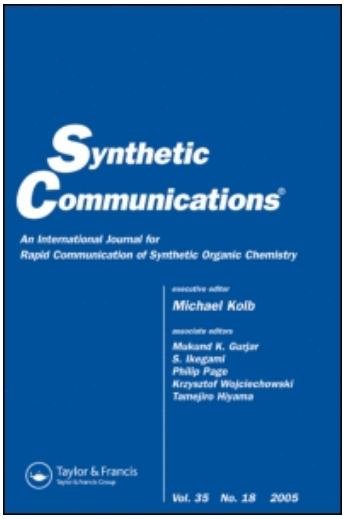

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Synthesis of Methyl-6-methyl Tricyclo[5.2.1.0^{2,6}]decan-9-one-2-carboxylate: Potential Intermediate to Isocomene and Cuprenolide

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SYNTHESIS OF METHYL-6-METHYL TRICYCLO[5.2.1.$0^{2,6}$]DECAN-9-ONE-2-CARBOXYLATE : POTENTIAL INTERMEDIATE TO ISOCOMENE AND CUPRENOLIDE

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ABSTRACT: A facile synthesis of methyl-6-methyl tricyclo [5.2.1.$0^{2,6}$]decan-9-one-2-carboxylate **7**, a potential intermediate to isocomene **6** and cuprenolide **8** is described.

Functionalised tricyclo[5.2.1.$0^{,2,6}$]decanes are attractive building blocks for the synthesis of natural products. Because of the strain associated with them, C-C bond cleavage is facile and leads to a variety of structural patterns.[1,2] Recently we have demonstrated[2] that C_2-C_6 bond cleavage in the tricyclo[5.2.1.$0^{2,6}$]-decene **2**, prepared from Diels-Alder reaction of the unsaturated anhydride **1** with cyclopentadiene (**Scheme 1**) has led to an easy access to otherwise difficultly accessible bridged eight-membered rings **3** present in taxanes.[3] We envisaged that the title keto-ester **7** would be an ideal intermediate to the sesquiterpene isocomene

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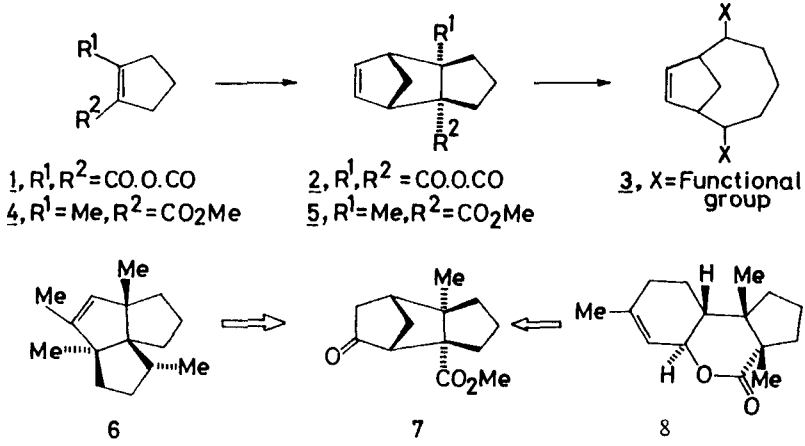
Scheme-1

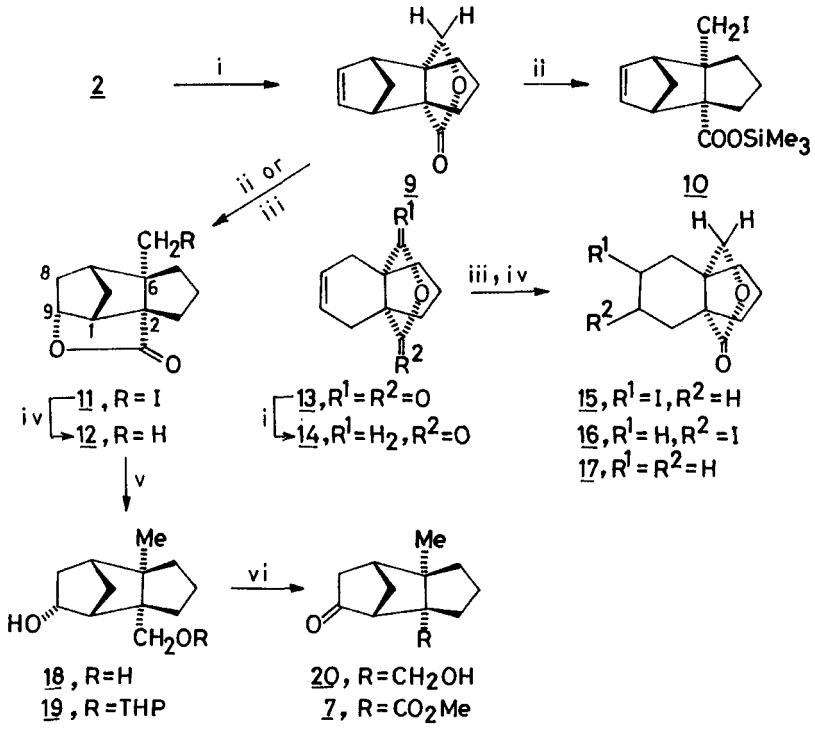


6.[1b] The COOMe group at C_2 and the carbon residue at C_1, after cleavage of the two carbon bridge in 7, could be employed to construct the third 5-membered ring. On the otherhand, the keto-ester 7, on reductive cleavage[2a,4] of the C_1-C_2 bond, may provide a stereoselective route to cuprenolide 8.[5] A retrosynthetic analysis depicts the adduct 5, derivable in principle from Diels-Alder reaction of the dienophile 4 with cyclopentadiene,, to be the right choice. However, the inefficiency of the unsaturated ester 4 towards Diels-Alder reaction precluded a direct synthesis of the ester 5. We here demonstrate that the unsaturated anhydride 1 can act as the dienophilic equivalent of the unsaturated ester 4 offering an easy access to the title keto-ester 7.

Results and Discussion

The tricyclic anhydride 2 was transformed to the known lactone 9[2c] through reduction with $NaHB_4$ in THF (**Scheme-2**). The lactone 9 was then treated with NaI-Me_3-SiCl[6] in acetonitrile with a view to obtain the iodo-carboxylate 10 which was expected to afford the desired

Scheme-2



Reagents : i, $NaBH_4$, THF; ii, NaI, TMSCl, CH_3CN; iii, HCl(g), NaI, CH_3CN, rt; iv, TBTH, AIBN(cat), C_6H_6, reflux; v, $LiAlH_4$, Et_2O; vi, a) Dihydropyran, PPTS, CH_2Cl_2; b) Swern Oxidation; c) PPTS, EtOH; d) Jones Oxidation; e) CH_2N_2, Et_2O.

ester 5 through C-I bond reduction. Surprisingly, the desired iodo-carboxylate 10 was not obtained. The only product m.p. 102°C, obtained in 87% yield from this reaction was assigned the iodo-lactone structure 11 based on spectral data. The appearance of a new lactone band in IR at 1770 cm^{-1} instead of IR absorption at 1755 cm^{-1} of the starting lactone 9 indicated the formation of a new

lactone. The absence of C_8,C_9 olefinic protons coupled with the presence of a two-proton quartet at δ 3.34 (J=8 Hz) for CH_2 of CH_2I and a one proton triplet at δ 4.80 (J=6 Hz) for C_9-H in ^1H NMR spectrum of the product suggested the structure of the new lactonic product as **11**. This structural assignment was further corroborated by its transformation to the lactone **12**. Thus, reduction of the iodo-lactone **11** with tributyltin hydride in refluxing benzene in presence of AIBN (cat) afforded the lactone **12**, m.p.84°C in 82% yield. In addition to a lactone band at 1770 cm^{-1}, the appearance of a quaternary Me at δ 1.06 and a broad triplet at δ 4.56 (J=7 Hz) for C_9-H in ^1H NMR of the reduction product is indicative of the structure **12**. The formation of the iodo-lactone **11** from the unsaturated lactone **9** could be rationalised by the trace amount of HCl present in TMSCl that initiated trans-lactonisation through protonation of the C_8,C_9 double bond. The trans-lactonisation was facilitated through nucleophilic attack by $I^{\ominus}$ on the lactone CH_2. In fact, the unsaturated lactone **9** underwent smooth trans-lactonisation to afford the same iodo-lactone **11** on treatment with NaI in CH_3CN in presence of dry HCl(g). The lactone **12**, in principile, should be available through lactonisation from the Diels-Alder adduct **5**. Thus it may be concluded that the unsaturated anhydride **1** can be used as the dienophilic equivalent of the unsaturated ester **4** towards Diels-Alder reaction with cyclopentadiene.

It is worth mentioning that the unsaturated lactone **14**, m.p. 112°C, prepared from the known Diels-Alder adduct **13**[7] failed to undergo trans-iodolactonisation under similar condition. Instead, addition of HI to the double bond of **14** took place to afford a mixture of the iodo-lactones **15** and **16** as indicated by the presence of two lactone CH_2 units at δ 3.83 and 3.90 and absence of olefinic protons in ^1H NMR spectrum of the crude product.

The formation of the iodo-lactones **15** and **16** was confirmed by their transformation through reduction with TBTH to the lactone **17**, m.p. 121°C. The facile trans-lactonisation of the unsaturated lactone **9** in contrast to the failure of the lactone **14** to undergo trans-lactonisation is attributed to be the result of the proximity of the lactone ring to the syn-olefinic bridge in the former.

Transformation of the lactone **12** to the desired keto-ester **7** was finallly achieved in the following way. Reduction of the lactone **12** with $LiALH_4$ afforded the diol **18**, m.p. 98°C in 89% yield. The primary OH group in the diol **18** was then selectively protected as tetrahydro pyranyl ether to afford the hydroxy compound **19** as a liquid in 83% yield. Swern oxidation of the hydroxy compound **19** followed by deprotection afforded the hydroxy-ketone **20** as a viscous liquid in 62% yield. The product **20** as obtained was then oxidised with Jones reagent and the resulting acid was treated with diazomethane to afford the title keto-ester **7** as a clear liquid in 47% yield.

Experimental Section

Melting points were taken in open capillary in sulphuric acid bath and are uncorrected. IR spectra were recorded on a Perkin Elmer 298 Spectrometer in $CHCl_3$ solution. Unless otherwise stated ^1H NMR spectra were recorded at 60 MHz on Varian EM-360L Spectrometer in CCl_4 solution using TMS as internal standard. Organic extracts were dried over anhydrous Na_2SO_4. Petroleum refers to fraction of petroleum ether boiling in the range 60-80°C. Column chromatography was performed on silica gel (60-120 mesh).

cis-endo-6-Iodomethyl-9-hydroxy tricyclo[5.2.1.$0^{2,6}$]-decan-2-carboxylic acid lactone (11). Method A : To a well stirred solution of the lactone **9** (100 mg, 0.52 mmol)

in CH_3CN (3 ml), anhydrous NaI (240 mg, 1.6 mmol) and TMSCl (168 mg, 1.56 mmol) were added successively. Stirring was continued for additional 4h. The reaction mixture on dilution with water was extracted with ether (3x15 ml). The ether layer was washed with aqueous saturated $NaHCO_3$, aqueous $Na_2S_2O_3$ (5%) solution and dried. The solvent was removed and the residual mass was chromatographed with ether-petroleum (1:19) as eluent to afford the solid iodo-lactone **11** (120 mg, 70%), m.p. 102°C, IR: 1770 cm^{-1}; ^1H NMR (200 MHz) δ: 1.2-2.1 (9H,m), 2.44 (1H, quintet, J=6 Hz), 2.6 (1H,brs), 3.1 (1H,d,J=7 Hz), 3.34 (2H,ABq,J=8 Hz, CH_2) and 4.8 (1H,t,J=6 Hz).

Method B: To a solution of the lactone **9** (1.9 gm, 10 mmol) in CH_3CN (20 ml) saturated with dry HCl(g), was added anhydrous NaI (2.25 gm, 15 mmol) with stirring. Stirring was continued for additional 6h. The reaction mixture was then worked up as above to afford the iodo-lactone **11** (2.8 gm, 87%), m.p. and m.m.p. with the sample prepared by method A 102°C. The IR and ^1H NMR spectra of this compound was found identical with those of the sample prepared by method A.

cis-endo-6-Methyl-9-Hydroxy tricyclo[5.2.1.$0^{2,6}$]decan-2-carboxylic Acid Lactone (12). A solution of the iodo-lactone **11** (2.8 gm, 7.8 mmol) in benzene (40 ml) was refluxed with TBTH (3.3 gm, 11.7 mmol) and AIBN (cat) for 7h under N_2 atmosphere. Benzene was then removed under reduced pressure. To the residue were added ether (45 ml) and saturated KF solution (35 ml). The resulting mixture was vigorously stirred for 20h. The precipitated solid was filtered off. The ether layer was separated from the aqueous layer and the latter was dried and concentrated to afford the lactone **12** (1.38 gm, 82%), m.p. 84°C; IR: 1770 cm^{-1}; ^1H NMR δ 1.06 (3H,s), 1.20-2.43 (11H,m), 2.62-

2.82 (1H,m)) and 4.39-4.69 (1H,m). Anal.calcd for $C_{12}H_{16}O_2$: C, 74.97, H; 8.37. Found: C, 74.76, H; 8.37.

cis-9-Hydroxymethyl bicyclo[4.3.$0^{8,9}$]non-5-ene-8-carboxylic Acid Lactone (14). A solution of the anhydride 13 (480 mg, 2.5 mmol) in THF (10 ml) was reduced with $NaBH_4$ (140 mg, 3.75 mmol) according to the procedure described for preparation of the lactone 9 to afford the lactone 14 (350 mg, 80%), m.p.112°C; IR: 1750 cm^{-1}; ^1H NMR δ 1.06-2.63 (10H, m), 3.83 (2H,s) and 5.93 (2H,t,J=2 Hz).

Reaction of the lactone 14 with NaI-HCl-CH_3CN.Synthesis of the iodo-lactones 15 and 16. Reaction of the lactone 14 (350 mg, 2 mmol) with NaI-HCl-CH_3CN following the method B afforded a mixture of the iodo-lactones 15 and 16 as a semi solid mass; ^1H NMR: δ 1.26-2.73 (12H,m), 3.83(s) and 3.90(s) merged under a m at 3.73-4.4 (total 3H).

cis-9-Hydroxymethyl bicyclo[4.3.$0^{8,9}$]nonane-8-carboxylic Acid Lactone (17). A mixture of the lactones 15 and 16 (310 mg, 1 mmol) in benzene (40 ml) was refluxed with TBTH (420 mg, 1.5 mmol) and AIBN (cat) for 7h. Work up of the reaction mixture according to the procedure for preparation of the lactone 12 afforded the lactone 17 (110 mg, 61%) as a crystalline solid, m.p. 121°C; IR: 1750 cm^{-1}; ^1H NMR δ: 1.33-2.06 (14H,m) and 3.93 (2H,s).

cis-endo-2-Hydroxymethyl-6-methyl-9-hydroxy tricyclo [5.2.1.$0^{2,6}$]decane (18). To a magnetically stirred suspension of LAH (500 mg, 13 mmol) in ether (25 ml) was added dropwise a solution of the lactone 12 (1.2 gm, 6.25 mmol) in ether (10 ml) under N_2. The mixture was then refluxed for 2.5h. The reaction mixture was cooled in ice and quenched by addition of saturated Na_2SO_4 solution. The granular precipitate was filtered off, and washed

with ether. The combined filtrate and washing were dried. The solvent was removed to afford the diol **18** (1.1 gm, 89%), m.p. 98°C; IR: 2230 cm^{-1}; ^1H NMR: δ 0.96 (3H,s), 1.1-2.1 (12H,m), 3.05 (1H,d,J=11 Hz), 3.93 (1H,d,J=11 Hz) and 3.7 (1H,brs). Anal.calcd for $C_{12}H_{20}O_2$: C, 73.43; H; 10.27. Found C, 73.91; H, 10.12.

cis-endo-Methyl-6-methyl tricyclo[5.2.1.$0^{2,6}$]dec-9-one-2-carboxylate (7). A solution of the diol **18** (1 gm, 5.1 mmol) in CH_2Cl_2 (10 ml) was treated with dihydropyran (0.51 ml, 5.61 mmol) and PPTS (30 mg) for 4h. The residual mass after removal of CH_2Cl_2 was chromatographed with ether-petroleum (1:10) as eluent to afford **19** (1.2 gm, 83%) as a semi solid mass. It was directly oxidised and deprotected as follows.

To a solution of oxalylchloride (0.5 ml, 5.8 mmol) in CH_2Cl_2 (3 ml) at -60°C, was added DMSO (0.55 ml, 7.8 mmol), dissolved in CH_2Cl_2 (1 ml) with stirring under N_2 atmosphere. After 15 min at this temperature a solution of the hydroxy compound **19** (1.1 gm, 3.9 mmol) in CH_2Cl_2 (1 ml) was added. Stirring was continued for additional 30 min at -60°C and then Et_3N (4.8 ml, 85 mmol) was added to it and stirring was continued for 15 min. The reaction mixture was then allowed to attain rt and water (5 ml) was added. The aqueous layer after separation from the organic layer was extracted with CH_2Cl_2 (3x15 ml). The combined organic layer was washed successively with aqueous HCl(1%), water, aqueous $NaHCO_3$ (5%), brine and dried. Solvent was removed and the residual mass was treated with EtOH (4 ml) and PPTS (30 mg) at about 55°C for 3h. The reaction mixture was diluted with water, extracted with ether, washed with saturated $NaHCO_3$,and dried.Removal of solvent followed by filtration through a short column afforded the keto alcohol **20** (0.48 gm, 62%) as a viscous liquid. This crude product was directly oxidised with Jones reagent as follows.

To an ice-cold stirring solution of the keto-alcohol **20** (200 mg, 1.04 mmol) in acetone (5 ml) Jones reagent was added dropwise untill the colour of the Jones reagent persisted for 15 min. Stirring was continued for additional 1.5h. The reaction mixture was then extracted with ether and the ether layer was repeatedly washed with 5% $NaHCO_3$ solution. The basic aqueous washing was acidified with ice-cold HCl (conc.) and extracted with ether (3x10 ml). The organic extract was washed with brine and dried. Removal of solvent followed by treatment of the residual mass with ethereal diazomethane afforded a viscous mass. This mass was filtered through a short alumina column [ether-petroleum (1:19)] to afford the keto-ester **7** (110 mg, 47%) as a colourless liqud; IR: 1740 cm^{-1}; ^1H NMR: δ 1.23 (3H,s), 1.35-1.84 (8H,m), 2.1-2.59 (4H,m), 3.56 (3H,s). Anal.calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.89; H, 8.05.

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