Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

# Synthesis of bridged bicyclic amino alcohols as compact modules for medicinal chemistry

Guolong Wu, Di Wang, Wei Zhu, Hong Shen, Haixia Liu & Lei Fu

**To cite this article:** Guolong Wu, Di Wang, Wei Zhu, Hong Shen, Haixia Liu & Lei Fu (2018): Synthesis of bridged bicyclic amino alcohols as compact modules for medicinal chemistry, Synthetic Communications, DOI: 10.1080/00397911.2018.1528615

**To link to this article:** https://doi.org/10.1080/00397911.2018.1528615

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2018.1528615



# Synthesis of bridged bicyclic amino alcohols as compact modules for medicinal chemistry

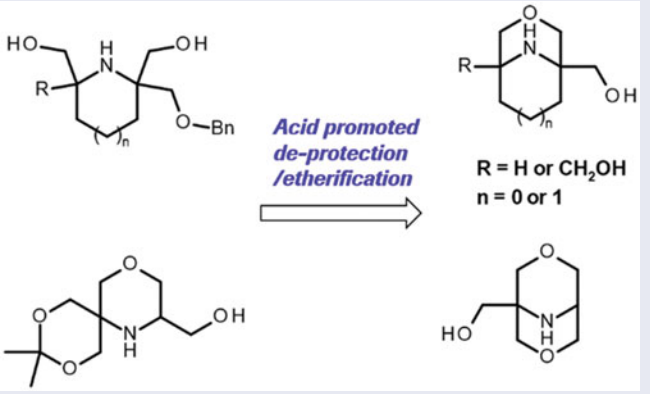
Guolong Wu[a,b], Di Wang[a], Wei Zhu[b], Hong Shen[b], Haixia Liu[b], and Lei Fu[a]

[a]School of Pharmacy, Shanghai Jiao Tong University, Shanghai, P. R. China; [b]Department of Medicinal Chemistry, Roche Innovation Center Shanghai, Roche Pharmaceutical Research & Early Development, Pudong, Shanghai, P. R. China

**ABSTRACT**

The efficient synthetic routes of three bridged bicyclic amino alcohols were reported. It is conceivable that these compounds could be readily used as compact modules in medicinal chemistry to fine-tune physicochemical and pharmacokinetic properties, in order to eventually improve the overall quality of small molecule drug candidates.

**GRAPHICAL ABSTRACT**




**ARTICLE HISTORY**
Received 23 July 2018

**KEYWORDS**
Amino alcohol; bridged bicyclic morpholine; compact module; medicinal chemistry

## Introduction

The drug-like properties of amino alcohols have drawn increasing awareness of the medicinal chemistry community since the introduction of Lipinski's 'rule of five'.[1] Many molecular properties such as molecular weight (MW), lipophilicity (as measured by LogP for example), polar surface area (PSA), rotatable bonds, and hydrogen bond donor/acceptor are calculated, evaluated[2], and set within a certain range during the hit-to-lead and lead-to-candidate optimizations in drug discovery. In addition to those

CONTACT Haixia Liu haixia.liu@roche.com Department of medicinal chemistry, Roche Innovation Center Shanghai, Roche Pharmaceutical Research & Early Development, 720 Cailun Road, Building 5, Pudong, Shanghai 201203, P. R. China.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/lsyc.

Supplemental data for this article can be accessed on the publisher' website.

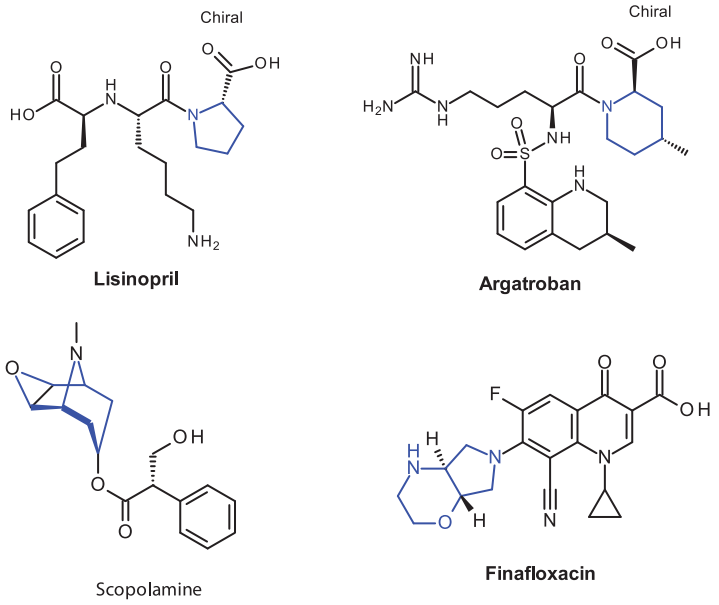



**Figure 1.** Representatives of marketed drugs containing pyrrolidine, piperidine or morpholine.

descriptors, molecular complexity, as measured by the fraction of $sp^3$ carbons ($Fsp^3$) and the presence of chiral centers may impact the transition of small molecule entities from discovery stage through clinical investigations to marketed drugs.[3] Taking into account the potential factors that may have an influence on compound quality, medicinal chemists adopt concepts such as 'escape from flatland'[3] and conformation restriction[4] in the design and synthesis of novel compact modules with targeted physicochemical properties, favorable conformations, and pre-set exit vectors for derivatization. These modules may be incorporated into small molecular entities to improve their quality and performance in various aspects.[5] For example, the recent identification of spirocyclic and oxetane containing modules[6] opens up new chemical space and offers multiple options for medicinal chemists to modulate physicochemical and pharmacokinetic properties, which may eventually improve the quality of small molecule drug candidates.

The aliphatic nitrogen-containing heterocycles such as piperidine, morpholine, and pyrrolidine are the most prevalent structural motifs in the marketed drugs (Figure 1) and clinical candidates.[7] To explore new chemistry space derived from these classic scaffolds, we designed a series of bridged bicyclic amino alcohol building blocks, which contain monocyclic nitrogen aliphatic heterocycle with an attached hydroxyl group (Figure 2, compound **1–3**). We envision that these compact modules will find their applications in the multidimensional optimization of drug discovery projects. First of all, these modules adopt compact 3D-shaped conformations which may help the host molecules to 'escape from flatland' and increase solubility and permeability. Moreover, the bridged tether introduces steric hindrance to the metabolically labile spots, potentially enhancing the building block's metabolic stability. In the meantime, the tether may further fill the receptor pockets and increase binding affinity to the protein target.

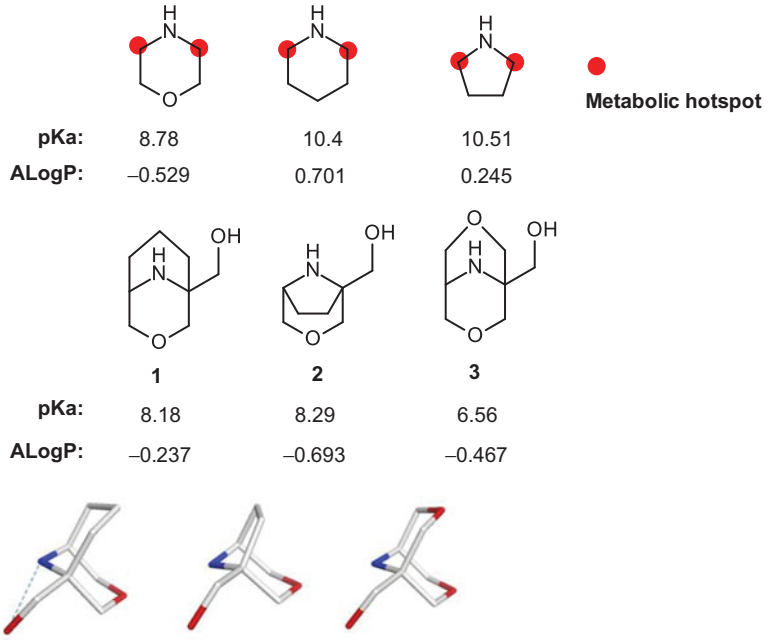



Figure 2. Calculated molecular properties: pKa, LogP and lowest energy conformations.[8]]

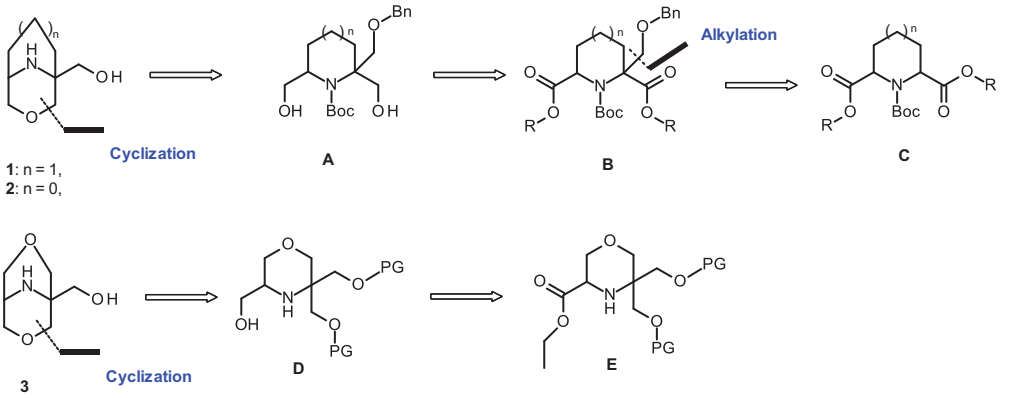
In addition, according to the calculated perameters,[8] these modules exhibit distinct physicochemical properties such as basicity and lipophilicity. Medicinal chemists can select the appropriate building blocks to fine-tune compound properties. To test their potential use in drug discovery, we successfully obtained several building blocks and herein we report our synthetic approach to access these modules.

## Retrosynthetic analysis

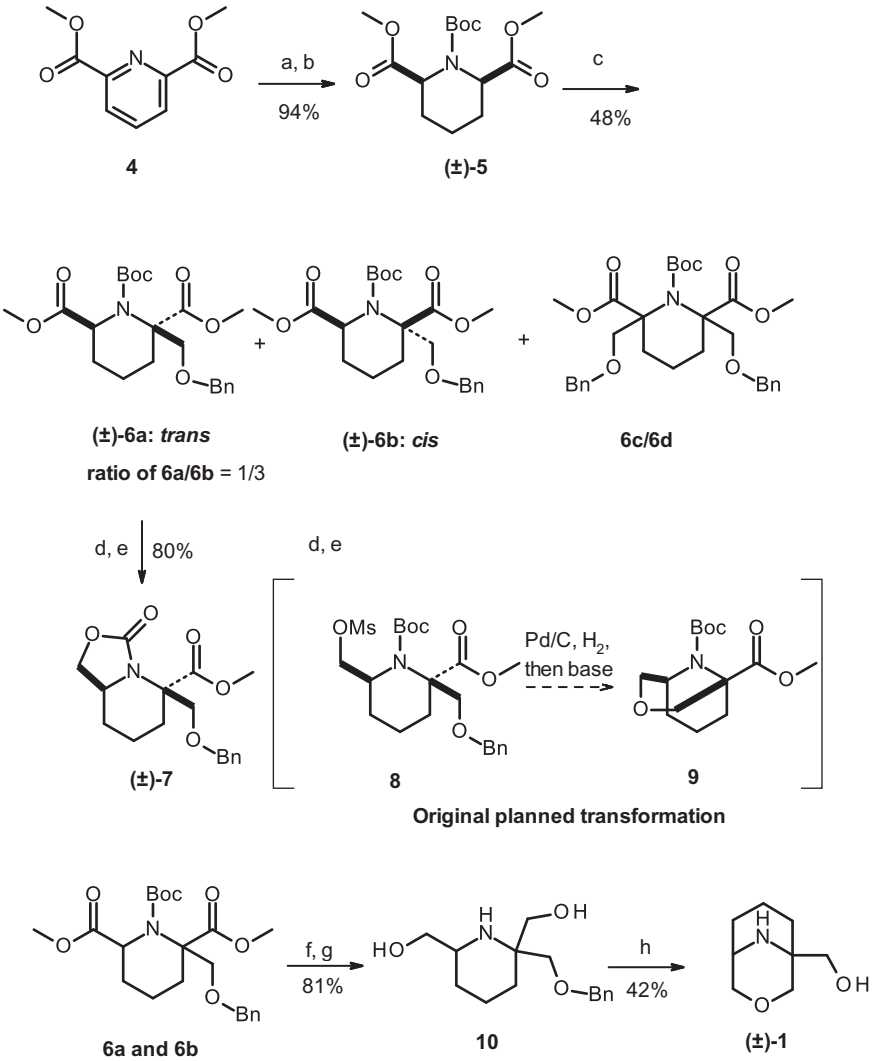
The retro analysis of compound **1–3** is outlined in Scheme 1 : in general the morpholine ring of compound **1–3** can be formed through an acid promoted one-pot deprotection and ring closure. The advanced intermediate **A** is converted from compound **B** by $LiAlH_4$ reduction, which was obtained by *C*-alkylation of dicarboxylate **C** with chloromethylbenzyl ether in the presence of LDA. The morpholine derivative **D** is accessible through ester reduction of compound **E** with $LiAlH_4$ which is built up from SnAP chemistry.[9]

## Results and discussion

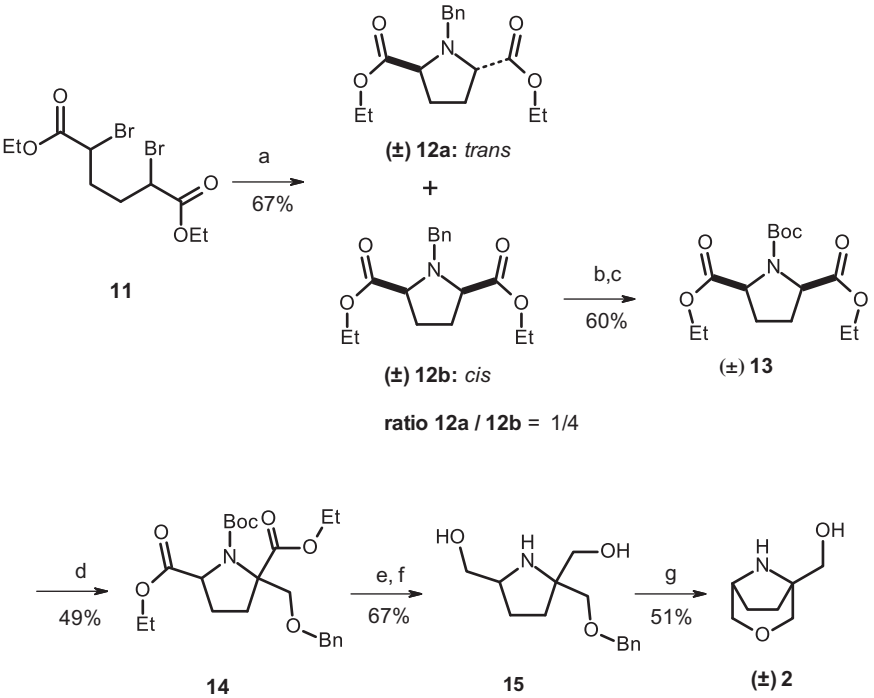
The synthesis of compound (±)-**1** (Scheme 2) commenced with dimethyl pyridine-2,6-dicarboxylate **4.** Hydrogenation in the presence of palladium on carbon followed by Boc-protection gave *cis*-substituted piperidine derivative (±)-**5** in high yield.[10] The subsequent α-alkylation using benzyl chloromethyl ether afforded the desired mono alkylated products as a 1:3 mixture of *trans/cis* isomers (±)-**6a**/(±)-**6b**[11] together with minor double alkylated products **6c/6d**.




**Scheme 1.** Retrosynthetic approach for compound **1-3**.




**Scheme 2.** Preparation of compound 1. Reagents and conditions: (a) Pd/C, $H_2$, MeOH; (b) $(Boc)_2O$, toluene, 95 °C; (c) LDA, chloromethylbenzyl ether, THF, −78 °C to RT; (d) $BH_3$, THF, 0 °C to RT; (e) MsCl, $Et_3N$, DCM, RT; (f) 1N HCl in EtOAc; (g) $LiAlH_4$, THF, 0 °C to RT; (h) $CH_3SO_3H$, 140 °C.

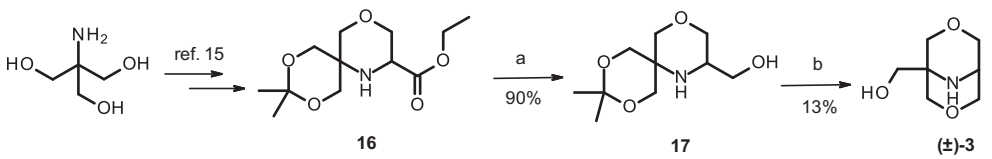



**Scheme 3.** Preparation of compound 2. Reagents and conditions: (a) $BnNH_2$, $K_2CO_3$, toluene/water, 80 °C; (b) $Pd(OH)_2/C$, $H_2$, MeOH; (c) $(Boc)_2O$, toluene, 95 °C; (d) LDA, chloromethylbenzyl ether, THF, −78 °C to RT; (e) 1N HCl in EtOAc; (f) $LiAlH_4$, THF, 0 °C to RT; (g) $CH_3SO_3H$, 140 °C.

Next, we planned to construct the second bridged morpholine ring. A selective reduction of the less hindered methyl ester of compound (±)-**6a** with borane followed by mesylation afforded a bicyclic compound (±)-**7** instead of the originally desired mesylate **8**. The synthetic strategy was then revised. After Boc-deprotection of the mixture of compound (±)-**6a** and (±)-**6b**, both methyl esters were reduced to give diol **10**, which was treated with $MeSO_3H$ at elevated temperature to afford the final building block (±)-**1** with modest yield.[12]

Building block (±)-**2** is a close analog of compound **1** with one methylene group lesser at the bridged linker region. A similar synthesis strategy was utilized (Scheme 3). In order to construct dicarboxylated pyrrolidine **12**, treatment of *cis*-diethyl-2,5-dibromohexanedioate with benzylamine and $K_2CO_3$ in toluene/water afforded the pyrrolidine product as a 1:4 mixture of *trans/cis* isomers (±)-**12a**/(±)-**12b**.[13–15] The *N*-Bn group of *cis* isomer (±)-**12 b** was switched to *N*-Boc through a two-step deprotection–protection reaction to facilitate the subsequent alkylation. Following the same synthetic scheme as described for compound (±)-**6a**/(±)-**6b**, the final module (±)-**2** was achieved with a moderate yield.

Next, we investigated the synthesis of building block (±)-**3** (Scheme 4). By utilizing a literature procedure and SnAP chemistry,[9] we were able to synthesized compound **16**. Reduction of the ethyl ester of **16** with $LiAlH_4$ afforded alcohol **17**, which cyclized to form the second morpholine ring upon heating in methanesulfonic acid. Unfortunately, the yield of the final product 3,7-dioxa-9-azabicyclo[3.3.1]nonan-5-ylmethanol (±)-**3** was relatively low.




**Scheme 4.** Preparation of compound 4. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to RT; (b) $CH_3SO_3H$, 140 °C.

## Conclusion

In summary, the synthesis of the three novel bridged amino alcohols was achieved. In our synthetic strategy, by utilizing commercially available starting materials, we constructed a 5- or 6-membered ring with required functional groups first and then formed the second bridged morpholine ring under strong acidic cyclization condition without protecting and differentiating the alcohol groups, which greatly simplified the synthesis. The synthetic methods described herein are very concise and reproducible, paving the way for their applications in structure-activity relationship (SAR) and structure-property relationship (SPR) studies in drug discovery projects. These bridged modules contain embedded pyrrolidine, piperidine and morpholine structures. Thus they can serve as novel bioisosteres for those motifs. Considering their unique 3-dimensional conformations and distinct physicochemical properties in terms of lipophilicity and basicity, these modules may be incorporated in analogs in order to solve absorption and safety related issues such as off-targets, cytotoxicity, hERG, and phospholipidosis. Furthermore, these modules might be also leveraged to introduce intellectual property (IP) relative to simpler scaffolds. The application of these building blocks is currently ongoing, and their impacts on biological targets as well as pharmacokinetics properties will be reported in due course.

## Experimental

All reactions involving air-sensitive reagents were performed under an argon atmosphere. Analytical thin-layer chromatography was performed using glass plates precoated with silica gel impregnated with a fluorescent indicator and visualized by exposure to ultraviolet light (254 nm) and/or stained by submersion in iodine on silica gel or aqueous ceric ammonium molybdate followed by heating with a heat gun. Analytical LC/MS spectra were obtained using a Waters UPLC-SQD Mass. Proton and carbon nuclear magnetic resonance ($^1$H and $^{13}$C NMR) spectra were recorded at 400 MHz on Brucker spectrometers. Reagents were used as received from commercial suppliers without further purification unless otherwise noted.

### *Typical experimental procedure for the key compounds*

#### *[6-(benzyloxymethyl)-6-(hydroxymethyl)-2-piperidyl]methanol 10*

Compound **6a/6b** (1.00 g, 2.4 mmol) was treated with HCl in EtOAc (1 N, 60 mL) at room temperature (RT). The mixture was stirred at RT for 18 h. The solvent was removed and the residue was purified by plash column chromatography eluting with a gradient of MeOH/DCM (10:100 to 30:100) to afford dimethyl 2-(benzyloxymethyl)piperidine-2,6-

dicarboxylate (0.84 g, 98%) as a white solid. ESI-HRMS: Calculated for $C_{17}H_{23}NO_5$ [$(M + H)^+$]: 322.1576. Found: 322.1677. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$: 7.39–7.24 (m, 5H), 4.53 (d, $J$ = 0.9 Hz, 2H), 3.91–3.84 (m, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.59 (d, $J$ = 9.5 Hz, 1H), 3.38 (dd, $J$ = 3.1, 10.9 Hz, 1H), 2.00–1.90 (m, 1H), 1.86–1.77 (m, 1H), 1.77–1.69 (m, 1H), 1.66–1.49 (m, 2H), 1.48–1.35 (m, 1H). To a solution of dimethyl 2-(benzyloxymethyl) piperidine-2,6-dicarboxylate (1.00 g, 3.2 mmol) in THF (50 mL) was added $LiAlH_4$ (2.0 M in THF, 3.25 mL, 6.5 mmol,) at 0 °C. The reaction mixture was then warmed to RT and stirred overnight. The reaction mixture was then cooled to 0 °C and quenched with aq NaOH (2.0 M, 2 mL). The resulting white precipitate was filtered and washed with THF (50 mL). The filtrate was dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with a gradient of MeOH:DCM (10:100 to 30:100) to afford compound **10** (0.70 g, 81%) as a yellow oil. ESI-HRMS: Calculated for $C_{15}H_{23}NO_3$ [$(M + H)^+$]: 266.1678. Found: 266.1772. The product was further purified to give samples of *trans*- and *cis*- isomers for NMR analysis: *trans*-isomer: $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.41–7.32 (m, 4H), 7.32–7.26 (m, 1H), 4.56 (s, 2H), 3.82–3.76 (m, 1H), 3.73–3.66 (m, 1H), 3.55 (dd, $J$ = 4.3, 10.8 Hz, 1H), 3.47 (d, $J$ = 8.9 Hz, 1H), 3.43–3.35 (m, 2H), 3.04–2.89 (m, 1H), 1.77–1.54 (m, 4H), 1.43–1.30 (m, 1H), 1.18–1.05 (m, 1H). $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$: 138.2, 128.0, 127.4, 127.3, 75.1, 73.2, 65.2, 58.7, 56.5, 51.8, 27.3, 26.9, 18.9. *cis*-isomer: $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.29–7.20 (m, 5H), 7.20–7.15 (m, 1H), 4.46 (s, 2H), 3.58 (d, $J$ = 9.5 Hz, 1H), 3.46–3.37 (m, 3H), 3.36–3.31 (m, 1H), 3.28 (dd, $J$ = 7.5, 10.9 Hz, 1H), 2.82 (dt, $J$ = 3.2, 7.6 Hz, 1H), 1.60–1.48 (m, 3H), 1.47–1.34 (m, 1H), 1.31–1.20 (m, 1H), 1.07–0.92 (m, 1H). $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$: 138.2, 128.0, 127.5, 127.3, 73.0, 66.7, 66.5, 65.1, 56.7, 52.1, 27.4, 26.7, 19.0.

### *3 -oxa-9-azabicyclo[3.3.1]nonan-5-ylmethanol (±)-1*

Compound **10** (600 mg, 2.26 mmol) was dissolved in methanesulfonic acid (6 mL). The solution was heated at 140 °C for 18 h under argon. After cooling to RT, the mixture was poured slowly into a mixture of ice (15 g) and water (15 mL). The mixture was then neutralized with 50% NaOH solution (9 mL) at 0 °C. To the mixture was added MeOH (150 mL). The white precipitate was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by spherical C18 column filled with 20–45$\mu$m spherical C18 bonded silica with 100 Å pores using a MPLC system (CombiFlash Companion, Isco Icn.) eluting with a gradient of MeOH: water (0.5% TFA) (5:100 to 95:100) to afford compound **(±)-1** (150 mg, 42%) as a light brown oil. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 4.11–4.03 (m, 1H), 3.99–3.93 (m, 2H), 3.93–3.87 (m, 1H), 3.51–3.42 (m, 3H), 2.60 (tq, $J$ = 6.4, 13.0 Hz, 1H), 2.14–2.03 (m, 2H), 1.99–1.83 (m, 2H), 1.78–1.71 (m, 1H). $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 70.2, 67.8, 63.5, 55.7, 48.6, 29.1, 26.2, 18.1. ESI-HRMS: Calculated for $C_8H_{15}NO_2$ [$(M + H)^+$]: 158.1103. Found: 158.1175.

### *[6-(benzyloxymethyl)-6-(hydroxymethyl)-2-piperidyl]methanol 15*

Compound **14** (1.00 g, 2.4 mmol) was treated with HCl in EtOAc (1 N, 60 mL) at RT. The solution was stirred at RT for 18 h, then solvent was removed. The residue was

purified by column chromatography eluting with a gradient of MeOH/DCM (10:100 to 30:100) to the intermediate (0.80 g, quant) as a white solid. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.42–7.19 (m, 5H), 4.63–4.53 (m, 1H), 4.53–4.45 (m, 1H), 4.24–4.12 (m, 4H), 3.98–3.63 (m, 2H), 3.61–3.44 (m, 1H), 2.24–2.03 (m, 2H), 2.01–1.75 (m, 2H), 1.34–1.20 (m, 6H). To a solution of this intermediate (0.80 g, 2.4 mmol) in dry THF (5 mL) was added $LiAlH_4$ solution (2 M in THF, 2.4 ml, 4.8 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred overnight, then quenched aq NaOH (2 M, 2 mL). The resulting white precipitate was filtered and washed with THF (20 mL). The filtrate was dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with a gradient of MeOH/DCM (10:100 to 30:100) to afford compound **15** (0.40 g, 67%) as a yellow oil. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.41–7.33 (m, 4H), 7.31–7.25 (m, 1H), 4.61–4.52 (m, 2H), 3.63–3.56 (m, 1H), 3.56–3.48 (m, 4H), 3.48–3.43 (m, 1H), 3.40–3.35 (m, 1H), 1.96–1.86 (m, 1H), 1.85–1.73 (m, 2H), 1.72–1.59 (m, 1H). IR (neat) $\nu_{max}$ 1680, 1353, 1203, 1061, 723 $cm^{-1}$. ESI-HRMS: Calculated for $C_{14}H_{21}NO_3$ [$(M + H)^+$]: 252.1521. Found: 252.1611.

### 3 -oxa-8-azabicyclo[3.2.1]octan-5-ylmethanol (±)-2

Compound **15** (400 mg, 1.59 mmol) was dissolved in methanesulfonic acid (8 mL). The solution was heated at 140 °C for 8 h under argon. After cooling to RT, the mixture was poured slowly into a mixture of ice (20 g) and water (20 mL), and neutralized with 50% sodium hydroxide solution (24 mL) at 0 °C. The mixture was then diluted with MeOH (200 mL). The formed white precipitate was filtered, the filtrate concentrated under reduced pressure. The residue was purified by spherical C18 column filled with 20–45$\mu$m spherical C18 bonded silica with 100 Å pores using a MPLC system (CombiFlash Companion, Isco Icn.) eluting with a gradient of Methanol:0.5% TFA in water (5:100 to 95:100) to afford compound **(±)-2** (115 mg, 51%) as a light yellow oil. $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 3.95 (d, $J$ = 5.7 Hz, 1H), 3.90–3.83 (m, 2H), 3.82–3.76 (m, 1H), 3.76–3.65 (m, 3H), 2.25–2.12 (m, 3H), 1.98–1.89 (m, 1H). $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 70.9, 68.4, 67.8, 60.4, 56.5, 26.9, 25.2. IR (neat) $\nu_{max}$ 1676, 1203, 1136, 723 $cm^{-1}$. ESI-HRMS: Calculated for $C_7H_{13}NO_2$ [$(M + H)+$]: 144.0946. Found: 144.1026.

### 3 ,7-dioxa-9-azabicyclo[3.3.1]nonan-5-ylmethanol (±)-3

To a solution of compound **16** (0.50 g, 1.9 mmol) in dry THF (30 mL) was added $LiAlH_4$ (2 M in THF, 1.4 mL, 2.8 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred overnight, then quenched with aq. NaOH (2 M, 1.0 mL). The resulting white precipitate was filtered and washed with THF (50 mL). The filtrate was dried over $Na_2SO_4$ and concentrated under reduced pressure to afford (9,9-dimethyl-4,8,10-trioxa-1-azaspiro[5.5]undecan-2-yl)methanol (378 mg, 90%) as a light yellow oil which was directly used. To this intermediate (110 mg, 0.51mmol) was added methanesulfonic acid (1 mL). The solution was heated at 140 °C for 8 h under argon. After cooling to room temperature, the mixture was poured slowly into a mixture of ice (5 g) and water (5 mL), and neutralized with 50% sodium hydroxide solution (3 mL) at 0 °C. The

mixture was diluted with methanol (50 mL). The formed white precipitate was filtered, the filtrate concentrated under reduced pressure. The residue was purified by spherical C18 column filled with 20–45$\mu$m spherical C18 bonded silica with 100 Å pores using a MPLC system (CombiFlash Companion, Isco Icn.) eluting with a gradient of MeOH/water (0.5% TFA) (5:100 to 95:100) to afford compound **(±)-3** (31 mg, 38%) as a light yellow oil. $^{1}$H NMR (400 MHz, DMSO-d6) $\delta$ 4.64 (t, $J$ = 5.4 Hz, 1H), 3.82–3.72 (m, 4H), 3.63 (dd, $J$ = 2.9, 10.4 Hz, 2H), 3.41 (d, $J$ = 10.3 Hz, 2H), 3.17 (d, $J$ = 5.3 Hz, 1H), 3.01 (d, $J$ = 5.5 Hz, 2H), 2.68–2.62 (m, 1H). $^{13}$C NMR (101 MHz, DMSO-d6) $\delta$ 72.8, 69.9, 65.6, 51.0, 48.2. IR (neat) $\nu_{max}$ 1648, 1048, 1025, 1002, 826, 765 cm$^{-1}$. ESI-HRMS: Calculated for $C_7H_{13}NO_3$ [$(M + H)^+$]: 160.0895. Found: 160.0956.

## Acknowledgments

The authors gratefully acknowledge the Hoffmann-La Roche AG and Shanghai Jiao Tong University for analytical support.

## References

[1] (a) Lovering, F. Escape from Flatland 2: Complexity and Promiscuity. *Med. Chem. Commun.* **2013**, *4*, 515–519. doi:10.1039/c2md20347b

[2] Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Adv. Drug Delivery Rev.* **1997**, *23*, 3–25. doi:10.1016/S0169-409X(96)00423-1

[3] Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J. Med. Chem.* **2002**, *45*, 2615–2623. doi:10.1021/jm020017n

[4] Mann, A. Conformational Restriction and/or Steric Hindrance in Medicinal Chemistry. In *The Practice of Medicinal Chemistry*, 3rd ed.; Wermuth C., Ed.; Academic Press/Elsevier: Amsterdam, **2008**; p 363.

[5] (a) Carreira, E.; Fessard, T. C. Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **2014**, *114*, 8257–8322. (b) Rogers-Evans, M.; Knust, H.; Plancher, J.-M.; Carreira, E. M.; Wuitschik, G.; Burkhard, J.; Li, D. B.; Guérot, C. Adventures in Drug-like Chemistry Space: From Oxetanes to Spiroazetidines and beyond!. *Chimia. (Aarau).* **2014**, *68*, 492–499. (c) Goldberg, F. W.; Kettle, J. G.; Kogej, T.; Perry, M. W. D.; Tomkinson, N. P. Designing Novel Building Blocks Is an Overlooked Strategy to Improve Compound Quality. *Drug Discov. Today.* **2015**, *20*, 11–17. (d) Druzhenko, T.; Denisenko, O.; Kheylik, Y.; Zozulya, S.; Shishkina, S. S.; Tolmachev, A.; Mykhailiuk, P. K. Design, Synthesis, and Characterization of SO2-Containing Azabicyclo[3.n.1]Alkanes: Promising Building Blocks for Drug Discovery. *Org. Lett.* **2015**, *17*, 1922–1925. (e) Wu, G.; Kou, B.; Tang, G.; Zhu, W.; Shen, H. C.; Liu, H.; Hu, T. Synthesis of Novel and Conformationally Constrained Bridged Amino Acids as Compact Modules for Drug Discovery. *Tetrahedron Lett.* **2016**, *57*, 599–602. (f) Kou, B.; Zhu, W.; Liu, H.; Shen, H. C.; Wu, J.; Hu, T. Synthesis of Bridged Bicyclic Morpholine Amino Acids as Compact Modules for Medicinal Chemistry. *Chem. Lett.* **2017**, *46*, 566–568. (g) Chalyk, B.; Isakov, A.; Butko, M.; Hrebeniuk, K.; Savych, O.; Kucher, O.; Gavrilenko, K.; Druzhenko, T.; Yarmolchuk, V.; Zozulya, S.; Mykhailiuk, P. Synthesis of 6-Azaspiro[4.3]Alkanes: Innovative Scaffolds for Drug Discovery. *Eur. J. Org. Chem.* **2017**, *2017*, 4530–4542. (h) Kirichok, A. A.; Shton, I.; Kliachyna, M.; Pishel, I.; Mykhailiuk, P. K. 1-Substituted 2-Azaspiro[3.3]Heptanes: Overlooked Motifs for Drug Discovery. *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 8865–8869. (i) Feskov, I. O.; Chernykh, A. V.; Kondratov,

I. S.; Klyachina, M.; Daniliuc, C. G.; Haufe, G. Cyclobutyl-Containing Rigid Analogues of Threonine: Synthesis and Physical Chemical Properties. *J. Org. Chem.* **2017**, *82*, 12863–12868. (j) Druzhenko, T.; Skalenko, Y.; Samoilenko, M.; Denisenko, A.; Zozulya, S.; Borysko, P. O.; Sokolenko, M. I.; Tarasov, A.; Mykhailiuk, P. K. Photochemical Synthesis of 2-Azabicyclo[3.2.0]Heptanes: Advanced Building Blocks for Drug Discovery. Synthesis of 2,3-Ethanoproline. *J. Org. Chem.* **2018**, *83*, 1394–1401. doi:10.1021/cr500127b

[6] Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. Oxetanes as Promising Modules in Drug Discovery. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 7736–7739. doi:10.1002/anie.200602343

[7] (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274. (b) Blizzard, T. A.; Singh, S.; Patil, B.; Chidurala, N.; Komanduri, V.; Debnath, S.; Belyakov, S.; Crespo, A.; Struck, A.; Kurtz, M.; et al. Heterocyclic Core Analogs of a Direct Thrombin Inhibitor. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1111–1115. (c) Bianchini, F.; Cini, N.; Trabocchi, A.; Bottoncetti, A.; Raspanti, S.; Vanzi, E.; Menchi, G.; Guarna, A.; Pupi, A.; Calorini, L. 125I-Radiolabeled Morpholine-Containing Arginine–Glycine–Aspartate (RGD) Ligand of $\alpha v\beta 3$ Integrin as a Molecular Imaging Probe for Angiogenesis. *J. Med. Chem.* **2012**, *55*, 5024–5033. doi:10.1021/jm501100b

[8] pKa is calculated by MoKa developed by Molecular Discovery **2016**. http://www.moldiscovery.com/software/moka/; AlogP is calculated by pipeline pilot developed by Biovia; Lowest energy conformations are calculated by MOE 2016 developed by CCG.

[9] Geoghegan, K.; Bode, J. W. Bespoke SnAP Reagents for the Synthesis of C-Substituted Spirocyclic and Bicyclic Saturated N-Heterocycles. *Org. Lett.* **2015**, *17*, 1934–1937. doi:10.1021/acs.orglett.5b00618

[10] Ding, D. R.; Dwoskin, L. P.; Crooks, P. A. Efficient Synthesis of cis-2,6-di-(2- quinolylpiperidine). *Tetrahedron Lett.* **2013**, *54*, 5211–5213. doi:10.1016/j.tetlet.2013.07.067

[11] Knoop, C. A.; Studer, A. Hydroxy- and Silyloxy-Substituted TEMPO Derivatives for the Living Free-Radical Polymerization of Styrene and n-Butyl Acrylate: Synthesis, Kinetics, and Mechanistic Studies. *J. Am. Chem. Soc.* **2003**, *125*, 16327–16333. doi:10.1021/ja037948o

[12] Lai, J. T. 3,3,5,5-Tetrasubstituted-2-Oxomorpholines and Derivatives. *Synthesis* **1984**, *1984*, 122–123. doi:10.1055/s-1984-30746

[13] Kubyshkin, V. S.; Mikhailiuk, P. K.; Komarov, I. V. Synthesis of 7-Azabicyclo[2.2.1]Heptane-1,4-Dicarboxylic Acid, a Rigid Non-Chiral Analogue of 2-Aminoadipic Acid. *Tetrahedron Lett.* **2007**, *48*, 4061–4063. doi:10.1016/j.tetlet.2007.04.019

[14] Karaki, F.; Kabasawa, Y.; Yanagimoto, T.; Umeda, N.; Firman; Urano, Y.; Nagano, T.; Otani, Y.; Ohwada, T. Visible-Light-Triggered Release of Nitric Oxide from N-Pyramidal Nitrosamines. *Chem. Eur. J* **2012**, *18*, 1127–1141. doi:10.1002/chem.201101427

[15] Fanton, J.; Camps, F.; Castillo, J. A.; Guérard-Hélaine, C.; Lemaire, M.; Charmantray, F.; Hecquet, L. Enzymatic and Organocatalyzed Asymmetric Reactions for the Synthesis of Thiosugar Scaffolds. *Eur. J. Org. Chem.* **2012**, *2012*, 203–210. doi:10.1002/ejoc.201101137