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GUAIANOLIDES : THE TOTAL SYNTHESIS OF (±)-ESTAFIATIN

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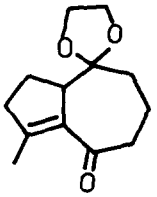
SUMMARY

An efficient synthesis of the trans fused perhydroazulenic epoxy ketone 5 is described. The potentiality of 5 is illustrated by its transformation into (±)-estafiatin 1.

Despite a long history, a wide distribution in nature, and extensive studies in relation to interconversions with other sesquiterpene classes[2], no total synthesis of a naturally occurring guaianolide has been reported until recently[3]. This stands in sharp contrast with a large number of recent, successful approaches to the biogenetically related pseudoguaianolides[4]. From our experience this discrepancy in synthetic activities on both series is related to the different position of the 15-methyl substituent. In pseudoguaianolides the C-5 angular position of the methyl group is an important factor allowing good stereo- and regiocontrol for the formation of other substituents.

Since most guaianolides are cis fused perhydroazulenes (αH) with a trans fused γ-lactone closed at C-6(α), a general approach implies the control of the relative configuration at C-1,C-5,C-6 and C-7, while permitting the formation of additional functionalities in the five-membered ring and at C-10. In a previous communication we have demonstrated the viability of a general route to guaianolides based upon the reductive cleavage of keto-epoxide 4 which yielded the desired stereochemical set-up at the ring-fusions (cf. 7). This route, however, centered upon keto-epoxide 3 which could only be obtained in modest yield (cumylhydroperoxide, triton B, THF, 5 days, r.t.; 48 %).

We now report on an alternative route, starting from the more readily obtained isomeric epoxide 5, and illustrate its potentiality with the total synthesis of (±)-estafiatin (1)[5]. The modified route is based upon the following assumptions : (1) the enolate formed upon initial reductive opening of keto-epoxides such as 4 and 6 is protonated internally[6] via the 4-oxy group, thus dictating the configuration at C-5 (4 → 7 and 6 → 8); (2) at an appropriate stage of the sequence inversion at C-1 will establish the naturally observed stereochemistry (cf. 1).



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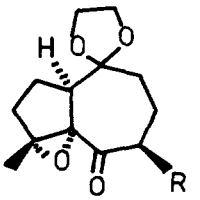
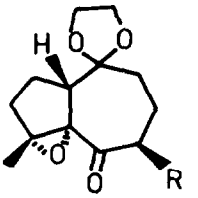
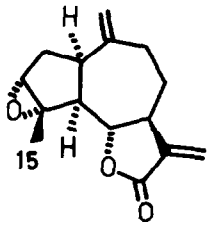


3 R = H
4 R = $CH_2CH{=}CMe_2$



5 R = H
6 R = $CH_2CH{=}CMe_2$



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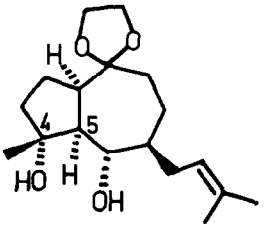

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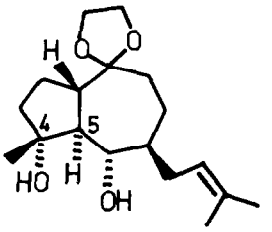

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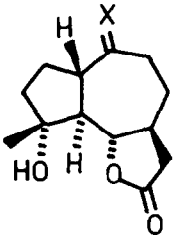
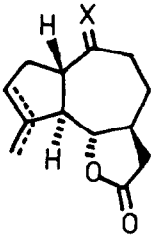
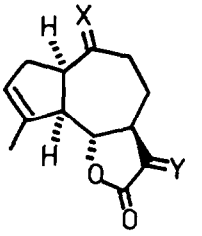


9 X = OCH_2CH_2O
10 X = O



11 X = OCH_2CH_2O
12 X = O



13 X = O; Y = H_2
14 X = CH_2; Y = H_2
15 X = CH_2; Y = CH_2

The epoxidation of 2[7] (H_2O_2, NaOH, MeOH, -20° to -5°C, 24 hr) yielded the diastereoisomeric epoxides 5 and 3 (ratio 9:1) from which 5 was obtained after column chromatography (SiO_2, ether-isooctane 1:1) in 70 % isolated yield. |5 : m.p. 110-111°C; ν 1720, 1070, 960 cm^{-1}; δ ($CDCl_3$) 3.92 (4H, m), 2.8 (1H, dd, 7 and 10.5 Hz); 2.69 (2H, m), 1.42 (3H, s); m/z at 238 ($M^{+\cdot}$, 8), 99 (100)|. Alkylation of ketone 5 with isoprenylbromide (LDA, 1.1 eq. HMPA, THF, -78° to -40°C, 2 h) and column chromatography (SiO_2, ethylacetate-isooctane 8:7) provided pure 6 (60 %) and the C-7(α)epimer (16 %)[8]. Treatment of the latter α-epimer with LDA and HMPA (10 eq) in THF and subsequent quenching with NH_4Cl gave a 6:4 ratio in favour of 6 (after this recycling 69 % combined yield). |6 : ν 1720, 1460, 1170, 1050, 960 cm^{-1}; δ ($CDCl_3$) 5.03 (1H, m), 3.9 (4H, m), 2.66 (1H, dd, 8 and 10 Hz), 2.85 (1H, m), 1.68 (3H, s), 1.61 (3H, s), 1.35

(3H, s); m/z at 306 ($M^{+\cdot}$; 3), 263 (3), 237 (4), 181 (20), 99 (100)|. A solution of 6 in liq. ammonia-THF was twice treated successively with lithium (10 eq) and NH_4Cl (11 eq) and provided diol 8 as the only isolated isomer (71 % yield). |8 : 113°C; ν 3500, 1400, 1170 cm^{-1}; δ ($CDCl_3$) 5.19 (1H, m), 3.95 (4H, m), 3.43 (1H, m), 2.99 (1H, s), 2.88 (1H, d, 2.5 Hz), 2.3 (1H, m), 2.15 (1H, ddd, 10.5, 10.5 and 2.5 Hz), 1.72 (3H, s), 1.64 (3H, s), 1.31 (3H, s); m/z at 310 ($M^{+\cdot}$, 5), 292 (40), 274 (25), 99 (100)|. Ozonolysis (CH_2Cl_2, -78°C; Me_2S work-up) of 8 and Jones oxidation of the resulting lactol gave 9 (80 %). |Subl. 132-134°C; 3450, 1785, 1480, 1070 cm^{-1}; δ ($CDCl_3$) 4.0 (4H, m), 3.89 (1H, m), 2.6 (2H, m), 2.2 (1H, m), 1.34 (3H, s); m/z 282 ($M^{+\cdot}$, 10), 99 (100)|. The structure of 9 was unambiguously proven by X-ray diffraction[9].

As indicated (vide supra) we now needed to invert the configuration at C-1. Ketone 10, however, obtained from 9 by hydrolysis (HCl-MeOH, 3N, r.t., 30 min, 73 % yield), |10 : ν 3550, 1790, 1720, 1450, 1210, 980 cm^{-1}; δ ($CDCl_3$) 4.09 (1H, t, 10.0 Hz), 2.83 (1H, ddd, 8.0, 11.5 and 15 Hz), 2.64 (3H, m), 2.5 (1H, m), 2.38 (3H, m), 1.36 (3H, s); m/z 238 ($M^{+\cdot}$, 10), 223 (3), 220 (10), 181 (60), 43 (100)| could not be epimerized : e.g., treatment with acid (HCl, MeOH, 3N). Examination of the preferred seven-membered ring conformations of both trans- and cis-fused perhydroazulenones 10 reveals the presence of severe non-bonded interactions between the methyl group at C-4 and the γ-lactone in the cis-fused series. We therefore decided to examine the possibility for inversion after dehydratation in the five-membered ring.

Treatment of 9 with Burgess reagent ($MeOOC\bar{N}SO_2\overset{+}{N}Et_3$; benzene, 50°, 3 h) led to 11 (61 %; unseparable mixture of endo- and exo-double bond isomers, ratio 3:1 from ^1H NMR) and the $\Delta^{4,5}$ isomer (17 %). Rapid hydrolysis of 11 (HCl-MeOH, 3N, r.t.) gave 12 : |$\Delta^{4,15}$: δ ($CDCl_3$) 5.37 (1H, m), 5.03 (1H, m), 4.07 (1H, t, 9.5 Hz)|; |$\Delta^{3,4}$: ν 1780, 1720, 1460, 1150, 810 cm^{-1}, δ ($CDCl_3$) 5.43 (1H, br. s), 4.0 (1H, t, 10 Hz), 3.14 (1H, ddd, 10, 10 and 7.5 Hz), 2.9 (2H, m), 1.83 (3H, br. s); m/z 220 ($M^{+\cdot}$, 100), 79 (98)|. Prolonged acid treatment led, as anticipated, to an equilibrium mixture of 12 and 13 (ratio 1:3, respectively). Preparative HPLC (Waters Ass. Prep LC/System 500) gave 13 (60 % isolated yield). |13 : m.p. 87°C; ν 1780, 1720, 1460 cm^{-1}, δ ($CDCl_3$) 5.5 (1H, br. s), 3.82 (1H, t, 10 Hz), 3.55 (1H, ddd, 9.0, 9.0 and 6.0 Hz), 3.08 (1H, br. t, 10 Hz), 1.84 (3H, br. s); m/z 220 ($M^{+\cdot}$, 88), 205 (10), 80 (100)|. Wittig reaction on ketone 13 ($Ph_3PCH_3.Br$, NaOt.Am, toluene, r.t., 30 min) led to 14 (75 % yield) |semi-solid oil; ν 3095, 1790, 1660, 1470, 1030 cm^{-1}; δ ($CDCl_3$) 5.54 (1H, br. s), 4.87 (1H, s), 4.84 (1H, s), 4.07 (1H, t, 9.5 Hz), 3.11 (1H, ddd, 7.5, 7.5 and 5.0 Hz), 2.83 (1H, br. t, 8.5 Hz) 2.65 (1H, m), 1.82 (3H, br. s); m/z 218 ($M^{+\cdot}$, 30), 138 (100)|.

α-Hydroxymethylation of the enolate anion of 14 (LDA, THF, -30°, CH_2O), formation of the mesylate ($MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C) and elimination (DBU, r.t., 3 h) yielded (79 %) 15 |oil, ν 1775, 1655, 1640, 1450, 1270, 1010; δ

($CDCl_3$) 6.2 (1H, d, 3.3 Hz), 5.54 (1H, br. s), 5.49 (1H, d, 3.3 Hz), 4.89 (1H, s), 4.86 (1H, s), 4.05 (1H, dd, 9 and 9 Hz), 3.15 (1H, m), 2.85 (2H, m), 1.86 (3H, br. s); m/z 230 ($M^{+\cdot}$)|. Epoxidation of triene 15 (mCPBA, $CHCl_3$, -5°C, 3 h) and column chromatography (SiO_2, ethylacetate-hexane 1:9) gave (±)-estafiatin 1 (69 %) |m.p. 92°-93°; ν 1760, 1660, 1645, 1150 cm^{-1}, δ ($CDCl_3$) 6.21 (1H, d, 3.5 Hz), 5.48 (1H, d, 3.5 Hz), 4.95 (1H, br. s), 4.86 (1H, br. s), 4.07 (1H, dd, 8.5 and 11 Hz, 3.37 (1H, s), 2.98 (1H, ddd, 7.5, 7.5 and 10.5 Hz), 2.87 (1H, m), 1.6 (1H, s)|. Both 1 and 15 were found identical (TLC behavior and spectral properties) with optically active samples described by Edgar, Greene and Crabbé[2b,10].

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6. See e.g. (a) M. Samson, P. De Clercq and M. Vandewalle, Tetrahedron, 33, 249 (1977); (b) P.A. Grieco, M. Nishizawa, T. Oguri, S.D. Burke and N. Marinovic, J. Amer. Chem. Soc., 99, 5773 (1977).
7. See ref. 8 in previous communication[3].
8. Comparison of spectral data and Rf values of all four isomeric alkylated epoxy-ketones (two from 3 and two from 5) suggested the β-configuration of the isoprenyl group in the major isomer. Conclusive proof was obtained with the X-ray study of intermediate 9.
9. J.P. Declercq, G. Germain, M. Van Meerssche and A. Devreese, P. De Clercq and M. Vandewalle, Bull. Soc. Chim. Belges, 90, 899 (1981).
10. We thank Dr. Greene for kindly sending samples of (-)-1 and (+)-15.

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