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Synthesis and absolute configuration of (−)-chettaphanin II

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Abstract—An efficient synthesis of chettaphanin II has been achieved from *ent*-halimic acid. The absolute configuration of the natural product was established and corroborated by X-ray analysis of chettaphanin II.

Chettaphanin I and II are the two main components of 'chettaphangki' a digestive remedy used in Thailand, and isolated from *Adenochlaena siamensi*, Ridl (Euphorbiaceae).[1,2] These two components are furanoditerpenes with an *ent*-halimane skeleton, whose structures have been determined by chemical and spectroscopic correlations. The structure and stereochemistry have been corroborated by X-ray crystallography of a chettaphanin II derivative,[2] the absolute configuration remaining undetermined.

In this paper the synthesis of chettaphanin II starting from *ent*-halimic acid, is described confirming the structure and establishing the absolute configuration of the natural product.

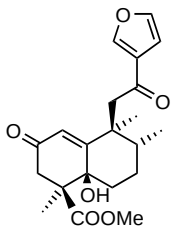
ent-Halimic acid is the main component of *Halimium viscosum* (Villarino de los Aires) and has been used as starting material in the synthesis of *ent*-halimanolides[3] and sestertepenolides,[4] similar to dysidiolide,[5] that show high antitumoural activity.

The structure of chettaphanin II, an *ent*-halimane diterpene, displays a third ring as a consequence of the C–C bond between C_1 and C_{12} in the *ent*-halimane skeleton.

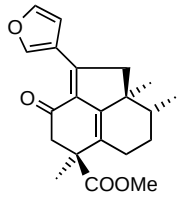
The synthesis was designed following the retrosynthetic scheme below (Scheme 1).

The key step in the synthesis is an intramolecular aldol condensation of protected diketone I. The furan ring of the side chain was added to a tetranorderivative II of *ent*-halimic acid **1**.

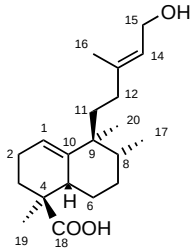
The synthesis was achieved as shown in Scheme 2. Degradation of the side chain of methyl ester of *ent*-halimic acid **2**, was performed in two stages, each of which resulted in the deletion of two carbons. The first was done by OsO_4[6] oxidation and treatment with LTA.[7] The reaction with OsO_4 was totally regioselective, with no derivative of the annular double bond being observed. The resulting triol was oxidised with LTA, giving ketone **3** in a 94% global yield for the two steps.



chettaphanin I



chettaphanin II



***ent*-halimic acid**

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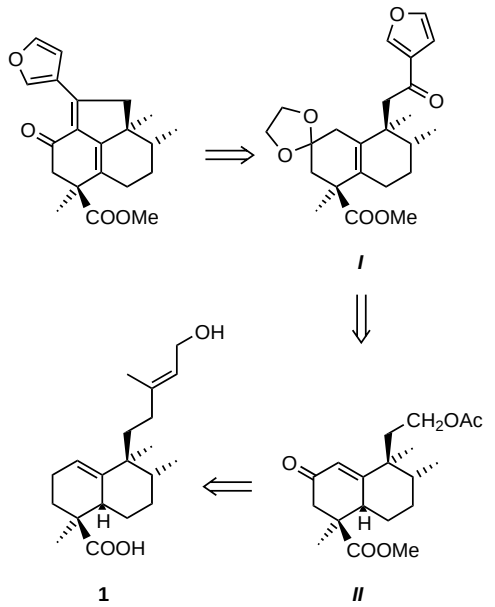


Scheme 1.

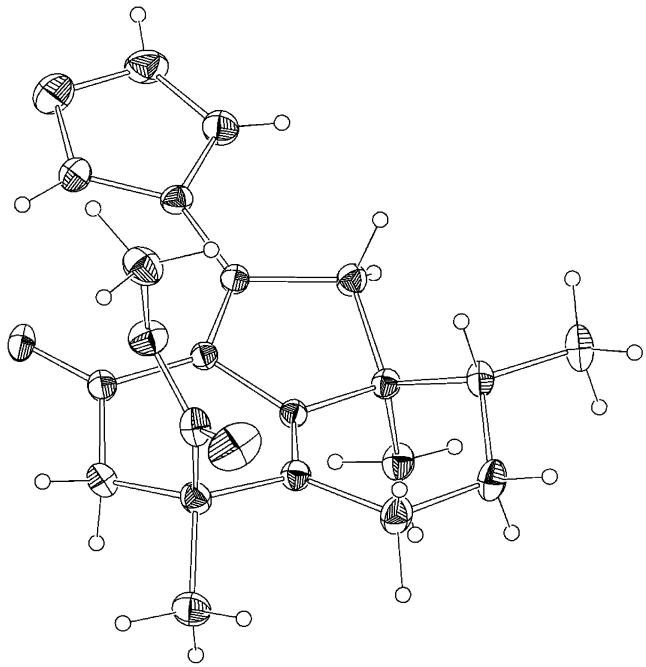
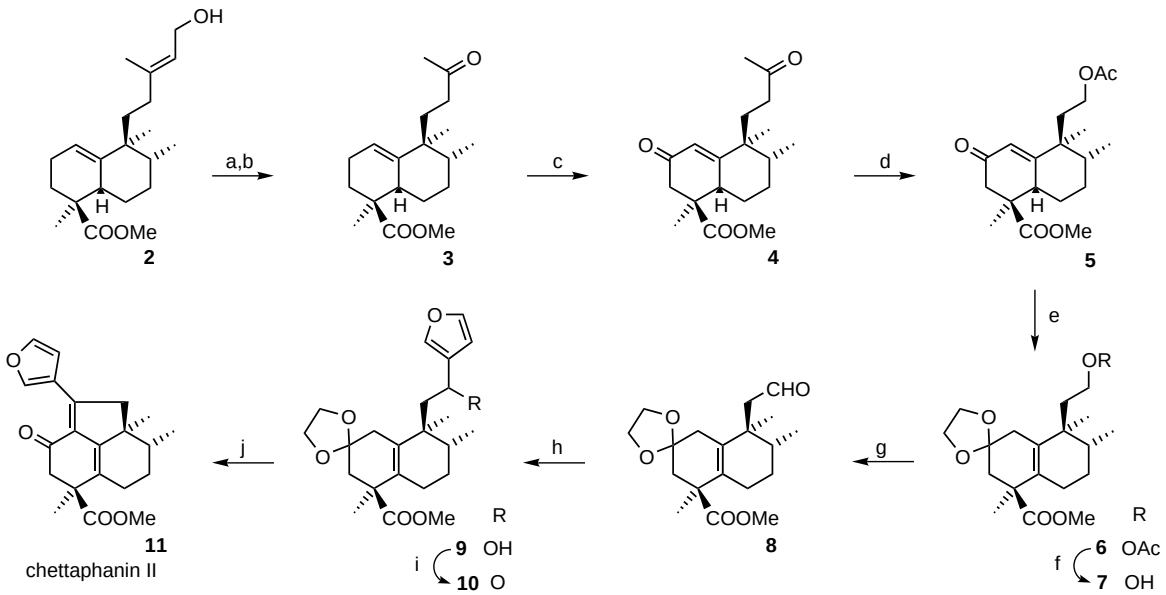


Figure 1. ORTEP view of compound **11**.

The degradation of the other two carbons was done by a Baeyer–Villiger reaction. In order to prevent electrophilic attack, on the annular double bond, this was deactivated by allylic oxidation at C_2 with Na_2CrO_4 in presence of Ac_2O/AcONa at 60°C[8] to give the α,β-unsaturated ketone **4** that already had the required carbonyl group at C_2. The Baeyer–Villiger oxidation of **4** was done with trifluoroacetic acid anhydride in the presence of urea-hydroperoxide,[9] to give **5** in a 61% yield.

In order to introduce the furan ring fragment in the side chain by means of an organometallic reagent, it was necessary to protect the carbonyl group at C_2 as a dioxolane. This was achieved by reaction of **5** with ethylene glycol in acidic media, giving **6**. Subsequent saponification with K_2CO_3 in MeOH gives alcohol **7** in 75% global yield for the two steps. Oxidation of **7** with PDC in DMF[10] gives aldehyde **8** in an excellent 98% yield. This aldehyde proved to be very stable and quite difficult to oxidise. Treatment of 3-bromofuran with



Scheme 2. (a) OsO_4, NMO, *t*-BuOH/THF/H_2O (7:2:1), 24 h, (99%); (b) LTA, C_6H_6, 20 min, (95%); (c) Na_2CrO_4, Ac_2O/AcOH, NaOAc, benzene, 55°C, 15 h, (64%); (d) UHP/TFAA, CH_2Cl_2, 60 min, (61%); (e) ethylene glycol, *p*-TsOH, benzene, reflux, 8 h, (76%); (f) K_2CO_3, MeOH, 3%, 60 min, (99%); (g) PDC, DMF, 3 h, (98%); (h) 3-bromofurane, BuLi, THF, −78°C, 20 min, (90%); (i) TPAP, NMO, CH_2Cl_2, 45 min, (93%); (j) *p*-TsOH, acetone, 5 h, (72%).

n-BuLi gave the corresponding 3-furyllithium,[11] to which was added aldehyde **8** to produce a 1:1 mixture of hydroxy derivatives, **9**. This mixture of epimers at C_{12} was oxidised with TPAP and NMO[12] as cooxidant to furnish ketone **10** in excellent yield. Treatment of **10** with TsOH lead to **11** in a 72% yield. Physical properties of **11**[13] were coincident with the ones described in the literature for chettaphanin II,[2] whose structure has been confirmed by X-ray analysis.[14]

In this paper *ent*-halimic acid, a diterpene of known absolute configuration,[15] has been transformed into chettaphanin II so the absolute configuration for this compound is that shown in Fig. 1.

Acknowledgements

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13. Chettaphanin II, **11**: mp 127°C (Et_2O); $[\alpha]_D^{25}=-435°$ ($c=0.81$, Me_2CO); UV (EtOH) 356, 264, 208 nm; IR (film) 3163, 1728, 1682, 1574, 1464, 1433, 1377, 1265, 1167, 1109, 1017 cm^{-1}; ^1H NMR δ 8.57 (1H, m, H_{16}), 7.43 (1H, m, H_{15}), 7.00 (1H, m, H_{14}), 3.57 (3H, s, COOMe), 2.81 ($1H_A$, d, $J=15.7$ Hz, H_3), 2.71 ($1H_A$, d, $J=16.9$ Hz, H_{11}), 2.66 ($1H_B$, d, $J=16.9$ Hz, H_{11}), 2.45 ($1H_B$, d, $J=15.7$ Hz, H_3), 2.37 (1H, ddd, $J=18.0$, 6.2 and 1.0 Hz, H_6), 2.25 (1H, ddd, $J=18.0$, 9.2 and 1.0 Hz, H_6), 1.66 (1H, m, H_7), 1.58 (1H, m, H_7), 1.57 (1H, m, H_8), 1.38 (3H, s, Me_{19}), 0.99 (3H, s, Me_{20}), 0.97 (3H, d, $J=6.2$ Hz, Me_{17}); ^{13}C NMR δ 127.9 (C_1), 195.1 (C_2), 52.1 (C_3), 48.4 (C_4), 125.1 (C_5), 23.7 (C_6), 27.0 (C_7), 37.1 (C_8), 42.4 (C_9), 150.3 (C_{10}), 50.3 (C_{11}), 139.7 (C_{12}), 121.8 (C_{13}), 111.0 (C_{14}), 142.7 (C_{15}), 146.3 (C_{16}), 16.4 (C_{17}), 174.6 (C_{18}), 22.3 (C_{19}), 20.3 (C_{20}), 52.3 (-COOMe). EIHRMS calcd for $C_{21}H_{24}O_4$ (M^+) 340.1674, found ($M+H^+$) 341.1658.
14. Crystal data for **11**: $C_{21}H_{21}O_4$, $M=304.4$, monoclinic, space group $P21$ (no. 4), $a=7.0648(4)$, $b=9.0525(5)$, $c=14.367(1)$ Å, $\alpha=90$, $\beta=103.38(1)$, $\gamma=90°$, $V=893.89(1)$ $Å^3$, $Z=2$, $D_c=1.265$ Mg/m^3, m(Cu-Kγ)$=0.698$ mm^{-1}, $F(000)=364$. Data (1629 independent reflections, theta range 3.15–65.00°) were measured on a Seifert 3003 SC rotating anode diffractometer with Cu-Kγ radiation (graphite monochromator) using 2θ–ω scans at 268 K. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically by full-matrix least-squares based on F_2 to give, $R_1=0.0376$, $wR_2=0.0867$ [$I>2\sigma(I)$]. The positions of the hydrogen atoms were located from difference Fourier method and refined isotropically. The absolute chirality was determined by internal reference. Computations were carried on an Digital 300 MHz workstation using the XRAY80 and SHELX93 programs. Crystallographic data for the structure reported in this paper has been deposited at the Cambridge Crystallographic Data Centre as supplementary material CCDC No. 145501.
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