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Total Syntheses of Echinopines

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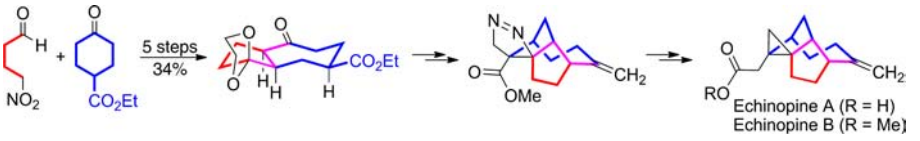
ABSTRACT



A concise and scalable synthesis of a *cis*-fused bicyclo[5.3.0]decane ring system has been developed for the total synthesis of echinopines. The core of the natural products was constructed efficiently through an intramolecular 1,3-dipolar cycloaddition and ring contraction strategy.

Echinopines A and B, **1** and **2** (Figure 1), are a pair of novel terpenoids isolated from the root of *Echinops spinosus* by Shi and Kiyota in 2007.[1] Their unprecedented 3−5−5−7 carbon framework contains five contiguous stereogenic centers, two of which are all-carbon quaternary centers adjacent to each other. The unique structural features rendered them noteworthy targets for synthesis. A number of innovative and elegant strategies have been documented to address the synthetic challenge presented by the molecular architecture of echinopines.[2]

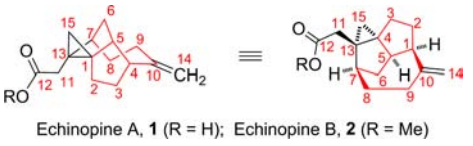
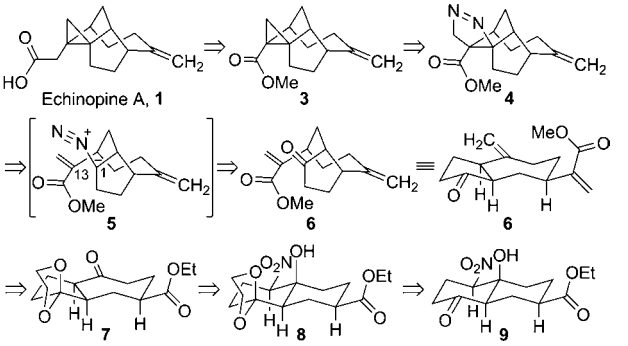


Figure 1. Molecular structures of echinopines A and B.

Although not obvious at first sight, echinopines possess a *cis*-fused bicyclo[5.3.0]decane ring system (highlighted in red). This feature prompted us to construct echinopines from such a carbon framework.[3] As illustrated in Scheme 1, we conceived that a much more complex tetracyclic framework **4** could be built by "stitching" C1 and C13 in **5** through an intramolecular 1,3-dipolar cycloaddition. The pyrazoline in **4** could be readily converted to a cyclopropane in **3** bearing the core structure of the natural product. A subsequent one-carbon homologation on **3** would delivery echinopine A. As far as the synthesis of *cis*-fused 5,7-carbocyles is concerned, we were inspired by a brilliant Tiffeneau−Demjanov rearrangement[4] strategy for preparing **13** from *trans*-decalin **12** reported by Seebach and coworkers (Scheme 2).[5] We envisioned that the same chemistry could be exploited to synthesize **7** from **9** and further functional group manipulation on **7** would give **6** as a precusor of **5** for the 1,3-diploar cycloaddition.

Scheme 1. Retrosynthetic Analysis of Echinopine A



To examine the feasibility of our strategy, we initiated a forward synthesis of **9**, which has a *trans*-decalin ring

(1) 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.
(2) (a) Magauer, T.; Mulzer, J.; Tiefenbacher, K. *Org. Lett.* **2009**, *11*, 5306–5309. (b) Nicolaou, K. C.; Ding, H.; Richard, J.-A.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2010**, *132*, 3815–3818. (c) Peixoto, P. A.; Richard, J.-A.; Severin, R.; Tseng, C.-C.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2011**, *50*, 3013–3016. (d) Peixoto, P. A.; Richard, J.-A.; Severin, R.; Chen, D. Y.-K. *Org. Lett.* **2011**, *13*, 5724–5727. (e) Michels, T. D.; Dowling, M. S.; Vanderwal, C. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 7572–7576.

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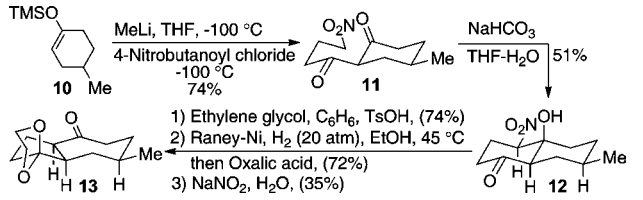
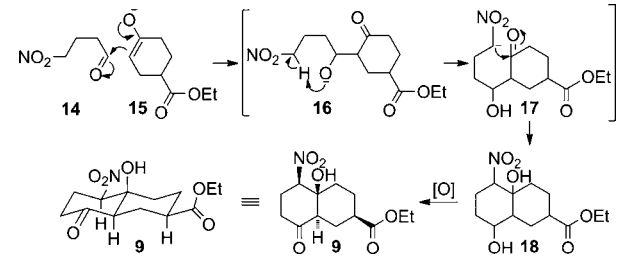
Scheme 2. Seebach's Synthesis of **13**[a]



[a] Note: the stereochemistry of the methyl group in **12** and **13** was not firmly determined.[5]

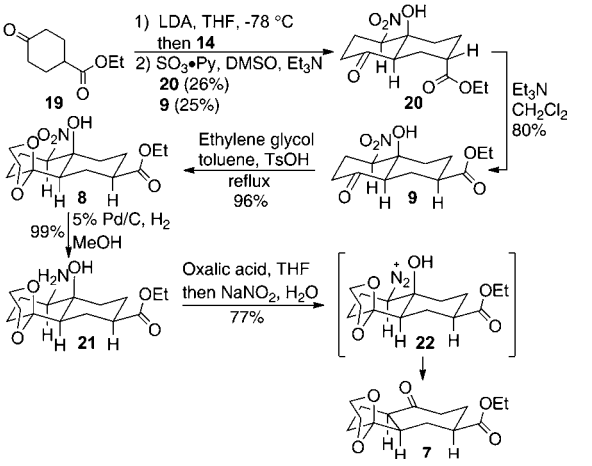
system structurally similar to **12**, by employing Seebach's two-step sequence (**10** → **12**, Scheme 2). In Seebach's synthesis, a Claisen type condensation at −100 °C between an enolate generated from **10** and 4-nitrobutanoyl chloride produced the 1,3-dicarbonyl compound **11**,[6] which then underwent a Henry reaction[7] upon treatment with $NaHCO_3$ to afford **12** in 38% yield in two steps. Unfortunately, our application of the same chemistry to the preparation of **9** resulted in a scarce amount of the desired product (2−8% yield) with poor reproducibility. Therefore, we gave up this route and proposed an alternative aldol−Henry reaction cascade and oxidation reaction sequence for the rapid construction of **9** (Scheme 3).

Scheme 3. Aldol−Henry Reaction Cascade and Oxidation Reaction Sequence for a Rapid Construction of **9**



We envisioned that an aldol adduct **16** between enolate **15** and 4-nitrobutanal **14**[8] could readily undergo intramolecular proton transfer to generate a carbanion **17** which is then converted to **18** through a facile intramolecular Henry reaction. Equilibration following oxidation of **18** is anticipated to eventually afford **9**, presumably the most stable epimer with both nitro and ester groups in equatorial positions in the *trans*-decalin system (Scheme 3).

Scheme 4. Concise Synthesis of *Cis*-fused Bicyclo[5.3.0]decane Ring System **7**



The synthetic plan was carried out using commercially available ketone **19** (Scheme 4). Gratifyingly, the successful aldol−Henry cascade and subsequent Parikh−Doering oxidation[9] allowed us to isolate the desired product **9** in 25% yield together with its epimer **20** in 26% yield. The stereochemistry of both **9** and **20** was unambiguously confirmed through single-crystal X-ray crystallographic analysis (Figure 2).[10] The undesired product **20** can be epimerized to **9** in 80% yield upon the treatment of triethylamine. Taken together, this convenient sequence generated the rather complex *trans*-decalin **9** in an overall yield of 46% using inexpensive chemicals **19** and **14**. Notably, this robust reaction sequence can be readily scaled up to produce over 10 g of **9** in one batch. Next, protection of the carbonyl group in **9** provided **8**, which underwent facile palladium-catalyzed hydrogenation of the nitro group to afford the corresponding amine **21** in nearly quantitative yield.[11] Following Seebach's procedure for the Tiffeneau−Demjanov rearrangement, we obtained the desired *cis*-fused 5,7-carbocycles **7** in 77% yield with complete stereochemical control. Importantly, the in situ hydrolysis of the ketal protecting group during the rearrangement which was observed in Seebach's synthesis did not occur with our substrate, and the desired product **7** was produced in relatively high yield.[12] This short synthetic

(3) Chen and Vanderwal reported construction of echinopines from *cis*-fused bicyclo[5.3.0]decane carbon frameworks through metal-mediated ene−yne cycloisomerizations, see ref 2d,2e.

(4) For a review on the Tiffeneau−Demjanov rearrangement, see: Fattori, D.; Henry, S.; Vogel, P. *Tetrahedron* **1993**, *49*, 1649–1664.

(5) Weller, T.; Seebach, D.; Davis, R. E.; Laird, B. B. *Helv. Chim. Acta* **1981**, *64*, 736–760.

(6) 4-Nitrobutanoyl chloride was prepared in three steps from nitromethane and methyl acrylate; for details and the preparation of **11**, see: Seebach, D.; Weller, T.; Protschuk, G.; Beck, A. K.; Hoekstra, M. S. *Helv. Chim. Acta* **1981**, *64*, 716–735.

(7) For a review on the Henry reaction, see: Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945.

(8) 4-Nitrobutanal was prepared in one step from nitromethane and acrolein; for details, see: Blidi, L. E.; Crestia, D.; Gallienne, E.; Demuynck, C.; Bolte, J.; Lemaire, M. *Tetrahedron:Asymmetry* **2004**, *15*, 2951–2954.

(9) Parikh, J. R.; Doering, W. V. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

(10) See the Supporting Information for the X-ray crystal structure of **20**.

(11) (a) Grundmann, C.; Ruske, W. *Chem. Ber.* **1953**, *86*, 939. (b) Kaneko, S.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 2302–2312.

(12) An undesired diketone product (40% yield) was observed during the production of **13** (35% yield) in Seebach's synthesis; for details, see ref 5.

sequence allowed us to conveniently synthesize **7** from the inexpensive commercially available **19** in an overall yield of 34%.

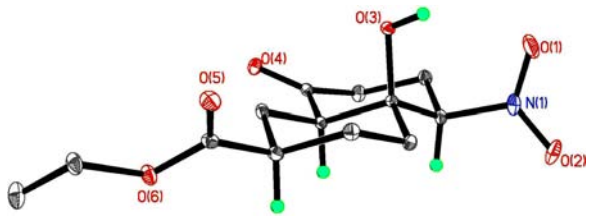
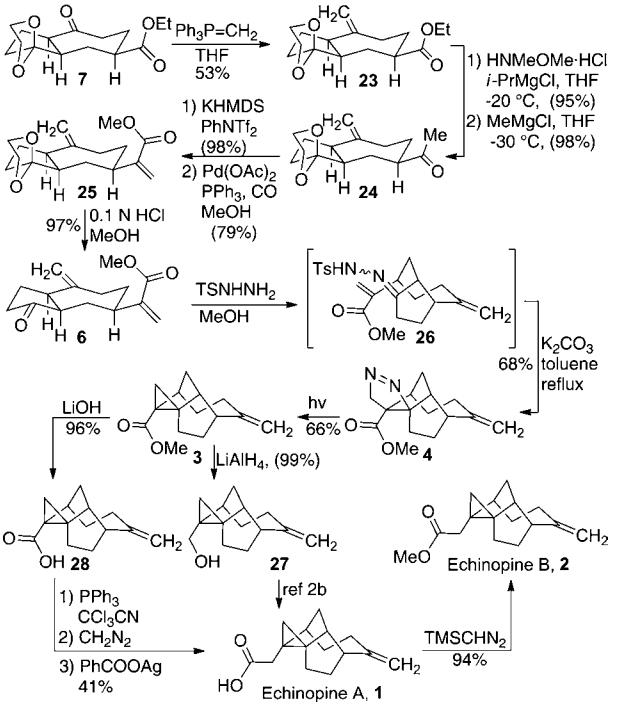


Figure 2. X-ray crystal structure of the *trans*-decalin system **9**.

With a sufficient supply of the key intermediate **7**, we proceeded to prepare the advanced intermediate **26** so as to examine the key 1,3-dipolar cycloaddition reaction (Scheme 5). Wittig olefination[13] of **7** installed the requisite methylene group on the seven-membered ring. A high-yielding conversion of ester **23** to methyl ketone **24** was carried out through a standard sequence involving a Weinreb amide intermediate.[14] Upon treatment with KHMDS and then $PhNTf_2$,[15] methyl ketone **24** was transformed to a vinyl triflate in nearly quantitative yield. A palladium-catalyzed carbonylation[16] of the vinyl triflate in methanol afforded the unsaturated ester **25** in good yield. Hydrolysis in 0.1 N hydrochloric acid and subsequent tosylhydrazone formation in methanol converted **25** smoothly to the advanced intermediate **26**. To our great excitement, the "cross-ring" 1,3-dipolar cycloaddition went smoothly, and we were able to acquire the desired pyrazoline **4** in 68% yield by heating the tosylhydrazone **26** to reflux in toluene in the presence of K_2CO_3.[17] Notably, although the intramolecular cycloaddition of a diazo alkane to an alkene has been studied extensively in the literature, its application in the context of natural product total synthesis is rarely reported.[18] Our study demonstrated that this superb reaction can be exploited to transform the simple bicyclic precursor **26** to a tetracyclic compound **4** with significantly higher structural complexity. Next, irradiation of **4** led to **3** in 66% yield.[19] Reduction of the ester group in **3** to a primary hydroxyl group afforded a literature-known intermediate **27** which was reported by Nicolaou, Chen, and co-workers.[2b] Following their Swern oxidation, Wittig olefination, hydrolysis, and Pinnick oxidation sequence, we obtained echinopine A (**1**), which upon methylation with $TMSCHN_2$ was further elaborated to echinopine B (**2**) in 94% yield.

Scheme 5. Total Synthesis of Echinopines A and B



Alternatively, **3** can also be converted to echinopine A through an Arndt–Eistert homologation.[20] Specifically, hydrolysis of the ester in **3** with LiOH afforded the carboxylic acid **28** in excellent yield. A mild chlorination with the use of PPh_3 and CCl_3CN converted **28** to an acid chloride.[21] The corresponding α-diazoketone underwent a $PhCO_2Ag$-catalyzed Wolff rearrangement[22] to produce echinopine A. Taken together, the entire sequence of homologation from carboxylic acid **28** was achieved in an overall yield of 41%.

In summary, we have developed a new approach for total syntheses of echinopines A and B. The syntheses features rapid construction of a *trans*-decalin through an aldol–Henry reaction cascade and its facile transformation to *cis*-fused bicyclo[5.3.0]decane ring system through a Tiffeneau–Demjanov rearrangement. This methodology allowed us to construct the rather complex echinopines

(13) For a review on the Wittig reaction, see:Edmonds, M.; Abell, A. The Wittig reaction. In *Modern Carbonyl Olefination* 2004, p.1.

(14) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.

(15) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979–982.

(16) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109–1112.

(17) Taber, D. F.; Guo, P. *J. Org. Chem.* **2008**, *43*, 9479–9481.

(18) For selected reports on the 1,3-dipolar cycloadditions, see: (a) Padwa, A.; Ku, H. *J. Org. Chem.* **1980**, *45*, 3756–3766. (b) Brinker, U. H.; Schrievers, T.; Xu, L. *J. Am. Chem. Soc.* **1990**, *112*, 8609–8611. (c) Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurumurthy, R. *J. Org. Chem.* **1993**, *58*, 424–437. (d) Jung, M. E.; Huang, A. *Org. Lett.* **2000**, *2*, 2659–2661. (e) Taber, D. F.; Guo, P.; Guo, N. *J. Am. Chem. Soc.* **2010**, *132*, 11179–11182. (f) Kang, T.; Kim, W.-Y.; Yoon, Y.; Kim, B. G.; Lee, H.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 18050–18053. There is only a single instance of the use of intramolecular cycloaddition of a diazo alkane to an alkene in natural product synthesis; see: (g) Schultz, A. G.; Puig, S. *J. Org. Chem.* **1985**, *50*, 915–916.

(19) (a) Rinehart, K. L., Jr.; Van Auken, T. L. *J. Am. Chem. Soc.* **1960**, *82*, 5251. (b) Van Auken, T. L.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1962**, *84*, 3736–3743.

(20) Kirmse, W. *Eur. J. Org. Chem.* **2002**, *14*, 2193–2256.

(21) Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *40*, 5323–5326.

(22) Kende, A. S.; Dong, H.-Q.; Mazur, A. W.; Ebetin, F. H. *Tetrahedron Lett.* **2001**, *42*, 6015–6018.

from common and inexpensive building blocks and reagents through straightforward chemical transformations. In addition, this new approach showcased the power of the 1,3-dipoloar cycloaddition reaction between a diazo alkane and alkene functionality in the preparation of complex molecular architecture using convenient substrates. Considering both *trans*-decalins and bicyclo[5.3.0]decanes are common motifs in terpenoids, we envision our facile synthesis of such carbon frameworks would have great potential in the total synthesis of versatile terpenoids. Further expansion and application of the chemistry are under investigation in our laboratory.

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Supporting Information Available. Experimental details and procedures, compound characterization data, copies of ^{1}H and ^{13}C NMR spectra for new compounds, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.