

Total Synthesis of Echinopines A and B

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Abstract: Echinopines A and B [(+)-**1** and (+)-**2**], two naturally occurring compounds characterized with a unique [3.5.5.7] carbon framework, have been synthesized in both enantiomeric and racemic forms. Their total synthesis involves a novel intramolecular rhodium-catalyzed cyclopropanation (**4** → **16**) and a samarium diiodide-mediated ring closure (**3** → **37**).

Introduction

The root of *Echinops spinosus* has proven its richness in bioactive secondary metabolites with considerable molecular diversity, including polyacetylene thiophenes, alkaloids, flavone glycosides, and benzothiophene glycosides.¹ In 2008, and after extensive chemical investigations of the constituents of *E. spinosus*, two sesquiterpenes with unprecedented molecular architectures were reported by Shi, Kiyota and co-workers.² Designated as echinopines A and B (**1** and **2**, Figure 1), these structures are characterized by a unique [3.5.5.7] carbon framework onto which a methylene group and a carboxymethyl group are appended. A total synthesis of these compounds has recently been disclosed.³ Herein we report an asymmetric total synthesis of natural echinopines A and B [(+)-**1** and (+)-**2**] and racemic echinopines A and B [(±)-**1** and (±)-**2**].

Results and Discussion

Retrosynthetic Analysis. The devised synthetic strategy toward echinopines A (**1**) and B (**2**) (Figure 2) was based on the premise that a diazo-derived carbenoid intramolecular addition to an exocyclic olefinic bond would form concurrently the cyclopropane ring and one of the cyclopentane rings of the molecule (see **4** → **3**, Figure 2), while an intramolecular SmI₂-mediated⁴ pinacol coupling (see **3** → **1**, **2**, Figure 2) at a later

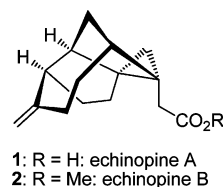


Figure 1. Structures of echinopines A (**1**) and B (**2**).

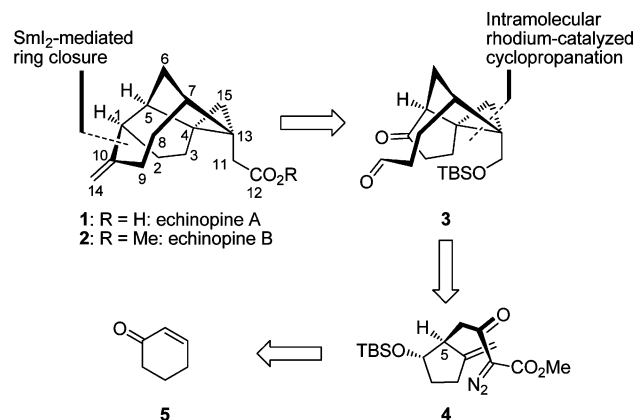


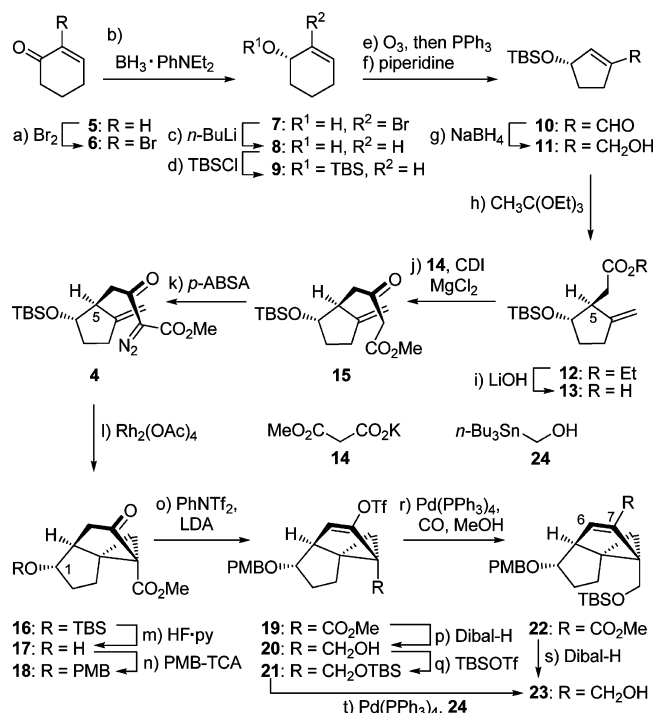
Figure 2. Retrosynthetic analysis of echinopines A (**1**) and B (**2**).

stage would generate the cycloheptane ring. Intermediate **4** was traced back to cyclohexenone (**5**) as shown retrosynthetically in Figure 2.

Construction of [5.5.3] Tricyclic Dialdehyde **3 via Diazo Ketoester **4**.** The construction of [5.5.3] tricyclic dialdehyde **3** commenced from cyclohexenone (**5**) and proceeded through diazo ketoester **4** as summarized in Schemes 1–3. Thus, bromination of **5** afforded 2-bromocyclohexenone (**6**, 98% yield), whose reduction under modified CBS conditions (see Scheme 1) afforded 2-bromocyclohexenol (**7**) in 90% yield and greater than 95% ee (by Mosher ester analysis). Treatment of the latter with *n*-BuLi followed by aqueous workup furnished enantioenriched 2-cyclohexenol (**8**) in 80% yield.⁵ Ring contrac-

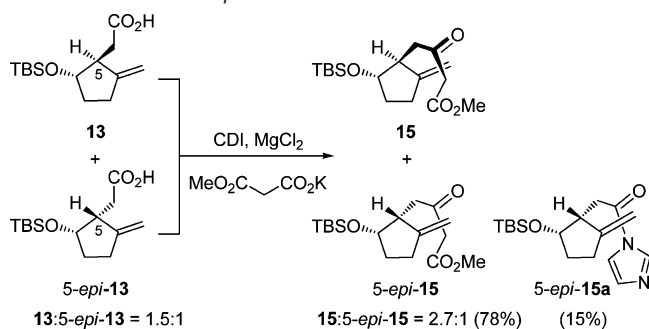
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Scheme 1. Synthesis of Tricyclic Allylic Alcohol **23**^a

^a Reagents and conditions: (a) Br₂ (1.02 equiv), CH₂Cl₂, 0 °C, 1 h; then Et₃N (1.7 equiv), 0 → 25 °C, 1.5 h, 98%; (b) (*R*)-α,α-diphenylprolinol (0.10 equiv), B(OMe)₃ (0.12 equiv), THF, 25 °C, 1 h; then BH₃·*N,N*-diethylaniline (1.0 equiv), 5, -5 → 25 °C, 16 h, 90%, ≥95% ee (Mosher ester analysis); (c) *n*-BuLi (3.5 equiv), Et₂O, -78 → -10 °C, 2.5 h, 80%; (d) TBSCl (1.3 equiv), Et₃N (1.5 equiv), DMAP (0.1 equiv), CH₂Cl₂, 25 °C, 6 h; (e) O₃, CH₂Cl₂, -78 °C; then PPh₃ (1.0 equiv), -78 → 25 °C, 16 h; (f) piperidine (0.04 equiv), AcOH (0.04 equiv), benzene, 90 °C, 1 h; (g) NaBH₄ (1.0 equiv), MeOH, 0 °C, 45 min, 84% for the four steps; (h) CH₃C(OEt)₃ (10.0 equiv), *o*-nitrophenol (0.05 equiv), xylenes, 150 °C, 21 h, 86% [ca. 1.5:1 mixture of *anti*:*syn* isomers (*anti* isomer shown)]; (i) LiOH (2.0 equiv), THF/MeOH/H₂O (3:1:1), 25 °C, 16 h, 100%; (j) **14** (3.0 equiv), MgCl₂ (3.0 equiv), CDI (2.2 equiv), THF, 25 °C, 16 h, 78% [ca. 2.7:1 mixture of *anti*:*syn* isomers (*anti* isomer shown)]; (k) *p*-ABSA (1.5 equiv), Et₃N (2.0 equiv), MeCN, 25 °C, 4 h, 97% [ca. 2.7:1 mixture *anti*:*syn* isomers (*anti* isomer shown)]; (l) Rh₂(OAc)₄ (0.01 equiv), benzene, 90 °C, 70 min, 70%; (m) HF·py (15 equiv), THF, 25 °C, 1 h; (n) *p*-MeOC₆H₄CH₂OC(N)CCl₃ (2.5 equiv), PPTS (0.1 equiv), CH₂Cl₂, 25 °C, 24 h, 73% for the two steps; (o) LDA (0.51 M in THF, 2.0 equiv), THF, -78 °C, 1 h; then PhNTf₂ (1.5 equiv), -78 → 0 °C, 2 h, 77%; (p) Dibal-H (1.0 M in toluene, 2.5 equiv), CH₂Cl₂, -78 °C, 1 h; (q) TBSOTf (2.0 equiv), 2,6-lutidine (4.0 equiv), CH₂Cl₂, 25 °C, 1 h, 89% for the two steps; (r) Pd(PPh₃)₄ (0.05 equiv), Et₃N (3.0 equiv), MeOH/DMF (1.8:1), CO (1 atm), 50 °C, 1 h, 85%; (s) Dibal-H (1.0 M in toluene, 2.5 equiv), CH₂Cl₂, -78 °C, 0.5 h, 100%; (t) Pd(PPh₃)₄ (0.05 equiv), LiCl (3.0 equiv), *n*-Bu₃SnCH₂OH (**24**, 3.0 equiv), THF, 70 °C, 2 h, 82%.

tion of TBS protected 2-cyclohexenol (TBSCl, Et₃N, **9**) was carried out by a three-step sequence⁶ involving ozonolysis, piperidine-catalyzed intramolecular aldol condensation, and NaBH₄-mediated reduction, to give cyclopentyl allylic alcohol **11** in 84% overall yield. Claisen rearrangement⁷ of **11** was effected by heating with CH₃C(OEt)₃ in the presence of *o*-nitrophenol (cat.) to afford, after saponification of the resulting ethyl ester (**12**), γ,δ-unsaturated carboxylic acid **13** in 86% overall yield as a mixture of C-5 diastereoisomers in which the desired *anti* product was predominating (*dr* ca. 1.5:1). This

Scheme 2. Homologation of Carboxylic Acids **13** and 5-*epi*-**13** to Ketoesters **15** and 5-*epi*-**15**

mixture was taken through the next three steps, at which stage the undesired diastereoisomer was conveniently and completely removed as we shall see below. Thus, conversion of carboxylic acid **13** to α-diazo-β-ketoester **4** was carried out through a two-step procedure⁸ involving reaction with methyl potassium malonate (**14**) in the presence of carbonyl diimidazole (CDI) and MgCl₂, followed by exposure of the resulting β-ketoester (**15**) to *p*-acetamidobenzenesulfonyl azide (*p*-ABSA),⁹ in 76% overall yield. The modest enhancement in diastereoisomeric purity from carboxylic acid **13** (*dr* ca. 1.5:1) to β-ketoester **15** (*dr* ca. 2.7:1) was noteworthy. Apparently, *anti* acid **13** was converted exclusively to the corresponding β-ketoester **15**, whereas the conversion of *syn* acid 5-*epi*-**13** to β-ketoester 5-*epi*-**15** was accompanied by significant amounts (15%) of acyl imidazole byproduct 5-*epi*-**15a**, which was easily removed from the mixture of ketoesters, as shown in Scheme 2. Pleasantly, heating diazo compound **4** in the presence of Rh₂(OAc)₄ (cat.) in benzene at 90 °C resulted in the formation of the expected [5.5.3] tricyclic system **16** in 70% yield and as a single diastereoisomer. No cyclization product corresponding to 5-*epi*-**4** (not shown) was observed, presumably due to steric shielding of the α-face of the olefin by the OTBS group. Although consumed, the fate of this diastereoisomer was not determined.

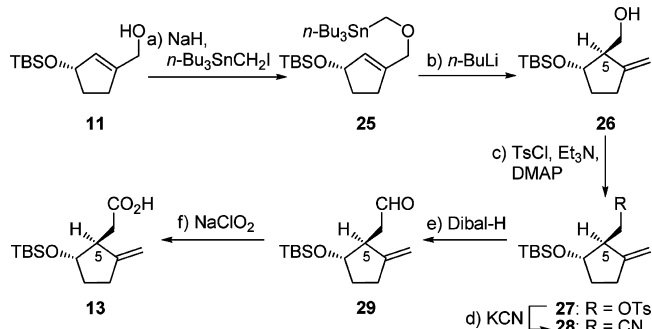
With tricyclic intermediate **16** in hand in multigram quantities we then proceeded to the next key intermediate, allylic alcohol **23**. To this end, **16** was subjected to a protecting group exchange (HF·py, **17**; then *p*-MeOC₆H₄CH₂OC(N)CCl₃, PPTS, **18**, 73% overall yield) and triflate formation (LDA, PhNTf₂, 77% yield) to give vinyl triflate **19**. The stability of triflate derivative **19** allowed its elaboration to the corresponding triflate TBS ether (Dibal-H, **20**; TBSOTf, 2,6-lut., **21**, 89% overall yield), which underwent palladium-catalyzed carboxymethylation [MeOH, CO, Pd(PPh₃)₄ (cat.), **22**] and subsequent reduction (Dibal-H) to afford allylic alcohol **23** in 85% yield over the two steps. Alternatively, Stille coupling of vinyl triflate **21** with hydroxymethyl stannane **24** in the presence of Pd(PPh₃)₄ (cat.) directly afforded allylic alcohol **23** in 82% yield as shown in Scheme 1.

While the synthetic sequence outlined in Scheme 1 provided sufficient supplies of allylic alcohol **23**, the modest diastereoselectivity of the Claisen rearrangement (**11** → **12**, *dr* ca. 1.5:1), albeit with slight enhancement in its conversion to β-ketoester **15** (*dr* ca. 2.7:1), left something to be desired and called for an improvement. To this end, allylic alcohol **11** was converted to stannane **25** (NaH, *n*-Bu₃SnCH₂I, 80% yield), a substrate for a

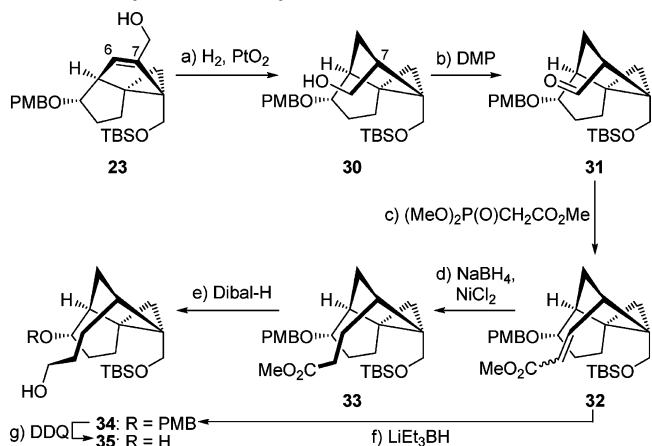
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Scheme 3. Alternative Construction of Alkenyl Carboxylic Acid **13** through [2,3]-Wittig Rearrangement^a

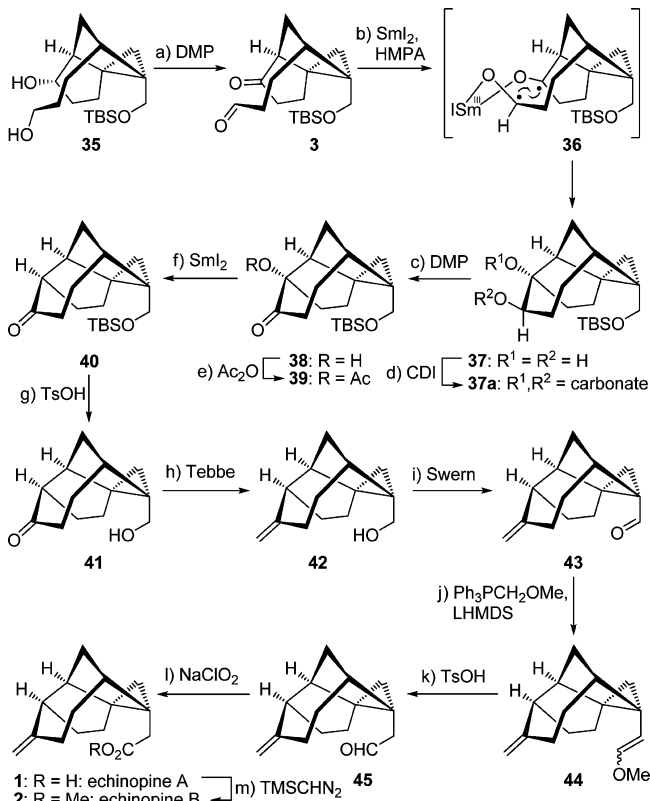
^a Reagents and conditions: (a) NaH (1.0 equiv), $n\text{-Bu}_3\text{SnCH}_2\text{I}$ (0.5 equiv), THF/HMPA (3:1), 25 °C, 16 h, 80%; (b) $n\text{-BuLi}$ (1.5 equiv), THF, -78 °C, 0.5 h, 49% [ca. 7:1 mixture of *anti:syn* isomers (*anti* isomer shown)]; (c) TsCl (4.0 equiv), Et₃N (8.0 equiv), DMAP (1.0 equiv), CH₂Cl₂, 8.5 h, 85%; (d) KCN (4.0 equiv), DMF, 60 °C, 12 h, 86%; (e) Dibal-H (1.0 M in toluene, 3.0 equiv), CH₂Cl₂, -78 °C, 1.5 h, 90%; (f) NaClO₂ (2.0 equiv), 2-methyl-2-butene (10.0 equiv), *t*-BuOH/pH 7 phosphate buffer (1:1), 25 °C, 2 h, 94%.

Scheme 4. Synthesis of Tricyclic Diol **35**^a

^a Reagents and conditions: (a) PtO₂·H₂O (60 wt %/wt, 0.88 equiv), H₂, benzene, 25 °C, 2 h, 69%; (b) DMP (2.0 equiv), NaHCO₃ (6.0 equiv), CH₂Cl₂, 25 °C, 2 h, 93%; (c) (MeO)₂P(O)CH₂COOMe (3.0 equiv), $n\text{-BuLi}$ (2.5 equiv), THF, 0 → 25 °C, 2 h, 96%; (d) NaBH₄ (2.0 equiv), NiCl₂·6H₂O (0.3 equiv), MeOH, 0 → 25 °C, 1 h, 98%; (e) Dibal-H (1.0 M in toluene, 2.5 equiv), CH₂Cl₂, -78 → 0 °C, 50 min; (f) LiEt₃BH (1.0 M in THF, 7.8 equiv), THF, -78 °C, 3 h, 63%; (g) DDQ (3.0 equiv), CH₂Cl₂/phosphate buffer (pH 7) (10:1), 0 °C, 80 min, 96% over the two steps.

planned [2,3] Wittig rearrangement,¹⁰ as shown in Scheme 3. Thus, treatment of alkenyl stannane **25** with $n\text{-BuLi}$ furnished homoallylic alcohol **26**, through the corresponding lithio species, in 49% yield as a mixture of C-5 diastereoisomers in which the desired *anti* product was predominating (ca. 7:1 *dr*). Conversion of alcohol **26** to the previously obtained carboxylic acid **13** was carried out through a four-step sequence involving tosylate **27** (TsCl, Et₃N, DMAP), cyanide **28** (KCN) and aldehyde **29** (Dibal-H, 66% yield over the three steps), which was subjected to Pinnick oxidation¹¹ (NaClO₂, 94% yield). In this instance, carboxylic acid **13** was obtained as a single diastereoisomer (by ¹H and ¹³C NMR analysis), presumably due to chromatographic enrichment during the sequence from alcohol **26**.

The next task was to reduce the Δ^{6,7} double bond of allylic alcohol **23** stereoselectively and extend the side chain to its

Scheme 5. Completion of the Total Synthesis of (+)-Echinopine A (**1**) and (+)-Echinopine B (**2**)^a

^a Reagents and conditions: (a) DMP (4.0 equiv), NaHCO₃ (16 equiv), CH₂Cl₂, 25 °C, 2 h, 81%; (b) SmI₂ (0.1 M in THF, 5.0 equiv), HMPA (20 equiv), THF, -78 → 25 °C, 1.5 h, 50%; (c) DMP (1.5 equiv), NaHCO₃ (6.0 equiv), CH₂Cl₂, 25 °C, 45 min; (d) CDI (6.0 equiv), benzene, 80 °C, 3 h, 87%; (e) Ac₂O (20 equiv), Et₃N (20 equiv), DMAP (1.0 equiv), CH₂Cl₂, 25 °C, 48 h, 81% for the two steps; (f) SmI₂ (0.1 M in THF, 2.0 equiv), MeOH (5.0 equiv), THF, -78 °C, 15 min, 92%; (g) TsOH·H₂O (1.0 equiv), MeOH/CH₂Cl₂ (1:1), 25 °C, 1 h, 100%; (h) Tebbe reagent (0.5 M in toluene, 2.2 equiv), pyridine (4.4 equiv), THF, -78 → 0 °C, 50 min, 87%; (i) (COCl)₂ (5.0 equiv), DMSO (10.0 equiv), CH₂Cl₂, -78 °C, 1 h; then Et₃N (15 equiv), -78 → 25 °C, 35 min; (j) Ph₃PCH₂OMe (5.0 equiv), LHMDS (4.7 equiv), THF, -5 °C, 45 min; (k) TsOH·H₂O (1.5 equiv), acetone, 25 °C, 3.5 h, 58% for the three steps; (l) NaClO₂ (2.0 equiv), 2-methyl-2-butene (10.0 equiv), *t*-BuOH/phosphate buffer (pH 7) (1:1), 25 °C, 1 h, 94%; (m) TMSCHN₂ (2.0 M in Et₂O, 1.5 equiv), benzene/MeOH (4:1), 25 °C, 0.5 h, 92%.

desired 3-carbon length. To this end, and as shown in Scheme 4, **23** was hydrogenated under optimized conditions, employing platinum catalyst (PtO₂, H₂) to afford the desired alcohol (**30**, 69% yield) as a single product. The latter was oxidized with DMP leading to aldehyde **31** (93% yield), whose HWE olefination [(MeO)₂P(O)CH₂COOMe, $n\text{-BuLi}$] gave enoate **32** as an inconsequential mixture of geometrical isomers (96% yield, *E:Z* ca. 4:1). Sequential reduction of **32** with NaBH₄–NiCl₂·6H₂O (98% yield) and Dibal-H, followed by DDQ-mediated PMB deprotection (**33**, 96% yield over the two steps), furnished primary alcohol **35** via PMB ether **34**. Alternatively, alcohol **34** could be accessed directly from enoate **32** through LiEt₃BH-facilitated reduction (63% yield).

The forging of the remaining seven-membered ring within the growing molecule was carried out as shown in Scheme 5, which also summarizes the final stages of the synthesis. Thus, exposure of diol **35** to DMP led to keto aldehyde **3** (81% yield), whose intramolecular pinacol coupling under SmI₂–HMPA conditions,⁴ as planned, smoothly furnished tetracyclic system

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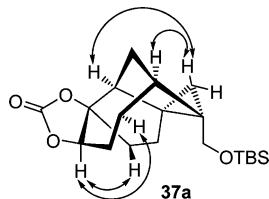


Figure 3. Key NOEs in support of the stereochemical assignment of carbonate **37a** and thereby diol **37**.

37 in 50% yield as a single diastereoisomer. Supported by NOE studies (see Figure 3) on the corresponding carbonate (**37a**, prepared from **37** and CDI, Scheme 5), this stereochemical outcome can be rationalized by postulating the cyclic chelated transition state **36** as shown in Scheme 5. Oxidation of the secondary hydroxyl group of **37** (DMP, **38**), followed by excision of the superfluous tertiary acetate (Ac_2O , Et_3N , DMAP, **39**, 81% for the two steps; SmI_2 –MeOH, 92% yield), then led to ketone **40**. Removal of the TBS group from the latter (TsOH), followed by Tebbe olefination of the resulting hydroxy ketone **41** (87% yield for the two steps) and Swern oxidation of the resulting hydroxyl olefin (**42**), furnished aldehyde **43**. Homologation of the latter through the standard procedure ($\text{Ph}_3\text{PCH}_2\text{OMe}$ –LHMDS, **44**; TsOH) afforded aldehyde **45** (58% yield for the three steps), whose Pinnick oxidation led first to echinopine A (**1**, NaClO_2 , 94% yield) and thence echinopine B (**2**, TMSCHN_2 , 92% yield). Synthetic (+)-**1** and (+)-**2** exhibited identical spectroscopic (^1H and ^{13}C NMR) data and satisfactory optical rotations [**1**: $[\alpha]_D^{25} = +27.6$ ($c = 0.54$, CHCl_3), $[\alpha]_D^{22} = +23$ ($c = 0.11$, CHCl_3)² and Lit. $[\alpha]_D^{22} = +26.1$

($c = 0.70$, CHCl_3)³; **2**: $[\alpha]_D^{25} = +21.5$ ($c = 0.50$, CHCl_3), $[\alpha]_D^{22} = +21$ ($c = 0.14$, CHCl_3)² and Lit. $[\alpha]_D^{22} = +21.6$ ($c = 0.60$, CHCl_3)³] and mass spectrometric data with those reported for the natural products.^{2,3}

In our initial studies, and by employing racemic allylic alcohol **8**, we have also synthesized ($\pm$)-echinopines A and B [($\pm$)-**1** and ($\pm$)-**2**]. Their spectroscopic (^1H and ^{13}C NMR) data were in agreement with those of the published data.^{2,3}

Conclusion

In summary, an asymmetric total synthesis of the novel natural products echinopines A (**1**) and B (**2**) has been achieved through a highly stereoselective and efficient strategy that highlights the growing importance of rhodium catalysis and samarium redox chemistry in chemical synthesis.

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

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