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Total synthesis of coronafacic acid through 6-*endo*-*trig* mode intramolecular cyclization of an enone-aldehyde to a hydrindanone using samarium(II) iodide

Masakazu Sono, Atsuko Hashimoto, Katsuyuki Nakashima and Motoo Tori*

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro cho, Tokushima 770-8514, Japan

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Abstract

Coronafacic acid has been synthesized from a hydrindanone prepared by a 6-*endo*-*trig* mode cyclization reaction of the enone-aldehyde with samarium(II) iodide. The stereochemistry of the hydrindanone was controlled by the coordinated samarium species resulting in *cis* in respect of the hydroxyl group at C-4 and the juncture proton at C-3a.

Keywords: biologically active compounds; carboxylic acids and derivatives; esters; indanes/hydrindanes.

We have previously reported an intramolecular cyclization reaction of an aldehyde and α,β-unsaturated ketone using samarium(II) iodide.[1–6] The reaction depends on the following conditions: with or without a proton source and/or HMPA resulting in formation of hydridanones with *trans* or *cis* selectivity in respect of the hydroxyl group at C-4 and the juncture proton at C-3a.[1,2] We have now successfully applied this reaction to the synthesis of coronafacic acid.[7]

Coronafacic acid (**1**) is itself a natural product isolated from the culture broth of *Pseudomonas syringae* by Ichihara and his group in 1977.[7] It has a *cis*-fused hydrindanone moiety (H-3a and H-7a) with an ethyl group at C-6 and a trisubstituted double bond (Δ4,5).[7] The synthesis of this compound has been reported by several groups.[8–21] The cyclization of the cyclopentenone derivative **3** to ketol **2** is the key step of this synthesis. The stereochemical problem is to adjust the stereochemistry at both the C-3a and C-7a positions relative to the ethyl group. However, this inversion may be feasible by the base-catalyzed equilibration (Scheme 1).

The precursor for the cyclization was prepared starting from 4-ethylcyclohexanol (**4**) (Scheme 2). Jones oxidation, Baeyer–Villiger oxidation, methanolysis, protection with the THP ether, and $LiAlH_4$ reduction afforded alcohol **5** in 57% yield (five steps). Swern oxidation and the Grignard reaction with the C3 unit, followed by deprotection of the TBDMS ether, yielded diol **6** in 60%

* Corresponding author. Tel: +81-88-622-9611; fax: +81-88-655-3051; e-mail: tori@ph.bunri-u.ac.jp

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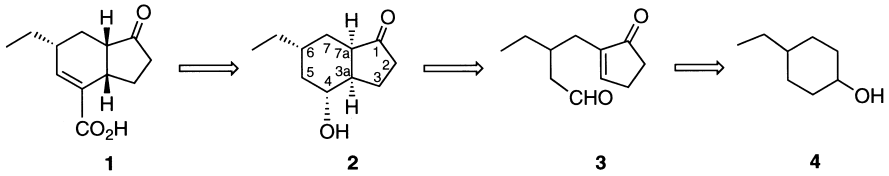
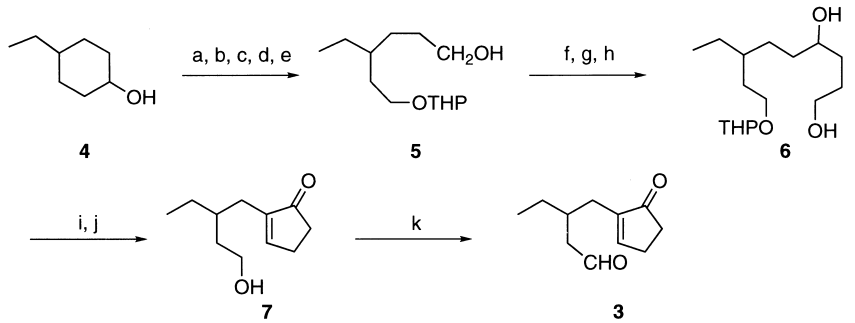


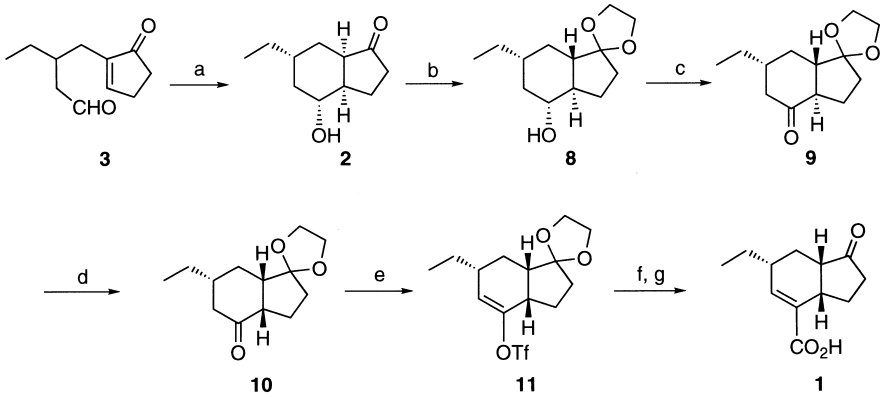
Scheme 1. Synthetic plan

yield (three steps). Swern oxidation into keto-aldehyde, KOH-catalyzed intramolecular aldol cyclization, and deprotection of the THP ether gave alcohol **7** in 47% yield (two steps). Swern oxidation of **7** afforded the desired enone-aldehyde **3** in 72% yield.



Scheme 2. (a) Jones' oxidation; (b) *m*CPBA, CH_2Cl_2, reflux, 4 h; (c) NaOMe, MeOH, rt, 2 h; (d) DHP, PPTS, CH_2Cl_2, rt, 10 h; (e) LAH, ether, rt, 10 h (five steps 75%); (f) Swern oxidation; (g) $BrMgCH_2CH_2CH_2OTBDMS$, THF, rt, 10 h; (h) TBAF, THF, rt, 2 h (three steps 66%); (i) Swern oxidation; (j) 5% KOH, MeOH, rt, 10 h; then 1 M HCl (two steps 47%); (k) Swern oxidation (72%)

The enone-aldehyde **3** was treated with SmI_2 in anhydrous THF at 0°C to yield a mixture of four stereoisomers of hydrindanones, the composition of which was determined by GC–MS (Scheme 3).[22] Separation of this mixture afforded alcohol **2** as a major product.[22] Treatment of **2**



Scheme 3. (a) SmI_2 (3 equiv.), 0°C, THF (61%); (b) $HOCH_2CH_2OH$, TsOH, PhH (56%); (c) PDC, CH_2Cl_2, rt, 5 h (quant.); (d) K_2CO_3, MeOH, reflux, 10 h (50%); (e) LDA, Cl-Py-$N(Tf)_2$, THF, –78°C (70%); (f) CO, $Pd(OAc)_2$, PPh_3, Et_3N, MeOH, DMF (58%); (g) 3 M HCl (80%)

with ethyleneglycol in the presence of TsOH afforded epimerized ketal **8**, stereochemistry of which was determined by the NOESY spectrum.[23] After oxidation of **8**, the resulting ketone **9** was subjected to base-catalyzed equilibration (KOH–MeOH) to give *cis*-hydrindanone **10** along with the starting ketone **9** in the ratio of **10**:**9** = 50:27. The ketone **10** was treated with LDA followed by chloropyridine triflate[24] at –78°C to provide a tri-substituted enol triflate in 70% yield. The palladium chemistry of carboxylation under standard conditions[25] afforded the corresponding methyl ester in 58% yield, which was hydrolyzed with 1 M aqueous HCl under reflux to yield coronafacic acid (**1**) in 80% yield.[7] The spectral data and mp (121–124°C) [lit. 125–128°C][7] were identical with those of the natural product.

Herein we have demonstrated a new route to the hydrindanones by a 6-*endo-trig* mode of intramolecular cyclization using SmI_2 and its successful application to the total synthesis of coronafacic acid (**1**).

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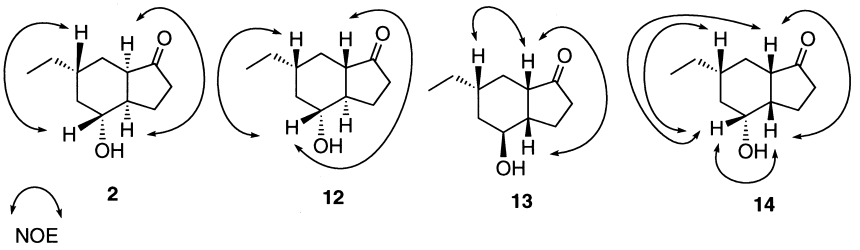
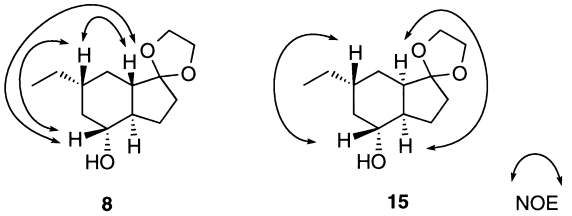
22. This reaction yielded four compounds (**2**:**12**:**13**:**14** = 50:18:19:13), whose structures were unambiguously determined by 2D NMR after separation (HPLC). Compounds **12**–**14** can also be used for synthesis.



23. The minor product was the normal ketal **15**, the yields of **8** and **15** being 56 and 12%, respectively.



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