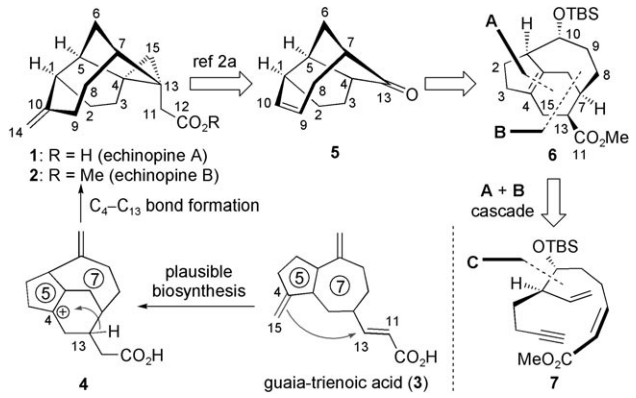
Natural Products

DOI: 10.1002/anie.201008000

Formal Asymmetric Synthesis of Echinopine A and B**

*Philippe A. Peixoto, Rene Severin, Chih-Chung Tseng, and David Y.-K. Chen**

In 2008, Shi, Kiyotam, and co-workers reported the isolation and structural elucidation of two novel sesquiterpenoids from the root of *Echinops spinosus* and subsequently named them echinopines A and B (**1** and **2**; Scheme 1).[1] Their unique carbocyclic framework, characterized by a [3,5,5,7] ring system, has been suggested to originate biosynthetically from a guaiane-type precursor (**3**; Scheme 1).[1] Although



Scheme 1. Molecular structures of echinopines A (**1**) and B (**2**), their plausible biosynthesis from guaia-trienoic acid (**3**), and the retrosynthetic analysis leading to [5,5,7] tricycle **5**, [5,6,7] tricycle **6**, and enyne enoate **7**. **A** = Palladium-catalyzed cycloisomerization; **B** = Intramolecular Diels–Alder reaction; **C** = Hosomi–Sakurai/asymmetric aldol reaction. TBS = *tert*-butyldimethylsilyl.

not noted for their biological properties, the unprecedented architectures of echinopines A (**1**) and B (**2**) presented an enticing challenge to the synthetic community.[2] Herein, we disclose a conceptually contrasting approach to the recently disclosed total synthesis of echinopine A (**1**) and B (**2**),[2] by using a novel strategy that intercepted the reported late-stage intermediate **5**,[2a] and thereby constitutes a formal synthesis of these structurally intriguing natural products.

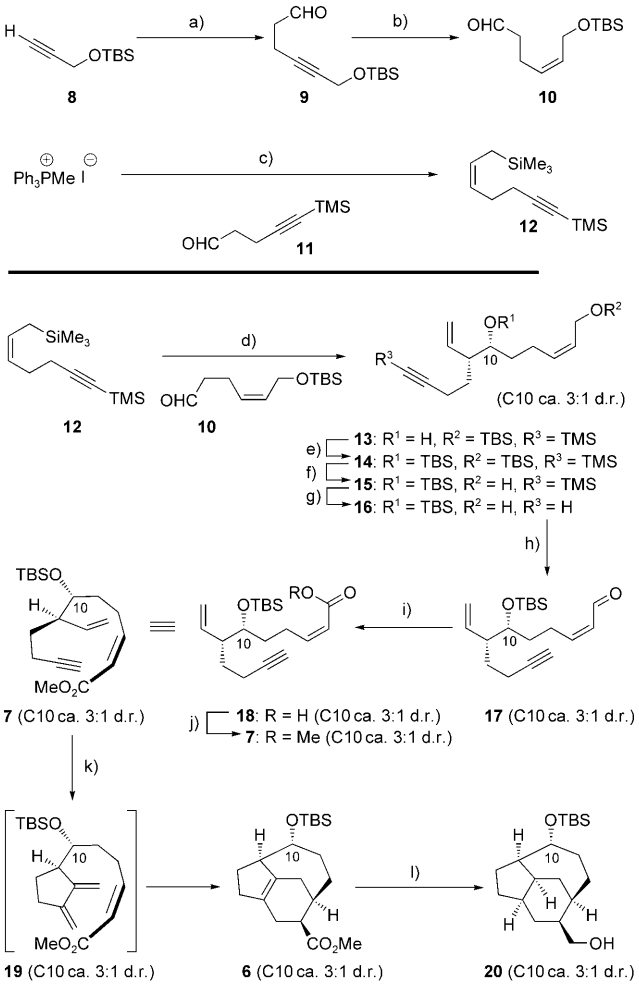
[*] Dr. P. A. Peixoto, Dr. R. Severin, Dr. C.-C. Tseng, Prof. Dr. D. Y.-K. Chen
Chemical Synthesis Laboratory@Biopolis, Institute of Chemical and Engineering Sciences (ICES)
Agency for Science, Technology and Research (A*STAR)
11 Biopolis Way, The Helios Block, #03–08
Singapore 138667 (Singapore)
Fax: (+65) 6874-5869
E-mail: david_chen@ices.a-star.edu.sg

[**] We thank Doris Tan (ICES) for high resolution mass spectrometric (HRMS) assistance. Financial support for this work was provided by A*STAR, Singapore.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201008000.

Inspired by the biosynthetic proposal,[1] we speculated on the possibility of transforming a late-stage [5,6,7] tricyclic ring system, that has a carbocyclic framework represented by the hypothetical biosynthetic intermediate **4** (Scheme 1), to access echinopines A (**1**) and B (**2**). Along these lines, the alkenyl methyl ester **6** was identified as a plausible synthetic precursor that would require a late-stage C4–C13 bond formation to give **5**. Further inspection of the intermediate **6**, which contains a cyclohexene, revealed an intramolecular Diels–Alder[3] process for its construction, in which the diene component of this venerable reaction could be derived from the cycloisomerization of the enyne-bearing substrate **7**.[4] With a cascade process in mind,[5] we envisaged that the transition-metal-mediated cycloisomerization reaction may be followed spontaneously by the intramolecular Diels–Alder event in the presence of the proximal dienophile upon generation of the transient diene. The stereochemically defined acyclic substrate **7** was carefully chosen to provide a conformationally favored transition state for the proposed intramolecular Diels–Alder reaction. Finally, preparation of the acyclic substrate **7** could be conceived from a Hosomi–Sakurai[6] or an asymmetric aldol reaction (leading to optically active **7**).

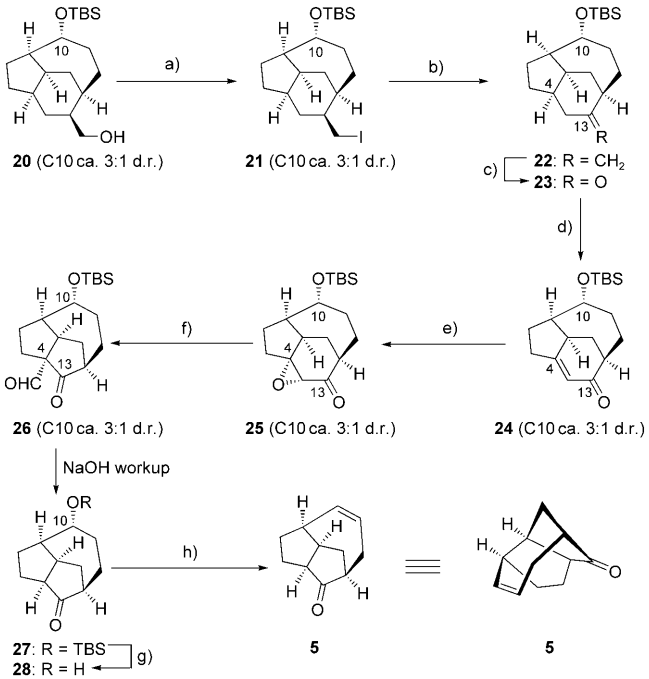
As shown in Scheme 2, the realization of our synthetic strategy commenced with the construction of the acyclic, cycloisomerization/intramolecular Diels–Alder precursor **7**. In preparation for the proposed Hosomi–Sakurai reaction,[6] alkenyl aldehyde **10** was synthesized from alkyne **8** through its conjugate addition to acrolein to afford alkynyl aldehyde **9**,[7] and subsequent partial hydrogenation of the latter compound under the conditions reported by Lindlar[8] (48% yield over the two steps). Correspondingly, allyl silane **12** was prepared in a 62% yield through an in situ generated $TMSCH_2CH_2PPh_3^+I^-$ and its reaction with alkynyl aldehyde **11**.[9] The Hosomi–Sakurai reaction,[6] engaging **10** and **12** in the presence of $TiCl_4$, afforded alcohol **13** in a 75% yield as an inseparable diastereomeric mixture in favor of the *syn* isomer (*syn*/*anti* ca. 3:1). A three-step protecting group manipulation was subsequently performed; this sequence involved silyl protection of **13** (**14**, 92% yield), selective removal of the primary allylic TBS ether (**15**, 95% yield), and removal of the TMS group (**16**, 98% yield). In preparation for the proposed cycloisomerization/intramolecular Diels–Alder cascade reaction, the allylic alcohol terminus of **16** was additionally functionalized to afford the corresponding enoate, through sequential oxidation (**18**, 81% overall yield) and methylation (**7**, 99% yield). Gratifyingly, upon treatment of **7** with $Pd(OAc)_2/PPh_3$ at an elevated temperature (80 °C), the proposed cycloisomerization took place smoothly to give diene enoate **19** (epimeric at C10, ca. 3:1) as the only detectable component in the ^1H NMR analysis of the crude reaction mixture. The efficiency of this transformation, in the



Scheme 2. Synthesis of tricyclic alcohol **20**. Reaction conditions: a) *n*BuLi (1.6 M in hexane, 1.1 equiv), THF, −78→−15 °C, 30 min; then CuI (1.1 equiv), −15 °C, 1 h; then acrolein (1.2 equiv), TMSI (1.1 equiv), −78→25 °C, 16 h, 48%; b) Lindlar catalyst (0.15 equiv), quinoline (0.5 equiv), H_2 (1 atm), toluene, 25 °C, 5 h, 99%; c) *n*BuLi (2.0 M in cyclohexane, 1.1 equiv), THF, −78 °C, 30 min; then $TMSCH_2I$ (1.2 equiv), 25 °C, 10 h; then *n*BuLi (2.0 M in cyclohexane, 0.9 equiv), 0 °C, 1 h; then **11**, −78→25 °C, 2 h, 62%; d) **10** (1.0 equiv); then $TiCl_4$ (1.0 equiv), CH_2Cl_2, −78 °C, 1 h, 75%; e) Et_3N (3.5 equiv), TBSOTf (1.2 equiv), CH_2Cl_2, 25 °C, 1 h, 92%; f) *p*-TsOH (0.10 equiv), CH_2Cl_2/MeOH (4:1.3), 0 °C, 2.5 h, 95%; g) K_2CO_3 (10.1 equiv), MeOH, 25 °C, 4 h, 98%; h) $NaHCO_3$ (10.0 equiv), DMP (1.5 equiv), CH_2Cl_2, 25 °C, 1.5 h, 85%; i) 2-methyl-2-butene (25.0 equiv), *t*BuOH; then $NaHPO_3$ (7.0 equiv), $NaClO_2$ (2.5 equiv), 25 °C, 2 h, 95%; j) $KHCO_3$ (10.0 equiv), MeI (4.0 equiv), DMF, 25 °C, 4 h, 99%; k) $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv), toluene, 80 °C, 2 h; then 160 °C, 6 h, 75%; l) DIBAL-H (1.0 M in toluene, 2.4 equiv), CH_2Cl_2, −78 °C, 45 min; then PtO_2 (0.10 equiv), H_2 (1 atm), EtOAc, 25 °C, 3 h, 100% over the two steps. DIBAL-H = diisobutylaluminium hydride, DMF = *N*,*N*′-dimethylformamide, DMP = Dess–Martin periodinane, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, *p*-TsOH = *p*-toluenesulfonic acid.

absence of the Thorpe–Ingold effect,[10] is also noteworthy. Whilst the stability of **19** permitted its isolation and purification, this in situ generated intermediate participated in the subsequent intramolecular Diels–Alder reaction upon prolonged heating at a higher temperature (160 °C), to furnish [5,6,7] tricycle **6** in an 75% overall yield from **7** (epimeric at C10, ca. 3:1). We hypothesized that an *endo* transition state, which was electronically stabilized through secondary orbital interactions, was involved during the intramolecular Diels–Alder process, and the configuration of the TBS ether (C10) had no noticeable impact on the efficiency and selectivity of either the cycloisomerization or the Diels–Alder reaction (i.e., no kinetic resolution). The tetra-substituted olefin within the Diels–Alder product **6** was found to be particularly labile towards oxidation, both upon exposure to oxidants or prolonged storage. As such, the sequential reduction of the tricyclic methyl ester **6** under DIBAL-H and PtO_2/H_2 conditions gave tricyclic alcohol **20** in quantitative yield (epimeric at C10, ca. 3:1); a key synthetic intermediate that could be stored and further elaborated (see below).

The further elaboration of tricyclic alcohol **20** is outlined in Scheme 3. In this instance, primary alcohol **20** was elaborated to ketone **23** through the intermediacy of iodide **21** (86% yield) and alkene **22** (76% yield), which was then oxidatively cleaved under the $OsO_4/Pb(OAc)_4$ conditions (91% yield). At this point, the C10-epimeric mixture of

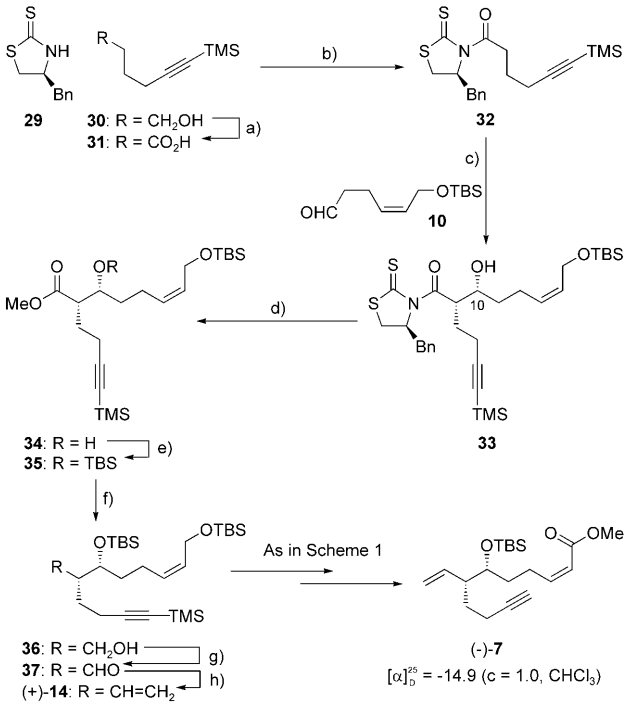


Scheme 3. Synthesis of intermediate **5** and formal synthesis of echinopine A (**1**) and B (**2**). Reagents and conditions: a) Et_3N (5.0 equiv), MsCl (2.0 equiv), CH_2Cl_2, 25 °C, 45 min; then NaI (0.93 equiv), acetone, 60 °C, 35 h, 86%: b) DBU (20 equiv), THF, 25 °C, 32 h, 76%; c) OsO_4 (0.5 equiv), NMO (2.0 equiv), THF/H_2O (4:1), 25 °C, 8 h; then $Pb(OAc)_4$ (2.0 equiv), CH_2Cl_2, 0 °C, 10 min, 91%; d) LDA (0.5 M in THF, 3.0 equiv), PhSeBr (2.0 equiv), THF, −78 °C, 90 min; then CH_2Cl_2/pyridine (9:1), H_2O_2 (6.2 equiv), CH_2Cl_2, 0 °C, 15 min, 51%; e) NaOH (34 equiv), H_2O_2 (128 equiv), MeOH, 0 °C, 30 min, 85%; f) montmorillonite K10 (cat.), benzene, 80 °C, 30 min; then NaOH (95 equiv), Et_2O, 0→10 °C, 1 h, **27**: 71%, **28**: 23%; g) *p*-TsOH (10.0 equiv), MeOH, 25 °C, 3 h, 83%; h) Martin's sulfurane (10.0 equiv), Et_3N (27 equiv), CH_2Cl_2, 25 °C, 16 h, 60%. Ms = methanesulfonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, NMO = *N*-methylmorpholine-*N*-oxide, LDA = lithium diisopropylamide.

tricyclic ketone **23** permitted chromatographic separation, although the configuration at this stereocenter is inconsequential. In accordance to our synthetic proposal that necessitates a C4–C13 bond construction, we speculated the feasibility of a ring-contraction process, in which epoxy ketone **25** could serve as a suitable substrate.[11] Thus, the formation of enone **24** from ketone **23** took place uneventfully through a two-step procedure that involved α selenation (PhSeBr) and oxidative elimination (H_2O_2) to give **24** in a 51% overall yield. Next, nucleophilic epoxidation of enone **24** upon its exposure to basic H_2O_2 afforded epoxy ketone **25** (85% yield), thus setting the stage for the proposed ring contraction. Gratifyingly, treatment of a benzene solution of **25** with montmorillonite K10[11] smoothly delivered keto aldehyde **26** as a single detectable component in the ^{1}H NMR analysis of the crude reaction mixture, thereby establishing the required C4–C13 linkage. Basic aqueous workup (NaOH) of the crude reaction mixture resulted in spontaneous deformylation, thus giving the tricyclic ketone **27** together with the hydroxy ketone **28** in 71% and 23% overall yields, respectively, from **25**. At this juncture, we serendipitously recognized the striking structural resemblance between tricyclic ketone **28** and alkenyl ketone **5**, which is a previously reported late-stage intermediate en route to the echinopines.[2a] Thus, conveniently, **5** was prepared from **28**, which can also be obtained from **27** by mild acidic desilylation (83% yield), through dehydration (60% yield, unoptimized). All physical characteristics of tricycle **5** matched identically to those reported previously,[2a] thus constituting a formal synthesis of echinopine A (**1**) and B (**2**).[12]

Thus, having demonstrated the synthetic utility of the Hosomi–Sakurai reaction[6] in our initial foray towards the synthesis of the cycloisomerization/Diels–Alder precursor **7**, an asymmetric version was subsequently pursued together with greatly improved diastereoisomeric purity at C10 (Scheme 4). In this instance, an auxiliary-controlled asymmetric aldol reaction engaging thiazolidinethione[13] **32** and aldehyde **10** in the presence of $TiCl_4$ furnished alcohol **33** as a single diastereoisomer in an 81% yield. Removal of the thiazolidinethione auxiliary (87% yield) and protection of the resulting hydroxy methyl ester (**34**) as its TBS ether (93% yield) gave the enyne methyl ester **35**. This compound was further subjected to a series of functional group manipulations and oxidation state adjustments at both its methyl ester and allylic TBS ether termini that, together with the liberation of its TMS-protected alkyne, delivered the targeted enyne enoate (−)-**7** in its optically active form as a single diastereoisomer.

In summary, the asymmetric formal synthesis of (+)-echinopine A (**1**) and B (**2**) was accomplished. Particularly noteworthy are the cascade construction of the tricyclic [5,6,7] tricyclic ring system **6** from the acyclic enyne precursor **7** through a palladium-catalyzed cycloisomerization with subsequent intramolecular Diels–Alder reaction, and the strategic application of a late-stage ring contraction of epoxy ketone **25.**[14] Further expansion and application of the developed synthetic strategies and technologies are currently under investigation.



Scheme 4. Asymmetric synthesis of enyne enoate (−)-**7**. Reagents and conditions: a) PDC (3.5 equiv), DMF, 0°C, 15 min; then 25°C, 12 h; b) DCC (1.0 equiv), **31** (1.0 equiv), CH_2Cl_2, −15°C, 30 min; then **29** (1.0 equiv), −15°C, 5 min; then DMAP (1.1 equiv), −15→25°C, 1 h, 56%; c) $TiCl_4$ (1.05 equiv), CH_2Cl_2, −78°C, 15 min; then iPr_2NEt (1.05 equiv), −78°C, 45 min; then NMP (2.1 equiv), −78°C, 15 min; then **10** (1.05 equiv), −78→−30°C, 2 h, 81%; d) imidazole (10.0 equiv), DMAP (1.0 equiv), MeOH, 25°C, 14 h, 87%; e) TBSOTf (2.0 equiv), Et_3N (5.0 equiv), CH_2Cl_2, 25°C, 1 h, 93%; f) DIBAL-H (1.0 M in toluene, 4.0 equiv), CH_2Cl_2, −78°C, 45 min, 91%; g) $NaHCO_3$ (10.0 equiv), DMP (2.0 equiv), CH_2Cl_2, 25°C, 1.5 h, 85%; h) methyl triphenylphosphonium bromide (4.0 equiv), *n*BuLi (2.0 M in cyclohexane, 3.5 equiv), THF, −20→−5°C, 45 min; then **37** (1.0 equiv), −20→0°C, 2 h, 56%. Bn = benzyl, DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, NMP = *N*-methylpyrrolidone, PDC = pyridinium dichromate.

Received: December 17, 2010
Published online: February 18, 2011

Keywords: cascade reactions · Diels–Alder reaction · natural products · terpenoids · total synthesis

[1] M. Dong, B. Cong, S.-H. Yu, F. Sauriol, C.-H. Huo, Q.-W. Shi, Y.-C. Gu, L. O. Zamir, H. Kiyota, *Org. Lett.* **2008**, *10*, 701–704.
[2] a) T. Magauer, J. Mulzer, K. Tiefenbacher, *Org. Lett.* **2009**, *11*, 5306–5309; b) K. C. Nicolaou, H. Ding, J.-A. Richard, D. Y.-K. Chen, *J. Am. Chem. Soc.* **2010**, *132*, 3815–3818.
[3] K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem.* **2002**, *114*, 1742–1773; *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698.
[4] V. Michelet, P. Y. Toullec, J.-P Genet, *Angew. Chem.* **2008**, *120*, 4338–4386; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315.
[5] For a recent review on cascade reactions in total synthesis, see: a) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551–564; b) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim,

2006, p. 617; c) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292 – 7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134 – 7186.
[6] a) A. Hosomi, M. Endo, H. Sakurai, *Chem. Lett.* **1976**, 941 – 942; b) I. Fleming, *Org. React.* **1989**, *37*, 57 – 575; c) I. Fleming, *Comprehensic Organic Synthesis*, *Vol. 6*, Pergamon, Oxford, **1991**, pp. 563 – 593.
[7] K. Takeishi, K. Sugishima, K. Sasaki, K. Tanaka, *Chem. Eur. J.* **2004**, *10*, 5681 – 5688.
[8] H. Lindlar, R. Dubuis, *Org. Synth. Coll. Vol. 5* **1973**, 880 – 883.
[9] K.-I. Imamura, E. Yoshikawa, V. Gevorgyan, Y. Yamamoto, *J. Am. Chem. Soc.* **1998**, *120*, 5339 – 5340.
[10] R. M. Beesley, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc. Trans.* **1915**, *107*, 1080 – 1106.
[11] J. Elings, H. Lempers, R. Sheldon, *Eur. J. Org. Chem.* **2000**, 1905 – 1911.
[12] Having demonstrated the feasibility of this novel approach to access late-stage intermediates **27** and **5**, several end-game strategies leading to echinopines A (**1**) and B (**2**) involving pedestrian functional transformations could be conceived, and these studies will be reported in the full account of this work.
[13] a) Y. Nagao, W.-M. Dai, M. Ochiai, S. Tsukagochi, E. Fujita, *J. Am. Chem. Soc.* **1988**, *110*, 289 – 291; b) M. T. Crimmins, B. W. King, E. A. Tabet, K. Chaudhary, *J. Org. Chem.* **2001**, *66*, 894 – 902; c) J. Patel, G. Clave, P.-Y. Renard, X. Franck, *Angew. Chem.* **2008**, *120*, 4292 – 4295; *Angew. Chem. Int. Ed.* **2008**, *47*, 4224 – 4227.
[14] In comparison to the previously reported total syntheses of the echinopines, where a [5,5]→[5,5,7]→[3,5,5,7] (reference [2a]) and a [5]→[3,5,5,]→[3,5,5,7] (reference [2b]) ring-forming sequence were executed, we demonstrated herein a conceptually contrasting sequence involving a one-pot preparation of a [5,6,7] system and its conversion to the [5,5,7] ring framework.

