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Asymmetric synthesis of α,α-disubstituted amino acids by diastereoselective functionalization of enantiopure phenyloxazinones, derivatives of asymmetric Strecker reaction products of aldehydes

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Abstract—Esterification of the asymmetric Strecker reaction products of a suitable aldehyde and (*R*)-phenylglycinol followed by lactonization and alkylation provides chiral oxazinones **5**. Treatment of the enolates of **5** with active alkyl halides, or aldehydes provided the corresponding functionalization products with high diastereoselectivity. The configuration of newly created quaternary carbon is *S* for the products coupled with simple alkyl halides and aldehydes, and *R* for the products coupled with methyl bromoacetate. Deprotection of these products afforded the corresponding enantiopure α,α-dialkyl amino acids.

1. Introduction

Owing to their remarkable pharmacological and conformational properties as either free amino acids or components of bioactive peptides, enantiopure α,α-disubstituted amino acids have attracted much synthetic attention.[1] Among the established methods, diastereolective functionalization of an enantiopure α-amino acids via a nonracemic enolate is one of the most popular ways.[1] In order to achieve the high diastereoselectivity, some cyclic derivatives of α-amino acids were developed, which include Schollkopf's bislactam ethers **1**,[2] Seebach's oxa- and imidazolidinones **2**,[3] and Williams' diphenyloxazinones **3**[4] and oxazinones **4**[5] recently developed by Najera and coworkers. However, most of them needed to take more reaction steps to build their structures and acidic cleavage of α-functionalization products at high reaction temperature. In addition, some of them were restricted by the source of enantiopure α-amino acids. Thus, the discovery of new enantiopure cyclic templates to overcome these drawbacks is still required (Fig. 1).

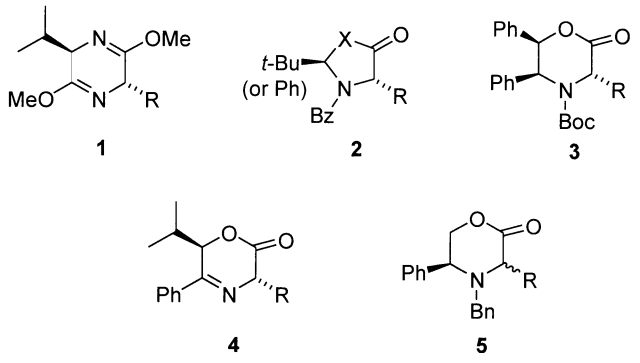

Figure 1. Structures of chiral templates for the asymmetric synthesis of α,α-dialkyl amino acids.

Inspired from our studies on asymmetric Strecker reactions starting with chiral amines,[6] we developed a new method for preparing chiral oxazinones **5**,[11] which took three steps and started from the asymmetric Strecker reaction products of suitable aldehydes, as illustrated in Scheme 1. After treatment of **5** with a suitable base, the nonracemic enolates generated might react with various electrophiles to provide functionalization products **6**. If the diastereoselectivity in this step was good we would be able to obtain enantiopure α,α-disubstituted amino acids by deprotection. Thus, we could synthesize either α-monosubstituted[8] or α,α-disubstituted amino acids using the asymmetric Strecker reaction of aldehyde. Herein, we wish to describe our results.[7]

2. Result and discussion

As shown in Scheme 1, the chiral oxazinones **5** were

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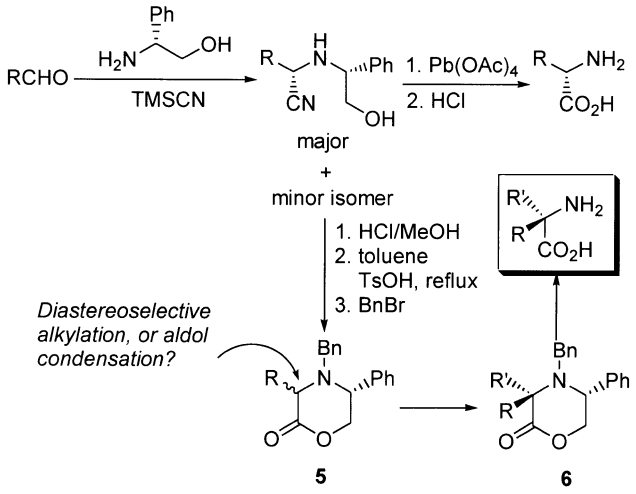
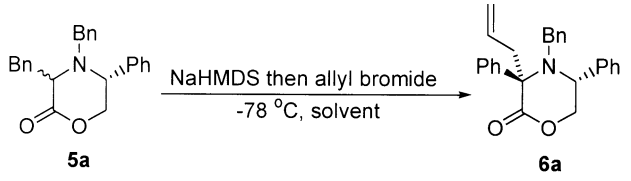


Scheme 1.

Table 1. Alkylation of **5a** in different solvents



Entry	Solvent	Reaction time (h)	Yield (%)[a]
1	THF	24	<10
2	Et_2O	24	<10
3	Toluene	24	–
4	THF/toluene	18	45
5	THF/HMPA	15	62
6	THF/DME	12	65
7	DME	8	87

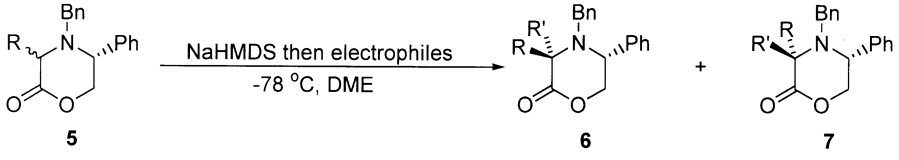
Reaction conditions: see text.
[a] Isolated yield.

prepared from aldehyde by following steps: (1) asymmetric Strecker reaction according to the known procedure[8] except for using NaCN instead of TMSCN; (2) esterification of nitrile moiety with methanolic hydrochloride; (3) cyclization in refluxing toluene catalyzed by TsOH; (4) alkylation with benzyl bromide mediated by K_2CO_3 in DMF. The overall yields for preparing **5a–d** from the corresponding aldehyde were 33–48% and the diastereoselectivities were 66–80%.

Initially, we chose the coupling reaction of **5a** with allyl bromide as a model to explore the optimum reaction conditions. It was found that the reaction was highly dependent on the solvents used. From the results summarized in Table 1 we could see using DME alone gave the highest yield in a shorter time (entry 7), while THF, ether, and toluene were the worst solvents for this reaction (entries 1–3). The reaction could also be carried out in mixed solvents such as THF/toluene, THF/DME and THF/HMPA to give the alkylation product in moderate yields (entries 4–6).

Under this optimized reaction condition other substrates and electrophiles were tested and the results are listed in Table 2. It was found that only active electrophiles could react with the sodium enolates generated from oxazinones **5** to give the corresponding products. For examples, apart from allyl bromide, other active alkyl halides such as benzyl bromide (entries 3, 5, 7, and 13), ethyl iodide (entry 8) and methyl bromoacetate (entries 2, 4, 9 and 14) were also worked for this reaction. However, less active alkyl halides such as ethyl bromide (entry 11) could not be used as the coupling reagents. In these cases, the corresponding oxazinone **5** was completely recovered after quenching the reaction. The aldol reaction of the sodium enolates generated from oxazinones **5** with an aldehyde proceeds in a much faster manner (entries 6 and 10). Two isomers were detected in this reaction and their ratio was about 8:1. By recrystalization the

Table 2. Diastereoselective functionalization of oxazinones **5**



Entry	Substrate (R)	Electrophile	Reaction time (h)	Product (R′)		Yield (%)[a]
				6	**7**	
1	Bn (**5a**)	Allyl bromide	8	Allyl (**6a**)	–	87
2	Bn (**5a**)	$BrCH_2CO_2Me$	9	–	CH_2CO_2Me (**7a**)	79
3	Bn (**5a**)	BnBr	8	Bn (**6b**)		83
4	*n*-Pr (**5b**)	$BrCH_2CO_2Me$	12	–	CH_2CO_2Me (**7b**)	76
5	*n*-Pr (**5b**)	BnBr	8	Bn (**6c**)	–	85
6	*n*-Pr (**5b**)	CH_3CHO	0.1	(*S*)-CH(OH)Me (**6d**)	–	85[b]
7	Me (**5c**)	BnBr	8	Bn (6e)	–	90
8	Me (**5c**)	EtI	24	Et (6f)	–	50
9	Me (**5c**)	$BrCH_2CO_2Me$	12	–	CH_2CO_2Me (**7c**)	87
10	Me (**5c**)	*n*-PrCHO	0.1	(*S*)-CH(OH)Pr-*n*(**6g**)	-	80[b]
11	Me (**5c**)	EtBr	12	–	–	–
12	$BnO(CH_2)_2$ (**5d**)	Allyl bromide	6	Allyl (**6h**)	–	90
13	$BnO(CH_2)_2$ (**5d**)	BnBr	6	Bn (**6i**)	–	89
14	$BnO(CH_2)_2$ (**5d**)	$BrCH_2CO_2Me$	8	–	CH_2CO_2Me (**7d**)	83

Reaction conditions: see text.
[a] Isolated yield.
[b] Based on 50% starting material recovery.

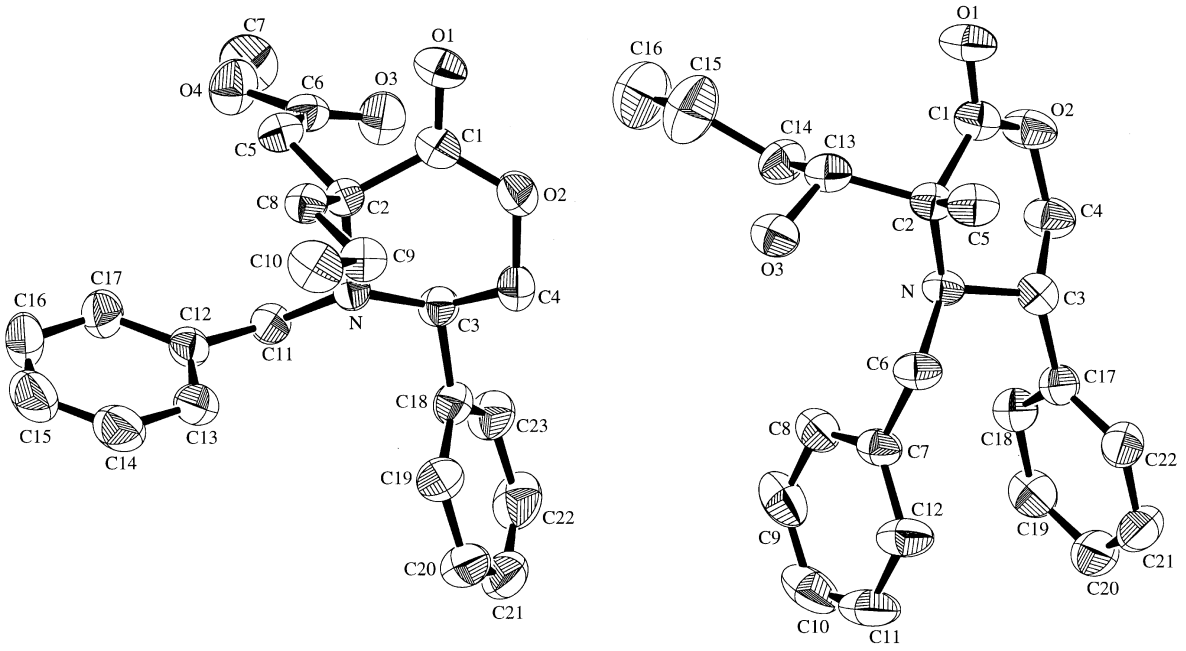
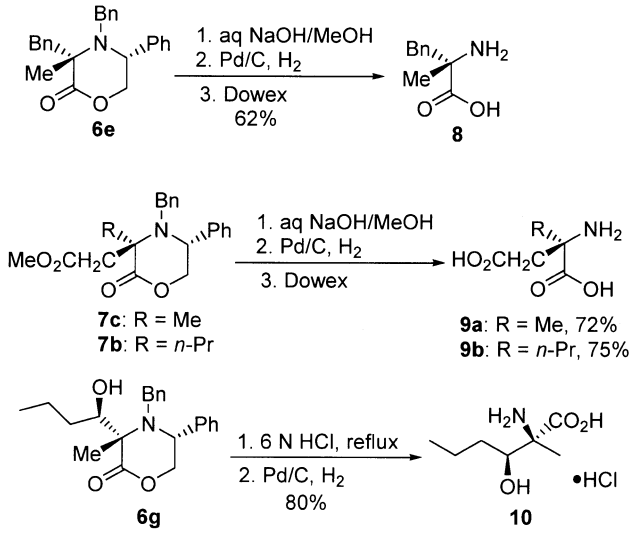


Figure 2. X-ray structures of **7b** (left) and **6g** (right).

pure major isomer **6d** or **6g** was obtained and their stereochemistry was assigned by X-ray structure analysis (see below). The conversion of this reaction was about 50% because a retro-aldol reaction might occur. Prolonging the reaction time would result in the formation of some side products. Although the reason for less reactivity of enolates generated from oxazinones **5** was not clear, one obvious explanation was because of their steric hindrance. The side chain in oxazinone substrates could be simple alkyl groups or some functionalized alkyl groups (entries 12–14), which would allow the preparation of more complicated α,α-disubstituted amino acids.

The diastereoselectivity of these coupling reactions was found to be very high. For example, HPLC analysis of the reaction product of **5b** with methyl bromoacetate indicated the diastereoselectivity was over 250:1. In order to determine the stereochemistry of the present products, both X-ray structure analysis and further conversion of the products to known α,α-disubstituted amino acids were undertaken. As shown in Fig. 2, the X-ray structure of **7b**, a coupling product of **5b** with methyl bromoacetate, clearly indicated that the 5-*n*-propyl group was *cis* to the 3-phenyl group, which implied that the configuration of 5-position was *R*. However, the X-ray structure of **6g**, an aldol reaction product, demonstrated that its configuration was 3*R*,5*S*,1′*S*. These surprising results prompted us to check the stereochemistry of **6a–c**, **6e–f**, and **6h–i** that were generated by alkylation with simple alkyl halides. We decided to solve this problem by conversion of **6e** to the known amino acid **8**. Thus, **6e** was treated with aqueous NaOH to open the lactone ring, the generated sodium salt was neutralized with HCl and then it was deprotected by Pd/C-catalyzed hydrogenation (40 atm and 40°C) to give the crude amino acid, which was purified with Dowex-50W to afford **8** ($[\alpha]_D^{19}=-22.2$ (*c* 2.8, H_2O), lit.[9]: $[\alpha]_D^{25}=-22$ (*c* 1.0, H_2O) for (*S*)-α-methylphenylalanine) in 62% yield (Scheme 2). This result implied that the quarternary carbon in **6a–c**, **6e–f**, and **6h–i** might have *S*-form configuration.

Taking the above investigations together, we concluded that when sodium enolates of **5** reacted with aldehydes or some simple alkyl halides, the (3*R*,5*S*)-products were provided. This stereochemistry could be explained by Fig. 3. When **5** was used as a substrate, the generated enolate would prefer the conformation A in which the *N*-benzyl group and the phenyl group are *trans* each other. This enolate would attack favorably the electrophile from the back side of the benzyl group and give the (3*R*,5*S*)-product. However, as mentioned above, when sodium enolates of **5** attacked methyl bromoacetate, the coupling products had a (3*R*,5*R*)-configuration. The reason for this exception is not clear, but one possible explanation is that this stereochemistry might come from some chelation that formed between the ester moiety of



Scheme 2.

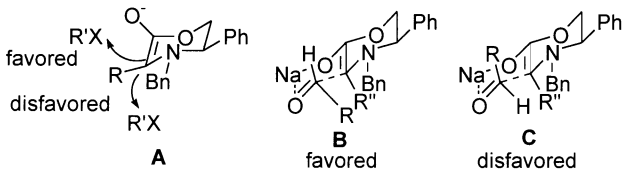


Figure 3.

methyl bromoacetate and sodium enolates thereby giving different stereochemistry. The predominant formation of 1′*S* isomer of aldol reaction was explained by Fig. 3. The conformation B is obviously more favorable than the conformation C because of bigger steric hindrance between R′ and R groups.

Following the same reaction sequence from **6e** to **8**, the lactones **7c** and **7b** were converted into (*R*)-α-methyl-aspartic acid and (*R*)-α-propylaspartic acid in 72 and 75% yields, respectively (Scheme 2). From the functionalization products α,α-disubstituted amino acids could be obtained in another manner that was demonstrated by the conversion of **6g** to **10**. Refluxing of **6g** in 6N HCl to open the lactone ring followed by Pd/C-catalyzed hydrogenation to cleavage the benzyl groups afforded **10** in 80% yield.

As a summary, we have developed a new class of chiral oxazinones that is suitable for preparing enantiopure α,α-dialkyl amino acids, especially α-alkyl aspartic acids and α,α-disubstituted analogues of serine and threine. These chiral oxazinones could be easily synthesized from aldehydes and chiral phenylglycinol in three working-up steps and the generated α,α-disubstituted amino acid precursors could be deprotected in convenient manner. Further optimization of the procedure and its application to prepare biologically active α,α-disubstituted amino acids are in progress.

3. Experimental

3.1. General procedure of preparing oxazinones 5

To a solution of aldehyde (1.0 equiv.), (*R*)-phenylglycinol (1.1 equiv.), ammonium chloride (1.3 equiv.) in MeOH–H_2O (1:1) was added sodium cyanide (1.0 equiv.) at 0°C. The solution was stirred at room temperature for 12 h and then MeOH was evaporated in vacuo. The aqueous phase was extracted with ethyl acetate three times, the combined organic phase was washed with brine and dried over Na_2SO_4. The solvent was evaporated by rotavapor and the residue was dissolved in methanolic hydrochloride. The resultant solution was stirred overnight before it was concentrated. The residue was dissolved in water and the solution was neutralized with aqueous $NaHCO_3$ to pH=8. After the solution was extracted with ethyl acetate three times, the combined organic phase was washed with brine and dried over Na_2SO_4. The solvent was removed to give crude amino ester, which was dissolved in toluene (20 mL/mmol) and then TsOH (0.2 equiv.) was added. The resultant solution was refluxed for 2 days under argon. Removal of the solvent followed by chromatography of the residue afforded the lactone, which was dissolved in dry DMF (2 mL/mmol). To this solution were added benzyl bromide (1 equiv.) and anhydrous potassium carbonate (1 equiv.) with stirring. The mixture was warmed to 60–65°C slowly and then the stirring was continued for 8 h. After the solvent was evaporated in vacuo, the residue was purified by chromatography to give **5**.

3.1.1. Compound 5a. 40% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.02 (m, 15H), 4.30–4.14 (m, 2H), 3.97 (dd, *J*=10.8, 3.7 Hz, 0.8H), 3.80–3.65 (m, 2.2H), 3.56 (d, *J*=13.6 Hz, 0.3H), 3.48 (d, *J*=13.6 Hz, 0.8H), 2.75–2.50 (m, 2H), 2.02–1.92 (m, 2H); EIMS *m*/*z* 371 (M^+), 266, 91.

3.1.2. Compound 5b. 48% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.17 (m, 10H), 4.31–4.14 (m, 2H), 3.97 (dd, *J*=11.1, 3.6 Hz, 0.7H), 3.80 (d, *J*=13.7 Hz, 0.7H), 3.67–3.63 (m, 1.6H), 3.51 (d, *J*=13.7 Hz, 0.7H), 1.72–1.60 (m, 2H), 1.51–1.27 (m, 2H), 0.89 (t, *J*=7.2 Hz), 0.77 (t, *J*=7.3 Hz, 2H); EIMS *m*/*z* 308 (M^+-H^+), 266, 91.

3.1.3. Compound 5c. 33% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.20 (m, 10H), 4.33–4.14 (m, 2H), 3.96 (dd, *J*=10.3, 3.8 Hz, 0.8H), 3.84–3.80 (m, 1H), 3.70–3.63 (m, 1H), 3.54–3.50 (m, 1.2H), 1.39 (d. *J*=7.1 Hz, 1H), 1.36 (d. *J*=7.1 Hz, 2H); EIMS *m*/*z* 282 (M^+-H^+), 132, 91.

3.1.4. Compound 5d. 38% overall yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.14 (M, 15H), 4.56–4.44 (m, 2H), 4.30–4.11 (m, 2H), 3.97–3.79 (m, 1.8H), 3.71–3.65 (m, 1.2H), 3.58–3.32 (m, 3H), 1.82–3.65 (m, 3H); EIMS *m*/*z* 415 (M^+), 324, 91.

3.2. General procedure of functionalization of 5

A solution (0.2 M) of **5** in DME was cooled to −78°C under argon. To this solution was added NaHMDS (1.0 M in THF, 1.2 equiv.) over 15 min. After the stirring was continued for 1 h, a solution of a suitable electrophile (1.2 equiv.) in THF was added at the same temperature. After the stirring was continued for a time indicated in Table 1, saturated aqueous ammonium chloride was added to quench the reaction. The mixture was partitioned between ethyl acetate and brine, and then the organic phase was separated and dried over Na_2SO_4. After the solvent was evaporated in vacuo, the residue was purified by chromatography to give the coupling product.

3.2.1. (3*S*,5*R*)-3-Allyl-4-benzyl-3-phenethyl-5-phenyl-morpholin-2-one 6a. $[\alpha]_D^{26}$=+26.2 (*c* 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–6.98 (m, 15H), 6.10 (m, 1H), 5.30 (dd, *J*=15.8, 9.3 Hz, 2H), 4.56–4.43 (m, 2H), 4.29 (dd, *J*=10.0, 2.0 Hz, 1H), 4.02 (d, *J*=14.9 Hz, 1H), 3.80 (d, *J*=15.0 Hz, 1H), 3.12 (dt, *J*=13.0, 4.5 Hz, 1H), 3.00 (dd, *J*=14.5, 7.0 Hz, 1H), 2.81 (dd, *J*=14.5, 7.0 Hz, 1H), 2.50 (dt, *J*=13.0, 4.3 Hz, 1H), 2.03 (dt, *J*=13.3, 4.3 Hz, 1H), 1.69 (dt, *J*=13.3, 4.2 Hz, 1H); EIMS *m*/*z* 412 (M^++H^+), 370. HRMS found *m*/*z* 370.1760 ($M^+-C_3H_5$); $C_{25}H_{24}NO_2$ requires 370.1794.

3.2.2. (3*R*,5*R*)-(4-Benzyl-2-oxo-3-phenethyl-5-phenyl-morpholin-3-yl)acetic acid, methyl ester 7a.

$[\alpha]_D^{26}$=+21.6 (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.03 (m, 15H), 4.63 (dd, *J*=10.2, 2.9 Hz, 1H), 4.53 (t, *J*=10.4 Hz, 1H), 4.34 (dd, *J*=9.9, 3.0 Hz, 1H), 3.84 (d, *J*=15.1 Hz, 1H), 3.78 (s, 3H), 3.51 (d, *J*=15.2 Hz, 1H), 3.25 (d, *J*=17.3 Hz, 1H), 3.24 (m, 1H), 3.06 (d, *J*=17.6 Hz, 1H), 2.53 (m, 1H), 1.73 (dt, *J*=13.0, 4.3 Hz, 1H), 0.78 (m, 1H); EIMS *m/z* 444 (M^++H^+), 370, 338; HRMS found *m/z* 443.2103 (M^+); $C_{28}H_{29}NO_4$ requires 443.2122.

3.2.3. (3*S*,5*R*)-2,4-Dibenzyl-3-phenethyl-5-phenylmorpholin-2-one 6b. $[\alpha]_D^{26}$=−33.8 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–6.85 (m, 20H), 4.47 (t, *J*=10.0 Hz, 1H), 4.21 (d, *J*=15.4 Hz, 1H), 3.99 (dd, *J*=10.9, 3.0 Hz, 1H), 3.83 (d, *J*=15.4 Hz, 1H), 3.66 (dd, *J*=10.6, 3.0 Hz, 1H), 3.49 (d, *J*=14.2 Hz, 1H), 3.37 (d, *J*=14.2 Hz, 1H), 3.04 (dt, *J*=12.9, 4.1 Hz, 1H), 2.59 (dt, *J*=13.0, 4.4 Hz, 1H), 2.21 (dt, *J*=13.0, 4.5 Hz, 1H), 1.93 (dt, *J*=13.3, 4.3 Hz, 1H); EIMS *m/z* 462 (M^++H^+), 370; HRMS found *m/z* 461.2406 (M^+); $C_{32}H_{31}NO_2$ requires 461.2454.

3.2.4. (3*S*,5*R*)-(4-Benzyl-2-oxo-5-phenyl-3-propylmorpholin-3-yl)acetic acid, methyl ester 7b. $[\alpha]_D^{20}$=−20.2 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–7.22 (m, 10H), 4.61 (dd, *J*=10.3, 3.0 Hz, 1H), 4.47 (t, *J*=10.8 Hz, 1H), 4.28 (dd, *J*=11.0, 3.2 Hz, 1H), 3.79 (s, 3H), 3.75 (d, *J*=15.2 Hz, 1H), 3.40 (d, *J*=15.2 Hz, 1H), 3.24 (d, *J*=17.6 Hz, 1H), 3.03 (d, *J*=17.6 Hz, 1H), 2.06 (m, 1H), 1.51–1.10 (m, 3H), 0.79 (t, *J*=7.1 Hz, 3H); EIMS *m/z* 381 (M^+); HRMS found *m/z* 381.1917 (M^+); $C_{23}H_{27}NO_4$ requires 381.1894.

3.2.5. (3*S*,5*R*)-3,4-Dibenzyl-5-phenyl-3-propylmorpholin-2-one 6c. $[\alpha]_D^{25}$=−53.6 (*c* 3.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–6.79 (m, 15H), 4.40 (t, *J*=10.3 Hz, 1H), 4.19 (d, *J*=15.5 Hz, 1H) 3.94 (dd, *J*=10.8, 3.0 Hz, 1H), 3.77 (d, *J*=15.5 Hz, 1H), 3.60 (dd, *J*=10.0, 2.9 Hz, 1H), 3.50 (d, *J*=14.2 Hz, 1H), 3.34 (d, *J*=14.1 Hz, 1H), 1.98–1.84 (m, 2H), 1.53–1.36 (m, 2H), 0.81 (t, *J*=7.1 Hz, 3H); EIMS *m/z* 308 (M^+−Bn); Anal. calcd for $C_{27}H_{29}NO_2$: C: 81.11, H 7.31, N 3.51, found C: 80.81, H: 7.08, N: 3.45.

3.2.6. (1′*S*,3*S*,5*R*)-4-Benzyl-3-(1-hydroxyethyl)-5-phenyl-3-propylmorpholin-2-one 6d. $[\alpha]_D^{14}$=+20.5 (*c* 2.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.16 (m, 10H), 4.53 (t, *J*=9.7 Hz, 1H), 4.36–4.32 (m, 2H), 4.26–4.21 (m, 1H), 3.88 (d, *J*=11.2 Hz, 1H), 3.80 (m, 2H), 2.17–2.07 (m, 1H), 1.89–1.80 (m, 1H), 1.28–1.22 (m, 2H), 0.82 (t, *J*=7.0 Hz, 3H); EIMS *m/z* 354 (M^++H^+), 308, 266, 91; Anal. calcd for $C_{22}H_{27}NO_3$: C: 74.75, H: 7.69, N: 3.96, found C: 74.87, H: 7.75, N: 4.06.

3.2.7. (3*S*,5*R*)-3,4-Dibenzyl-3-methyl-5-phenylmorpholin-2-one 6e. $[\alpha]_D^{14}$=−53.3 (*c* 2.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.07 (m, 15H), 4.40 (dd, *J*=10.7, 3.6 Hz, 1H). 4.11–4.04 (m, 2H), 3.85–3.80 (m, 2H), 3.30 (d, *J*=13.9 Hz, 1H), 3.14 (d, *J*=13.9 Hz, 1H), 1.32 (s, 3H); EIMS *m/z* 280 (M^+−Bn); HRMS found *m/z* 280.1355 (M^+−Bn); $C_{18}H_{18}NO_2$ requires 280.1373.

3.2.8. (3*S*,5*R*)-4-Benzyl-3-ethyl-3-methyl-5-phenylmorpholin-2-one 6f. $[\alpha]_D^{14}$=−65.3 (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.09 (m, 10H), 4.78 (dd, *J*=10.8, 3.7 Hz, 1H), 4.66 (dd, *J*=10.8, 3.7 Hz, 1H), 4.00 (m, 1H), 3.90 (d, *J*=14.8 Hz, 1H), 3.69 (d, *J*=14.8 Hz, 1H), 2.00–1.85 (m, 2H), 1.21–1.10 (m, 6H); EIMS *m/z* 309 (M^+); HRMS found *m/z* 309.1734 (M^+); $C_{20}H_{23}NO_2$ requires 309.1739.

3.2.9. (3*R*,5*R*)-(4-Benzyl-3-methyl-2-oxo-5-phenylmorpholin-3-yl)acetic acid, methyl ester 7c. $[\alpha]_D^{14}$=+47.1 (*c* 4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.26 (m, 10H), 4.87 (dd, *J*=10.6, 3.5 Hz, 1H), 4.66 (dd, *J*=10.6, 3.5 Hz, 1H), 3.97 (m, 1H), 3.82 (s, 3H), 3.75 (d, *J*=8.8 Hz, 1H), 3.65 (d, *J*=8.8 Hz, 1H), 3.18 (d, *J*=16.4 Hz, 1H), 2.96 (d, *J*=16.4 Hz, 1H), 1.21 (s, 3H); EIMS *m/z* 353 (M^+); HRMS found *m/z* 353.1636 (M^+); $C_{21}H_{23}NO_4$ requires 353.1645.

3.2.10. (1′*S*,3*S*,5*R*)-4-Benzyl-3-(1′-hydroxybutyl)-3-methyl-5-phenylmorpholin-2-one 6g. $[\alpha]_D^{14}$=+17.5 (*c* 2.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–6.92 (m, 10H), 4.59 (t, *J*=10.7 Hz, 1H), 4.22–4.09 (m, 2H), 3.84 (d, *J*=15.0 Hz, 1H), 3.77 (br s, 1H), 3.60 (d, *J*=15.0 Hz, 1H), 3.38–0.93 (m, 7H), 0.85 (dd, *J*=13.1, 6.1 Hz, 3H). EIMS *m/z* 354 (M^++H^+), 280, 132; Anal. calcd for $C_{22}H_{27}NO_3$: C: 74.75, H: 7.69, N: 3.96, found C: 74.77, H: 7.39, N: 3.98.

3.2.11. (3*S*,5*R*)-3-Allyl-4-benzyl-3-(3-benzyloxypropyl)-5-phenylmorpholin-2-one 6h. $[\alpha]_D^{26}$=18.2 (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.02 (m, 15H), 6.05 (m, 1H), 5.28 (dd, *J*=15.5, 9.0 Hz, 2H), 4.46 (s, 1H), 4.43–4.38 (m, 2H), 4.21 (m, 1H), 3.97 (d, *J*=14.9 Hz, 1H), 3.72 (d, *J*=14.9 Hz, 1H), 3.35–3.20 (m, 2H), 2.96 (dd, *J*=14.4, 8.1 Hz, 1H), 2.77 (dd, *J*=14.4, 6.9 Hz, 1H), 2.17 (m, 1H), 1.81–1.25 (m, 3H). EIMS *m/z* 456 (M^++H^+), 414, 308; HRMS found *m/z* 414.2043 (M^+−C_3H_5), $C_{27}H_{28}NO_3$ requires 414.2069.

3.2.12. (3*S*,5*R*)-3,4-Dibenzyl-3-(3-benzyloxypropyl)-5-phenylmorpholin-2-one 6i. $[\alpha]_D^{26}$=−22.0 (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–6.81 (m, 20H), 4.49 (s, 2H), 4.42 (t, *J*=10.0 Hz, 1H), 4.18 (d, *J*=15.4 Hz, 1H), 3.94 (m, 1H), 3.78 (d, *J*=15.4 Hz, 1H), 3.64 (dd, *J*=9.6, 4.1 Hz, 1H), 3.49 (d, *J*=14.3 Hz, 1H), 3.36 (d, *J*=14.2 Hz, 1H), 3.31–3.12 (m, 2H), 2.16 (m, 1H), 1.98 (t, *J*=10.7 Hz, 1H), 1.75–1.65 (m, 2H); EIMS *m/z* 506 (M^++H^+), 414, 306; HRMS found *m/z* 414.2074 (M^+−Bn), $C_{27}H_{28}NO_3$ requires 414.2089.

3.2.13. (3*R*,5*R*)-[4-Benzyl-3-(3-benzyloxypropyl)-2-oxo-5-phenylmorpholin-3-yl]-acetic acid, methyl ester 7d. $[\alpha]_D^{26}$=+4.4 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.15 (m, 15H), 4.58 (dd, *J*=10.3, 3.1 Hz, 1H), 4.47 (s, 2H), 4.51–4.43 (m, 1H), 4.28 (dd, *J*=10.7, 3.0 Hz, 1H), 3.82 (s, 3H), 3.79–3.73 (m, 2H), 3.50 (d, *J*=15.2 Hz, 1H), 3.31–3.20 (m, 2H), 3.03 (d, *J*=15.5 Hz, 1H), 2.28 (m, 1H), 1.67–1.24 (m, 3H). EIMS *m/z* 488 (M^++H^+), 414, 338. HRMS found *m/z* 487.2336, $C_{30}H_{33}NO_5$ requires 487.2345.

3.3. General procedure for converting 6 or 7 to the corresponding α,α-disubstituted amino acid

Method A. The substrate was suspended in 6N HCl and the

resultant mixture was refluxed for 24 h. The cooled solution was concentrated and the residue was dissolved in mixture of MeOH/H_2O (v/v, 1:1). After 10% Pd/C was added, the mixture was stirred under H_2 (40 atm, 40°C) for 36 h. The catalyst was filtered off and the filtrate was concentrated, the residue was purified by the residue was purified by Dowex-50W using water as eluent to give the product.

Method B. A solution of **6** or **7** in MeOH and 10% NaOH (v/v, 1:1) was stirred at room temperature until no more starting material was detected, as monitored by TLC. The solution was added 2N HCl to adjust pH=4 before it was evaporated in vacuo to dryness. After the residue was dissolved in ethanol, 10% Pd/C was added. The mixture was stirred under H_2 (40 atm, 40°C) for 36 h and then the catalyst was filtered off. The filtrate was concentrated and the residue was purified by Dowex-50W using water as eluent to give the product.

3.3.1. (*S*)-α-Methyl phenylalanine 8. 62% yield. ($[\alpha]_D^{19}=-22.2$ (*c* 2.8, H_2O), lit.[9]: $[\alpha]_D^{25}=-22$ (*c* 1.0, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 7.36–7.240 (m, 5H), 3.32 (d, *J*=14.5 Hz, 1H), 3.03 (d, *J*=14.5 Hz, 1H), 1.58 (s, 3H); ESIMS *m*/*z* 179 (M^+), 201, 224.

3.3.2. (*R*)-α-Methyl aspartic acid 9a. 72% yield. $[\alpha]_D^{17}=-57.8$ (*c* 0.41, H_2O), (lit.[10] $[\alpha]_D^{20}=-52.9$ (*c* 0.68, H_2O)); ^{1}H NMR (300 MHz, D_2O) δ 3.17 (d, *J*=18.2 Hz, 1H), 2.90 (d, *J*=18.2 Hz, 1H), 1.56 (s, 3H); ESIMS *m*/*z* 148 ($M^+ + H^+$).

3.3.3. (*R*)-α-Propyl aspartic acid 9b. 75% yield. $[\alpha]_D^{18}=-15.7$ (*c* 0.6, H_2O); ^{1}H NMR (300 MHz, D_2O) δ 2.89 (d, *J*=17.5 Hz, 1H), 2.64 (d, *J*=17.5 Hz, 1H), 1.78–1.63 (m, 2H), 1.41–1.14 (m, 2H), 0.89 (dd, *J*=14.1, 6.9 Hz, 3H); ESIMS *m*/*z* 176 ($M^+ + H^+$).

3.3.4. (2*S*,3*S*)-2-Amino-3-hydroxy-2-methylpentanoic acid 10. 80% yield. $[\alpha]_D^{25}=-7.0$ (*c* 1, MeOH). ^{1}H NMR (300 MHz, D_2O) δ 3.78 (m, 1H), 1.53–1.31 (m, 7H), 0.81 (t, *J*=6.9 Hz, 3H); ESIMS *m*/*z* 162 ($M^+ + H^+$).

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