Pergamon

Tetrahedron Letters 40 (1999) 2209–2212

TETRAHEDRON
LETTERS

Synthesis of *threo*- and *erythro*-bis(2,2'-Tetrahydrofuran). A Novel Serendipitous Synthesis of a Spiroketal

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Received 2 December 1998; accepted 19 January 1999

Abstract. Racemic *threo*-bis(2,2'-tetrahydrofuran) and *meso-erythro*-bis(2,2'-tetrahydrofuran) have been prepared by stereochemically unambiguous routes. Treatment of 2-(1'-bromo-4'-hydroxybutyl)-tetrahydrofuran with base or silver(I) tetrafluoroborate effected cyclisation to 1,6-dioxa-spiro[4.5]decane.

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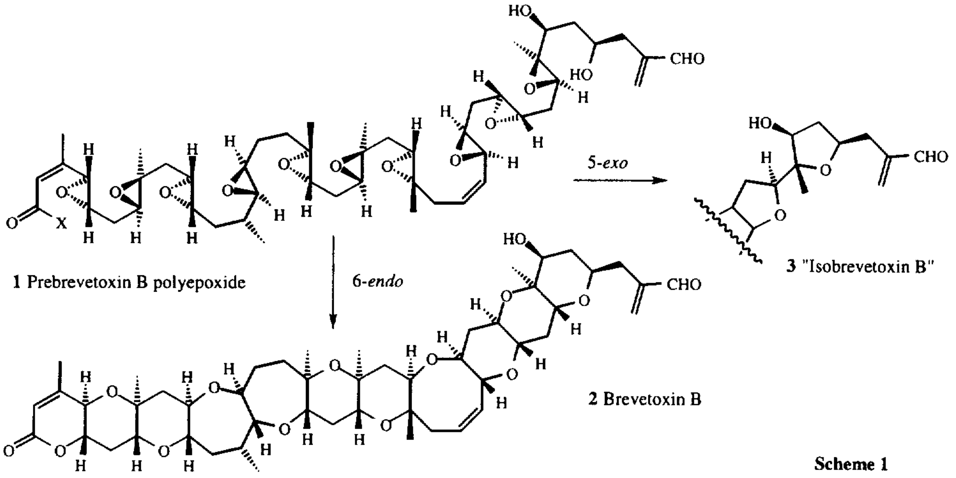
The extra-ordinary structures of the "ladder" polyethers (e.g. brevetoxin B **2**[1]) have inspired many attempts to mimic their biosynthesis.[2] The "right to left" polyepoxide cascade is *prima facie* the simplest conceivable mechanism (Scheme 1). However, it requires the first epoxide to be opened by a 6-*endo-tet* process, whereas simple 5-hydroxy-epoxides undergo cleavage predominantly by the 5-*exo-tet* mode. Application of this process to prebrevetoxin B polyepoxide **1** results in a 2,2'-bis-tetrahydrofuran **3** structure for the first two rings. It appeared possible that such a structure might undergo acid catalysed ring enlargement to a fused bis-pyran **7** *via* an exocyclic carbonium ion rearrangement (Scheme 2, path a). This process has been demonstrated for the expansion of furans to pyrans where an oxiranium ion **6**[3] is generated from an exocyclic iodide[4] or a mesylate.[5] We sought to test this proposal by preparing and rearranging the simplest possible analogues, *threo*- and *erythro*-2,2'-bis-tetrahydrofuran **4**, **5**.



1 Prebrevetoxin B polyepoxide

3 "Isobrevetoxin B"

2 Brevetoxin B

Scheme 1

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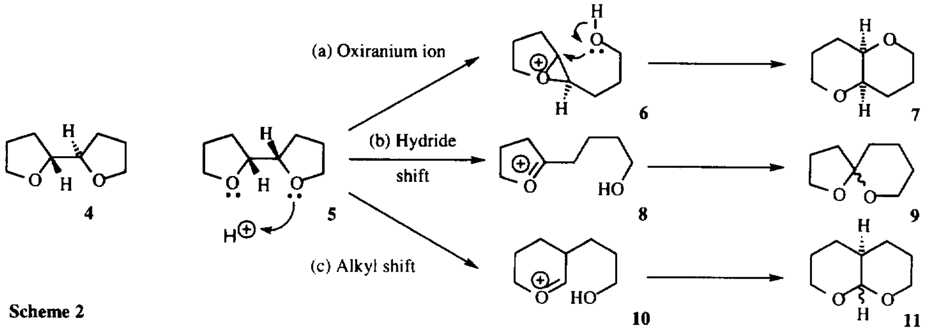
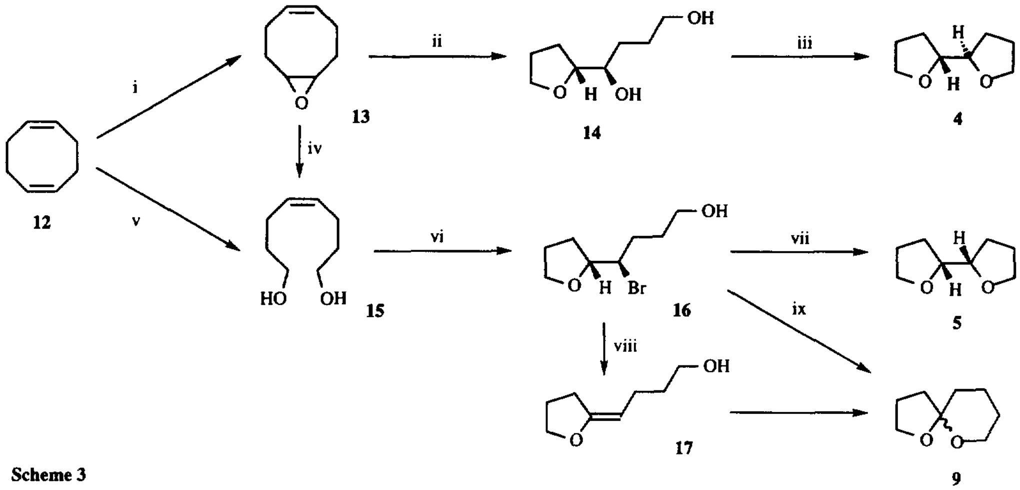


Scheme 2

There are twenty (mostly unintentional) reported syntheses of 2,2'-bis-THF.[6] Fifteen involve coupling of 2-tetrahydrofuranyl radicals[7] and three hydrogenation of 2,2'-bis-furan or related compounds.[8] In every case mixtures of racemic-*threo*-2,2'-bis-THF **4** and the *meso-erythro*-isomer **5** were obtained, which were not separated. An enantiospecific synthesis of *threo*-(-)-(2*R*,2'*R*)-bis-THF **4** in 13 steps from 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol has been reported in a thesis[9] and the racemic *threo*-isomer **4** by a carbonium ion induced epoxide cleavage.[10] The data presented in these reports do not enable the two diastereoisomers to be distinguished or even confirm that the material produced by the two routes has the same relative stereochemistry.

Initially, free radical dimerisation was re-investigated as a means to prepare reference materials. Photolysis of mercury(II) chloride in THF with a low pressure mercury lamp[11] was slow and gave a product which was difficult to purify. In contrast the *t*-butyl peroxide induced dimerisation of THF at 200-220°C in a sealed glass tube[12] gave material which was easily purified to afford the desired dimers **4**, **5** in good yield (65% based on *t*-butyl peroxide). On the largest scale attempted, 300g of THF was converted into 15g of 2,2'-bis-THF **4**, **5**. The 50:50 mixture of diastereoisomers was barely separable by column chromatography and the spectral data of the individual diastereoisomers was insufficient to distinguish their structures.[13] Moreover, as the oxiranium ion rearrangement was anticipated to be stereospecific, we planned stereoselective syntheses.

1,5-Cyclooctadiene **12** was ideal for our purposes. It is cheap, contains the complete carbon skeleton required and methods for mono-epoxidation and mono-ozonolysis are well developed. Treatment of 1,5-cyclooctadiene **12** with peracetic acid cleanly gave the mono-epoxide **13** (Scheme 3). This was treated with ozone and reduced sequentially to the dialdehyde and the diol which spontaneously underwent 5-*exo-tet* cyclisation *in situ* to give the tetrahydrofuranyl diol **14**. Selective formation of the primary triflate and *in situ* cyclisation gave the desired *threo*-isomer **4** in 15% overall yield. The low yield in the ozonolysis/reduction sequence reflects the difficulty in extracting the hydrophilic diol **14** from aqueous solution. The stereochemical integrity of this process relies on *cis*-epoxide formation, followed by *trans*-ring opening of the epoxide and closure of the second ring without affecting the stereochemistry. A complementary sequence was envisaged for *erythro*-2,2'-bis-THF **5** in which *trans*-addition to the *cis*-alkene would be followed by inversion at one centre in the second cyclisation.



Scheme 3

Reagents and conditions: (i) CH_3CO_3H, CH_3CO_2Na, $CHCl_3$, 50°C 2h, RT 24h (72% yield); (ii) (a) O_3; cyclohexane, methanol, 5:1, (b) Me_2S, (c) $NaBH_4$, MeOH , H_2O (36% yield); (iii) Tf_2O, pyr., CH_2Cl_2, -78°C (61% yield); (iv) (a) HIO_4, cat. Bu_4NOAc, H_2O, THF, 9:1, 0°C, 2.5h (90% crude yield of dialdehyde), (b) $NaBH_4$, EtOH (55% yield); (v) (a) O_3; cyclohexane, ethanol 15:1, (b) Me_2S, (c) $NaBH_4$, EtOH (60% yield); (vi) NBS, CCl_4, dark, 2h (100% yield); (vii) KH, DME, RT, 12h (**5** 45%, **9** 10% yield); (viii) Et_3N, cat. DMAP, $CHCl_3$, reflux, 24h (**9** 52% yield) ***or*** NaOH, MeOH, H_2O 9:1 (**9** 75% yield) ***or*** K_2CO_3, MeOH (**9** 26% yield); (ix) $AgBF_4$, PhH, RT, 12h (81% yield).

Periodate cleavage of the mono-epoxide **13** to the alkenic dialdehyde followed by sodium borohydride reduction to the diol **15** was a capricious process in our hands.[14] Eventually after much experimentation it was found that acceptable results could be achieved by using catalytic amounts of tetrabutylammonium acetate in a THF/water mixture. Alternatively the same diol **15** could be accessed by mono-ozonolysis of 1,5-cyclooctadiene **12** in a non-polar solvent which precipitates the hydroperoxide intermediate.[15] Intramolecular bromoetherification with *N*-bromosuccinimide in carbon tetrachloride resulted in precipitation of succinimide and enabled isolation of the unstable bromo-alcohol **16** in excellent yield without further purification. Intramolecular nucleophilic displacement of the bromo substituent by the alkoxide was anticipated to be difficult because of the deactivating effect of the β-alkoxy substituent.[16] Treatment with DBU in refluxing ether or THF effected no conversion, whereas triethylamine in chloroform or methanolic sodium hydroxide afforded the spiroketal **9**[17] as evinced by a singlet at δ 105.6 in the ^{13}C-NMR off resonance spectrum.[18] Potassium hydride in DMF gave a low yield of *erythro*-2,2'-bis-THF **5** after several days at 100°C. Acceptable yields were eventually achieved by using potassium hydride in dimethoxyethane at room temperature for 12 hours.

With both isomers in hand we attempted the proposed acid catalysed rearrangement. Treatment of *threo*-2,2'-bis-THF **4** with sulfuric acid, trifluoroacetic acid, aluminium trichloride or boron trifluoride etherate in methylene chloride returned starting material, whilst concentrated sulfuric acid, titanium tetrachloride and stannic chloride caused rapid polymerisation. Essentially identical results were obtained with the *erythro*-stereoisomer **5**. Apparently the ether-acid complex was insufficiently reactive and/or the product was unstable under the reaction conditions. Ionisation of the bromoether **16** with a silver salt offered the prospect of accessing the oxiranium ion **6** under milder conditions. However treatment with silver(I) tetrafluoroborate gave exclusively the spiroketal **9** in good yield. The formation of the spiroketal **9** under basic conditions *can* be rationalised by an E2 mechanism *via* the vinyl ether **17**, whereas the silver induced reaction most likely involves ionisation with concerted migration of hydride[19] (Scheme 2, path b), however this latter process cannot be excluded for the base catalysed reactions. In the precedents[4,5] that we used as justification for attempting an oxiranium ion rearrangement, the substrates bear an alkyl group at the position comparable to the migrating hydrogen in our substrates. It appears that this may be a prerequisite for achieving oxiranium ion rearrangements.

References

1. Shimizu, Y.; Bando, H.; Chou, H.-N.; Van Duyne, G.; and Clardy, J. C. *J. Chem. Soc., Chem. Commun.*, **1986**, 1656-1658.
2. For reviews see Kelly, D. R. in *The Chemistry of Natural Products*, Thompson, R. H. (ed), Blackie, Glasgow, 2nd edition, **1993**, 382-441; Elliot, M. C. *Contemp. Org. Synth.* **1997**, *4*, 238-259 and reference 10 below.
3. c.f. Alder, R. W.; Miller, A. J.; Rushbrook, D. I. *J. Chem. Soc., Chem. Commun.* **1989**, 277-279.
4. Bartlett, P. A.; Mori, I. and Bose, J. A. *J. Org. Chem.* **1989**, *54*, 3236-3239.
5. Nakata, T.; Nomura, S.; Matsukura, H. and Morimoto, M. *Tetrahedron Lett.* **1996**, *37*, 217-220; Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933-2935.
6. See octahydro-(2,2')bifuranyl, *Beilstein* registry no. 104583, *Chem. Abstr.* registry nos. [1592-33-2], [90334-38-6], [90334-40-0].
7. e.g. Gevorgyan, V.; Priede, E.; Liepins, E.; Gavars, M.; Lukevics, E. *J. Organomet. Chem.*, **1990**, *393*, 333-338.
8. Dana, G.; Girault, J.-P. *Bull. Chem. Soc. Fr.* **1972**, 1650-1656.
9. Nakayama, K. *Diss. Abstr. Int. B* **1986**, *47*, 1562; *Chem. Abst.* **1986**, *106*, 67029s.
10. Hayashi, H.; Fujiwara, K.; Murai, A. *Tetrahedron* 1997, **53**, 12425-12468.
11. Odaira, Y.; Matsuo, H.; Sakakibara, T.; Tsutsumi, S. *Nippon Kagaku Zasshi* **1967**, *88*, 39-42; *Chem. Abstr.* **1967**, *67*, 2591a.
12. Naarmann, H.; Zdenek, J.; Veihe, H. G.; Beaujean, M. and Merenyi, R. *Ger. Offen.* **1981**, 29 29 250; Naarmann, H.; Beaujean, M.; Merenyi, R. and Veihe, H. G., *Polymer Bull.* **1980**, *2*, 363-372, 417-425.
13. The most reliable method was ^{13}C-NMR. δ_C (90MHz, $CDCl_3$) *threo*-2,2-bis-THF **4** 81.5, 68.4, 28.2, 25.9; *erythro*-2,2'-bis-THF **5** 80.7, 68.1, 27.9, 25.5. Both stereoisomers give only four signals because the *threo*-enantiomers **4** have a C_2 axis and the *erythro*-stereoisomer **5** a plane of symmetry.
14. Nagarkatti, J. P. and Ashley, K. R. *J. Ind. Chem. Soc.* **1976**, *53*, 666-669; Nagarkatti, J. P. and Ashley, K. R. *Tetrahedron Lett.* **1973**, 4599-4600.
15. Tolstikov, G. A.; Odinokov, V. N.; Galeeva, R. I. and Bakeeva, R. S. *Tetrahedron Lett.* **1978**, 1857-1858.
16. Hanessian, S.; Thavonekham, B. and Dehoff, B. *J. Org. Chem.* **1989**, *54*, 5831-5833.
17. Fletcher, M. T. and Kitching, W. *Chem. Rev.* **1995**, *95*, 768-828; Perron, F. and Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617-1661.
18. This material was identical to an authentic sample of the spiroketal **9** which was kindly provided by Prof. Witko Francke. Francke, W.; Reith, W.; Sinnwell, V. *Chem. Ber.* **1980**, *113*, 2686-2693.
19. Nishiyama, H.; Naritomi, T.; Sakuta, K. and Itoh, K. *J. Org. Chem.* **1983**, *48*, 1557-1559.