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Asymmetric ammonium ylid rearrangements: the effect of nitrogen asymmetry

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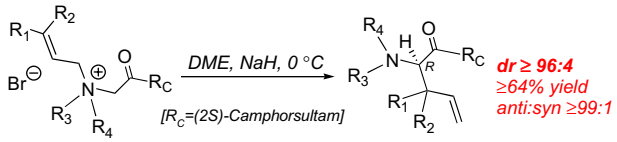
Abstract—[2,3]-Sigmatropic rearrangements of allylic ammonium ylids derived from glycinoylcamphorsultams are highly selective in terms of relative *and* absolute stereocontrol only when acyclic alkenes are present. When chiral esters of ylids derived from *N*-methyltetrahydropyridine ('NMTP') undergo rearrangement, the reactions show exclusive cis-stereoselectivity but the products are obtained with virtually no absolute stereocontrol. These observations support the notion that sigmatropic rearrangements of *N*-chiral ammonium ylids are controlled by nitrogen stereogenicity.

1. Introduction

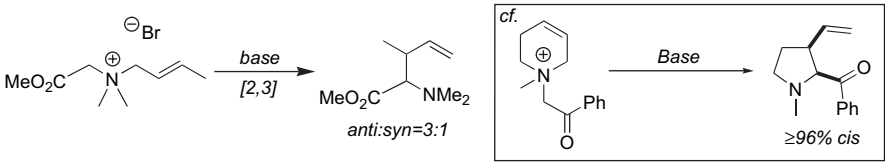
We have recently described our studies on the asymmetric [2,3]-sigmatropic rearrangements of allyl ammonium ylids derived from *N*-glycinoylcamphorsultam, which proceed with high levels of stereoselectivity (Scheme 1).[1]



Scheme 1.

[2,3]-Rearrangements of ammonium ylids derived from *N*-methyltetrahydropyridine ('NMTP') are inherently more stereoselective than nonasymmetric rearrangements of acyclic allylic ylids, due to the preference of a rigid *endo*-configured transition state (Scheme 2).[2]

Furthermore, NMTP ylids contain a stereogenic nitrogen atom[†] (yet, to our knowledge, simple[‡] enantiomerically-enriched ammonium ylids have never been prepared); though there is a paucity of examples of sigmatropic rearrangements of ammonium ylids involving N→C chirality transfer, the work of Hill and Chan[3] has shown that an asymmetric nitrogen atom *can* lead to enantioselective rearrangement reactions, which suggested in turn that nitrogen in NMTP ylids should exert a powerful stereotopic influence. However, the preparation of enantiomerically-pure NMTP ylids is currently an inaccessible goal, and we, therefore, initially sought to carry out stereoselective N-alkylations of chiral derivatives of NMTP as a means of preparing *diastereomerically* enriched ylids. We were also cognizant of the fact that, even if these alkylations proved unselective, the presence of two chiral elements in, say, sultam ylids **1** could in theory leads to an internal double asymmetric induction and a concomitant kinetic resolution to give only one of the two possible pyrrolidine products of rearrangement, plus a single diastereoisomer of unreacted salt precursor (Scheme 3).



Scheme 2.

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† *N*-chiral ammonium salts are historic compounds, having been prepared and used to greatly effect during the famous debate concerning the 'quinquevalence' of nitrogen: see, for instance, Pope, W. J.; Peachey, S. J. *J. Chem. Soc.*, **1899**, 1127.
‡ i.e., ammonium ylids where nitrogen is the only asymmetric component.

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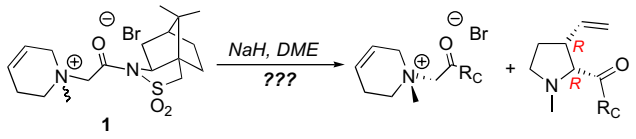
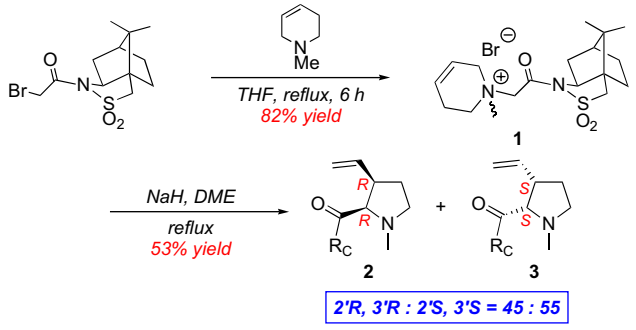


Scheme 3.

We report here that the [2,3]-rearrangements of diastereomeric NMTP ylids are highly diastereoselective, but proceed with little control of absolute stereochemistry, indicating that the asymmetric nitrogen atom completely dominates the stereochemical course of the reaction.

2. Results and discussion

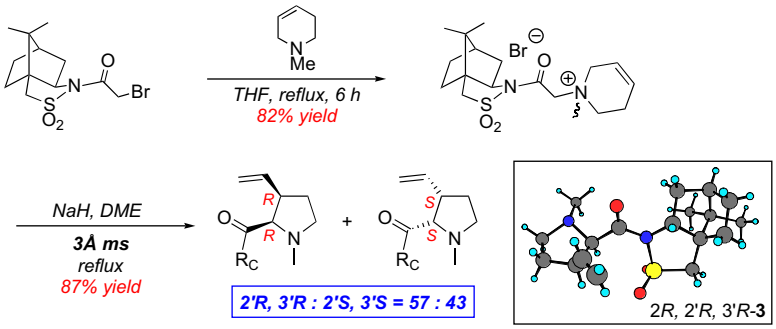
(2*S*)-Camphorsultam-NMTP salt **1** was synthesized in a routine manner from *N*-bromoacyl camphorsultam,[4] by alkylation with NMTP in THF at reflux (Scheme 3). Though many different conditions for this reaction were examined, we were unable to prepare this salt as anything more than a ~50:50 mixture of diastereoisomers (as judged from ^{1}H NMR spectra), indicating that the asymmetric auxiliary has little or no effect upon the diastereoselectivity of the N-alkylation reaction. In addition, to date we have found no means of separating the diastereomeric salts using a range of chromatographic and crystallization methods. When **1** was treated with stoichiometric[§] NaH in DME at 0 °C, no reaction occurred and starting material was recovered quantitatively; when the process was carried out in the same solvent at reflux (Scheme 4), [2,3]-rearrangement proceeded to give a pair of diastereomeric pyrrolidine carboxylate derivatives, **2** and **3**, which were tentatively assigned cis-stereochemistry by analogy with the racemic reactions previously carried out in our labs. These isomers were obtained in approximately equal amounts, indicating that virtually no selectivity had been induced in the absolute configuration of the products during the rearrangement reaction.



Scheme 4.

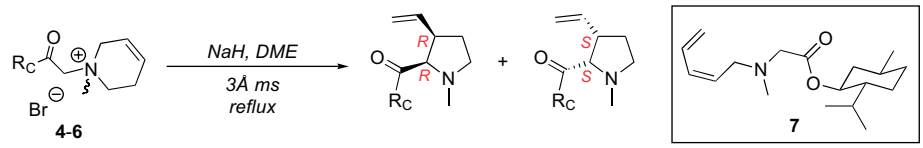
The rearrangement reaction could not be persuaded to proceed at lower temperatures for salts derived from either antipode of camphorsultam, though the yield of the process could be improved by the addition of 3 Å molecular sieves to the reaction medium. X-ray analysis of 2*R*,2′*R*,3′*R*-product of rearrangement confirmed the original conclusion that the pyrrolidine carboxylates obtained were cis-configured (Scheme 5).

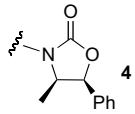
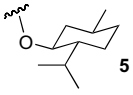
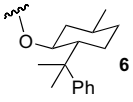
These initial data indicated two facts: firstly, the stereoselective N-alkylation of bromoacyl sultams is not feasible and, secondly, the NMTP ylids of either absolute configurations at nitrogen will undergo efficient rearrangement. We next investigated the preparation of NMTP salts by a reverse sequence of alkylation events, i.e., by acylmethylating tetrahydropyridine itself, and then carrying out a methylation reaction. However, under all of the conditions we have examined (using alkyl halides [with or without silver salts or other activators] or other electrophiles [triflates, oxonium salts, etc.]) the low or ambient-temperature alkylations of 2-(1′-tetrahydropyridinyl)acylsultams proceeded at a rate too slow to be practical (typically ≤5% yield of the salts would be obtained after 21 days reaction time). Furthermore, the very small amounts of salts isolated from these reactions did not seem to be enriched with either absolute configurations at nitrogen (though the deliquescent nature of the salts often precluded detailed analysis). Forced to consider, in the light of this experimental evidence, that perhaps the sultam auxiliary was too hindered, we next turned to other auxiliaries. Thus, oxazolidinone and menthyl derivatives of NMTP ylids were prepared using a range of alkylative procedures; once again, the only practical method to obtain the ylid precursors was by the alkylation of NMTP with the corresponding bromoacetylated auxiliaries. When these salts (**4**–**6**) were deprotonated and reacted in an analogous manner to the sultam ylids shown above, it was found that only the menthyl derivatives underwent efficient rearrangement; the oxazolidine-derived salt underwent preferential cleavage to give the parent heterocycle, even when the reaction was



Scheme 5.

[§] Reactions using *sub*-stoichiometric base are inefficient, and to date we have seen no evidence for kinetic resolution.



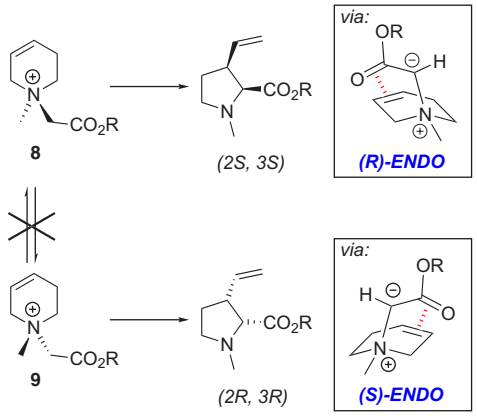
R_C	Yield/%	Dr (2'R, 3'R : 2'S, 3'S)
 4	0[a]	-
 5	53	51:49
 6	54	55:45

[a] (4R, 5S)-4-Methyl-5-phenyloxazolidinone obtained

Scheme 6.

carried out in the presence of desiccants (such as molecular sieves) (Scheme 6). Even where rearrangement did occur, side reactions were observed, such as the obtention of elimination product **7**[5] from the rearrangement reaction of menthyl salt **5**.

Thus, it is clear from these data that nitrogen stereogenicity dominates the course of the rearrangements of NMTP ylids; N_R-isomers **8** will lead to 2*S*,3*S*-pyrrolidines, whilst the N_S-isomers **9** will give 2*R*,3*R*-products (Scheme 7). Moreover, the effect of any chiral auxiliary is so small as to preclude any kinetic resolution and both ylid diastereoisomers undergo efficient rearrangement. Given the dominant effect of nitrogen chirality, these data also provide the tantalizing prospect that enantiomerically pure NMTP ylids can indeed be used to prepare enantiomerically enriched pyrrolidine carboxylates.



Scheme 7.

3. Conclusion

The [2,3]-sigmatropic rearrangements of NMTP ylids are not rendered stereoselective, in terms of absolute stereocontrol, by the attachment of chiral substituents at the periphery of the molecules. In addition, the diastereoselective alkylation of tetrahydropyridine derivatives has proved to be an elusive transformation. The pursuit of methods to prepare simple enantiomerically-enriched *N*-chiral ylids continues to dominate our aspirations and we shall report in due course the results of our further studies in this arena.

4. Experimental

4.1. General

All organic solvents were distilled prior to use and all reagents were purified by standard procedures.[6] 'Petrol' refers to the fraction of petroleum ether with the boiling range 40–60 °C and 'ether' refers to diethyl ether. Ether and THF were distilled from sodium benzophenone ketyl, toluene from sodium and dichloromethane from calcium hydride. Other chemicals were purchased from Aldrich Chemical Co. or prepared by literature methods.

Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. Spectra were recorded on Perkin–Elmer 881 or Paragon 1000 spectrophotometers. Optical rotations were measured using a Perkin–Elmer 241 MC polarimeter and are quoted in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on VG9090 or Fisons Autospec mass spectrometers. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-250 or AX-400 spectrometers. Unless otherwise stated, deuterochloroform was used as solvent and tetramethylsilane was the internal standard. Chemical shifts in ^{1}H NMR spectra are expressed as parts per million downfield from tetramethylsilane and in ^{13}C NMR, relative to the internal solvent standard. Coupling constants (*J*) are quoted in hertz.

Reactions involving chemicals or intermediates sensitive to air or moisture were conducted under a nitrogen or argon atmosphere in oven- or flame-dried apparatus. Flash chromatography was performed using Merck Kieselgel 60 or Fluka

Kieselgel 60 silica gel. Analytical thin-layer chromatography was performed using either precoated Merck Kieselgel 60 F_{254} glass-backed plates, or precoated Merck Kieselgel 60 F_{254} aluminium backed plates and was visualized under UV at 254 nm and by staining with iodine and/or an acidic ammonium molybdate dip.

4.2. *N*′-Methyl-*N*′-(*N*-carbonyl-(1*R*,2*S*)-bornane-10,2-sultam)methyl-1,2,3,6-tetrahydropyridinium bromide 1

A solution of *N*-methyl-1,2,3,6-tetrahydropyridine hydrochloride (5.0 g, 37.4 mmol) in 2 M aqueous sodium hydroxide (56.1 ml, 112.2 mmol, 3 equiv) was extracted with pentane (4×25 ml). The combined organic extracts were dried ($MgSO_4$) and removal of solvent in vacuo gave *N*-methyl-1,2,3,6-tetrahydropyridine as a colourless liquid (2.98 g, 82%), which was used without further purification. *N*-Bromoacetyl-(1*R*,2*S*)-bornane-10,2-sultam (1.73 g, 5.15 mmol) dissolved in THF (10 ml) was added dropwise over 5 min to a stirred solution of *N*-methyl-1,2,3,6-tetrahydropyridine (0.50 g, 5.15 mmol) in THF (10 ml) under nitrogen atmosphere. The reaction mixture was refluxed for 6 h during which the product began to precipitate. Once cooled, the mixture was triturated with petrol, the precipitate was collected over a glass sinter, washed with a small amount of methanol and the solvents were removed in vacuo to give *N*′-methyl-*N*′-(*N*-carbonyl-(1*R*,2*S*)-bornane-10,2-sultam)-methyl-1,2,3,6-tetrahydropyridinium bromide (1.82 g, 82%) as a colourless deliquescent solid; $[\alpha]_D^{20}$ +84.8 (*c* 1, $CHCl_3$); mp 178.2–180.5 °C; ν_{max}/cm^{-1} ($CHCl_3$) 1697, 1603, 1342, 1170; δ_H (250 MHz, $CDCl_3$) 0.99 (3H, s), 1.15 (3H, s), 1.39–1.59 and 1.78–2.04 (7H, br m), 2.23 (1H, br m), 2.48 (1H, br m), 3.46 (2H, m), 3.55 (2H, m), 3.66 (1.5H, s), 3.69 (1.5H, s), 4.17 (1H, m), 4.53 (1H, br m), 4.65 (1H, br m), 4.83 (1H, br m), 5.37 (1H, br m), 5.74 (1H, br m), 6.03 (1H, br m); δ_C (62.5 MHz, $CDCl_3$) 20.2, 21.5, 21.8, 26.5, 33.3, 38.6, 45.4, 48.6, 49.8, 49.9, 53.1, 57.9, 58.6, 61.7, 65.1, 119.8, 125.0, 163.8; *m*/*z* (CI) 353.1878 (M^+-Br, $C_{18}H_{29}N_2O_3S$ requires 353.1899), 353 (11%), 339 (57), 110 (16), 96 (100), 82 (13), 42 (11).

4.3. (2′*R*,3′*R*)-*N*′-Methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine 2 and (2′*S*,3′*S*)-*N*′-methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine 3

4.3.1. Method 1. Sodium hydride (27.6 mg, 1.15 mmol) was added to a vigorously stirred suspension of *N*′-methyl-*N*′-(*N*-carbonyl-(1*R*,2*S*)-bornane-10,2-sultam)methyl-1,2,3,6-tetrahydropyridinium bromide (0.50 g, 1.15 mmol) in DME (20 ml), under nitrogen atmosphere. The reaction mixture was heated at reflux for 16 h, after which it was cooled and diethyl ether (15 ml) was added. This mixture was then filtered through a small pad of Celite®, supported on a glass sinter, and washed well with further diethyl ether (2×10 ml). Solvents were removed in vacuo to give a solid, which was purified by column chromatography, eluting with ethyl acetate/petrol (1:1), to give (2′*S*,3′*S*)-*N*′-methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine (119 mg, 29%) and (2′*R*,3′*R*)-*N*′-methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine (98 mg, 24%) as colourless crystalline solids.

(2′*R*,3′*R*)-*N*′-Methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine **2**: R_f 0.24 (ethyl acetate/petrol, 1:1); $[\alpha]_D^{20}$ +135.4 (*c* 1, $CHCl_3$); mp 211.9–213.2 °C; ν_{max}/cm^{-1} ($CHCl_3$) 1702, 1642, 1331, 1165; δ_H (250 MHz, $CDCl_3$) 0.88 (3H, s), 1.05 (3H, s), 1.20–1.47 and 1.63–1.87 (5H, m), 1.93 (1H, m), 1.98 (1H, m), 2.00–2.12 (2H, m), 2.29 (3H, s), 2.32 (1H, ddd, *J* 7.6, 8.5, 8.7), 3.09 (1H, ddd, *J* 2.0, 8.5, 8.7), 3.15 (1H, dddd, *J* 7.5, 7.9, 8.0, 8.7), 3.36 (1H, d, *J* 13.8), 3.43 (1H, d, *J* 13.8), 3.71 (1H, d, *J* 8.4), 3.87 (1H, dd, *J* 5.2, 7.5), 4.84 (1H, dd, *J* 1.9, 9.9), 4.94 (1H, ddd, *J* 0.7, 1.9, 17.0), 5.70 (1H, ddd, *J* 9.7, 9.9, 17.0); δ_C (62.5 MHz, $CDCl_3$) 20.3, 21.3, 26.8, 31.5, 33.3, 38.9, 40.7, 45.0, 47.1, 48.0, 48.6, 53.7, 55.7, 65.7, 71.8, 116.3, 138.9, 171.3; *m*/*z* (CI) 353.1889 (MH^+, $C_{18}H_{29}N_2O_3S$ requires 353.1898), 353 (20%), 110 (100).

(2′*S*,3′*S*)-*N*′-Methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine **3**: R_f 0.32 (ethyl acetate/petrol, 1:1); $[\alpha]_D^{20}$ +49.6 (*c* 1, $CHCl_3$); mp 154.6–156.5 °C; ν_{max}/cm^{-1} ($CHCl_3$) 1693, 1642, 1334, 1165; δ_H (250 MHz, $CDCl_3$) 0.90 (3H, s), 1.10 (3H, s), 1.20–1.29 and 1.72–1.87 (5H, m), 1.89 (1H, m), 1.98 (1H, m), 2.02–2.16 (2H, m), 2.31 (3H, s), 2.47 (1H, ddd, *J* 7.1, 8.7, 8.8), 3.01 (1H, ddd, *J* 2.5, 8.7, 8.8), 3.12 (1H, dddd, *J* 8.4, 8.5, 8.5, 8.6), 3.37 (1H, d, *J* 13.8), 3.46 (1H, d, *J* 13.8), 3.85 (1H, dd, *J* 5.4, 7.2), 3.85 (1H, d, *J* 8.4), 4.90 (1H, ddd, *J* 0.7, 1.9, 10.1), 4.98 (1H, ddd, *J* 1.0, 1.9, 17.1), 5.77 (1H, ddd, *J* 8.5, 10.1, 17.1); δ_C (62.5 MHz, $CDCl_3$) 20.3, 21.4, 26.7, 31.6, 33.4, 39.3, 40.5, 45.2, 46.6, 48.1, 48.8, 53.7, 55.8, 65.9, 71.5, 116.1, 139.1, 171.4; *m*/*z* (CI) 353.1877 (MH^+, $C_{18}H_{29}N_2O_3S$ requires 353.1898), 353 (30%), 110 (100).

4.3.2. Method 2. Sodium hydride (55 mg, 2.30 mmol) was added to a vigorously stirred suspension of *N*′-methyl-*N*′-(*N*-carbonyl-(1*R*,2*S*)-bornane-10,2-sultam)methyl-1,2,3,6-tetrahydropyridinium bromide (1.00 g, 2.30 mmol) in DME (40 ml) containing molecular sieves, under nitrogen atmosphere. The reaction mixture was heated at reflux for 16 h, after which it was cooled and diethyl ether (30 ml) was added. This mixture was then filtered through a small pad of Celite® supported on a glass sinter, and washed well with further diethyl ether (2×15 ml). Solvents were removed in vacuo to give a solid, which was purified by column chromatography, eluting with ethyl acetate/petrol (1:1), to give (2′*R*,3′*R*)-*N*′-methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)-carbonyl-3′-ethenylpyrrolidine **2** (278 mg, 34%) and (2′*S*,3′*S*)-*N*′-methyl-2′-((1*R*,2*S*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine **3** (352 mg, 43%) as a colourless crystalline solids (data as previously recorded).

4.4. *N*′-Methyl-*N*′-(*N*-carbonyl-(1*S*,2*R*)-bornane-10,2-sultam)methyl-1,2,3,6-tetrahydropyridinium bromide (*ent*-1)

Following the method described above, *N*-bromoacetyl-(1*S*,2*R*)-bornane-10,2-sultam (1.73 g, 5.15 mmol) dissolved in THF (10 ml) was added to a stirred solution of *N*-methyl-1,2,3,6-tetrahydropyridine (0.50 g, 5.15 mmol) in THF (10 ml) to give *N*′-methyl-*N*′-(*N*-carbonyl-(1*S*,2*R*)-bornane-10,2-sultam)methyl-1,2,3,6-tetrahydropyridinium bromide (1.78 g, 80%) as a colourless deliquescent solid; $[\alpha]_D^{20}$ −79.7 (*c* 1, $CHCl_3$), other physical data as for **1**.

4.5. (2′*R*,3′*R*)-*N*′-Methyl-2′-((1*S*,2*R*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine and (2′*S*,3′*S*)-*N*′-methyl-2′-((1*S*,2*R*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine

Following method 2 described above, sodium hydride (27.6 mg, 1.15 mmol) was added to a vigorously stirred suspension of *N*′-methyl-*N*′-(*N*-carbonyl-(1*S*,2*R*)-bornane-10,2-sultam)methyl-1,2,3,6-tetrahydropyridinium bromide (0.50 g, 1.15 mmol) in DME (20 ml) over molecular sieves to give the crude product, which was purified by column chromatography, eluting with ethyl acetate/petrol (1:1), to furnish (2′*R*,3′*R*)-*N*′-methyl-2′-((1*S*,2*R*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine (198 mg, 49%) and (2′*S*,3′*S*)-*N*′-methyl-2′-((1*S*,2*R*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine (152 mg, 38%) as a colourless crystalline solids.

(2′*R*,3′*R*)-*N*′-Methyl-2′-((1*S*,2*R*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine: R_f 0.34 (ethyl acetate/petrol, 1:1); $[\alpha]_D^{20}$ −47.8 (*c* 1, $CHCl_3$), other physical data are identical to **3**.

(2′*S*,3′*S*)-*N*′-Methyl-2′-((1*S*,2*R*)-bornane-10,2-sultam)carbonyl-3′-ethenylpyrrolidine: R_f 0.23 (ethyl acetate/petrol, 1:1); $[\alpha]_D^{20}$ −136.0 (*c* 1, $CHCl_3$), other physical data are identical to **2**.

4.6. *N*-Methyl-*N*-((4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidone-*N*-carbonylmethyl)-3,4-didehydropiperidinium bromide 4

(4*R*,5*S*)-4-Methyl-5-phenyl-2-oxazolidone-*N*-bromoacetate (1.0 g, 3.35 mmol [prepared using an adaptation of the method used to prepare bromoacyl sultams[4] and utilized without further purification]) was added dropwise over 5 min to a stirred solution of *N*-methyl-3,4-didehydropiperidine (0.33 g, 3.35 mmol) in THF (20 ml) under argon. The reaction mixture was heated under reflux for 6 h, resulting in the precipitation of the title compound, which was filtered and washed with diethyl ether (2×25 ml) to give *N*-methyl-*N*-((4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone-*N*-carbonylmethyl)-3,4-didehydropiperidinium bromide **4** (1.01 g, 76%) as a colourless deliquescent solid and a 50:50 mixture of diastereoisomers; mp 120.9–121.1 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} (CH_2Cl_2) 1781, 1709; δ_H ($CDCl_3$) 0.93 (1.5H, d), 0.94 (1.5H, d), 2.41 (1H, m), 2.52 (1H, m), 3.62 (1.5H, s), 3.62 (1.5H, s), 4.15 (1H, m), 4.22 (0.5H, m), 4.31 (0.5H, m), 4.47 (0.5H, br d, *J* 16.9), 4.57 (0.5H, br d, *J* 16.9), 4.69 (0.5H, br d, *J* 16.9), 4.81 (0.5H, m), 4.84 (1H, m), 5.44 (1H, d, *J* 17.9), 5.59 (1H, d, *J* 17.9), 5.74 (1H, m), 5.98 (1H, d), 6.14 (1H, m), 7.27–7.42 (5H, m); δ_C ($CDCl_3$) 15.1, 21.5, 21.7, 42.8, 47.5, 47.8, 55.5, 58.2, 58.5, 60.5, 60.7, 64.5, 64.7, 119.6, 119.9, 124.4, 124.8, 126.2, 129.0, 129.1, 133.2, 153.1, 164.5; *m*/*z* (CI) 315.1712 (M^+−Br, $C_{18}H_{23}N_2O_3$ requires 315.1709), 298 (24%), 220 (75), 178 (100), 134 (26), 96 (72), 98 (21).

4.7. *N*-Methyl-*N*-((1*S*)-menthyloxycarbonyl)methyl-3,4-didehydropiperidinium bromide 5

(1*S*,2*R*,5*S*)-Menthol bromoacetate (1.0 g, 3.61 mmol) was added dropwise over 5 min to a stirred solution of *N*-methyl-3,4-didehydropiperidine (0.35 g, 3.61 mmol) in THF (20 ml) under argon. The reaction mixture was heated under reflux for 6 h resulting in the precipitation of the title compound, which was filtered and washed with diethyl ether (2×25 ml) to give *N*-methyl-*N*-((1*S*)-menthyloxycarbonyl)-methyl-3,4-didehydropiperidinium bromide **5** (1.2 g, 92%) as a colourless deliquescent solid; mp 172.1–172.6 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} (CH_2Cl_2) 2955, 2933 and 2868, 1734; δ_H ($CDCl_3$) 0.68 (1.5H, d, *J* 6.9), 0.69 (1.5H, d, *J* 6.9), 0.79 (1H, m), 0.82–0.86 (6H, m), 0.97 (1H, m), 1.03 (1H, m), 1.34 (1H, m), 1.40 (1H, m), 1.61 (1H, m), 1.65 (1H, m), 1.76 (1H, m), 1.90 (1H, m), 2.37 (1H, br d, *J* 17.2), 2.50 (1H, br d, *J* 17.2), 3.62 (1.5H, s), 3.63 (1.5H, s), 4.04 (1H, m), 4.14 (1H, m), 4.48 (1H, br m), 4.64 (1H, d, *J* 17.07), 4.73 (1H, m), 4.82 (1H, m), 4.98 (1H, d, *J* 17.07), 5.67 (1H, d, *J* 10.4), 5.96 (1H, d, *J* 10.4); δ_C ($CDCl_3$) 16.5, 21.2, 21.8, 22.4, 23.5, 23.6, 26.5, 26.7, 31.9, 34.3, 40.9, 41.0, 47.0, 47.1, 49.1, 49.4, 57.5, 57.8, 60.0, 60.4, 60.5, 60.8, 78.0, 119.8, 119.9, 124.9, 164.8, 164.8; *m*/*z* (CI) 294.2431 (M^+−Br, $C_{18}H_{32}NO_2$ requires 294.2433), 280 (100%), 156 (9), 142 (33), 110 (23), 96 (72), 82 (11), 69 (19), 42 (8).

4.8. (2*R*,3*R*)- and (2*S*,3*S*)-*N*-methyl-2-(1*S*)-menthyloxycarbonyl-3-ethenylpyrrolidine and (1*S*)-menthyl-3-aza-3-methyl-octa-5,7-dienoate 7

Sodium hydride (33.3 mg, 1.39 mmol) was added to a suspension of *N*-methyl-*N*-((1*S*,2*R*,5*S*)-menthyloxycarbonyl)-methyl-3,4-didehydropiperidinium bromide (0.50 g, 1.39 mmol) in DME (20 ml), vigorously stirred under argon. The reaction mixture was heated under reflux for 16 h, after which it was cooled and quenched by careful addition of methanol. Solvents were removed in vacuo to give a solid, which was partitioned between water (20 ml) and diethyl ether (20 ml). The organic layer was separated and the aqueous layer was further extracted with diethyl ether (4×20 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to leave a yellow solid, which was purified by column chromatography, eluting with diethyl ether/petrol, to give a mixture of (2*R*,3*R*)- and (2*S*,3*S*)-*N*-methyl-2-(1*S*,2*R*,5*S*)-menthyloxycarbonyl-3-ethenylpyrrolidine (210 mg, 53%) and (1*S*,2*R*,5*S*)-menthyl-3-aza-3-methyl-octa-5,7-dienoate **7** (27 mg, 7%) both as colourless oils.

(2*R*,3*R*)- and (2*S*,3*S*)-*N*-methyl-2-(1*S*,2*R*,5*S*)-menthyloxycarbonyl-3-ethenylpyrrolidine: R_f 0.36 (diethyl ether/petrol 2:1); ν_{max}/cm^{-1} 2955, 2869 and 2786 (NR_3), 1743 and 1725; δ_H ($CDCl_3$) 0.70 (1.5H, d, *J* 6.9), 0.76 (1.5H, d, *J* 6.9), 0.86 (3H, d, *J* 6.9), 0.88 (1.5H, d, *J* 6.9), 0.89 (1.5H, d, *J* 6.9), 0.92–1.05 (3H, m), 1.39 (1H, m), 1.44–1.52 (1H, m), 1.65 (1H, m), 1.68 (1H, m), 1.82 (1H, m), 1.90 (1H, m), 1.96 (1H, m), 2.05 (1H, m), 2.36 (1.5H, s), 2.37 (1.5H, s), 2.41 (1H, m), 3.05 (1H, m), 3.12 (0.5H, d, *J* 8.06), 3.14 (0.5H, d, *J* 8.4), 3.17 (1H, m), 4.69 (0.5H, ddd, *J* 4.4, 10.9, 10.9), 4.77 (0.5H, ddd, *J* 4.4, 10.9, 10.9), 4.95 (0.5H, dd, *J* 1.8, 9.9), 4.96 (0.5H, dd, *J* 1.8, 9.9), 5.02 (0.5H, dd, *J* 1.8, 16.8), 5.03 (0.5H, dd, *J* 1.8, 16.8), 5.77 (0.5H, ddd, *J* 9.2, 9.9, 16.8), 5.79 (0.5H, ddd, *J* 9.5, 9.9, 16.8); δ_C ($CDCl_3$) 15.7, 16.1, 20.70, 20.8, 22.0, 22.8, 23.2, 25.5, 26.2, 30.6, 30.7, 31.3,34.2, 40.3, 40.3, 41.1, 41.1, 46.1, 46.3, 46.6, 46.8, 55.2, 71.9, 72.4, 74.2, 74.7,

115.8, 115.9, 138.4, 171.0, 171.1; *m/z* (CI) 294.2421 (M^++H, $C_{18}H_{32}NO_2$ requires 294.2433), 156 (14%), 131 (12), 110 (100), 69 (7).

(1*S*,2*R*,5*S*)-Menthyl-3-aza-3-methyl-octa-5,7-dienoate: R_f 0.46 (diethyl ether/petrol 1:2); ν_{max}/cm^{-1} 2955, 2923 and 2871 (NR_3), 1736, 1686 and 1643; δ_H ($CDCl_3$) 0.75 (3H, d, *J* 6.9), 0.86 (3H, d, *J* 6.9), 0.88 (3H, d, *J* 6.9), 0.95–1.05 (2H), 1.11 (1H, m), 1.27 (1H, m), 1.31 (1H, m), 1.59 (1H, m), 1.66 (1H, m), 1.84 (1H, m), 1.97 (1H, m), 2.41 (3H, s), 3.26 (2H, s), 3.35 (2H, d, *J* 7.3), 4.76 (1H, ddd, *J* 4.4, 10.9, 10.9), 5.16 (1H, d, *J* 10.09), 5.25 (1H, d, *J* 16.8), 5.55 (1H, dt, *J* 10.6, 7.3), 6.18 (1H, dd, *J* 10.6, 11.2), 6.65 (1H, dddd, *J* 10.09, 11.2, 16.8, 1.1); δ_C ($CDCl_3$): 16.2, 20.7, 22.0, 23.3, 26.2, 31.4, 34.2, 40.9, 42.3, 46.9, 53.4, 57.7, 74.4, 118.7, 128.2, 131.7, 132.5, 170.4; *m/z* (CI) 294.2443 (M^++H, $C_{18}H_{32}NO_2$ requires 294.2433), 156 (13%), 110 (64), 96 (53), 67 (12).

4.9. *N*-Methyl-*N*-((1*R*)-8-phenylmenthyloxycarbonyl)-methyl-3,4-didehydropiperidinium bromide 6

(1*R*,2*S*,5*R*)-8-Phenylmenthyl bromoacetate (0.5 g, 1.41 mmol) was added dropwise over 5 min to a stirred solution of *N*-methyl-3,4-didehydropiperidine (0.14 g, 1.41 mmol) in THF (10 ml) under argon. The reaction mixture was heated under reflux for 12 h resulting in the precipitation of the title compound, which was filtered and washed with diethyl ether (2×15 ml) under argon to give *N*-methyl-*N*-(8-phenylmenthyloxycarbonyl)methyl-3,4-didehydropiperidinium bromide **6** (503 mg, 79%) as a colourless deliquescent solid; mp 169.9–170.2 °C (CH_2Cl_2/petrol); ν_{max}/cm^{-1} (CH_2Cl_2) 2958, 2935 and 2875, 1735, 1685, 1653 and 1636 (aromatic C=C); δ_H ($CDCl_3$) 0.87 (1.5H, d, *J* 6.9), 0.91 (1.5H, d), 0.97 (1H, m), 1.09 (1H, m), 1.18 (3H, m), 1.23 (1H, m), 1.29 (3H, m), 1.47 (1H, m), 1.71 (1H, m), 1.85 (1H, m), 1.94 (1H, m), 2.16 (1H, m), 2.33 (1H, br m), 2.50 (1H, br m), 3.49 (3H, s), 3.87 (1H, m), 3.98 (1H, m), 4.14 (1H, br m), 4.29 (1H, m), 4.38 (1H, m), 4.44 (1H, d, *J* 17.9), 4.86 (1H, m), 5.69 (1H, br m), 6.01 (1H, br m), 7.17 (1H, m), 7.31 (2H, m), 7.34 (2H, m); δ_C ($CDCl_3$) 21.1, 21.2, 21.5, 22.2, 22.5, 22.5, 25.9, 26.0, 28.1, 28.9, 30.1, 30.3, 34.0, 41.1, 41.2, 48.4, 48.7, 49.2, 49.3, 56.9, 57.7, 58.8, 59.2, 59.3, 60.2, 118.8, 119.1, 124.3, 124.6, 125.1, 125.2, 125.3, 128.2, 151.6, 151.8, 163.4, 163.5; *m/z* (CI) 370.2763 (M^+−Br, $C_{24}H_{36}NO_2$ requires 370.2746), 156 (19%), 110 (100).

4.10. (2*R*,3*R*)-*N*-methyl-2-(1*R*)-8-phenylmenthyloxycarbonyl-3-ethenylpyrrolidine and (2*S*,3*S*)-*N*-methyl-2-(1*R*)-8-phenylmenthyloxycarbonyl-3-ethenylpyrrolidine 6

Sodium hydride (26.6 mg, 1.11 mmol) was added to a suspension of *N*-methyl-*N*-((1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl)methyl-3,4-didehydropiperidinium bromide (0.50 g, 1.11 mmol) and powdered molecular sieves (200 mg) in THF (20 ml), vigorously stirred under argon. The reaction mixture was heated under reflux for 16 h, after which it was cooled and quenched by careful addition of methanol. Solvents were removed in vacuo to give a solid, which was partitioned between water (20 ml) and diethyl ether (20 ml). The organic layer was separated and the aqueous layer was further extracted with diethyl ether (4×20 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to leave a yellow oil, which was purified by column chromatography, eluting with diethyl ether/petrol (1:2), to give (2*R*,3*R*)-*N*-methyl-2-(1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl-3-ethenylpyrrolidine (120 mg, 29%) and (2*S*,3*S*)-*N*-methyl-2-(1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl-3-ethenylpyrrolidine (99 mg, 24%) both as colourless oil.

(2*S*,3*S*)-*N*-Methyl-2-(1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl-3-ethenylpyrrolidine: R_f 0.33 (diethyl ether/petrol 1:2); $[\alpha]_D^{20}$ −13.04 (*c* 1.3, CH_2Cl_2); ν_{max}/cm^{-1} 2955, 2876 and 2789 (NR_3), 1735, 1684 and 1653; δ_H ($CDCl_3$) 0.78 (1H, m), 0.84 (3H, d, *J* 6.2), 0.88 (1H, m), 0.96 (1H, m), 1.22 (3H, s), 1.34 (3H, s), 1.43 (1H, m), 1.50 (1H, m), 1.83 (1H, m), 1.92 (1H, m), 1.95 (1H, m), 2.07 (2H, m), 2.33 (3H, s), 2.48 (1H, m), 2.92 (1H, m), 2.96 (1H, m), 3.07 (1H, m), 4.74 (1H, ddd, *J* 4.03, 10.9, 10.9), 5.03 (1H, dd, *J* 1.8, 9.9), 5.07 (1H, dd, *J* 1.8, 17.2), 5.67 (1H, ddd, *J* 9.4, 9.9, 17.2), 7.15 (1H, m), 7.26 (2H, m), 7.28 (2H, m); δ_C ($CDCl_3$) 21.2, 24.3, 27.2, 29.0, 30.3, 31.3, 34.6, 40.2, 41.8, 46.1, 50.5, 54.9, 71.6, 74.4, 116.3, 125.2, 125.7, 128.0, 138.4, 151.1, 171.9; *m/z* (CI) 370.2744 (M^++H, $C_{24}H_{36}NO_2$ requires 370.2740), 282 (9%), 197 (11), 156 (15), 110 (100), 69 (12).

(2*R*,3*R*)-*N*-Methyl-2-(1*R*,2*S*,5*R*)-8-phenylmenthyloxycarbonyl-3-ethenylpyrrolidine: R_f 0.17 (diethyl ether/petrol 1:2); $[\alpha]_D^{20}$ −10.77 (*c* 0.9, CH_2Cl_2); ν_{max}/cm^{-1} 2955, 2876 and 2789 (NR_3), 1735, 1684 and 1653; δ_H ($CDCl_3$) 0.82 (1H, m), 0.84 (3H, d, *J* 6.5), 0.87 (1H, m), 1.06 (1H, m), 1.31 (3H, s), 1.43 (3H, s), 1.57 (1H, m), 1.59 (1H, m), 1.67 (1H, m), 1.72 (1H, m), 1.87 (1H, m), 2.01 (2H, m), 2.34 (3H, s), 2.43 (1H, m), 2.94 (1H, m), 2.96 (1H, m), 3.14 (1H, m), 4.82 (1H, ddd, *J* 4.3, 10.7, 10.7), 4.89 (1H, dd, *J* 1.8, 10.1), 4.94 (1H, dd, *J* 1.8, 17.0), 5.67 (1H, ddd, *J* 9.6, 10.1, 17.03) 7.15 (1H, m), 7.27 (2H, m), 7.34 (2H, m); δ_C ($CDCl_3$) 15.3, 21.8, 26.7, 29.7, 30.3, 31.2, 34.6, 39.8, 42.1, 45.9, 50.1, 55.2, 70.8, 74.6, 115.7, 125.0, 125.4, 128.1, 138.9, 151.7, 170.5; *m/z* (CI) 370.2744 (M^++H, $C_{24}H_{36}NO_2$ requires 370.2740), 282 (9%), 197 (11), 156 (15), 110 (100), 69 (12).

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