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CONTROLLING BENZYLIC FUNCTIONALITY AND STEREOCHEMISTRY: 2. SYNTHESIS OF THE PSEUDOPTEROSIN AGLYCONE

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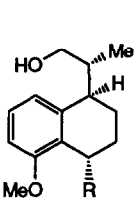
Abstract: Homologation, cyclisation, and reduction converted the tetralin (2) to the hexahydrophenalenol (8), which was methylated to afford (19) *via* alkoxide-directed metalation. The degree of stereoselectivity resulting from reactions of (19) and congeners with allylsilane - Lewis acid combinations was markedly dependent upon substitution patterns, whereas Et_2AlCN-$SnCl_4$ produced *pseudo*axial nitriles. The trimethyl nitrile (24) was elaborated to the pseudopterosin aglycone (4).

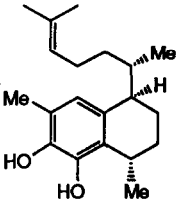
In the accompanying paper,[1] we described a highly stereocontrolled route from 5-methoxytetralone *via* (1) to (2), which in turn was elaborated to (3), the aglycone of the secopseudopterosins.[2]

Relative stereocontrol in the synthesis of (3) was achieved through *intra*molecular reductive processes. In this paper, we outline new aspects of the *inter*molecular reactions of benzylic carbonium ions with nucleophiles, and their application to the conversion of (2) to (4), the aglycone of the anti-inflammatory pseudopterosins.[3] Conversion of (2) to (4) requires formation of the third ring, Ar ring functionalisation, and introduction of the *pseudo*axial C-1 substitutient.

Alcohols (1) and (2) were transformed [TsCl, pyr, 23°; NaCN, DMSO, 65°; $MeSO_3H$, 1,2-$C_2H_4Cl_2$, 85°, 2 h, then NaOAc-H_2O, 85°, 2 h,[4]] to the tricyclic ketones (5) and (6) in 60-70% overall yield. Reduction of these ketones [$NaBH_4$] afforded alcohols (7) and (8) as C-1 epimer mixtures (α:β = 4:1).



1 R = H
2 R = Me



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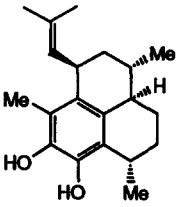
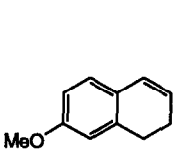


4

5 R = H, X = O
6 R = Me, X = O
7 R = H, X = H,OH
8 R = Me, X = H,OH

Model studies in which 6-methoxy-1-tetralol was treated with Lewis or protic acids in CH_2Cl_2 containing 1.5-5 eq. of a nucleophilic agent showed that *only highly reactive traps led to efficient C-C1 bond formation.* Competing proton loss affords the dihydronaphthalene (9), a *p*-methoxystyrene which is itself an excellent carbonium ion trap. A variety of potentially useful agents (CH_2=$CHSiMe_3$, $(CH_2$=$CH)_4Sn$, CH_2=CHOEt and Me_3SiCN) gave mixtures containing <30% of trapping product, with substantial amounts of the known[5] dimer (10). As anticipated from their highly nucleophilic character,[6] and some precedents in benzylic systems,[7] allylsilanes were excellent traps: (11) was obtained quantitatively using $SnCl_4$ - CH_2=$CHCH_2SiMe_3$ in CH_2Cl_2 at -70°. Under the same conditions, tricyclic alcohol (7) afforded a 92% yield of products, with a predominance of the desired *pseudo*axial compound (the ratio of (12):(13) was 12:1). In a cyclohexanone ketal system, axial allylation was also preferred.[8] The reversed sequence (CH_2=$CHCH_2MgBr$, then excess

Et_3SiH, $SnCl_4$ in CH_2Cl_2 at -70°) converted (7) to (13), *via* axial delivery of hydride. Characteristic PMR shift differences for H-10 were seen in these 3α-methyl compounds, and also in the 3-desmethyl series.[9]



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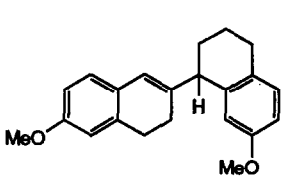

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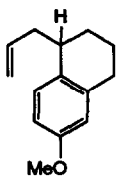

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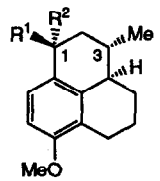
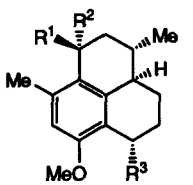


12 $R^1 = CH_2CH{=}CH_2$, $R^2 = H$
13 $R^1 = H$, $R^2 = CH_2CH{=}CH_2$
22 $R^1 = CN$, $R^2 = H$

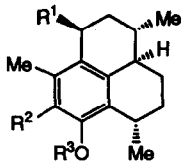
Local steric effects easily offset the stereoselectivity of the allylation. Under comparable conditions, the ratios of *ax:eq* substituted product from (7) and $CH_2{=}C(R)CH_2SnBu_3$[10] were 10:1 and 6:1 for **R** = H and Me, respectively. A *pseudo*axial 3β-methyl group had a pronounced effect; the alcohol[11] (14) afforded exclusively (15), the product of equatorial attack. This was also the major product (15:17 = 2:1) from reaction of (16) with Et_3SiH - $SnCl_4$; the smaller nucleophile still favours the axial direction. In the well-studied C-1 allylation of carbohydrate derivatives, dominant axial attack (α-C-glycoside formation) can usually be secured by selecting the appropriate solvent, promoter and leaving group, taking advantage of the additional effect of the oxygen lone pairs in conditions favoring the more "open" carbonium ion.[12]

14 $R^1,R^2 = H,OH$
15 $R^1 = H$, $R^2 = CH_2CH{=}CH_2$
16 $R^1,R^2 = OH,CH_2CH{=}CH_2$
17 $R^1 = CH_2CH{=}CH_2$, $R^2 = H$

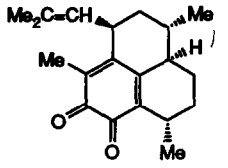


18 $R^1,R^2 = H,OH$; $R^3 = H$
19 $R^1,R^2 = H,OH$; $R^3 = Me$
20 $R^1 = CH_2C(Me){=}CH_2$, $R^2 = R^3 = H$
21 $R^1 = R^3 = H$, $R^2 = CH_2C(Me){=}CH_2$
23 $R^1 = CN$, $R^2 = R^3 = H$
24 $R^1 = CN$, $R^2 = H$, $R^3 = Me$

The trend towards less selective attack was further exacerbated by the presence of the C-10 methyl group characteristic of the natural products. We installed this group by alkoxide-directed metalation, taking advantage of the poor directing effect of the 8-MeO group in these systems; alcohols (7) and (8) were converted [4 eq. *t*-BuLi, Et_2O-pentane, 35°, 15 min., then 10 eq. MeI, 0°] to (18) and (19), respectively.[13] Reaction of (18) with $CH_2{=}C(Me)CH_2SnBu_3$ - $SnCl_4$ gave the desired *pseudo*axial product (20) in only 3:2 ratio with (21), a result little affected by varying the reaction conditions. While the reason for this effect of the *Ar* methyl group remains obscure,[14] an alternative was clearly needed to achieve our goal of high stereoselectivity; we found this in the use of *a smaller C-nucleophile*. Although Me_3SiCN was not an effective trap, more nucleophilic cyanide sources, in combination with a Lewis acid, were suitable. Thus, reaction of the 7,10-desmethyl alcohol (7) with Et_2AlCN (5 eq.) and $SnCl_4$ or $BF_3.Et_2O$ (2 eq.) in CH_2Cl_2 afforded 60-70% of nitrile (22) [7:1 at 25°, 16:1 at -70°][15], easily separated from minor products.[16] Significantly, this new method was *insensitive* to the presence of a 10-methyl group; both (18) and (19) gave the nitriles (23) and (24) containing <5% of their *eq* epimers. [The 3β-methyl alcohol (14), however, produced mostly the *pseudo*equatorial nitrile].



25 R^1 = CHO, R^2 = H, R^3 = Me
26 R^1 = CH=CMe$_2$, R^2 = H, R^3 = Me
27 R^1 = CH=CMe$_2$, R^2 = R^3 = H
29 R^1 = CH=CMe$_2$, R^2 = OAc, R^3 = Ac



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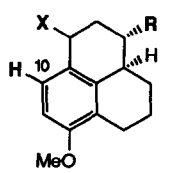
Compound (24) has the correct stereocenters for the target aglycone, and was converted to (4) as follows: Reduction [*i*-Bu$_2$AlH, toluene, -70°] gave the sensitive aldehyde (25),[17] which was converted to the deoxypseudopterosin derivative (26) through the β-hydroxysulfone[18] [Me$_2$C(Li)SO$_2$Ph, THF, -70°; Na-Hg, K$_2$HPO$_4$, MeOH] in 55% overall yield. Demethylation [BBr$_3$, 2,6-di-*t*-butylpyridine, CH$_2$Cl$_2$, 0°] gave phenol (27), which was oxidised cleanly [ON(SO$_3$K)$_2$, KH$_2$PO$_4$, acetone-H$_2$O, 0°][19] to the sensitive *o*-quinone (28). After extraction, this was reduced [Na$_2$S$_2$O$_4$, H$_2$O, CH$_2$Cl$_2$][21] to the aglycone (4), acetylation of which gave diacetate (29). Authentic samples of (4), (28), and (29) were prepared from pseudopterosin E,[22] and were spectroscopically and chromatographically identical with our synthetic materials.[23]

Acknowledgements: We thank the Physical-Analytical department for spectra and analyses. Special thanks to Professor William Fenical, for a generous gift of pseudopterosin E.

References and Notes:

1. Preceding paper
2. Look, S. A.; Fenical, W. *Tetrahedron*, **1987**, *43*, 3363-3370.
3. (a) Look, S. A.; Fenical, W.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.*, **1986**, *51*, 5140-5145. (b) Look, S. A.; Fenical, W.; Jacobs, R. S.; Clardy, J. *Proc. Nat. Acad. Sci. U.S.A.* **1986**, *83*, 6238-6240.
4. A rather stable intermediate imine formed in the first step, and required hydrolysis with hot buffer.
5. Johnson, W. S.; Anderson, J. M.; Shelberg, W. E. *J. Am. Chem. Soc.*, **1944**, *66*, 218-222; Clark-Lewis, J. W.; Nair, V. *Aust. J. Chem.*, **1967**, *20*, 2137-2149.
6. Mayr, H.; Pock, R. *Tetrahedron*, **1986**, *42*, 4211-4214. For a comprehensive review of allyl- and vinylsilane chemistry, see: Fleming, I.; Dunoques, J.; Smithers, R. *Org. Reacts.*, **1989**, *37*, 57-575.
7. Allylsilanes with arylcarbinols: Cella, J. A. *J. Org. Chem.*, **1982**, *47*, 2125-2130; with tetralol-Cr(CO)$_3$ complexes: Uemura, M; Kobayashi, T.; Hayashi, Y. *Synthesis*, **1986**, 386-388.
8. Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Letts.*, **1980**, *21*, 71-74.
9. PMR shifts (δ, in CDCl$_3$) for H-10 in compounds (i) are shown in the table:



(i)

X	R = H	R = Me
α-OH	7.34	7.38
β-OH	7.19	7.19
α-Allyl	7.08	7.10
β-Allyl	6.99	6.98
α-PhSO$_2$CH$_2$	6.84	6.83
β-PhSO$_2$CH$_2$	6.73	6.74
α-CN	-	7.25
β-CN	-	7.14

The 1-($PhSO_2CH_2$) derivatives were prepared from the 1-ketones (excess $PhSO_2CH_2CeCl_2$, followed by reduction of the resulting unsaturated sulfones). X-Ray crystallography confirmed the stereochemistry of the 3-desmethyl-1α-(phenylsulfonyl)-compound.

10. Silanes and stannanes both gave high yields. The allylsilanes afforded slightly higher *ax:eq* ratios.
11. Prepared from the diastereoisomer of alcohol (**1**) [ref. 1] by the route used to obtain (**5**) from (**1**).
12. Giannis, A.; Sandhoff, K. *Tetrahedron Letts.*, **1985**, *26*, 1479-1482; Kozikowski, A. P.; Sorgi, K. L. *ibid*, **1983**, *24*, 1563-1566; *indem, ibid*, **1982**, *22*, 2281-2284; Hosomi, A,; Sakata,H.; Sakurai, H. *ibid*, **1984**, *25*, 2283-2286; Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.*, **1982**, *104*, 4976-4978.
13. 95% recovery of product, which usually contained 10-15% starting material, possibly from competing electron transfer followed by proton abstraction. Since the alcohols tended to dehydrate on chromatography, separation was deferred until the C-C1 bond had been established in the next step. For metalation of benzyl alkoxides, see: Meyer, N.; Seebach, D. *Angew. Chem. Int. Edit. Engl.*, **1978**, *17*, 521-522.
14. In simple product stability terms, the more pronounced A(1,3) interaction in the *eq* isomer should compete with the usual cyclohexane *ax* isomer destabilisation. Clearly, this is not kinetically significant in these reactions, as it would be expected to *increase* the proportion of axial attack in the 10-methyl series.
15. Deprotonation-reprotonation ($LiN(SiMe_3)_2$; HOAc) returned a 1:1 isomer mixture.
16. Small amounts of recovered alcohol, 1-EtCO compound, and olefin were detected. With Bu_3SnCN in place of Et_2AlCN, a modest yield of nitrile was accompanied by much olefin, and the latter was the major product with $Bu_4N^+CN^-$ - $SnCl_4$.
17. Equilibration with DBU in $CDCl_3$ gave an approximately 2:3 *ax:eq* mixture. The 10-desmethyl aldehydes isomerised more readily, and decomposed on treatment with DBU.
18. Julia, M.; Paris, J-M. *Tetrahedron Letts*, **1973**, 4833-4836. With aldehyde (**25**), we observed some epimerisation on reaction with $Me_2C{=}PPh_3$; during the course of our studies, Wittig olefination of a related aldehyde was reported in a synthesis of pseudopterosins: Corey, E. J.; Carpino, P. *J. Am. Chem. Soc.*, **1989**, *111*, 5472-5474. In an earlier synthesis, olefination via a β-hydroxyester was used: Broka, C. A.; Chan, S.; Peterson, B. *J. Org. Chem.*, **1988**, *53*, 1584-1586.
19. Teuber, H-J.; Staiger, G. *Chem. Ber.*, **1955**, *88*, 802-827.
20. The *o*-quinone (**28**) was unstable to prolonged contact with silica gel, and decomposed somewhat on concentrating solutions. A washed $CDCl_3$ extract of the oxidation mixture gave the following PMR spectrum: δ = 1.03(*d*,3), 1.07(*d*,3), 1.72(*s*,6), 1.80(*s*,3), 2.96(*m*, 1), 3.61(*m*,1), and 5.06(*d*,1). From reduction of this material, we obtained the catechol (**4**), PMR (CDCl3): δ = 1.03(*d*,3), 1.16(*d*,3), 1.16(*s*,3), 2.03(*s*,3), 3.23(*m*,1), 3.59(*m*,1), 4.85(*s*,1, exch. by D_2O), 5.06(*s*,1, exch. by D_2O), and 5.12(*d*,1).
21. $Na_2S_2O_4$, in contrast to Na_2SO_3, effected rapid, clean reduction of *o*-quinones in this biphasic system.
22. Anaerobic hydrolysis gave catechol (**4**), oxidised to *o*-quinone (**28**) with Fremy"s salt; see ref. 20 for PMR spectra.
23. All new compounds gave PMR, MS, and HRMS or microanalytical data fully consistent with the assigned structures.

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