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Enantiospecific synthesis of substituted 1-norbornyl trifluoromethanethiosulfonates and 1-norbornanethiols

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Abstract: New homochiral 1-norbornylthiotriflates **6** and **7** and 1-norbornanethiols **8** and **9** are easily prepared starting from naturally occurring 2-norbornanones **1**. The key step is the reaction of chiral 2-norbornanethiones **2** with Tf_2O under mild conditions. © 1997 Published by Elsevier Science Ltd

Thiosulfonates R-SO_2S-R′ are less common than their oxygen analogues, sulfonates, although they constitute an important class of organic compounds which have found interesting applications as antifungical,[1] bactericidal,[1] radioprotectant[1] and sulfhydryl blocking reagents for enzymes.[2] Furthermore, they are useful synthons for the preparation of certain β-lactam antibiotics[3] such as 3-norcephems, penams, penems and other biologically active compounds such as enzyme inhibitors.[4] Thiosulfonates react with nucleophiles at the sulfenyl sulfur, due to the good nucleofugacity of sulfinate anions,[5] giving S–S bond cleavage products. This makes them powerful sulfenylating agents,[6] especially in the thioalkylation of thiols[7] to form unsymmetrical disulfides which play significant roles in diverse biochemical processes as regulatory hormones, drugs and enzyme activators or inhibitors.[8]

The most common synthetic methods for the preparation of thiosulfonates involve alkylation of thiosulfonic acids salts,[4,6b,9] sulfenylation of sulfinic acids or their salts,[10] reaction of thiols with sulfonyl halides[11] and oxidation of thiosulfinates, thiols or disulfides[3c,12] (only suitable for the symmetrical ones). However, all these procedures have limitations (mainly in the preparation of unsymmetrical thiosulfonates),[10c,12] derived from side reactions or unstability and unavailability of starting materials. Very recently, a procedure for the preparation of alkyl- and aryl- thiotriflates by sulfenylation of sodium triflinate has been described.[13] Thiotriflates could be more potent sulfenylating agents than nonfluorinated thiosulfonates.

In this communication we present an easy and convenient procedure for the preparation of different substituted 1-norbornylthiotriflates **5–7** and 1-norbornanethiols **8** and **9** from 1-methyl-2-norbornanones **1**. Both thiotriflates and thiols are promising as precursors for the preparation of other optically active bridgehead sulfur compounds (e.g. sulfonic acids, sulfides, disulfides, etc.).

As we have earlier shown, the reaction of 1-methyl-2-norbornanones **1** such as fenchone **1a** and camphor **1b** with trifluoromethanesulfonic anhydride in the presence of a hindered base takes place under Wagner–Meerwein rearrangement of the triflyloxycarbenium ions formed by electrophilic attack at the carbonyl oxygen, giving 2-methylidene-1-norbornyltriflates in good yields.[14] These homochiral bridgehead triflates have been widely used by us as starting materials for the preparation of other homochiral bridgehead compounds of great interest such as 1-norbornylamines with antiviral activity,[15] 1,2-norbornanediols,[14b,16] β-aminoalcohols,[17] bicyclo [2.1.1] hexane derivatives[18] and homochiral cyclopentane derivatives.[14b]

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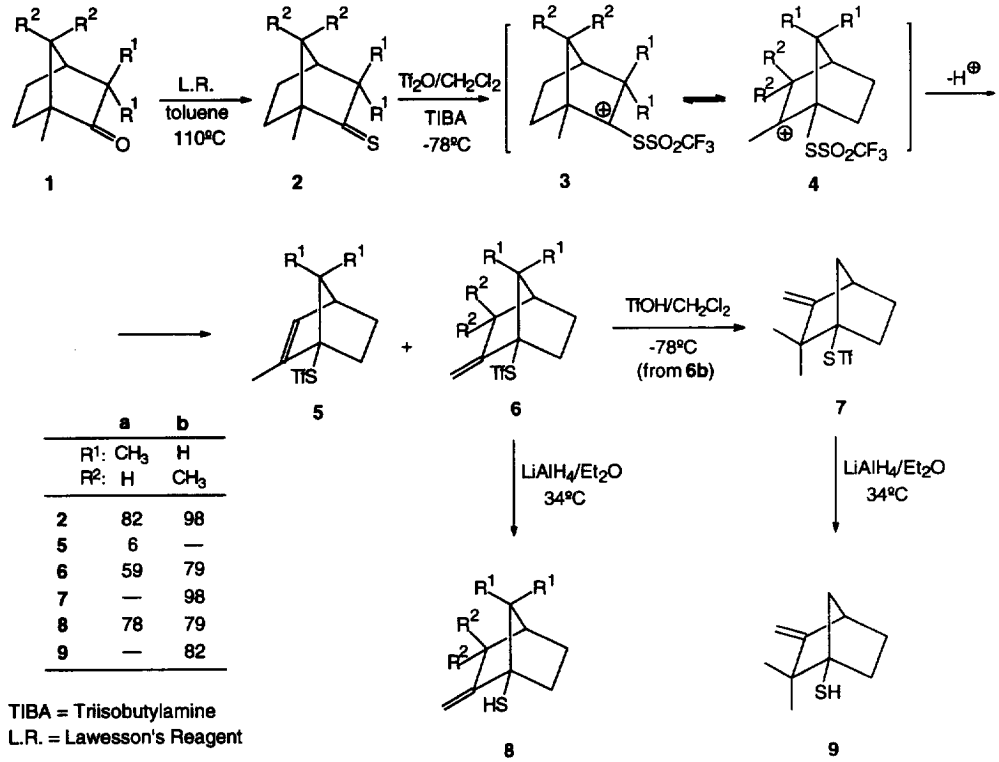
Following our work plan on the preparation and chemistry of bridgehead homochiral compounds starting from naturally occurring 1-methyl-2-norbornanones **1**,[14,19] we report here on the synthesis of new homochiral thiotriflates like **6a**, **6b** and **7** and thiols **8a**, **8b** and **9** based on the reaction of thioketones **2** with trifluoromethanesulfonic anhydride (Tf_2O). The results are summarized in Scheme 1.



	a	b
	R^1: CH_3	H
	R^2: H	CH_3
2	82	98
5	6	—
6	59	79
7	—	98
8	78	79
9	—	82

TIBA = Triisobutylamine
L.R. = Lawesson's Reagent

Scheme 1.

Thioketones **2**[20] were obtained by reaction of ketones **1** with Lawesson's reagent.[21] As expected, the reaction of **2** with Tf_2O proceeds as with the parent ketones,[14] leading to the trifluoromethylsulfonylthiocarbenium ion **3** which undergoes a Wagner–Meerwein rearrangement to **4** and subsequent deprotonation giving the thiotriflates **5** and **6** in good yields.[22] The thus obtained thiotriflate **6b** is pure enough (>95% by ^{1}H-NMR) to be employed in further reactions. Nevertheless, analytical pure samples of **6b** can be obtained by flash column chromatography (silica gel/*n*-pentane). Thiotriflate **6b** quantitatively isomerizes to **7** when treated with two equivalents of TfOH in CH_2Cl_2 at −78°C through a Nametkin rearrangement, similar to its analogous triflate.[14a,23] In the case of **2a**, thiotriflates **5** and **6** were easily separated by column chromatography (silica gel/*n*-pentane).

The reduction of thiotriflates **6** and **7** was straightforwardly achieved by reaction with $LiAlH_4$ in Et_2O at 34°C, affording the bridgehead thiols **8** and **9**, through S–S bond cleavage. Thiols **8** and **9** were purified by column chromatography (silica gel/*n*-pentane).

In summary, we have presented a facile and convenient method for the preparation of new homochiral bridgehead thiotriflates and thiols,[24] which are promising as precursors of chiral ligands[25] and other interesting bridgehead sulfur derivatives. Further work in this area is in progress.

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22. **General procedure**: To a stirred solution, cooled at −78°C, of **2** (11.9 mmol) and TIBA (30.0 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise a solution of Tf_2O (15.5 mmol for **2a** or 28.5 mmol for **2b**) in CH_2Cl_2 (10 mL). The mixture was stirred for 30 min and the reaction was monitored by GC. After completion of the reaction, the solvent was removed and pentane (50 mL) was added. The mixture was washed with 10% hydrochloric acid (3×20 mL), 10% $NaHCO_3$ (20

mL) and dried ($MgSO_4$). After evaporation of the solvent, the crude oil was purified by column chromatography (silica gel/*n*-pentane).

23. Unlike its analogous triflate, two equivalents of TfOH are required for the complete isomerization of **6b**.
24. Specific rotations and spectral data of the synthesized products. **5**: $[\alpha]_D^{20}=-18.3$ (c=0.77, CH_2Cl_2). ^{13}C-NMR (62 MHz, $CDCl_3$) δ=141.6, 129.3, 119.3, (q, J=324.0 Hz), 75.5, 62.1, 49.7, 30.0, 26.7, 20.5, 19.7, 14.9 ppm. **6a**: $[\alpha]_D^{20}=+47.5$ (c=1.02, CH_2Cl_2). ^{13}C-NMR (62 MHz, $CDCl_3$) δ=151.3, 119.3 (q, J=323.6 Hz), 108.3, 73.1, 52.0, 43.1, 36.8, 33.0, 28.5, 19.7, 19.4 ppm. **6b**: $[\alpha]_D^{20}=-89.1$ (c=0.28, CH_2Cl_2). ^{13}C-NMR (62 MHz, $CDCl_3$) δ=161.8, 119.2 (q, J=323.7 Hz), 103.2, 66.2, 45.9, 44.3, 43.6, 35.9, 29.3, 25.9, 25.0. ppm. **7**: $[\alpha]_D^{20}=-18.5$ (c=1.05, CH_2Cl_2). ^{13}C-NMR (62 MHz, $CDCl_3$) δ=161.6, 119.1 (q, J=326.8 Hz), 101.7, 69.9, 47.8, 44.2, 42.3, 31.2, 30.3, 28.0, 23.7 ppm. **8a**: $[\alpha]_D^{20}=-37.8$ (c=0.59, CH_2Cl_2). ^{13}C-NMR (62 MHz, $CDCl_3$) δ=156.2, 104.5, 61.2, 49.4, 42.9, 37.4, 36.8, 28.2, 19.4, 19.1 ppm. **8b**: $[\alpha]_D^{20}=-49.0$ (c=0.68, CH_2Cl_2). ^{13}C-NMR (62 MHz, $CDCl_3$) δ=166.3, 100.7, 55.1, 48.0, 46.5, 42.8, 38.3, 29.7, 26.2, 25.8 ppm. **9**: $[\alpha]_D^{20}=-28.9$ (c=2.26, CH_2Cl_2) ^{13}C-NMR (62 MHz, $CDCl_3$) δ=164.1, 100.9, 56.8, 46.1, 45.3, 34.9, 31.2, 30.7, 28.0, 20.6 ppm.
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