Tetrahedron Letters,Vol.23,No.22,pp 2285-2288,1982 0040-4039/82/222285-04$03.00/0
Printed in Great Britain

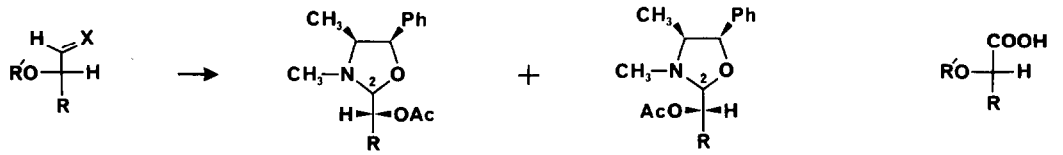
A METHOD FOR THE SYSTEMATIC RESOLUTION OF UNBRANCHED α-ACETOXYALKYL- AND ARALKYLALDEHYDES: SYNTHESIS OF 11R AND 11S-HETE

George Just, Corinne Luthe and Pierre Potvin[1]
Department of Chemistry, McGill University
Montreal, Canada H3A 2K6

It is shown that oxazolidines derived from racemic unbranched α-acetoxyaldehydes and ℓ-ephedrine have predictable chromatographic mobilities, with the R-isomer always having a higher R_f-value. This resolution has been used to prepare 11R and 11S-HETE.

Separation by thin-layer chromatography (t.l.c.) of the reaction mixture of (±) α-acetoxyheptanal 3e with ℓ-ephedrine gives, in order of decreasing R_f-values, two major oxazolidines, 4R-e and 4S-e, and two minor oxazolidines 4R'-e and 4S'-e, where the major and minor isomers differ in their stereochemistry at the 2-position, since they are interconverted upon exposure to silica gel. This finding forms the basis for a micromethod to establish the absolute stereochemistry at C-15 of compounds having a prostaglandin-like side-chain[2,3]. In this paper, we demonstrate that this method can be extended to other α-acetoxyalkanals, and scaled up for preparative purposes.

Allylic alcohols 1a-c are commercially available; 1d was obtained by reaction of benzaldehyde with vinyl lithium. Their respective acetates 2 were ozonolyzed[2] to give the corresponding aldehydes 3. Reaction 3 with ℓ-ephedrine gave, not unexpectedly, two major and two minor oxazolidines 4, as established by t.l.c. In the case of the lower homologues, 4a in particular, 0.5-1% NEt_3 had to be added to the eluting solvents to prevent partial hydrolysis of the oxazolidine ring on the t.l.c. plates. The R_f-values of the isomers of 4a and 4b respectively were quite close, and h.p.l.c. was required to effect separation; those of 4c,d,e were easily separated by flash chromatography[16]. The two major isomers for each set had very similar p.m.r. spectra to those described for 4R-e and 4S-e[2]. Appropriate transformation[2] of the least polar isomers 4R-a,b,c,d gave the corresponding



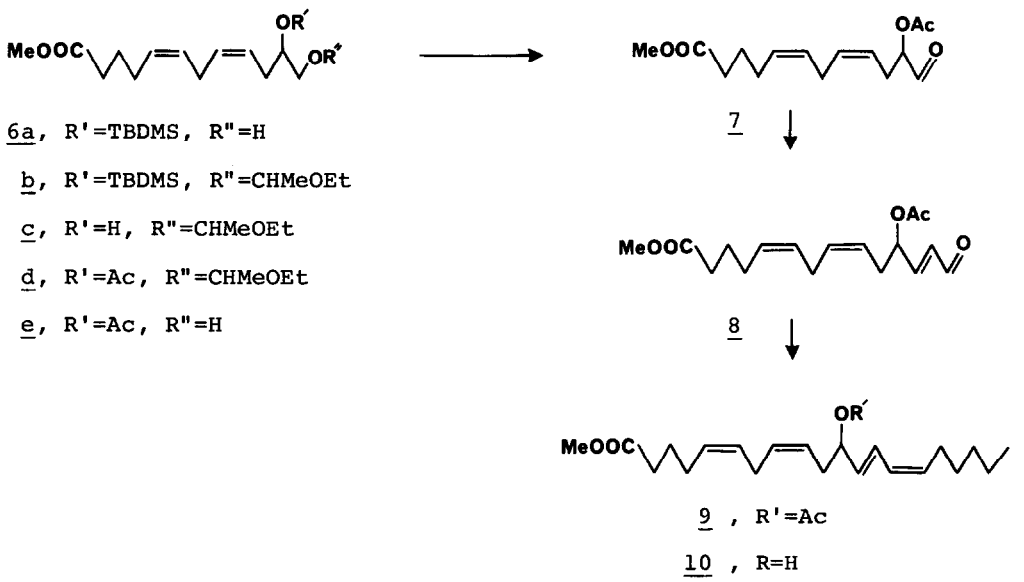
1, R'=H, X=CH_2

2, R'=Ac, X=CH_2 4R , major isomer 4S , major isomer 5 , R'=H

3, R'=Ac, X=O 4R', minor isomer 4S', minor isomer

a, R=CH_3 b, R=CH_2CH_3 c, R=$CH_2CH_2CH_3$ d, R=Ph

e, R=$CH_2(CH_2)_3CH_3$ f, R= 



6a, R'=TBDMS, R"=H

b, R'=TBDMS, R"=CHMeOEt

c, R'=H, R"=CHMeOEt

d, R'=Ac, R"=CHMeOEt

e, R'=Ac, R"=H

7

8

9 , R'=Ac

10 , R=H

hydroxy acids 5R-a,b,c,d. [5a, $[\alpha_D^{21}]$ in H_2O -2.0° (lit. -2.6°[4]); 5b, 2.5° (2.3°[5], 6.0°[6]); 5c, -1.4° (-1.4°[6]), 5d, -155° (-157.5°[7])].

In order to establish the practicality of the method, the recently described alcohol 6a[8] was transformed by a routine sequence (6a → 6e)[8] to

acetoxyalcohol 6e. Low temperature oxidation of 6e with dimethylsulfoxide-oxalyl chloride[9] gave α-acetoxyaldehyde 7 in ∿ 85% yield. Treatment of 7 with ephedrine (2 eq) in CH_2Cl_2 at 40° for 3 h gave 4R-f and 4S-f (separable by flash chromatography), accompanied by relatively large amounts of the minor isomers 4'-f. Addition of a catalytic amount of pyridinium tosylate effected a rapid isomerization of the minor to the major isomers. Acid hydrolysis of 4R-f and 4S-f[17] gave aldehydes 7R and 7S respectively. Treatment of 7R and 7S with formylmethylenetriphenylphosphorane[8] gave 8R and 8S, which, upon reaction with hexyltriphenylphosphorane[8], provided 9R and 9S, contaminated by 10-15% of the 14E-isomer. Separation was effected as described[8] after methanolysis of acetates 9, using catalytic NaOMe.

Hydroxy esters 10R and 10S had 200 MHz p.m.r. spectra and g.c.-mass spectrometric behaviour indistinguishable from that of 10R,S[8,10]. 10R had $[\alpha_D^{21}]$ 11.2° (10.97°[10]), and 10S $[\alpha_D^{21}]$ -11.3° (CH_2Cl_2).

A clear-cut conformational model could not be found to explain the remarkable chromatographic and p.m.r. spectral behaviour[11,12] of our oxazolidines. An examination of the literature revealed some contention among workers on the subject of configuration at C_2 of similar oxazolidines. We had made the *a priori* intuitive assumption that any substituent in the 2-position would rather be *trans* to the C_4-methyl and C_5-phenyl groups of an oxazolidine ring derived from ephedrine, a structural assignment buttressed by the published crystal structure of an oxazolidine derived from *para*-bromobenzaldehyde and ℓ-ephedrine by Neelakantan[13]. It now appears to have been a mistake to neglect the steric requirements and the configuration of the N-methyl group, because Beckett and Jones[14], and Baudet and Gelbcke[15] present convincing arguments to the contrary, based on a large volume of spectroscopic data. Pending the resolution of these conflicting reports, no firm assignment of the stereochemistry at C-2 of the oxazolidine ring is made.

ACKNOWLEDGEMENTS

We wish to thank the Natural Sciences and Engineering Research Council of Canada for financial support.

REFERENCES AND NOTES

1. Holder of a Natural Sciences and Engineering Research Council of Canada Scholarship, 1980-81 and of a "Ministère de l'Education de la Province de Québec" Scholarship, 1980-82.
2. G. Just and H. Oh, Tetrahedron Lett., 3667 (1980).
3. G. Just and H. Oh, Can. J. Chem., 59, 2729 (1981).
4. H. Borsook, H.M. Huffman and Y.-P. Liu, J. Biol. Chem., 102, 452 (1933).
5. M. Winitz, L. Bloch-Frankenthal, H. Izumiya, S.M. Birnbaum, C.G. Baker and J.P. Greenstein, J. Am. Chem. Soc., 78, 2423 (1956).
6. P.A. Levene and H.L. Haller, J. Biol. Chem., 77, 558 and *ibid.*, 74, 346.
7. G.M. Schwab, E. Bamann and P. Laeverenz, Z. Physiol. Chem., 215, 121 (1933).
8. For experimental details, see G. Just and C. Luthe, Tetrahedron Lett., 0000 (1982) and references therein.
9. A.J. Mancuso, S.L. Huang and D. Swern, J. Org. Chem., 43, 2480 (1978).
10. E.J. Corey and J. Kang, J. Am. Chem. Soc., 103, 4618 (1981).
11. H. Oh, Ph.D. Thesis, McGill University, 1981.
12. P. Potvin, Ph.D. Thesis, McGill University, 1982.
13. L. Neelakantan and J. Molin-Case, J. Org. Chem., 36, 2261 (1971).
14. A.H. Beckett and G.R. Jones, Tetrahedron, 33, 3313 (1977); A.H. Beckett, G.R. Jones and D. Hollingsbee, J. Pharm. Pharmacol., 30, 15 (1978).
15. M. Baudet and M. Gelbcke, Anal. Letters, 12, 325 and 641 (1979).
16. W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 43, 2923 (1978).
17. 0.2 mmol, 0.8 ml, 0.5 N HCl, 4 ml MeOH, 33°, 4 h; ether extraction with no prior removal of MeOH.

(Received in USA 22 February 1982)