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Synthesis of Optically Active α-Alkylidene-β-hydroxy-γ-methylenebutyrolactones. Isoobtusilactones and Isomahubalactones (Isomahubanolide and Isomahubenolide)

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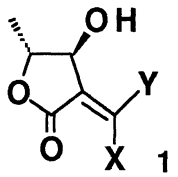
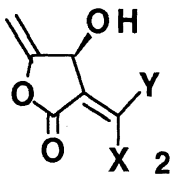
The title compounds were prepared via stereoselective aldol reaction of α,β-unsaturated carboxylate α-anion equivalent, derived from optically active α-(arylsulfinyl)carboxylate and bromomagnesium diisopropylamide, with propargyl aldehyde as a key step.

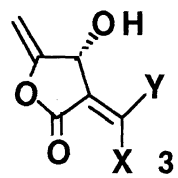
Litsenolides (**1**), the lactonic components of the Lauraceae family which have α-alkylidene-β-hydroxy-γ-valerolactone structure, have been isolated from *Litsea japonica* by Ishii et al.[1] in 1972. Similar lactones such as obtusilactones (**2**) and mahubalactones (**3**)[mahubanolides (**3a**), mahubenolides (**3b**), and mahubynolides (**3c**)], charactrized by α-alkylidene-β-hydroxy-γ-methylenebutyrolactone structure, have been isolated from japanese Lauraceae *Lindera obtusiloba* Blume as physiologically active substances by Yamamura et al.[2] in 1975, and from amazonian Lauracea *Licaria mahuba* Kosterm by Martinez et al.[3] in 1979, respectively.



1a Litsenolide A_1 X=$(CH_2)_9CH=CH_2$, Y=H;
1a' Litsenolide A_2 X=H, Y=$(CH_2)_9CH=CH_2$;
1b Litsenolide B_1 X=$(CH_2)_9C\equiv CH$, Y=H;
1b' Litsenolide B_2 X=H, Y=$(CH_2)_9C\equiv CH$;
1c Litsenolide C_1 X=$(CH_2)_{12}CH_3$, Y=H;
1c' Litsenolide C_2 X=H, Y=$(CH_2)_{12}CH_3$;



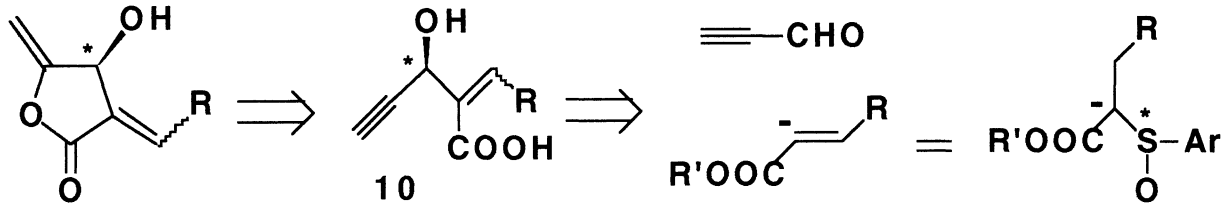
2 Obtusilactone X=$(CH_2)_9CH=CH_2$, Y=H;
2' Isoobtusilactone X=H, Y=$(CH_2)_9CH=CH_2$;
2a Obtusilactone A X=$(CH_2)_{12}CH_3$, Y=H;
2a' Isoobtusilactone A X=H, Y=$(CH_2)_{12}CH_3$;
2b Obtusilactone B X=cis-$(CH_2)_5CH=CH(CH_2)_7CH_3$, Y=H;
2b' Isoobtusilactone B X=H, Y=cis-$(CH_2)_5CH=CH(CH_2)_7CH_3$;



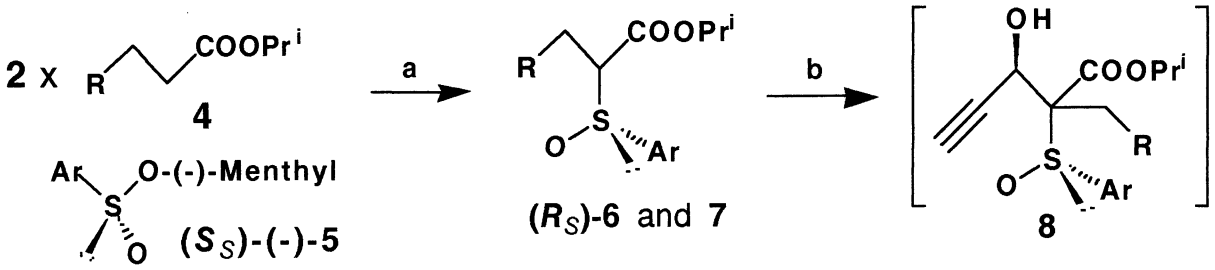
3a Mahubanolide X=$(CH_2)_{14}CH_3$, Y=H;
3a' Isomahubanolide X=H, Y=$(CH_2)_{14}CH_3$;
3b Mahubenolide X=$(CH_2)_{13}CH=CH_2$, Y=H;
3b' Isomahubenolide X=H, Y=$(CH_2)_{13}CH=CH_2$;
3c Mahubynolide X=$(CH_2)_{13}C\equiv CH$, Y=H;
3c' Isomahubynolide X=H, Y=$(CH_2)_{13}C\equiv CH$;

The syntheses of optically active litsenolides[4] and of racemic obtusilactones and mahubalactones[5] have been reported. However, to the best of our knowledge, no effort has been made on the synthesis of optically active obtusilactones and mahubalactones. Here we wish to report a new synthesis of optically active α-alkylidene-β-hydroxy-γ-methylenebutyrolactones (isoobtusilactones and isomahubalactones) by employing the stereoselective reaction of optically active sulfoxide.

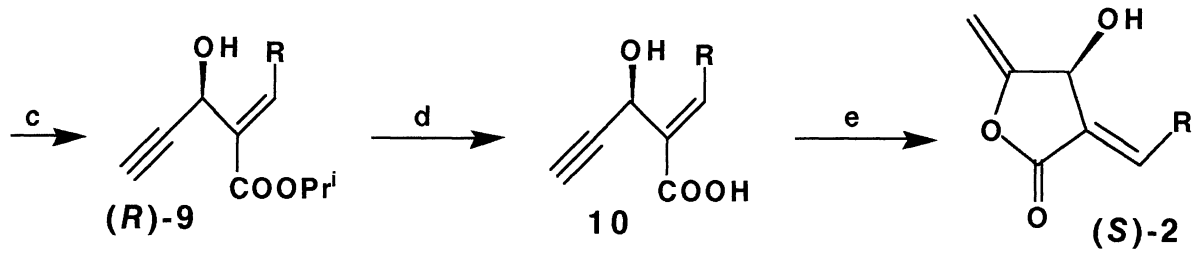
Our synthetic strategy for the title compounds is to build α-alkylidene-β-hydroxy-γ-pentynoic acid (**10**) by enantioselective reaction of α,β-unsaturated carboxylate α-anion (acrylate α-anion) with propargylaldehyde, and to build the α-alkylidene-β-hydroxy-γ-methylenebutyrolactone by intramolecular addition reaction of the carboxylic acid to the internal terminal-yn functionarity. In particular, optically active α-(arylsulfinyl)carboxylate is used as the acrylate α-anion equivalent possessing a possibility of considerable asymmetric induction to give an optically active alcohol.[6]



Diastereomeric mixtures of optically active isopropyl (R_S)-α-(p-tolylsulfinyl)carboxylates (**6** and **7**)[7] were prepared by sulfinylation of the corresponding esters **4**, derived from commercially available hexadecanoic acid and *cis*-octadec-9-enoic acid, with lithium cyclohexylisopropylamide and (-)-*l*-menthyl (S_S)-p-tolylsulfinate [(S_S)-**5**] in THF at -60 °C or by alkylation of isopropyl (R_S)-α-(p-tolylsulfinyl)acetate with sodium hydride and dodec-11-enyl iodide in DMSO at r.t. quantitatively.[8] The less polar diastereoisomer **6** (silica gel TLC, EtOAc/hexane=1/3) was treated with bromomagnesium diisopropylamide and then with propargylaldehyde in ether at -50 °C to give aldol product **8**.[9] The crude product **8** was heated in benzene at 60 °C for one hour in the presence of acid scavenger (sodium hydrogencarbonate) to afford the corresponding (*E*)-α-alkylidene-β-hydroxy ester **9** (sometimes with a trace of *Z* isomer) in 50% yield from **6**. On the other hand, the more polar isomer **7** did not give the aldol product and was recovered quantitatively after the same treatment as in the case of **6**.[10] However, the less reactive diastereoisomer **7** was also used effectively after stereoconversion at the α-position of α-(arylsulfinyl)carboxylate to the less polar isomer **6**. The ester **9** was converted to the carboxylic acid **10** by hydrolysis with Claisen's alkali[11] and then the acid was lactonized to isoobtusilactones **2** by treatment with a catalytic amount of silver carbonate[12] in 40-45% yield based on **9**. The specific rotations of the prepared isoobtusilactone (**2**), isoobtusilactone A (**2a**), and isoobtusilactone B (**2b**) were $[\alpha]_D$ -60.4° (c 0.278, dioxane); 92%ee [lit.[2] -56° (c 0.67, $CHCl_3$)], -50.0° (c 0.382, dioxane); 90%ee [lit.[2] -54° (c 0.50, $CHCl_3$)], and -30.6° (c 0.320, dioxane); 82%ee, respectively. The optical purities of the products were determined by HPLC (Daisel Chiralcel OD, i-PrOH/hexane=1/9) analysis.

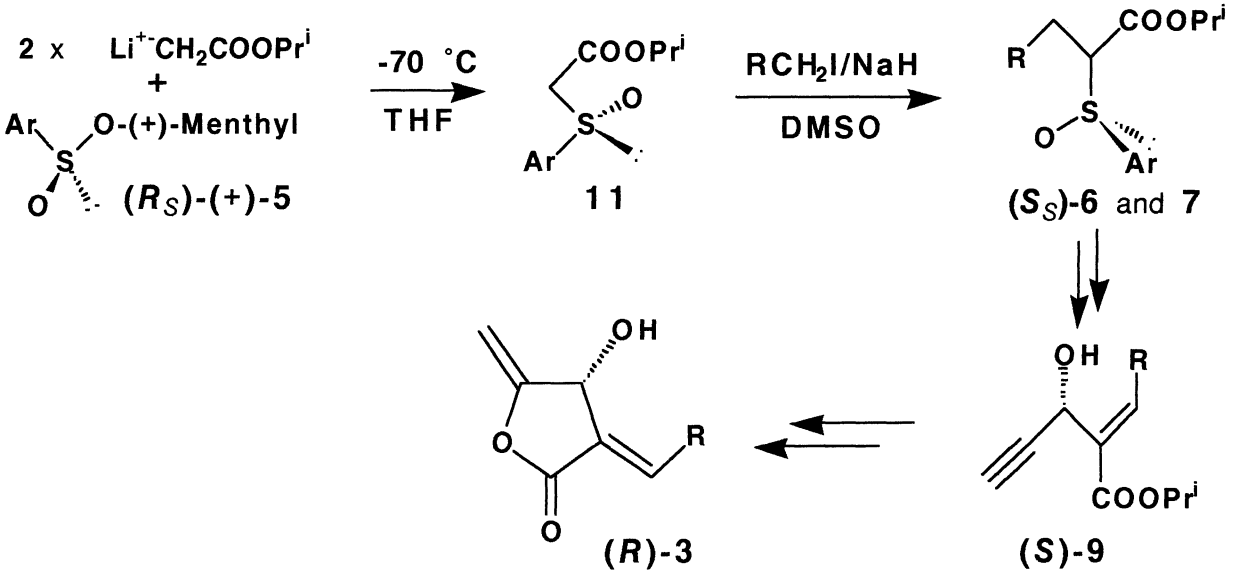


a. (2 x) $LiNPr^iC_6H_{11}$, (S_S)-(-)-**5**, -60 °C, THF; b. $BrMgNPr^i_2$, HC≡CCHO, -40 °C, ether;



c. 60 °C, $NaHCO_3$, benzene; d. KOH, H_2O, MeOH, r.t., ether, then H^+;
e. Ag_2CO_3 (cat.), 80 °C, benzene

The levorotatory α-alkylidene-β-hydroxy-γ-methylenebutyrolactones, isoobtusilactones, which have *S* configuration were prepared from (R_S)-**6** as described above. Therefore, the synthesis of dextrorotatory mahubalactones was carried out from (S_S)-**6** by the manner similar to that described in the synthesis of isoobtusilactones, and we obtained isomahubanolide (**3a**), $[\alpha]_D$ +35.9° (c 0.674, dioxane); 75%ee, and isomahubenolide (**3b**), $[\alpha]_D$ +37.1° (c 0.340, dioxane); 82%ee [lit.[3] +22.0° (dioxane)].



Through this investigation, we have found out the following facts; 1) the anion derived from less polar diastereoisomer of α-(arylsulfinyl)carboxylates reacts with propargyl aldehyde, 2) the anion derived from *R* configurational sulfoxide by the treatment with bromomagnesium diisopropylamide reacts with propargyl aldehyde enantioselectively to give (*R*)-propargylic alcohol [(*S*)-β-hydroxy-γ-methylenebutrylolactone], and 3) the (*E*)-α-alkylidene-γ-butyrolactones (isoobtusilactones and isomahubalactones) are predominantly prepared by this method.

References

1) K. Takeda, K. Sakurawi, and H. Ishii, *Tetrahedron*, **28**, 3757 (1972).
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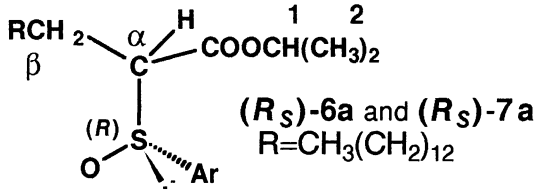
4) S. Wakabayashi, H. Ogawa, N. Ueno, N. Kunieda, T. Mandai, and J. Nokami, *Chem. Lett.*, **1987**, 875; W. W. Wood and G. M. Watson, *J. Chem. Soc., Chem. Commun.*, **1986**, 1599; S-Y. Chan and M. M.

Joullie, *Tetrahedron Lett.*, **24**, 5027 (1983).

5) S. W. Rollinson, R. A. Amos, and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **103**, 4114 (1981).

6) C. Papageorgiou and C. Benezra, *Tetrahedron Lett.*, **25**, 1303 (1984).

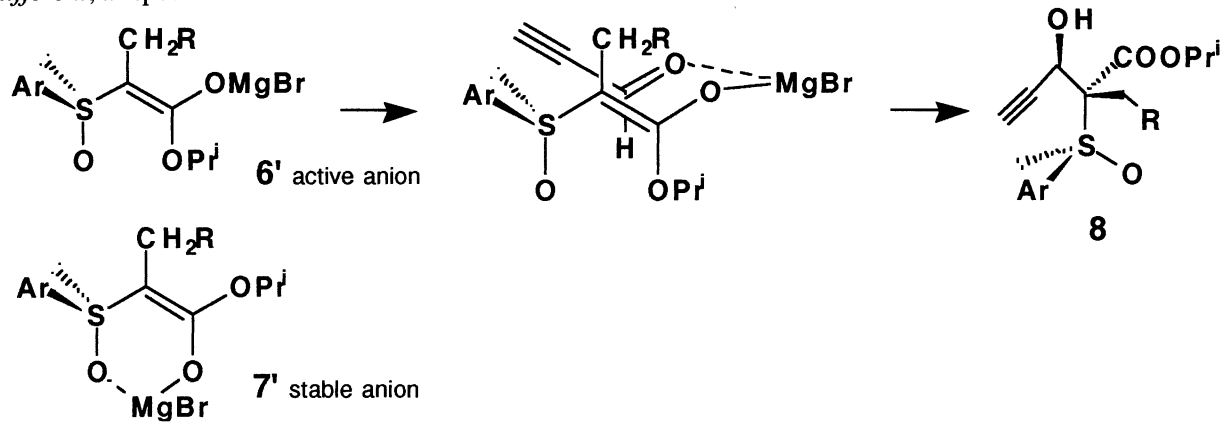
7) The absolute configuration of the diastereoismers **6** and **7** is not clear. The properties for isopropyl (R_S)-α-(p-tolylsulfinyl)hexadecanoate [(R_S)-**6a** and (R_S)-**7a**] are as follows. **6a**: $[\alpha]_D$ 33.1 (c 1.00, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ=72.7 (Cα); ^1H NMR ($CDCl_3$) δ=3.40 (dd, J=4.7 and 9.9 Hz, Hα), 2.10 (m, Hβ), 4.82 (quint, J=6.2 Hz, H_1), 0.93 (d, J=6.2 Hz, H_2), 1.14 (d, J=6.2 Hz, H_2). **7a**: $[\alpha]_D$ 112.2 (c 1.00, $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ=69.5 (Cα); 1H NMR ($CDCl_3$) δ=3.50 (dd, J=4.8 and 10.3 Hz, Hα), 1.73 (m, Hβ), 4.95 (quint, J=6.2 Hz, H_1), 1.11 (d, J=6.2 Hz, H_2), 1.20 (d, J=6.2 Hz, H_2). The R_f values on silica gel TLC (EtOAc/hexane = 1/3) were 0.52 and 0.47 for (*R*s)-**6a** and (*R*s)-**7a**, respectively.



8) The notations R_S and S_S denote the absolute configuration of the sulfinyl group.

9) The aldol reaction of ethyl α-(phenylsulfinyl)acetate with aldehyde, by using Grignard reagent as a base, was previously found; N. Kunieda, J. Nokami, and M. Kinoshita, *Tetrahedron Lett.*, **1974**, 3997; J. Nokami, N. Kunieda, and M. Kinoshita, *ibid.*, **1975**, 2179.

10) It is reasonable to understand the difference of the reactivity between the reactive isomer **6** and the inactive isomer **7** as follows. *The structural properties of the anions* **6'** *and* **7'** *derived from* **6** *and* **7** *must be quite different*, as speculated for the inactive anion as **7'** and for the active anion as **6'** for instance.



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