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The first route toward oxygenated monocarbocyclic terpenoids: synthesis of elegansidiol, a new sesquiterpene from *Santolina elegans*

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Abstract

This paper describes the isolation of elegansidiol (**1**), a new monocyclic sesquiterpenic alcohol, together with the known monocyclic triterpene achilleol A (**2**), both from *Santolina elegans*. The structure of **1** was confirmed by synthesis starting from 6,7-epoxygeranyl acetate (**6**), constituting the first route towards this type of compound.

Keywords: terpenoids; cyclization.

From the hexane extract of the aerial parts of *S. elegans*, we isolated both elegansidiol (*cis*-3-[(*E*)-5-hydroxy-3-methyl-3-pentenyl]-2,2-dimethyl-4-methylenecyclohexanol) (**1**) and the known triterpene achilleol A (**2**).[1] Elegansidiol was isolated for the first time as a new natural product. Its structure was established on the basis of its spectroscopic properties, which resemble those exhibited by **2**.

Compound **1** is a colourless oil presenting an $[\alpha]_D$ value of –4.0 (c=1, $CHCl_3$). Its HRFABMS shows $[M+H]^+$ at m/z 239.201432 (calcd for $C_{15}H_{27}O_2$: 239.201105). The IR spectrum presented absorption bands due to a hydroxyl group (3384 cm^{-1}) and carbon–carbon double bond (1645 cm^{-1}). In the ^1H NMR spectrum it is worth noting the signals of the protons geminal to the hydroxyl group appearing at δ 3.42, (dd, *J*=9.6 and 4.2 Hz, 1H) and at δ 4.15 (d, *J*=6.9 Hz, 2H), and those corresponding to the olefinic protons, triple quartet at δ 5.40 (tq, *J*=6.9 and 1.3 Hz) and two singlets at δ 4.60 and 4.88. In the ^{13}C NMR spectrum, we observed the signals due to both the olefinic carbons (δ 147.1, 140.1, 132.1 and 108.3) and the two oxygenated carbons (δ 59.3 and 77.2).

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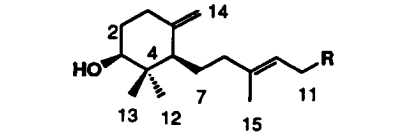
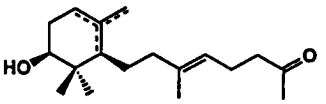
The isolation of both **1** and **2** in *S. elegans* points to a second hypothesis for the biogenesis of achilleol A (**2**). This triterpene could be biosynthesized either by squalene oxide monocyclization[2] or by tail-to-tail condensation of the corresponding monocyclic and acyclic sesquiterpenes.

The occurrence of this rather unusual structure not only in **1** and **2**, but also in the closely related and recently reported **3–5**,[3] led us to confirm these structural assignments via chemical synthesis.



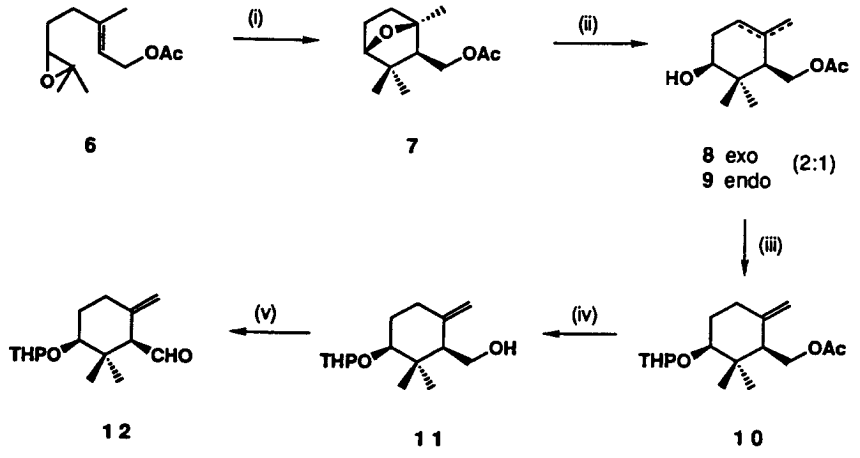
1 R : OH

2 R : -CH_2



3 exo C=C
4 trisubstituted C=C
5 tetrasubstituted C=C

The synthesis of **1** was approached by condensation of a monocyclic synthon C_{10} with an acyclic synthon C_5. The elaboration of the C_{10} moiety was carried out through electrophilic cyclization of 6,7-epoxygeranyl acetate (**6**), on the basis of previous studies by the present authors.[4] Scheme 1 depicts the first synthetic approach using aldehyde **12** as the C_{10} electrophile synthon. The efficient cyclization of **6** to **7** and subsequent opening of the bicyclic ether in anhydrous conditions led to a mixture of regiosomers **8** and **9** (ratio 2:1), the combined yield being higher than 60%. Transformation of **8** into **12** was achieved under standard conditions. Nevertheless, all the attempts to condense this aldehyde with nucleophiles such as 2-oxopropylidentriphenylphosphorane were unsuccessful. This difficulty has also been described in related structures,[5] and can be accounted for by considering the steric hindrance exerted on the aldehyde group by both the *gem*-dimethyl and the exocyclic double bond.



6 **7** **8** exo **9** endo (2:1) **10** **11** **12**

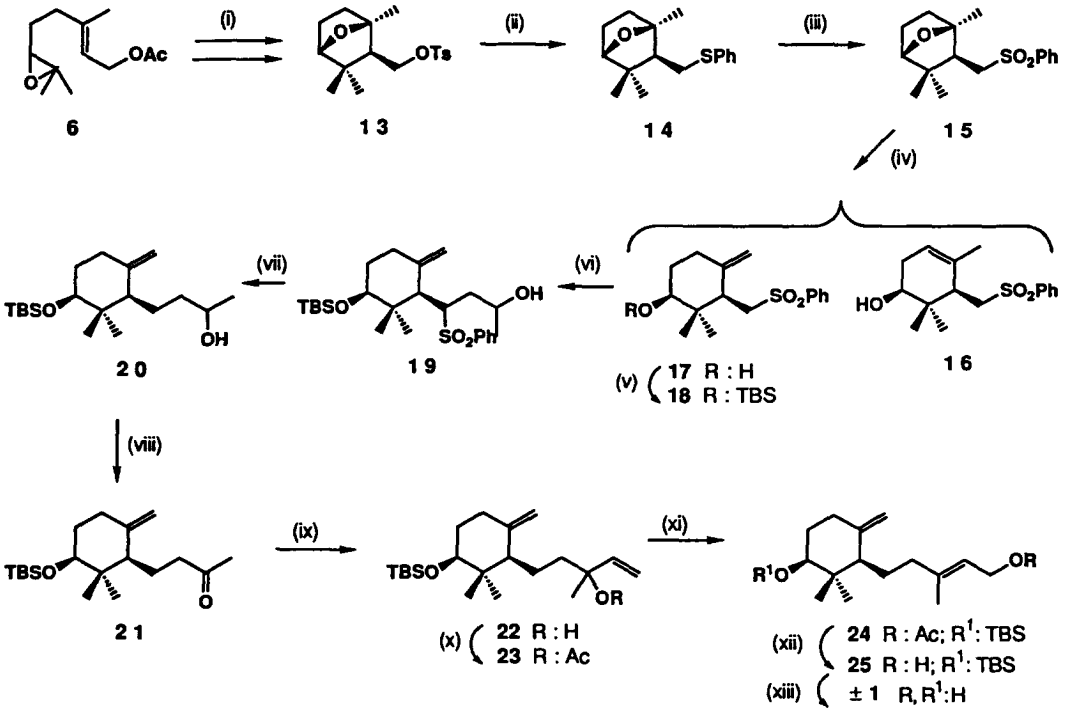
Scheme 1. (i) See Barrero et al.[4] (ii) BBr_3, CH_2Cl_2, rt, 10 min; collidine, CH_2Cl_2 (72%). (iii) DHP, PPTS, CH_2Cl_2, rt, 6 h (85%). (iv) 2 N KOH–MeOH, rt, 12 h (90%). (v) PDC, CH_2Cl_2, rt, 24 h (80%)

The sulphone **17** was therefore studied as a new C_{10} nucleophilic synthon. This sulphone was formed starting from the tosyl derivative **13**, which is easily obtained from **6**.[4] Treatment of **13** with potassium thiophenoxide provided the sulfide **14**, which was oxidized to **15** with *m*CPBA. In this case, the opening of the bicyclic ether furnished a mixture of the regioisomers **16** and **17** (ratio 1:1), which was easily separated by column chromatography. After protecting the hydroxyl group of **17** as its *t*-butyldimethylsilylether, alkylation of the carbanion generated from **18** by treatment with butyllithium was attempted with the C_5 allylic bromide, the tetrahydropyranyl derivative of 4-bromo-3-methyl-2(*E*)-

butenol. Unfortunately, the use of the monocarbocycle as the nucleophile did not lead to a successful reaction. In fact, at room temperature starting materials remained unaltered and only decomposition of the allylic derivative was observed after heating.

This task could only be accomplished by treatment of the sulphone anion with the much more stable propylene oxide at 65°C to give the β-hydroxysulphone **19**. Reduction of the sulphone group with sodium amalgam and further oxidation of the hydroxyl group with Jones reagent gave the ketone **21**, which afforded **22** after being exposed to vinylmagnesium bromide. Acetate **23** underwent allylic rearrangement after treatment with palladium dichloride bis acetonitrile to afford the carbon skeleton of elegansidiol. Saponification of the ester group and fluoride-induced cleavage of the silyl ether completed the synthesis of **1**, whose spectroscopic properties turned out to be identical to those of the natural product.[6]

This work reflects the inherent difficulties in lengthening the lateral chain of monocyclic derivatives such as **12** or **18**. The synthetic sequence depicted in Scheme 2 constitutes the first route to oxygenated monocyclic terpenoids of the type exemplified by **2–5**.



Scheme 2. (i) See Barrero et al.[4] (ii) KH, PhSH, EtOH, reflux, 4 h (92%). (iii) MCPBA, CH_2Cl_2, rt, 1 h (98%). (iv) BBr_3, CH_2Cl_2, 15 min; collidine (82%). (v) TBSCl, DMF, imidazole, DMAP, 10 h, rt (90%). (vi) BuLi, THF, 0°C, 30 min; propylene oxide, 0°C–65°C, 1 h 45 min (87%). (vii) Na–Hg 6%, Na_2HPO_4, EtOH, reflux, 4 h (85%). (viii) Jones, acetone, 30 min, 0°C (95%). (ix) CH_2=CHMgBr, THF, 0°C, 30 min (95%). (x) Ac_2O, Et_3N, DMAP, THF, reflux, 26 h (90%). (xi) $PdCl_2(CH_3CN)_2$, THF, rt, 45 min (95%). (xii) KOH, MeOH, rt, 45 min (94%). (xiii) TBAF, THF, rt, 6 h (89%)

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6. All new compounds were obtained in an analytically pure form and fully characterized by spectroscopic techniques. Elegansidiol (**1**): colourless oil; $[\alpha]_D$ –4.0° (c 0.9, $CHCl_3$); IR (film) ν_{max}: 3384, 2930, 2852, 1717, 1645, 1449, 1379, 1261, 1183, 1082, 1023, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.73 (s, 3H, Me-12), 1.03 (s, 3H, Me-13), 1.50 (m, 2H, H-2α, H-7), 1.65 (m, 2H, H-5, H-7), 1.68 (s, 3H, Me-15), 1.75 (m, 1H, H-8), 2.00–1.85 (m, 2H, H-1β, H-2β), 2.10 (m, 1H, H-8), 2.32 (dt, J=13.1, 4.4 Hz, 1H, H-1α), 3.42 (dd, J=9.6, 4.2 Hz, 1H, H-3), 4.15 (d, J=6.9 Hz, 2H, H-11), 4.60 (bs, 1H, H-14), 4.88 (bs, 1H, H-14′), 5.40 (tq, J=6.9, 1.3 Hz, 1H, H-10); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.7 (C-14), 16.2 (C-12), 23.8 (C-7), 26.0 (C-13), 32.0 (C-2), 32.7 (C-1), 38.7 (C-8), 40.4 (C-4), 51.2 (C-5), 59.3 (C-11), 77.2 (C-3), 108.3 (C-14), 123.1 (C-10), 140.1 (C-9), 147.1 (C-6); EIMS *m/z* 238 [M^+], (1), 220 (8), 205 (35), 187 (27), 175 (24), 159 (18), 134 (27), 119 (45), 107 (62), 96 (100), 81 (64), 67 (44), 55 (54), 43 (85), 41 (83); HRFABMS *m/z* $[M+H]^+$ 239.201432 (calcd for $C_{15}H_{27}O_2$, 239.201105). Compound **21**: ^1H NMR (300 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.81 (s, 3H), 0.88 (s, 9H), 0.91 (s, 3H), 1.51 (m, 2H, H-4, H-4′α), 1.60 (m, 1H, H-1′), 1.65 (m, 1H, H-4), 1.84 (m, 1H, H-4′β), 1.96 (m, 1H, H-3′β), 2.08 (s, 3H, H-1), 2.21 (ddd, J=17.1, 8.1, 4.6 Hz, H-3), 2.30 (m, 1H, H-3′α), 2.44 (ddd, J=17.1, 7.4, 7.1 Hz, H-3), 3.38 (dd, J=7.1, 3.6 Hz, H-5′), 4.48 (bs, H-7′), 4.80 (bs, H-7′); ^{13}C NMR (75 MHz, $CDCl_3$): δ –4.1 (C-Si), –4.9 (C-Si), 20.7 (C-4′), 20.9 (C-4), 21.9 (C-8′), 25.9 (C-9′), 26.0 (CH_3)$_3$CSi), 27.0 (C-1), 32.0 (C-3′), 40.4 (C-6′), 43.2 (C-3), 52.3 (C-1′), 76.8 (C-5′), 109.1 (C-7′), 148.1 (C-2′), 209.7 (C-2).