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Total Syntheses of Echinopines A and B, Sesquiterpenes with a Unique Tetracyclic [3-5-5-7] Skeleton

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ABSTRACT

This review covers the different syntheses of two sesquiterpenes with unprecedented tetracyclic [3-5-5-7] framework, echinopines A and B. The synthetic strategies and ring-forming sequences are presented with emphasis on the methods for the stereoselective construction of the stereogenic centers in the echinopane skeleton.

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1. Introduction

The synthesis of natural products of unique structure often allows innovation in strategy and can afford opportunities to develop new methodology. In this context, terpenoids occupy a unique position and pose significant synthetic challenges.

Echinopines A (**1**) and B (**2**), are two novel sesquiterpenoids isolated from the roots of *Echinops spinosus*, in 2008, by Shi and Kiyota.¹ These minor metabolites (0.12% yield) are characterized by an unprecedented tetracyclic [3-5-5-7] skeleton. This complex architecture features five contiguous stereogenic centers, two of them being quaternary; noteworthy, the 7-membered cycle adopts a chair-like form (Figure 1).²

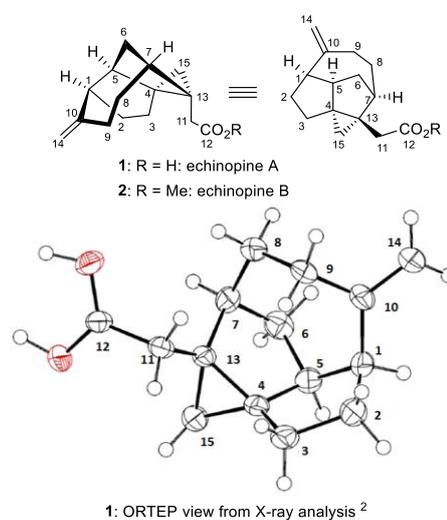
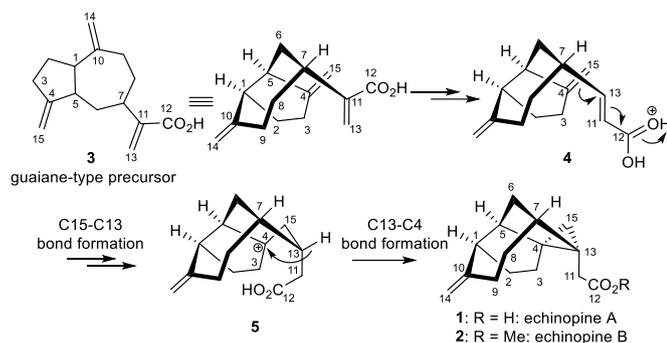


Figure 1. Structure of echinopines A (**1**) and B (**2**).

It has been suggested that the biosynthetic pathway of this unique echinopane framework may involve skeletal rearrangements from the guaianes type precursor **3**.¹ More particularly, a sequence including transformation of the [5-7] bicyclic ring system **4** into the [5-6-7] carbocation **5**, was proposed for the construction of the [3-5-5-7] tetracyclic echinopane skeleton (Scheme 1).



Scheme 1. Proposed biosynthetic pathway for the echinopane skeleton.

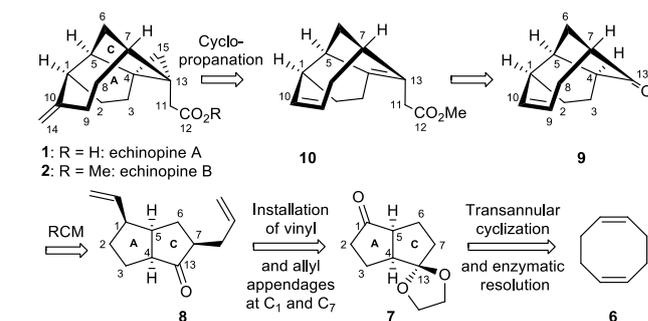
Although no biological activity has been uncovered so far, the original and complex structure of these natural products has motivated several research groups to embark on their total synthesis. Hence, only one year after their isolation, in 2009, Magauer, Mulzer and Tiefenbacher reported the first enantioselective total synthesis and determined the absolute configuration of these sesquiterpenes.² Thereafter, in 2010, 2011 and 2012, Nicolaou, Chen and Vanderwal described four total or formal bioinspired syntheses of these two natural products.³⁻⁷ More recently, in 2013 and 2015, Liang and Misra respectively achieved one total and one formal synthesis proceeding through original sequences.^{8,9} However, it is important to note that only the first syntheses, developed by Tiefenbacher *et al.*, Nicolaou and Chen have been performed in asymmetric form.²⁻⁶

Design of strategies for the stereoselective synthesis of such complex skeletons is particularly challenging. Thus, in this review, which surveys the synthesis of echinopines, emphasis will be laid on the strategies and ring-forming sequences. An overview of the methods developed for the stereoselective construction of stereogenic centers in the echinopane skeleton will also be presented.

2. Magauer, Mulzer and Tiefenbacher first total synthesis (2009)

The first total synthesis of echinopines A (**1**) and B (**2**) was achieved by Magauer, Mulzer and Tiefenbacher in 2009.² The strategy was based on the elaboration of the diquinane **8** bearing two *cis*-appendages at C1 and C7 (numbering identical to the final compounds). This intermediate was found suitable to build up the seven-membered ring by RCM and led to the tricyclic [5-5-7] intermediate **9**.

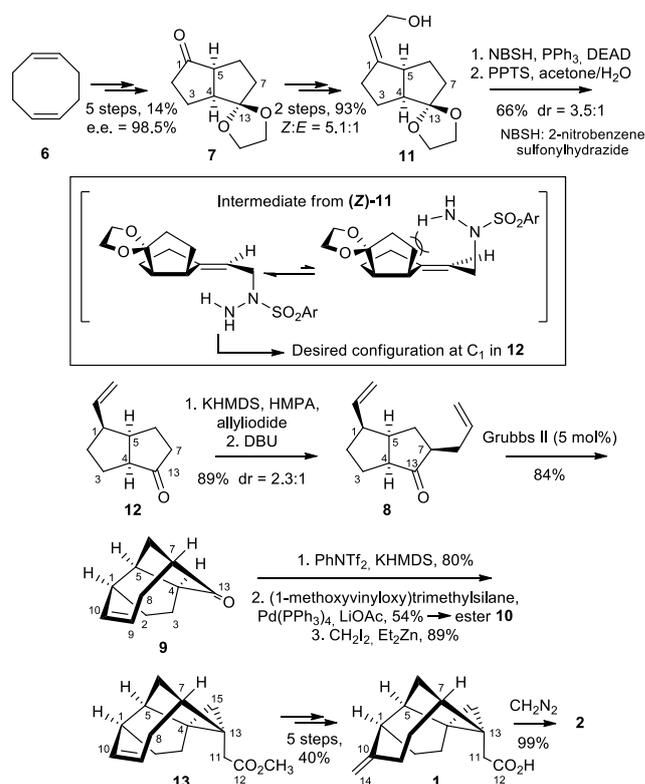
In turn, the precursor **7** of bicycle **8**, was easily prepared following a known procedure including a palladium chloride-mediated transannular cyclization and subsequent enzymatic resolution from commercially available cyclooctadiene **6**.¹⁰ Installation of the cyclopropane ring was accomplished at the end of the synthesis from [5-5-7] framework **10** (Scheme 2).



Scheme 2. Magauer, Mulzer and Tiefenbacher total synthesis: retrosynthetic analysis.

The synthesis started by converting cyclooctadiene **6** to optically active ketone **7** on multigram scale. Then, preparation of the RCM precursor **8** from bicyclic allylic alcohol **11** involved two key steps. The stereoselective installation of the vinyl moiety at C1 on the concave side of the bicyclo[3.3.0]octane core **11** was carried out through Myers [3,3]-sigmatropic rearrangement to give diastereomer **12** in 66% yield and 3.5:1 *dr*.¹¹ The stereochemical outcome of this efficient reductive transposition of allylic alcohol **11** could be rationalized by steric interactions with the adjacent cyclopentane ring. Then, allylation at C7, next to the ketone function of **12**, followed by epimerization under basic conditions, allowed the formation of the desired pure *cis*-diastereomer **8** (an easily separable 2.3:1 diastereomeric mixture was obtained).

The RCM reaction of the highly strained seven-membered ring of **8** smoothly occurred to yield tetracyclic adduct **9**. With **9** in hand, late-stage functionalization began with the unusual Pd-catalyzed C2-homologation of a vinyl triflate with a ketene silyl acetal (formation of ester **10**),¹² followed by regioselective cyclopropanation to afford the tetracyclic derivative **13**. Compound **13** was finally transformed into the target echinopines **1** and **2** (Scheme 3).

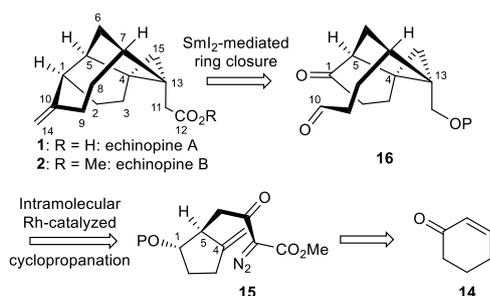


Scheme 3. Magauer, Mulzer and Tiefenbacher total synthesis.

The total syntheses of echinopines A (**1**) and B (**2**) were achieved in an overall 1% yield for 20(21) steps. The relative configuration of **1** was confirmed by single crystal analysis, whereas the absolute configuration of **1** and **2** unambiguously follows from the synthesis.

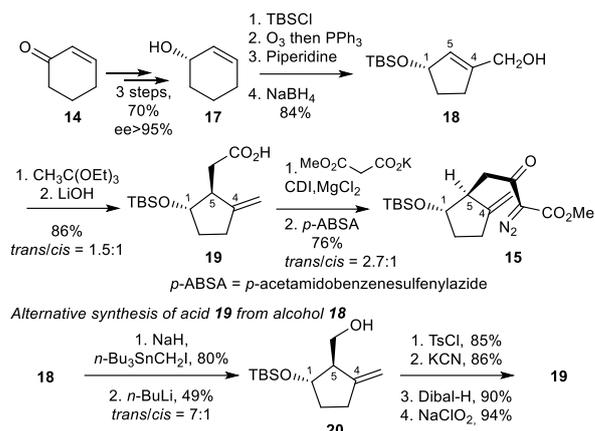
3. Nicolaou and Chen total synthesis (2010) “Chen’s first generation synthesis”

In 2010, inspired by the bond forming sequence suggested by the biosynthetic proposal of Shi and Kiyota,¹ Nicolaou and Chen considered a chemically equivalent intramolecular cyclopropanation process *i.e.* a late stage transformation of the [5-6-7] tricyclic ring system **5** into [3-5-5-7] echinopane skeleton of **1** and **2**. Unfortunately, this strategy met with failure primarily due to difficulties associated with the preparation of a suitable intramolecular cyclopropanation precursor. Therefore, in their first generation synthesis, they opted for a revised strategy that involved the simultaneous formation of the cyclopropane and one cyclopentane rings by means of a carbenoid intramolecular addition to the exocyclic olefinic bond of α -diazo- β -ketoester **15**, to afford the tricyclic [3-5-5] aldehyde **16**.³ The cycloheptane was generated at a later stage through an intramolecular SmI₂-mediated pinacol coupling reaction, from **16**. Diazo compound **15** was elaborated from cyclohexenone **14** (Scheme 4).



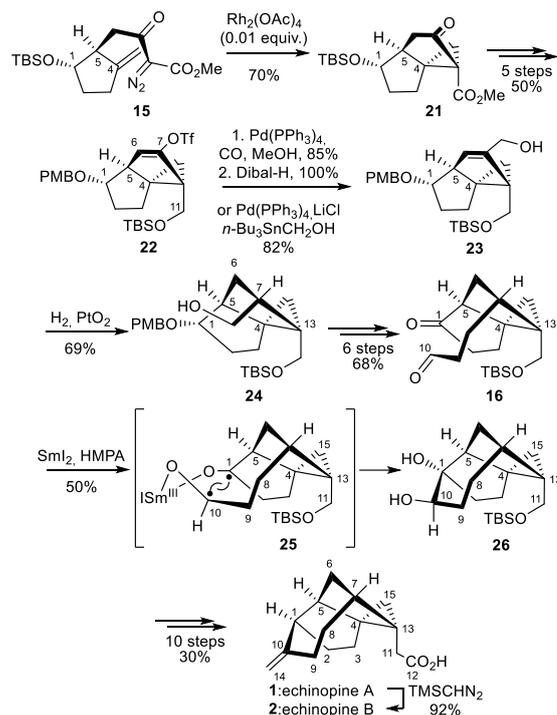
Scheme 4. Nicolaou and Chen total synthesis: retrosynthetic analysis.

Preparation of diazo ketoester **15** began from cyclohexenone **14** which was rapidly transformed into cyclopentyl allylic alcohol **18** by ring contraction of **17**. Subsequent Johnson-Claisen rearrangement afforded carboxylic acid **19** as a 1.5:1 mixture of *trans/cis* C5 diastereomers after saponification. Conversion into desired diazo ketoester **15** was carried out by a two-step procedure in the presence of methyl potassium malonate followed by exposure to *p*-acetamidobenzenesulfonyl azide (*p*-ABSA), with only a modest enhancement in the diastereomeric purity (*dr*: 2.7:1).¹³ Therefore, an alternative synthesis of carboxylic acid **19** from cyclopentyl allylic alcohol **18**, allowed to improve the diastereoselectivity to 7:1. The sequence involved [2,3] Wittig rearrangement of the alkenyl stannane derived from **18** and a one-carbon homologation of homoallylic alcohol **20** (Scheme 5).



Scheme 5. Nicolaou and Chen total synthesis. Formation of the α -diazo- β -ketoester intermediate **15**.

At this stage, heating diazo compound **15** in the presence of Rh₂(OAc)₄ (cat.) resulted in the formation of the desired tricyclic [3-5-5] system **21** in 70% yield as a single diastereomer. The synthesis of allylic alcohol **23** from **21** required seven or six steps *via* vinyltriflate derivative **22**. The next task was the elaboration of aldehyde **16**. To this end, the double bond of allylic alcohol **23** was stereoselectively reduced to afford **24** and the side chain was extended to the required 3-carbon length in a six-step sequence (Scheme 6).



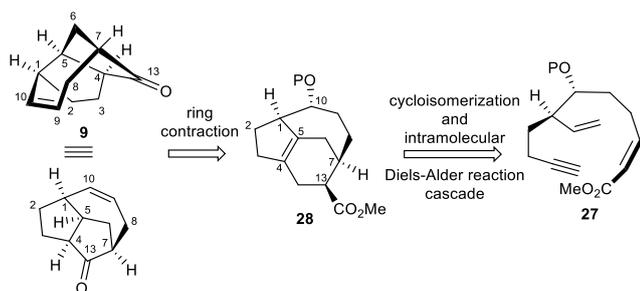
Scheme 6. Nicolaou and Chen total synthesis.

The forging of the remaining seven-membered ring was carried out by intramolecular pinacol coupling under SmI₂-HMPA conditions, to afford the desired tetracyclic compound **26** as a single diastereomer in 50% yield, *via* the cyclic chelated transition state **25**.¹⁴ Finally, the remaining functionalities (C14 of the exocyclic alkene and the C12-carboxylic acid) were introduced in a 10 step sequence.

This total synthesis of echinopines A (**1**) (and B (**2**)) was achieved in an overall 0.79% (0.73%) yield for 37 (38) steps.

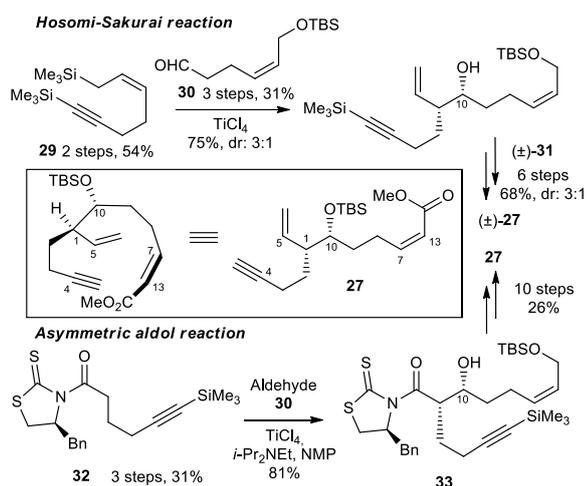
4. Chen's formal synthesis (2011) "Chen's second generation synthesis"

The formal synthesis developed by Chen in 2011 featured another ring-forming sequence: the key step was based on the preparation of a [5-6-7] tricyclic intermediate **28** by means of the cycloisomerization/intramolecular Diels-Alder cascade reaction of an enyne-bearing substrate **27**.^{4,15,16} This tricyclic compound **28** was identified as a synthetic precursor of the [5-5-7] tricyclic ketone **9** already described by Magauer, Mulzer and Tiefenbacher,² through a late-stage C4-C13 bond formation (Scheme 7).



Scheme 7. Chen's formal synthesis: retrosynthetic analysis.

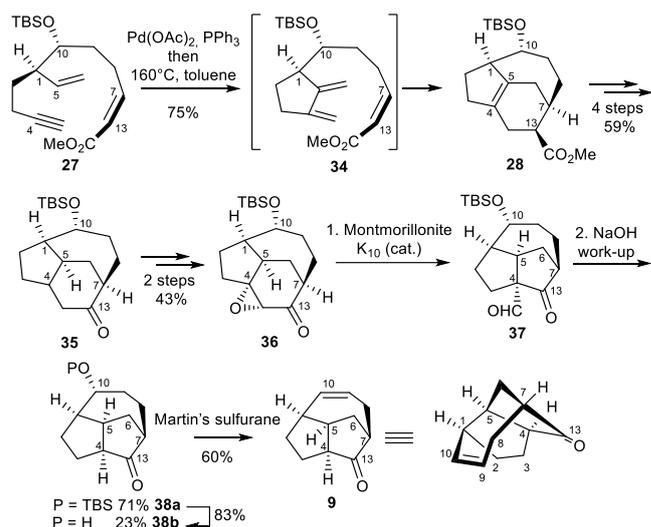
The acyclic precursor **27** was prepared in racemic and asymmetric forms. The preparation of racemic (\pm)-**27** has demonstrated the synthetic utility of Hosomi-Sakurai reaction: this reaction, involving allylsilane **29** and aldehyde **30** in the presence of TiCl_4 , afforded alcohol (\pm)-**31** in 75% yield as an inseparable mixture of diastereomers, in favor of the *syn* isomer (*dr*: 3:1 at C10).¹⁷ A six-step manipulation was subsequently performed to afford the desired intermediate (\pm)-**27** (*dr*: 3:1 at C10). An auxiliary-controlled asymmetric aldol reaction involving thiazolidinethione **32** and aldehyde **30** in the presence of TiCl_4 was next carried out to provide alcohol **33** as a single diastereomer, in 81% yield. Finally, enyne enolate **27** in optically active form was delivered in ten steps from **33** as a single diastereomer (Scheme 8).



Scheme 8. Chen's formal synthesis: formation of enoate **27**.

Upon treatment of **27** with $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ at 80°C followed by prolonged heating at 160°C , the cycloisomerization/Diels Alder cascade reaction occurred to give the [5-6-7] tricycle **28** in 75% overall yield *via* intermediate **34**. An *endo* transition state has been postulated. Noteworthy, the efficiency of the enyne cycloisomerization reaction in the absence of Thorpe-Ingold effect, is remarkable. Tricyclic intermediate **28** was next transformed into epoxy-ketone **36** through ketone **35**, thus setting

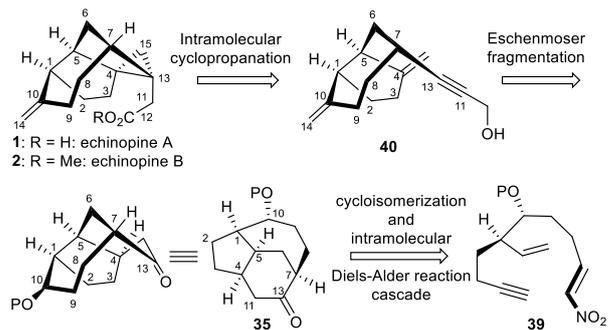
the stage for the ring contraction step. This was readily achieved by treatment of **36** with Montmorillonite K10 to deliver keto-aldehyde **37** as a single component. Subsequent basic aqueous work-up resulted in deformylation with concomitant partial desilylation, thus providing tricyclic ketone **38a** ($\text{P} = \text{TBS}$, 71% yield) and **38b** ($\text{P} = \text{H}$, 23% yield). At this stage, the targeted alkenyl ketone **9** was smoothly prepared in one step from **38b**, thus constituting a formal synthesis of echinopines A (**1**) and B (**2**) (Scheme 9). This synthesis of the optically active [5-5-7] tricyclic ketone **9**, already described by Magauer, Mulzer and Tiefenbacher, was attained in an overall 0.6% yield for 25 steps.¹⁸



Scheme 9. Chen's formal synthesis.

5. Chen's total synthesis (2011) "Chen's third generation synthesis"

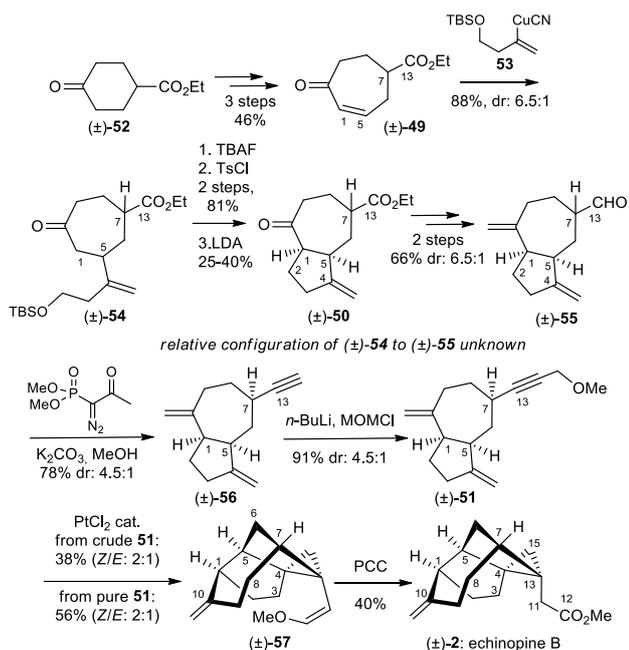
Finally, Chen reported the realization of the late-stage intramolecular cyclopropanation process proposed in the biosynthetic pathway, through an extension of its second generation strategy, in a conceptually distinct [5-6-7] \rightarrow [5-7] \rightarrow [3-5-5-7] ring-forming sequence to access echinopines **1** and **2**.^{5,6}



Scheme 10. Chen's total synthesis: retrosynthetic analysis.

In analogy with the proposed biosynthesis (*cf.* Scheme 1), the [5-7] ene-yne **40** was established as intramolecular cyclopropanation precursor. Its elaboration involved an Eschenmoser fragmentation to cleave the C4-C11 bond of the [5-6-7] tricyclic ketone **35**. This ketone was synthesized in accordance with the previously developed cycloisomerization/Diels-Alder pathway, from nitroalkene **39** (Scheme 10).

A TiCl_4 -mediated Hosomi-Sakurai reaction between allyl silane **29** and aldehyde **41** afforded the desired racemic alcohol in 74% yield as a mixture of C10 epimers (*dr*: 7:3) which was then



Scheme 13. Vanderwal's total synthesis.

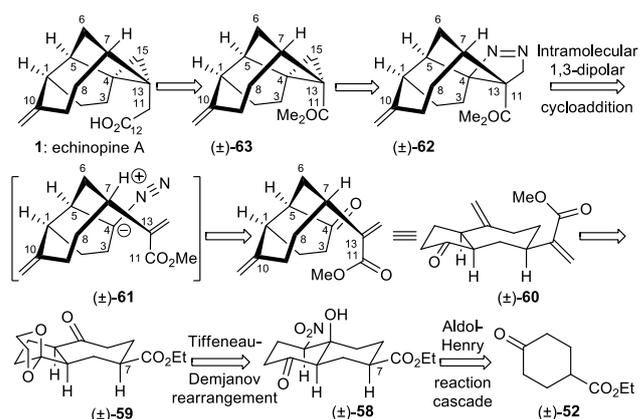
After transformation of (±)-56 into methyl ether (±)-51, the cycloisomerization step was carefully examined. In the first experiments, subsection of the crude ene-propargylic ether (±)-51 to PtCl_2 (cat.) provided the desired echinopane skeleton (±)-57 in a modest 38% yield as a 2:1 mixture of (*Z*)/(*E*) enol ether; the minor diastereomer of the starting material remaining unreacted.

Successful reaction can only occur if the C7 configuration allows the projection of the alkyne onto the concave face of the *cis*-fused bicyclic ring system. Therefore, it was hypothesized that the previous conjugate addition of **53** to (±)-49, predominantly generated (±)-54 as the undesired diastereomer. Fortunately, the epimerization at the alkylation step mainly corrected the C7 configuration and enabled the desired cycloisomerization to occur. In later experiments, the reaction was conducted from pure (±)-51, thus providing (±)-57 in 56% yield. Final enol ether oxidation provided racemic echinopine B (±)-2 in 40% yield.

This route to racemic echinopine B (±)-2 stands at 13 steps in 0.9% overall yield.

7. Liang's total synthesis (2013)

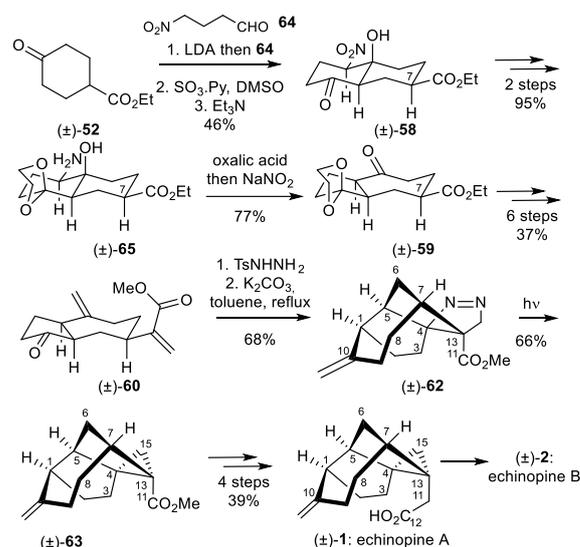
In 2013, Liang developed a new approach for the total synthesis of echinopines A (**1**) and B (**2**).⁸ The construction of the cyclopropane ring in tetracyclic framework (±)-63 bearing the core structure of the natural product, involved intramolecular 1,3-dipolar cycloaddition reaction from diazo intermediate (±)-61 and subsequent irradiation of pyrazoline (±)-62. Additionally, the synthesis featured rapid construction of the *trans*-decalin intermediate (±)-58 through an aldol-Henry cascade reaction from ketone (±)-52 and subsequent transformation to *cis*-fused bicyclo[5.3.0]decane ring system (±)-59 by means of a Tiffeneau-Demjanov rearrangement. Further group manipulation provided (±)-60 as precursor of (±)-61 for the 1,3-dipolar cycloaddition reaction (Scheme 14).



Scheme 14. Liang's synthesis: retrosynthetic analysis.

An aldol-Henry reaction cascade between enolate of ketone (±)-52 and 4-nitrobutanal **64** followed by oxidation and equilibration allowed the isolation of the desired *trans*-decalin (±)-58 in 46% yield along with epimer at C7 in 5% yield.²⁴ Notably, this robust reaction sequence can be readily scaled up to produce over 10 g of (±)-58 in one batch. After protection and reduction, a Tiffeneau-Demjanov rearrangement generated the *cis*-fused 5,7-carbocycle (±)-59 in 77% from (±)-65, with complete stereochemical control.²⁵ At this stage, the key "cross-ring" 1,3-dipolar cycloaddition reaction was examined from ketone (±)-60, elaborated from (±)-59 in a six step sequence.²⁶ The cycloaddition occurred smoothly by heating the corresponding tosylhydrazone to give the required pyrazolone (±)-62 in 68% yield. Next, irradiation of (±)-62 led to the tetracyclic compound (±)-63, advanced intermediate in the total synthesis of echinopines **1** and **2**.²⁷ The targeted natural products were finally isolated after homologation in 39% yield (Scheme 15).

This total synthesis in racemic version has been accomplished in 2.2% overall yield for 18 steps.

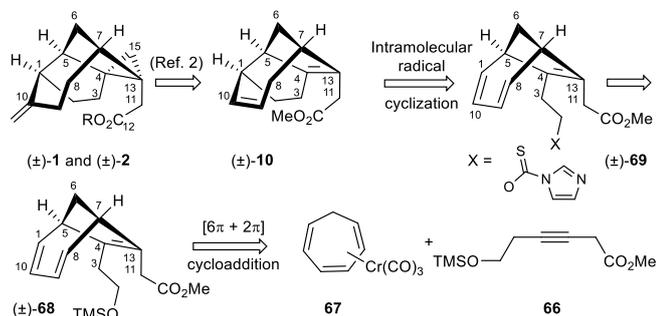


Scheme 15. Liang's total synthesis.

8. Misra's formal synthesis (2015)

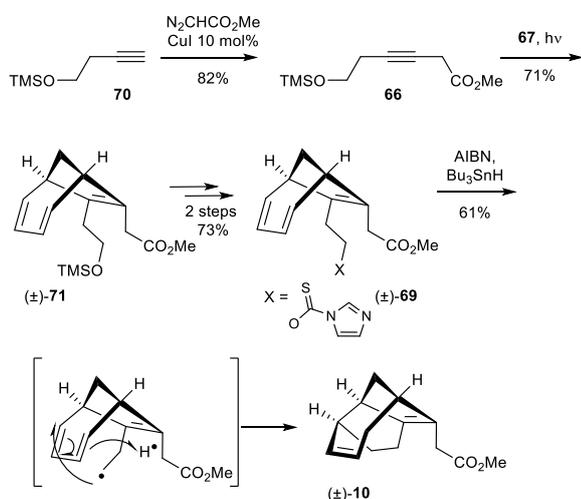
Very recently (in 2015), Misra described a formal synthesis of racemic echinopines (±)-1 and (±)-2 using a distinctly different strategy from those previously reported.⁹ Hence, the advanced tricyclic intermediate (±)-10, already reported by Magauer, Mulzer and Tiefenbacher in 2009,² was obtained by a regioselective 5-*exo*

trig intramolecular radical cyclization from xanthate (\pm)-**69**. In turn, the bicyclo[4.2.1]nonane precursor (\pm)-**68** was easily built by employing a photochemical Cr(0)-promoted $[6\pi + 2\pi]$ cycloaddition reaction of alkyne **66** and tricarbonyl chromium-(0) complex **67** (Scheme 16).²⁸



Scheme 16. Misra's formal synthesis: retrosynthetic analysis.

The requisite alkyne **66** was smoothly prepared on multigram scale by means of a CuI catalyzed C-H insertion method reported by Fu from terminal alkyne **70**.²⁹ Then, a dilute solution of chromium complex **67** and alkyne **66** was irradiated using a 450-W medium-pressure mercury vapor lamp to afford the bicyclic intermediate (\pm)-**71** in 71% yield. Numerous conditions were tested for the optimization of the key radical cyclization involving an inactivated cyclic diene. Finally, from xanthate (\pm)-**69**, the tricyclic methyl ester derivative (\pm)-**10** was obtained in an acceptable 61% yield, through the slow addition of a $\text{Bu}_3\text{SnH/AIBN}$ mixture to a refluxing dilute toluene solution (Scheme 17).



Scheme 17. Misra's formal synthesis.

Thus, a formal synthesis of racemic echinopines A and B has been achieved in a five step sequence (26% overall yield) to the known intermediate (\pm)-**10**.³⁰

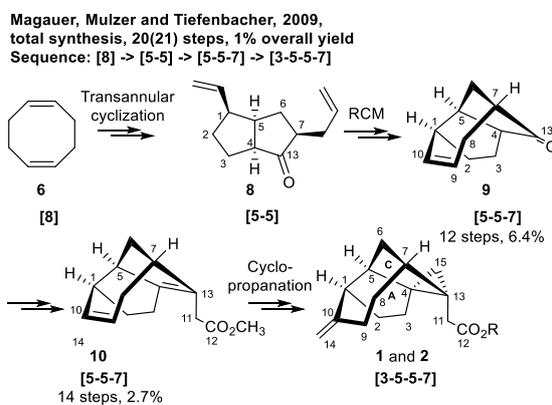
9. Conclusion

In this account, the different syntheses of echinopines have been highlighted and discussed. A number of innovative and elegant strategies (seven) have been developed to succeed in this synthetic challenge. For clarity, the different synthetic pathways established for the set-up of the echinopane framework are summarized below (Scheme 18).

One key feature of the echinopine synthesis is clearly the establishment of the original [3-5-5-7] skeleton through conceptually contrasting ring-forming sequences. Remarkably,

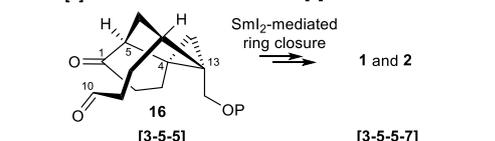
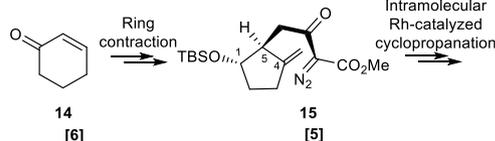
four of the seven approaches are bioinspired,³⁻⁷ including the highly challenging simultaneous formation of the cyclopropane ring and one of the cyclopentane rings, generally conducted at a late-stage of the synthesis.

Finally, it is interesting to mention that the most recent syntheses have been elaborated in a sake of originality, albeit in racemic form.

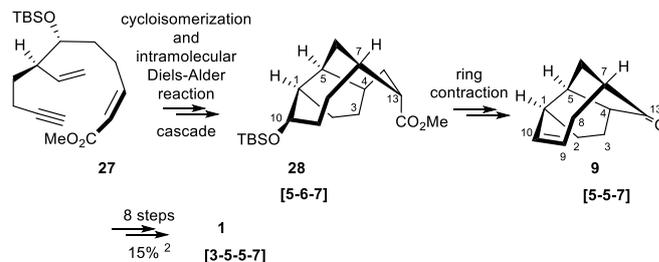


Magauer, Mulzer and Tiefenbacher, 2009, total synthesis, 20(21) steps, 1% overall yield
Sequence: [8] -> [5-5] -> [5-5-7] -> [3-5-5-7]

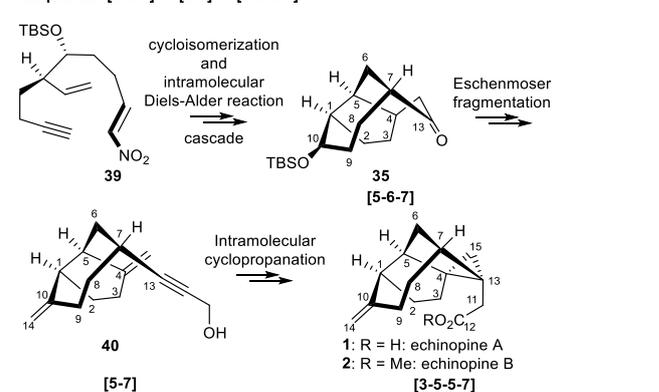
Nicolaou and Chen, 2010, "first generation synthesis", total synthesis, 37 (38) steps, 0.79% (0.73%) overall yield
Sequence: [6] -> [5] -> [3-5-5] -> [3-5-5-7]



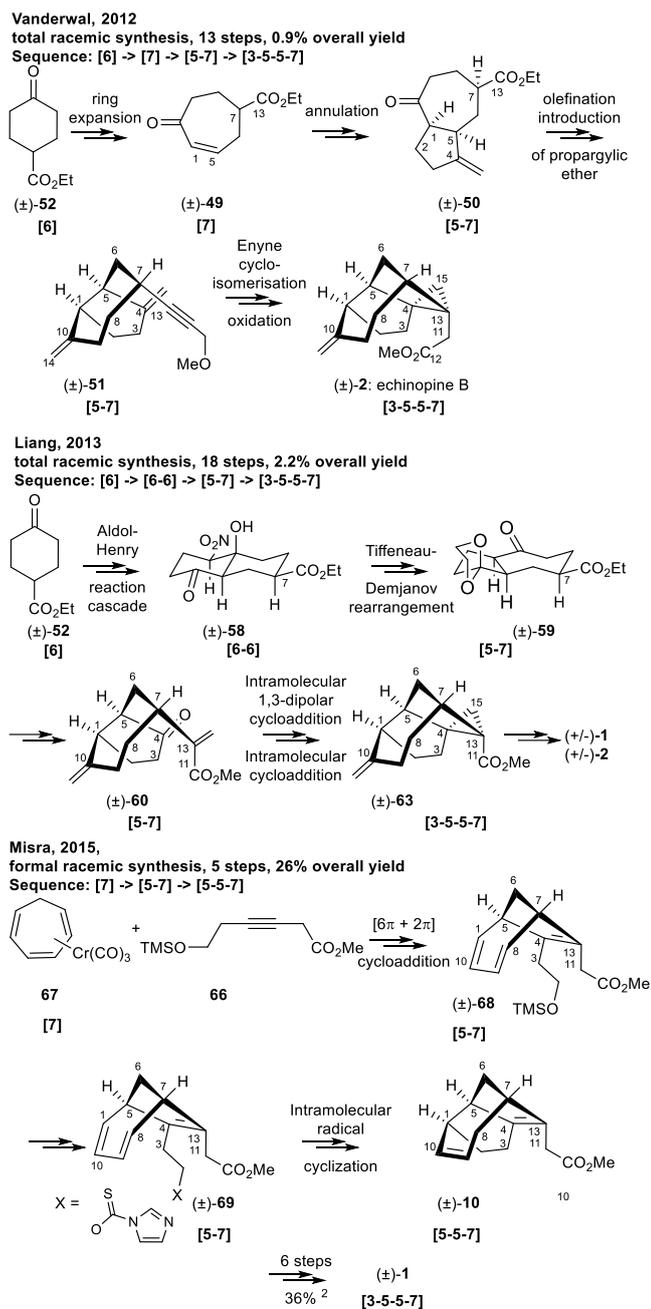
Chen, 2011, "second generation synthesis", formal synthesis 25 steps, 1.0% overall yield
Sequence: [5-6-7] -> [5-5-7]



Chen, 2011, "third generation synthesis", total synthesis 25(26) steps, 0.5(0.4)% overall yield
Sequence: [5-6-7] -> [5-7] -> [3-5-5-7]



Chen, 2011, "third generation synthesis", total synthesis 25(26) steps, 0.5(0.4)% overall yield
Sequence: [5-6-7] -> [5-7] -> [3-5-5-7]



Scheme 18. Overview of the synthetic strategies towards the echinopines and ring-forming sequences.

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