Pergamon

Tetrahedron Letters, Vol. 35, No. 41, pp. 7677-7680, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01603-8

An Efficient Synthesis of a Chiral Carbocyclic 2'-Deoxyribonucleoside Synthon by Directed Reduction

Alan D. Borthwick*, Andrew J. Crame, Anne M. Exall, and Gordon G. Weingarten.

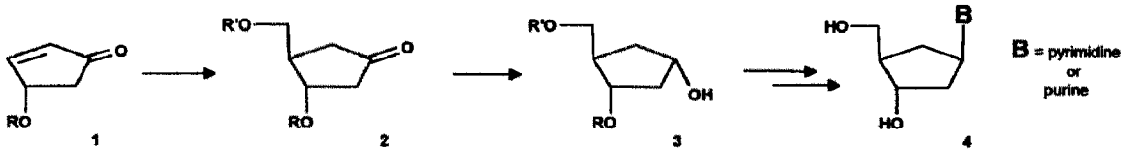
Department of Medicinal Chemistry II, Glaxo Research and Development Ltd, Greenford, Middlesex UB6 OHE. UK

Abstract: Directed reduction of the 1,4 hydroxy-ketone **9** and the 1,4 aldehydo-ketone **12** with $NaBH(OAc)_3$ gave stereoselectively in high yield the 1,4 diol **10**, a key intermediate required in our synthesis of chiral carbocyclic 2'- deoxyribonucleosides.

Chiral carbocyclic nucleosides have attracted considerable attention as antiviral[1], antitumour[2] and purinergic agents[3] as well as antisense oligonucleotides[4]. As a result there are a large number of synthetic approaches[5] to chiral carbocyclic nucleosides, the more efficient and flexible of which are the convergent approaches where the intact base is coupled directly to a suitably functionalised carbocylic moiety. This has been illustrated by a variety of convergent syntheses to chiral carbocyclic *ribo*nucleosides[5]. In contrast there are relatively few convergent syntheses[6,4c] tailored to chiral carbocyclic *2'-deoxyribo*nucleosides **4**.

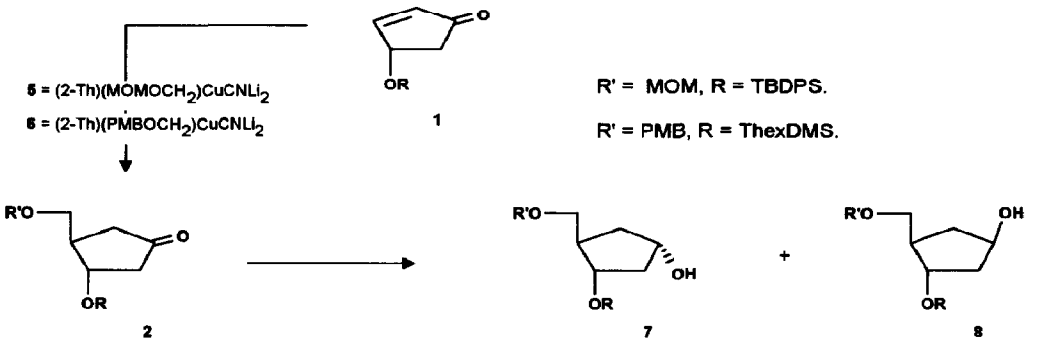
In our search for a short, efficient and convergent synthesis of chiral carbocyclic 2'-deoxyribonucleosides we were attracted by the simplicity of forming the required carbocyclic ring **3** in two stages. First by 1,4 addition of a one carbon fragment to a chiral cyclopentenone **1**, a strategy that has been successfully exploited in the prostaglandin field[7] and in the synthesis of aristeromycin[8], followed by stereoselective reduction of the resulting ketone **2** as illustrated in Scheme 1.

Scheme 1



Our initial approach is illustrated in Scheme 2. Conjugate 1,4-addition of the higher order cuprate **5** derived from the methoxymethoxymethyllithium[9] and lithium 2-thienyl cyanocuprate[10], to the S-enone[11] **1** (R = TBDPS) gave the cyclopentanone **2** (R' = MOM, R = TBDPS) in 67% yield. Similarly the PMB analogue **6** derived from *para*methoxybenzyloxymethyllithium[13] was added to enone **1** (R = ThexDMS) to give **2** (R' = PMB, R = ThexDMS) in 69% yield. Stereoselective reduction of ketone **2** was expected to give, via steric control, predominantly the required α alcohol **7**, based on literature precedents[14,15]. However with a range of different reagents (Scheme 2) only marginal stereoselective reduction was seen. The mixtures of alcohols **7** and **8** were produced in ≥ 70% isolated yield.

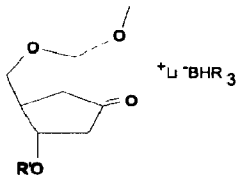
Scheme 2



R' = MOM, R = TBDPS				
	Red-Al / -70°	1	:	1
	DIBAL /-70°	1	:	1
	$NaBH_4$ / IPA / -70° to RT	3	:	2
	$LiBu^s_3BH$ /-70°	1	:	3
R' = PMB;R = ThexDMS				
	Red-Al / -70°	3	:	2
	DIBAL /-70°	3	:	2
	$NaBH_4$ / IPA / -70° to RT	3	:	2
	$LiBu^s_3BH$ /-70°	3	:	2

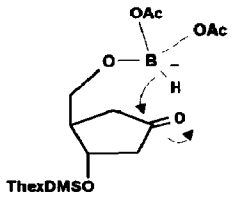
Surprisingly the use of L-selectride gave predominantly the unwanted β-alcohol when the primary alcohol was protected with MOM. A possible explanation for this is that the L-selectride is chelated to the top face of the ketone in a manner similar to that shown in Scheme 3, this would then favour attack on the opposite face by another molecule of hydride to give **8** (R' = MOM, R = TBDPS) as the predominant isomer.

Scheme 3



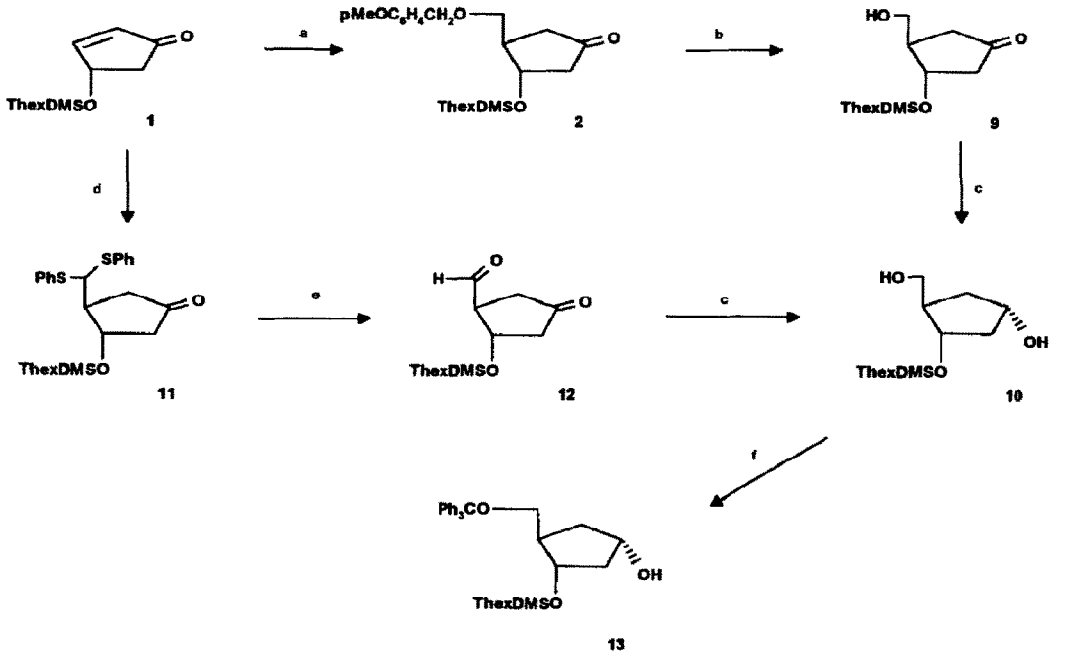
A way round the lack of steric control in this attempted stereoselective reduction is to use a directed reduction[16] to the top face of the ketone utilising the primary alcohol as the directing functionality (Scheme 4). Triacetoxyborohydrides[16] are known to reduce 1,3-hydroxy ketones stereoselectively, not simply because the intermediate alkoxydiacetoxyborohydride does so intramolecularly but because it is actually a more potent reducing agent than the triacetoxyborohydride parent.

Scheme 4



Until recently[17] this has been limited to 1,3-hydroxy ketones, while 1,5-, 1,6- and 1,8-hydroxy ketones failed to reduce[18] under similar conditions. Deprotection of the PMB group in **2** with DDQ gave the 1,4-hydroxy ketone **9** in 86% yield. Reduction of **9** with sodium triacetoxyborohydride gave exclusively the 1,4-diol **10** as a white solid in 75% yield (Scheme 5). The stereochemistry of **10** was unambiguously determined by an NOE experiment[18].

Scheme 5



Reagents and conditions: (a) (2-Th)(PMBOCH$_2$)CuCNLi$_2$ / TMSCl, THF, -78° (b) DDQ, CH_2Cl_2. (c) $NaBH(OAc)_3$, EtOAc, Δ. (d) $(PhS)_2CH_2$, nBuLi, THF, DMPU, -78° (e) CuO/$CuCl_2$, acetone, Δ (f) Ph_3CCl / DMAP reagent, CH_2Cl_2, Δ

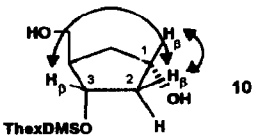
We have extended this concept of directed reduction It was noted that while sodium triacetoxyborohydride is extremely sluggish to reduce ketones intermolecularly, it does reduce aldehydes[19]. Thus in-situ reduction of an aldehyde to form the reactive *alkoxy*diacetoxyborohydride intermediate should also lead to directed reduction of the cyclopentanone, to give the diol **10** This strategy made it feasible to replace the difficult 1,4-cuprate addition, which requires careful control of temperatures and times , by a more robust addition of a formyl synthon to the cyclic enone The best of several formyl anion equivalents tried proved to be bis(phenylthio)methane which added regio- and stereo-selectively to the enone **1** to give the 1,4 -adduct **11** in 78% yield. As a substitute for HMPA, which is normally required to ensure that the carbanion adds 1,4 rather than 1,2[20], N,N'-dimethylpropyleneurea (DMPU)[21] was used. Although this reaction is reported to go satisfactorily at 0° [20], we found that the molecule decomposed when the reaction was allowed to warm up from -78°. The reagent of choice for the dethiation step proved to be copper oxide and copper chloride in refluxing acetone[22], which gave the aldehyde **12** in 77% yield (Scheme 5) Other reagents (isoamyl

nitrite/dichloromethane/RT/5days)[23] and ($Tl(CF_3CO_2)_3$ /Na_2HPO_4/THF)[24] gave lower yields. Reduction of the 1,4 -keto aldehyde **12** with sodium triacetoxyborohydride in ethyl acetate at reflux for 1/2 hour gave the diol **10** in 91% yield.

Selective protection of the primary alcohol in the diol **10** by acylation or silylation under a variety of conditions failed to give the required product in high enough yield or with the selectivity needed. However, tritylation[25] of **10** with a preformed DMAP/Ph_3CCl complex in dichloromethane at reflux gave **13** in 80% yield (Scheme 5). The alcohol **13** may now be coupled to a variety of purine or pyrimidine bases to give chiral carbocyclic *2'-deoxyribo*nucleosides.

References:

1. Marquez, V. E.; Lim, M.-I. *Med.Res.Rev.* **1986**, *6*, 1.
2. MacCoss, M.; Robins, M.J. In *The Chemistry of Antitumour Agents;* Wilman, D. E. V., Ed.; Blackie and Sons: U.K., 1990; pp 261, 299.
3. Chen, J.; Grim, M.; Rock, C.; Chan, K. *Tetrahedron Lett.*,**1989**, *30*, 5543.
4. (a) Prebost, M.; Lucas, M.; Chavis, C.; Pompon, A.; Baumgartner, H.; Rayner, B.; Griengl, H.; Imbach, J.-L. *Biochem. Biophys. Res. Commun.***1989**, *165*, 742. (b) Szemzo, A.; Szecsi, J.; Sagi, J.; Otvos, L. *Tetrahedron Lett.*,**1990**, *31*, 1463. (c) Mosher,H. E. In *Prospectives in Medicinal Chemistry*; Testa. B.,Ed.; VCH.; Basel, 1993, p 277-297.
5. Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571.
6. Biggadike, K.; Borthwick, A. D.; Exall, A. M.; Kirk, B. E.; Roberts, S. M.; Youds, P. *J.Chem.Soc.Chem.Comm.*1987, 1083.
7. Noyori, R.; Suzuki, M. *Angew.Chem., Int. Ed. Engl.* **1984**, *23*, 847.
8. (a) Bestmann, H. J.; Roth, D. *Syn.Lett.***1991**, 751. (b) Wolfe, M. S.; Anderson, B. L.; Borcherding, D. R.; Borchardt, R. T. *J.Org.Chem.***1990**, *55*, 4712.
9. Johnson, C. R.; Medich, J. R. *J.Org.Chem.***1988**, *53*, 4131.
10. Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.*,**1987**, *28*, 945.
11. The S-enone 1 (R = TBDPS) and 1 (R = ThexDMS) were prepared from the commercially available (1S,4R)-cis-4-acetoxy-2-cyclopenten-1-ol (Fluka) by analogy to the literature method[12] used to prepare the TBDMS derivative.
12. (a) Tanaka, T.; Kurozumi, S.; Toru, T.; Miura, S.; Kobayashi, M.; Ishimoto, S. *Tetrahedron* **1976**, *32*, 1713. (b) Danishefsky, S. M.; Cabal, M. P.; Chow, K. *J.Amer.Chem.Soc.***1989**, *111*, 3456.
13. Buchwald, S. L.; Nielsen, R. B.; Dewan, J. C. *Organometallics*, **1989**, *8*, 1593.
14. Hanessian, S.; Roy, P. J. *J.Org.Chem.* **1990**, *55*, 5766.
15. Takahashi, K.; Shiro, M.; Kishi, M. *J.Org.Chem.* **1988**, *53*, 3098.
16. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J.Amer.Chem.Soc.***1988**, *110*, 3560 and the references therein, for a review of directed reactions see Hoveyda, A. H.; Evans, D. A.; Fu, G. H. *Chem.Reviews* **1993**, *93*, 1307.
17. Adams, J.; Poupart, M.-A.; Grenier, L. *Tetrahedron Lett.*, **1989**, *30*, 1753.
18. Major NOE's were observed between H1β and H2β, and between H2β and H3β as depicted below.



10

19. Gribble, G. H.; Nutaitis, C. F. *Org.Prep.Proced.Int.* **1985**, *17*, 317.
20. Ager, D. J.; East, M. B. *J.Org.Chem.*, **1986**, *51*, 3983.
21. Mukhopadhyay, T.; Seebach, D. *Helvetica Chimica Acta*, **1982**, *65*, 385.
22. Stutz, P.; Stadler, P.A. *Org.Synth.,Coll. Vol. VI*, **1988**, 109.
23. Fuji, K.; Ichikawa, K.; Fujita, E. *Tetrahedron Lett.*, **1978**, *19*, 3561.
24. Jones, P. S.; Ley, S. V.; Simpkin, N. S.; Whittle, A. J. *Tetrahedron* **1986**, *42*, 6519.
25. Hernandez, O.; Chausharz, S. K.; Cox, R. H.; Porter, J. *Tetrahedron Lett.*,**1981**, *21*, 1491.

(*Received in UK* 4 *August* 1994; *accepted* 19 *August* 1994)