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Asymmetric Michael Addition of Thiols to (1R,2R,4R)-(-)-2,10-*N*-Enoylcamphorsultam

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Abstract: Lithium base promoted stereoselective Michael addition of thiols to *N*-methacryloyl-camphorsultam produced the corresponding addition products in 66% to 90% diastereoselectivity. Hydrolysis of the Michael product with three equivalents of lithium hydroxide in THF/H_2O gave the corresponding optically active β-thioester with no sign of any racemization, and recovered camphorsultam quantitatively.

Optically active β-thioesters bearing an α-stereogenic center are important intermediates for the synthesis of important molecules with therapeutic activities, such as diltiazem,[1] thiazesim,[2] and captopril.[3] Asymmetric synthesis through the nucleophilic conjugate addition to α,β-unsaturated carbonyl compounds is one of the most efficient method for this purpose.[4~5] Although synthesis of optically active β-thioesters from the Michael addition of thiols to electron deficient olefins has been reported,[6~14] the search for a better chiral auxiliary for the synthesis of optically active β-thioesters from achiral precursors remains as a worthwhile challenge. (1R,2R,4R)-(-)-2,10-Camphorsultam **1**, prepared from (1R)-(+)-10-camphorsulfonic acid,[15] have been demonstrated to direct stereoselective reactions with a high degree of diastereoselectivity.[16~24] Herein we report our findings on the asymmetric Michael addition reaction of thiols to chiral *N*-methacryloylcamphorsultam **2**.

N-Methacryloylcamphorsultam **2** was prepared according the literature procedure.[18] Additions of thiols **3** to *N*-methacryloylcamphorsultam **2** in the presence of a basic promoter gave the corresponding Michael adducts **4** in excellent yields and the result are listed in Table I. When tetrabutylammonium hydroxide was used as the promoter there is no asymmetric induction at all. However, when a lithium base was used as the promoter up to 90% of asymmetric induction could be observed. This result suggested that there might be some chelation effect operating with the lithium ion. (entry 1 to 4) The reaction presumably proceeded through 1,4-addition of thiolate anion to the chelated intermediate **A** followed by a kinetic controlled protonation on the less hindered face.[14] More acidic thiols gave lower asymmetric induction. Interestingly, when the reaction was performed in the presence of Lewis acidic promoters such as $TiCl_4$, $ZnCl_2$, or BF_3OEt_2 complicated mixture were obtained.

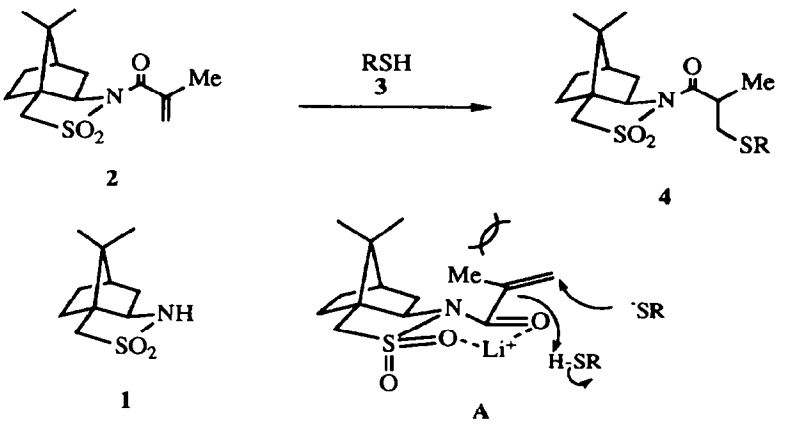


Table I Michael Addition of Thiols 3 to *N*-Methacryloylcamphorsultam 2

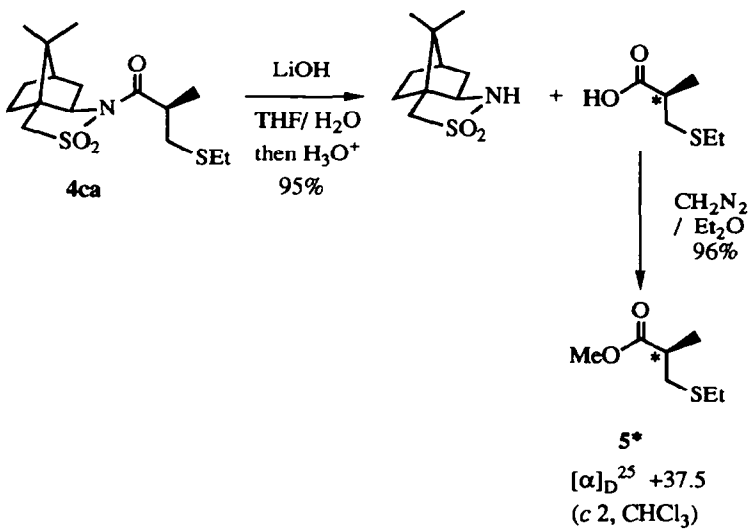
entry	RSH[a] (equivalent)	promoter (equivalent)	reaction condition	reaction time(hr)	yield (%)	ratio $C_\alpha R:C_\alpha S$
1	**3a** (2.0)	*n*-BuLi (0.2)	-78°C→0°C	2.75	99[b]	5 : 1
2	**3a** (2.0)	LiOH (0.2)	-20°C	3	89[b]	5.5 : 1
3	**3a** (2.0)	$LiN(i\text{-}Pr)_2$ (0.2)	-78°C→-40°C	4.5	99[b]	3 : 2
4	**3a** (2.0)	$n\text{-}Bu_4NOH$(0.2)	0°C	4.75	85	1 : 1
5	**3b** (10.0)	*n*-BuLi (0.2)	0°C	1.5	99	10 : 1
6	**3b** (5.0)	*n*-BuLi (0.2)	-10°C	1.5	99	10 : 1
7	**3c** (1.2)	*n*-BuLi (0.2)	-78°C→0°C	3.5	98	19 : 1
8	**3c** (1.1)	*n*-BuLi (0.2)	-78°C	2.0	97	19 : 1

[a] **3a** R = PhCO-, **3b** R = Ph-, **3c** R = Et- [b] conversion

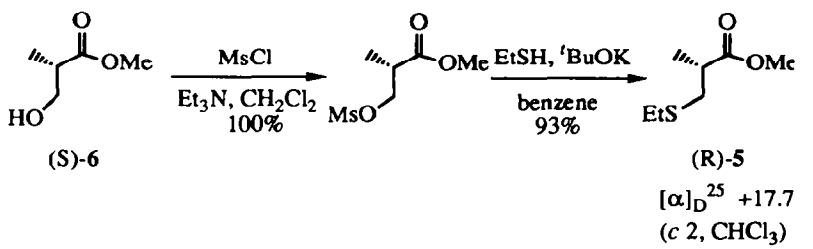
Compound **4ca**,[25] the major product of **4c**,[25] was easily obtained in pure form after a single recrystallization from CH_2Cl_2/*n*-hexane. In order to assign the configuration of the newly formed stereogenic center, **4ca** was hydrolyzed with three equivalents of lithium hydroxide in aqueous tetrahydrofuran (THF) followed by esterification with diazomethane in ether to give the corresponding methyl ester **5***[25] in 95% yield and recovered the chiral auxiliary **1** quantitatively.(Scheme I) When the reaction was carried out in THF/D_2O there is no deuterium incorporation on the product, and therefore there should be no epimerization of the newly formed stereogenic center during the hydrolysis stage. A sample of (*R*)-(+)-**5**[26] was prepared from the mesylation of methyl (*S*)-(+)-3-hydroxy-2-methylpropionate **6**[27] with methanesulfonyl chloride in the presence of triethylamine in dichloromethane followed by treatment of ethanethiol in benzene in the presence of potassium *t*-butoxide.[28] (Scheme II) After comparison of the optical rotation of methyl ester **5***,[29] prepared from asymmetric synthesis, with (*R*)-(+)-**5**, prepared from (*S*)-(+)-**6**, we found both to have positive signs of rotation. As expected, each of the newly formed stereogenic centers in the major products of **4a-4c**[25] and methyl ester **5*** was assigned the *R* configuration. This reaction mode is quite different from Oppolzer's conjugate addition reaction of Grignard reagents to *N*-methacryloylcamphorsultam.[18] However

the result is similar to Oppolzer's catalytic hydrogenation on *N*-methacryloylcamphorsultam.[30] We also noticed that methyl ester **5*** had more than twice in magnitude of the specific rotation value than that of (*R*)-(+)-**5**. This suggested that there was serious racemization while preparing (*R*)-(+)-**5** from (*S*)-(+)-**6**.

SCHEME I



SCHEME II



In summary, thiol addition to *N*-enoylcamphorsultam could be achieved with good diastereoselectivity. Pure Michael adduct could be obtained after a single recrystalization. Removal of chiral auxiliary could be achieved without racemization at α-stereogenic center. Thus an asymmetric synthetic method for the preparation of β-alkylthioester bearing an α-stereogenic center has been demonstrated.

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25. These compounds give satisfactory spectroscopic data.; The major product of **4** shows a doublet-doublet pattern (J= ~5.0, ~7.5 Hz) at δ 3.88±0.04, whereas the minor product of **4** shows a triplet pattern (J= ~6.3 Hz) on the same region in their ^{1}H NMR spectra. These peaks are designated to the chemical shift of the C_{7a} proton.
26. $[\alpha]_D^{22}$ +17.7 (*c* 2, $CHCl_3$).
27. Methyl (S)-(+)-3-hydroxy-2-methylpropionate, $[\alpha]_D^{19}$ +26 (*c* 4, CH_3OH), was purchased from Alderich Co., Milwaukee, U.S.A.
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