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AN EFFICIENT SYNTHETIC METHOD FOR MACROCYCLIC KETONES BY INTRAMOLECULAR ALKYLATION OF PROTECTED CYANOHYDRINS, AND ITS APPLICATION TO THE SYNTHESES OF MUSCONE AND EXALTONE

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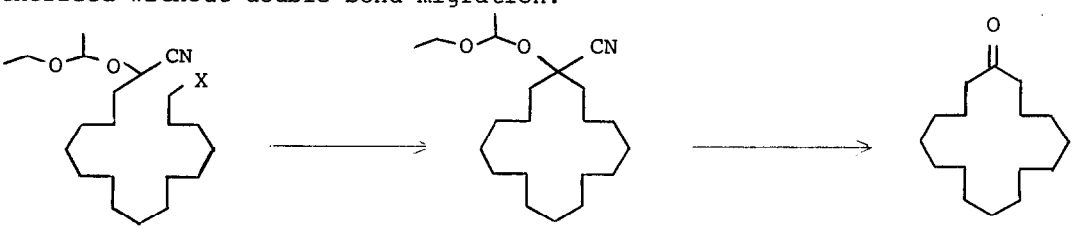
Summary: A simple synthetic method for macrocyclic ketones based on intramolecular alkylation of carbanion, generated from protected cyanohydrin is reported. Subsequent mild treatment with acid and base of the cyclized products leads to macrocyclic ketones in high yields. The reaction is rapid and irreversible, and hence required short reaction time. The method was successfully applied to the syntheses of cyclohexadecanone and *trans*-2-cyclopentadecenone as a precursor of (±)-muscone and exaltone.

A number of naturally occurring macrocyclic ketones are known. Civetone, muscone, and exaltone are representative macrocyclic ketones. An efficient construction of these macrocarbocycles is a target of active investigation in current organic chemistry.[1] Synthetic methods previously reported for the macrocyclic ketones are ring expansion[2] and intramolecular condensations such as aldol,[3] Dieckmann,[4] and acyloin.[5] More recently new approaches based on intramolecular Wittig reaction[6] and intramolecular acylation[7] have been reported. Some of these methods are quite efficient. However, in most of these methods, there remains one serious problem which is associated with lack of control of proton transfer or regioselective generation of carbanion, because carbonyl groups are present in molecules before and after the cyclization.

We have reported before an efficient method of macrolide formation based on intramolecular alkylation on ω-haloalkyl phenylthioacetates, and the method was successfully applied to the total syntheses of recifeiolide and 9-decanolide.[8] Also lasiodiplodin[9] and zearalenone[10] were synthesized by the intramolecular alkylation of ω-haloalkyl 2-phenylthiomethyl-4,6-dimethoxybenzoate. In this paper we wish to report a simple and efficient method for macrocyclic ketones based on intramolecular alkylation of a carbanion generated from protected cyanohydrins 1.[11] The cyclized product 2 is converted in high yields to the macrocyclic ketone 3 by mild treatment with an acid and a base. The present method is superior to the previous ones in several respects. Only monocarbanion is generated from the cyanohydrins and the cyclized product is stable in base. Therefore the reaction is simple. Also the alkylation reaction proceeds rapidly. The cyclized product is neutral and hence the reaction is irreversible. Therefore, it is not necessary to

carry out the reaction under high dilution conditions. The reaction can be carried out in a short period of time simply by adding the protected cyanohydrin to a solution of sodium hexamethyldisilazane. The selection of sodium hexamethyldisilazane as a base is important. With this base, α,β-unsaturated ketones can be synthesized without double bond migration.

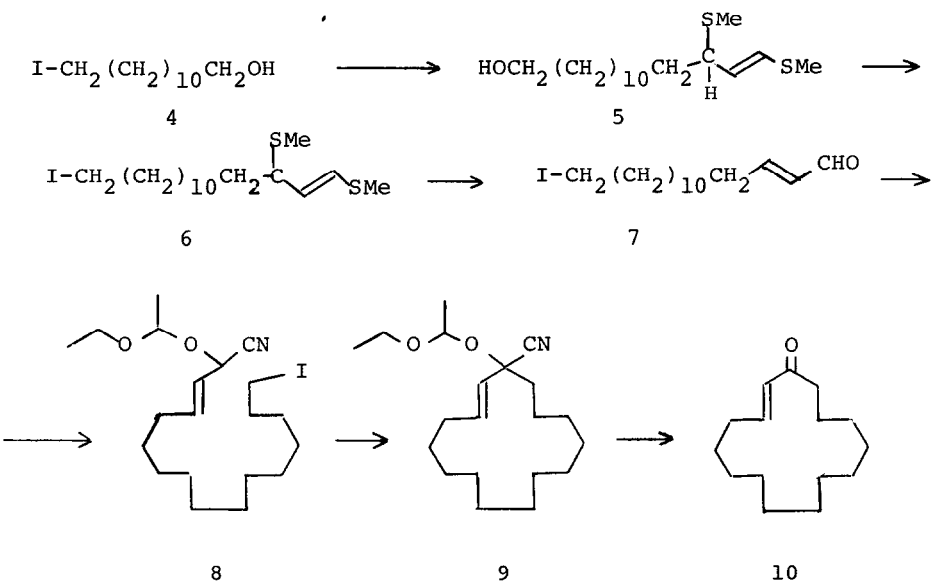


1 2 3

At first, the 16-membered ketone was synthesized. The protected cyanohydrin 1 was easily prepared from 16-iodohexadecanal ($NaHSO_3$/NaCN, then ethyl vinyl ether/H^+). The cyclization of 1 was carried out by the following way. The cyanohydrin 1 (200 mg, 0.43 mmol) in dry THF (7 mL) was added slowly over 2 h at 40°C under a nitrogen atmosphere to sodium hexamethyldisilazane (2.15 mmol) in dry THF (15 mL). The cyclized product 2 was isolated as an oil in 71% yield after chromatographic purification (silica gel) : NMR (CCl_4) δ 1.90-1.25 (m, 6 H, CH_3), 3.50 (q, J = 6.6 Hz, 2 H, OCH_2), 4.96 (q, J = 5.6 Hz, 1 H, OCHO). Removal of the protecting group (3N-HCl/THF, 0°C) generated the cyclohexadecanone cyanohydrin, which was dissolved in ether and washed vigorously with 5% NaOH solution in a separatory funnel. Cyclohexadecanone (3) was isolated as crystals in 85% overall yield from 2 after chromatographic purification: mp 66-67°C;[12] IR (film) 1712 cm^{-1}; NMR (CCl_4) δ 1.00-1.85 (m, 26 H, CH_2), 2.31 (t, J = 6.4 Hz, 4 H, CH_2CO); MS m/e 238 (M^+); Anal. Calcd for $C_{16}H_{30}O$, C, 80.61, H, 12.69; Found: C, 80.62; H, 12.93.

Then we prepared *trans*-2-cyclopentadecenone (10), as a precursor of (±)-muscone and exaltone. The alkylation (LDA, THF, -78°C) of 1,3-bis(methylthio)-2-methoxypropane[13] with 1.1 equiv. of ethyl vinyl ether addcut of 12-iodododecanol (4) and subsequent removal (3N-HCl, THF, 0°C) of the protecting group of alcohol gave 1,3-bis(methylthio)-15-hydroxy-1-pentadecene (5) in 90%: IR (film) 3320 and 2925 cm^{-1}; NMR (CCl_4) δ 1.91 (s, 3 H, SCH_3), 2.22 (s, 3 H, SCH_3), 3.17 (m, 1 H, allylic), 3.52 (m, 2 H, OCH_2), 4.85-5.20 (m, 1 H, olefinic), 6.00 (d, J = 14 Hz, 1 H, olefinic). The primary alcohol was converted into the iodide 6 (*p*-TsCl/pyridine, NaI/acetone, overall yield 90%) which was hydrolyzed with mercuric chloride (CH_3CN : H_2O = 8 : 1)[13] to give 15-iodo-2-pentadecenal (7): IR (film) 1690 cm^{-1}; NMR (CCl_4) δ 2.10-2.60 (m, 2 H, allylic), 3.13 (t, J = 6.5 Hz, 2 H, $-CH_2I$), 6.0 (dd, J = 15.6 Hz, J = 7.9 Hz, 1 H, olefinic), 6.80 (dt, J = 15.6 Hz, J = 6.4 Hz, 1 H, olefinic), 9.43 (d, J = 7.9 Hz, CHO). The enal 7 was treated for 2 h at 0°C with 3.0 equiv. of trimethylsilyl cyanide in the presence of a

catalytic amount of zinc iodide. Trimethylsilyl protecting group was changed to ethoxy ethyl ether (3N-HCl/THF at 0°C, 70% yield, then ethyl vinyl ether/H^+, 93% yield) to give the protected cyanohydrin 8: IR (film) 2910 cm^{-1}; NMR (CCl_4) δ 0.90-1.30 (m, 6 H, CH_3), 1.89-2.30 (m, 2 H, allylic), 3.15 (t, J = 6.4 Hz, 2 H, CH_2I), 3.30-3.80 (m, 2 H, CH_2O-), 4.5-5.06 (m, 2 H, -$OCHCH_3O$-, -OCH-CN), 5.15-6.30 (m, 2 H, olefinic). The protected cyanohydrin 8 (0.269 mmol in 4 mL of THF) was added over 1 h to a THF solution (9 mL) of sodium hexamethyldisilazane (1.34 mmol) at 40°C. The cyclized product 9 was obtained in 75% yield after chromatography, which was easily converted, as above, to 2-cyclopentadecenone (10): IR (film) 1692, 1664, 1622, and 980 cm^{-1}; NMR (CCl_4) δ 1.48-1.95 (m, 2 H, allylic), 2.00-2.55 (m, 2 H, -$COCH_2$), 6.10 (d, J =15.9 Hz, 1 H, olefinic), 6.68 (dt, J = 15.9 Hz, J = 6.4 Hz, olefinic); Ms m/e 222 (M^+). The trans configuration of the double bond was fully confirmed by the NMR spectrum. The conversion of 10 to muscone and exaltone is known.[6,14]



The results reported in this paper clearly indicate the usefulness and generality of the present method for the efficient preparation of macrocyclic ketones. The method is applicable not only to macrocyclic ketones, but also to medium-membered cyclic ketones. Also we have confirmed that the reaction tolerates the presence of ester group. We are actively investigating further application of this cyclization method to the syntheses of naturally occurring large and medium-membered cyclic ketones including sesquiterpenes and keto lactones.

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