Pergamon

Tetrahedron, Vol. 53, No. 32, pp. 11141-11152, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00372-4

Enantioselective Synthesis of α-Amino Acids from Glycine *t*-Butyl Ester

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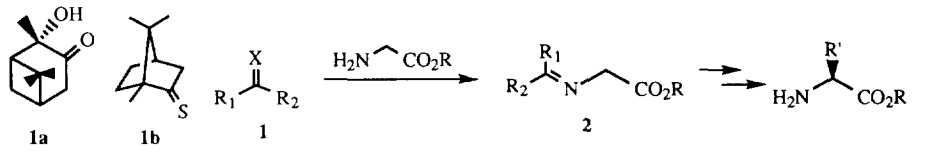
Abstract: Enantioselective syntheses of optically active α-amino acids from glycine *t*-butyl ester through Schiff base employing (+)-*N*-alkyl-10-camphorsulfonamides as chiral auxiliaries were described. Methylation of Schiff base **5** gave high asymmetric inductions, whereas ethylation, allylation and benzylation gave fair asymmetric inductions. The stereochemistry of the major alkylation product was *S* configuration at the newly formed stereogenic center with the exception of the benzylation reaction in which the *R* configuration was generated. © 1997 Elsevier Science Ltd.

(This paper is dedicated to Professor Samuel J. Danishefsky, an inspiring mentor whom I sincerely admire.)

Introduction

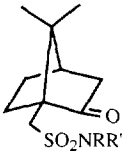
Optically active α-amino acids are important in biological systems; they are also found as components of many antibiotics.[1] The synthesis of optically active α-amino acids has been intensively investigated,[2,3] and many approaches has been devised. Products obtained from the asymmetric enolate alkylation of Schiff bases derived from glycine and ketones as chiral auxiliaries is one approach[4] which was first reported by Yamada's group.[4a] They employed (1*S*,2*S*,5*S*)-(-)-2-hydroxypinan-3-one **1a** as the chiral auxiliary and observed 66-83% enantioselectivity. McIntosh and coworkers reported that the enolate alkylation of Schiff base **2b**, derived from the condensation of glycine ester with thiocamphor **1b**, gave no induction when using methyl iodide as the alkylating agent, and >98% induction when using benzyl bromide.[5] In this approach the optical yield for bulkier alkylating agent such as benzyl bromide had been upgraded. However the optical yield for smaller alkylating agent such as methyl iodide was significantly worse than that in the previous approach (Scheme 1).

Scheme 1

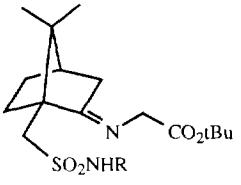


1a **1b** **1** **2**

We have reported an asymmetric synthesis of α-amino acids from glycine *t*-butyl ester employing (+)-*N*,*N*-diisopropyl-10-camphorsulfonamide **3** as a chiral auxiliary with improved enantioselectivity.[6] Using the lithium enolate we observed a similar result to McIntosh. However, we observed 50% induction for methylation and >98% induction for benzylation using the potassium enolate in the reaction. The zinc enolate and magnesium enolate gave asymmetric inductions between the results obtained using lithium enolate and potassium enolate. To obtain higher induction for small alkylating agents and broader scope in the synthesis of optically active α-amino acids from glycine *t*-butyl ester, modification of camphorsulfonamide **3** was required. One would expect that a modification on the sulfonamido group of **3** to *N*-monosubstituted sulfonamide **4** may provide a more rigid conformation for enolate **6**, derived from Schiff base **5**, and improve the diastereoselectivity for the alkylation. Here we report our findings in the preparation of optically active α-amino acids from glycine *t*-butyl ester employing (+)-*N*-alkyl-10-camphorsulfonamides **4** as chiral auxiliaries.



3 R = R' = Pr^i
4 R = H, R' = alkyl



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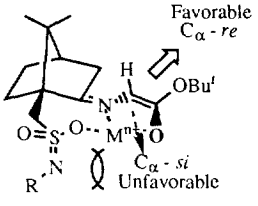

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Results and Discussion

Chiral auxiliaries **4a** and **4b** were prepared according to a modified procedure.[6,7] Thus, reaction of D-10-camphorsulfonyl chloride with cyclohexylamine, and *t*-butylamine in dichloromethane and the presence of triethylamine gave chiral auxiliaries **4a~b** in 98%, and 96% yields respectively. Direct condensation of glycine *t*-butyl ester with **4a~b** in refluxing toluene gave the corresponding Schiff bases **5a~b** in 48~50% yield. However separation of **5a** from **4a**, and **5b** from **4b** were difficult due to their similar polarity behavior on silica gel column. According to the literature[5] and our previous experiences,[6] the yields on the formation of Schiff bases could be improved and the separation problem could be solved by using the thione version of the chiral auxiliaries. Conversion of **4a** to thione **4c** could be achieved by treating **4a** with hydrogen sulfide and trimethyl orthoformate in the presence of hydrogen chloride. However a concomitant formation of **4d** makes the purification of **4c** very difficult. The mixture of **4c** and **4d** was used and reacted with glycine *t*-butyl ester to give Schiff base **5a** and unchanged **4d**. Separation of **5a** and **4d** could be achieved with ease by silica gel column chromatography at this stage. Similarly, **4b** was converted to Schiff base **5b** through thione **4e** (Scheme 2). Schiff bases **5a** and **5b** could be obtained in pure form and good yields in this manner.

Treatment of Schiff base **5a** with 2.2 equivalents of lithium diisopropylamide in tetrahydrofuran followed by 1.2 equivalent of methyl iodide at -78 °C gave two diastereomers **7a** and **8a** in 53% yield with a 3.3 to 1 ratio. It is well documented that simple lithio enolates are not monomeric, and that the addition of an appropriate amount of hexamethylphosphoroustriamide (HMPA) would at least partially deaggregate the clusters and improve the yield of alkylation without affecting the diastereoselectivity.[4c,5b,8] When the reaction was carried out in the presence of 2~4 equivalents of HMPA not only was the diastereoselectivity improved to

8.0~8.7 to 1 but also the chemical yield was improved to 87% (Table 1). On a 2.35 mmol reaction scale the diastereoselectivity was further improved to a ratio of 11 to 1 (Table 2, entry 1). This reaction condition was used for the following investigations.

Scheme 2

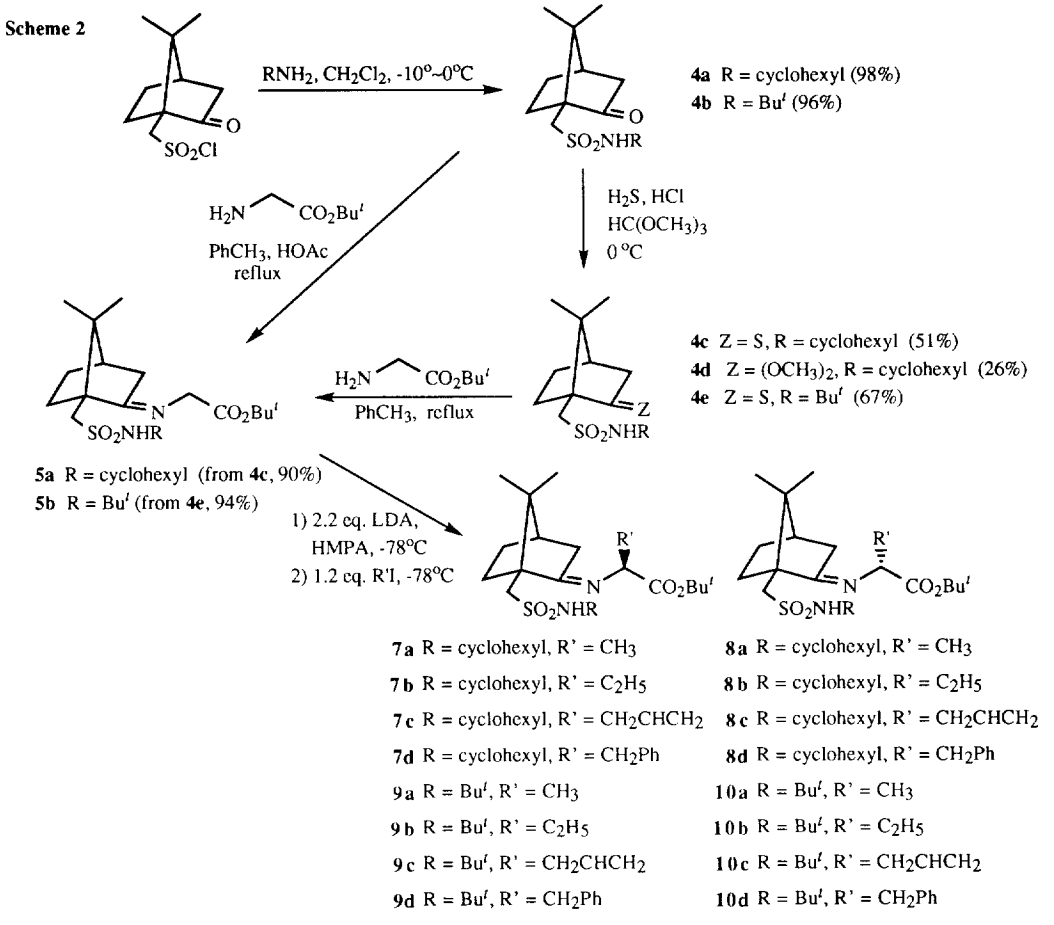


Table 1 The effect of HMPA on the diastereoselective alkylation of Schiff base **5a**

entry	HMPA(eq)	CH_3I(eq)	conversion(%)	**7a:8a**[a]	yield(%)[b]
1	0	1.2	75	3.3:1	53
2	1	1.2	90	6.0:1	72
3	2	1.2	100	8.0:1	85
4	4	1.2	100	8.7:1	87
5	6	7.5	100	10:1	82

[a] The ratios were determined by ^1H NMR analysis. [b] Isolated yield.

Unexpectedly, the diastereoselectivity for ethylation, allylation, and benzylation of **5a** were found to be only 2.2 to 1, 2.3 to 1, and 1 to 1.5 ratio respectively (Table 2, entry 2~4). We then turned to investigate the asymmetric alkylation reaction of **5b**, and the results were summarized in Table 2. The results for the asymmetric alkylation were found to be similar to those observed with Schiff base **5a**. Methylation gave the best result with any Schiff base **5**. Schiff base **5b** gave a diastereoselectivity better than 20 to 1 on α-methylation. In most cases, the yields were very high. After a single recrystallization of crystalline product from acetone-hexane, the major alkylation product from **5b** could be obtained in >98% diastereomeric purity. We had observed metal ion effects in our previous studies.[6] However, attempts to improve the diastereoselectivity by changing the metal ion in enolate **6** were fruitless. There was no apparent improvement on the diastereoselectivity for the methylation of Schiff base **5b** upon changing the metal ion from lithium to potassium, cerium, or magnesium ions which had been found to be effective for the alkylation of Schiff base derived from glycine *t*-butyl ester and chiral auxiliary **3** (Table 3).

Table 2 Diastereoselective alkylation of Schiff base **5**

entry	Schiff base	R'I	diastereoselectivity[a]	yield(%)[b]
1	**5a**	CH_3I	11:1	91
2	**5a**	C_2H_5I	2.2:1	98
3	**5a**	CH_2=$CHCH_2Br$	2.3:1	74
4	**5a**	$PhCH_2Br$	1:1.5	96
5	**5b**	CH_3I	>20:1	95
6	**5b**	C_2H_5I	3:1(>100:1)[c]	98(41)[d]
7	**5b**	CH_2=$CHCH_2Br$	2.4:1(>100:1)[c]	96(70)[d]
8	**5b**	$PhCH_2Br$	1:3(>100:1)[c]	98(64)[d]

[a] The ratios were determined by ^1H NMR analysis for entries 1~6, 8, and HPLC analysis for entry 7. [b] Isolated yield. [c] Diastereomeric ratio after recrystallization from acetone-hexane. [d] Isolated yield after recrystallization from acetone-hexane.

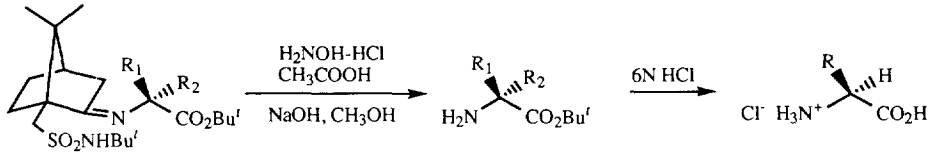
Table 3 The effect of metal ion on the diastereoselective alkylation of Schiff base **5b**

entry	M^{n+}	HMPA(eq)	R'X	**9:10**[a]	yield(%)[b]
1	Li^+(LDA)	2	CH_3I	>20:1	95
2		2	C_2H_5I	3:1	98
3		2	CH_2=$CHCH_2Br$	2.4:1	96
4		2	$PhCH_2Br$	1:3	98
5	K^+(KHMDS)	2	CH_3I	>20:1	31
6		2	C_2H_5I	3:1	64
7		2	CH_2=$CHCH_2Br$	2.4:1	7
8		2	$PhCH_2Br$	1:3	25
9	Ce^{3+}	0	CH_3I	>20:1	16
10		2	CH_3I	>20:1	50
11		2	CH_2=$CHCH_2Br$	---	0

[a] The ratios were determined by ^1H NMR analysis. [b] Isolated yield.

In order to determine the stereochemistry on the alkylation of enolate **6**, the major alkylation products **9a~c** and **10d** were hydrolyzed to the corresponding *t*-butyl α-amino esters **11a~d** in good yield by the treatment of the alkylation product with hydroxylamine and acetic acid in methanol.[5] Chiral auxiliary **4** was recovered quantitatively (Scheme 3). *t*-Butyl α-amino esters **11a~c** were further converted to the corresponding hydrochloride salt **12a~c** in 100% yields. After comparison of our measured $[\alpha]_D$ value for *t*-butyl α-ammonium ester **12a~c** and α-amino ester **11d** with literature data,[5c,9~11] we found that almost no racemization occurred during the hydrolysis stage and each of the newly formed stereogenic centers in **11a~b** and **12a~b** was assigned as *S* configuration, whereas in **11d** the newly formed stereogenic center was assigned as *R* configuration (Table 4). The stereochemistry of **11c** and **12c** were based upon the $[\alpha]_D$ value of the series. Since **9a~c**, **12a~c** had the same sign of $[\alpha]_D$ value and **9a~b**, **12a~b** had *S* configuration at the newly formed stereogenic center, we temporally assigned **9c** and **12c** also had an *S* configuration at the newly formed stereogenic center. Interestingly, in our previous studies we found that the Schiff base derived from chiral auxiliary **3** gave (*R*)-amino ester as the major product,[5] whereas Schiff base **5** gave (*S*)-amino ester as the major product except benzylation. In addition, the change of preferred stereoselectivity on the α-alkylation of Schiff base **5** was noted. To date, there is no chiral auxiliary that has been found to show a reversed stereoselectivity on the α-alkylation of Schiff base derived from glycine ester. The detailed mechanism for the asymmetric alkylation of enolate **6** is not clear at present, and further investigation is necessary to understand the mode of alkylation.

Scheme 3



9a R_1 = CH_3, R_2 = H
9b R_1 = C_2H_5, R_2 = H
9c R_1 = $CH_2CH{=}CH_2$, R_2 = H
10d R_1 = H, R_2 = CH_2Ph

11a R_1 = CH_3, R_2 = H (60%)
11b R_1 = C_2H_5, R_2 = H (85%)
11c R_1 = $CH_2CH{=}CH_2$, R_2 = H (92%)
11d R_1 = H, R_2 = CH_2Ph (92%)

12a R = CH_3 (100%)
12b R = C_2H_5 (100%)
12c R = $CH_2CH{=}CH_2$ (100%)

Table 4 The assignment of the stereochemistry for amino ester **11d** and amino acids **12a~c**

α-amino ester	$[\alpha]_D$	lit. $[\alpha]_D$ (configuration)	C_α configuration on **11/12**
12a	+6.1°(*c* 1.31, H_2O)	+6.3°(*c* 1.20, H_2O)[10](*S*)	*S*
12b	+9.8°(*c* 1.31, H_2O)	+10.1°(*c* 1.11, H_2O)[10](*S*)	*S*
12c	+0.7°(*c* 1.18, H_2O)	--	*S*
11d	-32.9°(*c* 2.25, ethanol)	-32.6°(*c* 1.90, ethanol)[9](*R*)	*R*

Conclusion

Diastereoselective syntheses of α-amino esters from glycine *t*-butyl ester employing (+)-*N*-alkyl-10-camphorsulfonamide **4b** as a chiral auxiliary works well for α-alkylation with small alkylating agents;

diastereoselectivities for alkylating agents other than methyl iodide were fair. The pure diastereomer could be obtained by single recrystallization of the products from acetone-hexane in good yield. This provides an opportunity for the synthesis of enantiomerically pure α-amino acids employing this method. The change of preferred stereoselectivity on the α-alkylation of Schiff base **5** was unanticipated.

Experimental section

General. Unless otherwise noted, infrared spectra were run as neat films on a sodium chloride window. The NMR spectra were run at 400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR in $CDCl_3$ solution on a Bruker AM-400 NMR spectrometer except a few that were run in D_2O, and chemical shifts are expressed in ppm units relative to internal standard TMS (tetramethylsilane). Mass spectra and high-resolution mass spectra (HRMS) were measured on Jeol SX102 and JMS-HX110 instruments respectively with the electron-impact (EI, 75 eV) technique unless otherwise noted. All crystalline products were recrystallized from acetone-hexane, and melting points of crystalline products were measured by a Buchi 512 apparatus and were uncorrected.

General procedure for the preparation of 4

To a two-necked flask (500mL) containing 4-*N*,*N*-dimethylaminopyridine (0.37 g, 0.003 mol), alkylamine (0.30 mol) and dichloromethane (120 mL), was added 10-camphorsulfonyl chloride (25.1 g, 0.10 mol) in dichloromethane (120 mL) at 0°C over a period of 1h. The mixture was stirred for an additional hour and neutralized with 10% citric acid, then extracted with dichloromethane twice. The combined organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was recrystallized from acetone-hexane to give crystalline product.

4a: White crystal, mp 103 °C; $[\alpha]_D^{20}$ +20.82° (*c* 1, $CHCl_3$); IR ν 3288(s), 2935(s), 1740(s), 1324(s),1145(s)cm^{-1}.; ^1H NMR: 0.91(s, 3H), 1.06(s, 3H), 1.16-1.29(m, 1H), 1,31-1.44 (m, 4H), 1.55-1.63(m, 1H), 1.72-1.75(m, 2H), 1.94(d, J=18.5Hz, 1H), 1.85-2.10(m, 5H), 2.13 (dd, J=4.5, 4.4Hz, 1H), 2.27-2.35 (m, 1H), 2.41(ddd, J=18.5, 3.9, 3.9Hz, 1H), 2.98, 3.43 (ABq, J=15.1Hz, 2H), 3.30-3.40(m, 1H), 5.34(d, J=7.1Hz, 1H); ^{13}C NMR: 19.4(CH_3), 19.6(CH_3), 24.5(CH_2), 24.6(CH_2), 25.0(CH_2), 26.1(CH_2), 26.7(CH_2), 33.6(CH_2), 34.4(CH_2), 42.5(CH_3), 42.6(CH), 48.2(C), 51.1(CH_2), 52.7(CH), 58.9(C), 217.0(C); MS(12eV), *m/z*(rel. intensity) 313(M^+, 3), 260(2), 215(13), 151(15), 141(35), 123 (35), 109(60), 98(100); HRMS: Calcd for $C_{16}H_{27}NO_3S$:313.1712, Found: 313.1702.; Anal: Calcd for $C_{16}H_{27}NO_3S$: C,61.34; H, 8.63; N, 4.47; S, 10.22. Found : C, 61.41; H, 8.69; N, 4.48; S, 10.24.

4b: White crystal, mp 91.5-92.5 °C; $[\alpha]_D^{20}$ +23.18° (*c* 1, $CHCl_3$); IR ν 3284(br,s), 2955(s), 1741(s), 1391(m), 1367(m), 1321(s), 1140(s)cm^{-1}.; ^1H NMR: 0.91(s, 3H), 1.05(s, 3H), 1.41(s, 9H), 1,43-1.47(m, 1H), 1.84-1.94(m, 1H), 1.94(d, J=18.7Hz, 1H), 1.99-2.08(m, 1H), 2.12(dd, J=4.5, 4.4Hz, 1H), 2.29-2.45(m, 2H), 2.99, 3.49(ABq, J=14.9Hz, 2H), 5.12(s, 1H); ^{13}C NMR: 19.5(CH_3), 19.7(CH_3), 25.9(CH_3), 26.8(CH_2), 30.1(CH_3), 42.6(CH), 42.7(CH_2), 48.3(C), 53.4(CH_2), 54.6(C), 59.1(C), 217.2(C); MS(12eV), *m/z*(rel. intensity): 272(M^+-CH_3, 42), 215(74), 167(12), 151(37), 115(63), 109(27),

58(100); HRMS: Calcd for $C_{13}H_{22}O_3SN$ (M^+-CH_3):272.1321, Found :272.1314; Anal: Calcd for $C_{14}H_{25}NO_3S$: C, 58.54; H, 8.71; N, 4.88; S, 11.15.; Found: C, 58.52; H, 8.73; N, 4.85; S, 11.19.

The preparation of 4e

To a 250mL three-necked flask containing **4b** (8.0 g, 0.0279 mol), methanol(50 mL), and trimethyl orthoformate (18 mL, 0.0174 mol) was bubbled with streams of excess hydrogen chloride and hydrogen sulfide at 0 °C for 1 h. The reaction mixture was stirred at 28 °C for 12 h. The resulting orange color solution was concentrated *in vacuo*. The residue was purified on a silica gel column (dichloromethane-ethyl acetate-hexane/1:3:15) to give **4e** (5.68 g, 67%) and recovered **4b** (2.13 g, 27%).

4e: Orange crystal, mp 132-133 °C; $[\alpha]_D^{20}$ +174.5° (*c* 1,$CHCl_3$).; IR ν 3283(s), 2941(s), 1430(m), 1390(m), 1370(m), 1318(s), 1138(s), 1002(s)cm^{-1}.; ^1H NMR: 0.84(s, 3H), 1.21(s, 3H), 1.42(s, 9H), 1.42-1.49(m, 1H), 1.52-1.63(m, 1H), 2.05-2.13 (m, 1H), 2.16(dd, J=4.4, 4.3Hz, 1H), 2.48(d, J=20.9Hz, 1H), 2.65-2.75(m, 1H), 2.76-2.84 (m, 1H), 3.09, 4.17(ABq, J=14.8Hz, 2H), 4.62(s, 1H).; ^{13}C NMR: 19.7(CH_3), 20.4(CH_3), 22.0(CH_2), 29.0(CH_2), 30.4(CH_3), 44.8(CH), 50.1(C), 54.7(C), 54.9(CH_2), 55.5(CH_2), 69.9(C), 237.0(C).; MS *m/z*(rel. intensity): 303(M^+, 28), 231(7), 167(61), 151(33), 134(17), 133(100), 123(44), 107(41), 91(39), 74(67), 59(52).; HRMS: Calcd for $C_{14}H_{25}NO_2S_2$: 303.1327, Found: 303.1324.; Anal: Calcd for $C_{14}H_{25}NO_2S_2$: C, 55.45; H, 8.25; N, 4.62; S, 21.12.; Found: C, 55.51; H, 8.28; N, 4.62; S, 21.22.

The preparation of 5a

To a 250mL three-necked flask containing **4a** (15.65 g, 0.05 mol), methanol(60 mL), and trimethyl orthoformate (46 mL, 0.42 mol) was bubbled with streams of excess hydrogen chloride and hydrogen sulfide at 0 °C for 1.5 h. The reaction mixture was stirred at 28 °C for 10 h. The resulting orange color solution was concentrated *in vacuo*. The residue was purified on a silica gel column (dichloromethane-ethyl acetate-hexane/1:3:7) to give a mixture (13.1 g) of **4c** (51%) and **4d** (26%). Since separation of **4c** and **4d** was difficult at this stage, the mixture was carried over to the next operation where easy separation could be achieved after the reaction.

A solution containing the mixture of **4c** and **4d** (3.29 g, about 0.01 mol), glycine *t*-butyl ester (1.57 g, 0.012 mol), and toluene (30 mL) in a 50 mL flask was heated under reflux for 24 h, then concentrated *in vacuo*. The residue was purified on a silica gel column (dichloromethane-ethyl acetate-hexane/1:3:7) to give **5a** (2.54 g, 90%) and **4d** (0.39 g).

5a: White crystal, mp 132-133 °C.; $[\alpha]_D^{20}$ +7.26°(*c* 1, CHCl3).; IR ν 3300(m), 2928(s), 1737(s), 1690(m), 1392(m), 1368(m), 1323(s), 1151(s)cm^{-1}.; ^1H NMR: 0.86(s, 3H), 0.95(s, 3H), 1.11-1.19(m, 1H), 1.28-1.41(m, 5H), 1.48(s, 9H), 1.53-1.60(m, 1H), 1.71-1.74(m, 2H), 1.83(d,J=1.72Hz, 1H), 1.90-2.70(m, 5H), 2.12-2.20(m, 1H), 2.30-2.34(m, 1H), 3.07, 3.42(ABq, J=15.0Hz, 2H), 3.36(m, 1H), 3.38, 3.92(ABq, J=17.9Hz, 2H), 7.69(d, J=6.3Hz, 1H).; ^{13}C NMR: 19.0(CH_3), 19.7(CH_3), 25.2(CH_2), 25.3(CH_2), 25.4(CH_2), 27.3(CH_2), 28.0(CH_3), 29.3(CH_2), 33.0(CH_2), 34.8(CH_2), 35.7(CH_2), 43.5(CH), 49.6(C), 53.2(CH), 53.7(CH_2), 54.7(CH_2), 56.5(C), 81.4(C), 169.2(C), 183.9(C).; MS *m/z*(rel. intensity): 426(M^+, 17), 370(6), 325(6), 272(28), 208(100), 197(39), 57(61).; HRMS: Calcd for

$C_{22}H_{38}N_2O_4S$: 426.2553, Found: 426.2572.; Anal: Calcd for $C_{22}H_{38}N_2O_4S$: C, 61.97; H, 8.92; N, 6.57; S, 7.51.; Found : C, 61.90; H, 8.94; N, 6.57; S, 7.58.

4d: White crystal, mp 105-107 °C.; $[\alpha]_D^{20}$ +5.13°(*c* 1.95, $CHCl_3$).; IR ν 3280(s), 2926(s), 1446(m), 1320(s), 1138(s)cm^{-1}.; ^1H NMR: 0.92(s, 3H), 0.99(s, 3H), 1.15-1.40(s, 6H), 1.45-1.65 (m, 2H), 1.68-1.74(m, 4H), 1.96-2.03(m, 3H), 2.15-2.19(m, 2H), 2.89, 3.64(ABq, J=15.6Hz, 2H), 3.19(s, 3H), 3.26-3.31(m, 1H), 3.34(s, 3H), 4.47(d, J=6.9Hz, 1H).; ^{13}C NMR: 20.4(CH_3), 21.3(CH_3), 24.8(CH_2), 24.9(CH_2), 25.3(CH_2), 27.0(CH_2), 34.4(CH_2), 34.5(CH_2), 39.9(CH_2), 43.3(CH), 47.8(CH_3), 50.5(CH_3), 51.2(C), 52.3(CH_2), 52.8(CH), 53.9(C), 108.9(C).; MS(12eV), *m/z*(rel. intensity): 344(M^+-CH_3, 5),328(86), 297(90), 264(20), 197(100), 165(90).; HRMS: Calcd for $C_{18}H_{33}NO_4S$: 359.2093; Found: 359.2112.

The preparation of 5b

A solution containing **4e** (3.03 g, 0.01 mol), glycine *t*-butyl ester (1.57 g, 0.012 mol), and toluene(30 mL) in a 50 mL flask was heated under reflux for 24 h, then concentrated *in vacuo*. The residue was purified on a silica gel column (acetone-hexane/1:3) to give **5b** (3.74 g, 94%).

5b: White crystal, mp 93-93.5 °C.; $[\alpha]_D^{20}$ -3.70°(*c* 1, $CHCl_3$).; IR ν 3200(w), 2935(s), 1735(s), 1687(s), 1390(m), 1367(m), 1325(s), 1150(s)cm^{-1}.; ^1H NMR: 0.88(s, 3H), 0.96(s, 3H), 1.30-1.40(m, 1H), 1.30(s, 9H), 1.47(s, 9H), 1.88(d, J=17.3Hz, 1H), 1.90-2.20(m, 4H), 2.32-2.38(m, 1H), 2.99, 3.56 (ABq, J=15.0Hz, 2H), 3.95, 3.99(ABq, J=16.5Hz, 2H), 7.80(s, 1H).; ^{13}C NMR: 19.0(CH_3), 19.6(CH_3), 27.3(CH_2), 27.9(CH_3), 28.7(CH_2), 30.2(CH_3), 35.5(CH_2), 43.2(CH), 49.6(C), 53.9(CH_2), 54.4(C), 55.7(CH_2), 56.2(C), 81.7(C), 168.4(C), 185.5(C).; MS *m/z*(rel. intensity): 401(M^++1, 2), 385(27), 329(7), 272(40), 208(100).; HRMS: Calcd for $C_{20}H_{36}N_2O_4S$: 400.2396, Found: 400.2401.; Anal: Calcd for $C_{20}H_{36}N_2O_4S$: C, 60.00; H, 9.00; N, 7.00; S, 8.00.; Found: C, 60.01; H, 8.92; N, 7.00; S, 7.82.

General procedure for the alkylation of 5

To a round bottomed flask containing Schiff base **5** (2.35 mmol) and tetrahydrofuran (4.7 mL) was added lithium diisopropylamide (5.17 mmol) at -78 °C. The mixture was stirred for 30 min. then was added hexamethylphosphoroustriamide (4.70 mmol) and alkyl halide(2.82 mmol) at -78 °C. After 1h at -78 °C, the mixture was warmed to 0 °C and stirred for 10 min. The mixture was added water (2.5 mL) to quench the reaction and extracted with ether. The organic layer was washed with brine, dried with anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the alkylation products. Crystalline product was recrystallized from acetone-hexane to give pure diastereomer.

7a: oil; $[\alpha]_D^{20}$ -41.01° (*c* 1.87, $CHCl_3$).; IR ν 3250(s), 2931(s), 1730(s), 1679(s), 1390(m), 1370(m), 1310(s), 1149(s).cm^{-1}; ^1H NMR: 0.83(s, 3H), 0.85(s, 3H), 1.10-1.20(m, 1H), 1.29-1.48(m, 5H), 1.32(d, J=6.4Hz, 3H), 1.48(s, 9H), 1.58-1.64(m, 1H), 1.73-1.75(m, 2H), 1.88-2.20(m, 7H), 2.35(ddd, J=17.1, 3.8, 3.8Hz, 1H), 3.04, 3.42(ABq, J=14.8Hz, 2H), 3.30-3.40(m, 1H), 3.65(q, J=6.4Hz, 1H), 7.38(d, J=6.7Hz, 1H).; ^{13}C NMR: 18.3(CH_3), 19.1(CH_3), 19.5(CH_3), 25.2(CH_2), 25.4(CH_2x2), 27.4(CH_3), 28.0(CH_3), 28.9(CH_2), 33.6(CH_2), 34.8(CH_2), 35.0(CH_2), 43.4(CH), 49.1(C), 53.1(CH), 54.5(CH_2),

56.2(C), 60.2(CH), 81.4(C), 171.6(C), 181.6(C).; MS *m/z*(rel. intensity): 440(M^+, 18), 349(12), 286(16), 278(8), 222(100), 197(46).; HRMS: Calcd for $C_{23}H_{40}N_2O_4S$: 440.2710, Found: 440.2715.

7b: oil; $[\alpha]_D^{20}$ -70.40° (*c* 2.97, $CHCl_3$).; IR ν 3300-3100(br), 2927(s), 1731(s), 1682(m), 1391(m), 1368(m), 1325(s), 1149(s)cm^{-1}.; ^1H NMR: 0.84(s, 3H), 0.90(t, J=7.5Hz, 3H), 1.08-1.18(m, 1H), 1.25-1.38(m, 5H), 1.48(s, 9H), 1.58-1.65(m, 1H), 1.70-1.80(m, 4H), 1.85-2.12(m, 10H), 2.35(ddd, J=17.4, 3.8, 3.8Hz, 1H), 3.05, 3.44(ABq, J=14.9Hz, 2H), 3.35-3.42(m, 1H), 3.74(dd, J=8.0, 5.6Hz, 1H), 7.40(d, J=7.2Hz, 1H).; ^{13}C NMR: 10.6(CH_3), 19.1(CH_3), 19.6(CH_3), 25.3(CH_2), 25.4(CH_2x2), 26.1(CH_2), 27.4(CH_2), 28.0(CH_3), 28.9(CH_2), 33.8(CH_2), 34.9(CH_2), 35.3(CH_2), 43.4(CH), 48.8(C), 52.9(CH), 54.6(CH_2), 56.3(C), 67.1(CH), 81.4(C), 170.6(C), 182.7(C).; MS *m/z*(rel. intensity): 454(M^+, 12), 353(12), 292(7), 236(100).; HRMS: Calcd for $C_{24}H_{42}N_2O_4S$: 454.2866; Found: 454.2875.

7c: $[\alpha]_D^{20}$ -69.22° (*c* 1.47, $CHCl_3$).; IR ν 3300-3050(br, m), 2926(s), 1732(s), 1678(m), 1650(m), 1391(m), 1370(m), 1320(s), 1150(s)cm^{-1}.; ^1H NMR: 0.78(s, 3H), 0.91(s, 3H), 1.05-1.15(m, 1H), 1.25-1.35(m, 5H), 1.43(s, 9H), 1.58-1.68(m, 3H), 1.85-2.10(m, 7H), 2.16(ddd, J=10.1, 4.1, 3.4Hz, 1H), 2.36-2.46(m, 1H), 2.55-2.65(m, 1H), 2.99, 3.39(ABq, J=14.8Hz, 2H), 3.30-3.40(m, 1H), 3.85(dd, J=8.2, 5.3Hz, 1H), 5.01(d, J=10.6Hz, 1H), 5.07(dd, J=16.4, 1.4Hz, 1H), 5.61-5.72(m, 1H), 7.25(d, J=4.2Hz, 1H).; ^{13}C NMR: 19.1(CH_3), 19.7(CH_3), 25.3(CH_2x2), 25.5(CH_2), 27.4(CH_2), 28.0(CH_3), 28.8(CH_2), 33.9(CH_2), 34.9(CH_2), 35.5(CH_2), 37.2(CH_2), 43.5(CH), 48.9(C), 52.9(CH), 54.5(CH_2), 56.4(C), 65.4(CH), 81.8(C), 117.9(CH_2), 134.0(CH), 170.2(C), 183.0(C).; MS *m/z*(rel. intensity): 466(M^+, 15), 409(5), 365(10), 312(8), 288(14), 249(100).; HRMS: Calcd for $C_{25}H_{42}N_2O_4S$: 466.2865, Found: 466.2861.

8c: White crystal, mp 103-104 °C.; $[\alpha]_D^{20}$ +49.63° (*c* 1, $CHCl_3$).; IR ν 3250(s), 2926(s), 1731(s), 1680(m), 1650(w), 1391(m), 1367(m), 1325(s), 1149(s)cm^{-1}.; ^1H NMR: 0.83(s, 3H), 0.93(s, 3H), 1.08-1.18(m, 1H), 1.20-1.40(m, 5H),1.43(s, 9H), 1.56-1.59(m, 1H), 1.70-1.71(m, 2H), 1.86-2.15(m, 7H), 2.41-2.47(m, 2H), 2.58-2.68(m, 1H), 3.07, 3.39, (ABq, J=14.9Hz, 2H), 3.30-3.38(m, 1H), 3.86(dd, J=8.1, 5.4Hz, 1H), 5.06(d, J=9.8Hz, 1H), 5.12(d, J=17.0Hz, 1H), 5.69-5.79(m, 1H), 7.45(d, J=7.3Hz, 1H).; ^{13}C NMR: 19.1(CH_3), 19.6(CH_3), 25.3(CH_2x2), 28.0(CH_3), 29.8(CH_2), 33.2(CH_2), 34.9(CH_2), 35.8(CH_2), 37.3(CH_2), 43.3(CH), 49.4(C), 53.5(CH), 55.1(CH_2), 56.5(C), 64.6(CH), 81.4(C), 118.2(CH_2), 133.5(CH), 170.2(C), 183.2(C).; MS *m/z*(rel. intensity): 466(M^+, 16), 409(4), 365(10), 312(10), 288(14), 249(100), 197(24).; HRMS: Calcd for $C_{25}H_{42}N_2O_4S$: 466.2865, Found: 466.2861.; Anal: Calcd for $C_{25}H_{42}N_2O_4S$: C, 64.38; H, 9.01; N, 6.01; S, 6.88.; Found: C, 64.27; H, 9.11; N, 6.08; S, 6.85.

7d: White crystal, mp 116-116.5 °C.; $[\alpha]_D^{20}$ -120.35° (*c* 1, $CHCl_3$).; IR ν 3300-3200(br), 2939(s), 1730(s), 1682(m), 1600(w), 1500(w), 1391(m), 1368(m), 1320(s), 1151(s)cm^{-1}.; ^1H NMR: 0.22(s, 3H), 0.85(s, 3H), 1.29-1.41(m, 5H), 1.46(s, 9H), 1.61-2.17(m, 12H), 2.91, 3.39(ABq, J=14.9Hz, 2H), 2.96(dd, J=13.5, 9.9Hz, 1H), 3.26(dd, J=13.5, 4.3Hz, 1H), 3.42-3.43(m, 1H), 4.07(dd, J=9.9, 4.3Hz, 1H), 7.14-7.28(m, 5H), 7.51(d, J=6.6Hz, 1H).; ^{13}C NMR: 18.3(CH_3), 18.9(CH_3), 25.2(CH_2), 25.3(CH_2), 25.4(CH_2), 27.2(CH_2), 27.9(CH_3), 28.3(CH_2), 34.3(CH_2), 34.9(CH_2), 35.4(CH_2), 38.8(CH_2), 43.1(CH), 48.7(C), 52.1(CH), 54.1(CH_2), 56.0(C), 66.9(CH), 81.7(C), 126.5(CH), 128.3(CH), 129.2(CH), 137.9(C), 169.9(C), 183.6(C).; MS *m/z*(rel. intensity): 516(M^+, 35), 460(5), 415(11), 354(11), 298(100), 197(9), 149(35).; HRMS: Calcd for $C_{29}H_{44}N_2O_4S$: 516.3022, Found:

516.3025; Anal: Calcd for $C_{29}H_{44}N_2O_4S$: C, 67.44; H, 8.53; N, 5.43; S, 6.20.; Found: C, 67.47; H, 8.61; N, 5.65; S, 6.20.

9a: oil; $[\alpha]_D^{20}$ -82.59° (*c* 1.55, $CHCl_3$).; IR ν 3250(m), 2933(s), 1730(s), 1685(s), 1391(m), 1368(m), 1325(s), 1140(s)cm^{-1}.; ^1H NMR: 0.81(s, 3H), 0.96(s, 3H), 1.30-1.40(m, 1H), 1.37(d, J=6.8Hz, 3H), 1.40(s, 9H), 1.46(s, 9H), 1.83-2.17(m, 5H), 2.30-2.38(m, 1H), 2.94, 3.56(ABq, J=15.0Hz, 2H), 3.94(q, J=6.8Hz, 1H), 7.56(s, 1H).; ^{13}C NMR: 18.3(CH_3), 19.0(CH_3), 19.4(CH_3), 22.3(CH_2), 22.9(CH_3), 28.2(CH_2), 30.5(CH_3), 35.1(CH_2), 43.29(CH), 49.1(C), 54.6(C), 55.5(CH_2), 59.9(CH), 81.3(C), 171.0(C), 182.8(C).; MS *m/z*(rel. intensity): 415(M^++1, 1), 399(23), 353(10), 313(13), 286(21), 278(7), 222(100), 176 (10).; HRMS: Calcd for $C_{21}H_{38}N_2O_4S$: 414.2553, Found: 414.2521.

9b: White crystal, mp 82-83 °C.; $[\alpha]_D^{20}$ -121.90° (*c* 1, $CHCl_3$).; IR ν 3300-3200(br), 2938(s), 1730(s), 1681(m), 1391(m), 1368(m), 1313(s), 1147(s)cm^{-1}.; ^1H NMR: 0.82(s, 3H), 0.89(t, J=7.5Hz, 3H), 0.97(s, 3H), 1.29-1.35(m, 1H), 1.40(s, 9H), 1.47(s, 9H), 1.73-1.82(m, 1H), 1.90-2.08(m, 5H), 2.18-2.28(m, 1H), 2.35-2.44(m, 1H), 2.93, 3.57(ABq, J=15.0Hz, 2H), 3.72(dd, J=8.8, 4.9Hz, 1H), 7.46(s, 1H).; ^{13}C NMR: 10.6(CH_3), 18.9(CH_3), 19.5(CH_3), 25.7(CH_2), 27.3(CH_2), 27.9(CH_3), 28.0(CH_2), 30.5(CH_3), 35.6(CH_2), 43.2(CH), 48.9(C), 54.7(C), 55.3(CH_2), 55.9(CH_2), 66.6(CH), 81.3(C), 170.2(C), 183.9(C). ; MS *m/z*(rel. intensity): 429(M^++1, 0.5), 413(42), 357(5), 355(3), 327(10), 292(15), 264(6), 236(100).; HRMS: Calcd for $C_{22}H_{40}N_2O_4S$: 428.2709, Found: 428.2682.; Anal: Calcd for $C_{22}H_{40}N_2O_4S$: C, 61.68; H, 9.35; N, 6.54; S, 7.48.; Found: C, 61.62; H, 9.39; N, 6.84; S, 7.45.

9c: White crystal, mp 94-94.5 °C.; $[\alpha]_D^{20}$ -16.77° (*c* 1, $CHCl_3$).; IR ν 3300-3200(br), 2951(s), 1731(s), 1680(m), 1391(m), 1367(m), 1326(s), 1146(s)cm^{-1}.; ^1H NMR: 0.89(s, 3H), 0.90(s, 3H), 1.29-1.35(m, 1H), 1.42(s, 9H), 1.45(s, 9H), 1.88-2.09(m, 5H), 2.37-2.54(m, 2H), 2.65-2.74(m, 1H), 3.02, 3.55(ABq, J=15.0Hz, 2H), 3.89(dd, J=8.6,5.4Hz, 1H), 5.08(d, J=10.1Hz, 1H), 5.14(dd, J=17.1, 1.2Hz, 1H), 5.67-5.79(m, 1H), 7.32(s, 1H).; ^{13}C NMR: 19.3(CH_3), 19.8(CH_3), 22.6(CH_2), 28.2(CH_3), 29.6(CH_2), 30.6(CH_3), 30.7(C), 36.3(CH_2), 37.0(CH_2), 43.4(CH), 49.86(C), 55.0(C), 56.4(CH_2), 65.2(CH), 81.6(C), 118.2(CH_2), 133.8(CH), 170.2(C), 184.3(C).; MS(12eV), *m/z*(rel. intensity): 440(M^+, 2), 425(43), 383(2), 369(5), 339(9), 305(18), 288(7), 248(100).; HRMS: Calcd for $C_{23}H_{40}N_2O_4S$: 440.2709, Found:440.2693.; Anal: Calcd for $C_{23}H_{40}N_2O_4S$: C, 62.73; H, 9.09; N, 6.36; S, 7.28.; Found: C, 62.84; H, 9.11; N, 6.50; S, 7.26.

9d: White crystal, mp 117-118 °C.; $[\alpha]_D^{20}$ -164.67° (*c* 1.2, $CHCl_3$).; IR ν 3070(s), 2940(s), 1728(s), 1680(s), 1600(w), 1500(w), 1391(m), 1367(m), 1287(s), 1146(s)cm^{-1}.; ^1H NMR: 0.12(s, 3H), 0.84(s, 3H), 1.19-1.25(m, 1H), 1.47(s, 18H), 1.75-2.18(m, 5H), 2.15-2.28(m, 1H), 2.78, 3.43(ABq, J=15.2Hz, 2H), 3.02(dd, J=13.4, 10.6Hz, 1H), 3.27(dd, J=13.4, 13.6Hz, 1H), 4.04(dd, J=10.6, 3.6Hz, 1H), 7.13-7.27(m, 5H), 7.07(s, 1H).; ^{13}C NMR: 18.7(CH_3), 18.9(CH_3), 27.3(CH_2), 27.8(CH_2), 28.0(CH_3), 30.7(CH_3), 35.8(CH_2), 38.6(CH_2), 43.1(CH), 48.9(C), 54.9(C), 55.2(CH_2), 55.9(C), 66.7(CH), 81.8(C), 126.5(CH), 128.4(CH), 129.3(CH), 138.1(C), 169.7(C).; MS *m/z*(rel. intensity): 491(M^++1, 0.5), 475(22), 419(6), 389(10), 362(10), 354(6), 298(100).; HRMS: Calcd for $C_{27}H_{42}N_2O_4S$: 490.2866, Found: 490.2851.

10d: White crystal, mp 178-178.5 °C.; $[\alpha]_D^{20}$ +46.19° (*c* 1, $CHCl_3$).; IR ν 3250(w), 3030(m), 2951(m), 1720(s), 1680(m), 1600(w), 1500(w), 1390(m),1365(m), 1324(s), 1142(s)cm^{-1}.; ^1H NMR: 0.69-0.72(m, 1H), 0.79(s, 3H), 0.86(s, 3H), 0.96(d, J=17.0Hz, 1H), 1.45(s, 9H), 1.46(s, 9H), 1.65-1.95(m, 4H),

2.22(ddd, J=17.0, 4.0, 4.0Hz, 1H), 2.94(d, J=13.3Hz, 1H), 2.97, 3.52(ABq, J=14.9Hz, 2H), 3.29(dd, J=13.3, 3.4Hz, 1H), 3.97(dd, J=10.3, 3.4Hz, 1H), 7.19-7.30(m, 5H), 7.54(s, 1H).; ^{13}C NMR: 19.0(CH_3), 19.4(CH_3), 27.1(CH_2), 28.0(CH_3), 28.7(CH_2), 30.5(CH_3), 35.5(CH_2), 38.4(CH_2), 42.9(CH), 49.4(C), 54.9(C), 56.2(CH_2), 56.5(C), 66.9(CH_2), 81.5(C), 126.5(CH), 128.3(CH), 129.8(CH), 137.8(C), 170.5(C), 184.8(C).; MS*m/z*(rel. intensity): 491(M^++1, 0.6), 419(6), 389(10), 362(11), 354(7), 298(100).; HRMS: Calcd for $C_{27}H_{42}N_2O_4S$: 490.2866, Found: 490.2851.; Anal: Calcd for $C_{27}H_{42}N_2O_4S$: C, 66.12; H, 8.57; N, 5.71; S, 6.53.; Found: C, 66.27; H, 8.73; N, 5.93; S, 6.50.

General procedure for the hydrolysis of alkylation product 9a~c and 10d

A mixture containing **9** or **10d** (1 mmol), sodium hydroxide (1.1 mmol), hydroxylamine-hydrochloride (76.5 mg, 1.1 mmol), acetic acid (1.1 mmol), methanol (4 mL), chloroform (3 mL) in a flask (25 mL) was stirred at 25 °C for 24h. The mixture was concentrated *in vacuo*, and acidified with 2 *N* HCl (~7.5 mL), then extracted with ether (80 mL). The organic layer was washed with water (8 mL), dried with anhydrous sodium sulfate, and concentrated *in vacuo* to recover the chiral auxiliary **4b**. The combined aqueous solution was adjusted to *p*H 10 with 2*N* NaOH, then was extracted with ether (80 mL). The organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, and concentrated to give amino ester **11**.

11a: $[\alpha]_D^{20}$ +0.97° (*c* 2.08, $CHCl_3$).; IR ν 3342(m), 3300(m), 2967(s), 1728(s), 1606(w), 1391(m), 1368(m), 1250(m), 1157(s) cm^{-1}.; ^{1}H NMR: 1.21(d, J=7.0Hz, 3H), 1.38(s, 9H), 1.87(br, 2H), 3.43(q, J=7.0Hz, 1H).; ^{13}C NMR: 20.6(CH_3), 27.9(CH_3), 50.5(CH), 80.7(C), 175.8(C).; MS(70eV), *m/z*(rel. intensity): 146(M^++1, 58), 90(100).

11b: $[\alpha]_D^{20}$ +4.97° (*c* 0.4, $CHCl_3$).; IR ν 3350(w), 3310(w), 2971(s), 1728(s), 1367(m), 1157(s)cm^{-1}.; ^{1}H NMR: 0.95(t, J=6.3Hz, 3H), 1.51(s, 9H), 1.55-1.80(m, 4H), 3.28(t, J=6.1Hz, 1H).; ^{13}C NMR: 9.7(CH_3), 27.9(CH_2), 28.1(CH_3), 56.2(CH), 80.8(C), 175.3(C).; MS(70eV), *m/z*(rel. intensity): 160(M^++1, 22), 104(100), 58(56).

11c: $[\alpha]_D^{20}$ -0.91° (*c* 0.98, $CHCl_3$).; IR ν 3378(w), 3300(w), 3078(w), 2960(s), 1729(s), 1640(w), 1620(w), 1368(m), 1157(s)cm^{-1}.; ^{1}H NMR: 1.47(s, 9H), 1.64(br s, 2H), 2.34-2.48(m, 2H), 3.42(dd, J=6.7, 5.2Hz, 1H), 5.12-5.17(m, 2H), 5.70-5.78(m, 1H).; ^{13}C NMR: 28.0(CH_3), 39.3(CH_2), 54.3(CH), 81.1(C), 118.3(CH_2), 133.6(CH), 174.5(C).; MS(70eV), *m/z*(rel. intensity): 172(M^++1, 56), 116(100), 70(24), 57(18).

11d: $[\alpha]_D^{20}$ -32.9° (*c* 2.25, ethanol), lit[9]: $[\alpha]_D^{30}$ -32.6° and lit[11]: $[\alpha]_D^{20}$ -24.8° (neat).; IR ν 3377(m), 3300(w), 3070(w),2960(s), 1727(s), 1599(w), 1496(w), 1454(m), 1392(m), 1368(s), 1158(s), 700(m)cm^{-1}. ; ^{1}H NMR: 1.40(s, 9H), 1.54(br, 2H), 2.81(dd, J=13.4, 7.8Hz, 1H), 3.00(dd, J=13.4, 5.6Hz, 1H), 3.58(dd, J=7.8, 5.6Hz, 1H), 7.18-7.27(m, 5H).; ^{13}C NMR: 27.9(CH_3), 41.2(CH_2), 56.2(CH), 81.0(C), 126.6(CH), 128.3(CH), 129.3(CH), 137.5(C), 174.2(C).; MS(70eV) *m/z*(rel. intensity): 222(M^++1, 100), 166(58), 120(93), 91(22), 74(22), 65(11), 57(33).

General procedure for the formation of amino ester hydrochloride salt 12a~c

A mixture containing **11** (0.50 mmol) and 6*N* HCl (5 mL) was heated under reflux for 1.5h then was concentrated under vacuum (0.2 mmHg, 25 °C, 14~30 h) to give **12** as white solid.

12a: $[\alpha]_D^{20}$ +6.09° (*c* 1.31, H_2O), lit[10]: $[\alpha]_D^{20}$ +6.3° (*c* 1.20, H_2O).; ^1H NMR(D_2O): 1.53(d, J=7.4Hz, 3H), 4.07(q, J=7.4Hz, 1H).
12b: $[\alpha]_D^{20}$ +9.80° (*c* 1.05, H_2O), lit[10]: $[\alpha]_D^{20}$ +10.1° (*c* 1.11, H_2O).; ^1H NMR: 1.01(t, J=7.5Hz, 3H), 1.91-2.01(m, 2H), 4.00(t, J=6.0Hz, 1H).
12c: $[\alpha]_D^{20}$ +0.66° (*c* 1.18, H_2O).; ^1H NMR: 2.62-2.78(m, 2H), 4.13(dd, J=7.2, 5.0Hz, 1H), 5.27-5.32(m, 2H), 5.71-5.82(m, 1H).

Acknowledgment. Support of this work from the National Science Council, Republic of China under Grant number NSC81-0208-M007-078, and a generous gift of D-10-camphorsulfonic acid, starting material for **4**, from China Camphor Co. are gratefully acknowledged. We thank Tainan Regional Instrumentation Center, Tainan, Taiwan, Republic of China for the assistance on handling elementary analyses.

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(*Received* 29 *August* 1996; *accepted* 11 *December* 1996)