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Electrospray ionisation mass spectrometric studies of *N*-substituted 10-(aminosulfonyl)bornyl acrylate derivatives

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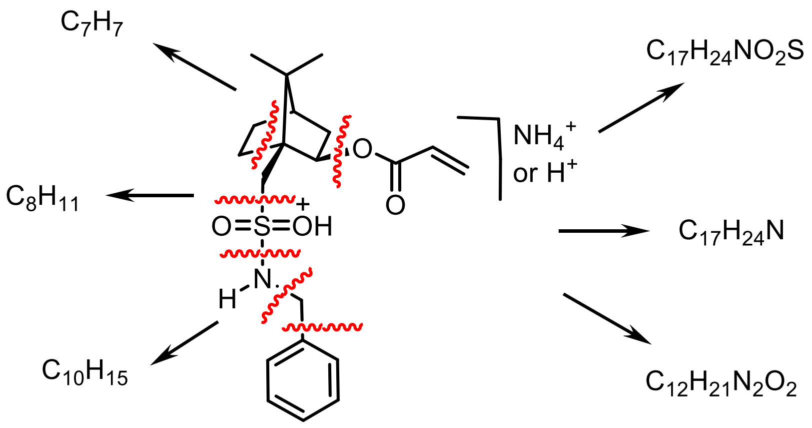
Abstract

Fragmentation patterns in the positive-ion electrospray ionization (ESI) mass spectra of representative *N*-substituted 10-(aminosulfonyl)bornyl acrylate derivatives have been explored using high-resolution methods. Evidence is presented for the involvement of common fragmentation pathways.



Keywords: Mass spectrometry, bornyl derivatives, sulfonamides, electrospray ionisation, fragmentation pathways

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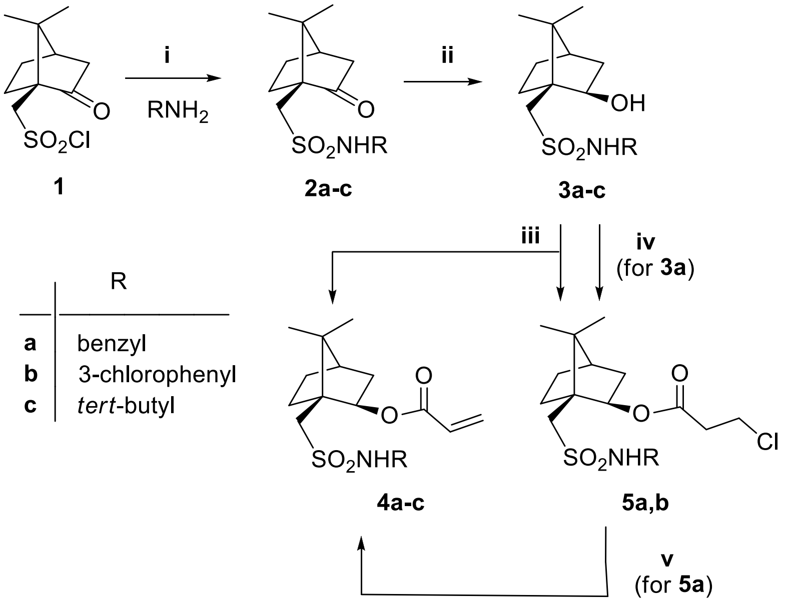
Introduction

The naturally occurring terpenoid borneol has found use in traditional medicine, and a number of bornyl esters have been shown to exhibit a range of pharmacological activities.[1] Bambagiotti *et al*.[2] have identified diagnostic fragment ions in the electron impact (EI) mass spectra of various bornyl esters, and Selva *et al*.[3] have used negative ion chemical ionization (CI) mass spectrometry (MS) to explore the fragmentation of a variety of bornyl esters as well. We have previously studied[4] fragmentation patterns in the gas chromatography-MS study[5] mass spectra of selected chiral silyl enol ethers, including a bornyl ester derivative. Examples of applications of MS methods focusing on the analysis of bornyl systems in natural products include a gas chromatography-EIMS study[5] of *Alpinia mutica* fruit oils and efficient differentiation of *C. camphora* chemotypes[6] using Desorption Atmospheric Pressure Chemical Ionization (DAPCI-MS).

We have previously reported[7] the synthesis of a series of optically pure camphor-10-sulfonamide-derived bornyl alcohol derivatives (**3**) (Scheme 1) as chiral auxiliaries, and the use of the subsequently derived acryloyl esters (**4**) as synthons in diastereoselective Baylis-Hillman reactions. To our knowledge, no Electrospray Ionisation (ESI) MS studies of such compounds have been undertaken and, in this communication, we now report our investigation of fragmentation patterns in the positive-ion ESI MS spectra of the representative bornyl acrylate derivatives **4a-c** and **5a**.

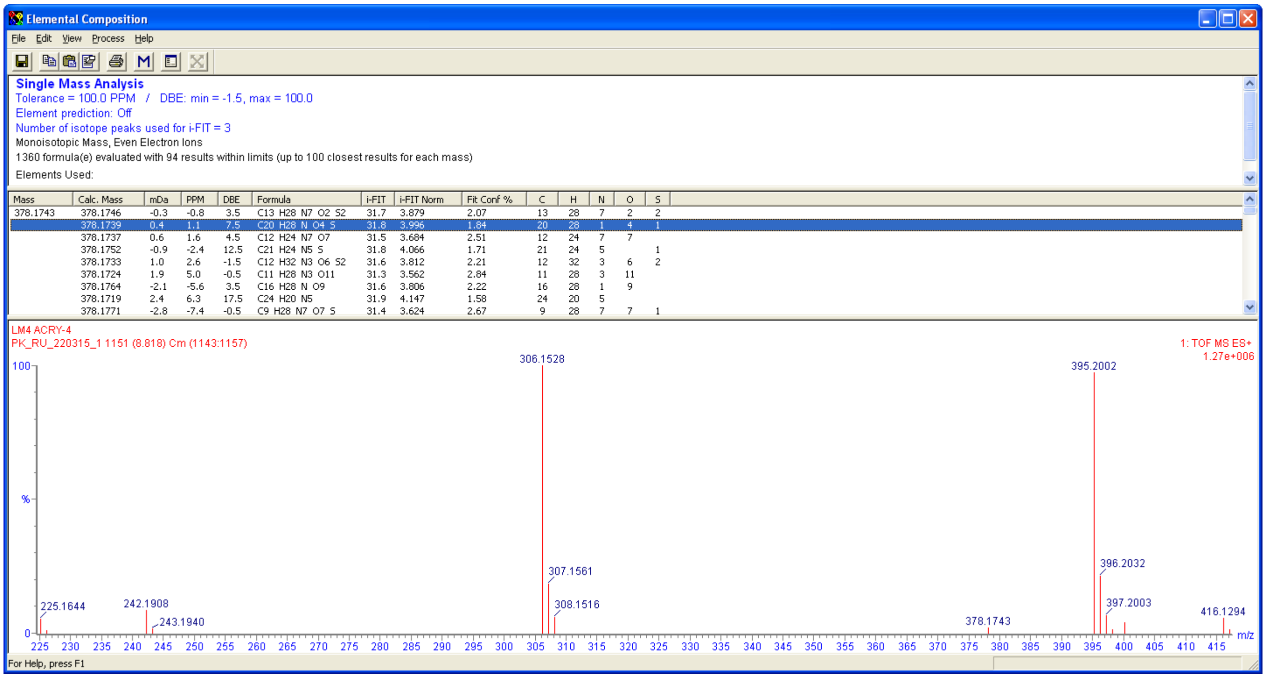
Results and Discussion

Access to the acryloyl esters **4a-c** was achieved in three steps as outlined in Scheme 1: i) formation of the camphor-10-sulfonamides **2a-c** from D-camphor-10-sulfonyl chloride **1**; ii) diastereoselective reduction to the epimeric bornyl alcohol derivatives **3a-c**, with clear predominance of the 2-*exo*-hydroxy analogues; and iii) reaction with acryloyl chloride to afford the esters **4a-c**, accompanied, in some cases, by the hydrochlorinated derivative (*i.e.*, **5a** and **5b**). Access to the acryloyl ester **4a** has also been achieved *via* direct generation of the 3-chloropropanoyl ester **5a**, followed by base-catalysed dehydrochlorination – as shown in Scheme 1. We now report on the results of a detailed exploration of the mass spectrometric fragmentation pathways exhibited by the representative compounds **4a-c** and **5a**.



Scheme 1. Preparation of bornyl acrylate derivatives.[7] *Reagents and conditions:* i) DMAP, CH_3CN, 0 °C; ii) $NaBH_4$, $EtOH\text{-}H_2O$, 0 °C; iii) Al_2O_3, $CH_2{=}CHCOCl$; iv) Al_2O_3, $ClCH_2CH_2COCl$; v) Et_3N, N_2.

Positive-ion ESI mass spectra of the representative system, 2-*exo*-acryloyloxy-*N*-benzylbornane-10-sulfonamide **4a** (Figure 1), reveal a "base peak" at *m/z* 306 and peaks at *m/z* 378.1743, 395.2002 and 400.1558 corresponding, respectively, to the pseudo-molecular ion **4a-H$^+$**, the ammonio-molecular ion **4a-NH$_4^+$** and the sodio-molecular ion **4a-Na$^+$**.



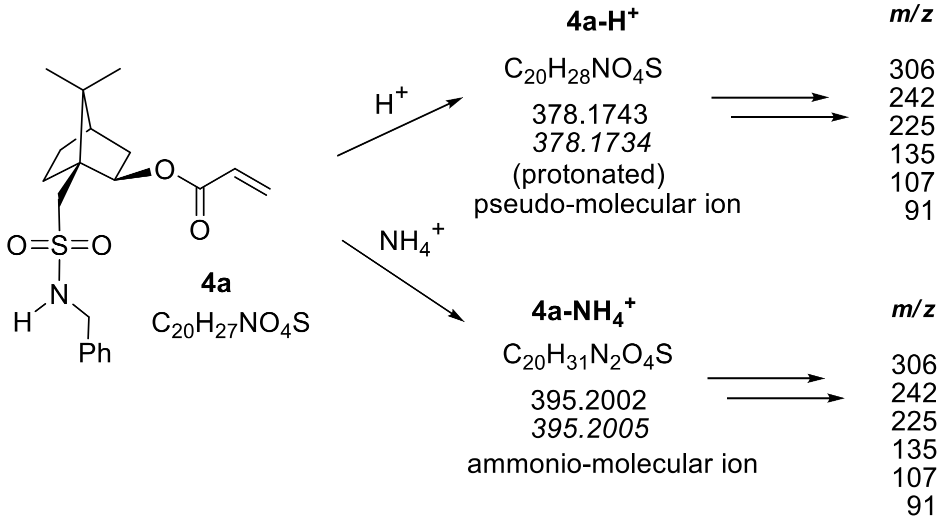
Single Mass Analysis
Tolerance = 100.0 PPM / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
1360 formula(e) evaluated with 94 results within limits (up to 100 closest results for each mass)
Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT Norm	Fit Conf %	C	H	N	O	S
378.1743	378.1746	-0.3	-0.8	3.5	C13 H28 N7 O2 S2	31.7	3.879	2.07	13	28	7	2	2
	378.1739	0.4	1.1	7.5	C20 H28 N O4 S	31.8	3.996	1.84	20	28	1	4	1
	378.1737	0.6	1.6	4.5	C12 H24 N7 O7	31.5	3.684	2.51	12	24	7	7	
	378.1752	-0.9	-2.4	12.5	C21 H24 N5 S	31.8	4.066	1.71	21	24	5		1
	378.1733	1.0	2.6	-1.5	C12 H32 N3 O6 S2	31.6	3.812	2.21	12	32	3	6	2
	378.1724	1.9	5.0	-0.5	C11 H28 N3 O11	31.3	3.562	2.84	11	28	3	11	
	378.1764	-2.1	-5.6	3.5	C16 H28 N O9	31.6	3.806	2.22	16	28	1	9	
	378.1719	2.4	6.3	17.5	C24 H20 N5	31.9	4.147	1.58	24	20	5		
	378.1771	-2.8	-7.4	-0.5	C9 H28 N7 O7 S	31.4	3.624	2.67	9	28	7	7	1

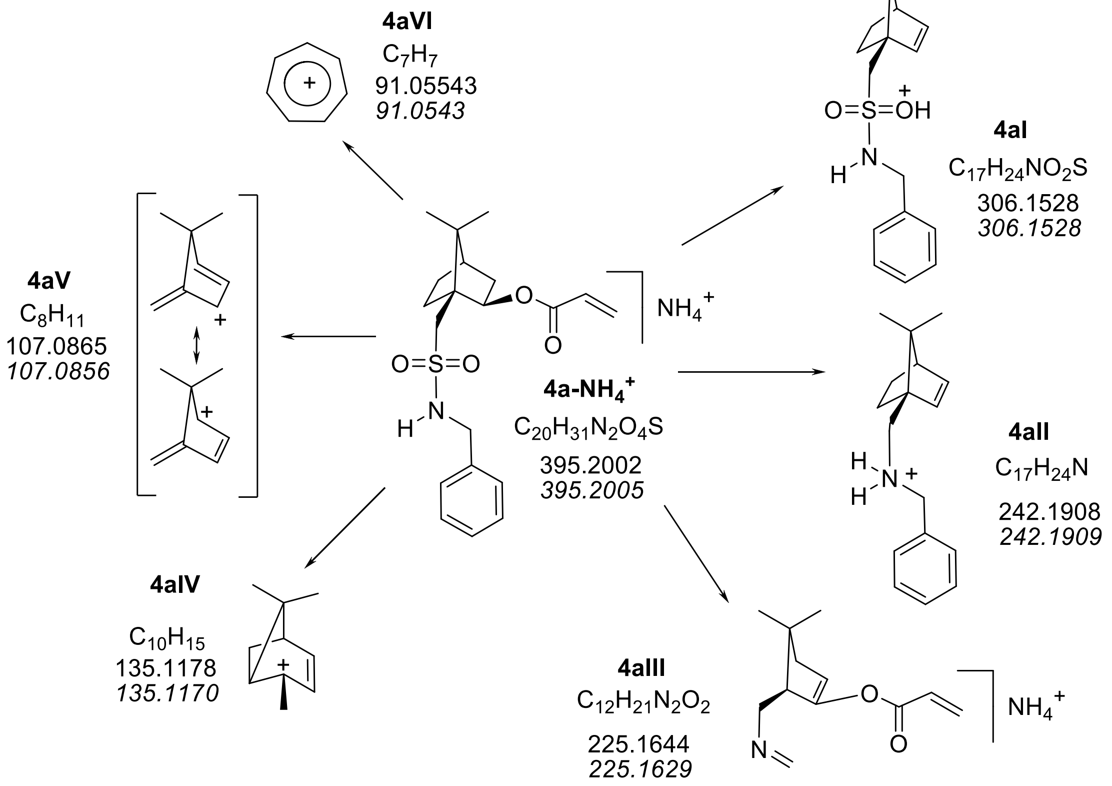
LM4 ACRY-4
PK_RU_220315_1 1151 (8.818) Cm (1143:1157)
1: TOF MS ES+
1.27e+006

Figure 1. Positive-ion ESI MS spectrum of compound **4a**.

LC-MS/MS analyses indicate that the pseudo-molecular ion **4a-H⁺** and the ammonio-molecular ion **4a-NH₄⁺** exhibit parallel, but independent fragmentation pathways, *i.e.*, independent in the sense that loss of NH_3 from **4a-NH₄⁺** to form **4a-H⁺** is not evident (Scheme 2).



Scheme 2. Significant ESI MS fragmentation series of the pseudo-molecular ion **4a-H⁺** and the ammonio-molecular ion **4a-NH₄⁺**; italicised data reflect the calculated *m/z* values.

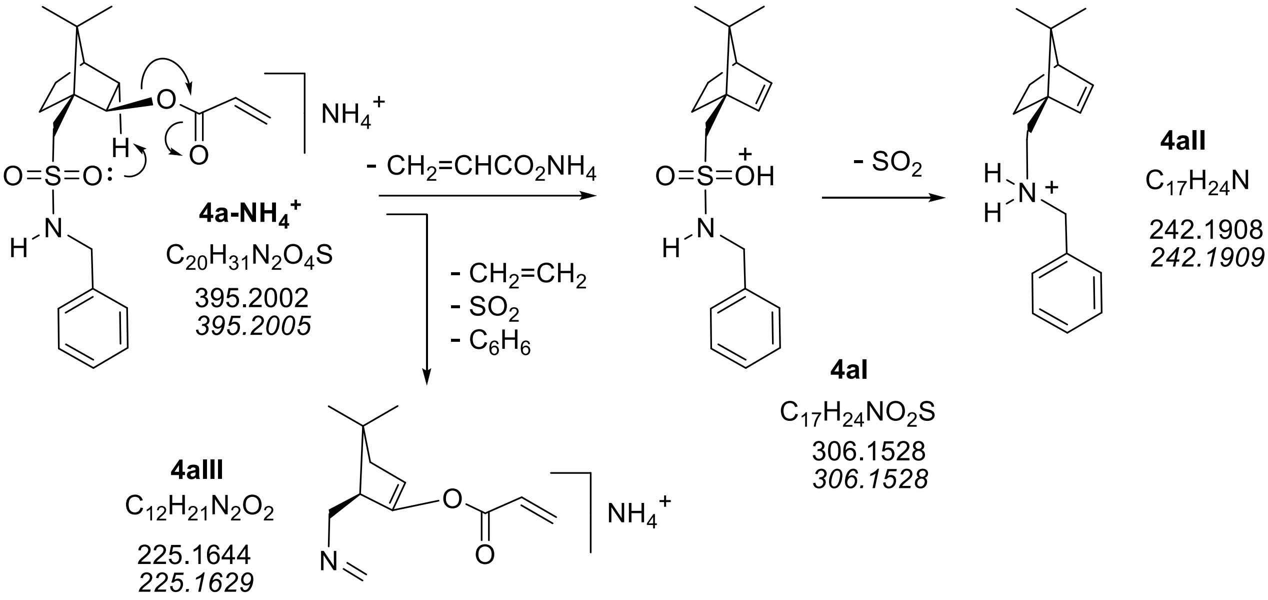


Scheme 3. ESI MS fragmentation pathways of the ammonio-molecular ion **4a-NH₄⁺** ; italicised data reflect the calculated *m/z* values.

In their ESI MS research on sulfonamides and tetracyclines, Tso and Aga[8] attribute formation of an ammonio-molecular ion [M+NH_4^+] to "gas-phase chemical ionisation induced by ammonium ions". Subsequent loss of NH_3 then leads to a pseudo-molecular ion. In our study, however, the MS/MS spectrum of the ammonio-molecular ion **4a-NH$_4^+$** reveals no evidence of the formation of the pseudo-molecular ion at *m/z* 378. On the other hand, the species corresponding to the base peak at *m/z* 306 originates from both **4a-NH$_4^+$** and **4a-H$^+$**, and MS/MS analysis of this species (*m/z* 306} reveals further fragmentation to the species responsible for the peaks at *m/z* 135, 107 and 91 (Scheme 3).

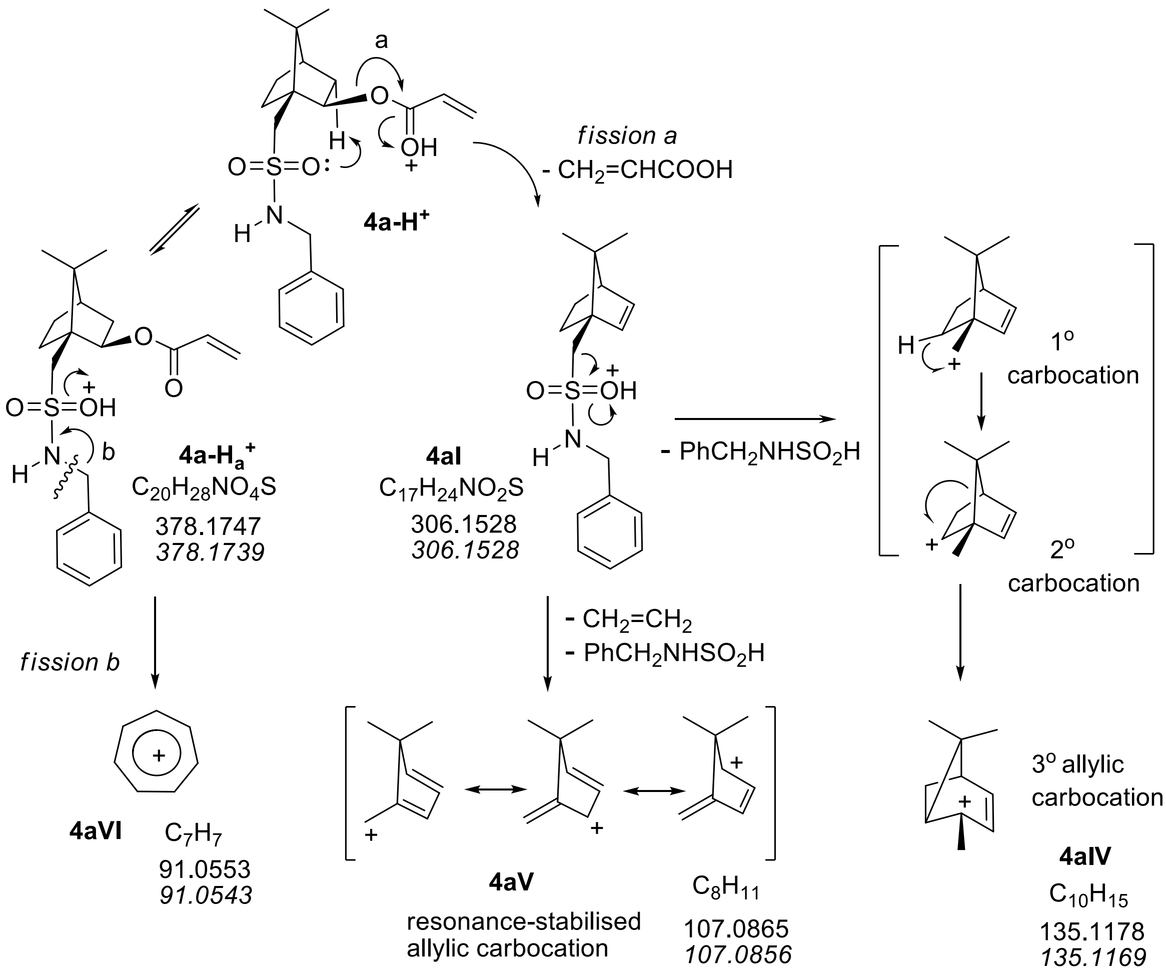
Attention was initially focused on formation of the fragments corresponding to six significant peaks in the positive-ion ESI MS spectra of the ammonio-molecular ion **4a-NH$_4^+$** (*m/z* 395), as illustrated in Scheme 3. Mechanistic rationalisations of the formation of these fragments are provided in Schemes 4 and 5.

As illustrated in Scheme 4, cleavage of the bornyl-oxygen bond and concomitant transfer of the 3-*endo* proton to a sulfonyl oxygen atom leads to fragment **4aI**, which is responsible for the base peak at m/z 306, and loss of ammonium acrylate from the ammonio-molecular ion **4a-NH$_4^+$** (or, in the case of the pseudo-molecular ion **4a-H$^+$**, loss of acrylic acid). Subsequent extrusion of SO_2 then leads to fragment **4aII** (*m/z* 242). The loss of SO_2 in the positive-ion mass spectra of sulfonamides has been reported by Sun *et al.*[9] and by Niessen and Correa.[10] The odd *m/z* value of the fragment with *m/z* 225 is consistent with an even-electron cation containing two nitrogen atoms and with the putative structure **4aIII**. Formation of this fragment is attributed to the tandem loss of three neutral molecules: i) ethylene, *via* intramolecular rearrangement; ii) sulfur dioxide, *via* precedented[9,10] extrusion from a sulfonamide moiety; and iii) benzene from the benzylamine moiety. The presence of the same fragment (**4aIII**) in the MS/MS spectrum of the pseudo-molecular ion **4a-H$^+$** suggests the possibility of a collision-induced dissociation[3] cascade initiated by impact of NH_3 with the pseudo-molecular ion.[8]



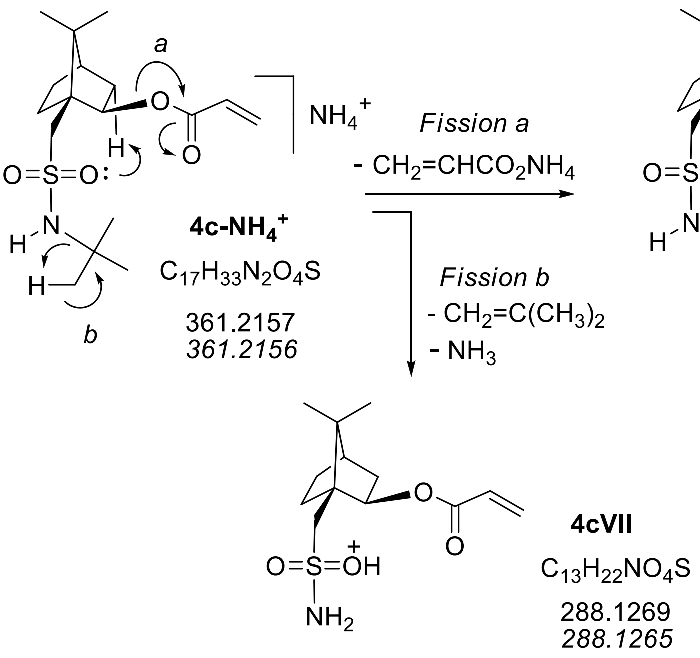
Scheme 4. Formation of the "base peak" fragment **4aI** and the fragment ions **4aII** and **4aIII** from the ammonio-molecular ion **4a-NH$_4^+$**; italicised data reflect the calculated *m/z* values.

The proposed pathways from the base-peak fragment **4aI** (*m/z* 306) to the three, even-electron cationic fragments, **4aIV, 4aV** and **4aVI**, which are outlined in Scheme 5, are consistent with MS/MS data for **4aI**. Loss of benzylaminosulfinic acid from **4aI** leads, following sequential rearrangement of a primary carbocation (*via* a hydride shift) and a secondary carbocation (*via* Wagner-Meerwein rearrangement) to the even more stable tertiary allylic carbocation **4aIV** (*m/z* 135). Tandem loss of benzylaminosulfinic acid and ethylene (*via* a *retro*-Diels Alder reaction) accounts for the resonance-stabilised secondary allylic cation **4aV** (*m/z* 107). Finally, cleavage of the *N*-benzylic bond in **4a-H$_a^+$** (fission b) affords a neutral camphor-10-sulfonamide tautomer and the observed aromatic tropylium cation **4aVI** at *m/z* 91.



Scheme 5. Generation of the even-electron cationic fragments **4aIV**, **4aV** and **4aVI**; italicised data reflect the calculated *m/z* values.

The mass spectrum of the hydrochlorinated analogue **5a** of compound **4a** reveals the corresponding **M-H$^+$** and **M-NH$_4^+$** peaks at *m/z* 414 and 431, respectively. Fragments in common with those observed for compound **4a**, are evidenced by the ions at *m/z* 306, 242 and 225. The **M-H$^+$** and **M-NH$_4^+$** peaks for the *N*-(3-chlorophenyl) derivative **4b** are evident at *m/z* 398 and 415, respectively. Fragmentation of the latter, ammonio-molecular ion **4b-NH$_4^+$** affords a fragment (*m/z* = 326.0982) which clearly contains a Cl^{35} atom, with the Cl^{37} isotopologue having *m/z* = 328.0959; this fragment is responsible for the base peak and corresponds to the base-peak fragments at *m/z* 306 in the spectra of the analogues **4a** and **5a**. The mass spectrum of 2-*exo*-(acryloyloxy)-*N*-(*t*-butyl)bornane-10-sulfonamide **4c** reveals clear pseudo-, ammonio- and sodio-molecular ion peaks at *m/z* 344.1892, 361.2157 and 366.1711, respectively. Formation of the sulfonamide **4cVII** (*m/z* 288.1269) is attributed to loss of isobutylene and NH$_3$ from the ammonio-molecular ion **4c-NH$_4^+$** *via* "*fission b*" in Scheme 6, although similar loss of isobutylene alone from the pseudo-molecular ion would have the same effect. The base peak (*m/z* 216.1059) corresponds to the sulfonamide fragment **4cVIII** formed *via* similar elimination of isobutylene from the intermediate **4cI** (*m/z* 272.1681). While the latter fragment could equally well arise from the loss of acrylic acid from the pseudo-molecular ion, the MS/MS data obtained for the formation of analogous *N*-benzyl fragment **4aI** supports involvement of the corresponding ammonio-molecular ion **4c-NH$_4^+$**.



Scheme 6. Selected fragmentation pathways from the ammonio-molecular ion **4c-NH$_4^+$**; italicised data reflect the calculated *m/z* values.

Conclusions

High-resolution ESI MS and LC-MS/MS studies have provided insights into competing parallel, common and compound-specific fragmentation pathways in a series of representative *N*-substituted 10-(aminosulfonyl)-bornyl acrylate derivatives. Fragmentation pathways have been proposed with the aid of the MS/MS data and provide evidence of the involvement, *inter alia*, of *retro*-Diels-Alder, bicyclic terpenoid carbocation rearrangement and SO$_2$-extrusion processes.

Experimental Section

General. The synthesis and characterisation of compounds **4a-c** and **5a** have been reported previously.[7] In an alternative approach to obtain a purer sample of the parent system **4a**, the diastereomeric alcohols **3a** were acylated with 3-chloropropanoyl chloride, followed by Et$_3$N-mediated dehydrochlorination and chromatographic (HPLC) purification as detailed below.

Neutral Al_2O_3 (0.244 g, 2.4 mmol) was added to the mixture of the diastereomeric alcohols **3a** (0.50 g, 1.6 mmol), followed by 3-chloropropanoyl chloride (0.38 g, 3 mmol). The resulting dispersion was shaken, sealed and kept unstirred at r.t. for 72 h. The mixture was then taken up in $CHCl_3$ (3 x 1 mL), filtered and the filtrate dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give an oil which was then treated with triethylamine (0.46 g, 3.1 mmol). The resulting mixture was stirred under N_2 at *ca.* 25 ^{0}C for 1 h and then taken up in EtOAc (5 mL); the organic solution was washed with brine and dried over anhydrous $MgSO_4$. Solvent was removed *in vacuo* to give an oil which was chromatographed [HPLC; elution with hexane-EtOAc (8: 2)] to afford four fractions.

Fraction 1. **2-*Exo*-acryloyloxy-*N*-(benzyl)bornane-10-sulfonamide 4a** as white crystals (0.39 g, 49%); δ_H (400 MHz; $CDCl_3$) 0.82 and 0.98 (6H, 2 x s, 8- and 9-Me), 1.23-2.03 (7H, series of multiplets, 3-, 5- and 6-CH_2 and 4-CH), 2.81 and 3.44 (2H, 2 x d, 10-CH_2), 4.25 (2H, d, $PhCH_2$), 4.47 (1H, br s, NH), 5.04 (1H, d, 2-CH), 5.79 (1H, d, *J* 10.4 Hz, 3’-CH_E), 6.09 (1H, dd, *J* 10.2 and 17.4 Hz, 2’-CH) and 6.33 (1H, d, *J* 17.4, 3’-CH_Z) and 7.33 (5H, overlapping signals, ArH); δ_C (100 MHz; $CDCl_3$) 19.9 and 20.3 (C-8 and C-9), 27.1, 29.8 and 39.5 (C-3, C-5 and C-6), 44.4 (C-4), 47.2 (C-11), 49.2 and 49.4 (C-1 and C-7), 51.9 (C-10), 77.9 (C-2), 128.9 (C-2’), 130.3 (C-3’), 127.97, 128.0, 128.8 and 137.0 (ArC) and 164.8 (C=O); HRMS: *m/z* Calc. for $C_{20}H_{28}NO_4S$ (MH^+) 378.1734, Found 378.1743, *and* for $C_{20}H_{31}N_2O_4S$ (MNH_4^+) 395.2005, Found 395.2002.

Positive-ion high-resolution electrospray ionisation MS and LC-MS/MS data were recorded on a Waters Synapt G2 spectrometer by the Central Analytical Laboratory at the University of Stellenbosch, South Africa. Relevant mass spectrometric data and instrumental conditions are available in the supporting information.

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Supplementary Material

ESI MS data for the representative compounds, and NMR data for compound **4a** can be found in the Supplementary Material accompanying this paper.

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