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Synthesis of optically active α-aminobenzolactam via an oxidative–cyclization reaction

Ching-Yao Chang and Teng-Kuei Yang*

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

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Abstract—A convergent pathway for the asymmetric synthesis of (–)-α-aminobenzolactam **1** is described. For the first time, the key intermediate *N*-methoxybenzolactam **8** was prepared from L-homophenylalanine ethyl ester hydrochloride (LHPE·HCl) **5** by employing an oxidative cyclization in the presence of trifluoroacetic acid (TFA).

1. Introduction

(3*S*)-3-Amino-1,3,4,5-tetrahydrobenzo[*b*]azepin-2-one [(–)-α-aminobenzolactam] **1** is a key intermediate in the total synthesis of Benazepril·HCl **2**,[1] an angiotensin converting enzyme (ACE) inhibitor which has recently become a blockbuster antihypertensive drug. Compound **1** is also an important precursor for the new class of antithrombotic agent **3**[2] as derivatives of CVS-1778, as well as for the nonpeptidyl growth hormone secretagogue **4**, L-692428[3] (Fig. 1).

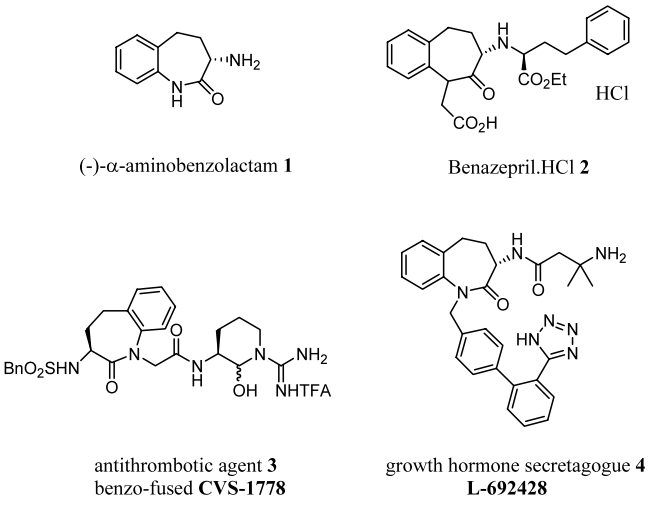

Figure 1.

Numerous reports related to the synthesis of (–)-α-aminobenzolactam **1** have been reported. These methods mainly consist of the resolution of racemates by fractional crystallization of diastereomeric tartaric acid salts[4a] or enantioselective synthesis employing catalytic hydrogenation in the presence of an external chiral ligand.[4b] On the other hand, a synthesis of (–)-α-aminobenzolactam **1** was recently published in which an organozinc reagent of *N*-protected γ-halo-α-amino ester was used to react with 2-iodoaniline followed by cyclization and hydrogenation to give compound **1**.[5] Herein we report a more convenient synthesis of enantiopure compound **1** based on the oxidative cyclization of *N*-methoxyamide **7** by employing the commercially and readily available L-homophenylalanine ethyl ester hydrochloride (LHPE·HCl) **5** as a starting material.

2. Results and discussion

As part of our studies towards the development of an asymmetric synthesis of Benazepril·HCl **2**, we discovered an oxidative cyclization procedure for the preparation of *N*-methoxybenzolactam **8** from *N*-methoxyamide **7**. The readily available LHPE·HCl **5** suggested that an effective asymmetric synthesis of (–)-α-aminobenzolactam **1** could be achieved.

The synthetic strategy for (–)-α-aminobenzolactam **1** is illustrated in Scheme 1. The synthesis began with the protection of the amino group of LHPE using benzyl chloroformate to give compound **6** in 99% yield.[6] The *N*-methoxyamide **7** was produced in a 70% yield overall through amidation of benzyloxycarbonyl LHPE **6** by

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

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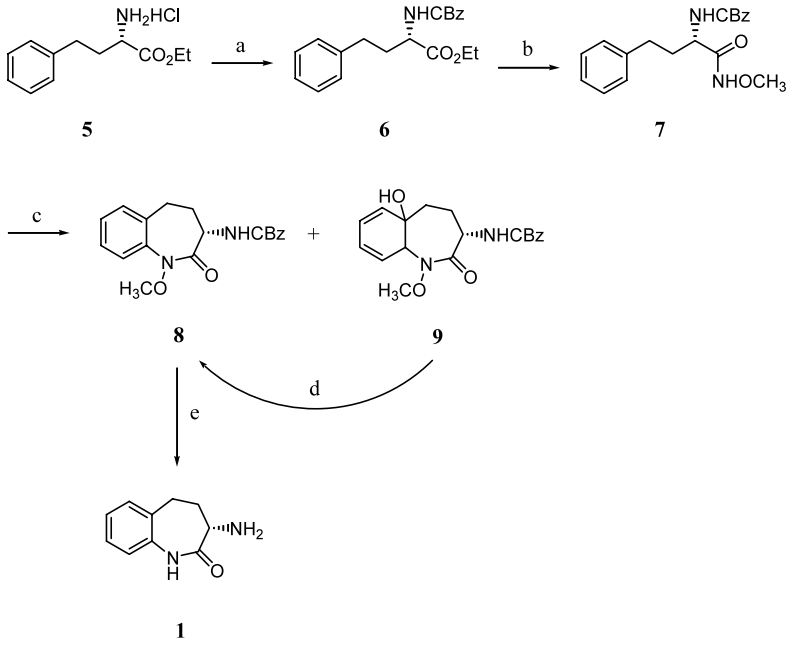


Scheme 1. *Reagents and conditions*: (a) CBzCl, $NaHCO_3$, THF/H_2O (99%); (b) $HONH_2HCl$, KOH, CH_3OH, 0°C, then CH_3I (70%); (c) PIFA, TFA, CH_2Cl_2, 0°C (**8**, 40%; **9**, 45%); (d) $BF_3{\cdot}Et_2O/THF$/reflux (75%); (e) H_2, $Pd(OH)_2/C$, C_2H_5OH, rt (97%).

hydroxylamine followed by an in-situ methylation of hydroxamic acid using iodomethane as the methylating agent.[7]

The key step in our synthetic strategy is the generation of *N*-methoxybenzolactam **8** through the acid induced cyclization of *N*-methoxyamide **7**. When we employed a literature procedure[8] for the treatment of *N*-methoxyamide **7** in dichloromethane with [bis(trifluoroacetoxy)iodo]benzene (PIFA) at 0°C for 15 min it afforded the cyclized *N*-methoxybenzolactam **8** in a disappointingly low yield of 22%. Therefore, we undertook a comprehensive investigation to circumvent the low yield in the cyclization of *N*-methoxyamide **7** to *N*-methoxybenzolactam **8**. In another related report, Romero et al.[9] observed a dramatic increase in yield during a cyclization reaction in the presence of protic acids. Therefore various protic acids were used in our investigation to obtain the *N*-methoxybenzolactam **8** and the results obtained are summarised in Table 1.

To date, the overall yield has reached 74% for the cyclization of *N*-methoxyamide **7** to the desired *N*-methoxybenzolactam **8**. We found that the treatment of *N*-methoxyamide **7** with 3 equiv. of trifluoroacetic acid in dichloromethane at 0°C produced 40% of *N*-methoxybenzolactam **8** and 45% of hydroxyl compound **9** (Table 1, entry 4). The mechanism of this cyclization

Table 1. Study for oxidative–cyclization reaction of *N*-methoxyamide **7**

Entry	Solvent	Acid catalyst	Acid equiv.	Temperature (°C)	**8**[a] yield (%)
1	CH_2Cl_2	–	–	0	57
2	CH_2Cl_2	TFA	0.2	0	64
3	CH_2Cl_2	TFA	1.0	0	69
4	CH_2Cl_2	TFA	3.0	0	74
5	CH_2Cl_2	TFA	6.0	0	72
6	CH_2Cl_2	TFA	10.0	0	71
7	CH_2Cl_2	TFA	3.0	−15	54
8	CH_2Cl_2	TFA	3.0	rt	72
9	CH_2Cl_2	PTSA	0.2	0	56
10	$CHCl_3$	–	–	0	61
11	$CHCl_3$	TFA	3.0	0	67
12	$CHCl_3$	TFA	3.0	rt	65
13	CH_3CN	TFA	3.0	rt	57
14	CH_3CN	TFA	3.0	Reflux	63
15	Toluene	TFA	3.0	rt	70
16	Toluene	TFA	3.0	Reflux	61

[a] The yield of *N*-methoxybenzolactam **8** was reported according to combined yields of oxidative–cyclization of **7** and dehydration of **9**.

process is illustrated in Scheme 2. The cationic intermediate **12** generated in the acidic cyclization would produce not only the desired *N*-methoxybenzolactam **8** but also hydroxyl compound **9**, because the anion of trifluoroacetic acid eliminated from PIFA during the reaction, would act as a nucleophile to generate trifluoroacetate **13** which was then hydrolyzed during aqueous work-up to give alcohol **9**.[10] The hydroxyl compound **9** would gain back its aromaticity by treatment with $BF_3{\cdot}Et_2O$ to give compound **8** in 75% yield. The overall yield of the desired *N*-methoxybenzolactam **8** was 74%.

Subsequent treatment of *N*-methoxybenzolactam **8** by hydrogenation in the presence of Pearlman's catalyst at 100 psi hydrogen pressure produced the target compound **1** in a 97% yield.[9] The HPLC analysis demonstrated that the enantiomeric purity of (−)-α-aminobenzolactam **1** was greater than 98% e.e. which indicated there was almost no racemization during the whole synthetic process.[11]

3. Conclusion

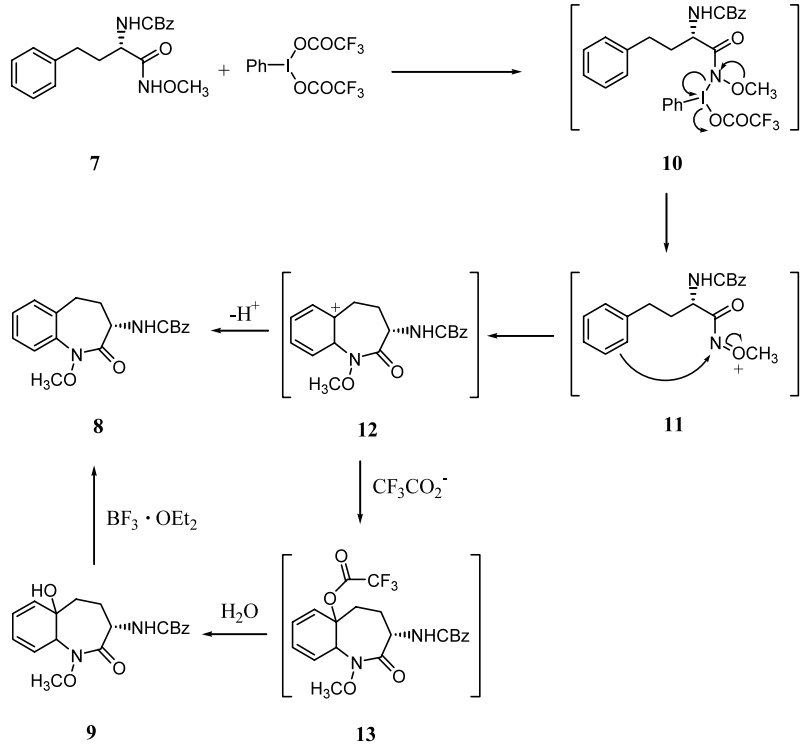
We have accomplished a novel chiral synthesis of (−)-α-aminobenzolactam **1** through a unique oxidative cyclization of *N*-methoxyamide **7**. Our synthesis demonstrated the first example by employing commercially available LHPE·HCl **5** from the chiral pool to prepare (−)-α-aminobenzolactam **1**. Further condition optimization of the synthesis and application of this important chiral synthon **1** are currently under investigation.

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 nitrogen at room temperature 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 spectrophtometer. NMR spectra were recorded on a Varian Mercury 400 or Varian Inova 600. The chemical shifts are reported as δ value in ppm relative to TMS ($\delta = 0$), which was used as the internal standard in $CDCl_3$ for ^1H NMR spectra and the center peak of $CDCl_3$ ($\delta = 77.0$ ppm), which was used as the internal standard in ^{13}C NMR spectra. FAB-mass spectra were collected on a JMS-700 double-focusing mass spectrometer. Elemental analyses were collected on a Foss Heraeus CHN-O-Rapid elemental analyzer.

4.1. (2*S*)-2-Benzyloxycarbonylamino-4-phenylbutyric acid ethyl ester, 6

To a solution of the LHPE·HCl **5** (4.87 g, 20 mmol) and sodium bicarbonate (3.53 g, 42 mmol) in 1:1 THF:water (100 ml), benzyl chloroformate (3.58 g, 21 mmol) was added dropwisely at 0°C. The solution was allowed to slowly warm to ambient temperature and stirred overnight. The THF was removed in vacuo, after which water (50 ml) was added, and the aqueous



Scheme 2.

solution extracted with ethyl acetate (3×50 ml). The combined organic layers were washed with brine and dried over magnesium sulphate. The solvent was removed in vacuo and purified by flash chromatography (hexane/ethyl acetate = 10:1) to afford **6** (6.75 g, 99%) as a white solid: $[\alpha]_D = +25.1$ (*c* 1.08, $CHCl_3$); mp 55–56°C; IR (neat): 3364, 2968, 1728, 1528, 1212 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.12 (m, 10H, CH), 5.37 (br, 1H, NHCBz), 5.13 (s, 2H, CO_2CH_2Ph), 4.45–4.40 (m, 1H, CHNHCBz), 4.18 (q, $J = 7.0$ Hz, 2H, $CO_2CH_2CH_3$), 2.75–2.60 (m, 2H, CCH_2), 2.24–2.14 (m, 1H, CH_2CH), 2.06–1.94 (m, 1H, CH_2CH), 1.28 (t, $J = 7.0$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 155.8, 140.6, 136.2, 128.5, 128.4, 128.3, 128.1, 128.0, 126.1, 66.9, 61.4, 53.6, 34.2, 31.4, 14.1; MS (FAB): *m*/*z* 342 (MH^+), 298, 224, 117, 91 (100%), 77. Anal. calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10; O, 18.75. Found: C, 70.38; H, 6.85; N, 4.25; O, 18.99.

4.2. (1*S*)-(1-Methoxycarbamoyl-3-phenylpropyl)-carbamic acid benzyl ester, 7

To a solution of *N*-protected LHPE **6** (3.41 g, 10 mmol) and hydroxylamine hydrochloride (2.08 g, 30 mmol) in methanol (20 ml) was cooled to 0°C and a methanolic solution of potassium hydroxide (3.95 g, 85%, 60 mmol) was added dropwisely. The solution was stirred at 0°C for 6 h, after which iodomethane (2.13 g, 15 mmol) was added. The solution was allowed to slowly warm to ambient temperature and stirred overnight. The methanol was removed in vacuo, whereupon water (50 ml) was added, and the aqueous solution extracted with ethyl acetate (3×50 ml). The combined organics were washed with brine and dried over magnesium sulphate. The solvent was removed in vacuo and purified by flash chromatography (hexane/ethyl acetate = 2:1) to obtain **7** (2.40 g, 70%) as a white solid: $[\alpha]_D = -29.5$ (*c* 1.03, $CHCl_3$); mp 140–141°C; IR (neat): 3304, 1690, 1664, 1536, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (br, 1H, $NHOCH_3$), 7.38–7.12 (m, 10H, CH), 5.31 (br, 1H, NHCBz), 5.14–5.05 (m, 2H, CO_2CH_2Ph), 4.04–3.94 (m, 1H, CHNHCBz), 3.74 (s, 3H, $NHOCH_3$), 2.72–2.64 (m, 2H, CCH_2), 2.20–2.10 (m, 1H, CH_2CH), 2.02–1.92 (m, 1H, CH_2CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 156.4, 140.5, 135.9, 128.5, 128.4, 128.3, 128.2, 127.9, 126.1, 67.1, 64.1, 52.0, 33.8, 31.6; MS (FAB): *m*/*z* 343 (MH^+), 307, 289, 224, 154 (100%), 136, 91. Anal. calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18; O, 18.69. Found: C, 66.65; H, 6.26; N, 8.05; O, 19.16.

4.3. (3*S*)-(1-Methoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl)carbamic acid benzyl ester, 8

To a solution of *N*-methoxyamide **7** (1.71 g, 5 mmol) in dichloromethane (40 ml) was cooled to 0°C, and trifluoroacetic acid (1.71 g, 15 mmol) was added. PIFA (2.25 g, 5.25 mmol) was added in portions over 10 min, and the mixture was stirred at 0°C for 15 min. Cooled water (5 ml) was then added, and the aqueous solution extracted with dichloromethane (2×50 ml). The combined organics were washed with brine and dried over magnesium sulphate. The solvent was removed in vacuo and purified by flash chromatography (hexane/ethyl acetate = 3:1) to obtain the desired **8** (0.68 g, 40%) as a white solid and hydroxyl compound **9** (0.81 g, 45%) as a viscous liquid.[9] The hydroxyl compound **9** was dissolved in THF (20 ml) with $BF_3{\cdot}Et_2O$ (0.96 g, 6.75 mmol) being added and the reaction solution being allowed to reflux for 4 h. The mixture was vaporized in vacuo and purified by flash chromatography (hexane/ethyl acetate = 3:1) to get more **8** (0.57 g, 75%) as a white solid. Therefore the total yield of the desired compound **8** was 74%: $[\alpha]_D = -120.7$ (*c* 1.03, $CHCl_3$); mp 151–152°C; IR (neat): 3336, 1724, 1690, 1530, 1488, 1256, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.24 (m, 9H, CH), 5.74 (d, $J = 7.6$ Hz, 1H, NHCBz), 5.05 (s, 2H, CO_2CH_2Ph), 4.22–4.15 (m, 1H, CHNHCBz), 3.83 (s, 3H, OCH_3), 2.94–2.82 (m, 1H, CCH_2), 2.70–2.62 (m, 2H, CH_2CH_2), 2.05–1.97 (m, 1H, CH_2CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 155.3, 137.4, 136.2, 133.7, 129.3, 128.4, 128.1, 128.0, 128.0, 127.9, 122.6, 66.8, 62.3, 50.8, 36.2, 28.3; MS (FAB): *m*/*z* 341 (MH^+), 297, 265, 175, 154, 91 (100%), 77. Anal. calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23; O, 18.80. Found: C, 66.74; H, 5.80; N, 8.13; O, 18.96.

4.4. (3*S*)-3-Amino-1,3,4,5-tetrahydrobenzo[*b*]azepin-2-one, (−)-α-aminobenzolactam, 1

To a solution of *N*-methoxybenzolactam **8** (0.68g, 2mmol) and 20% palladium hydroxyl on carbon (0.14 g) in absolute ethanol (20 ml) was shaken in a Parr apparatus under hydrogen pressure of 100 psi for 6 h. The mixture was filtered through Celite and the filtered cake washed with methanol (30 ml). The solvent was then removed in vacuo to afford **1** (0.34 g, 97%) as pale yellow solid with e.e. = 98% based on the HPLC analysis on the chiral column: $[\alpha]_D = -447.0$ (*c* 1.02, CH_3OH) [lit.[5] $[\alpha]_D = -446.0$ (*c* 1.0, CH_3OH)]; mp 150–151°C (lit.[5] mp 147–149°C); IR (neat): 1670, 1588, 1492, 1416, 1292 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.28–7.23 (m, 2H, CH), 7.17–7.13 (m, 1H, CH), 7.02 (d, $J = 8.0$ Hz, 1H, CH), 3.44–3.39 (m, 1H, $CHNH_2$), 2.90–2.83 (m, 1H, CCH_2), 2.72–2.65 (m, 1H, CCH_2), 2.53–2.42 (m, 1H, CH_2CH), 2.01–1.92 (m, 1H, CH_2CH); ^{13}C NMR (150 MHz, CD_3OD) δ 176.2, 138.3, 135.4, 130.6, 128.7, 127.1, 123.3, 51.9, 38.9, 29.6; MS (FAB): *m*/*z* 177 (MH^+), 154 (100%), 136, 132, 107, 89. Anal. calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90; O, 9.08. Found: C, 68.28; H, 6.93; N, 15.98; O, 9.36.

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10. The compound **9** was identified by mass spectroscopy, $C_{19}H_{22}N_2O_5$ MS (FAB): m/z 359.2 (MH^+); HRMS (FAB): m/z calcd for $C_{19}H_{22}N_2O_5$ MH^+ 359.1607, found MH^+ 359.1608.
11. The e.e. of **1** was determinated by high-performance liquid chromatography equipped with a Daicel CROWNPAK CR(+) column, 150×4.0 mm, eluted (0.8 ml/min) with aq. $HClO_4$ (pH 2) and detected by a UV lamp at $\lambda = 254$ nm. The retention times of the *R*- and *S*-forms were 9.4 min and 11.6 min, respectively.