Pergamon

Tetrahedron Letters 40 (1999) 4093–4096

TETRAHEDRON LETTERS

A General Synthesis of Homochiral ß-Hydroxy *N*-Acetylcysteamine Thioesters

Christine Le Sann[a], Thomas J. Simpson[a*], David I. Smith[b], Paul Watts[a] and Christine L. Willis[a]

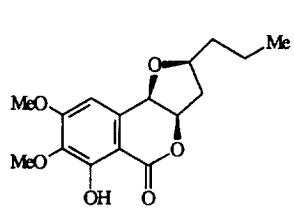
[a]School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK

[b] Sanofi Research, Alnwick Research Centre, Willowburn Avenue, Alnwick, Northumberland, NE66 2JH, UK

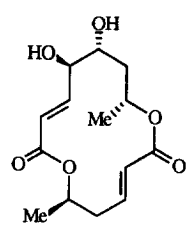
Received 10 March 1999; accepted 29 March 1999

Abstract. A convenient and efficient route for the enantioselective synthesis of functionalised ß-hydroxy *N*-acetylcysteamine thioesters is described. The route allows the facile incorporation of vicinal ^{13}C labelling to produce intermediates required for biosynthetic studies on a wide range of polyketide metabolites, e.g. 6-MSA, monocerin, colletodiol and strobilurins.

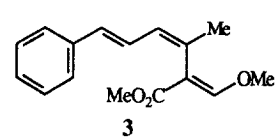
In vivo and *in vitro* studies to establish the exact sequence of events in the chain assembly phase of polyketide biosynthesis require the synthesis of the putative intermediates, often in enantioenriched form and ideally incorporating adjacent ^{13}C labels for sensitivity of detection in incorporation experiments, and in the form of their *N*-acetylcysteamine (NAC) thioesters.[1] These have been shown to be recognised and processed by the polyketide biosynthetic enzymes.[2,3] There are few generally applicable methods and so a range of methods have had to be developed for their synthesis. Studies on the biosynthesis of monocerin **1**[4] and colletodiol **2**[5] require the synthesis of both enantiomers of the NAC thioesters of 3-hydroxyhexanoic and 3-hydroxybutanoic acids respectively, whereas studies on the important antifungal strobilurins, e.g. **3**,[6] require the corresponding NAC thioesters of 3-hydroxy-3-phenylpropanoic acid. While some of these compounds have been prepared previously,[7] the routes differ widely, and are not suitable for the facile synthesis of both enantiomers or for incorporation of vicinal ^{13}C-labelling. We now report an efficient general method for the synthesis of ß-hydroxy NAC thioesters which fulfils the above criteria.



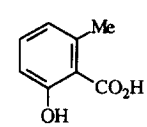
1



2



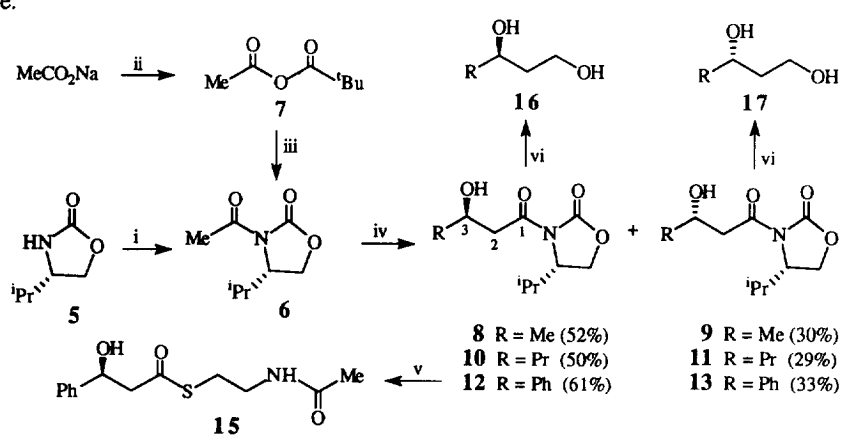
3



4

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)00657-7

ß-Hydroxycarbonyl compounds can be prepared by directed aldol methods using chiral auxiliaries such as Evans' oxazolidinones. The chiral boron[8] and titanium[9] enolates derived from α-substituted acetyl oxazolidinones give high *syn*-selective aldol condensations. In contrast, their simple acetyl analogues give low degrees of diastereoselectivity. This is generally seen to be a severe disadvantage and a range of methods have been developed to improve the selectivities observed.[10] However, in biosynthetic studies, when both enantiomers are often required for incorporation studies, this lack of stereoselectivity can be used to advantage for the efficient, cost-effective preparation of the desired biosynthetic intermediates, provided the diastereomeric aldol products are readily separable.[11]



Reagents: (i) BuLi, MeCOCl (95%); (ii) ^{t}BuCOCl, THF, then (iii) BuLi, THF (78%); (iv)$TiCl_4$, $^{i}Pr_2NEt$, DCM, -78°C, then RCHO; (v) $HSCH_2CH_2NHCOMe$ **14**, Me_3Al (65%); (vi) $LiAlH_4$, THF

Scheme 1

The known[8] acetyl oxazolidinone **6** was prepared in 95% yield from the valine-derived Evans' auxiliary **5** (Scheme 1). It can also be prepared in labelled form in high yield from sodium [1,2-$^{13}C_2$]acetate which can be easily converted with pivaloyl chloride to the mixed anhydride **7**, and can then be used to form the vicinally labelled acetyl oxazolidinone.[12] Reaction of the titanium enolate of **6** with ethanal, butanal and benzaldehyde gave the aldol products **8** - **13** in high yields (79-94%).[13] In each case, the diastereomeric pairs were produced in a *ca.* 2:1 ratio and could be readily separated by flash chromatography. Interestingly, the diastereotopic methylene protons adjacent to the imide carbonyl showed a characteristic well-resolved coupling pattern for the minor component, whereas the major component gave a less well-resolved ABX multiplet (Figure). These are diagnostic of the stereochemistry of the aldol product as was demonstrated by conversion of the aldol products to the corresponding homochiral 1,3-diols[14] or ß-hydroxy acids[8], and comparison with literature $[\alpha]_D$ values to confirm that, in each case, the major component has the hydroxyl group *anti* to the isopropyl substituent in the oxazolidinone ring.

It has been shown that ß-hydroxyacylimidazolides can be efficiently converted to the corresponding Weinreb amide derivatives using trimethylaluminium and *N,O*-dimethylhydroxylamine hydrochloride.[15] We were gratified to find that similar treatment of the phenyl analogue **12** with *N*-acetylcysteamine **14**[16] and trimethylaluminium allowed direct conversion to the NAC thioester **15** in 65% yield.[17] This obviates problems

arising from *retro*-aldol cleavage on hydrolysis to give the free acid and the poor yields sometimes observed in conversion of ß-hydroxy acids to their NAC thioesters using standard carbodiimide coupling condensations.[7]

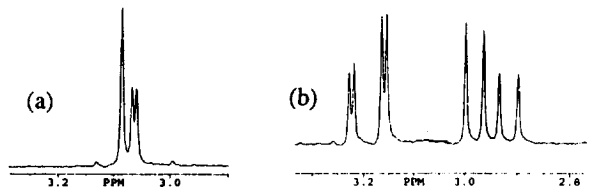
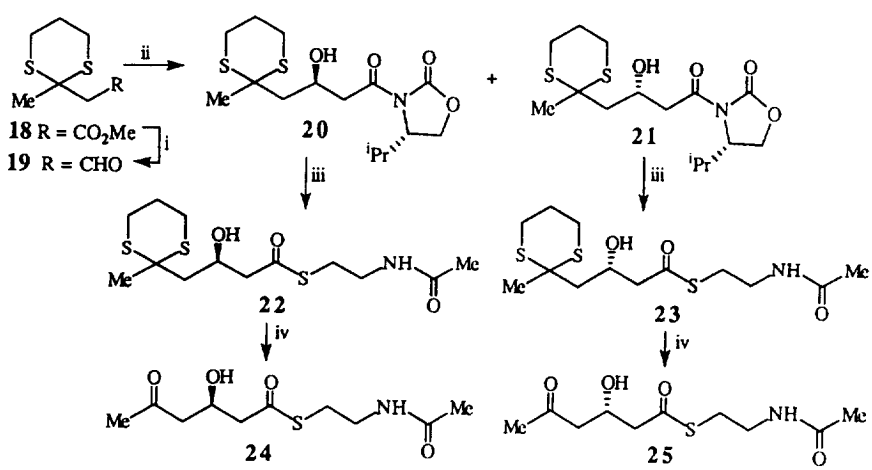


Figure. Signals observed for the 2-methylene hydrogens in the 300 MHz ^{1}H NMR spectra of (a) **10** and (b) **11**, both in $CDCl_3$

To prove further the generality of the route and its applicability to more highly functionalised ß-hydroxy thioesters, we have prepared both enantiomers, **24** and **25**, of the NAC thioesters of 3-hydroxy-5-oxohexanoic acid. This has previously been prepared in racemic form,[18,19] and on incubation with purified 6-MSA synthase[20] and malonyl CoA, 6-MSA production is observed.[19] The enantiomers are required to study the overall stereochemistry of the ketoreduction and elimination reactions in 6-MSA biosynthesis.[21] The synthesis is summarised in Scheme 2. 3-Oxobutanal, protected as the dithiane **19** was prepared in 91% yield by DIBAL-H reduction of the ester **18**.[22] Condensation with the enolate of **6** gave, as expected, a 2:1 mixture of the aldol products **20** and **21**, which were separated by flash chromatography. The more polar minor component **21** showed the diagnostic signals for the diastereotopic methylene hydrogens consistent with the predicted 3*R* stereochemistry for the aldol product. The diastereomers were separately converted to the protected NAC thioesters **22** and **23** and the 5-oxo functionality was released by removal of the dithiane protection[23] to give the desired enantiomers in 3 steps from the acetyl oxazolidinone **6**.



Reagents: (i) DIBAL-H, DCM, -78°C (94%); (ii) **6**, $TiCl_4$, $^iPr_2NEt$, DCM, -78°C (71%); (iii) $HSCH_2CH_2NHAc$ **14**, Me_3Al (54%); (iv) MeI, $CaCO_3$, MeCN, H_2O, 40°C (86%)

Scheme 2

Acknowledgements: We thank the Engineering and Physical Sciences Research Council, University of Bristol and Sanofi Research for financial support, and Dr G J Ellames for help and encouragement.

References and Notes

1. Simpson, T.J., *Chem. Ind.*, **1995**, 407
2. Cane, D.E.; Ott, W.R.; Prabhakatau, P.C.; Tan, W., *Tetrahedron Lett.*, **1991**, *32*, 5454
3. Weissman, K.J.; Bycroft, M.; Cutter, A.L.; Hanefeld, U.; Frost, E.J.; Timoney, M.C.; Harris, R.; Handa, S.; Roddis, M.; Staunton, J.; Leadlay, P.F., *Chem. Biol.*, **1998**, *5*, 743
4. Scott, F.E.; Simpson, T.J.; Trimble, L.A.; Vederas J.C., *J. Chem. Soc., Chem. Commun.*, **1984**, 756
5. O'Neill, J.A.; Simpson, T.J.; Willis, C.L., *J. Chem. Soc., Chem. Commun.*, **1993**, 738
6. Clough, J.M., *Nat. Prod. Rep.*, **1993**, *10*, 565
7. Jacobs, A.; Staunton, J., *J. Chem. Soc., Chem. Commun.*, **1995**, 863; Dillon, M.P.; Simpson, T.J.; Sweeney, J.B., *Biorg. Med. Chem. Lett.*, **1991**, *1*, 223; Bjorklund, J.A.; Leete, E., *Phytochemistry*, **1992**, *31*, 3887
8. Evans, D.A.; Bartoli, J.; Shih, T.L., *J. Am. Chem. Soc.*, **1981**, *103*, 2127
9. Evans, D.A.; Urpi, F.; Somers, T.C.; Clark, J.S.; Bilodeau, M.T., *J. Am. Chem. Soc.*, **1990**, *112*, 8215
10. For a recent review, see Regan, A.C., *J. Chem. Soc., Perkin Trans. 1*, **1999**, 357
11. Jacobs, A.; Hill, A.; Staunton, J., *J. Chem. Soc., Chem. Commun.*, **1995**, 859
12. Simpson, T.J.; Willis, C.L., Proceedings of the Chiral Europe '96 Symposium, Strasbourg, **1996**, pp 49-55
13. A solution of titanium chloride in dichloromethane (8.0 ml, 1M, 8.0 mmol) was added to a stirred solution of **6** (670 mg, 3.92 mmol) in dichloromethane (30 ml) at -78°C under nitrogen. After 10 minutes, diisopropylethylamine (1.40 ml, 8.04 mmol) was added, followed 1 hour later by freshly distilled benzaldehyde (0.8 ml, 7.87 mmol). The reaction mixture was maintained at -78°C for 5 hours and allowed to warm to room temperature overnight. Saturated ammonium chloride solution was added (20 ml) and the mixture was extracted with dichloromethane (3 x 100 ml). The dichloromethane was washed with water (50 ml), dried over magnesium sulphate and concentrated *in vacuo* to give a yellow oil which was purified by flash column chromatography. The diastereomers were isolated in an overall yield of 94%. Elution with 20% ethyl acetate in petrol gave **12** (360 mg, 33%) as a colourless oil; $[\alpha]_D^{22}$ +45.1 (*c* 1.22,$CHCl_3$). Found M^+, 277.1313; $C_{15}H_{19}NO_4$ requires 277.1314; υ_{max}/cm^{-1} 3500, 1782 and 1697; δ_H (300 MHz) 0.86, 0.92 (both 3H, d, *J* 7, $CH(CH_3)_2$, 2.37 (1H, spd, *J* 7 and 3, $CH(CH_3)_2$), 3.23 (1H, brs, O*H*), 3.28 (1H, dd, *J* 17 and 3, 2-*H*H), 3.49 (1H, dd, *J* 17 and 9, 2-H*H*), 4.22 (1H, dd, *J* 9 and 3.5, OC*H*H), 4.27 (1H, t, *J* 9, OCH*H*), 4.46 (1H, dt, *J* 9 and 3.5, NC*H*), 5.19 (1H, m, 3-*H*), 7.27-7.42 (5H, m, Ar-*H*); m/z 277 (M^+, 39%), 259 (24), 171 (20), 131 (100), 105 (75), 83 (96) and 68 (21). Elution with 25% ethyl acetate in petrol gave **13** (660 mg, 61%) as a white crystalline solid; m.pt. 115-117°C; $[\alpha]_D^{22}$ +114.2 (*c* 0.46,$CHCl_3$). Found M^+, 277.1313; $C_{15}H_{19}NO_4$ requires 277.1314; υ_{max}/cm^{-1} 3500, 1782 and 1697; δ_H (300 MHz) 0.80, 0.85 (both 3H, d, *J* 7, $CH(CH_3)_2$), 2.30 (1H, spd, *J* 7 and 3, $CH(CH_3)_2$), 3.15 (1H, brs, O*H*), 3.29 (2H, m, 2-H_2), 4.13 (1H, dd, *J* 9 and 3, OC*H*H), 4.19 (1H, t, *J* 9, OC*H*H), 4.37 (1H, dt, *J* 9 and 3, NC*H*), 5.16 (1H, m, 3-*H*), 7.18-7.35 (5H, m, Ar-*H*); m/z 277 (M^+, 72%), 171 (35), 130 (100), 107 (86), 79 (81) and 68 (39).
14. Boaz, N.W., *J. Org. Chem.*, **1992**, *57*, 4289
15. Evans, D.A.; Bender, S.L.; Morris, J., *J. Am. Chem. Soc.*, **1988**, *110*, 2506
16. Schwab, J.M.; Klassen, J.B., *J. Am. Chem. Soc.*, **1984**, *106*, 7217
17. Trimethylaluminium (0.80 ml, 2M, 1.60 mmol) was added to a stirred solution of *N*-acetylcysteamine (220 mg, 1.85 mmol) in THF (20 ml) at -10°C under nitrogen. After 1.5 hours, a solution of oxazolidinone **12** (100 mg, 0.36 mmol) in THF (10 ml) was added and the solution was allowed to warm to room temperature overnight. The reaction mixture was acidified to pH 5 using dilute hydrochloric acid and extracted using ethyl acetate (5 x 50 ml). The ethyl acetate was washed with brine (20 ml), dried over magnesium sulphate and concentrated *in vacuo* to give an oil which was purified by flash column chromatography on a flash silica column with *ca.* 3cm of copper sulphate impregnated silica on the top. Elution with 50% ethyl acetate in petrol gave **15** (62 mg, 65%) as a colourless oil; $[\alpha]_D^{22}$ +25.6 (*c* 4.33,$CHCl_3$); δ_H (300 MHz) 1.96 (3H, s, $COCH_3$), 2.89-3.12 (5H, m, CH_2S, 2-H_2 and 3-O*H*), 2.42 (2H, m, CH_2N), 5.20 (1H, m, 3-*H*), 6.13 (1H, brs, N*H*), 7.28-7.38 (5H, m, Ar-*H*); δ_c (75 MHz) 23.0 (CH_3), 28.8 (CH_2), 39.2 (SCH_2), 52.8 (NCH_2), 70.9 (CHO), 125.7, 127.9, 128.6, 142.4 (Ar), 170.8 (CON), 198.7 (COS).
18. Oldfield, M.F., PhD Thesis, University of Bristol, **1995**
19. Shoolingin-Jordan, P.M., personal communication
20. Spencer, J.B.; Jordan, P.M., *Biochem. J.*, **1992**, *288*, 839
21. Simpson, T.J. in "Topics in Current Chemistry", Vol 195 "Biosynthesis - Polyketides and Vitamins", eds Leeper, F.J. and Vederas, J.C., Springer-Verlag, Berlin, **1997**, pp 1-48
22. Ong, B.S., *Tetrahedron Lett.*, **1980**, *21*, 4225
23. Trost, B.M.; Preckel, M.; Leichter, L.M., *J. Am. Chem. Soc.*, **1975**, *97*, 2224