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Synthesis and absolute configuration of (−)-chrysolic acid and (+)-isofregenedol

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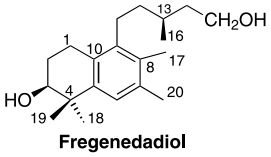
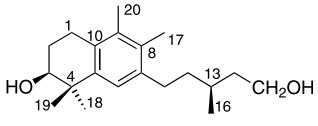
Abstract—An efficient synthesis of (−)-chrysolic acid and (+)-isofregenedol has been achieved from zamoranic acid and sclareol. The characteristic tetrahydronaphtalenic system was obtained by use of a cationic rearrangement of bicyclic systems adequately functionalized. The absolute configuration of the natural products was established using Sharpless asymmetric epoxidation.

Bicyclic diterpenes with an aromatic B ring are not very usual in nature.[1] Compounds of this kind have mainly two carbon skeletons, fregenedanes and isofregenedanes,[2,3] fregenedadiol and isofregenedadiol being representatives of these skeletons.

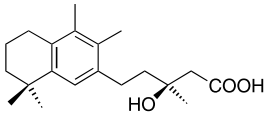
Chrysolic acid[4] isolated from *Chrysothamnus paniculatus* and 14-isofregeneden-13-ol[5] (isofregenedol) isolated from *Haplopappus parvifolius* are isofregenedane diterpenes whose structures were determined spectroscopically, but their proposed absolute configuration is based on biogenetic grounds and still not proved.



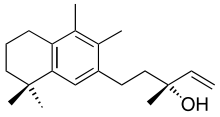
Fregenedadiol



Isofregenedadiol



Chrysolic acid



Isofregenedol

In this paper we present the synthesis of chrysolic acid and isofregenedol from ketone **8**, easily obtained from zamoranic acid and sclareol, which establishes the absolute configuration of the natural products. The synthesis is designed as shown in a retrosynthetic scheme (Scheme 1), having the above ketone **8** as key compound.

The key step in the synthesis of the tetrahydronaphtalenic system (THN) characteristic of these compounds is a cationic rearrangement of bicyclic systems adequately functionalised, previously described by us.[3] Intermediate **8** could be obtained from **5** and/or **11** that have allylic groupings in ring B. These compounds are easily synthetised from zamoranic acid and sclareol, respectively. Successive Wittig and Sharpless reactions on methylketone **8**, make it possible to obtain both natural compounds with total control of the absolute configuration.

Synthesis of 8 from zamoranic acid (Scheme 2).

The transformation of zamoranic acid methyl ester **3** into methylketone **4** has been previously reported by our group.[6] Diacetate **5**, having the groups necessary for the cationic rearrangement to ketone **8** that possesses the THN system, was achieved from **4** by conventional reactions of reduction and acetylation. Treatment of **5** with I_2 in C_6H_6, 1 h, under reflux gave **6** in a 60% yield after column chromatography on silicagel, reduction of **6** with LAH afforded **7** (96%). Oxidation with PCC/DCM[7] of **7** led to ketone **8** in an excellent yield (90%).

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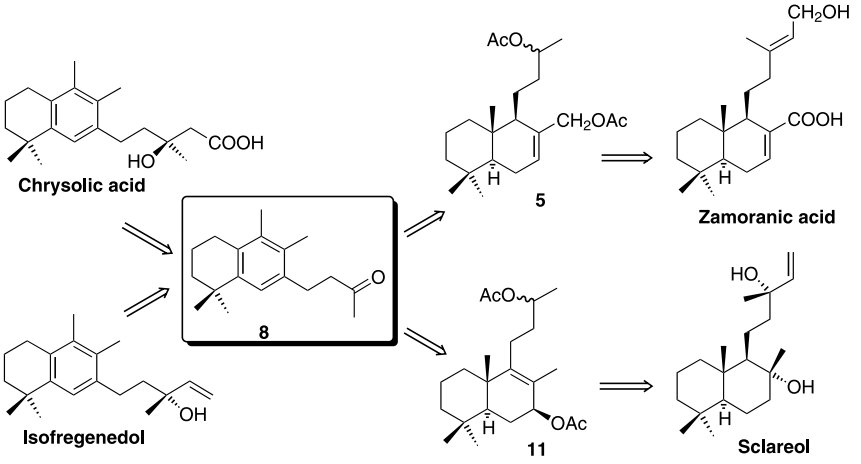
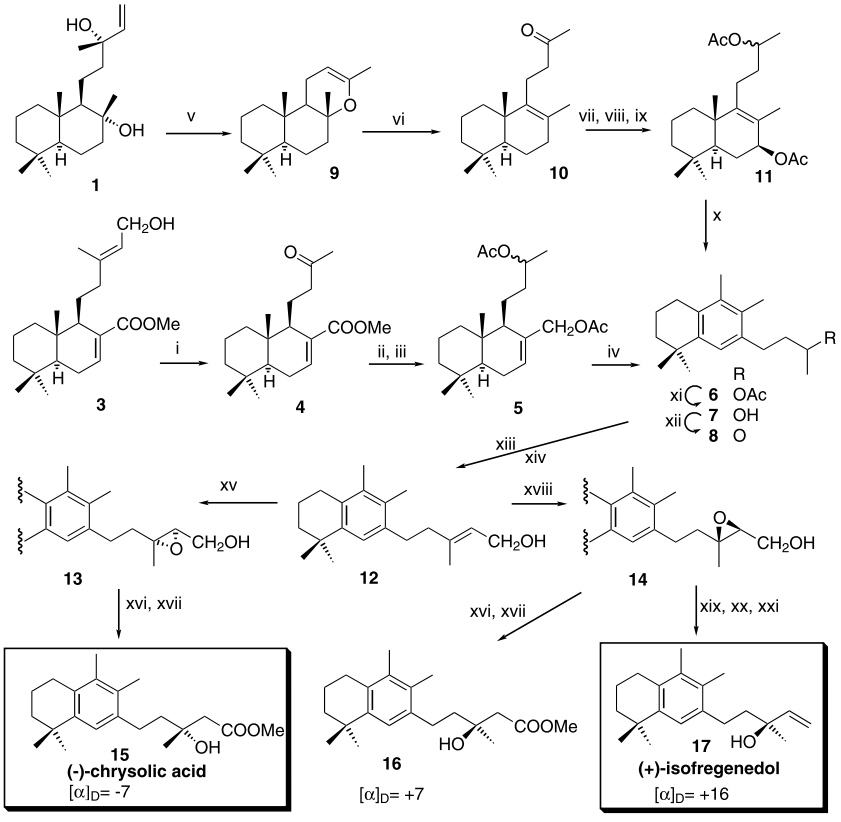
Synthesis of 8 from sclareol 1 (Scheme 2)

$KMnO_4$ oxidation in the presence of $MgSO_4$[8] and filtering the mixture on a silicagel column gave **9** as the only product in a 65% yield, in multigram scale. Treatment of **9** with HI in C_6H_6 at room temperature over 30 min, gives ketone **10** quantitatively. Allylic oxidation of **10** in anhydrous conditions followed by LAH reduction and acetylation gave **11** (63% overall yield 3 steps) required for the cationic rearrangement. Treatment of **11** with HI in C_6H_6 at room temperature over 1 hour gives **6** in a 65% yield after column chromatography on silicagel; **6** was transformed into ketone **8** as before.



Scheme 1.



Scheme 2. *Reagents and conditions*: (i) Ref. 6; (ii) LAH, THF (98%); (iii) Ac_2O, Py (100%); (iv) I_2, C_6H_6, reflux, 1 h (60%); (v) $KMnO_4$, $MgSO_4$, SiO_2 (65%); (vi) HI, C_6H_6, rt (98%); (vii) Na_2CrO_4, Ac_2O, AcONa, AcOH, 60°C (65%); (viii) LAH, THF (97%); (ix) Ac_2O, Py (100%); (x) HI, C_6H_6 reflux, 1 h (65%); (xi) LAH (96%); (xii) PCC, DCM (90%); (xiii) $(EtO)_2P(O)CH_2COOMe$, HNa (90%) (*E*/*Z*, 9/1); (xiv) DIBAL-H (90%); (xv) D-(−)-DET, *t*-BuOOH, Ti(*i*-PrO)$_4$, −24°C, 24 h (90%); (xvi) LAH, THF (93%); (xvii) a. PDC, DMF; b. CH_2N_2 (94%); (xviii) L-(+)-DET, *t*-BuOOH, Ti(*i*-PrO)$_4$, −24°C, 24 h (90%); (xix) CITs, Py (75%); (xx) Zn–Cu, ICu, THF, 2 h (84%); (xxi) Zn, AcOH, 2 h (80%).

Synthesis of chrysolic acid and isofregenedol from ketone 8 (Scheme 2)

Horner–Emmons reaction of **8** with excess of the phosphonate $(EtO)_2POCH_2COOMe$[9] gave a mixture E/Z 9:1 of the esters in good yield. DIBAL-H[10] reduction of the mixture led to the corresponding mixture of allylic alcohols, from which **12** was isolated in an 81% yield. Sharpless epoxidation of **12** gives the corresponding enantiomeric epoxides **13** or **14** using D-(−)-DET or L-(+)-DET[11], respectively. [12]

Reduction of **13** with LAH gave a diol that by oxidation with PDC in DMF, followed by esterification with diazomethane lead to **15** $[\alpha]_D=-7$ (c 0.78, $CHCl_3$). The same sequence with **14** gave the enantiomer of **15**, **16** $[\alpha]_D=+7$ (c 1.25, $CHCl_3$).

Spectroscopic properties for **15**[13] and **16** are identical to the ones described for chrysolic acid methyl ester. The $[\alpha]_D=-12$ (c 2.39, $CHCl_3$) described, for the last compound implies that the absolute configuration is 13*R*, the one of **15**, opposite to the described one.[4]

The hydroxy derivative **17** was synthesised starting from **14** in three steps, tosylation,[14] iodide sustitution[15] and Zn/AcOH reduction,[16] in a good overall yield.

The physical properties for **17**[17] $[\alpha]_D=+16$ (c 1.28, $CHCl_3$) agree with those described for the natural product ($[\alpha]_D=+20$), establishing the absolute configuration as 13*S* for the natural product (+) isofregenedol, opposite to the one proposed on the base of biogenetic hypotheses.

Acknowledgements

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12. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543 The e.e. of epoxides was controlled by comparison of Mosher's ester of the Sharpless products with those of the racemic epoxides obtained with *m*-CPBA. The e.e. for **13** was 86% and 87%, for **14**.
13. *Methyl 13R-hydroxy-15-isofregenedanoate*, **15** R_f *(Hex/AcOEt 8/2)*=0.40; $[\alpha]_D=-7$ (c 0.78, $CHCl_3$); IR (film): 3522, 1738, 1678, 1593, 1456, 1383, 1362 and 1209 cm^{-1}. The assignments for the spectra, ^1H NMR and ^{13}C NMR for **15** and **16** were done by bidimensional experiments HMQC and HMBC. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.04 (1H, s, H-6), 3.73 (3H, s, COOMe), 3.64 (1H, s, OH), 2.70–2.60 (4H, m, H-1 and H-11), 2.61 (1H, d, $J=15.0$ Hz, H-14), 2.53 (1H, d, $J=15.0$ Hz, H-14), 2.21 (3H, s, Me-17), 2.15 (3H, s, Me-20), 1.90–1.70 (4H, m, H-2 and H-12), 1.36 (3H, s, Me-16), 1.29 (6H, s, Me-18 and Me-19); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5 (C_1), 19.8 (C_2), 38.9 (C_3), 33.8 (C_4), 143.4 (C_5), 125.0 (C_6), 137.4 (C_7), 132.4 (C_8), 134.8 (C_9), 131.3 (C_{10}), 29.8 (C_{11}), 43.4 (C_{12}), 71.0 (C_{13}), 45.1 (C_{14}), 171.5 (C_{15}), 26.7 (C_{16}), 15.3 (C_{17}), 32.0 (C_{18}), 32.0 (C_{19}), 15.6 (C_{20}), 51.5 (COO<u>Me</u>). EIMS (rel. intensity): m/z 332 (7) [M^+], 314 (10), 299 (82), 258 (6), 243 (35), 225 (14), 201 (30), 185 (100). EIHRMS calcd. for $C_{21}H_{32}O_3$: 332.2351, found: 332.2344.
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17. *14-isofregeneden-13S-ol*, **17**. R_f *(Hex/AcOEt 8/2)*=0.47; $[\alpha]_D=+16$ (c 1.28, $CHCl_3$); IR (film): 3453, 1462, 1362, 1107, 997, 920 and 756 cm^{-1}. The assignments for the spectra, ^1H NMR and ^{13}C NMR for **17** were done by

bidimensional experiments HMQC and HMBC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (1H, s, H-6), 6.02 (1H, dd, $J_{XA}=10.7$ and $J_{XB}=17.3$ Hz, H-14), 5.32 (1H, dd, $J_{AX}=10.7$ and $J_{AB}=1.0$ Hz, H_A-15), 5.16 (1H, dd, $J_{BX}=17.3$ and $J_{BA}=1.0$ Hz, H_B-15), 2.70–2.60 (4H, m, H-1 and H-11), 2.19 (3H, s, Me-20), 2.15 (3H, s, Me-17), 1.90–1.70 (4H, m, H-2 and H-12), 1.60 (2H, m, H-3), 1.36 (3H, s, Me-16), 1.28 (6H, s, Me-18 and Me-19); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.5 (C_1), 19.8 (C_2), 38.9 (C_3), 33.8 (C_4), 143.3 (C_5), 125.0 (C_6), 137.5 (C_7), 132.5 (C_8), 134.9 (C_9), 131.2 (C_{10}), 29.0 (C_{11}), 43.6 (C_{12}), 73.4 (C_{13},) 145.1 (C_{14}), 112.0 (C_{15}), 28.0 (C_{16}), 15.4 (C_{17}), 32.0 (C_{18}), 32.0 (C_{19}), 15.6 (C_{20}). EIMS (rel. intensity): m/z 286 (35) [M^+], 271 (58), 253 (63), 216 (41), 185 (68), 71 (100). EIHRMS calcd. for $C_{20}H_{30}O$: 286.2296, found: 286.2297.