Tetrahedron Letters Vol. 21, pp 4767 - 4770
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0040-4039/80/1201-4767$02.00/0

A GENERAL ENTRY TO GUAIANOLIDES.
AN ILLUSTRATIVE SYNTHESIS OF (±)-COMPRESSANOLIDE

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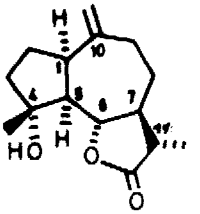
SUMMARY

A short and efficient synthesis of a key intermediate 2 for the formation of guaianolides is described. The potentiality of 2 is illustrated by its transformation into the natural occurring guaianolide, (±)-compressanolide 1.

Guaianolides, with ca 200 known naturally occurring compounds, represent one of the largest groups of sesquiterpene lactones[2]. In contrast to pseudoguaianolides[3], they have so far only been approached by relay syntheses involving rearrangements of eudesmanolides[4] and germacranolides[5,6]. With only a few exceptions guaianolides possess a cis-fused (α,H) hydroazulene skeleton (when C-1 and/or C-5 are not sp^2 hybridized) and display a functionalized C-10 (double bond or oxyfunction). Furthermore in 85 % of the cases the γ-lactone is closed in a trans manner toward C-6 (α, C-O). The wide diversity among the natural representatives arises from additional functionalities, especially in the five-membered ring and at C-8.

A general synthetic approach to the guaianolides calls for a key intermediate which meets these structural requirements and is yet simple enough to be efficiently prepared. In this paper we describe a short synthesis of such an intermediate 2 and illustrate its potentiality by its transformation into (±)-compressanolide (1)[6], which is the first naturally occurring guaianolide obtained in racemic form by total synthesis.

The starting diketone 3 is readily available from 2-cyclopentenone[7]. Selective protection of the isolated ketofunction by transacetalisation (butanone-2-ethylene ketal, p-TsOH in chloroform at reflux for 6 h) led to 4 in 74 % yield |oil; ν(neat) 1610, 1675 cm^{-1}; m/z at 222 (M^+; 12), 221 (72), 99 (100)|. The epoxidation of 4 with cumylhydroperoxide (80 % sln.) and triton B in THF (5 days, r.t.) yielded the diastereoisomeric epoxides 5 and 6 (ratio 6:1, respectively); pure α-epoxide 5 was obtained after purification on silica gel (48 % isolated yield) |mp 103-104°C; ν 1720, 1115 cm^{-1}; δ($CDCl_3$) 2.71 (1H, dd, 9.0 and 2.5 Hz), 2.65 (2H, m), 1.42 (3H, s); m/z at 238 (M^+; 17), 99 (100)|[8]. Deprotonation of 5 at -78°C with LDA followed by treatment with isopentenyl bromide and HMPA (1.0 equiv) led to a mixture of two ketones 7 and 8 (ratio 2:1, respectively) from which the desired β-isomer at C-7 (7) was readily separated by chromatography on silica gel (56 % isolated yield) |mp 74°C; ν 1720, 1115 cm^{-1}; δ (CDCl$_3$) 5.06 (1H, m), ~3.94 (4H), 2.73 (1H, dd, 8.0 and 2.5 Hz), 2.69 (1H, m), 1.69 (3H, s), 1.60 (3H, s), 1.55 (3H, s); m/z at 306 (M$^{+\cdot}$; 8), 181 (61), 99 (100)|.



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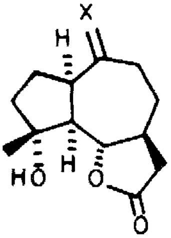
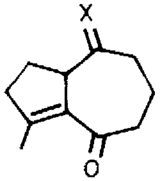
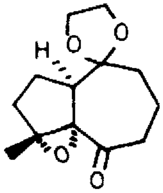


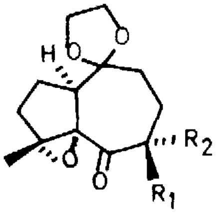
2 X=OCH$_2$CH$_2$O
10 X=O



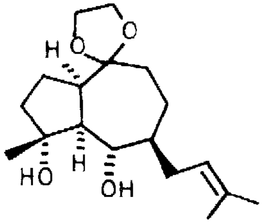
3 X=O
4 X=OCH$_2$CH$_2$O



5
6 β-epoxide



7 R$_1$ = CH$_2$CH = CMe$_2$; R$_2$=H
8 R$_1$ = H ; R$_2$= CH$_2$CH = CMe$_2$



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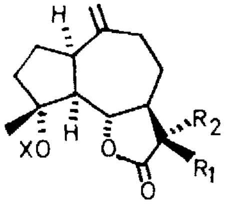

11 X = R$_1$ = R$_2$ = H
12 X = TMS ; R$_1$ = R$_2$ = H
13 X = H ; R$_1$ = Me ; R$_2$ = H

Recycling of the α-isomer 8 (mp 79-81°C) was possible via equilibration (DBU, methylene chloride) leading to a 1:1 ratio of both isomers. Reductive cleavage of keto-epoxide 7 by repetitive (2 times) treatment with lithium (7.3 equiv) in liquid ammonia[9], directly followed by ammonium chloride (8.0 equiv) gave diol 9 as sole isolated reaction product (57 % yield) |semisolid oil; ν(neat) 3400 cm^{-1}; δ(CDCl$_3$) 5.21 (1H, m), 2.63 (1H, dt, 9.0, 9.0 and 12.3 Hz), 2.29 (1H), 2.12 (1H, m), 2.04 (1H, dd, 10.5 and 12.5 Hz), 1.73 (3H, s), 1.64 (3H, s), 1.34 (3H, s)|. Oxidative fission of the double bond (ozone at -78°C, followed by dimethyl sulfide) followed by Jones oxidation of the intermediate lactol gave lactone 2 (80 % yield) |mp 158-160°C; ν 1795 cm^{-1}; δ(CDCl$_3$) 4.52 (1H, dd, 9.5 and 11.0 Hz), 2.73 (1H, ddd, 8.5, 10.0 and 12.5 Hz), 2.60 and 2.27 (2H, AB of ABX), 2.36 (1H, dd, 11.5 and 12.3 Hz), 1.34 (3H, s); m/z at 282 (M$^{+\cdot}$; 4.2), 99 (100)|. Structure 2 was unambiguously determined by X-ray diffraction[10], hereby also settling the stereochemical outcome of the previous reactions.

In nine steps, starting from 2-cyclopentenone, an ideal key intermediate for guaianolide synthesis is thus obtained : it features the desired stereochemistry at C-1, C-5, C-6 and C-7, a functionality at C-4 for various functionalizations of the five-membered ring and the necessary active sites for the introduction of the two remaining carbons of the guaiane skeleton at C-11 and C-10.

Full advantage of the stereochemical and structural features of lactone 2 was taken in the following sequence which eventually led to (±)-compressanolide (1). Deketalization to 10 (methanol, 3 N hydrochloric acid, 6 h) |mp 150-152°C; ν 1785, 1720, 1240 and 1150 cm^{-1}; δ(CDCl$_3$) 3.92 (1H, dd, 9.5 and 11.3 Hz), 3.50 (1H, dt, 8.75, 8.75 and 12.6 Hz), 2.71 (1H, dd, 8.0 and 17.0 Hz), 2.56 (1H), 2.48 (1H, dd, 11.3 and 12.5 Hz), 2.30 (1H, dd, 12.0 and 17.0 Hz), 2.18 (2H), 1.66 (1H), 1.53 (1H), 1.27 (3H, s); m/z at 238 (M$^{+\cdot}$; 11), 181 (60), 43 (100)|, followed by treatment with methylene phosphorane in THF (r.t., 20 min) led to olefin 11 (55 % yield from 3) |semi-solid oil; ν(neat) 1790, 1270, 1100, 1030 and 800 cm^{-1}; δ(CDCl$_3$) 4.98 (1H, s), 4.95 (1H, s), 4.12 (1H, dd, 9.5 and 11.5 Hz), 3.00 (1H, m), 2.62 (2H), 2.11 (1H, m), 1.30 (3H, s); m/z at 236 (M$^{+\cdot}$; 0.4), 43 (100)|. The tertiary alcohol in 11 was protected as the trimethylsilyl ether 12 (80 % yield; trimethylsilyl chloride, triethyl amine in methylene chloride, in the presence of 4-dimethylaminopyridine[11]; 4 h) and methylated (LDA, methyliodide, HMPA, -78°C, 10 min); acid work-up (methanol, 3 N hydrochloric acid, 1 h) gave a mixture of diastereosiomers 1 and 13 (79 % yield; ratio 1:8, respectively) which were readily separated on silica gel. The inversion of configuration at C-11 in the undesired β-epimer 13 (mp 86-87°C) was partially achieved by treatment with LDA, followed by quenching with ammonium chloride, leading to a 1:2 mixture of 1 and 13, respectively. The TLC behavior and spectral properties of synthetic 1 |oil; ν 1785 cm^{-1}; δ(CDCl$_3$) 4.98 (1H, s), 4.95 (1H, s), 4.05 (1H, dd, 9.5 and 11.0 Hz), 2.99 (1H, m), 2.65 (1H, dt, 3.75, 3.75 and 12.5 Hz), 2.27 (1H, dd, 11.0 and 12.0 Hz), 2.22 (1H, dd, 7.0 and 11.8 Hz), 2.12 (1H, m), 1.30 (3H, s), 1.24 (3H, d, 7.0 Hz); m/z at 250 (M$^{+\cdot}$; 2.0), 43 (100)| showed it to be identical with an authentic sample of compressanolide[12].

ACKNOWLEDGMENT

We thank the N.F.W.O. (Nationaal Fonds voor Wetenschappelijk Onderzoek) and the "Ministerie voor Wetenschapsbeleid" for financial support to the laboratory.

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12. We are indebted to Dr. G.A. Cordell for kindly sending a sample of natural compressanolide.

(Received in UK 24 September 1980)