EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201300136

Unusual Skeletal Rearrangement of Unsaturated Seven-Membered Lactams into Fused Pyrrolidinolactones

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Keywords: Nitrogen heterocycles / Lactones / Lactams / Ylides / Diastereoselectivity / Rearrangement

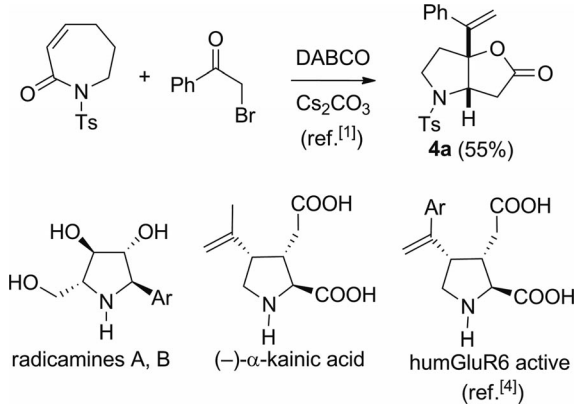
Unsaturated ε-lactams undergo a novel process involving a skeletal reorganization to give fused pyrrolidine-lactones by reaction with aromatic α-bromo ketones in the presence of 1,4-diazabicyclo[2.2.2]octane and a base. The process involves the formation of an ammonium salt and subsequently a nitrogen ylide, which initiates the rearrangement reaction. This species reduces undesired side-reactions such as double-bond shifts or Morita–Baylis–Hilman-type processes. The resulting products are structurally related to kainoids and the transformation of the lactone moiety in the rearranged product paves the way to the synthesis of these potentially bioactive natural products and their derivatives.

Introduction

Skeletal rearrangements are among the most fascinating chemical transformations and the understanding of their reaction mechanisms is often a challenge. In the course of our studies on the synthesis of highly functionalized cyclopropanes by the cyclopropanation of unsaturated lactams with nitrogen ylides, we discovered an unprecedented rearrangement of a seven-membered unsaturated lactam.[1] This process led to a bicyclic homoallylamine fused to a lactone ring structurally related to natural products such as kainic acid or radicamines (Scheme 1).

(–)-α-Kainic acid has attracted attention because of its neuroexcitatory properties and also its insecticidal and anthelmintic activities.[2] The potent neuroexcitatory activity of kainic acid is attributed to its action as a conformationally restricted analogue of glutamic acid. The synthesis of this product and potentially active derivatives will continue to attract the attention of synthetic chemists for years to come.[3] Some aryl kainic acid analogues have been reported to show activity towards the human GluR6 receptor.[4] Radicamines A and B, isolated from Lobelia chinensis Lour,[5] are pyrrolidine alkaloids that exhibit α-glucosidase inhibition and have received considerable synthetic attention.[6]

Therefore this new rearrangement could be a really interesting chemical tool because it presents a new and unknown reactivity. Herein we present all our synthetic efforts to investigate the scope and limitations of this new process by varying the α-bromo ketone, the protecting group and the ring size of the unsaturated lactam employed. We also envisioned investigating the potential of applying this process, as a starting point, to the synthesis of analogues of natural products containing the pyrrolidine core. A plausible mechanism for this reaction is proposed that postulates the participation of nitrogen ylides as reagents. In addition to the synthetically important phosphonium and sulfonium ylides, ammonium ylides have been developed and reviewed in recent years as important precursors in organic chemistry.[7] Although they are involved in many different types of reactions, the cyclopropanation of activated double bonds with nitrogen ylides is probably the most useful synthetic reaction in which these species are involved.[8]



Scheme 1. Rearrangement of a seven-membered unsaturated lactam to give homolallylamine **4a** and structures of related natural and bioactive products.

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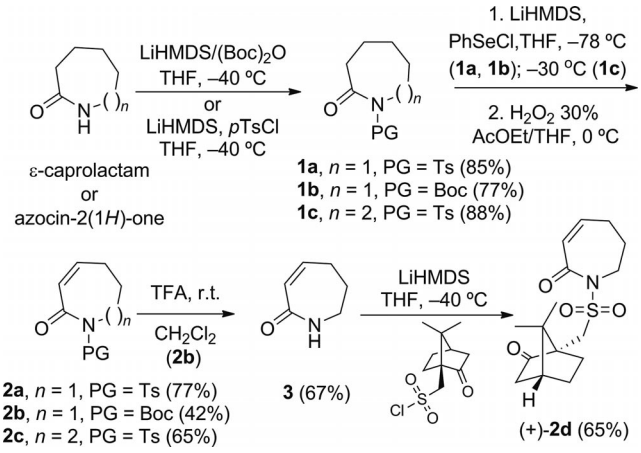
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300136.

Results and Discussion

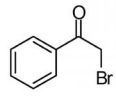
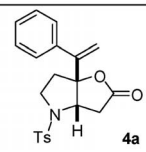
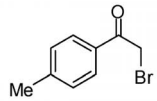
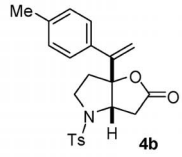
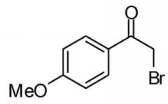
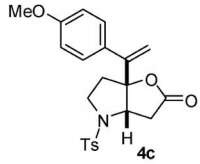
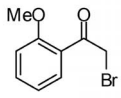
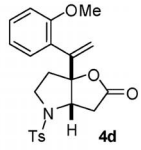
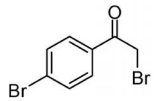
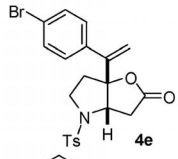
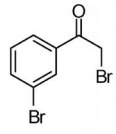
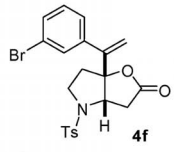
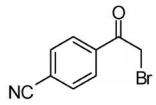
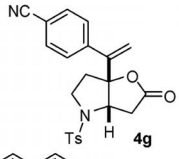
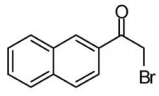
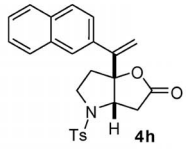
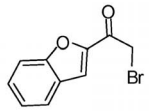
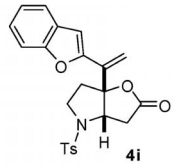
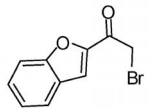
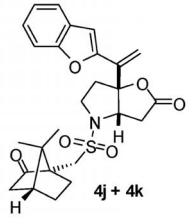
To extend the study of the rearrangement of seven-membered unsaturated lactams, we optimized the synthesis of the starting materials, the unsaturated lactams **2**, by the route shown in Scheme 2. The choice of the nitrogen protecting group was important because electron-withdrawing properties seem to be necessary for the initiation of the rearrangement process. Thus, we prepared unsaturated lactams **2a**–**d** bearing sulfonamides and carbamate protecting groups. ε-Caprolactam was transformed into compounds **1a** and **1b**, which were converted into the corresponding α,β-unsaturated analogues by seleniation of the lactam enolates, oxidation into the corresponding selenoxide and elimination. Oxidation of the selenide with aqueous hydrogen peroxide generated the selenoxide, which spontaneously eliminated PhSeOH to give the desired compounds in better global yields than when the oxidation was performed with *m*-CPBA.[9] In addition, we prepared the eight-membered unsaturated lactam **2c** following the same methodology starting from azocin-2(1*H*)-one. For the synthesis of (+)-**2d** it was necessary to carry out the protection step after constructing the unsaturated lactam as the selenation process did not take place with *N*-camphorsulfonylcaprolactam. Therefore **2b** was treated with TFA and the resulting lactam **3** was treated with (+)-10-camphorsulfonyl chloride to give (+)-**2d** in an overall yield of 43% starting from **2b**.



Scheme 2. Synthesis of the starting unsaturated lactams **2a**–**d**.

Thus, the reaction of phenacyl bromide with 1 equiv. of 1,4-diazabicyclo[2.2.2]octane (DABCO) followed by the addition after stirring for 1 h of 1.2 equiv. of Cs_2CO_3 and **2a** gave product **4a** in 55% yield. It was necessary to form the quaternary ammonium salt previous to the addition of the base to avoid secondary reactions such as condensation and double-bond shifts. Increasing the amount of base to 2 equiv. of Cs_2CO_3 raised the yield to 70%. If the lactam **2a** was added 30 min after the addition of the base, the reaction was cleaner and **4a** was isolated in 79% yield (entry 1). The solvent of choice was acetonitrile because the

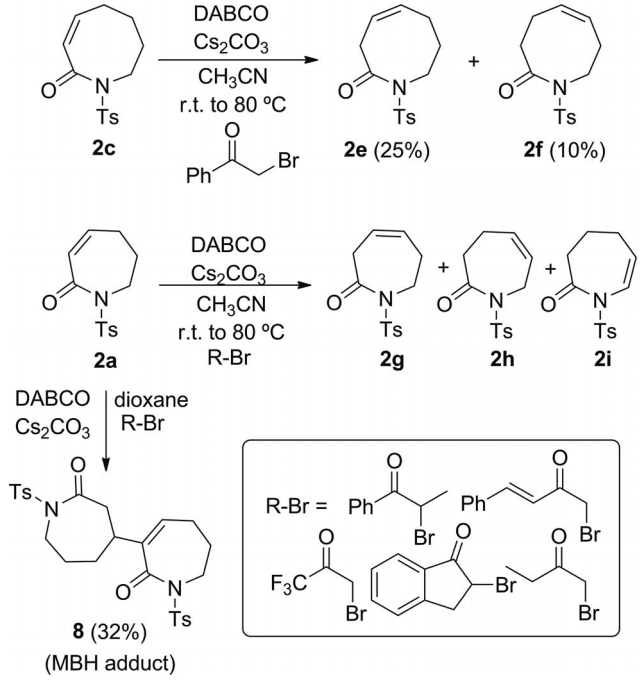
Table 1. Scope of the rearrangement reaction of lactams **2**.

No.	α-Bromo ketone	Product	Yield[a] (%)
1		 **4a**	79
2		 **4b**	75
3		 **4c**	84
4		 **4d**	45
5		 **4e**	55
6		 **4f**	60
7		 **4g**	35
8		 **4h**	68
9		 **4i**	85
10		 **4j + 4k**	58

[a] Reaction conditions: DABCO (1 equiv.), α-bromo ketone (1.1 equiv.), Cs_2CO_3 (2 equiv.), **2a** or **2d** (1 equiv.), anhydrous acetonitrile, argon. [b] In pure product.

yields were slightly lower with dichloroethane or dichloromethane whereas with THF or dioxane we detected important amounts of side-products (see below). With these optimized conditions in hand, the scope of the reaction was explored with various α-bromo ketones and the results are shown in Table 1. Conversion to the corresponding fused heterocyclic compounds was observed for the aromatic α-bromo ketones tested. Only lactams bearing sulfonamides as protecting groups displayed desirable properties under the reaction conditions to yield the desired compounds as no rearrangement was observed for **2b**. Phenyl derivatives bearing either an electron-withdrawing or -donating group reacted well under the conditions (entries 2–7), but the reaction is favoured by electronic-rich aromatic rings. Thus, **4b** and **4c** were isolated in good yields, whereas **4e**–**g** were formed in much lower yields. The *o*-methoxy derivative **4d** was only obtained in moderate yield probably due to the steric hindrance. Naphthalene and benzofuran derivatives, following these trends, gave the corresponding products **4h** and **4i** in good yields (entries 8 and 9).

The structures of compounds **4** were assigned according to their NMR spectroscopic data. An X-ray diffraction analysis supported the structure of compound **4a** and showed the *cis* stereochemistry of the ring fusion, which was assigned to the rest of the series due to the similarity of the NMR spectra.[10] Other α-bromo ketones without aromatic rings were tested, but we did not observe conversion into the rearranged products. In addition, secondary bromides did not react. These unreactive bromo ketones are shown in Scheme 3. Finally, we treated chiral substrate (+)-**2d** with (1-benzofuran-2-yl)-2-bromoethanone (entry 10) and isolated the corresponding mixture of diastereomeric



Scheme 3. Main side-reactions in the reactions of lactams **2** with bromo ketones.

rearranged products **4j** and **4k** in a combined yield of 58% in a ratio of 1:1, which we were not able to separate by chromatography.

In an attempt to develop an asymmetric version of this process we substituted DABCO by a chiral amine. Thus, two isomers of (8-ethylquinuclidin-2-yl)methanol and 3-(–)-(*R*)-quinuclidinol (commercial compounds) were acetylated to give the amines **5**–**7** depicted in Figure 1.[11] We treated these amines with (1-benzofuran-2-yl)-2-bromoethanone but in the first two cases we did not observe the formation of ammonium salts, possibly due to a steric effect. On the other hand, the reaction of **7** gave the salt, which was treated with **2a**. Rearrangement occurred to give scalemic **4i** in 57% yield with an *ee* of only 15%.[12]

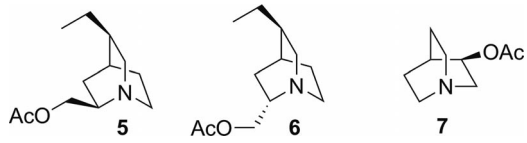
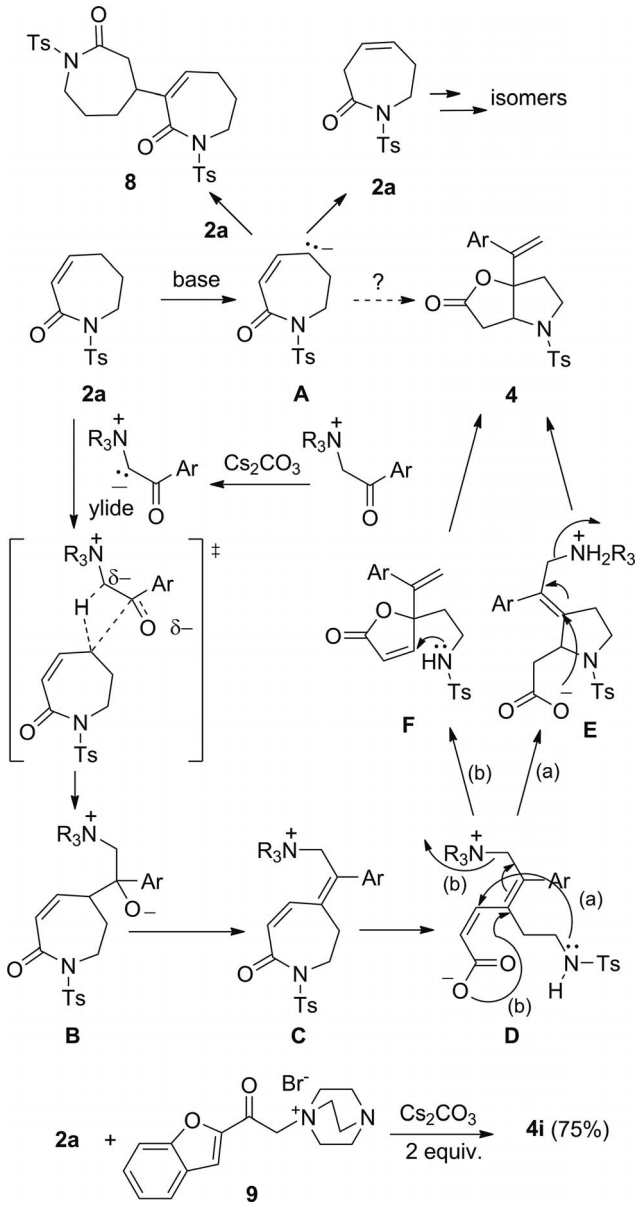


Figure 1. Chiral amines used for the reaction with (1-benzofuran-2-yl)-2-bromoethanone and **2a**.

The side-reactions detected in these reactions proved to be interesting. In some reactions we detected mixtures of isomers of the starting lactam in which the double bond had shifted to various positions within the ring. Significant yields of these products were obtained when using the α-bromo ketones depicted in Scheme 3.[13] In addition, this was the only process observed when the eight-membered lactam **2c** was treated with phenacyl bromide. With this starting material we isolated **2e** and **2f** in variable yields depending on the reaction conditions. The other competing reaction was a Morita–Baylis–Hillman-type (MBH) reaction of lactam **2a**, which gave product **8**.[14] As indicated above, acetonitrile was found to be the best solvent, with THF and dioxane giving **8** as the major product (32% isolated yield with dioxane) along with mixtures of **2g**–**i**. The use of harder bases (Na_2CO_3, NaOH) led to the formation of variable amounts of **8** as a result of the MBH-type reaction.

With these results we proposed a reaction pathway that could explain the formation of the fused heterocyclic products **4** (Scheme 4). It is reasonable to assume the formation of enolate **A** to start the reaction. This should subsequently react with the carbonyl group of the preformed ammonium salt and proceed to intermediate **B**. We checked that ammonium salts are intermediates in this reaction by isolating **9**, which gave the corresponding product **4i** in 75% yield upon reaction with **2a** and 2 equiv. of Cs_2CO_3. Moreover, if the lactam was added before the formation of the ammonium salt no rearrangement was observed and a mixture of double-bond-shifted products was produced. In addition, bases like NaOH or Na_2CO_3 resulted in MBH-type reactions, which shows that the way in which the enolate is formed is critical for a particular reaction course. This tendency towards isomerization reactions was reduced or eliminated if the ammonium salt was stirred with the base prior to the addition of the lactam. During this period bright-

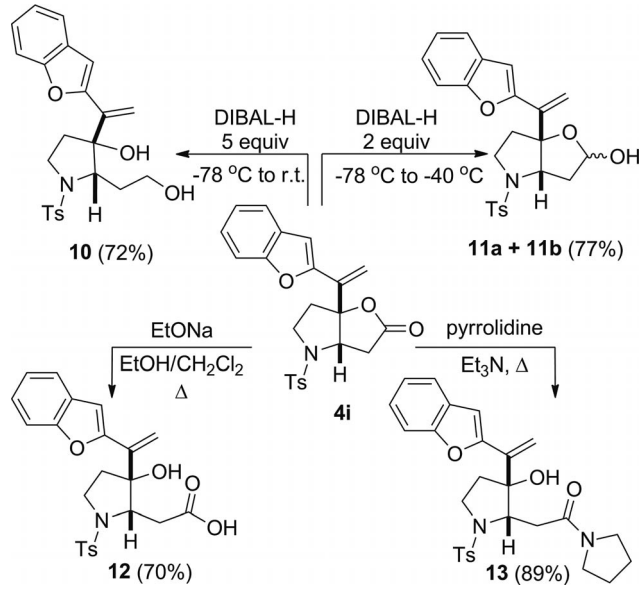
coloured species were formed, which indicates the formation of nitrogen ylides. In view of these observations, we postulate that the formation of intermediate **B** might proceed via the transition state depicted in Scheme 4, the nitrogen ylide being the species that removes the proton thereby avoiding competitive side-reactions.



Scheme 4. Proposed reaction pathway for the synthesis of the fused heterocyclin products **4**.

The protonation of **B** and an E1cB-type process would lead to **C**. Stabilization of the new double bond by the aromatic ring should be essential and this could be the reason for the lack of reactivity of non-aromatic reagents. Furthermore, opening of the lactam to form **D** and conjugate attack of the amino group produces intermediate **E** (path a). Cyclization assisted by the leaving of the ammonium group gives the final product **4**. Alternatively, the addition of the carboxylate anion in **D** to the new tetrasubstituted double bond with elimination of the tertiary amine and then intramolecular 1,4-addition of the TosNH group to the α,β-unsaturated lactone **F** could be possible (path b). Compounds **4** were shown to have *cis* stereochemistry.[10]

The products obtained by this new rearrangement process have structural similarities with certain natural products as we have indicated above. Therefore we explored some transformations leading to structures more closely related to kainoids and radicamines. Scheme 5 shows the results of these reactions with **4i**. Reduction of the lactone group with DIBAL-H allowed the selective synthesis of both the diol **10** and the mixture of hemiacetals **11**. If 5 equiv. of DIBAL-H were used and the reaction allowed to reach room temp., the major product was **10** (72%), whereas milder conditions (2 equiv. of reagent and lower temperatures not above –40 °C) produced only the hemiacetals **11** in high yields (77%). Cleavage of the lactone to give hydroxy acid **12** was accomplished by using EtONa and we were able to obtain this product as a single spot on TLC. However, after a few minutes in solution, this product started to cyclize to **4i**. Finally, we performed an aminolysis reaction on **4i** with pyrrolidine to obtain **13** in an excellent yield (89%).[15]



Scheme 5. Transformations of product **4i**.

Conclusions

The reactions of unsaturated seven-membered lactams with aromatic α-bromo ketones by a novel rearrangement process have been described herein. The reaction is mediated by tertiary amines, which form quaternary salts with the bromo ketones and subsequently nitrogen ylides that initiate the rearrangement process. The participation of nitrogen ylides is postulated as necessary to avoid competitive side-reactions. Thus, new fused heterocyclic compounds related to kainoids and other natural products such as radicamines have been obtained. The transformation of the lact-

one group present in the rearranged product paves the way for the synthesis of these natural products and their derivatives.

Experimental Section

General: Melting points (uncorrected) were determined with a Stuart Scientific SMP3 apparatus. ^{1}H and ^{13}C NMR spectra were taken with a Bruker DPX 300 MHz BACS60. Chemical shifts (δ) are expressed in parts per million relative to internal tetramethylsilane at δ = 0.00 ppm. IR spectra were recorded with a Perkin-Elmer Spectrum a 100 FT-IR spectrophotometer. Mass spectra were recorded with a 1100 HPLC (Xterra MS C18 5 mm reverse-phase columns) coupled to MS (API-ES) with a 1946D Ms detector, all from Agilent. Elemental analyses (C, H, N) were performed with a LECO CHNS-932 apparatus at the Microanalyses Service of the Universidad Complutense of Madrid. Thin layer chromatography (TLC) analyses were performed on commercial aluminium sheets bearing a 0.25 mm layer of Merck silica gel 60 F254. Merck silica gel 60 of 230–400 mesh ASTM was used for standard column chromatography. All solvents were purchased from VWR and distilled just before their use. Tetrahydrofuran was refluxed in the presence of sodium/benzophenone and acetonitrile and dichloromethane in the presence of calcium hydride. All reactions were conducted under argon in flame-dried flasks. All reagents were purchased from Aldrich or Across Organics. The syntheses of compounds **1a**, **1b**,[1] **1c**,[16] **2a**, **2b**,[1] **3**,[17] **2g**, **2h** and **2i**[12] have been described in the literature.

(*Z*)-1-Tosyl-5,6,7,8-tetrahydroazocin-2(1*H*)-one (2c): A 1 M LiHMDS solution (3.00 mL, 3.0 mmol) in THF was added to a 0.2 M solution of 1-tosyl-2-azacyclooctanone (0.20 mL, 1.0 mmol) in anhydrous THF under argon at –30 °C. The reaction mixture was stirred for 1 h and then a 0.4 M solution of phenylselenyl chloride (383 mg, 2.0 mmol) was added at the same temperature. The mixture was stirred for a further 1 h and then warmed up to room temperature over 1 h and stirred 30 min more at this temperature. The reaction mixture was washed with a 1 M HCl aqueous solution (20 mL) and then the aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, washed with a 10% aqueous solution of $NaHCO_3$ and brine, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was dissolved in THF and a 30% aqueous solution of hydrogen peroxide (0.34 mL, 3.00 mmol) was added to the mixture at 0 °C. This mixture was stirred for 15 min at 0 °C and then warmed up to room temperature over 30 min. The reaction mixture was then dissolved in dichloromethane (15 mL) and washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted three times with dichloromethane (15 mL). The organic layers were combined, washed with brine, dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography to give **2c** as a white solid (m.p. 99–101 °C), yield 182 mg (65%; hexane/ethyl acetate, 6:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56–1.71 (m, 2 H, CH_2CH$_2$CH=), 1.95 (br. s, 2 H, CH_2CH$_2$N), 2.33 (br. s, 2 H, CH$_2$CH_2CH=), 2.43 (s, 3 H, CH$_3$), 4.11 (t, J = 11.3 Hz, 2 H, CH$_2$CH_2N), 5.65 (dt, J_1 = 12.8, J_2 = 1.9 Hz, 1 H, HC=C*H*CO), 6.13 (dt, J_1 = 12.8, J_2 = 5.2 Hz, 1 H, *H*C=CHCO), 7.31 (d, J = 8.1 Hz, 2 H, Ts), 7.94 (d, J = 8.4 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7 (CH$_2$), 21.6 (CH$_3$), 29.8 (CH$_2$), 30.9 (CH$_2$), 46.5 (CH$_2$), 121.6 (CH), 129.0 (CH), 129.2 (CH), 136.2 (C), 141.1 (CH), 144.7 (C), 168.1 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2931, 1672, 1632, 1595 cm^{-1}. MS (ESI): m/z = 280 [M + H]$^+$. $C_{14}H_{17}NO_3S$ (279.35): calcd. C 60.19, H 6.13, N 5.01, S 11.48; found C 60.32, H 6.03, N 4.86.

1-{[(1*S*,4*R*)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methylsulfonyl}-6,7-dihydro-1*H*-azepin-2(5*H*)-one [(+)-2d]: A 1 M LiHMDS solution (1.00 mL, 1.00 mmol) in THF was added to a 0.2 M solution of 6,7-dihydro-1*H*-azepin-2(5*H*)-one (**3**; 0.18 mL, 0.90 mmol) in anhydrous THF under argon at –40 °C. The reaction mixture was stirred for 1 h and then a 0.4 M solution of (1*S*)-(+)-10-camphorsulfonyl chloride in THF (2.50 mL, 1.00 mmol) was added at the same temperature. The reaction was stirred for a further 1 h and then warmed to room temperature over 30 min. The mixture was washed with a 1 N HCl aqueous solution (20 mL) and then the aqueous layer was extracted three times with ethyl acetate (3 × 20 mL). The organic layers were combined, washed with a 10% aqueous solution of $NaHCO_3$ (20 mL) and brine (20 mL) and dried with anhydrous $MgSO_4$. Reaction time: 2.5 h, yield 190 mg (65%; hexane/ethyl acetate, 6:1) of **2d** as a white solid (m.p. 91–94 °C). $[\alpha]_D^{26}$ = +38 (c = 0.024, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (s, 3 H, CH_3, camphor), 1.11 (s, 3 H, CH_3, camphor), 1.42–1.50 (m, 1 H, camphor), 1.75–1.85 (m, 1 H, camphor), 1.92 (d, J = 18.5 Hz, 1 H, camphor), 2.01–2.13 (m, 4 H, CH$_2$CH_2CH$_2$ and camphor), 2.34–2.49 (m, 4 H, CH_2CH= and camphor), 3.53 (d, J = 14.9 Hz, 1 H, camphor), 3.67–3.77 (d, J = 6.0 Hz, 1 H, CH_2N), 3.94–4.03 (d, J = 6.0 Hz, 1 H, CH_2N), 3.99 (d, J = 14.9 Hz, 1 H, camphor), 6.04 (d, J = 11.8 Hz, 1 H, *H*C=CO), 6.47–6.55 (m, 1 H, CH$_2$C*H*=) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2 (2 CH$_3$), 26.2 (CH$_2$), 26.6 (CH$_2$), 27.5 (CH$_2$), 28.7 (CH$_2$), 43.0 (CH$_2$), 43.2 (CH), 45.2 (CH$_2$), 48.9 (C), 52.5 (CH$_2$), 59.4 (C), 127.1 (CH), 143.0 (CH), 170.2 (CO), 215.2 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 1738, 1694 cm^{-1}. MS (ESI): m/z = 326 [M + H]$^+$. $C_{16}H_{23}NO_4S$ (325.42): calcd. C 59.05, H 7.12, N 4.30, S 9.85; found C 59.14, H 7.24, N 4.11.

(*Z*)-1-Tosyl-1,6,7,8-tetrahydroazocin-2(3*H*)-one (2e) and (*Z*)-1-Tosyl-3,4,7,8-tetrahydroazocin-2(1*H*)-one (2f): Following the general procedure for the rearrangement reaction from 2-bromo-1-phenylethanone (77 mg, 0.39 mmol), Cs_2CO_3 (232 mg, 0.71 mmol), DABCO (40 mg, 0.36 mmol) and **2c** (100 mg, 0.36 mmol). Reaction time: 16 h, yield 25 mg (25%; (hexane/ethyl acetate, 9:1) of **2e** as a yellow syrup and 10 mg (10%) of **2f** as a yellow syrup unpurified by **2e**.

Data for 2e: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84–1.92 (m, 2 H, CH_2), 2.04–2.11 (m, 2 H, CH_2), 2.43 (s, 3 H, CH$_3$), 3.18 (dd, J_1 = 5.1, J_2 = 1.7 Hz, 2 H, CH_2CO), 4.09 (t, J = 5.6 Hz, 2 H, CH_2N), 5.47–5.54 (m, 1 H, *H*C=), 5.67–5.77 (m, 1 H, *H*C=), 7.30 (d, J = 8.2 Hz, 2 H, Ts), 7.91 (d, J = 8.4 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7 (CH$_2$), 21.6 (CH$_3$), 29.8 (CH$_2$), 30.9 (CH$_2$), 46.5 (CH$_2$), 121.6 (CH), 129.0 (CH), 129.2 (CH), 136.2 (C), 141.1 (CH), 144.7 (C), 168.1 (CO) ppm. IR (NaCl): $\tilde{\nu}$ = 2930, 1632, 1495 cm^{-1}. $C_{14}H_{17}NO_3S$ (279.35): calcd. C 60.19, H 6.13, N 5.01, S 11.48; found C 60.42, H 6.26, N 5.15.

Data for 2f: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83–0.88 (m, 4 H, 2 CH_2), 2.43 (s, 3 H, CH_3), 2.52–2.58 (m, 2 H, CH_2CO), 4.06 (t, J = 6.6 Hz, 2 H, CH_2N), 5.85 (d, J = 9.8 Hz, 1 H, *H*C=), 6.77–6.83 (m, 1 H, *H*C=), 7.32 (d, J = 8.1 Hz, 2 H, Ts), 7.93 (d, J = 8.4 Hz, 2 H, Ts) ppm. IR (NaCl): $\tilde{\nu}$ = 2929, 1630, 1490 cm^{-1}.

General Procedure for the Rearrangement Reaction: DABCO (1 equiv.) was added to a solution of the α-bromo ketone (1.1 equiv.) in dry acetonitrile (0.20 M) under argon and the resulting mixture was stirred at room temp. for 60 min. Then Cs_2CO_3 (2 equiv.) was added and the mixture stirred for 30 min. Finally, the corresponding lactam (1 equiv.) dissolved in dry acetonitrile (0.20 M) was added slowly over 30 min. The reaction mixture was stirred at 80 °C. Once completed, as shown by TLC analysis, the reaction was quenched by filtering through Celite and washing with a 2.5% HCl aqueous solution (15 mL). The mixture was extracted

with CH_2Cl_2 (3 × 15 mL) and the organic layers combined, washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product, which was purified by flash chromatography.

(3a*S,6a*R**)-6a-(1-Phenylvinyl)-4-tosylhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one (4a):** Following the general procedure starting from 2-bromo-1-phenylethanone (84 mg, 0.42 mmol), Cs_2CO_3 (244 mg, 0.75 mmol), DABCO (43 mg, 0.38 mmol) and **2a** (100 mg, 0.38 mmol). Reaction time: 16 h, yield 115 mg (79%; hexane/ethyl acetate, 3:1) of **4a** as a white solid (m.p. 236–240 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75–1.86 (m, 1 H, CH_2CH$_2$N), 2.05–2.13 (m, 1 H, CH_2CH$_2$N), 2.35 (s, 3 H, CH_3), 2.66 (dd, J_1 = 18.4, J_2 = 6.1 Hz, 1 H, CH_2CO), 2.84 (d, J = 18.4 Hz, 1 H, CH_2CO), 3.43–3.49 (m, 2 H, CH$_2$CH_2N), 4.27 (d, J = 6.6 Hz, 1 H, CH), 5.12 (s, 1 H, H_2C=C), 5.41 (s, 1 H, H_2C=C), 6.95 (d, J = 6.8 Hz, 2 H, Ph), 7.12–7.26 (m, 5 H, Ph and Ts), 7.47 (d, J = 8.3 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 34.8 (CH_2), 36.6 (CH_2), 47.1 (CH_2), 62.8 (CH), 95.4 (C), 117.7 (CH_2), 126.8 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 129.9 (CH), 134.5 (C), 138.1 (C), 143.9 (C), 145.8 (C), 174.4 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2953, 2900, 1789, 1696, 1597 cm^{-1}. MS (ESI): m/z = 384 [M + H]$^+$. $C_{21}H_{21}NO_4S$ (383.46): calcd. C 65.78.05, H 5.52, N 3.65, S 8.36; found C 65.73, H 5.48, N 3.47.

(3a*S,6a*R**)-6a-[1-(*p*-Tolyl)vinyl]-4-tosylhexahydro-2*H*-furo[3,2-*b*]-pyrrol-2-one (4b):** Following the general procedure starting from 2-bromo-1-(4-methylphenyl)ethanone (89 mg, 0.42 mmol), Cs_2CO_3 (244 mg, 0.75 mmol), DABCO (43 mg, 0.38 mmol) and **2a** (100 mg, 0.38 mmol). Reaction time: 16 h, yield 113 mg (75%; hexane/ethyl acetate, 9:1) of **4b** as an orange solid (m.p. 114–116 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82–1.93 (m, 1 H, CH_2CH$_2$N), 2.11–2.17 (m, 1 H, CH_2CH$_2$N), 2.38 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 2.73 (dd, J_1 = 18.3, J_2 = 6.1 Hz, 1 H, CH_2CO), 2.91 (d, J = 18.3 Hz, 1 H, CH_2CO), 3.49–3.55 (m, 2 H, CH$_2$CH_2N), 4.35 (d, J = 6.0 Hz, 1 H, CH), 5.17 (s, 1 H, H_2C=C), 5.44 (s, 1 H, H_2C=C), 6.90 (d, J = 8.0 Hz, 2 H, Ar), 7.06 (d, J = 8.0 Hz, 2 H, Ar), 7.21 (d, J = 8.2 Hz, 2 H, Ts), 7.55 (d, J = 8.3 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 21.6 (CH_3), 35.0 (CH_2), 36.7 (CH_2), 47.2 (CH_2), 62.9 (CH), 95.5 (C), 117.5 (CH_2), 127.0 (CH), 128.3 (CH), 129.1 (CH), 129.9 (CH), 134.8 (C), 135.3 (C), 137.9 (C), 143.9 (C), 145.9 (C), 174.5 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2924, 1789, 1595 cm^{-1}. MS (ESI): m/z = 398 [M + H]$^+$. $C_{22H23}NO_4S$ (397.49): calcd. C 66.48, H 5.83, N 3.52, S 8.07; found C 66.18, H 5.62, N 3.71.

(3a*S,6a*R**)-6a-[1-(4-Methoxyphenyl)vinyl]-4-tosylhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one (4c):** Following the general procedure starting from 2-bromo-1-(4-methoxyphenyl)ethanone (95 mg, 0.42 mmol), Cs_2CO_3 (244 mg, 0.75 mmol), DABCO (43 mg, 0.38 mmol) and **2a** (100 mg, 0.38 mmol). Reaction time: 16 h, yield 132 mg (84%; hexane/ethyl acetate, 9:1) of **4c** as a yellow solid (m.p. 236–240 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.83–1.94 (m, 1 H, CH_2CH$_2$N), 2.12–2.17 (m, 1 H, CH_2CH$_2$N), 2.43 (s, 3 H, CH_3), 2.72 (dd, J_1 = 18.4, J_2 = 6.2 Hz, 1 H, CH_2CO), 2.90 (d, J = 18.3 Hz, 1 H, CH_2CO), 3.51–3.57 (m, 2 H, CH$_2$CH_2N), 3.83 (s, 3 H, OCH_3), 4.34 (d, J = 6.0 Hz, 1 H, CH), 5.16 (s, 1 H, H_2C=C), 5.43 (s, 1 H, H_2C=C), 6.76 (d, J = 8.6 Hz, 2 H, Ar), 6.95 (d, J = 8.8 Hz, 2 H, Ar), 7.23 (d, J = 8.3 Hz, 2 H, Ts), 7.56 (d, J = 8.3 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 35.0 (CH_2), 36.7 (CH_2), 47.2 (CH_2), 55.3 (OCH_3), 62.9 (CH), 95.6 (C), 113.8 (CH), 117.4 (CH_2), 127.0 (CH), 129.6 (CH), 130.0 (CH), 130.4 (C), 134.8 (C), 144.0 (C), 145.5 (C), 159.4 (C), 174.5 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2926, 1791, 1693, 1605 cm^{-1}. MS (ESI): m/z = 414 [M + H]$^+$. $C_{22}H_{23}NO_5S$ (413.49): calcd. C 63.90, H 5.61, N 3.39, S 7.75; found C 63.78, H 5.49, N 3.57.

(3a*S,6a*R**)-6a-[1-(2-Methoxyphenyl)vinyl]-4-tosylhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one (4d):** Following the general procedure starting from 1-(2-methoxyphenyl)-2-bromoethanone (95 mg, 0.42 mmol), Cs_2CO_3 (244 mg, 0.75 mmol), DABCO (43 mg, 0.38 mmol) and **2a** (100 mg, 0.38 mmol). Reaction time: 16 h, yield 70 mg (45%; hexane/ethyl acetate, 9:1) of **4d** as a yellow solid (m.p. 172–174 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.71–1.76 (m, 1 H, CH_2CH$_2$N), 2.05–2.17 (m, 1 H, CH_2CH$_2$N), 2.39 (s, 3 H, CH_3), 2.87–2.88 (m, 2 H, CH_2CO), 3.47–3.54 (m, 2 H, CH$_2$CH_2N), 3.78 (s, 3 H, OCH_3), 4.31 (dd, J_1 = 3.8, J_2 = 2.8 Hz, 1 H, CH), 5.01 (s, 1 H, H_2C=C), 5.57 (s, 1 H, H_2C=C), 6.84–6.89 (m, 3 H, Ar), 7.11 (d, J = 8.2 Hz, 2 H, Ts), 7.28–7.36 (m, 1 H, Ar), 7.43 (d, J = 8.3 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3), 35.2 (CH_2), 36.9 (CH_2), 47.2 (CH_2), 55.5 (OCH_3), 63.2 (CH), 96.0 (C), 111.0 (CH), 118.5 (CH_2), 120.6 (CH), 126.7 (CH), 128.5 (C), 129.6 (CH), 129.8 (CH), 131.2 (CH), 134.9 (C), 143.2 (C), 143.6 (C), 156.5 (C), 174.9 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2924, 1792, 1695, 1599 cm^{-1}. MS (ESI): m/z = 414 [M + H]$^+$, 436 [M + Na]$^+$. $C_{22}H_{23}NO_5S$ (413.49): calcd. C 63.90, H 5.61, N 3.39, S 7.75; found C 63.99, H 5.74, N 3.20.

(3a*S,6a*R**)-6a-[1-(4-Bromophenyl)vinyl]-4-tosylhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one (4e).** Following the general procedure starting from 2-bromo-1-(4-bromophenyl)ethanone (117 mg, 0.42 mmol), Cs_2CO_3 (244 mg, 0.75 mmol), DABCO (43 mg, 0.38 mmol) and **2a** (100 mg, 0.38 mmol). Reaction time: 16 h, yield 97 mg (55%; hexane/ethyl acetate, 9:1) of **4e** as a yellow solid (m.p. 129–131 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75–1.80 (m, 1 H, CH_2CH$_2$N), 2.10–2.12 (m, 1 H, CH_2CH$_2$N), 2.47 (s, 3 H, CH_3), 2.77 (dd, J_1 = 18.4, J_2 = 6.1 Hz, 1 H, CH_2CO), 2.94 (d, J = 18.4 Hz, 1 H, CH_2CO), 3.51–3.58 (m, 2 H, CH$_2$CH_2N), 4.27 (d, J = 5.9 Hz, 1 H, CH), 5.19 (s, 1 H, H_2C=C), 5.50 (s, 1 H, H_2C=C), 6.89 (d, J = 8.4 Hz, 2 H, Ar), 7.24 (d, J = 8.1 Hz, 2 H, Ar), 7.38 (d, J = 8.4 Hz, 2 H, Ts), 7.53 (d, J = 8.3 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 35.1 (CH_2), 36.6 (CH_2), 47.2 (CH_2), 62.7 (CH), 95.1 (C), 118.3 (CH_2), 122.5 (C), 126.9 (CH), 130.0 (CH), 130.1 (CH), 131.6 (CH), 134.6 (C), 137.0 (C), 144.3 (C), 145.0 (C), 174.1 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2922, 1783, 1694, 1595 cm^{-1}. MS (ESI): m/z = 462 [M + H]$^+$. $C_{21}H_{20}BrNO_4S$ (462.36): calcd. C 54.55, H 4.36, Br 17.28, N 3.03, S 6.94; found C 54.44, H 4.48, N 2.94.

(3a*S,6a*R**)-6a-[1-(3-Bromophenyl)vinyl]-4-tosylhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one (4f):** Following the general procedure starting from 2-bromo-1-(3-bromophenyl)ethanone (117 mg, 0.42 mmol), Cs_2CO_3 (244 mg, 0.75 mmol), DABCO (43 mg, 0.38 mmol) and **2a** (100 mg, 0.38 mmol). Reaction time: 16 h, yield 105 mg (60%; hexane/ethyl acetate, 9:1) of **4f** as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76–1.80 (m, 1 H, CH_2CH$_2$N), 2.13–2.14 (m, 1 H, CH_2CH$_2$N), 2.43 (s, 3 H, CH_3), 2.79 (dd, J_1 = 18.4, J_2 = 6.1 Hz, 1 H, CH_2CO), 2.95 (d, J = 18.4 Hz, 1 H, CH_2CO), 3.51–3.58 (m, 2 H, CH$_2$CH_2N), 4.29 (d, J = 5.9 Hz, 1 H, CH), 5.19 (s, 1 H, H_2C=C), 5.51 (s, 1 H, H_2C=C), 6.97 (d, J = 7.7 Hz, 1 H, Ar), 7.14 (t, J = 7.8 Hz, 1 H, Ar), 7.19 (t, J = 1.7 Hz, 1 H, Ar), 7.23 (d, J = 8.1 Hz, 2 H, Ts), 7.47 (dt, J_1 = 8.0, J_2 = 1.8 Hz, 1 H, Ar), 7.54 (d, J = 8.3 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 35.1 (CH_2), 36.6 (CH_2), 47.2 (CH_2), 62.7 (CH), 95.0 (C), 118.7 (CH_2), 122.6 (C), 126.9 (CH), 128.6 (CH), 129.3 (CH), 130.0 (CH), 131.2 (CH), 131.6 (CH), 134.5 (C), 140.2 (C), 144.2 (C), 144.8 (C), 174.1 (CO) ppm. IR (NaCl): $\tilde{\nu}$ = 2918, 1788, 1694, 1594 cm^{-1}. MS (ESI): m/z = 462 [M + H]$^+$. $C_{21}H_{20}BrNO_4S$ (462.36): calcd. C 54.55, H 4.36, Br 17.28, N 3.03, S 6.94; found C 54.71, H 4.25, N 3.13.

4-{1-[(3a*S,6a*R**)-2-Oxo-4-tosylhexahydro-2*H*-furo[3,2-*b*]pyrrol-6a-yl]vinyl}benzonitrile (4g):** Following the general procedure start-

ing from 2-bromo-1-(4-cyanophenyl)ethanone (94 mg, 0.42 mmol), Cs_2CO_3 (244 mg, 0.75 mmol), DABCO (43 mg, 0.38 mmol) and **2a** (100 mg, 0.38 mmol). Reaction time: 16 h, yield 54 mg (35%; hexane/ethyl acetate, 9:1) of **4g** as a yellow solid (m.p. 126–128 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77–1.88 (m, 1 H, CH_2CH$_2$N), 2.17–2.22 (m, 1 H, CH_2CH$_2$N), 2.47 (s, 3 H, CH_3), 2.77 (dd, J_1 = 18.5, J_2 = 6.3 Hz, 1 H, CH_2CO), 2.94 (d, J = 18.5 Hz, 1 H, CH_2CO), 3.48–3.56 (m, 1 H, CH$_2$CH_2N), 3.59–3.66 (m, 1 H, CH$_2$CH_2N), 4.33 (d, J = 5.9 Hz, 1 H, CH), 5.27 (s, 1 H, H_2C=C), 5.53 (s, 1 H, H_2C=C), 7.21 (d, J = 8.4 Hz, 2 H, Ar), 7.27 (d, J = 8.4 Hz, 2 H, Ar), 7.57 (d, J = 8.4 Hz, 2 H, Ar), 7.60 (d, J = 8.3 Hz, 2 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 35.7 (CH_2), 36.5 (CH_2), 47.1 (CH_2), 62.7 (CH), 94.7 (C), 112.4 (CN), 118.1 (C), 119.0 (CH_2), 127.1 (CH), 129.2 (CH), 130.1 (CH), 132.2 (CH), 134.9 (C), 142.9 (C), 144.4 (C), 145.0 (C), 173.7 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 2912, 2226, 1790, 1596 cm^{-1}. MS (ESI): m/z = 409 [M + H]$^+$, 431 [M + Na]$^+$. $C_{22}H_{20}N_2O_4S$ (408.47): calcd. C 64.69, H 4.94, N 6.86, S 7.85; found C 64.49, H 4.79, N 6.98.

(3a*S,6a*R**)-6a-[1-(2-Naphthyl)vinyl]-4-tosylhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one (4h):** Following the general procedure starting from 2-bromo-1-(2-naphthylethanone (105 mg, 0.42 mmol), Cs_2CO_3 (244 mg, 0.75 mmol), DABCO (43 mg, 0.38 mmol) and **2a** (100 mg, 0.38 mmol). Reaction time: 2.5 h, yield 112 mg (68%; hexane/ethyl acetate, 9:1) of **4h** as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81–1.86 (m, 1 H, CH_2CH$_2$N), 2.14–2.20 (m, 1 H, CH_2CH$_2$N), 2.19 (s, 3 H, CH_3), 2.84 (dd, J_1 = 18.3, J_2 = 5.8 Hz, 1 H, CH_2CO), 2.96 (d, J = 18.2 Hz, 1 H, CH_2CO), 3.51–3.56 (m, 2 H, CH$_2$CH_2N), 4.43 (d, J = 5.4 Hz, 1 H, CH), 5.27 (s, 1 H, H_2C=C), 5.60 (s, 1 H, H_2C=C), 6.77 (d, J = 8.0 Hz, 2 H, Ar), 7.12 (d, J = 8.4 Hz, 1 H, Ar), 7.38 (d, J = 8.3 Hz, 2 H, Ar), 7.49 (s, 1 H, Ar), 7.55–7.58 (m, 2 H, Ar), 7.72–7.80 (m, 2 H, Ar), 7.87 (d, J = 8.3 Hz, 1 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 35.0 (CH_2), 36.7 (CH_2), 47.2 (CH_2), 62.8 (CH), 95.5 (C), 118.2 (CH_2), 126.4 (CH), 126.7 (CH), 126.7 (CH), 126.8 (CH), 127.6 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 129.7 (CH), 132.7 (C), 132.9 (C), 134.4 (C), 135.6 (C), 143.8 (C), 145.9 (C), 174.4 (CO) ppm. IR (NaCl): $\tilde{\nu}$ = 2912, 1789, 1695, 1543 cm^{-1}. MS (ESI): m/z = 434, [M + H]$^+$. $C_{25}H_{23}NO_4S$ (433.52): calcd. C 69.26, H 5.35, N 3.23, S 7.40; found C 69.15, H 5.25, N 3.38.

(3a*S,6a*R**)-6a-[1-(Benzofuran-2-yl)vinyl]-4-tosylhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one (4i):** Following the general procedure starting from 1-benzofuran-2-yl-2-bromoethanone (100 mg, 0.42 mmol), Cs_2CO_3 (244 mg, 0.75 mmol), DABCO (43 mg, 0.38 mmol) and **2a** (100 mg, 0.38 mmol). Reaction time: 2.5 h, yield 137 mg (85%; hexane/ethyl acetate, 9:1) of **4i** as a yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35–2.42 (m, 2 H, CH_2CH$_2$N), 2.50 (s, 3 H, CH_3), 2.82 (dd, J_1 = 18.5, J_2 = 6.1 Hz, 1 H, CH_2CO), 3.08 (d, J = 18.5 Hz, 1 H, CH_2CO), 3.64–3.78 (m, 2 H, CH$_2$CH_2N), 4.61 (d, J = 5.6 Hz, 1 H, CH), 5.61 (s, 1 H, H_2C=C), 5.98 (s, 1 H, H_2C=C), 6.37 (s, 1 H, Ar), 7.20–7.30 (m, 3 H, Ar), 7.35 (d, J = 8.0 Hz, 2 H, Ts), 7.42 (dd, J_1 = 7.1, J_2 = 1.0 Hz, 1 H, Ar), 7.77 (d, J = 8.3 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (CH_3), 36.4 (CH_2), 36.5 (CH_2), 48.0 (CH_2), 63.5 (CH), 94.4 (C), 105.4 (CH), 111.5 (CH), 117.1 (CH_2), 121.6 (CH), 123.7 (CH), 125.7 (CH), 127.9 (CH), 128.3 (C), 130.6 (CH), 135.2 (C), 135.6 (C), 144.7 (C), 152.2 (C), 154.6 (C), 174.4 (CO) ppm. IR (NaCl): $\tilde{\nu}$ = 2924, 1799, 1694, 1596 cm^{-1}. MS (ESI): m/z = 462 [M + K]$^+$. $C_{23}H_{21}NO_5S$ (423.48): calcd. C 65.23, H 5.00, N 3.31, S 7.57; found C 65.11, H 4.87, N 3.39.

(3a*R*,6a*S*)- and (3a*S*,6a*R*)-6a-[1-(Benzofuran-2-yl)vinyl]-4-{[(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl]methylsulfonyl}hexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one (4j and 4k): Following the general procedure starting from (1-benzofuran-2-yl)-2-bromoethanone (82 mg, 0.34 mmol), Cs_2CO_3 (202 mg, 0.62 mmol), DABCO (35 mg, 0.31 mmol) and **2d** (100 mg, 0.31 mmol). Reaction time: 4 h, yield 88 mg (58%; hexane/ethyl acetate, 9:1) of a mixture of **4j** and **4k** as a brown syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 and 0.91 (s, 3 H, CH_3, camphor), 1.13 and 1.14 (s, 3 H, CH_3, camphor), 1.40–1.49 (m, 1 H, camphor), 1.63–1.73 (m, 1 H, camphor), 1.96 and 1.97 (d, J = 24.8 and J = 24.4 Hz, 1 H, camphor), 2.01–2.14 (m, 2 H, camphor), 2.35–2.53 (m, 3 H, CH_2CH$_2$N and camphor), 2.61–2.77 (m, 1 H, camphor), 2.81–3.06 (m, 3 H, CH_2CO and camphor), 3.50 and 3.54 (d, J = 30.1 and J = 28.0 Hz, 1 H, camphor), 3.60–3.73 (m, 1 H, CH_2CH_2N), 3.91–4.00 (m, 1 H, CH$_2$CH_2N), 4.92 and 5.01 (d, J = 5.8 and J = 7.9 Hz, 1 H, CH), 5.71 (s, 1 H, H_2C=C), 6.02 (s, 1 H, H_2C=C), 6.90 and 6.91 (s, 1 H, Ar), 7.20–7.33 (m, 2 H, Ar), 7.46–7.55 (m, 1 H, Ar), 7.57 (d, J = 7.6 Hz, 1 H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8 and 19.9 (CH_3), 20.0 (both CH_3), 25.2 and 25.3 (CH_2), 26.8 and 26.9 (CH_2), 36.2 (both CH_2), 36.5 and 36.6 (CH_2), 42.6 (both CH_2), 42.8 and 42.9 (CH), 47.3 and 47.5 (C), 47.9 (both CH_2), 48.1 and 48.4 (CH_2), 58.4 and 58.5 (C), 62.9 (both CH), 94.2 and 94.3 (C), 105.5 and 105.6 (CH), 111.2 and 111.3 (CH), 116.7 (both CH_2), 121.4 (both CH), 123.4 and 123.5 (CH), 125.4 (both CH), 128.0 and 128.1 (C), 135.3 and 135.4 (C), 152.1 and 152.2 (C), 154.4 and 154.5 (C), 174.1 and 174.2 (CO), 215.1 (both CO) ppm. IR (NaCl): $\tilde{\nu}$ = 2964, 1741, 1691 cm^{-1}.

(*Z*)-3-(2-Oxo-1-tosylazepan-4-yl)-1-tosyl-6,7-dihydro-1*H*-azepin-2(5*H*)-one (8): Following the general procedure starting from 2-bromo-1-phenylethanone (84 mg, 0.42 mmol), Cs_2CO_3 (244 mg, 0.75 mmol), DABCO (43 mg, 0.38 mmol) and **2a** (100 mg, 0.38 mmol) in dioxane. Reaction time: 16 h, yield 32 mg (32%; hexane/ethyl acetate, 3:1) of **8** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63–1.70 (m, 2 H, CH_2), 1.98–2.07 (m, 2 H, CH_2), 2.16–2.26 (m, 2 H, CH_2), 2.31–2.47 (m, 3 H, CH_2CO and CH_2), 2.42 (s, 6 H, 2 CH_3), 2.63–2.70 (m, 1 H, CH), 2.77 (dd, J_1 = 13.3, J_2 = 9.9 Hz, 1 H, CH_2CO), 3.64–3.76 (m, 2 H, CH_2N), 3.90 (dt, J_1 = 14.9, J_2 = 5.7 Hz, 1 H, CH_2N), 4.32 (dd, J_1 = 15.4, J_2 = 7.2 Hz, 1 H, CH_2N), 6.11 (t, J = 7.3 Hz, 1 H, HC=C), 7.28 (m, 4 H, Ts), 7.84 (d, J = 8.4 Hz, 2 H, Ts), 7.88 (d, J = 8.4 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 21.7 (CH_3), 22.7 (CH_2), 28.1 (CH_2), 28.4 (CH_2), 35.0 (CH), 37.5 (CH_2), 43.6 (CH_2), 44.5 (CH_2), 45.9 (CH_2), 128.4 (CH), 128.6 (CH), 129.3 (CH), 129.5 (CH), 133.4 (CH), 136.3 (C), 136.5 (C), 141.9 (C), 144.7 (2 C), 169.8 (CO), 172.9 (CO) ppm. IR (NaCl): $\tilde{\nu}$ = 2956, 2927, 1684, 1596, 1353 cm^{-1}. MS (ESI): m/z = 553 [M + Na]$^+$. $C_{26}H_{30}N_2O_6S_2$ (530.66): calcd. C 58.85, H 5.70, N 5.28, S 12.09; found C 59.12, H 5.81, N 5.36.

1-[2-(Benzofuran-2-yl)-2-oxoethyl]-4-aza-1-azoniabicyclo[2.2.2]-octane (9): DABCO (43 mg, 0.38 mmol) was added to a solution of 1-benzofuran-2-yl-2-bromoethanone (91 mg, 0.38 mmol) in dry acetonitrile (0.20 M) under argon and the mixture was stirred at room temp. until the formation of a precipitate (1 h). The solvent was eliminated under reduced pressure to give the salt **9** without any further purification, yield 132 mg (99%) of **9** as a white solid (m.p. 238–241 °C). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.18 (t, J = 7.5 Hz, 6 H, $^+$NCH$_2$CH_2N), 3.68 (t, J = 7.1 Hz, 6 H, $^+$NCH_2CH$_2$N), 5.13 (s, 2 H, CH_2CO), 7.50 (t, J = 7.8 Hz, 1 H, Ar), 7.70 (t, J = 8.3 Hz, 1 H, Ar), 7.86 (d, J = 8.4 Hz, 1 H, CH), 7.99 (d, J = 7.8 Hz, 1 H, Ar), 8.23 (s, 1 H, Ar) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 43.3 (CH_2), 51.5 (CH_2), 62.8 (CH_2), 111.2 (CH), 115.3 (CH), 123.0 (CH), 123.4 (CH), 125.2 (CH), 128.5 (C), 149.1 (C), 154.1 (C), 179.8 (CO) ppm. IR (KBr): $\tilde{\nu}$ = 1732, 1694, 1601, 1554 cm^{-1}. MS (ESI): m/z = 271 [M]$^+$.

(2*S,3*R**)-3-[1-(Benzofuran-2-yl)vinyl]-2-(2-hydroxyethyl)-1-tosylpyrrolidin-3-ol (10):** Compound **4i** (100 mg, 0.24 mmol) was dissolved in anhydrous dichloromethane (0.9 mL) and cooled to –78 °C. A solution of 1 M DIBAL-H in toluene (1.2 mL, 1.2 mmol) was added dropwise to the reaction mixture. The solution was warmed to room temperature and stirred for 1 h. Once completed, as shown by TLC analysis, the reaction was quenched by adding a 1 M solution of NaOH (20 mL). The aqueous layer was extracted with dichloromethane (4× 15 mL) and the combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting mixture was purified by flash chromatography on silica gel (hexane/ethyl acetate, 3:1) to give compound **10** as a white solid (74 mg, 72%; m.p. 58–60 °C) along with 7 mg (7%) of **11**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99–2.12 (m, 1 H, CH_2CH$_2$N), 2.08 (t, J = 6.9 Hz, 2 H, CH_2CH$_2$OH), 2.25–2.35 (m, 1 H, CH_2CH$_2$N), 2.43 (s, 3 H, CH_3), 3.36 (dt, J_1 = 14.0, J_2 = 10.7 Hz, 1 H, CH$_2$CH_2N), 3.67 (dt, J_1 = 13.8, J_2 = 10.7 Hz, 1 H, CH$_2$CH_2N), 3.86–3.93 (m, 1 H, CH$_2$CH_2OH), 3.97–4.04 (m, 1 H, CH$_2$CH_2OH), 4.17 (dd, J_1 = 6.8, J_2 = 5.1 Hz, 1 H, CH), 5.19 (s, 1 H, H_2C=C), 5.55 (s, 1 H, H_2C=C), 6.63 (s, 1 H, Ar), 7.10 (d, J = 8.0 Hz, 2 H, Ts) 7.20–7.40 (m, 3 H, Ar), 7.50–7.55 (m, 3 H, Ar and Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 32.9 (CH_2), 36.9 (CH_2), 46.7 (CH_2), 58.2 (CH_2), 64.5 (CH), 80.6 (C), 105.4 (CH), 110.8 (CH), 115.6 (CH_2), 121.3 (CH), 123.0 (CH), 124.8 (CH), 127.5 (CH), 128.6 (C), 129.6 (CH), 134.2 (C), 139.9 (C), 143.6 (C), 153.5 (C), 154.0 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3469, 3337, 2950, 1595 cm^{-1}. MS (ESI): m/z = 428 [M + H]$^+$. $C_{23}H_{25}NO_5S$ (427.51): calcd. C 64.62, H 5.89, N 3.28, S 7.50; found C 64.48, H 5.95, N 3.07.

(2*S,3a*S**,6a*R**)- and (2*R**,3a*S**,6a*R**)-6a-[1-(Benzofuran-2-yl)-vinyl]-4-tosylhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-ol (11a and 11b):** Compound **4i** (100 mg, 0.24 mmol) was dissolved in anhydrous dichloromethane (0.9 mL) and cooled to –78 °C. A solution of 1 M DIBAL-H in toluene (0.48 mL, 0.48 mmol) was added dropwise to the reaction mixture. The reaction was warmed to –40 °C and then stirred for 1 h at this temperature. Then the reaction was quenched by adding a solution of 1 M NaOH (20 mL). The aqueous layer was extracted with dichloromethane (4× 15 mL) and the combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting mixture was purified by flash chromatography on silica gel (hexane/ethyl acetate, 3:1). A mixture of compounds **11a** and **11b** was obtained as a white syrup (78 mg, 77%) together with 10 mg (10%) of compound **10**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05–2.30 (m, 3 H, CH_2CH$_2$N and CH_2CHOH), 2.49 and 2.51 (s, 3 H, CH_3), 2.58 and 2.71 (d, J = 14.5 Hz, and ddd, J_1 = 14.3, J_2 = 5.2, J_3 = 2.1 Hz, 1 H, CH_2CHOH), 2.81 and 3.30 (d, J = 5.0 Hz, and d, J = 9.0 Hz, 1 H, OH), 3.60–4.55 (m, 2 H, CH$_2$CH_2N), 4.39 and 4.53 (d, J = 5.0 Hz, and dd, J_1 = 5.7, J_2 = 2.1 Hz, 1 H, NCH), 5.61 and 5.64 (s, 1 H, H_2C=C), 5.61 and 5.76 (m and q, J = 5.0 Hz, 1 H, CHOH), 5.90 and 5.92 (s, 1 H, H_2C=C), 6.23 and 6.37 (s, 1 H, Ar), 7.19–7.42 (m, 6 H, Ar and Ts), 7.81 and 7.79 (d, J = 8.3 Hz, and d, J = 8.3 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 (CH_3), 36.6 and 37.6 (CH_2), 39.9 and 41.2 (CH_2), 48.1 and 48.3 (CH_2), 66.7 (CH), 93.8 and 95.0 (C), 99.7 and 100.4 (CH), 104.5 and 104.8 (CH), 111.0 (CH), 116.1 (CH_2), 120.9 (CH), 122.9 and 123.0 (CH), 124.8 and 124.8 (CH), 127.5 and 127.8 (CH), 128.3 and 128.5 (C), 130.0 and 130.0 (CH), 137.6 (C), 138.7 (C), 143.8 and 144.0 (C), 153.2 (C), 154.1 (C) ppm. IR (NaCl): $\tilde{\nu}$ = 3505, 3298, 2951, 1601 cm^{-1}.

2-{(2*S,3*R**)-3-[1-(Benzofuran-2-yl)vinyl]-3-hydroxy-1-tosylpyrrolidin-2-yl}acetic Acid (12):** Compound **4i** (90 mg, 0.21 mmol) in EtOH/CH_2Cl_2 (2.4 mL, 1:1) was added to a solution of EtONa (440 mg, 6.5 mmol) in absolute EtOH (2.2 mL), generated in situ, and the mixture was heated at reflux for 4 h. Then the mixture was allowed to cool to room temperature and water (2 mL) was poured over the mixture followed by ethyl acetate. The organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography, yield 65 mg (70%; hexane/ethyl acetate, 3:1) of **12** as a yellow syrup that evolved in a few minutes to a mixture of **12** and **4i** (data taken from the mixture). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.12–2.23 (m, 2 H, CH_2CH$_2$N), 2.44 (s, 3 H, CH_3), 2.59 (dd, J_1 = 16.7, J_2 = 4.5 Hz, 1 H, CH_2CO), 2.81 (dd, J_1 = 16.7, J_2 = 6.4 Hz, 1 H, CH_2CO), 3.42–3.70 (m, 2 H, CH$_2$CH_2N), 4.27 (dd, J_1 = 6.3, J_2 = 4.5 Hz, 1 H, CH), 5.44 (s, 1 H, H_2C=C), 5.65 (s, 1 H, H_2C=C), 6.67 (s, 1 H, Ar), 7.26–7.30 (m, 5 H, Ar and Ts), 7.42 (d, J = 8.0 Hz, 1 H, Ar), 7.64 (d, J = 8.2 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 21.1 (CH_3), 35.7 (CH_2), 36.7 (CH_2), 46.7 (CH_2), 62.4 (CH), 79.7 (C), 104.9 (CH), 110.6 (CH), 116.0 (CH_2), 121.0 (CH), 122.9 (C), 124.6 (CH), 127.3 (CH), 127.7 (CH), 128.3 (C), 129.6 (CH), 134.0 (C), 139.2 (C), 143.3 (C), 153.2 (C), 172.6 (CO) ppm. IR (NaCl): $\tilde{\nu}$ = 3480, 3250, 2900, 1720, 1590 cm^{-1}.

2-{(2*S,3*R**)-3-[1-(Benzofuran-2-yl)vinyl]-3-hydroxy-1-tosylpyrrolidin-2-yl}-1-(pyrrolidin-1-yl)ethanone (13):** Et_3N (1.00 mL) and pyrrolidine (0.42 mL, 5.00 mmol) were added to a solution of **4i** (106 mg, 0.25 mmol) under argon. The resulting mixture was heated at reflux with stirring for 2 h, cooled and diluted with diethyl ether (5 mL). Then it was treated with a solution of potassium carbonate (10 mL) and the aqueous phase was extracted with two portions of diethyl ether (2× 10 mL). The organic extracts were combined, dried with anhydrous $MgSO_4$ and evaporated under reduced pressure to yield the crude product, which was purified by flash chromatography, yield 110 mg (89%; hexane/ethyl acetate, 4:1) of **13** as a brown syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87–1.90 (m, 4 H, CH_2CH$_2$N and pyrrolidine), 2.13 (t, J = 6.9 Hz, 2 H, pyrrolidine), 2.43 (s, 3 H, CH_3), 3.00 (dd, J_1 = 14.9, J_2 = 2.5 Hz, 1 H, CH_2CO), 3.14 (dd, J_1 = 14.9, J_2 = 8.4 Hz, 1 H, CH_2CO), 3.25 (dt, J_1 = 14.2, J_2 = 10.3 Hz, 1 H, CH$_2$CH_2N), 3.50 (t, J = 7.1 Hz, 2 H, pyrrolidine), 3.55–3.59 (m, 1 H, pyrrolidine), 3.63 (dt, J_1 = 13.1, J_2 = 10.3 Hz, 1 H, CH$_2$CH_2N), 3.73–3.81 (m, 1 H, pyrrolidine), 4.27 (dd, J_1 = 8.4, J_2 = 2.6 Hz, 1 H, CH), 5.01 (s, 1 H, H_2C=C), 5.58 (s, 1 H, H_2C=C), 6.79 (s, 1 H, Ar), 6.86 (s, 1 H, OH), 7.14 (d, J = 8.0 Hz, 2 H, Ts), 7.20–7.31 (m, 2 H, Ar), 7.36 (d, J = 8.2 Hz, 1 H, Ar), 7.51 (d, J = 8.2 Hz, 1 H, Ar), 7.58 (d, J = 8.2 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 24.5 (CH_2), 26.1 (CH_2), 36.8 (CH_2), 37.0 (CH_2), 46.2 (CH_2), 46.7 (CH_2), 47.7 (CH_2), 62.9 (CH), 80.9 (C), 105.5 (CH), 110.7 (CH), 115.8 (CH_2), 121.2 (CH), 122.8 (CH), 124.6 (CH), 127.4 (CH), 128.8 (C), 129.7 (CH), 134.0 (C), 139.9 (C), 143.7 (C), 153.8 (C), 154.0 (C), 170.6 (CO) ppm. IR (NaCl): $\tilde{\nu}$ = 2944, 1604 cm^{-1}. MS (ESI): m/z = 495 [M + H]$^+$. $C_{27}H_{30}N_2O_5S$ (494.60): calcd. C 65.57, H 6.11, N 5.66, S 6.48; found C 65.33, H 6.31, N 5.39.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{1}C NMR spectra of compounds (+)-**2d**, **4a**–**k**, **8**–**13**; ORTEP drawing of **4a**.

Acknowledgments

Funding of this project by the Spanish Ministerio de Educación y Ciencia (MEC) (MINECO, project number CTQ2012-31063) is acknowledged. S. A. thanks the Spanish Ministerio de Ciencia e Innovación (MCINN) for a pre-doctoral fellowship.

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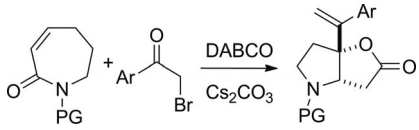
Received: January 29, 2013
Published Online: ■

Lactam Rearrangement

Unsaturated ε-lactams undergo a novel skeletal reorganization to give fused pyrrolidine-lactones by reaction with aromatic α-bromo ketones in the presence of DABCO and **a** base. The process involves the formation of an ammonium salt and subsequently a nitrogen ylide, which initiates the rearrangement reaction to produce compounds structurally related to kainates and radicamines.



Keywords: Nitrogen heterocycles / Lactones / Lactams / Ylides / Diastereoselectivity / Rearrangement

