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A FIRST TOTAL SYNTHESIS OF GERMACRONE BY INTRAMOLECULAR ALKYLATION OF PROTECTED CYANOHYDRIN

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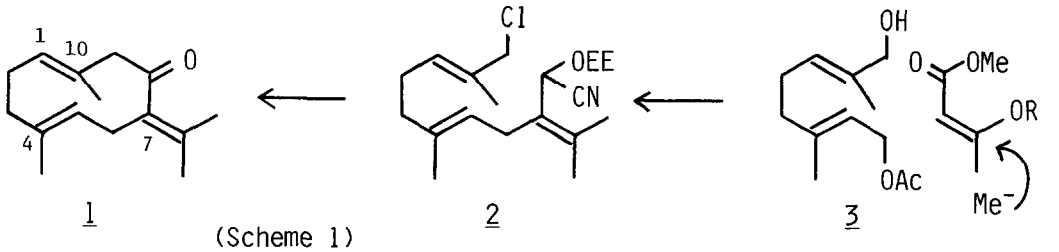
Summary: A total synthesis of Germacrone by the intramolecular alkylation of a carbanion generated from protected cyanohydrin is presented.

(*E*,*E*)-Germacra-1(10),4,7(11)trien-8-one (*E*,*E*-germacrone) (1) was first isolated from the essential oil of Bulgarian "zdravets" (Geranium macrorhizum L.) by Wienhaus and Scholz[1] and its structure was assigned by Sorm.[2] Transannular reactions,[3] epoxidation,[4] and photoisomerization[5] of germacrone (1) were well studied in connection with sesquiterpene biogenesis, but so far the synthetic study of 1 has not been reported. Germacrone has the labile (*E*,*E*)-1,5-cyclodecadiene system and β,γ-unsaturated ketone. The presence of these two labile groups in the strained ten-membered ring causes various reactions. For example, the thermal treatment of 1 affords the monocyclic sesquiterpene β-elemenone via Cope rearrangements.[3a] Base treatment results in an isomerization of C(1,10) double bond to provide isogermacrone.[6] Acid treatment gives the bicyclic selinane type sesquiterpenes.[3b] Thus the stereoselective elaboration of the labile (*E*,*E*)-1,5-cyclodecadiene system and β,γ-unsaturated ketone and an efficient cyclization are the major problems to be solved in the synthesis of germacrone.

Recently we have reported a general synthetic method for the preparation of (*E*,*E*)-2,6-cyclodecadienones based on intramolecular carbon-carbon bond formation.[7] We describe herein the first total synthesis of germacrone by intramolecular alkylation of a carbanion generated from protected cyanohydrin. In our synthetic plan (Scheme 1), 1,5-diene fragment 3 was prepared from geranyl acetate

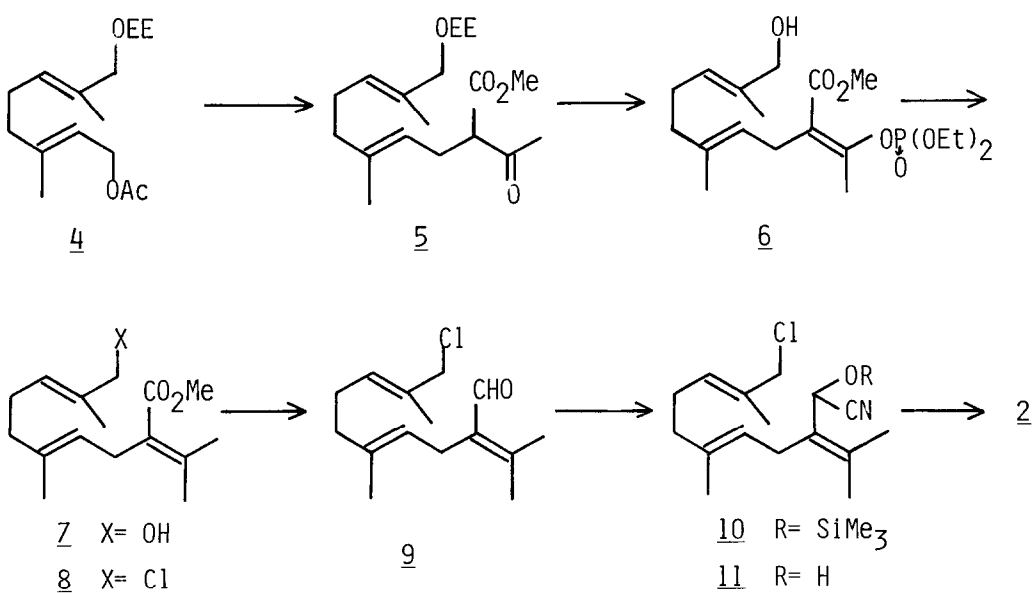


1 2 3

(Scheme 1)

and the exocyclic enone moiety was constructed from methyl acetoacetate and lithium dimethylcuprate. The attachment of methyl acetoacetate to 3 and the cyclization of 2 were carried out by palladium-catalyzed allylation and the intramolecular alkylation of carbanion generated from 2 with sodium bis(trimethylsilyl)amide, respectively, with retention of olefin geometry.

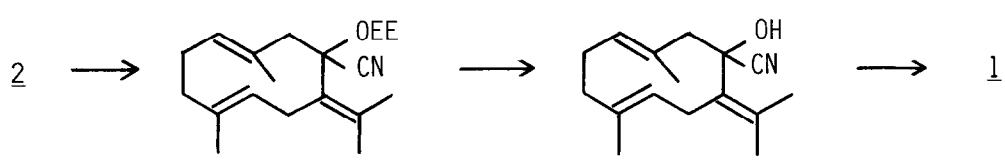
The key intermediate 2 was prepared from the allyl alcohol 3 as outlined in Scheme 2. The protection of the alcohol 3, obtained from the geranyl acetate by the method previously reported,[7] with ethyl vinyl ether gave the allyl acetate 4. The palladium-catalyzed alkylation[8] of methyl acetoacetate with 4 was carried out in the following way. A mixture of 4, 2 mol% of palladium acetate, 8 mol% of triphenylphosphine, and 3.5 equiv. of sodium salt of methyl acetoacetate was refluxed in THF (20 mL) for 5 hours to give the acetoacetate derivative 5 in 65% yield [NMR (CCl_4): δ 1.61 (br s, 6H, Me), 2.13 (s, 3H, Me), 3.67 (s, 3H, OMe); IR: 1745 and 1720 cm^{-1}]. The acetoacetate moiety was converted to the conjugated ester 7 in two steps. Deprotonation of 5 with sodium hydride in dry ether at 0°C and reaction of the resultant enolate with 3 equiv. of diethyl chlorophosphate gave the enol phosphate 6 in 95% yield [NMR (CCl_4): δ 1.60 (br s, 3H, Me), 1.64 (br s, 3H, Me), 3.67 (s, 3H, OMe); IR 3450 and 1725 cm^{-1}]. A conjugate addition of lithium dimethylcuprate to 6 and elimination of the phosphate group[9] at -10°C in dry ether gave the isopropylidene ether 7 in 70% yield [NMR (CCl_4): δ 1.61 (br s, 6H, Me), 1.81 (s, 3H, Me), 1.94 (s, 3H, Me), 3.66 (s, 3H, OMe); IR: 3400 and 1710 cm^{-1}; Mass M^+=266].



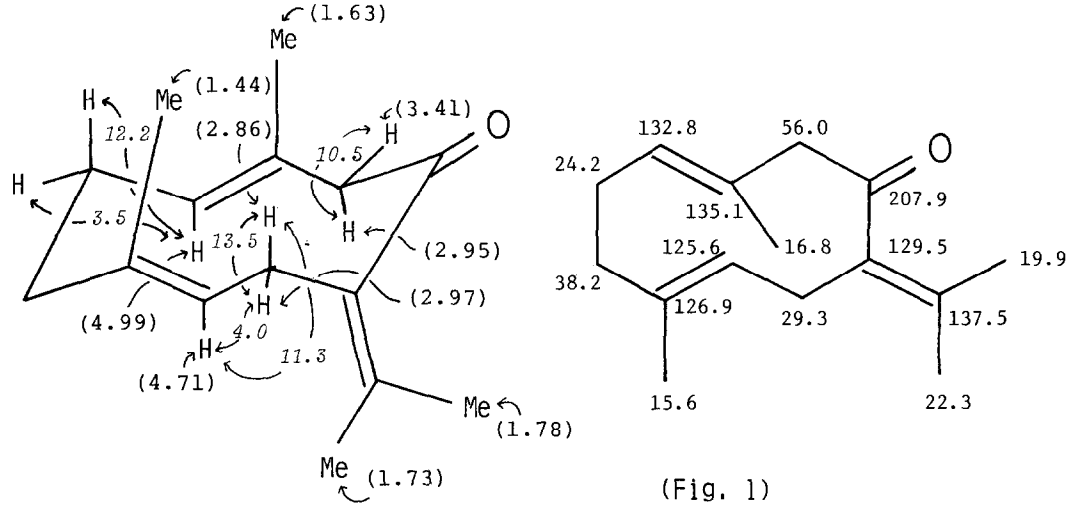
(Scheme 2)

The allylic chlorination of 7 with 2 equiv. of triphenylphosphine in refluxing carbon tetrachloride for 12 hours gave the allyl chloride 8 in 90% yield. The ester 8 was converted to the aldehyde 9 in two steps. The reduction of 8 with 2 equiv. of diisobutylaluminium hydride in THF at -40°C to the allyl alcohol and the oxidation of the resultant alcohol with manganese dioxide in *n*-hexane at room temperature gave the aldehyde 9 in 56% overall yield {NMR (CCl_4): δ 1.70 (br s, 6H, Me), 1.95 (s, 3H, Me), 2.20 (s, 3H, Me), 10.13 (br s, 1H, aldehyde H); IR: 1760 cm^{-1}; Mass M^+=254}. The protected cyanohydrin formation of the aldehyde 9 was carried out in the following way. The enal 9 was treated for one hour at 0°C under nitrogen atmosphere with 2 equiv. of trimethylsilyl cyanide in the presence of a catalytic amount of KCN/18-crown-6 to give the cyanohydrin trimethylsilyl ether 10. The removal of trimethylsilyl group with trimethylbenzylammonium fluoride in THF and H_2O at 0°C and the protection of the resultant cyanohydrin 11 with ethyl vinyl ether gave the protected cyanohydrin 2 in 85% overall yield {NMR (CCl_4): δ 1.67 (br s, 6H, Me), 1.72 (s, 3H, Me), 1.79 (s, 3H, Me); IR: 2950 cm^{-1}}.

The cyclization of the protected cyanohydrin 2 was carried out in the following way. The protected cyanohydrin 2 (300 mg, 0.85 mmol) in THF (10 mL) was added, using a Hershberg dropping funnel, over 30 min at 56°C under nitrogen atmosphere to a solution of sodium bis(trimethylsilyl)amide (4.25 mmol) in THF (10 mL). The reaction mixture was quenched with cold sat. aq. ammonium chloride solution. The cyclized product 12 was isolated in 79% yield after column chromatografic purification. Acid treatment of the cyclized product 12 with *p*-toluenesulfonic acid in methanol at 0°C for one hour gave the cyanohydrin 13, which was dissolved in ether and shaken vigorously for 20 min with 2% aqueous sodium hydroxide in a separatory funnel. Germacrone (1) was isolated in 84% yield after column chromatografic purification {IR: 1680 cm^{-1}; mp 51-52°C (from $MeOH/H_2O$); High-resolution mass spectrum calcd. for $C_{15}H_{22}O$; m/e 218.1671. Found; m/e 218.1675}. The structure of synthetic germacrone (1) was confirmed by the ^{1}H-NMR (400 MHz) and ^{13}C-NMR spectrum (Fig. 1).



12 13



(Fig. 1)

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