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A novel stereoselective total synthesis of (±)-hirsutene from saligenin

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Abstract—A total synthesis of hirsutene, a tricyclic sesquiterpene, from saligenin, is described.

The efficient generation of complex molecular architecture from simple precursors is one of the most important aspects of development of new methodologies and synthesis design.[1,2] Occasionally reactions in tandem,[2b,c,3] or a cascade of reactions,[2d,e] or multicomponent reactions[4] are developed to achieve this objective. In view of the recent interest in the chemistry of polyquinanes which is continuing unabated,[5,6] we have developed a method for rapid generation of molecular complexity from simple precursors.[7] Among various polyquinanes, hirsutene **1** (Fig. 1), a triquinane metabolite of *Coriolus consors*,[8] has been a popular target[5a,9] for developing and testing new methodologies for cyclopentanoid synthesis. Though several ingenious syntheses of hirsutene have been reported,[5a,9] a majority of these generate the triquinane framework iteratively in a multistep sequence often in a non-stereoselective fashion. In continuation of our interest in this area,[7] we wish to report herein a total synthesis of hirsutene **1** from saligenin **2**. The key features of our methodology are efficient generation of molecular complexity by in-situ generation and cycloaddition of a highly labile spiroepoxycyclohexa-2,4-dienone **3**, an unusual alkylation at the ring junction in the tricyclo-[5.2.2.0^{2,6}]undecane frame and a photochemical 1,2-acyl shift, as delineated below.

The cornerstone of our plan is the correlation of structural and stereochemical features of hirsutene **1** with the tricyclic system **5** through the intermediates **6** and **7**.

We considered that the triquinane **7** could be elaborated to hirsutene via transformation of the spirocyclopropane ring into the geminal methyl groups followed by oxidation and Wittig reaction. It was further contemplated that tetracyclic intermediate **6** could be obtained by a triplet sensitized 1,2-acyl shift[10,11] (or oxa di-π-methane rearrangement) in **5** (Scheme 1). The key tricyclic precursor **5** could be derived from the readily available ketoepoxide **4** via manipulation of the oxirane ring, allylic oxidation of the five-membered ring and alkylation at the appropriate ring junction.

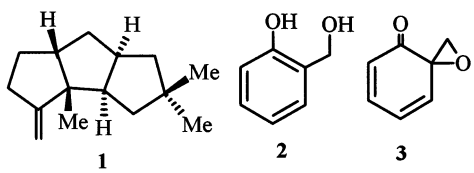
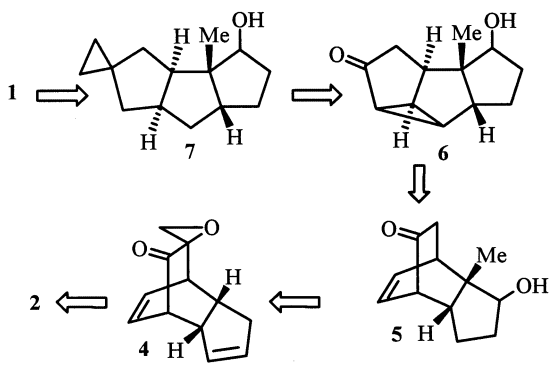


Figure 1.



Scheme 1.

Keywords: saligenin; cyclohexa-2,4-dienone; alkylation; oxa-di-π-methane rearrangement.

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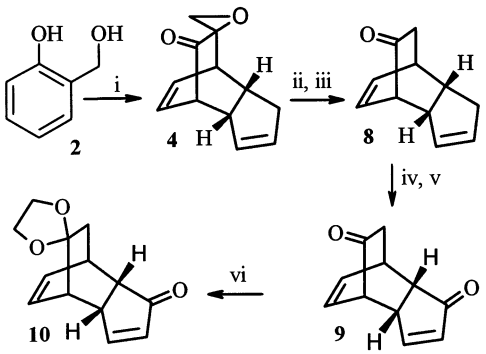
There are several noteworthy features of the present methodology and strategy. For example, the *cis*:*anti*:*cis* triquinane framework of hirsutene disposed with appropriate functionalities and angular methyl group, is generated in a single stereoselective photochemical reaction. Moreover, the angular methyl group and the three rings of hirsutene including the two five-membered rings in latent fashion are present in the tricyclic system **5** which is readily derived from the ketoepoxide **4**. Further, the epoxide **4** having a β,γ-enone chromophore is assembled from saligenin **2** and cyclopentadiene in a single step thus *generating molecular complexity at the beginning of the synthetic route itself*, one of the most desirable features in synthesis design.[1] However, the success of our approach appeared to be highly dependent on the introduction of the methyl group at the ring junction during transformation of **4** to **5**, especially since such types of alkylations are generally not observed.

Thus, the oxidation of saligenin **2** with sodium *meta*periodate in aqueous acetonitrile containing cyclopentadiene, gave the tricyclic ketoepoxide **4**.[11] Reduction of the oxirane ring in **4** with Zn–NH_4Cl in aqueous methanol and oxidation of the resulting β-hydroxyketone followed by decarboxylation gave the precursor **8** (Scheme 2). Allylic oxidation of dienone **8** with SeO_2 followed by further oxidation of the resulting alcohols with PDC gave a mixture of enones from which the major enone **9** was isolated. Selective ketalization in **9** gave the keto–ketal **10** in excellent yield, whose structure was clearly revealed from its spectroscopic data.[12]

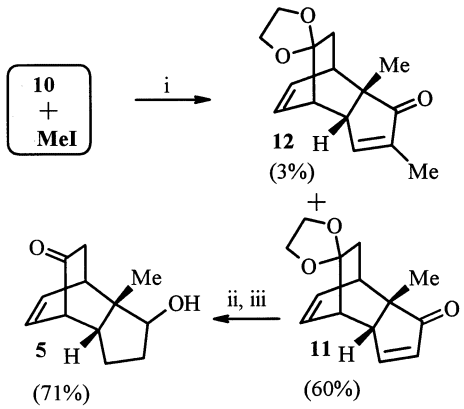
At this juncture, introduction of the methyl group at the ring junction α′ to carbonyl group in **10** was required. In general, alkylation of α,β-enones having a γ-methine or methylene results in α-alkylation via the extended thermodynamic dienolate.[13] We thought it possible to generate the kinetic enolate by abstraction of the proton at the α′ carbon and alkylate with methyl iodide. However, treatment of the keto–ketal with excess LDA at −78°C followed by addition of methyl iodide did not give the desired alkylated product. After considerable experimentation, *we discovered that simultaneous addition of enone* ***10*** *and methyl iodide to a solution of LDA at −78°C gave the desired alkylated product* ***11*** *as the major product (60%)*, in addition to a small amount of dialkylated product **12** (3%). The structure of the compound **11** was deduced from its spectroscopic data. Thus, the ^1H NMR spectrum of **11** exhibited characteristic signals at δ 7.36 (dd, $J=5.7$, 2.7 Hz, 1H) and 6.11 (dd, $J=5.7$, 1.5 Hz, 1H) for the β and α protons of the α,β-enone, respectively. The olefinic protons of its bicyclo[2.2.2] moiety showed their signals at δ 6.21 (superimposed dd, $J=7$ Hz, 1H) and δ 5.8 (superimposed dd, $J=7$ Hz, 1H). It showed signals at δ 3.06 (m, 1H), 2.75–2.71 (m, 1H), 2.70–2.67 (m, 1H) for the three methine protons and a multiplet at δ 3.98–3.89 for the protons of the ketal group. Furthermore, a signal for the methyl group was observed at δ 1.20. Interestingly, the methylene group present in the bicyclo[2.2.2]octane frame appeared as an AB system at δ 2.11(d of part of an AB system, $J_{AB}=14$, 2.4 Hz, 1H) and at 1.62 (d of part of an AB system, $J_{AB}=14$, 3.1 Hz, 1H). These spectral features, especially the multiplicities of the enone protons and the chemical shift of methyl group, clearly suggested the structure **11** for the alkylated product. The ^{13}C NMR (75 MHz) spectrum also corroborated with the structure **11** as it exhibited signals at δ 213.2, 163.2, 135.0, 134.5, 127.9, 113.6, 64.3, 64.09, 50.1, 48.6, 43.2, 38.8, 35.5, 18.9.

Reduction of the dienone **11** with sodium borohydride followed by deprotection of the ketal group readily gave the desired precursor **5** (Scheme 3) as a single diastereomer [^1H NMR (300 MHz) and ^{13}C NMR (75 MHz)]. However, no attempts were made to ascertain the orientation of the hydroxyl group since it would later be converted to a carbonyl group (vide infra). It may be mentioned that the tricyclic compounds of type **5** and **9–12** are not readily accessible otherwise.

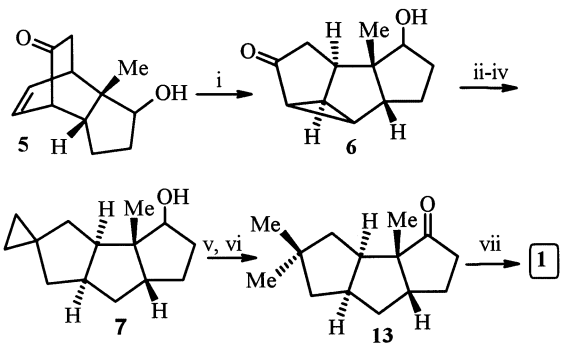
Towards a synthesis of hirsutene, a solution of **5** in acetone (both as solvent and triplet sensitizer) was irradiated for 1 h to give the tetracyclic intermediate **6** in good yield (70%) (Scheme 4) as a result of a stereoselective 1,2-acyl shift.[10,11] Reductive cleavage of the



Scheme 2. *Reagents and conditions*: (i) $NaIO_4$, cyclopentadiene, CH_3CN–H_2O, 0–5°C, 88%; (ii) Zn, NH_4Cl, MeOH–H_2O, 90%; (iii) (a) Jones' reagent, acetone, 0–5°C, (b) THF–H_2O, Δ, 50%; (iv) SeO_2, KH_2PO_4, dioxane–H_2O, 110°C, 52%; (v) PDC, CH_2Cl_2, 70%; (vi) ethylene glycol, *p*-TsOH, benzene, Δ, 96%.



Scheme 3. *Reagents and conditions*: (i) LDA, THF, −78°C; (ii) $NaBH_4$, MeOH; (iii) HCl, acetone–H_2O.



Scheme 4. *Reagents and conditions*: (i) *hv*, acetone, 1 h, 70%; (ii) Bu_3SnH, AIBN, benzene, Δ, 65%; (iii) $Ph_3P{=}CH_2$, toluene, 0°C, 80%; (iv) CH_2I_2, Et_2Zn, benzene, 46%; (v) H_2, PtO_2, AcOH, 74%; (vi) PCC, CH_2Cl_2, 71%; (vii) $Ph_3P{=}CH_2$, toluene, Δ, 44%.

peripheral cyclopropane bond in **6** with tributyltin hydride–AIBN[14] followed by a Wittig reaction and cyclopropanation with methylene diiodide[15] and diethyl zinc gave the cyclopropyl alcohol **7**. Hydrogenation of **7** with PtO_2–H_2 followed by oxidation gave the known ketone **13** whose spectroscopic features[16] are in good agreement with those reported in the literature.[17] Finally, Wittig olefination of **13** furnished hirsutene whose ^{1}H NMR spectrum (300 MHz) exhibited characteristic signals at δ 4.81 (br s, 1H) and 4.77 (br s, 1H) due to the exocyclic olefinic protons. It also displayed resonances at δ 1.04 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H) for the three methyl groups, in addition to other signals at δ 2.65–2.42 (m, 4H), 2.16–2.10 (m, 1H), 1.79–1.59 (m, 2H), 1.49–1.38 (m, 4H) 1.20 (m, 1H) and 1.0 (m, 1H). The ^{13}C NMR spectrum (75 MHz) also gave characteristic signals at δ 162.9, 103.52 for the olefinic carbons in addition to signals at δ 55.96, 53.41, 49.91, 48.90, 44.27, 41.85, 40.88, 38.61, 30.89, 29.71, 27.22, 26.80 and 23.19. These spectroscopic features are in good agreement with those reported in literature.[18]

In summary, a novel synthesis of hirsutene has been described. It involves transformation of saligenin and cyclopentadiene into the tricyclo[5.2.2.0^{2,6}]undecane system endowed with a β,γ-enone chromophore such as **10**. Introduction of the methyl group at the ring junction and reduction of the enone gave the key precursor **5** containing 12 of the carbons of hirsutene. A photochemical reaction of **5** furnished the tetracyclic compound **6** which was elaborated to hirsutene.

Acknowledgements

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12. Data for compound **10**: mp 127–129°C; IR ν_{max}: 1696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (dd, $J=6$, 3 Hz, 1H, β proton of α,β-enone), 6.16 (dd, $J=6$, 2 Hz, 1H), 6.12 (superimposed dd with structure, $J=7$ Hz, 1H), 5.89 (superimposed dd with structure, $J=7$ Hz, 1H), 3.98–3.92 (m, 4H, -OCH_2CH_2O-), 3.48–3.43 (m, 1H), 3.16–3.09 (m, 1H), 2.76 (m of d, $J=6$ Hz, 1H), 2.49 (dd, $J=6$, 3 Hz, 1H), 1.82 (d of part of an AB system, $J_{AB}=13.5$, 3 Hz, 1H), 1.78 (d of part of an AB system, $J_{AB}=13.5$, 3.7 Hz, 1H); ^{13}C NMR (75 MHz, CCl_4+$CDCl_3$): δ 209.7, 164.6, 136.8, 131.8, 128.3, 112.9, 64.2, 64.1, 48.1, 42.4, 41.9, 39.6, 34.2; MS (m/z): 218 (M^+).
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16. Data for compound **13**: IR (neat) ν_{max}: 1738 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.8 (dd with structure, $J=19$, 8.8 Hz, 1H), 2.5 (complex m, 1H), 2.44–2.2 (m, 3H), 2.06–1.93 (m, 1H), 1.76–1.62 (m, 3H partly merged

with signal due to H_2O present in $CDCl_3$), 1.48–1.37 (m, 2H), 1.18 (superimposed dd, $J=12$ Hz, 1H), 1.04 (s, 3H, CH_3), 1.01–0.96 (m, 1H), (0.94 s, 3H CH_3), 0.90 (s, 3H CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 229.68, 59.44, 48.97, 46.82, 43.41, 41.94, 41.22, 37.68, 34.33, 29.80, 29.32, 26.63, 22.48, 17.39; MS (m/z): 206 (M^+).

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