Pergamon

Tetrahedron Letters, Vol. 38, No. 43, pp. 7609-7612, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01806-6

The Biomimetic Synthesis of Marine Epoxylipids : Bisepoxides to Tetrahydrofurans

Robert J. Capon,* Russell A. Barrow, Colin Skene and Simone Rochfort

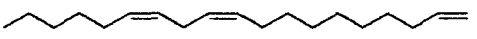
School of Chemistry, University of Melbourne, Parkville Victoria 3052, Australia

Abstract : The biomimetic synthesis of novel lipids **1**, **2**, **8** and **10** obtained from the southern Australian marine brown alga, *Notheia anomala* has been achieved, and features the acid mediated conversion of methylene interrupted bisepoxides to tetrahydrofurans. © 1997 Elsevier Science Ltd.

We recently reported the acid mediated conversion of methylene interrupted bisepoxides to substituted tetrahydrofurans, a transformation that is high yielding and demonstrates both regiospecificity and stereospecificity. [1] Those investigations were prompted by studies[2-6] into the chemistry of the marine brown alga, *Notheia anomala*, which features an array of novel oxylipids (>30). In this report we describe a highly convergent biomimetic synthesis that proceeds via the triene **1** and bisepoxide **2** to the dihydroxytetrahydrofurans **8** and **10**, all of which are co-metabolites in *N. anomala*.

The 2,5-*trans* disubstituted tetrahydrofuran **8** has been the focus of several total syntheses since first being reported[2] in 1980 from the southern Australian marine brown alga *Notheia anomala*. Although ascribed no particular biological properties, **8** has proved a useful vehicle with which to demonstrate new synthetic methodologies targeting chiral 2,5-substituted tetrahydrofurans. Such methodologies are of considerable value given the large number of bioactive molecules that incorporate the tetrahydrofuran functionality (macrolides, pheromones, polyether antibiotics, annonaceous acetogenins etc...). The first total synthesis of racemic **8** was achieved in 14 steps by Williams *et al*, who employed the NBS oxidation of 1,3-dioxolane precursors and subsequent chelation controlled Grignard coupling. Although the yields for many steps were high, an advanced precursor was required, and several reactions required chromatographic resolution of stereoisomeric products.[7] This effort was followed in 1985 by the >10 step (~17%) enantioselective synthesis of Takano *et al*, which proceeded from diethyl L-tartrate and culminated in a Grignard coupling to establish the "alkene" end of the carbon skeleton. It should be noted that this synthesis also employed chromatographic fractionation to resolve key stereoisomeric intermediates.[8] A second enantiospecific synthesis was achieved in 1990 by Gurjar *et al*, who converted a protected deoxysugar in 5 steps to the same aldehyde intermediate

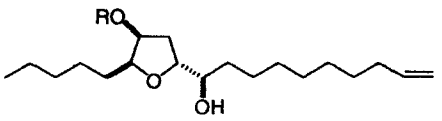
as secured by Takano *et al,*[8] for a formal 7 step synthesis (~20%).[9] Since Gurjar employed the same final coupling as Takano, this synthesis also featured a chromatographic resolution at the final step. The most recent asymmetric synthesis of **8** was by Chikashita *et al* in 1993, who employed a 10 step (~3%) cyclodehydration route starting from (S)-glycidol.[10] As with those described above, this synthesis required chromatographic resolution of stereoisomeric products. Our interest in **8** and its co-metabolites was prompted both by the need to solve the complete stereostructures of new epoxylipids, and by the *in vitro* anthelmintic properties of these compounds and our desire to secure structure analogues for SAR investigations. In pursuit of these objectives we chose to explore a highly convergent biomimetic approach to the synthesis of substituted tetrahydrofurans.



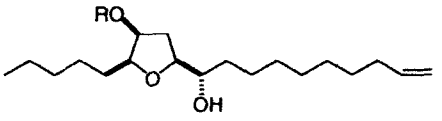
1

2

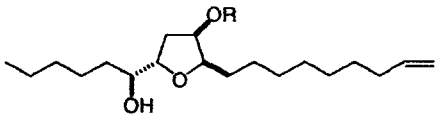
3



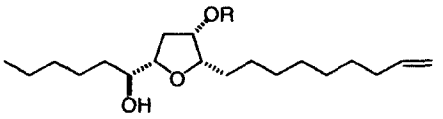
4 R=Ac
8 R=H



6 R=Ac
10 R=H



5 R=Ac
9 R=H



7 R=Ac
11 R=H

Commercially available linoleic acid was readily converted to the corresponding aldehyde before being extended via a Wittig coupling to the triene **1**, identical in all respects to that obtained naturally from *N. anomala*.[3] Treatment of **1** with m-CPBA yielded a 1:1.4 mixture of *syn* and *anti* bisepoxides (**2**+**3**) (84%) that were readily separated by MPLC (silica, 20% EtOAc/hexane). As described earlier[1] the ^{1}H NMR multiplicity for the bisepoxymethylene 8-H_2 resonance is diagnostic of the *syn* vs *anti* diastereomers, such that the *syn cis, cis* relative stereochemistry for the bisepoxide obtained from *N. anomala*[3,11] can now be confirmed for the first time. Furthermore, given the established stereospecific synthetic relationship between bisepoxides and tetrahydrofurans,[1] and the known absolute stereochemistry of the co-metabolite **8**,[2] the absolute stereochemistry of naturally occurring **2** is most likely 6S,7R,9S,10R.

Treatment of the mixture of *syn* and *anti* bisepoxides (**2**+**3**) with glacial acetic acid at 100°C overnight returned an aproximately equal mixture of tetrahydrofuran acetates (**4**-**7**) (98%) that could be resolved by preparative reverse phase HPLC (C_{18}, 30% H_2O/MeOH) into 1:1 mixtures of the *trans* isomers (**4**+**5**) (41%) and *cis* isomers (**6**+**7**) (36%). Independent treatment of these mixtures with methanolic ammonium hydroxide returned the *trans* (**8**+**9**) (98%) and *cis* (**10**+**11**) (97%) diols. Normal phase HPLC (silica, 20% EtOAc/hexane) successfully resolved the *trans* diols **8** and **9**, and the *cis* diols **10** and **11**. All compounds were subjected to detailed spectroscopic analysis, and their assigned structures were in full accord with this data. Most significantly, the synthetic sample of **8** proved to be identical (NMR, IR, MS, TLC) with an authentic natural sample. Likewise, a synthetic sample of **10** proved to be identical (NMR, IR, MS, TLC) to an authentic natural sample.[6]

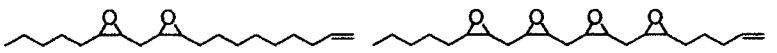
The overall transformation from **1** to tetrahydrofuran diols is a two pot process that is high yielding and employs simple procedures and safe reagents. This biomimetic synthesis not only yields the natural products **1**, **2**, **8** and **10**, but provides ready access to a host of other analogues through selective chemical manipulation of the tetrahydrofuran acetates (**4**-**7**). For example, oxidation/reduction cycles have yielded oxo analogues plus all possible stereoisomeric diols, while treatment of the mesylate of **6** with aqueous KOH returned a rare 1,4-dioxabicyclo[2.2.1]heptane ring system that features in metabolites isolated from a Pacific sea-hare[12] and a Mediterranean sponge.[13] Application of asymmetric synthetic methodology to the preparation of enantiomerically pure bisepoxides would see this biomimetic procedure yield enantiomerically pure tetrahydrofurans.

Acknowledgements

This research was supported by the Australian Research Council.

References and Notes

1. Capon, R. J.; Barrow, R. A., *J. Org. Chem.*, **1997**, submitted.
2. Warren, R. G.; Wells, R. J.; Blount, J. F., *Aust. J. Chem.*, **1980**, *33*, 891-898.
3. Barrow, R. A.; Capon, R. J., *Aust. J. Chem.*, **1990**, *43*, 895-911.
4. Murray, L. M.; Barrow, R. A.; Capon, R. J., *Aust. J. Chem.*, **1991**, *44*, 843-854.
5. Rochfort, S.; Murray, L. M.; Capon, R. J., *J. Nat. Prod.*, **1992**, *55*, 1332-1335.
6. Capon, R. J., unpublished results (manuscripts in preparation)
7. Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'sa, A., *J. Am. Chem. Soc.*, **1984**, *106*, 2641-2644.
8. Hatakeyama, S.; Sakurai, K.; Saijo, K.; Takano, S., *Tetrahedron Lett.*, **1985**, *26*, 1333-1336.
9. Gurjar, M. K.; Mainkar, P. S., *Heterocycles*, **1990**, *31*, 407-410.
10. Chikashita, H.; Nakamura, Y.; Uemura, H.; Itoh, K., *Chem. Lett.*, **1993**, 477-480.
11. The structures reported for the mono and bisepoxide natural products in ref 3 are in error. The correct structures are the bisepoxide and tetraepoxide respectively, as shown below. [6]



12. Schutte, G. R.; Chung, M. C. H.; Scheuer, P. J., *J. Org. Chem.*, **1981**, *46*, 3870-3873.
13. Giordano, F.; Magol, L.; Notaro, G.; Piccialli, V.; Sica, D., *J. Chem. Soc. Chem. Comm.*, **1990**, 1559-1561.

(*Received in UK* 25 *June* 1997; *revised* 26 *August* 1997; *accepted* 29 *August* 1997)