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An Oxy-Cope Rearrangement Route for the Enantioselective Construction of 5,11-Fused Framework of Dolabellane Diterpenes

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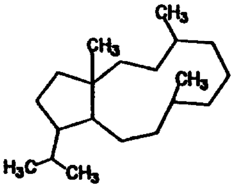
Abstract: A sequence for generating the dolabellane diterpene framework from (R)-limonene is delineated.

Among the plethora of C_{20}-diterpene frameworks present in Nature, the 5,11-fused dolabellane skeleton 1 is a relatively new addition.[1a] Natural products based on this ring system have rapidly proliferated and many densely functionalized compounds e.g., 2[1b] & 3[1c], with impressive biological activity, have been isolated. The ring system of dolabellanes also occupies pivotal position in the biogenesis of several novel diterpene skeleta like dolastanes, fusiccocanes and crinipellins. However, a total synthesis of any dolabellane natural product has not been accomplished so far. A recent Letter[2] on the synthetic studies towards dolabellanes prompts us to record our own endeavors towards the construction of ring system 1 from (R)-limonene employing an oxy-Cope rearrangement as the key step.



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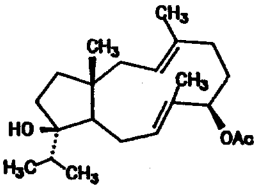

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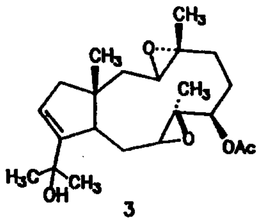

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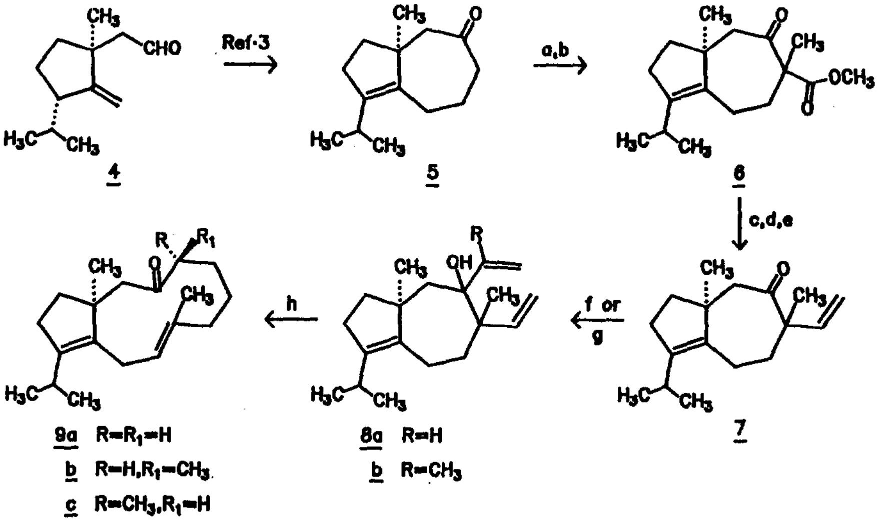
We have previously described[3] a synthesis of the bicyclic enone 5 from (R)-limonene derived precursor 4. Elaboration of 5 to the 5,11-fused dolabellane skeleton required recourse to a 4-carbon annulative ring expansion protocol employing the carbonyl group as the handle. Successive, regioselective α-substitution in 5 led to 6 as a diastereomeric mixture (2:3) whose separation was not required.[4] The ester group in 6 was elaborated to a vinyl group through a routine 3-step sequence to furnish 7, Scheme.[4] Addition of vinylmagnesium bromide to 7 led to the oxy-Cope precursor 8a. Thermal activation of 8a resulted in a smooth [3s.3s]-shift to furnish the nordolabellane enone 9a (70% from 7).[5] Similarly, addition of isopropenyl magnesium bromide to 7 gave 8b, which underwent thermal oxy-Cope rearrangement to furnish dolabellane enones (-)-9b,c (2:3, 70%).[6] The enones 9b and 9c could be readily separated and characterized and also equilibrated (NaOMe-MeOH) to a single enone 9b or 9c in quantitative yield.[6] Thus,



Scheme: (a) NaH, $(CH_3O)_2C{=}O$, Δ, 78%; (b) K_2CO_3-Acetone, CH_3I, Δ, 85%; (c) LAH, Et_2O, RT, 65%; (d) PCC, DCM, 4Å mol.sieves, RT, 30%; (e) $Ph_3P^+CH_3Br^-$, Na-t-amyloxide, RT, 90%; (f) $CH_2{=}CHMgBr$, THF; (g) $CH_2{=}CCH_3MgBr$, THF; (h) 200°C (sealed tube), 1h, 70% from 7.

5,11-fused bicyclic dolabellane enones (−)-9b,c, in enantiomerically pure form and suitably functionalized for further elaboration could be readily realized.

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(4). All new compounds were characterized on the basis of IR, ^1H and ^{13}C NMR and analytical data but diastereomers were not separated until the last step i.e., 9b and 9c.

(5). The trans-stereochemistry to the trisubstitited double bond is assigned on the basis of comparison of characteristic ^1H and ^{13}C NMR signals in 9a,b,c with natural dolabellanes.

(6). It was not possible to unambiguously distinguish between 9b and 9c on the basis of available spectral evidence; however, they were individually fully characterized: 9b/c ^{13}C NMR: δ 213.6, 143.6, 138.5, 136.1, 127.3, 50.3, 48.7, 47.5, 39.2, 37.8, 34.6, 27.3, 27.1(2C), 26.4, 23.6, 21.0, 20.8, 18.2, 17.7. 9b/c ^{13}C NMR: δ 212.7, 144.5, 135.7, 134.0, 128.8, 52.2, 48.4, 46.3, 41.0, 34.5, 34.1, 31.0, 28.3, 27.2, 21.3, 21.0, 19.5, 15.1.

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