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A General, Enantioselective Synthesis of 1-Azabicyclo[*m.n*.0]alkane Ring Systems

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Abstract

In this Letter, we describe a novel approach for the general and enantioselective synthesis of a diverse array of small to large 1-azabicyclo[*m.n*.0]alkyl ring systems with an embedded olefin handle for further functionalization. The stereochemistry is established via a highly diastereoselective indium-mediated allylation of an Ellman sulfinimine in greater than 9:1 dr., which is readily separable by column chromatography to afford a single diastereomer. This methodology allows for the rapid preparation of 1-azabicyclo[*m.n*.0]alkane ring systems that are not readily accessible through any other chemistry in excellent overall yields and, for many systems, the only enantioselective preparation reported to date.

Keywords

azabicyclo; olefin metathesis; enantioselective; allylation; alkaloid

Natural products and pharmaceutical compositions that possess azabicyclic ring systems **1–9** are very common; however, synthetic approaches to access these 1-azabicyclo[*m.n*.0]alkane systems (Fig. 1) are limited.^{1–8} In general, the existing strategies for the construction of azabicyclic ring systems rely on Staudinger-aza-Wittig approaches,⁹ 7-exo-*tet*-cyclizations,^{10,11} cycloadditions ([5+2], [4+2] and [2+2+2]),¹² ring-closing metathesis (RCM) strategies,¹³ Mitsunobu approaches¹⁴ and rearrangements (nitron and intramolecular Schmidt rearrangements)^{15,16} For the larger azabicyclic ring systems, routes are very rare, and those reported lack stereocontrol.^{8,17}

Towards the development of an enantioselective toolbox of synthetic routes to access these valuable azaheterocycles, we recently reported a novel six step approach for the rapid and enantioselective synthesis of azabicyclic systems such as **1–3** (Scheme 1).¹⁸ Here, an indium-mediated allylation of a chiral aldimine substrate **10**, *N*-alkylation to afford **11**, ring-closing metathesis (RCM) to provide **12**, and finally a one-pot deprotection/acetal hydrolysis/reductive amination sequence to afford enantiopure azabicyclic ring systems **1–**

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3.¹⁸ This methodology was then employed for the enantioselective total syntheses of (+)-grandisine D,¹⁸ cremastrine¹⁹ and amabiline.²⁰

While this was a notable advance, we also wanted to develop a streamlined route to access the higher homologs **4–9** in an enantioselective manner. De Kimpe and co-workers recently demonstrated the asymmetric synthesis of 2-arylpyrrolidines **15** from γ -chloro *N*-(*tert*-butanesulfinyl)ketimines **13**,¹¹ and Brown and co-workers employed a related strategy for the total synthesis of (–)-tashiromine **17** and (–)-epilupinine **18** (Scheme 2, eq. 1).²¹

Inspired by these results and our internal efforts, we envisioned a protocol that would subject various chloroalkyl *N*-(*tert*-butanesulfinyl)aldehydes **19** to an asymmetric allylation reaction to provide **20** in high diastereomeric ratio (dr).^{18,22,23} Deprotection and alkylation of the pyrrolidine would provide azocines **21**, substrates for a ring closing metathesis reaction²⁴ to provide general, enantioselective access to 1-azabicyclo[*m.n.0*]alkane cores **1–9** with an embedded olefin as a handle for further functionalization (Scheme 3).

The requisite chloroalkyl *N*-(*tert*-butanesulfinyl)aldehydes **19** were easily prepared in 92–94% yields by condensing the corresponding chloroaldehydes **22** with the Ellman (*S*)-*tert*-butanesulfinamide **23** employing CuSO₄ in DCM.^{25,26} A subsequent indium-mediated allylation reaction affords the anticipated (*R*)-anti-adducts **20** in >9:1 diastereoselectivity and up to 86% yield.^{18,22,23} After column chromatography, single diastereomers of analogs **20** resulted, which were carried forward. Following modification of the known protocols,^{11,21} acid-mediated deprotection and base-induced, microwave-assisted cyclization and alkylation with the required allyl, butenyl and pentenyl bromides smoothly afforded the chiral *N*-alkyl azocines **21** in 63–83% yields for the three step, one-pot reaction sequence (Scheme 4).²⁷ To enable the one-pot sequence, a number of bases, solvents and temperatures were evaluated; however, K₂CO₃, NaI in DMF under microwave irradiation (120 °C, 15 min) proved to be general for all substrates, even the larger 7-azocine rings.

With all of the chiral *N*-alkyl azocines **21** in hand, we focused on the RCM to provide the 1-azabicyclo[*m.n.0*]alkane systems **1–9**. Initial attempt following several known reaction conditions with Grubbs II^{18,20,24,28,29} failed to provide the desired unsaturated 1-azabicyclo[5.4.0]tridecane core of **7**. A perusal of the literature regarding RCM methods with tertiary amines, suggested that ‘protection’ of the amine by *in situ* generation of ammonium salts enabled facile ring-closing.^{29–31} Thus, treatment of **21c1** with 1.1 equivalent of camphor sulfonic acid (CSA) in 0.05 M toluene, followed by the addition of 10 mol% of Grubbs II and microwave heating for 1 hour at 100 °C, provided the unsaturated 1-azabicyclo[5.4.0]tridecane core of **7** in 70% isolated yield (Scheme 5).²⁷ An evaluation of additional acids led to the use of trifluoroacetic acid (TFA), which was equally effective (68% yield) and allowed for simpler purification.

With a robust protocol in hand for the RCM, all of the chiral *N*-alkyl azocines **21** were converted, under these optimal conditions, into the desired unsaturated 1-azabicyclo[5.4.0]alkane cores **22** of **1–9** (Scheme 6). Yields for the RCM reaction averaged 70% for all the substrates **21**, providing high yielding, enantioselective access to each of the key 1-azabicyclo[*m.n.0*]alkane systems **1–9** in short order (Fig. 2). Overall yields from the commercial aldehydes **22** ranged from 29 to 59%, and offer the synthetic and medicinal chemist a general route to access these important azabicyclic ring systems.

In summary, we have developed a novel approach for the general and enantioselective synthesis of a diverse array of small to large 1-azabicyclo[*m.n.0*]alkane ring systems with an embedded olefin handle for further functionalization. The stereochemistry is established via a highly diastereoselective indium-mediated allylation of an Ellman sulfinimine in greater

than 9:1 dr., which is readily separable by column chromatography to afford a single diastereomer. This methodology allows for the rapid preparation of 1-azabicyclo[*m.n*.0]alkane ring systems that are not readily accessible through any other chemistry in excellent overall yields and, for many systems, the only enantioselective preparation reported to date.

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27. Representative experimental:

(*S,E*)-*N*-(6-chlorohexylidene)-2-methylpropane-2-sulfonamide **19c**: To a solution of 6-chlorohexanal (7.37 g, 54.79 mmol) in DCM (219 ml) at ambient temperature was added CuSO₄ (20.11 g, 126.02 mmol) and (*S*)-2-methylpropane-2-sulfonamide (7.64 g, 63.01 mmol) in a single batch. The reaction was stirred for 12 h, at which point the starting material was fully consumed

by TLC analysis (4:1 Hex/EtOAc, $r_f = 0.35$). The heterogeneous mixture was filtered through a silica pad and concentrated *in vacuo* to yield a viscous oil, which was purified by flash chromatography (4:1 Hex/EtOAc) to afford the desired product as a clear oil (12.34 g, 94%). $[\alpha]_D^{20} = +157.9^\circ$ ($c = 1.5$, MeOH). ^1H NMR (400.1 MHz, CDCl_3) δ (ppm): 8.05 (t, $J = 4.5$ Hz, 1H); 3.52 (t, $J = 6.5$ Hz, 2H); 2.53 (m, 2H); 1.79 (m, 2H); 1.66 (m, 2H); 1.51 (m, 2H); 1.18 (s, 9H). ^{13}C NMR (100.6 MHz, CDCl_3) δ (ppm): 169.26, 56.64, 44.82, 35.96, 32.37, 26.56, 24.78, 22.42. HRMS (TOF, ES+) $\text{C}_{10}\text{H}_{21}\text{NOSCl}$ $[\text{M}+\text{H}]^+$ calc'd 238.1032, found 238.1034.

(*S*)-*N*-((*R*)-9-chloronon-1-en-4-yl)-2-methylpropane-2-sulfonamide **20c**: NaBr (380 g) was dissolved in 841 mL of deionized H_2O . To this fully dissolved saturated NaBr solution was added aldimine **19c** (10.00g, 42.05 mmol) and indium powder (19.31 g, 168.2 mmol). The mixture was stirred vigorously for 5 min., then allyl bromide (20.35 g, 168.2 mmol) added in a single batch. Vigorous stirring was continued for 9 h, at which point the starting material was consumed by TLC analysis (1:1 Hex/EtOAc, $r_f = 0.34$). The mixture was quenched with NaHCO_3 and extracted x5 with EtOAc. The organic fractions were combined, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo* to yield crude oil. Purification by flash chromatography (1:1 Hex/ EtOAc) afforded the desired product as a clear oil (10.10 g, 86%). $[\alpha]_D^{20} = +25.7^\circ$ ($c = 1.5$, MeOH). ^1H NMR (400.1 MHz, CDCl_3) δ (ppm): 5.77 (m, 1H); 5.15 (m, 2H); 3.52 (t, $J = 6.5$ Hz, 2H); 3.30 (sextet, $J = 6.1$ Hz, 1H); 3.21 (br d, $J = 6.1$ Hz, 1H); 2.35 (dp, $J_1 = 6.5$ Hz, $J_2 = 10.4$ Hz, 2H); 1.763 (quint., $J = 6.5$ Hz, 2H); 1.53-1.32 (m, 5H). ^{13}C NMR (100.6 MHz, CDCl_3) δ (ppm): 134.23, 119.14, 55.92, 54.83, 45.08, 40.56, 34.91, 32.60, 26.88, 24.92, 22.79. HRMS (TOF, ES+) $\text{C}_{13}\text{H}_{27}\text{NOSCl}$ $[\text{M}+\text{H}]^+$ calc'd 280.1502, found 280.1504.

(*S*)-1,2-diallylazepane **21c1**: A 4N solution of HCl / dioxanes (14.92 ml) was cooled to 0°C and slowly added to a microwave vial containing sulfinamide **20c** (2.0 g, 7.15 mmol). Solution was then brought to ambient temperature and stirred for an additional 45 min, and concentrated *in vacuo* to afford the deprotected amine as the HCl salt in quantitative yield. The amine was dissolved in DMF (35.9 mL), then K₂CO₃ (1.98 g, 14.34 mmol) and NaI (1.18 g, 7.89 mmol) were added in a single batch. The vial was sealed and submitted to microwave irradiation at 120°C for 15 min. LC/MS analysis showed full consumption of starting material to the cyclized secondary amine. Allyl bromide (0.954 g, 7.89 mmol) and an additional equivalent of K₂CO₃ (0.99 g, 7.15 mmol) was then added to the pale yellow solution at ambient temperature, and stirring was continued for 4 h. Mixture was dissolved in 5% LiCl solution and extracted with Et₂O (5 x 40 mL). Organic fractions were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to yield a pale yellow crude oil. Purification by flash chromatography (1:1 Hex/EtOAc) afforded the desired product as a clear oil (0.82g, 64%). [α]_D²⁰ = -5.0° (*c* = 0.9, MeOH). ¹H NMR (400.1 MHz, CDCl₃) δ (ppm): 5.82 (m, 2H); 5.19-4.93 (m, 4H); 3.22 (m, 2H); 2.85 (m, 1H); 2.70 (m, 2H); 2.26 (m, 1H); 2.06 (m, 1H); 1.75 (m, 1H); 1.66-1.38 (m, 7H). ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 137.98, 137.51, 115.99, 115.66, 62.45, 55.71, 49.83, 39.34, 32.65, 28.88, 27.53, 25.78. HRMS (TOF, ES+) C₁₂H₂₂N [M+H]⁺ calc'd 180.1752, found 180.1751.

(*S*)-octahydropyrido[1,2-*a*]azepine **unsat-7**: To a solution of diene **21c1** (106 mg, 0.59 mmol) in toluene (11.8 mL) was added trifluoroacetic acid (71 mg, 0.62 mmol), and Grubbs 2nd generation catalyst (49 mg, 0.06 mmol). Solution was submitted to microwave irradiation for 1 h at 100°C. The toluene was removed *in vacuo*, and the crude residue purified to afford the desired product as the TFA salt (105 mg, 68%). [α]_D²⁰ = +45.2° (*c* = 1.25, MeOH). ¹H NMR (400.1 MHz, CDCl₃) δ (ppm): 5.88 (m, 1H); 5.64 (m, 1H); 3.94 (m, 1H); 3.57 (m, 2H); 3.18-3.04 (m, 2H); 2.73 (t, 1H);

2.25 (m, 1H); 2.24-1.92 (m, 3H); 1.89-1.72 (m, 3H); 1.58 (m, 2H). ^{13}C NMR (100.6 MHz, CDCl_3) δ (ppm): 126.83, 120.24, 63.64, 55.70, 54.32, 31.93, 30.59, 27.21, 26.00, 21.96. HRMS (TOF, ES+) $\text{C}_{10}\text{H}_{18}\text{N}$ $[\text{M}+\text{H}]^+$ calc'd 152.1439, found 152.1440.

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1, $m = 1$, 1-azabicyclo[4.3.0]nonane
(indolizine)

2, $m = 2$, 1-azabicyclo[5.3.0]decane
(octahydro-1*H*-pyrrolo[1,2-*a*]azepine)

3, $m = 3$, 1-azabicyclo[6.3.0]undecane
(decahydropyrrolo[1,2-*a*]azocine)

4, $m = 1$, 1-azabicyclo[4.4.0]dodecane
(quinolizidine)

5, $m = 2$, 1-azabicyclo[5.4.0]tridecane
(decahydropyrido[1,2-*a*]azepine)

6, $m = 3$, 1-azabicyclo[6.4.0]tetradecane
(decahydro-1*H*-pyrido[1,2-*a*]azocine)

7, $m = 1$, 1-azabicyclo[5.4.0]tridecane
(decahydropyrido[1,2-*a*]azepine)

8, $m = 2$, 1-azabicyclo[5.5.0]tetradecane
(decahydro-1*H*-azepino[1,2-*a*]azepine)

9, $m = 3$, 1-azabicyclo[6.5.0]pentadecane
(dodecahydroazepino[1,2-*a*]azocine)

Figure 1.

Representative 1-azabicyclo[*m.n.0*]alkane ring systems, including their alternative IUPAC nomenclature, of interest in both natural product synthesis and drug discovery.

Figure 2. Mono-unsaturated 1-azabicyclo[*m.n.0*]alkane ring systems **22** synthesized that encompass all of the key azabicyclic ring systems **1–9**. Yields are overall from commercial aldehydes **22**, and ranged from 29–59%.

Scheme 1.

First generation rapid, enantioselective synthesis of azabicyclic ring systems **1–3**.

Scheme 2.

Application of γ -chloro *N*-(*tert*-butesulfinyl)ketimines to access pyrroles and azabicyclic systems in high enantioselectivity.

Scheme 3.

Envisioned route to employ chloroalkyl *N*-(*tert*-butanesulfinyl)aldehydes, an asymmetric allylation and a subsequent RCM to access diverse 1-azabicyclo[*m.n.0*]alkane cores in high enantioselectivity.

Scheme 4. Enantioselective synthesis of *N*-alkyl azocines **24**.

Scheme 5.RCM approaches to access the 1-azabicyclo[*m.n.0*]alkane cores.

Scheme 6.

Optimal RCM conditions for the enantioselective synthesis of the unsaturated 1-azabicyclo[*m.n.0*]alkane cores **22** of **1-9**.