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DMSO mediated novel oxidative skeletal rearrangement of ring-A in lupenone†

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A novel one-step stereospecific synthesis of C-2-nor-1β-hydroxy-2-oxa-lupenone **3** is described through potassium hydroxide (KOH)-dimethyl sulphoxide (DMSO) mediated oxidation of lupenone **2**. Formation of **3** is associated with an unusual oxidative skeletal rearrangement of ring-A in lupenone under the condition of oxidation.

Lupeol **1** is a biologically active naturally occurring pentacyclic triterpene[1-3]. To explore its potential for delivering bioactive molecules, regioselective reactions[4,5] of the isopropenyl side chain attached to the E-ring of lupeol have been carried out earlier, and in continuation of this work, selective oxidation of A-ring has now been attempted. Literature precedence[6,7] for a multi-step oxidative rearrangement of ring-A in similar triterpene exists. Lupeol is known to undergo skeletal rearrangement in acids[8-11]. Selective oxidation of ring-A in lupenone was, therefore, attempted under basic conditions and this led to the first observation of DMSO-mediated oxidative skeletal rearrangement of ring-A in lupenone. The details of the first report are presented here.

Results and Discussion

Lupeol, extracted from the ethanolic extract of *Crataeva nurvula*, was oxidised with pyridinium chlorochromate (PCC) to yield lupenone **2** (91.5%). This on treatment with powdered KOH in dry DMSO at room temperature gave the compound **3** in excellent yield (81.7%). This oxidative skeletal rearrangement also proceeded smoothly in an atmosphere of nitrogen. Extensive 2D NMR studies were carried out to establish the structure and the stereochemistry of compound **3**. High resolution ^{1}H NMR experiment on **3** showed the appearance of one-proton singlet at δ 5.28 suggesting a –O–CH–O– grouping in the molecule. ^{13}C DEPT experiment revealed the absence of two methylene carbons (C-1 and C-2) in **3** in comparison to the parent lupenone molecule, and also the appearance of a downfield methine carbon at δ 100.89 which further lent support in favour of a –O–CH–O– grouping in the molecule. ^{1}H-^{13}C correlation study on the basis of Heteronuclear Multiple Quantum Coherence experiment confirmed the absence of C-1 and C-2 methylene carbons in A-ring of the product and the presence of oxomethine group as their replacement. The chemical shifts of all other protons and carbons in rings B, C, D and E remained unaffected. FAB-MS of this compound exhibited M^+ peak at m/z 442. These observations and other spectroscopic data supported the structure of compound **3**. The stereochemistry of C-1 in **3** was determined by ROESY experiment in which C-1(H) was found to show nOe with C-5 (α-H) instead of C-10 (β-CH_3). This clearly indicated compound **3** was formed exclusively as one stereoisomer in which C-1 has α-H and β-OH. Thus, it is presumed that during the formation of **3**, recyclisation of the product of oxidatively cleaved ring-A in lupenone occurred stereospecifically. Chemical evidences in support of **3** were obtained from the results of some classical reactions. Compound **3** when treated with methyl iodide in the presence of anhydrous K_2CO_3 and dry acetone led to the formation of A-ring cleaved product **4** (97%) with a cyclopentano-perhydrophenanthrene skeleton. Reductive recyclisation of **4** with $NaBH_4$/MeOH[12] led to the

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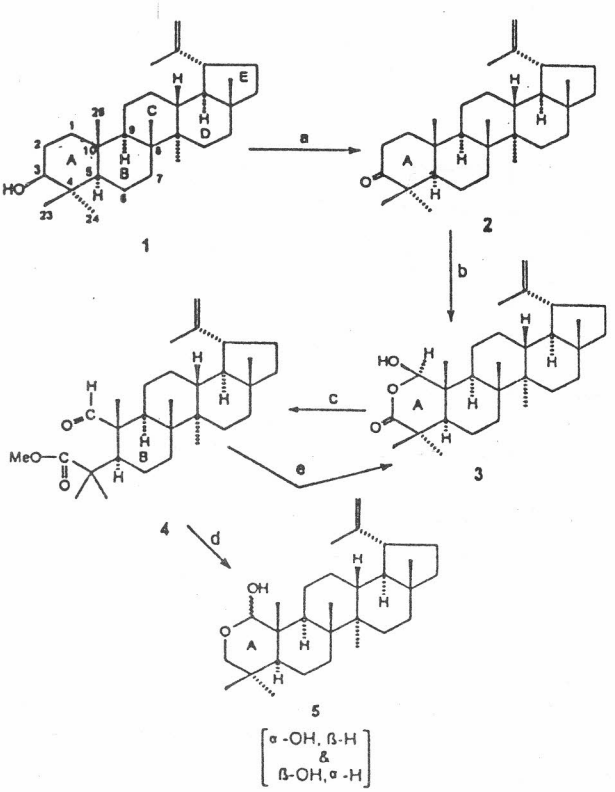

Reagents and conditions: (a) PCC, CH_2Cl_2, 5 hr.; (b) KOH, DMSO, 16 hr.; (c) MeI, K_2CO_3, Acetone, 14 hr.; (d) $NaBH_4$, MeOH, 24 hr.; (e) NaOH, H_2O, EtOH, 20 hr. [All the reactions were carried out at room temperature (25°C)].

Scheme I

formation of an stereoisometric mixture of **5** [46.6%, 1-hydroxy-2-oxa-lupan-20(29)-ene] as evident from the NMR spectrum. The C-1 proton of only one of the stereoisomers of **5** showed nOe with C-5 (α-H) while the other stereoisomer showed nOe with C-10 (β-CH_3). Alkaline hydrolysis of **4** with NaOH/EtOH-H_2O resulted back to the stereospecific formation of the parent compound **3** (42.5%). The schematic representation of all these reactions are shown in Scheme I.

Experimental Section

General. Melting points were determined on a hot stage melting point apparatus and are uncorrected. IR spectra were measured on a Beckmann Acculab-10 spectrophotometer. Optical rotations were recorded on a Rudolph Research Polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 FT NMR instrument using $CDCl_3$ as solvent and TMS as internal standard. FAB mass spectra were obtained on a JOEL SX 102/DA 6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Chemical analyses were carried out on a Carlo-Erba-1108 strumentazeone.

Reaction of lupenone 2 with KOH and DMSO: Formation of C-2-nor-1β-hydroxy-2-oxa-lupenone 3. To solution of lupenone (4.7 mmoles) in dry DMSO (30 mL) was added powdered KOH (9.4 mmoles) and the reaction mixture was allowed to stir at room temperature (25°C) for 16 hr. Excess DMSO was then removed *in vacuo* and the resulting mixture acidified to *p*H 6 by an aqueous solution (20%) of ammonium chloride and extracted with *n*-butanol (2×50 mL). Combined organic layer was washed with water (2×50 mL), dried over anhydrous $MgSO_4$, filtered and evaporated to give an oily residue which was column chromatographed over silica gel. Elution with methanol-chloroform (0.2-99.8, v/v) as eluent yielded the compound **3** as white solid, mp 183-84°C; MS: m/z 443 (M^++1), 425 (M^+–OH); IR (KBr): 1710 cm^{-1} (C=O); $[\alpha]_D^{25}$ +23.33° (*c* 0.0015, $CHCl_3$); ^{1}H NMR: δ 5.28 (s, 1H, C*H*OH), 1.28 [m, 1H, C-5 (proton)], 1.22 (s, 3H, C-23(CH_3)], 1.16 (s, 3H, C-24)CH_3)], 1.08 (s, 3H, C-25(CH_3)]; ^{13}C NMR (100 MHz): δ 179.29 (C=O), 100.89 (*C*HOH), 43.26 (C-4), 40.10 (C-5), 28.61 (C-23), 23.49 (C-24), 14.58 (C-25). Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.73; H, 10.40. Found: C, 79.05; H, 10.28%.

Reaction of compound 3 with potassium carbonate and methyl iodide: Formation of A-ring cleaved product 4. To a solution of compound **3** (2.2 mmoles) in dry acetone (35 mL) were added potassium carbonate (4.4 mmoles) and methyl iodide (4.4 mmoles) and the reaction mixture was stirred at room temperature for 14 hr. After the completion of the reaction, it was filtered, the solid residue was washed with acetone (2×10 mL) and the combined organic extract evaporated at reduced pressure to give a solid residue which was column chromatographed over silica gel. Elution with chloroform:hexane (7:3, v/v) as eluent gave compound **4**, mp 165-66°C, MS: m/z 457 (M^++1), 425 (M^+–OMe); IR (KBr): 1720 cm^{-1} (C=O); ^{1}H NMR: δ 9.23 (s, 1H, CHO), 3.70 (s, 3H, OMe), 1.67 [s, 3H, C-23(CH_3)], 1.36 [m, 1H, C-5(proton)], 1.28 [s, 3H, C-24(CH_3)], 1.18 [s, 3H, C-25(CH_3)], ^{13}C NMR (100 MHz):

δ 205.50 (CHO), 178.07 (CO_2Me), 52.10 (C-4), 5.55 (OMe), 39.19 (C-5), 25.11 (C-23), 23.77 (C-24), 14.35 (C-25). Anal. Calcd for $C_{30}H_{48}O_3$: C, 78.94; H, 10.52. Found: C, 79.13; H, 10.38%.

Reaction of compound 4 with sodium borohydride: Formation of 1-hydroxy-2-oxa lupan-20(29)-ene 5. To a solution of compound **4** (1.7 mmoles) in methanol (25 mL) was added sodium borohydride (3.5 mmoles, in portions) under stirring at 0-5°C. The stirring was continued for 24 hr at room temperature after which the excess of methanol was removed *in vacuo*. The reaction mixture was then diluted with water (30 mL) and extracted with chloroform (2×40 mL). Usual work-up of the organic layer furnished a crude residue which was purified by column chromatography over silica gel using chloroform:hexane (9:1, v/v) as eluent to yield the compound **5**, mp 110-11°C; MS: m/z 429 (M^++1); 411 (M^+–OH); IR (KBr): 3420 cm^{-1} (OH); $[\alpha]_D$ –0.00 (*c* 0.0014 in $CHCl_3$); ^{1}H NMR: δ 4.25, 4.24 (2, s's, C*H*OH), 3.65, 3.00 (2, d's, *J*=12 Hz, 6 Hz, OCH_2), 3.56, 3.20 (2, d's, *J*=9 Hz, 12 Hz, OCH_2), 1.03 (s, 3H, C-23(CH_3)], 1.00 [s, 3H, C-24(CH_3)], 0.95 [s, 3H, C-25(CH_3)], 0.85 [m, 1H, C-5(H)]; ^{13}C NMR (100 MHz): δ 103.5, 99.2 (*C*HOH), 78.3, 70.2 (OCH_2), 45.4 (C-5), 42.9 (C-4), 27.3 (C-23), 25.4 (C-24), 17.9 (C-25). Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.31; H, 11.21. Found: C, 81.05; H, 11.36%. Only those ^{1}H and ^{13}C NMR data which have a direct bearing on structures have been included.

Reaction of compound 4 with sodium hydroxide: Reformation of compound 3. To a solution of compound **4** (1.5 mmoles) in ethanol (15 mL) and water (15 mL) was added sodium hydroxide (1.5 mmoles) and the mixture stirred at room temperature for 24 hr. Solvent was removed under reduced pressure and the residue obtained acidified to *p*H 6.0 by an aqueous NH_4Cl solution (20%) and extracted with chloroform (2×40 mL). Usual work-up of the organic layer furnished a solid residue which on purification by column chromatography over silica gel using methanol-chloroform (0.2:98.8, v/v) as eluent gave pure **3**.

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