a\text{-}2} = J_{1a\text{-}5b} = 2.8$ Hz, $J_{1a\text{-}1b} = 9.7$ Hz, 1 H, H-1a), 1.4 (m, 1 H, H-4a), 1.55 (m, $J_{10a\text{-}9a} = 5.5$ Hz, 1 H, H-10a), 1.56 (m, 1 H, H-2), 2.01 (ddd, $J_{9b\text{-}10a} = 5.5$ Hz, $J_{9b\text{-}10b} = 2.3$ Hz, $J_{9b\text{-}9a} = 15.4$ Hz, 1 H, H-9b), 2.08 (ddd, $J_{9a\text{-}10a} = 1.1$ Hz, $J_{9a\text{-}10b} = 6.5$ Hz, $J_{9a\text{-}9b} = 15.4$ Hz, 1 H, H-9a), 2.13 (d, $J_{9\text{-}7'a} = 2.8$ Hz, 1 H, H-7); ^{13}C NMR ($CDCl_3$) δ 23.1 (CH_3-11a), 23.4 (CH_3-12b), 23.6 (C-5), 25.4 (CH_3-11b), 26.5 (C-4), 32.7 (CH_3-12a), 33.5 (C-11), 36.7 (C-1), 37.8 (C-10), 38.3 (C-12), 40.1 (C-9), 49.0 (C-2), 59.9 (C-6), 60.5 (C-7), 211.3 (C=O).

2.4. Ketone 5

A suspension of ketone **4** (40 mg) and alumina (2 g) in petrol ether (4 ml) was stirred for 22 h at room temperature, filtration from the alumina provided pure ketone **5** (39 mg) [3]. ^1H NMR ($CDCl_3$) δ 0.90 (s, 3 H, CH_3-11a), 0.91 (s, 3 H, CH_3-12a), 0.97 (s, 3 H, CH_3-11b), (m, 1 H, H-4b), 1.06 (dd, $J_{1b\text{-}2} = 6.1$ Hz, $J_{1b\text{-}1a} = 12.0$ Hz, 1 H, H-1b), 1.17 (s, 3 H,

CH_3-12b), 1.23 (m, 1 H, H-5a), 1.48 (ddd, $J_{4a\text{-}5b} = 7.7$ Hz, $J_{4a\text{-}4b} = 13.8$ Hz, $J_{4a\text{-}5a} = 2.6$ Hz, 1 H, H-4a), 1.60 ($J_{1a\text{-}2} = 6.1$ Hz, $J_{1a\text{-}1b} = 12.3$ Hz, 1 H, H-1a), 1.72 (m, 1 H, H-5b), 1.73 (m, 1 H, H-7), 1.80 (m, 1 H, H-2), 1.93 (dddq, $J_{10a\text{-}9b} = 8.1$ Hz, $J_{10a\text{-}9a} = 11.1$ Hz, $J_{10a\text{-}10b} = 19.2$ Hz, $J_{10a\text{-}11} = 0.5$ Hz, 1 H, H-10a), 2.27 (ddd, $J_{9b\text{-}10a} = 8.0$ Hz, $J_{9b\text{-}10b} = 2.7$ Hz, $J_{9b\text{-}9a} = 19.4$ Hz, 1 H, H-9b), 2.36 (dddd, $J_{9a\text{-}10a} = 11.1$ Hz, $J_{9a\text{-}10b} = 7.7$ Hz, $J_{9a\text{-}9b} = 19.4$ Hz, $J_{9a\text{-}2} = 1.3$ Hz, 1 H, H-9a); ^{13}C NMR ($CDCl_3$) δ 23.2 (CH_3-11a), 24.5 (C-5), 25.9 (CH_3-11b), 26.0 (CH_3-12a), 28.1 (CH_3-12b), 30.9 (C-5), 31.6 (C-7), 34.9 (C-10), 37.1 (C-9), 37.9 (C-1), 44.1 (C-3), 48.4 (C-2), 56.3 (C-6), 63.9 (C-7), 214.5 (C=O).

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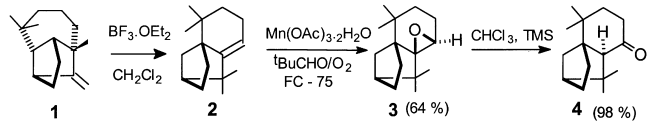
Appendix A.

Epoxidation of isolongifolene could be realized cleanly and selectively under aerobic conditions using a fluorous phase.



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