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2-Azabicyclo[3.2.1]octane scaffold: synthesis and applications

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2-Azabicyclo[3.2.1]octanes are nitrogen containing heterocycles with significant potential in the field of drug discovery. This core has been applied as key synthetic intermediate in several total synthesis, while their unique structure can make them a challenging scaffold to acquire. This Minireview summarizes the synthetic approaches to access this bicyclic architecture and highlights its presence in the total synthesis of several target molecules.

1. Introduction

Nitrogen-containing heterocycles can be found in a variety of products of natural and synthetic origin.[1] Due to their known bioactive properties, *N*-based compounds are particularly interesting from a pharmaceutical point of view.[1c,2] Among these, the 2-azabicyclo[3.2.1]octane system, consisting of a six-membered nitrogen heterocycle fused to a cyclopentane ring (Fig. 1), has gained significant interest in the past decades due to its synthetic and pharmacological potential.[3]

Interest in this core by the scientific community has spiked since 2014 after Massiot's group reported a series of structurally related cytisine-like alkaloids from the roots and stems of *Ormosia hosier*, a plant employed in traditional Chinese herbal medicine. These compounds, of the hosieine family (Fig. 2), exhibited high affinity for α4β2 neuronal nicotinic acetylcholine receptor. For instance, (−)-hosieine A, the most potent molecule in this class (IC_{50} = 0.96 nM, K_i = 0.32 nM), exhibits an activity five times stronger than nicotine.[4] The remarkable high activity of (−)-hosieine A and its complex skeleton have already inspired its asymmetric total synthesis, as well as its enantiomer, which are discussed in this manuscript.

Other synthetic compounds containing the 2-azabicyclo[3.2.1]octane scaffold have also shown diverse biological activities. Ong and Anderson were pioneers in showcasing its medicinal potential as efficient analgesic agents. The most promising compounds **2a** and **2b** showed a combined agonist-antagonist effect with efficiency close to morphine (Fig. 2).[5] In a similar line, Andreotti's group explored the effect of aryl sub-

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(±)-1

Fig. 1 General structure of 2-azabicyclo[3.2.1]octanes.

stitution in the bridgehead carbon of the azabicyclo[3.2.1]octane. Compound **3**, mimicking the 3D conformation of cocaine, proved to be a potent *in vitro* triple re-uptake inhibitor (TRUI).[3b] The introduction of a second nitrogen group attached to the bicyclic structure grants this class of molecules relevant biological activity. Agonist activity in κ-opioid receptors (KOR) was observed for compound **4**[6] and cytotoxic activity on different tumor cell lines, such as glioblastoma (GBM), medulloblastoma (MB) and hepatocellular carcinoma (HCC) cell lines (Fig. 2) were reported for **5**.[7] Overall, the medicinal and biological effect of azabicyclo[3.2.1]octane derivatives appears to derive from its structural similarity with bioactive alkaloids such as nicotine, cocaine and morphine, while its bicyclic backbone provides additional rigidity to the molecular structure, which is an important feature in medicinal chemistry.[8]

2-Azabicyclo[3.2.1]octane system is chiral and, unless constructed from enantiomerically pure precursors, it is often present as a mixture of two enantiomers. In this review, we represent it in a consistent 3D configuration for the sake of clarity and consistency, adding (±) notation whenever a racemic mixture is present.

In this Minireview we discuss the reported methodologies for the synthesis of 2-azabicyclo[3.2.1]octanes, namely intramolecular cyclization and rearrangements, such as Beckmann rearrangement. Moreover, their application in total synthesis is also covered in this manuscript. We also include the synthesis of 2-azabicyclo[3.2.1]octan-3-ones, since they are

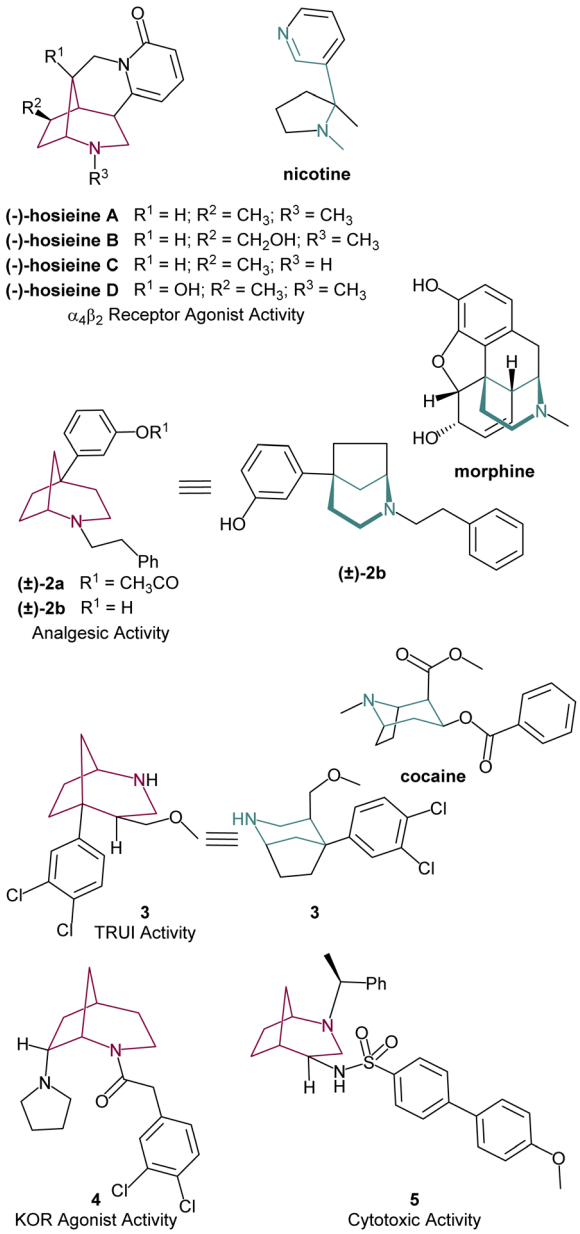

Fig. 2 Selected examples of 2-azabicyclo[3.2.1]octane scaffolds with biological activity.

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common precursors to the 2-azabicyclo[3.2.1]octane core, typically accessed *via* reduction with $LiAlH_4$.

2. Synthesis of 2-azabicyclo[3.2.1]octanes by intramolecular cyclization

The assembly of the 2-azabicyclo[3.2.1]octanes is often achieved *via* nucleophilic attack and concomitant intramolecular cyclization. This strategy typically uses cyclopentanes[3b,9] and piperidine derivatives[6,9c] as starting materials, however other scaffolds have also been successfully applied.[10]

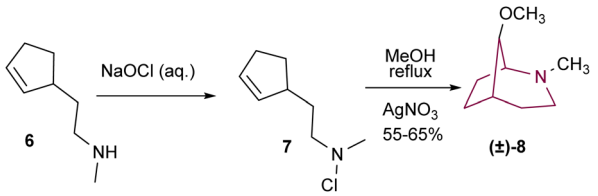
One of the first examples in the literature comes from Gassman and co-workers that, in 1968, reported the preparation of 8-methoxy-2-methyl-2-azabicyclo[3.2.1]octane **8** (Scheme 1). Treatment of amine **6** with aqueous sodium hypochlorite resulted in **7**. Reflux of a methanolic solution of **7** in the presence of silver nitrate resulted in product **8** in 55–65% yield.[11]

In 1977, Takeda and co-workers[9c] were the first to prepare 5-aryl substituted 2-azabicyclo[3.2.1]octane scaffolds (Scheme 2), inspired by the conventional synthesis of phenylmorphan.[12] The azabicyclo-core was accessed through intramolecular cyclization using cyclopentanone **10** or cyclopentenone **13** (Scheme 2). The synthetic strategy commences with the α-alkylation of cyclopentanone **9** to afford **10**. From there, two synthetic routes emerge: cyclopentanone **10** may be submitted to α-bromination, which is followed by ring closing. Demethylation of the resulting tetraalkyl ammonium is achieved under high temperatures to yield ketone **11** (Scheme 2). In a different approach, **10** may be turned to the corresponding carbamate and then oxidized to the enone **13**. Carbamate deprotection leads to intramolecular 1,4-addition of the secondary amine to give bicyclic amino ketone **14** (Scheme 2). Compounds **11** and **14** underwent Wolff–Kishner reduction to yield the desired azabicycloalkane **12**. In a convergent manner, ketone **14** could also be obtained *via* acid catalysed cyclization of **16** (Scheme 2).[9c] A year later, a similar procedure was described by Ong and co-workers, in which optimization of the reaction conditions applied to **10**, **11** and **12** led to improvement of yields and the extension of the reaction scope.[5]

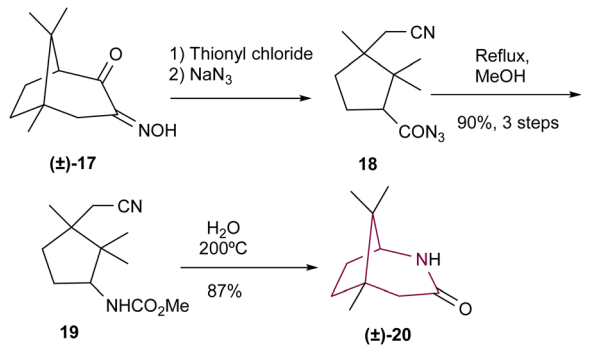
Fleming and coworkers[10a] reported the synthesis of 2-azabicyclo[3.2.1]octane **20** from urethane **19** (Scheme 3). Compound **17** was reacted with thionyl chloride and then sodium azide, resulting in the formation of azide **18** through C–C bond cleavage and ring opening. Compound **18** was then heated under reflux in methanol, resulting in **19**. Finally, **19** was heated at 200 °C to produce lactam **20**, in 87% yield.

Fourrey and co-workers[10b] reported in 1999 the preparation of 2-azabicyclo[3.2.1]octane core through Tsuji–Trost reaction followed by intramolecular cycloaddition. Palladium catalyzed intramolecular cyclization of hydrazine derivative **22** delivered the compound **23** in high yield. Bicyclic **23** was transformed into cyclopentane **24**, a key intermediate in the synthesis of homocarbocyclic nucleosides (Scheme 4).

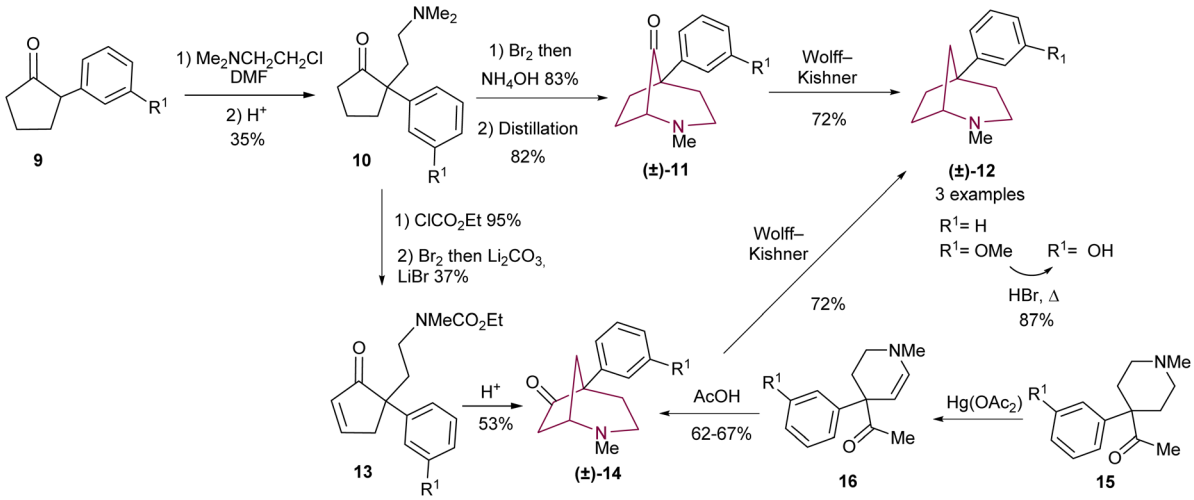
In the same year, the 2-azabicyclo[3.2.1]octan-3-one core was shown once more to be an important precursor to other carbocyclic nucleosides by Lundt's group.[10c] Bicyclic system **27** was accessed from **26** *via* epoxide ring opening with ammonia



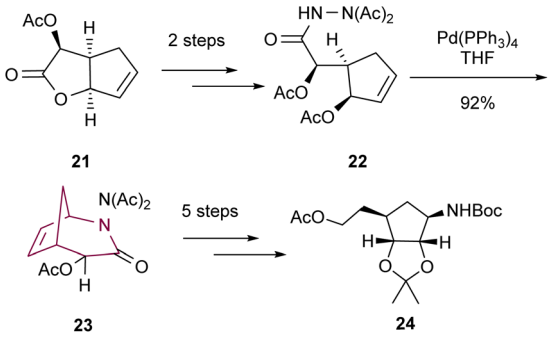
Scheme 1 Synthesis of 2-azabicyclo[3.2.1]octane **8**.



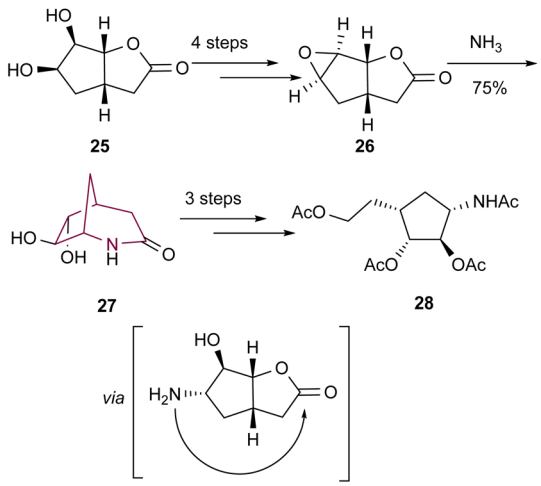
Scheme 3 Synthesis of 2-azabicyclo[3.2.1]octane (±)-**20** *via* intramolecular amide formation.



Scheme 2 Synthesis of 5-aryl-2-azabicyclo[3.2.1]octanes **12** by intramolecular cyclization.



Scheme 4 Synthesis of 2-azabicyclo[3.2.1]octan-3-one **23** by palladium catalyzed intramolecular cyclization.



Scheme 5 Synthesis of bicyclic system **27** by intramolecular cyclization.

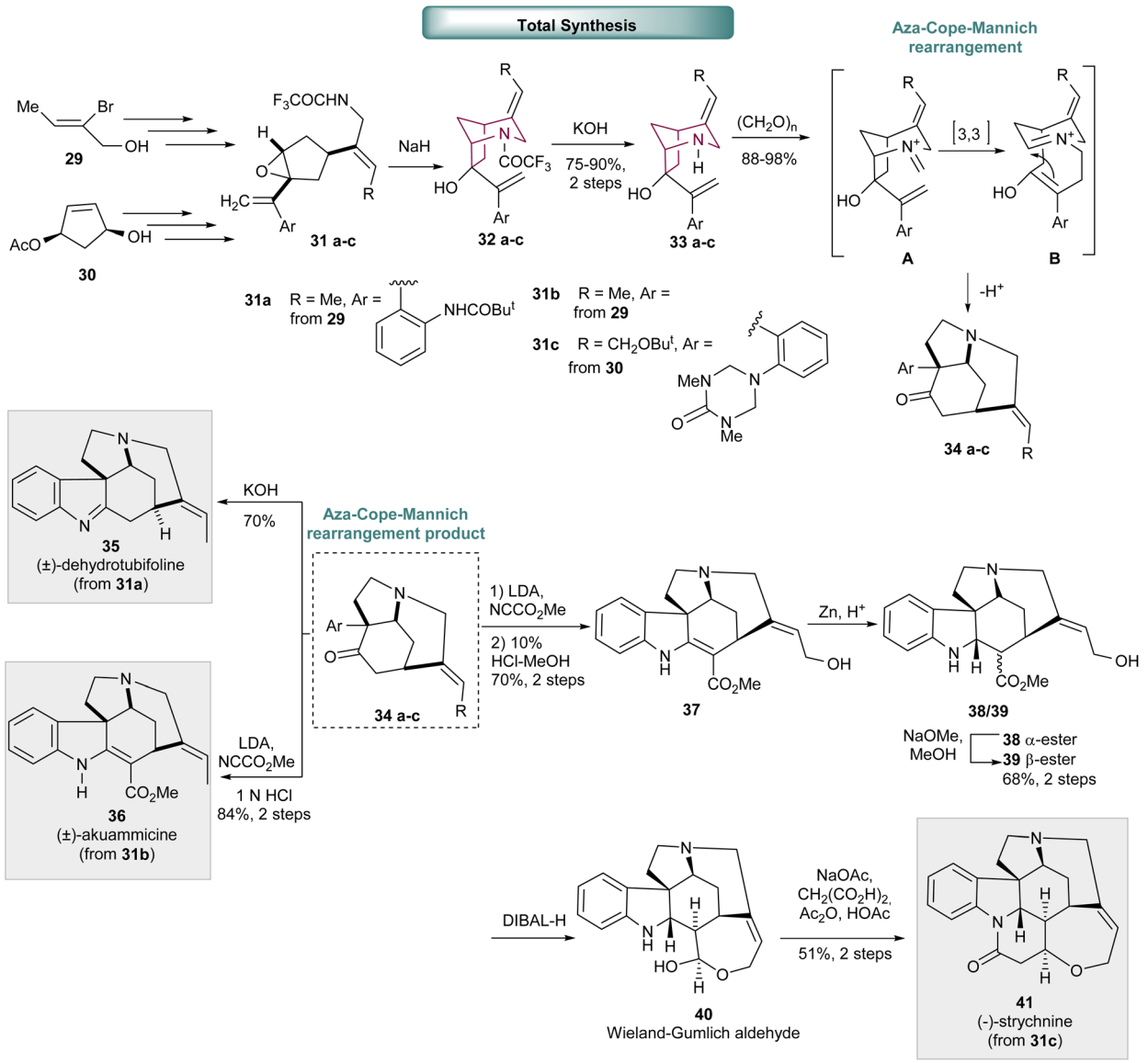
followed by subsequent nucleophilic attack of the amine to the ester (Scheme 5). Amide cleavage and other operations led to the desired highly functionalized cyclopentane **28**.

In a similar manner, 2-azabicyclo[3.2.1]octane core **32a–c**, was prepared *via* intramolecular epoxide ring opening reaction of **31a–c** with trifluoroacetamide (Scheme 6). Trifluoroacetamide removal led to bicyclic compound **33a–c**, the precursor for the Aza-Cope-Mannich rearrangement, the key transformation in the total synthesis of Strychnos alkaloids: (±)-dehydrotubifoline **35**, (±)-akuammicine **36**[13] and (−)-strychnine **41**.[14] The synthetic strategy to obtain (±)-dehydrotubifoline **35** and (±)-akuammicine **36** is very similar and commences from compound **29**. While the synthesis of (−)-strychnine started with an enantioselective hydrolysis of *cis*-3,5 diacetoxycyclopentene to access compound **30**. Epoxide **31a–c** was synthesized by applying several standard manipulations, that include hydroxyl protection, Pd-catalyzed carbonylation, epoxide formation and Wittig methylenation towards compound **29** and **30**. The desired azabicyclo[3.2.1]octane **33a–c**, was accessed *via* epoxide ring opening with trifluoroacetamide, followed by trifluoroacetamide removal. The Aza-Cope-Mannich rearrangement of **33a–c** proceeds *via* the formation of an iminium intermediate **A**, that undergoes a [3,3] rearrangement to intermediate **B**. Cyclization leads exclusively to the formation of tricyclic compound **34a–c** already containing three stereogenic centers present in the final molecules. Hydrolysis of **34a** delivered the desired (±)-dehydrotubifoline **35**. (±)-Akuammicine **36** was obtained after acylation, that furnished the correspondent β-keto ester, and acid catalyzed hydrolysis. (−)-Strychnine **41** was furnished after carbomethoxylation of **34c**, that afforded the correspondent β-keto ester derivative mostly in the enol form, followed by *tert*-butyl and triazone removal. Selective reduction of vinylogous carbamate double bond provided a mixture of α-ester **38** and β-ester **39**, that under basic conditions, efficiently converted to the desired β-ester **39**. Finally, ester reduction with DIBALH led to Wieland-Gumlich aldehyde **40** that, upon treatment with malonic acid under Perkin condensation conditions, originated the desired (−)-strychnine **41**.

In 2018, Wood and co-workers reported the total synthesis of (+)-hosieine A, an alkaloid containing the 2-azabicyclo[3.2.1]octane core, in just 7 steps with an overall yield of 16% (Scheme 7).[15] The synthesis of (+)-hosieine A commences with *N*-alkylation of pyridinone **42** to provide (±)-**43** by modification of Lee and Knochel's organozinc allylation reaction, nucleophilic alkynylation and sequential homologation, *O*-acylation and desilylation. The key step, a catalytic asymmetric Rautenstrauch reaction, was applied to (±)-**43** and provided intermediate **45** with good enantiocontrol (90 : 10 er). Sequential Michael-cyclization, reductive amination and lactamization delivered azabicyclo[3.2.1]octan-3-one core (+)-**48** in moderate yield (42% from **45**). Amide reduction with BH_3/THF furnished (+)-hosieine A **49**.

In 2010, Profeta and Andreotti[3b] employed cyclopentanone **50** for the synthesis of the 2-azabicyclo[3.2.1]octane system in a candidate molecule as TRUI (Scheme 8). The synthetic methodology involved the conversion of ketone **50** to **51** through Knoevenagel condensation. After a sequence of reactions involving cuprate 1,4-addition, Boc cleavage with TFA and basic treatment, a mixture of isomers **53** (*anti*/*syn* = 5/95) was obtained in 43% yield over three steps. Preparative HPLC separated both isomers which were subjected to amide and ester reduction and alcohol methylation (through amine protection/deprotection sequence), to give the desired cocaine analogue **3**.

More recently, Wünsch and co-workers[9b] reported the synthesis of several 2-azabicyclo[3.2.1]octan-7-amines to study their KOR agonist activity. In this procedure, sulfonamide **55** afforded good yields of bicyclic compound **56** as a racemic mixture by intramolecular S_N2 reaction upon deprotonation with NaH (Scheme 9). Then, tosylate **56** reacted with NaN_3 to originate the corresponding azide, with unexpected retention of configuration, which after reduction yielded the primary amine **57**. Alkylation of **57** afforded amines **58a** and **58b**. Tosyl removal and acylation provided the correspondent bicyclic compounds **59a** and **59b**.

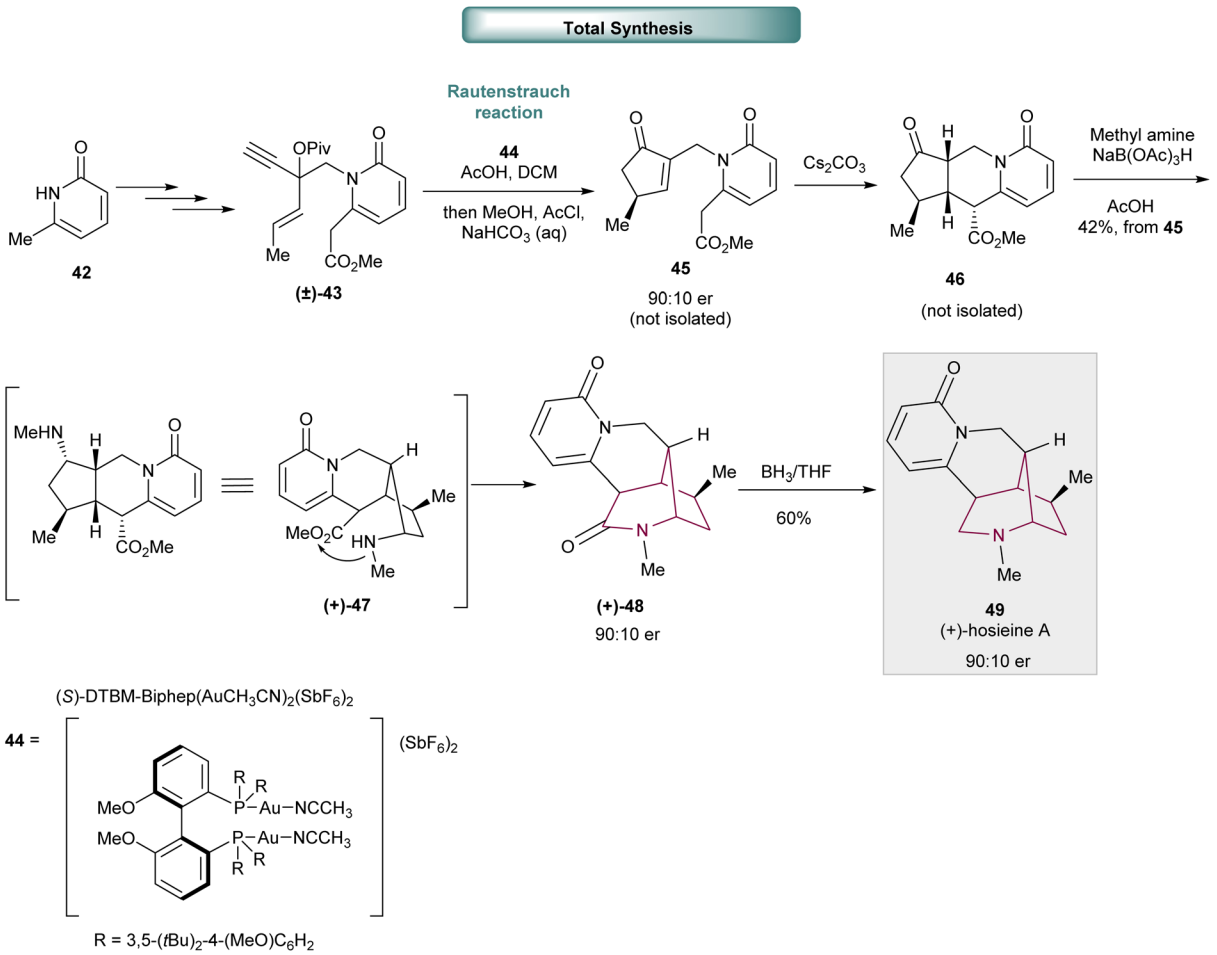


Scheme 6 Synthesis of bicyclic system **32a–c** by intramolecular epoxide ring opening reaction. Aza-Cope-Mannich rearrangement of **33a–c** to **34a–c**, a key intermediate in the total synthesis of (±)-dehydrotubifoline **35**, (±)-akuammicine **36** and (–)-strychnine **41**.

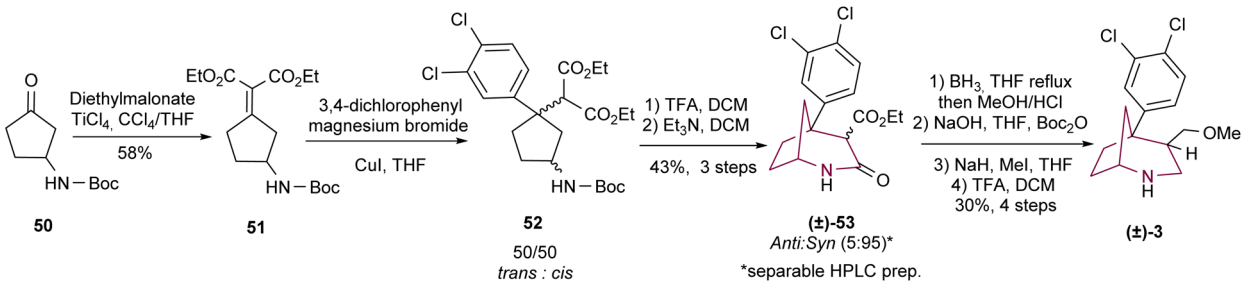
The same group[6] has also described the synthesis of 2-azabicyclo[3.2.1]octane core through Dieckmann cyclization of piperidine derivative **60** (Scheme 10). High temperatures were necessary to ensure that both ester substituents on **60** have an axial orientation and to prompt the inversion of configuration of *trans*-**60**. Compounds **61** were obtained in good yields, as a mixture of enantiomers (1*S*,5*R*) and (1*R*,5*S*) in a 3 : 1 ratio. Deethoxycarbonylation using Krapcho conditions, followed by Boc removal with EtOH and H_2O and subsequent acylation resulted in bicyclic amide **62**. Compound **62** underwent reductive amination. $NaBH(OAc)_3$ adds to the less hindered side of the iminium intermediate, resulting in 2-azabicyclo[3.2.1]octanes **4** and **63** with an *endo*-configuration.

Dondas and co-workers synthesized bicyclic *N*-hydroxylamine **66a** and amine **66b** from compounds **64a** and **64b**, respectively (Scheme 11). Upon treatment with phenylselenyl bromide, aldoxime **64a** was converted to bridged nitrone salt **65a** *via* phenylselenyl induced cyclization, in a stereo- and regioselective manner. After reaction with $NaBH_4$, compound **65a** resulted in 2-azabicyclo[3.2.1]octane **66a** in 69% yield. However, when the same conditions were applied to oxime **64b**, only trace amounts of the desired product **66b** were obtained. The authors attributed this lack of reaction to the steric inhibition of the *gem*-dimethyl group. The synthesis of azabicyclo[3.2.1]octane **69** was achieved in 34% yield, by using analogous conditions, starting from compound **67**.[9a]

A unique way to access the azabicyclo[3.2.1]octane core was discovered by Namba and Tanino *via* construction of a *N*-acyl-*N*-tosylhydrazine **72** from an intramolecular palladium(II)-catalyzed cyclization reaction of **70** (Scheme 12). Treatment of **72**



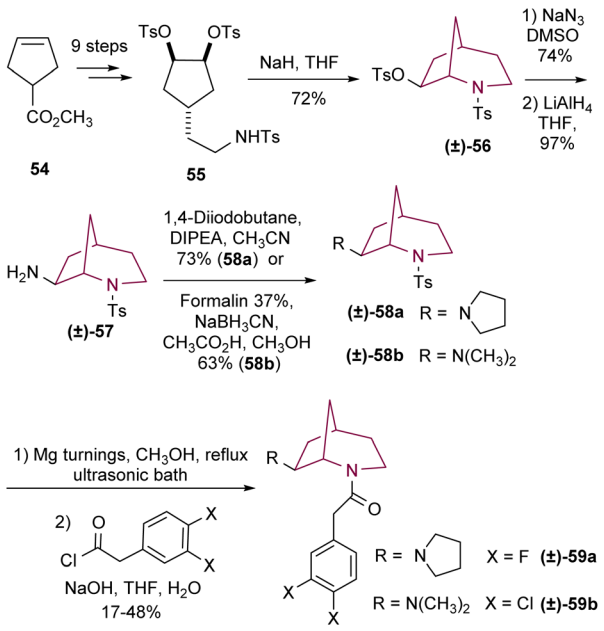
Scheme 7 Total synthesis of (+)-hosieine A **49**.



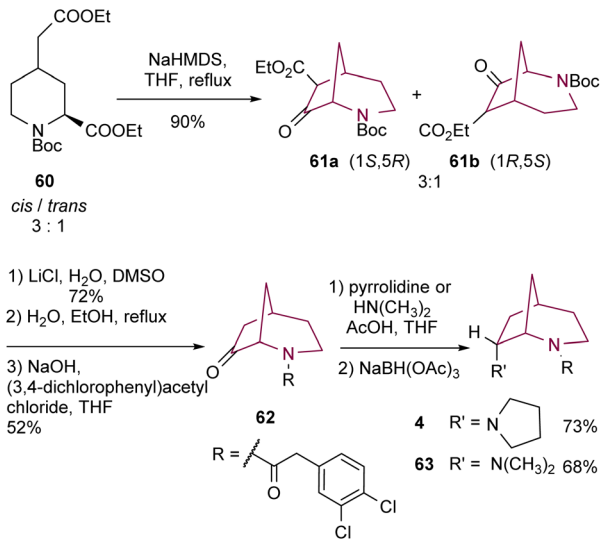
Scheme 8 Synthesis of 5-aryl-2-azabicyclo[3.2.1]octane **3** by intramolecular cyclization.

with trifluoracetic anhydride followed by epoxide formation provided access to **74**. Then, samarium(II) iodide promoted the sequential N–N bond cleavage, epoxide ring opening/cyclization to furnish the azabicyclo[3.2.1]octane core.[9d]

In 2015, Hong and co-workers achieved the first asymmetric synthesis of (−)-hosieine A, an alkaloid containing the 2-azabicyclo[3.2.1]octane core (Scheme 13).[3c] The key transformation was the elegant nitroso-ene cyclization to form the 2-azabicyclo[3.2.1]octane core. The synthetic approach began with α-methyl aldehyde **76**, that after several standard operations such as Horner–Wadsworth–Emmons olefination, 1,4-addition, and ring closing metathesis (RCM) provided hydroxamic acid **77**. Hydroxamic acid oxidation delivered **78** that underwent retro-Diels–Alder to afford the unstable acylnitroso intermediate **79**, that suffers intramolecular nitroso–ene cyclization. The major product 2-aza-bicyclo[3.2.1]octane **80**, was obtained *via* 6-*endo*-type reaction, in 9 : 1 ratio, and the minor 2-azabicyclo[3.3.0]octane **81**, obtained *via* 5-*endo*-type. *N*-hydroxy acetylation and treatment with SmI_2 resulted in the cleavage of N–O bond, followed by amide methylation to give



Scheme 9 Synthesis of 2-azabicyclo[3.2.1]octane by intramolecular cyclization.



Scheme 10 Synthesis of 2-azabicyclo[3.2.1]octanes **4** and **63** by Dieckmann cyclization of a piperidine derivative.

compound **82**. Bromohydrination, using an innovative methodology with NBS and phosphine, afforded the desired bicyclic ring **84**, obtained in 84% combined yield (2 : 1) with a minor product **83**. Radical debromination delivered compound **85**. Hydroxyl activation and *N*-alkylation with 2-pyridone furnished **86**. 1,6-Conjugate addition and subsequent protonation resulted in **87**. Dehydrogenation with activated MnO_2 and amide reduction in the presence of borane finally originated (−)-hosieine A **49**.

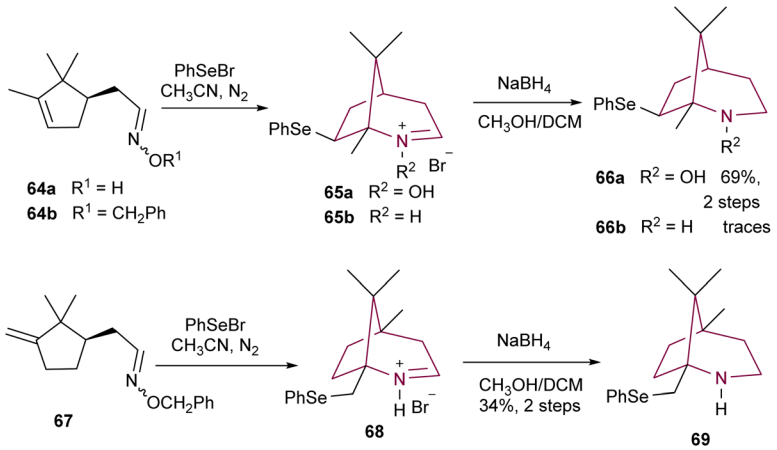
3. Synthesis of 2-azabicyclo[3.2.1] octanes by rearrangements

The bicyclic core of the 2-azabicyclo[3.2.1]octane scaffold may also be accessed through different types of rearrangement reactions, typically through ring-enlargement reactions. Such reactions include Beckmann rearrangements,[16] norbornadiene cascade rearrangements,[17] and rearrangement of bicyclo[2.2.1] heptanes.[18]

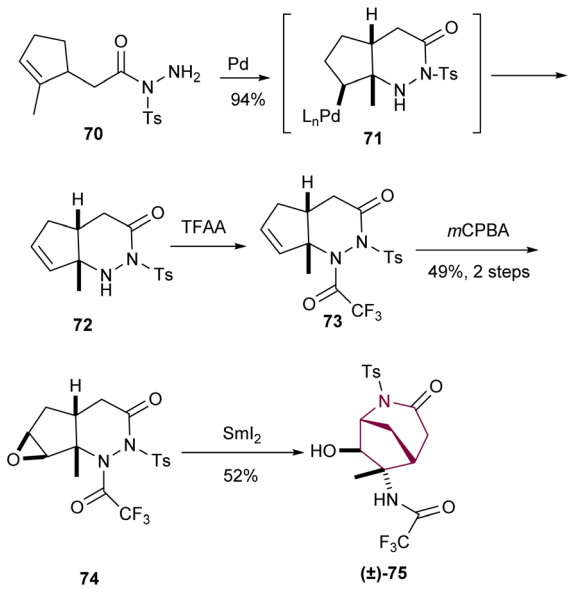
3.1. Beckmann rearrangement

In 1960, Hall[16a] reported the first example of a Beckmann rearrangement in norcamphor derived oximes to 2-azabicyclo [3.2.1.]octan-3-one. Treatment of norcamphor derived oximes with benzenesulfonyl chloride or sulfuric acid/NH_4OH, provided 2-azabicyclo[3.2.1.]octan-3-one **89a** in 38% yield after migration of the bridgehead C–C bond (Scheme 14). Since then, a series of research groups have published their findings in such rearrangement in similar cores, with yields of **89a** ranging from 35 to 90%. These results have been already summarized in an excellent review work by Krow in 1981 and will not be covered here extensively.[19] Nevertheless, several of the old papers before 1981 report unspecified yields and uncertainty on the nature of some molecules, as well as unreproducible results.[20] Scheme 14 presents the main limitations associated with this transformation, which for norcamphor is the formation of a regiosiomer **89′a**, *via* migration of the other C–C bond (depicted in green). The related fenchone oxime **88b** also undergoes Beckmann rearrangement with additional side-reactions involving formation of unsaturated nitriles such as **90** *via* cleavage of the bridgehead C–C bond (depicted in green, Scheme 14) forming a stable tertiary carbocation **91**. Interestingly, camphor fails to give the 2-azabicyclo[3.2.1]octanone regioisomer in more than 12% yield,[21] giving as major product the 3-aza isomer in 42% yield.[19] Photo-Beckmann conditions have been explored in attempts to improve the yield and selectivity of the process but without success.[22] For more complex substrates, the Beckmann rearrangement has also been observed to fail.[21a] Despite the various challenges associated with this transformation, the Beckmann rearrangement remains a useful protocol for the synthesis of 2-azabicyclo [3.2.1]octane core since the obtained amides can be cleanly reduced with $LiAlH_4$.[23]

In 2008, Gin and co-workers applied the Beckmann rearrangement towards the synthesis of chlorocyclopentane cores of the proposed original and revised structures of palau'amine **95a** and **95b**, respectively (Scheme 15).[24] For that, ketone **97** and **103** were prepared in several steps from dihydroquinone **96**. The corresponding oxime was formed, and thionyl-chloride mediated Beckmann rearrangement in a regioselective manner to 2-azabicyclo[3.2.1.]octan-3-one **98** (Scheme 15A), and **104**, the last obtained after Boc protection (Scheme 15B). Regarding the proposed original structure of palau'amine (Scheme 15A), **98** suffers cyclopentene ozonolysis with subsequent reductive work up and diol acetylation to



Scheme 11 Synthesis of 2-azabicyclo[3.2.1]octanes **66a,b** and **69** *via* phenylselenyl induced cyclization.



Scheme 12 Synthesis of azabicyclo[3.2.1]octane core taking profit of an intramolecular palladium(II)-catalyzed cyclization.

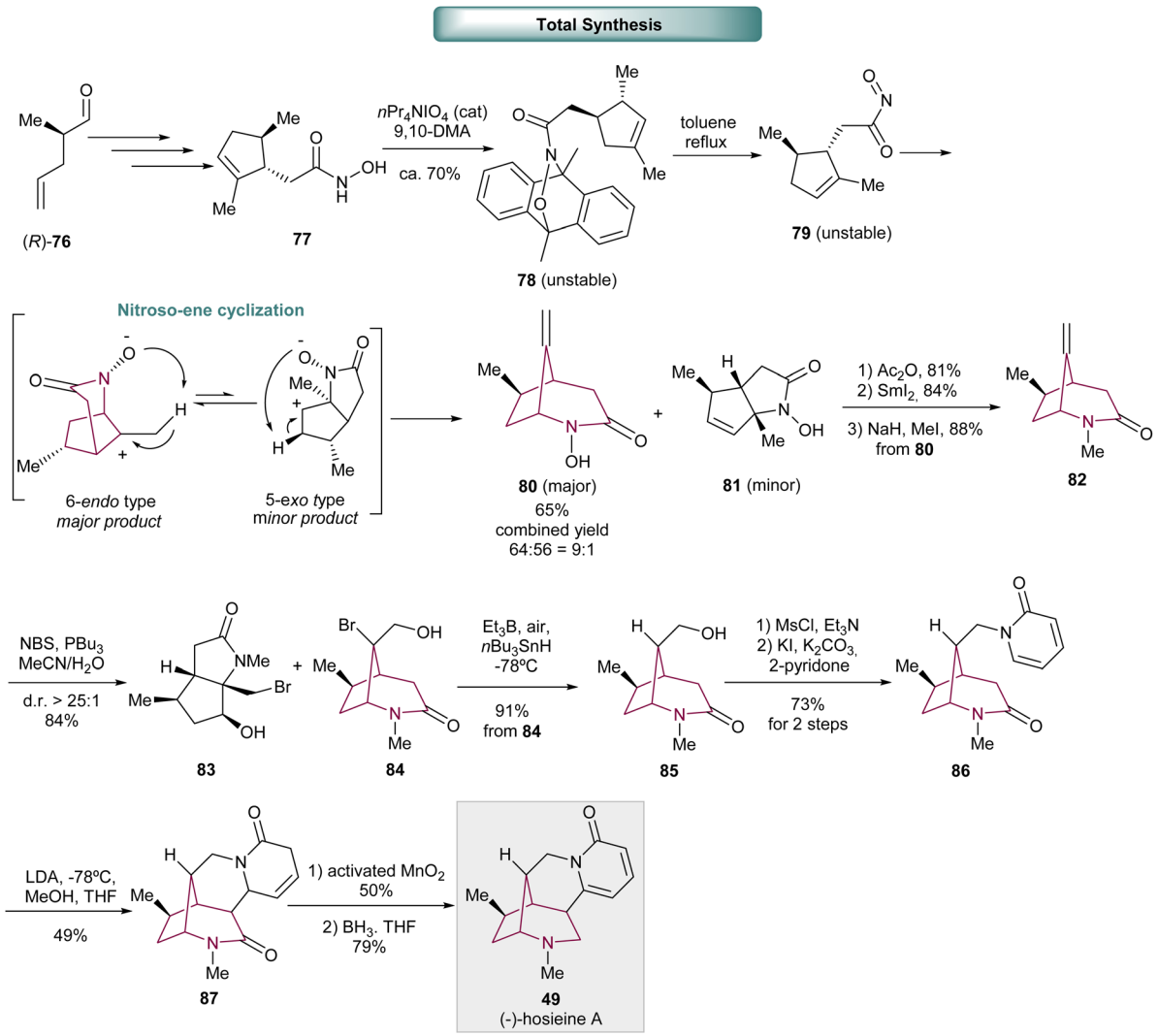
furnish **99**. Lactam Boc protection gave **100**. Lastly, acetal saponification, imide hydrolysis and subsequent acidic treatment resulted in lactone **102** in 96% yield, over the 2 steps. Compounds **101** and **102** represent the cyclopentane cores of the originally proposed structure of palau'amine, **95a**. Concerning the revised chlorocyclopentane cores of palau'amine **95b** (Scheme 15B), from compound **104** two synthetic routes emerge. Lemieux–Johnson oxidation of **104** and subjection to silica gel and Et_3N provided di-aldehyde **105** with C12 epimerization. The bridged chlorocyclopentanes **105** and **100** are stereochemically distinct at C12 and C17. Cyclopentene ring of **104** also undergoes ozonolysis followed by reduction with $NaBH_4$ and treatment with TsOH. This led to intramolecular alcoholysis of the imide and lactone formation. Hydroxy protection delivers **106** in 91% yield, over the 2 steps. Benzyl ether removal led to the formation of **107**. Finally, lactone hydrolysis, methyl ester formation, and C12 oxidation/epimerization yielded aldehyde **108**, that is the C12,C17 diastereomer of chlorocyclopentane **102** (Scheme 15A).

A way to access the bicyclic core from camphor is to initiate rearrangement with camphor hydrazone **109**, as demonstrated by Tezuka and co-workers (Scheme 16). Treatment of **109** with *m*-chloroperbenzoic acid resulted in compounds **110** in high yield, as a 1 : 1 mixture of *endo* (**110a**) and *exo* (**110b**) isomers. Upon reflux in ethanol in the presence of acid or base, lactam **112** was formed in 40% yield from **110a**. This reaction proceeds *via* formation of the corresponding alcohol intermediate **111a** (Scheme 16).[16c] The thermal decomposition reaction of α-azohydroperoxide **113** was also reported by the same group. When **113** was refluxed in benzene, a mixture of products were obtained, among them lactam **114** in 22% yield (Scheme 16B).[16b]

3.2. Schmidt reaction

The synthesis of azabicyclo[3.2.1]octane can also be achieved by Schmidt reaction of ketones with hydroxyalkyl azides (Scheme 17). However, the preferred product from such rearrangement in most norcamphor derivatives is the 3-azolactam regioisomer, in low yields,[25] which is in contrast with the Beckmann rearrangement. This difference in regioselectivity was studied in detail by Krow in 1996,[26] who subjected various norcamphor derivatives to Beckmann and Schmidt conditions (Table 1). For most cases, Beckmann conditions delivered almost exclusively the 2-azolactam isomer, while Schmidt conditions gave a mixture of isomers, in which 3-azolactam was predominant (except for entry 5). Krow postulates that the difference in regioselectivity arises from the poor selectivity in the formation of the iminodiazonium intermediate in Schmidt conditions, whilst the oxime-*O*-sulfonic acid intermediate in Beckmann conditions forms with *syn* selectivity (Scheme 17).

In 2016, Aubé and co-workers[18f] implemented a new version of Schmidt reaction using triflic acid, in the presence of HFIP (Scheme 18). The reaction proceeds in two stages, first



Scheme 13 Total synthesis of (−)-hosieine A **49**.

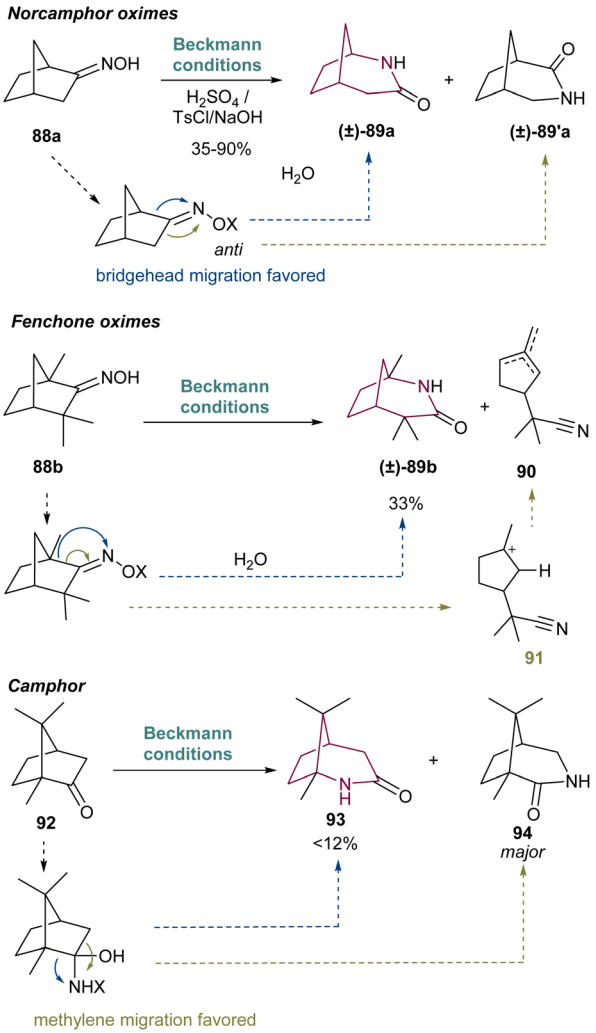
the ketone reacts with hydroxyalkyl azide and then is trapped intramolecularly by the hydroxyl to form the correspondent iminium ether. Finally, the iminium ether is hydrolyzed to deliver the amide. This new methodology was applied towards the synthesis of azabicyclo[3.2.1]octanes **116** and **117**. While HFIP and the intramolecular hydroxyl group significantly improve the reaction yield, the poor selectivity in the C–C migration step continues to limit the applicability of the Schmidt rearrangement in the synthesis of azabicyclo[3.2.1] octanes as the resulting regioisomers are usually inseparable.

3.3. Norbornadiene rearrangement

A more robust synthetic method for the obtention of 2-azabicyclo[3.2.1]octane is through the rearrangement of norbornadiene **118**. Reaction with tosyl azide proceeds through (2 + 3)-cycloaddition to form a transient triazoline **119**, which is labile, and ring opens to the diazonium betaine **120**. Subsequent loss of nitrogen leads to formation of the fused-ring aziridine **121**. Compound **121** then slowly undergoes electrocyclic reaction opening the aziridine ring and providing the bicyclo[3.1.0]hexene imine **122**. Then, through an aza-Cope rearrangement, *N*-tosyl-2-azabicyclo[3.2.1]octa-3,6-diene **123** is formed (Scheme 19), which is the main precursor for the 2-azabicyclo[3.2.1]octane family.[17a,c]

Following the synthesis of 2-azabicyclo[3.2.1]octadiene **123** from norbornadiene **118**, Young and co-workers[17b] obtained the desired 2-azabicyclo[3.2.1]octane **125** through a two-step sequence reduction, using $LiAlH_4$ and hydrogenation. Direct hydrogenation of 2-azabicyclo[3.2.1]octadiene **126** with palladium catalyst results in 2-azabicyclo[3.2.1]octane **127** (Scheme 20).

Another approach to prepare 2-azabicyclo[3.2.1]octane core from norbornadiene was reported by Bergmeier and co-workers.[17d] In this case, a dihydroxylation of the C6–C7 olefin of **128** was performed using either AD-mix α or β, achieving excellent yields in both cases. The resulting diol was protected to

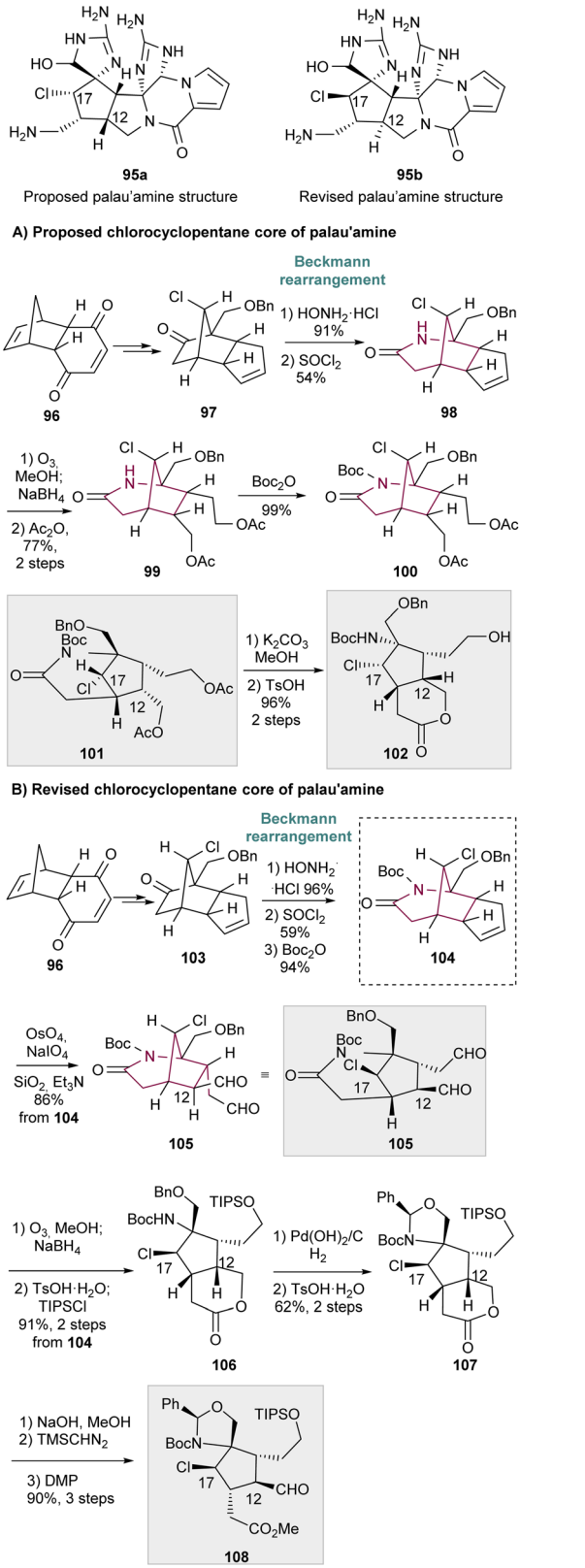


Scheme 14 Synthesis of 2-azabicyclo[3.2.1.]octan-3-ones **89a,b**.

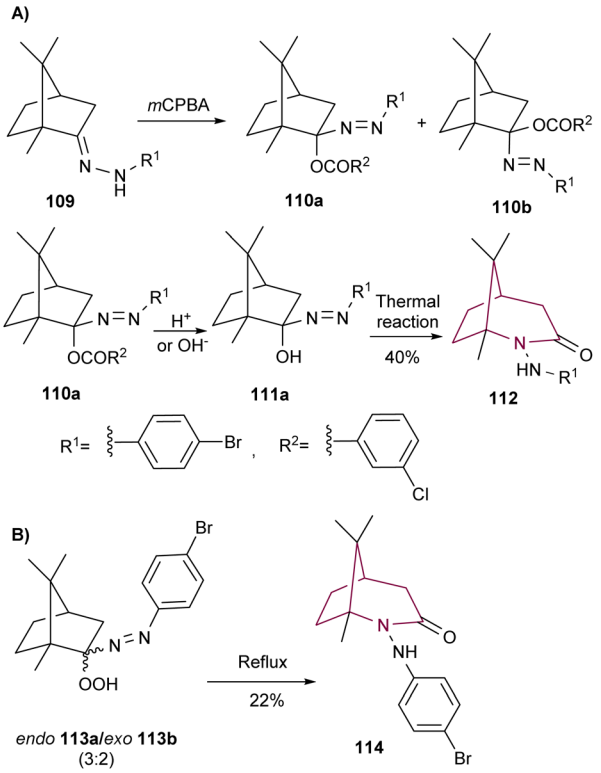
yield acetonide **129**. This was followed by insertion of a hydroxyl group at C4, yielding 4-*exo*-hydroxy-6,7-*exo*-isopropylidenedioxy-*N*-tosyl-2-azabicyclo[3.2.1]octane **130a** in 65% yield, together with the minor 4-*endo* isomer **130b** (Scheme 21).

The same research group reported another example of the selective functionalization of the double bonds of compound **128**.[17e] Selective reduction of the C6–C7 double bond of **128** resulted in bicyclic compound **131**. 4-Arylated and alkenylated products **132** were obtained with good yields *via* Suzuki coupling. Finally, hydrogenation of the C3–C4 olefin afforded saturated azabicyclo **133** (Scheme 22).

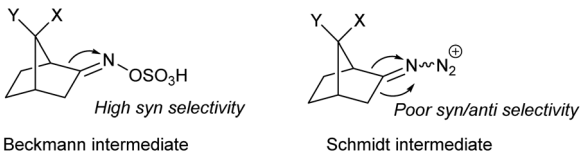
2-Azabicyclo[3.2.1]octane can also be prepared taking profit of traditional Cope rearrangement, which allows an equilibrium between compounds **134** and **135**, which are formed *via* epoxidation and rearrangement of norbornadiene. The mixture, when treated with excess methylamine, undergoes imine formation and 1,6-addition of methylamine, yielding **136** and **137** in equilibrium (Scheme 23). Only **137** reacts under hydrogenation conditions, resulting in 2-azabicyclo [3.2.1]octane **138** in 86% yield.[18b]



Scheme 15 (A) Synthesis of chlorocyclopentane cores of the proposed original structure of palau'amine. (B) Synthesis of chlorocyclopentane cores of the revised structures of palau'amine.



Scheme 16 Synthesis of 2-azabicyclo[3.2.l]octane **112** and **114**.



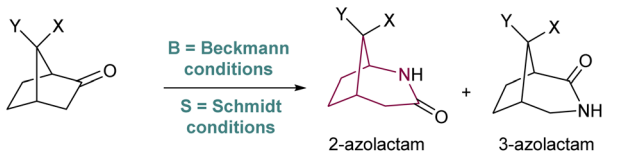
Scheme 17 Beckmann and Schmidt intermediates for the norcamphor system.

3.4. Photolysis

In addition to the Schmidt rearrangement, the azide group has also provided access to the azabicyclo[3.2.1]octane *via* photolysis. Lwowski and co-workers studied the irradiation of azidonorbornane **139** with UV light (310–410 nm or 254 nm) (Scheme 24). In alcoholic solvents, this reaction resulted in the formation of hemiaminal ethers **140** and **141** in 52–54% and 23–24% yields, respectively. Reduction of **140a** with $LiAlH_4$ resulted in 2-azabicyclo[3.2.1]octane **1a** in 33% yield, while reduction of **140b** gave **1b** in a much better 91% yield.[18a] A few years later, Sheridan and colleagues confirmed the reaction mechanism by methanol trapping experiments, showing that products **140** and **141** were formed through nucleophilic addition of alcohol to the highly reactive bridgehead imine intermediates.[18e]

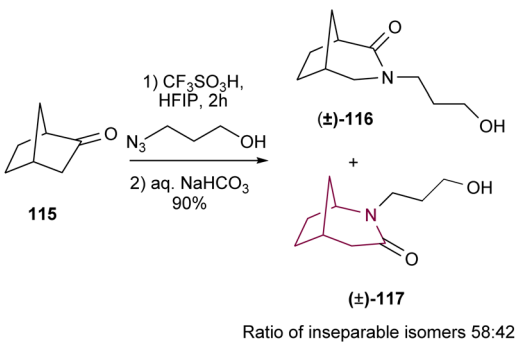
While some research groups have observed the formation of the 2-azabicyclo[3.2.1]octane system *via* rearrangement of oxaziridines of camphor[27] and norcamphor,[28] the low yields

Table 1 Regioselectivity studies of norcamphor derivatives under Beckman and Schmidt conditions



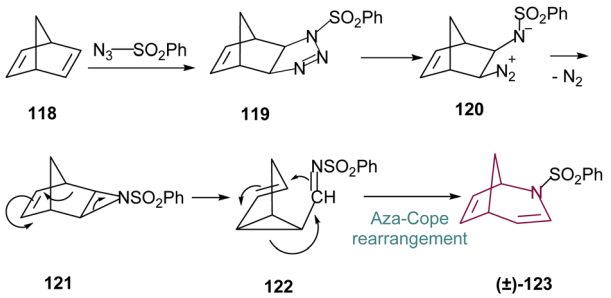
Entry	X	Y	Lactams yield	Ratio of lactams (2-aza : 3-aza)
1	H	H	B = 37% S = 35%	B = (90 : 10) S = (0 : 100)
2	OMe	H	B = 27% S = 48%	B = (100 : 0) S = (27 : 73)
3	Cl	H	B = 49% S = 22%	B = (100 : 0) S = (15 : 85)
4	Br	H	B = 53% S = 34%	B = (95 : 5) S = (19 : 81)
5	OTs	H	B = 27% S = 52%	B = (100 : 0) S = (65 : 35)
6	H	COOMe	B = 29% S = 31%	B = (100 : 0) S = (34 : 66)
7	H	Cl	B = 23% S = 29%	B = (100 : 0) S = (17 : 83)
8	H	Br	B = 57% S = 41%	B = (100 : 0) S = (0 : 100)
9	H	OTs	B = 38% S = 40%	B = (100 : 0) S = (64 : 36)
10	H (*exo*-5-Br)	COOMe	B = 64% S = 52%	B = (100 : 0) S = (48 : 52)

Beckmann conditions (B) = hydroxylamine-*O*-sulfonic acid in acetic acid; Schmidt conditions (S) = sulfuric acid and sodium azide in chloroform.

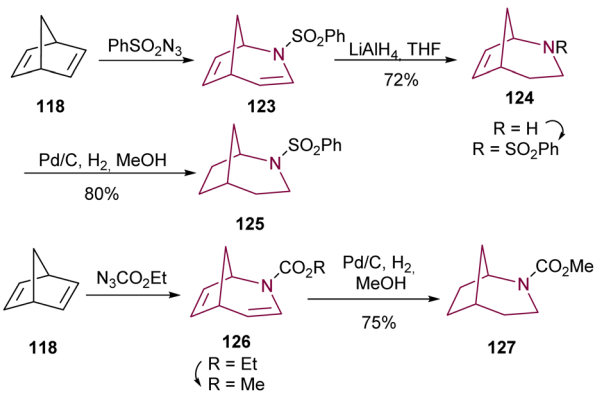


Scheme 18 Synthesis of azabicyclo[3.2.1]octane core *via* Schmidt reaction.

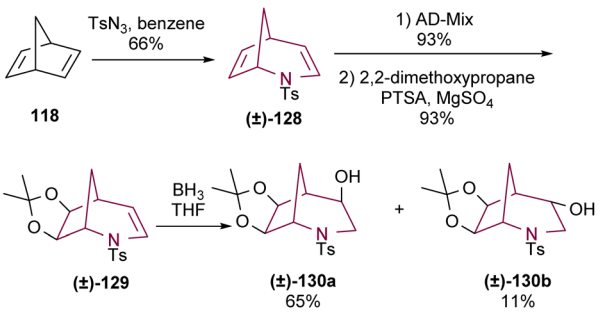
and poor selectivity have limited their applicability. Remarkably, Yamada and co-workers have tamed their reactivity through photochemical rearrangement of alkanenitronate anions like bicyclic nitro compounds **142a** and **142b**. After deprotonation and irradiation, isomerization of an oxaziridine intermediate gives access to the azabicyclo[3.2.1]octane hydroxamic acids **143a** and **143b** in good yields and selectivity. Then, reduction allowed the preparation of the corresponding azabicyclo[3.2.1]octane amides **144a** and **144b** (Scheme 25).[18c,d]



Scheme 19 Proposed mechanistic pathway for the synthesis of *N*-tosyl-2-azabicyclo[3.2.1]octa-3,6-diene **123**.



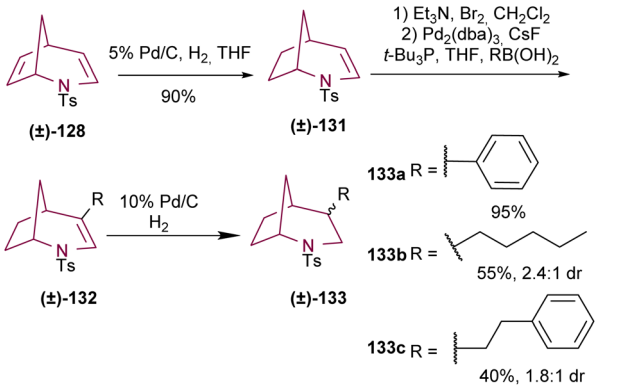
Scheme 20 Reduction of 2-azabicyclo[3.2.1]octadiene **123** and **126** to deliver 2-azabicyclo[3.2.1]octane **125** and **127**, respectively.



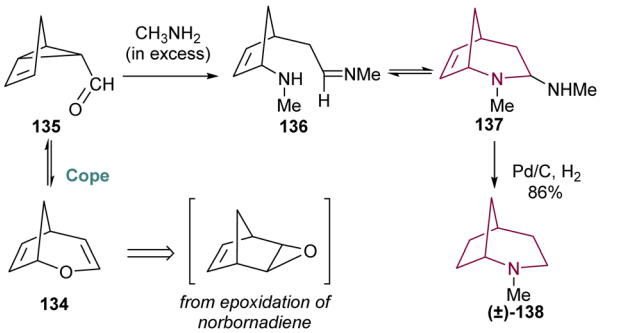
Scheme 21 Selective functionalization of 2-azabicyclo[3.2.1]octadiene **128**.

3.5. Mitsunobu promoted rearrangement

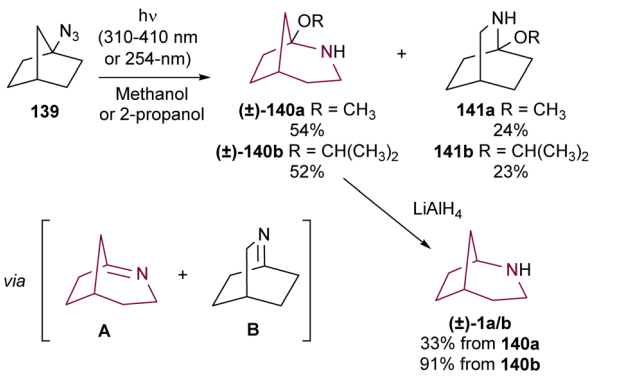
Wojaczyńska and co-workers reported the synthesis of 2-azabicyclo[3.2.1]octane system *via* rearrangement of 2-azabicyclo [2.2.1]heptane derivatives under Mitsunobu conditions[18g] or sulfonyl chloride/base (Scheme 26).[29] The reaction mechanism proceeds through activation of the primary alcohol and intramolecular nitrogen nucleophilic attack forming an aziridinium intermediate, which was then regioselectively opened by nucleophilic attack at the more substituted carbon, releasing ring strain in the [2.2.1]heptane system (Scheme 26A).



Scheme 22 Selective functionalization of 2-azabicyclo[3.2.1]octadiene **128**.

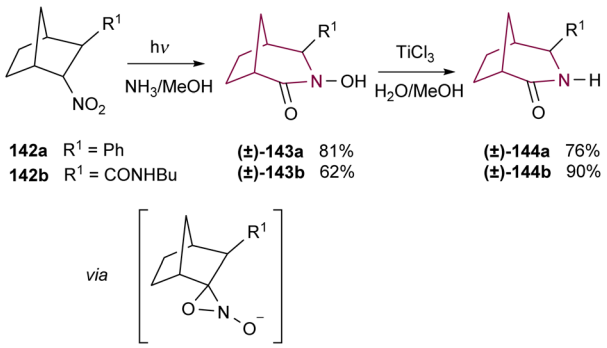


Scheme 23 Synthesis of 2-azabicyclo[3.2.l]octane **138** from **134**.

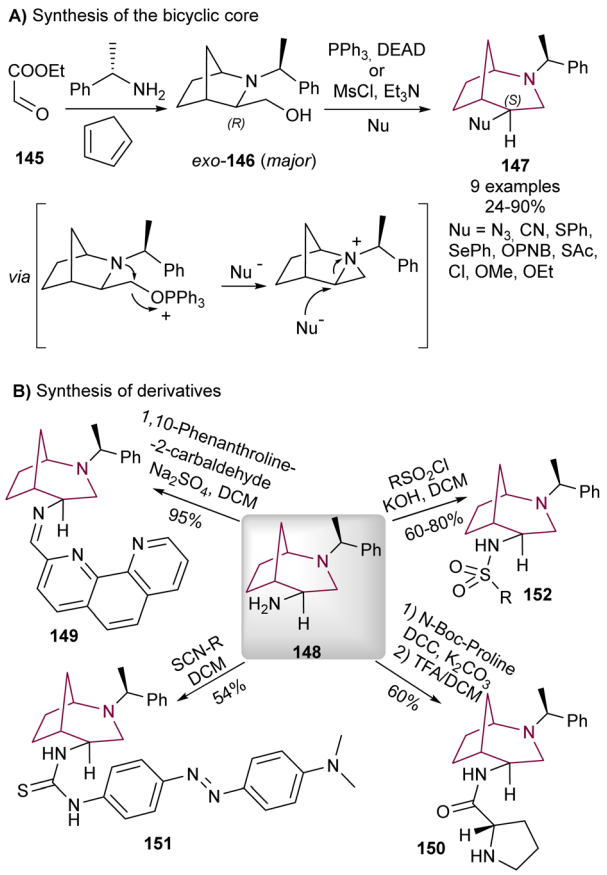


Scheme 24 Synthesis of 2-azabicyclo[3.2.1]octanes **140a,b** *via* photolysis of azidonorbornane **139**.

The correspondent rearranged products were obtained with inversion of configuration expected for S_N2 aziridine ring-opening reaction. The minor *endo*-**146** also undergoes the same aziridinium formation/regioselective ring opening isomer. The product derived from azide addition proved to be especially useful since after reduction to the amine **148**, it provided the bicyclic core a synthetic handle to install further functionalities (Scheme 26B).



Scheme 25 Synthesis of azabicyclo[3.2.1]octane core *via* rearrangement of alkanenitronate anions.



Scheme 26 Synthesis of 2-azabicyclo[3.2.1]octane **147** through Mitsunobu reaction (A), and synthesis of derivatives (B).

The same authors installed a 1,10-phenanthroline moiety *via* imine formation (**149**),[30] and a proline *via* amide bond (**150**).[29] These molecules were evaluated as catalysts for asymmetric aldol reactions, as the chiral and rigid core of the 2-azabicyclo[3.2.1]octane system could induce stereoselectivity. While a pioneer study in the utilization of the 2-azabicyclo [3.2.1]octane system in asymmetric organocatalysis, the *des* and *ees* obtained were not outstanding, and no other studies were performed in this topic. The free amine additionally proved useful for the synthesis of chiral thioureas (**151**)[31] and sulfonamides (**152**), the latter displaying promising antiviral[32] and antiproliferative activity,[18g] and also cytotoxicity to cancer cell lines.[7]

4. Summary and outlook

The 2-azabicyclo[3.2.1]octane system represents an important scaffold that is present in natural and synthetic products. The major interest in this structure lies in its prospective application as a class of bioactive molecules. Different biological activities have already been demonstrated by several research groups. On the other hand, it has also been shown that this core is often present as an important intermediate in the synthesis of other biologically active molecules. Therefore, efficient access to this scaffold is likely to bring new advancements within drug discovery. Current methods for its synthesis are still lacklustre, both in yield and in regioselectivity in most rearrangements. One major hindrance to the application of the 2-azabicyclo[3.2.1]octane in modern organic chemistry is the lack of direct asymmetric synthetic methods. Being a chiral highly rigid bicyclic system with a functional handle in the form of amine, its nearly absent use in asymmetric organocatalysis is surprising, which can be attributed by its synthetic challenge. In this Minireview, we have summarized several synthetic approaches for the obtention of the 2-azabicyclo[3.2.1] octane scaffold, highlighting their advantages and challenging limitations. Efforts are expected to be devoted to the development of more and efficient approaches to synthesize this bicyclic system, particularly in an asymmetric fashion.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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