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# Unexpected Synthesis of 1,6-Dioxadecalins by Desulfonylation of Phenylsulfonyl [4,5] spiroketals

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***Abstract***: *cis*- and *trans*-fused 5-hydroxy-1,6-dioxadecalins are obtained in good yields by desulfonylation with Na(Hg) of the readily available 4-phenylsulfonyl-1,6-dioxaspiro[4,5]decan-10-ones. **Copyright © 1996 Elsevier Science Ltd**

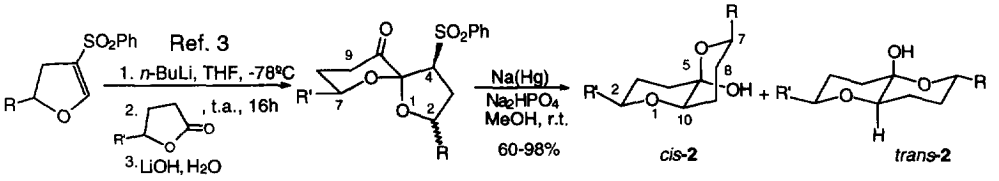
The 1,6-dioxadecalin unit is found in the polyether structure of many marine toxins,[1] such as brevetoxins, ciguatoxin, maitoxin, gambierol, and okadaic acid. Due to the impressive biological properties of these naturally occurring substances and their formidable molecular structures, a great attention has been recently paid to the development of methods for their synthesis.[2] We have recently described a one-step method for the synthesis of 4-phenylsulfonyl-1,6-dioxaspiro[4,5]decan-10-ones from readily available starting materials.[3] This procedure is based on the condensation of the α-lithiated carbanion of β-sulfonyl dihydrofurans with γ-lactones to give spiroketals **1**. We want to report here that the reductive elimination of the sulfonyl group in spiroketals **1** with Na(Hg) under the usual conditions[4] (excess of Na(Hg) 6%, MeOH, $Na_2HPO_4$, rt) occurs with concomitant cleavage of the spiroketal skeleton to afford 5-hydroxy-1,6-dioxadecalins **2**.[5]

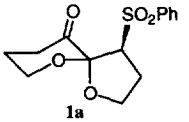
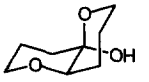
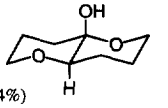
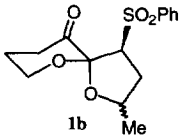
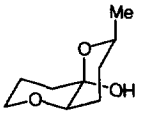
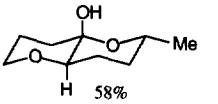
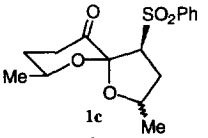
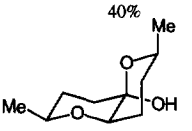
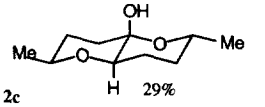
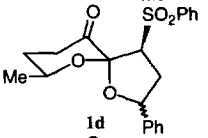
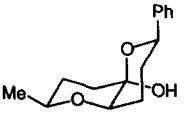
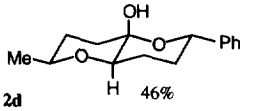
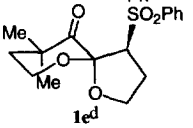
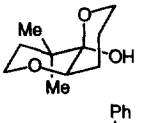
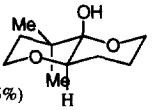
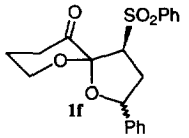
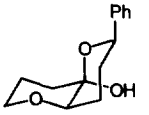
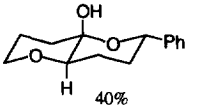
As it is shown in the table, the reaction was quite general. Regardless the substitution at C-2 or C-7 in spiroketals **1**, a mixture of a *cis*- and a *trans*-1,6-dioxadecalin (*cis*-**2** +*trans*-**2**) was obtained in high yield, both isomers being readily separated by flash chromatography[6]. Although compounds **2** have up to four stereogenic centers, a mixture of the most stable *cis*- and *trans*-1,6-dioxadecalin[7] (those with the substituents at C-2 and C-7 at equatorial positions) was almost exclusively detected, suggesting that the process was thermodynamically controlled.

A possible mechanistic explanation of this reaction is shown in scheme 1. First, desulfonylation of the β-alkoxy sulfones **1** (mixture of epimers at C-2) with Na(Hg) would occur by a Julia reaction[8], with cleavage of the axial $C_5$-$O_1$ bond and formation of the diastereomeric enones **3A** and **3B**[9]. Further stereoselective *in situ* reduction of the conjugated double bond of **3A** and **3B** would lead to the formation of the most stable diequatorial substituted pyrans **4A** and **4B**, respectively, which should cyclize to the most stable *cis* or *trans* - fused hemiketal form **2**. Thus, **4A** would afford *cis*-**2** stereoselectively, whereas **4B** would lead to the formation of *trans*-**2**.

Also studied was the reaction of **1a** with other reductive agents usually used in desulfonylations, such as $SmI_2$[10] and Raney Ni[11]. Whereas with $SmI_2$ a mixture of products was formed, in which 1,6-dioxadecalins **2** were detected by $^1$H-NMR, with Raney Ni the fastest reaction was the carbonyl reduction[12].

**Table 1**: Reaction of spiroketals **1** with Na(Hg)

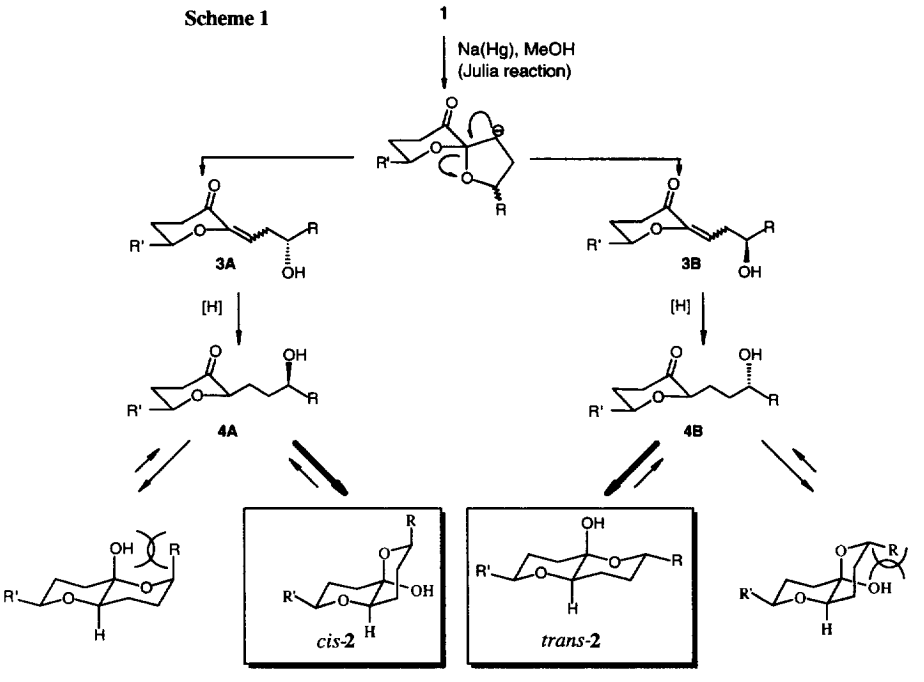



| Entry | Spiroketal 1[a] | Dioxadecalin and yield[b] | cis/trans ratio[c] |
|---|---|---|---|
| 1 |  **1a** |   **2a** (64%) | 64 : 34 |
| 2 |  **1b** |  40%  **2b** 58% | 45 : 55 |
| 3 |  **1c** |  31%  **2c** 29% | 50 : 50 |
| 4 |  **1d** |  30%  **2d** 46% | 40 : 60 |
| 5 |  **1e**[d] |   **2e** (85%) | 95 : 5 |
| 6 |  **1f** |  40%  **2f** 40% | 43 : 57 |

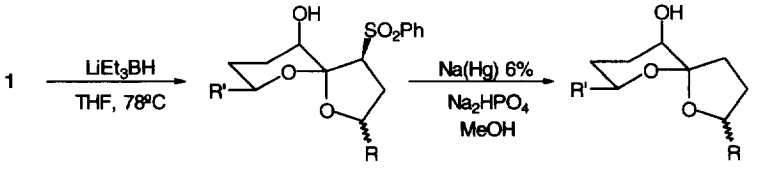
[a] As mixtures of isomers at C-2.[b] Of pure product after flash cromatography.[c] Determined by $^1$H-NMR spectroscopy on the crude mixtures.[d] **1e** was prepared by methylation of **1a** (NaH, MeI, THF, rt, 60% yield)

Unlike the behaviour of ketones **1**, the desulfonylation of alcohols **5** with Na(Hg) occurred without cleavage of the spiroketal skeleton (scheme 2). Reduction of **1a**, **1b**, and **1c** with $LiEt_3BH$ (THF, -78°C) was highly stereoselective in favour of the expected axial alcohols **5a** (ax/eq= 97/3), **5b** (ax/eq= 97/3), and **5c** (ax/eq= 90/10), respectively. The major axial alcohols were purified by flash chromatography (85-91% yield) and its further reduction with Na(Hg) ($Na_2HPO_4$, MeOH, rt) afforded the corresponding hydroxy spiroketals **6a**, **6b**, and **6c**, respectively (55-73% yield). This different behaviour of ketones **1** and alcohols **5** in the reaction with Na(Hg) suggests that the driving force of the C-O cleavage in the spiroketal skeleton of compounds **1** is the formation of the conjugated double bond of the intermediate enones **3**.

**Scheme 1**




**Scheme 2**




| | | |
|---|---|---|
| **1a**, R = R' = H | **5a**, 85% | **6a**, 73% |
| **1b**, R = Me, R' = H | **5b**, 86% | **6b**, 60% |
| **1c**, R = R' = Me | **5c**, 90% | **6c**, 55% |

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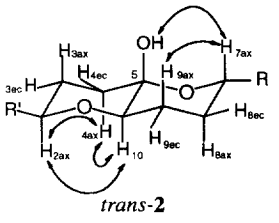
2. For some recent references, see: a) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, T.; Sato, M.; Untersteller, E.; Xiao, X. Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171. b) Sasaki, M.; Nonomura, T.; Murata, M.; Tachibana, K. *Tetrahedron Lett.* **1995**, *36*, 9007. c) Lee, E.; Park, C. M.; Yun, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 8017. d) Nicolaou, K. C.; Tiebes, J.; Theodorakis, E. A.; Rutjes, F. P. J. T. *J. Am. Chem. Soc.* **1994**, *116*, 9371. e) Burke, S. D.; Jung, K. W.; Phillips, J. R.; Perri, R. E. *Tetrahedron Lett.* **1994**, *35*, 703. f) Sasaki, M.; Monomura, T.; Murata, M.; Tachihana, K. *Tetrahedron Lett.* **1994**, *35*, 5023.
3. Carretero, J. C.; Rojo, J.; Díaz, N.; Hamdouchi, C.; Poveda, A. *Tetrahedron* **1995**, *51*, 8507.

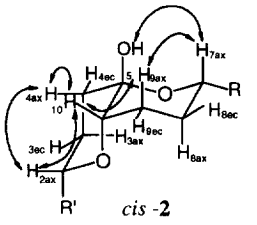
4. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
5. For other synthesis of 1,6-dioxadecalins from [4,5] spiroketals, see: Dona, R. I.; Preire, R.; Martín, A.; Suarez, E. *Tetrahedron Lett.* **1995**, *36*, 7309.
6. Only in the case of **2a** and **2e** was it not possible to separate the isomers.
7. Structure and configurational assignment

The structure and the configurational assignment of the steroisomers of 1,6-dioxadecalins **2** has been firmly established by mass spectrometry and specially by NMR studies ($^1$H-NMR, $^{13}$C-NMR, HMQC, TOCSY and NOESY experiments). In the figures shown below are summarized the criteria that were particularly diagnostic for the configurational assignment.




*trans*-**2**

| | J (Hz) |
|---|---|
| J2ax,3ax | 10.2-11.4 |
| J2ax,3ec | 2.3-3.8 |
| J7ax,8ax | 10.0-11.6 |
| J7ax,8ec | 2.3-2.6 |
| **J10,9ax** | **11.9-12.4** |
| **J10,9ec** | **4.2-4.7** |




*cis* -**2**

| | J (Hz) |
|---|---|
| J2ax,3ax | 10.7-11.7 |
| J2ax,3ec | 2.1-2.9 |
| J7ax,8ax | 11.1-11.7 |
| J7ax,8ec | 2.6-2.7 |
| **J10,9ax** | **2.8-3.2** |
| **J10,9ec** | **2.8-3.2** |

Significant coupling constants and NOE's of dioxadecalins *trans*-**2** and *cis*-**2**.

a) All protons in compounds *trans*-**2** and *cis*-**2** have the characteristic coupling constants of a six membered ring in chair conformation (usual *anti* and *gauche* coupling constants). Moreover, in substituted C-2 or/and C-7 dioxadecalins **2** the *anti* values of $J_{2,3ax}$ and $J_{7,8ax}$ (10.0-11.7 Hz) and the *gauche* values of $J_{2,3eq}$ and $J_{7,8eq}$ (2.1-3.8 Hz) indicate that in both *cis* and *trans* isomers **2** the substituents R and R' are in equatorial positions.

b) The *cis* or *trans* fusion stereochemistry of dioxadecalins **2** was deduced from the coupling constants of $H_{10}$: in *trans*-**2** $H_{10}$ is in axial position ($J_{10,9ax}$= 11.9-12.4 Hz and $J_{10,9eq}$= 4.2-4.7 Hz), whereas in *cis*-**2** $H_{10}$ is in equatorial position ($J_{10,9ax}$= $J_{10,9eq}$= 2.8-3.2 Hz).

c) A simple criteria to distinguish between hydroxy-1,6-dioxadecalins **2** and hydroxy spiroketals **6** (both have the same molecular weight) is the chemical shift of the quaternary carbon: in dioxadecalins **2** $\delta_{C5}$ appears at higher field (92-94 ppm) than $\delta_{C5}$ in spiroketals **5** or **6** (105-107 ppm).

d) The NOE's observed in compounds *cis*-**2** and *trans*-**2** are fully consistent with the proposed structures (see above figures).

Moreover, in agreement with the hemiketal structure of compounds **2**, the reduction of **2a** with $NaBH_4$ (MeOH, rt) afforded the corresponding diol and its treatment with dry MeOH under acid conditions (*p*-TsOH) led to the formation of a 1:1.6 mixture of *trans/cis* 5-methoxy-1,6-dioxadecalins.

8. Simpkins, N. S. , *Sulphones in Organic Synthesis*, Tetrahedron Organic Chemistry Series, Vol. 10, p 254-289, Pergamon Press, 1993.
9. Although the desulfonylation of arylsulfones with Na(Hg) usually tolerates the presence of ketones (see for instance: a) Anderson, M. B.; Ranasinghe, M. G.; Palmer, J. T.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 3125. b) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3554. c) Trost, B. M.; Vincent, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 5680. d) Trost, B. M.; Weber, L.; Streg, P.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3426) it is also possible to envisage another mechanism for the formation of intermediate enones **3** based on the double electron transfer to the carbonyl of **1** instead to the C-S bond. Thus, formation of the α-oxy carbanion, followed by cleavage of the axial $C_5$-$O_1$ bond to give the corresponding enolate and its further basic sulfinate elimination could afford enones **3**.
10. a) Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194. b) Künzer, H.; Stahnke, M.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1991**, *32*, 1949.
11. Trost, B. M. *Chem. Rev.* **1978**, *78*, 363.
12. Spiroketals **5a** and **6a** were two of the main products detected in the crude mixture of the reaction of **1a** with an excess of Ni-Raney (EtOH, reflux, 3 h).

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