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(+)-trans-Camphenesulfonamide: A Novel Enantiomerically Pure Primary Sulfonamide

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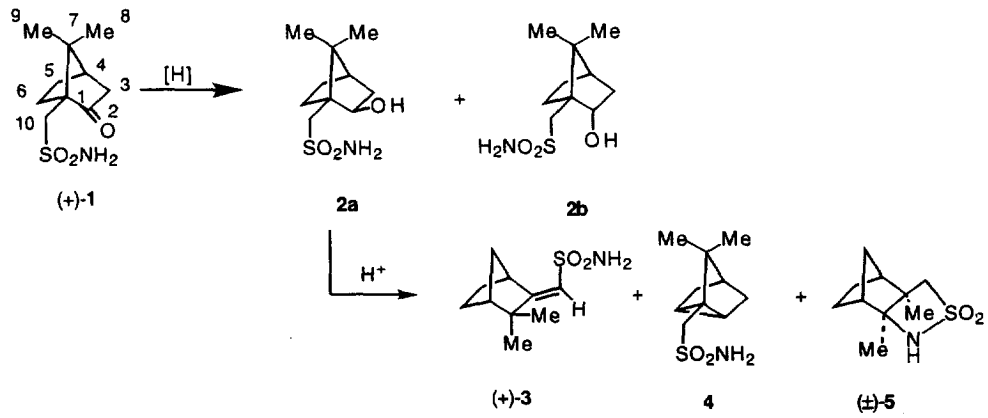
Summary: (+)-*trans*-Camphenesulfonamide (**3**) is prepared in two steps (54%) from camphorsulfonamide **1**, via a acid catalyzed rearrangement of the corresponding carbinol **2a**. Copyright © 1996 Elsevier Science Ltd

Primary sulfonamides (RSO_2NH_2) serve as precursors of building blocks widely used in organic synthesis, such as N-sulfinylsulfonamides, N-sulfonylimines, sulfonylisocyanates and N,N-dihalosulfonamides.[2] Enantiopure sulfonamides ($R^*SO_2NH_2$), required for all of the above reagents, are generally rare and not easily accessible. Recently we described the asymmetric synthesis of previously unavailable α-functionalized primary sulfonamides by reaction of electrophiles with the dianions of (camphorsulfonyl)imines.[3] While yields were good to excellent, the diastereoselectivities (2-90%) was variable. It occurred to us that (1*S*)-(+)-10-camphorsulfonamide (**1**) might serve as source of enantiopure primary sulfonamides, because of the well known ability of camphor and its derivatives to undergo a variety of acid catalyzed rearrangements.[4] Although **1** has been used in the asymmetric synthesis of N-sulfonyloxaziridines, it is less than ideal as a primary sulfonamide building block because of its conformationally mobility, the distance between the stereocenters and the active site, and the fact that it is easily dehydrated to

Scheme 1



(+)-1 **2a** **2b** (+)-3 **4** (±)-5

the camphorsulfonylimine.[5] In this letter we describe the enantioselective synthesis of *trans*-camphenesulfonamide (**3**), which does not suffer from these limitations, in two steps from (+)-**1** (Scheme 1).

(1*S*)-(+)-10-camphorsulfonamide (**1**), prepared as previously described from (+)-10-camphorsulfonyl chloride and ammonia,[5,6] was initially reduced with $NaBH_4$. Even under optimum conditions (-30 °C in MeOH) only an 88:12 mixture of the *exo*:*endo* carbinols **2a** and **2b** was isolated in 83% yield. Best results were obtained by addition of a THF solution of (+)-**1**, typically 0.44 molar, to 1.25 equivalents of $LiAlH_4$ (1.0 M in THF) at -78°C. Under these conditions **2a/2b** (97:3) were isolated in greater than 94% yield which could be separated by flash chromatography.[7,8] The assignment of *exo*-position to the hydroxyl group in the major isomer **2a** was based on the well known preference for *endo* reduction of norbornyl ketones[9] and NOE experiments. An NOE interaction was observed between the CHOH and the methyl protons in the minor carbinol **2b** which was absent in **2a**.

We next turned our attention to the acid catalyzed rearrangement of carbinols **2a/2b**. Typically 5.0 mmol of the 97:3 mixture of **2a/2b** was refluxed in the appropriate solvent with an acid catalyst (Table 1). Work-up consisted of washing the organic phase with water, brine and drying. Flash chromatography gave two products. The major product was identified as (+)-*trans*-camphenesulfonamide (**3**) and the minor product as tricyclane sulfonamide **4** based on their spectral properties. The absorption at δ 6.05 ppm in the ^1H NMR of **3** is indicative of a vinyl proton with the alkene carbons at δ 118.4 and 173.5 ppm, respectively in the ^{13}C NMR spectrum. The trans nature of the double bond was confirmed by single crystal X-ray analysis (Figure 1).[10,11] The single absorption for the two methyl group at δ 0.9 ppm, the fact that there are only five carbon resonances in the ^{13}C NMR and that it is not optically active support its highly symmetrical structure.[12] When **2a/2b** were dissolved in conc. H_2SO_4, stirred for 1 h and poured over ice camphenesultam (**5**) was isolated in 83% yield. The structure of **5** is based on the NH absorption at 3258 cm^{-1} in its IR spectrum and analysis of the ^1H, ^{13}C NMR spectra as well as HETCOR and NOE experiments. The structure of sultam **5** also finds precedent in the acid catalyzed rearrangement of 10- and 9-(2-hydroxy)bornanesulfonates to an optically inactive camphene sultone (**5**, NH = O).[13] Evaluation of **5** ($[\alpha]^{20}_D$ + 0.71) using the chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)-

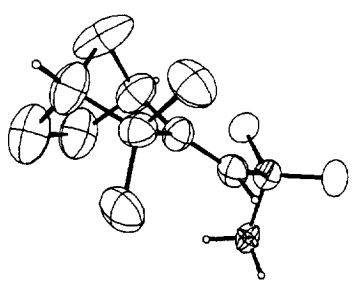


Figure 1. Structure of (+)-**3** in the solid state (some hydrogens not shown).

Table 1. Acid Catalyzed Rearrangement of Carbinols **2a/2b**[a]

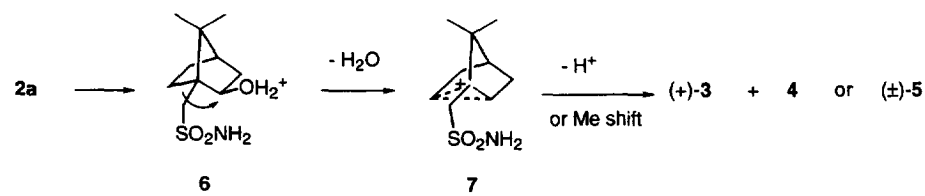
entry	Solvent (mL)	Acid Catalyst (mol %)	time (h)	(+)-**3** % yield[b] (% ee)[c]	**4**
1	Toluene (20)	TsOH (15)	0.5	54 (55)	9
2		TsOH (15)	2.0	58 (43)	4
3		TsOH (15)	12	59 (38)	4
4		TsOH (1-2)[d]	30	61 (72)	14
5		H_2SO_4 (1-2)	8	65 (73)	14
6		Amberlist Resin	16	67 (73)	12
7	Toluene (200)	TsOH (1-2)	120	67 (90)	5
8	Xylenes (20)	TsOH (1-2)	6	72 (71)	17
9	Xylenes (200)	TsOH (1-2)	16	64 (88)	8

a) Carried out on 5.0 mmol of carbinol substrate.
b) GLC yields using a 30m x 0.32 mm SPB-30 column
c) Based on the maximum observed rotation of optically pure (+)-**3**.
d) Values calculated based on 15% recovery of starting material.

ethanol indicated that it was racemic.

The results summarized in Table 1 reveal that the highest yields and ee's (88-90%) of (+)-**3** were obtained when the rearrangement was carried out in dilute toluene or xylene (entries 7 and 9). The lower temperature of toluene (110 °C) resulted in a significant increase in the reaction time compare to xylene (137 °C, compare entries 7 and 9). Two crystallization of the crude material ($[\alpha]^{20}_D$ +172.19) from acetone/*n*-hexane gave (+)-**3**, $[\alpha]^{20}_D$ +190.5 (c 1.0 $CHCl_3$) in 58% yield and >97% ee. The optical purity was verified by forming the sulfonyl urea with (*S*)-(-)-α-methylbenzylisocyanate followed by HPLC analysis using a reverse phase C-18 column (40% MeCN:H_2O).

The formation of the rearrangement products listed in Scheme 1 can be rationalized in terms of bridged ion **7** which loses a C-10 or C-6 proton to form (+)-**3** and **4**, respectively or undergoes a methyl shift to eventually give (±)-**5**. What remains unclear, and the subject of future studies, is the influence of dilution on the optical purity of (+)-**3** and the dominate shift in the rearrangement products to (±)-**5** in the presence of conc. H_2SO_4.



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References and Notes

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7. All new compounds gave satisfactory elemental analysis and their spectral properties were consistent with their structures.
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