An Improved Synthesis of 10-Isobornylsultone

Frank W. Lewis†,* and David H. Grayson

Centre for Synthesis and Chemical Biology, School of Chemistry, Trinity College, Dublin 2, Ireland

Abstract—A modified and improved synthesis of 10-isobornylsultone in three steps and in 81 % overall yield starting from (+)-camphor-10-sulfonic acid is described. The synthesis proceeds by methyl sulfonate ester formation, stereoselective reduction and base-catalyzed intramolecular cyclisation. © 2014 Elsevier Science. All rights reserved

1. Introduction

Derivatives of the bicyclic monoterpene (+)-camphor have been widely used both as chiral control elements in asymmetric synthesis and as chiral templates in enantiospecific natural product syntheses owing to its rigid bicyclic structure.1 One such derivative is (−)-10-isobornylsultone 1 (Figure 1). The known2 thermal rearrangement of sultone 1 to sultone 2 has been exploited in the enantiospecific total syntheses of β-santalol3 and β-santalene,4 which are the two main constituents of East Indian sandalwood oil. In addition, sultone 1 is a key precursor to several important chiral auxiliaries. Cleavage of the S–O bond of 1 with various nucleophiles gives rise to isoborneol sulfonamides 3,5 isoborneol arylsulfones 46 and to 10-mercaptoborneol 57 which have all been frequently employed as chiral auxiliaries in asymmetric synthesis.8–11

Sultone 1 has been previously synthesized by the sulfonation of camphene using acetic anhydride/fuming sulfuric acid,2a or by the reduction of (+)-camphor-10-sulfonic acid with sodium borohydride followed by exposure of the intermediate sodium isobornylsulfonate salt to p-toluenesulfonyl chloride in pyridine.2c,3,5,6a In a more recent report, Kaye obtained sultone 1 as a minor by-product (4 % yield) during the reduction of phenyl (+)-camphor-10-sulfonic acid with sodium borohydride followed by exposure of the intermediate sodium isobornylsulfonate salt to p-toluenesulfonyl chloride in pyridine.2c,5,6a

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2. Results and Discussion

During the course of our ongoing studies on the utility of camphor-derived sulfones as novel chiral auxiliaries in asymmetric synthesis,14 we required a short synthesis of the methyl sulfonate ether intermediate 9. We proposed to synthesize 9 by the route outlined in Scheme 1.

Figure 1. The structures of isobornylsultone 1, its thermal rearrangement isomer 2, and its derived chiral auxiliaries 3, 4 and 5.

Scheme 1.
Accordingly, methyl sulfonate ester 7 was conveniently obtained in 90 % yield by treating (+)-camphor-10-sulfonic acid 6 with trimethyl orthoacetate according to the procedure of Gopalan.15 Reduction of 7 with excess sodium borohydride in methanol proceeded with high stereoselectivity to afford the novel exo-configured isoborneol sulfonate ester 8 along with ca. 10 % of its endo-configured borneol isomer 10 in 95 % combined yield as determined by 1H NMR spectroscopy (Scheme 2). This mixture was used in the next step without further purification. The exo-alcohol 8 was characterized by a doublet at ca. δ 4.1 ppm for the C2 endo-methine proton as well as a pair of doublets at ca. δ 3.0 and 3.6 ppm corresponding to the methylene protons adjacent to the sulfonate ester group.

Treatment of 8 with sodium hydride in the presence of methyl iodide in dry THF at ambient temperature for 1 hour failed to afford the desired methyl ether 9 (Scheme 1). Instead, isobornyl sultone 1 was obtained as the sole product. When the reaction was repeated under identical conditions in the absence of methyl iodide, sultone 1 was obtained in 60 % yield. Performing the cyclisation reaction at 0 °C for 1 hour resulted in a greatly improved yield of 1 of 95 % (Scheme 3). The NMR spectroscopic details of 1 were identical to those published by Pinho e Melo.66 Interestingly, carrying out the reaction at ambient temperature for 24 hours afforded 1 in a much lower 15 % yield. Evaporation of the aqueous phase from this reaction furnished an off-white solid whose 1H NMR spectrum in D2O suggested the presence of the corresponding sodium isobornylsulfonate salt,16 which was most likely obtained by simple methanolation or hydrolysis of the sulfonate ester group of 8.

![Scheme 2](image)

Inspired by Kaye’s synthesis of 1 via reduction of the analogous phenyl sulfonate ester followed by cyclisation,12 we next sought to synthesize the sultone 1 from the ester 7 in a one-pot procedure via reduction of 7 and subsequent base-catalyzed cyclisation in situ. However, these attempts met with limited success. Various reductions of 7 with excess (3–4 equivalents) sodium borohydride in methanol or in isopropanol, and subsequent additions of potassium tert-butoxide (1 equivalent) led at best to mixtures of 8 and sultone 1 (8:1 ratio ranging from 1:7 to 1:1.3) in overall yields no higher than 44 %. The reduced tendency of sulfonate ester 8 to cyclise to 1 under these conditions compared to Kaye’s phenyl sulfonate ester (which cyclises smoothly to 1 in the absence of additional base)12 can be attributed to the greater leaving group ability of the phenoxy-group in the latter compound.

![Scheme 3](image)

However, the new synthesis of 10-isobornylsultone 1 reported herein has several advantages compared to previous syntheses reported in the literature. Firstly, the one-step esterification of (+)-camphor-10-sulfonic acid 6 to form 7 using trimethyl orthoacetate is superior to the literature synthesis of the analogous phenyl sulfonate ester,17 which has to be carried out in two steps from 6 (ie: conversion of 6 into (+)-camphor-10-sulfonyl chloride using thionyl chloride, followed by treatment of the product with phenol in pyridine), and which employs toxic (phenol, pyridine) and corrosive (thionyl chloride) reagents.18 Secondly, the optimized synthesis of 1 reported herein proceeds in higher overall yield (81 %) than previous syntheses of 1 from either (+)-camphor-10-sulfonyl chloride (76 %)12 or from (+)-camphor-10-sulfonic acid 6 (44 % overall by Kaye’s method,12 75 % overall when thionyl chloride is used to convert 6 to (+)-camphor-10-sulfonyl chloride19). Finally, our reduction of the sulfonate ester 7 to yield 8 requires a smaller excess of sodium borohydride (3 equivalents) than Kaye’s reduction of the analogous phenyl sulfonate ester (which requires 10 equivalents of sodium borohydride).12

3. Conclusion

We report herein an unexpected and improved synthesis of (+)-10-isobomylsultone 1 from (+)-camphor-10-sulfonic acid 6. This modified and convenient synthesis delivers 1 in three steps from 6 in a high overall yield of 81 % without the need for column chromatography or the use of toxic and corrosive reagents.

4. Experimental

4.1. General

NMR spectra were recorded using a Bruker AVANCE DPX 400 MHz spectrometer (400.1 MHz for 1H and 100.6 MHz for 13C). Chemical shifts are reported in parts per million. Coupling constants (J) are quoted in Hertz. Optical
rotations were measured using a Perkin-Elmer 141 polarimeter. IR spectra were recorded for Nujol mulls (N) or liquid films (L) on a Mattson Genesis II FTIR spectrometer. Mass spectra were obtained under electroosmotic conditions using a Micromass LCT instrument. Uncorrected melting points (Mp) were measured in unsealed capillary tubes using a Griffin melting point apparatus. Tetrahydrofuran (THF) was dried and distilled over sodium-benzophenone ketyl prior to use. All other solvents and reagents were purified by standard techniques. Organic extracts of reaction products were dried over anhydrous magnesium sulfate.

(15,5R,7R)-10-Dimethyl-4-oxa-3-thiatricyclo[5.2.1.01,5]decane 3,3-dioxol 1.

A solution of the sulfonate ester 8 (0.58 g, 2.33 mmol) in dry THF (10 mL) was added to a suspension of sodium hydride (0.14 g, 60 %, 3.50 mmol, 1.5 eq) in dry THF (5 mL) under an atmosphere of nitrogen. The solution was stirred at 0 °C for 1 hour. The solution was then diluted with H2O (50 mL) and extracted with DCM (3 × 50 mL). The combined organic extracts were dried and evaporated to yield a semi-solid material which crystallised in vacuo (0.1 mm Hg) to afford the title compound 1 as a white solid (0.48 g, 95 %). Mp 61–63 °C (DCM); Lit. 61 °C (ether); Lit. 114–116 °C; [α]D = −3.7 (c 0.33, CCl4, 27 °C); Lit. 6 = −4.05 (c 10, CCl4, 25 °C); IR ν max (N) 2923, 2723, 1658, 1456, 1352 (S=O), 1257, 1166 (S=O), 1076, 992, 879, 807, 746 cm −1; 1H NMR (CDCl3) 0.88 (s, 3H, 10- C H3), 1.12–1.17 (m, 1H), 1.45–1.51 (m, 1H), 1.69–1.88 (m, 5H), 2.83 (br s, 1H, 10-H), 2.99 (d, J = 14.0, 1H, CH2SO3CH3), 3.56 (s, [M + Na] +: 249.1161; found: 249.1153.

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16. This compound had 1H NMR (D2O) 0.74 (s, 3H, 7-C1), 2.35 (H, 7-C3), 0.90 (s, 3H, 7-CH3), 0.90 (s, 3H, 7-CH3), 1.00–1.03 (m, 1H), 1.28–1.32 (m, 1H), 1.59–2.09 (m, 1H), 2.76 (d, J = 14.6, 1H, CH2SO3Na). 3.21 (d, J = 14.6, 1H, CH2SO3Na). 3.95–3.98 (m, 1H, 2-C2) ppm.


18. Phenyl camphor-10-sulfonate was recently synthesized directly from (+)-camphor-10-sulfonic acid in 68 % yield using diphenyliodonium salts, see: Jalalian, N.; Petersen, T. B.; Olofsson, B. Chem. Eur. J. 2012, 18, 14140–14149.
