Tetrahedron Letters 54 (2013) 1645–1648

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A general, enantioselective synthesis of 1-azabicyclo[*m.n.*0]alkane ring systems

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ARTICLE INFO

Article history:
Received 19 December 2012
Revised 2 January 2013
Accepted 4 January 2013
Available online 24 January 2013

Keywords:
Azabicycle
Olefin metathesis
Enantioselective
Allylation
Alkaloid

ABSTRACT

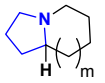
In this Letter, we describe a novel approach for the general and enantioselective synthesis of a diverse array of small to large 1-azabicyclo[*m.n.*0]alkyl ring systems with an embedded olefin handle for further functionalization. The stereochemistry is established via a highly diastereoselective indium-mediated 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.

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 approaches,[14] and rearrangements (nitrone and intramolecular Schmidt rearrangements)[15,16] For the larger azabicyclic ring systems, routes are very rare, and those reported lack stereocontrol.[8,17]

Toward 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 afforded enantiopure azabicyclic ring systems **1–3**.[18] This methodology was then employed for the enantioselective total syntheses of (+)-grandisine D,[18] cremastrine,[19] and amabiline.[20]

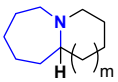
While this was a notable advance, we also wanted to develop a streamlined route to access the higher homologs **4**–**9** in an enantioselective manner. De Kimpe and co-workers recently demonstrated the asymmetric synthesis of 2-arylpyrrolidines **15** from γ-chloro *N*-(*tert*-butanesulfinyl)ketimines **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



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.

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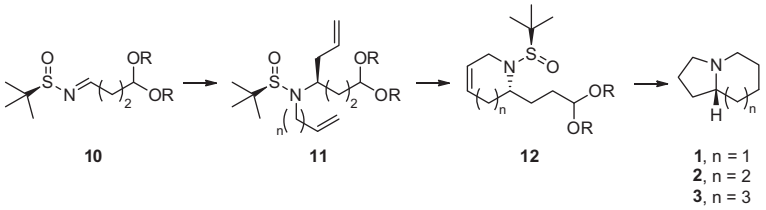
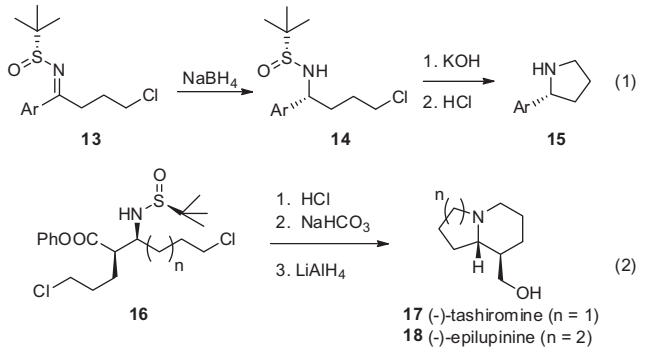
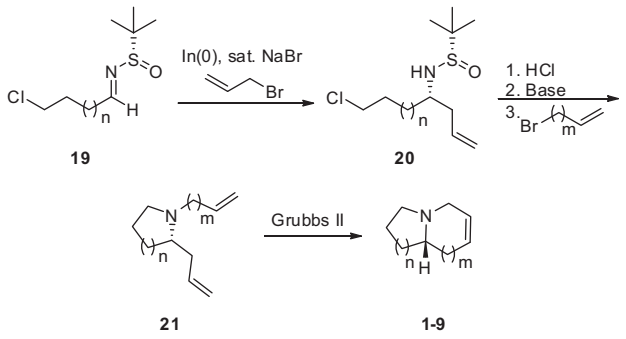
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.01.041



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



Scheme 2. Application of γ-chloro *N*-(*tert*-butanesulfinyl)ketimines to access pyrroles and azabicyclic systems in high enantioselectivity.

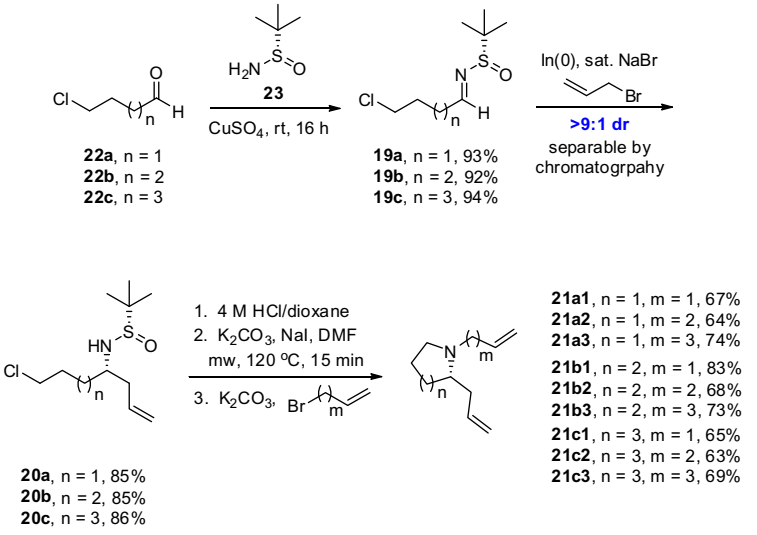


Scheme 3. Envisioned route to employ chloroalkyl *N*-(*tert*-butanesulfinyl)aldehydes, an asymmetric allylation and a subsequent RCM to access diverse 1-azabicyclo[*m.n.*0]alkane cores in high enantioselectivity.

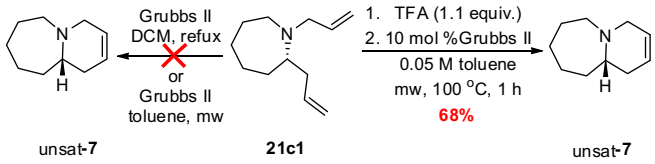
for a ring closing metathesis reaction[24] to provide general, enantioselective access to 1-azabicyclo[*m.n.*0]alkane cores **1–9** with an embedded olefin as a handle for further functionalization (Scheme 3).

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 $CuSO_4$ 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 diasteromers 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, K_2CO_3 and NaI in DMF under microwave irradiation (120 °C, 15 min) proved to be general for all substrates, even the larger 7-azocine rings.

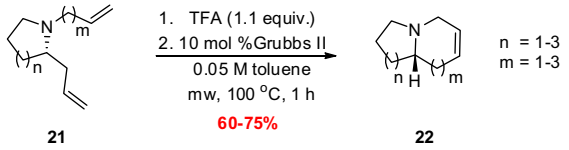
With all of the chiral *N*-alkyl azocines **21** in hand, we focused on the RCM to provide the 1-azabicyclo[*m.n.*0]alkane systems **1**–**9**. Initial attempt following several known reaction conditions with Grubbs II[18,20,24,28,29] failed to provide the desired unsaturated 1-azabicyclo[5.4.0]tridecane 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



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**.

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

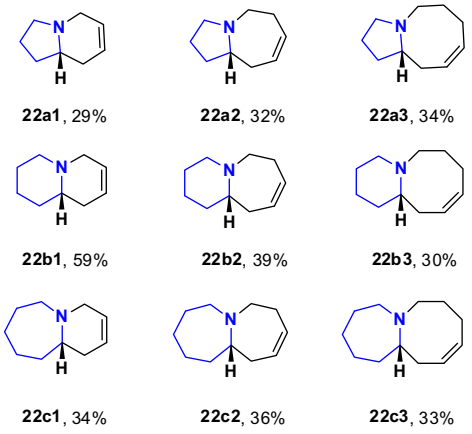


Figure 2. Mono-unsaturated 1-azabicyclo[*m.n.*0]alkane ring systems **22** synthesized that encompass all of the key azabicyclic ring systems **1–9**. Yields are overall from commercial aldehydes **22**, and ranged from 29–59%.

and, for many systems, the only enantioselective preparation reported to date.

Acknowledgments

The authors gratefully acknowledge funding from the Department of Pharmacology, Vanderbilt University Medical Center and the Warren Family & Foundation for funding the William K. Warren, Jr. Chair in Medicine. Vanderbilt houses the Vanderbilt Specialized Chemistry Center of the MLPCN and we acknowledge MLPCN support (U54MH084659).

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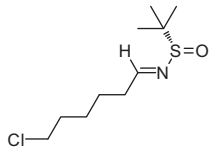
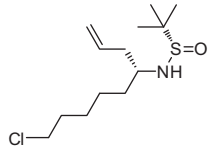
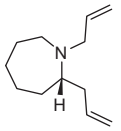
27. *Representative experimental*:



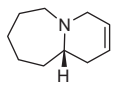
(S,E)-N-(6-Chlorohexylidene)-2-methylpropane-2-sulfinamide **19c**: To a solution of 6-chlorohexanal (7.37 g, 54.79 mmol) in DCM (219 ml) at ambient temperature was added $CuSO_4$ (20.11 g, 126.02 mmol) and (*S*)-2-methylpropane-2-sulfinamide (7.64 g, 63.01 mmol) in a single batch. The reaction was stirred 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° (*c* 1.5, MeOH). ^{1}H 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+) $C_{10}H_{21}NOSCl$ $[M+H]^+$ calcd 238.1032, found 238.1034.



(S)-N-((R)-9-Chloronon-1-en-4-yl)-2-methylpropane-2-sulfinamide **20c**: NaBr (380 g) was dissolved in 841 mL of deionized H_2O. To this fully dissolved saturated NaBr solution was added aldimine **19c** (10.00 g, 42.05 mmol) and indium powder (19.31 g, 168.2 mmol). The mixture was stirred vigorously for 5 min., then allyl bromide was (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 ×5 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° (*c* 1.5, MeOH). ^{1}H 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+) $C_{13}H_{27}NOSCl$ $[M+H]^+$ calcd 280.1502, found 280.1504.



(S)-1,2-diallylazepane ***21c1***: A 4 N 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 K_2CO_3 (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 K_2CO_3 (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 Et_2O (5 × 40 mL). Organic fractions were combined, washed with brine, dried over Na_2SO_4, 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 (0.82 g, 64%). $[\alpha]_D^{20}$ −5.0° (*c* 0.9, MeOH). ^{1}H NMR (400.1 MHz, $CDCl_3$) 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). ^{13}C NMR (100.6 MHz, $CDCl_3$) 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+) $C_{12}H_{22}N$ $[M+H]^+$ calcd 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%). $[\alpha]_D^{20}$ +45.2° (*c* 1.25, MeOH). ^{1}H NMR (400.1 MHz, $CDCl_3$) 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+) $C_{10}H_{18}N$ $[M+H]^+$ calcd 152.1439, found 152.1440.

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