

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

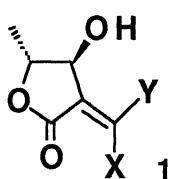
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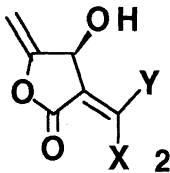
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The title compounds were prepared via stereoselective aldol reaction of α,β -unsaturated carboxylate α -anion equivalent, derived from optically active α -(arylsulfinyl)carboxylate and bromomagnesium diisopropylamide, with propargyl aldehyde as a key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

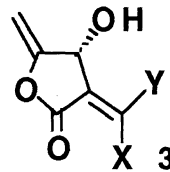
Litsenolides (1), the lactonic components of the Lauraceae family which have α -alkylidene- β -hydroxy- γ -valerolactone structure, have been isolated from *Litsea japonica* by Ishii et al.¹⁾ in 1972. Similar lactones such as obtusilactones (2) and mahubalactones (3)[mahubanolides (3a), mahubenolides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



- 1a Litsenolide A₁ X=(CH₂)₉CH=CH₂, Y=H;
 1a' Litsenolide A₂ X=H, Y=(CH₂)₉CH=CH₂;
 1b Litsenolide B₁ X=(CH₂)₉C≡CH, Y=H;
 1b' Litsenolide B₂ X=H, Y=(CH₂)₉C≡CH;
 1c Litsenolide C₁ X=(CH₂)₁₂CH₃, Y=H;
 1c' Litsenolide C₂ X=H, Y=(CH₂)₁₂CH₃;



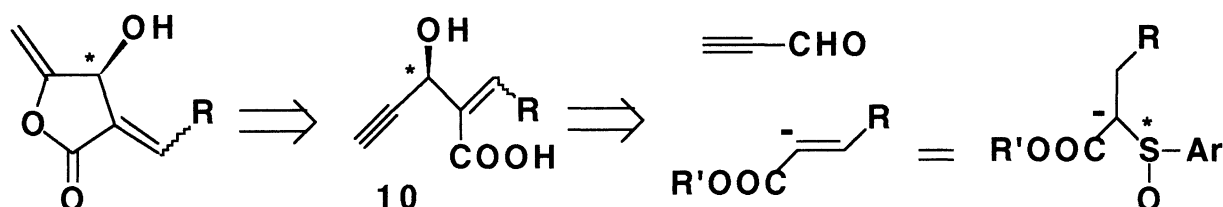
- 2 Obtusilactone X=(CH₂)₉CH=CH₂, Y=H;
 2' Isoobtusilactone X=H, Y=(CH₂)₉CH=CH₂;
 2a Obtusilactone A X=(CH₂)₁₂CH₃, Y=H;
 2a' Isoobtusilactone A X=H, Y=(CH₂)₁₂CH₃;
 2b Obtusilactone B X=cis-(CH₂)₅CH=CH(CH₂)₇CH₃, Y=H;
 2b' Isoobtusilactone B X=H, Y=cis-(CH₂)₅CH=CH(CH₂)₇CH₃;



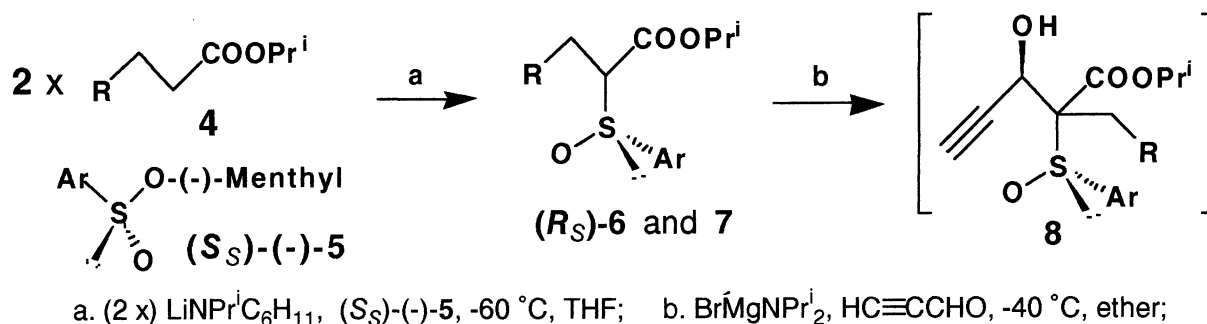
- 3a Mahubanolide X=(CH₂)₁₄CH₃, Y=H;
 3a' Isomahubanolide X=H, Y=(CH₂)₁₄CH₃;
 3b Mahubenolide X=(CH₂)₁₃CH=CH₂, Y=H;
 3b' Isomahubenolide X=H, Y=(CH₂)₁₃CH=CH₂;
 3c Mahubynolide X=(CH₂)₁₃C≡CH, Y=H;
 3c' Isomahubynolide X=H, Y=(CH₂)₁₃C≡CH;

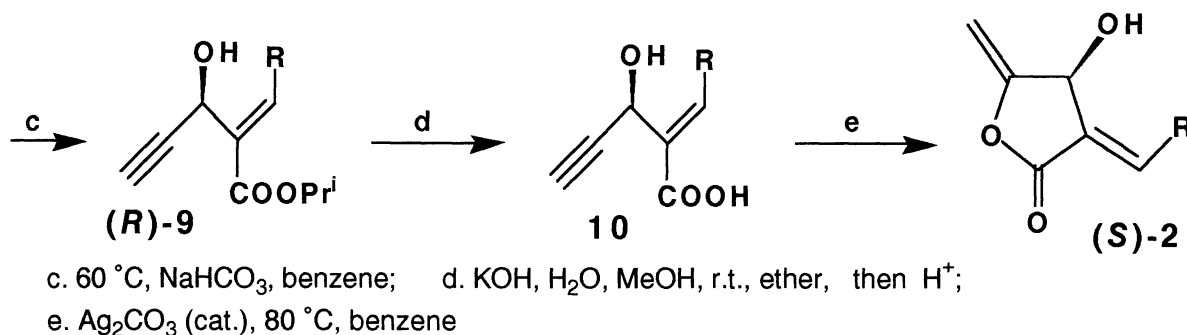
The syntheses of optically active litsenolides⁴⁾ and of racemic obtusilactones and mahubalactones⁵⁾ have been reported. However, to the best of our knowledge, no effort has been made on the synthesis of optically active obtusilactones and mahubalactones. Here we wish to report a new synthesis of optically 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 -methylenebutylolactone by intramolecular addition reaction of the carboxylic acid to the internal terminal-yn functionality. 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⁾

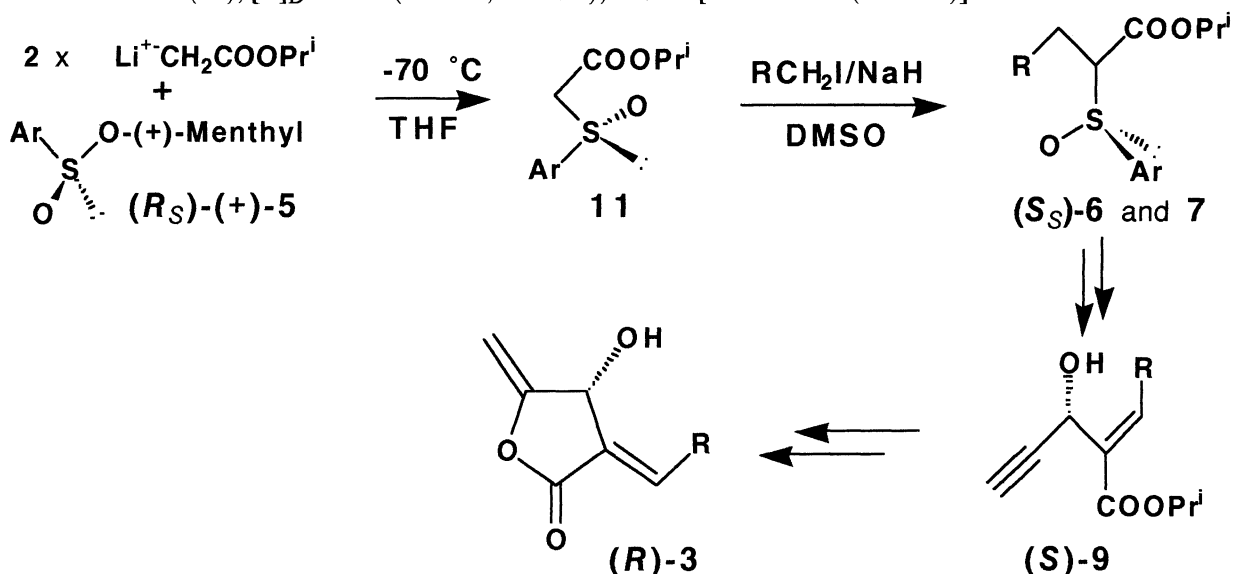


Diastereomeric mixtures of optically active isopropyl (R_S)- α -(*p*-tolylsulfinyl)carboxylates (**6** and **7**)⁷⁾ were prepared by sulfinylation of the corresponding esters **4**, derived from commercially available hexadecanoic acid and *cis*-octadec-9-enoic acid, with lithium cyclohexylisopropylamide 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 alkali¹¹⁾ and then the acid was lactonized to isoobtusilactones **2** by treatment with a catalytic amount of silver carbonate¹²⁾ in 40-45% yield based on **9**. The specific rotations of the prepared isoobtusilactone (**2**), isoobtusilactone A (**2a**), and isoobtusilactone B (**2b**) were $[\alpha]_D -60.4^\circ$ (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.





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), [α]_D +35.9° (c 0.674, dioxane); 75%ee, and isomahubenolide (3b), [α]_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 -methylenebutyrolactone], 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).
- 2) M. Niwa, M. Iguchi, and S. Yamamura, *Chem. Lett.*, **1975**, 655; *Tetrahedron Lett.*, **1975**, 1539, 4395.
- 3) J. C. Martinez V., M. Yoshida, and O. R. Gottlieb, *Tetrahedron Lett.*, **1979**, 1021.
- 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.

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