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ALKYLATION OF 2,4-DIMETHYL-3-FUROIC ACID AND SYNTHESIS OF 4,6-DIOXO-14-NORFURANOEUDESMANE

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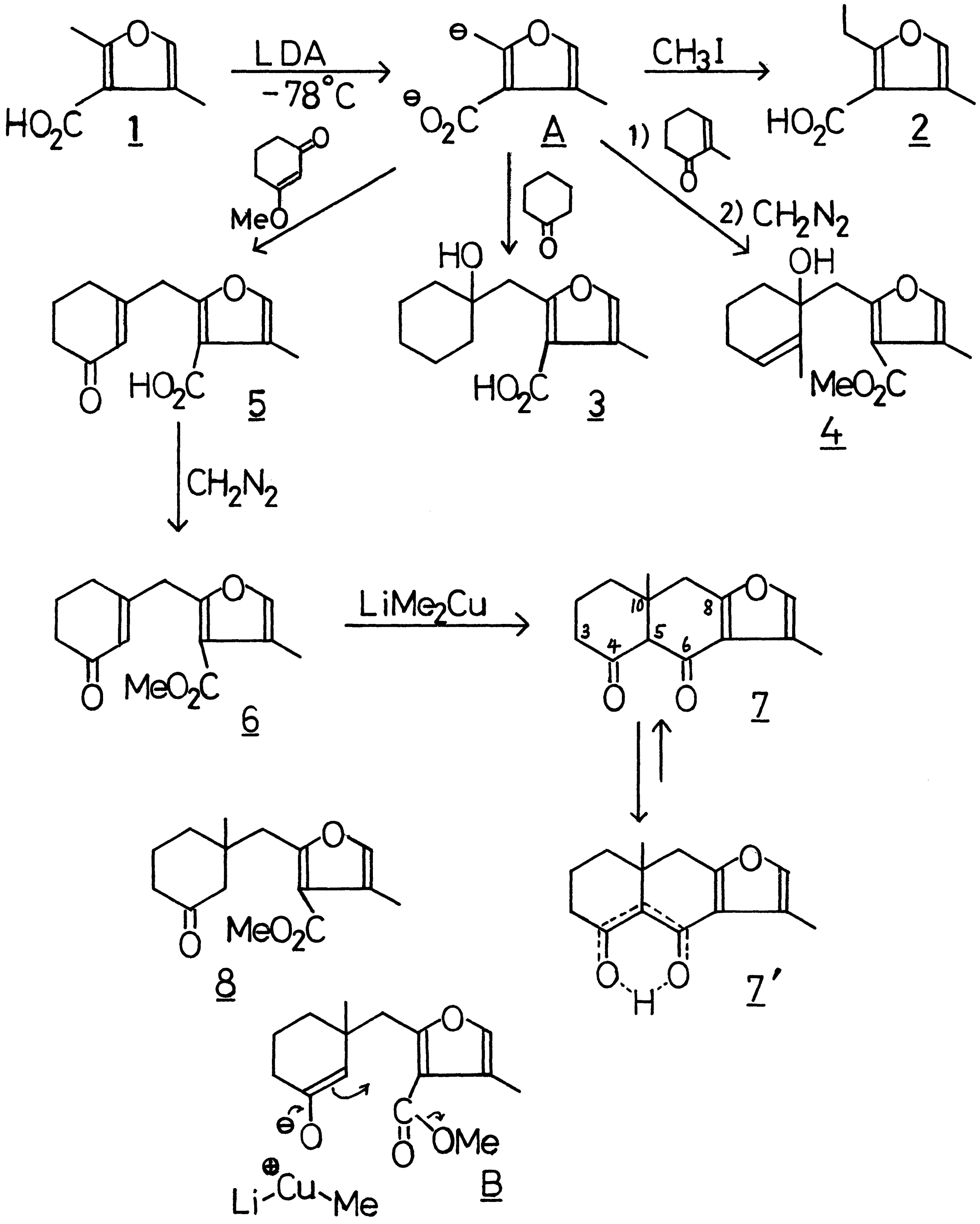
Treatment of 2,4-dimethyl-3-furoic acid in THF with LDA gave a dianion (A). Alkylation of A with methyl iodide, cyclohexanone, 2-methyl-2-cyclohexenone or 3-methoxy-2-cyclohexenone yielded the corresponding alkylated derivatives (2, 3, 4 or 5) respectively. The methyl ester (6) was treated with $LiMe_2Cu$ to give 4,6-dioxo-14-norfuranoeudesmane (7), a key intermediate for the synthesis of some eudesmanolides and elemanolides.

More than 500 sesquiterpene lactones and furans have been isolated and identified from many species of higher and lower plants, particularly from species of Compositae.[1] Many of them have been reported to reveal considerable anti-tumor, cytotoxic, anti-microbial, phytotoxic or allergic activity. Recently, a number of studies have been reported on the synthesis of eudesmane and certain elemane sesquiterpene lactones (e.g. vernolepin, vernomenin and isotelekin).[2] Most approaches, however, require rather many steps to construct the oxidized A and B rings and lactones. We report here novel alkylation of metalated 2,4-dimethyl-3-furoic acid with electrophilic reagents and new annelation reaction to show a potentially useful route to the relatively highly oxidized eudesmane and elemane sesquiterpene lactones and furans.

2,4-Dimethyl-3-furoic acid[3](1) in THF was added to two equivalent mole of lithium diisopropyl amide in THF-hexane at -78° C to produce a deep red homogeneous solution suggesting the formation of a dianion (A). Treatment of the deep red solution with one equivalent mole of methyl iodide at 0° C for 1 hr, followed by acidification with conc HCl gave 2-ethyl-4-methyl-3-furoic acid (2),


1
LDA
-78°C
A
CH3I
2
1)
2) CH2N2
MeO
HO
OH
5
3
4
CH2N2
6
LiMe2Cu
10
8
3
4
5
6
7
7′
8
Li
Cu
Me
OMe
B

m.p. 67.5∼69.5° C, IR (Nujol), ∼3000 (br) and 1680 cm^{-1}, NMR ($CDCl_3$): δ 7.03 (1H, m), 3.00 (2H, q, J = 7 Hz), 2.15 (3H, d, J = 1.5 Hz) and 1.25 (3H, t, J = 7 Hz) in quantitative yield. The formation of the acid 2 indicates the intermediacy of the dianion A. By the similar procedure, reactions with various types of electrophilic reagents were examined. The reaction of cyclohexanone with the dianion A afforded a hydroxy acid (3) (yield, 80 %), an oil, IR (Nujol): ∼3500 (br), ∼3000 (br) and 1685 cm^{-1}, NMR ($CDCl_3$): δ ∼7.5 (2H, br), 7.14 (1H, m), 3.16 (2H, s), 2.12 (3H, d, J = 1.2 Hz) and 1.8∼1.2 (10H, br). Then the reaction of the dianion A with 2-methyl-2-cyclohexenone was examined. The products were methylated with CH_2N_2 and separated by silica gel column chromatography to give a methyl ester (4) (70 %), an oil, IR (neat) ∼3450 (br) and 1710 cm^{-1}, NMR ($CDCl_3$) δ 7.11 (1H, m), 5.50 (1H, m), 3.84 (3H, s), 3.53 (1H, d, J = 14.5 Hz), 3.03 (1H, d, J = 14.5 Hz), 2.13 (3H, d, J = 1.2 Hz) and 1.83 (3H, br.s). The same 1,2-addition product 4 was obtained as a main product when one or two equivalent mole of CuI was added to the solution of the acid 1 and LDA, before the treatment with 2-methyl-2-cyclohexenone and CH_2N_2. The quenching of the dianion A with 3-methoxy-2-cyclohexenone and subsequent acidification with conc HCl gave an acid (5) (75 %), m.p. 89∼91° C, IR ($CDCl_3$): ∼3100 (br), 1710, 1670 and 1615 cm^{-1}, NMR ($CDCl_3$): δ ∼10.2 (1H, br), 7.15 (1H, m), 5.85 (1H, m), 3.94 (2H, br.s) and 2.18 (3H, d, J = 1.2 Hz). The acid 5 might be formed by the hydrolysis and subsequent dehydration of the addition product of the dianion A to the ketone moiety of 3-methoxy-2-cyclohexenone.

As the selective alkylation of 2,4-dimethyl-3-furoic acid was performed, 1,4-alkylation of the α,β-unsaturated ketone part of the acid 5 and subsequent annelation reaction of the product were attempted. The acid 5 was converted to its methyl ester (6), an oil, IR (neat): 1725, 1670, 1625 and 1610 cm^{-1}, NMR ($CDCl_3$): δ 7.12 (1H, m), 5.78 (1H, m), 3.88 (2H, m), 3.82 (3H, s) and 2.15 (3H, d, J = 1.5 Hz) by the reaction with CH_2N_2 in a quantitative yield. On treatment of the ester 6 with $LiMe_2Cu$ at 0° C for 45 hr, desired 4,6-dioxo-14-norfurano-eudesmane (7) (73 %), m.p. 91.5∼93° C, IR (KBr): ∼2960 and 1612 cm^{-1}, NMR ($CDCl_3$) δ 15.26 (0.7H, s), 3.82 (0.3H, s), 7.07 (1H, m), 2.69 (2H, s), 2.23 (3H, d, J = 1.8 Hz) and 1.18 (3H, s), Mass: M$^+$ at m/e 232 and base peak at m/e 217 (M$^+$ - 15) was produced by cyclization of an intermediate anion (B) which might be formed by the methylation of the α,β-unsaturated ketone moiety of 6 with $LiMe_2Cu$. The NMR spectrum of the diketone 7 in $CDCl_3$ shows that 7 in solution exists in equilibrium between diketone 7 and enol ketone (7') in a ratio of 3 : 7. On the treatment of 6 with $LiMe_2Cu$ in short time (3 hr), a keto ester (8), an oil, IR (neat): 1720 (br) cm^{-1}, NMR ($CDCl_3$): δ 7.16 (1H, m), 3.83 (3H, s), 3.51 (2H, br.s), 2.15 (3H, d, J=1.2 Hz) and 0.97 (3H, s), and the diketone 7 were obtained in a ratio of 1 : 3. Other alkyl groups (e.g. methoxymethyl) could be introduced at C-10 by the similar procedures. Moreover, furan moieties are easily oxidized to give the γ-lactones by peracid.4) These results could present the useful general route to the relatively highly oxidized eudesmane and elemane sesquiterpene lactones and furans. Studies on the total syntheses of natural eudesmanolides, elemanolides and eremophilanolides5) by this strategy are under way.

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