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Azabicycles Construction: the Transannular Ring Contraction with *N*-Protected Nucleophiles

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Synthetic strategies are one of the most critical factors for the success of a synthetic campaign, but most importantly they are crucial for the economy and the efficiency of the sequence. Within this perspective, the synthesis of azabicyclic scaffolds, constituents of many bioactive alkaloids, can be tackled using tandem transannular ring contractions-protecting group cleavages. Commonly these reactions feature medium-sized cyclic *N*-protected amines that carry a potential electrophilic site. Under the correct conditions this site is activated, and the protecting group is fragmented, inducing a transannular reaction. For the first time, we review in detail this strategy's applications, which span from the assembly of small molecules to complex molecular architectures.

Introduction

Azabicyclic systems are key frameworks in organic compounds. In particular, their bridgehead nitrogen motif is a feature in many alkaloids.[1] The synthesis of such structures poses challenges in regard to efficiency, *i.e.* the ability to minimize the number of steps and side-products, along with the use of high-yielding reactions.[2] The transannular cyclization of medium-sized rings is an excellent strategy towards the enhancement of molecular rigidity and structural complexity, two properties often associated with biological activity of alkaloids (Figure 1).

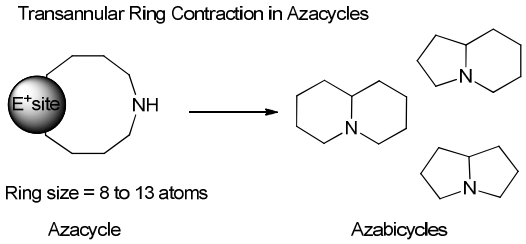


Fig. 1 TRCs in medium-sized azacyclic molecules exploit the presence of both a potential electrophilic site and nucleophile in the ring to deliver azabicycles.

Therefore, the adoption, in synthetic strategies, of tandem transannular ring contractions/*N*-protecting group cleavage reactions which allows to increase molecular complexity in the minimal amount of steps is of paramount importance. This tandem synthetic strategy has been successfully applied to the construction of azabicycles. The inherent difficulty to gather and categorize the literature regarding such synthetic strategies probably thwarted any previous reviewing efforts. In this review we will evaluate an attractive strategic choice for the construction of bicyclic amino compounds. In particular, the synthetic strategy which involves transannular ring contractions (TRCs) in concert with the deprotection of the nitrogen, applied to medium-sized azacycles (8 to 13 atoms) will be the main focus of the discussion (Figure 1).

In TRCs, nitrogen is the nucleophilic site, while the electrophilic site is commonly generated by activating a double bond.[3] The presence of an *E*-double bond within a medium-sized ring introduces stereogenic information to the ring structure due to planar chirality,[4] thus opening opportunities for stereoselective transformations. Furthermore, transannular reactions of the kind described above are generally regio- and diasteroselective, in most cases affording a single product.[5,6] This specificity is due to the strain experienced by the ring as a result of the cross-ring interactions. The strain locks the conformation of the molecule, thus setting a significantly different distance between the lone pair of the nitrogen and each of the sp^2 carbons.[7] This effect means that with careful planning and prior computational studies, it is possible to achieve reliable predictions as to the outcome of the reaction. Such TRCs (Figure 1) are applicable to the formation of pyrrolizidine (5,5), indolizidine (5,6) or quinolizidine (6,6) structures, although, in nine and ten membered rings an additional strain is needed to retard the normally rapid ring inversions. To this end, it is possible to rigidify the structure of the molecule introducing a lactam moiety and a protecting group.[7]

Transannular ring contractionspresent the possibility of introducing a protecting group at the nitrogen atom, and subsequently remove it in concomitance with the transannulation reaction (Figure 2). Considering that in the multi-step synthesis of complex natural products it is necessary, in most cases, to protect secondary amines, this approach presents a clear advantage.[8]Additionally, due to the wide variety of protecting groups available for amines[9] and corresponding cleavage conditions, which can concurrently trigger the transannulation, TRCs are a powerful and tunable tool for the synthesis of

azabicycles.

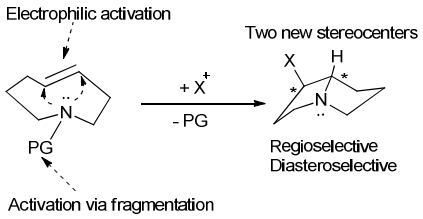


Fig. 2 The formation of a pyrrolizidine *via* transannular nucleophilic attack from a protected secondary amine. The same approach is also applicable to nine and ten-member rings.

However, the range of factors that regulate transannular reactions, such as those described thus far, makes it somewhat difficult to categorize them and, to group their reaction mechanisms under general headings. Nevertheless, the characteristics that hold true for the various systems can be found in seminal publications,[3,6,7] and from those we can appreciate the various distinctions between mechanisms.

Herein, we review transannular ring contractions involving *N*-protected nucleophiles. First, the factors that control the transannular nucleophilic attack by unprotected nitrogen will be introduced, followed by the effect of the presence of various protecting groups, on the result of the reaction. Afterwards, a series of substrates and activators will be presented and compared to other approaches to build the same scaffolds. Finally, the application of tandem transannular *N*-alkylations and protecting group cleavage on complex natural products will be discussed.

The Essential Classics

The mechanism of "classical" transannular cyclizations in eight-membered rings, with secondary amines and soft electrophile activation, was studied extensively by Sawicki and Wilson at the end of the 1970s.[7] In their seminal publications, they underlined the importance of this methodology in the synthesis of alkaloids by virtue of its stereospecificity and the concomitant introduction of a functional group at the C1 position of the newly formed pyrrolizidine.[7]

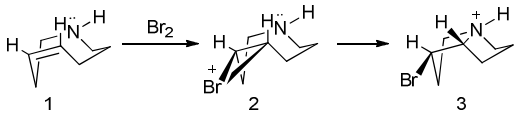


Fig. 3 Example of the mechanism of activation in the transannular reaction of olefinic cyclic amines through formation of a bromonium ion and subsequent regiospecific attack by the nitrogen.[7]

In their study, amino olefin **1** (Figure 3) was treated with a range of soft electrophiles (Br_2, I_2, $HgCl_2$, PhSeBr, PhSBr). These electrophiles approach the double bond preferentially from the less hindered face with formation of an onium ion. If Br_2 is used to activate **1**, bromonium ion **2** is obtained. Subsequently, the latter is attacked by the nitrogen atom, affording only *trans* geometry. This *anti* addition mechanism precludes a mechanism involving dibromide formation, which would lead to a different stereochemistry.[7] Additionally, transannular interactions between the nitrogen lone pair and the olefinicπ-electrons were found to be absent, in contrast to the case of smaller rings,[10] thus indicating that it is the conformation that controls the reaction.

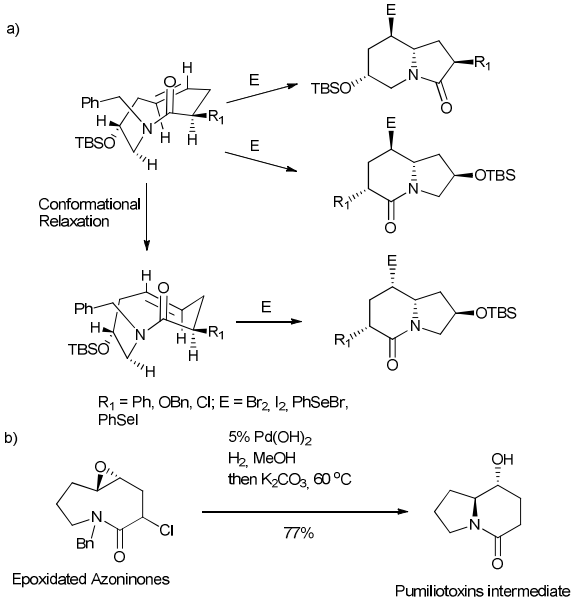
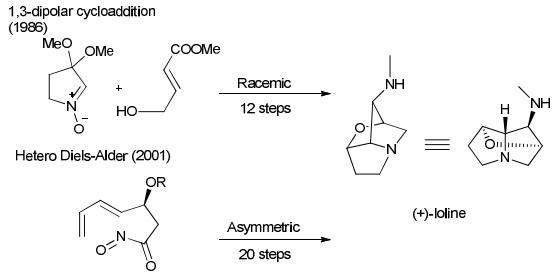


Fig. 4 a) Challenges presented by nine membered ring lactams: conformational relaxation and low regioselectivity lead to stereochemically distinct products[11]; b) The bicyclic core of Pumiliotoxins can be prepared through Pd mediated deprotection, with concomitant C-Cl bond reduction and an epoxide opening.[13]

Azoninones (nine membered cyclic amino olefins), on the other hand, present more stereochemically allowed pathways than hexahydroazocine (Figure 4a), even when the additional constraint of a lactam is added. This difference is due to conformational relaxation that flips the lactam with respect to the olefin, hereby modifying the two planes of chirality that are present. Additionally, depending on the substitution pattern on the ring, the distance between the nitrogen and the two olefinic carbons changes, affecting regioselectivity.[11]

What remains as the common feature with the TRCs in eight-membered rings is the onium ion formation and *anti* addition.[11] Furthermore, the substrates, shown in Figure 4, undergo tandem TRCs-cleavage reactions. Specifically, protected lactams (Bn, Dmb) undergo transannular reactions with various electrophiles with concomitant deprotection of the resulting cyclized acylammonium moiety.[11, 12]

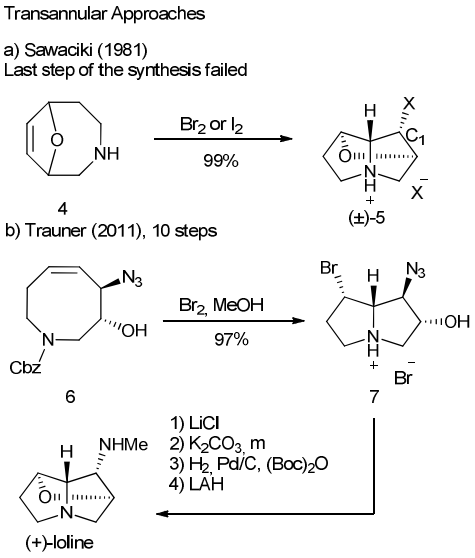


Scheme 1 Key steps and features of previous strategies towards the synthesis (+)-loline.

These "classical" features of the TRCs are illustrated elegantly in the total synthesis of (+)-loline, an alkaloid found in tall fescue grass.[14] The loline family of azabicycles is characterized by a strained pyrrolizidine and morpholine three ring-systems. Of the previously reported syntheses,[15,16,17] the racemic one from

Tufariello *et al*.[15] was achieved in 12 steps (Scheme 1), while the first asymmetric approach featured a total of 20 transformations to reach the target.[16]

The first transannular approach to loline was attempted by Wilson and Sawicki, featuring a five-step synthesis of unprotected bicycle **4**from furan (Scheme 2a). The bicycle **4**, underwent regioselective and stereospecific transannular ring-contraction to afford racemic **5**.[3,18]



Scheme 2 Transannular approaches to loline: a) the reaction is high yielding and does not produce sideproducts b) in a single transannular reaction the olefin is activated and the Cbz group, which protects the bromonium ion from the solvent, is cleaved.

Unfortunately, the following and final S_N2 displacement at the C1 position could not take place due to the hindered norbornane scaffold and the electronic repulsion between the incoming nucleophile and the nitrogen lone-pair.[18] Despite the possibilities in the framework construction offered by TRCs, in this case the limitations lied in the electrophile scope, since only Br_2 and I_2 afforded **5**. Aminopalladation was attempted as an alternative, but failed to yield the desired product delivering a palladium-amine-olefin complex instead.[7,18]

In 2011, the Trauner group exploited a similar strategy using Cbz-protected amino olefin **6**, which was synthesized *via* RCM in five steps (Scheme 2b).[19] Amine **6** undergoes a transannular reaction under mild conditions affording the salt **7**. Here, the Cbz group, required for a previous metathesis step shields the bromonium ion from rapid attack by the solvent, which, instead, subsequently to the acylammonium formation, cleaves the carbamate. This asymmetric ten-step synthesis follows, in its key step, the already described rules: conformational preorganization dictates the regio- and stereochemistry, and the protecting group is cleaved during the stereospecific reaction step

Alexine Alkaloids

Alexine alkaloids (polyhydroxylated pyrrolizidine) are a family of potent bioactive compounds, particularly glycosidase inhibitors.[20] The dense hydroxyl decorations and the pyrrolizidine scaffold make these alkaloids attractive targets for a transannular synthetic strategy. Thus, many of their representative compounds have been synthesized using this approach (Figure 5).

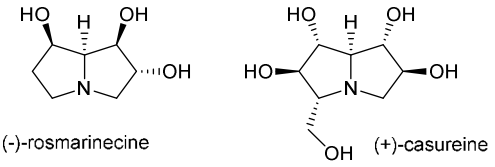
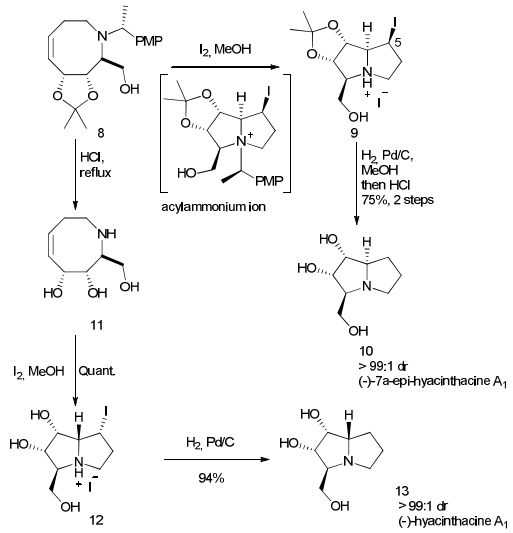


Fig. 5 Two representative compounds of the alexine alkaloids: (-)-rosmarinecine and (+)-casureine.[20]

For example, in 2011, the Davis group developed a "*transannular iodoamination with concomitant N-debenzylation*".[21] This reaction was applied on the hexahydroazocine **8**,provided with an *N*-α-methylbenzyl amine protecting group and an acetonide-protected *cis*-diol that introduce conformational strain (Scheme 3). Amino-olefin **8** can undergo a reversible iodonium formation, which is attacked by the protected nitrogen, affording a transient ammonium ion. The protecting group is then cleaved leading to product **9**.[21]Alternative protecting groups other than carbamates, such as *N*-benzyl for instance, can be employed successfully, provided that their elimination is not hindered.

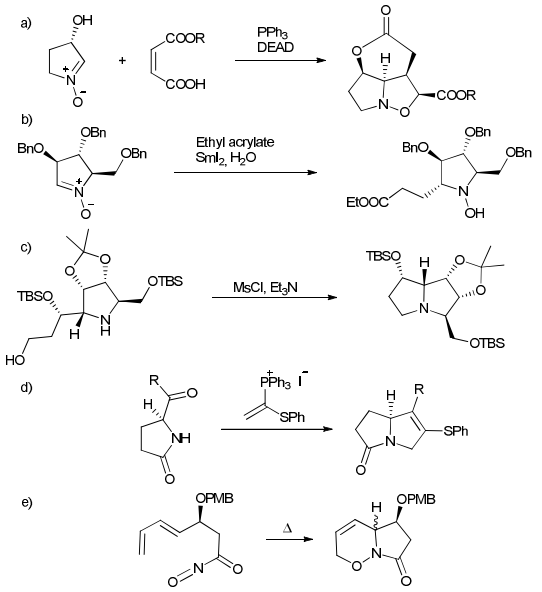
The transannular strategy for this alkaloid family permits fine-tuning of the reaction's stereochemical outcome, as Davis *et al*. have demonstrated in the synthesis of the epimeric natural products **10** and **13** from a common precursor-hexahydroazocine **8** (Scheme 3).[22] When **8** is directly subjected to the iodoamination reaction, iodine adds from the *Si* face with respect to C5, affording compound **9**, and subsequently, **10** with complete stereocontrol. On the other hand, the removal of the protecting groups from **8** to afford **11,** followed by iodoamination, has enabled the stereospecificity to be inverted with addition to the *Re* face (**12**).



Scheme 3 Tuning of the transannular reaction permits control over the stereochemistry of the product.

This work demonstrates that the obtained stereochemistry is directly controlled by the conformation of the ring. Compound **8**leads to intermediate **9** due to the conformation that avoids the

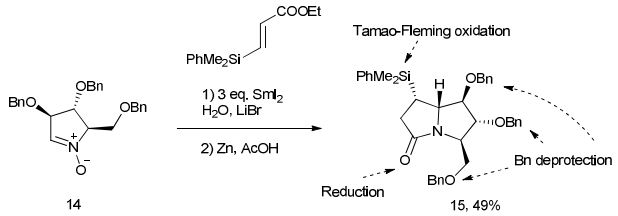
1,2-strain between the substituents on the nitrogen and on C1, while the transformation of **11** to **12** prefers the 1,2-strain, hereby changing conformation and thus result.[22]



Scheme 4 Selected routes to pyrrolizidine synthesis: a) [3+2]-cycloadditions; b) nitroneumpolung; c) intramolecular alkylation; d) Wittig vinylphosphonium ring-closure; e) hetero Diels-Alder.

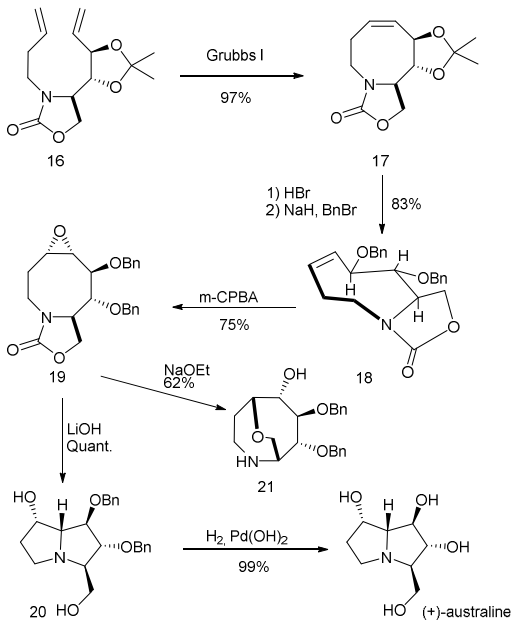
A number of non-TRC methods to assemble the pyrrolizidine core have been developed as well and can be compared (Scheme 4).[23]For instance, nitrones are an important tool in [3+2]-cycloadditions that lead to isoxazolidine formation (Scheme 4a).[24,25,26]Another approach can be to use nitrone umpolung mediated by SmI_2 (Scheme 4b).[27] These are attractive methods, but the products then require a reduction and a second ring closure.[28]Alternatively a common intramolecular alkylation can be used (Scheme 4c).[29] The Wittig reaction, using a vinylphosphonium salt (Scheme 4d),[30]enables in one step both ring-closing and introduction of an easy to functionalize substituted olefin. As noted in section 2, hetero Diels-Alder[31]reactions have been used with success to access pyrrolizidine scaffolds in a stereocontrolled manner (Scheme 4e). However, again further transformations are necessary.

Perhaps a more readily comparable example is the synthesis of (+)-australine, a representative compound of the alexine alkaloids, featuring five contiguous stereocenters (Schemes 5 and 6). To date, the two most efficient and shortest syntheses that have been reported both comprise 11 steps. The first, which exploits a "*SmI_2 mediated cross-coupling of nitrones with β-silyl acrylates*" was accomplished with an overall yield of 21% (Scheme 5).[28]The second synthesis was completed with an overall yield of 35% and employed a transannular ring-contraction strategy (Scheme 6).[32] Even though the yield of the second synthesis is higher, it is important to note that the starting material in the latter approach is an epoxide that was prepared in three steps. In the former approach L-xylose was employed, which was converted to nitrone **14**. This compound was reacted with a silyl acrylate in diasteroselective manner, followed by reduction of the N-O bond with zinc to afford bicyclic amide **15**(Scheme 5). A notable drawback of this synthetic strategy lies in its key step, which is relatively low-yielding (49%) and the need for additional reduction of the newly formed amide.[28]



Scheme 5 Non-TRC synthetic strategy employed in the synthesis of (+)-australine: samarium-mediated coupling and subsequent reduction-annulation with zinc.

On the other hand, the transannular approach to (+)-australine resulted in a quantitative yield (99%) in regard to the ring-contraction reaction (Scheme 6).[33] Moreover, ring closing metathesis (RCM) was employed to build the hexahydroazocine scaffold, with excellent yield (97%).[32]The high yield of this RCM to form **17** from **16** can be rationalized by consideration of the conformational strain induced by the acetonide and the templating effect of the 2-oxazolidinone *N*-protecting group that tethers the reacting alkenes.[34] Subsequently, the acetonide group was replaced by a bis benzyl ether (**18**). The replacement is necessary because transannulation attempts on an acetonide protected substrate failed. To rationalize this, the authors have proposed that a conformational reorganization of the ring is necessary to orient the nitrogen for internal S_N2 on the epoxide. If the *trans*-fused five-membered acetonide is present on the ring the energy barrier for the reorganization is too high and thus the displacement does not take place.[33a]



Scheme 6 Construction of hexahydroazocine scaffold **19** and execution of the transannular reaction to afford precursor **20** and ultimately (+)-australine.

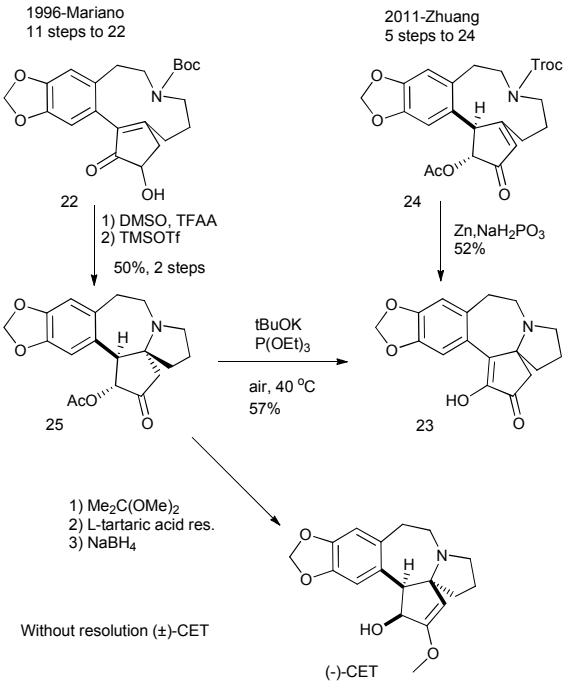
The conformation of **18** shields the β face of the olefin, resulting in a fully selective epoxidation to **19**. At this stage the double bond is activated as an epoxide, and the TRC triggering step is

the removal of the 2-oxazolidinone. The benefit of having a carbamate group is again highlighted in this elegant strategy. Additionally, it is important to notice that only CO is lost in the deprotection, while the methanol fragment is retained within the compound's structure. This reaction was performed with LiOH affording di-*O*-benzyl australine **20** in quantitative yield. Lithium as an oxygen coordinating cation is crucial in this step. Indeed, a cation with lower affinity (Na^+) affords ether **21**. Tandem TRCs-cleavages are thus highly dependent on the substrate, and hence require detailed planning.

The Opportunities for Divergence

The TRC strategies that have been discussed above were applied to the synthesis of small molecular scaffolds, mostly concerning eight-membered rings. However, TRCs are not limited to this set of compounds and, indeed, have been applied successfully in the total synthesis of more complex structures. They deviate from the previously described "classical" features (a double bond activated by forming an onium ion or epoxide) although they fall within the general TRC-approach.

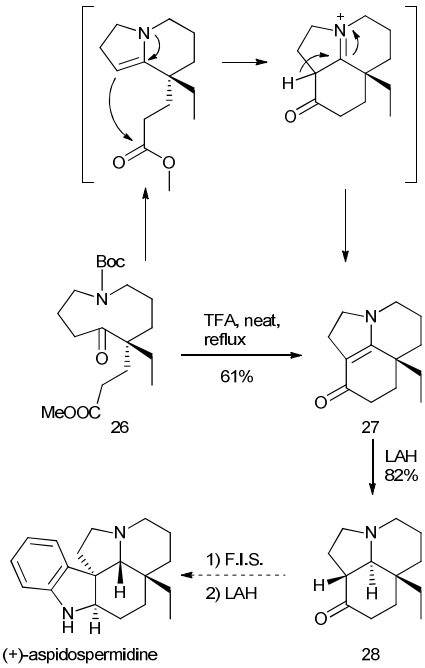
A notable example is that of Cephalotaxine ((-)-CET), an alkaloid whose ester derivatives exhibit anti-cancer activity.[35] Its structure is composed of a benzazepine core fused to a spirocyclopentane bicycle (Scheme 7).[36] The bioactive esters were recently submitted for pharmacological licensing, which prompted the development of several racemic and asymmetric syntheses.[37] These syntheses were in general quite efficient and involved the use of a benzazepine scaffold[37c] or a spiroamine[37a] as the starting material. Additionally, two syntheses exploiting a transannular strategy were reported,[38,39] differing in the amine protecting groups and electrophilic sites that have been used (Scheme 7).



Scheme 7 Two transannular approaches to the racemic synthesis of (-)-CET and subsequent resolution.

The first synthesis from Mariano *et al.*[38] starts form (iodopiperonyl)ethanol to afford compound **22** in eleven steps. Following a Swern oxidation, this compound was treated with TMSOTf to remove the Boc protecting group, which enabled an aza-Michael cyclization to yield **23**. Here, the electrophilic olefin in the Michael system defines the regioselectivity of the addition. It is noteworthy that, although the chirality of compound **22** can be observed on ^{1}H NMR scale[38] due to the slow rotation around the double bond, the TRC does not proceed with a defined stereochemical outcome. Under other conditions it may be possible to obtain **23** avoiding the probable racemizing retro-reaction. Fifteen years after this report,[39] a racemic synthesis followed a similar strategy, with some notable differences, namely the protecting group and the positioning of the electrophilic site. Starting from dihydro(dioxolo)isoquinoline, Zhuang *et al.*[39] synthesized Troc-protected azecine **24** through a stereospecific oxy-Nazarov cyclization. Subsequently, the Michael system, which in this case is exocyclic, was activated by protonation. Simultaneously, the Troc group was cleaved by reduction with zinc, affording **25** in a diasteroselective manner, albeit with the wrong configuration at the newly formed stereocenter. The main drawback of this strategy is determined by the subsequent oxidation, which removes one asymmetric center and racemises the other. Therefore, both had to be reset, reducing the effectiveness of the synthesis through additional steps and chiral resolution,[40] in order to obtain (-)-CET.

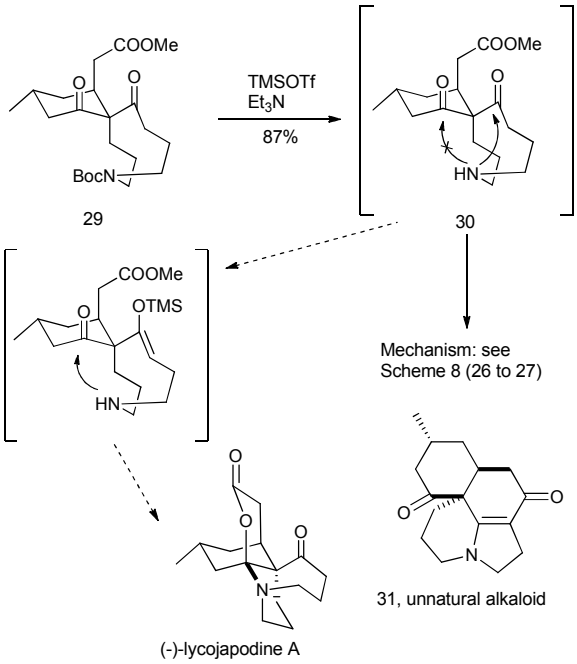
These examples highlight how electrophilic sites in TRC strategies can be quite complex to understand, in contrast to the "classical" double bond functionality. Nevertheless, the reaction pattern is still recognizable, and remarkably the same strategy (aza-Michael-driven TRC) can be applied in two distinct ways, to obtain the same target intermediate **23**.



Scheme 8 Substrate **26** undergoes a cascade reaction upon treatment with TFA. The obtained vinylogous amide **27** can be readily reduced to tricyclic ketone **28**. (+)-Aspidospermidine can be synthesized from this intermediate in two steps; F.I.S. = Fischer Indole Synthesis.

The continued diversification in the range of applications where

TRCs are used to construct ever more complex frameworks is exemplified in the case of a recent formal enantioselective synthesis of aspidospermidine.[41,43] It features an "*intramolecular cascade transannular cyclization*" to form a tricyclic vinylamide (Scheme 8).[42] This reaction, whose product **27** is one step away from Stork's tricyclic ketone **28**,[43] was carried out under relatively harsh conditions,[44]and yet delivered in 61% yield. Under these conditions the TFA cleaves the Boc group and promotes condensation with the ketone. Subsequently, the resulting iminium ion tautomerizes to the enamine. The latter attacks the ester moiety intramolecularly, closing the tricycle to provide **27**.[42]Finally, through a reduction it is possible to obtain **28**, which can be readily transformed in (+)-aspidospermidine (Scheme 8). For comparison, other enantioselective syntheses of (+)-aspidospermidine have been reported,[45] of which the most successful was reported by MacMillan.[45d]This synthesis features an impressive catalytic organocascade step to achieve a core tetracyclic scaffold, that permits transformations to different natural products. Thanks to this, the linear synthesis is short, highly enantioselective, and high yielding and not least, elegant.

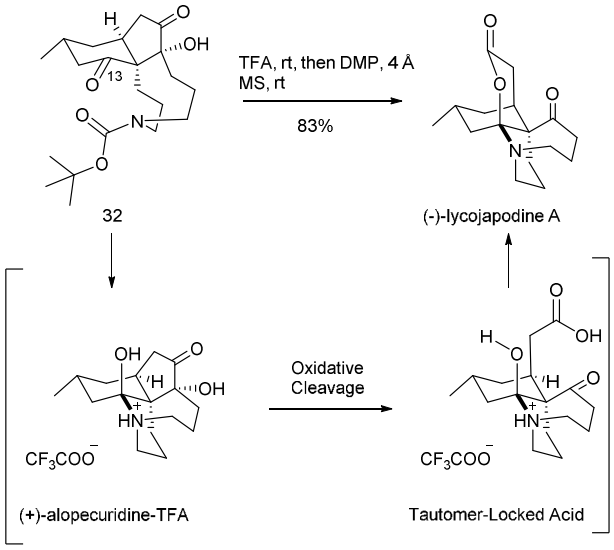


Scheme 9 Attempt to synthesize (-)-lycojapodine A. TRC were unfruitful delivering instead vinylogus amide **31**.

TRCs with concomitant protective group cleavage offer the possibility of positioning the electrophilic moiety exocyclic to the ring. An example hereof are the syntheses of (-)-lycojapodine A.[46,47] The first strategic attempt of the synthesis involved the treatment of compound **29** with TMSOTf (Scheme 9).[46]Both a selective protection of the most reactive carbonyl group and the triggering of a TRC to obtain (-)-lycojapodine A were expected. Instead, compound **31** was obtained in 87% yield, which is clearly the product of the same reaction pathway illustrated in Scheme 8.

In 2013, another attempt to achieve this synthesis was reported by Lei *et al*.,[47] starting from the acid analogue of ester **29**. Treatment of this acid with TFAA resulted in the formation of a mixed anhydride and TFA *in situ*. Subsequent Boc deprotection leads to a similar to **30** reactive intermediate, consisting of mixed anhydride and free amine moieties. At this point the equilibrium between the reversible carbinolamine formation and the irreversible transannulation/dehydration leads to **31**. Seemingly, the ring strain released by the tricycle formation out-competes formation of the hemiaminal.

The described approaches were part of a biomimetic[48] synthetic strategy based on the proposed biogenetic pathways for this kind of *Lycopodium* alkaloids.[47] The synthesis of (-)-lycojapodine A was achieved *via* a biomimetic strategy that exploits a one-pot protocol. When substrate **32** (Scheme 10) was treated with TFA, the Boc group was cleaved and the corresponding hemiaminal was formed. Hence, the formed (+)-alopecuridine-TFA salt undergoes oxidative cleavage and lactonization to afford (-)-lycojapodine A upon addition of DMP and molecular sieves.[47]

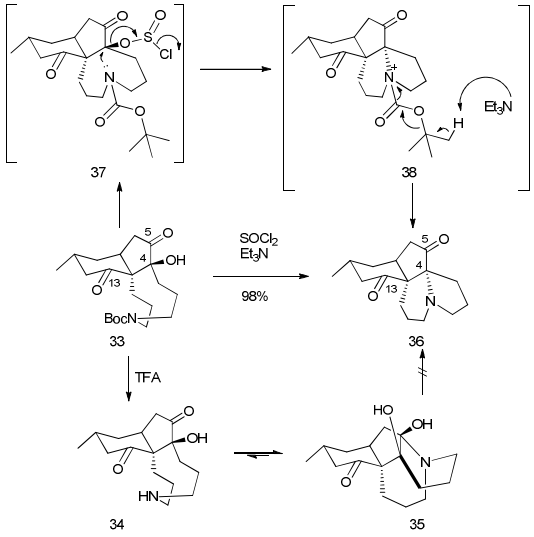


Scheme 10 Biomimetic synthesis of (-)-lycojapodine A *via* TRC-PG cleavage with subsequent oxidative cleavage and lactonization.

The azabicycles forming reaction can be viewed as an example of TRC where the electrophilic site, in **32,** is the exocyclic ketone (C13). This can be regarded as a substituent on the Boc protected azecine. Interestingly, the group of Wang *et al*.[46] obtained the natural product by first isolating the (+)-alopecuridine-TFA salt, by treatment of **32** with TFA, and then employing MnO_2 in a separate oxidative-cleavage/lactonization step.

The TRC strategy was also applied for the preparation of other *Lycopodium* alkaloid family members. The key step in the synthesis of (-)-8-deoxyserratinine, (+)-fawcettidine, (+)-fawcettimine, from the group of Lei,[47,49] was a "*tandem transannular N-alkylation and removal of the Boc group*" (Scheme 11).Cleavage of the protecting group with TFA, from compound **33**, was attempted. Although this provided the desired amine (**34**), the following transannular reaction lacked the desired regioselectivity at the electrophilic site, attacking C5 to give carbinolamine **35**. The acidic medium failed to promote the removal of the alcohol and instead activated the ketone. It is remarkable that treatment of **33** with $SOCl_2$ and Et_3N circumvented this issue and delivered compound **36** in nearly quantitative yield. This efficiency underlines the importance of the protecting group, which is still present after the displacement

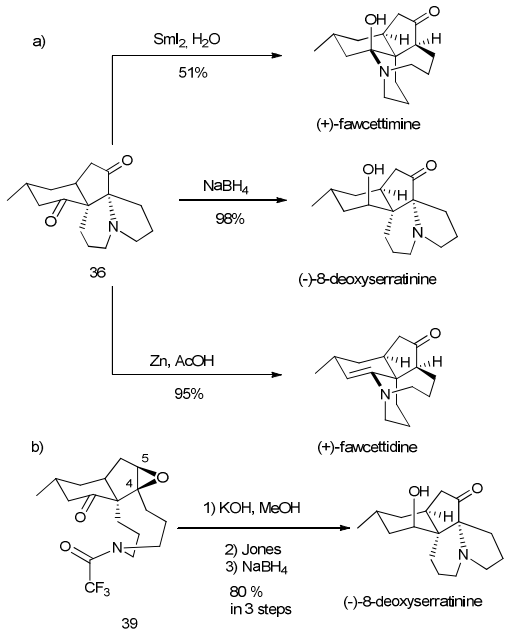
from the nitrogen of the newly formed leaving group (**38**).[49] Subsequently, the base is strong enough to trigger the cleavage of the acylammonium ion to afford **36**.



Scheme 11 Biomimetic TRC with concomitant Boc removal affords product **36**.[47] This reaction proceeds through a functional group interconversion (**37**) and acylammonium formation (**38**). Instead, if the Boc is cleaved first (**34**) then carbinolamine **35** is obtained.

Additionally, the importance of the ring conformation and the orientation of the nitrogen lone pair were confirmed by submitting the C4 epimer of **33** to the same conditions. Due to the *syn* orientation of the nitrogen lone pair the molecule underwent solely dehydration.[49]

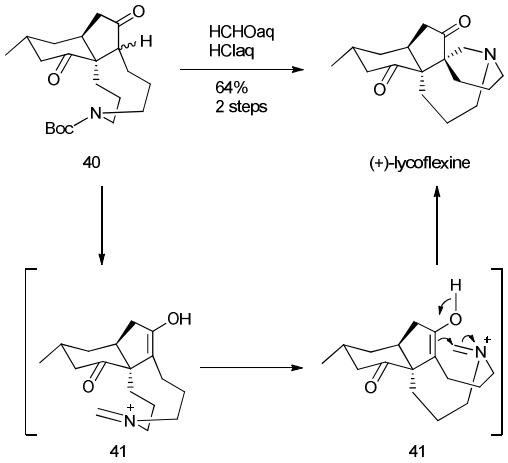
To conclude the syntheses, compound **36** was treated under different conditions to deliver various *Lycopodium* alkaloids as single stereoisomers (Scheme 12a).[49]



Scheme 12 a) Under specific conditions compound **36** can be transformed selectively in one of the following products: (-)-8-deoxyserratinine, (+)-fawcettidine, (+)-fawcettimine;[49]b) under basic treatment epoxide **39** undergoes TRC. Subsequent oxidation and reduction affords (-)-8-deoxyserratinine.[50]

In 2011, the group of Wei prepared epoxide **39** (structurally related to **33**), and protected the nitrogen with a trifluoroacetate group (Scheme 12b).[50] With this compound they were able to trigger the tandem cleavage-TRC reaction with KOH. A subsequent oxidation of the resulting alcohol at C5 afforded **36**, which could readily be transformed to (-)-8-deoxyserratinine.

Finally, an interesting natural product synthesis, that represents a paradigm shift in transannular ring contractions with correspondent protecting group cleavage, is (+)-Lycoflexine.[51]The first synthesis of (+)-lycoflexine involved the treatment of **40** with dilute HCl and formaldehyde (Scheme 13). This reaction triggered the deprotection of the Boc protected amine and subsequent iminum formation (**41**). Then **41** was attacked by the tautomerized ketone through a transannular Mannich reaction. Hence, (+)-Lycoflexine was isolated as one stereoisomer. This synthesis represents a paradigm shift since the nitrogen, which is presented throughout this review as the nucleophile, becomes part of the electrophilic moiety.



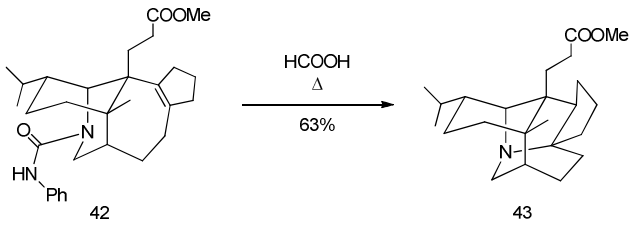
Scheme 13 In a single reaction **40** is deprotected and, subsequently, iminium **41** is formed, which then undergoes an intramolecular Mannich reaction to afford (+)-Lycoflexine.[51]

Summary and Perspectives

The aim of this review is not only to present the diverse features of a synthetic methodology but also to obtain a wider perspective on the context of the synthesis of azabicycles.

The concept of transannular ring contractions by *N*-protected nucleophilesis has shown to be useful in the synthesis of azabicyclic scaffolds with varying sizes. Moreover, in most cases the reactions are regioselective and stereospecific by virtue of the conformational strain, intrinsic to medium-sized rings. Additionally, a "classical" group of these specific transannular reactions is described and the several, albeit not an exhaustive list, of the more important syntheses that involve TRCs are discussed. The insights into the mechanisms governing TRCs are the most important factor described herein, facilitating application of the methodology. Indeed, the mechanisms proposed are evident for the transannular strategy for the preparation of (+)-loline, described in the second section. It is

important to note the possibilities that are opened up by the strategic use of protecting groups and activators. These can be implemented more generally, as was demonstrated for the synthesis of alexine alkaloids. Nevertheless, it is apparent from the literature that the "classical" TRCs are not used in the construction of quaternary stereocenters. Though presumably not a trivial task, the same strategy could be implemented on azacycles with tri- or tetrasubstituted alkenes to prepare stereodefined quaternary carbons in one step.



Scheme 14 The *N*-phenyl urea protected amino olefin **42** undergoes protecting group cleavage and stereocontrolled TRC to afford **43**.

Indeed such an example has been reported by Heathcock e*t al*.[52] in the synthesis of (±)-methyl homodaphniphyllate **43** (Scheme 14).

The possibilities available in terms of electrophilic partners in transannular ring contractions were discussed, as part of the strategy to obtain complex natural products. The successes and limitations of the approach where juxtaposed with other strategies. The limited scope of electrophiles used to activate the olefins in the rings is perhaps the most surprising feature. In fact, an expansion of the repertoire of electrophiles has been relatively limited over the last thirty years. For example, aziridination with iodinanes reagents have yet to be applied in TRCs.[53] As a final remark, it is of note that tandem TRC methodologies are still being developed, and continued expansion of the scope in terms of scaffolds can be expected in the near future.[54]

Notes and references

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