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Annulation strategy for the biomimetic synthesis of cis-fused diterpenoids

Shanta S. Bhar and M. M. V. Ramana*

Department of Chemistry, University of Mumbai, Santacruz(E), Mumbai 400 098, India

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Abstract—Concise and efficient formal syntheses of the A/B cis-fused ring C-aromatic tricyclic diterpenes, xanthoperol, and *cis*-A/B-coleon V are reported, via the application of domino reactions followed by a novel annulation method, in which the highly substituted target molecules are assembled from an acyclic precursor, namely the easily accessible monoterpene, citral.
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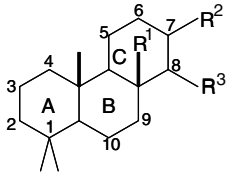
1. Introduction

The 1,1,4a-trimethyl- and 1,1,4a,8-tetramethylperhydrophenanthrene ring systems **1** and **2** (Fig. 1) form all, or part of, the basic carbocyclic framework of several classes of terpenes.[1] In addition, the B and C rings in many of the natural products incorporate carbonyl, hydroxyl, epoxide, and/or olefin moieties at various positions and ring C is often aromatic in nature.

Strategies for the total synthesis of these terpenes most commonly employ consecutive Robinson annulation reactions, or linear substitution strategies based on sequential electrophilic substitution and metalation–alkylation reactions. A more effective approach to highly substituted aromatic compounds, however, involves the application of annulation methods: convergent strategies in which the aromatic system is assembled from acyclic precursors in a single step, with all (or most) substituents already in place. Significantly, annulation routes avoid the regiochemical ambiguities associated with aromatic substitution reactions, and their intrinsic convergent character facilitates the efficient assembly of highly substituted aromatics that would require long, multistep routes using classical substitution methodology.



1, R^1=H, R^2, R^3=H or alkyl
2, R=CH_3, R^2, R^3=H or alkyl

Figure 1. Basic carbocyclic framework of various classes of terpenes.

We have previously shown that the application of a novel type of domino reaction provides the basis for a very efficient route for the one-pot construction of highly substituted aromatic diterpene systems.[2] The strategy, provided extremely direct synthetic routes to tricyclic ring C-aromatic diterpenes with A/B trans-fused ring junctions. In order to further define the scope of this methodology, we have examined its application to the construction of substituted 1,1,4a-trimethyl-1,2,3,4,4a,9a-hexahydrofluorenones.

In the larger context, substituted hexahydrofluorenones have attracted attention as intermediates for the synthesis of β-norditerpenoids, β-norsteroids,[3] C-nor-D homosteroids,[4] and the gibberellins.[5] These compounds, after expansion of the B-ring, have the potential to be used for the synthesis of compounds with cis A/B ring junctions such as the opium alkaloids and some bile acids. However, the lack of methods to prepare these compounds has restricted their use in organic synthesis.

As in all hexahydrofluoren-9-ones, the more stable of the two possible hydrindanone ring junctions has been

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* Corresponding author. Tel.: +91 22 26526091; fax: +91 22 26528547; e-mail: b_shanta@yahoo.com

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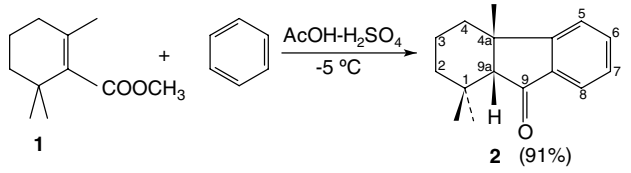
shown by thermodynamic and kinetic considerations, by House and co-workers,[6] to be the isomer with cis A/B-ring fusion, and this was later confirmed by Kai[7] (synthesis of β-norditerpenoids) and Merchant[8] (synthesis of β-norsteroids).

Encouraged by our previous work[2] employing novel domino reactions for the synthesis of abietane-type diterpenes, we envisioned the formation of the cis A/B ring fused hexahydrofluoren-9-one system via domino alkylation–cycloacylation of methyl β-cyclogeranate **1**, easily obtained[9] from the readily accessible monoterpene, citral, with aromatic substrates. To test this hypothesis, we first subjected methyl β-cyclogeranate to an AcOH–H_2SO_4 (1:9) (−5 °C) promoted domino alkylation–cycloacylation with benzene (Scheme 1). The resulting product **2** was shown to have a 6-5-6 fused ring skeleton by analyzing the COSY and HMBC spectra. Further spectral analysis indicated it to be 1,2,3,4,4a,9a-hexahydro-1,1,4a-trimethyl-9-fluorenone, and its relative stereochemistry was assigned as cis by nuclear Overhauser enhancement exchange spectroscopy (NOESY), where a 16% enhancement of H9a (at δ 1.90) was caused by irradiation of Me-4a (at δ 1.25).

To apply this mild method to the synthesis of other substituted hexahydroflorenones, methyl β-cyclogeranate **1** was reacted (AcOH–H_2SO_4 (1:9) (−5 °C)) with 1-isopropyl-2-methoxybenzene[10] **3** (Scheme 2). The product **4** was also shown to possess a 6-5-6 skeleton

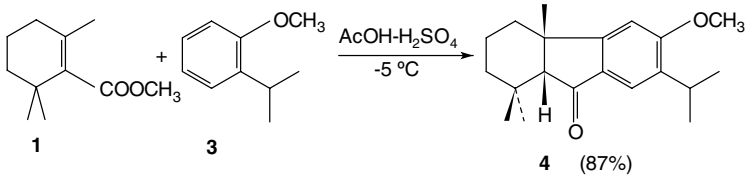


Scheme 1. Fluorenone **2** via domino alkylation–cycloacylation.

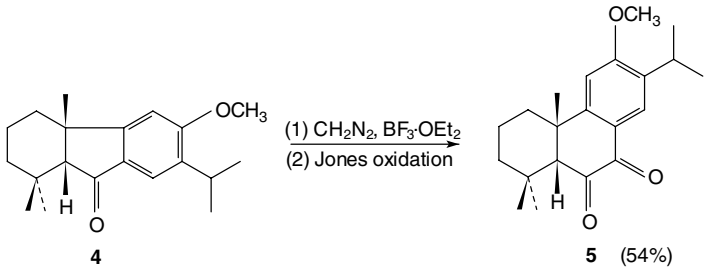
(by COSY and HMBC experiments) and its stereochemistry was deduced as cis by the 12% enhancement of H9a (at δ 2.05) through irradiation of Me-4a (at δ 1.35) in the NOESY spectral data. Analysis of its IR, NMR (due to lack of coupling, the two aromatic protons are assumed to be para to each other) and elemental analysis indicated compound **4** to be 6-methoxy-7-isopropyl-1,2,3,4,4a,9a-hexahydro-1,1,4a-trimethyl-9-fluorenone.

The ring expansion of the hexahydrofluorenone **4** with diazomethane and subsequent Tiffeneau–Demjanov annulation, followed by Jones oxidation of the reaction mixture gave compound **5** in good yield (Scheme 3). The identification of synthetic **5** as (±)-xanthoperyl methyl ether was established by mixed melting point experiments and from IR and ^{1}H NMR comparisons with an authentic sample. Since **5** has previously been converted into the A/B cis-fused diterpene, (±)-xanthoperol,[11] this method can be regarded as a formal total synthesis, utilizing citral as the starting material.

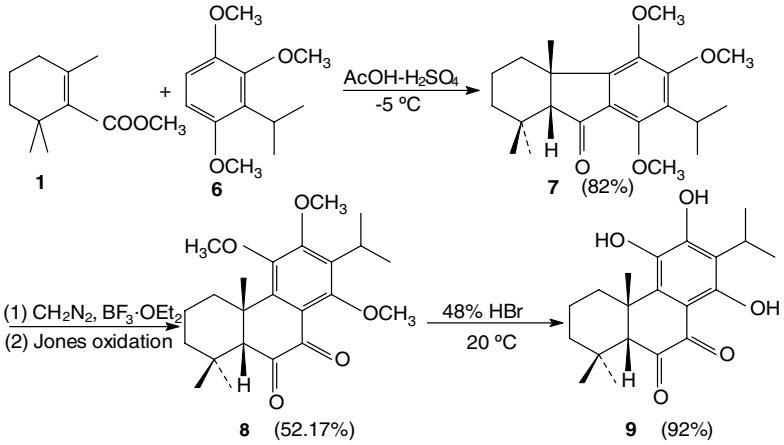
As a further example, methyl β-cyclogeranate **1** was reacted with highly substituted 1,2,4-trimethoxy-3-isopropylbenzene[12] **6**, the resulting product **7** also having a 6-5-6 ring-skeleton (by COSY and HMBC experiments), cis-fused (12% enhancement of H9a (at δ 2.05) caused by irradiation of Me-4a (at δ 1.35)). Analysis of its IR, NMR (2D NMR peak of isopropyl –CH is at 2.75, and its coupling is observed with H at 3.8 and 3.9) and elemental analysis data indicated **7** to be 5,6,8-trimethoxy-7-isopropyl-1,2,3,4,4a,9a-hexahydro-1,1,4a-trimethyl-9-fluorenone. When this hexahydrofluorenone was ring expanded with diazomethane and subsequent Tiffeneau–Demjanov annulation, followed by Jones oxidation and demethylation with 48% HBr, compound **9** was obtained in moderate yield (Scheme 4). The identification of synthetic **9** as *cis*-A/B-coleon V[13] was established by IR, NMR, and mass spectroscopy and through elemental analysis.



Scheme 2. Fluorenone **4** via domino alkylation–cycloacylation.



Scheme 3. Synthesis of xanthoperyl methyl ether **5**.



Scheme 4. Total synthesis of *cis*-A/B-coleon V **9**.

2. Conclusion

In conclusion, the transformation of the acyclic monoterpene, citral, into highly substituted A/B cis-fused ring-C aromatic tricyclic diterpenes was effected via ring homologation of cyclic ketones by the Tiffeneau–Demjanov ring expansion. This new method should allow the rapid production of a large array of diterpenoids with cis stereochemistry due to the wide substrate scope with respect to the aromatic co-reactant used.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.082.

References and notes

1. (a) Hanson, J. R. *Nat. Prod. Rep.* **1988**, *5*, 211–227; (b) Hanson, J. R. *Nat. Prod. Rep.* **1986**, *3*, 123–132; (c) Connolly, D.; Hill, R. A. *Nat. Prod. Rep.* **1985**, *2*, 1–17; (d) Apsimon, J. W.; Fyfe, K. E.; Greaves, A. M. In *The Total Synthesis of Natural Products*; Apsimon, J. W., Ed.; Wiley-Interscience: New York, 1984; Vol. 6, p 85; (e) Nakanishi, K.; Goto, T.; Ito, S.; Natori, S.; Noze, S. In *Natural Products Chemistry*; Academic Press: New York, 1974; Vol. 1; (f) Hanson, J. R. In *Terpenoids and Steroids—Specialist Periodical Report of the Royal Society of Chemistry*; The Royal Society of Chemistry: London, 1971; Vol. 1–12.
2. Bhar, S. S.; Ramana, M. M. V. *J. Org. Chem.* **2004**, *69*, 8935–8937.
3. France, D. J.; Hand, J. J.; Los, M. *J. Org. Chem.* **1970**, *35*, 468–473.
4. Green, M. J.; Abraham, N. A.; Fleischer, E. B.; Case, J.; Fried, J. *J. Chem. Soc., Chem. Commun.* **1970**, 234–235.
5. Grove, J. F. *Q. Rev. Chem. Soc.* **1961**, *15*, 56–70.
6. House, H. O.; Carlson, R. G. *J. Org. Chem.* **1964**, *29*, 74–78.
7. Kai, S. N.; Roberts, J. L.; Rutledge, D. S.; Wilson, M. A.; Woodgate, P. D. *Aust. J. Chem.* **1976**, *29*, 2683–2692.
8. Merchant, J. R.; Waghulde, V. *Ind. J. Chem.* **1987**, *26B*, 1084–1085.
9. Heather, J. B.; Mittal, R. S. D.; Sih, C. J. *J. Am. Chem. Soc.* **1976**, *98*, 3661–3668.
10. Chang, H. M.; Cheng, K. P.; Choang, T. F.; Chow, H. F.; Chui, K. Y.; Hon, P. M.; Tan, F. W. L.; Yang, Y.; Zhong, Z. P. *J. Org. Chem.* **1990**, *55*, 3537–3543.
11. Nasipuri, D.; Guha, M. *J. Chem. Soc.* **1962**, 4248–4252.
12. Carreno, M. C.; Garcia Ruano, J. L.; Toledo, M. A.; Urbano, A. *Tetrahedron: Asymmetry* **1997**, *8*, 913–921.
13. Miyase, T.; Ruedi, P.; Eugster, H. C. *Helv. Chim. Acta* **1977**, *60*, 2770–2779.