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Total Synthesis of Echinopines A and B

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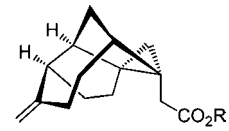
Abstract: Echinopines A and B [(+)-**1** and (+)-**2**], two naturally occurring compounds characterized with a unique [3.5.5.7] carbon framework, have been synthesized in both enantiomeric and racemic forms. Their total synthesis involves a novel intramolecular rhodium-catalyzed cyclopropanation (**4**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

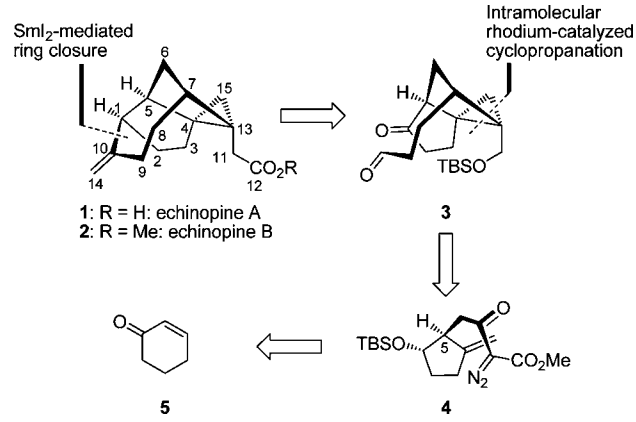


1: R = H: echinopine A
2: R = Me: echinopine B

Figure 1. Structures of echinopines A (**1**) and B (**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 SmI_2-mediated[4] pinacol coupling (see **3** → **1**, **2**, Figure 2) at a later stage would generate the cycloheptane ring. Intermediate **4** was traced back to cyclohexenone (**5**) as shown retrosynthetically in Figure 2.



1: R = H: echinopine A
2: R = Me: echinopine B

3

4

5

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

(1) (a) Shih, C. In *Flora Sinica*; Scientific Press: Beijing, China, 1987; Vol. 78, p 1. (b) Guo, D.; Cui, Y.; Lou, Z.; Gao, C.; Huang, L. *Chin. Trad. Herb. Med.* **1992**, *23*, 3–5. (c) Guo, D.; Cui, Y.; Lou, Z.; Wang, D.; Huang, L. *Chin. Trad. Herb. Med.* **1992**, *23*, 512–514. (d) Lam, J.; Christensen, L. P.; Thomasen, T. *Phytochemistry* **1991**, *30*, 1157–1159. (e) Chaudhuri, P. K. *J. Nat. Prod.* **1992**, *55*, 249–259. (f) Ram, S. N.; Roy, R.; Singh, B.; Singh, R. P.; Pandey, V. B. *Planta Med.* **1996**, *62*, 187. (g) Koike, K. K.; Jia, Z. H.; Nikaido, T.; Liu, Y.; Zhao, Y. Y.; Guo, D. A. *Org. Lett.* **1999**, *1*, 197–198.

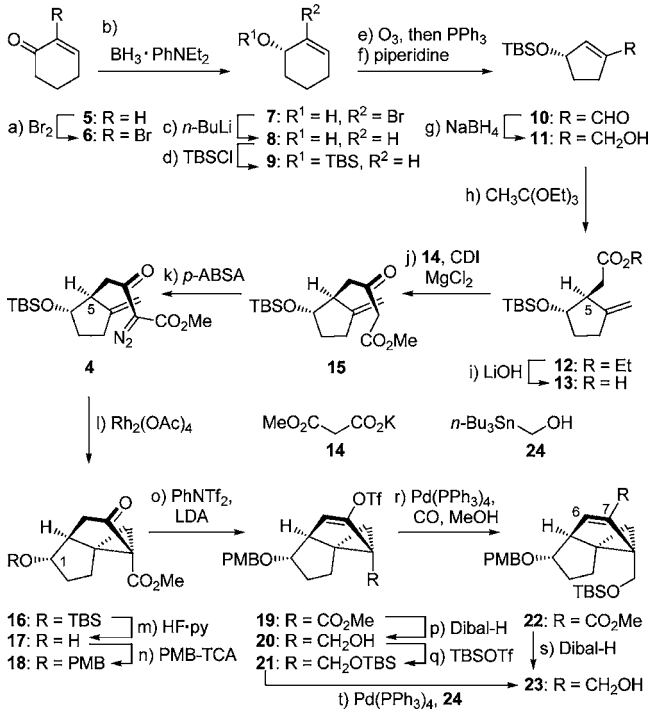
(2) Dong, M.; Cong, B.; Yu, S.-H.; Sauriol, F.; Huo, C.-H.; Shi, Q.-W.; Gu, Y.-C.; Zamir, L. O.; Kiyota, H. *Org. Lett.* **2008**, *10*, 701–704.

(3) Magauer, T.; Mulzer, J.; Tiefenbacher, K. *Org. Lett.* **2009**, *11*, 5306–5309.

(4) For selected reviews on the use of samarium diiodide in chemical synthesis, see: (a) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140–7165. (b) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371–3403. (c) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351–10372. (d) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338.

(5) Holub, N.; Neidhöfer, J.; Blechert, S. *Org. Lett.* **2005**, *7*, 1227–1229.

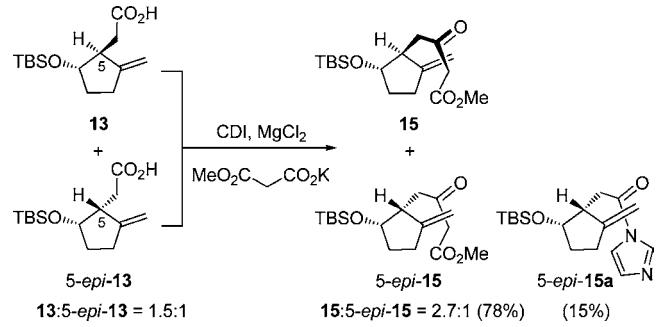
Scheme 1. Synthesis of Tricyclic Allylic Alcohol **23**[a]



[a] Reagents and conditions: (a) Br_2 (1.02 equiv), CH_2Cl_2, 0 °C, 1 h; then Et_3N (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 $BH_3 \cdot N,N$-diethylaniline (1.0 equiv), **5**, −5 → 25 °C, 16 h, 90%, ≥95% ee (Mosher ester analysis); (c) *n*-BuLi (3.5 equiv), Et_2O, −78 → −10 °C, 2.5 h, 80%; (d) TBSCl (1.3 equiv), Et_3N (1.5 equiv), DMAP (0.1 equiv), CH_2Cl_2, 25 °C, 6 h; (e) O_3, CH_2Cl_2, −78 °C; then PPh_3 (1.0 equiv), −78 → 25 °C, 16 h; (f) piperidine (0.04 equiv), AcOH (0.04 equiv), benzene, 90 °C, 1 h; (g) $NaBH_4$ (1.0 equiv), MeOH, 0 °C, 45 min, 84% for the four steps; (h) $CH_3C(OEt)_3$ (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/H_2O (3:1:1), 25 °C, 16 h, 100%; (j) **14** (3.0 equiv), $MgCl_2$ (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), Et_3N (2.0 equiv), MeCN, 25 °C, 4 h, 97% [ca. 2.7:1 mixture *anti*:*syn* isomers (*anti* isomer shown)]; (l) $Rh_2(OAc)_4$ (0.01 equiv), benzene, 90 °C, 70 min, 70%; (m) HF·py (15 equiv), THF, 25 °C, 1.5 h; (n) *p*-$MeOC_6H_4CH_2OC(N)CCl_3$ (2.5 equiv), PPTS (0.1 equiv), CH_2Cl_2, 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 $PhNTf_2$ (1.5 equiv), −78 → 0 °C, 2 h, 77%; (p) Dibal-H (1.0 M in toluene, 2.5 equiv), CH_2Cl_2, −78 °C, 1 h; (q) TBSOTf (2.0 equiv), 2,6-lutidine (4.0 equiv), CH_2Cl_2, 25 °C, 1 h, 89% for the two steps; (r) $Pd(PPh_3)_4$ (0.05 equiv), Et_3N (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), CH_2Cl_2, −78 °C, 0.5 h, 100%; (t) $Pd(PPh_3)_4$ (0.05 equiv), LiCl (3.0 equiv), *n*-Bu_3SnCH_2OH (**24**, 3.0 equiv), THF, 70 °C, 2 h, 82%.

tion of TBS protected 2-cyclohexenol (TBSCl, Et_3N, **9**) was carried out by a three-step sequence[6] involving ozonolysis, piperidine-catalyzed intramolecular aldol condensation, and $NaBH_4$-mediated reduction, to give cyclopentyl allylic alcohol **11** in 84% overall yield. Claisen rearrangement[7] of **11** was effected by heating with $CH_3C(OEt)_3$ 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**



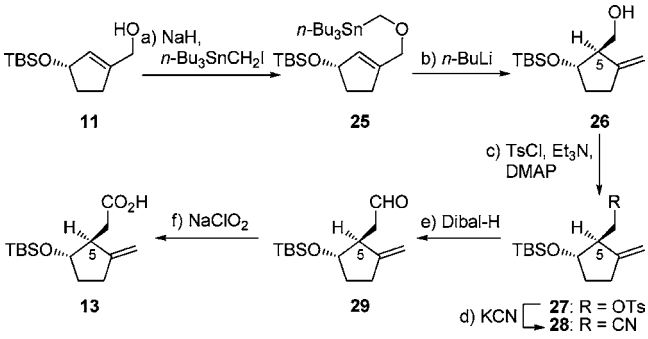
mixture was taken through the next three steps, at which stage the undesired diastereoisomer was conveniently and completely removed as we shall see below. Thus, conversion of carboxylic acid **13** to α-diazo-β-ketoester **4** was carried out through a two-step procedure[8] involving reaction with methyl potassium malonate (**14**) in the presence of carbonyl diimidazole (CDI) and $MgCl_2$, followed by exposure of the resulting β-ketoester (**15**) to *p*-acetamidobenzenesulfenyl 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 $Rh_2(OAc)_4$ (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*-$MeOC_6H_4CH_2OC(N)CCl_3$, PPTS, **18**, 73% overall yield) and triflate formation (LDA, $PhNTf_2$, 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, $Pd(PPh_3)_4$ (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 $Pd(PPh_3)_4$ (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*-Bu_3SnCH_2I, 80% yield), a substrate for a

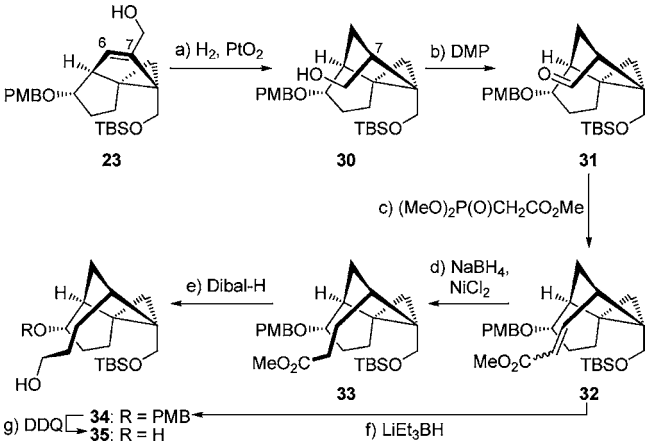
(6) (a) Kozikowski, A. P.; Tuckmantel, W. *J. Org. Chem.* **1991**, *56*, 2826–2837. For an alternative synthesis of allylic alcohol **9**, see: (b) Fukuzaki, T.; Kobayashi, S.; Hibi, T.; Ikuma, Y.; Ishihara, J.; Kanoh, N.; Murai, A. *Org. Lett.* **2002**, *4*, 2877–2880.
(7) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002.
(8) Brooks, D. W.; Lu, D. L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72–74.
(9) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, D. H. *Synth. Commun.* **1987**, *17*, 1709–1716.

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*-Bu_3SnCH_2I (0.5 equiv), THF/HMPA (3:1), 25 °C, 16 h, 80%; (b) *n*-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), Et_3N (8.0 equiv), DMAP (1.0 equiv), CH_2Cl_2, 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), CH_2Cl_2, −78 °C, 1.5 h, 90%; (f) $NaClO_2$ (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]



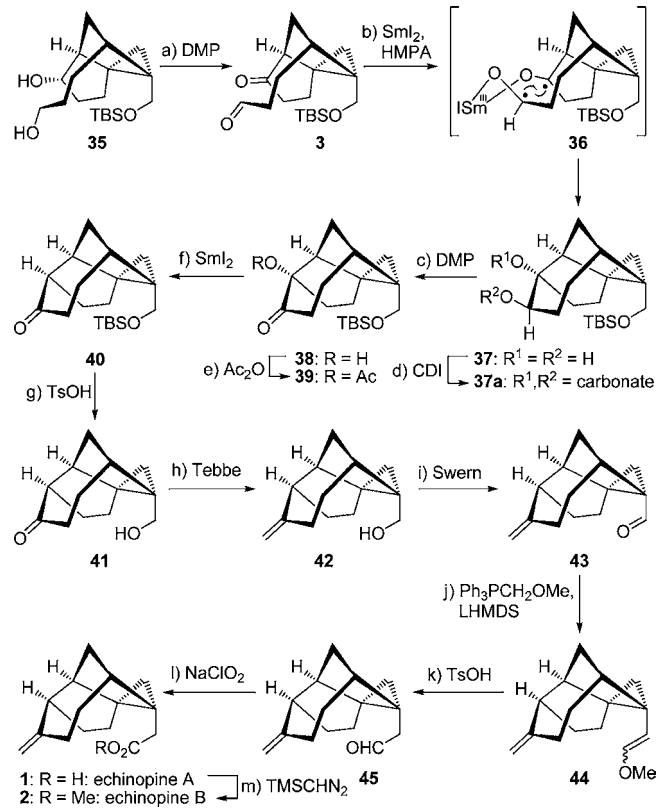
[a] Reagents and conditions: (a) $PtO_2 \cdot H_2O$ (60 wt %/wt, 0.88 equiv), H_2, benzene, 25 °C, 2 h, 69%; (b) DMP (2.0 equiv), $NaHCO_3$ (6.0 equiv), CH_2Cl_2, 25 °C, 2 h, 93%; (c) $(MeO)_2P(O)CH_2COOMe$ (3.0 equiv), *n*-BuLi (2.5 equiv), THF, 0 → 25 °C, 2 h, 96%; (d) $NaBH_4$ (2.0 equiv), $NiCl_2 \cdot 6H_2O$ (0.3 equiv), MeOH, 0 → 25 °C, 1 h, 98%; (e) Dibal-H (1.0 M in toluene, 2.5 equiv), CH_2Cl_2, −78 → 0 °C, 50 min; (f) $LiEt_3BH$ (1.0 M in THF, 7.8 equiv), THF, −78 °C, 3 h, 63%; (g) DDQ (3.0 equiv), CH_2Cl_2/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*-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, Et_3N, DMAP), cyanide **28** (KCN) and aldehyde **29** (Dibal-H, 66% yield over the three steps), which was subjected to Pinnick oxidation[11] ($NaClO_2$, 94% yield). In this instance, carboxylic acid **13** was obtained as a single diastereoisomer (by ^1H and ^{13}C NMR analysis), presumably due to chromatographic enrichment during the sequence from alcohol **26**.

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

(10) Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105–209.
(11) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.

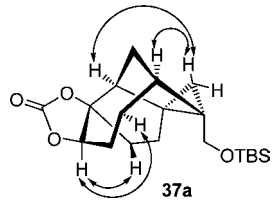
Scheme 5. Completion of the Total Synthesis of (+)-Echinopine A (**1**) and (+)-Echinopine B (**2**)[a]



[a] Reagents and conditions: (a) DMP (4.0 equiv), $NaHCO_3$ (16 equiv), CH_2Cl_2, 25 °C, 2 h, 81%; (b) SmI_2 (0.1 M in THF, 5.0 equiv), HMPA (20 equiv), THF, −78 → 25 °C, 1.5 h, 50%; (c) DMP (1.5 equiv), $NaHCO_3$ (6.0 equiv), CH_2Cl_2, 25 °C, 45 min; (d) CDI (6.0 equiv), benzene, 80 °C, 3 h, 87%; (e) Ac_2O (20 equiv), Et_3N (20 equiv), DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 48 h, 81% for the two steps; (f) SmI_2 (0.1 M in THF, 2.0 equiv), MeOH (5.0 equiv), THF, −78 °C, 15 min, 92%; (g) $TsOH \cdot H_2O$ (1.0 equiv), $MeOH/CH_2Cl_2$ (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), CH_2Cl_2, −78 °C, 1 h; then Et_3N (15 equiv), −78 → 25 °C, 35 min; (j) Ph_3PCH_2OMe (5.0 equiv), LHMDS (4.7 equiv), THF, −5 °C, 45 min; (k) $TsOH \cdot H_2O$ (1.5 equiv), acetone, 25 °C, 3.5 h, 58% for the three steps; (l) $NaClO_2$ (2.0 equiv), 2-methyl-2-butene (10.0 equiv), *t*-BuOH/phosphate buffer (pH 7) (1:1), 25 °C, 1 h, 94%; (m) $TMSCHN_2$ (2.0 M in Et_2O, 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 (PtO_2, H_2) 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 [$(MeO)_2P(O)CH_2COOMe$, *n*-BuLi] gave enoate **32** as an inconsequential mixture of geometrical isomers (96% yield, *E*:*Z* ca. 4:1). Sequential reduction of **32** with $NaBH_4$−$NiCl_2 \cdot 6H_2O$ (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 $LiEt_3BH$-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 SmI_2−HMPA conditions,[4] as planned, smoothly furnished tetracyclic system



37a

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 ($Ph_3PCH_2OMe-LHMDS$, **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 (±)-echinopines A and B [(±)-**1** and (±)-**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.

Acknowledgment. Professor K. C. Nicolaou is also at the Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037 (USA), and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093 (USA). We thank Ms. Doris Tan (ICES) for high resolution mass spectrometric (HRMS) assistance. Financial support for this work was provided by A*STAR, Singapore.

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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