Stereospecific Total Synthesis of Amberketal and a Homologue

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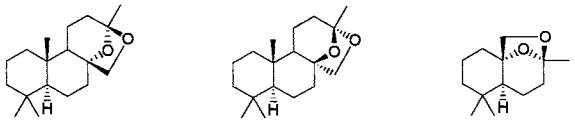
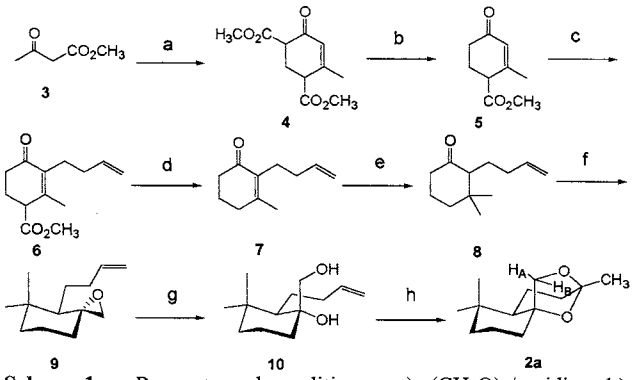
Amberketal (**1a**) and acetal homologue (**2a**) have been synthesised from a commercially available methyl acetoacetate involving palladium catalysed cyclisation as a key step.

There is a constant interest in ambergris derivatives as demonstrated by numberous recent publications on this topic.[1] However, most of this activity is concentrated on Ambrox and its racemate,[2-6] little attention has been paid to amberketal (**1a**) and epi-8-amberketal (**1b**), the two cyclic ketals which occurs in small amounts in the bark of the western white pine (*Pinus montcola*).[7] The synthesis of both **1a** and **1b** which have been reported in the literatures appeared to be a partial synthesis starting from naturally occuring compounds such as sclareol and manool via a common keto alkene intermediate.[8-13]



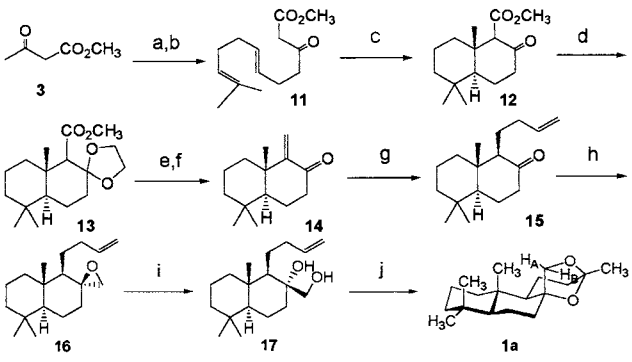
1a **1b** **2a**

It has been established by us that the bicyclic ketal of this type can be obtained by palladium catalysed cyclization of the corresponding diols.[14] We report herein the first stereo-specific total synthesis of amberketal (**1a**), and the acetal homologue **2a** from methyl acetoacetate which is outlined in Schemes 1 and 2. The key steps of this approach are the stereo-specific formation of epoxides **9** and **16** and the palladium catalysed cyclization of the corresponding diols **10** and **17** to (**2a**) and (**1a**), respectively.



Scheme 1. Reagents and conditions : a) $(CH_2O)_n$/pyridine, b) CH_3ONa, CH_3OH, c) NaH, toluene, 4-bromo-1-butene, d) KOH, CH_3OH, e) CH_3MgI, CuBr.S($CH_3)_2$, $(C_2H_5)_2O$, f) NaH, DMSO, $(CH_3)_3SO^+I^-$, g) aq.H_2SO_4, THF, h) $PdCl_2$, $CuCl_2$, O_2, DME, 65 °C.

Hagemann's ester (**5**) was prepared in two steps from methyl acetoacetate (**3**) according to the method described by Rouault and Smith.[15] We were able to obtain the butenyl keto ester **6** in 93% yield by conducting the alkylation in toluene using sodium hydride to prepare the enolate. The carboxylate salt, prepared in situ by heating keto ester **6** with methanolic potassium hydroxide for 24 h gave dienone **7** [16] in about 50% yield. The conjugate addition of the methyl group to the unreactive α,β-disubstituted dienone **7** was accomplished by employing Grignard reagent and cuprous bromide dimethylsulfide complex at -78 °C to give ketone **8** (94%). The reactions of cyclic ketones with trimethyl oxosulphonium iodide to give epoxides are frequently stereospecific.[17] Attack of the ylide occurs from the less hindered side of the molecule and tends to form an equatorial carbon-carbon bond. Thus, epoxidation of ketone **8** with trimethyl oxosulphonium iodide (prepared from dimethylsulphoxide and methyl iodide) and sodium hydride in anhydrous dimethylsulphoxide at 50-55 °C gave epoxide **9** (91%) The NMR spectrum of **9** showed only one set of epoxy methylene protons as an AB double doublet at δ 2.53 (J = 5.0 Hz) and 2.58 (J = 5.0 Hz). In addition, one of these protons has a long-range coupling (J =1.0 Hz) with a proton in the cyclohexane ring. The NMR spectra indicate that nucleophilic attack of the ylide occured from the less hindered side of the molecule to give the epoxide **9**. Hydrolysis of the epoxide **9** in aqueous sulphuric acid gave the diol **10** in 44% yield. Cyclization of the diol **10** under Wacker type conditions[18] provided ketal **2a** in 55% yield. GLC analysis of the ketal showed that it was a single isomer and its NMR spectrum showed it to be amberketal (**2a**). The signal due to H_A was observed as a doublet at δ 4.25 (J = 7.5 Hz) as well as that of H_B at δ 3.39 (J = 7.5 Hz). These are in agreement with that reported by Ohloff whereas in the case of its isomer, H_A and H_B appeared as double doublet at δ 3.22 (J = 7.0 Hz) and 3.69 (J = 7.0 Hz).[19] In addition, the assignment of this structure was also based on NOE data. Irradiation of the axial methyl proton at δ 0.86 caused enhancement of the signal of H_A (δ 4.25).



Scheme 2. Reagents and Conditions: a) NaH/THF, HMPA, 0 °C; b) *n*-BuLi, geranyl bromide; c) $SnCl_4/CH_2Cl_2$; d) $(CH_2OH)_2$, *p*TsOH, toluene; e) $LiAlH_4$, ether; f) *p*TsOH, C_2H_5OH; g) $TiCl_4$, CH_2Cl_2, allyltrimethylsilane; h) NaH, $(CH_3)_3SO^+I^-$, DMSO; i) aq.H_2SO_4,THF; j) $PdCl_2/O_2$, DME, 65 °C

Cyclic ketoester **12** was prepared in two steps according to the method described by White.[20] Alkylation of the dianion derived from methyl acetoacetate with geranyl bromide afforded ketoester **11** (70%). Lewis acid catalysed cyclization of **11** using 6 mole equivalents of stannic chloride in methylene chloride gave a single cyclic product **12** (45%) after chromatographic purification. Ketalization of **12** using excess ethylene glycol and a catalytic amount of *p*-toluene sulfonic acid in benzene afforded bicyclic ketal ester **13** (94%) after crystalzation from dry hexane. Conversion of **13** to the exo-methylene ketone **14** was accomplished by $LiAlH_4$ reduction and subsequently acid deketalization and dehydration. After exploring a variety of conditions for the Michael addition to **14** in methylene chloride with 3 mole equivalents of allyltrimethylsilane and titanium tetrachloride (Sakurai reaction),[22] it was found that exposure of **14** at -55 °C gave the product **15** (42%). Epoxidation of **15** with trimethyl oxo- sulphonium iodide afforded epoxide **16** (68%). The NMR spectrum of epoxide **16** showed only one set of epoxy methylene protons as two doublets at δ 2.40 (J = 5.0 Hz) and 2.53(J = 5.0 Hz) which indicated that only one isomer of the epoxy compound was obtained from the reaction.

The configuration of the epoxy moiety was established through its hydrolysis with acid to diol **17** then palladium catalysed cyclisation to give amberketal (**1a**). The NMR spectrum of **1a** showed the signal due to H_A as a doublet at δ 4.21 (J = 7.0 Hz) and H_B as a doublet at δ 3.36 (J = 7.0 Hz). These are in agreement with data reported by Scheidegger whereas in the case of the its isomer, H_A and H_B appeared as two doublet at δ 3.31 and 3.37.[12]

In conclusion the first total stereoselective syntheses of amberketal (**1a**) and homologue (**2a**) have been completed. The overall yields for 10 and 8 steps processes were 1.2% and 14.8%, respectively. Stereospecific addition of **15** and **8** by acid hydrolysis of the derived epoxides **16** and **9** gave the respective diols **17** and **10**. Stereospecific cyclization of **17** and **10** using the Wacker process afforded **1a** and **2a,** respectively.

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