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# Synthesis of the *trans–syn–trans* perhydrobenz[*e*]indene moiety of the stellettins and of the stelliferins

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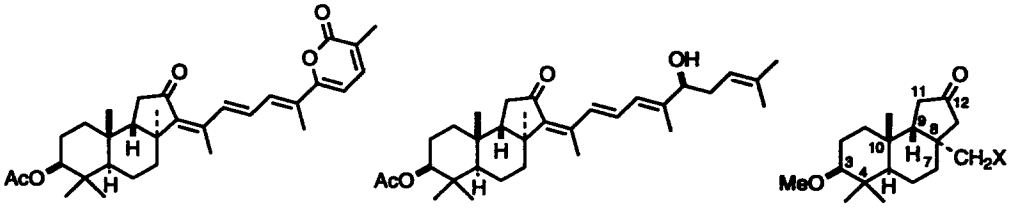
**Abstract**

The perhydrobenz[*e*]indene moiety of the stellettins and of the stelliferins, two families of isomalabaricane-type triterpenes with *trans–syn–trans* ring junctions, has been built from a bicyclic γ,δ-unsaturated aldehyde by a reaction sequence including a Lewis acid catalysed ene cyclisation to form a cyclopentanol, a hydroxyl-directed cyclopropanation, and the ring opening of a cyclopropyl ketone with trimethylsilyl iodide. 

*Keywords:* terpenes; ene reaction; cyclopropanation; trimethylsilyl halide.

Several cytotoxic triterpenes called stellettins and stelliferins have been isolated in recent years from Indian and Pacific sponges of the genera *Stelletta* and *Jaspis*.[1] Embedded in their rather rare isomalabaricane framework is a 4,4,8,10-tetramethylperhydrobenz[*e*] indene system with *trans–syn–trans* ring junctions which force the central ring into an unfavourable twist-boat conformation. In this letter, we describe the obtention of the tricyclic ketone **15** that we plan to use as an intermediate in the synthesis of some of these triterpenes (Scheme 1).




Scheme 1.

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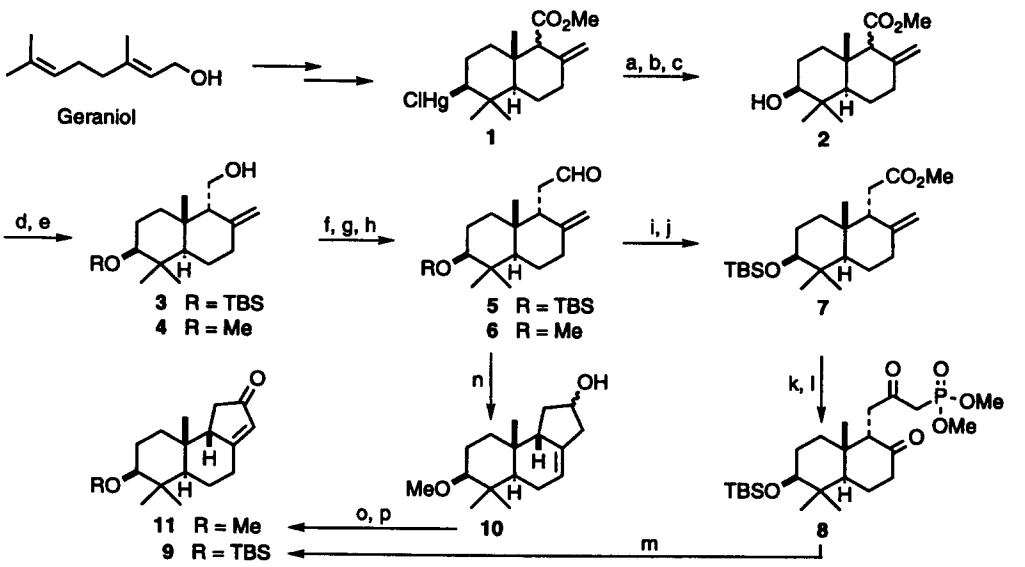
*PII:* S0040-4039(99)01240-X

*trans–syn–trans* Perhydrobenz[*e*]indenes have been obtained by others either by cyclisation of epoxy polyenes[2,3] or by transannular Diels–Alder reactions.[4] Earlier work in our group has resulted in the obtention of a *trans–syn–trans* perhydrophenanthrenic compound by hydroxyl-directed introduction of the 8-methyl on the concave α face of (9βH)-podocarp-8(14)-en-13α-ol.[5] The synthesis of **15** is based on the same strategy. However, changing from a 6/6/6 to a 6/6/5 ring system required several major modifications.

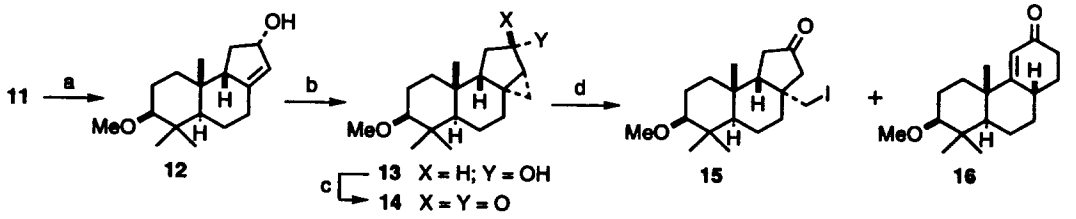
Our first target was the α,β-unsaturated ketone **9** and hence its Horner–Wadsworth–Emmons (HWE) precursor **8** (Scheme 2). The synthesis of **8** was undertaken from ester **1** (7/1 mixture of 9α-**1**/9β-**1**) prepared in five steps from geraniol, according to Weiler.[6] Introduction of the equatorial 3-hydroxyl was achieved by treatment of the chloromercury derivatives **1** with sodium borohydride in the presence of oxygen,[7] oxidation of the resulting diastereomeric (C-3, C-9) hydroxy esters to keto esters, and selective reduction to the hydroxy esters **2**. After protection as *t*-butyldimethylsilyl (TBS) ethers,[8] C-11 homologation was undertaken by a somewhat long reaction sequence imposed by the severe steric hindrance at C-11, the propensity of C-11 leaving groups to undergo elimination, and the sensitivity of the molecule to acidic conditions (TBS and *exo*-methylene groups). It involved reduction of the methoxycarbonyl into an hydroxyl, chromatographic separation of the alcohol **3** from its 9-epimer, mesylation, substitution with sodium cyanide, reduction with diisobutylaluminium hydride to aldehyde **5**, oxidation with sodium chlorite,[9] and esterification. Treatment of the so-obtained ester **7** with lithium dimethyl methylphosphonate followed by ozonolysis of the 8-*exo*-methylene yielded the β,ε-diketo phosphonate **8**. HWE cyclisation was then tested with five bases, keeping in mind that the enone **9** was prone to epimerisation at C-9. Mixtures of **9** and of its epimer were actually obtained with three of them.[10] However, **9** was the only product when tetrabutylammonium hydroxide in 1/1 benzene/water[11] was used (up to 47% yield) and also under the Masamune–Roush conditions (DBU, LiCl, MeCN; 13% yield).[12]

While these attempts were underway, an alternative route was explored which allowed the obtention of enone **11**[13] (mp 61–62°C) in three steps and 43% yield from the γ,δ-unsaturated aldehyde **6**[14] (instead of five steps and 22% yield for the transformation of **5** to **9**). It started with the chlorodimethylaluminium-catalysed cyclisation of **6** to the strained homoallylic alcohol **10** in 66% yield and went on with the oxidation[15] of **10** to the corresponding ketone and the isomerisation of the 7,8-double bond in basic medium.[16] It is worth mentioning that an ene reaction has seldom been used so far for the preparation of 3-methylene cyclopentanols.[17]

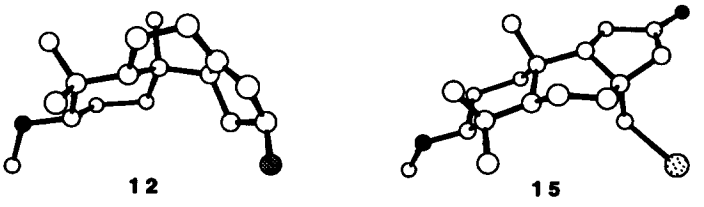
Reduction of **11** under Luche conditions[18] led to the exclusive obtention of the α-oriented allylic alcohol **12** (mp 114–115°C; X-ray structure,[19] Scheme 4) which, when subjected to the Furukawa modification[20] of the Simmons–Smith cyclopropanation, gave **13** (mp 110.5–111.5°C) as the only product (Scheme 3). After oxidation to the cyclopropyl ketone **14** (mp 120–121°C), reaction with lithium in ethylamine[21] furnished an unseparable 1/2 mixture of two compounds the most abundant of which was probably ketone **17** (Scheme 1).[22] This outcome led us to treat **14** with trimethylsilyl iodide.[23] The resulting 6/4 mixture of iodide **15**[13] (mp 121°C; decomposes) and of an enone (mp 79–80°C), to which we assign structure **16**,[24] could be separated by column chromatography and the structure of **15** confirmed by X-ray crystallography (Scheme 4). However, reduction of **15** to **17** was more difficult than anticipated. It is still being investigated and will be reported in due course.




Scheme 2. (a) $NaBH_4$, $O_2$ bubbling, DMF, rt, 2 h (82%); (b) $(COCl)_2$, DMSO, $CH_2Cl_2$, –60°C, 4 h, then $NEt_3$ (80%); (c) $NaBH_4$, EtOH, 0°C, 1 h (100%); (d) for **3**: TBSOTf, $CH_2Cl_2$, 0°C, 15 min, then $NEt_3$, 20 min (100%); for **4**: $KN(SiMe_3)_2$, THF, 0°C, then MeI, 0°C, 10 min (91%); (e) $LiAlH_4$, ether, reflux, 2 h (R=TBS: 77%; R=Me: 88%); (f) MsCl, $NEt_3$, $CH_2Cl_2$, 0°C, 0.5 h; (g) NaCN, DMSO, 110°C, 6.5 h (steps f+g: R=TBS: 75%; R=Me: 62%); (h) $(i\text{-Bu})_2AlH$, toluene, –78°C, 1.5 h, then $H_3O^+$ (R=TBS: 95%; R=Me: 100%); (i) $NaClO_2$, *t*-BuOH, $NaH_2PO_4$ (pH 3.5), $Me_2C{=}CHMe$, rt, 23 h (91%); (j) $CH_2N_2$, ether, 0°C, 20 min (77%); (k) $LiCH_2P(O)(OMe)_2$, THF, –78°C, 1 h (76%); (l) $O_3$, $CH_2Cl_2$, –78°C, 20 min, then $Me_2S$, rt, 2 h (89%); (m) $n\text{-Bu}_4NOH$, 1/1 $C_6H_6/H_2O$, rt, 6.5 h (47%); (n) $Me_2AlCl$, $CH_2Cl_2$, 0°C, 1.5 h (66%); (o) $n\text{-Pr}_4NRuO_4$, *N*-methylmorpholine-*N*-oxide, 13X molecular sieves, $CH_2Cl_2$, rt, 6.5 h (80%); (p) $Na_2CO_3$, MeOH, rt, 25 min (critical reaction time) (81%)




Scheme 3. (a) $NaBH_4$, $CeCl_3$, MeOH, rt, 25 min (critical reaction time) (98%); (b) $ICH_2Cl$, $ZnEt_2$, $(CH_2Cl)_2$, 0°C, 2 h (85%); (c) $n\text{-Pr}_4NRuO_4$, *N*-methylmorpholine-*N*-oxide, 13X molecular sieves, $CH_2Cl_2$, rt, 3 h (86%); (d) $Me_3SiI$, $CCl_4$, rt, 0.5 h (88%; **15/16**=6/4)




Scheme 4. X-Ray crystal structures

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13. Enone **11**. $^1$H NMR (500 MHz, $CDCl_3$) δ 0.84 (s, 3H); 0.88 (dd, *J*=11.9, 5.0 Hz, 1H); 0.95 (s, 3H); 1.20 (s, 3H); 1.32 (br td, *J*=14.0, 3.4 Hz, 1H); 1.40–1.51 (m, 2H); 1.75–1.90 (m, 3H); 2.37 (d, *J*=5.5 Hz, 2H); 2.60 (m and dd, *J*=11.3, 4.1 Hz, 2H); 2.68 (m, 1H); 2.74 (ddd, *J*=15.1, 9.8, 5.1 Hz, 1H); 3.34 (s, 3H); 5.81 (t, *J*=1.9 Hz, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 16.1; 20.0; 22.4; 25.2; 27.1; 28.1; 35.2; 37.8; 39.1; 39.4; 47.7; 54.1; 57.6; 88.3; 128.0; 185.4; 208.4. Ketone **15**. $^1$H NMR (500 MHz, $CDCl_3$) δ 0.81 (s, 3H); 1.02 (s, 3H); 1.04 (s, 3H); 1.31 and 1.32 (br d and td, *J*=12.4 Hz and *J*=13.0, 3.8 Hz, 2H); 1.40–1.50 (m, 2H); 1.55 (ddt, *J*=4.2, 11.6, 13.4 Hz, 1H); 1.60–1.70 (m, 2H); 1.93 (dd, *J*=17.8, 3.4 Hz, 1H); 1.99 (br dq, $J_{app}$=13.7, 3.9 Hz, 1H); 2.07 (ddd, *J*=14.5, 9.9, 9.1 Hz, 1H); 2.18 (2 d, *J*=12.3 Hz and *J*=10.2 Hz, 2H); 2.33 (dd, *J*=10.2, 12.3 Hz, 1H); 2.74 (d and dd, *J*=17.8 Hz and *J*=11.6, 4.9 Hz, 2H); 3.24 (dd, *J*=10.2, 1.5 Hz, 1H); 3.38 (s, 3H); 3.72 (dd, *J*=10.2, 3.3 Hz, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 16.6; 17.4; 21.8; 22.6; 23.7; 29.1; 33.6; 34.8; 35.5; 35.9; 39.1; 43.6; 48.6; 51.9; 57.8; 59.6; 88.4; 215.6.
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22. Major compound: $^1$H NMR (200 MHz, $CDCl_3$) δ 0.80 (s, 3H); 1.00 (s, 3H); 1.01 (s, 3H); 1.14 (s, 3H); 2.73 (dd, *J*=5.0, 10.9 Hz, 1H); 3.37 (s, 3H).
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