SYNTHESIS OF SOME *CIS*-4,4-DIMETHYL-2-ISOPROPENYLCYLOPENTANE DERIVATIVES AS POTENTIAL INTERMEDIATES TOWARDS THE PROTOILLUDANE SKELETON

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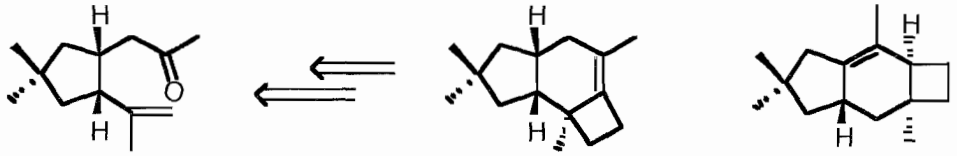
ABSTRACT

The three gem-dimethyl-substituted cyclopentane derivatives 1-(2-propionyl)-4,4-dimethyl-2-isopropenylcyclopentane, 2-isopropenyl-4,4-dimethylcyclopentanecarboxyaldehyde and 1-hydroxymethyl-2-isopropenyl-4,4-dimethylcyclopentane have been synthesized employing a thermally induced ene reaction as a key step. Each of the three compounds has been obtained predominantly as the cis isomer. The successful synthesis of these compounds affords opportunities for their further ellaboration towards sesquiterpenes of the protoilludane skeleton.

INTRODUCTION

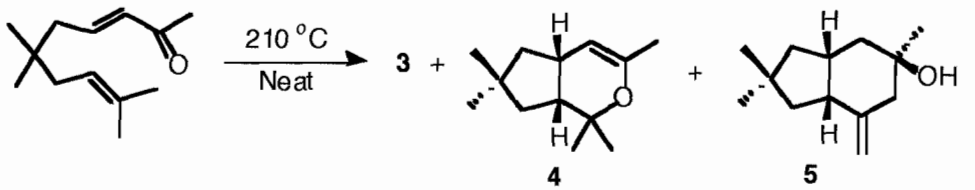
Over the past two and half decades several tricyclic sesquiterpenes with the unique 4/5/6 ring system have been isolated from natural sources and characterised (Mdachi 1995, Hansen *et al.* 1998). The compounds are divided into two subclasses, namely the protoilludanes and sterpuranes; here represented by Δ^6-protoilludene (**1**) and sterpurene (**2**), respectively. Both classes of compounds show interesting biological activities, but equally interesting is their postulation as intermediates in the biosyntheses of other sesquiterpenes (Murata *et al.* 1981, Ayer and Browne 1981, Arnone *et al.* 1989). The unique skeleton of Δ^6-protoilludene (**1**) presents a synthetic challenge, but still some syntheses of these compounds have been reported (Furukawa *et al.* 1985, Oppolzer and Nakao 1986, Hansen *et al.* 1998). With compound **1** as the ultimate target, retrosynthetic analysis may lead to a *gem*-dimethyl-substituted cyclopentane derivative such as **3** (Scheme 1).



3 **1** **2**

Scheme 1

This paper reports on the synthetic efforts towards some *gem*-dimethyl-substituted cyclopentane derivatives, which are potentially capable of being transformed to Δ^6-protoilludene (**1**). The *gem*-dimethyl-substituted cyclopentane derivative **3** was previously prepared as a 3:7 mixture of the *cis* and *trans* isomers, respectively, from the thermally induced ene reaction (Scheme 2, Mdachi 1995, Birkenes *et al.* 1998). In this preparation, however, the Diels-Alder product **4** was formed as the major component, together with the bicyclic alcohol **5**.

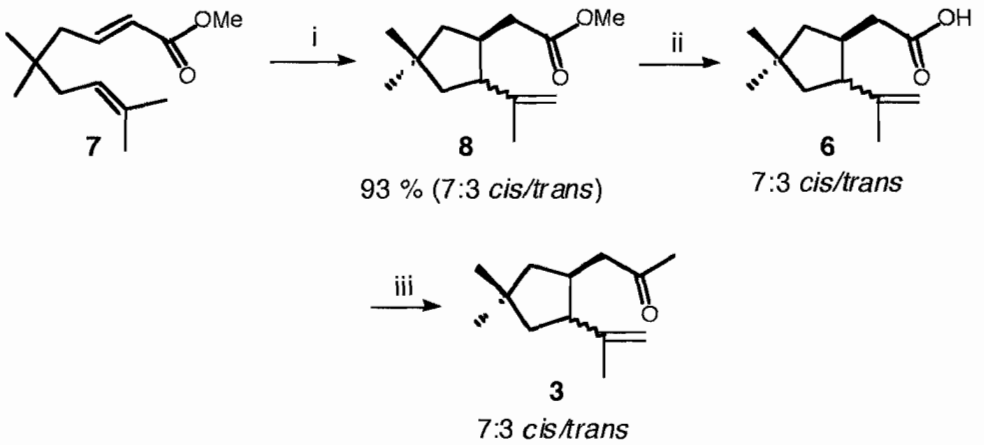


Scheme 2

Consequently, there was a need to improve both the yield and stereoselectivity (in favour of the *cis* isomer) of the desired ketone **3**. Thus, one strategy to achieve this goal would be to transform the readily available 4,4-dimethyl-2-isopropenylcyclopentylacetic acid (**6**) to compound **3**. It was also envisioned that the acid **6** could be synthetically manipulated to form other *gem*-dimethyl-substituted cyclopentane derivatives, besides compound **3**, which are potential intermediates towards assembling the protoilludane skeleton.

RESULTS AND DICUSSION

Thompson and Heathcock (1992) reported the preparation of 4,4-dimethyl-2-isopropenylcyclopentylacetic acid (**6**) from the thermally induced ene reaction of methyl 5,5,8-trimethyl-2,7-nonadiennoate (**7**). In the work reported herein, the procedure by Thompson and Heathcock was used to prepare compound **6**, which was further converted to the desired ketone **3** (Scheme 3). Unlike the closely related ene reaction in Scheme 2, compound **7** gave exclusively the ene product, that is compound **8** in 93% yield. None of the Diels-Alder product corresponding to compound **4** was formed. Furthermore, compound **8** was formed as a 7:3 mixture of the *cis* and *trans* isomers, respectively.



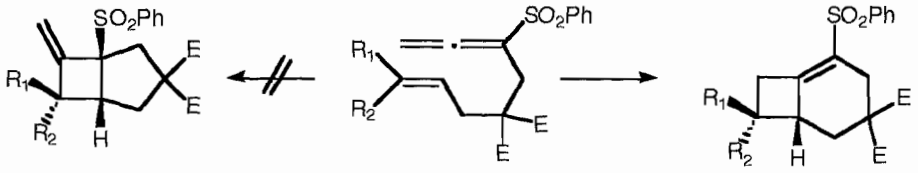
(i) 235 °C, Neat (ii) NaOH (100 %) (iii) 2 equiv. MeLi, 0 °C then H_2O

Scheme 3

Base-catalysed hydrolysis of ester **8** quantitatively afforded the acid **6**, which was treated with two equivalents of MeLi at 0 °C to give 88% yield of ketone **3** as a 7:3 mixture of the *cis* and *trans* isomers, respectively. Thus, the desired ketone

became available in 82% overall yield from ester **7**. This is, indeed, a significant improvement both in the yield and stereoselectivity (in favour of the desired *cis* isomer) of ketone **3**. It is worthwhile to recall that previously (Mdachi, 1995, Birkenes *et al.*, 1998) an overall yield of 35% of ketone **3** was achieved as a 3:7 mixture of the *cis* and *trans* isomers, respectively. Thus, besides the low yield, even the stereochemistry of the product was biased towards the undesired *trans* isomer.

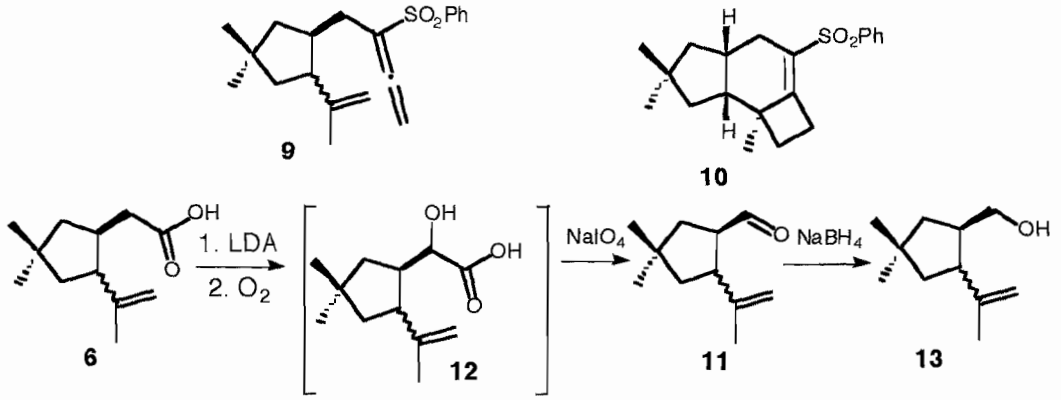
Having accomplished the preparation of the desired ketone **3** from the acid **6**, attention was then focused on strategies of synthetically transforming the latter compound into other *gem*-dimethyl-substituted cyclopentane derivatives, which are potential intermediates towards assembling the protoilludane skeleton. Padwa *et al.* (1993) have reported the thermally induced rearrangement of phenylsulphonyl-substituted allenes to cycloadducts corresponding to bicyclo[4.2.0]octene as sole products (Scheme 4).



$E = SO_2Ph$ or CO_2Me
$R_1, R_2 = H$ or Me

Scheme 4

Accordingly, the study of a thermally induced [2+2] ene-allene cycloaddition of derivative **9** was conceived, anticipating the formation of compound **10**, which consists of the 4/5/6 tricyclic ring system present in several protoilludanes (Scheme 5).



Scheme 5

In order to transform the acid **6** (prepared according to Scheme 3) to compound **9**, which is the immediate precursor of the target compound **10**, a synthetic route (Scheme 5) was designed. Even though the synthetic strategy towards compound **9** was not executed to its completion in the present study, the success obtained in the initial steps of this synthetic route are worth reporting. The first objective in this strategy was to prepare aldehyde **11** from the carboxylic acid **6** *via* intermediate **12**. LDA mediated a-hydroxylation of **6** followed by sodium metaperiodate cleavage (Andelic *et al.*, 1985) gave the desired aldehyde **11** in 34% overall yield. The aldehyde was obtained as a 7:3 mixture of the *cis* and *trans* isomers, respectively. Treatment of the aldehyde **11** with $NaBH_4$ in methanol afforded the alcohol **13** (96%), again as a 7:3 mixture of the *cis* and *trans* isomers, respectively.

CONCLUSION

The paper reports on the significant improvement in the yield and stereoselectivity (in favour of the *cis* isomer) of 1-(2-propionyl)-4,4-dimethyl-2-isopropenylcyclopentane (**3**), which is a key intermediate towards assembling the 4/5/6 tricyclic ring system present in several protoilludane and sterpurane sesquiterpenes. Even though the synthetic strategy towards the preparation of compound **9** was not executed to its completion in the present study, the preliminary results obtained thus far give a strong motivation for future follow-up of this synthetic strategy towards the protoilludane skeleton.

EXPERIMENTAL

General Procedures

NMR spectra were recorded on a Varian Gemini 200 instrument using $CDCl_3$ as the solvent and TMS as an internal standard at 200 MHz (^1H NMR) and 50 MHz. (^{13}C NMR). IR spectra were recorded on either a Perkin-Elmer Paragon 500 FT spectrophotometer or a Magna-IR 550 instrument. MS spectra were measured on a GC-MS JEOL DX-303 spectrometer with direct inlet at 70 eV. For analytical GLC a 25 m SP2100 capillary column was used.

1-(2-Propionyl)-4,4-dimethyl-2-isopropenylcyclopentane (**3**). A solution of MeLi in Et_2O (10.25 ml of 1.6 M, 16.40 mmol) was added dropwise to a solution of the acid **6** (1.61 g, 8.20 mmol) in dry Et_2O (100 ml) kept at 0 °C under an argon atmosphere and stirred for 20 min. after addition of MeLi and then 50 ml of saturated NH_4Cl was added to quench the reaction. The aqueous phase was extracted with Et_2O (3 x 25 ml) and the combined organic solution washed with 10% $NaHCO_3$ (20 ml), brine (20 ml) and dried ($MgSO_4$). Evaporation of the solvent left an oil, which was purified by column chromatography (silica gel, pet. ether/EtOAc, 95:5 v/v) to afford 1.32 g (88%) of ketone **3**. MS: *m/z* (% rel. int.) 194 (M^+, 10), 179 (21), 161 (13), 151 (22), 137 (19), 136 (28), 125 (8), 121 (63), 110 (18), 109 (18), 107 (12), 105 (10), 95 (41), 93 (15), 83 (11), 81 (11), 79 (11), 69 (14), 67 (14), 55 (23), 53 (11), 43 (100), 41 (32). ^1H NMR (200 MHz, $CDCl_3$): d 0.98 (s, 3 H major isomer), 0.99 (s, 3 H), 1.02 (s, 3 H), 1.06 (s, 3 H major isomer), 1.20 (m, 2 H), 1.35-1.60 (m, 3 H), 1.63 (s, 3 H), 1.67 (s, 3 H major isomer), 1.76 (m, 2 H), 2.07 (s, 3 H major isomer), 2.08 (s, 3 H), 2.09-2.40 (m, 5 H), 2.50-2.69 (m, 4 H), 4.62 (s, 1 H), 4.69 (s, 2 H), 4.78 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): d 19.59, 23.92, 31.13, 31.51, 31.95, 32.13, 32.33, 37.02, 37.54, 38.95, 44.07, 46.00, 46.90, 47.64, 48.36, 49.00, 49.14, 54.59, 111.35, 111.53, 146.17, 146.55, 209.14. IR (film): 3082 (w), 2953 (s), 2874 (m), 1720 (s), 1648 (w), 1368 (m), 895 (m) cm^{-1}.

2-Isopropenyl-4,4-dimethylcyclopentanecarboxyaldehyde (**11**). (a) LDA mediated a-hydroxylation of

carboxylic acid **6**: A solution of the acid **6** (3.23 g, 16.5 mmol) in dry THF (20 ml) was added to LDA (*ca* 40 mmol) at 0 °C. The latter was prepared by dropwise addition of MeLi (25.2 ml of 1.6 M Et_2O solution, 40.3 mmol) to di*iso*propylamine (5.75 ml, 40.6 mmol) dissolved in THF (100 ml) at 0 °C under a N_2 atmosphere. HMPTA (7 ml, 39.8 mmol) was added after 15 min. since complete addition of the acid to LDA. The reaction mixture was stirred for 6 h at room temperature, then cooled to 0 °C and oxygen bubbled-in for 1 h. The reaction mixture was poured in water (300 ml), acidified, extracted with Et_2O and dried ($MgSO_4$). Evaporation of the solvent gave 3.48 g of crude a-hydroxylated acid as a viscous oil. IR (film): 3500-3000 (s), 2910 (s), 1720 (s), 1630 (m), 1440 (s), 880 (m) cm^{-1}.

(b) Sodium metaperiodate mediated cleavage of the crude a-hydroxyl acid **12**: The crude material obtained above and $NaIO_4$ (5.1 g, 24 mmol) were mixed together with 70 ml of acetone-acetic acid-water (40:20:10 v/v) and stirred at 45 °C for 20 h. The reaction mixture was poured in water (200 ml) and extracted with ether. The organic phase was washed with saturated $NaHCO_3$ (aq.) and dried ($MgSO_4$). Evaporation of the solvent left an oil which was purified by column chromatography (silica gel, 19:1 v/v pet. ether/EtOAc) to give 0.915 g (34%) of the aldehyde **11** as a 7:3 mixture of the *cis* and *trans* isomers, respectively. MS: *m/z* (% rel. int.) 166 (M^+, 9), 151 (5), 138 (8), 137 (44), 123 (34), 111 (10), 110 (14), 109 (13), 107 (10), 97 (16), 96 (14), 95 (64), 93 (9), 91 (10), 83 (14), 82 (16), 81 (33), 79 (14), 77 (11), 70 (100), 69 (44), 67 (28), 57 (10), 55 (32), 53 (18), 43 (19), 41 (63), 39 (26), 29 (18), 27 (19). ^1H NMR (200 MHz, $CDCl_3$): d 1.00 (s, 3 H), 1.06 (s, 3 H), 1.13 (s, 3 H), 1.40-1.86 (multiplets, 8 H), 1.70 (3, 3 H minor isomer), 1.75 (s, 3 H major isomer), 2.80 (m, 2 H), 2.95 (m, 2 H), 4.74 (d, *J* 7 Hz, 2 H minor isomer), 4.81 (d, *J* 7 Hz, 2 H major isomer), 9.51 (d, *J* 3 Hz, 1 H major isomer), 9.53 (d, *J* 3 Hz, 1 H minor isomer). ^{13}C NMR (50 MHz, $CDCl_3$): d 21.03, 23.35, 29.83, 30.44, 30.56, 37.96 (quart. C, major), 38.47 (quart. C, minor), 40.53 (CH_2, major), 41.62 (CH_2, minor), 44.80 (CH_2, major), 46.88 (CH_2, minor), 47.99 (CH, minor), 48.25 (CH, major), 52.92 (CH, major), 55.85 (CH, minor), 110.90 (=CH_2, minor), 111.83 (=CH_2, major), 143.43 (quart. =C, major), 145.68 (quart. =C, minor), 203.98 (HC=O, minor), 204.50 (HC=O, major). IR (film): 3089 (w), 2955 (s), 2867 (m), 2727 (w), 1724 (s), 1648 (w), 1463 (w), 1446 (w), 896 (m) cm^{-1}.

1-Hydroxymethyl-2-isopropenyl-4,4-dimethylcyclopentane (**13**). To a solution of the aldehyde **11** (0.856 g, 5.12 mmol) in methanol (35 ml) was added 0.15 ml water containing $NaBH_4$ (0.223 g, 5.89 mmol) and NaOH (0.062 g, 1.55 mmol). The mixture was stirred for 20 h at room temperature under a nitrogen atmosphere. The reaction mixture was diluted with Et_2O (150 ml) and poured in water (100 ml). Solid NaCl was added and the aqueous phase extracted with Et_2O. The combined organic phase was washed with 1% HCl aq., 5% $NaHCO_3$ aq., brine and dried ($MgSO_4$). Evaporation of the solvent left 0.824 g (96%) of the alcohol **13** which was > 99% pure according to GLC. MS: *m/z* (% rel. int.) 168 (M^+, 3), 153 (11), 138 (12), 137 (100), 135 (29), 121 (8), 111 (10), 109 (8), 107 (27), 95 (40), 93 (20), 91 (8), 81 (23), 79 (27), 69 (23), 67 (16), 57 (11), 55 (21), 53 (11), 43 (19), 41 (32), 39 (12), 29 (10), 27 (8). ^1H NMR (200 MHz, $CDCl_3$): d 0.99 (s, 3 H), 1.02 (s, 3 H), 1.03 (s, 3 H), 1.09 (s, 3 H), 1.16-1.47 (multiplets, 4 H), 1.41 (s, 1 H), 1.54-1.69 (multiplets, 4 H), 1.62 (s, 1 H), 1.70 (s, 3 H minor isomer), 1.81 (s, 3 H major isomer), 2.15 (m, 1 H), 2.39 (m, 2 H), 2.72 (m, 1 H), 3.31 (m, 1 H), 3.49 (m, 2 H), 3.59 (m, 1 H), 4.76 (d, *J* 12 Hz, 2 H minor isomer), 4.78 (d, *J* 12 Hz, 2 H major isomer). ^{13}C NMR (50 MHz, $CDCl_3$): d 18.70 (CH_3), 23.20 (CH_3),

29.70 (CH_3), 30.37 (CH_3), 30.51 (CH_3), 30.59 (CH_3), 35.92 (quart. C, major), 36.08 (quart. C, minor), 43.69 (CH, major), 44.08 (CH_2, major), 44.20 (CH_2, major), 44.93 (CH_2, minor), 45.46 (CH, minor), 47.38 (CH_2, minor), 47.80 (CH, major), 51.35 (CH, minor), 64.93 (CH_2-O, minor), 67.25 (CH_2-O, major), 110.53 (=CH_2, major), 110.94 (=CH_2, minor), 145.84 (quart. =C, major), 146.80 (quart. =C, minor). IR (film): 3342 (s), 3086 (m), 2948 (s), 2860 (s), 1644 (m), 1464 (s), 1373 (s), 1034 (s), 889 (s) cm^{-1}.

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