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An efficient, asymmetric synthesis of pipecolic acid and 2-alkyl pipecolic acids

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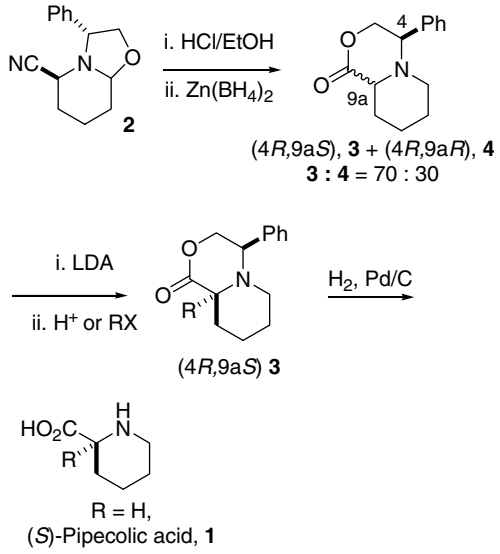
Received 21 September 2005; accepted 21 October 2005

Abstract—Both (*R*)- and (*S*)-pipecolic acids and their 2-alkyl derivatives have been synthesized via diastereoselective alkylations of (*R*)-5-phenylmorpholin-2-one **5**.

1. Introduction

Pipecolic acid **1** and its derivatives occur in numerous natural products with important biological properties.[1,2] Synthetic routes to these compounds have been developed featuring enzymatic reactions,[1e,3] asymmetric hydrogenation,[4] diastereoselective alkylation,[5] ring closing metathesis,[6] and other transformations derived from known chiral building blocks.[7] Among the stereoselective methodologies to form pipecolic acid, Royer and Husson's method is probably the most practical. They used (*R*)-2-cyano-6-phenyloxazolopiperidine **2** to form diastereomers of 4-phenylhexahydropyrido[2,1-*c*][1,4]-oxazin-1-ones **3** and **4**, which were converted to (*S*)-pipecolic acids after epimerization and hydrogenation (Scheme 1).[7a] This method has also been adopted to synthesize isotopically labeled pipecolic acids[8a] and a serotonin (5-hydroxytryptamine, 5-HT) agonist.[8b]



Scheme 1.

However, applying Royer and Husson's method to prepare (*R*)-pipecolic acid is held back since separating diastereomeric mixtures of **3** and **4**, or using the other enantiomer of the chiral auxiliary, that is, (*S*)-phenyl glycinol, is required.[8] This is important because (*R*)-pipecolic acid does not occur naturally, current access to this enantiomer is limited to resolution,[3b] kinetic resolution of its precursor,[1e] and a few diastereoselective syntheses.[5b,d] Recent studies show that derivatives of (*R*)-pipecolic acid are found to have higher affinity toward to muscarinic receptors than those of (*S*)-enantiomer.[9]

A diastereoselective synthesis of (4*R*,9*aR*)-oxazin-1-one **4** is reported herein. Access to diastereomerically pure **4** provides the route to both (*R*)- and (*S*)-pipecolic acid using a single chiral auxiliary. In addition, both enantiomers of 2-alkyl pipecolic acids can also be prepared by alternating the sequence of alkylations.

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doi:10.1016/j.tetasy.2005.10.025

2. Results and discussion

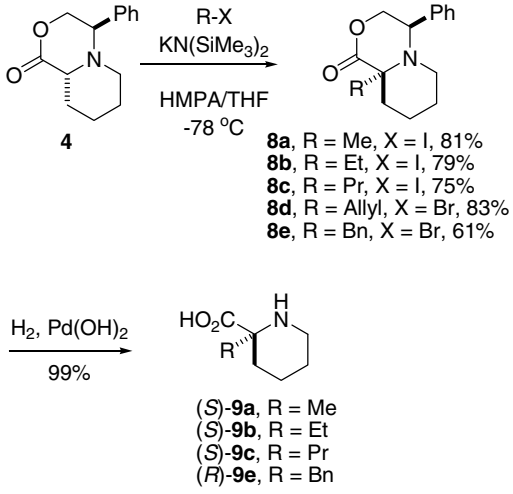
2.1. Synthesis of (*R*)- and (*S*)-pipecolic acid

Chiral glycine enolate synthon, 5-phenyl morpholin-2-one **5**, was prepared from the commercially available, and inexpensive, (*R*)-2-phenylglycinol in three steps.[10a] The enolate of **5** was formed then monoalkylated with diiodobutane based on Williams' procedure to give (3*R*,5*R*)-4-iodobutyl substituted compound **6**.[10b] The (3*S*,5*R*)-diastereomer was not detected by ^{1}H and ^{13}C NMR spectrometry. This result was consistent with Williams' and Dellaria's reports that the diastereoselectivity of this process is very high (>96% de).[10] Removal of the Boc group by trifluoroacetic acid (TFA) and cyclization under basic conditions provided the desired (4*R*,9*aR*)-oxazin-1-one **4**. The configuration and diastereomeric purity of **4** was known by comparing its NMR spectra with Royer's data.[7a] The epimerization of **4** by deprotonation/protonation protocol provided only the (4*R*,9*aS*)-diastereomer **3**. In contrast to Royer's procedure, we found that potassium bis(trimethylsilyl)amide (KHMDS) is more effective than sodium bis(trimethylsilyl)amide (NaHMDS) and lithium diisopropylamide (LDA), which gave <10% and 50% conversion, respectively. This difference may arise because deprotonating the minor isomer **4** (30%) is sufficient in Royer's procedure, but complete enolate formation is required in our transformation of **4** to **3**. This intriguing reactivity difference of the substrates **5** and **4** toward bases (NaHMDS versus KHMDS) allowed us to control the alkylation effectively, that is, excess NaHMDS (1.5 equiv) used in the diastereoselective alkylation of **5** did not compromise the stereochemical outcome. On the other hand, to form the enolates on tertiary carbons, such as **4** and **10** (see below), KHMDS was applied. Both (*R*)- and (*S*)-pipecolic acids were prepared after hydrogenation of morpholin-2-one **4** and **3**, respectively (Scheme 2). Here, we found that Pearlman's catalyst[11] gave better yields than previous reports using Pd/C.

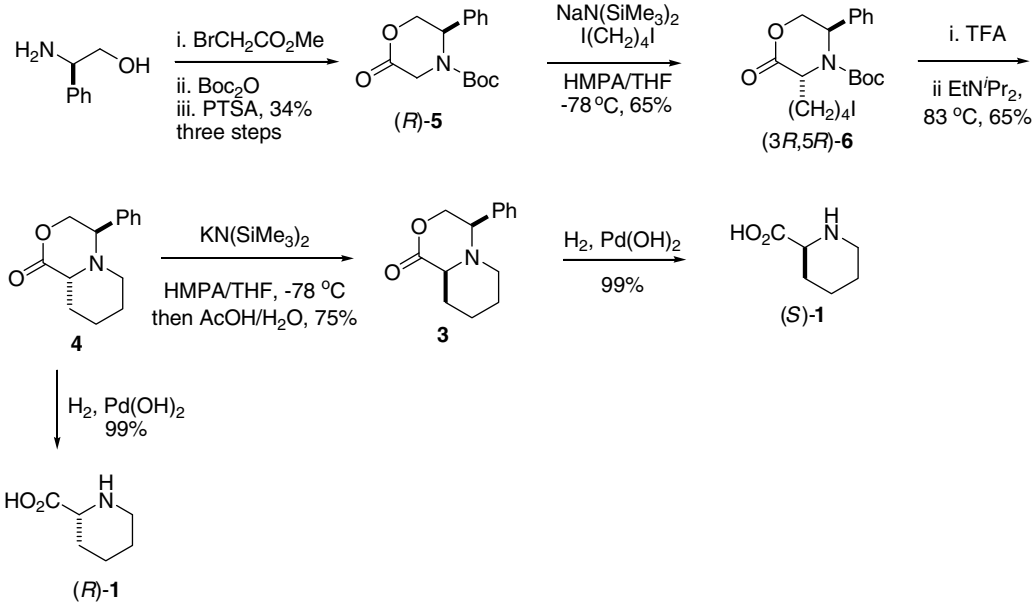
2.2. Synthesis of 2-alkylpipecolic acids

Replacing the proton source with alkyl halides in the transformation of compound **4** into **3** provided an access to 2-substituted pipecolic acids **9** (Scheme 3).

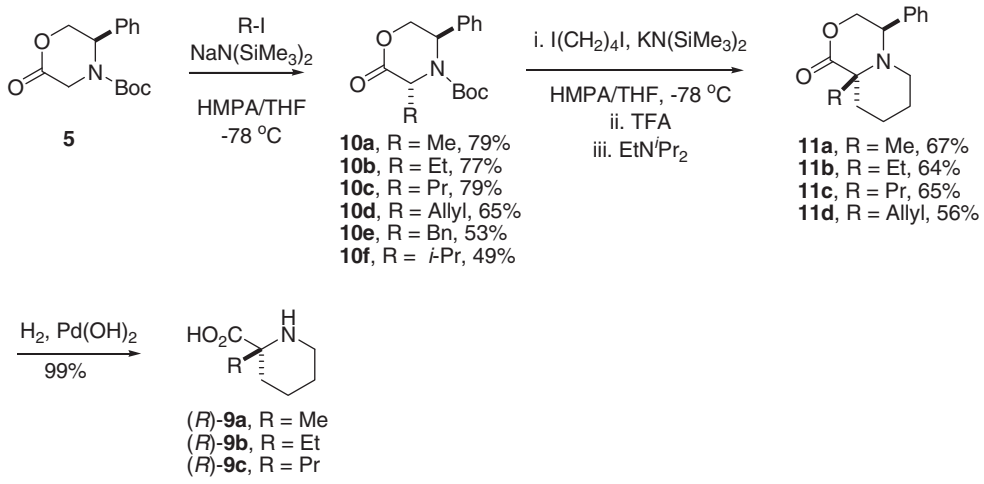
The other enantiomer of 2-alkyl pipecolic acids **9** can also be prepared. To have reversed stereocenters, the quaternary stereogenic carbons of **9** were assembled by incorporating the substituents onto morpholin-2-one **5** first, then forming the piperidine moiety later. The enolate from **5** and NaHMDS reacted with various electrophiles at −78 °C to give (3*R*)-morpholin-2-ones **10a**–**f** (Scheme 4).



Scheme 3.



Scheme 2.



Scheme 4.

In the ^{13}C NMR, the sp^3 carbons of compounds **10** with larger substituents, such as allyl **10d**, benzyl **10e** and isopropyl **10f**, gave weak resonances at room temperature (Fig. 1b). We propose this is due to conformational isomers that equilibrate slowly on the NMR time scale, since coalescence was observed at elevated temperature (45 °C, Fig. 1a).[12]

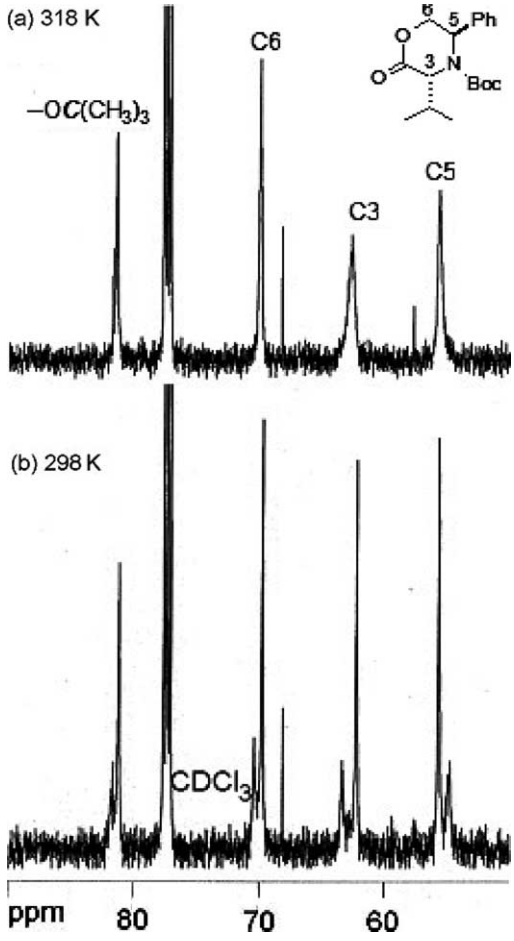


Figure 1. ^{13}C NMR spectroscopies of **10f**: (a) 45 °C, (b) 25 °C.

Following alkylation of **10a–f** with diiodobutane, deprotection and cyclization generated the desired diastereomers **11a–d**. KHMDS was used to facilitate the second alkylation. Unfortunately, alkylation of benzyl or isopropyl substituted compounds, **10e** and **10f**, with diiodobutane did not proceed, and the starting materials **10e–f** were recovered without epimerization. The failure to generate enolates of **10e** and **10f** may be due to the steric hindrance of the large base (KHMDS) in accessing the proton geminal to the more hindered isopropyl and benzyl group attached to a cyclic framework. Compounds **11a–d** have distinctive NMR spectra compared to their diastereomers **8a–d**. Thus, both diastereomers **8a–d** and **11a–d** were independently synthesized and no cross-contamination was observed within the detection limits of ^1H and ^{13}C NMR. Finally, hydrogenation gave (*R*)-pipecolic acids **9a–c** with good yields. The specific rotations of these pipecolic acids **1**, **9**, and their precursors **8**, **11** are listed in Table 1.

In summary, we have developed a diastereoselective synthesis of both enantiomers of pipecolic acids and 2-alkyl-pipecolic acids, using the same chiral auxiliary **5**. Our route is complementary to Royer's method to prepare oxazin-1-one **4** insofar as the stereochemical control is concerned. We believe that the methodology described in this paper provides a reliable and simple way to prepare pipecolic acids enantioselectively.

3. Experimental

All purchased chemicals were used without further purification. THF was distilled from sodium benzophenone ketyl. ^1H and ^{13}C NMR spectra were obtained on Brüker 200, 400, or 500 MHz spectrometers and referenced to TMS or residual $CHCl_3$. Concentration of solutions was accomplished by rotary evaporation at water aspirator pressure. Analytical TLC was carried out using Merck aluminum-backed 0.2 mm silica gel 60 F254 plates. Column chromatography was conducted using Merck silica gel 60 (230–400 mesh).

Table 1. Specific rotations of pipecolic acids and precursors **8** and **11**

Entry	Compound	R	$[\alpha]_D^{25}$	Lit. $[\alpha]_D^{25}$
1	(*R*)-**1**	H	+25.8[a]	+25.5[b]
2	(*S*)-**1**	H	−25.8[a]	−26.0[c]
3	(*R*)-**9a**	Me	+3.6[a]	
4	(*S*)-**9a**	Me	−3.7[a]	−3.7[d]
5	(*R*)-**9b**	Et	+11.3[a]	
6	(*S*)-**9b**	Et	−11.9[a]	−12.0[e]
7	(*R*)-**9c**	Pr	+21.7[a]	
8	(*S*)-**9c**	Pr	−22.3[a]	
9	(*R*)-**9e**	Bn	−2.8[a]	−3.3[f]
10	**8a**	Me	−119.9[g]	−120.7[h]
11	**11a**	Me	−50.3[g]	
12	**8b**	Et	−91.2[g]	−90.7[i]
13	**11b**	Et	−47.7[g]	
14	**8c**	Pr	−107.3[g]	
15	**11c**	Pr	−49.1[g]	
16	**8d**	Allyl	−109.3[g]	
17	**11d**	Allyl	−23.9[g]	
18	**8e**	Bn	−143.1[g]	−143.7[j]

[a] $c = 1.0$ in water.
[b] $c = 1.0$ in water; Ref. 13.
[c] $c = 2.9$ in water; Ref. 7a.
[d] $c = 0.2$ in water; Ref. 14.
[e] $c = 1.1$ in water; Ref. 5a.
[f] $c = 0.6$ in water; Ref. 7a.
[g] $c = 1.0$ in $CHCl_3$.
[h] $c = 0.45$ in $CHCl_3$; Ref. 7a.
[i] $c = 0.97$ in $CHCl_3$; Ref. 7a.
[j] $c = 0.48$ in $CHCl_3$; Ref. 7a.

3.1. General procedure to perform diastereoselective alkylation of 5

3.1.1. Preparation of (3*R*,5*R*)-3-(4-iodobutyl)-2-oxo-5-phenyl-morpholine-4-carboxylic acid *tert*-butyl ester 6. Sodium bis(trimethylsilyl)amide (2 M, 7.5 mL, 15 mmol) was added to a solution of **5** (2.77 g, 10 mmol), 1,4-diiodobutane (6.5 mL, 49 mmol) and HMPA (2.6 mL, 15 mmol) in THF (100 mL) at −78 °C dropwise. After 3 h at −78 °C, the reaction mixture was added with saturated ammonium chloride (30 mL) and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (SiO_2–ethyl acetate/hexanes, 1:3; R_f 0.31) to provide compound **6** (2.98 g, 6.5 mmol, 65%) as a light yellow oil. $[\alpha]_D^{25} = -124.2$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.22 (m, 3H), 7.07 (d, $J = 7.3$ Hz, 2H), 5.02 (br, 1H), 4.84 (br, 1H), 4.76 (dd, $J = 3.0$, 11.9 Hz, 1H), 4.40 (br, 1H), 3.19 (t, $J = 7.0$ Hz, 2H), 2.08–1.98 (m, 1H), 1.96–1.78 (m, 3H), 1.65–1.60 (m, 2H), 1.3 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 153.4, 140.0, 128.9, 127.8, 125.4, 81.3, 69.7, 56.1, 55.0, 33.2, 32.7, 28.0, 26.7, 5.9; HRMS (FAB) $[M+H]^+$ ($C_{19}H_{27}INO_4$) calcd 460.0985, found 460.1008.

3.1.2. (3*R*,5*R*)-4-*tert*-Butyloxycarbonyl-3-methyl-5-phenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one 10a.[10a] R_f 0.28 (ethyl acetate/hexanes 1:4); $[\alpha]_D^{25} = -181.9$ (*c* 1, $CHCl_3$); −176.0 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.23 (m, 3H), 7.07 (d, $J = 7.3$ Hz, 2H), 5.05 (br, 1H), 4.92 (br, 1H), 4.74 (dd, $J = 2.9$, 11.8 Hz, 1H), 4.45 (br, 1H), 1.61 (d, $J = 7.1$ Hz, 3H), 1.49–1.19 (br, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 153.2, 139.6, 128.8, 127.8, 125.4, 81.3, 69.9, 54.8, 52.2, 28.1, 20.0; HRMS (FAB) $[M+H]^+$ ($C_{16}H_{22}NO_4$) calcd 292.1549. found 292.1548.

3.1.3. (3*R*,5*R*)-4-*tert*-Butyloxycarbonyl-3-ethyl-5-phenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one 10b. R_f 0.31 (ethyl acetate/hexanes 1:4); $[\alpha]_D^{25} = -177.3$ (*c* 1, $CHCl_3$), −174.9 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.23 (m, 3H), 7.07 (d, $J = 7.3$ Hz, 2H), 5.01 (br, 1H), 4.75 (dd, $J = 3.0$, 11.8 Hz, 2H), 4.38 (br, 1H), 2.11–2.01 (m, 1H), 1.90–1.79 (m, 1H), 1.44–1.16 (br, 9H), 1.08 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 153.6, 140.0, 128.8, 127.7, 125.4, 81.2, 69.6, 57.9, 54.9, 27.9, 10.4; HRMS (EI) $[M]^+$ ($C_{17}H_{23}NO_4$) calcd 305.1627, found 305.1629.

3.1.4. (3*R*,5*R*)-4-*tert*-Butyloxycarbonyl-5-phenyl-3-propyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one 10c. R_f 0.31 (ethyl acetate/hexanes 1:5); $[\alpha]_D^{25} = -182.1$ (*c* 1, $CHCl_3$), −180.3 (*c* 1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.33–7.21 (m, 3H), 7.05 (d, $J = 6.6$ Hz, 2H), 5.00 (br, 1H), 4.74 (dd, $J = 3.0$, 11.8 Hz, 2H), 4.36 (br, 1H), 2.06–1.86 (m, 1H), 1.82–1.67 (m, 1H), 1.60–1.13 (m, 11H), 0.96 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.0, 153.4, 140.0, 128.7, 127.6, 125.2, 80.9, 69.6, 56.3, 54.8, 36.3, 27.9, 19.0, 13.5; HRMS (EI) $[M]^+$ ($C_{18}H_{25}NO_4$) calcd 319.1784, found 319.1790.

3.1.5. (3*R*,5*R*)-3-Allyl-4-*tert*-butyloxycarbonyl-5-phenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one 10d.[10a] R_f 0.35 (ethyl acetate/hexanes 1:6); $[\alpha]_D^{25} = -186.7$ (*c* 1, $CHCl_3$), −183.8 (*c* 1, CH_2Cl_2), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.29 (m, 3H), 7.12 (d, $J = 6.8$ Hz, 2H), 5.91 (m, 1H), 5.20–5.17 (m, 2H), 4.98 (br, 1H), 4.80 (dd, $J = 2.9$, 11.8 Hz, 2H), 4.36 (br, 1H), 2.80–2.72 (m, 2H), 1.46–1.17 (br, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.7, 153.6, 140.0, 132.2, 128.8, 127.8, 125.4, 119.5, 81.2, 69.6, 56.6, 54.8, 38.3, 27.9; HRMS (FAB) $[M+H]^+$ ($C_{18}H_{24}NO_4$) calcd 318.1705, found 318.1709.

3.1.6. (3*R*,5*R*)-3-Benzyl-4-*tert*-butyloxycarbonyl-5-phenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one 10e.[10a] R_f 0.32 (ethyl acetate/hexanes 1:6); $[\alpha]_D^{25} = -159.7$ (*c* 1, $CHCl_3$), −203.6 (*c* 1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.45–7.23 (m, 8H), 7.06 (d, $J = 6.6$ Hz, 2H), 5.20 (br, 1H), 4.82 (br, 1H), 3.96 (br d, $J = 11.4$ Hz, 1H), 3.57 (br, 1H), 3.32 (dd, $J = 3.5$, 13.6 Hz, 2H), 1.56–1.23 (br, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 153.8, 140.2, 136.3, 129.9, 128.8, 128.5, 128.2, 128.0, 127.7, 127.5, 125.3, 81.2, 69.1, 58.5, 54.3, 38.8, 28.2; HRMS (FAB) $[M+H]^+$ ($C_{22}H_{26}NO_4$) calcd 368.1862, found 368.1869.

3.1.7. (3*R*,5*R*)-4-*tert*-Butyloxycarbonyl-3-isopropyl-5-phenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one 10f. R_f 0.35 (ethyl acetate/hexanes 1:5); $[\alpha]_D^{25} = -135.5$ (*c* 1, $CHCl_3$), −130.3 (*c* 1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.22 (m, 3H), 7.06 (d, $J = 7.4$ Hz, 2H), 5.05 (br, 1H), 4.66 (dd, $J = 3.1$, 12.0 Hz, 1H), 4.56 (br, 1H), 4.27 (br, 1H), 2.20–2.13 (m, 2H), 1.42–1.09 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 154.5,

140.8, 128.7, 127.6, 125.4, 80.9, 69.8, 62.5, 55.0, 33.4, 27.9, 19.4; HRMS (FAB) $[M+H]^+$ ($C_{18}H_{26}NO_4$) calcd 320.1862, found 320.1862.

3.2. General procedure of piperidine ring formation

Preparation of (4*R*,9a*R*)-4-Phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one **4**

Trifluoroacetic acid (TFA, 30 mL) was added to a solution of **6** (2.98 g) in 1,2-dichloroethane (30 mL). After stirred at rt for 24 h, the reaction mixture was concentrated to remove TFA. Another 30 mL of 1,2-dichloroethane and diisopropyl ethylamine (5.7 mL, 32.7 mmol) were added to the residue, and the reaction mixture was heated to reflux for 6 h. The solvent was removed under vacuum and the crude product was purified by column chromatography (SiO_2: ethyl acetate/hexanes, 1:3; R_f 0.41) to provide compound **4** (0.98 g, 65%) as a light yellow oil.[7a] $[\alpha]_D^{25} = -6.7$ (*c* 1, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.29 (m, 5H), 4.66 (dd, $J = 4.9$, 11.1 Hz, 1H), 4.43 (dd, $J = 4.9$, 11.1 Hz, 1H), 3.97 (dd, $J = 4.9$, 4.9 Hz, 1H), 3.30 (dd, $J = 3.2$, 9.4 Hz, 1H), 2.77 (m, 1H), 2.31 (m, 1H), 2.06–2.03 (m, 1H), 1.84–1.73 (m, 2H), 1.57–1.48 (m, 1H), 1.44–1.41 (m, 1H), 1.36–1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.8, 135.5, 128.6, 128.3, 128.2, 72.2, 60.0, 57.8, 51.7, 26.7, 23.9, 23.4.

3.3. Epimerization

3.3.1. Preparation of (4*R*,9*aS*)-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one 3. Potassium bis(trimethylsilyl)amide (0.5 M, 1.7 mL, 0.86 mmol) was added to a solution of **4** (100 mg, 0.43 mmol) in THF (3 mL) at −78 °C dropwise. After 30 min at −78 °C, HMPA (150 μL, 0.86 mmol) and acetic acid (125 μL, 2.2 mmol) were added to the reaction sequentially. The reaction mixture was added with saturated ammonium chloride (3 mL) and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (SiO_2: ethyl acetate/hexanes, 1:4; R_f 0.41) to provide compound **3** (75 mg, 75%).[7a] $[\alpha]_D^{25} = +17.4$ (*c* 1, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.33 (m, 5H), 4.28 (br, 1H), 4.18 (dd, $J = 3.5$, 11.0 Hz, 1H), 3.54 (d, $J = 8.1$ Hz, 1H), 2.91 (d, $J = 11.0$ Hz, 1H), 2.75 (d, $J = 10.9$ Hz, 1H), 2.38 (d, $J = 13.0$ Hz, 1H), 1.87 (d, $J = 12.7$ Hz, 1H), 1.71–1.64 (m, 2H), 1.52–1.43 (m, 2H), 1.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 136.5, 128.9, 128.6, 128.4, 72.8, 64.9, 64.7, 52.7, 28.2, 24.9, 24.6.

3.4. General procedure of deprotection

3.4.1. Preparation of (*R*)-pipecolic acid 1. A mixture of compound **4** (50 mg, 0.22 mol) and palladium hydroxide on carbon (20%, 60 mg) in methanol (2.5 mL) and water (250 μL) was put into an autoclave, and hydrogen pressure (5 bar) was applied. After stirred at rt for 24 h, the solution was filtered, concentrated and purified by column chromatography (DOWEX 50WX4-400, eluted with ether and methanol) to provide compound (*R*)-**1** (49 mg, 99%). $[\alpha]_D^{25} = +25.8$ (*c* 1, H_2O), ^1H NMR (200 MHz, D_2O): δ 3.55 (dd, $J = 3.5$, 11.2 Hz, 1H), 3.39 (d, $J = 12.5$ Hz, 1H), 3.0–2.9 (m, 1H), 2.3–2.1 (m, 1H), 1.9–1.5 (m, 5H); ^{13}C NMR (50 MHz, D_2O): δ 174.4, 66.8, 43.4, 26.3, 21.6, 21.3. HRMS (FAB) $[M+H]^+$ ($C_6H_{12}NO_2$) calcd 130.0868, found 130.0866.

3.4.2. (*S*)-Pipecolic acid 1. $[\alpha]_D^{25} = -25.8$ (*c* 1, H_2O), ^1H NMR (200 MHz, D_2O): δ 3.55 (dd, $J = 3.5$, 11.2 Hz, 1H), 3.38 (d, $J = 12.4$ Hz, 1H), 3.0–2.9 (m, 1H), 2.3–2.1 (m, 1H), 1.9–1.5 (m, 5H); ^{13}C NMR (50 MHz, D_2O): δ 174.4, 66.9, 43.4, 26.3, 21.6, 21.3. HRMS (FAB) $[M+H]^+$ ($C_6H_{12}NO_2$) calcd 130.0868, found 130.0871.

3.4.3. (*S*)-2-Methyl-2-piperidinecarboxylic acid 9a. $[\alpha]_D^{25} = -3.7$ (*c* 1, H_2O), ^1H NMR (200 MHz, D_2O): δ 3.22–3.08 (m, 2H), 2.27–2.10 (m, 1H), 1.85–1.55 (m, 5H), 1.47 (s, 3H); ^{13}C NMR (50 MHz, D_2O): δ 185.6, 62.6, 41.7, 31.7, 22.8, 21.2, 19.1; HRMS (FAB) $[M+H]^+$ ($C_7H_{14}NO_2$) calcd 144.1025, found 144.1030.

3.4.4. (*R*)-2-Methyl-2-piperidinecarboxylic acid 9a. $[\alpha]_D^{25} = +3.6$ (*c* 1, H_2O); ^1H NMR (200 MHz, D_2O): δ 3.22–3.08 (m, 2H), 2.20–2.14 (m, 1H), 1.75–1.60 (m, 5H), 1.47 (s, 3H); ^{13}C NMR (50 MHz, D_2O): δ 185.6, 62.6, 41.7, 31.7, 22.8, 21.2, 19.1; HRMS (FAB) $[M+H]^+$ ($C_7H_{14}NO_2$) calcd 144.1025, found 144.1031.

3.4.5. (*S*)-2-Ethyl-2-piperidinecarboxylic acid 9b. $[\alpha]_D^{25} = -11.9$ (*c* 1, H_2O); ^1H NMR (200 MHz, D_2O): δ 3.20–2.89 (m, 2H), 2.26–2.19 (m, 1H), 1.90–1.39 (m, 7H), 0.89 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (50 MHz, D_2O): δ 176.2, 62.9, 38.3, 27.2, 26.6, 17.6, 15.5, 3.0; HRMS (FAB) $[M+H]^+$ ($C_8H_{16}NO_2$) calcd 158.1181, found 158.1174.

3.4.6. (*R*)-2-Ethyl-2-piperidinecarboxylic acid 9b. $[\alpha]_D^{25} = +11.3$ (*c* 1, H_2O); ^1H NMR (200 MHz, D_2O): δ 3.20–2.80 (m, 2H), 2.26–2.19 (m, 1H), 1.90–1.50 (m, 7H), 0.89 (t, $J = 7.6$, 3H); ^{13}C NMR (50 MHz, D_2O): δ 176.1, 63.0, 38.3, 27.2, 26.6, 17.6, 15.5, 3.0; HRMS (FAB) $[M+H]^+$ ($C_8H_{16}NO_2$) calcd 158.1181, found 158.1182.

3.4.7. (*S*)-2-Propyl-2-piperidinecarboxylic acid 9c. $[\alpha]_D^{25} = -22.3$ (*c* 1, H_2O); ^1H NMR (200 MHz, D_2O): δ 3.40–2.75 (m, 3H), 2.26–2.19 (m, 1H), 1.91–1.33 (m, 8H), 0.69 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (50 MHz, D_2O): δ 174.2, 69.5, 53.5, 41.8, 37.6, 32.9, 30.8, 19.9, 18.2; HRMS (FAB) $[M+H]^+$ ($C_9H_{18}NO_2$) calcd 172.1338, found 172.1343.

3.4.8. (*R*)-2-Propyl-2-piperidinecarboxylic acid 9c. $[\alpha]_D^{25} = +21.7$ (*c* 1, D_2O); ^1H NMR (200 MHz, D_2O): δ 3.20–2.75 (m, 3H), 2.09 (m, 1H), 1.91–1.75 (m, 3H), 1.62–1.50 (m, 3H), 1.40 (m, 2H), 0.99–0.85 (m, 3H); ^{13}C NMR (50 MHz, D_2O): δ 174.2, 69.5, 53.5, 42.3, 37.5, 33.2, 30.7, 19.9, 18.3, 8.3; HRMS (FAB) $[M+H]^+$ ($C_9H_{18}NO_2$) calcd 172.1338, found 172.1342.

3.4.9. (*R*)-2-Benzyl-2-piperidinecarboxylic acid 9e. $[\alpha]_D^{25} = -2.8$ (*c* 0.5, MeOH); ^1H NMR (500 MHz, 1:1 D_2O–CD_3OD): δ 7.31–7.19 (m, 5H), 3.16 (d, $J = 14.1$ Hz, 1H), 3.05 (d, $J = 14.1$ Hz, 1H), 2.95–2.91 (m, 2H), 2.41–2.29

(m, 1H), 1.79–1.72 (m, 3H), 1.69–1.62 (m, 2H); ^{13}C NMR (125 MHz, D_2O+CD_3OD): δ 170.0, 138.9, 131.1, 130.0, 127.9, 68.3, 44.0, 35.4, 32.4, 22.7, 20.5; HRMS (FAB) $[M+H]^+$ ($C_{13}H_{18}NO_2$) calcd 220.1338, found 220.1338.

3.5. Diastereoselective alkylation to form chiral quaternary carbon

3.5.1. Preparation of (4*R*,9*aS*)-9a-propyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one 8c. Potassium bis-(trimethylsilyl)amide (0.5 M, 1.7 mL, 0.86 mmol) was added to a solution of **4** (100 mg, 0.43 mmol) in THF (3 mL) at −78 °C dropwise. After 30 min at −78 °C, HMPA (150 μL, 0.86 mmol) and propyl iodide (214 μL, 2.2 mmol) were added to the reaction sequentially. The reaction was maintained at −70 to −78 °C for 1.5 h, and then quenched with saturated ammonium chloride (3 mL), diluted with water (5 mL), and extracted with ethyl acetate. The organic layer was washed with water and saturated sodium chloride, dried over anhydrous sodium sulfate, filtered, concentrated, and purified by column chromatography (SiO_2: ethyl acetate/hexanes) to provide compound **8c** (88 mg, 0.32 mmol 75%). R_f 0.45 (ethyl acetate/hexanes: 1/5); $[\alpha]_D^{25} = -107.3$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.29 (m, 5H), 4.42–4.36 (m, 2H), 4.21–4.17 (m, 1H), 2.41 (br, 2H), 2.13 (dd, $J = 8.5$, 13.0 Hz, 1H), 2.01 (m, 1H), 1.84–1.76 (m, 2H), 1.52–1.42 (m, 3H), 1.23 (m, 3H), 0.96 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 138.9, 128.9, 128.5, 128.3, 71.9, 62.9, 57.0, 44.2, 37.5, 29.7, 25.3, 20.3, 17.5, 14.6; HRMS (FAB) $[M+H]^+$ ($C_{17}H_{24}NO_2$) calcd 274.1807, found 274.1811.

3.5.2. (4*R*,9*aS*)-9a-Methyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one 8a. R_f 0.43 (ethyl acetate/hexanes 1:5); $[\alpha]_D^{25} = -119.9$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.25 (m, 5H), 4.28 (t, $J = 10.6$ Hz, 1H), 4.23 (dd, $J = 4.7$, 10.6 Hz, 1H), 3.97 (dd, $J = 4.7$, 10.6 Hz, 1H), 2.40 (dt, $J = 3.4$, 11.9 Hz, 1H), 2.17 (dt, $J = 3.2$, 11.9 Hz, 1H), 2.11–2.08 (m, 1H), 1.84 (dt, $J = 4.3$, 13.1 Hz, 1H), 1.66–1.63 (m, 1H), 1.59–1.50 (m, 1H), 1.47–1.38 (m, 2H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.7, 137.6, 128.8, 128.4, 128.4, 73.1, 60.3, 58.2, 43.7, 34.5, 29.7, 25.3, 19.9, 13.5; HRMS (EI) $[M]^+$ ($C_{15}H_{19}NO_2$) calcd 245.1416, found 245.1416.

3.5.3. (4*R*,9*aS*)-9a-Ethyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one 8b. R_f 0.45 (ethyl acetate/hexanes 1:5); $[\alpha]_D^{25} = -91.2$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28–7.26 (m, 5H), 4.41 (t, $J = 6.4$ Hz, 1H), 4.39 (m, 1H), 4.18 (dd, $J = 6.4$, 8.4 Hz, 1H), 2.41 (t, $J = 5.4$ Hz, 2H), 2.17–2.08 (m, 2H), 1.91–1.84 (m, 1H), 1.77 (dt, $J = 4.0$, 12.3 Hz, 1H), 1.56 (t, $J = 4.5$ Hz, 1H), 1.52–1.46 (m, 1H), 1.44–1.41 (m, 2H), 0.98 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 138.8, 128.8, 128.1, 127.9, 71.9, 63.2, 56.8, 44.1, 30.5, 25.3, 20.3, 20.0, 8.6; HRMS (FAB) $[M+H]^+$ ($C_{16}H_{22}NO_2$) calcd 260.1651, found 260.1651.

3.5.4. (4*R*,9*aS*)-9a-Allyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one 8d. R_f 0.41 (ethyl acetate/hexanes: 1/7); $[\alpha]_D^{25} = -109.3$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.29 (m, 5H), 5.98–5.79 (m, 1H), 5.17–5.13 (m, 2H), 4.39–4.35 (m, 2H), 4.26–4.07 (m, 1H), 2.83–2.55 (m, 3H), 2.46–2.40 (m, 1H), 2.12 (dt, $J = 3.9$, 13.8 Hz, 1H), 1.81–1.68 (m, 1H), 1.59–1.52 (m, 2H), 1.50–1.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 137.8, 133.4, 128.9, 128.3, 128.1, 118.1, 72.9, 65.5, 56.8, 42.2, 38.0, 30.9, 25.2, 20.5; HRMS (FAB) $[M+H]^+$ ($C_{17}H_{22}NO_2$) calcd 272.1651; found 272.1648.

3.5.5. (4*R*,9*aR*)-9a-Benzyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one 8e. R_f 0.44 (ethyl acetate/hexanes 1:8); $[\alpha]_D^{25} = -143.1$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.25 (m, 7H), 7.25–7.20 (m, 3H), 4.27–4.25 (m, 2H), 4.06 (dd, $J = 6.3$, 7.7 Hz, 1H), 3.40 (d, $J = 13.7$ Hz, 1H), 3.27 (d, $J = 13.7$ Hz, 1H), 2.65 (dt, $J = 3.0$, 11.8 Hz, 1H), 2.53–2.50 (m, 1H), 2.10–2.07 (m, 1H), 1.78–1.69 (m, 3H), 1.55–1.52 (m, 1H), 1.56–1.50 (m, 1H), 1.49–1.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 138.7, 137.0, 130.3, 128.8, 128.3, 128.3, 128.1, 126.8, 72.7, 64.9, 57.6, 44.0, 33.8, 32.3, 25.4, 20.3; HRMS (FAB) $[M+H]^+$ ($C_{21}H_{24}NO_2$) calcd 322.1807, found 322.1804.

3.5.6. (4*R*,9*aR*)-9a-Methyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one 11a. R_f 0.45 (ethyl acetate/hexanes: 1/5); $[\alpha]_D^{25} = -50.3$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.31 (m, 5H), 4.36 (dd, $J = 3.5$, 10.5 Hz, 1H), 4.25 (t, $J = 10.5$ Hz, 1H), 4.16 (dd, $J = 3.5$, 10.6 Hz, 1H), 2.79 (dt, $J = 3.0$, 14.0 Hz, 1H), 2.57–2.54 (m, 1H), 2.16 (m, 1H), 1.75–1.69 (m, 2H), 1.66 (s, 3H), 1.63 (m, 1H), 1.46–1.41 (m, 1H), 1.05 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.6, 137.1, 128.9, 128.5, 128.3, 73.0, 61.1, 56.8, 43.2, 29.0, 22.6, 20.2, 18.9; HRMS (FAB) $[M+H]^+$ ($C_{15}H_{20}NO_2$) calcd 246.1494; found 246.1501.

3.5.7. (4*R*,9*aR*)-9a-Ethyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one 11b. R_f 0.41 (ethyl acetate/hexanes: 1/6); $[\alpha]_D^{25} = -47.2$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.29 (m, 5H), 4.39 (dd, $J = 3.2$, 10.6 Hz, 1H), 4.19 (t, $J = 10.6$ Hz, 1H), 4.10 (dd, $J = 3.2$, 10.6 Hz, 1H), 2.65 (dt, $J = 2.8$, 15.0 Hz, 1H), 2.53 (dd, $J = 1.9$, 15.0 Hz, 1H), 2.31 (m, 1H), 2.17–2.11 (m, 1H), 1.86 (m, 1H), 1.76–1.63 (m, 4H), 1.47–1.36 (m, 1H), 1.02 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 137.4, 128.9, 128.5, 128.3, 73.1, 65.5, 56.4, 42.1, 29.5, 26.7, 20.6, 18.7, 8.9; HRMS (FAB) $[M+H]^+$ ($C_{16}H_{22}NO_2$) calcd 260.1651; found 260.1653.

3.5.8. (4*R*,9*aR*)-9a-Propyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one 11c. R_f 0.44 (ethyl acetate/hexanes: 1/6); $[\alpha]_D^{25} = -49.1$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.33 (m, 5H), 4.38 (dd, $J = 2.7$, 10.5 Hz, 1H), 4.19 (t, $J = 10.5$ Hz, 1H), 4.10 (dd, $J = 2.7$, 10.5 Hz, 1H), 2.65 (dt, $J = 2.0$, 14.6 Hz, 1H), 2.53 (dt, $J = 2.0$, 14.6 Hz, 1H), 2.27 (dt, $J = 3.7$, 12.4 Hz, 1H), 2.13 (dt, $J = 5.3$, 12.9 Hz, 1H), 1.81 (dt, $J = 4.4$, 12.6 Hz, 2H), 1.76–1.71 (m, 3H), 1.64 (m, 1H), 1.45–1.37 (m, 1H), 31–1.26 (m, 2H), 0.97 (t, $J = 7.1$ Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.3, 137.4, 128.9, 128.5, 128.3, 73.1, 65.0, 56.4, 42.3,

35.9, 29.6, 20.7, 18.7, 18.0, 14.3; HRMS (FAB) $[M+H]^+$ ($C_{17}H_{24}NO_2$) calcd 274.1807, found 274.1819.

3.5.9. (4*R*,9*aR*)-9a-Allyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one 11d. R_f 0.46 (ethyl acetate/hexanes: 1/6); $[\alpha]_D^{25} = -23.9$ (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.38–7.25 (m, 5H), 6.08–5.87 (m, 1H), 5.17 (dd, $J = 1.8$, 6.0 Hz, 1H), 5.10 (br 1H), 4.43 (dd, $J = 2.8$, 10.5 Hz, 1H), 4.29 (t, $J = 10.5$ Hz, 1H), 4.09 (dd, $J = 2.8$, 10.5 Hz, 1H), 3.22–3.08 (m, 1H), 2.78 (dt, $J = 2.8$, 13.9 Hz, 1H), 2.58 (dt, $J = 3.8$, 14.4 Hz, 2H), 2.23–2.00 (m, 1H), 1.78–1.62 (m, 3H), 1.48–1.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0, 136.3, 133.5, 129.0, 128.7, 128.4, 118.0, 72.5, 65.7, 56.7, 42.4, 37.8, 29.0, 20.2, 18.5; HRMS (FAB) $[M+H]^+$ ($C_{17}H_{22}NO_2$) calcd 272.1645; found 272.1648.

Acknowledgments

The authors thank Professor K. Burgess (Texas A&M University) for his helpful comments. This research was supported by National Central University and the National Science Council (NSC 93-2113-M-008-010), Taiwan.

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12. The known single crystal X-ray structure of **10e** showed that both C_5-phenyl and C_3-benzyl groups were locked in the axial positions of the oxazinone ring to avoid the unfavored A(1,3)-interaction.[10a] Except the carbons of oxazinone, only the *tert*-butyl carbon clearly showed the minor absorptions in ^{13}C NMR, which indicates that the *tert*-butyl group is more sensitive to the conformational change than the phenyl and isopropyl groups of **10j**. Thus, we suspect that the conformers may be due to the rotation of the urethane group.
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