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Total Synthesis of Echinopines A and B: Exploiting a Bioinspired Late-Stage Intramolecular Cyclopropanation

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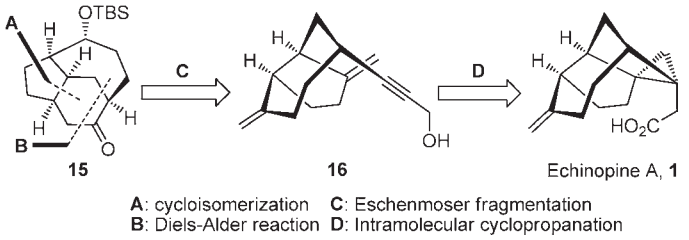
ABSTRACT



Total synthesis of echinopine A and B have been accomplished, based on a strategy that involved two transition-metal-mediated ene-yne cycloisomerizations. A modified Pd-catalyzed enyne cycloisomerization/intramolecular Diels–Alder cascade rendered a more streamlined synthesis of tricyclic ketone 15, and a Ru-catalyzed ene-yne cycloisomerization/cyclopropanation resembled the late-stage [5/7] → [3/5/5/7] ring-forming sequence in the proposed biosynthetic pathway.

The terpenoids occupy a unique position among the structurally diverse natural products and pose significant synthetic challenges primarily attributed to their unusual three-dimensional architectures and the lack of functional group handles. As such, a terpenoid-based synthetic campaign often required additional considerations in terms of conformational analysis, carbon–carbon bond-forming sequence, and strategic introduction/removal of functional groups.[1] Echinopines A and B (Scheme 1, **1** and **2**) are two recently reported sesquiterpenoids isolated from the root of *Echinops spinosus*, with their unique carbon framework signified by a [3/5/5/7] ring system.[2] Biosynthetically, the echinopines have been proposed to originate from a guaiane-type precursor (**6**) through a series of programmed carbon–carbon bond-forming/breaking events (Scheme 1).[2]

In 2010, we reported an asymmetric total synthesis of echinopines A (**1**) and B (**2**) that featured a [5] → [3.5.5] → [3/5/5/7] ring-forming sequence through the application of an intramolecular cyclopropanation followed by a SmI_2-mediated diradical coupling (Scheme 2i).[3a] Subsequently in 2011, we demonstrated an alternative ring-forming sequence toward the echinopines that involved a cycloisomerization/intramolecular Diels–Alder cascade followed by a late-stage ring-contraction to intercept a [5/5/7] tricyclic intermediate (**12**)[3b] en route to the total synthesis reported by Mulzer, Tiefenbacher, and Magauer (Scheme 2ii).[3c] Revisiting the biosynthetic proposal (**4** → **1**, Scheme 1), in fact, we had considered a chemically

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(1) (a) Hudlicky, T.; Reed, J. W. *The Way of Synthesis: Evolution of Design and Methods for Natural Products*; Wiley-VCH: Weinheim, 2007. For a recent review on the synthesis of challenging terpenes, see: (b) Maimone, T. J.; Baran, P. S. *Nat. Chem. Biol.* **2007**, *3*, 396–407 and references therein.

(2) Dong, M.; Cong, B.; Yu, S.-H.; Sauriol, F.; Huo, C.-H.; Shi, Q.-W.; Gu, Y.-C.; Zamir, L. O.; Kiyota, H. *Org. Lett.* **2008**, *10*, 701–704.

(3) (a) Nicolaou, K. C.; Ding, H.; Richard, J.-A.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2010**, *132*, 3815–3818. (b) Peixoto, P. A.; Severin, R.; Tseng, C.-C.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3013–3016. (c) Magauer, T.; Mulzer, J.; Tiefenbacher, K. *Org. Lett.* **2009**, *11*, 5306–5309.

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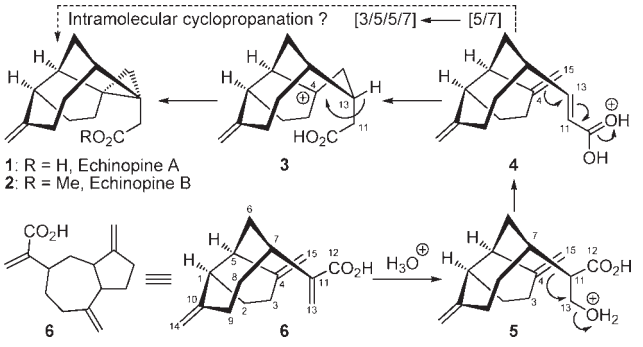
Scheme 1. Proposed Biosynthesis of Echinopines A (**1**) and B (**2**) from Guaiane-Type Triene (**6**) and Intermediates **3**, **4**, and **5**

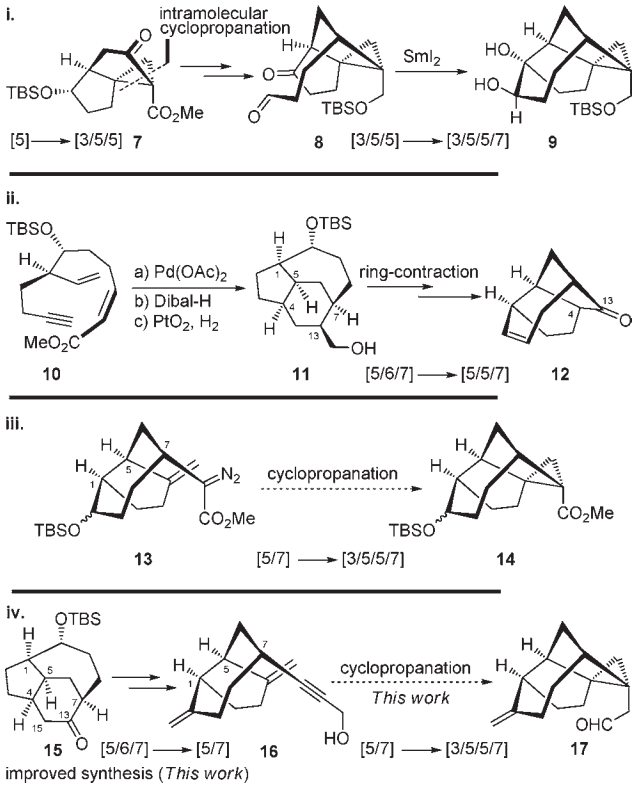


equivalent intramolecular cyclopropanation process (**13** → **14**, Scheme 2iii) but unfortunately met with failures primarily due to the difficulties associated with the preparation of a suitable intramolecular cyclopropanation precursor (**13**). Here, we report the realization of this late-stage intramolecular cyclopropanation process through an extension of our second-generation strategy, culminating in a conceptually contrasting [5/6/7] → [5/7] → [3/5/5/7] ring-forming sequence to access the echinopines (Scheme 2iv).

One challenge faced during our preparation of the proposed intramolecular cyclopropanation precursor **13** was the control of the relative stereochemistry at C1, C5, and C7. To overcome this problem, we recognized tricycle **11** described in our second-generation, formal synthesis of the echinopines was prepared as a single stereoisomer, where the C7, C1, and C5 stereocenters had been faithfully controlled through the intramolecular Diels–Alder reaction and a facial-selective hydrogenation (PtO_2, H_2), respectively (Scheme 2ii, **10** → **11**).[3b] With this observation in mind, we pondered whether a late-stage intermediate along our second-generation synthesis could be converted to a plausible intramolecular cyclopropanation precursor. As a consequence, the six-membered ring within the [5/6/7] tricycle (for example, **11**) had to be ruptured to unveil a [5/7] bicyclic system. Because such a bond-cleavage process could potentially be achieved through tricyclic ketone intermediate **15** (Scheme 2iv),[3b] it was deemed an important objective to improve its synthesis that previously required a seven-step post-Diels–Alder functional group transformations.[3b] In this context, in accordance to our previously developed synthetic strategy, a revised cycloisomerization/Diels–Alder cascade precursor **26** was envisaged, and its preparation is outlined in Scheme 3. A $TiCl_4$-mediated Hosomi–Sakurai reaction[4] between allyl silane **18** and aldehyde **19** took place smoothly to afford a mixture of hydroxy ene-yne **20** and diol **21** (*ca.* 1.2:1), which on treatment with TBSOTf cleanly funneled to a common bis-TBS ether **22** (*ca.* 7:3 mixture of C10 epimers)

(4) (a) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941–942. (b) Fleming, I. *Org. React.* **1989**, *37*, 57–575. (c) Fleming, I. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 6, pp 563–593.

Scheme 2. Synthetic Strategies Towards the Echinopines Illustrating Conceptually Contrasting Ring-Forming Sequences[a]



[a] (i) First-generation synthesis, (ii) second-generation synthesis, (iii) initial attempt of α-diazo-based intramolecular cyclopropanation, and (iv) ene-yne cycloisomerization based intramolecular cyclopropanation.

in 65% yield (from **18**).[5] Sequential desilylations of **22** (PTSA; then K_2CO_3, MeOH, 69% yield over the two steps) followed by oxidation of the so-obtained primary alcohol **24** (Swern) delivered aldehyde **25**, which underwent a two-step Henry reaction[6] (nitromethane, TMG) and dehydration (Ac_2O, py) to produce the targeted nitroalkene **26** in 75% overall yield. Pleasingly, the anticipated cycloisomerization/intramolecular Diels–Alder cascade engaging ene-yne **26** containing an internal nitroalkene moiety proceeded faithfully under less drastic reaction conditions (80 °C versus previously described 160 °C for the intramolecular Diels–Alder reaction)[3b] to furnish nitro-[5/6/7] tricycle **28** in 73% yield as an inconsequential mixture of C10 epimers (*ca.* 7:3). With tricycle **28** in hand, its conversion to ketone **15** first required a modified diimide reduction under the Myers' protocol,[7] followed by a Nef reaction[8] that required a set of carefully

(5) Optically active bis-TBS ether (−)-**22** was prepared using a chiral auxiliary-based aldol approach. For details, see Supporting Information.

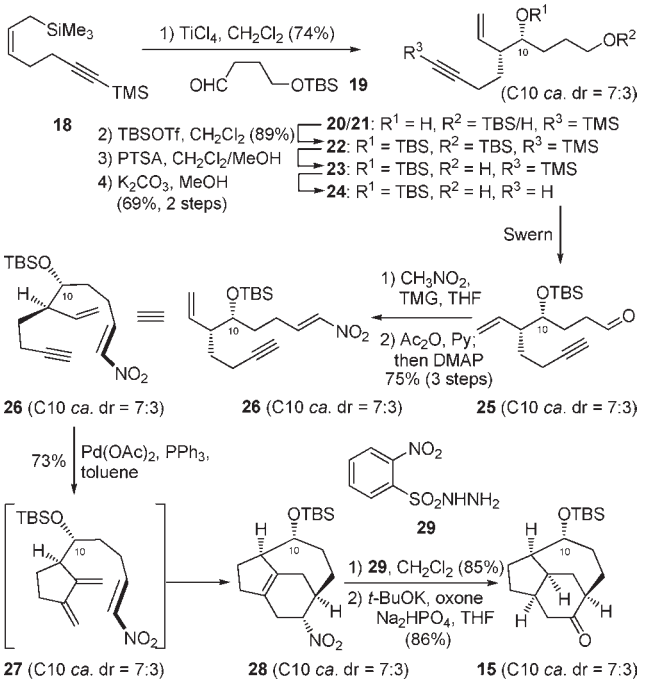
(6) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945.

(7) (a) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507. For a review of methods for generating diimide and its use in the reduction of multiple bonds in homogeneous environments, see: (b) Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91–155. (c) Miller, C. E. *J. Chem. Educ.* **1965**, *42*, 254–259.

(8) (a) Grierson, D. S.; Husson, H.-P. *Comp. Org. Synth.* **1991**, *6*, 937–944. (b) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017–1047.

optimized reaction conditions (*t*-BuOK, oxone, Na_2HPO_4). As such, our first objective of developing a more streamlined synthesis of the tricyclic ketone **15** had been realized, where both a pre- and post-Diels–Alder transformation had been significantly reduced in comparison to our previously reported synthesis.[3b]

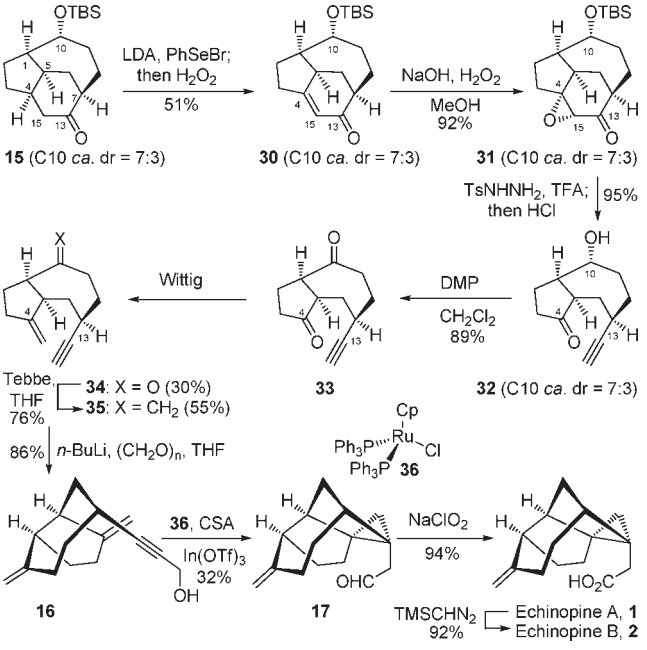
Scheme 3. Improved Synthesis of Tricyclic Ketone **15**[a]



[a] Ac = acetyl, Ph = phenyl, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, OTf = trifluoromethanesulfonate, PTSA = *p*-toluenesulfonic acid, TMG = 1,1,3,3-tetramethylguanidine, DMSO = dimethyl sulfoxide, THF = tetrahydrofuran, DMAP = 4-dimethylaminopyridine.

Advancing the synthesis from tricyclic ketone **15** next entailed the rupture of its six-membered cyclohexanone ring. At this juncture, intelligence gathering from our second-generation formal synthesis of the echinopines once again proved insightful, where we envisaged an Eschenmoser fragmentation[9] of the epoxy ketone **31** to affect the C4–C15 bond cleavage. Indeed, as shown in Scheme 4, on treatment of epoxy ketone **31** with $TsNHNH_2$ followed by acidic workup, alkynyl ketone **32** was obtained in 95% yield with concomitant desilylation. As such, the [5/6/7] → [5/7] skeletal conversion had been successfully accomplished, with complete stereochemical fidelity at C1, C5, and C7. Next, we turned our attention to the final objective, namely the bioinspired [5/7] → [3/5/5/7] skeletal conversion that called for a chemically equivalent intramolecular cyclopropanation process. With contemplation of the possibilities and recognition of the alkynyl moiety residing in **32**, the recent advent of transition-metal-mediated ene-yne cycloisomerization developed by Trost[10] became an enticing option to be tested in a complex molecular setting. Thus, oxidation of hydroxy ketone **32** (DMP, 89% yield) followed by double Wittig olefination afforded a mixture of diene-yne **35** (55% yield) and ene-yne **34** (30% yield), where the latter was transformed to the former under Tebbe conditions (76% yield). Direct treatment of diketone **33** with Tebbe reagent afforded diene-yne **35** but generally with inconsistent results, and the conversion from ene-yne **34** to diene-yne **35** was best performed under Tebbe conditions. As such, both the alkene component for the proposed ene-yne cycloisomerization and the C10–C14 exocyclic alkene required in the echinopines were introduced. The cycloisomerization precursor **16** was obtained through lithiation chemistry (*n*BuLi, paraformaldehyde, 86% yield), in readiness for the final ring-forming events. Our initial attempts employing the venerable platinum- or gold-mediated reactions provided little success despite extensive experimentations. Gratifyingly, switching to the reaction conditions reported by Trost and co-workers [$CpRu(PPh_3)_2Cl$, CSA, $In(OTf)_3$],[10] followed by extensive optimization, delivered the aldehyde **17** in 32% yield. While we speculate the modest yield of this

Scheme 4. Completion of the Total Synthesis of Echinopine A **1** and B **2**[a]



[a] LDA = lithium diisopropylamide, DMP = Dess-Martin periodinane, TFA = trifluoroacetic acid, Ts = *p*-toluene sulfonic, CSA = camphorsulfonic acid.

(9) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708–713.

(10) Trost, B. M.; Breder, A.; O'Keefe, B. M.; Rao, M.; Franz, A. W. *J. Am. Chem. Soc.* **2011**, *133*, 4766–4769.

(11) Asymmetric synthesis of echinopine A described herein proceeded in 24 steps with 0.23% overall yield. In comparison with the reported syntheses, see: ref 3a: 39 steps, 0.17% overall yield; ref 3b: 32 steps, 0.10% overall yield; ref 3c: 20 steps, 0.53% overall yield. Steps were counted based on the longest linear sequence from commercially available starting material.

(12) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668–1698.

transformation could originate from either the reaction conditions or the conformational preference of **16** (and the intermediates leading to **17**), the construction of the [3/5/5/7] tetracyclic system through application of ene-yne cycloisomerization in this complex molecular setting is noteworthy. Finally, oxidation ($NaClO_2$) of aldehyde **17** provided echinopine A (**1**, 94% yield), and its conversion to echinopine B (**2**) was effected through the action of $TMSCHN_2$ in 92% yield.

In summary, a novel synthetic entry to the echinopines has been demonstrated that featured two transition-metal-mediated ene-yne cycloisomerizations.[11] The palladium-catalyzed ene-yne cycloisomerization/intramolecular Diels–Alder cascade of **26** culminated in an improved preparation of tricyclic ketone **15**, whereas a ruthenium-promoted cycloisomerization of **16** induced an intramolecular cyclopropanation that resembles the late-stage bond constructions in the proposed biosynthetic pathway (**4** → **1**, Scheme 1). Conceptually, this [5/6/7] → [5/7] → [3/5/5/7] ring-forming sequence is in stark contrast to those reported previously[3] and rendered further conformational understanding of the echinopines molecular architecture. While the **31** → **32** bond-cleavage sequence (through Eschenmoser fragmentation) may appear counterintuitive at first glance, application of the venerable intramolecular Diels–Alder reaction[12] followed by hydrogenation to cast the C1, C5 and C7 stereocenters which otherwise proved challenging in the direct preparation of a [5/7] bicyclic system (for example, **13**, Scheme 2iii) was a strategically noteworthy maneuver.

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Supporting Information Available. Experimental procedures and compound characterization (PDF). This material is available free of charge via Internet at http://pubs.acs.org.

Note Added after ASAP Publication. The authors recognize that they inadvertently inserted spectra for compounds **17** and echinopine A and B from their earlier report in JACS (ref 3a). The Supporting Information has been corrected to include the proper spectra. The revised version was published on the Web October 3, 2011.