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Studies on Furoterpenes: Stereoselective Total Synthesis of (±)-Ambliol-A and Dendrolasin

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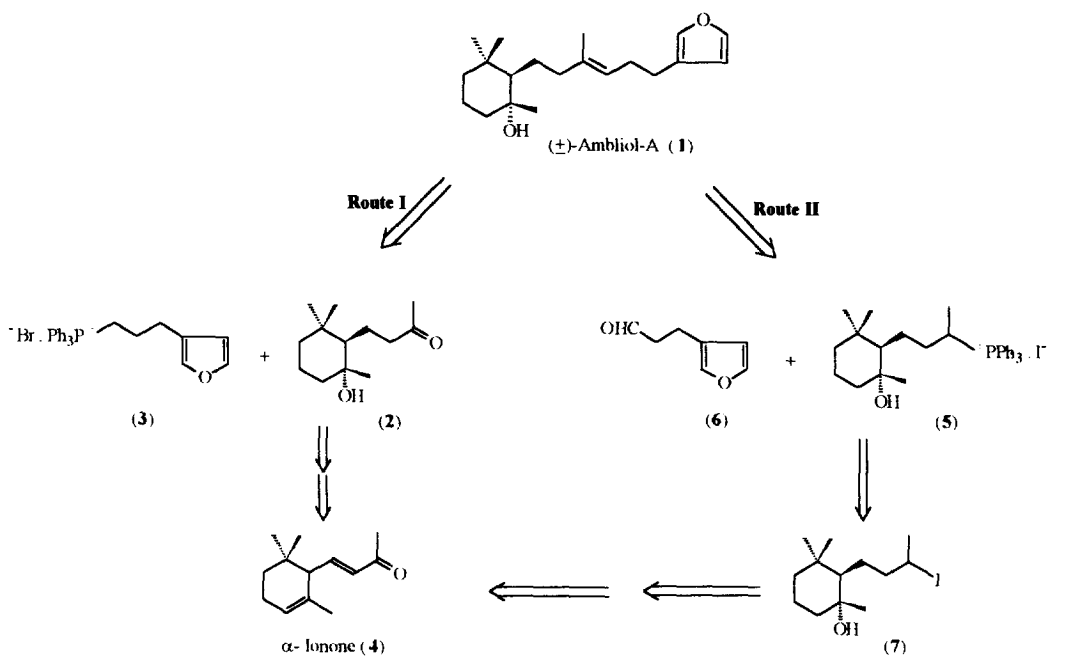
Abstract : (±)-Ambliol-A (**1**) is totally synthesised with high stereoselectivity starting from α-ionone and [3-(3′-furyl)propyl]triphenylphosphonium bromide (**3**). In another attempt utilising **3** with the commercially available ketone **11** the total synthesis of Dendrolasin (**12**) has also been achieved.

Furoterpenes are desirable synthetic targets due to their important biological activities. Ambliol-A (**1**)[1] is the first furoditerpenoid isolated from the marine sponge *Dysidea amblia*. The characteristic of the structure of this new class of furoterpenes is the presence of unique E-geometry of the double bond, tertiary hydroxyl group and the furan moiety. Nishizawa *et. al.*[2] have reported the biomimetic total synthesis of **1** in very poor yield starting from furnesyl bromide. Herein we describe a short and convenient total synthesis of Ambliol-A. Retrosynthetic analysis of Ambliol-A readily identified the keto alcohol (**2**) and [3-(3′-furyl)propyl]triphenylphosphonium bromide (**3**) (via route I) and **5** and **6** (via route II) as key intermediates. We adopted the reconnection approach by Wittig reaction between **2** and **3** for the synthesis of Ambliol-A as per Scheme - 1.

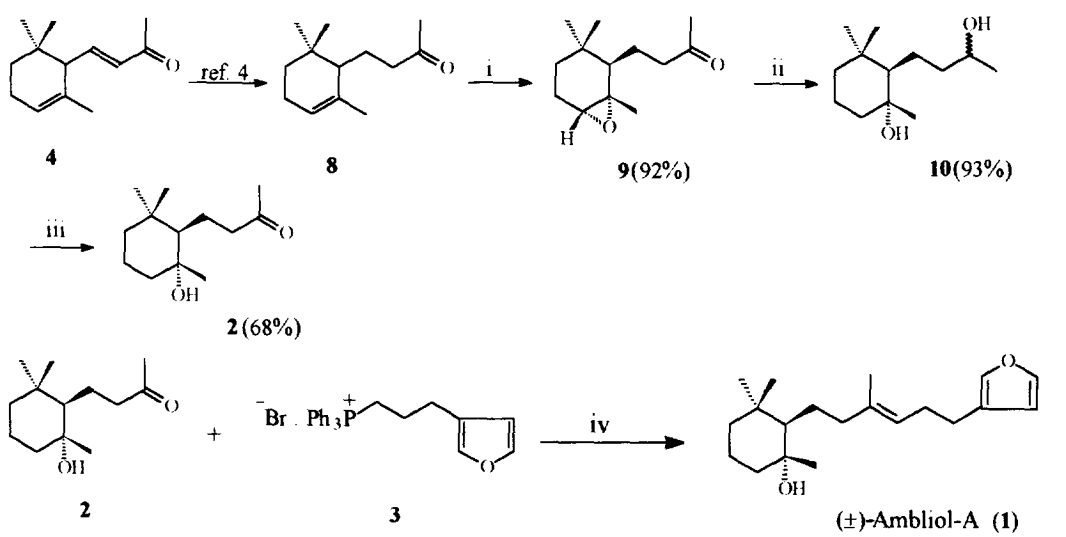
Compound **8** was obtained by selective reduction of α-ionone[3] following the method of Camps *et. al.*,[4] although in our hands it took seven days instead of 2 h as reported for completion of the reaction. Compound **8** was then converted to the epoxy ketone (**9**) in 92% yield by oxidation with m-CPBA. The compound was analysed by ^{1}H-NMR as well as ^{13}C and DEPT analysis. The stereochemistry as depicted for the epoxy ketone is in conformity with the favoured transition state of its formation because the axial approach of the per acid will be sterically hindered by 1, 3-diaxial interaction (Figure 1).

An attempt at Wittig olefination of the epoxy ketone **9** with the ylide generated from **3** (using NaH or n-BuLi as base) met with failure. Unreacted epoxyketone was recovered from the reaction mixture. Compound **9** was then reduced with $LiAlH_4$ to produce the diol (**10**) as a colourless solid in ~93% yield. The stereochemistry of the product was unambiguously determined by NMR analysis and by analogy.[5] Partial oxidation of **10** with Ag_2CO_3 - celite[6] in refluxing benzene afforded the ketoalcohol **2** as a colourless oil in 68% yield. The ketoalcohol when subjected to Wittig olefination with the ylide generated from two equivalents of **3**[7] and n-BuLi afforded (±) Ambliol-A (**1**) in ~31% yield. All the compounds have been characterised by the usual spectral data and analysis.

Retrosynthetic analysis:



SCHEME 1

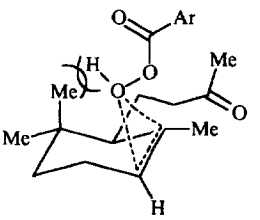


Reagents and conditions : i. m-CPBA, CH_2Cl_2, 0° C-r.t., 12 h. ii. $LiAlH_4$, THF, r.t., 20 h. iii. Ag_2CO_3-celite, benzene, reflux, 4 h. iv. n-BuLi, THF, -30°C to r.t., overnight.

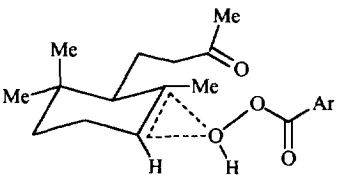
The pre-dominance of the Z-diastereomer in Wittig reaction was the result of early studies, now it is about to be challenged by a moderate combination of base and Wittig salt to produce the E-diastereomer.[8]

One of the crucial steps in the synthesis consists of a stereoselective epoxidation and reduction. The second difficulty was solved by chemoselective oxidation of the diol (**10**) by Ag_2CO_3-celite without undergoing any protection/deprotection protocol.

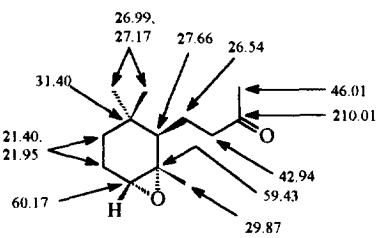
Figure 1 :



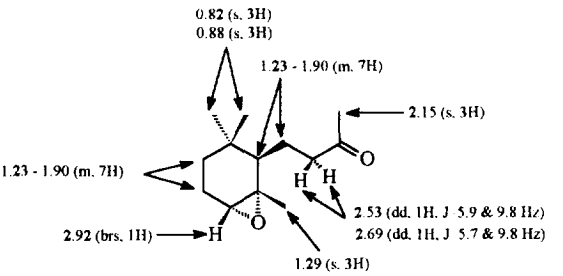
Unfavourable T. S.



Favourable T. S.



^{13}C-NMR of **9**

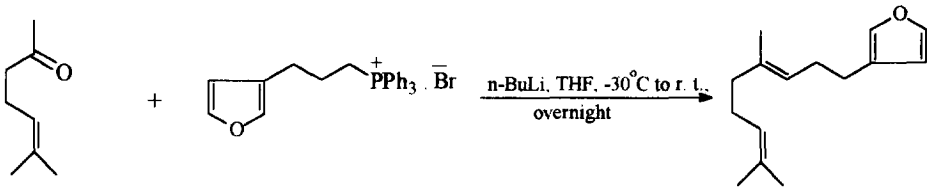


^{1}H-NMR of **9**

The alternative attempt to synthesise the title compound (**1**) via route II failed since the synthesis of the Wittig salt **5** by reaction of **7** and PPh_3 was unsuccessful.

We have also utilized the Wittig salt (**3**) for the synthesis of another naturally occuring furosesquiterpene, Dendrolasin,[9,10] the major product of the mandibular gland of the ant *Lasius (Dendrolasius) fulginosus Latr.* The reaction of the commercially available ketone **11** with **3** in THF and n-BuLi afforded Dendrolasin in 27% yield. The structural data of the product are in agreement with that reported in literature.[11]

SCHEME 2



11 **3** Dendrolasin (**12**)

In conclusion, we have described here the total synthesis of (±)Ambliol-A and Dendrolasin and currently we are investigating the extension of this methodology to the total synthesis of Pouoside-A.[12]

Experimental Section :

All the reactions were carried out under argon atmosphere. NMR spectra were recorded in $CDCl_3$ solution on 200 MHz Brucker machine. IR spectra were recorded on a Perkin Elmer 883 machine. Mass spectra were produced at IICB, Calcutta, India.

4-(2,6,6-Trimethyl-2,3-epoxycyclohexyl)butan-2-one (9) :

A solution of 70% m-chloroperbenzoic acid (5.00 g, 28.97 mmol) in dry CH_2Cl_2(140 mL) was added to a solution of **8** (3.22g, 16.57 mmol) in dry CH_2Cl_2 (20 mL) cooled in an ice bath and stirred at r.t. for 12 h. The reaction mixture was then washed with 10% aqueous $NaHSO_3$ solution (4 x 100 mL), $NaHCO_3$ solution (4 x 100 mL), water, dried over anhydrous Na_2SO_4. Solvent evaporation provided **9** as a colourless liquid (3.23 g, 92%) which was used for the next reaction without further purification. The epoxide is unstable at r.t. and should be stored in a refrigerator. An analytical sample of epoxy ketone was prepared by sublimation under high vacuum. IR (neat) 1712 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ : 0.82 (s, 3H), 0.88 (s, 3H), 1.23-1.90 (m, 7H), 1.29 (s, 3H), 2.15 (s, 3H), 2.53 (dd, 1H, J~5.9 & 9.8 Hz), 2.69 (dd, 1H, J~5.7 & 9.8 Hz), 2.92 (brs, 1H) ppm. ^{13}C-NMR ($CDCl_3$) δ : 21.40, 21.95, 26.54, 26.99, 27.17, 27.66, 29.87, 31.40, 42.94, 46.01,59.43, 60.17, 210.01 ppm. MS(m/z) : 210(M$^+$), 192, 177, 174, 159, 139, 121, 119, 111, 109, 107, 105. Anal. Calcd. for $C_{13}H_{22}O_2$: C, 74.29; H, 10.48. Found: C, 73.89, ; H, 10.13.

4-(2,6,6-Trimethyl-2-hydroxycyclohexyl)butan-2-ol (10) :

To a stirred suspension of LAH (1.44 g, excess) in dry THF (50 mL) a solution of **9** (3.23 g, 15.36 mmol) in dry THF (10 mL) was added dropwise. Stirring was continued at r.t. for 20 h. It was then cooled in an ice-bath and poured onto ice-water. Extraction with ether followed by usual workup afforded the diol **10** as a colourless solid (3.05 g, 93%). An analytical sample was prepared by repeated crystallisation from petroleum ether (60-80^{0}C). IR (KBr) : 3362 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ : 0.88 (s, 3H), 0.97 (s, 3H), 1.18 (s, 3H), 1.21 (d,

3H, J~ 6.2 Hz), 1.58 (brs, 2H), 1.07-1.85 (m, 11H), 3.78 (m,1H) ppm.^{13}C-NMR ($CDCl_3$) δ :18.26, 21.38, 21.86, 23.46, 30.87, 32.06, 34.77, 41.16, 41.78, 43.19,54.16, 68.51, 73.04 ppm. MS (m/z) : 214 (M$^+$). Anal. Calcd. for $C_{13}H_{26}O_2$: C, 72.90; H, 12.15. Found: C, 72.74 ; H, 11.98.

4-(2,6,6-Trimethyl-2-hydroxycyclohexyl)butan-2-one (2) :

A mixture of the diol **10** (30 mg, 0.14 mmol) and Ag_2CO_3 - Celite (400 mg, 1mmol of Ag_2CO_3 / 0.57 g of the reagent) in dry benzene (7 mL) was heated under reflux for 4 h. After cooling to r. t.. it was then filtered and the residue was washed with a little dry benzene. The filtrates were combined and the solvent was evaporated to afford the desired ketone **2** (20 mg, 68%). IR(neat) : 3495(br), 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ : 0.77-2.00 (m, 9H), 0.87 (s, 3H), 0.98 (s, 3H), 1.15 (s, 3H), 2.14 (s, 3H), 2.47 (dd, 1H, J~2.8 Hz & 6.8 Hz), 2.52 (dd, 1H, J~3.2 Hz & 6.8 Hz) ppm. Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.59; H, 11.32. Found: C, 73.21; H, 10.95.

Ambliol-A (1) :

1M solution of n-BuLi (0.20 mL) was injected slowly into a cold (-30^0 C) stirred suspension of **3** (102 mg, 0.226 mmol) in dry THF (1.5 mL). An orange-yellow mixture resulted which was stirred for 35-40 min at -30^0 C. Now to this a THF solution (0.5 mL) of **2** (20 mg, 0.094 mmol) was injected dropwise. Stirring was continued for 30 min at -30^0 C. It was then allowed to attain r.t. and stirred overnight. The reaction mixture was quenched with one drop of ice-water and the solvent was stripped out under reduced pressure. The residue was thoroughly extracted with ether, dried (Na_2SO_4) and the solvent removed. The crude product thus obtained was purified by column chromatography [neutral Al_2O_3/Petroleum ether (60-80^0 C)] to furnish the title compound (9 mg, 31%) as colourless oil. ^{1}H-NMR ($CDCl_3$) δ : 0.85 (s, 3H), 0.88 (s, 3H), 1.16 (s, 3H), 1.60 (s, 3H), 1.1 - 1.95 (m, 8H), 2.11 - 2.31 (m, 4H), 2.41 (t, 2H, 6.7 Hz), 5.41 (t, 1H, J~4.5 Hz), 6.23 (brs, 1H), 7.18 (brs, 1H), 7.31 (brs, 1H) ppm [lit.[2] ^{1}H-NMR ($CDCl_3$) δ : 0.82 (s, 3H), 0.93 (s, 3H), 1.15 (s, 3H), 1.60 (s, 3H), 5.13 (br t, 1H, J ~ 6 Hz), 6.22 (d, 1H, J ~ 1 Hz), 7.17 (d, 1H, J ~ 1 Hz), 7.29 (t, 1H, J ~ 1 Hz) ppm].

Dendrolasin (12) :

1M solution of n-BuLi (0.11 mL) was injected slowly into a cold (-30^0 C) stirred suspension of **3** (56 mg, 0.12 mmol) in dry THF (1mL). An orange-yellow mixture resulted which was stirred for 35-40 min at -30^0 C. Then to this a THF solution (0.5 mL) of **11** (13 mg, 0.1 mmol) was injected dropwise. Stirring was continued for 30 min at -30^0 C. It was then allowed to attain r.t. and stirred overnight. The reaction mixture was quenched with one drop of ice-water and the solvent was stripped out under reduced pressure. The residue was thoroughly extracted with ether, dried (Na_2SO_4) and the solvent removed. The crude product thus obtained was purified by column chromatography [neutral Al_2O_3/Petroleum ether (60-80^0 C)] to furnish the Dendrolasin (6 mg, 27%) as colourless oil. ^{1}H-NMR ($CDCl_3$) δ : 1.60 (s, 6H), 1.68 (s, 3H), 2.01 (br, 4H), 2.21 - 2.30 (m, 2H), 2.44 (t, 2H, J~7.1 Hz), 5.14 (m, 1H), 5.39 (m, 1H), 6.24 (s, 1H), 7.19 (s, 1H), 7.32

(s, 1H) ppm [lit.[11] ^{1}H-NMR ($CDCl_3$) δ : 1.59 (s, 6H), 1.68 (s, 3H), 2.01 (br, 4H), 2.00 - 2.60 (m, 4H), 5.10 (m, 2 H), 6.26 (br, 1H), 7.19 (br, 1H), 7.31 (t, 1H, J ~ 2 Hz) ppm].

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