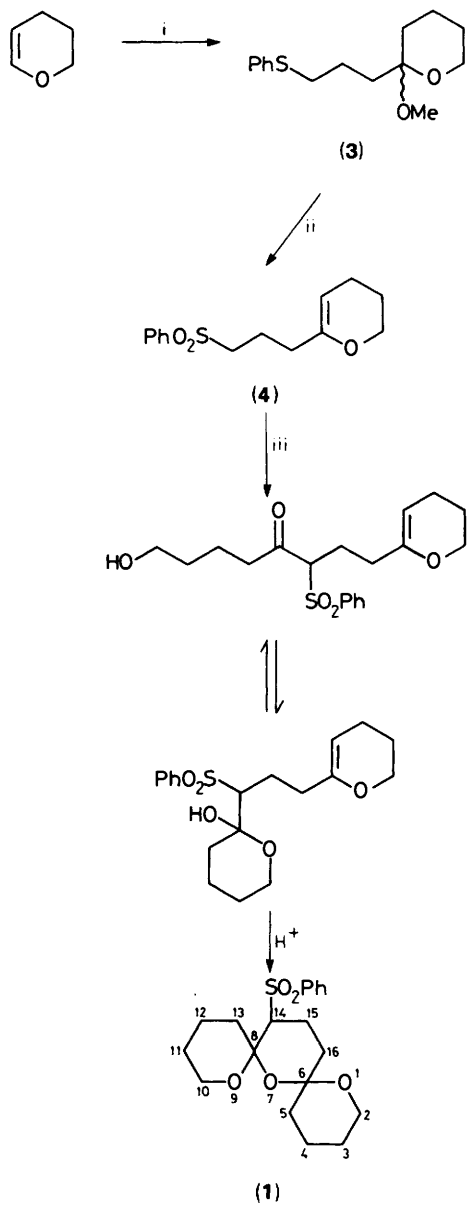
# The Chemistry of Bis-spiroacetals.[1] Synthesis of the Novel 1,7,9-Trioxadispiro[5.1.5.3]hexadecane Ring System

**Margaret A. Brimble,* Carolyn J. Rush, Geoffrey M. Williams, and Edward N. Baker**
*Department of Chemistry and Biochemistry, Massey University, Private Bag, Palmerston North, New Zealand*

The synthesis of the novel bis-spiroacetal (**1**) *via* the addition of an α-sulphonyl carbanion to δ-valerolactone followed by an acid catalysed cyclization is described. The stereochemistry was determined by X-ray crystallography and $^1$H NMR spectroscopy.

The spiroacetal unit is a principal structural feature of many biologically active natural products and has consequently attracted attention from synthetic chemists.[2] Examples of the preparation of bis-spiroacetals include the construction of the 1,6,8-trioxadispiro[4.1.4.2]tridec-13-ene[3] the 1,6,8-trioxadispiro[4.1.4.3]tetradecane[4] and the 1,6,8-trioxadispiro[4.1.5.3]-pentadec-13-ene[5] ring systems. We now wish to report the synthesis of the novel 1,7,9-trioxadispiro[5.1.5.3]hexadecane ring system (**1**) (Scheme 1) in which the phenylsulphonyl group at C-14 conferred crystallinity on the product thus allowing the stereochemistry to be determined using X-ray crystallography.

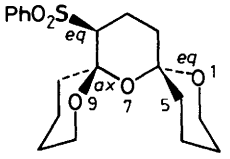
The synthesis of the tricyclic bis-spiroacetal (**1**) is an extension of our previously reported work[6] on the synthesis of the simpler bicyclic spiroacetals *via* the addition of α-sulphonyl



**Scheme 1.** *Reagents and Conditions:* i, BuLi (1.0 equiv.), 55 °C, 2.5 h, $BrCH_2CH_2CH_2SPh$ (**2**) then Amberlite IR 120 resin, MeOH, room temp., 16 h, 50%; ii, $NaBO_3{\cdot}4H_2O$, KOH, MeOH, 5 h, 60 °C, then Amberlite IR 120 resin, toluene, reflux, 3 h, 55%; iii, BuLi (2.0 equiv.), −78 °C, 0.25 h, δ-valerolactone, THF, then camphorsulphonic acid (cat.), $CH_2Cl_2$, 57%.

carbanions to lactones. Thus, lithiation of dihydropyran using butyl-lithium (1.0 equiv.) in tetrahydrofuran at 55 °C for 2.5 h followed by the addition of the bromide (**2**) afforded the sulphide (**3**)* after treatment with acidic methanol. After oxidation of the sulphide to a sulphone using sodium perborate in 50% methanolic potassium hydroxide the methoxyacetal group was eliminated to a double bond by heating with Amberlite IR 120 resin in toluene to give the sulphone dihydropyran (**4**). Generation of the α-sulphonyl carbanion using butyl-lithium (2.0 equiv.) at −78 °C, followed by reaction with δ-valerolactone afforded an equilibrium mixture of the open chain ketol alcohol and the cyclic hemiketals. This crude mixture was then subjected to an acid catalysed cyclization using a catalytic quantity of camphorsulphonic acid in dichloromethane at room temperature for 24 h to give the bis-spiroacetal (**1**) as a mixture of two stereoisomers.

The stereochemistry of the less polar isomer, isolated in 28% yield after purification by flash chromatography, was determined by X-ray crystallography† as the *trans*-isomer (**1a**) [$R_f$ 0.78 (hexane–ethyl acetate, 2:1) colourless crystalline prisms, m.p. 116–117 °C (from hexane–diethyl ether) (Found: C, 62.6; H, 7.3; S, 8.6. $C_{19}H_{26}O_5S$ requires C, 62.3; H, 7.15; S, 8.75); $\nu_{max}$(Nujol) 1 315s and 1 140s ($SO_2$) $cm^{-1}$; $\delta_H$(270 MHz; $CDCl_3$) 1.37–1.95 (15 H, m, 7 × $CH_2$ and $13_{eq}$), 2.66 (1 H, ddd, $J_{13ax,12ax}$ 13.2 Hz, $J_{13ax,13eq}$ 13.2, $J_{13ax,12eq}$ 4.4 Hz, $13_{ax}$-H), 3.52–3.91 (5 H, m, 2 × $CH_2O$ and CHS), 7.48–7.64 (3 H, m, 5′-H, 3′-H, and 4′-H), and 7.91 (2 H, d, $J_{2',3'}$ 7.7 Hz, 6′-H and 2′-H)]. The conformation adopted (Figures 1 and 2) was found to be that in



*trans*-(**1a**)

3 anomeric effects

**Figure 1.**

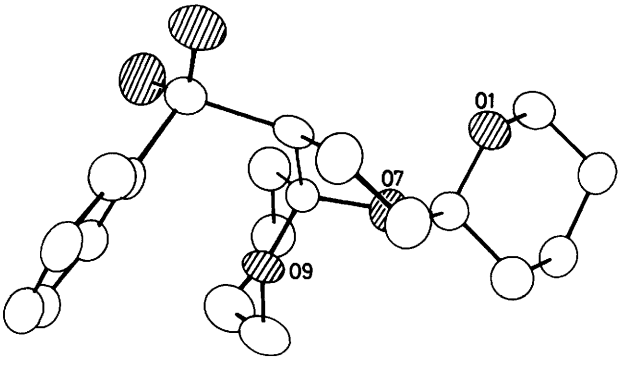


**Figure 2.** Structure of 14-Phenylsulphonyl-1,7,9-trioxadispiro[5.1.5.3]-hexadecane (**1a**).

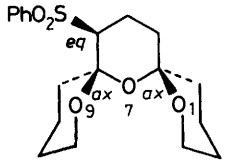
which the oxygen of one of the terminal rings occupies a pseudo-equatorial position whilst the oxygen of the other ring occupies an axial postion relative to the oxygen of the central ring. The phenylsulphonyl group at C-14 occupies an equatorial position *syn* to the C(8)–O(9) bond of the neighbouring six-membered ring. The central ring adopts a skew-boat conformation thereby relieving the steric interactions between the oxygen atom (0–9) and the methylene group at C-5. In this conformation, the

* All new compounds gave satisfactory spectroscopic and analytical data.

† *Crystal data for* (**1a**)—$C_{19}H_{26}O_5S$, $M$ = 3.66.0, orthorhombic, space group *P*(*bca*), $a$ = 10.500(1), $b$ = 13.987(1), $c$ = 24.537(2) Å, $D_c$ = 1.351 g $cm^{-3}$ for $Z$ = 8, μ(Cu-$K_\alpha$) = 17.8 $cm^{-1}$. Data (Cu-$K_\alpha$ radiation) were collected in the range $1.5 \leq \theta \leq 70°$ on an Enraf-Nonius CAD4 diffractometer (3 745 unique reflections). Lorentz and polarisation corrections were made, and data were corrected for absorption from an azimuthal scan. The structure was solved by direct methods (MULTAN) and subsequent Fourier syntheses, and refined by least squares (program SHELX). All non-hydrogen atoms were given anisotropic thermal parameters, and hydrogen atoms were included in their calculated positions (but not refined). For the final model, $R$ = 0.0408, $R_w$ = 0.0478 for 2 739 reflections with $I > 3\sigma(I)$. Atomic co-ordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre. [See 'Instructions for Authors (1990),' *J. Chem. Soc., Perkin Trans. 1*, 1990, Issue 1.]

molecule exhibits three anomeric effects and the two carbon-oxygen bonds of rings A and C are *anti* to each other thus avoiding any unfavourable dipole–dipole interactions. A similar conformation was observed for the analogous 1,6,8-trioxadispiro[4.1.4.3]tetradecane ring system.[4]

The second more polar isomer was isolated in 29% yield after purification by flash chromatography and was assigned as the *cis*-isomer (**1b**) (Figure 3) using $^1$H NMR spectroscopy. [$R_F$




*cis*-(**1b**)

4 anomeric effects
dipole–dipole interactions unfavourable

**Figure 3.**

0.72 (hexane–ethyl acetate, 2:1) colourless needles, m.p. 104.5–105.5 °C (from hexane–diethyl ether); $\delta_H$(270 MHz; $CDCl_3$) 1.41–1.97 (14 H, m, 6 × $CH_2$, $13_{eq}$-H and $15_{eq}$-H), 2.17–2.23 (1 H, m, $15_{ax}$-H), 2.66 (1 H, ddd, $J_{3ax,12ax}$ 13.0 Hz, $J_{13ax,13eq}$ 13.0 Hz, and $J_{13ax,12eq}$ 4.4 Hz, $13_{ax}$-H), 3.14 (1 H, dd, $J_{14ax,15ax}$ 8.6 Hz, $J_{14ax,15eq}$ 5.7 Hz, $14_{ax}$-H), 3.57–3.60 (2 H, m, $2_{eq}$-H and $10_{eq}$-H), 3.83–3.97 (2 H, m, $2_{ax}$-H and $10_{ax}$-H), 7.47–7.62 (3 H, m, 5′-H, 3′-H, and 4′-H), and 7.89 (2 H, m, 6′-H and 2′-H)]. The downfield shift of $15_{ax}$-H to $\delta_H$ 2.17–2.23 in this isomer from $\delta_H$ 1.37–1.95 in the *trans*-isomer was consistent with its assignment as the *cis*-isomer in which $15_{ax}$-H is deshielded due to the two 1,3-diaxial interactions with the C–O bonds of the adjacent rings (Figure 4). In the *trans*-isomer only one such 1,3-diaxial interaction is found.

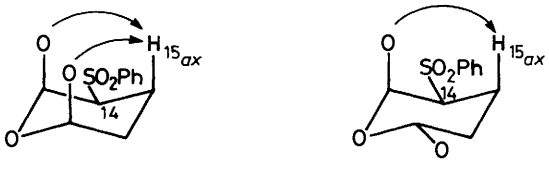
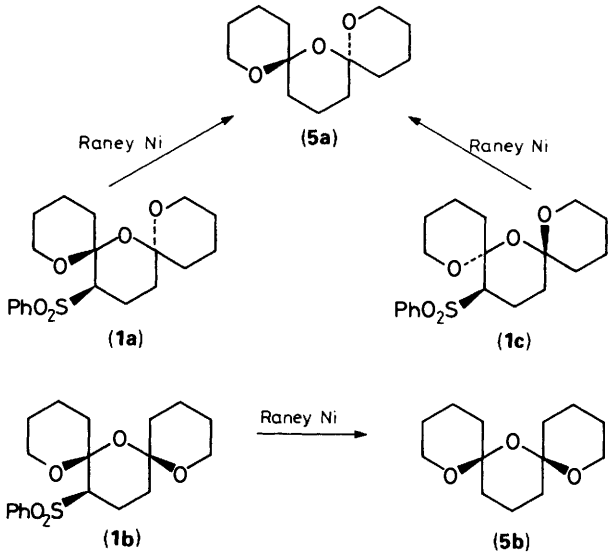
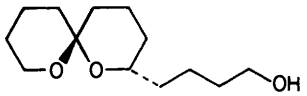



**Figure 4.**

Further evidence for the assignment of the two bis-spiroacetals isolated as the *trans*-isomer (**1a**) (Figures 1 and 2) and the *cis*-isomer (**1b**) (Figure 3) was obtained upon removal of the phenylsulphonyl group. Thus, separate removal of the sulphone group from the *cis*- and *trans*-sulphones (**1a**) and (**1b**) using W-2 Raney nickel gave the *cis*- and *trans*-isomers of the parent bis-spiroacetal (**5a**), and (**5b**) respectively, albeit in 10% yield (Scheme 2). This supported the assignment of the two isomeric sulphones as the *trans*-isomer (**1a**) and the *cis*-isomer (**1b**), in that, if these were assigned as the two *trans*-isomers (**1a**) and (**1c**) only one isomer of the parent bis-spiroacetal (**5a**) would have been formed upon removal of the sulphone functionality. In both cases, however, the major product formed in this reduction step was the spiroacetal alcohol (**6**) (82% yield). Spiroacetal alcohol (**6**) underwent oxidative cyclization to the parent bis-spiroacetals (**5a**, **b**). Thus, irradiation of a mixture of alcohol, (**6**), iodobenzene diacetate (1 equiv.), and iodine (0.5 equiv.) in cyclohexane for 1 h gave a 1:1 mixture of the parent bis-spiroacetals (**5a**, **b**) in 76% yield that were easily separated by flash chromatography.




**Scheme 2.**




(6)

In summary, this synthetic sequence provided an efficient entry to the bis-spiroacetal ring system (**5a**, **b**) combining the use of two recently developed reactions for the construction of spiroacetals, namely condensation of an α-sulphonyl carbanion with δ-valerolactone[3] and an oxidative cyclization using iodobenzene diacetate and iodine.[1]

## Acknowledgements

We thank Dr. K. W. Jolley for the high field NMR spectroscopy and the Massey University Research Fund for financial support.

## References

1 For a previous paper see: R. Baker and M. A. Brimble, *J. Chem. Soc., Perkin Trans. 1*, 1988, 125.
2 For a review see: T. L. B. Boivin, *Tetrahedron*, 1987, **43**, 3309.
3 A. A. Ponomarev and I. A. Markushina, *Zh. Obschch. Khim.*, 1963, **33**, 3955 (*Chem. Abstr.*, 1964, **60**, 10649b–e; A. A. Ponomarev and I. A. Markushina, *Geterotsiki Soedin., Akad. Navk. Latv. SSR*, 1965, **1**, 43 (*Chem. Abstr.*, 1965, **63**, 4256f.
4 L. Cottier, G. Descotes, M. F. Grenier, and F. Metras, *Tetrahedron*, 1981, **37**, 2525; L. Cottier and G. Descotes, *ibid.*, 1985, **41**, 409.
5 Y. Kishi, S. Hatakeyama, and M. D. Lewis, Front. Chem. Plenary Keynote Lect., 28th IUPAC congress, 1981, ed. K. J. Laidler, Pergamon Press Ltd., Oxford, 1982, p. 287; K. Horita, S. Nagato, Y. Oikawa, and O. Yonemitsu, *Tetrahedron Lett.*, 1987, **28**, 3253; F. Perron and K. F. Albizati, *J. Org. Chem.*, 1989, **54**, 2047; P. Kocienski, Y. Fall, and R. Whitby, *J. Chem. Soc., Perkin Trans. 1*, 1989, 841.
6 M. A. Brimble, D. L. Officer, and G. M. Williams, *Tetrahedron Lett.*, 1988, **29**, 3609.

*Paper* 9/03883C
*Received* 12*th September* 1989
*Accepted* 6*th November* 1989