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Synthesis and characterization of novel spirooxazacamphorsultam derivatives

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ABSTRACT

Derivatives of camphorsultam which contain novel spirooxazolidine and spirooxazine structures have been prepared in high yield and purity. Though it was expected that the ketone moiety would undergo acetal formation, the imine instead underwent reaction and was proven by X-ray crystallography and 2D NMR techniques. The initial ketone-containing derivatives were then reduced to produce *exo*-hydroxy analogs that have potential as a new family of chiral auxiliaries.

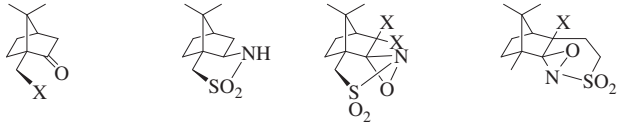
1. Introduction

Camphor (**1a**, Scheme 1) has long been utilized as a source of chirality in asymmetric synthesis. Well known for its synthetic utility as a compound found in the chiral pool, camphor has been functionalized in a number of positions on its bornane skeleton to form a number of synthetically-diverse derivatives. A few examples of camphor derivatives that have found wide use in organic synthesis are (1*S*)-(+)-10-camphorsulfonic acid (**1b**), which has been widely used as a resolving agent;[1,2] Oppolzer's sultam (**2**), a versatile chiral auxiliary found throughout the literature;[3–10] and Davis' oxaziridines (**3**[11,12] and **4**[13]), which have found wide application as chiral reagents.

2. Results and discussion

We have long been interested in *N*-sulfonyloxaziridines as chiral, aprotic oxidizing agents. The synthetic utility that these compounds have contributed to the field of asymmetric organic synthesis is well documented in the literature, as these compounds have found a number of uses in the synthesis of a wide variety of natural and synthetic products.[14–18] The structural diversity of this family of compounds and the enantioselectivity displayed by the derivatives, in particular dichloro derivative **3b** and acetal **3c**, sparked our interest in expanding on these structures. It is well known that the rigidity, steric demands, and electronic interactions of the oxaziridines play a large role in the enantioselectivity they exhibit.[11,19] We envisioned expansion of Davis' acetal oxaziridines, and attempted to produce a cyclic acetal version of oxaziridine **3c**. Although we anticipated difficulty in the incorporation of another ring into an already rigid multicyclic ring system, the formation of a cyclic acetal at the C-3 position (as in dioxolane **5a** and dioxane **5b**, Scheme 2) seemed a natural extension of dimethyl acetal **3c** published by Davis and co-workers.[20] Our initial target was the formation of acetal imines **6a** and **6b**.

Synthesis of the desired acetal derivatives was begun with (1*S*)-(+)-10-camphorsulfonic acid (**1b**) following the literature



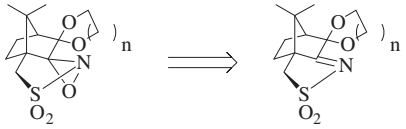
1a X = H
b X = SO_3H

2

3a X = H
b X = Cl
c X = OCH_3

4a X = H
b X = Cl

Scheme 1.



5a n = 1
b n = 2

6a n = 1
b n = 2

Scheme 2.

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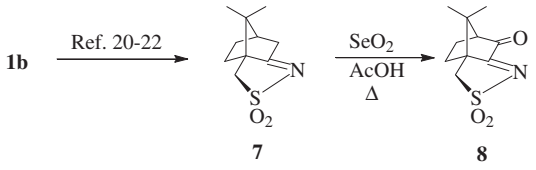
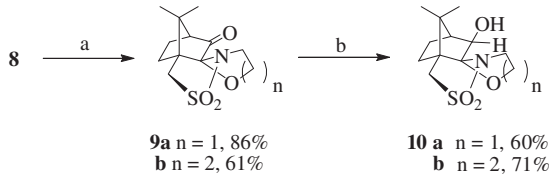


Scheme 3.



Scheme 5. Reagents and conditions: (a) $BrCH_2CH_2OH$ (**9a**) or $BrCH_2CH_2CH_2OH$ (**9b**), DBU, CH_2Cl_2, reflux; (b) $LiAlH_4$, THF, 0 °C to reflux.

methods[20–22] (Scheme 3). The oxidation of imine **7** using SeO_2 led to α-ketoimine **8** as a mixture with an over-oxidation product. Allowing this mixture to sit overnight led to pronounced over-oxidation of the desired ketone **8** and drastically lowered yields of the desired product. Simple vacuum filtration through silica gel afforded the removal of oxidant that remained after vacuum filtration through Celite, as well as the oxidation byproduct, and led to a 90% yield of α-ketoimine **8** in sufficient purity with an extended shelf life.[23]

Table 1 shows a number of methods of acetal formation attempted which ultimately led to successful formation of a crystalline product. Standard acetal formation conditions (acid-catalyzed, Dean–Stark trap, entry 1) and use of a 'bulky proton' source of ethylene glycol[24–26] (entry 2) showed no signs of reaction. It was found that use of 2-chloroethanol[27] led to the formation of product (entry 3), but the yield was limited by polymerization of 2-chloroethanol under basic conditions; lower reaction temperatures in a non-polar solvent showed no signs of the desired product (entries 4 and 5). The yield of the desired product was improved using 2-bromoethanol[28] (entry 6) with lessened observation of polymerization; the reaction was optimized at a lower temperature (entry 7) to produce compound **9a** in an 86% yield.[29]

Initial data, primarily ^1H and ^{13}C NMR, led us to believe that we had formed desired acetal imine **6a** (Scheme 4); upon X-ray crystallography[30] and 2D NMR techniques (DEPT, COSY, and HETCOR), it was discovered that the imine functionality had actually undergone reaction instead of the ketone to produce spirooxazoline

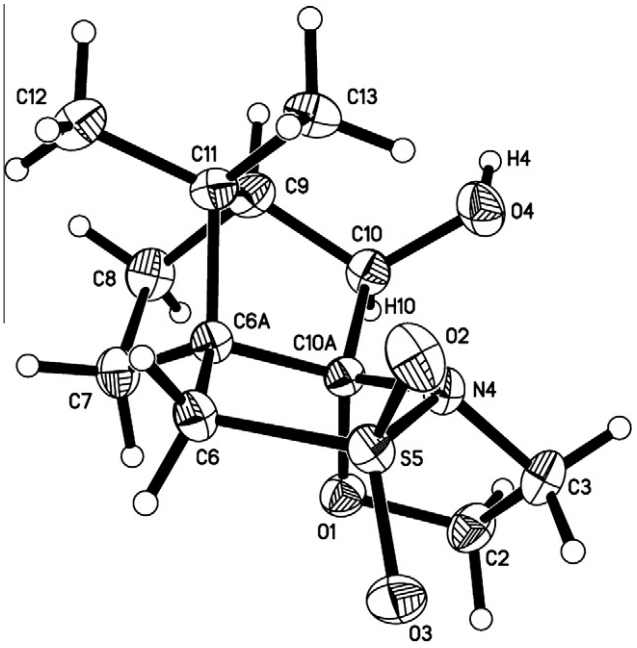
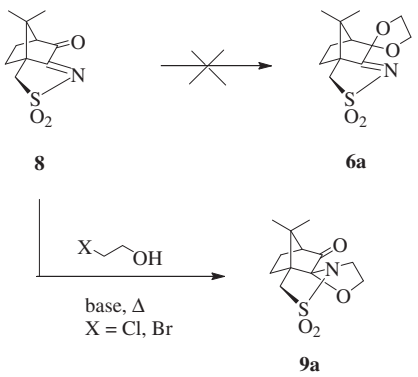


Figure 1. ORTEP of alcohol **10a**.

Table 1
Methods of acetal formation for acetal **9a**

Entry	Conditions	Yield (%)
1	Ethylene glycol, *p*TsOH, toluene, reflux	0
2[24–26]	$TMSOCH_2CH_2OTMS$, TMSOTf, CH_2Cl_2, −78 to 0 °C	0
3[27]	2-Chloroethanol, Li_2CO_3, 130 °C	54
4	2-Chloroethanol, Li_2CO_3, toluene, reflux	0
5	2-Chloroethanol, Li_2CO_3, xylenes, reflux	0
6[28]	2-Bromoethanol, DBU, toluene, reflux	60
7[29]	2-Bromoethanol, DBU, CH_2Cl_2, reflux	86



Scheme 4.

derivative **9a**. The novelty of these compounds and their potential as a new category of camphor-based chiral auxiliaries redirected our attention toward the synthetic utility of these spirooxazolines.

To expand the scope and utility of this novel camphor-derived spirooxazoline and explore its potential as a chiral auxiliary, we not only produced the dioxolane-type oxazolidine **9a**,[29] but also its dioxane counterpart oxazine **9b** through a similar procedure (Scheme 5).[31] Both ketones were then reduced with $LiAlH_4$ in reasonable yields to produce the *exo* alcohols **10a**[32] and **10b**.[33] The structure and orientation of the reduction products were again proven by X-ray crystallography, as seen in the ORTEP of alcohol **10a** (Fig. 1). The ketone and/or alcohol functionalities may provide a useful attachment point for the application of these compounds as chiral auxiliaries.

3. Conclusions

We have produced a new family of chiral, non-racemic compounds which contain a novel multicyclic ring system. Produced by reaction of the imine functionality instead of the ketone, the structures of keto spirooxazolidine **9a** and spirooxazine **9b** were confirmed by X-ray diffraction, which subsequently underwent reduction to produce the *exo*-hydroxy analogs **10a** and **10b** as confirmed by X-ray diffraction as well.[30] We are continuing to study these compounds for their potential as chiral auxiliaries, as well as investigating methods of acetal formation in order to produce sulfonylimines **6**.

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23. Synthesis of (−)-(3-oxocamphorsulfonyl)imine (**8**) was accomplished following the procedure delineated by B.-C. Chen et al. (Ref.[20]) with the following additions: The reaction mixture was vacuum filtered through a pad of Celite and rinsed with CH_2Cl_2 until the filtrate was colorless. The filtrate was concentrated in vacuo and the resulting yellow and orange solids were dissolved in minimal CH_2Cl_2. The solution was vacuum filtered through silica gel and rinsed with CH_2Cl_2 until the filtrate was colorless. The filtrate was concentrated in vacuo to yield (−)-(3-oxocamphorsulfonyl)imine (**8**) as a yellow crystalline solid (90%). This product has spectroscopic data identical to Chen et al. and was used in a timely manner to avoid decomposition. We have also shelved the purified imine for over three months and have seen no signs of decomposition.
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29. General procedure for the preparation of derivatives **9**: To a solution of (−)-(3-oxocamphorsulfonyl)imine (**8**; 7.00 g, 30.7 mmol) in CH_2Cl_2 (105 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (23.0 mL, 153 mmol, 5 equiv), and 2-bromoethanol (11.0 mL, 153 mmol, 5 equiv). The mixture was heated to reflux and stirred for 1 h. The mixture was allowed to cool to rt and dichloromethane (100 mL) was added. The reaction mixture was washed with satd aq NH_4Cl (2 × 100 mL) and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield the crude product as a mix of yellow and orange solids. The solid was crystallized from 100% ethanol to yield spirooxazolidine **9a** as long, white needle-like crystals (7.23 g, 86%). Mp 234–235 °C; $[\alpha]_D$ +34.1 ($CHCl_3$, *c* 1.0); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05–4.12 (m, 2H), 3.99 (dd, *J* = 8.55, 15.96 Hz, 1H), 3.65–3.72 (m, 1H), 3.43 (AB quartet, *J* = 13.81 Hz, 2H), 2.38 (d, *J* = 5.70 Hz, 1H), 2.31 (ddd, *J* = 3.25, 9.13, 12.29 Hz, 1H), 2.11 (dddd, *J* = 3.26, 5.70, 11.70, 13.90 Hz, 1H), 1.96 (ddd, *J* = 5.23, 11.70, 11.70 Hz, 1H), 1.82 (ddd, *J* = 5.33, 9.13, 13.90 Hz, 1H), 1.29 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 100.5, 65.1, 58.9, 52.2, 49.8, 46.3, 44.0, 26.1, 22.9, 22.2, 18.5; DEPT (125 MHz, 135°, $CDCl_3$) δ 65.1 (−), 58.9 (+), 49.8 (−), 46.3 (−), 26.1 (−), 22.9 (−), 22.2 (+), 18.5 (+). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16. Found: C, 53.20; H, 6.28; N, 5.24.
30. Details of X-ray diffraction analysis for compounds **9a**, **9b**, **10a**, and **10b** will be published elsewhere: Wilke, B.I.; Goodenough, A.K.; Bausch, C.C.; Cline, E.N.; Abrams, M.L.; Fayer, E.L.; Swenson, D.C.; Cermak, D.M. *Acta Cryst.* **2010**, *C66*, o600–o605.
31. Compound **9b**: The solid was crystallized from 100% ethanol to yield spirooxazine **9b** as a white crystalline solid (61%). Mp 184–185 °C; $[\alpha]_D$ −5.5 ($CHCl_3$, *c* 1.0); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.51 (ddd, *J* = 2.67, 11.65, 13.20 Hz, 1H), 3.99–4.02 (m, 1H), 3.78 (ddd, *J* = 3.56, 13.06, 14.72 Hz, 1H), 3.64–3.68 (m, 1H), 3.34 (s, 2H), 2.37–2.47 (m, 1H), 2.34 (d, *J* = 5.70 Hz, 1H), 2.29–2.33 (m, 1H), 2.00–2.07 (m, 1H), 1.77–1.85 (m, 2H), 1.34–1.38 (m, 1H), 1.19 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.3, 87.5, 63.2, 59.3, 54.5, 48.2, 44.0, 38.0, 24.6, 23.1, 22.0 (2C), 19.1; DEPT (125 MHz, 135°, $CDCl_3$) δ 63.1 (−), 59.3 (+), 48.2 (−), 38.0 (−), 24.6 (−), 23.1 (−), 22.0 (+), 22.0 (−), 19.1 (+). Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91. Found: C, 54.69; H, 6.70; N, 4.88.
32. General procedure for the preparation of *exo*-hydroxy derivatives **10**: To a mixture of $LiAlH_4$ (1.21 g, 31.8 mmol, 1.2 equiv) in THF (450 mL) at 0 °C was added spirooxazolidine **9a** (7.24 g, 26.7 mmol) in portions. The mixture was heated to reflux while stirring for 12 h. The mixture was cooled to 0 °C and methanol (250 mL) was added dropwise. Solvent was removed from the mixture in vacuo until a white solid/gray residue remained. The solid was dissolved in 20% KOH (150 mL). The resulting mixture was continuously extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield a mix of white and yellow solids. The solid was crystallized from 100% ethanol to yield *exo*-hydroxy spirooxazolidine **10a** as white needle-like crystals (4.34 g, 60%). Mp 201–205 °C; $[\alpha]_D$ −6.2 ($CHCl_3$, *c* 1.0); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.11 (ddd, *J* = 4.80, 8.07, 12.57 Hz, 1H), 3.97 (dd, *J* = 7.77, 14.68 Hz, 1H), 3.81 (ddd, *J* = 4.80, 7.77, 8.43 Hz, 1H), 3.68 (d, *J* = 4.68 Hz, 1H), 3.44 (ddd, *J* = 6.84, 8.72, 12.25 Hz, 1H), 3.38 (AB quartet, *J* = 13.60 Hz, 2H), 2.07 (ddd, *J* = 2.98. 9.17, 12.25 Hz, 1H), 1.89–2.01 (m, 3H), 1.68–1.76 (m, 1H), 1.46 (s, 3H), 1.29–1.39 (m, 1H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 110.0, 83.1, 63.0, 53.2, 52.1, 50.6, 48.6, 46.4, 25.7, 24.6, 22.6, 21.6; DEPT (125 MHz, 135°, $CDCl_3$) δ 83.1 (+), 63.0 (−), 52.1 (+), 50.6 (−), 46.4 (−), 25.7 (−), 24.6 (−), 22.6 (+), 21.6 (+). Anal. Calcd for $C_{12}H_{19}NO_4S$: C, 52.73; H, 7.01; N, 5.12. Found: C, 52.97; H, 6.76; N, 5.08.
33. Compound **10b**: Purification by flash column chromatography (5:95 acetone/chloroform) gave *exo*-hydroxy spirooxazine **10b** as a white crystalline solid (71%). Mp 186–188 °C; $[\alpha]_D$ −27.0 °C ($CHCl_3$, *c* 1.0); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03–4.06 (m, 3H), 3.65–3.76 (m, 2H), 3.27 (AB quartet, *J* = 13.54 Hz, 2H), 2.37–2.49 (m, 1H), 2.00–2.06 (m, 2H), 1.83–1.91 (m, 2H), 1.49–1.56 (m, 1H), 1.42 (s, 3H), 1.22–1.31 (m, 2H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.7, 81.9, 62.9, 55.6, 52.6, 48.9, 48.7, 39.5, 25.0, 23.9, 22.3, 22.0, 21.9; DEPT (125 MHz, 135°, $CDCl_3$) δ 81.9 (+), 62.9 (−), 52.6 (+), 48.9 (−), 39.5 (−), 25.0 (−), 23.9 (−), 22.3 (+), 22.0 (+), 21.9 Anal. Calcd for $C_{13}H_{21}NO_4S$: C, 54.33; H, 7.37; N, 4.87. Found: C, 54.40; H, 7.46; N, 4.90.