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Asymmetric synthesis of ACE inhibitor-Benazepril HCl via a bioreductive reaction

Ching-Yao Chang and Teng-Kuei Yang*

Department of Chemistry, National Chung-Hsing University, Taichung 402, Taiwan, ROC

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Abstract—An enantioselective synthesis of the potent angiotensin converting enzyme (ACE) inhibitor (2*S*, 3′*S*)-2-(1-carboxymethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-ylamino)-4-phenylbutyric acid ethyl ester hydrochloride, Benazepril HCl **4**, has been achieved through an asymmetric reduction of 4-(2-nitrophenyl)-2,4-dioxobutyric acid ethyl ester **6b** employing baker's yeast as the reductive catalyst.

1. Introduction

Fulfilling the increasing medical need for antihypertensive drugs has been an important task for synthetic scientists in recent years. Over the past two decades, angiotensin converting enzyme (ACE) inhibitors[1] have proved to be a major class of antihypertensive agents. The best known examples of this class are Captopril **1**,[2] Enalapril **2**[3] and Lisinopril **3** (Fig. 1).[4]

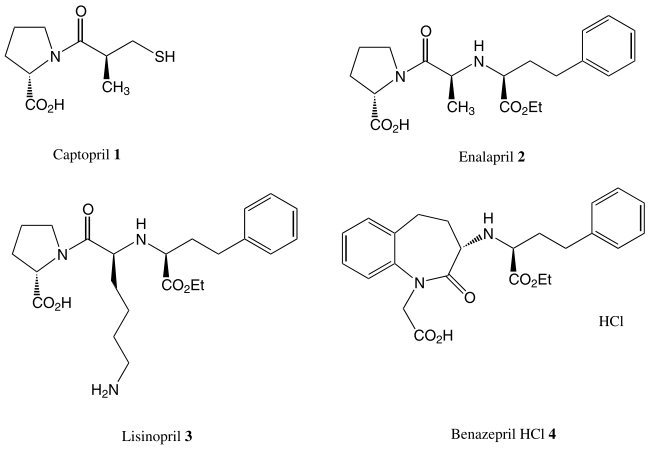
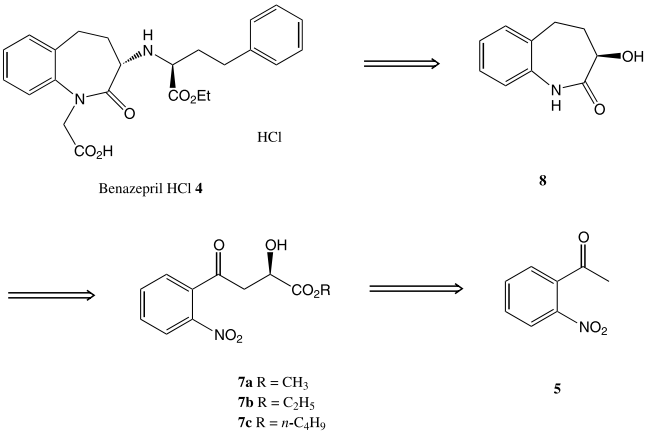


Figure 1.

Our study, has focused on the asymmetric synthesis of Benazepril HCl **4**, one of the most potent ACE inhibitor, which has a quite different skeleton from the others. To the best of our knowledge, only a few examples have been published of the synthesis of Benazepril HCl **4**.[1c,1e] These reports are generally achiral syntheses using a crystallization-based resolution to get the desired enantiomerically pure product. On the other hand, we found only one asymmetric synthesis in the literature involving asymmetric reduction in an imine intermediate to produce the chiral aminobenzolactam in moderate d.e. Herein, we report an efficient enantioselective synthesis for Benazepril HCl **4** with high d.e. through the stereoselective reduction at the 2-carbonyl group of 4-(2-nitrophenyl)-2,4-dioxobutyric acid ethyl ester **6b** employing a bioreductive agent.

Our retrosynthetic approach to the Benazepril HCl **4** is shown in Scheme 1, our strategy focused on the utiliza-



Scheme 1.

* Corresponding author. Tel.: +886 (4) 22856603; fax: +886 (4) 22856597; e-mail: tkyang@mail.nchu.edu.tw

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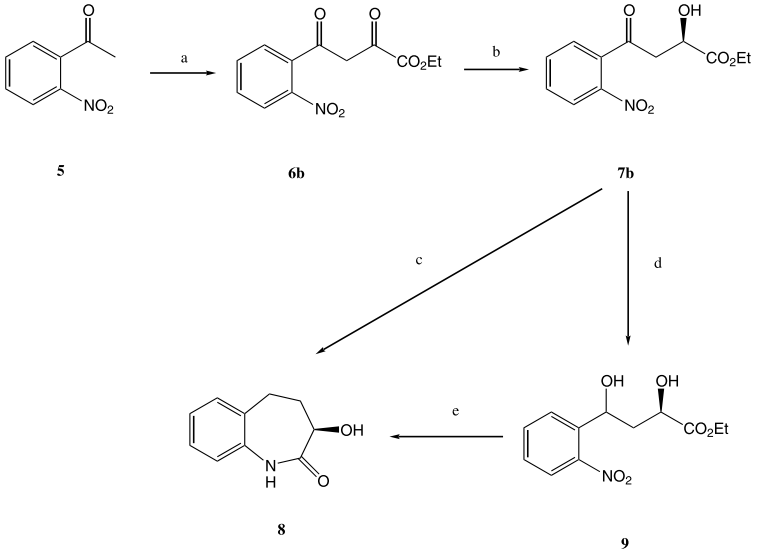
tion of α-hydroxy-γ-keto ethyl ester **7b** as a building block to generate the non-racemic (*R*)-3-hydroxybenzolactam moiety through the reduction of the aryl nitro group to the aniline followed by the intramolecular lactamization of the amino and ester functionalities. The stereospecific displacement of the derivatized hydroxyl group of (*R*)-3-hydroxybenzolactam by *L*-homophenylalanine ethyl ester (LHPE)[5] led to the desired Benazepril HCl **4** in enantiomerically pure form.

2. Results and discussion

As a part of our studies towards the synthetic development of enantiomerically pure ACE inhibitors, we designed a novel synthetic route for the preparation of enantiomerically pure Benazepril HCl **4**, which began with *o*-nitroacetophenone **5** as shown in Scheme 2. Claisen condensation[6] of *o*-nitroacetophenone **5** and diethyl oxalate provided α,γ-dioxo ethyl ester **6b** in a nearly quantitative yield. According to the literature,[7] α-carbonyl esters can be reduced by baker's yeast to produce chiral α-hydroxy ester. On the other hand, both carbonyl groups of the α,γ-dioxo ester were reduced on asymmetric hydrogenation using a transition metal complex with chiral ligand in preparation of α-hydroxy-γ-butyrolactones.[8] However, the key step in our present strategy is the asymmetric reduction of the α-carbonyl without affecting the γ-carbonyl group. In fact, we have successfully reduced compound **6b** to the desired α-hydroxy-γ-keto ethyl ester **7b** with high chemical yield and e.e.[9] by employing baker's yeast in the presence of phenacyl chloride as the enzyme inhibitor.[10] In order to optimize the reaction conditions for this enantioselective reduction, a variety of different esters were used to explore the effects of the ester alkoxyl group on the baker's yeast reduction. The results obtained are summarized in Table 1.

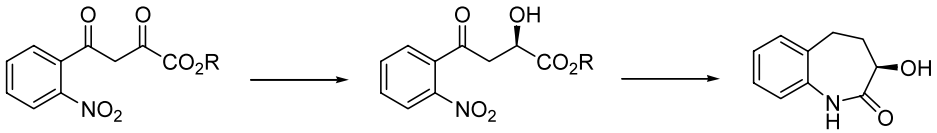
α-Hydroxy-γ-keto ethyl ester **7b** was subjected to hydrogenation[11] in the presence of palladium–charcoal in methanol which afforded α-hydroxybenzolactam **8** in 42% yield without any racemization at the hydroxyl bearing carbon. In another process, the γ-keto group of α-hydroxy-γ-keto ethyl ester **7b** was reduced with sodium triacetoxyborohydride ($NaBH(OAc)_3$)[12] to give the α,γ-diol ethyl ester **9** in quantitative yield followed by hydrogenation[13] over palladium–charcoal in hydrogen atmosphere to achieve α-hydroxybenzolactam **8** in 74% yield with the same enantiomeric purity as ester **7b** (Scheme 3).

The desired (2*S*,3′*S*)-2-(2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-ylamino)-4-phenylbutyric acid ethyl ester **11** was obtained from the displacement of the protected hydroxyl group of α-hydroxybenzolactam **8** by LHPE.[1a,1b] In order to optimize this coupling reaction, various leaving group derivatives of the hydroxyl group were studied with the results summarized in Table 2. Although these substitution reactions went to completion, epimerization was observed when the tosyl[1b] or mesyl[1a] derivatives (Table 2, entries 1 and 2) of the α-hydroxybenzolactam **8** were employed. As the S_N2 reaction occurred on a relatively hindered secondary carbon, a higher reaction temperature was required to pursue the reaction. Unfortunately, a higher reaction temperature caused an epimerization at the 3α-carbon of benzolactam. Therefore, a better leaving group was needed to lower the reaction temperature in this S_N2 reaction. In fact, the reaction of *p*-nitrobenzenesulfonylate **10c** with LHPE[1c,14] in *N*,*N*-dimethylacetamide at 50°C over 2.5 days produced mainly the desired compound **11** and its epimer **12** with nearly the



Scheme 2. *Reagents and conditions*: (a) diethyl oxalate, NaOEt, THF, 0°C (99%); (b) baker's yeast, phenacyl chloride, Et_2O/H_2O, 30°C (85%); (c) H_2, Pd–C, HCl, MeOH, then HOAc/toluene, 80°C (42%); (d) $NaBH(OAc)_3$, THF, 0°C; (e) H_2, Pd–C, HCl, MeOH, then HOAc/toluene, 80°C (74%, two steps).

Table 1. The baker's yeast reduction for α,γ-dioxo ester



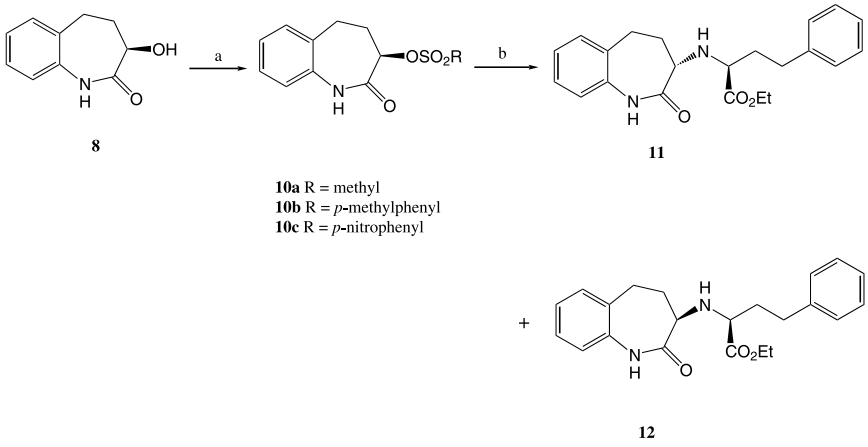
6a R = CH_3
6b R = C_2H_5
6c R = *n*-C_4H_9

7a R = CH_3
7b R = C_2H_5
7c R = *n*-C_4H_9

8

Entry	Substrate R =	Preincubation time (h)	Phenacyl chloride (mM)	Conversion[a] (%)	Yield[a] (%)	E.e.[b] (%)
1	C_2H_5	–	6.4	95	75	72
2	C_2H_5	2	6.4	100	85	80
3	C_2H_5	4	6.4	100	82	78
4	C_2H_5	6	6.4	93	74	74
5	C_2H_5	2	3.2	95	80	73
6	C_2H_5	2	1.6	91	77	71
7	C_2H_5	2	–	70	57	70
8	CH_3	2	6.4	100	75	53
9	*n*-C_4H_9	2	6.4	70	48	70

[a] The conversion and yield were determined after baker's yeast reduction at 30°C for 24 h and purified by flash chromatography.
[b] The e.e. of **8** was determined by using HPLC equipped with a Daicel CHIRALCEL OC column, 250×4.6 mm, eluted (1.5 ml/min) with hexane/isopropanol = 97/3 and detected by a UV lamp at $\lambda = 254$ nm. The retention time of the (*R*)-form and (*S*)-form was 62.3 and 75.5 min, respectively.



8

10a R = methyl
10b R = *p*-methylphenyl
10c R = *p*-nitrophenyl

11

12

Scheme 3. *Reagents and conditions*: (a) RSO_2Cl, NEt_3, THF, rt; (b) LHPE, DMA, heat.

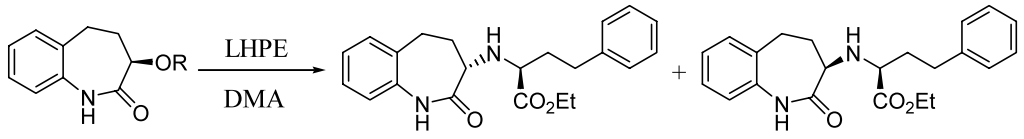
same isomeric ratio as the starting material **10c** (Table 2, entry 6). Our observation indicated that this substitution reaction proceeded in a stereospecific fashion with complete inversion of the configuration at the 3α-carbon of benzolactam (Scheme 4).

The amido nitrogen of (2*S*,3′*S*)-2-(2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-ylamino)-4-phenylbutyric acid ethyl ester **11** was alkylated[1e,15] with *t*-butyl chloroacetate to give the desired (2*S*,3′*S*)-2-(1-*tert*-butoxycarbonylmethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-azepin-3-ylamino)-4-phenylbutyric acid ethyl ester **13** in 98% yield. The *t*-butyl ester was hydrolyzed[16] by hydrochloride gas in toluene to give Benazepril HCl **4** as a crystalline compound in higher than 90% yield with more than 98% diastereomeric purity.[17]

3. Conclusion

In summary, we have reported a new asymmetric synthesis of Benazepril HCl **4** starting from *o*-nitroacetophenone **5**. This synthesis revealed a methodology using chiral α-hydroxy-γ-keto ethyl ester **7b** which was prepared by baker's yeast catalyzed enantioselective reduction of α,γ-dioxo ethyl ester **6b**, as an effective synthon for the chiral synthesis of 3-functionalized

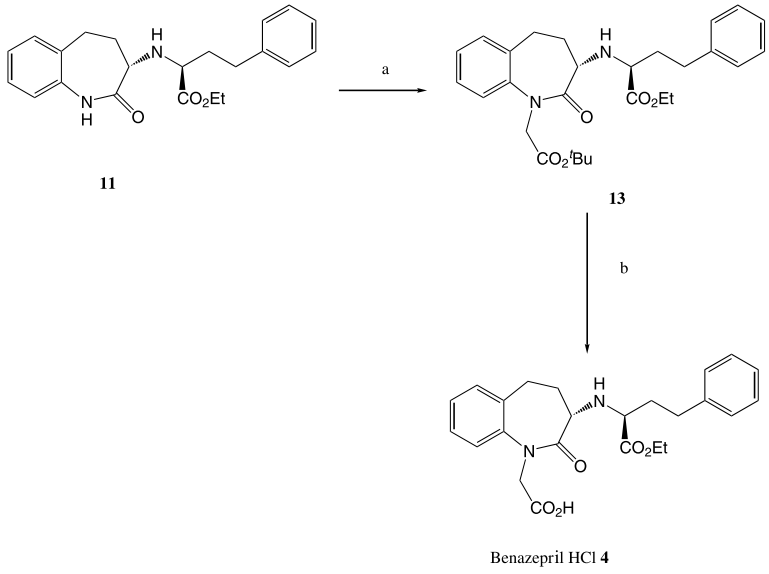
Table 2. The effect of leaving group for coupling reaction



10 **11** **12**

Entry	Substrate **10**[a] R =	Temperature (°C)	Reaction time (h)	Conversion (%)	**11**/**12**[c]
1	Ms[b]	100	48	100	67:33
2	Ts[b]	100	48	100	71:29
3	Ns	100	12	100	83:17
4	Ns	80	36	100	85:15
5	Ns	60	48	100	86:14
6	Ns	50	60	100	89:11

[a] The e.e. of compound **10** was based on compound **8** with e.e. = 80%.
[b] No reaction at 80°C.
[c] The **11**/**12** was determined by HPLC equipped with a Thermo Quest Hypersil BDS C18 column, 150×4.6 mm, eluted (1.0 ml/min) with 0.05M $KH_2PO_{4(aq.)}$/methanol = 40/60 and detected by a UV lamp at $\lambda = 254$ nm. The retention time of **11** and **12** was 12.1 and 24.2 min, respectively.



11 **13** Benazepril HCl **4**

Scheme 4. *Reagents and conditions*: (a) $ClCH_2CO_2^tBu$, KOH, TBAB, THF (98%); (b) $HCl_{(g)}$, toluene (90%).

benzolactam molecules. Subsequent coupling reaction of LHPE and benzolactam **10c** produced Benazepril HCl **4** in good yield with high diastereomeric purity.

4. Experimental

Starting materials were obtained from commercial suppliers and used without further purification unless otherwise stated. All reactions were performed in flame-dried apparatus under an atmosphere of nitrogen at rt unless otherwise stated. THF was distilled from sodium/benzophenone under nitrogen. Flash chromatography was carried out using Merck silica gel 60, 70–230 mesh ASTM. Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Infrared spectra were recorded on a Hitachi 270-30 Infrared Spectrophotometer. NMR spectra were recorded on a Varian Mercury 400 or Varian INOVA 600. The chemical shift are reported as δ value in ppm relative to TMS ($\delta = 0$) was used as internal standard in $CDCl_3$ for ^1H NMR spectra and the center peak of $CDCl_3$ ($\delta = 77.0$ ppm) was used as internal standard in ^{13}C NMR spectra. FAB-mass spectra were collected on JMS-700 double focusing Mass Spectrometer. Elemental analyses were collected on a Foss Heraeus CHN-O-RAPID Elemental Analyzer.

4.1. 4-(2-Nitrophenyl)-2,4-dioxobutyric acid ethyl ester, 6b

To a stirred solution of *o*-nitroacetophenone **5** (16.5 g, 0.1 mol) and diethyl oxalate (29.2 g, 0.2 mol) in anhydrous THF (50 ml) was added sodium ethoxide solution, which had been freshly prepared from sodium (4.6 g, 0.2 mol) and absolute ethanol (100 ml) at 0°C. The reaction solution was allowed to stir at 0°C for 2 h. After the TLC

analysis of the aliquot indicated the completion of reaction, the reaction mixture was poured into an ice-cold hydrochloride solution (2 M, 120 ml) and stirred at ambient temperature until the precipitation of yellow solid was completed. The yellow solid was filtered and washed sequentially with water (2×100 ml) and cold hexane (2×100 ml) to afford the crude product **6b** (26.3 g, 99%). The crude product was pure enough to use without further purification for the next reaction: mp 90-91°C; IR (neat): 3110, 1728, 1632, 1612, 1522, 1264 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, $J=8$, 1.2 Hz, 1H, CH), 7.75-7.73 (m, 1H, CH), 7.68-7.66 (m, 1H, CH), 7.60 (dd, $J=7.2$, 1.6 Hz, 1H, CH), 6.65 (s, 1H, CH), 4.38 (q, $J=7.2$ Hz, 2H, $CO_2CH_2CH_3$), 1.39 (t, $J=7.2$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 165.7, 161.4, 147.1, 133.5, 133.2, 131.9, 128.7, 124.5, 102.0, 62.7, 13.9; MS (FAB): m/z 266 (MH^+), 154 (100%), 136, 106, 89, 77, 57. Anal. calcd for $C_{12}H_{11}NO_6$: C, 54.34; H, 4.18; N, 5.28; O, 36.20. Found: C, 54.08; H, 4.30; N, 5.34; O, 36.36.

4.2. (2*R*)-2-Hydroxy-4-(2-nitrophenyl)-4-oxobutyric acid ethyl ester, 7b

To a three-necked flask containing diethyl ether (1.5 L) and water (108 ml) equipped with a mechanical stirrer, was added phenacyl chloride (1.5 g) and baker's yeast (180 g). The mixture was preincubated at 30°C for 2 h while being stirred. The α,γ-dioxo ethyl ester **6b** (7.95 g, 30 mmol) was added in one portion and the reaction allowed to proceed at 30°C for 24 h. The reaction mixture was filtered through a Celite pad and the filter cake washed with ethyl acetate (2×500 ml). The combined filtrate was concentrated under reduced pressure to give a brownish viscous oil. The residual oil was purified by flash chromatography (hexane/ethyl acetate = 2:1) to afford **7b** (6.8 g, 85%) as a pale yellow solid: $[\alpha]_D=+4.24$ (c 1.25, $CHCl_3$); mp 33-34°C; IR (neat): 3516, 2980, 1742, 1718, 1528, 1345 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, $J=8$ Hz, 1H, CH), 7.77-7.73 (m, 1H, CH), 7.65-7.61 (m, 1H, CH), 7.49 (d, $J=8$ Hz, 1H, CH), 4.64-4.61 (m, 1H, CHOH), 4.30 (q, $J=7.2$ Hz, 2H, $CO_2CH_2CH_3$), 3.36 (dd, $J=6.4$, 4 Hz, 1H, CH_2), 3.32 (dd, $J=6.4$, 4 Hz, 1H, CH_2), 1.33 (t, $J=7.2$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 173.1, 145.3, 136.7, 134.1, 130.6, 127.5, 124.0, 66.8, 61.7, 45.9, 13.7; MS (FAB): m/z 268 (MH^+), 194, 150 (100%), 137, 57. Anal. calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24; O, 35.92. Found: C, 54.26; H, 4.88; N, 5.37; O, 36.08.

4.3. (3*R*)-3-Hydroxy-1,3,4,5-tetrahydrobenzo[*b*]azepin-2-one, 8

A solution of $NaBH(OAc)_3$ was prepared by adding $NaBH_4$ (3.04 g, 80 mmol) to glacial acetic acid (50 ml) in small portions while maintaining the temperature between 10 ~ 20°C. After the hydrogen evolution ceased, anhydrous THF (50 ml) was added and the solution cooled to 0°C in a brine bath. α-Hydroxy-γ-keto ethyl ester **7b** (5.34 g, 20 mmol) was then added in one portion and the reaction mixture allowed to stir at 0°C for 2 h. The reaction was quenched with cold water (30 ml). The volatiles were removed in vacuo at 50°C. The residue was dissolved in ethyl acetate (100 ml) and washed with cold water (2×50 ml). The organic layer was concentrated under reduced pressure to give the crude α,γ-diol ethyl ester **9** (5.33 g, 99%) as a yellow liquid. The crude **9** was dissolved in methanol (20 ml) and stirred in presence of palladium–charcoal (1 g, 10%) under hydrogen atmosphere for 24 h. The reaction mixture was then added to 12 M hydrochloric acid (5 ml) and stirred again under hydrogen atmosphere for another 36 h. The reaction mixture was then filtered and concentrated in vacuo. The oily residue was diluted with water and the pH adjusted to 4 ~ 5 by saturated sodium bicarbonate solution (20 ml). The aqueous layer was extracted with ethyl acetate (3×100 ml) and the combined organic layer concentrated to give a pale yellow oil. The residual oil was heated in acetic acid (5 ml) and toluene (50 ml) at 80°C for 16 h. The mixture was then concentrated and purified with flash chromatography (hexane/ethyl acetate = 3:1) to afford **8** (2.63 g, 74%) as a white solid with e.e. = 80% based on the HPLC analysis on the chiral column: $[\alpha]_D=+287.2$ (c 1.08, $CHCl_3$); mp 138-139°C; IR (neat): 3302, 2948, 1674, 1586, 1494, 1316 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (br, 1H, CONH), 7.28-7.15 (m, 3H, CH), 7.01-6.99 (m, 1H, CH), 4.17-4.11 (m, 1H, CHOH), 3.01-2.92 (m, 1H, CH_2), 2.74-2.63 (m, 2H, CH_2), 2.11-2.04 (m, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 135.7, 133.9, 129.6, 127.6, 126.2, 122.0, 67.8, 38.5, 28.0; MS (FAB): m/z 178 (MH^+, 100%), 154, 136, 132, 77, 57. Anal. calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90; O, 18.06. Found: C, 67.87; H, 6.26; N, 8.05; O, 17.70.

4.4. 4-Nitrobenzenesulfonic acid (3*R*)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl ester 10c

To a solution of **8** (0.89 g, 5 mmol) in anhydrous THF (30 ml) at 0°C was added triethylamine (1.01 g, 10 mmol) and *p*-nitrobenzenesulfonyl chloride (1.66 g, 7.5 mmol) in portions. The reaction mixture was allowed to stir at rt for 16 h. The reaction mixture was then added to ethyl acetate (100 ml) and diluted HCl (1 M, 10 ml). The aqueous layer was separated and extracted with ethyl acetate (3×50 ml). The combined organic layer was washed with saturated sodium bicarbonate solution (2×20 ml) followed by cold water (2×30 ml). The organic layer was dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford the crude product **10c** (1.78 g, 98%) as a white solid. The ^1H NMR of the product **10c** showed it was pure enough for the subsequent reaction and therefore was used without further purification: $[\alpha]_D=+215.0$ (c 0.98, DMF); mp 217-218°C (dec.); IR (neat): 3102, 1688, 1523, 1374, 1184, 1008, 844 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 10.11 (br, 1H, CONH), 8.41 (d, $J=9.0$ Hz, 2H, CH), 8.10 (d, $J=9.0$ Hz, 2H, CH), 7.28-7.25 (m, 2H, CH), 7.15-7.12 (m, 1H, CH), 6.97 (d, $J=8.4$ Hz, 1H, CH), 4.86 (dd, $J=8.4$, 8.4 Hz, 1H, CHO), 2.75-2.67 (m, 2H, CH_2), 2.53-2.46 (m, 1H, CH_2), 2.29-2.24 (m, 1H, CH_2); ^{13}C NMR (150 MHz, d^6-DMSO) δ 167.0, 150.7, 141.5, 136.5, 132.8, 129.9, 129.3, 127.9, 125.7, 124.8, 122.2, 78.0, 35.1, 26.9; MS (FAB): m/z 363 (MH^+), 307, 289, 154 (100%), 136, 106, 89; HRMS (FAB): m/z calcd for $C_{16}H_{14}N_2O_6S$ MH^+ 363.0651, Found MH^+ 363.0650.

4.5. (2*S*,3′*S*)-2-(2-Oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-azepin-3-ylamino)-4-phenyl-butric acid ethyl ester, 11 and the (2*S*,3′*R*) isomer 12

A mixture of **10c** (1.81 g, 5 mmol) and LHPE (3.10 g, 15 mmol) in *N*,*N*-dimethylacetamide (5 ml) was heated at 50°C for 2.5 days and gave the two isomers in a ratio of 89:11 by HPLC. The reaction mixture was purified by flash chromatography (hexane/ethyl acetate = 2:1) to give **11** (1.43 g, 78%) as a white solid: $[\alpha]_D = -168.1$ (*c* 1.09, $CHCl_3$); mp 110-111°C; IR (neat): 3224, 2948, 1734, 1676, 1494, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (br, 1H, CONH), 7.29-7.13 (m, 8H, CH), 6.99 (d, $J = 8.0$ Hz, 1H, CH), 4.12-4.03 (m, 2H, $CO_2CH_2CH_3$), 3.33-3.26 (m, 2H, CHNH), 2.91-2.84 (m, 1H, CH_2), 2.75-2.61 (m, 3H, CH_2), 2.55-2.42 (m, 1H, CH_2), 2.10-1.88 (m, 3H, CH_2), 1.15 (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 174.2, 141.3, 136.6, 134.3, 129.6, 128.3, 128.2, 127.5, 125.9, 125.8, 122.0, 60.5, 60.0, 56.6, 37.8, 35.0, 32.1, 28.9, 14.1; MS (FAB): *m*/*z* 367 (MH^+, 100%), 293, 206, 154, 91, 77, 51. Anal. calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64; O, 13.10. Found: C, 71.88; H, 7.36; N, 7.63; O, 12.77. and **12** (0.18 g, 10%) as a white solid: $[\alpha]_D = +63.5$ (*c* 1.10, $CHCl_3$); mp 100-101°C; IR (neat): 2944, 1732, 1674, 1492, 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (br, 1H, CONH), 7.26-7.11 (m, 8H, CH), 6.97 (d, $J = 7.2$ Hz, 1H, CH), 4.20-4.05 (m, 2H, $CO_2CH_2CH_3$), 3.28-3.23 (m, 1H, COCHNH), 3.13-3.10 (m, 1H, COCHNH), 2.97-2.85 (m, 1H, CH_2), 2.72-2.60 (m, 3H, CH_2), 2.55-2.40 (m, 1H, CH_2), 2.09-1.80 (m, 3H, CH_2), 1.25-1.10 (m, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 174.2, 141.5, 136.5, 134.4, 129.6, 128.4, 128.3, 127.6, 126.0, 125.8, 122.1, 60.7, 59.3, 56.7, 37.9, 34.6, 31.6, 28.9, 14.2; MS (FAB): *m*/*z* 367 (MH^+ 100%), 307, 293, 206, 154, 136. Anal. calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64; O, 13.10. Found: C, 71.97; H, 7.07; N, 7.68; O, 13.18.

4.6. (2*S*,3′*S*)-2-(1-*tert*-Butoxycarbonylmethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-azepin-3-ylamino)-4-phenylbutyric acid ethyl ester, 13

To a solution of **11** (0.732 g, 2 mmol) and tetrabutylammonium bromide (64 mg, 0.2 mmol) in anhydrous THF (20 ml) was added KOH (0.16 g, 85%, 2.4 mmol) at 0°C. The reaction solution was stirred at 0°C for 30 min, after which *t*-butyl chloroacetate (0.36 g, 2.4 mmol) added and the reaction solution allowed to proceed at rt for 5 h. The resulting solution was passed through a short column with silica gel and then purified by flash chromatography (hexane/ethyl acetate = 3:1) to afford **13** (0.94 g, 98%) as a colorless liquid: $[\alpha]_D = -145.6$ (*c* 1.05, $CHCl_3$); IR (neat): 3344, 2988, 1738, 1670, 1370, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.09 (m, 9H, CH), 4.58 (d, $J = 17.2$ Hz, 1H, NCH_2), 4.33 (d, $J = 17.2$ Hz, 1H, NCH_2), 4.13-4.01 (m, 2H, $CO_2CH_2CH_3$), 3.35-3.20 (m, 3H, NHCH, CH_2), 2.73-2.65 (m, 2H, CH_2), 2.59-2.38 (m, 2H, CH_2), 2.15-1.95 (m, 3H, CH_2), 1.43 (s, 9H, $C(CH_3)_3$), 1.13 (t, $J = 7.0$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 173.6, 167.7, 141.3, 140.9, 136.0, 129.3, 128.3, 128.2, 127.6, 126.6, 125.8, 122.1, 81.8, 60.4, 60.1, 56.8, 51.1, 37.6, 34.9, 32.0, 28.4, 27.9, 14.0; MS (FAB): *m*/*z* 481 (MH^+, 100%), 425, 351, 319, 246, 190, 144, 91, 57. Anal. calcd for $C_{28}H_{36}N_2O_5$: C, 69.98; H, 7.55; N, 5.83; O, 16.65. Found: C, 70.05; H, 7.48; N, 5.82; O, 16.13.

4.7. (2*S*,3′*S*)-2-(1-Carboxymethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-ylamino)-4-phenylbutyric acid ethyl ester hydrochloride, Benazepril HCl 4

To a solution of **13** (2.4 g, 5 mmol) in toluene (50 ml) was bubbled HCl gas at 0°C for 30 min. The reaction solution was then allowed to proceed at rt for 1 h. The reaction solution was concentrated in vacuo to give a crude white solid and washed with hexane (3×30 ml) to afford Benazepril HCl **4** (2.07 g, 90%) with d.e. >98% based on the HPLC analysis: $[\alpha]_D = -142.6$ (*c* 0.98, EtOH) [lit.[1e] $[\alpha]_D = -141.0$ (*c* 0.9, EtOH)]; mp 188-189°C (lit.[1e] mp 188-190°C); IR (neat): 3460, 2988, 1738, 1674, 1216 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 7.42-7.18 (m, 9H, CH), 4.62 (s, 2H, CH_2CO_2H), 4.26-4.08 (m, 2H, $CO_2CH_2CH_3$), 3.98-3.89 (m, 2H, CHNH·HCl), 3.40-3.28 (m, 1H, CH_2), 2.90-2.55 (m, 4H, CH_2), 2.40-2.15 (m, 3H, CH_2), 1.20 (t, $J = 7.2$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (150 MHz, CD_3OD) δ 171.6, 169.4, 168.1, 141.0, 140.9, 135.5, 130.7, 129.6, 129.5, 128.8, 127.5, 124.0, 63.8, 60.1, 58.9, 51.4, 34.7, 33.0, 31.8, 28.1, 14.3; MS (FAB): *m*/*z* 425 ($MH-HCl^+$, 100%), 351, 190, 154, 91, 77, 51. Anal. calcd for $C_{24}H_{29}ClN_2O_5$: C, 62.54; H, 6.34; N, 6.08; O, 17.35. Found: C, 62.37; H, 6.34; N, 5.62; O, 17.02.

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