Synthesis of Optically Active Litsenolide C

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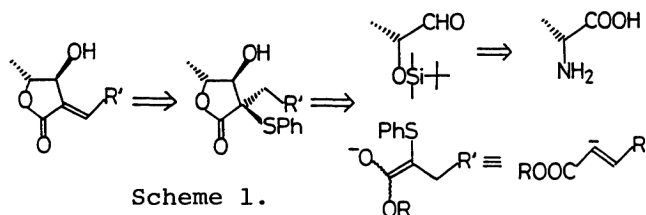[+]Faculty of Engineering, Osaka City University, Sumiyoshi, Osaka 558

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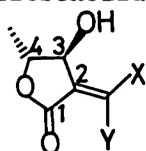
Litsenolide A_1 X=H, Y=$(CH_2)_9CH=CH_2$; A_2 X=$(CH_2)_9CH=CH_2$, Y=H;
B_1 X=H, Y=$(CH_2)_9C\equiv CH$; B_2 X=$(CH_2)_9C\equiv CH$, Y=H;
C_1 X=H, Y=$(CH_2)_{12}CH_3$; C_2 X=$(CH_2)_{12}CH_3$, Y=H.

Our synthetic strategy for
the optically active litsenolide
is to build the required absolute
configuration at C(3) and C(4)

Scheme 1.

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 diethyl-
aluminum chloride to give (4R)-2-phenylthio-2-alkyl-3-hydroxy-4-tert-butyldimethyl-
silyloxypentanoate in good yield. Then, our synthesis of the title compound was
carried out by employing this method as follows (Scheme 2).

Scheme 2.   litsenolide C

R =(CH₂)₁₃CH₃

R'=(CH₂)₁₂CH₃
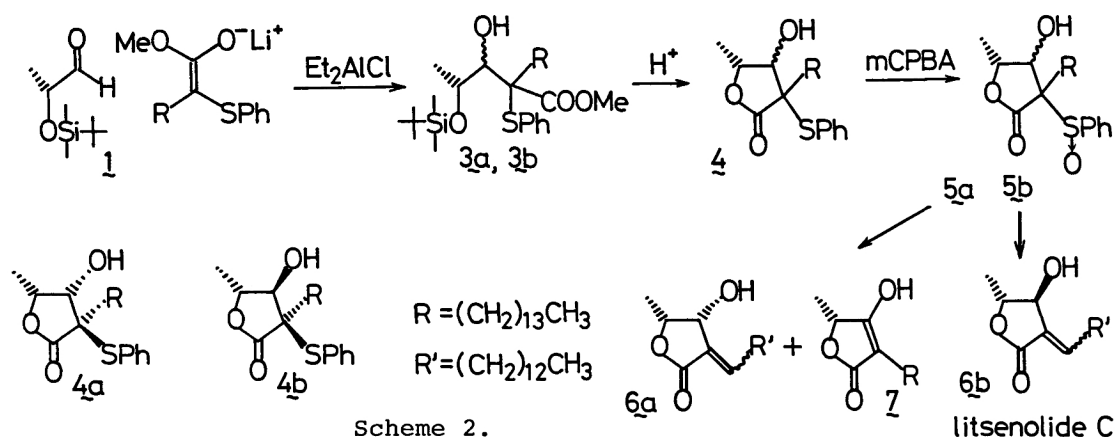
To a stirred solution of LDA was added methyl 2-(phenylthio)hexadecanoate (**2**) at 0 °C. The aldehyde **1** and diethylaluminum chloride (2 M hexane solution, 1.2 equiv.) were added successively to the reaction mixture at -70 °C and the stirring was continued for 1 hour.[10] Workup (acid hydrolysis 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$_3$CHCOOMe
  |
  SPh
	benzaldehyde	-78 °C
		0.5 h
			76
			(3/1) [a]
				65 [c]
				(3/1) [a]

CH$_3$CH$_2$CHCOOEt
  |
  SPh
	CH$_3$(CH$_2$)$_5$CHO	-78 °C
		1 h
			93
			(2/1) [a]
				47 [c]
				(1/1) [a]

	CH$_3$CH=CHCHO	-78 °C 0.5 h	93 (2/1) [d]	
	cyclopentanone	-78 °C 0.5 h	81	

CH$_3$(CH$_2$)$_{13}$CHCOOMe
  |
  SPh
	(R) CH$_3$CHCHO
	   |
	   OSiMe$_2$Bu^t
		-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[13] 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^{t}Me$_2$SiCl, imidazole, DMF) followed by DIBAH reduction (CH$_2$Cl$_2$, -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)].

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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 $\underline{1}$ (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) $\underline{3a}$: $[\alpha]_D^{20}$+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}.

$\underline{3b}$: $[\alpha]_D^{20}$-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) $\underline{4a}$: $[\alpha]_D^{20}$+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}.

$\underline{4b}$: $[\alpha]_D^{20}$-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) $\underline{6a}$ (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}.

$\underline{7}$: $[\alpha]_D^{20}$-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 $\underline{4a}$ and $\underline{4b}$ can be explained by assuming the occurrence of cis-elimination of the corresponding sulfoxides ($\underline{5a}$ and $\underline{5b}$) [C. A. Kingsbury and D. J. Cram, J. Am. Chem. Soc., $\underline{82}$, 1810 (1960)].

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