99. Preparation and Photochemistry of Cross-Conjugated Cyclohexadienone Ring A of Friedelane Triterpene

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Key words : *Cross-conjugated cyclohexadienone, Friedelin, Photochemistry, Lumiproduct*

Because of the presence of 4,4,10-trimethyl ring A system in triterpenes α-amyrin, β-amyrin and lupane series, the introduction of photolabile cross-conjugated cyclohexadienone chromophore in ring A is not feasible. In contrast, in friedelane triterpene having 4,5-dimethyl ring A system this can be introduced. Thus, by a sequence of reactions starting from friedelane the key compound friedel-1(10), 3-dien-2-one, a cross-conjugated cyclohexadienone system in ring A, was synthesised. This upon UV irradiation at 254 nm in neutral and non-nucleophilic solvent, dioxane, in nitrogen atmosphere at ambient temperature yielded the bicyclo (3.1.0) hex-3-en-2-one derivative (lumiproduct) in good yield (62%). Its structure has been elucidated by the combination of UV, IR, PMR, CMR and EI mass spectral analysis. The stereochemistry has been studied by chiroptical (CD) measurements. Prolonged irradiation results in a complex reaction mixture.

100. Synthesis of Some New Arylamides as Biologically Active Agents

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Key words : *Arylamides, Antimicrobial Activity*

The study of arylamides has revealed valuable drugs for the diseases like Cancer,. Malaria, Tuberculosis, Fungal, Viral and

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Note

Preparation and molecular rearrangement of 2α, 3α-epoxy lupan-1-one catalysed by boron trifluoride and by ultraviolet irradiation†

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Using lupeol **7** as lead compound 2α, 3α-epoxy lupan-1-one **11** has been synthesised by a sequence of reactions. Boron trifluoride catalysed molecular rearrangement of **11** in benzene yields 2-formyl-A-nor-lupan-1-one **15** (enolized). Same rearrangement is also achieved in dioxane under photolytic condition.

House and Watson[1] have observed that cyclic epoxy ketones of the type (1:n>1) in the presence of boron trifluoride-etherate undergo molecular rearrangement (**Chart 1**) with reduction in ring size of ketones and produce the keto aldehydes **2**. Later, Kartha and Chakravarti[2] studied the action of boron trifluoride on some sesquiterpene epoxy ketones and epoxides and found that in each case an aldehyde was formed by contraction of a six-membered ring to a five-membered one. Ganguly *et. al.*[3] carried out BF_3–catalysed rearrangement of 1α, 2α-epoxy lupan-3-one **3** and obtained the product 1 – methyl-2α-hydroxy-lup-1(10)en-3-one **4**. Here, most probably due to the presence of a neopentyl system adjacent to the epoxy ketone system, methyl migration occurred instead of ring contraction. In contrast. Chatterjee *et. al.*[4] also studied the same rearrangement on the same substrate **3** and reported the formation of the nor-ketone **5**, presumably formed by the elimination of formyl group from the initial product, 2-formyl cyclopentanone **6**. In this note we wish to report first the partial synthesis of the isomeric epoxy ketone **11** possessing a neopentyl system adjacent to the epoxy ketone moiety and then the molecular rearrangement of **11** induced by BF_3-etherate as well as induced by ultraviolet irradiation to give 2-formyl-Anor-lupan-1-one **15.**

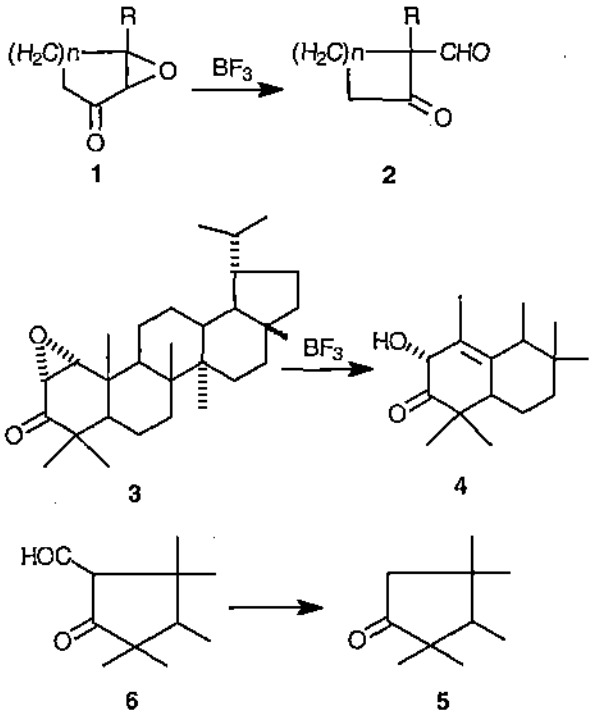

Chart 1

The starting material for the preparation of **11** is the triterpene lupeol **7**, obtained abundantly from the benzene extract of *Zanthoxylum budrunga*[5] followed by chromatographic purification. Compound **7** on catalytic reduction (**Scheme I**) furnished lupanol **8**, which on dehydration with phosporus oxychloride in pyridine afforded lup-2-ene **9**. Oxidation of **9** with sodium dichromate in benzene-acetic acid mixture (1:1) yielded the conjugated ketone, lup-2-en-1-one **10**, λ_{max} 220nm, ν_{max} 1667cm^{-1}. Though it was expected to give the key compound 2α, 3α-epoxy lupan-1-one **11** on treatment with alkaline hydrogen peroxide, our repeated attempts failed to obtain the desired epoxy ketone **11**. At this juncture, a literature survey revealed that the system 2-en-1-one of ring-A in triterpenes is stable towards alkaline hydrogen peroxide as noted by Barton and coworkers[6]. Consequently, we adopted an alternative method for the preparation of the epoxy ketone **11**. Lup-2-ene **9** on selenium dioxide oxidation in dioxane with a few drops of water added in it, gave the allylic alcohol, lup-2-ene-1α-ol **12** following the reaction conditions

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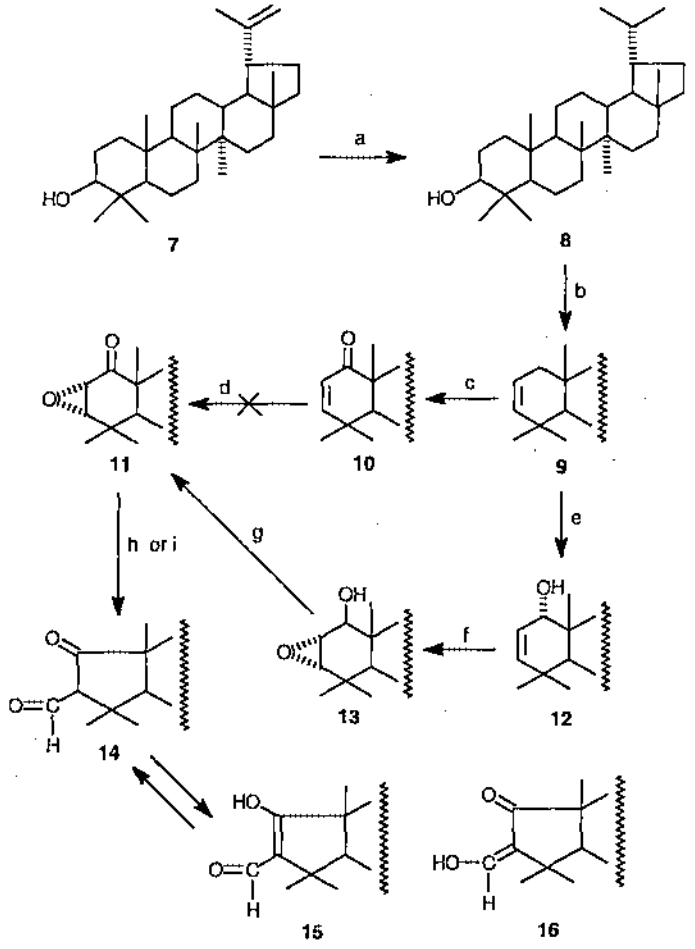

Scheme I

Reagents and conditions. (a) H_2/Pd-C, ETOAc, rt, 4hr (b) $POCl_3$, Py, 4hr, water-bath (c) $Na_2Cr_2O_7$, C_6H_6-AcOH (1:1), 3hr, reflux (d) H_2O_2, NaOH, rt (e) SeO_2, dioxane, traces of water, 6hr, reflux (f) *m*-CPBA, $CHCl_3$, 5°C, 72hr (g) CrO_3, Py, 5°C, 48h (h) BF_3 -- etherate, C_6H_6, 1hr, rt (i) hv > 290 nm, dioxone, 0.5hr, rt.

prescribed by Vystrcil *et. al*[7]. Compound **12** was epoxidised[7] with metachloro-perbenzoic acid in chloroform to yield the epoxy alcohol, 2α, 3α-epoxy lupan-1α-ol **13.** We have prepared the key compound, 2α, 3α-epoxy lupan-1-one **11** by the chromium trioxide-pyridine oxidation of **13.** In ^{1}HNMR spectrum, appearance of resonances at δ 3.1 (doublet, J = 4Hz) and δ 3.27 (doublet, J = 4Hz) enabled us to assign 2α, 3α-epoxy ketone stereochemistry for **11.** Vystrcil and coworkers[7] settled the stereochemistry of **13**, the precursor of **11**, as 2α, 3α-epoxy lupan-1α-ol by carrying out its conversion with LAH to 2α, 3α-dihydroxy lupane of known structure. Boron trifluoride catalysed rearrangement of **11** in dry benzene at ambient temperature afforded the ring A contracted keto aldehyde, 2-formyl-A-nor-lupan-1-one **14** in 60% yield. It practically exists in solution as the enolized form **15.** The structure of the rearranged product was deduced by the physical techniques UV, IR, NMR and mass spectra (see Experimental). Of the two possible enolized forms **15** and **16,** the former one **15** was supported by aldehydic proton singlet at δ 9.4 in the ^{1}H NMR analysis.

The mechanistic aspects of the ring contraction reaction have been thoroughly investigated[1,2]. Most possibly the ion **17 (Chart 2)** generated by the attack of BF_3 on 11 gives rise to carbocation **18** which eventually rearranges to the ring contracted product **14.** The whole process might be synchronous.

The photorearrangement of cyclic epoxy ketones is well documented[8,9]. Upon photolysis, they afford 1,3-diketones or keto-aldehydes. We have carried out irradiation of **11** in dioxane at λ> 290 nm at ambinet temperature under argon-atmosphere for 0.5 hr. We have been able to isolate the same keto-aldehyde **14** in good yield (52%). Since the initial product **14** is also

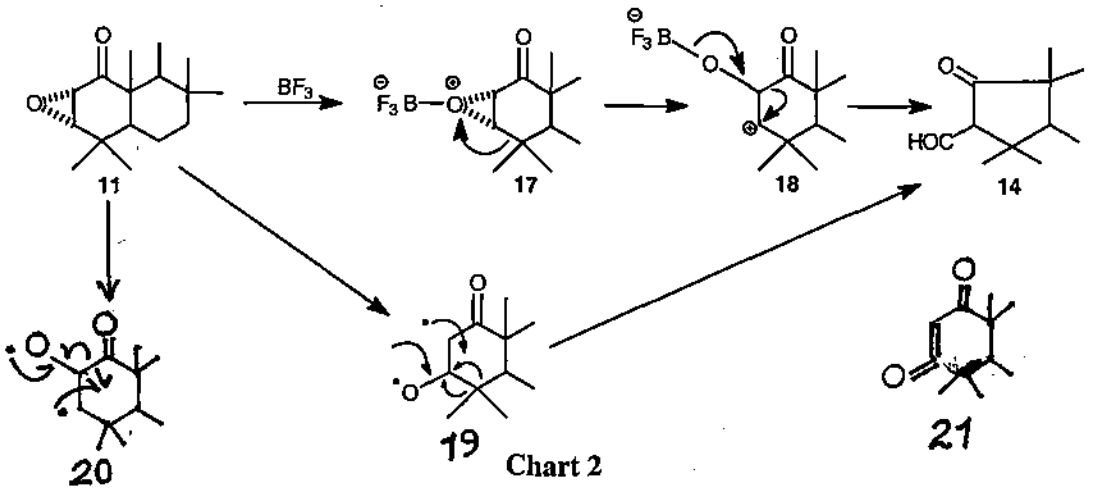

Chart 2

photolabile, irradiation for an extended period results in a complex reaction mixture giving a low yield of **14**.

This photoreaction occurs from excited singlet manifold[8,9] via a diradical generated by homolysis of C_α–O bond, the retention of configuration[9] α in the resulting β-diketones obtained from the stereoisomeric steroidal epoxy ketones supports the proposition of a predominantly concerted rearrangement maintaining close orbital overlap throughout the entire radical migration[9]. Accordingly, the mechanistic pathway of the photorearrangement of **11** studied by us can be depicted as in Chart 2. The diradical **19** or **20** generated initially on photoexcitation rearranges to the keto-aldehyde **14** by a process in which the bond-migration and carbonyl-formation steps are concerted.

Though the ketoketene **21** could be an attractive intermediate, no product corresponding to this intermediate has been isolated.

In conclusion, the molecular rearrangement conducted by us on isomeric epoxy ketone **11**, induced by either BF_3-etherate at ambient temperature or under photolytic condition, enabled us to obtain the ring contracted keto-aldehyde **14** in line with the finding of the original workers[1]. Though Chatterjee *et al.*[4] did not obtain the rearranged ring contracted keto-aldehyde **6**, but obtained a ring contracted ketone **5**, presumably formed by deformylation of the intermediate keto-aldehyde **6**. Incidentally, we did not observe the formation of methyl migrated product of the type **4** isolated by Ganguly *et al*[3].

Experimental Section

General. Melting points were determined in a sulphuric acid bath and are uncorrected. The pet.ether used throughout the investigation had B.P. 60-80°C. ^{1}H NMR spectra were recorded on a VNXL-200 spectrophotometer in $CDCl_3$ solution using TMS as internal reference; IR spectra on a Pye Unicam-Sp-300S and UV on a shimad Zu UV-240 spectrophotometers; and mass spectra (EIMS) on a Jeol JMS-D300 mass spectrophotometer, using direct sample introduction into the ion source at 70 eV. TLC was done on chromatoplate of silica gel G (E.Merck) and spots were visualised by exposing the plates in iodine vapour.

Isolation of lupeol 7. Stem-bark of *Zanthoxylum budrunga*[5] was extracted in a soxhlet apparatus for 20 hr. with benzene. The extract was concentrated and purified by column chromatography over silica gel. Elution with pet-ether-ethyl acetate (9:1) as eluent gave lupeol **7** as white solid, crystallised from chloroform-methanol as needless mp 214-15°C (lit.[10] mp 215-16°C); IR (nujal): 3420 (OH), 1630, 890 cm^{-1} (=CH_2).

Lupanol 8. To a solution of lupeol **7** (21 mmoles) in ethyl acetate (450 mL) was added Pd-C (5%, 1g) and hydrogenated for 5 hr. Pd-C was removed by filtration and the filtrate on concentration afforded fine white needles of lupanol **8**, mp 202-03°C (lit[11] mp 201-02°C), IR (nujal : 3390 cm^{-1} (OH), $C_{30}H_{52}O$ (M^+ 428 m/z).

Preparation of lup-2-ene 9. To a solution of lupanol **8** (16 mmoles) in dry pyridine (200 mL) was added phosphorus oxychloride (25 mL). The reaction mixture was refluxed on a water-bath for 4 hr and then overnight at room temperature. It was poured on ice-water. The precipitated brown solid obtained on filtration was chromatographed on silica gel. Elution

with pet. ether gave lup-2-ene **9** (65%) as, white solid mp 190-192°C (lit.[12] mp 192-93°C); IR (nujal) :1630, 850 cm^{-1} (C = C).

Preparation of lup-2-en-1-one 10. To a solution of lup-2-ene **9** (11 mmoles) in benzene-acetic acid (1:1, 300 mL) sodium dichromate (15 mmoles) was added and the mixture refluxed for 3 hr. The excess oxidant was destroyed by addition of methanol (20 mL). The reaction mixture was extracted with ether (500 mL), washed with Na_2CO_3 and then with water until neutral. The brown mass obtained on evaporation was chromatographed over silica gel. Elution with pet. ether—ethyl acetate (4:1) as eluent gave **10** as white solid (55%), mp 194-95°C, UV (CH_3OH): λ_{max} 220 nm, IR (nujal): 1667, 1625cm^{-1} (conjugated ketone).

Alkaline hydrogen peroxide treatment of lup-2-en-1-one 10. To a solutin of **10** (2.5 mmoles) in dioxane (50 mL) was added aquous hydrogen peroxide (30%, 8 mL) and aqueous NaOH (6*N*, 10 mL) and stirred over a period of 2 hr. After usual work-up unchanged starting material **10** was recovered in almost quantitative yield (mp and mmp).

Preparation of lup-2-en-1α-ol[7] 12. To a solution of **9** (5.2 mmoles) in dioxane (200 mL) SeO_2 (6.7 mmole) was added. After addition of traces of water (4 drops) the reaction was refluxed for 8 hr. The warm filtrate obtained on removal of Se was poured into aquous KOH solution (2.5%, 1.2L). The precipitated solid was chromatographed over silica gel. Elution with pet.ether-ethyl acetate (3:1) gave a white solid which on crystallisation from chloroform-methanol gave needles of lup-2-en-1α-ol **12,** mp 201-02°C (lit.[7] mp 203-04°C), $C_{30}H_{50}O$ (M^+426 m/z), IR (nujal) : 3424 (OH), 1625, 862 cm^{-1} (C=C), ^{1}HNMR : δ0.7 – 1.1 ($8CH_3S$), 3.6 (m, 1H, CHOH), 5.5 (d, 1H, J =12 Hz C_3 -H) and 5.7 (q, 1H, C_2 - H). Anal. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.12; H, 11.61%.

Preparation of 1α-hydroxy-2α, 3α-epoxy lupane 13. To a solution of **12** (10.5 mmoles) in chloroform (55 mL) was added *m*-CPBA (14.6 mmoles). The reaction mixture was kept at 5°C for 72 hr, extracted with ether (250 mL), washed with Na_2CO_3 solution and then with water until neutral. The white solid obtained on evaporation of solvent, was crystallised from chloroform-methanol to furnish pure **13** (72%), mp 233-34°C (lit.[7] mp 232°C); $C_{30}H_{50}O_2$ (M^+ 442 m/z), Anal. Calcd for $C_{30}H_{50}O_2$; C, 81.33, H, 11.35. Found: C, 81.47; H, 11.09%.

Preparation of 2α, 3α-epoxy lupan-1-one 11. To a solution of **13** (2.5 mmoles) in pyridine (20 mL) was added a slurry of CrO_3 (3.6 mmoles) in pyridine (15 mL) at 5°C and kept at this temperature for 48 hr. The reaction mixture was diluted with ethyl acetate (200 mL). The precipitate was filtered off. The clear brown filtrate was treated with aqueous HCl (10%), washed with water until neutral. Evaporation of the solvent left a brown mass which was chromatographed over silica gel. Elution with pet. ether-ethyl acetate (4:1) yielded a white solid which on crystallisation from chloroform-methanol afforded fine needles of **11** (48%) mp 191°C; IR (nujal): 1695 cm^{-1} (C = O); 1H NMR: δ 0.72 – 1.1 ($8CH_3S$), 3.11 (d, 1H, J = 4Hz, C_3- H) and 3.27 (d, 1H, J =4Hz, C_2-H); Mass : 440 (M^+), 397 m/z(M^+–isopropyl). Anal. Calcd. for $C_{30}H_{50}O_2$: C, 81.81; H, 10.91. Found: C, 81.45; H 10.68%.

BF_3-etherate rearrangement of 11. Preparation of 2-formyl-A-nor-lupan-1-one 14. The epoxy ketone **11** (1.2 mmoles) in dry benzene (25 mL) was treated with freshly distilled BF_3-etherate (5 mL) at room temperature for 1 hr. The reaction mixture was diluted with water, extracted with ether and washed with water. On evaporation a thick gum was obtained which was purified by chromatography over silica gel. Pet. ether-ethyl acetate (7:3) eluted a white solid (60%), mp 93-94°C, UV (MeOH); λ_{max}227 nm, shifted to 292 nm in 0.1*M* NaOH, IR (nujal): 3450(OH), 1710 (unsaturated aldehyde), 1595 (C=C) cm^{-1}, ^{1}H NMR : δ 0.7-1.2 ($8CH_3S$), ~~3.11(d, 1H, J = 4Hz C_3-H), 3.27 (d, 1H, J = 4Hz, C_2-H)~~ and 9.4 (s, 1H, –CHO); Mass : 440 (M^+), 397 m/z (M^+-isopropyl). Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.81; H, 1091. Found: C, 81.55; H, 16.72%.

Photolysis of 11 : Formation of 2-formyl-A-nor-lupan-1-one 14. A solution of 11 (1.1 mmole) in dry dioxane (100 mL) was irradiated for 0.5 hr with medium pressure mercury lamp placed in a central water-cooled pyrex immersion well under argon atmosphere at ambient temperature. Evaporation of the solvent in a rotary vacuum evaporator followed by chromatography of the crude product on silica gel using pet. ether-ethyl acetate (7 : 3) as eluent gave a white solid (52%) which was found to be identical with **14** by mp and mmp determinations and by comparison of spectral (UV, IR, ^{1}H NMR and mass) data .

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