Stereocontrolled synthesis of (±)-α-pinguisene and (±)-pinguisenol

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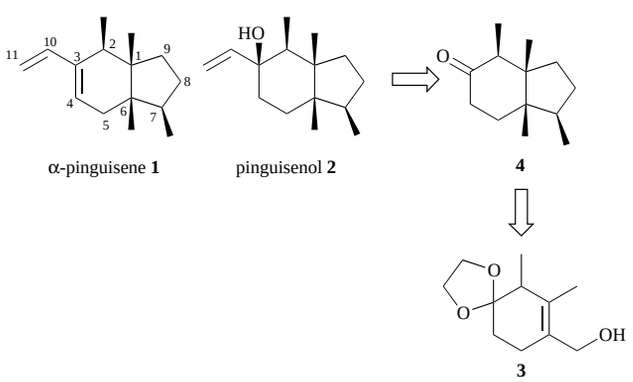
1 PERKIN COMMUNICATION

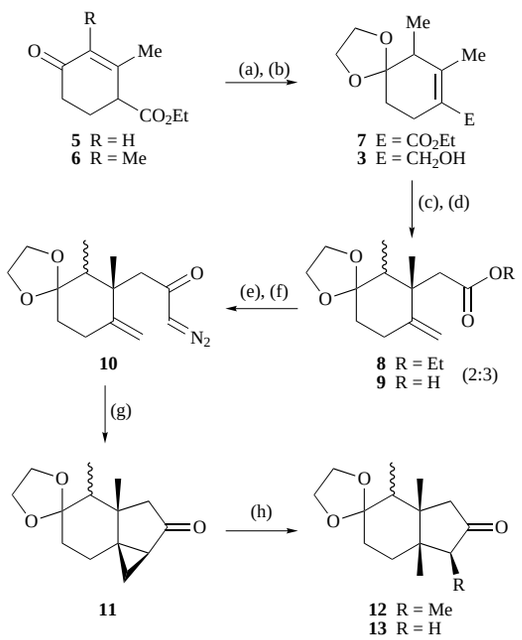
Total synthesis of (±)-α-pinguisene 1 and (±)-pinguisenol 2, employing an orthoester Claisen rearrangement and an intramolecular diazo ketone cyclopropanation reaction for the stereospecific construction of vicinal quaternary carbon atoms, is described.

The sesquiterpenes α-pinguisene **1** and pinguisenol **2** were isolated from the liverworts, *Porella vernicosa* and its complex (*P. macroloba* and *P. gracillima*) which show some interesting biological activities, such as allergenic contact dermatitis, anticancer, antimicrobial and antifeedant activities, along with several other pinguisanes.[1] The interesting carbon skeleton, 1,2,6,7-tetramethylbicyclo[4.3.0]nonane, incorporating two vicinal quaternary centres and four methyl groups attached to four contiguous carbon atoms in an all-*cis* fashion, makes the pinguisanes challenging synthetic targets.[2] Recently Schinzer and co-workers have reported the first total synthesis of α-pinguisene and pinguisenol based on propargylsilane-terminated cyclisation of an enone.[2] Herein, we report a stereocontrolled synthesis of **1** and **2** starting from Hagemann's ester *via* the allyl alcohol **3** and the bicyclic ketone **4**.



α-pinguisene **1** pinguisenol **2** **4** **3**

The synthetic sequence starting from Hagemann's ester **5** is depicted in Schemes 1 and 2. The two quaternary carbon centres were stereoselectively created using a combination of Claisen rearrangement and intramolecular diazo ketone cyclopropanation reactions. The requisite starting material, allyl alcohol **3**, for the projected Claisen rearrangement was obtained from Hagemann's ester. Thus, generation of the dienolate of **5** and low temperature alkylation furnished the γ-methylated product **6**. Simultaneous protection of the ketone and isomerisation of the olefin in **6** was achieved using the standard ketalisation conditions to generate the α,β-unsaturated ester **7**, which on reduction with lithium aluminium hydride furnished the allyl alcohol **3**. The first quaternary carbon was created using an orthoester variant of the Claisen rearrangement. Thus, thermal activation of the allyl alcohol **3** and triethyl orthoacetate in the presence of a catalytic amount of propionic acid furnished the ene ester **8**, which on hydrolysis with methanolic sodium hydroxide yielded the ene acid **9**. The formation of two isomers in the Claisen rearrangement has no significance as they can be equilibrated at a later stage. Anhydrous copper sulfate–copper[3] catalysed decomposition of



5 R = H
6 R = Me

7 E = CO_2Et
3 E = CH_2OH

10

8 R = Et
9 R = H (2:3)

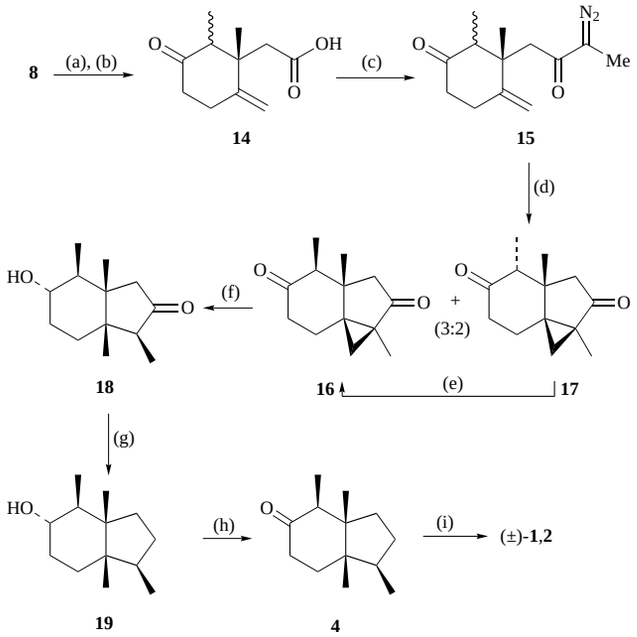
11

12 R = Me
13 R = H

Scheme 1 *Reagents conditions:* (a) NaH, MeI, −50 °C, 95%; (b) $(CH_2OH)_2$, toluene-*p*-sulfonic acid (*p*-TSA), C_6H_6, 48 h; 52%; (c) $LiAlH_4$, Et_2O, −70 °C, 97%; (d) $MeC(OEt)_3$, $EtCO_2H$ (cat.), 180 °C, 48 h, 75%; (e) 10% NaOH, MeOH, 4 h, reflux, 92%; (f) $(COCl)_2$, C_6H_6, room temp., 2 h; CH_2N_2, Et_2O, 0 °C, 2 h; (g) Cu, $CuSO_4$, cyclohexane, reflux, 3 h; 33% from **9**; (h) Li, liq. NH_3; MeI (excess), 45 min, 84%

the diazo ketone **10**, obtained from the acid **9** *via* the acid chloride, in refluxing cyclohexane furnished, stereospecifically, a 3:2 mixture of the tricyclic keto ketal **11**. Reductive cleavage of the cyclopropane ring using lithium in liquid ammonia followed by alkylation of the intermediate enolate with methyl iodide was attempted for the introduction of the fourth methyl group to generate the keto ketal **12**. However, the alkylation step was unsuccessful and only the keto ketal **13** was obtained. Hence, it was decided to introduce the methyl group at an early stage and diazoethane was opted for in the place of diazomethane.

Thus, hydrolysis of the ketal moiety in **8** followed by ester hydrolysis furnished the keto acid **14**, which was transformed into diazo ketone **15**. Copper–copper sulfate catalysed[3] intramolecular cyclopropanation of the diazo ketone **15** followed by chromatography on silica gel furnished the tricyclic ketones **16** and **17** in a 3:2 ratio. The *sec*-methyl group was assigned as equatorial in the major compound **16**, which was further confirmed by the equilibration of the minor isomer **17** into the thermodynamically more stable major isomer **16**. Simultaneous reductive cleavage of the cyclopropane ring and reduction of the ketone in the six-membered ring (thereby differentiating the two ketone functionalities as well as avoiding the equilibration of the C-2 *sec*-methyl)[4] was achieved using lithium in liquid ammonia to stereoselectively transform the diketone **16** into the keto alcohol **18**. It is interesting to note the generation of the required stereochemistry at C-7 which may be the consequence of base catalysed equilibration during work-up. Modified Wolff–Kishner reduction of the keto alcohol **18** followed by



Scheme 2 *Reagents conditions:* (a) 3 M HCl, THF, 2 h, 98%; (b) 10% NaOH, MeOH, reflux, 4 h, 90%; (c) $(COCl)_2$, C_6H_6, room temp., 2 h; $MeCHN_2$, Et_2O, 0 °C, 2 h; (d) Cu, $CuSO_4$, cyclohexane, reflux, 1.5 h; 24% from **14**; (e) K_2CO_3, MeOH, room temp., 48 h, 86%; (f) Li, liq. NH_3, THF, 67%; (g) NH_2NH_2, diethylene glycol, $(CH_2OH)_2$, 180 °C, 2 h; Na, 4 h; (h) PCC, CH_2Cl_2, 2 h; 68% from **18**; (i) ref. 2

pyridinium chlorochromate (PCC) oxidation of the resulting alcohol **19** furnished the bicyclic ketone **4**, which exhibited spectral data (IR, 400 MHz ^{1}H NMR, ^{13}C NMR and mass) identical to that of the authentic sample. Since Schinzer and co-workers[2] have transformed the ketone **4** into pinguisenol (by addition of vinyl Grignard reagent) and α-pinguisene (*via* Pd catalysed coupling of the enol triflate with vinyltrialkylstanane), the present sequence constitutes a formal synthesis of **1** and **2**. Currently, we are investigating the extension of this methodology for the chiral synthesis of **1** and **2**.

Experimental

3α,6β,7β- and 3α,6β,7α-Trimethyltricyclo[4.4.0.0^{1,3}]decane-4,8-diones (16 and 17)

To a magnetically stirred solution of the acid (1.2 g, 6.12 mmol) in dry benzene (6 ml) was added oxalyl chloride (2.6 ml, 30.6 mmol). The reaction mixture was stirred for 2 h at room temperature, concentrated under reduced pressure to afford the acid chloride and then was used without further purification. To an ice-cold magnetically stirred solution of ethereal diazoethane (0.12 mol in 125 ml of diethyl ether, prepared from *N*-nitrosoethylurea) was added, dropwise, a solution of the acid chloride obtained above in anhydrous diethyl ether (5 ml) and the resulting solution was stirred for 2 h at ice temperature. The excess diazoethane and diethyl ether were removed by careful evaporation on a water bath and the residue was rapidly filtered through a short silica gel column using 1 : 5 ethyl acetate and hexane as eluent, to furnish the diazo ketone **15** as a yellow oil. [ν_{max}(neat)/cm^{-1} 3095, 2100, 1710, 1640, 900]. A mixture of copper (1.9 g, 29.9 mmol) and anhydrous $CuSO_4$ (480 mg, 3 mmol) was added to a magnetically stirred solution of the diazo ketone **15** in 100 ml of anhydrous cyclohexane under a blanket of nitrogen and refluxed for 1.5 h. After the completion of the reaction, the solids were filtered off and the solvent was evaporated under reduced pressure. Purification of the residue on a silica gel column using ethyl acetate and hexane (1 : 20 ⟶ 1 : 5) as eluent furnished the two diketones **16** (180 mg, 14.2% from the acid **14**) and **17** (122 mg, 9.7% from the acid **14**). For the diketone **16**: ν_{max}(neat)/cm^{-1} 1715; δ_H(400 MHz, $CDCl_3$) 0.84 (1 H, dd, *J* 5 and 1 †) and 1.39 (1 H, d, *J* 5) [H-2], 0.97 (3 H, d, *J* 6.5, *sec*-Me), 0.98 (3 H, s) and 1.34 (3 H, s) [2 × *tert*-Me], 1.99 (1 H, d, *J* 17.5) and 2.07 (1 H, d, *J* 17.5) [H-5], 2.23 (1 H, q, *J* 6.5, H-7), 1.60–1.72 (1 H, m) and 2.28–2.48 (3 H, m) [H-9 and 10]; δ_C(22.5 MHz, $CDCl_3$) 213.3, 210.8, 52.0, 46.4, 45.0, 42.8, 40.7, 38.2, 27.0, 25.1, 16.6, 10.2, 8.7; *m*/*z* 206 (M^+, 20%), 135 (20), 121 (10), 107 (20), 69 (100) (HRMS: found M^+, 206.1316. $C_{13}H_{18}O_2$ requires M, 206.1307). For the diketone **17**: ν_{max}(neat)/cm^{-1} 1715; δ_H(400 MHz, $CDCl_3$) 0.72 (1 H, d, *J* 5) and 1.19 (1 H, d, *J* 5) [H-2], 1.03 (3 H, d, *J* 7.5, *sec*-Me), 1.18 (3 H, s) and 1.31 (3 H, s) [2 × *tert*-Me], 1.97 (1 H, d, *J* 18) and 2.02 (1 H, d, *J* 18) [H-5], 1.64 (1 H, dd, *J* 13.5, 7, H-10$_{eq}$), 2.37 (1 H, q, *J* 7.5, H-7), 2.45 (1 H, ddd, *J* 13.5, 13.5 and 5.5, H-10$_{ax}$), 2.25 (1 H, dd, *J* 14 and 5.5, H-9$_{eq}$), 2.57 (1 H, ddd, *J* 14, 13.5 and 7, H-9$_{ax}$); δ_C(22.5 MHz, $CDCl_3$) 213.7 (2C), 54.7, 43.9, 43.2, 39.2, 38.2, 35.9, 25.3, 23.3, 22.9, 13.5, 10.6; *m*/*z* 206 (M^+, 26%), 135 (18), 121 (10), 107 (20), 69 (100) (HRMS: found M^+, 206.1310. $C_{13}H_{18}O_2$ requires *M*, 206.1307).

† *J* Values are given in Hz.

Acknowledgements

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References

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2 So far there is only one approach reported for α-pinguisene **1** and pinguisenol **2**, see: D. Schinzer, K. Ringe, P. G. Jones and D. Döring, *Tetrahedron Lett.*, 1995, **36**, 4051; D. Schinzer and K. Ringe, *Tetrahedron*, 1996, **52**, 7475. The authors referred to α-pinguisene as β-pinguisene. For the synthesis of pinguisone and its derivatives see, S. Bernasconi, P. Gariboldi, G. Jommi, S. Montanari and M. Sisti, *J. Chem. Soc.*, *Perkin Trans. 1*, 1981, 2394; T. Uyehara, Y. Kabasawa and T. Kato, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2521; R. Baker, D. L. Selwood, C. J. Swain, N. M. H. Webster and J. Hirshfield, *J. Chem. Soc.*, *Perkin Trans. 1*, 1988, 471 and references cited therein.

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4 It is worth noting that as per the molecular mechanics calculations, unlike in the diketone **16**, in 1,2,6,7-tetramethylbicyclo[4.3.0]nonan-3,8-diones the 1β,2α,6β,7α-isomer is more stable than the 1β,2β,6β,7β-isomer.

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