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TOTAL SYNTHESIS OF (±)-ISOALANTOLACTONE AND (±)-DIHYDROCALLITRISIN

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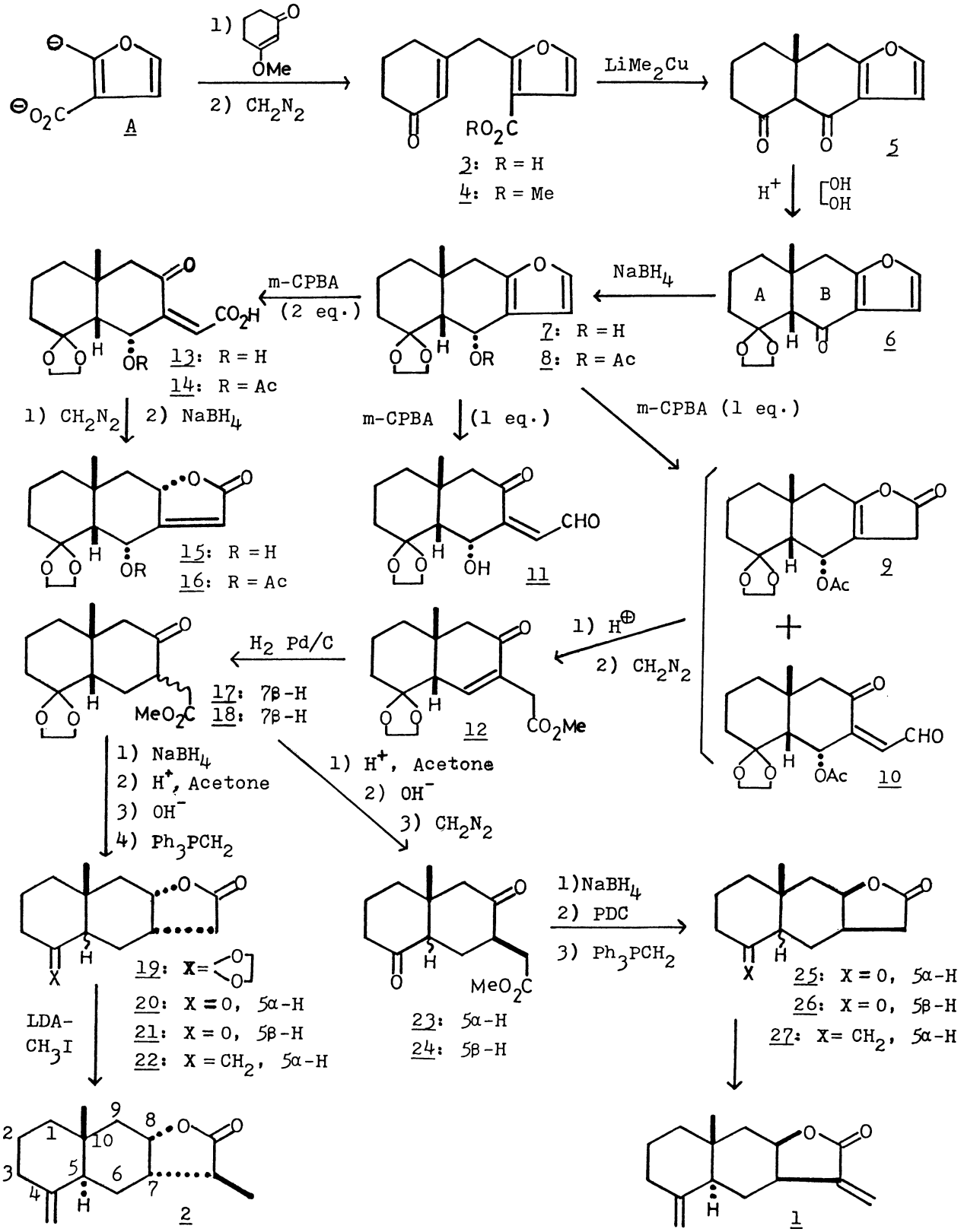
Two eudesmanolides having opposite stereochemistry of lactone ring each other, (±)-isoalantolactone and (±)-dihydrocallitrisin were synthesized stereoselectively by a route involving alkylation of 2-methyl-3-furoic acid and oxidation of furan ring.

Sesquiterpene lactones have attracted much synthetic interest because of the structural variety of the compounds having considerable biological activity as allergenic agents, growth inhibitor, antibacterial agents and antitumor agents.[1] Eudesmanolides can be distingushed into four groups in consideration of stereochemistry of γ-lactone ring.[2] In this report, we describe stereoselective total synthesis of two eudesmanolides which have opposite stereochemistry of γ-lactone ring each other, (±)-isoalantolactone (1)[3] and (±)-dihydrocallitrisin (2)[4] by a route involving the alkylation reaction of 2-methyl-3-furoic acid[5] and oxidation of furan ring. Previously we reported efficient synthesis of furanoeremophilane and 14-norfuranoeudesmane derivatives by a route involving alkylation of 2,4-dimethyl-3-furoic acid.[6] We planned to create the γ-lactone ring by oxidation of furan ring, and then to introduce an α-methylene or α-methyl group on the γ-lactone ring. According to this strategy, 2-methyl-3-furoic acid was used for the starting material of our synthesis of eudesmanolides.

A dianion A was generated from 2-methyl-3-furoic acid with LDA as described previously.[6] The reaction of the dianion A with 3-methoxy-2-cyclohexen-1-one gave an acid (3) (yield: 70 %). Methylation of the acid 3 with diazomethane formed an ester (4) which was treated with $LiMe_2Cu$ at 0 °C for 45 hr to produce a cyclized compound (5) directly (89 %). Ketalization of the dione 5 (reflux in PhH-ethylene glycol-TsOH) afforded an A/B cis-ketone (6) (88 %).[7] The alcohol (7) was obtained stereoselectively by reduction of 6 with $NaBH_4$ in DGM-H_2O-NaOH


A
1) 2) CH_2N_2
3: R = H
4: R = Me
$LiMe_2Cu$
5
H^+
6
A B
$NaBH_4$
7: R = H
8: R = Ac
m-CPBA (2 eq.)
13: R = H
14: R = Ac
1) CH_2N_2 2) $NaBH_4$
15: R = H
16: R = Ac
m-CPBA (1 eq.)
11
m-CPBA (1 eq.)
9
1) $H^{\oplus}$ 2) CH_2N_2
10
12
H_2 Pd/C
17: 7β-H
18: 7β-H
1) $NaBH_4$ 2) H^+, Acetone 3) OH^- 4) Ph_3PCH_2
1) H^+, Acetone 2) OH^- 3) CH_2N_2
19: X=
20: X = O, 5α-H
21: X = O, 5β-H
22: X = CH_2, 5α-H
23: 5α-H
24: 5β-H
1) $NaBH_4$ 2) PDC 3) Ph_3PCH_2
25: X = O, 5α-H
26: X = O, 5β-H
27: X = CH_2, 5α-H
LDA-CH_3I
2
1

at 120 °C (94 %). Acetylation of 7 in Ac_2O-pyridine at ambient temperature formed the acetate 8 (92 %). The stereochemistry of the compounds 6, 7 and 8 was assigned by ^{1}H-NMR spectra of the alcohol 7 and the ester 8. The ^{1}H-NMR spectrum of the acetate 8 showed the C-6 proton as a broad doublet at δ 5.94 (J = 6 Hz). The chemical shift of C-10 methyl group of 8 appears at δ 1.14 (s) which is near to that of 7 at δ 1.09 (s). These indicate the only possible stereochemistry of the alcohol 7 and the ester 8 should be shown in the formulae.

Oxidation of furan ring with peracid was then studied to create γ-lactone ring. Tekeda obtained a β,γ-unsaturated γ-lactone by oxidation of a furan compound with perbenzoic acid.[8] Oxidation of the acetate 8 with 1 equivalent mole of m-CPBA in CH_2Cl_2, gave a mixture of a lactone (9) and a keto-aldehyde (10) (9 : 10 = 6 : 4, total yield: 90 %), whereas the alcohol 7 produced only keto-aldehyde (11) by the same treatment (90 %). Treatment of the mixture (9 and 10) with p-TsOH in THF at ambient temperature for 44 hr, followed by esterification with diazomethane, afforded an ester (12) (57 % overall yield from 7). The ester 12 was converted to two eudesmanolides 1 and 2 stereoselectively. Oxidation of the alcohol 7 and the acetate 8 with 2 equivalent mole of m-CPBA gave acids (13) (96 %) and (14) (87 %), respectively. The stereochemistry of the double bond of 13 and 14 was deduced from the conversion of 13 and 14 to lactones (15) (81 %) and (16) (78 %) (CH_2N_2 in Et_2O; $NaBH_4$ in MeOH). These acids 13 and 14 should be important intermediates for synthesis of highly oxidized eudesmanolides. Catalytic hydrogenation of the ester 12 with 5%-Pd/C in AcOEt yielded esters (17) and (18) (5 : 1) quantitatively. The stereochemistry of major ester 17 was assumed from the reaction mechanism of the hydrogenation.

The major ester 17 which was separated by MPLC was converted into dihydrocallitrisin as follows. Reduction of the ester 17 with $NaBH_4$ in MeOH gave a lactone (19) quantitatively. Treatment of 19 in acetone-TsOH gave an A/B *cis*-compound (21), and the product 21 was equilibrated in MeOH-KOH to afford a mixture of A/B *trans*- and *cis*- compounds (20) and (21) (10 : 1, 89 % from 19). The A/B *trans*-compound 20 which was crystallized selectively from a solution of 20 and 21 in Et_2O-hexane, was methylenated with Ph_3PCH_2 in THF-HMPT to produce a compound (22) (90 %). Methylation of 22 with LDA-CH_3I formed stereoselectively (±)-dihydrocallitrisin 2 which was identical (IR and ^{1}H-NMR spectra) to the natural product 2.[4]

(±)-Isoalantolactone 1 was then synthesized from the ester 17 and 18. The

mixture of the esters 17 and 18 was successively submitted to deketalization with acetone-TsOH, to equilibration in MeOH-KOH and then to methylation with diazomethane to give diketo-esters (23) and (24) (3 : 1, 85 % overall yield from a mixture of 17 and 18). Both of the diketo-esters (23 and 24) have 7β side chain, which was confirmed by conversion of 23 and 24 to isoalantolactone 1. The mixture (23 and 24) was reduced by $NaBH_4$ in MeOH, without separation. The product was oxidized with PDC[10] to give keto-lactones (25) and (26) (3 : 1, 95 % overall yield from a mixture of 23 and 24).[11] After separation by MPLC, the A/B cis-keto-lactone 26 was equilibrated in 1%-KOH-MeOH to give the similar mixture of 25 and 26. Wittig reaction of the A/B trans-compound 25 (Ph_3PCH_2 in THF-HMPT) produced the lactone (27) (88 %) which was led to isoalantolactone 1 according to the procedures described in the literature.[12] The synthesized compound 1 was identical (IR and ^{1}H-NMR spectra) to isoalantolactone 1.[2,3,12]

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