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## Stereospecific synthesis of the aglycone of pseudopterosin E

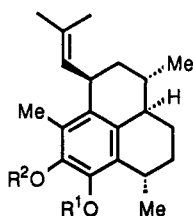
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Abstract - Aglycone 1 of pseudopterosin E has been synthesized from the tetralone 2 using several novel reactions to control stereoselectivity.

The pseudopterosins and secopseudopterosins are diterpene glycosides isolated (ref. 1) from the Caribbean Seawhip *Pseudoptero-gorgia 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

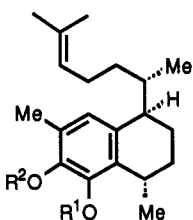


PSEUDOPTEROSINS

A - D : R<sup>1</sup> = (acetylated) D-Xylose , R<sup>2</sup> = H

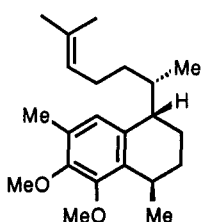
E : R<sup>1</sup> = H, R<sup>2</sup> = Fucose ; F : R<sup>1</sup> = H, R<sup>2</sup> = Arabinose

G - J : R<sup>1</sup> = (acetylated) Fucose , R<sup>2</sup> = H :



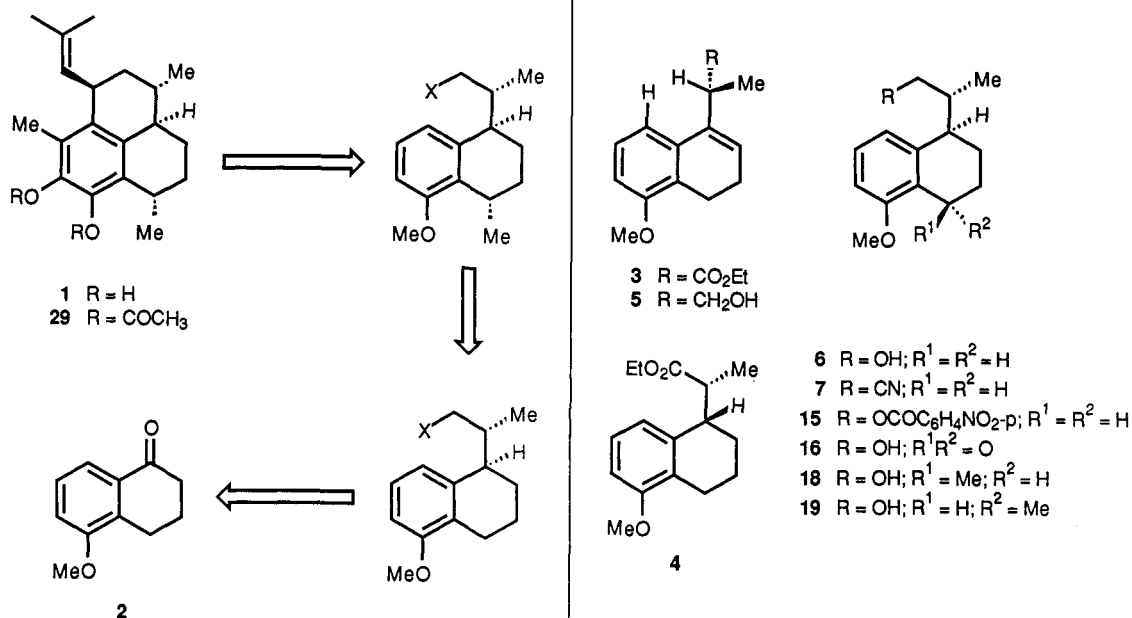
SECOPTEROSINS

Seco A - D : R<sup>1</sup> = (acetylated) Arabinose , R<sup>2</sup> = H :

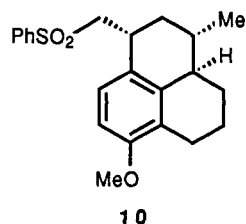
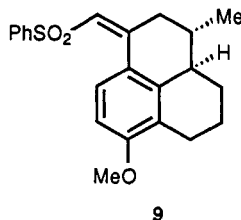
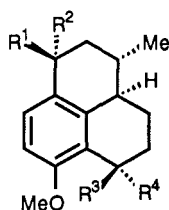


Derived from *Eremophila terpenoids*

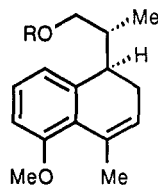
Scheme 1



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<sub>3</sub> and C<sub>4</sub> 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 *Eremophila* 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<sub>1</sub>. 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

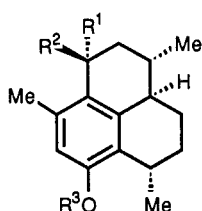


- 8 R<sup>1</sup>R<sup>2</sup> = O; R<sup>3</sup> = R<sup>4</sup> = H  
11 R<sup>1</sup>, R<sup>2</sup> = H, OH; R<sup>3</sup> = R<sup>4</sup> = H  
12 R<sup>1</sup> = CH<sub>2</sub>CH=CH<sub>2</sub>; R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = H  
13 R<sup>1</sup> = CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>; R<sup>2</sup> = R<sup>3</sup> = R<sup>4</sup> = H  
21 R<sup>1</sup>R<sup>2</sup> = O; R<sup>3</sup> = H; R<sup>4</sup> = Me  
22 R<sup>1</sup>, R<sup>2</sup> = H, OH; R<sup>3</sup> = H; R<sup>4</sup> = Me  
10 R<sup>1</sup> = R<sup>3</sup> = R<sup>4</sup> = H; R<sup>2</sup> = CH<sub>2</sub>SO<sub>2</sub>Ph  
14 R<sup>1</sup> = R<sup>3</sup> = R<sup>4</sup> = H; R<sup>2</sup> = CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>

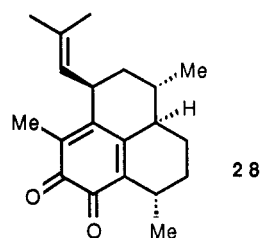


- 17 R = H  
20 R = *t*-Bu<sub>2</sub>SiH

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<sub>1</sub>, C<sub>3</sub> and C<sub>4</sub>. The structure of **12** was proven by conversion to **13** and comparing its nmr spectrum with the C<sub>1</sub> epimer **14** obtained from **10**. H<sub>10</sub> in **13** appeared at  $\delta$ 6.94 and the corresponding proton in **14** appeared at  $\delta$ 7.05. Having achieved the synthesis of **12** possessing the tricyclic skeleton and correct stereochemistries of C<sub>1</sub>, C<sub>3</sub> and C<sub>4</sub> of pseudopterosins we turned our attention towards stereoselectively introducing substitution at C<sub>7</sub>. 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<sub>7</sub>. 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 on reaction (ref. 7) with trifluoroacetic acid should deliver hydride intramolecularly from the  $\beta$ -face thus yielding the C<sub>7</sub>-methyl group in the desired  $\alpha$ -orientation. Thus when the above reaction was carried out at high dilution favoring intramolecular reaction, we obtained almost exclusively ( $\geq$  95:5) **19** from **20**. With all the required reactions for stereocontrolled incorporation of substituents at C<sub>1</sub>, C<sub>3</sub>, C<sub>4</sub> and C<sub>7</sub> in hand, we next turned our attention towards incorporating proper functionalities at C<sub>1</sub> and the aromatic ring. Compound **19** was converted to (**21**) [compare (6)  $\rightarrow$  (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  $\beta$ -isobutenyl group at C<sub>1</sub>. Compound **26** thus possessed the tricyclic system of



- 23** R<sup>1</sup>, R<sup>2</sup> = H, OH; R<sup>3</sup> = Me  
**24** R<sup>1</sup> = H; R<sup>2</sup> = CN; R<sup>3</sup> = Me  
**25** R<sup>1</sup> = H; R<sup>2</sup> = CHO; R<sup>3</sup> = Me  
**26** R<sup>1</sup> = H; R<sup>2</sup> = CH=CMe<sub>2</sub>; R<sup>3</sup> = Me  
**27** R<sup>1</sup> = R<sup>3</sup> = H; R<sup>2</sup> = CH=CMe<sub>2</sub>



pseudopterosin E with correct substitution and stereochemistry at C<sub>1</sub>, C<sub>3</sub>, C<sub>4</sub> and C<sub>7</sub>. 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<sub>2</sub>S<sub>2</sub>O<sub>4</sub> 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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