The Partial Syntheses of 7β-Hydroxyatisenolide and Atisagibberellin A_{12} Dimethyl Ester

Braulio M. Fraga,[a]* Ricardo Guillermo,[a] and James R. Hanson[b]

[a]*Instituto de Productos Naturales Orgánicos, La Laguna, 38206-Tenerife, Canary Islands, Spain*
[b]*School of Molecular Sciences, University of Sussex, Brighton, Sussex BN1 9QJ, U.K.*

Reprinted from

JOURNAL OF CHEMICAL RESEARCH (S)

1990

The Partial Syntheses of 7β-Hydroxyatisenolide and Atisagibberellin A_{12} Dimethyl Ester

J. Chem. Research (S), 1990, 99
J. Chem. Research (M), 1990, 0729–0741

Braulio M. Fraga,[a,*] Ricardo Guillermo,[a] and James R. Hanson[b]

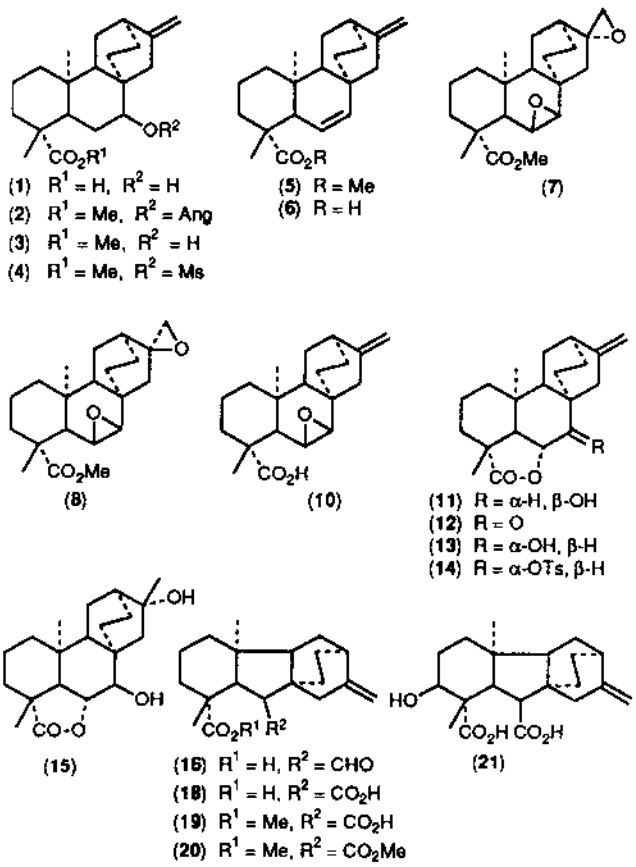
[a]*Instituto de Productos Naturales Orgánicos, La Laguna, 38206-Tenerife, Canary Islands, Spain*
[b]*School of Molecular Sciences, University of Sussex, Brighton, Sussex BN1 9QJ, U.K.*

Gummiferolic acid has been transformed into 7β-hydroxyatisenolide and 7β,16α-dihydroxyatisanolide *via* atisa-6,16-dien-19-oic acid. The 7β-hydroxyatisenolide was subsequently converted into atisagibberellin A_{12} dimethyl ester in several steps.

In a previous paper[1] we have described the microbiological transformation of *ent*-7α-hydroxyatis-16-en-19-oic acid (**1**) by the fungus *Gibberella fujikuroi* and shown that it was converted into the atisene analogues of gibberellins A_{12} and A_{14}, (**18**) and (**21**), respectively. We have now synthesized 7β-hydroxyatisenolide following a method similar to that employed in the preparation of 7β-hydroxykaurenolide.[2] This revealed an interesting contrast with the *ent*-kaurane series.

Hydrolysis of the methyl ester of gummiferolic acid[3] (**2**) gave the alcohol (**3**), which was treated with methanesulphonyl chloride in pyridine to afford the corresponding methanesulphonate (**4**). Elimination of the methanesulphonate (**4**) gave methyl *ent*-atisa-6,16-dien-19-oate (**5**). This was epoxidized with *m*-chloroperbenzoic acid to give a 16-epimeric mixture of the 6,16-diepoxides (**7**) and (**8**). The 6β,7β-stereochemistry of the epoxide followed from the position of the H-6 resonance (δ 3.90) in which, by analogy with the kaurene series, it is deshielded by the C-19 substituent. However, unlike the kaurene series, there is less to differentiate the faces of the 16-ene and, consequently, epimers were obtained at this centre. The 16-epoxide was removed with potassium selenocyanate and the ester hydrolysed with ethanethiolate to afford *ent*-6α,7α-epoxyatis-16-en-19-oic acid (**10**), which differed from its kaurene analogue in that it could be chromatographed and was stable to pH 5. However, on treatment with dilute hydrochloric acid at room temperature for 8 days, it was converted into *ent*-6β,7α-dihydroxyatis-16-en-19-oic acid 19,6β-lactone (7β-hydroxyatisenolide) (**11**) and the 16-alcohol (**15**). The synthetic atisenolide (**11**) was identical with that obtained from the microbiological transformation of (**6**).

Oxidation of 7β-hydroxyatisenolide (**11**) with Jones reagent gave the ketone (**12**), which was reduced with sodium borohydride in methanol to afford the 7α-alcohol (**13**). This compound was treated with tosyl chloride in pyridine to give the corresponding toluene-*p*-sulphonate (**14**). This underwent ring contraction to form the aldehyde (**16**) on treatment with potassium hydroxide in aqueous t-butyl alcohol. This rearrangement is analogous to that used in the kaurenolide series for ring contraction of ring B.[5] Compound (**16**) was methylated with diazomethane and oxidized with Jones reagent to afford the acid (**19**). Further methylation gave compound (**20**) which was identical with the dimethyl ester of atisagibberellin A_{12}, obtained by methylation of one of the compounds formed in the microbiological transformation of *ent*-7α-hydroxyatis-16-en-19-oic acid (**1**) by *G. fujikuroi*.[1]



This study completes our earlier works on the partial synthesis of analogues of gibberellins with the C and D rings of beyerene[10,11] and trachylobane[12] diterpenes.

Techniques used: NMR, MS

References: 11

Received, 20th September 1989; Paper E/9/04031E

References cited in this synopsis

1 J. R. Hanson, F. Y. Sarah, B. M. Fraga, and M. G. Hernández, *Phytochemistry*, 1979, **18**, 1875.
2 M. H. Beale, J. R. Bearder, G. H. Down, M. Hutchison, J. MacMillan, and B. O. Phinney, *Phytochemistry*, 1982, **21**, 1279.
3 M. Pinar, B. Rodriguez, and A. Alemany, *Phytochemistry*, 1978, **17**, 1978.
5 R. H. B. Galt and J. R. Hanson, *J. Chem. Soc.*, 1965, 1565.
10 B. M. Fraga, A. G. González, M. G. Hernández, A. San Martin, Z. J. Duri, and J. R. Hanson, *Tetrahedron Lett.*, 1983, **24**, 1945.
11 B. M. Fraga, A. G. González, M. G. Hernández, Z. J. Duri, and J. R. Hanson, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1105.
12 B. M. Fraga, R. Guillermo, J. D. Arraez, J. G. Luis, A. Perales, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1513.

*To receive any correspondence.