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Synthetic studies on sugar-fused erinacines

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Samarium-mediated 7-*endo-trig* radical cyclization afforded excellent stereocontrol of the four contiguous asymmetric centers present in the 6-7-6 tricyclic cores of the (sugar-fused) erinacines E, F, and G.

The erinacines were isolated by Kawagishi from myceria of the fungus *Hericium erinaceum*, as potent stimulators of nerve growth factor (NGF) synthesis.[1] Erinacines E **1**, F **2**, and G **3**[2] share carbocyclic E-rings that are not seen in other cyathan diterpenes,[3] thus constituting a unique subgroup among the erinacine family (Fig. 1). These E-rings are probably biosynthesized by fusion of a sugar unit with a diterpenoid aglycon (cyathan skeleton). In 1998, Saito *et al.* investigated erinacine E **1** from the fermentation broth of a basidiomycete (*Hericium ramosum* CL24240), and that it had κ-opioid receptor agonist activity.[4] Despite their intriguing structure and biological activities, no synthetic studies have focused on the substructural family containing erinacines E, F, and G.[5,6] We report here the efficient construction of the common 6-7-6 tricyclic core **4**. A notable challenge in this synthesis was the construction of the central 7-membered ring, which possesses four contiguous asymmetric centers.

Our synthetic plan is outlined in Scheme 1. Disconnection at the C13–C14 bond of **4** gives the ald-enone **5**, a key precursor in our study. We chose samarium-mediated radical cyclization for this transformation.[7,8] Only a few examples of 7-*endo-trig* radical cyclization have been reported,[9] but we predicted that its mild reaction conditions would be suitable for polyfunctionalized target molecules.

Our synthesis commenced with chemoselective reduction of **6** (96% ee) (Scheme 2).[10] Swern oxidation of the resulting primary alcohol gave an aldehyde with a *syn* relative configuration. Treatment of the *syn*-aldehyde with DBU afforded an equilibrium mixture of aldehydes (*syn* : *anti* = 1 : 1). The desired *anti*-isomer **7** was isolated, and the recovered *syn*-isomer was treated again. After two cycles of these processes, **7** was obtained in 70% yield. The *anti*-isomer **7** was then converted into homologated aldehyde **8** by a Wittig reaction and hydrolysis of the resulting enol ether without any epimerization at C-5. The installation of 2-cyclohexen-1-one with the Morita–Baylis–Hillman reaction[11] proved to be more difficult than anticipated. Numerous reaction

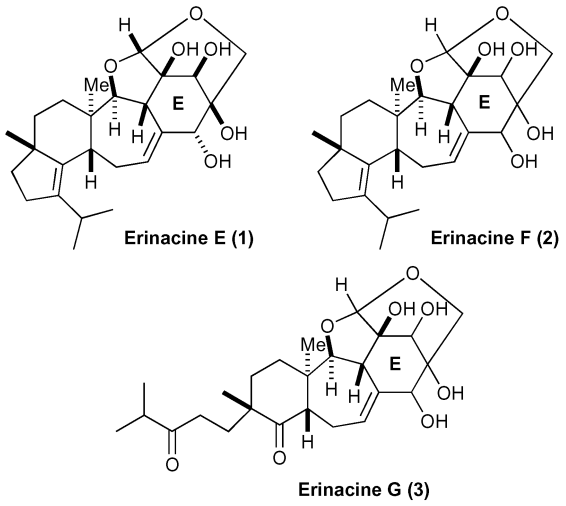
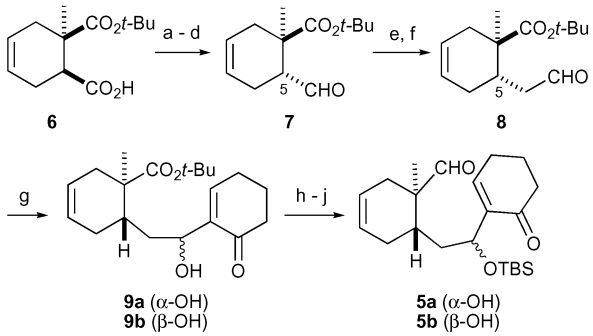
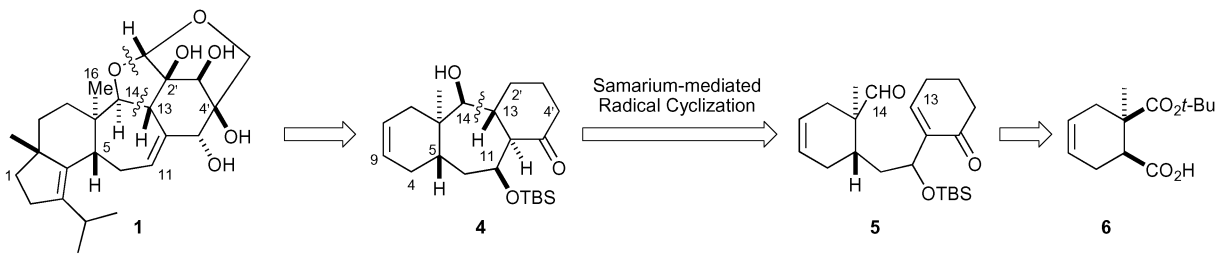


Fig. 1 Sugar-fused erinacines.



Scheme 2 *Reagents and conditions*: a) i) *i*-BuOCOCl, Et_3N, Et_2O; ii) $NaBH_4$, THF, 87% (2 steps); b) $(COCl)_2$, DMSO; Et_3N, CH_2Cl_2, 90%; c) DBU, MeOH; d) separation of isomers, 70% of **7** after 2 cycles; e) *t*-BuOK, $MeOCH_2PPh_3Cl$, toluene, 68%; f) TFA, THF–H_2O (1 : 1), 94%; g) 2-cyclohexen-1-one, DBU, Et_2O–MeOH (9 : 1), 47% for **9a** and 47% for **9b**; h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 78% from **9a** and 82% from **9b**; i) DIBAL, toluene; j) TPAP, NMO, 4 Å MS, CH_2Cl_2, 66% for **5a** and 81% for **5b**.



Scheme 1 Synthetic plan.

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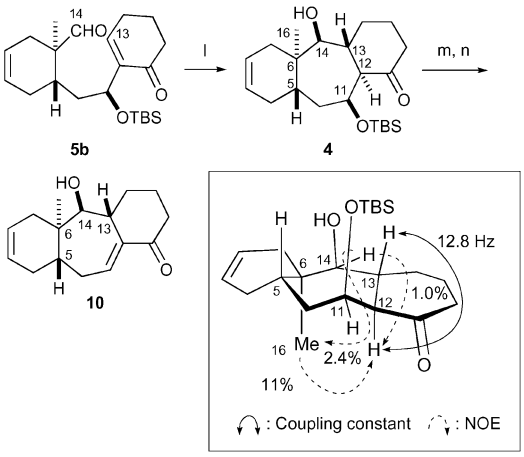
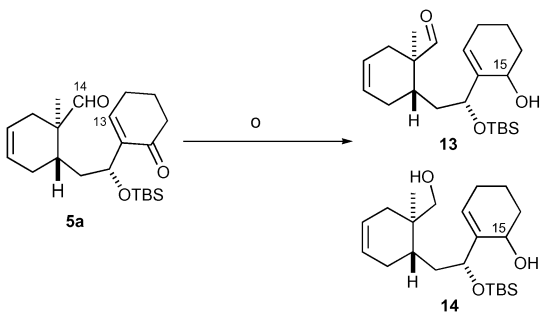
systems were surveyed, and finally, aldehyde **8** and 2-cyclohexen-1-one were treated with DBU in Et_2O–MeOH, and the desired product **9** was obtained in 94% yield. The use of MeOH as a co-solvent was found to be essential, with **9** being obtained in poor yield (<30%) in the absence of MeOH. Diastereomeric secondary alcohols **9a** and **9b**[12] were protected as their *tert*-butyldimethylsilyl ethers. Reduction of the *tert*-butyl ester and the enone moiety, followed by oxidation of the resulting diol with TPAP, gave ald-enones **5a** and **5b**, respectively.

With the key precursor **5** in hand, we attempted the samarium-mediated radical cyclization. With ald-enone **5b** as a starting material, the cyclization reaction proceeded smoothly to give **4** in 86% yield as a single diastereomer. Structural assignment of cycloadduct **4** was initially obtained through ^{1}H-NMR, ^{13}C-NMR, COSY, HMBC, and HOHAHA experiments, and these spectra showed that **4** has the 6-7-6 tricyclic core as a platform. The NOE correlations between H-12 and Me-16, and H-12 and H-14 indicated that both H-12 and H-14 protons are oriented in an α configuration. The 12, 13-*trans* stereochemistry was assigned on the basis of the coupling constant ($J_{12,13}$ = 12.8 Hz). These experiments revealed that compound **4** has the correct stereochemistry on four contiguous carbons, C-5, C-6, C-14, and C-13.[13] Finally, desilylation of **4** afforded a diol, and acetylation and subsequent elimination of the resulting acetate afforded **10** with the same configuration of functional groups as in erinacines E, F, and G (Scheme 3).



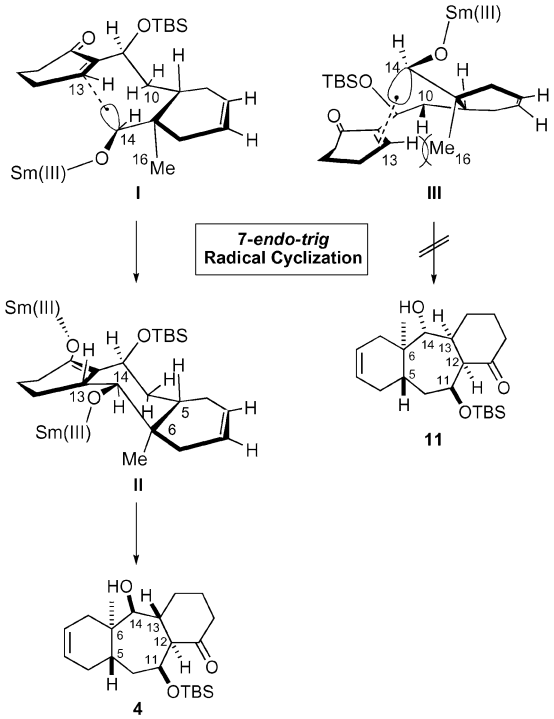
Scheme 3 *Reagents and conditions*: l) SmI_2 (20 eq.), THF–*t*-BuOH, (100 : 1), 0 C, 2 h, 86%; m) TBAF, AcOH, THF, 67%; n) Ac_2O, DBU, CH_2Cl_2, 96%.

Unexpectedly, the radical cyclization with ald-enone **5a** failed under the conditions described above. The products were inseparable mixtures of **13** and **14** (*ca.* 1 : 1). When a Lewis-basic additive, HMPA, was added to increase the reduction potential,[14] the sole product was **14** in 76% yield. The stereochemistry of the newly formed chiral centers at C-15 in **13** and **14** was not determined (Scheme 4).



Scheme 4 *Reagents and conditions*: o) SmI_2 (20 eq.), THF–*t*-BuOH (100 : 1), 0 C, 3.5 h, 76%

The stereochemical outcomes of the 7-*endo-trig* radical cyclization of **5b** might be explained as follows (Scheme 5). The cyclization from intermediate **I** leads to a *cis* arrangement between the newly formed hydroxy group at C-14 and the hydrogen atom at C-13. This process is preferable to approach **III**, which suffers from repulsion between Me-16, H-10, and H-13. The resulting samarium enolate is protonated stereoselectively to afford thermodynamically more stable **4** as a single isomer.



Scheme 5

In summary, we have succeeded in constructing the central 6-7-6 core ring system that exists in sugar-fused erinacines by an efficient samarium-mediated radical cyclization. These synthetic studies should constitute a firm basis for synthesis of the sugar-fused erinacine subfamily. Further efforts toward the synthesis of erinacine E will be reported in due course.

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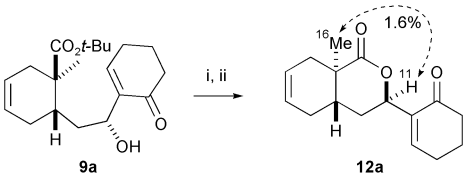
12 The configuration at C-11 in **9a** and **9b** was confirmed by converting them to lactones **12a** and **12b**, respectively; a NOE was observed between H-11 and Me-16 in **12a** .



9a **12a**

Reagents and conditions: i) TFA, CH_2Cl_2, 0 °C, 2 h; ii) azeotropic removal of water with toluene, 40 °C, 20 mmHg, 55% for **12a**, 65% for **12b**

13 Compound **4**: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.56 (2H, m, H-8 and H-9), 4.76 (1H, d, $J = 10.8$ Hz, OH), 4.69 (1H, d, $J = 5.4$ Hz, H-11), 3.20 (1H, d, $J = 10.8$ Hz, H-14), 2.70 (1H, dd, $J = 3.0$, 16.8 Hz, H-7), 2.49 (1H, d, $J = 12.8$ Hz, H-12), 2.36 (1H, ddd, $J = 1.8$, 3.6, 13.8 Hz, H-4′), 2.22 (1H, ddd, $J = 1.8$, 12.8, 13.2 Hz, H-13), 2.20 (1H, m, H-4′), 2.16 (1H, m, H-5), 2.05 (1H, dd, $J = 3.0$, 13.2 Hz, H-2′), 2.03 (1H, m, H-3′), 1.99 (1H, m, H-4), 1.86 (1H, m, H-10), 1.83 (1H, m, H-2′), 1.69 (2H, m, H-4 and H-3′), 1.49 (1H, dd, $J = 1.8$, 16.8 Hz, H-7), 1.30 (1H, ddd, $J = 1.8$, 12.6, 13.2 Hz, H-10), 0.94 (3H, s, H-16), 0.88 (9H, s, *t*-BuSi), 0.20 (3H, s, MeSi), 0.15 (3H, s, MeSi); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 209.6, 125.8, 124.5, 82.9, 67.4, 60.3, 48.6, 42.2, 40.7, 40.6, 39.5, 33.6, 31.7, 29.6, 25.9, 25.8, 18.2, 15.3, −4.80, −4.90; IR (film, cm^{-1}) 3396, 2929, 1712, 1209, 788, 670, 424; HRMS calcd. for $C_{22}H_{38}O_3SiNa$ 401.2488, found 401.2496; $[\alpha]_D^{27}$ −3.54 ($c = 0.427$, $CHCl_3$).

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