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# Highly Efficient Asymmetric Access to 1-Azaspiro[4.4]nonane Skeleton

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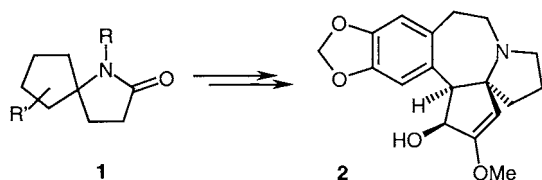
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**Abstract:** Vinylogous Mukaiyama aldol type reaction of chiral non-racemic silyloxypyrroles followed by acidic treatment affords an efficient asymmetric access to 1-azaspiro[4.4]nonanes in high diastereoisomeric excess (up to 79%).

**Keywords:** spiro compounds, asymmetric synthesis, ring expansion, rearrangement, pyrroles

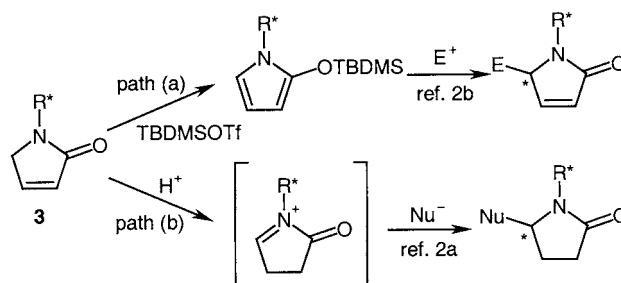
1-Azaspiro[4.4]nonanes are building blocks difficult to access since the formation of quaternary spiro centers has always been a tricky exercise in organic synthesis. Nevertheless, methods to form a spiro center  $\alpha$  to the nitrogen of a pyrrolidine have been developed, and they are based upon a wide variety of different methodologies.<sup>1</sup> Among them, the use of radicals,<sup>1a</sup> cycloadditions,<sup>1b</sup> ring closure reaction,<sup>1c</sup> palladium,<sup>1d</sup> *N*-acyliminiums,<sup>1e</sup> phenol oxidation<sup>1f</sup> and more recently the use of aluminium amide in domino reactions,<sup>1g</sup> have been described. It is noteworthy that only few of these methods are stereoselective<sup>1b,e</sup> and can be used for asymmetric synthesis of natural products containing this moiety.

We planned to develop a new asymmetric entry to 1-azaspiro[4.4]nonane, like the lactam **1**, as a key intermediate in the synthesis of (–)-cephalotaxine **2** (Scheme 1).



Scheme 1

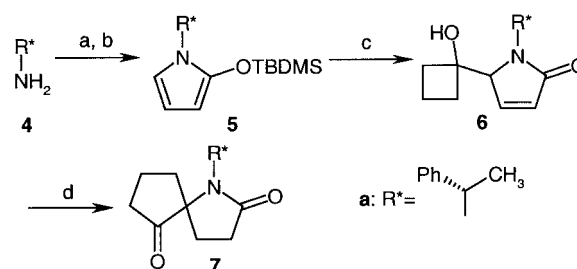
We anticipated that this could be possible by the use of chiral non racemic  $\alpha,\beta$ -unsaturated  $\gamma$ -lactams **3** that we have been developing for some years.<sup>2</sup> The possibility to diastereoselectively substitute  $\gamma$ -lactams **3** at the C-5 position with either an electrophile [via the silyloxypyrrole, path (a)] or a nucleophile [via a *N*-acyliminium, path (b), Scheme 2], permits to construct a quaternary spiro center at this carbon. As a matter of fact, the application of path (a) maintains the  $\alpha,\beta$ -unsaturation, allowing further use of path (b).



Scheme 2

The ring expansion of cyclobutanol derivatives giving rise to spiro compound via a semi-pinacol type reaction is known for a decade. It was well described by Paquette with dihydrofuran and tetrahydropyran derivatives,<sup>3</sup> and recently, an example with piperidine compounds has been published.<sup>4</sup> The key step for this reaction is the formation of a carbocation  $\alpha$  to the carbinol of cyclobutanol, may it be an oxonium or a *N*-acyliminium.

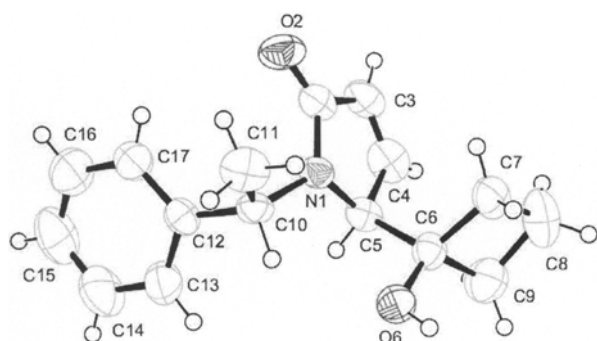
This method appeared very attractive for us, since we anticipated that the cyclobutanol derivative required for the semi-pinacol rearrangement should be the  $\alpha,\beta$ -unsaturated  $\gamma$ -lactam **6** (Scheme 3). It could be quite readily accessible by a vinylogous Mukaiyama aldol condensation of the silyloxypyrrole **5** with cyclobutanone.



**Scheme 3** Reagents and conditions: (a) 2,5-Dihydro-2,5-dimethoxyfuran, HCl, H<sub>2</sub>O, r.t.; (b) TBSOTf, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, r.t.; (c) cyclobutanone, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C; (d) aq conc. HCl, CH<sub>2</sub>Cl<sub>2</sub>, r.t.

In order to check this two step sequence we prepared silyloxypyrrole **5a** derived from  $\alpha$ -methylbenzylamine **4a** using the methodology already reported, namely condensation of **4a** with dimethoxydihydrofuran to give **3a** followed by TBDMSOTf treatment in presence of base. The expected compound (**6a**) was obtained in 85% yield and 83% diastereoisomeric excess when silyloxypyrrole **5a** was reacted with cyclobutanone (Scheme 3).<sup>5</sup>

The major isomer could be crystallized and allowed us to determine the absolute configuration of the new chiral center by X-ray analysis to be *S* (Figure 1).



**Figure 1** Crystal structure of **6a**, determined by X-ray.<sup>6</sup>

Then, **6a** was placed under acidic conditions to achieve the ring expansion. Depending on the reaction conditions (Table 1), we observed either degradation or the elimination product or the expected product as a mixture of two diastereoisomers. The reaction could be carried out under different conditions but the best result was obtained by the use of concentrated hydrochloric acid in dichloromethane (Table 1, entry 7), as described for *N*-tosyliminiums by Dake's group.<sup>4</sup>

We can suggest that water was needed for this reaction, to ensure the spiro center formation instead of elimination (Scheme 4).

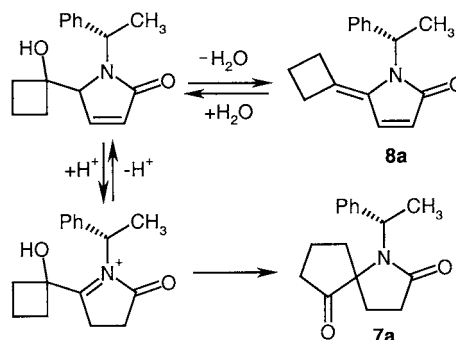
**Table 1** Semi-pinacolic Rearrangement of Cyclobutanol Derivative **6a** Under Various Acidic Conditions

Entry	Acid	Solvent	Temp	<b>7a</b> <sup>a</sup>	<b>8a</b>
1	CSA	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	degradation	
2	PTSA	toluene	reflux	degradation	
3	TfOH	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	degradation	
4	Amberlyst 15	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	70%	30%
5	Amberlyst 15	toluene	r.t.	75%	25%
6	Dowex 50X8-100	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	90%	10%
7	concd HCl	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	>99%	<1%

<sup>a</sup> Product ratios are determined by integration of <sup>1</sup>H NMR spectra.

Unfortunately, despite the excellent chemical yield, the diastereoisomeric excess was modest (20%), and we then decided to investigate other chiral auxiliaries in order to improve this result.

Various silyloxypyrroles **5a–e** were prepared using our standard methodology from amines **4a–e** in 41–73% overall yields. These silyloxypyrroles were engaged in the vinylous Mukaiyama reaction followed by acidic treatment to give rise to the spiro compounds (Table 2).



**Scheme 4**

In all cases, this two steps sequence occurred in very high yield. Using phenylglycinol derivatives allowed us to improve the diastereoisomeric excess of the ring expansion reaction, but a real hit was obtained with (*S*)-1-(1-naphthyl)ethylamine. This chiral amine has already been used in asymmetric syntheses with good stereochemical results<sup>7</sup> and is a suitable source of nitrogen and chirality for our target alkaloid. The diastereoisomeric excess could be further enhanced from 74% to 79%, operating at 0 °C instead of 20 °C, while time to reaction completion was raised from 2 hours to 9 hours. Nevertheless, at –20 °C, no reaction occurred after 24 hours.

**Table 2** Diastereoselectivity in the Rearrangement Reaction to 1-Azaspiro[4.4]nonane Skeleton<sup>8</sup>

Entry	Starting Amine	<b>6</b> , <sup>a,b</sup> Yield (de) %	<b>7</b> , <sup>b</sup> Yield (de) %
1	<b>4a</b> (Ph-CH(CH <sub>3</sub> )-NH <sub>2</sub> )	85 (83)	99 (20)
2	<b>4b</b> (Ph-CH(CH <sub>2</sub> OBz)-NH <sub>2</sub> )	84 (18)	99 (40)
3	<b>4c</b> (Ph-CH(CH <sub>2</sub> OMe)-NH <sub>2</sub> )	75 (48)	99 (63)
4	<b>4d</b> (α-Naph-CH(CH <sub>3</sub> )-NH <sub>2</sub> )	77 (4)	99 (74-79) <sup>c</sup>
5 <sup>d</sup>	<b>4e</b> (α-Naph-CH(CH <sub>2</sub> OMe)-NH <sub>2</sub> )	62 (30)	99 (68)

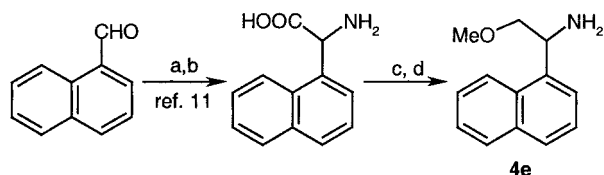
<sup>a</sup> Yield of isolated product.

<sup>b</sup> De determined by integration of corresponding signal in the <sup>1</sup>H NMR spectra of the crude reaction product.

<sup>c</sup> Reaction at 0 °C.

<sup>d</sup> Using racemic material.

Because of the improved de observed with *O*-substituted phenylglycinols, we envisioned the use of *O*-methyl-naphthylglycinol (Table 2, entry 5). Different asymmetric syntheses of naphthylglycinol exist,<sup>9</sup> but we preferred to prepare the more accessible racemic one. Thus, **4e** was prepared in four steps from 1-naphthaldehyde as shown in Scheme 5.

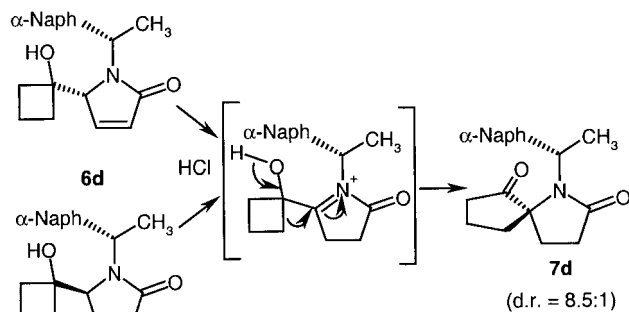


**Scheme 5** Reagents and conditions: (a) NaCN,  $(\text{NH}_4)_2\text{CO}_3$ , EtOH/ $\text{H}_2\text{O}$  50/50, 50 °C, 24 h; (b) NaOH,  $\text{H}_2\text{O}$ , reflux, 2.5 h; (c) LAH, THF (89%); (d) KH, THF, overnight then MeI (75%).

The amino acid was first obtained from the corresponding aldehyde through a modified Strecker synthesis as described.<sup>10</sup> The reduction of the carboxylic acid function by  $\text{LiAlH}_4$  furnished the aminoalcohol which was regioselectively methylated<sup>11</sup> (KH, THF, MeI) to give **4e** in 67% for the two steps.

Unfortunately this new chiral auxiliary did not allow any improvement in the diastereoselectivity of the semi-pinacol rearrangement.

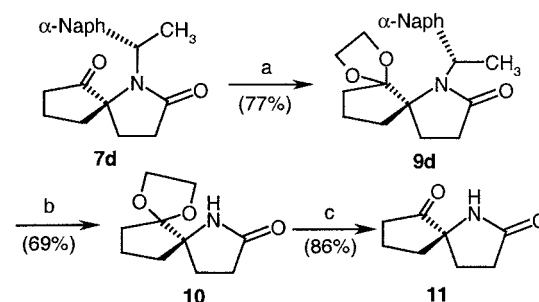
As suggested by the mechanism of the rearrangement and by the discrepancy between diastereoisomeric excesses of compounds **6** and **7**, the stereochemical information of compound **6** was lost in the semi-pinacol rearrangement. This was definitively proved by placing each diastereoisomer of **5d**, easily separable by crystallization, under the same experimental conditions (Scheme 6). We did not notice any measurable difference between the two crude products, proving that there was no kind of survival of the initial configuration.<sup>12</sup> So, the chirality of the new center was only controlled by the chiral auxiliary, due to the free rotation in the intermediate *N*-acyliminium.



**Scheme 6**

Major diastereoisomer **7d** could be easily separated through crystallization by triturating the crude product in ether (68% of the diastereopure product could be obtained). We then derivatised it, on the way to determine the absolute configuration of the newly created spiro center (Scheme 7). First, the ketone was protected as the cyclic ketal **9d** with ethylene glycol (77% yield), and the latter was treated with lithium in liquid ammonia,<sup>13</sup> to remove the chiral auxiliary. The ketal **10** (69% yield) could be deprotected to obtain the simple spiro amide **11** in 86% yield.

This compound was described in the Nagasaka's cephalotaxine synthesis and the comparison of its optical rotation ( $[\alpha]_D -64$ , lit.<sup>14</sup>  $-68$ ) allowed us to assign the *R*-configuration to the spiro center of **7d**. Following identical process, we also attributed the *R*-configuration to the spiro center of **7c**.

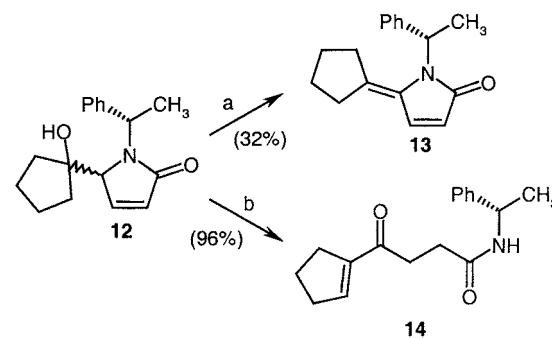


**Scheme 7** Reagents and conditions: (a) Ethyleneglycol, PTSA, toluene, reflux; (b) Li/ $\text{NH}_3$ , ethanol,  $-78$  °C; (c) HOAc/ $\text{H}_2\text{O}$  50/50, reflux.

Since the ring enlargement of cyclopentanol derivatives has been described with dihydrofuran compounds<sup>3</sup> we envisaged this reaction starting with our  $\gamma$ -lactam.

The aldol product **12** was readily obtained from the silyloxypyrrole **5a** under the same conditions as above, in good yield (78%) and an excellent diastereoisomeric excess (90%).

However, this compound did not undergo rearrangement reaction. By varying the conditions, we obtained either the elimination product or the product of hydrolysis of the *N*-acyliminium moiety<sup>4</sup> (Scheme 8).



**Scheme 8** Reagents and conditions: (a) Amberlyst 15,  $\text{CH}_2\text{Cl}_2$ , r.t.; (b) concd HCl, THF, r.t.

To summarize, we developed a highly efficient method for the diastereoselective formation of 1-aza-spiro[4.4]nonanes, allowing us to construct the spiro bicyclic system of (–)-cephalotaxine. Work is on progress to complete a new asymmetric synthesis of (–)-cephalotaxine based on this methodology.

## Acknowledgement

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- (4) Fenster, M. D. E.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2001**, 3, 2109.
- (5) **Typical Procedure for Silyloxypyrroles 5.** To a solution of 2,5-dimethoxy-2,5-dihydrofuran (1 equiv) and chiral amine **4a-c-e** (1 equiv) in water (0.25 M) was added a concd solution of HCl (1.5 equiv). The mixture was stirred at r.t. for 3 h then neutralized with solid NaHCO<sub>3</sub> and extract with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over MgSO<sub>4</sub> and the solvent distilled off. A red oil, mixture of the  $\alpha,\beta$  and  $\beta,\gamma$  unsaturated lactams was then obtained. *tert*-Butyldimethylsilyl triflate (1 equiv) was slowly added to a solution of either the crude product or the purified lactams (1 equiv) and NEt<sub>3</sub> (2 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (0.1 M) and the mixture was stirred at r.t. for 1 h. The solvent was evaporated under vacuum and the residue purified by filtration on a pad of alumina with a mixture of heptane and EtOAc. (Note: silyloxypyrroles are used to be kept under argon at -20 °C). **Analyses for 5d:** [ $\alpha$ ]<sub>D</sub><sup>25</sup> +11.7 (c 0.69, CH<sub>2</sub>Cl<sub>2</sub>). Mp = 97 °C (heptane-EtOAc). IR (KBr):  $\nu$  = 2929, 2858, 1560, 1492, 1438 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = -0.05 (s, 3 H), 0.23 (s, 3 H), 0.80 (s, 9 H), 1.89 (d, *J* = 7.0 Hz, 3 H), 5.31 (dd, *J* = 2.0, 3.6 Hz, 1 H), 6.01 (t, *J* = 3.5 Hz, 1 H), 6.16 (q, *J* = 7.0 Hz, 1 H), 6.35 (dd, *J* = 1.9, 3.4 Hz, 1 H), 7.10 (d, *J* = 7.2 Hz, 1 H), 7.42 (t, *J* = 7.9 Hz, 1 H), 7.50–7.55 (m, 2 H), 7.77 (d, *J* = 8.3 Hz, 1 H), 7.88 (d, *J* = 7.4 Hz, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = -5.0, -4.6, 18.2, 21.4, 25.7, 49.5, 87.7, 105.2, 109.8, 123.2, 125.8, 126.5, 128.1, 129.1, 131.0, 134.1, 139.7, 142.2. HRMS (CI, NH<sub>3</sub>): *m/z* calcd for C<sub>22</sub>H<sub>30</sub>NOSi (MH<sup>+</sup>): 352.2097. Found: 352.2101. **Typical Procedure for Cyclobutanols 6.** To a solution of silyloxypyrrole **5a-e** (1 equiv) in anhyd CH<sub>2</sub>Cl<sub>2</sub> (0.15 M) with 3 Å MS, under argon, was added cyclobutanone (or cyclopentanone) (1.6 equiv). After 15 min at r.t., the solution was cooled at -78 °C and BF<sub>3</sub>·OEt<sub>2</sub> (1.5 equiv) was added in the course of 15 min. The solution was stirred at -78 °C for 2 h and allowed to warm to 0 °C. The reaction was quenched by addition of H<sub>2</sub>O, the aq phase was separated and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic phases were combined, dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under vacuum. The resulting oil was purified by flash chromatography. **Analyses for 6d: Minor diastereoisomer:** [ $\alpha$ ]<sub>D</sub><sup>25</sup> -264.1 (c 0.52, CHCl<sub>3</sub>). Mp = 245 °C (CH<sub>2</sub>Cl<sub>2</sub>). IR (KBr):  $\nu$  = 3388, 2976, 2937, 1660 cm<sup>-1</sup>. MS (CI, NH<sub>3</sub>): *m/z* = 308 (MH<sup>+</sup>), 238 (MH<sup>+</sup> - C<sub>4</sub>H<sub>6</sub>O). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 0.35–0.5 (m, 1 H), 1.01 (s, 1 H, D<sub>2</sub>O exch.), 1.35–1.55 (m, 2 H), 1.55–1.70 (m, 2 H), 1.78 (d, *J* = 7.1 Hz, 3 H), 1.85–2.00 (m, 1 H), 4.25 (t, *J* = 1.6 Hz, 1 H), 6.30 (m, 2 H), 6.94 (dd, *J* = 7.0, 6.0 Hz, 1 H), 7.40–7.60 (m, 4 H), 7.83 (d, *J* = 8.1 Hz, 1 H), 7.90 (d, *J* = 8.3 Hz, 1 H), 8.23 (d, *J* = 8.4 Hz, 1 H). <sup>13</sup>C NMR (75 MHz, DMSO):  $\delta$  = 17.7, 24.4, 36.2, 40.6, 55.1, 74.8, 81.3, 128.5, 130.3, 130.8, 131.7, 132.9, 134.3, 134.5, 136.1, 139.0, 143.5, 151.3, 177.6. **Major diastereoisomer:** [ $\alpha$ ]<sub>D</sub><sup>25</sup> -13.8 (c 0.97, CHCl<sub>3</sub>). Mp = 196–198 °C (Et<sub>2</sub>O). IR (KBr):  $\nu$  = 3382, 2977, 2934, 1658, 1394 cm<sup>-1</sup>. MS (CI, NH<sub>3</sub>): *m/z* = 308 (MH<sup>+</sup>), 238 (MH<sup>+</sup> - C<sub>4</sub>H<sub>6</sub>O). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.36 (m, 1 H), 1.80–2.10 (m, 5 H), 1.75 (s, 1 H), 1.86 (d, *J* = 7.0 Hz, 3 H), 3.51 (t, *J* = 1.5 Hz, 1 H), 6.07 (q, *J* = 7.0 Hz, 1 H), 6.28 (dd, *J* = 1.6, 6.0 Hz, 1 H), 6.81 (dd, *J* = 1.8, 6.0 Hz, 1 H), 7.47 (m, 3 H), 7.63 (m, 2 H), 7.84 (m, 2 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 13.6, 19.1, 31.9, 36.2, 49.0, 69.6, 75.9, 123.2, 125.2, 125.8, 126.1, 127.3, 128.5, 129.1, 129.2, 132.0, 134.0, 136.2, 145.7, 173.3. Anal. Calcd for C<sub>20</sub>H<sub>21</sub>NO<sub>2</sub>: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.03; H, 7.06; N, 4.60.
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- (8) **Typical Procedure for Spiro Compounds 7.** To a solution of cyclobutanol **6a-e** (1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (0.05 M) was added concd aq HCl (1.5 equiv). After 9 h at 0 °C, the solvent was removed under vacuum. The crude product was redissolved twice in CH<sub>2</sub>Cl<sub>2</sub> and reevaporated to eliminate trace amount of acid. **Analyses for 7d** (crystallized from Et<sub>2</sub>O): [ $\alpha$ ]<sub>D</sub><sup>25</sup> -48.4 (c 1.04, CHCl<sub>3</sub>). Mp = 140 °C (Et<sub>2</sub>O). IR (KBr):  $\nu$  = 2968, 1750, 1679, 1380, 1347, 780 cm<sup>-1</sup>. MS (CI, NH<sub>3</sub>): *m/z* = 308 (MH<sup>+</sup>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.07–1.17 (m, 2 H), 1.34–1.55 (m, 2 H), 1.62 (ddd, *J* = 6.5, 8.5, 12.3 Hz, 1 H), 1.67 (d, *J* = 7.0 Hz, 3 H), 1.87 (ddd, *J* = 9.5, 11.6, 18.9 Hz, 1 H), 1.93 (ddd, *J* = 6.8, 8.9, 12.3 Hz, 1 H), 2.23 (dd, *J* = 6.1, 18.9 Hz, 1 H), 2.43 (dd, *J* = 6.8, 8.5, 16.8 Hz, 1 H), 2.53 (ddd, *J* = 6.5, 8.9, 16.8 Hz, 1 H), 6.25 (q, *J* = 7.1 Hz, 1 H), 7.30–7.60 (m, 4 H), 7.83 (d, *J* = 9.7 Hz, 1 H), 7.79 (d, *J* = 7.6 Hz, 1 H), 8.00 (d, *J* = 8.3 Hz, 1 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.8, 18.9, 29.0, 31.7, 32.3, 35.7, 47.5, 72.3, 124.0, 125.1, 125.9, 126.3, 127.2, 129.1, 129.3, 132.7, 133.9, 136.1, 175.7, 217.0. Anal. Calcd for C<sub>20</sub>H<sub>21</sub>NO<sub>2</sub>: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.96; H, 7.15; N, 4.41.
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