AN EFFICIENT TOTAL SYNTHESIS OF AC-5-1 : NOVEL 5-LIPOXYGENASE INHIBITOR ISOLATED FROM ARTOCARPUS COMMUNIS

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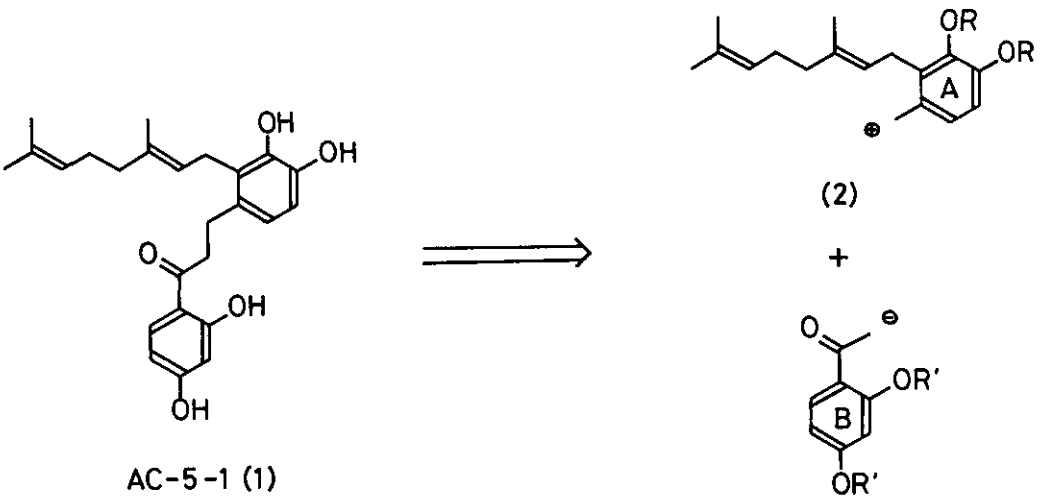
Abstruct———The first total synthesis of the highly potent 5-lipoxygenase inhibitor, AC-5-1, from Artocarpus communis has been accomplished by using the oxazoline method of Meyers as a key step.

Recently, AC-5-1 (1), a novel dihydrochalcone with highly potent and selective 5-lipoxygenase inhibiting activity has been isolated from the Indonesian plant Artocarpus communis[1,2] In view of its interesting structure and attractive bioactivity, we undertook its total synthesis. Here, we wish to report the first total synthesis of (1).



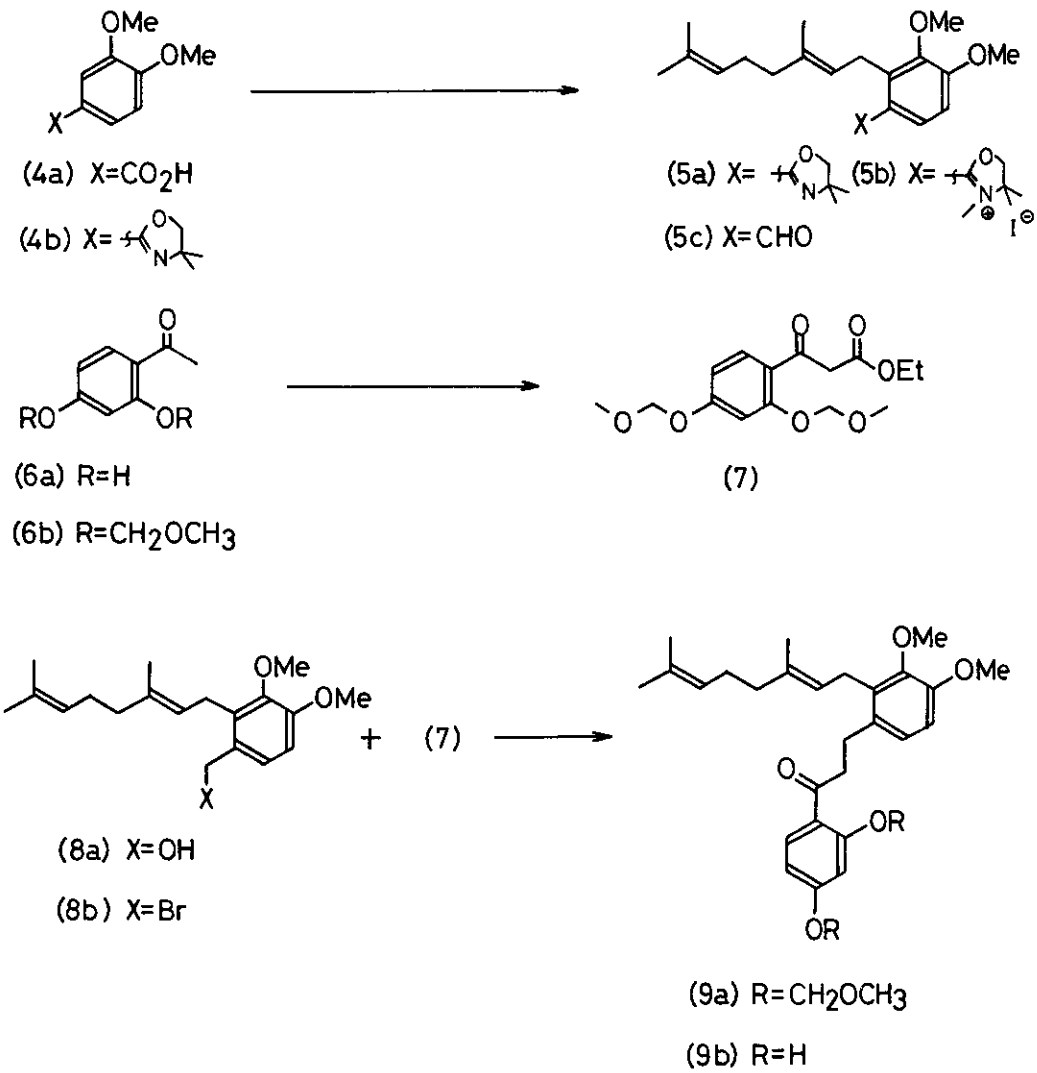
Scheme 1

On the consideration that the A ring part (2) (Scheme 1) would be constructed by

using the oxazoline method of Meyers[3], the regioselective introduction of a geranyl group into 2-(3,4-dimethoxyphenyl)-4,4-dimethyloxazoline (4b) derived from 3,4-dimethoxybenzoic acid (4a) and 2-amino-2-methylpropanol[4] was performed according to the standard procedure of Meyers[5]. Thus, the oxazoline (4b) was lithiated with n-butyllithium in dry tetrahydrofuran (THF) at -45°C under an argon atmosphere, and subsequently treated with geranyl bromide to give regioselectively 2-(2-geranyl-3,4-dimethoxyphenyl)-4,4-dimethyloxazoline (5a) in 60% overall yield from (4a). Reduction of the oxazolinium salt (5b) derived from (5a) and methyl iodide, using K-selectride[6] in THF at 0°C, followed by a hydrolytic ring opening with oxalic acid in aqueous THF yielded the aldehyde (5c) in 78% overall yield, ir $\nu_{max}(CHCl_3)$ 1680cm^{-1}; ^{1}H nmr $\delta(CDCl_3)$ 1.56(3H, br s), 1.64(3H, br s), 1.80(3H, br s), 2.01(4H, br s), 3.81(2H, d, J=7 Hz), 3.82(3H, s), 3.95(3H, s), 4.98-5.07(1H, br t, J=8 Hz), 5.10-5.19(1H, br t, J=8 Hz), 6.91(1H, d, J=9 Hz), 7.68(1H, d, J=9 Hz), 10.12(1H, s); ms(m/z) 302(M^+), 283, 219, 205, 191, 109.

In order to prepare a dihydrochalcone skeleton, (5c) was converted to the bromide (8b) via the benzyl alcohol (8a) in 90% overall yield by the sodium borohydride reduction and the following bromination with phosphorous tribromide. On the other hand, the masked acetophenone (6b) derived from 2,4-dihydroxyacetophenone (6a) and methoxymethyl chloride was refluxed with diethyl carbonate in dry toluene in the presence of sodium hydride (NaH) to give rise to the masked benzoylacetate (7) in 85% yield[7,8] which was used for the following condensation reaction with (8b). Condensation of (8b) with the keto ester (7) in the presence of NaH in dry dimethylformamide (DMF), followed by the successive hydrolysis and decarboxylation with 15% ethanolic potassium hydroxide at 60°C afforded the masked dihydrochalcone (9a) in 65% yield. Deprotection of two methoxymethyl groups of (9a) proceeded under stirring with 15% hydrochloric acid in methanol-THF (7:3) to give the 3,4-O,O-dimethyl-AC-5-1 (9b) in 86% yield, ir ν_{max}(neat) 3250, 1630cm^{-1}; ^{1}H nmr $\delta(CDCl_3)$ 1.52(3H, br s), 1.62(3H, br s), 1.73(3H, br s), 1.97(4H, br s), 2.91-3.00(2H, br t, J=10 Hz), 3.05-3.18(2H, br t, J=10 Hz), 3.40(2H, d, J=7 Hz), 4.97-5.13(2H, m), 5.76(1H, br s, OH), 6.33(1H, dd, J=9 Hz, 2 Hz), 6.36(1H, d, J=2 Hz), 6.74(1H, d, J=9 Hz), 6.88(1H, d, J=9 Hz), 7.58(1H, d, J=9 Hz), 12.77(1H, s, OH); ms(m/z) 438(M^+), 406, 316, 296, 286, 273, 255, 217, 203, 193 (Found: $\underline{M}^+$, 438.2427. $C_{27}H_{34}O_5$ requires $\underline{M}$, 438.2425). Treatment of (9b) with boron tribromide in dry methylene chloride at 0°C under an argon atmosphere gave the crude product, which was stirred in the

presence of zinc powder in acetic acid to give AC-5-1 (1) in 77% yield as a colorless powder, mp 132-136°C. Spectral data(ir, ^{1}H nmr, and ms) of the synthesized (1) were identical in every respect with those of the natural (1). Furthermore, the retention time (5.05 min) of compound (1) on high performance liquid chromatography (HPLC) also coincided with that of the natural product[9].



Scheme 2

ACKNOWLEDGEMENT

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9. HPLC conditions; Column: Cosmosil 5Ph, 4.6X150 mm,
   Mobile phase: acetonitrile:0.01% aqueous acetic acid=70:30,
   Flow Rate: 1 ml/min, Detection: UV 254 nm.

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