Tetrahedron Letters, Vol.32, No.19, pp 2083-2086, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

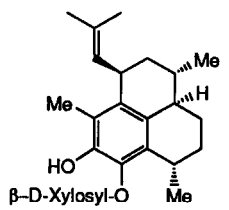
CONTROLLING BENZYLIC FUNCTIONALITY AND STEREOCHEMISTRY: 1. SYNTHESIS OF THE SECOPSEUDOPTEROSIN AGLYCONE

Stuart W. McCombie, Brian Cox, Sue-Ing Lin and Ashit K. Ganguly*
Chemical Research, Schering-Plough Corporation, 60 Orange Street, Bloomfield, N.J. 07003, U.S.A.
and
Andrew T. McPhail
Paul M. Gross Chemical Laboratories, Duke University, Durham, N.C. 27706, U.S.A.

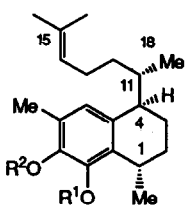
Abstract: Directed, homogeneous hydrogenation of 1-(1-hydroxymethylethyl)-5-methoxy-3,4-dihydronaphthalene (**7**), followed by protection and selective benzylic oxidation gave the 1-oxo-(*4R*, 11R**) compound (**13**). After addition of $MeCeCl_2$, the natural C-1 stereochemistry was established by intramolecular hydride delivery from the di-t-butylsilylether. Final elaboration of the sidechain and the Ar ring substituents gave the secopseudopterosin aglycone ether (**3**).

Pseudopterosin A (**1**)[1] and secopseudopterosin A (**2**)[2] are members of a family of diterpenes isolated from *pseudopterogorgia sp.* by Fenical and co-workers. The potent anti-inflammatory activity of these substances[3] gives good reason to regard them as targets for flexible, stereocontrolled syntheses. Two routes to the tricyclic system have appeared,[4,5] having in common the annelation of an aromatic ring onto a terpene-derived unit in which three stereocenters were already established. In this paper, we outline a conceptually different, tetralone-based route to the racemic secopseudopterosin aglycone ether (**3**), with >20:1 relative stereocontrol at each stereocenter.

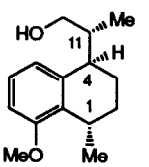
Our route to key intermediate (**4**) from 5-methoxytetralone (**5**) utilises a directed hydrogenation in conjunction with a selective functionalisation of a benzylic methylene group. The final stereocenter is established by a different type of directed reduction, using *intramolecular ionic hydrogenation* as a new method for controlling benzylic stereochemistry. In the accompanying paper, we describe the conversion of (**4**) to the tricyclic series, and other aspects of chemo- and regioselectivity in benzylic carbonium ion chemistry.



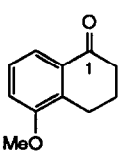
1



2 R^1 = α-D-Arabinosyl, R^2 = H
3 R^1 = H, R^2 = Me

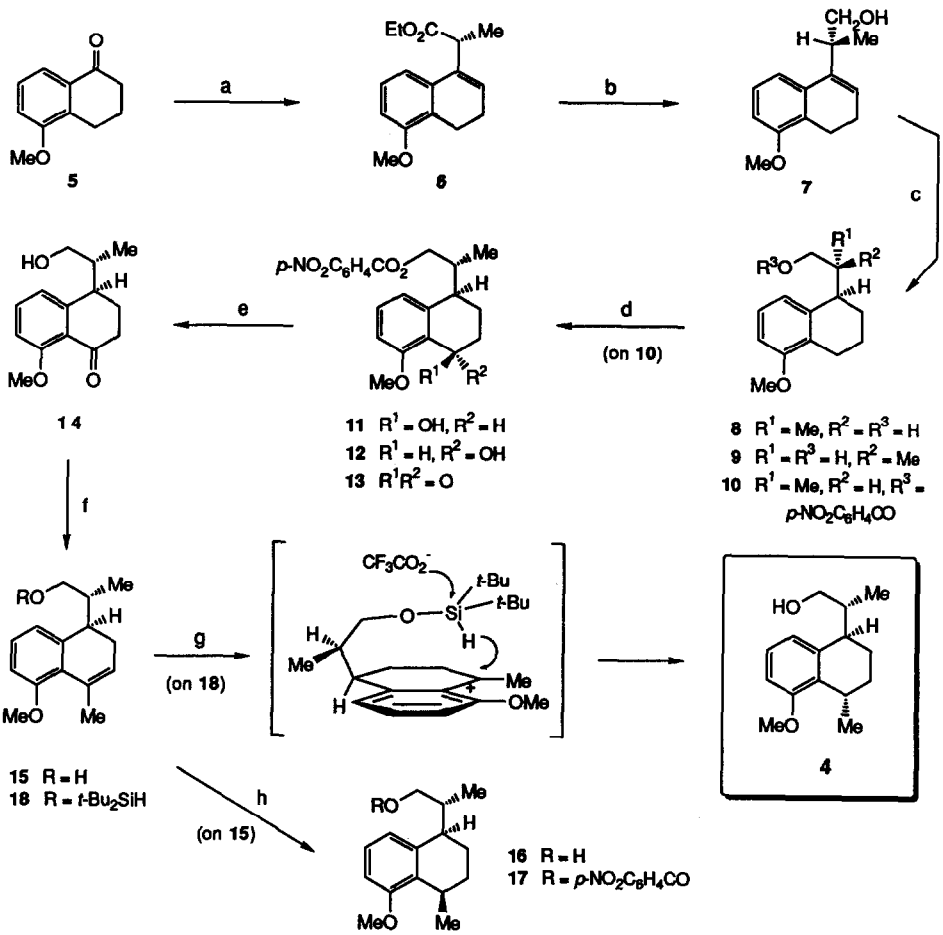


4



5

The conversion of (**5**) to (**4**) is shown in **Scheme 1**. Reformatsky reaction[6] [Zn, $MeCHBrCO_2Et$, Me_3SiCl activation, THF, 65°], followed by dehydration [MsOH, 1,2-$C_2H_4Cl_2$, 80°] afforded racemic[7] ester (**6**), which was reduced [$NaH_2Al(OCH_2CH_2OMe)_2$, Et_2O] to homoallylic alcohol (**7**) [mp 63-65°; 75-85%]. Dihydronaphthalenes (**6**) and (**7**) have a strongly preferred solution conformation,[8] depicted for (**7**), which minimises interactions with the *peri*-ArH and differentiates the diastereotopic faces of the olefin, permitting stereoselective reduction.



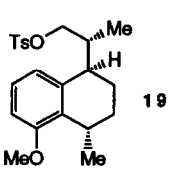
Reagents (see text for details): **a:** Zn, $MeCHBrCO_2Et$; MsOH. **b:** Red-Al. **c:** $ClRh(PPh_3)_3$, H_2, *t*-BuOK *or* H_2, Pd-C; *p*-$NO_2C_6H_4COCl$, py. **d:** $K_2S_2O_8$, $CuSO_4$. **e:** PCC; NaOMe. **f:** $MeCeCl_2$; TsOH; *t*-Bu_2SiHCl, imidazole. **g:** CF_3CO_2H (high dilution); *n*-Bu_4NF. **h:** H_2, Pd-C.

Scheme 1

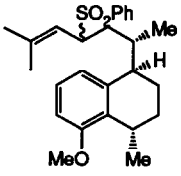
Although normal reduction [H_2, Pd-C] of (**7**) gave a 3:2 mixture of (**8**) and epimer (**9**)[9] [δ values ($CDCl_3$) for $CHCH_3$ *in* (**8**) *and* (**9**) *were* 0.77 *and* 1.04, *respectively*], directed homogeneous reduction[10] by the method of Thompson[11] [0.05 eq. $ClRh(PPh_3)_3$, 0.1 eq. *t*-BuOK, 60 psi H_2, THF, 23°, 50 h] afforded (**8**)/(**9**) in >95:5 ratio. Complete purity was secured upon one recrystallization of the derived *p*-nitrobenzoate (**10**) [mp 90-92°; 86% from (**7**)]. Selective oxidation was obtained by modifiying a known procedure:[12] treatment of (**10**) with $K_2S_2O_8$ (2 eq.), $CuSO_4$ (0.2 eq.) and *sym*-collidine[13] (2 eq.) in MeCN-H_2O [1:1, 80°, 1.5 h] gave a mixture of alcohols (**11**)/(**12**) and ketone (**13**). Oxidation of this mixture [PCC,[14] *celite*, CH_2Cl_2] *provided* (**13**) [63% *from* (**10**)]. *Following hydrolysis*, treatment with $MeCeCl_2$[15] [THF, -70 to 23°] and subsequent dehydration [TsOH] gave olefin (**15**) in 72% yield from (**13**).

Olefin (15) was inert to H_2/*t*-BuOK/ClRh(PPh_3)$_3$, but was reduced [H_2, Pd-C] from the less hindered face to isomer (16), epimeric[16] at C-1 with the natural series. With Et_3SiH-CF_3CO_2H, a 2:3 mixture of (16) and the desired (4) was produced [δ values ($CDCl_3$) for $CHCH_3$: for (4), 0.87 and 1.16, and for (16), 0.68 and 1.18]. The rapid, clean nature of this "ionic hydrogenation"[17] suggested the application of an *intramolecular* version[18] to secure the needed stereochemistry. Accordingly, (15) was converted [2 eq. *t*-Bu_2SiHCl, 3 eq. imidazole, DMF, 23°] to the ether[19] (18). Syringe pump addition[20] [16-20 h] of (18) in CH_2Cl_2 to CF_3CO_2H [5 eq., 0.1M in CH_2Cl_2] followed by desilylation [*n*-Bu_4NF, THF, 23°] gave (4) of >95% isomeric purity in 65-75% yield from (15), 19-24% overall from 5-methoxytetralone.

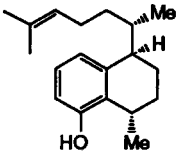
Alcohol (4) was converted to the aglycone ether (3) as follows: tosylate (19), treated with Me_2C=CHCH(Li)SO_2Ph [THF, -70 to 23°], afforded diastereoisomer mixture (20).[21] Desulfonylation of (20) [Li, $EtNH_2$][22] was accompanied by demethylation to yield (21) containing 8-13% of (22). After protection [$MeOCH_2Cl$, *i*-Pr_2NEt] to afford (23), metalation[23] was effected [*t*-BuLi, Et_2O, 0°]. Workup with $B(OMe)_3$ followed by H_2O_2-H_2O-K_2CO_3[24] gave catechol ether (24), and Mannich reaction [aq. CH_2O, morpholine, EtOH, 80°] produced (25).



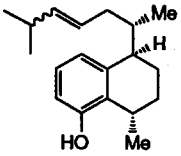
19



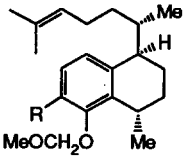
20



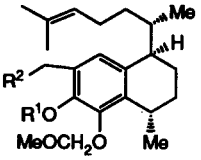
21



22



23 R = H
24 R = OH



25 R^1 = H, R^2 = $N(CH_2CH_2)_2O$
26 R^1 = COCl, R^2 = Cl
27 R^1 = R^2 = H

Mannich base (25) was resistant to both hydride reagents and Na-NH_3, but was efficiently converted to the chloromethyl compound (26) [3 eq. CCl_3OCOCl, 4 eq. *sym*-collidine or *i*-Pr_2NEt, CH_2Cl_2, 0-23°, 6 h]. Reduction [$NaBH_4$, DMSO] followed by hydrolysis[25] [NaOH, aq. EtOH] gave C6-methyl compound (27), which was O-methylated [MeI, K_2CO_3, acetone]. Final hydrolysis of the MOM ether [TsOH, MeOH] then provided (3), identical (TLC, MS, 400MHz PMR) with a sample prepared[2] from secopseudopterosin.

Acknowledgements: We thank Professor W. Fenical for an authentic sample of (3), and the Physical-Analytical department for spectra and analyses.[26]

References and Notes:

1. Look, S. A.; Fenical, W.; Matsumoto, G. K.; Clardy, J. *J. Org Chem.*, **1986**, *51*, 5140-5145
2. Look, S. A.; Fenical, W. *Tetrahedron*, **1987**, *43*, 3363-3370.
3. Look, S. A.; Fenical, W.; Jacobs, R. S.; Clardy, J. *Proc. Nat. Acad. Sci. USA*, **1986**, *83*, 6238-6240.
4. Broka, C. A.; Chan, S.; Peterson, B. *J. Org. Chem.*, **1988**, *53*, 1584-1586.

5. Corey, E. J.; Carpino, P. *J. Am. Chem. Soc.*, **1989**, *111*, 5472-5474.
6. *Review:* Furstner, A. *Synthesis*, **1989**, 571-590.
7. The derived acid is an obvious point for chiral intervention; these studies are in progress.
8. The *peri*-ArH in (**6**) showed a strong NOE with the allylic methine, but very weak effects with other protons.
9. Over Pd-C, (**6**) was reduced with 94:6 selectivity for the *epimeric* series. This provides potentially useful intermediates for the serrulatane series of diterpenes (see: Croft, K. D.; Ghisalberti, E. L.; Jefferies, P. R,; Proudfoot, G. M. *Aust. J. Chem.*, **1981**, *34*, 1954-1957.). For a very recent synthesis of dihydroxy serrulatic acid *via* Tetralin-$Cr(CO)_3$ complexes, see; Uemura, M.; Nishimura, H.; Hayashi, Y. *Tetrahedron Letts.*, **1990**, *31*, 2319-2322.
10. *Review:* Brown, J. M. *Angew. Chem. Int. Edit. Engl.*, **1987**, *26*, 190-203.
11. Thompson, H. W.; McPherson, E. *J. Am. Chem. Soc.*, **1974**, *96*, 6232-6233. This process, which utilises the anionic species to ensure entry into the coordination sphere of the metal complex, permits the use of the air-stable $ClRh(PPh_3)_3$, and also allowed highly diastereoselective reduction of the corresponding *carboxylate* [H_2, $ClRh(PPh_3)_3$ in $EtOH\text{-}H_2O\text{-}NaHCO_3$]. $LiAlH_4$ reduction of the dihydroacid afforded pure (**8**).
12. Bhatt, M. V.; Perumal, P. T. *Tetrahedron Letts.*, **1981**, *22*, 2605-2608.
13. This more hindered buffer was tried on the assumption that pyridine (which gave ca. 30% of the alcohol/ketone mixture) was intercepting radical and/or cationic intermediates.
14. Corey, E. J.; Suggs, J. W. *Tetrahedron Letts.*, **1975**, 2647-2650.
15. Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Letts.*, **1984**, *25*, 4233-4236. Other organometallics (MeMgBr, $Ph_3P{=}CH_2$ and Me_3SiCH_2MgCl) caused extensive enolate formation from (**14**).
16. Confirmed by an X-ray structure determination on the *p*-nitrobenzoate (**17**). Details may be obtained from A. T. McP.
17. *Review:* Kursanov, D. N.; Parnes, Z.; Loim, N. M. *Synthesis*, **1974**, 633-651.
18. One reaction of this type, involving reduction of a ketone through a 6-membered transition state, has been described: Anwar, S.; Davis, A. P. *J. C. S. Chem. Commun.* **1986**, 831-832.
19. $RCH_2OSiHt\text{-}Bu_2$ showed acid stability similar to $RCH_2OSiMe_2t\text{-}Bu$; the less hindered $RCH_2OSiHMe_2$ and $RCH_2OSiHPh_2$ were labile to weak acids and to silica gel.
20. From rapid addition of excess CF_3CO_2H to solutions of (**18**), the ratios of (**3**):(**16**) were 3:2 at $5x10^{-2}$M and 5:1 at $5x10^{-3}$ M. High dilution ensured dominance of the intramolecular transfer, through the 9-membered transition state depicted in **Scheme 1**. We believe that this type of process will be of general use for stereocontrol, and we are currently examining the scope and limitations with respect to tether, ring size and functionality in systems involving benzylic, oxocarbonium and iminium ions.
21. A variety of cuprate-based, direct prenylations of (**19**) or the corresponding chloride gave regioisomer mixtures.
22. Greico, P. A.; Masaki, Y. *J. Org. Chem.*, **1974**, *39*, 2135-2136.
23. The MeO group was not an effective director of *ortho*-metalation in 5-methoxytetralins.
24. Compare: Kidwell, R. L.; Murphy, M.; Darling, S. D. *Org. Syn. Coll. Vol. V*, Wiley, New York, **1973**, 918-921.
25. The major product from the $NaBH_4$ step was the symmetrical carbonate of phenol (**27**).
26. All new compounds gave satisfactory elemental analyses and/or high resolution mass spectra.

(Received in USA 9 October 1990)