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# TOTAL SYNTHESIS OF ( ±)-BISABOLANGELONE

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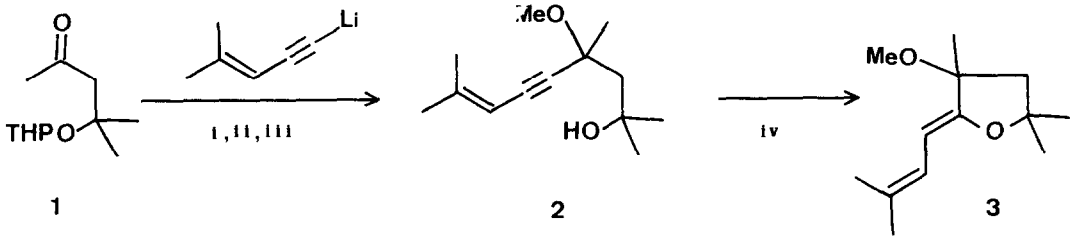
Summary : The total synthesis of the sesquiterpenoid ( ±) bisabolangelone 21 is described. The key step utilizes the heterocyclic five membered ring formation by cyclisation of a γ-acetylenic alcohol with the formation of an exocyclic conjugated enol ether in high yield.

Bisabolangelone 21 is a well known sesquiterpenoid isolated from the seeds of *Angelica silvestris* (1), and interesting for its strong insect antifeeding properties (2). Starting from the natural product, we obtained several biologically active derivatives (3). However this work suffered some limitation in view of the very unstable nature of the natural product, and required a synthetic approach. Our general goal for the synthesis of 21 is to form the heterocyclic ring by cyclisation of a γ-acetylenic alcohol, which is already a known procedure (4). Since no closely related example was found in the litterature, we started our investigation with a model study.

Scheme 1



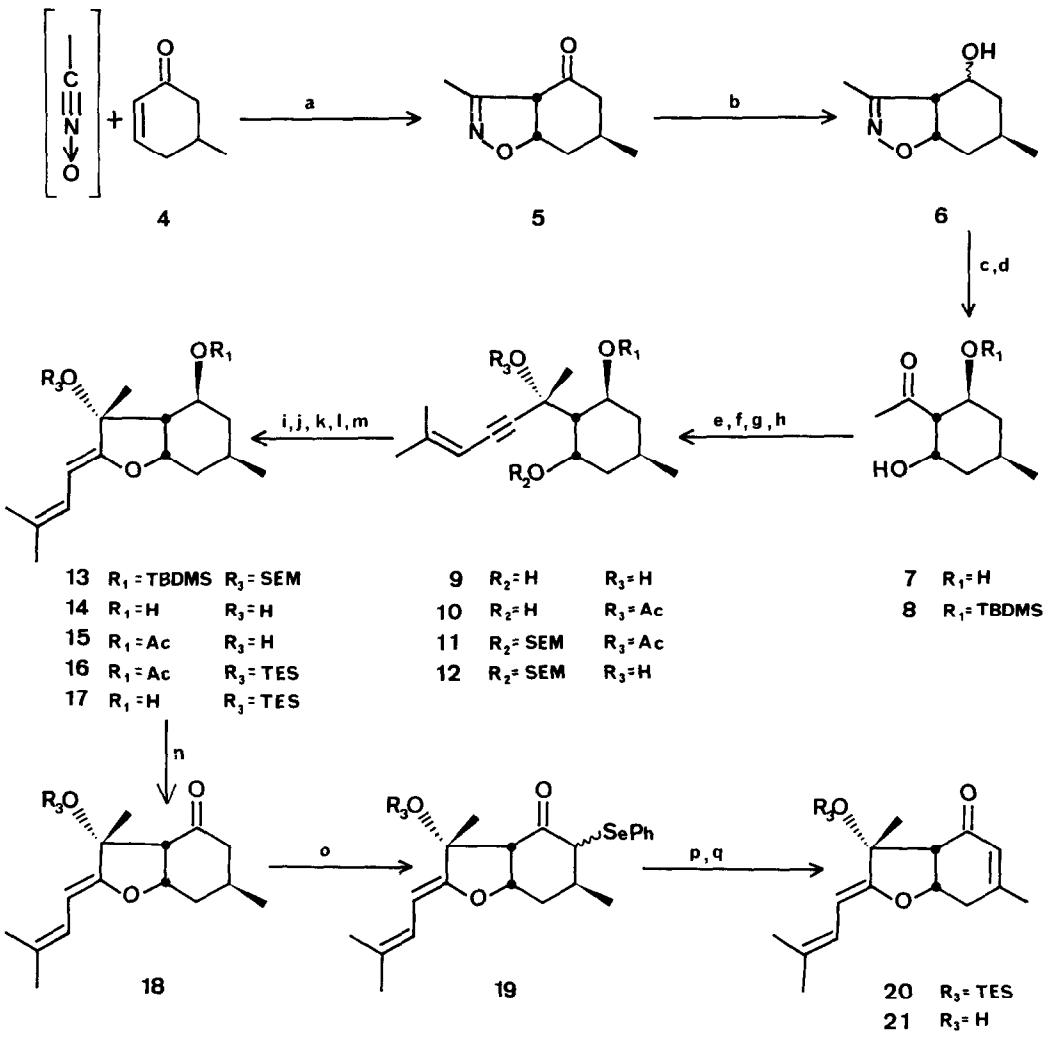

i) $H_3C$-C($CH_3$)=CH-C≡C-Li/THF - 78°C (94 %) ; ii) MeI/KOH/DMSO, 30 min. r.t. (80 %) ; iii) PPTS/MeOH over night at r.t. (90 %) ; iv) 3 eq t-BuOK/DMSO - THF, 5 min r.t. (95 %).

Treatment of the protected diacetone-alcohol 1 with the lithium acetylide of 2-methyl-pent-2-ene-4-yne (5) in THF at -78°C, followed by methylation of the propargylic alcohol with MeI/KOH/DMSO at r.t. and removal of the THP group, yielded 2 in 70 % overal yield. Upon treatment with a strong base (t-BuOK/DMSO - THF 5 min r.t.) the γ-acetylenic alcohol 2 was cyclized to give 3 in 95 % yield. Other strong bases such as $KN(SiMe_3)_2$/THF, KH/THF/HMPA gave similar results, whereas NaOMe/MeOH (4) left the starting material unchanged after 20 h at reflux.

When the tertiary propargylic alcohol was unprotected, no cyclisation occured and 2 was cleaved to regenerate the starting materials. We then searched for a hydroxyl protective group which could be removed from the acid sensitive end-product. This was accomplished with a tetrahydropyranyl ether (THP), a methylthiomethylether (MTM) or a [2(trimethylsilyl)ethoxy] methylether (SEM). The yield of deprotection is respectively 10, 47 and 73 %.

Application of the outlined method to our goal provided (±)-bisabolangelone 21 as described below (Scheme 2). Starting with the 5-methylcyclohexenone 4 (6) and acetonitrile oxide generated *in situ* from acetohydroxamic acid chloride and triethylamine (7), yielded 61 % of the Δ2-isoxazoline 5 (mp 46-47°C). After reduction with $NaBH_4$ in methanol, we obtained 6 as a mixture of epimers in quantitative yield. Despite similar chromatographic behaviour, the two diastereoisomers (50 % each) could be separated by crystallization (the α-OH isomer is a solid mp 110.5-111.5°C whereas the β-OH isomer is a liquid). Treatment of 6 (β-OH) with 10 eq Raney nickel in water at 0°C followed by 20 eq of conc. HCl over 30 min gave after stirring for 4 h 100 % of the acetylcyclohexanediol 7 (mp 74-74.5°C) with no isomerisation. Selective monoprotection with t-butyldimethylsilylchloride/imidazole (TBDMS-Cl) in DMF occured in quantitative yield at the β-OH 8. To this product we added the acetylide in a highly stereoselective manner : 2.5 eq of 2-methylpent-2-ene-4-yne in THF lithiated with n-butyllithium in hexane at -10°C, followed after 30 min by the ketone 8 at -78°C for 3 h, then 10 hours at -20°C gave the monoprotected triol 9 (mp 65-67°C) in 98 % yield. The same sequence of reactions applied to the α-OH isomer 6 yields also single products corresponding to 7, 8 and 9 but the following steps do not succeed. The secondary hydroxyl was selectively acetylated with $Ac_2O$/pyridine affording 10 (mp 70-71°C) in 94 % yield. The tertiary propargylic hydroxyl was protected as a SEM ether 11 (mp 50-52°C) in 96 % yield. The acetyl moiety was then removed with $LiAlH_4$ in ether at 0°C to give 12 in quantitative yield. Treatment of 12 in THF with 1.2 eq dimsyl-potassium 0.6 M at - 20°C gave a deep red solution which was quenched after 15 minutes with AcOH/THF to leave a slightly yellow solution which afforded 13 in 66 % yield after column chromatography. This surprisingly clean reaction gave rise to the bisabolangelone skeleton with all steric requirements. Deprotection of the two hydroxyl groups (8 eq $Bu_4NF$/THF 2M, 6 days at 30°C) gave the diol 14 (mp 56-57°C) in 83 % yield, and was necessary since the SEM protective group could not be removed in the last steps. After acetylation of the secondary hydroxyl with $Ac_2O$/pyridine in 85 % yield, we obtained 15 as a crystalline solid (mp 115-116°C). The tertiary hydroxyl was then protected as a triethylsilyl (TES) ether with TES-Cl/DMF/imidazole for 3 days at 30°C in quantitative yield. (No protection occurred with TES-Cl/pyridine even at 70°C and TES-triflate gave a single product which showed to be a bridged triethylsilyl orthoester arising from the reaction with the acetate). Product 16 was a crystalline solid (mp 115-116°C). Removal of the acetyl group was performed with DIBAH in toluene at 0°C, 100 %. ($LiAlH_4$, or $K_2CO_3$/methanol cleaved the TES protective group). 17 was submitted to Swern oxidation ($(COCl)_2$/DMSO) (8) and gave 18 (mp 65-66°C) in 75 % yield which was α-lithiated at the desired position with LDA/THF -78°C (1 h) then -20°C (10 h). Subsequent reaction with PhSeCl (9) at -78°C (1/2 h) gave 65 % of 19 as a mixture of two diastereoisomers easily separable by column chromatography. One isomer gave the protected bisabolangelone 20 in 40 % yield upon treatment with $NaIO_4$/methanol buffered with 2,6-lutidine. The other isomer gave the selenoxide, which on heating, furnished only traces of 20 (∿15 %).

Scheme 2




Conditions

a) 30 eq 4/$Et_2O$, $H_3CClNOH$, $Et_3N$, 61 % ; b) $NaBH_4$/MeOH, 100 % ; c) Raney Ni/$H_2O$, HCl, 100 % ; d) 1,2 eq TBDMS-Cl/DMF/imidazole, 100 % ; e) 2,5 eq $H_3C$-C($CH_3$)=CH-C≡C-Li/THF, 98 % ; f) 20 eq $Ac_2O$/pyridine 94 % ; g) 3 eq SEM-Cl/EtN(isoPr)$_2$, 96 % ; h) 1 eq $LiAlH_4$/ $Et_2O$, 100 % ; i) 1,2 eq dimsyl-K/THF, 66 % ; j) 8 eq $nBu_4NF$/THF, 83 % ; k) 20 eq $Ac_2O$/pyridine, 85 % ; l) 5 eq TES-Cl/DMF/imidazol, 100 % ; m) excess DIBAH/toluene, 100 % ;n)$(COCl)_2/CH_2Cl_2$, DMSO, EtN(isoPr)$_2$, 75 % ; o) 1,2 eq LDA/THF, PhSeCl, 65 % ; p) 3 eq $NaIO_4$/ MeOH, 2,6-lutidine, 40 % ; q) 50 eq HF/pyridine, $CH_2Cl_2$, 62 %.

( ±)-bisabolangelone 21 (mp 130-132°C) was obtained upon treatment of 20 with excess HF/pyridine in methylene chloride for 3 days at 30°C in 62 % yield. These neutral conditions were the only ones compatible with the highly sensitive product. 21 proved to be identical with the natural bisabolangelone by means of its spectral data (NMR, IR, MS, UV) and TLC behaviour.

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**Spectral data of some selected intermediates** ; 5 m/z 167 ($M^+$ 31 %), IR ($CHCl_3$) : ν 1720, 1395, 1235, 920 $cm^{-1}$, $^1H$ NMR ($CDCl_3$) δ 1.04 (d, 3, J = 6,4), 1.57 (ddd, 1, J = 15.2, 12.3, 3.6) ; 1.90 (ddd, 1, J = 16.6, 12.2, 0.8) ; 2.09 (d, 3, J = 0.9) ; 2.23 (dm, 2, d, J = 15.2) ; 2.50 (dm, 1, J = 16.6) ; 3.54 (d, 1, J = 10.3) ; 4.91 (ddd, 1, J = 10.0, 3.4, 2.9) ; Found C 64.6, H 7.88, N 8.23 %; Calc. for $C_9H_{13}O_2N$ : C 64.6, H 7.78, N 8.38 %. 9 : ν 3530, 3400, 2200w, 1255, 1040, 835 $cm^{-1}$. 0.17 (d, 6, J = 5.8) ; 0.91 (s, 9) ; 0.93 (d, 3, J = 7) ; 1.03 - 1.27 (m, 3) ; 1.59 (d, 3, J = 1) ; 1.81 (d, 3, J = 1.2) ; 1.89 (d, 3, J = 0.8) ; 1.89 - 2.10 (m, 3) ; 4.3 (sl, 1) ; 4.6 (td, 1, J = 10.8, 4.1); 5.29 (m, 1). 13 : ν (neat) 1670, 1635, 1250, 1020, 835 $cm^{-1}$. δ 0.03 (s, 9) ; 0.07 (s, 6) ; 0.88 (s, 9) ; 0.92 (m, 2) ; 1.03 (d, 3, J = 6.5 ; 1.1. (m, 2) ; 1.52 (s, 3) ; 1.72 (s, 3) ; 1.78 (s, 3) ; 1.90 (m, 3) ; 2.07 (dd, 1, J = 7, 5) ; 3.64 (td, 2, J = 10, 0.5), 4.20 (m, 1) ; 4.74 (dd, 2, J = 28.7, 7.5); 5.29 (d, 1, J = 11.2) ; 6.23 (dm, 1, J = 11.2).

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