Tetrahedron Letters,Vol.25,No.35,pp 3841-3844,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

PRACTICAL ENANTIOSPECIFIC SYNTHESES OF (+) ERYTHRO-9-(2S-HYDROXY-3R-NONYL) ADENINE [1].

Elie ABUSHANAB *+
Department of Medicinal Chemistry, University of Rhode Island
Kingston, R.I. 02881, USA.

Michel BESSODES* and Kostas ANTONAKIS
Laboratoire de Chimie Organique Biologique
Institut de Recherches Scientifiques sur le Cancer, CNRS
Boite Postale 8, 94802 Villejuif Cedex, France.

Abstract : Three enantiospecific syntheses of 1S (2S-benzyloxethyl) oxirane (9) from L-ascorbic acid, L(+) tartaric acid, and Z-butene 1,4-diol are reported. The conversion of 9 to 2S-hydroxy-3R-nonylamine (19) is also described.

(+)-Erythro-9-(2S-hydroxy-3R-nonyl) adenine (+)-EHNA (1) has been recently identified, among its enantiomer and diastereomers, to be the most active inhibitor of the enzyme adenosine deaminase (ADA)[2,3]. The inhibition of ADA potentiates the anti-tumor and anti-viral activity of a number of adenosine analogs [4]. (+)EHNA is a semi-tight binding inhibitor that dissociates within minutes from ADA, thus avoiding immunosuppression and other toxic side effects associated with long term inhibition of the enzyme [5,6]. This has renewed interest in (+)-EHNA as a potential drug.

The reported syntheses[2,3] are rather lengthy indicating the need for a practical and versatile route to (+)-EHNA and certain analogs. Amine 19, in its racemic [7] and chiral [2] forms, has been incorporated into EHNA. Therefore a suitable synthesis of 19 would satisfy the above objective.

Retrosynthetic analysis led to 1S-(2S-hydroxyethyl) oxirane (10). The epoxide provides the necessary functionality for further elaboration into a 9-carbon fragment and subsequently to 19. This paper describes synthetic routes for 9 starting with L(+)-ascorbic acid, L(+)-tartaric acid, and Z-butene-1,4-diol, followed by its conversion to the target compound (19).

+ On sabbatical leave from URI at INSERM, France, 1983-1984.

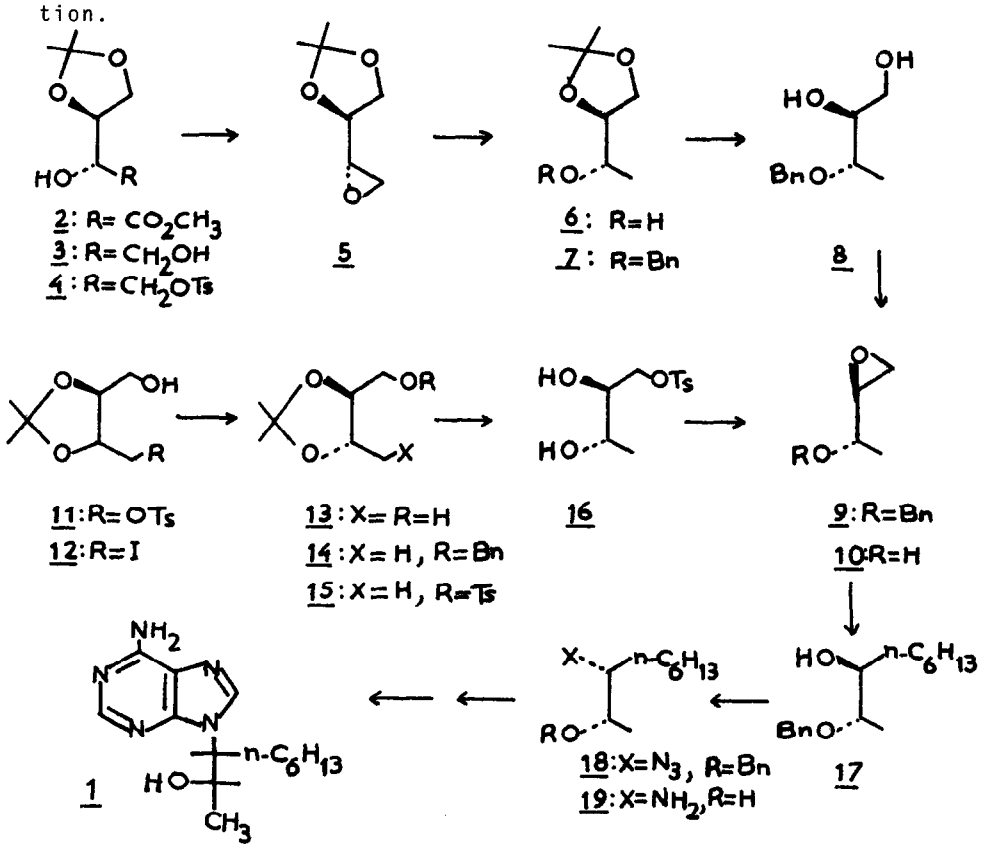
5,6-O-Isopropylidene-L-ascorbic acid [8] was oxidatively cleaved [9] to potassium-3,4-O-isopropylidene-L-threonate [10]. This was converted directly to its methyl ester 2 (CH_3I, CH_3CN, 75 % overall yield). LAH reduction of 2 furnished 3,4-O-isopropylidene-L-threitol (3,$[\alpha]_D$ = +3.99, C = 2.1) from which 4 was obtained by selective tosylation (TsCl, Pyr., 0°C, overnight). Treatment of an ether solution of 4 with one equivalent of $NaOCH_3$ gave epoxide 5 which was reduced with LAH to alcohol 6. This compound could be directly prepared from 4 using LAH. Benzylation of 6 (NaH/DMF, BnBr, 25°C) furnished 7 ($[\alpha]_D$ = -10.76, C = 1.69), which upon hydrolysis (CH_3OH, H_2O, Dowex-50) gave diol 8 ($[\alpha]_D$ = +25.6, C = 0.89). The sequence of reactions starting with 3 when carried out without purification of intermediates 4-7, [11] led to 8 in 51 % overall yield after purification by flash chromatography (initially EtOAc : Hexane 1 : 9 then 1 : 1). When diol 8 was subjected to the Mitsunobu reaction [12] (Ph_3P, DEAD, 110°, neat) epoxide 9 ($[\alpha]_D$ = -10.66, C = 2.88) could be distilled off in 88 % yield.

Epoxide 9 was also obtained from L(+)tartaric acid and Z-butene-1,4-diol. Tosylate 11 [13], upon treatment with NaI (acetone, 100°), furnished the iodo compound (12). Hydrogenation of 12 without purification (10 % Pd/C, EtOH) resulted in 13 (80 % yield from 11). The latter compound was also obtained following the Sharpless chiral oxidation method [14]. Isopropylidene 14 ($[\alpha]_D$ = +2.67, C = 1.58) was obtained by treatment of 1-O-benzyl-2S,3R-butane-2,3-diol with acetone/$CuSO_4$. The latter compound was obtained from Z-butene-1,4-diol [15]. Debenzylation of 14 gave 13 which was tosylated to give 15 ($[\alpha]_D$ = -3.67, C = 1.09). Hydrolysis of 15 furnished the crystalline diol 16 ($[\alpha]_D$ = -4.53, C = 1.6). The volatile epoxide 10 was obtained in quantitative yield upon treatment of a cold (0°C) ethereal solution of 16 with $NaOCH_3$.

On the other hand, when 16 was treated with two equivalents of NaH/DMF followed by the immediate addition (2min) of benzyl bromide, resulted in the formation of 11, identical to that obtained previously.

Completion of the synthesis of 19 followed. Treatment of 9 with $(n\text{-}C_5H_{11})_2CuLi$ (2 eq., 0°C, 2hr, ether)[16] gave adduct 17 ($[\alpha]_D$ = +2.04, C = 2.45) [17], from which azide 18 ($[\alpha]_D$ =+13.4, C = 1.31) was obtained [18] (2 Ph_3P 2 DEAD, $2HN_3$, benzene, 25°C, 3 hr). Reduction of the azido function and deprotection were accomplished by catalytic reduction (PtO_2, EtOH, overnight). The amino alcohol (19, $[\alpha]_D$ = +12.7, C = 0.40) obtained was identical to that obtained from L-rhamnose [2].

The developed synthetic methodology is currently being used to prepare analogs of EHNA for further biological evaluation.



ACKNOWLEDGEMENTS : The authors thank Dr. Marie Thérèse Chenon for the ^{13}C NMR spectra. The technical assistance of Aude Dapoigny and David W. Cabral is also acknowledged.

References

1. A preliminary account of this work has been presented at the ACS 185th National Meeting, Seattle, 1983 ; Abstr. N° 81.

2. G. Bastian, M. Bessodes, R.P. Panzica, E. Abushanab, S.F. Chen J.D. Stoeckler and R.E. Parks, Jr., J. Med. Chem., 24, 1383 (1981).

3. D.C. Baker, and L.D. Hawkins, J. Org. Chem., 47, 2179 (1982).

4. R.P. Agarwal, S. Cha, G.W. Crabtrée and R.E. Parks, Jr., in "Chemistry and Biology of Nucleosides and Nucleotides", R.E. Harmon, R.K. Robins and L.B. Townsend, Eds., Academic Press, New York, 1978, pp. 159-197.

5. M.F.E. Siaw, B.S. Mitchell, C.A. Koller, M.S. Coleman and J.J. Hutton, Proc. Natl. Acad. Sci., 77, 6157 (1980).

6. M.R. Grever, M.F.E. Siaw, W.F. Jacob, J.A. Neidhart, J.S. Miser, M.S. Coleman, J.J. Hutton and S.D. Balarzak, Blood, 57, 406 (1981).

7. H.J. Schaeffer and C.F. Schwender, J. Med. Chem., 17, 6 (1974)

8. F. Micheel and K. Hasse, Ber., 69B, 879 (1936).

9. N. Cohen, B.L. Banner, R.J. Lopresti, F. Wong, M. Rosenberger, Y.Y. Liu, E. Thom and A.A. Liebman, J. Am. Chem. Soc., 105, 3661 (1983).

10. J.M. Perel and P.G. Dayton, J. Org. Chem., 25, 2044 (1960).

11. A ditosylate was always formed. Its separation from 4 was avoided by reducing the mixture directly with LAH. Satisfactory elemental analysis, ^{1}H and ^{13}C NMR spectra were obtained for key compounds. Optical rotations were taken in ethanol.

12. O. Mitsanobu, Synthesis, 1 (1981).

13. H. Meyer and D. Seebach, Ann., 2261 (1975).

14. T. Katsuki, A.W.M. Lee, P. Ma, V.S. Martin, S. Masamune, K.B. Sharpless, D. Tuddenham and F.J. Walker, J. Org. Chem., 47, 1373 (1982).

15. K.B. Sharpless, C.H. Behrens, T. Katsui, A.W.M. Lee, V.S. Martin, M. Takatani, S.M. Viti, F.J. Walker and S.S. Woodward, Pure and Applied Chem., 55, 589 (1983).

16. G.H. Posner, Org. React., 22, 287 (1975).

17. n-pentyl lithium was prepared from 1-chloropentane. The use of 1-bromopentane resulted in competitive bromide opening of the epoxide to give the corresponding bromohydrin. The epoxide was recovered by treatment of this compound with methanolic KOH.

18. H. Loibner and E. Zbiral, Helv. Chim. Acta, 59, 2100 (1976).

(Received in France 13 June 1984)