Stereoselective Route to Functionalized *cis*-Hydrindanes from Tricyclo[5.2.1.$0^{2,6}$]decan-10-ones. A Total Synthesis of (±)-Coronafacic Acid

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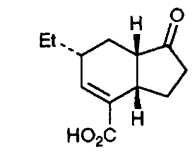
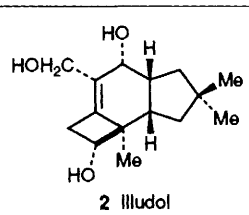
A flexible approach to functionalized *cis*-hydrindanes *via* Haller–Bauer type cleavage of *endo*-tricyclo[5.2.1.$0^{2,6}$]decan-10-ones is delineated and its efficacy demonstrated through a concise synthesis of (±)-coronafacic acid.

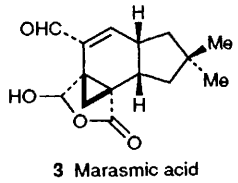
Natural products based entirely on the *cis*-hydrindane skeleton or embodying this system as the core unit in their structure, *e.g.* **1–3** have been frequently encountered in recent years and evoked considerable synthetic interest.[1] That many of these compounds also exhibit biological activity and are endowed with diverse functionalization and stereochemical patterns has further enhanced their synthetic appeal. We have conceived a short, stereocontrolled approach, offering considerable latitude in terms of functionalization, to the *cis*-hydrindane system from readily and abundantly available *endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-diene-3,10-dione **4**.[2] The tricyclic ring system of **4** has been deployed previously in natural product synthesis, but these efforts have focused on the extraction of either the *endo*-five membered ring *via* a retro-Diels–Alder reaction[3a] or the diquinane moiety through



1 Coronafacic acid



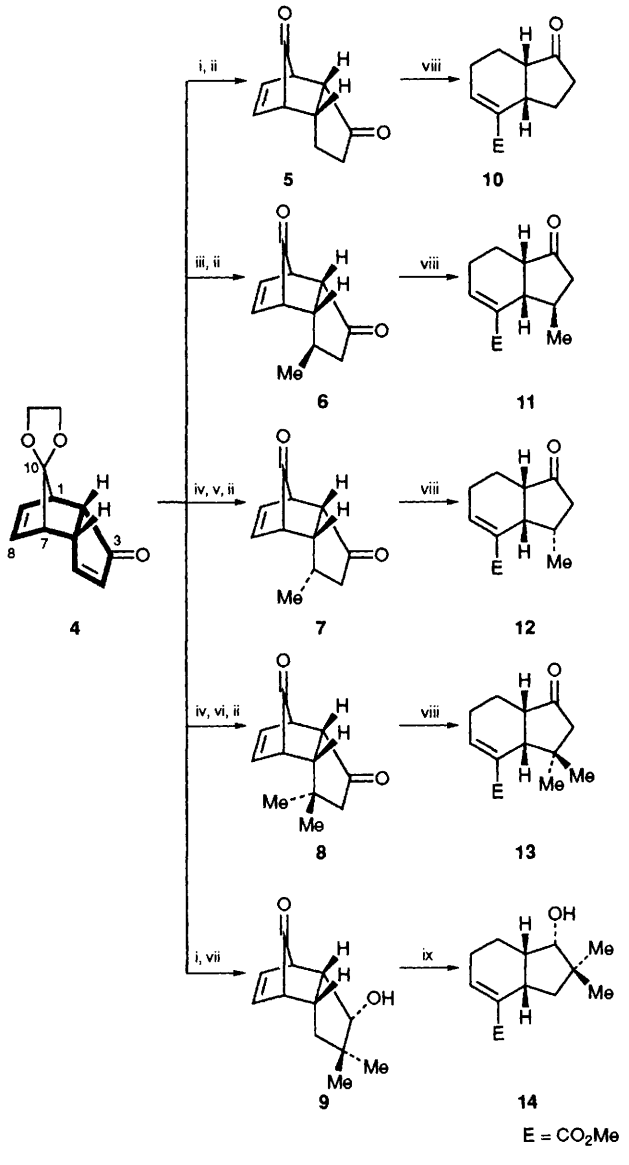
2 Illudol



3 Marasmic acid

the oxidative cleavage of the norbornene double bond from appropriately elaborated precursors.[2c,3] Our interest was to retrieve the hydrindane moiety (heavy lined) from **4** through the removal of the C-10-bridge and towards this end we have employed the hydroxide mediated Haller–Bauer type cleavage of the non-enolizable ketones as the key step.[4]† Herein, we describe a very short entry into several *cis*-hydrindanes, with variation in substitution from a single precursor **4** and as an illustration of their utility report a synthesis of (±)-coronafacic acid **1**, a phytotoxin isolated from the culture broth of *Pseudomonas coronafacience*.[5]

The *endo*-tricyclic enone **4**[2] with a masked C-10-carbonyl group proved to be a highly profitable starting material in which the enone moiety could be readily elaborated to generate the desired features before unmasking the C-10-carbonyl group for a variant of the Haller–Bauer cleavage.



Scheme 1 *Reagents and conditions*: (i) ref. 2(*c*); (ii) 60% aq. H_2SO_4–CH_2Cl_2, room temp., 2–3 h, 90%; (iii) MeLi–CuBr, $(Me)_2S$, diethyl ether, −23 °C, 68%; (iv) MeLi–diethyl ether and pyridinium chlorochromate–CH_2Cl_2 (Celite), 67%; (v) $LiAlH(OMe)_3$–tetrahydrofuran, CuBr, −78 °C, 60%; (vi) $Li(Me)_2Cu$–BF_3–Et_2O, diethyl ether, −15 °C, room temp., 60%; (viii) Amberlyst-15, moist $(Me)_2CO$, room temp., 10 h, 85–90%; (viii) 30% aq. NaOH–benzene, heat, 2–3 h, 60–70%; (ix) as (viii) but 36 h

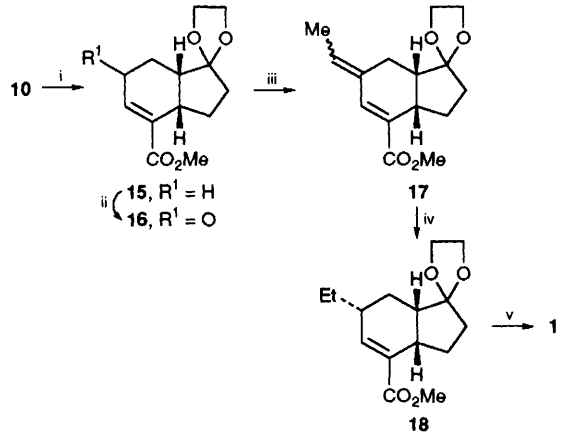
† To our knowledge, Haller–Bauer cleavage on the tricyclo-[5.2.1.$0^{2,6}$]decan-10-one system has not been reported before.

Thus, in short sequences **4** could be elaborated into Haller–Bauer precursors **5–9**‡ as summarized in Scheme 1.

On refluxing **5–9** in a biphasic medium (30% aq. NaOH–benzene) for few hours and subjecting the crude product to diazomethane esterification, bicyclic esters **10–14** could be obtained readily in 60–70% yield. The structures of the bicyclic esters follow from their ^1H and ^{13}C NMR data‡ and the X-ray crystal structure of a derivative of **14**. Some features with regard to the ready formation of *cis*-hydrindanes **10–14** merit further comment. The Haller–Bauer cleavage consistently exhibits good regioselectivity with preferential C(1)–C(10) bond scission, possibly guided by the bystander C(3)-electron withdrawing substituent.§ The isolated double bond in the product migrated under the basic reaction conditions to furnish α,β-unsaturated esters **10–14** in all cases but no epimerization at the ring junction was observed.

While **10–14** are serviceable for the synthesis of various natural products, we exemplify their utility through a new synthesis of (±)-coronafacic acid **1**, a frequently pursued synthetic objective.[6] Protection of the carbonyl group in **10** to **15** and allylic oxidation [Bu^tO_2H–pyridinium dichromate (PDC)][7] furnished the enone ester **16**. Ethylidenation of **16** led to **17**, which underwent regio- and stereo-selective hydrogenation from the convex face to **18** in which the *endo*-ethyl group stereochemistry was fully secured. Exposure of **18** to dil. HCl led to the hydrolysis of both the acetal and the ester groups and coronafacic acid **1**, m.p. 120 °C, identical (IR, ^1H and ^{13}C NMR) with the natural product, was obtained in a short, simple sequence, Scheme 2.

Since recent reports indicate that tricyclodecane systems related to **4** can be obtained in both the enantiomeric forms through biotransformations,[3c,d] our approach can be readily adapted for the synthesis of chiral *cis*-hydrindanes as well.



Scheme 2 *Reagents and conditions*: (i) $(CH_2OH)_2$, toluene-*p*-sulfonic acid, benzene, 95%; (ii) PDC, Bu^tO_2H, C_6H_6, Celite, room temp., 61%; (iii) Ph_3P^+–$CH_2CH_3Br^-$, BuLi, C_6H_6, room temp., 57%; (iv) 10% Pd-C, EtOAc, room temp., 5 min, 86%; (v) HCl (2.5 mol dm^{-3}), heat, 3 h, 70%

‡ All compounds in Scheme 1, except **4** and **5**, are new and were characterized on the basis of their spectral (IR, ^1H and ^{13}C NMR) and analytical data. ^{13}C NMR values for the key compounds are as follows. **10**: δ 220.6, 167.2, 140.6, 131.6, 51.5, 46.5, 36.9, 35.6, 27.2, 23.8 and 19.3. **11**: δ 220.5, 167.7, 140.6, 132.1, 51.6, 45.3, 44.9, 42.2, 35.0, 23.0, 20.7 and 20.0. **12**: δ 220.2, 167.9, 141.4, 130.1, 51.5, 46.4, 45.3, 38.7, 32.3, 24.2, 21.8 and 18.3. **13**: δ 220.4, 169.3, 140.6, 132.1, 53.4, 51.7, 46.8, 44.7, 39.9, 30.2, 25.8, 22.9 and 22.3. **14**: 162.0, 139.8, 133.4, 83.2, 51.4, 46.0, 42.0, 40.9, 33.8, 30.0, 25.2, 25.0 and 18.4. **1**: δ 220.1, 171.4, 146.9, 131.0, 46.7, 38.2, 38.0, 36.2, 28.2, 27.8, 25.9 and 11.3.

§ In the case of the **7** → **12** transformation, a small amount (≈15%) of the other isomer was detected (NMR) but not isolated.

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