



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

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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. © 2000 Elsevier Science Ltd. All rights reserved.

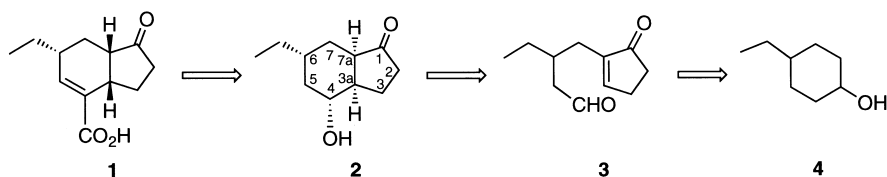
Keywords: biologically active compounds; carboxylic acids and derivatives; esters; indanes/hydrindanes.

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 hydrindanones 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 ($\Delta 4,5$).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).

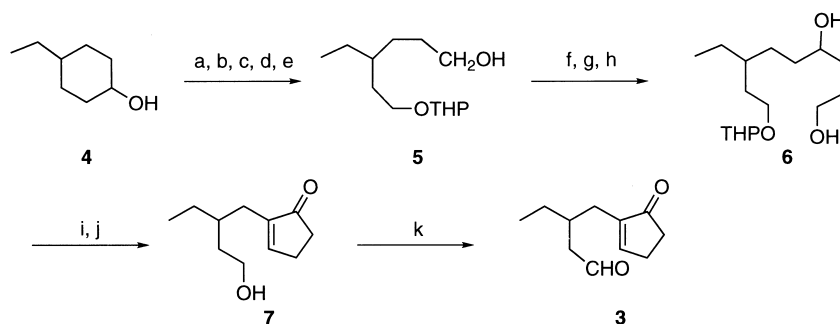
The precursor for the cyclization was prepared starting from 4-ethylcyclohexanol (**4**) (Scheme 2). Jones oxidation, Baeyer–Villiger oxidation, methanolysis, protection with the THP ether, and LiAlH_4 reduction afforded alcohol **5** in 57% yield (five steps). Swern oxidation and the Grignard reaction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

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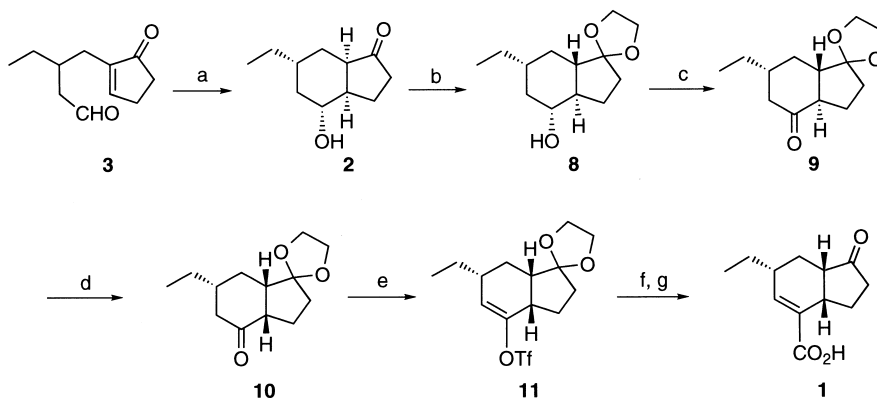
Scheme 1. Synthetic plan

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, CH₂Cl₂, reflux, 4 h; (c) NaOMe, MeOH, rt, 2 h; (d) DHP, PPTS, CH₂Cl₂, rt, 10 h; (e) LAH, ether, rt, 10 h (five steps 75%); (f) Swern oxidation; (g) BrMgCH₂CH₂CH₂OTBDMS, 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 SmI₂ 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) SmI₂ (3 equiv.), 0°C, THF (61%); (b) HOCH₂CH₂OH, TsOH, PhH (56%); (c) PDC, CH₂Cl₂, rt, 5 h (quant.); (d) K₂CO₃, MeOH, reflux, 10 h (50%); (e) LDA, Cl-Py-N(Tf)₂, THF, -78°C (70%); (f) CO, Pd(OAc)₂, PPh₃, Et₃N, 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 triflate²⁴ at -78°C to provide a tri-substituted enol triflate in 70% yield. The palladium chemistry of carboxylation under standard conditions²⁵ 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 ($121\text{--}124^{\circ}\text{C}$) [lit. $125\text{--}128^{\circ}\text{C}$]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**).

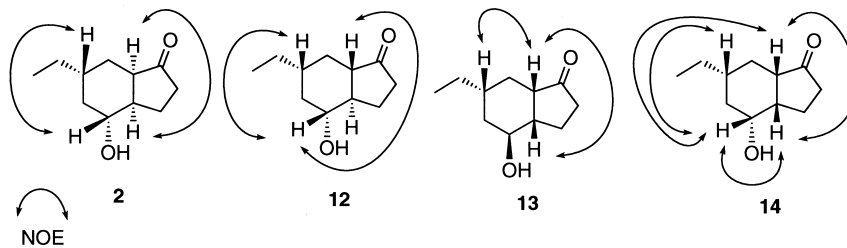
Acknowledgements

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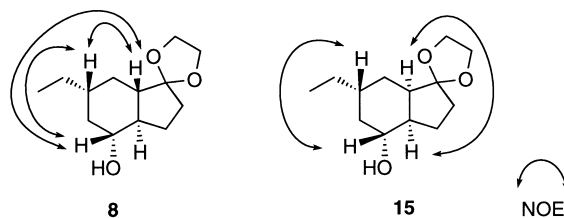
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 22. This reaction yielded four compounds (**2**:**12**:**13**:**14** = 50:18:19:13), whose structures were unambiguously determined by 2D NMR after separation (HPLC). Compounds **12–14** can also be used for synthesis.



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



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