Unexpected reactivity of 10-hydroxycamphor under triflic anhydride treatment: formation of a C_2-pseudosymmetric camphor-derived sulfite

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Dedicated to Prof. Benito Alcaide Alañón on the occasion of his 60th birthday

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Abstract

Treatment of enantiopure 10-hydroxycamphor with triflic anhydride and triethylamine yields enantiopure bis(10-camphoryl) sulfite, a novel interesting camphor-based C_2-pseudosymmetric chiral sulfite with a prochiral sulfonyl group. The process takes place by initial formation of 10-camphoryl triflinate, which undergoes an unexpected nucleophilic substitution with displacement of trifluoromethyl anion (attack of a second equivalent of 10-hydroxycamphor on the sulfur atom). The mentioned pseudosymmetric sulfite has also been obtained by standard reaction of 10-hydroxycamphor with thionyl chloride.

Keywords: Triflic anhydride, camphor derivatives, chiral sulfites, triflinates

Introduction

During the last years we have developed a methodology for the straightforward synthesis of enantiopure 10-substituted camphor derivatives starting from natural camphor.[1] This class of compounds has been used for many years as interesting intermediates for the preparation of a large variety of valuable chirality transfer agents, namely chiral resolving agents, auxiliaries, ligands, catalysts, etc. (some examples are depicted in Figure 1). However, those derivatives having an atom different from sulfur at position 10 of camphor were usually hard to obtain. In

contrast, 10-S-derivatives were easily prepared from commercially available 10-camphorsulfonic acid. It was in this context that we developed the stereocontrolled synthetic route shown in Scheme 1 for the preparation of differently substituted 10-substituted camphors from camphor in just three steps.[1a]

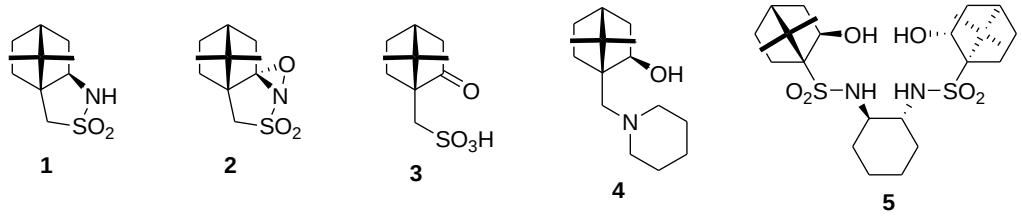
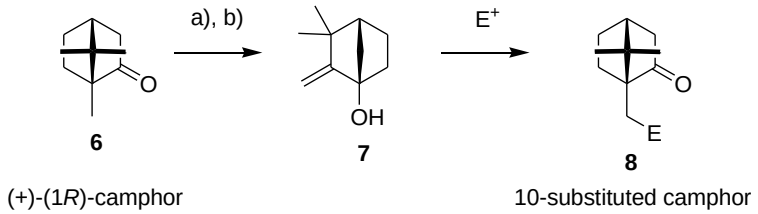


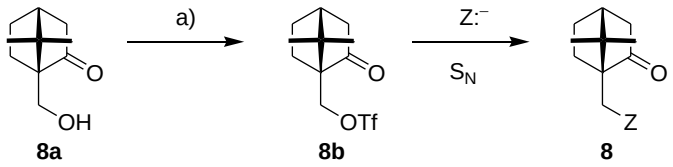
Figure 1. Some selected 10-substituted camphor derivatives.



Scheme 1. Stereocontrolled route to 10-substituted camphor derivatives **8** based on electrophilic reagents (E^+). a) Tf_2O / TIBA, DCM, r.t.; b) LAH, Et_2O, reflux.

The introduction of a substituent at position 10 of camphor was achieved by reaction of intermediate **7** with an appropriate electrophile, capable of adding to the olefin and promoting a pinacol-type Wagner-Meerwein rearrangement. By this synthetic route, we have introduced different atoms at position 10 of camphor (halogens, oxygen, sulfur, selenium, carbon, etc.).[1a] However, certain heteroatoms could not be introduced at such position by this electrophile-based methodology. With the aim of finding alternative ways to obtain all kinds of 10-substituted camphor derivatives, we decided to prepare 10-triflyloxycamphor (**8b)** from 10-hydroxycamphor (**8a**).[2] The nucleofugacity of the triflyloxyl group would make this derivative a versatile intermediate from which a particular substituent could be introduced at such position by an S_N reaction.[3]

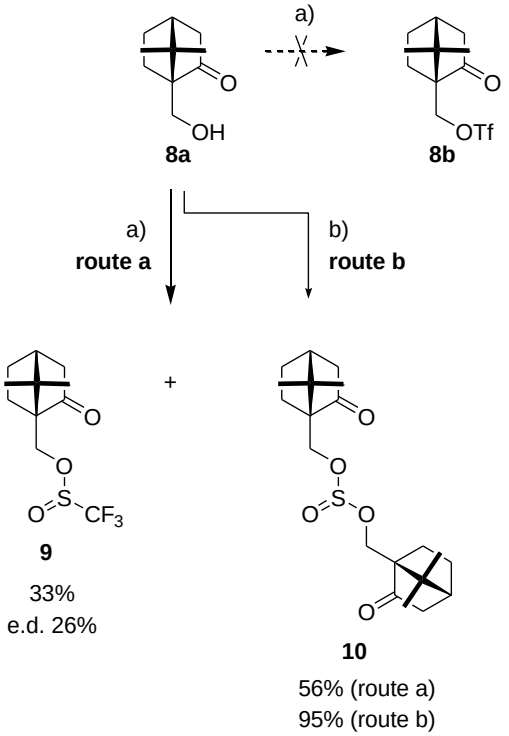
Thus, treatment of 10-hydroxycamphor (**8a**) with triflic anhydride (in the absence of base) gave place to 10-triflyloxycamphor (**8b**). This derivative proved to be a versatile intermediate for the preparation of other 10-substituted camphors, such as amino or amido derivatives (Scheme 2).[1d]



Scheme 2. Stereocontrolled route to 10-susbtituted camphors derivatives **8** based on nucleophilic reagents (Z:⁻). a) Tf_2O.

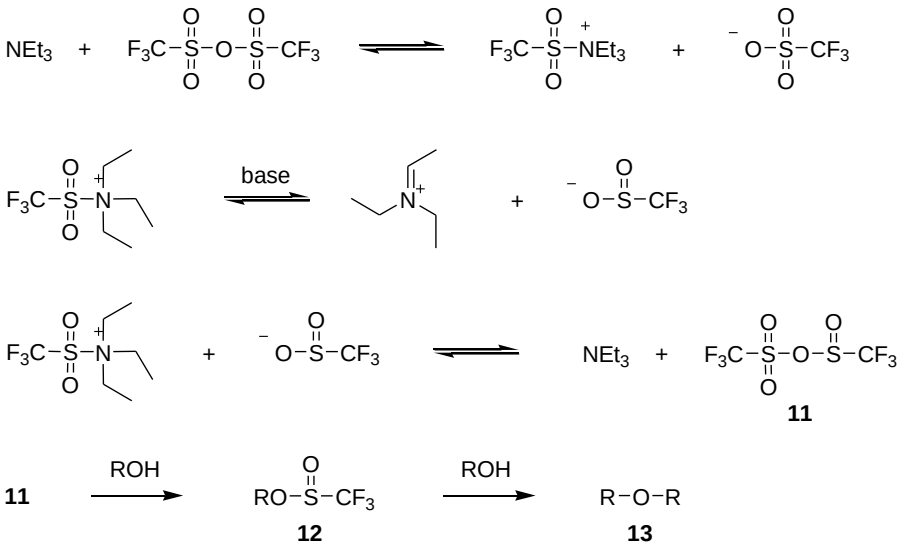
Results and Discussion

In the search for conditions for the preparation of 10-triflyloxycamphor (**8b**), we found an interesting and unexpected reactivity of 10-hydroxycamphor (**8a**) with triflic anhydride. Thus, when 10-hydroxycamphor (**8a**) was treated with triflic anhydride in standard conditions (triethylamine as base and dichloromethane as solvent), enantiopure C_2-pseudosymmetric sulfite **10** and triflinate **9** (as a diastereomeric mixture, e.d. 26%) were obtained instead of the expected triflate **8b** (route a, Scheme 3). The same sulfite **10** was obtained in the reaction of **8a** with thionyl chloride using pyridine as both catalyst and base (route b, Scheme 3).[4,5] This new pseudosymmetric chiral sulfite is a potential interesting precursor for the enantioselective preparation of chiral sulfoxides[6] from asymmetric sulfites, according to Kagan´s methodology.[7]



Scheme 3. Generation of C_2-pseudosymmetric sulfite **10**. a) Tf_2O/Et_3N. b) $SOCl_2$/pyridine.

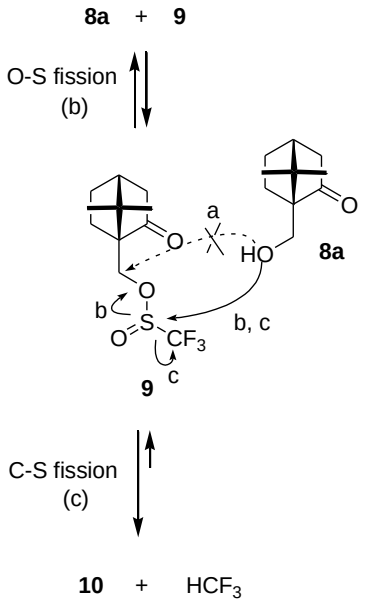
Formation of triflinates is well-known in the reaction of sterically hindered alcohols with triflic anhydride and triethylamine. Under these conditions, a mixed anhydride, triflinyl triflate **11**, is formed. This new anhydride can react with an alcohol to give rise to the corresponding triflinate **12**.[8] These highly reactive electrophilic triflinates **12** usually undergo a subsequent *in situ* nucleophilic substitution reaction with a second molecule of the starting alcohol to yield the symmetric ethers **13** (Scheme 4).[8]



Scheme 4. Formation of triflinyl triflate **11** from triflic anhydride and base, and general reaction with alcohols.

Unexpectedly, no ether was detected in our case, but C_2-pseudosymmetric sulfite **10** was isolated instead. This fact must be due to the neopenthylic character of both, the starting alcohol **8a** and the triflinate **9**, which favors the nucleophilic attack of a second molecule of alcohol on the sulfur atom (b or c, Scheme 5) over the more hindered neopenthylic carbon atom (a, Scheme 5).

On the other hand, the mentioned nucleophilic attack can take place with O-S fission and alkoxide as leaving group (b, Scheme 5) or with C-S fission and trifluormethyl anion as leaving group (c, Scheme 5).[9] The first option would lead to the same mixture of products (**8a** and **9**), whereas the second would yield sulfite **10** and trifluoromethane. The formation of volatile and less nucleophilic trifluoromethane must be the driving force for the equilibrium displacement towards the sulfite formation.



Scheme 5. Unexpected electrophilic reactivity of triflinate **9**.

Conclusions

In summary, unexpected reactivity of 10-hydroxycamphor (**8a**) with triflic anhydride has been described. Treatment of **8a** with triflic anhydride and base affords *C*$_2$-symmetric sulfite **10**, instead of the expected triflate **8b**. The synthetic process involves the formation of a key intermediate triflinate **9** by reaction of the corresponding starting alcohol with Tf_2O/Et_3N. In mechanistic terms, the described sulfite formation implies an unexpected sterically-controlled electrophilic reactivity of the mentioned triflinate.

Experimental Section

General Procedures. Et_2O and CH_2Cl_2 were distilled over sodium / benzophenone and calcium hydride, respectively, immediately prior to use. Triethylamine was dried with KOH and distilled over CaH_2. Pyridine was dried and distilled over KOH. Thionyl chloride was purchased from Aldrich and used without further purification. Triflic anhydride was prepared from triflic acid according the previously described procedure[10] and distilled over P_2O_5 immediately prior to use. Flash chromatography was performed over silica gel (230-400 mesh).^{1}H and ^{13}C NMR were recorded in a Bruker AC-200 spectrometer (200 MHz for ^{1}H and 50 MHz for ^{13}C) in $CDCl_3$ at room temperature. Chemical shift values are reported in ppm, using chloroform as internal reference (7.27 ppm for ^{1}H and 77.0 ppm for ^{13}C) and coupling constants are in hertz. IR spectra were recorded on a Shimadzu FTIR-8300 spectrometer. Wave numbers are reported in cm^{-1}.

Mass spectra were recorded on a 60-eV mass spectrometer. HRMS were recorded on a mass VG-spectrometer using the FAB technique.

Reaction of 10-hydroxycamphor with triflic anhydride (route a). Over a cooled (0 ºC) solution of **8a** (1.00 g, 5.9 mmol) and NEt_3 (1.80 g, 17.7 mmol) in 30 mL of dry CH_2Cl_2 under argon, freshly distilled Tf_2O (2.00 g, 7.1 mmol) was added dropwise. After stirring at room temperature for 48 h, the reaction mixture was treated with sat. $NaHCO_3$ solution (15 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with 10% HCl (2 x 15 mL), H_2O (1 x 15 mL) and brine (1 x 15 mL) and dried over $MgSO_4$. After solvent evaporation under reduced pressure, the crude was purified by flash chromatography (silica gel / CH_2Cl_2). **9** (33% yield, inseparable diastereomeric mixture, e.d. 26% by ^{1}H NMR) and **10** (55% yield)[11] were obtained.

(1*R*,*R*s)- and (1*R*,*S*s)-10-(Triflinyloxy)camphor (9). Colorless oil. HRMS (mixture): 215.0752 [calcd. for $C_{10}H_{15}O_3S$ ($M^{+\cdot}$ - CF_3): 215.0742]. ^{1}H NMR (mixture), δ: 4.54 (AB, d, *J* = 11.2 Hz, 1H), 4.50 (AB, d, *J* = 11.2 Hz, 1H´), 4.29 (ABX, dd, *J* = 11.2 Hz, *J* = 0.7 Hz, 1H´), 4.24 (ABX, dd, *J* = 11.2 Hz, *J* = 0.7 Hz, 1H), 2.45 (dm, *J* = 18.5 Hz, 1H+1H´), 2.18 – 1.90 (several m, 4H+4H´), 1.44 (d, *J* = 10.2 Hz, 2H), 1.43 (d, *J* = 11.8 Hz, 2H´), 1.09 (s, 3H+3H´), 0.99 (s, 3H+3H´). ^{13}C NMR (mixture), δ: 215.2, 215.1, 122.8 (c, *J* = 338.5 Hz, CF_3), 122.8 (c, *J* = 332.2 Hz, CF_3), 65.8, 65.6, 60.7, 47.2, 43.9, 43.1, 26.5, 25.3, 24.9, 20.6, 20.5, 19.8, 19.7. IR (CCl_4), ν: 1751 (s), 1205 (s), 1134 (s). MS (mixture), *m/z*: 215 (10), 81 (100).

Bis[(1*R*)-10-camphoryl] sulfite (10). White solid. Mp: 115 - 117 ºC. HRMS: 405.1706 [calcd. for $C_{20}H_{30}NaO_5S$: 405.1712] $[\alpha]_D^{20}$ +44.0 (0.11, $CHCl_3$). ^{1}H NMR, δ: 4.27 (AB, d, *J* = 11.2 Hz, 1H), 4.21 (AB, d, *J* = 11.2 Hz, 1H), 4.10 (AB, d, *J* = 11.2 Hz, 1H), 4.06 (AB, d, *J* = 11.2 Hz, 1H), 2.43 (dm, *J* = 18.5 Hz, 2H), 2.05 – 1.88 (m, 6H), 1.88 (d, *J* = 18.5 Hz, 2H), 1.55 – 1.32 (m, 4H), 1.08 (s, 6H), 0.99 (d, *J* = 3.4 Hz, 6H). ^{13}C NMR, δ: 215.8, 215.6, 60.2, 58.4, 58.3, 47.1, 43.9, 43.8, 43.2, 26.6, 25.5, 20.8, 20.4, 20.0. IR (CCl_4), ν: 1747, 1375, 1197. MS, *m/z*: 267 (4), 100 (100).

Bis[(1*R*)-10-camphoryl] sulfite (10) (route b). Over a cooled (0 ºC) solution of **8a** (1.81 g, 10.8 mmol) and pyridine (1.71 g, 21.6 mmol) in 20 mL of dry Et_2O under argon atmosphere, $SOCl_2$ (0.64 g, 5.4 mmol) was added dropwise. After stirring for 1h at room temperature, the reaction mixture was filtrated over celite, washing with Et_2O. The filtrated was then washed with 10% HCl (2 x 10 mL), sat. $NaHCO_3$ (1 x 10 mL), H_2O (1 x 10 mL) and brine (1 x 10 mL) and dried over $MgSO_4$. After solvent evaporation under reduced pressure, the crude was purified by recrystalization from hexanes (95% yield).

Acknowledgements

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