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A New Total Synthesis of (±)-Norprezizanone[1]

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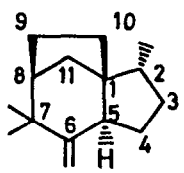
(Key words: Cycloaddition; stereospecific 1,4-addition; sesquiterpene synthesis)

Summary: Acid catalyzed rearrangement of *endo* 1-methoxytricyclo[6.2.2.$0^{3,8}$]dodec-2-en-10-ol **8c** afforded the ketone **9** which has been transformed into (±)-norprezizanone **19** thus completing a formal synthesis of (±)-zizaene. A key step in this strategy is a stereospecific 1,4-addition of a methyl group.

Zizaene **1**, a tricyclic sesquiterpene, has been isolated[2] from vetiver oil, *Vetiveria zizanoides* (L.) Nash and possesses the novel tricyclo[6.2.1.$0^{1,5}$]undecane skeleton. Prezizaene **2** and prezizanol **3** were isolated from the essential oil of *Eremophila georgei* Diels by Ghisalberti and coworkers[3]. A number of syntheses of zizaene and its congeners have been reported[4]. We have earlier prepared[5] the Coate's ketone[4b] **6**, by the acid catalyzed rearrangement of *endo* 7-methoxy-2-methyltricyclo[5.2.2.$0^{1,5}$]undec-5-en-8-ol **4** into 2-methyltricyclo[6.2.1.$0^{1,5}$]undec-5-en-7-one **5**, followed by subsequent transformations. Although the conversion of



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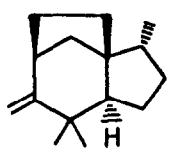

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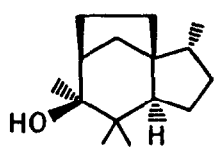

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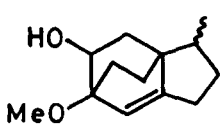

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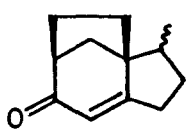

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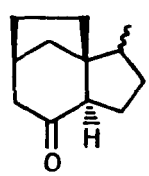

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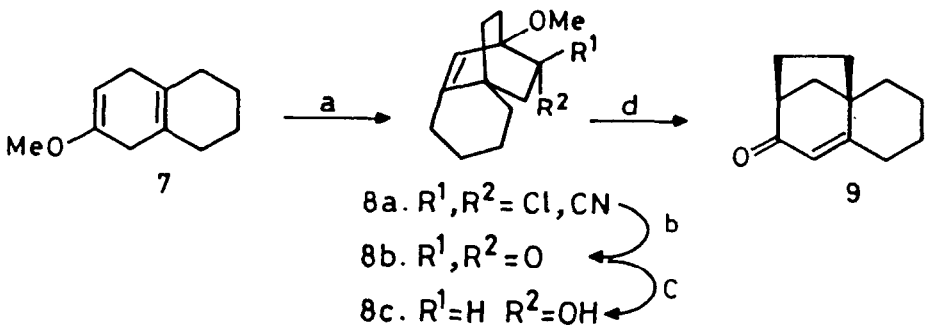
the ketones, **5** and **6** into an epimeric mixture of zizaene has been achieved[6], separation of these C-2 epimers was a difficult problem. We now report a stereospecific synthesis of (±)-norprezizanone **19**, an intermediate which has been transformed into zizaene **1**, prezizaene **2** and prezizanol **3**.

The adduct **8a**, obtained by refluxing the diene **7** with α-chloroacrylonitrile in benzene, afforded the ketone **8b** on hydrolysis[7]. Reduction of **8b** with DIBAL-H gave the *endo*-alcohol **8c** which was smoothly rearranged to the tricyclic α,β-unsaturated ketone **9** with $BF_3.OEt_2$ in benzene.

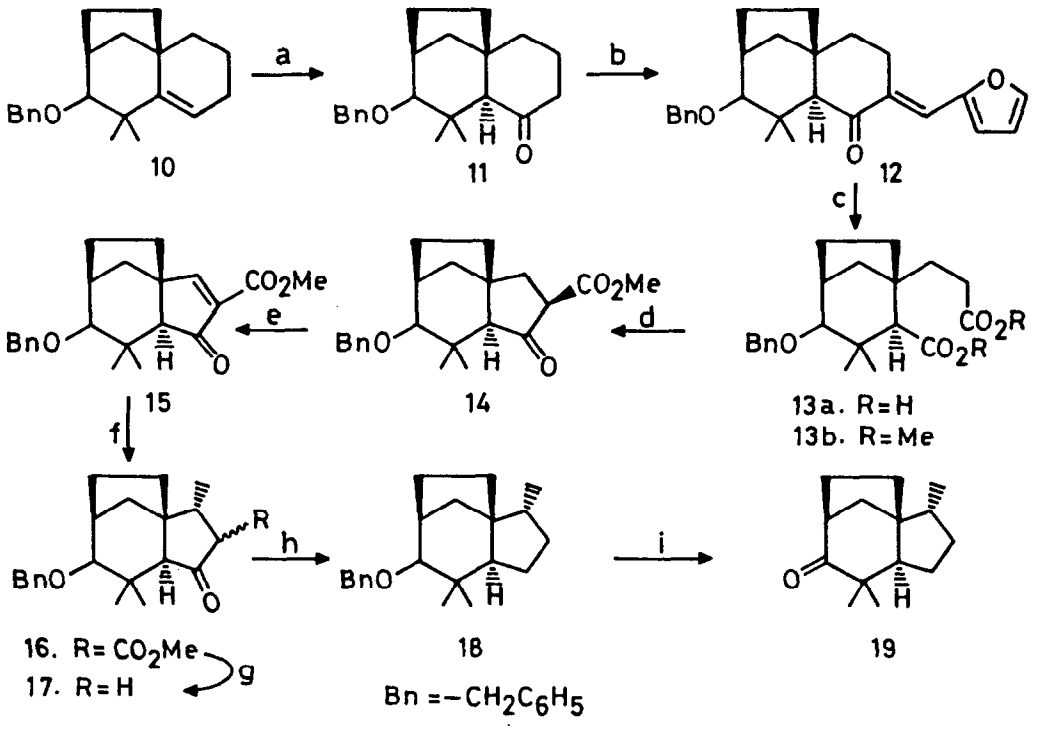
Methylation of **9** with MeI/KO^{t}Bu/^{t}BuOH afforded the ketone, which was reduced with sodium borohydride and the resulting alcohol was benzylated to yield the compound **10**. Hydroboration of **10** gave the alcohol which was oxidized to the ketone **11**. The furfurylidine derivative **12** of **11** was subjected to ozonolysis, followed by an oxidative work up to yield the dicarboxylic acid **13a**. The diester **13b** afforded the β-ketoester **14** on Dieckmann cyclisation.



Reagents & Conditions : a) CH_2=C(Cl)CN, C_6H_6, reflux, 20h, 95%; b) 30% aq.KOH, DMSO, 65°C, 48h, 60%; c) DIBAL-H, THF, -78°C → r.t., 4h, 92%; d) $BF_3.OEt_2$, C_6H_6, reflux, 17h, 86%.

Reaction of **14** with phenylselenylchloride[8] followed by oxidation with hydrogen peroxide resulted in the unsaturated keto-ester **15**. Addition[9] of dimethylcopper lithium to the keto-ester **15** at 0°C gave a mixture (1:1) of C-2 epimeric compounds **16**. However when the reaction was performed at -100°C, the addition of methyl group occurred stereospecifically resulting in a single isomer **16**. The stereochemistry of the methyl group appears to be α-equatorial as the addition of the methyl group is favoured from the least hindered side.

Decarboxylation[10] of **16** under mild conditions afforded the ketone **17**. During this reaction, no trace of epimerization at C-5 was observed. Wolff-Kishner reduction of **17** led to a mixture of compounds, presumably due to epimerization at C-5. However reduction of **17** with sodium borohydride gave a mixture of alcohols, whose xanthate ester was deoxygenated[11] with tributyltin hydride and AIBN to yield the **18** as a single product. Hydrogenolysis of **18** followed by oxidation afforded (±)-norprezizanone **19** in good yield, identical with the authentic spectrum, kindly provided by Prof. Kenji Mori.



Reagents & Conditions: a) [i] BH_3,THF,24h,H_2O_2,NaOH; [ii] PCC/CH_2Cl_2,rt,1h,70%; b) NaOH/Furfural, 0°C → rt.,100%; c) [i]O_3/EtOAc,-78°C; [ii] H_2O_2/HOAc,H^+; [iii] CH_2N_2,67%; d) KO^{t}Bu/C_6H_6,reflux, 16h,77%; e) NaH/PhSeCl/H_2O_2,THF,88%; f) Me_2CuLi, Et_2O,-100°C,89%; g) DABCO/o-Xylene,95°C,8h, 84%; h) [i] DIBAL-H/THF,-78°C → rt.; [ii] NaH/CS_2/MeI,THF,reflux; [iii] ^{n}Bu$_3$SnH/AIBN/Toluene,reflux, 8h,88%; i) [i] Pd-C/H_2/EtOH; [ii] PDC/CH_2Cl_2,1h,94%.

(±)-Norprezizanone **19** has been converted into zizaene[2c,12]**1**, prezizaene[4c]**2** and prezizanol **3**, thus completing a formal synthesis of these sesquiterpenes.

In conclusion an efficient method for the synthesis of the tricyclic sesquiterpenes of the zizaene type is described from 1-methoxytricyclo[6.2.2.$0^{3,8}$]dodec-6-en-8-one, readily obtained from the cycloaddition of 6-methoxy-1,2,3,4,5,8-hexahydronaphthalene and α-chloroacrylonitrile.

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