

A NOVEL SYNTHETIC METHOD FOR OPTICALLY ACTIVE TERPENES
BY THE RING-OPENING REACTION OF (R)-(+)- β -METHYL- β -PROPIOLACTONE

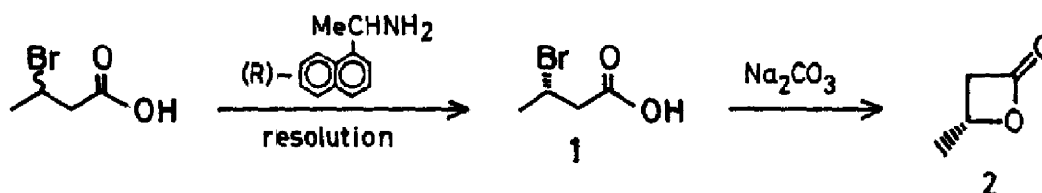
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Summary; Optically active terpene such as (R)-(+)-citronellol, (R)-(+)-pulegone or (S)- α -turmerone is prepared in high enantiomeric excess from an intermediate, (R)-(+)-citronellic acid or (S)-(+)-3-p-tolylbutyric acid, which is easily prepared by the SN2 type of ring opening reaction of (R)-(+)- β -methyl- β -propiolactone with homoprenylmagnesium bromide in the presence of a copper(I) salt or di-p-tolyleuprate.

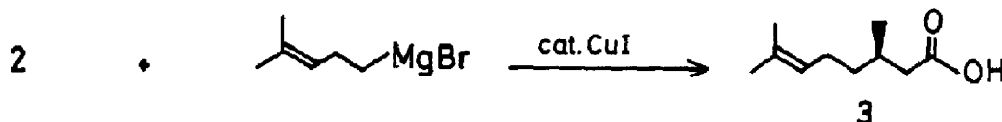
Many biologically active natural products, such as alkaloid, steroid, terpenoid, sugar, peptide and so on, have optical activity, and generally the *d*- and *l*-forms of each class of these compounds show different biological activities. In some cases, one of the two enantiomers has no activity. Thus, it is one of the most important problems in synthetic organic chemistry to prepare selectively only one enantiomer. Recent synthetic methods for the optically active terpenes have been classified into two groups, e.g., 1) conversion of naturally occurring amino acids, sugars or other easily available optically active compounds,¹ and 2) asymmetric synthesis from prochiral compounds.² In either case, the introduction of asymmetric carbon(S) should be conducted at the possible earliest stage in the synthesis. We wish to report here a convenient synthetic method for optically active terpenes such as (R)-(+)-citronellol (3), (R)-(+)-pulegone (5) and (S)-(+)- α -turmerone (9) by utilizing the SN2 type of reaction of (R)-(+)- β -methyl- β -propiolactone (2) with a Grignard reagent in the presence of a copper salt or with a cuprate, which proceeds with almost complete inversion.

A key step for the synthesis of optically active terpenes, i.e., the regio-specific reaction of β -methyl- β -propiolactone with a Grignard reagent in the presence of a copper catalyst or with a diorganocuprate, which has been developed in our laboratory,³ seemed to be SN2 type ring-opening. Accordingly, the reaction of optically active β -methyl- β -propiolactone would yield a corresponding β -substituted butyric acid with an asymmetric β -carbon, which could be easily converted into optically active terpenes.⁴

An important starting material, (R)-(+)- β -methyl- β -propiolactone (2) was easily obtained from 3-bromobutyric acid by a modified method of Shelton et al.⁵ Resolution of racemic 3-bromobutyric acid, which was prepared by the hydrobromination of crotonic acid, with (R)-(+)- α -(1-naphthyl)ethylamine afforded (S)-(+)-3-bromobutyric acid (1) of 90% e.e. ($[\alpha]_D^{25} +105^\circ$ (0.168M, 2N HClO₄), lit.⁶ $[\alpha]_D^{25} +116.5^\circ$ (0.1632M, 2N HClO₄)). Cyclization of 1 by the reaction with aq Na₂CO₃ in CHCl₃ yielded the lactone 2 in a yield of 72%; $[\alpha]_D^{20} +24.6^\circ$ (neat).

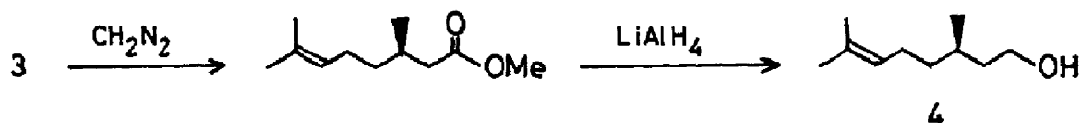


The key intermediate for the synthesis of (R)-(+)-citronellol (4) and (R)-(+)-pulegone (5), (R)-(+)-3,7-dimethyl-6-octenoic acid (citronellic acid) (3) was easily prepared by the S_N2 type ring-opening of the lactone 2 with homoprenylmagnesium bromide in the presence of copper(I) salt. Thus, when homoprenylmagnesium bromide was added to a mixture of 2 and copper(I) iodide (2 mol%) in THF-Me₂S (20:1) at -10 °C and the reaction mixture was stirred for 3 h at -10~



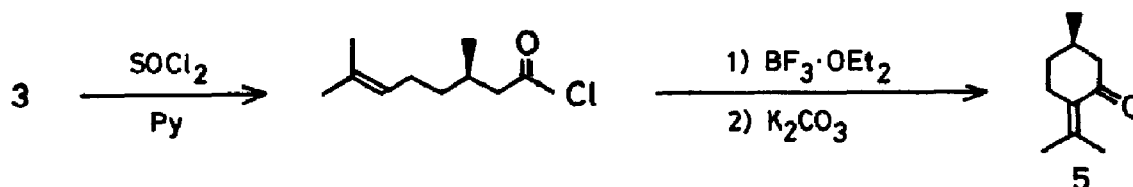
-5 °C, 3 was obtained in 90% yield; $[\alpha]_D^{25} +7.51^\circ$ (c 3.19, MeOH), lit.⁷ $[\alpha]_D^{25} +9.05^\circ$ (c 3.2, MeOH). Since the optical purity of 3 calculated from the rotation data showed 83%, the configuration of the β -carbon in (S)-3-bromobutyric acid (1) was transformed into 3 with retention of 92% through two-step inversion, i.e., cyclization (1 to 2) and the ring-opening of the β -propiolactone (2 to 3) proceed almost completely in S_N2 mechanism. Although the reaction of optically active secondary alkyl halides with organocuprates is well-known procedure for a carbon-carbon bond formation with inversion,⁸ the present one provides an efficient conversion of a carbon-halogen bond into a carbon-carbon bond with net retention

Esterification of 3 with diazomethane and reduction with lithium aluminum hydride furnished (R)-(+)-citronellol (4) of 84% e.e. in 99% yield; $[\alpha]_D^{25} +4.19^\circ$ (c 23.2, MeOH), lit.⁷ $[\alpha]_D^{20} +4.97^\circ$ (c 23.1, MeOH).

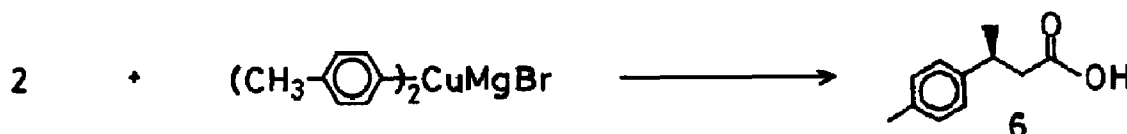


Treatment of 3 with thionyl chloride and pyridine followed by cyclization

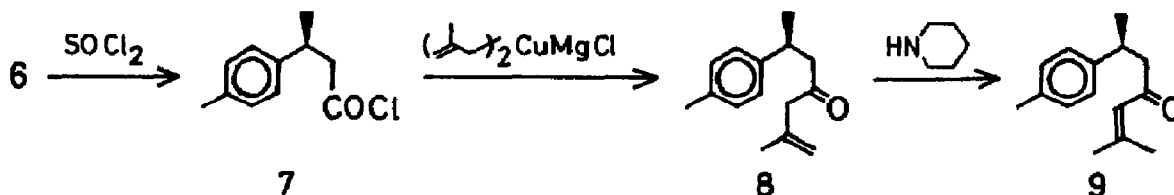
with $\text{BF}_3 \cdot \text{OEt}_2$ and by dehydrohalogenation with K_2CO_3 gave (R)-(+)-pulegone (5) in a yield of 63%; $[\alpha]_{\text{D}}^{26} +22.5^\circ$ (c 1.98, EtOH), lit.⁹ $[\alpha]_{\text{D}}^{23} +24^\circ$ (c 2, EtOH). The optical purity of 5 thus obtained was 94% based on the reported optical rotation, which was in conflict with that of 3. Since the transformation of 3 to 5 seemed to proceed without racemization, the purity of 5 should be 84%.



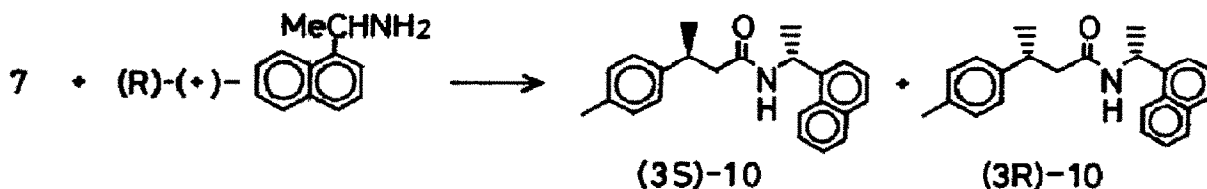
A monocyclic aromatic sesquiterpene, (S)-(+)-ar-turmerone (9) was also synthesized *via* (S)-(+)-3-p-tolylbutyric acid (6) which was easily provided by the reaction of the lactone 2 and di-p-tolylcuprate. When 2 was added into a



solution of di-p-tolylcuprate, prepared from p-tolylmagnesium bromide (2 equiv) and copper(I) iodide (1 equiv) in THF- Me_2S (10:1) at -30°C , and the reaction mixture was allowed to warm to 0°C for over 1 h, 6 was obtained in 60% yield; $[\alpha]_{\text{D}}^{24} +55.0^\circ$ (c 4.69, C_6H_6), lit.¹⁰ $[\alpha]_{\text{D}} +65^\circ$ (c 4.6, C_6H_6). The optical purity of 6 showed 84%, which is the same value as that of 3. Treatment of 6 with thionyl chloride afforded quantitatively the acid chloride 7. Coupling of 7 with



dimethylallylcuprate, prepared from methylallylmagnesium chloride (2 equiv) and copper(I) iodide (1 equiv) in THF at -78°C , gave (S)-(+)-iso-ar-turmerone (8) in a yield of 98%; $[\alpha]_{\text{D}}^{24} +24.7^\circ$ (c 2.38, $n\text{-C}_6\text{H}_{14}$). Treatment of 8 with piperidine in ether¹¹ gave (S)-(+)-ar-turmerone (9) in 93% yield; $[\alpha]_{\text{D}}^{22} +59.9^\circ$ (c 4.5, $n\text{-C}_6\text{H}_{14}$) lit.¹² $[\alpha]_{\text{D}}^{22} +64^\circ$ (c 4.5, $n\text{-C}_6\text{H}_{14}$). The optical purity of 9 was calculated as 94% based on the reported optical rotation, which was in conflict with that of 6. Thereupon, the optical purity of 6 was determined by an alternate procedure other than optical rotation. Direct determination procedure for the enantiomeric composition of the (S)-acid 6 was based on a separation of the diastereomeric amides (10) quantitatively obtained by the reaction of the acid chloride 7 and (R)-(+)- α -(1-naphthyl)ethylamine, by silica gel tlc ($\text{C}_6\text{H}_6:\text{Et}_2\text{O} =$



7:1), which gave two components in a ratio of 92:8, corresponded to the (3S)-amide and the (3R)-amide respectively.¹³ Thus, the optical purity of 6 was determined to be 84%, which is identical with that based on the rotation data. Since the transformation of 6 to ar-turmerone 9 seemed to proceed without racemization, the purity of 9 should be 84%.

As mentioned above, the S_N2 type of the ring-opening of optically active β-methyl-β-propiolactone with a Grignard reagent in the presence of a copper(I) catalyst or with a diorganocuprate provides a promising procedure for the synthesis of a wide variety of optically active terpenes in high enantiomeric excess.

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- Nmr data (CDCl₃) for (3S)-10; δ 1.18 (d, J=7Hz, 3H), 1.43 (d, J=5Hz, 3H), 2.19 (m, 5H), 3.20 (t, J=7Hz, 1H), 5.70 (m, 2H), 7.2~8.2 (m, 11H). (3R)-10 δ 1.27 (d, J=7Hz, 3H), 1.53 (d, J=6Hz, 3H), 2.19 (m, 5H), 3.20 (t, J=7Hz, 1H), 5.70 (m, 2H), 7.0~8.2 (m, 11H).

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