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SYNTHESIS OF AMBRACETAL AND EPI-8-AMBRACETAL

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Summary : A protection-deprotection sequence is used in order to control the formation of the exocyclic double bond of compound **10** which is further used for the synthesis of the title compounds

We have recently reported an efficient synthesis of ambracetal from sclareol (1) However when compared to the synthetic scheme involving manool **14** as starting material (2,3) the main problem encountered in our approach was the elimination of the C-8 tertiary acetate of **3**, so as to form exclusively the exomethylene group of **10** This reaction turned out to be difficult to reproduce and to scale up, and these problems could not be solved by carrying out the elimination on the corresponding alcohol **4** We report here the preparation of ambracetal **11** and epi-8-ambracetal **13** in a more reliable and reproducible way The use of an ethylene cetal as a protective group of the C-13 carbonyl as in **5**, was required The success of this scheme relies on i) the efficient preparation of **5** , ii) the chemioselective epoxidation of the trisubstituted double bond of **8** Ethyleneacetal **5** can be prepared in 96 % yield (on 3g scale) by percolating a solution of ethylene glycol, THF and ketoacetate **3** (5ml/5ml/1mM) on a column packed with Amberlyst 15 resin mixed with molecular sieves Reduction of **5** with $LiAlH_4$ gives a quantitative yield of alcohol **6** Treatment of the latter by $POCl_3$/Py yields a 87/13 mixture of **7** and **8** The epoxidation of this mixture with MCPBA, exclusively occurs on the trisubstituted double bond of **8**, to yield **9** which can now be easily separated by column chromatography from the unreacted olefin **7** Compound **10** is then obtained by hydrolysis of **7**, in presence of PPTS Ambracetal **11** and epi-8-ambracetal **13** are then prepared by known procedures (4,5) with respectively 38 % and 30 % overall yields from sclareol The overall yields we observe, compete well with those observed when manool **14** (10 % overall yield in a 2/1 mixture of **11** and **13**) is used as a starting material (2,3) Although the protection-deprotection steps obviously lengthen the synthetic scheme, we have not been able to avoid them

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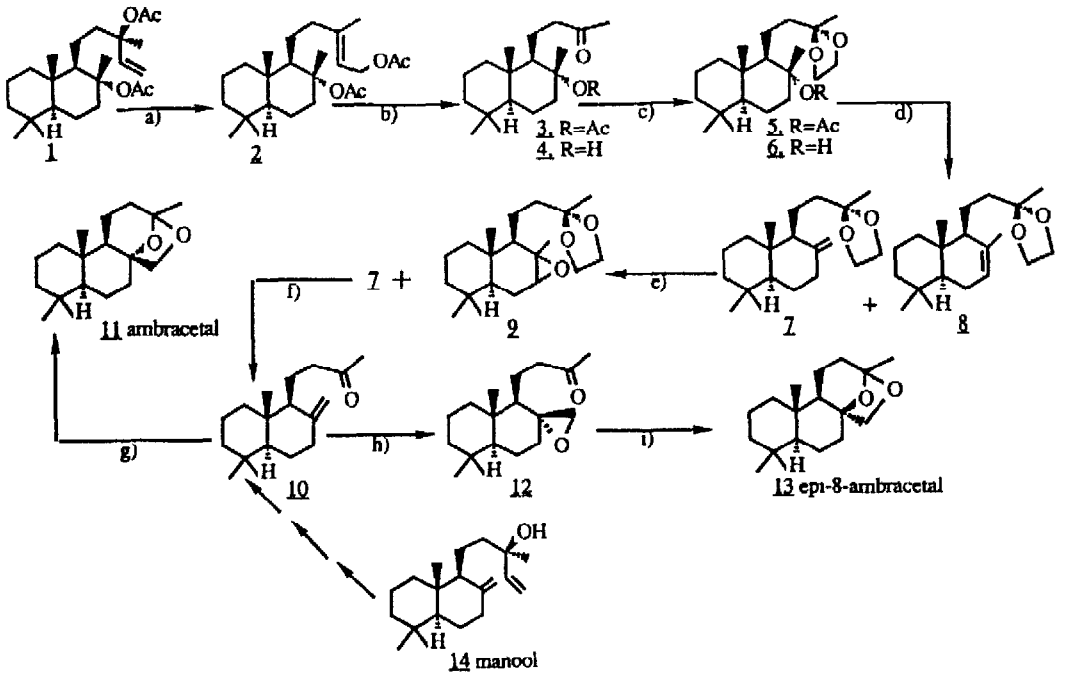

a) $PdCl_2(CH_3CN)_2$, THF, rt, 2h, 87 % , b) O_3, MeOH, CH_2Cl_2, $(CH3)_2S$, -70°C, 24h, 90% , c) 1°) THF, ethylene glycol, Amberlyst 15, molecular sieves, , 95 % , 2°) $LiAlH_4$, Et_2O d) $POCl_3$, Pyridine, CH_2Cl_2, -30°C, 48 h, 89 % , e) MCPBA 0,35 eq , CH_2Cl_2, Na_2CO_3 0 5 M, rt, 1 H, 78 % f) Acetone, PPTS, reflux, 3h, 98%, g) catalytic OsO_4, trimethyl amine oxide dihydrate, tBuOH, Pyridine, reflux, 6 h, 90 % , h) MCPBA, CH_2Cl_2, Na_2CO_3, 0 5 M, 3h, rt, 90 % , i) CH_2Cl_2, PPTS, reflux, 3 h, 90 %

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5 - All the compounds reported herein have been identified to known structures by the usual spectroscopic techniques except 7 which is new and has been fully characterised by RMN ^{13}C, ^{1}H, IR, a correct centesimal analysis have also been obtained Compound 9 has been described by Cambie, Aust. J Chem, 1990, 43, 1151

7, RMN ^{13}C ($CDCl_3$) 148 6 (s), 110 4 (s), 106 4 (t), 64 6 (t), 56 9 (d), 55 5 (d), 42 2 (t), 39 7 (s), 39 1 (t), 38 3 (t), 37 9 (t), 33 6 (s), 33.5 (t), 24 4 (t), 23 8 (q), 21 7 (q), 19 4 (t), 17 9 (t), 14 4 (q) RMN ^{1}H ($CDCl_3$) 0 75 (s,3H), 0 87 (s,3H), 0 94 (s,3H), 1.39 (s,3H), 4 0 (s,4H), 4 6 (s,1H), 4 9(s,1H) ,

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