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Stereocontrolled total synthesis of (±)-pisiferol and (±)-pisiferal

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Abstract—The stereoselective total synthesis of (±)-pisiferol (**1**) and (±)-pisiferal (**2**) has been successfully accomplished using the *trans*-octahydrophenanthrene derivative **20** as a key intermediate. Intramolecular cyclisation of the diazoketone **15** followed by catalytic hydrogenation provided, stereoselectively, the keto-ester **17** which was converted into the acetate **20** through the intermediates **18** and **19**.

The tricyclic diterpenes (+)-pisiferol (**1**) and (+)-pisiferal (**2**) were isolated[1,2] from the leaves of *Chamaecyparis pisifera* along with several closely related diterpenes and incorporate a *trans*-fused octahydrophenanthrene ring system as the basic carbocyclic framework. Strong antifungal activity of the diterpenes **1** and **2** against the rice blast fungus *Pyricularia oryzae* was reported by Tomita and co-workers.[3] Also, the diterpenes have been reported[4,5] to possess antimite, antioxidative, antibacterial and antitumour activities and have been used in pharmaceuticals and cosmetics for controlling acne and dandruff, for treatment of skin disorders and as deodorants. Widespread interest in pisiferol is reflected in the number of diverse synthetic approaches reported[6–11] in the literature over the last two decades. The total synthesis of the diterpenes **1** and **2** is associated with the difficulty in the generation of an oxygenated methyl group as an angular substituent and an appropriately substituted aromatic C ring in the *trans*-octahydrophenanthrene nucleus. Earlier methodologies for the synthesis of these diterpenes most commonly employed transannular oxidation of the angular methyl group[6,7] or Robinson annulation[8,9] of an appropriate Wieland-Miescher ketone as key reactions. Kametani et al. accomplished[10] the synthesis of pisiferol methyl ether **3** involving thermolysis of the olefinic benzocyclobutene **4** as the key step. Thermolysis of **4** proceeded through intramolecular Diels–Alder reaction of an *o*-quinodimethane to generate the angularly cyano substituted octahydrophenanthrenes **6** and **8** (Fig. 1) in the ratio of 1:4. Recently, Bush and Jones achieved[11] an improved synthesis of **6** using thermolysis of the benzocyclobutene **5** which provided **7** and **9** in the ratio of 1.5:1. The transformation of **7** into **6** was carried out in a straightforward manner. The transformation of pisiferol methyl ether **3** into the diterpene pisiferin (**10**) (Fig. 1) through skeletal rearrangement was reported by Kametani et al.[10]

Starting from the easily accessible tetrahydrophenanthrene **11**,[12] we report herein a stereoselective synthesis of the diterpenes **1** and **2** in racemic form employing an aryl participating diazoketone cyclisation[13] strategy to generate intermediate hydrophenanthrene derivatives suitable for the synthesis. 1,1-Dimethyl-6,9-dimethoxy-1,2,3,4-tetrahydrophenanthrene (**11**), easily prepared[12] from commercially available 1,6-dihydroxynaphthalene, was used as the starting material for the synthesis of the diterpenes **1** and **2** as shown in Scheme 1. Oxidation of **11** with pyridinium chlorochromate furnished the ketone **12** in 85% yield. The ketone was condensed with ethyl formate in the presence of sodium hydride and the resulting crude hydroxymethylene derivative was treated[14] with alkaline hydrogen peroxide followed by CH_2N_2 to afford the diester **13**[15] in 82% overall yield. Partial hydrolysis of the diester under controlled conditions yielded the acid–ester **14** (87%). Reaction of **14** with ethyl chloroformate in the presence of Et_3N followed by treatment of the resulting mixed anhydride with CH_2N_2 provided the diazomethyl ketone **15** in 90% yield. On treatment with trifluoroacetic acid in CH_2Cl_2 at −20 °C for a brief period, the diazoketone underwent intramolecular cyclisation to provide the enedione **16**[16] in 64% yield which on catalytic hydrogenation yielded the

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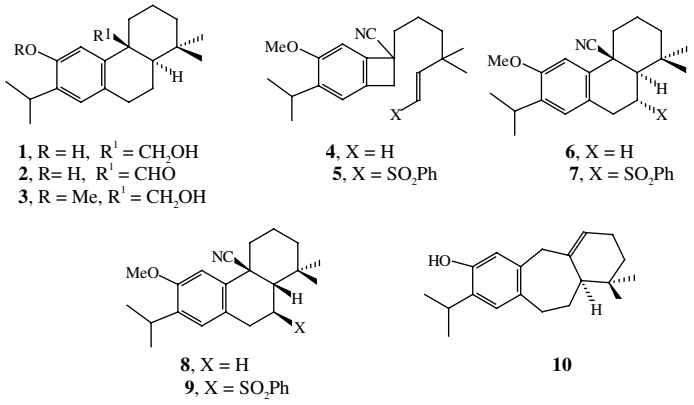


1, R = H, $R^1 = CH_2OH$
2, R= H, $R^1 = CHO$
3, R = Me, $R^1 = CH_2OH$

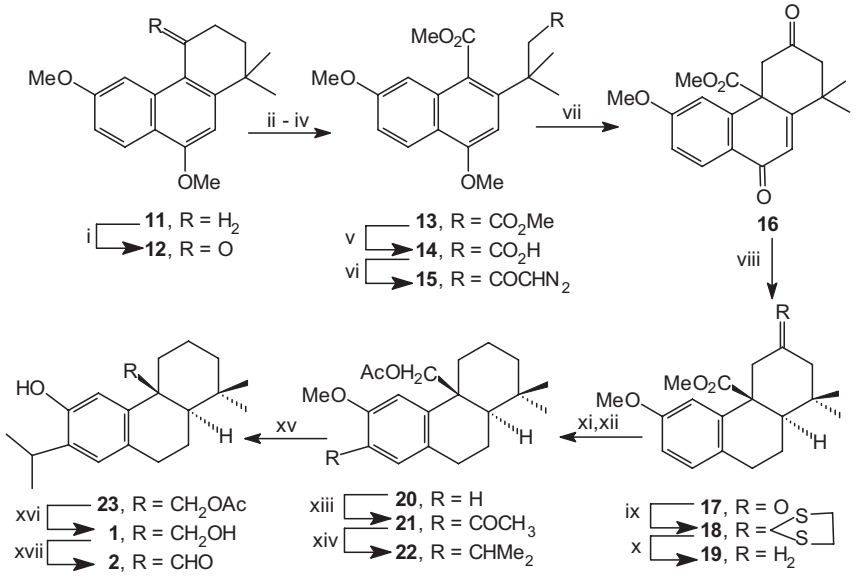
4, X = H
5, X = SO_2Ph

6, X = H
7, X = SO_2Ph

8, X = H
9, X = SO_2Ph

10

Figure 1.



Scheme 1. Reagents and conditions: (i) PCC, CH_2Cl_2, rt, 85%; (ii) NaH, HCO_2Et, C_6H_6, 0 °C to rt; (iii) aq NaOH, H_2O_2, 0 °C to rt, H_3O^+, 85%; (iv) CH_2N_2, Et_2O, 0 °C, 97%; (v) KOH, H_2O, THF, rt, 24 h, 60 °C, 1 h, H_3O^+, 87%; (vi) $ClCO_2Et$, Et_3N, Et_2O, THF, −10 °C, 1 h then CH_2N_2, Et_2O, 0 °C to rt, 16 h, 90%; (vii) TFA, CH_2Cl_2, −20 °C, 3 min, 64%; (viii) H_2, 10% Pd–C, EtOAc, 93%; (ix) $HSCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, MeOH, rt, 90%; (x) Raney nickel, EtOH, reflux, 85%; (xi) $LiAlH_4$, THF, reflux, 95%; (xii) Ac_2O, C_5H_5N, 70 °C, 86%; (xiii) AcCl, $AlCl_3$, CH_2Cl_2, 0 °C to rt, H_3O^+, 84%; (xiv) MeMgI, Et_2O, reflux, aq NH_4Cl then Ac_2O, C_5H_5N, 70 °C; H_2, 10% Pd–C, AcOH, $HClO_4$ (trace), 78%; (xv) $AlCl_3$, EtSH, rt, 75%; (xvi) $LiAlH_4$, THF, rt, 87%; (xvii) Jones' reagent, Me_2CO, 0 °C, 1 min, 48%.

trans-fused keto-ester **17** as the sole product (93%). The assignment of *trans* stereochemistry to **17** was confirmed by single crystal X-ray crystallography (Fig. 2) as well as by subsequent transformation of **17** into the diterpenes **1** and **2** possessing *trans*-stereochemistry at the A/B ring junction.

In order to remove the carbonyl group from the ring A, **17** was converted into the corresponding ethylene thioacetal **18** (90%) which on desulfurisation with Raney nickel furnished the ester **19** [16] in 85% yield. Reduction of **19** with $LiAlH_4$ followed by acetylation of the resulting primary alcohol provided the acetate **20** (82%) which on treatment with CH_3COCl in the presence of anhydrous $AlCl_3$ afforded the methyl ketone **21**[16] in 84% yield. Reaction of **21** with MeMgI followed by treatment of the crude product with Ac_2O and subsequent

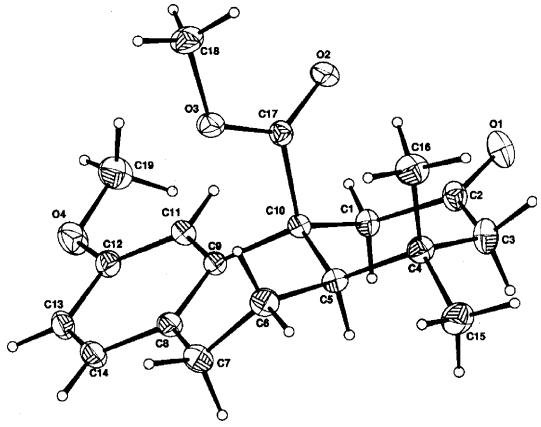


Figure 2. Single crystal X-ray structure of the keto-ester **17** (an ORTEP drawing).

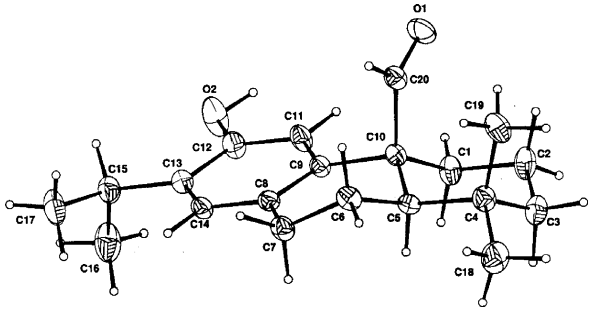


Figure 3. Single crystal X-ray structure of synthetic pisiferal **2** (an ORTEP drawing).

hydrogenation in the presence of a catalytic amount of $HClO_4$ furnished the acetate **22**[16] (78%). Fujita and co-workers reported[17] that a combination of aluminium halide and ethanethiol is very effective for demethylation of methyl ethers of phenols whilst acetoxy groups are stable to this reagent system. Demethylation of **22** with anhydrous $AlCl_3$ and EtSH afforded the phenol **23** (75%) which on reduction with $LiAlH_4$ furnished (±)-pisiferol (**1**)[16] in 87% yield. The phenol **23** exhibits significant antitumour activity and inhibits[5] the growth of human cervix uteri HeLa cells. Treatment of **1** with Jones' reagent at 0 °C for a brief period provided (±)-pisiferal (**2**)[16] (48%). The identity of synthetic **2** was secured through single crystal X-ray crystallography (Fig. 3). Also, the spectral data of **1** and **2** agreed very well with those reported in the literature.

In conclusion, a stereocontrolled synthesis of the abietane-type tricyclic diterpenes (±)-pisiferol and (±)-pisiferal has been accomplished involving aryl participated intramolecular cyclisation of an appropriately substituted diazomethyl ketone as a key reaction.

Acknowledgements

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16. Selected spectral data for the enedione **16**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (s, 3H), 1.37 (s, 3H), 2.34, 2.54 (AB_q, 2H, J = 15.7 Hz), 2.34, 3.80 (AB_q, 2H, J = 18 Hz), 3.63 (s, 3H), 3.88 (s, 3H), 6.71 (s, 1H), 6.94 (d, 1H, J = 2.4 Hz), 7.02 (dd, 1H, J = 8.7, 2.4 Hz), 8.17 (d, 1H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.5, 32.2, 38.1, 46.5, 51.7, 51.8, 53.6, 55.6, 110.3, 114.9, 123.7, 127.7, 129.1, 143.1, 162.4, 163.5, 171.8, 183.5, 206.2. For the ester **19**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.77 (s, 3H), 0.96 (s, 3H), 1.18–1.31 (m, 2H), 1.43–1.52 (m, 2H), 1.58–1.66 (m, 1H), 1.87–2.05 (m, 2H), 2.37–2.55 (m, 1H), 2.80–2.96 (m, 3H), 3.54 (s, 3H), 3.73 (s, 3H), 6.69 (dd, 1H, J = 8.4, 2.6 Hz), 6.84 (d, 1H, J = 2.6 Hz), 7.00 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.6, 20.0, 20.3, 29.2, 32.0, 33.9, 37.0, 41.7, 48.0, 51.5, 52.2, 55.1, 110.9, 112.4, 129.0, 130.3, 141.5, 157.4, 175.7. For the methyl ketone **21**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.98 (s, 6H), 1.25–1.84 (m, 8H), 1.93 (s, 3H), 2.54–2.60 (m, 1H), 2.59 (s, 3H), 2.81–3.00 (m, 2H), 3.88 (s, 3H), 4.16, 4.54 (AB_q, 2H, J = 11 Hz), 6.88 (s, 1H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.2, 18.7, 20.9, 22.2, 28.1, 31.7, 33.1, 33.4, 33.5, 41.1, 41.2, 50.0, 55.4, 65.5, 109.9, 126.0, 128.1, 130.7, 150.1, 156.0, 170.5, 199.4. For the acetate **22**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (s, 6H), 1.18 and 1.19 (2 d, 2 × 3H, J = 7.0 Hz each), 1.24–1.93 (m, 8H), 1.92 (s, 3H), 2.53–2.57 (m, 1H), 2.83–2.94 (m, 2H), 3.22 (sept, 1H, J = 7.0 Hz), 3.79 (s, 3H), 4.14, 4.55 (AB_q, 2H, J = 10.8 Hz), 6.76 (s, 1H), 6.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.6, 18.9, 21.0, 22.3, 22.6, 22.8, 26.4, 28.8, 33.3, 33.4, 33.6, 40.5, 41.5, 50.5, 55.5, 66.1, 109.2, 126.4, 127.5, 134.9, 142.0, 154.0, 170.8. For pisiferol **1**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (s, 3H), 0.94 (s, 3H), 1.22 (d, 6H, J = 6.9 Hz), 1.14–1.90 (m, 8H), 2.46–2.50 (m, 1H), 2.80–2.96 (m, 2H), 3.19 (sept, 1H, J = 6.9 Hz), 3.62, 3.99 (AB_q, 2H, J = 11 Hz), 6.65 (s, 1H), 6.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.4, 18.8, 22.3, 22.5, 22.7, 26.7, 28.7, 32.7, 33.2, 33.4, 41.6, 42.3, 50.1, 63.8, 112.8, 127.4, 127.7, 133.0, 141.3, 150.8. For pisiferal **2**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.82 (s, 3H), 1.00 (s, 3H), 1.22 (d, 6H, J = 6.9 Hz), 1.13–1.72 (m, 6H),2.00–2.14 (m, 2H), 2.83–2.99 (m, 3H), 3.14 (sept, 1H, J = 6.9 Hz), 4.83 (br s, 1H), 6.56 (s, 1H), 6.92 (s, 1H), 9.89 (d, 1H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.3, 19.6, 20.6, 22.4, 22.5, 26.9, 30.1, 31.5, 32.6, 33.9, 41.3, 51.7, 53.1, 113.8, 127.2, 130.4, 133.4, 134.2, 151.6, 200.9.
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