Pergamon

Tetrahedron Letters 42 (2001) 2389–2391

TETRAHEDRON
LETTERS

# Enantiospecific synthesis of 8-epipuupehedione from (*R*)-(−)-carvone

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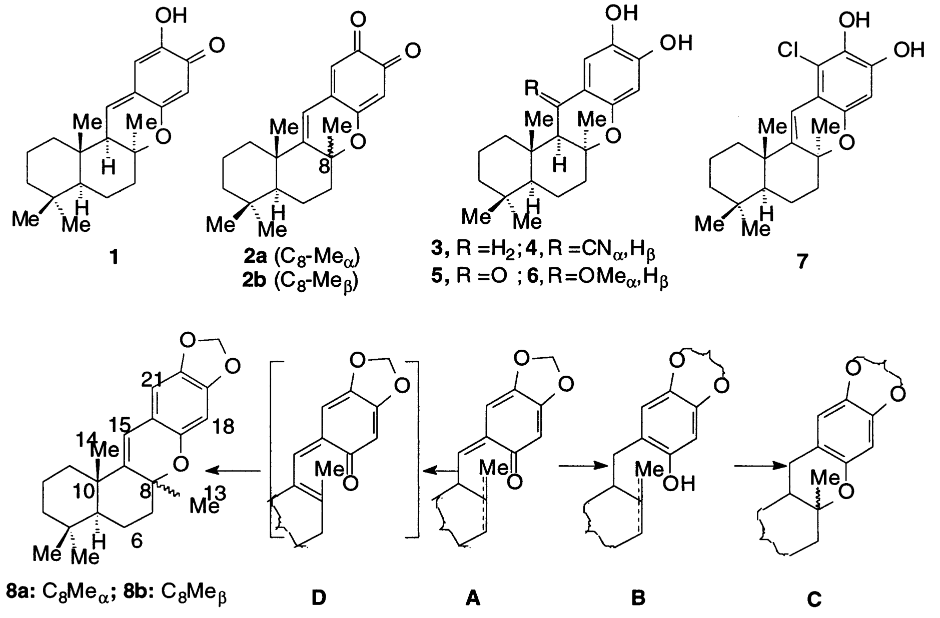
Received 17 November 2000; revised 10 January 2001; accepted 25 January 2001

**Abstract**—An enantiospecific synthesis of the antitumor marine sponge metabolite puupehedione (**2a**) and its $C_8$-epimer **2b** as their methylenedioxy derivatives **8a** and **8b** was achieved through concomitant *O*-allyl deprotection and electrocyclization of **20** derived from (−)-carvone. © 2001 Published by Elsevier Science Ltd.

Puupehenone (**1**), puupehedione (**2a**), puupehediol (**3**), 15-cyanopuupehenol (**4**), 15-oxopuupehediol (**5**), 15-α-methoxypuupehenol (**6**), 21-chloropuupehediol (**7**) and their derivatives belong to a group of recently characterized marine sponge metabolites of mixed biogenetic origin featuring a sesquiterpene unit joined to a $C_6$-shikimate moiety.[1] These compounds have been reported to display a wide range of important biological properties including cytotoxic, antiviral, antifungal, antitumor and antimalarial activities.[2] Moreover, a few of them have been shown[3] to inhibit topoisomerase II activity, cholesteryl ester transfer protein (CETP) properties as well as replication of the HIV virus, further heightening the interest in this class of compounds. The unique structural features and biological activities of these compounds has prompted chemists to study their synthesis.

The first synthesis of (±)-puupehenone (**1**) starting from farnesyl bromide and sesamol was reported in 1978 by Trammel.[4] Recently, total syntheses of both the enantiomers of 15-oxopuupehenol (as their methylenedioxy



**Scheme 1.**

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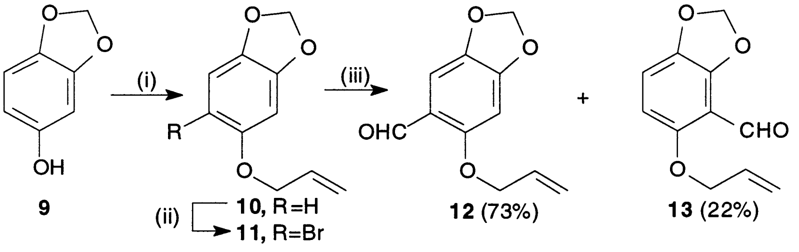
0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)00153-8

derivatives) starting from (+)- and (−)-driminal, prepared from farnesol, have been described.[5] More recently, Barrero et al. have published enantiospecific synthetic routes to puupehenone (**1**), puupehedione (**2a**) and 8-epipuupehedione (**2b**) from (−)-sclareol.[6] Significantly, **2b** was found to be the most antitumor-active compound against the cell lines P388, A-549, HT-29 and MEL-28.[6] The key element of most of the reported syntheses is the electrophilic cyclization of phenolic intermediates **B** to the respective tetrahydropyrans **C** with varying degrees of stereoselectivity (Scheme 1). The intermediate **B** is generated from the corresponding *o*-quinomethane **A**, prepared in several steps via the condensation of a bicyclic aldehyde with an appropriately functionalized *O*-TBS protected aryllithium. However, the recently disclosed[6b] acid-induced electrocyclization of **A** to a 1:4 mixture of the isomeric dihydropyrans **8a** ($C_8$-$Me_\alpha$) and **8b** ($C_8$-$Me_\beta$), via the conjugated dienone **D**, is the most attractive synthetic route to **2b**.

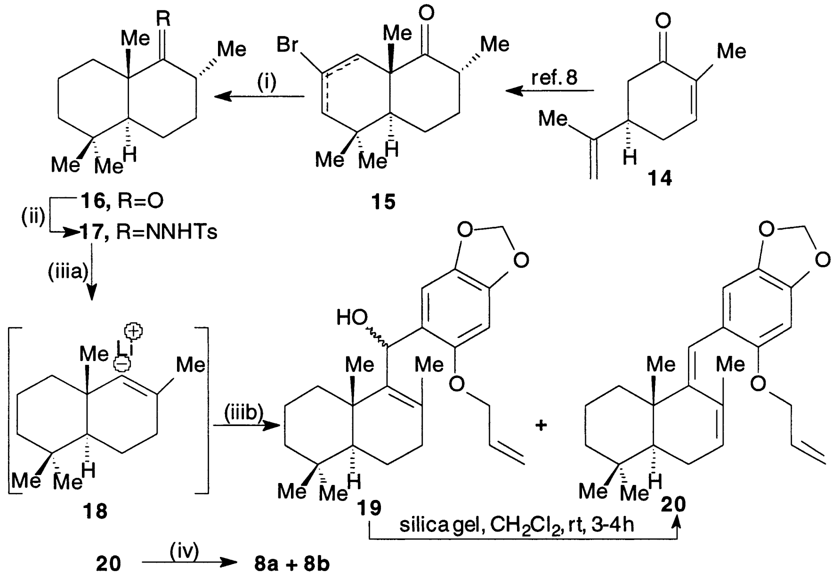
We describe herein a simple synthetic entry to 8-epipuupehedione (**2b**) along with puupehedione (**2a**) involving the key *O*-allyl protected intermediate **20**, which was readily derived by coupling the aldehyde **12** with the vinyl anion **18**, and its conversion to the desired methylenedioxypyrans **8a** and **b** in a one-pot process using $RhCl_3 \cdot 3H_2O$ in ethanol (Schemes 2 and 3).

The aromatic synthon **12** was obtained in high yield from sesamol (**9**) via allylation to **10**, electrophilic bromination to give the *O*-allylbromoether **11**, and formylation of the in situ generated lithio anion with DMF (Scheme 2). A minor amount of the chromatographically separable regioisomeric aldehyde **13** was also obtained in the reaction.[7]

The (−)-*trans*-decalone **16** was prepared from natural (*R*)-(−)-carvone (**14**) by modification of a reported procedure[8] through catalytic hydrogenation of the vinyl bromo ketone **15** in the presence of Pd–C (10%) containing $PdCl_2$ (5 mol%) in EtOH (Scheme 3). Addition[9] of the vinyl lithium species **18**, generated by exposure of the tosylhydrazone **17** to an excess of *n*-BuLi in THF, to **12** afforded a mixture of the unstable allyl alcohol **19** and the diene **20**. Treatment of the crude condensation product with silica gel in $CH_2Cl_2$ for 3–4 h at room temperature produced the diene **20** quantitatively. Finally, cleavage of the *O*-allyl ether of the diene **20** in refluxing EtOH containing a catalytic amount of $RhCl_3 \cdot 3H_2O$ led to spontaneous cyclization,[10] possibly through the intermediate dienone **D** (Scheme 1), afford-



Scheme 2. (i) $K_2CO_3$, allyl bromide, acetone, rt, 12 h, 99%; (ii) NBS, $CH_3CN$, −15°C, 30 min, 98%; (iii) *n*-BuLi (1.6 M), −78°C, 30 min, then DMF, −78°C, 6 h.



Scheme 3. (i) Pd–C, EtOH, $PdCl_2$ (5 mol%), 95%; (ii) *p*-$TsNHNH_2$, $MgSO_4$, *p*TsOH (cat.), THF, reflux, 72 h, 93% based on recovered starting ketone; (iii) (a) *n*-BuLi (1.6 M), −78°C (3 h) to −5°C (6 h), to rt (2 h); (b) −78°C, **12**, 5 h, 59%; (iv) $RhCl_3 \cdot 3H_2O$, EtOH, reflux, 7 h, quantitative.

ing a mixture of the isomeric pyrans **8a** ($C_8$-Me$_\alpha$) and **8b** ($C_8$-Me$_\beta$) in a ratio of ca. 1:4 ($^1$H and $^{13}$C NMR) in quantitative yield.[11] While the desired major isomer **8b** (43%) was separated from the mixture by chromatography, the minor natural isomer **8a** could only be obtained in a partially purified form. Since both the isomers **8a** and **b** have already been transformed to puupehedione **2a** and its epimer **2b**, the present work represents a shorter formal synthesis of these highly bioactive compounds from natural carvone. The concomitant oxaannulation in the RhCl$_3$-induced deprotection of an *O*-allylic phenolic group, virtually under neutral conditions, should emerge as a simple synthetic entry to this and a number of natural products and analogs.

## Acknowledgements

We are grateful to the DST (New Delhi) for financial support (Grant No. SP/SI/G-4/93), UGC (New Delhi) for a JRF to S.S., and Professor U. R. Ghatak of our institute for his suggestions and advice.

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11. **17**: mp 136–137°C; $[\alpha]_D^{29}$ +77.1 (*c* 0.14, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.83 (d, $J=8.5$ Hz, 2H), 7.30 (d, $J=8.5$ Hz, 2H), 7.17 (br s, 1H, exchangeable), 2.75 (m, 1H), 2.43 (s, 3H), 1.89 (d, $J=13$ Hz, 1H), 1.48–1.59 (m, 6H), 1.26–1.42 (m, 2H), 0.97–1.10 (m, 2H), 1.04 (d, $J=7.6$ Hz, 3H), 0.98 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 17.2 (CH$_2$), 18.3 (CH$_2$), 18.8 (CH$_3$), 21.5 (CH$_3$), 21.6 (CH$_3$), 21.8 (CH$_3$), 28.0 (CH$_3$), 32.1 (CH$_2$), 33.2 (CH), 33.7 (C), 36.1 (CH$_2$), 41.5 (CH$_3$), 43.2 (C), 52.8 (CH), 128.1 (CH), 129.2 (CH), 135.5 (C), 143.7 (C), 170.8 (C).
    **19**: $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.01 (s, 1H), 6.54 (s, 1H), 5.60–6.13 (m, 1H), 5.93 (m, 2H), 5.57 (br s, 1H), 5.43 (dd, $J=1.2$ and 17 Hz, 1H), 5.32 (dd, $J=1.2$ and 12 Hz, 1H), 4.59 (d, $J=4.8$ Hz, 2H), 3.29 (br s, 1H), 2.15 (m, 1H), 1.70 (s, 3H), 1.16 (s, 3H), 0.92 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 18.8 (CH$_2$), 18.9 (CH$_2$), 19.8 (CH$_3$), 21.7 (CH$_3$), 22.5 (CH$_3$), 33.3 (CH$_3$), 34.7 (CH$_2$), 35.9 (CH$_2$), 38.9 (C), 41.6 (CH$_2$), 51.9 (CH), 67.4 (CH), 69.9 (CH$_2$), 95.7 (CH), 101.1 (CH$_2$), 109.5 (CH), 118.0 (CH$_2$), 124.3 (C), 132.9 (CH), 133.2 (C), 139.2 (C), 140.8 (C), 147.1 (C), 151.9 (C). One aliphatic quaternary carbon signal could not be identified due to overlap.
    **20**: $[\alpha]_D^{29}$ −577 (*c* 0.27, CHCl$_3$); $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.63 (s, 1H), 6.46 (s, 1H), 6.22 (s, 1H), 5.90–6.01 (m, 1H), 5.89 (s, 2H), 5.57 (br s, 1H), 5.30 (dd, $J=1.2$ and 17 Hz, 1H), 5.23 (dd, $J=1.2$ and 11.3 Hz, 1H), 4.41–4.47 (m, 2H), 1.01–2.40 (m, several protons), 1.51 (d, $J=1.2$ Hz, 3H), 1.02 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 20.0 (CH$_2$), 20.3 (CH$_2$), 22.5 (CH$_3$), 22.7 (CH$_3$), 26.0 (CH$_2$), 33.3 (CH$_3$), 34.5 (C), 38.8 (CH$_2$), 39.4 (C), 43.1 (CH$_2$), 49.0 (CH), 71.3 (CH$_2$), 97.6 (CH), 111.4 (CH), 116.5 (CH), 117.5 (CH$_2$), 123.7 (C), 129.2 (CH), 132.2 (C), 134.4 (CH), 142.0 (C), 147.2 (C), 151.5 (C). One aliphatic quaternary carbon signal could not be identified due to overlap.
    **8b**: $[\alpha]_D^{29}$ +88.2 (*c* 0.14, CH$_2$Cl$_2$); $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.46 (s, 1H), 6.37 (s, 1H), 6.00 (s, 1H), 5.86 (s, 2H), 2.17 (m, 1H), 1.07–1.94 (m, several protons), 1.38 (s, 3H), 1.13 (s, 1H), 0.91 (s, 3H), 0.86 (s, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 18.9 (CH$_2$), 19.4 (CH$_2$), 21.7 (CH$_3$), 23.5 (CH$_3$), 25.9 (CH$_3$), 33.4 (CH$_3$), 33.6 (C), 38.1 (CH$_2$), 39.0 (C), 41.6 (2×CH$_2$), 52.2 (CH), 78.1 (C), 98.7 (CH$_2$), 100.8 (CH$_2$), 105.5 (CH), 114.4 (CH), 116.3 (C), 141.6 (C), 146.78 (C), 146.82 (C), 149.6 (C). The assigned[6b] chemical shift of 114.3 for $C_9$ is at variance with our data.