

A Versatile Enantioselective Synthesis of Azabicyclic Ring Systems: A Concise Total Synthesis of (+)-Grandisine D and Unnatural Analogues

Olugbeminiyi O. Fadeyi,^[b] Timothy J. Senter,^[b] Kristopher N. Hahn,^[b] and Craig W. Lindsley*^[a]

Azabicyclic ring skeletons are common structural subunits present in numerous alkaloid natural products and serve as important scaffolds in biologically active and pharmaceutically significant compounds.^[1] Of particular interest in our laboratory (Figure 1), are the indolizidine **1**, pyrrolo[1,2-*a*]

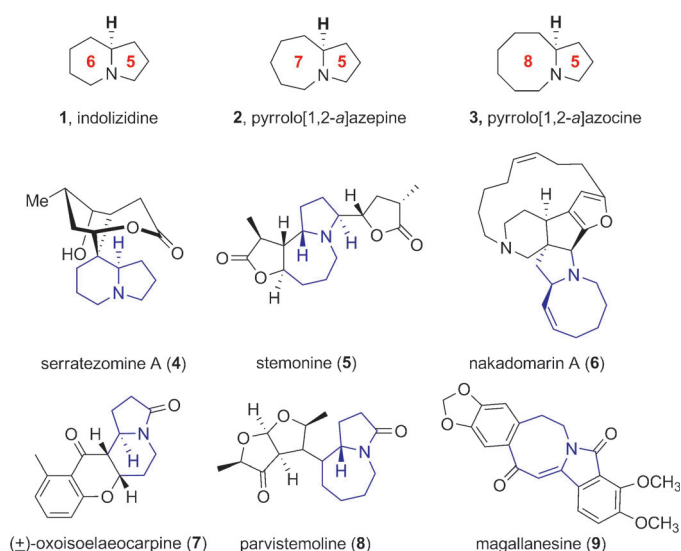


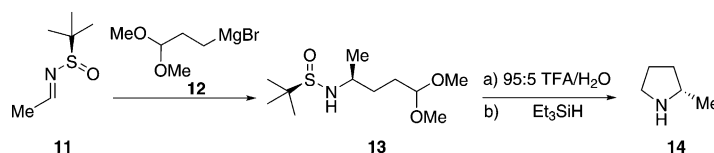
Figure 1. Structures of indolizidine **1**, pyrrolo[1,2-*a*]azepine **2**, and pyrrolo[1,2-*a*]azocine **3** alkaloid cores and natural products **4–9** that possess these azabicyclic ring systems.^[1–7]

a]azepine **2**, and pyrrolo[1,2-*a*]azocine **3** azabicyclic systems,^[1] which are found in a number of natural products such as the indolizidine alkaloid, serratezomine (**4**),^[2] the

stemona alkaloid, stemonine (**5**),^[3] and the manzamine alkaloid, nakadomarin A (**6**),^[4] to highlight but a few representative examples. Other related natural products contain the corresponding lactam moiety, such as **7–9**.^[5–7] More recently, these azabicyclic cores are key pharmacophores of high-throughput screening (HTS) hits from our MLPCN probe discovery efforts,^[8] requiring robust methodology to rapidly access the parent azabicyclic ring systems as well as flexibility to incorporate structural diversity for analogue synthesis.^[9]

Many synthetic strategies have been developed for the construction of azabicyclic ring systems,^[10] such as **1** and **2**, including Staudinger-aza-Wittig approaches,^[11] 7-*exo-tet*-cyclizations,^[12] [4+2] and [2+2+2] cycloadditions,^[13] ring-closing metathesis (RCM) strategies,^[14] nitron rearrangements^[15] and intramolecular Schmidt rearrangements.^[16] General approaches for the synthesis of the pyrrolo[1,2-*a*]azocine **3** system are rare and most lack stereocontrol.^[10,17] The majority of these were developed in the context of natural product target-oriented synthesis, and our laboratory required a general synthetic strategy to access **1–3** with considerable flexibility for both the synthesis of unnatural analogues and the ease of scale-up. Here, we detail our contributions to this dynamic field with the development of a rapid, general protocol for the enantioselective construction of azabicyclic ring systems **1–3** and the application of this new methodology to a concise total synthesis of (+)-grandisine D, the formal total synthesis of (+)-grandisine B, and unnatural analogues.

Our work was inspired by the chiral sulfinamide work of Ellman and co-workers for the synthesis of chiral 2-substituted pyrrolidines (Scheme 1).^[18] Addition of a Grignard re-



Scheme 1. Ellman's approach to the synthesis of chiral 2-substituted pyrrolidines. a) 95:5 TFA/H₂O, 10 min, then Et₃SiH.

agent **12** (with a latent aldehyde moiety) to a chiral aldimine **11** provides **13** in high yield and excellent diastereoselectivity. A one-pot deprotection/acetal hydrolysis facilitates an

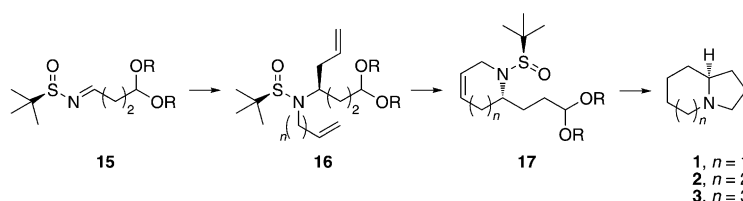
[a] Prof. C. W. Lindsley
Departments of Pharmacology & Chemistry
Vanderbilt Center for Neuroscience Drug Discovery
12415D MRBIV, Vanderbilt University Medical Center
Nashville, TN 37232 (USA)
Fax: (+) 615-345-6532
E-mail: craig.lindsley@vanderbilt.edu

[b] Dr. O. O. Fadeyi, T. J. Senter, K. N. Hahn
Department of Chemistry
Vanderbilt University
Nashville, TN 37232-6600 (USA)

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.201200629>.

intramolecular reductive amination reaction to produce chiral pyrrolidine **14** in high enantiomeric excess.^[18] In our hands,^[19] the addition of organometallic reagents such as **12** to aldimines **11** always proceed with high diastereoselectivity, but the relative stereochemistry can be substrate-dependent based on the ability of the dioxolane oxygens atoms to coordinate the metal, thus the addition may proceed through either a metal-chelated or non-metal-chelated transition state.^[20,21]

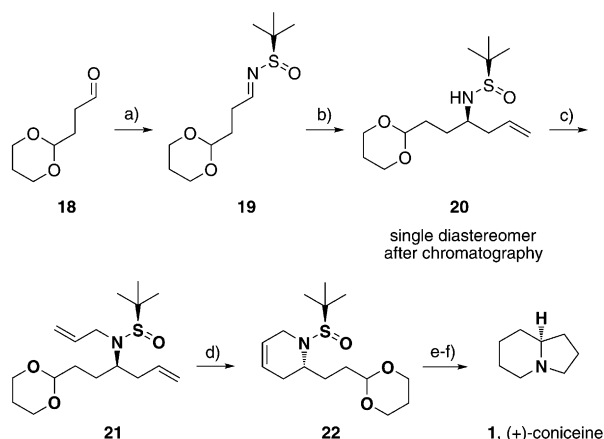
Based on the work of Ellman^[18,20] and our experience,^[19] we envisioned a protocol involving either diastereoselective Grignard or indium-mediated allylation of a chiral aldimine substrate **15**,^[18–21] N-alkylation to afford **16**, ring-closing metathesis (RCM) to provide **17**, and finally a one-pot deprotection/acetal hydrolysis/reductive amination sequence to afford enantiopure azabicyclic ring systems **1–3** (Scheme 2).



Scheme 2. Envisioned approach for the rapid, enantioselective synthesis of azabicyclic ring systems **1–3**.

In this sequence, the stoichiometric chiral auxiliary also serves as a protecting group throughout the synthesis.

We began by applying the strategy outlined in Scheme 2 to the synthesis of the indolizidine core **1** (Scheme 3). The commercially available aldehyde **18** was converted into the corresponding (*R*)-*N*-sulfinyl aldimine **19** under standard conditions^[18–20] in 91 % yield, followed by an indium-mediated allylation reaction that afforded **20** with greater than 15:1

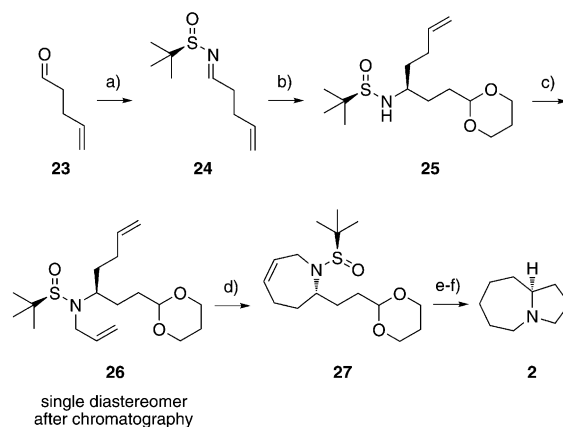


Scheme 3. Synthesis of (+)-coniceine (**1**), representing the basic indolizidine core. a) (*R*)-*tert*-butyl sulfinamide, CuSO₄, CH₂Cl₂, 91 %; b) In⁰, allyl bromide, satd aq. NaBr, RT, 16 h, 87 % (>19:1 d.r.); c) LiHMDS, allyl bromide, DMF, –20 °C to RT, 80 %; d) Grubbs II (5 mol %), CH₂Cl₂, 40 °C, 1 h, 84 %; e) H₂, Pd/C; f) 1. TFA/H₂O (95:5), RT, 45 min; 2. PS-BH(OAc)₃, 81 % for two steps. PS-BH(OAc)₃=polymer-supported triacetoxyborohydride; LiHMDS=lithium bis(trimethylsilyl)amide.

diastereoselectivity and in 87 % yield.^[19,21] After column chromatography, a single diastereomer of **20** resulted, which was carried forward. Alkylation of the sulfinamide with allyl bromide provided **21**, which smoothly underwent an RCM reaction with Grubbs II^[22] to deliver **22** in good yield.^[19] Hydrogenation to reduce the alkene, followed by a one-pot deprotection/acetal hydrolysis/reductive amination sequence produced the indolizidine alkaloid (+)-coniceine **1** with an enantiomeric excess (*ee*) of more than 98 %. This approach for the synthesis of (+)-coniceine,^[23] the simplest alkaloid possessing the azabicyclic core **1**, required only six steps and proceeded in 43 % overall yield.

Application of this approach for the enantioselective synthesis of the pyrrolo[1,2-*a*]azepine **2** proved more challenging. In this instance, we were unable to alkylate **20** with a number of butenyl substrates (Cl, Br, I, OMs, OTS, and

Otf) in reasonable yield to allow for the RCM to form the seven-membered ring. Therefore, we altered the approach (Scheme 4). For the azabicyclic core **2**, commercially available aldehyde **23** was converted into the corresponding (*R*)-*N*-sulfinyl aldimine **24** under Ti(OEt)₄-mediated conditions in

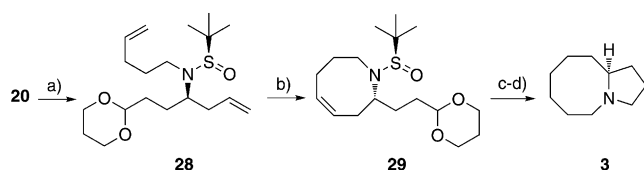


Scheme 4. Synthesis of the pyrrolo[1,2-*a*]azepine core **2**. a) (*R*)-*tert*-butyl sulfinamide, Ti(OEt)₄, CH₂Cl₂, 95 %; b) (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide, THF, –45 °C, 88 % (>9:1 d.r.); c) LiHMDS, allyl bromide, DMF, –20 °C to RT, 80 %; d) Grubbs II (5 mol %), CH₂Cl₂, 40 °C, 1 h, 78 %; e) H₂, Pd/C; f) 1. TFA/H₂O (95:5), RT, 5 min; 2. PS-BH(OAc)₃, 86 % for two steps.

95 % yield.^[18–21] Following the Ellman protocol, addition of Grignard reagent to **24** afforded the desired adduct **25** in 88 % yield and with a diastereomer ratio (d.r.) of more than 9:1.^[18–21] Alkylation of sulfinamide **25** with allyl bromide provided **26** as a single diastereomer after column chromatography in 80 % yield (Scheme 4). Once again, an RCM reaction with Grubbs II^[22] delivered the seven-membered ring **27** in 78 % yield. Hydrogenation to reduce the alkene, fol-

lowed by a one-pot deprotection/acetal hydrolysis/reductive amination sequence produced pyrrolo[1,2-*a*]azepine **2** in 86% yield for the two steps and with >98% *ee*. This variation of the approach outlined in Scheme 1 for the synthesis of **2** once again required only six steps and proceeded in 45% overall yield (Scheme 4).

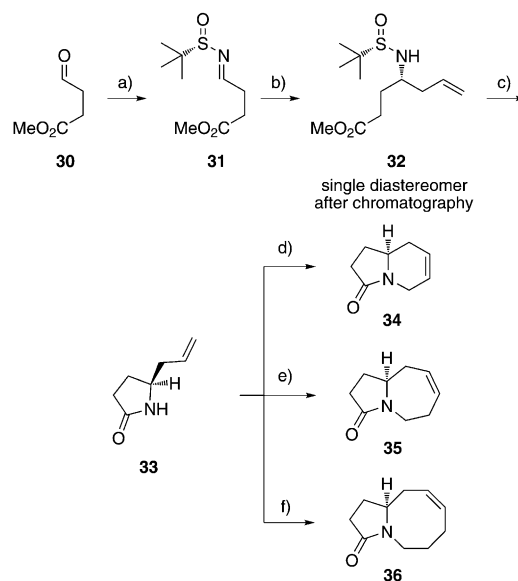
For the more rarely described pyrrolo[1,2-*a*]azocine azabicyclic system **3**, the protocol employed for the synthesis of the indolizidine core **1** (Scheme 3) proceeded smoothly. In this case, alkylation of sulfinamide **20** with 5-bromo-1-pentene provided **28**, that smoothly underwent an RCM reaction with Grubbs II^[22] to deliver **29** in 70% yield for the two steps (Scheme 5). Hydrogenation to reduce the alkene, fol-



Scheme 5. Synthesis of the pyrrolo[1,2-*a*]azocine core **3**. a) LiHMDS, 5-bromo-1-pentene, DMF, -20°C to RT, 85%; b) Grubbs II (5 mol %), CH_2Cl_2 , 40°C , 1 h, 82%; c) H_2 , Pd/C; d) 1. TFA/ H_2O (95:5), RT, 45 min; 2. PS-BH(OAc)₃, 87% for two steps.

lowed by a one-pot deprotection/acetal hydrolysis/reductive amination sequence produced pyrrolo[1,2-*a*]azocine **3** in 87% yield for the two steps and with more than 98% *ee*. Thus, from advanced intermediate **20**, azabicyclic core **3** could be accessed in four steps and in 60% overall yield (Scheme 5). Thus, this new methodology provided rapid, high yielding access to enantiopure azabicyclic rings systems **1–3** from commercial reagents, and either enantiomer of **1–3** can be prepared by the use of either the (*R*)- or (*S*)-*tert*-butyl sulfinamine.

Because many natural products, represented by **7–9**, possess the azabicyclic cores **1–3** with a γ -lactam moiety,^[5–7] we next applied our methodology to this molecular architecture. Starting from commercial aldehyde **30**, a highly convergent approach to the lactam congeners of **1–3** was developed (Scheme 6), in which **30** was first converted into the corresponding (*S*)-*N*-sulfinyl aldimine **31** under standard conditions in 90% yield.^[18–21] An indium-mediated allylation reaction afforded **32** in 88% yield with more than 10:1 diastereoselectivity, and, after column chromatography, a single diastereomer.^[19,21] A standard deprotection liberated the primary amine, which in the presence of sodium carbonate induced cyclization to form key linchpin intermediate (*S*)-5-allylpyrrolidin-2-one **33** in 97% yield. Allylation of lactam **33** and subsequent RCM with Grubbs II^[22] provided indolizidinone **34** in 87% yield for the two steps. Similarly, alkylation of **33** with either butenyl bromide or pentenyl bromide, followed by an RCM reaction with Grubbs II,^[22] afforded azepinone **35** or azocinone **36**, respectively. Thus, azabicyclic lactams **34–36** can be prepared in five steps from commercial aldehyde **30**, through linchpin **33**, in overall yields rang-



Scheme 6. Synthesis of azabicyclic lactams **34–36**. a) (*S*)-*tert*-butyl sulfinamide, CuSO_4 , CH_2Cl_2 , 90%; b) In^0 , allyl bromide, satd aq. NaBr, RT, 16 h, 88% (>10:1 d.r.); c) 1. HCl, MeOH, RT; 2. Na_2CO_3 , CH_2Cl_2 , 97%; d) 1. LiHMDS, allyl bromide, DMF, -20°C to RT; 2. Grubbs II (5 mol %), CH_2Cl_2 , 40°C , 1 h, 87% for two steps; e) 1. LiHMDS, butenyl bromide, DMF, -20°C to RT; 2. Grubbs II (5 mol %), CH_2Cl_2 , 40°C , 1 h, 86% for two steps; f) 1. LiHMDS, pentenyl bromide, DMF, -20°C to RT; 2. Grubbs II (5 mol %), CH_2Cl_2 , 40°C , 1 h, 73% for two steps.

ing from 56–69% (Scheme 6). Importantly, the alkene can either be reduced or used as a handle to install additional functionality and chemical diversity.

Efforts now focused on the application of this methodology towards targeted natural product total synthesis, with the focus of determining if our streamlined approach for the synthesis of azabicyclic ring systems would offer a tactical advantage. After a perusal of the literature, we were attracted to grandisines A–G (**37–46**), indolizidine alkaloids isolated by Carroll and co-workers from the leaves of the Australian rain-forest tree *Elaeocarpus grandis* (Figure 2).^[24] These alkaloids display selective human δ -opioid receptor affinity. Selective activation of the δ -opioid receptor is an attractive strategy for the development of new analgesics, thus grandi-

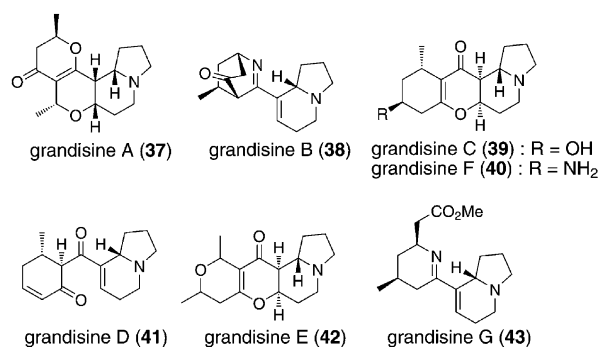
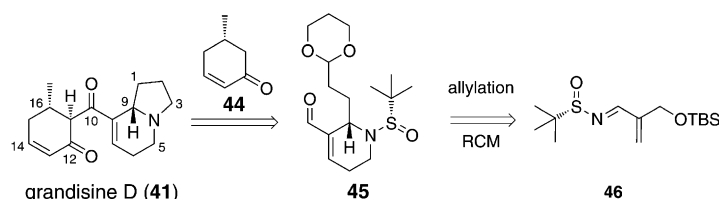


Figure 2. Structures of the indolizidine alkaloids, the grandisines A–G (**37–43**).

sines are potential potent analgesic agents.^[25] To highlight our new methodology, we elected to synthesize grandisine D (**41**). Grandisine D (**41**) was previously synthesized by Tamura and co-workers in 18 steps (12.5% overall yield) employing a Brønsted acid-mediated Morita–Baylis–Hillman ring-closure reaction as the key step; however, two steps suffered from poor stereocontrol.^[26] Tamura was also able to convert **41** into grandisine B (**38**) through a tandem imination/amination reaction sequence.^[26] Two years later, Taylor and co-workers improved on the synthesis of **41**, requiring only 13 steps (10% overall yield) from commercial starting materials, and featuring a new alkyne–acetal cyclization reaction.^[27]

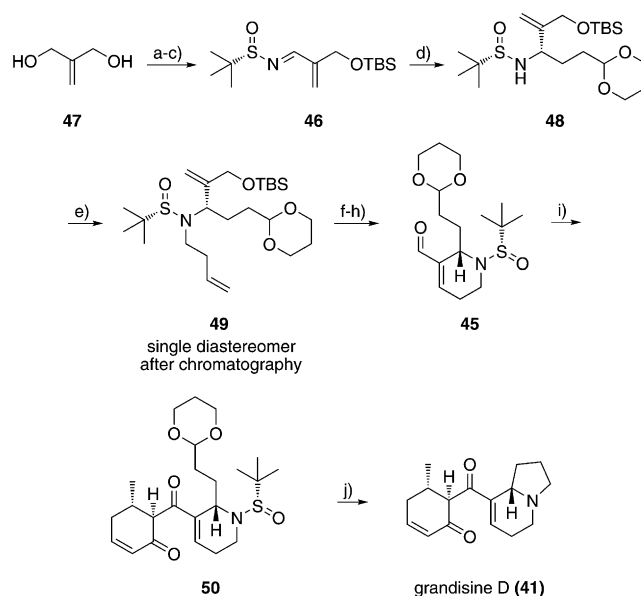
Our retrosynthesis led to the same key aldol chemistry as that employed by Tamura and Taylor,^[26,27] but a fundamentally new approach to the indolizidine core (Scheme 7).^[28]



Scheme 7. Retrosynthesis of grandisine D (**41**).

Thus, **41** would be accessed by an aldol reaction between 8-formylindolizidine **45** and known (*S*)-5-methylcyclohexanone **44**.^[29] 8-Formylindolizidine **45** would be prepared from Grignard addition and RCM of (*S*)-sulfanyl aldimine **46**.

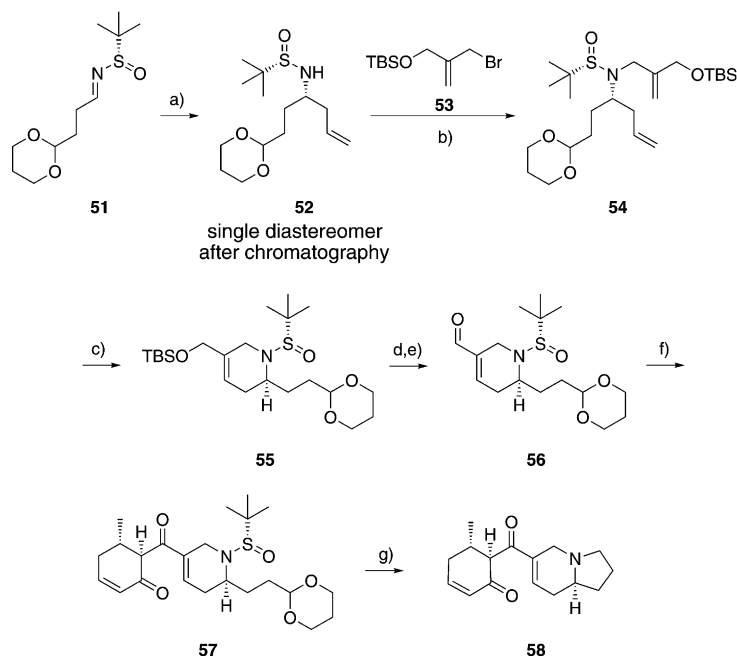
Our synthetic study began with the synthesis of (*S*)-sulfanyl aldimine **46** (Scheme 8). Starting from commercial diol **47**, a mono-silylation and oxidation sequence, followed by conversion into the corresponding (*S*)-*N*-sulfanyl aldimine **46** under $\text{Ti}(\text{OEt})_4$ -mediated conditions proceeded in 74% yield for the three steps.^[18–21] Following the Ellman protocol, addition of Grignard reagent to **46** afforded the desired adduct **48** in 79% yield with >10:1 d.r.^[18–21] Alkylation of sulfonamide **48** with butenyl triflate provided **49** as a single diastereomer after column chromatography in 87% yield (Scheme 8). Again, an RCM reaction with Grubbs II^[22] delivered the piperidine ring in 96% yield, followed by removal of the TBS group and oxidation to key aldehyde **45** in 93% yield for the two steps. Next, an Evan's aldol employing boron-enolate methodology^[30] with **45** and enone **44**,^[29] followed by oxidation provided **50** in 77% yield (Scheme 8). Finally, application of the one-pot deprotection/acetal hydrolysis/reductive amination sequence produced **41** in 47% yield. Our synthetic **41** was in complete agreement with the reported spectral and rotation data for the natural product^[24] as well as the previous synthetic efforts.^[26,27] Thus, the total synthesis of grandisine D (**41**), employing our azabicyclic methodology, required only 11 steps from commercial starting materials in 16.4% overall yield and with excellent stereocontrol throughout. Notably, based on the work of both Tamura^[26] and Taylor,^[27] the total synthesis of



Scheme 8. Synthesis of (+)-grandisine D (**41**). a) TBSCl, imidazole, CH_2Cl_2 , 95%; b) MnO_2 , CH_2Cl_2 , 90%; c) (*S*)-*tert*-butyl sulfonamide, $\text{Ti}(\text{OEt})_4$, CH_2Cl_2 , 87%; d) (2-(1,3-dioxan-2-yl)ethyl)magnesium bromide, THF, -78 to -45°C , 79% (>10:1 d.r.); e) LiHMDS , 3-butenyl triflate, HMPA/THF, -78°C , 87%; f) Grubbs II (5 mol%), CH_2Cl_2 , 40°C , 1 h, 96%; g) TBAF, THF, 0°C , 93%; h) MnO_2 , CH_2Cl_2 , 100%; i) 1. **44**, $n\text{Bu}_2\text{BOTf}$, $i\text{PrNEt}_2$, CH_2Cl_2 , -78°C to RT, 2. TFAA, DMSO, CH_2Cl_2 , -78°C , 77%; j) 1. TFA/ H_2O (95:5), RT, 45 min; 2. PS-BH(OAc)₃, DCE, 47%. HMPA = hexamethylphosphoramide; TFAA = trifluoroacetic anhydride, TBAF = tetrabutylammoniumfluoride.

(+)-grandisine (**41**) also constitutes a formal total synthesis of (–)-grandisine B (**38**).

To further highlight the power of this methodology for diversity-oriented synthesis, we applied it towards the synthesis of an unnatural analogue of **41**, in which the nitrogen atom was moved from 4-position to the 9-position, resulting in a fundamentally new molecular architecture. Starting with (*S*)-*N*-sulfanyl aldimine **51** (the (*S*)-enantiomer of **19**), an indium-mediated allylation reaction afforded **52** (the (*S,S*) enantiomer of (*R,R*)-**20**) in 87% yield with greater than 19:1 diastereoselectivity, and, after column chromatography, a single diastereomer (Scheme 9).^[18–21] Diol **47** was mono-protected as a TBS ether and the remaining hydroxyl was converted into the corresponding allylic bromide **53** in 85% yield for the two steps. Allylation of **52** with **53** provided **54** in 90% yield, followed by an RCM reaction with Grubbs II^[22] afforded **54** in 81% yield for the two steps. Deprotection of the TBS ether and oxidation delivered key aldehyde **56**, in 95% yield for the two steps. Once again, an Evan's aldol^[30] employing boron-enolate methodology with **56** and enone **44**,^[29] followed by oxidation provided **57** in 67% yield. Finally, application of the one-pot deprotection/acetal hydrolysis/reductive amination sequence produced the unnatural analogue of (+)-grandisine D **58** in 49% yield. The synthesis of **58** proceeded in 11 steps (the longest linear sequence was 9 steps) from commercial materials in 17.8% overall yield (Scheme 9).



Scheme 9. Synthesis of unnatural analogue (**58**). a) In^0 , allyl bromide, satd aq. NaBr, RT, 16 h, 87% (>19:1 d.r.); b) LiHMDS, **53**, DMF, -20°C to RT, 90%; c) Grubbs II (5 mol %), CH_2Cl_2 , 40°C , 1 h, 90%; d) TBAF, THF, 0°C , 95%; e) MnO_2 , CH_2Cl_2 , 100%; f) 1. **44**, $n\text{Bu}_3\text{BOTf}$, $i\text{PrNEt}_2$, CH_2Cl_2 , -78°C to RT; 2. TFAA, DMSO, CH_2Cl_2 , -78°C , 67%; g) 1. TFA/ H_2O (95:5), RT, 45 min; 2. PS-BH(OAc) $_3$, DCE, 49%.

In summary, we have developed a novel six step approach for the rapid and enantioselective synthesis of indolizidine **1**, pyrrolo[1,2-*a*]azepine **2**, and pyrrolo[1,2-*a*]azocine **3** azabicyclic systems and their respective lactam congeners **34–36**, that are found in a host of natural products as well as pharmaceutical preparations. The methodology described herein allows the preparation of either enantiomer, based on the stereochemistry of the *tert*-butyl sulfinamide employed and the nature of the transition state of the organometallic used in the initial allylation. To highlight this technology in natural product total synthesis, (+)-grandisine D (**41**) was prepared in 11 synthetic steps and in 16.4% overall yield, a notable advance over the two previous syntheses, and also constitutes a formal total synthesis of (–)-grandisine B (**38**). This methodology also lent itself to the rapid synthesis of an unnatural analogue **58**, expanding the utility of the methodology for diversity-oriented synthesis. Further refinements, applications to the related pyrrolizidine alkaloids and biological investigations are in progress and will be reported in due course.

Acknowledgements

The authors acknowledge the Vanderbilt Department of Pharmacology, VUMC and the NIH for funding our research, and in particular the MLPCN (U54MH084659) for the Vanderbilt Specialized Chemistry Center.

Keywords: alkaloids • enantioselectivity • grandisine D • lactams • synthetic methods • total synthesis

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Received: February 24, 2012
Published online: March 30, 2012