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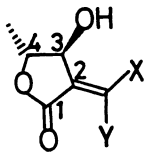
Synthesis of Optically Active Litsenolide C

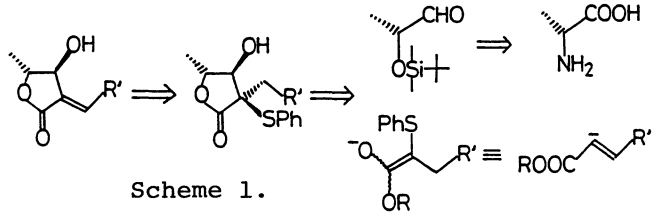
Shoji WAKABAYASHI, Hideki OGAWA, Naomi UENO, Norio KUNIEDA,[+]
Tadakatsu MANDAI, and Junzo NOKAMI*
Okayama University of Science, Ridai, Okayama 700
[+]Faculty of Engineering, Osaka City University, Sumiyoshi, Osaka 558

Lithium enolate, derived from alkyl 2-(phenylthio)alkanoate with lithium diisopropylamide, reacted with aldehyde in the presence of diethylaluminum chloride to give alkyl 2-phenylthio-2-alkyl-3-hydroxyalkanoate, which was converted to 2-alkylidene-3-hydroxy-alkanoate via thermolysis of the corresponding sulfoxide. The title compound was synthesized from methyl 2-(phenylthio)hexadecanoate and (R)-(+)-2-tert-butyldimethylsilyloxypropanal by employing the method.

Natural products containing the 2-alkylidene-3-hydroxy-4-methyl(or methylene)-4-butyrolactone functionality, litsenolides[1] (or obtusilactone and mehubanolides),[2] have been isolated from Lauraceae family. These 2-alkylidene-3-hydroxy-4-butyrolactones are well known to exhibit fairly remarkable bioactivity, and have been synthesized by C. Benezra et al.[3] and J. A. Katzenellenbogen et al.[4] Moreover, the syntheses of optically active litsenolides from D-ribonolactone[5a] and D-glucose[5b] have been reported. Here we describe new synthesis of optically active litsenolide C.

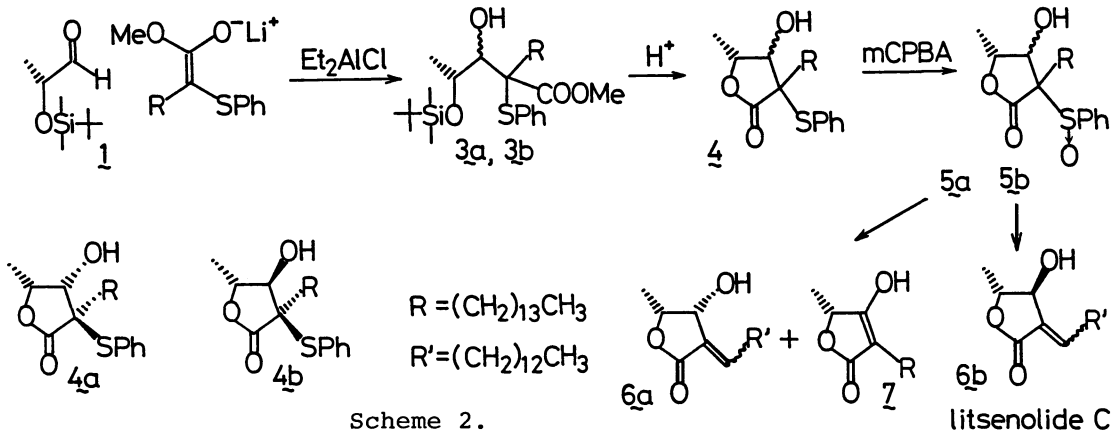


Litsenolide A_1 X=H, Y=$(CH_2)_9CH{=}CH_2$; A_2 X=$(CH_2)_9CH{=}CH_2$, Y=H;
B_1 X=H, Y=$(CH_2)_9C{\equiv}CH$; B_2 X=$(CH_2)_9C{\equiv}CH$, Y=H;
C_1 X=H, Y=$(CH_2)_{12}CH_3$; C_2 X=$(CH_2)_{12}CH_3$, Y=H.



Scheme 1.

Our synthetic strategy for the optically active litsenolide is to build the required absolute configuration at C(3) and C(4) of 3-hydroxy-4-valerolactone by diastereoface differentiation reaction of acrylate α-anion equivalent with (R)-(+)-2-tert-butyldimethylsilyloxypropanal (1)[6] and to form the C(2)-C(3) bond by erythro selective reaction of the aldehyde with lithium enolate derived from 2-(phenylthio)ester[7] as shown in Scheme 1. There are a few reports on the reaction of aldehyde with acrylate α-anion equivalent to form 2-alkylidene-3-hydroxy-4-butyrolactone derivatives.[8] However, the reported methods are not suitable for our purpose.[9] Meanwhile, we have found out that the aldol reaction of (R)-(+)-2-tert-butyldimethylsilyloxypropanal (1) with *the lithium enolate* derived from alkyl 2-(phenylthio)alkanoate and LDA is promoted by diethylaluminum chloride to give (4R)-2-phenylthio-2-alkyl-3-hydroxy-4-tert-butyldimethylsilyloxypentanoate in good yield. Then, our synthesis of the title compound was carried out by employing this method as follows (Scheme 2).



Scheme 2.

To a stirred solution of LDA was added methyl 2-(phenylthio)hexadecanoate (2) at 0 °C. The aldehyde 1 and diethylaluminum chloride (2 M hexane solution, 1.2 equiv.) were added successively to the reaction mixture at -70 °C and the stirring was continued for 1 hour.[10] Workup (acid hydrolysis by aq. tartaric acid and extraction) gave a crude product, which was purified by column chromatography on silica gel to give two stereoisomeric products, i.e. less polar product 3a (Rf 0.47, ether/hexane=1/5) and polar product 3b (Rf 0.40, ether/hexane=1/5) in 20% and 59% isolated yield respectively.[11] The products, 3a and 3b, were separately treated with a catalytic amount of p-toluenesulfonic acid in CH_2Cl_2 at room temperature to give 2-phenylthio-2-tetradecanyl-3-hydroxy-4-valerolactones (4a and 4b),[12] in quantitative yield. The 2-(phenylthio)lactones were oxidized by m-chloroperbenzoic acid to the corresponding sulfoxides, 5a and 5b,[13] which were heated at 80 °C in benzene to yield desulfurized lactones. (3R,4R)-2-Tetradecanylidene-3-hydroxy-4-valerolactone (6a) (*E*/*Z*=4/1) and (4R)-2-tetradecanyl-3-hydroxy-4-methyl-4-but-2-enolide (7) were obtained from 5a in 17% and 62% yield respectively,[14] and (3S,4R)-2-tetradecanylidene-3-hydroxy-4-valerolactone (6b) (*E*/*Z*=4/1) was obtained from 5b in 83% yield. Litsenolide C_2 (*E* isomer) and C_1 (*Z* isomer) were separated by flash column chromatography on silica gel eluted by a mixed solvent of benzene and ether.[15] Then, optically active litsenolides(C_1 and C_2) were obtained in ca. 40% yield based on the aldehyde 1. The configuration of the intermediates, e.g. 4a and 4b, may be shown in Scheme 2, in which the configuration of 4b is the same as that expected at the retrosynthetic study.[16]

We wish to show here chracteristics of the diethylaluminum chloride promoted aldol reaction of lithium enolate with aldehyde as follows: (1) The chemical yield is high. (2) The ratio of erythro/threo about the formed C-C bond is 2/1-3/1. (3) The diastereoface differentiation reaction about the aldehyde 1 seems to be performed by non-chelation-controlled stereoselectivity, and the ratio of erythro(anti)/threo(syn)=3/1. The typical results are listed in Table 1.

On the other hand, we could obtain the following result by employing the Hoye's method.[7] Diastereoface selectivity of the zinc enolate, derived from methyl 2-(phenylthio)hexadecanoate, with the aldehyde 1 was not observed (erythro/threo=1/1) though the reaction was performed erythro specifically about the formed C-C bond. Then, the Hoye's method seems to be advantageous for the synthesis of 3,4-cis isomers of 2-alkylidene-3-hydroxy-4-valerolactones.[4]

Table 1. Et_2AlCl Promoted Aldol Reaction of Lithium Enolate (Derived from 2-(Phenylthio)ester and LDA) with Aldehyde (and Ketone)

2-(Phenylthio)ester 2	Aldehyde or ketone	Reaction conditions	3 Yield/%[a] (erythro/threo)[b]	
$CH_3CH(SPh)COOMe$	benzaldehyde	-78 °C 0.5 h	76 (3/1)[a]	65[c] (3/1)[a]
$CH_3CH_2CH(SPh)COOEt$	$CH_3(CH_2)_5CHO$	-78 °C 1 h	93 (2/1)[a]	47[c] (1/1)[a]
	$CH_3CH=CHCHO$	-78 °C 0.5 h	93 (2/1)[d]	
	cyclopentanone	-78 °C 0.5 h	81	
$CH_3(CH_2)_{13}CH(SPh)COOMe$	(R) $CH_3CH(OSiMe_2Bu^t)CHO$	-70 °C 1 h	72 (3/1)[a]	47[c] (e)[a]

a) After isolation by column chromatography on silica gel.
b) The ratio shows the stereoselectivity about the formed C-C bond.
c) By the Hoye's method (reaction of the zinc enolate at 0 °C).
d) Measured by ^{13}C NMR.
e) Erythrospecificity about the formed C-C bond and no diastereoface selectivity about the optically active 1 were observed.

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6) The aldehyde 1 ($[\alpha]_D^{20}$+11° (c 1.0, $CHCl_3$)) was obtained from methyl (R)-(+)-lactate by silylation (Bu^tMe_2SiCl, imidazole, DMF) followed by DIBAH reduction (CH_2Cl_2, -78 °C). Methyl (R)-(+)-lactate was prepared from D-alanine by a modified method for the conversion of L-glutamic acid to (S)-(+)-4-ethoxycarbonyl-4-butyrolactone (M. Taniguchi, K. Koga, and S. Yamada, Tetrahedron, 30, 3547 (1974)].
7) Hoye et al. reported that the zinc enolate derived from 2-(phenylthio)ester reacts with aldehyde to give 2-phenylthio-2-alkyl-3-hydroxyalkanoate erythro selectively [T. R. Hoye and M. J. Kurth, J. Org. Chem., 45, 3549 (1980)].
8) Refs. 3, 4, and 6; A. Bernardi, M. G. Beretta, L. Colombo, C. Gennari, G. Poli, and C. Scolastico, J. Org. Chem., 50, 4442 (1985).
9) It seems to be difficult for us to prepare an optically pure (R)-2-acetoxypropanal to employ

the Benezra's method, and the reaction of zinc enolate with 1 (Hoye's method) gave an undesired results. Moreover, it is easy for us to get the 2-(phenylthio)ester rather than any other synthon for acrylate α-anion equivalent.

10) Et_2AlCl was added after addition of aldehyde to the reaction mixture. It is important to get the desired product in good yield.

11) 3a: $[\alpha]_D^{20}$+19.4° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.46 (3H, s, OCH_3), 3.9 (2H, m, O-CH); ^{13}C NMR ($CDCl_3$) δ -4.23 (q), -4.11 (q), 14.09 (q), 18.08 (s), 21.49 (q), 22.66 (t), 24.95 (t), 25.95 (3xq), 29.41 (t), 29.65 (7xt), 30.47 (t), 31.88 (2xt), 51.37 (q), 64.17 (s), 70.10 (d), 76.85 (d), 128.52 (2xd), 129.34 (d), 130.39 (s), 137.09 (2xd), 171.44 (s); IR (neat) 3530, 1735 cm^{-1}.
3b: $[\alpha]_D^{20}$-12.2° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.65 (3H, s, OCH_3), 3.80 (1H, d, J=6 Hz, 3-H), 4.07 (1H, quint, J=6 Hz, 4-H); ^{13}C NMR ($CDCl_3$) δ -4.24 (q), -4.14 (q), 14.08 (q), 18.08 (s), 20.86 (q), 22.71 (t), 24.41 (t), 25.97 (3xq), 29.68 (9xt), 31.97 (t), 32.99 (t), 51.85 (q), 64.42 (s), 70.61 (d), 78.21 (d), 128.59 (2xd), 129.33 (d), 130.64 (s), 137.23 (2xd), 172.94 (s); IR (neat) 3550, 1735, 1710 cm^{-1}.

12) 4a: $[\alpha]_D^{20}$+32.5° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.05 (1H, d, J=5 Hz, -OH), 4.10 (1H, dd, J=5 and 7 Hz, 3-H), 4.26 (1H, quint, J=7 Hz, 4-H); IR (neat) 3450, 1740 cm^{-1}.
4b: $[\alpha]_D^{20}$-24.7° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.36 (1H, d, J=7 Hz, -OH), 4.00 (1H, dd, J=7 and 8 Hz, 3-H), 4.20 (1H, dq, J=6 and 8 Hz, 4-H); IR (nujol) 3420, 1740 cm^{-1}.

13) It was difficult to isolate the pure sulfoxides without the contamination of desulfurized product at room temperature.

14) 6a (*E*/*Z*=4/1); $[\alpha]_D^{20}$+69.1° (c 0.1, $CHCl_3$); *E* isomer is characterized as follows; ^1H NMR ($CDCl_3$) δ 1.46 (3H, d, J=6 Hz, 4-CH_3), 2.40 (2H, q, J=8 Hz, C=C-CH_2), 4.52 (1H, quint, J=6 Hz, 4-H), 4.81 (1H, d, J=6 Hz, 3-H), 6.93 (1H, t, J=8 Hz, C=CH); IR (neat) 3450, 1740, 1670 cm^{-1}.
7: $[\alpha]_D^{20}$-5.0° (c 0.1, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 1.50 (3H, d, J=7 Hz, 4-CH_3), 2.20 (2H, m, C=C-CH_2), 4.83 (1H, q, J=7 Hz, 4-H); IR (neat) 3500-2500 (broad), 1730, 1660, 1640 cm^{-1}.

15) Litsenolide C_2: $[\alpha]_D^{20}$-45.3° (c 0.4, dioxane), -52.2° (c 0.4, $CHCl_3$) (lit.[1] $[\alpha]_D^{26}$-45.2° (c 1.0, dioxane)); ^1H NMR ($CDCl_3$) δ 1.35 (3H, d, J=7 Hz, 4-CH_3), 2.40 (2H, q, J=8 Hz, C=C-CH_2), 4.5 (2H, m, O-CH), 6.99 (1H, dt, J=1.5 and 8 Hz, C=CH); IR (neat) 3450, 1740, 1680 cm^{-1}.
Litsenolide C_1: $[\alpha]_D^{20}$-8.0° (c 0.1, dioxane) (lit.[1] $[\alpha]_D^{24}$-9.4° (c 0.6, dioxane)), ^1H NMR ($CDCl_3$) δ 1.38 (3H, d, J=7 Hz, 4-CH_3), 2.76 (2H, q, J=8 Hz, C=C-CH_2), 4.3 (2H, m, O-CH), 6.53 (1H, dt, J=1 and 8 Hz, C=CH).

16) The configuration of 4a and 4b can be explained by assuming the occurrence of cis-elimination of the corresponding sulfoxides (5a and 5b) [C. A. Kingsbury and D. J. Cram, J. Am. Chem. Soc., 82, 1810 (1960)].

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