A NEW STEREOSELECTIVE ROUTE TO γ-BUTYROLACTONES: ASYMMETRIC SYNTHESES OF (+)-*trans*-WHISKY AND (+)-*trans*-COGNAC LACTONES

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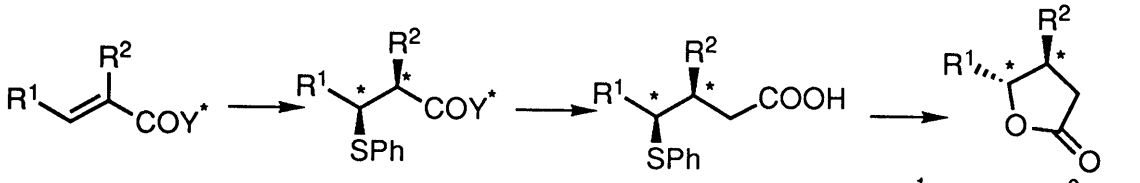
A new stereoselective route to γ-butyrolactones such as (+)-*trans*-whisky and (+)-*trans*-cognac lactones (**1a, b**) has been developed by a combination of three key reactions: diastereoselective nucleophilic addition of thiophenol, cleavage of chiral N-acylsultam *via* thioester, and intramolecular displacement of the sulfonium group with carboxylate anion.

KEYWORDS asymmetric synthesis; whisky lactone; cognac lactone; butyrolactone; nucleophilic addition; thiophenol; (+)-sultam; ate complex

Structurally simple γ-butyrolactones are widespread naturally occurring substances found not only as sex pheromones[1] but also as key flavor components.[2] The biological activities of these substances are strictly dependent on the absolute configuration of the chiral C4-carbon atom which is attached by oxygen to the lactone ring.[3] We have now provided a new method for the construction of two contiguous stereogenic centers at the C3- and C4-positions of γ-butyrolactones by demonstrating asymmetric syntheses of (+)-*trans*-whisky and (+)-*trans*-cognac lactones (**1a, b**), which are key components for the flavors of whisky, wine, and cognac.[4-6] Our synthetic strategy consists of two crucial reactions, diastereoselective nucleophilic addition of thiophenol to α,β-unsaturated acid derivatives (**2a, b**) having (+)-sultam and stereoselective displacement reaction of the corresponding sulfonium group with carboxylate anion.



1a: R^1=n-C_4H_9, R^2=Me
1b: R^1=n-C_5H_{11}, R^2=Me

Acylation of (+)-sultam, Oppolzer's reagent,[7] with β-(n-butyl)methacryloyl chloride in the presence of sodium hydride gave the chiral olefin **2a** in 90% yield, which was then treated with 10 eq of thiophenol in the presence of 0.3 eq of lithium thiophenoxide in THF at 0 °C[8,9] to give the chiral adduct **3a** in 83% yield in addition to small amounts of unidentified diastereoisomers. The stereostructure of the adduct **3a** was firmly established by its X-ray crystallography, which supported the nature of the addition reaction as *anti*-addition of thiophenol as in the case of our previous work.[10] The proposed mechanism for the diastereoselective *anti*-addition of thiophenol is as follows. The starting chiral olefin **2a** takes *s-trans*-conformation **A** due to steric hindrance between the vinyl methyl group and the C7-methylene part of the chiral auxiliary found in the corresponding *s-cis*-conformation. Lithium thiophenoxide would attack from

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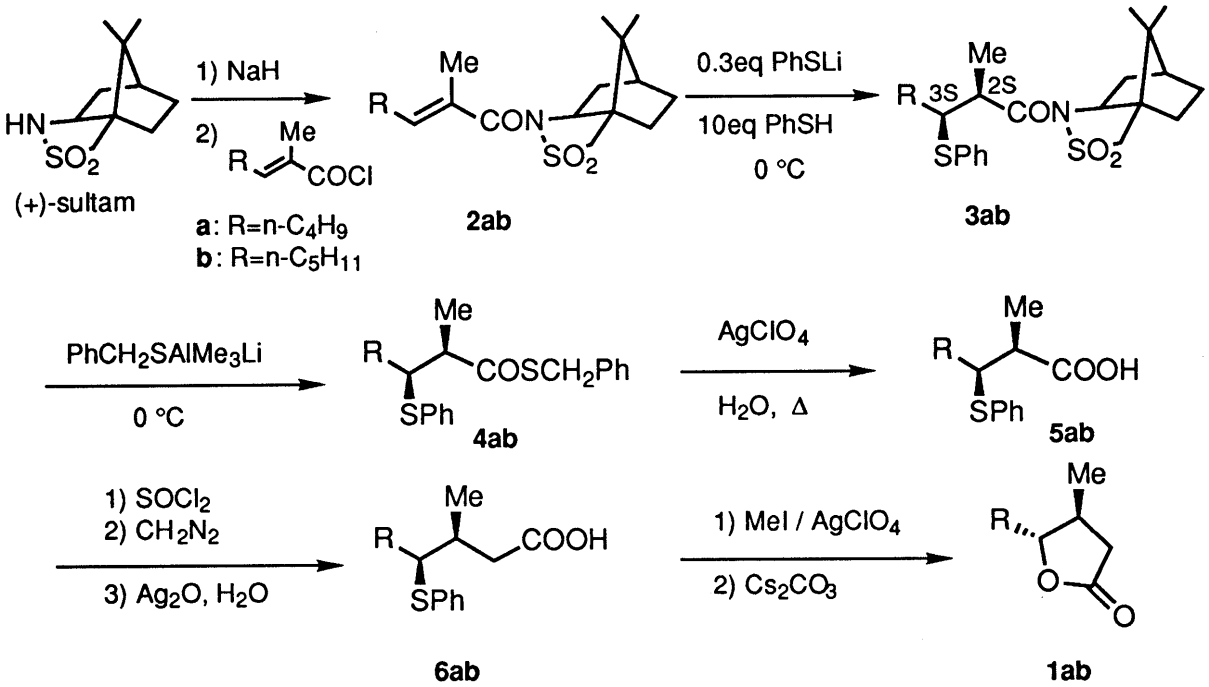
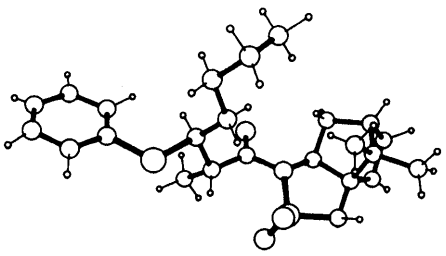
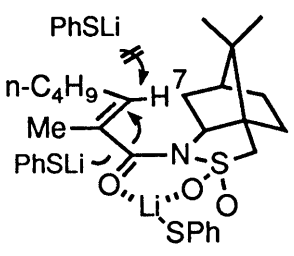
a convex α-face to form the enolate **B**, which is then protonated from β-face due to the stereoelectronic effect of the newly introduced sulfur group to give the (2*S*,3*S*)-adduct **3a**.

Since the application of conventional methods (LiOH,[7] LiOH-H_2O_2[11]) to the cleavage of N-acylcamphor sultam was unsuccessful, we have developed a new method for its cleavage without loss of the induced chirality and with virtually complete recovery of the chiral auxiliary. Treatment of the adduct **3a** with aluminum thiobenzyloxy "ate" complex, prepared from n-butyl lithium, benzyl mercaptan, and trimethylaluminum, gave the thioester **4a** in 84% yield. Both lithium benzylthiophenoxide and aluminum thiophenoxide "ate" complex were ineffective for the cleavage of N-acylcamphor sultam. Hydrolysis of the thioester **4a** in the presence of silver perchlorate proceeded smoothly to give the corresponding acid **5a** in 94% yield, which was then subjected to Arndt-Eistert reaction to afford the homologous acid **6a** in 51% yield with three steps from **5a**. S-Alkylation of the sulfide **6a** with methyl iodide in the presence of silver perchlorate followed by treatment of the resulting sulfonium salt with cesium carbonate underwent smooth lactonization[12,13] by intramolecular substitution reaction with the naked carboxylate anion.[14]

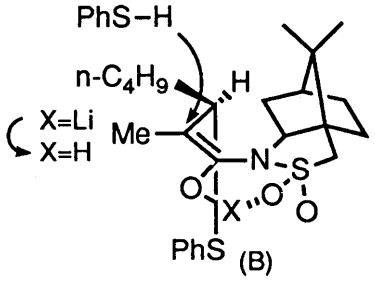




crystal structure of **3a**



[*s-trans*] (A)



(B)

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Products were found to be a diastereomeric mixture (98:2) by the NMR spectrum and carefully purified by preparative TLC. The major lactone **1a** thus prepared was identical with the authentic sample of (+)-*trans*-whisky lactone upon comparison of their spectral data and optical rotations ($[\alpha]_D$ +79 °(c=1.22, MeOH) (lit.[4] $[\alpha]_D$ +79 ° (c=1.04, MeOH)).

Similarly, asymmetric synthesis of (+)-*trans*-cognac lactone (**1b**) was accomplished by the same reaction sequence from β-(n-pentyl)methacryloyl chloride. The product **1b** was also identical with the authentic sample of (+)-*trans*-cognac lactone upon comparison of their spectral data and optical rotations ($[\alpha]_D$ +78 °(c=1.12, CH_2Cl_2)(lit.[15] $[\alpha]_D$ +79.5 °(CH_2Cl_2)).

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