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Stereospecific synthesis of the aglycone of pseudopterosin E

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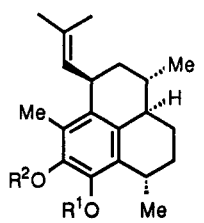
Abstract - Aglycone 1 of pseudopterosin E has been synthesized from the tetralone 2 using several novel reactions to control stereselectivity.

The pseudopterosins and secopseudopterosins are diterpene glycosides isolated (ref. 1) from the Caribbean Seawhip Pseudopterogorgia elisabethae. The pseudopterosins are the tricyclic compounds A-J and the secopseudopterosins are characterized by their bicyclic structures. All of these natural products possess potent antiinflammatory activity. Recently two routes (refs. 2,3) towards the synthesis of pseudopterosins have been published and in this paper we wish to disclose a stereospecific synthesis of the aglycone 1 of pseudopterosin E developed in our laboratories. Our retrosynthetic analysis starting from an inexpensive starting material 2 is shown in Scheme 1. Reformatsky

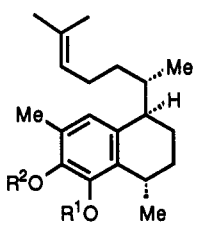


PSEUDOPTEROSINS

A - D : R^1 = (acetylated) D-Xylose , R^2 = H

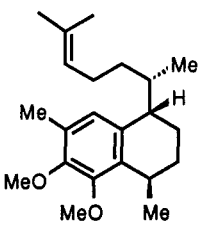
E : R^1 = H, R^2 = Fucose ; F : R^1 = H, R^2 = Arabinose

G - J : R^1 = (acetylated) Fucose , R^2 = H :



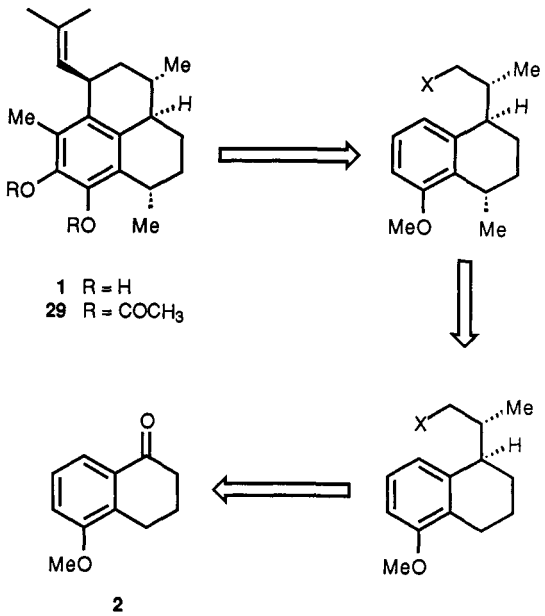
SECOPSEUDOPTEROSINS

Seco A - D : R^1 = (acetylated) Arabinose , R^2 = H :



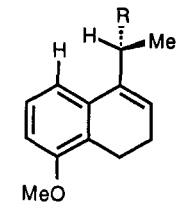
***Derived from Eremophila* terpenoids**

Scheme 1

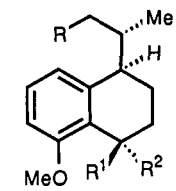


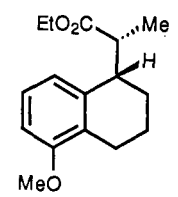
1 R = H
29 R = $COCH_3$

2



3 R = CO_2Et
5 R = CH_2OH





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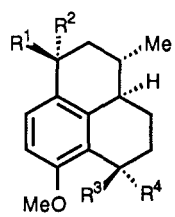
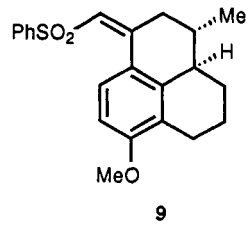
6 R = OH; $R^1 = R^2 = H$
7 R = CN; $R^1 = R^2 = H$
15 R = $OCOC_6H_4NO_2$-p; $R^1 = R^2 = H$
16 R = OH; $R^1R^2 = O$
18 R = OH; R^1 = Me; $R^2 = H$
19 R = OH; $R^1 = H$; R^2 = Me

reaction of 2 with ethyl 2-bromopropionate followed by dehydration of the reaction product yielded the olefin 3 which exists in the preferred conformation as shown, to avoid peri interactions. This, of course, has important consequences for establishing correct stereochemistries at C_3 and C_4 of pseudopterosin. Catalytic hydrogenation of 3 as expected delivered hydrogen from the least hindered side and yielded the undesired isomer 4 whose stereochemistry does not correspond to the pseudopterosins, but does correspond to the related Eremophilia terpenoids. To exploit the haptophilicity of alcohols and catalysts in hydrogenation processes, ester 3 was reduced to the homoallylic alcohol 5 which on homogenous hydrogenation (ref. 4) stereoselectively yielded compound 6 with the desired stereochemistry. Standard homologation and cyclization then gave the tricyclic ketone 8. Reaction of 8 with phenylsulfonylmethylcerium (III) chloride (ref. 5) yielded the olefin 9. Ionic hydrogenation of 9 with triethylsilane and trifluoroacetic acid yielded exclusively 10 possessing the undesired stereochemistry at C_1. The structure of 10 was proven using X-ray crystallographic analysis. Although 10 possessed the wrong stereochemistry because the hydride in the product was delivered from the axial side, we



8 $R^1R^2 = O$; $R^3 = R^4 = H$
11 R^1,R^2 = H,OH; $R^3 = R^4 = H$
12 $R^1 = CH_2CH{=}CH_2$; $R^2 = R^3 = R^4 = H$
13 $R^1 = CH_2CH_2CH_3$; $R^2 = R^3 = R^4 = H$
21 $R^1R^2 = O$; $R^3 = H$; R^4 = Me
22 R^1,R^2 = H,OH; $R^3 = H$; R^4 = Me
10 $R^1 = R^3 = R^4 = H$; $R^2 = CH_2SO_2Ph$
14 $R^1 = R^3 = R^4 = H$; $R^2 = CH_2CH_2CH_3$



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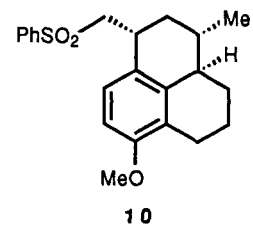

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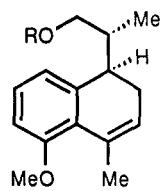
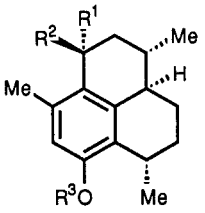
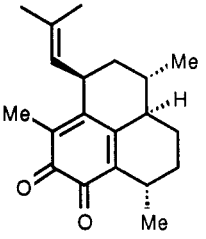


17 R = H
20 R = t-Bu_2SiH

asked whether the analogous 1-unsubstituted benzylic cation could be captured similarly on the axial side using "carbon nucleophiles" instead of a hydride donor. Thus the tricyclic ketone 8 was reduced to 11 and in the event when 11 was treated with allyltrimethylsilane and titanium tetrachloride, it yielded 12 with correct stereochemistry of the product at C_1, C_3 and C_4. The structure of 12 was proven by conversion to 13 and comparing its nmr spectrum with the C_1 epimer 14 obtained from 10. H_{10} in 13 appeared at δ6.94 and the corresponding proton in 14 appeared at δ7.05. Having achieved the synthesis of 12 possessing the tricyclic skeleton and correct stereochemistries of C_1, C_3 and C_4 of pseudopterosins we turned our attention towards stereoselectively introducing substitution at C_7. Thus, compound 15 was oxidized (ref. 6) with persulphate and cupric ion to obtain the benzylic ketone which upon methanolysis provided 16. Reaction of 16 with methylcerium chloride followed by dehydration yielded the olefin 17. Hydrogenation of 17 gave 18 with wrong stereoselectivity at C_7. However, trifluoroacetic acid-triethylsilane yielded a mixture of 18 and 19 and therefore decided to carry out the process in an intramolecular sense. We argued that the silane 20 on reaction (ref. 7) with trifluoroacetic acid should deliver hydride intramolecularly from the β-face thus yielding the C_7-methyl group in the desired α-orientation. Thus when the above reaction was carried out at high dilution favoring intramolecular reaction, we obtained almost exclusively (≥ 95:5) 19 from 20. With all the required reactions for stereocontrolled incorporation of substituents at C_1, C_3, C_4 and C_7 in hand, we next turned our attention towards incorporating proper functionalities at C_1 and the aromatic ring. Compound 19 was converted to (21) [compare (6)→(8)]. Reduction of 21 yielded 22, which on treatment (ref. 8) with tertiary butyl lithium followed by methyl iodide gave (23). Reactions of (23) with allylsilanes and Lewis acids indicated poor stereoselectivity compared with the 10-desmethyl series. However, use of a small incoming nucleophile restored high pseudoaxial selectivity: (23) reacted with diethylaluminum cyanide and stannic chloride to give (24) with >95% stereoselectivity. Reduction to aldehyde 25 followed by reaction with phenyl isopropyl sulphone anion and reduction of the crude product with sodium amalgam yielded 26 with the desired β-isobutenyl group at C_1. Compound 26 thus possessed the tricyclic system of



23 $R^1,R^2 = H,OH$; $R^3 = Me$
24 $R^1 = H$; $R^2 = CN$; $R^3 = Me$
25 $R^1 = H$; $R^2 = CHO$; $R^3 = Me$
26 $R^1 = H$; $R^2 = CH{=}CMe_2$; $R^3 = Me$
27 $R^1 = R^3 = H$; $R^2 = CH{=}CMe_2$



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pseudopterosin E with correct substitution and stereochemistry at C_1, C_3, C_4 and C_7. Demethylation of 26 with boron tribromide yielded the phenol 27 which underwent oxidation with Fremy's salt to give the ortho quinone 28. Reduction of 28 with $Na_2S_2O_4$ gave the desired quinol pseudopterosin aglycone 1 which was characterized as its diacetate 29. Authentic samples of 28, 1 and 29 were prepared from pseudopterosin E and the natural and synthetic samples were found to be identical in all respects (t.l.c., n.m.r., m.s., etc.).

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