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A Scalable Process to the Key Intermediate of Cilazapril: (S)-1-Benzyloxycarbonylhexahydropyridazine-3-carboxylic acid, Through a Novel Cascade Course

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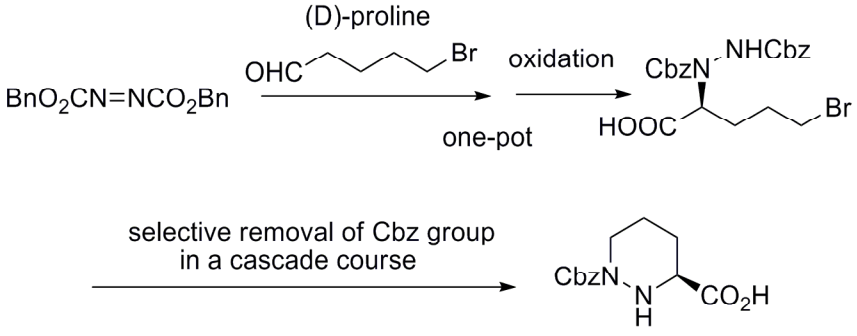
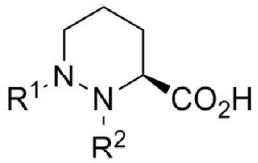


ABSTRACT: A novel and efficient manufacturing technology is disclosed in the present work for the preparation of (S)-1-benzyloxycarbonylhexahydropyridazine-3-carboxylic acid, which is a key intermediate of cilazapril. The whole process includes only three steps; the first two steps

were conducted in one pot, followed by a novel selective removal of Cbz group in a cascade course.

Introduction

(S)-Hexahydropyridazine-3-carboxylic acid[1] (**1**, Figure 1), an architecturally novel cyclic α-hydrazino acid, has been found to be an important component in a large of peptide natural substances, such as monamycins,[2] azinothricin,[3] aurantimycins,[4] polyoxypeptins[5], etc. Compound **1** shows appreciable biological activity, and appears to interfere with γ-amino-butyric acid (GABA) uptake.[6] Among (S)-hexahydropyridazine-3-carboxylic acid derivatives, (S)-1-benzyloxycarbonylhexahydropyridazine-3-carboxylic acid (**2**, Figure 1), a key intermediate of antihypertensive drug cilazapril,[7] is the most attractive.



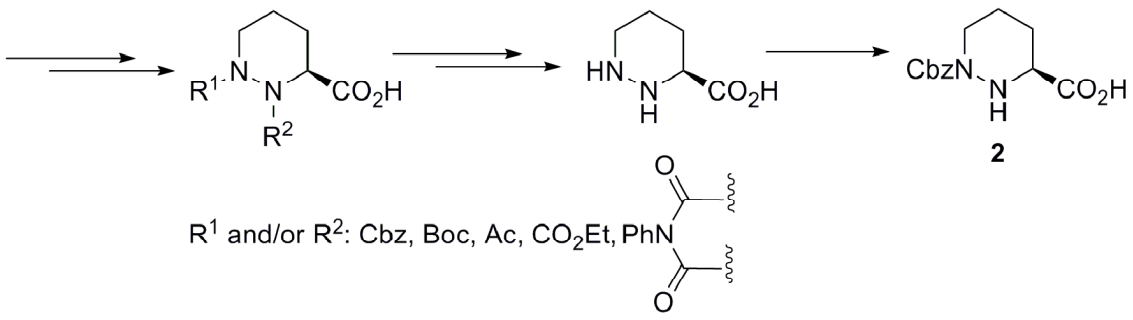
$R^1 = R^2 = H$ **(1)**
R^1 = Cbz, $R^2 = H$ **(2)**
$R^1 = R^2$ = Cbz **(3)**

Figure 1. (S)-Hexahydropyridazine-3-carboxylic acid derivatives.

However, it's still a challenge to construct this chiral six-membered nitrogen containing heterocyclic compound **2**. To the best of our knowledge, all methods reported by other groups for the synthesis of **2** are through removal of both substituent groups on two nitrogen atoms of (S)-1, 2-di-(benzyloxycarbonyl)hexahydropyridazine-3-carboxylic acid (**3**, Figure 1), followed by the rebuilding of Cbz group on one of the nitrogen atoms far away from carboxyl group. These methods suffer from the drawbacks such as long route, tedious operation as well as the use of

expensive regents (Scheme 1).[8] Herein, we report a novel scalable approach to (S)-1-benzyloxycarbonylhexahydropyridazine-3-carboxylic acid **2**.

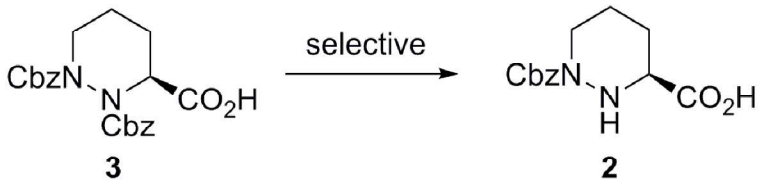
Scheme 1. Known methods reported by other groups



Results and Discussion

During the exploration of cilazapril, our group developed a novel synthetic method to **2**, which could be directly constructed by selective removal of one Cbz group on nitrogen atom adjacent to carboxyl group of **3** (Scheme 2).[9] However, **2** could be only synthesized in a very small scale (grams scale) in the early stage by using this method.

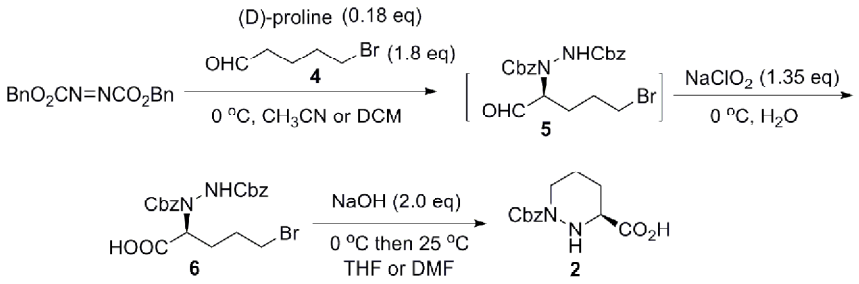
Scheme 2. Formation of 2 through selective removal of one Cbz group of 3



After careful optimization and deep exploration, we realized the synthesis of **2** in Kg scale. The whole process, as shown in Scheme 3, includes only three steps starting from the asymmetric α-hydrazination of bromoaldehyde **4**.[10] Only intermediate hydrazine acid **6** was isolated in the

whole course. Specially, selective removal of one Cbz group in a cascade course simplifies the operation, consequently brings more benefits to the industrial development.

Scheme 3. The whole process for the synthesis of 2



First, hydrazine aldehyde **5** was formed through proline-induced asymmetric α-hydrazination of **4** with DBAD (dibenzyl azodicarboxylate), which was commercially available or could be prepared easily according to the known method.[11] Since this asymmetric α-hydrazination was first reported by another group,[12] we just made simple modifications to the process. It was found that one of the key points was the amount of bromoaldehyde **4** because of its instability under these conditions even at −10 °C. The details are shown in Table 1. For example, when 1.3 equiv of **4** was used, the yield was only 57% without any **4** detected after reaction. Instead, several impurities appeared (Table 1, entry 1). The yield was improved with the increased amount of aldehyde. 1.8 equiv was found to be the best for yield of **5**. However, the yield was not helped when the amount of **4** increased further (Table 1, entries 2−4). According to the literature,[12] higher temperature resulted in poor yield. Nevertheless, we found it unnecessary to conduct the reaction under lower temperature, such as −10 °C, which on the contrary led to a very slow reaction (Table 1, entry 5). In addition to CH_3CN, DCM was found to be another good solvent (Table 1, entry 6).

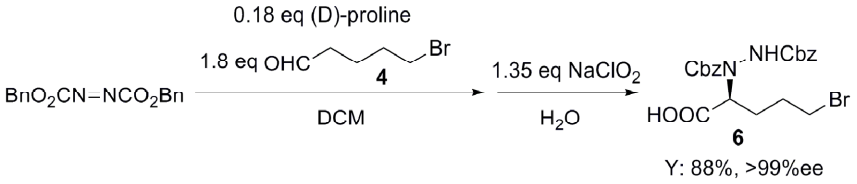
Table 1. Asymmetric α-hydrazination[a]

entry	**4** (equiv)	solvent	temp (°C)	time (h)	yield of **5** (%)[b]
1	1.3	CH_3CN	0	12	57
2	1.5	CH_3CN	0	12	75
3	1.8	CH_3CN	0	12	92[c]
4	2.0	CH_3CN	0	12	90
5	1.8	CH_3CN	−10	24	80
6	1.8	DCM	0	12	90[c]

[a]All reactions were carried out with DBAD (0.01 mol), **4** and D-proline (10 mol% related to the amount of **4**) in solvent. [b]Isolated yield. [c]>99% ee%. The enantiomeric excess was determined for **6** after direct oxidation of **5** without separation, because **5** was liable to be racemized.

The next step was to convert **5** to its acid **6**. When $KMnO_4$ was first used as the oxidant, the yield was good in small scale. Unfortunately, the yield decreased to less than 50% when scaled up. What made it even worse is that separation of the product was quite hard because large amounts of black materials formed during oxidation. After screening, $NaClO_2$ showed a good performance, not only for the reaction, but also for the separation. Strikingly, the transformation from DBAD to **6** could be completed in a one-pot course without separation of **5**, which was liable to be racemized.[13] If the reaction was performed in that way, it should be monitored by TLC or HPLC. For a typical reaction, 0.75 equiv of $NaClO_2$ with respect to aldehyde **4** is sufficient for a complete oxidation. When the reaction was carried out in one-pot, DCM had an advantage over CH_3CN, due to much easier separation from aqueous mixture. After simple purification, **6** was obtained in good yield as well as high enantiomeric excess from DBAD (Scheme 4).

Scheme 4. Formation of 6 from the reaction of DBAD with 4 in one-pot



The ring-closing reaction of **6** to **2** was unexpected but interesting. In the initial explorations, either δ-lactone **7** or the mixture of **7** and **3** was produced. As can be seen from table 2 and Scheme 5, when an organic base such as Et_3N, DMAP or an inorganic base such as Na_2CO_3 or NaH was used at 25 °C, δ-lactone **7** was the only product (Table 2, entries 1−4). Lower temperature decelerated the attack of carboxyl group on bromide, causing the formation of **3** as minor product, when at least 2 equiv of NaH was employed (Table 2, entries 5−6). But 1 equiv of NaH still generated **7** completely at 0 °C (Table 2, entry 7). In contrast to NaH, other bases like Et_3N, DMAP or Na_2CO_3 gave nothing at 0 °C with the starting material recovered (Table 2, entries 8−10). It seemed that the further freduction in temperature made the reaction proceed quite slowly even in the presence of NaH (Table 2, entry 11). It was surprising that **2** was unexpectedly observed, when the mixture of **3** and **7** stood with the temperature rising from 0 °C to 25 °C before quenching (Table 2, entry 12).

Scheme 5. Ring-closing reaction of compound 6

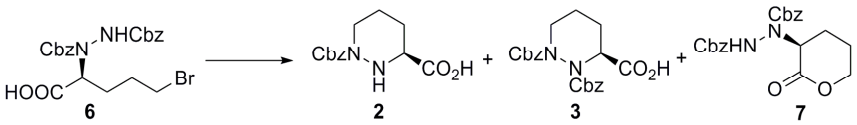


Table 2. Ring-closing reaction of compound 6[a]

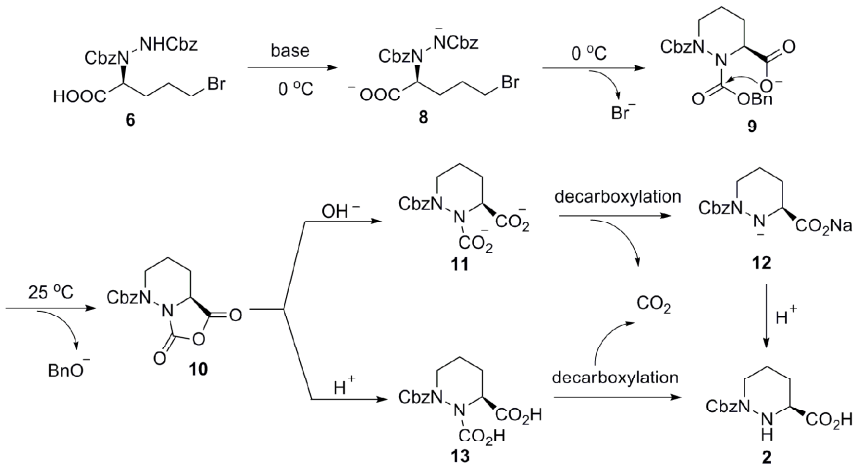
entry	base	solvent	temp (°C)	time (h)	yield (%)[b]		
					2	**3**	**7**
1	Et_3N, 2 equiv	DCM	25	24	−	−	83

2	DMAP, 2 equiv	DCM	25	24	–	–	79
3	Na_2CO_3, 2 equiv	DMF	25	12	–	–	80
4	NaH, 2 equiv	DMF	25	6	–	–	94
5	NaH, 2 equiv	DMF	0[c]	12	–	29	63
6	NaH, 3 equiv	DMF	0[c]	12	–	27	60
7	NaH, 1 equiv	DMF	0[c]	12	–	–	88
8	Et_3N, 2 equiv	DCM	0[c]	24	–	–	–
9	DMAP, 2 equiv	DCM	0[c]	24	–	–	–
10	Na_2CO_3, 2 equiv	DMF	0[c]	24	–	–	–
11	NaH, 2 equiv	DMF	−10	24	–	5	15
12	NaH, 2 equiv	DMF	0−25[d]	12[e]	15	10	60

[a]All reactions were carried out with **6** (0.01 mol) and base in solvent. [b]Isolated yield. [c]The reaction was quenched with HCl aq also at 0 °C. [d]The reaction was stirred at 0 °C for 12 h, was then warmed to 25 °C on standing. [e]The reaction time at 0 °C.

The direct formation of **2** from the reaction attracted our great attention, and compelled us to study it. We found that this transformation actually included two successive stages. In the first stage, **9**[14] (anion of **3**) was formed at lower temperature (0 °C). When temperature rose at next stage, the transformation of **9** to **2** occurred (25 °C). A possible mechanism is postulated in Scheme 6. The removal of hydrogen proceeded in the presence of at least 2 equiv of base to yield dianion **8** from **6** at 0 °C. After the attack of nitrogen anion on bromide, intermediate **9** was formed. At higher temperature such as 25 °C, **9** was then subjected to ring-closing reaction to form bicyclic-ring anhydride **10**,[15, 16] which was transformed to **2** through either an acid or base mediated hydrolysis-decarboxylation cascade course. It was obvious that temperature and the kind of base were the crucial factors for this cascade reaction.

Scheme 6. Postulated mechanism



Knowing the above information, we then turned our attention to other bases. The results arelisted in table 3 and Scheme 7. The reaction proceeded slowly in the presence of alkoxides such as NaOtBu, NaOEt, and only δ-lactone **7** was obtained with a trace of **3** detected by TLC (Table 2, entries 1−2). Surprisingly, NaOH exhibited perfect activity for the formation of **3** exclusively, and the yield of **3** was doubled to 92% when the reaction time was extended (Table 2, entries 3−4). As long as **3** was well-formed, the formation of **2** was quite easy. The selective removal of the Cbz group took place spontaneously at increasing temperature (Table 2, entry 5). In addition, KOH in THF was a good option (Table 2, entries 6−7).

Scheme 7. Condition screen for the formation 2 from 6

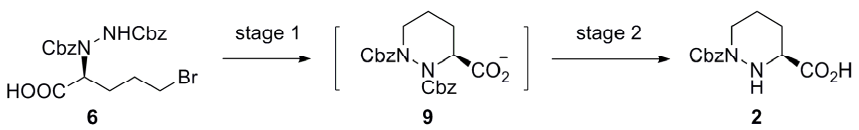


Table 3. Condition screen for the formation 2 from 6[a]

entry	condition[a]	yield (%)[b]

		2	**3**	**7**
1	Stage 1: NaO*t*Bu (2 equiv), DMF, 0 °C, 24 h[c]	–	trace	51
2	Stage 1: NaOEt (2 equiv), DMF, 0 °C, 24 h[c]	–	trace	34
3	Stage 1: NaOH (2 equiv), DMF, 0 °C, 12 h[c]	–	48	–
4	Stage 1: NaOH (2 equiv), DMF, 0 °C, 24 h[c]	–	96	–
5	Stage 1: NaOH (2 equiv), DMF, 0 °C, 24 h Stage 2: 3 h, 25 °C	90	–	–
6	Stage 1: NaOH (2 equiv), THF, 0 °C, 24 h Stage 2: 3 h, 25 °C	90	–	–
7	Stage 1: KOH (2 equiv), THF, 0 °C, 24 h Stage 2: 3 h, 25 °C	85	–	–

[a]All reactions were carried out with **6** (0.01 mol) and base in solvent. [b]Isolated yield. [c]The reaction was not proceeded to stage 2.

CONCLUSION

A novel and efficient manufacturing technology was developed for the preparation of (S)-1-benzyloxycarbonylhexahydropyridazine-3-carboxylic acid **2**, which is a key intermediate of antihypertensive drug cilazapril. Compound **2** was finally obtained in 75% overall yield with 99% purity and >99%ee after three steps. In the final step, a novel selective removal of Cbz group took place in a cascade course.

EXPERIMENTAL SECTION

General. Melting points were recorded on an RY-1 melting point apparatus and are uncorrected. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) as internal standards. *J* values are given in hertz. Mass spectra were recorded on a Finnigan MAT-95/711 spectrometer. Elemental analysis was performed on an MOD-1106 instrument. Optical resolutions were determined on a Jasco P-1020 polarimeter. HPLC analysis was performed by a standard method on an Intersil ODS-3 C_{18} column, 250 mm × 4.6 mm (5 μm); λ = 210 nm; mobile phase: A (CH_3CN) and B (0.2% H_3PO_4), 60:40 v/v. Enantiomeric excess was determined by HPLC using CHIRALCEL OJ-H column, 250 mm × 4.6 mm (5 μm); λ = 210 nm; mobile phase: A (hexane) and B (i-PrOH), 80:20 v/v. The HPLC analysis data are reported in area % and are not adjusted to weight %.

(S)-5-Bromo-2-*N*, *N'*-di-(benzyloxycarbonyl)hydrazino-1-pentanoic acid (6). To a stirred solution of **4** (1.49 kg, 9.0 mol) in DCM (12 L) was added D-Proline (103.5 g, 0.9 mol) and DBAD (1.49 kg, 5.0 mol) at 0 °C. DBAD disappeared after the mixture was stirred for 12 h at that temperature. Then NH_2SO_3H (873.0 g, 9.0 mol) was added in portion to the above mixture at 0 °C, followed by the slow addition of 80% $NaClO_2$ (763.6 g, 6.75 mol) in H_2O (6 L) with control of the temperature less than 0 °C. The reaction was finished after the addition of $NaClO_2$ solution. Then the mixture was quenched by addition of saturated Na_2SO_3 solution until the potassium iodide-starch test paper showed that no oxidant existed. Solid was removed after the mixture was stirred for 1 h at 25 °C. The aqueous layer was extracted with DCM (2 × 3 L) after separation. The combined organic layer was concentrated after washed with brine (10 L). Solid precipitate when solvent was concentrated to 10% of the total volume. This solid was dried at 50 °C under vacuum after filtration to afford **6** (2.11 kg, 88% from DBAD) as an off-white solid

with 98.5% purity by HPLC (retention time: 30.2 min), and >99%ee (retention time: 22.5 min for (S) and 18.7 min for (R)). Mp: 114−115 ^{o}C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.73−2.06 (br, m, 4H), 3.48 (br, s, 2H), 4.60 (br, s, 1H), 5.11−5.16 (br, s, 4H), 7.25−7.40 (br, m, 10H), 9.06−9.58 (br, s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 27.3, 27.5, 29.5, 35.1, 60.2, 61.2, 66.7, 67.7, 67.9, 127.6, 127.9, 128.1, 128.3, 128.4, 128.8, 136.6, 136.9, 155.9, 156.2, 157.2, 171.8; ESI-MS (m/z) 477, 479 $[M - H]^{-}$.

(S)-1-Benzyloxycarbonylhexahydropyridazine-3-carboxylic acid (2). The mixture of NaOH (352.0 g, 8.8 mol) with **6** (2.11 kg, 4.4 mol) in THF (15 L) was stirred for 24 h at 0 °C, followed by keeping stirring at 25 °C for another 3 h. To this mixture was added successively 1N NaOH aq (4.4 L) and sat $NaHCO_3$ aq (5 L). The organic layer was separated and extracted with sat $NaHCO_3$ aq (2 × 5 L), then discarded. The combined aqueous layer was washed with hexane (2 × 5 L), was then acidified with 37% HCl aq. to pH=4~5. The precipitated solid was collected and slurried with EtOAc (3 L) for 3 h. This solid was dried at 50 °C under vacuum to afford **2** (982.9 g, 85%) as a white solid with 99% purity by HPLC (retention time: 15.4 min), and >99%ee (retention time: 20.9 min for (S) and 17.7 min for (R)). Mp: 166−167 °C (lit. mp 168−169).[8c] $[\alpha]_D$ = −35.4 (T = 20 ^{o}C, c = 1 g/100 mL, MeOH), (lit. $[\alpha]_D$ = −35.0)[8c] ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 1.51−1.55 (br, m, 2H), 1.68−1.70 (br, m, 1H), 1.87−1.91 (br, m, 1H), 3.06 (br, s, 1H), 3.37 (dd, J = 9.6 Hz, 2.8 Hz, 1H), 3.82 (d, J = 12.8 Hz, 1H), 5.09 (dd, J = 15.2 Hz, 12.4 Hz, 2H), 7.30−7.38 (m, 5H), 12.75 (br, s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 23.4, 27.6, 44.5, 58.3, 66.8, 128.0, 128.3, 128.8, 137.4, 155.6, 173.2; ESI-MS (m/z) 265 $[M + H]^{+}$; Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.20; H, 6.18; N, 10.53.

(S)-5-Bromo-2-*N*, *N'*-(dibenzyloxycarbonyl)hydrazino-1-pentanal (5).

To a stirred solution of **4** (2.97 g, 0.018 mol) in CH_3CN (24 mL) was added D-Proline (0.21 g, 0.0018 mol) and DBAD (2.98 g, 0.01 mol) at 0 °C. DBAD disappeared after the mixture was stirred for 12 h at that temperature. The mixture was then concentrated to afford an oil, which was purified via silica gel column chromatography using EtOAc/hexane (1:4) as eluent to yield 4.26 g (92%) of **5** as an off-white solid. Mp: 84−85 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.65−2.20 (br, m, 4H), 3.35−3.50 (br, m, 2H), 4.50−4.80 (br, m, 1H), 5.11−5.16 (br, s, 4H), 6.68−6.82 (br, s, 1H), 7.25−7.35 (br, m, 10H), 9.50−9.60 (br, s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.3, 24.9, 28.9, 33.5, 33.9, 66.6, 67.7, 68.0, 68.7, 69.1, 127.8, 128.2, 128.7, 135.1, 135.4, 156.3, 156.9, 198.5, 199.0; ESI-MS (m/z) 461, 463 $[M - H]^-$.

(S)-1, 2-Di-(benzyloxycarbonyl)hexahydropyridazine-3-carboxylic acid (3). To a solution of **6** (4.79 g, 0.01 mol) in DMF (40 mL) was added NaOH (0.80 g, 0.02 mol) at 0 °C. The mixture was stirred for 24 h at 0 °C, then quenched by 1 N HCl aq (30 mL) at 0 °C. The aqueous layer was removed after extracted with EtOAc (2 × 80 mL). The combined organic layer was dried with anhydrous Na_2SO_4, then concentrated to afford an oil after filtration. The product was purified via silica gel column chromatography using EtOAc/hexane (1:2) as eluent to yield 3.83 g (96%) of **3** as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.56−2.21 (br, m, 4H), 2.90−3.20 (br, m, 1H), 4.00−4.25 (br, m, 1H), 5.05−5.29 (br, m, 5H), 7.25−7.40 (br, m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.0, 20.3, 23.9, 24.6, 43.7, 44.7, 55.7, 56.9, 68.0, 68.7, 69.1, 127.7, 127.9, 128.2,

128.4, 128.5, 128.6, 128.7, 135.2, 135.5, 136.1, 155.2, 155.6, 156.6, 171.4, 172.8; ESI-MS (m/z) 399 $[M + H]^+$.

(S)-3-*N*, *N'*-di-(benzyloxycarbonyl)hydrazinyltetrahydro-2*H*-pyran-2-one (7). The mixture of **6** (4.79 g, 0.01 mol) and Et_3N (2.02 g, 0.02 mol) was stirred in DCM (30 mL) for 24 h at 25 °C. After the reaction was finished, the mixture was concentrated, and then purified via silica gel column chromatography using EtOAc/hexane (1:8) as eluent to yield 3.30 g (83%) of **7** as an off-white solid. Mp: 93−94 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.95−2.45 (br, m, 4H), 4.20−5.20 (br, m, 7H), 6.60−6.95 (br, s, 1H), 7.20-7.35 (br, m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.8, 22.0, 22.6, 23.6, 57.2, 58.6, 67.8, 68.6, 69.0, 127.6, 128.1, 128.2, 128.4, 128.6, 135.5, 155.8, 156.2, 156.8, 169.9, 170.4; ESI-MS (m/z) 399 $[M + H]^+$; Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.41; H, 5.51; N, 7.14.

ASSOCIATED CONTENT

Supporting Information.

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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10. Compound **4** was synthesized according to the known method. Please see: (a) Chong, M.; Heuft, M. A.; Rabbat, P. *J. Org. Chem.* **2000**, *65*, 5837. (b) Shu, L.; Wang, P.; Radinov, R.; Dominique, R.; Wright, J.; Alabanza, L. M.; Dong, Y. *Org. Process. Res. Dev*. **2013**, *17*, 114.

11. DABD could be commercially purchased or easily prepared according to the known method. Please see: (a) Little, R. D.; Venegas, M. G. *Org. Syn., Coll.* **1990**, *7*, 56. (b) Mellor, J. M.; Pathirana, R. N. *J. Chem. Soc. Perkin Trans. 1.* **1984**, 753. (c) Starr, J. T.; Rai, G. S.; Dang, H.; McNelis, B. J. *Syn. Commun.* **1997**, *27*, 3197.

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13. >99% ee% was obtained for crude **6**, if the reaction was carried out in one-pot without separation of **5**. However, **6** was found to be completely racemized (0%ee and $[\alpha]_D = 0$), when the separated **5**, either by column chromatography or by recrystallization, was used under the same oxidation condition.

14. Compound **3** could be transformed to compound **2** in 95% yield in THF using NaOH as base at ambient temperature, which meant that **3** (or **9**) was one of the intermediate from **6** to **2**.

15. Compound **10** was synthesized according to literature listed in reference 16. To **3** (200 mg, 0.5 mmol) was added a solution of oxalyl chloride (318 mg, 2.5 mmol) in benzene (5 mL) at 25 ^{o}C. The reaction mixture was stirred for 18 h at that temperature, and then concentrated in vacuo to afford the **10** as a colorless oil mixed with BnCl. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.65−2.23 (br, m, 4H), 3.02−3.33 (br, m, 1H), 4.07−4.21 (br, m, 2H), 4.52 (s, C*H*$_2$ of BnCl), 5.14 (br, s, 2H), 7.12−7.29 (br, m, 5H, mixed with Ar-*H* of BnCl). ESI-MS (m/z) 265 [M − $CO_2 + H_3O]^+$. With **10** in hand, we then mixed the solution of **10** in THF with water under either acidic or basic condition. As expected, **2** was formed smoothly almost quantitatively.

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