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SYNTHESIS OF (-)-DIHYDROMAHUBANOLIDE B AND (-)-ISODIHYDROMAHUBANOLIDE B

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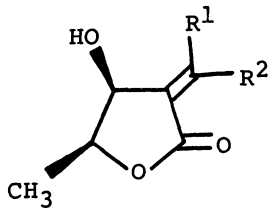
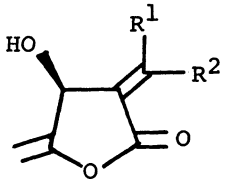
The total synthesis of (-)-dihydromahubanolide B and (-)-isodihydromahubanolide B isolated from the Amazonian Lauraceae *Licaria mahuba* (Samp.) Kosterm was achieved starting from (-)-methyl 5-hydroxy methyl -2,2-dimethyl-1,3-dioxolane-4-carboxylate which was readily available from L-(+)-tartaric acid.

In association with the synthetic work of optically active natural lactones having a variety of biological activities, our interest has been elicited in the synthesis of a series of structurally related γ-lactones found in the Lauraceae family. Among these are obtusilactones[1] and litsenolides[2] isolated from the Japanese Lauraceae, and mahuba lactones[3] from the Amazonian Lauraceae, all of which have similar structural characteristics; α-alkylidene-β-hydroxy-γ-lactone moiety and fatty acid-derived long chain substituents. Some components belonging to obtusilactones were reported to possess cytotoxic activity. Only a few reports concerning the synthetic studies of these compounds have been published to date.[4] In our synthetic approach[5] which would lead to obtusilactone (3) and congeners, we had chosen the known chiral hydroxy ester 7 as the starting material which is readily available in a four-step sequence from L-(+)-tartaric acid.





(1) R^1=H R^2=$C_{15}H_{31}$

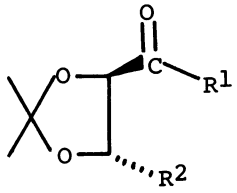
(2) R^1=$C_{15}H_{31}$, R^2=H

(3) R^1=H, R^2=$(CH_2)_9CH=CH_2$

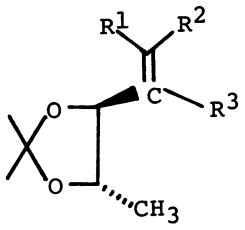
(4) R^1=H, R^2=$(CH_2)_{12}CH_3$

(5) R^1=$(CH_2)_{12}CH_3$, R^2=H

In this communication, we describe a synthesis of (-)-dihydromahubanolide B (1) and (-)-isodihydromahubanolide B (2), two members belonging to mahuba lactones, from this ester (7). Hydroxy ester (7) ($[\alpha]_D^{25}$ -17.0° (CH_3OH)) was prepared from L-(+)-tartaric acid *via* diester 6 in 37% overall yield by a slightly modified literature procedure.[6] This was then treated with methanesulfonyl chloride in pyridine to give mesylate (8)[6] which on refluxing with NaI in 2-butanone provided iodide (9)[7] in good yield. Deiodination of 9 to 10 proceeded smoothly by catalytic hydrogenolysis (5% Pd-C/CH_3OH) in the presence of triethylamine. Since ester 10 was now in hand, our attention was turned to modification of the ester group of 10. The sequential treatment of 10 with $Ba(OH)_2$ in CH_3OH, KOH in CH_3OH and oxalyl chloride in ether gave rise to acid chloride (12). Decomposition of diazomethyl ketone (13) obtained from 12 and excess diazomethane in ether was carried out with benzoic acid and Cu powder in boiling dioxane. Keto benzoate (14) (mp 58-9°, $[\alpha]_D^{23}$ +85.0° ($CHCl_3$)) thus obtained (86% yield from 12) was subjected to the Wittig reaction. The requisite ylide was generated by treatment with *n*-BuLi of the corresponding phosphonium salt[8] derived from hexadecyl bromide and triphenylphosphine in toluene. On brief treatment of 14 with the above ylide, the allylic benzoate (15) was predominantly produced as an inseparable mixture of geometrical isomers 15a and 15b, together with a small amount of the corresponding alcohol (16) which also consisted of *E* (16a) and *Z* isomers (16b) (*vide infra*). On prolonged treatment of 14 with the ylide, however, 16a and 16b were the major products apparently resulting from further nucleophilic attack of the excess ylide on the ester group of the adducts 15a and 15b. Without separation, the isomeric mixture of 15 was reduced with $LiAlH_4$ in ether, and allylic alcohols obtained were successfully separated into *E* (16a) ($[\alpha]_D^{21}$ +24.2° ($CHCl_3$)) and *Z* isomers (16b) ($[\alpha]_D^{21}$ +27.0° ($CHCl_3$)) (ca. 2 : 8) by repeated column chromatography. The stereochemistry of isomeric alcohols was determined as follows. Oxidation of the major (less mobile) and minor (more mobile) isomers of 16 with active MnO_2 in CH_2Cl_2 gave the corresponding aldehydes, respectively, without isomerization of unsaturated bond, although the reaction proceeded slowly, especially in the minor isomer. In the NMR spectra of the aldehydes obtained in this way, the formyl proton of 17b derived from the major alcohol (16b) resonates at 9.70 ppm, while that of another isomer resonates at 10.08 ppm.[9] Accordingly, the stereochemistry of 16a and 16b is as represented in the figure.



(6) $R^1=OCH_3$, $R^2=CO_2CH_3$
(7) $R^1=OCH_3$, $R^2=CH_2OH$
(8) $R^1=OCH_3$, $R^2=CH_2OMs$
(9) $R^1=OCH_3$, $R^2=CH_2I$
(10) $R^1=OCH_3$, $R^2=CH_3$
(11) $R^1=OH$, $R^2=CH_3$
(12) $R^1=Cl$, $R^2=CH_3$
(13) $R^1=CHN_2$, $R^2=CH_3$
(14) $R^1=CH_2OCPh$, $R^2=CH_3$



(15a) $R^1=H$, $R^2=C_{15}H_{31}$, $R^3=CH_2OCPh$
(15b) $R^1=C_{15}H_{31}$, $R^2=H$, $R^3=CH_2OCPh$
(16a) $R^1=H$, $R^2=C_{15}H_{31}$, $R^3=CH_2OH$
(16b) $R^1=C_{15}H_{31}$, $R^2=H$, $R^3=CH_2OH$
(17a) $R^1=H$, $R^2=C_{15}H_{31}$, $R^3=CHO$
(17b) $R^1=C_{15}H_{31}$, $R^2=H$, $R^3=CHO$
(18a) $R^1=H$, $R^2=C_{15}H_{31}$, $R^3=CO_2H$
(18b) $R^1=C_{15}H_{31}$, $R^2=H$, $R^3=CO_2H$

At this stage we encountered a difficulty in oxidizing 17a and 17b to the corresponding carboxylic acid (18a) and (18b). The conventional method with Ag_2O in a variety of aqueous bases such as KOH, $Ba(OH)_2$ and K_2CO_3 failed. Even the recently developed oxidation method using a combination of AgO and cyanide anion[10] gave no satisfactory result. Jones oxidation led to a complex mixture of products. Pyridinium dichromate oxidation[11] in DMF at low temperature is one of the efficient reaction conditions under which allylic alcohols are easily oxidized to the corresponding unsaturated aldehydes without affecting conjugated double bond. When an excess of this reagent was applied to 17a at ambient temperature, but not at lower temperature, the desired unsaturated carboxylic acid was found to be produced, although a considerable amount of the unchanged aldehyde was recovered. Unfortunately, the acid as well as the recovered aldehyde proved to be a mixture of geometrical isomers by NMR examination. Direct oxidation of 16a and 16b with this reagent also generated a mixture of 18a and 18b, accompanied by 17a and 17b.

Finally, the mixture of the acid isomers, without separation into its individual components, was treated with 80% aqueous acetic acid at reflux temperature

or 90% aqueous trifluoroacetic acid at room temperature to afford a mixture containing lactonic products. Purification by column chromatography followed by preparative TLC gave (-)-isodihydromahubanolide B (2) (mp 78-9°, $[\alpha]_D^{22}$ -102° (dioxane)), IR and NMR spectra of which were superimposable with those of the natural material (mp 70-1°, $[\alpha]_D$ -93.3° (dioxane)), and (-)-dihydromahubanolide B (1) (mp 66-7°, $[\alpha]_D^{21}$ -37° (dioxane)). The spectral examination of synthetic 1 thus obtained fully supported the structure proposed to (-)-dihydromahubanolide B, although natural 1 has not yet been isolated in the pure form and no physical data recorded.

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References and Notes

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