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A GENERAL SYNTHETIC METHOD FOR 2,6-CYCLODECADIENONE SYSTEM BY INTRAMOLECULAR ALKYLATION OF PROTECTED CYANOHYDRINS

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Summary: 2,6-Dimethyl-(*E*,*E*)-2,6-cyclodecadienone (12), 3,7-dimethyl-(*E*,*E*)-2,6-cyclodecadienone (15), 3,7-dimethyl-(*Z*,*E*)-2,6-cyclodecadienone (18) were synthesized by intramolecular alkylation of unsaturated cyanohydrin ethers.

The synthesis of medium and large rings by direct cyclization methodology continnues to be a major challenge. Application of the cyanohydrin methodology to large rings has previously been demonstrated in this laboratory.[1] This paper extends this methodology to the class of medium sized rings. Such a development is cleary significant since the chemistry of the medium rings is significantly different from that of the large or normal rings.

The germacranes are well known as typical ten-membered sesquiterpenes.[2] Most of germacranes have the chemically and thermally labile (*E*,*E*)-1,5-cyclodecadiene system possessing oxidized carbons at various positions as shown in Figure 1. Thus an efficient ring formation and the stereoselective introduction of 1,5-diene are required for syntheses of ten-membered sesquiterpenes However, previous approaches to ten-membered carbocycles involve indirect methods[3] such as ring-cleavage of bi- or tricyclic compounds[4] and ring expansions based on Cope,[5] oxy-Cope,[6] and Cope-Claisen[7] rearrangements. Anion-induced cyclization of epoxy sulfides is also reported,[8] but the isomerization of double bonds takes place. Thus the acceptable synthetic methods for (*E*,*E*)-1,5-cyclodecadiene are few. We wish to report here a general synthetic method for (*E*,*E*)-2,6-cyclodecadienones by intramolecular alkylation of cyanohydrin ethers.[9]

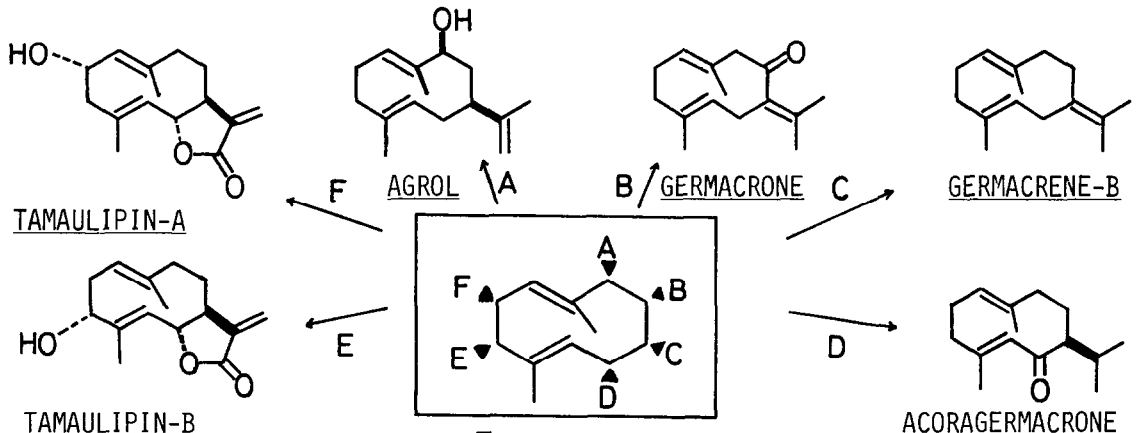
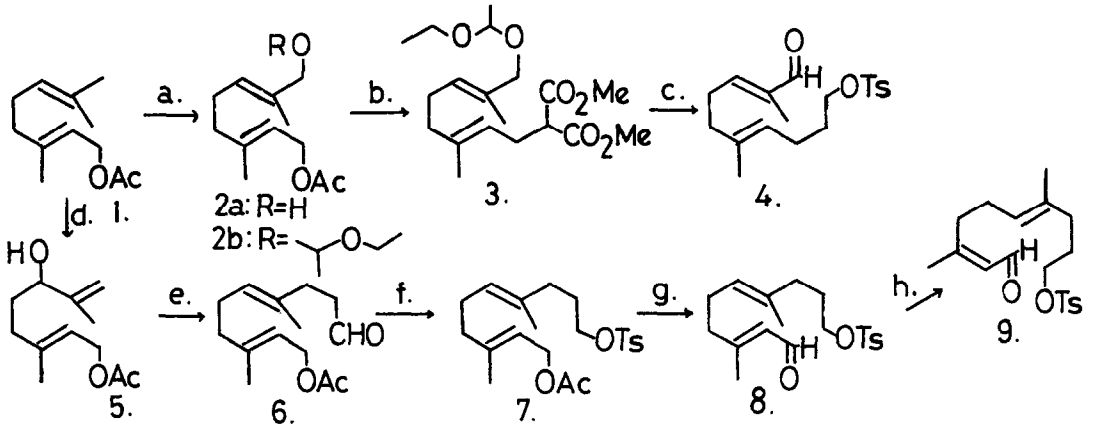


Figure 1

This cyclization has the following characteristic features. (1) High yields of cyclization without undergoing intermolecular alkylation. (2) The carbanion acts only as acyl anion equivalent without the isomerization of the double bonds. (3) It is possible to introduce the carbonyl group at various positions by selecting cyclization positions.

The (*E*)-enals 4 and 8 were prepared stereoselectively starting from geranyl acetate 1 as outlined in Scheme 1. The allyl alcohol 2a was obtained by the method previously reported.[10] The palladium catalyzed allylation[11] of dimethyl malonate with allyl acetate 2b gave the diester 3 in 58% yield with retention of olefin geometry. The conversion of malonate moiety to the tosylate, hydrolysis of 1-ethoxyethoxy group, and oxidation of the resulting alcohol gave the pure (*E*)-enal 4 in 34% overall yield from 3. While the enal 8 was obtained stereoselectively in the following way. The Claisen rearrangement of the vinyl ether of 5 at 180°C gave the aldehyde 6 in 85% yield. The reduction of the aldehyde and the tosylation gave 7 in 80% yield. Hydrolysis of the acetyl group and oxidation of the allyl alcohol gave the (*E*)-enal 8 in 67% yield. The (*Z*)-enal 9 was separated from a mixture of 8 and 9 (6 : 4), obtained by the acid-promoted isomerization of the (*E*)-enal 8. The pure enals 4, 8, and 9 were transformed into the protected cyanohydrins 10, 13, and 16, respectively, without isomerization of the olefins in three steps (Me_3SiCN/18-crown-6,[12] $PhCH_2N^+Me_3F^-$, ethyl vinyl ether/H^+; 90% overall yield).

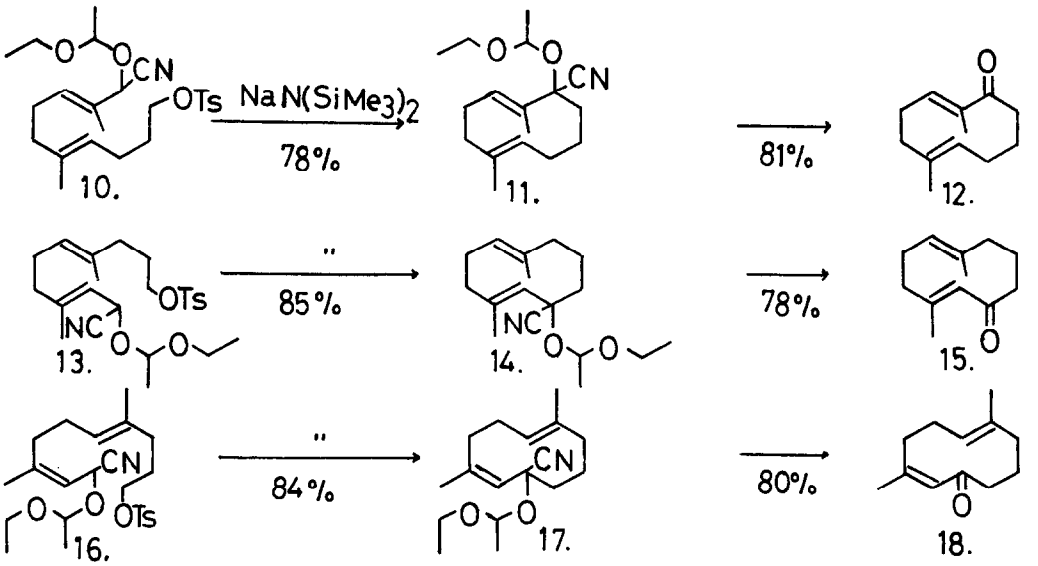


a) SeO_2/*t*-BuOOH; $NaBH_4$; CH_2=CHOEt/*p*-TsOH: b) $Pd(OAc)_2/PPh_3/NaCH(CO_2Me)_2$ in THF reflux, 16 h: c) NaI/HMPA/H_2O, 170°C; $LiAlH_4$; *p*-TsCl/Py.; *p*-TsOH/MeOH; PDC: d) NBS/H_2O; K_2CO_3/MeOH; *i*-Bu_3Al: e) CH_2=CHOEt/$Hg(OAc)_2$; 180°C: f) $NaBH_4$; *p*-TsCl/Py.: g) K_2CO_3/MeOH; MnO_2: h) *p*-TsOH in CH_2Cl_2, room temp., 3 h

Scheme 1

Cyclizations of 10, 13, and 16 were carried out in the following way (Scheme 2). The protected cyanohydrin (1 mmol) in THF (7 mL) was added, over 1 hour at 50-60°C under nitrogen atmosphere to sodium bis(trimethylsilyl)amide (5 mmol) in THF (7 mL). After usual work-up and short column chromatography, the cyclization products 11, 14, and 17 were obtained in 78, 85, and 84% yields respectively. TLC of each crude mixture showed the presence of only the cyclization product. The crude product 11 was converted to the enone 12 in 81% yield by acid treatment (PPTS/MeOH at

40°C for 30 min), followed by aqueous base treatment (2% aq NaOH/Et_2O at room temp for 5 – 10 min; Condition A). Even a trace of other isomers[13] could not be detected in the crude product 12[15] by NMR. The treatment of the crude product 14 with acid as above, followed by milder base treatment (1% aq $NaHCO_3$/Et_2O at room temp for 60 min; Condition B) gave only the enone 15[15] in 78% yield. It is noteworthy that under the condition A, a mixture of the enone 15 (60% yield) and 18[16] (25% yield) was obtained from 14. The crude product 17 was also converted to the pure (Z)-enone 18[15] in 80% yield under the condition B.



Scheme 2

We are actively investigating further application of this cyclization method to the syntheses of naturally occurring medium and large-membered terpenes.

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References and Notes:

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3) Cope rearrangement of 1,2-divinylcyclohexane to 1,5-cyclodecadiene is reversible. Oxy-Cope rearrangement of 1,2-divinylcyclohexenol usually gives (*Z*,*E*)-cyclodecadienone. In contrast, Cope-Claisen rearrangement leads to 1,6-cyclodecadiene.
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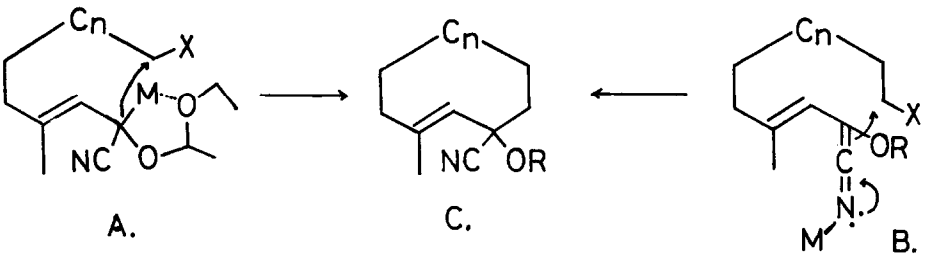
13) The regio-selective cyclization at α-position without ($E \leftrightarrow Z$) isomerization of double bond observed here (10 → 11, 13 → 14, 16 → 17) is tentatively thought to be a consequence of the metal chelating effect of the oxygen or the nitrogen atom as expressed by structures A or B.[14] Another reason is that placing an E double bond in eight membered ring (γ attack product) is highly improbable. Moreover the cyclization product C has no acidic proton, hence the isomerization of the unsaturated cyanohydrin ether does not occur.



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15) (E)-enone 12: IR(neat) 1680, 1620 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 5.80 (br t, J = 7.4 Hz, 1H), 4.59 (br t, J = 6.0 Hz, 1H), 1.70 (d, J = 1.0 Hz, 3H), 1.59 (br s, 3H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 208.4, 141.3, 139.4, 131.0, 130.6, 38.9, 38.6, 28.7, 25.2, 16.4, 14.0: Mass m/e 178; Anal. calcd. for $C_{12}H_{18}O$: C, 80.85, H, 10.18. Found. C, 80.12, H, 10.15.

(E)-enone 15: IR(neat) 1675, 1605 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 5.44 (br s, 1H), 4.78 (m, 1H), 1.89 (br s, 3H), 1.20 (br s, 3H); Mass m/e 178: HPLC retention time (Rt) 17.2-19.0 min (Silica gel; SI-60-5 μm, 7.5 o.d. × 550 mm, flow rate 4.8 mL/min, 5% ethyl acetate in n-hexane).

(Z)-enone 18: IR (neat) 1680, 1630 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 5.93 (br s, 1H), 4.88 (m, 1H), 1.76 (br s, 3H), 1.43 (br s, 3H); HPLC (Rt) 12.7-13.6 min.

16) The isomerization of the less stable (E)-enone 15 to the more stable (Z)-enone 18 with base treatment is known [see ref. 6) a)].

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