Tetrahedron Letters, Vol. 34, No. 2, pp. 261-264, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

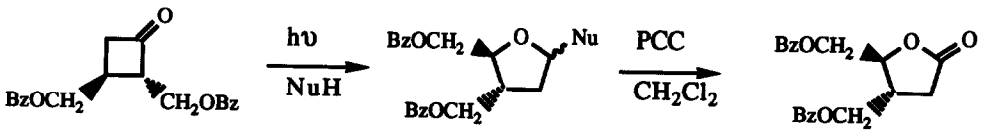
A Novel Approach Towards 2,3-Dideoxyriboside Synthesis

Edward Lee-Ruff*, Ji-Long Jiang and Wei-Qin Wan
Department of Chemistry
York University
Toronto, Ontario
Canada M3J 1P3

Summary: A short synthesis of 2,3-dideoxy-3(S)-C-hydroxymethyl ribosides is described. The key step involves a photochemical ring-expansion of a chiral cyclobutanone which occurs stereospecifically.

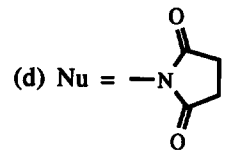
There has been a recent flurry of activity on the preparation of nucleoside analogues related to oxetanocin which exhibit potent antiviral activity.[1-4] These compounds possess a four membered carbocyclic or heterocyclic oxetane ring with *vicinal* trans-disubstituted hydroxymethyl groups. In a recent report,[5] a Swedish group showed that certain 2',3'-dideoxy-3'-C-hydroxymethyl nucleosides are very potent inhibitors of HIV. Our recent findings[6] that the photochemical ring-expansion of cyclobutanones gives N-H insertion products (2-aminotetrahydrofurans) and that these ring expansion reactions occur with retention of configuration of the ring substituents[7] prompted us to explore this route as a possible method for nucleoside synthesis. We report the successful application of this idea in the preparation of chiral 2,3-dideoxy-3(S)-C-hydroxymethyl ribosides starting with the optically pure protected 2,3-bishydroxymethylcyclobutanone **1**. This ketone was obtained by a modified procedure involving the stereospecific metal-catalyzed [2+2] cycloaddition of 1,1-dimethoxyethylene to (-)dimenthyl fumarate as the key step.[2,13]

UV irradiation of ketone **1** in THF/water[8] gave an epimeric mixture of hemiacetals **2**(a)[9] (58%) ($[\alpha]_D$ = +13.2, c = 1M, $CHCl_3$). The relative stereochemistry at the chiral centers C-3 and C-4 (sugar numbering) of **2**(a) was confirmed by its oxidation to lactone **3**.[9] A single stereoisomer was produced as was evident from the ^{1}H-nmr spectrum. Homonuclear decoupling of the C-5 methylene protons showed a doublet for H-4 (J = 3.4Hz) typical for trans vicinal coupled protons.



1

2 (a) Nu = OH
(b) Nu = *t*-OC_4H_9
(c) Nu = OCH_3



Furthermore, NOED experiments carried out for **3** indicated the trans relationship between the two benzoyloxymethyl groups. This is based on selective irradiation of the H-5 (δ 4.59) methylene protons and observation of signal enhancements for the H-4 (δ 4.80), H-3 (δ 2.95) and H-2β (δ 2.90) protons. Since epimerization could only occur at C-4 upon photolysis of ketone **1** and a single stereoisomer **3** is produced in this sequence, the initial photochemical ring expansion reaction of the optically pure ketone **1** must have proceeded stereospecifically. Furthermore since the absolute configuration for ketone **1** has been assigned by X-ray crystallography of one of its analogs,[3] the assignment of the 3(S), 4(R) configuration for hemiacetal **2**(a) is secure. Confirmation of the absolute configuration was obtained from the photoadduct **2**(c) obtained from the photolysis of **1** in methanol. The β-anomer which was separated by preparative chromatography has identical physical and spectral properties with those of a previously reported sample prepared by a different route.[10]

Similar irradiation of ketone **1** in THF containing *t*-butanol, methanol and succinimide gave adducts **2**(b)-(d) in varying yields (Table 1) depending on the extent to which water is rigorously excluded from the reaction. In addition to the photoadducts **2**, small amounts of the cycloelimination product, *E*-1,4-bis(benzoyloxy)-2-butene were produced. The extent of photocycloelimination in cyclobutanones is often solvent dependent.[11] In all cases, an anomeric mixture (about 1:1 mixture of α and β) was obtained as evident from the observation of two anomeric proton signals in the region δ 5.0-5.5 ppm in the ^{1}H-nmr spectra. Some stereoselectivity was observed in the case of the *t*-butanol photoadduct **2**(b) (4:1 in favour of the α epimer). The low yield in the case of *t*-butanol insertion may be attributable to steric factors in the bimolecular process favouring competing

unimolecular pathways such as photocycloelimination. Similar observations for other cyclobutanones have been reported.[12]

Table 1 YIELDS OF PHOTOADDUCTS 2(a) - (d)[a]

Solvent	Photoadducts (% Yield)	% Yield of Trans-Benzoyloxy-2-Butene
THF/H_2O	2(a) (58)	15
THF/*t*-C_4H_9OH	2(b) (9)	20
THF/CH_3OH	2(c) (62)	33
THF/Succinimide	2(d) (17)[b]	30

a. Isolated yields.
b. Actual yield is 20%, based on unreacted starting material.

Since the methanol adduct 2(c) has been coupled with cytosine[5] and a purine[10] our method constitutes a formal synthesis of nucleosides. The direct insertion of the oxacarbene derived from 1 into N-H functions of purine and pyrimidine bases is under current investigation.[6]

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for support of this work.

References and Notes

1. Slusarchyk, W.A.; Young, M.G.; Bisacchi, G.S.; Hockstein, D.R.; and Zahler, R. *Tetrahedron Lett.* **1989**, *30*, 6453
2. Ahmad, S.; *Tetrahedron Lett.* **1991**, *32*, 6997
3. Bisacchi, G.S.; Braitman, A.; Cianci, C.W.; Clark, J.M.; Field, A.K.; Hagen, M.E.; Hockstein, D.R.; Malley, M.F.; Mitt, T.; Slusarchyk, W.A.; Sundeen, J.E.; Terry, B.J.; Tuomari, A.V.; Weaver, E.R.; Young, M.G.; Zahler, R. *J. Med. Chem.* **1991**, *34*, 1415
4. Ichikawa, Y.; Narita, A.; Shiozawa, A.; Hayashi, Y.; Narasaka, K. *J. Chem. Soc. Chem. Commum.* **1989**, 1919

5. Svansson, L.; Kvarnström, I.; Chasson, B.; Samuelsson, B. *J. Org. Chem.* **1991**, *56*, 2993

6. Hayes, I.E.E.; Jandrisits, L.; Lee-Ruff, E. *Can. J. Chem.* **1989**, *67*, 2057

7. Lee-Ruff, E. in "Advances in Strain in Organic Chemistry" B. Halton (Ed.) *JAI Press* (1991) *vol. 1* p.167

8. The irradiation was carried out using a Hanovia 450W lamp in a quartz immersion well. Pyrex tubes containing 0.02M solutions of ketone 1 in THF and nucleophile scavenger in pyrex tubes were strapped around the well and irradiated for two hours.

9. Spectral data: **2a** ^{1}H-nmr δ(ppm) 7.94-8.16, 7.35-7.65 (10H, aromatic benzoyl-H), 5.66, 5.60 (1H two dxd, anomeric H-1), 4.28-4.66 (5H, m, Bz-OCH_2 plus H-4), 3.06 (1H, br.s., OH), 2.90, 2.55 (1H, m, H-3), 2.31-2.47, 2.16-2.26 (2H, m, H-2); IR (cm^{-1}): 3430 (OH), 1710 (C=O); MS. 339 (M^+-OH); analysis Calc. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66, Found C, 67.37; H, 5.90. Lactone **3**: ^{1}H-nmr δ(ppm): 8.01 (d, 4H, ortho benzoyl-H), 7.58 (t, 2H, para benzoyl-H), 7.44 (*t*, 4H, meta benzoyl-H), 4.80 (m, 1H, H-4), 4.59 (m, 2H, Bz-O-CH_2 at C-4), 4.44 (m, 2H, Bz-O-CH_2 at C-3), 2.95 (m, 1H, H-3), 2.90 (dd, 1H, H-2β), 2.57 (m, 1H, H-2α), IR(cm^{-1}): 1780 (C=O of lactone), 1715 (C=O of benzoyl group); MS.CI 355 (M^++H), 372 (M^+ + NH_4).

10. Acton, E.M.; Goerner, R.N.; Uh, H.S.; Ryan, K.J.; and Henry, D.W. *J. Med. Chem.* **1979**, *22*, 518

11. Lee-Ruff, E.; Hayes, I.E.E.; Kazarians-Moghaddam, H.; *Struct. Chem*, **1991**, *2*, 175

12. Newton, R.F. in "Photochemistry in Organic Synthesis" J.D. Coyle (Ed) *Royal Society of Chemistry Burlington House* **1988**, p. 39

13. Saleem, E. Eur. Patent Appl. 0458643A2 (1991). No acidic work-up was used to prepare the intermediate, (1S-trans)-3,3-dimethoxy-1,2-cyclobutanedimethanol, dibenzoate ester. Nevertheless, it was partially hydrolyzed and used directly in the subsequent acid hydrolysis step.

(Received in USA 5 August 1992; accepted 14 October 1992)