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Total Synthesis of both Enantiomers of 15-Oxopuupehenol Methylendioxy Derivatives

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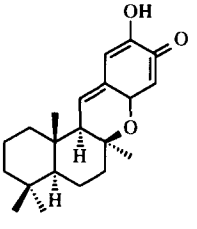
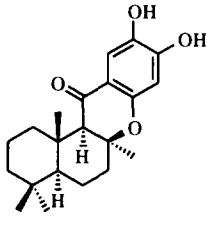
Dedicated to Prof. Luigi Minale *in memoriam*

Abstract :The total synthesis of both enantiomers of puupehenol and 15-oxopuupehenol as methylenedioxy derivatives is described. The key steps of the synthesis are the regioselective transformation of **10** to **11** and the stereoselective cyclization of **12** to **13**. © 1997 Elsevier Science Ltd.

(+)-Puupehenone **1** and (-)-15-oxopuupehenol **2** are metabolites isolated from two Hawaiian sponges *Hyrtios* sp[2] showing a sesquiterpene unit joined to a C-6 shikimate moiety. Both compounds show interesting biological properties including cytotoxic, antiviral and antifungal activities for **1** and antitumor, antimalarial and inhibition of Topoisomerase II activities for **2**.[2]

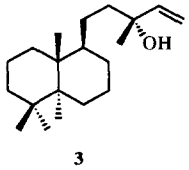


1



2

A previous synthesis of racemic **1** has been reported by Trammel[3] starting from farnesyl bromide and sesamol, whereas, to the best of our knowledge, the synthesis of **2** has never been published. A recent report of Barrero *et al.*[4] concerning the enantiospecific synthesis of (+)-**1** from (-)-sclareol **3** and protocatechualdehyde **4** involving 15 synthetic steps prompted us to report our results in this field.



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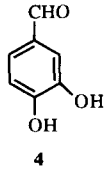
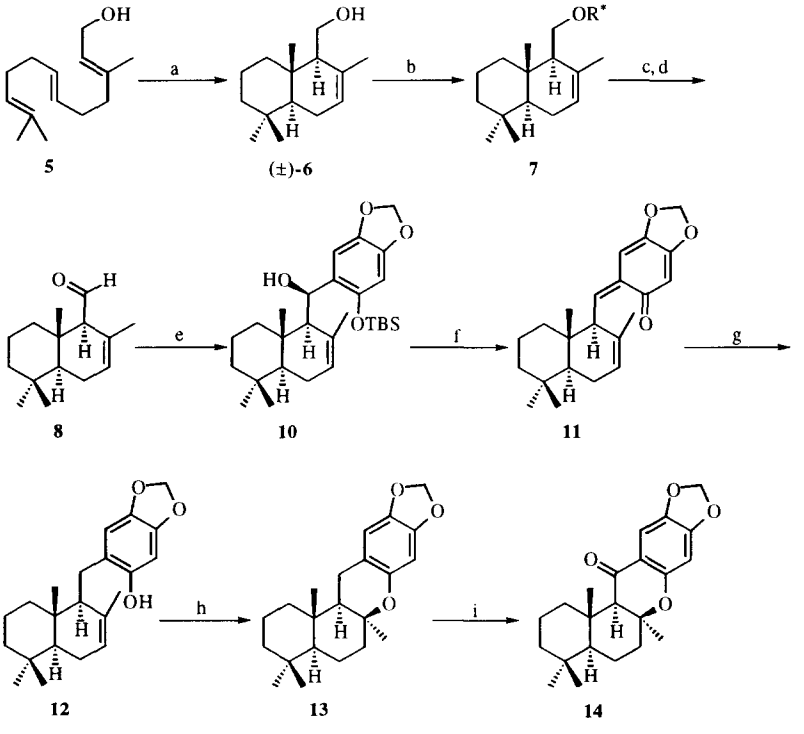


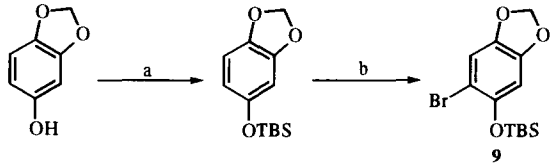
4

The present synthesis (Scheme 1) starts from *t,t*-farnesol **5** which was transformed to racemic drimenol **6** by reaction with fluorosulfonic acid.[5] The optical resolution of drimenol[6] was achieved by preparation of the canfanoates **7** followed by chromatographic separation of both diastereomers. Hydrolysis of **7a** and **7b** with $Ba(OH)_2$ gave optically pure (+) and (-)-drimenol, whose optical data are in agreement with those previously reported.[6] From this point, the synthetic sequence was continued with both separated enantiomers. Oxidation to drimenal **8** was achieved using pyridinium chlorocromate (PCC).[7] Further reaction of **8** with the protected bromosesamol **9**, prepared from sesamol in two synthetic steps (Scheme 2), gave alcohol **10** which was dehydrated to enone **11** using camphorsulfonic acid (CSA).[7] Conjugate reduction of **11** affords **12** which was cyclized to **13** by means of CSA. All attempts to transform **13** into the related dihydroxy derivative failed using the conditions previously described by Trammel and others.[8] Finally, benzylic oxidation of **13** with PDC afforded the protected 15-oxopuupehenol **14**.



Key: a) 1.1eq. $HFSO_3$; nitropropane-CH_2Cl_2 10:1;-78°C; 1h; 56%; b) 1.2eq. camfanoylchloride; pyridine-CH_2Cl_2; rt; 1h; 80%; c) i) chromatographic separation (SiO_2); Hexane-CH_2Cl_2 20:1; (+)-**7** $[\alpha]_D$=+8.9 (c=0.06 M, $CHCl_3$); (-)-**7** $[\alpha]_D$= -16.7 (c=0.33 M, $CHCl_3$); ii) 3eq. $Ba(OH)_2$; MeOH-CH_2Cl_2; rt; 2h; 85%; d) 1.5eq. PCC; CH_2Cl_2; rt; 1h; 68%; (+)-**8** $[\alpha]_D$=+18.8 (c=0.32 M, $CHCl_3$); (-)-**8** $[\alpha]_D$= -19.2 (c=0.17 M, $CHCl_3$) i) **9**; ^{t}BuLi; Et_2O; -78°C; ii) (+) and (-)-**8**; 1h; 68%. (+)-**10** from (+)-**8**, $[\alpha]_D$=+10.8 (c=0.08 M, $CHCl_3$); (-)-**10** $[\alpha]_D$=-9.5 (c=0.37 M, $CHCl_3$); f) 1eq. CSA; CH_2Cl_2; rt; 85%; (+)-**11** from (+)-**10**, $[\alpha]_D$=+264.5 (c=0.09 M, $CHCl_3$); (-)-**11** $[\alpha]_D$=-265.7 (c=0.09 M, $CHCl_3$); g) 4eq. $NaBH_4$; pyridine-CH_2Cl_2; rt; 30 min; 81%; (+)-**12** $[\alpha]_D$=+23.3 (c=0.08 M, $CHCl_3$); (-)-**12** from (+)-**11**, $[\alpha]_D$=-23.1 (c=0.02 M, $CHCl_3$); h) 2.5eq. CSA; CH_2Cl_2; rt; 15 min; 87%; (+)-**13** from (-)-**12**, $[\alpha]_D$=+35.7 (c=0.03 M, $CHCl_3$); (-)-**13** $[\alpha]_D$=-27.6 (c=0.01 M, $CHCl_3$); i) 6eq. PDC; CH_2Cl_2; rt; 24h; 45%. (+)-**14** $[\alpha]_D$=+54.3 (c=0.01 M, $CHCl_3$); (-)-**14** from (+)-**13**, $[\alpha]_D$=-56.0 (c=0.01 M, $CHCl_3$).

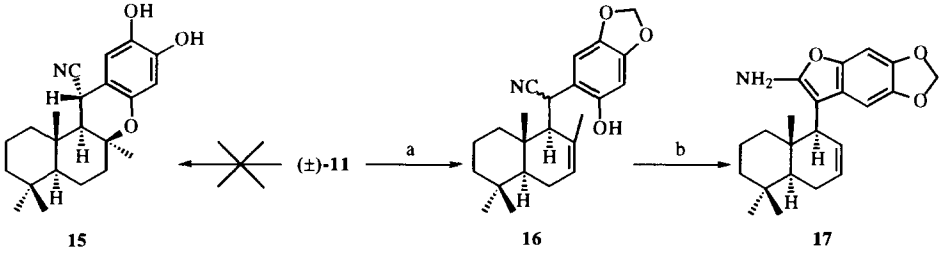
Scheme 1



Key: a) 2eq. TBSOTf; 2eq. Et_3N; CH_2Cl_2; -78°C;1h; 99%; b) 1eq. Br_2; CCl_4;10min; 95%.

Scheme 2

According to Scheuer *et al.*,[2] compound **2** can be derived from **1** by 1,6-addition of water followed by oxidation. In fact the conjugate reduction of **11** to **12** constitutes a related 1,8 process. In the same fashion, 15-cyanopuupehenol **15** isolated from a Verongide sponge[9] constitutes the adduct arising from the 1,6-addition of HCN to **1**. In this way, we speculate that the 1,8 addition of TMSCN to enone **11** could give the related cyano derivative **16** precursor of **15** by cyclization (Scheme 3). The reaction of **11** with TMSCN in the presence of Et_3Al[10] gives **16**.[11] All attempts at cyclization of **16** to **15** were unsuccesful (Scheme 3) compound **17** being isolated in all cases, arising from intramolecular alcoholysis of the cyano functionality followed by isomerization to the aminofurane derivative.



Key: a) TMSCN-Et_3Al; THF; 20 min.; 65%; b)Several conditions, for instance:1) $BF_3{\cdot}OEt_2$; THF-CH_2Cl_2; 2) p-toluenesulfonic acid-CH_2Cl_2; 3) β-naphthalensulfonic acid-CH_2Cl_2; 4) i) $Hg(OAc)_2$; acetone-H_2O; ii) $NaBH_4$, NaOH 3M.

Scheme 3

In summary, in this report we have described a general route to both enantiomers of methylenedioxy derivatives of puupehenol **13** (precursor of puupehenone **1**) and 15-oxopuupehenol **14** (10 steps from sesamol and *t,t*-farnesol for **13** and 11 steps for **14**) which, despite the problems related to the deprotection of the methylenedioxy group, is easily adaptable by use of other aromatic patterns such as **4**.[4] Intensive work in this way is now being undertaken achieved in our laboratory.

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11. The stereochemistry at the position 15 has not been determined. All new compounds described gave satisfactory spectroscopic and analytical data.

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