Suzuki–Miyaura Coupling Based Enantioselective Synthesis of (+)-*epi*-Clausenamide and the Enantiomer of Its 3-Deoxy Analogue

Lu Zhang, Yumei Zhou, Xiaoming Yu*

State Key Laboratory of Bioactive Substance and Function of Natural Medicine, Beijing Key Laboratory of Active Substance Discovery and Drugability Evaluation, Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, P. R. of China
Fax +86(10)63017757; E-mail: mingxyu@imm.ac.cn

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Abstract: The first enantioselective synthesis of two biologically interesting close analogues of clausenamide, namely (+)-*epi*-clausenamide and (–)-3-deoxy-*epi*-clausenamide, was reported. Key steps of the synthesis included construction of the chiral pyrrolinone intermediates from D- and L-serine derivatives, introduction of the C4-phenyl by Suzuki–Miyaura coupling and establishment of the C6 configuration by a *threo*-selective Grignard reaction. Optimization of the key Suzuki–Miyaura coupling reaction was described in detail.

Key words: (+)-*epi*-clausenamide, (–)-3-deoxy-*epi*-clausenamide, nootropics, osteoporosis, Suzuki–Miyaura coupling

Clausenamide [(±)-**1**, Figure 1] is a densely substituted pyrrolinone natural product found in the aqueous extract of Chinese herb medicine *Clausen alassium* (lour) skeels.[1] The compound contains four chiral centers, but was isolated as a racemate. Instead of the originally anticipated hepatoprotective property, the *levo*-enantiomer of clausenamide [(–)-**1**, Figure 1] was later found to be a useful nootropics.[2] It exhibited remarkable long-term potentiation (LTP) enhancing capability in hippocampus of rats,[3] and is now under clinical trial in China for its potential in treatment of Alzheimer's disease. (+)-*epi*-Clausenamide [(+)-**2**, Figure 1] is a non-natural diastereomer of (–)-**1** that showed twice the magnitude of LTP enhancement as that of (–)-**1**, and thereby a more promising nootropics.[3] Moreover, (–)-**3** (Figure 1), the 3-deoxy analogue of (–)-**2**, was identified as an inhibitor of 17-β-hydroxy-steroid dehydrogenase II (17-β-HSD II) and therefore could be useful in preventing the onset of osteoporosis.[4] Based upon these biological findings, enantioselective synthesis of (+)-**2** and (–)-**3** merits an interesting subject of study.

Hartwig and Born first reported the total synthesis of (±)-**1**.[5] Thereafter, Huang et al. contributed a more advanced five-step biomimetic synthesis, in which the cyclization of **4** was the key step to deliver the precursor named as clausenamidone (**5**, Figure 1).[6] Huang's strategy was later utilized in several asymmetric syntheses of (+)- and (–)-**1** in combination with varied asymmetric accesses to the 2,3-epoxy-cinnamyl moiety in the molecule of **4** (or its equivalence).[7] However, the same strategy is not applicable in the synthesis of **2** and **3** albeit their high resemblance to **1**, because the reduction of **5** is highly *erythro*-selective and compound **1** is usually the only product regardless the reducing agent. Therefore, different synthetic routes are to be sought. We recently finished an optical resolution based synthesis of (+)-**2**,[8] and herein report a Suzuki–Miyaura coupling based enantioselective synthesis of (+)-**2** and (–)-**3** from D- and L-serine, respectively.

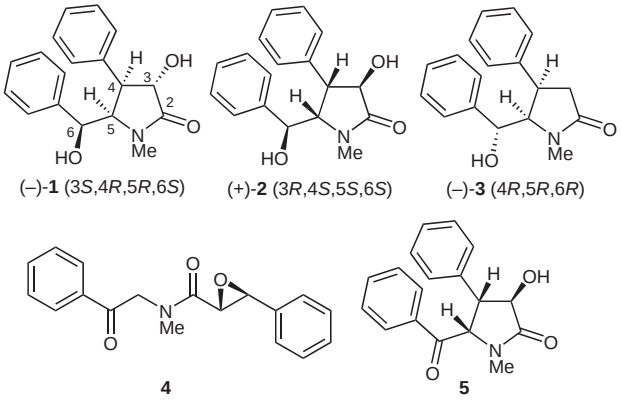

Figure 1 Structure of clausenamide, bioactive unnatural analogues, and synthetic precursors

As illustrated in Scheme 1, our synthetic plan for **2** and **3** started with the known condensation of serine derivative **6** with Meldrum's acid, which gives β-keto lactam **7**. For both antipodes of **6** are readily available, it is easy to define the C5 configuration in the molecule of **7**. After transfer of **7** into a suitable sulfonate (**8**), the C4-phenyl was to be introduced by Suzuki–Miyaura coupling to give **9** in enantiomerially pure form. Catalytic hydrogenation of **9** was then expected to give rise to the C4–C5 *cis* geometry (**10**). The *threo*-selective Grignard reaction of **10** first observed by Hartwig and Born,[5] nevertheless, would be utilized to introduce the C6-phenyl to afford **3**, and finally the C3–OH was to be installed by oxidation of the metal enolate to accomplish the enantioselective synthesis of **2**.

Based upon this plan, L-serine derivative L-**6** was selected the starting material of (–)-**3** (Scheme 2). The procedure previously reported by Ma[9] was followed to carry out the condensation of (+)-**6** with Meldrum's acid and the following ring closure. Because the resulting β-keto lactam suffered significant decomposition during chromato-

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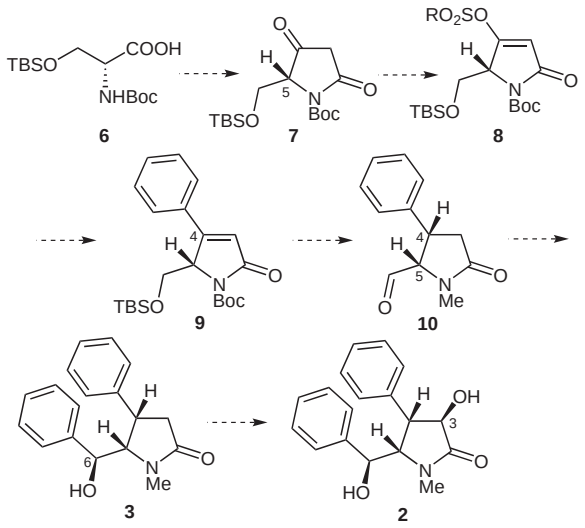
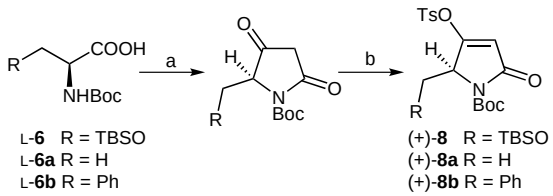


Scheme 1 Synthetic plan for **2** and **3**

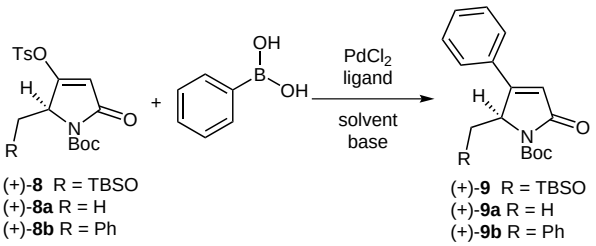
graphic purification, it was subjected to the next step of elaboration without isolation, and stable (+)-**8** was obtained in 74% yield over two steps.



Scheme 2 *Reagents and conditions*: (a) Meldrum's acid (1.0 equiv), EDCI (1.2 equiv), DMAP (1.48 equiv), r.t., 5% $KHSO_4$ workup, and then heated to reflux in EtOAc; (b) TsCl (1.2 equiv), Et_3N (1.3 equiv), 0 °C.

Simple tosylate substrates that differ from (+)-**8** only by lacking the C5 substituents were known to be able to undergo successful Suzuki coupling with phenylboronic acid in the presence of $PdCl_2$/DPPF.[10] However, our initial attempts on the reaction of (+)-**8** proved to be failure since no desired product was detected (Table 1, entry 1). In order to evaluate the quality of our sample of $PdCl_2$/DPPF, we synthesized substrates **8a** and **8b** (Scheme 2), both bearing all-carbon substituent at C5, and found both of them afforded coupling products **9a** and **9b** in good yield (Table 1, entries 2 and 3), implying that the presence of an oxygen-containing substituent at C5 exerted strong impact on the behavior of (+)-**8** during the process of $PdCl_2$/DPPF catalysis. Therefore, other commonly employed bidentate phosphine ligands, including DPPE, DPPB, and DPPP, were examined (Table 1, entries 4–6,), and fortunately, the last one was found to be helpful, even though the yield of (+)-**9** was extremely low. Upon further screening of a variety of additive bases other than Cs_2CO_3 (Table 1, entries 7–10),[11] we found that CsF helped to deliver the desired (+)-**9** in an optimal yield of 60% without affecting the TBS group. Furthermore, additional experiments revealed that a better yield could be achieved by us-

Table 1 Optimization of the Suzuki Coupling[a]



(+)-**8** R = TBSO
(+)-**8a** R = H
(+)-**8b** R = Ph

(+)-**9** R = TBSO
(+)-**9a** R = H
(+)-**9b** R = Ph

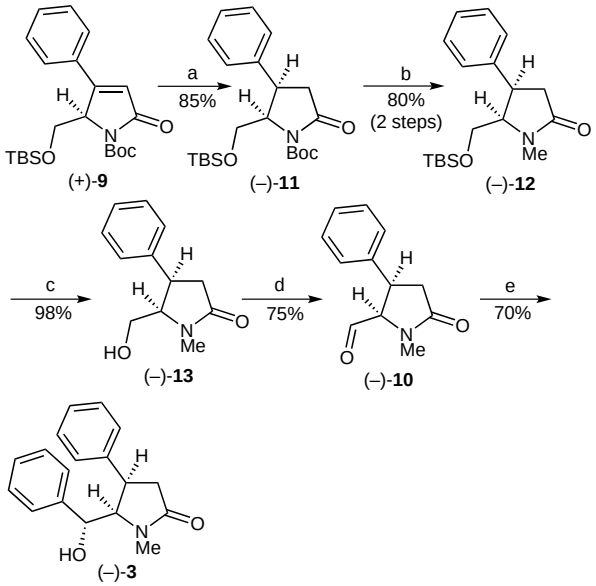
Entry	Tosylate	Ligand	Base[b]	Solvent[c]	Yield (%)[d]
1	**8**	DPPF	Cs_2CO_3	THF–H_2O (5:1)	0
2	**8a**	DPPF	Cs_2CO_3	THF–H_2O (5:1)	86
3	**8b**	DPPF	Cs_2CO_3	THF–H_2O (5:1)	81
4	**8**	DPPE	Cs_2CO_3	THF–H_2O (5:1)	0
5	**8**	DPPB	Cs_2CO_3	THF–H_2O (5:1)	0
6	**8**	DPPP	Cs_2CO_3	THF–H_2O (5:1)	8
7	**8**	DPPP	KF	THF–H_2O (5:1)	10
8	**8**	DPPP	K_2CO_3	THF–H_2O (5:1)	39
9	**8**	DPPP	NaOH	THF–H_2O (5:1)	48
10	**8**	DPPP	CsF	THF–H_2O (5:1)	62
11	**8**	DPPP	CsF	benzene–H_2O (5:1)	73

[a] Reaction conditions: phenylboronic acid (1.5 equiv), $PdCl_2$ (15 mol%), ligand (15 mol%), base (3.0 equiv), 65 °C.
[b] Other bases proved ineffective: KBr, NaOH, KOH, K_3PO_4.
[c] The $PdCl_2$/DPPP/CsF-promoted reaction failed to give coupling product in DMF.
[d] Isolated yield.

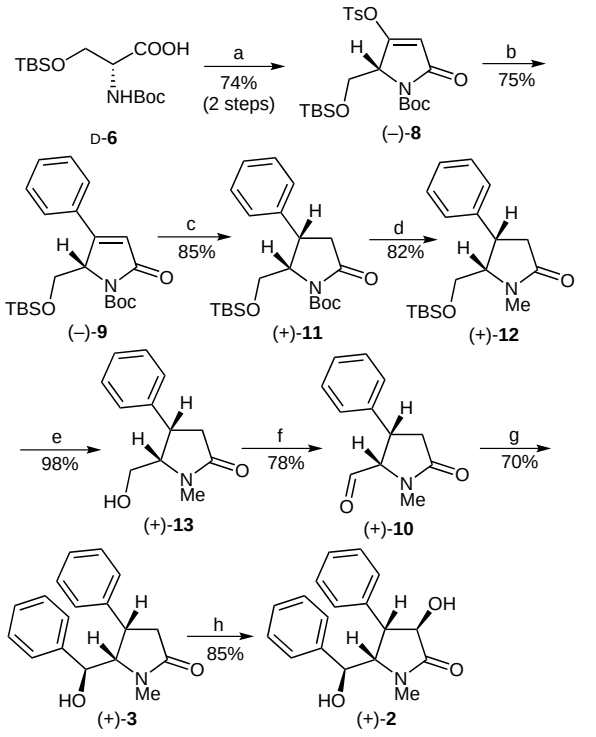
ing a benzene–H_2O mixture as solvent (Table 1, entry 11).[12]

With the key Suzuki–Miyaura coupling reaction optimized, we went on embarking the synthesis of (–)-**3** (Scheme 3). Compound (+)-**9** was hydrogenated at medium pressure (3.45 bar) in the presence of 10% Pd/C to give 4,5-*cis*-substituted (–)-**11** in 85% yield,[13] which was subsequently treated with TFA to remove the *N*-Boc group and N-methylated with MeI and NaH to give (–)-**12** in 80% overall yield.[14] After preparation of (–)-**13** in 98% yield from (–)-**12** by cleavage of the TBS ether with TBAF, the chemistry Hartwig and Born described[5] in racemic form was executed. Hence, (–)-**13** was subjected to the Swern oxidation delivering (–)-**14** and then Grignard reaction with phenyl magnesium bromide. As it was expected, the reported *threo*-selective addition was highly reproducible, and (–)-**3**[15] was isolated in 53% yield over two steps.

After successful enantioselective synthesis of (–)-**3**, we moved on to the preparation of (+)-**2** by following the same sequence. As it is shown in Scheme 4, the 11-step transformation starting from D-**6** to (+)-**3** proved straight-



Scheme 3 *Reagents and conditions*: (a) H_2 (3.45 bar), 10% Pd/C; (b) 1. TFA (1.2 equiv), CH_2Cl_2, 30 min, $NaHCO_3$ workup; 2. MeI (1.3 equiv), NaH (1.3 equiv), DMF; (c) TBAF (1.1 equiv), THF; (d) oxalyl chloride (1.5 equiv), DMSO (2.0 equiv), Et_3N (3.0 equiv), –78 °C; (e) PhMgBr (1.0 equiv), THF, 0 °C.



Scheme 4 *Reagents and conditions*: (a) 1. Meldrum's acid (1.0 equiv), EDCI (1.2 equiv), DMAP (1.48 equiv); 2. TsCl (1.2 equiv), Et_3N (1.3 equiv), 0 °C; (b) phenylboronic acid (1.5 equiv), $PdCl_2$ (15 mol%), DPPP (15 mol%), CsF (3.0 equiv), benzene–H_2O, reflux; (c) H_2, 10% Pd/C, 3.45 bar; (d) 1. TFA (1.2 equiv), CH_2Cl_2, 30 min, $NaHCO_3$ workup; 2. MeI (1.3 equiv), NaH (1.3 equiv), DMF; (e) TBAF (1.1 equiv), THF; (f) oxalyl chloride (1.5 equiv), DMSO (2.0 equiv), Et_3N (3.0 equiv), –78 °C; (g) PhMgBr (1.0 equiv), THF, 0 °C; (h) LDA (3.0 equiv), 2-(methylsulfonyl)-3-phenyl-1,2-oxaziridine (4.0 equiv), THF, –78 °C.

forward, giving the precursor of target molecule in 18.2% overall yield. Interestingly, the final step to (+)-**2** appeared to be different from literature report, because a similar Davis oxidation of lithium enolate was reported ineffective,[5] but in our case the desired product (+)-**2**[16] was isolated in 85% yield when the same oxidant was applied after treatment of (+)-**3** with excessive LDA.

In conclusion, we report for the first time the successful enantioselective synthesis of (+)-**2**[17] and (–)-**3**, two biologically important close analogues of clausenamide, from D- and L-serine derivatives, respectively. With the main content assigned to the optimization of a previously unknown Suzuki–Miyaura coupling reaction, this study provided a convenient approach to the target molecules and thereby will help facilitate the related biological studies.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **Typical Procedure for Suzuki–Miyaura Coupling:**
Compound (+)-**8** (100 mg, 0.2 mmol, 1.0 equiv), phenylboronic acid (37 mg, 0.3 mmol, 1.5 equiv), $PdCl_2$ (3.6 mg, 0.02 mmol, 0.1 equiv), and DPPP (8.3 mg, 0.02 mmol, 0.1 equiv) were placed in a three-necked flask with a magnetic stirring bar and a condenser. The reactor was evacuated with an oil pump and then flushed with argon. After this process was repeated for three times, benzene (2.0 mL) was added through a syringe. Upon a clear solution was formed under stirring, CsF (91 mg, 3.0 equiv in H_2O, 0.4 mL) was added through a syringe. The reaction mixture was stirred at r.t. for 1 h and then heated to reflux (about 12 h). After cooling to r.t., the reaction mixture was washed with a sat. aq solution of $NaHCO_3$ (2.0 mL), brine (2.0 mL), and dried over Na_2SO_4. Removal of the solvent in vacuo and chromatography (PE–EtOAc, 10:1) gave (+)-**9** (59 mg) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.455 (5 H, s, ArH), 6.297 (1 H, s, C3-H), 5.090 (1 H, s, C5-H), 4.231 (1 H, dd, *J* = 2.4, 10.4 Hz, C6-H), 3.808 (1 H, d, *J* = 10.4 Hz, C6-H), 1.590 (9 H, s, BocH), 0.731 (9 H, s, *t*-BuSi), –0.158 (3 H, s, CH_3Si), –0.228 (3 H, s, CH_3Si). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.063, 159.630, 149.756, 131.365, 130.571, 128.968, 127.122, 121.505, 82.754, 63.401, 60.440, 28.206, 25.581, 17.996, –5.875. ESI-HRMS: *m/z* calcd for $[C_{22}H_{33}NO_4Si + Na]^+$: 426.2071; found: 426.2060. $[\alpha]_D^{20}$ +55.0 (*c* 0.64, $CHCl_3$).

(13) **(2*R*,3*R*)-*tert*-Butyl-2-[(*tert*-butyldimethylsilyloxy)-methyl]-5-oxo-3-phenylpyrrolidine-1-carboxylate [(-)-11]:**
To a solution of (+)-**9** (400 mg, 1.0 mmol) in MeOH (20 mL), 10% Pd/C (40 mg) was slowly added. The mixture was hydrogenated (3.45 bar) for 12 h. After removal of the solid material, the filtrate was evaporated to dryness. Chromatograph of the residue (PE–EtOAc, 20:1) gave (–)-**11** (345 mg, 85%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.388 (5 H, m, ArH), 4.311 (1 H, d, *J* = 7.8 Hz, C6-H), 3.942 (1 H, d, *J* = 10.8 Hz, C6-H), 3.786 (1 H, m, C5-H), 3.289 (2 H, m, C3-H, C4-H), 2.642 (1 H, dd, *J* = 8.7, 16.5 Hz, C3-H), 1.613 (9 H, s, BocH), 0.911 (9 H, s, *t*-BuSi), –0.001 (3 H, s, CH_3Si), –0.021 (3 H, s, CH_3Si). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.975, 149.991, 136.679, 128.440, 128.127, 127.350, 82.768, 62.704, 60.348, 41.252, 37.340, 28.068, 25.731, 18.034, –5.884, –5.923. ESI-HRMS: *m/z* calcd for $[C_{22}H_{35}NO_4Si + Na]^+$: 428.2228; found: 426. 2207. $[\alpha]_D^{20}$ –3.0 (*c* 0.99, $CHCl_3$).

(14) **(4*R*,5*R*)-5-[(*tert*-Butyldimethylsilyloxy)methyl]-1-methyl-4-phenylpyrrolidin-2-one [(–)-12]:**
To a stirred solution of (–)-**11** (1.0 g, 2.5 mmol) in CH_2Cl_2 (17.0 mL) was added TFA (0.48 mL, 2.0 equiv in CH_2Cl_2 (4.8 mL)] through a syringe at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and then diluted with EtOAc (20.0 mL). A sat. aq solution of $NaHCO_3$ (ca. 1.0 mL) was added dropwise to adjust the pH to 7. The organic phase was then washed with H_2O (40.0 mL) and brine (40.0 mL) and dried over Na_2SO_4. Evaporation of the solvent in vacuo afforded a white solid (860 mg). The solid was dissolved in DMF (10.5 mL) and cooled to 0 °C. NaH (147 mg, 1.3 mmol) was carefully added to the solution under argon. The mixture was stirred until the evolution of gas had ceased. MeI (0.31 mL, 1.3 equiv) was added through a syringe, and the reaction was stirred at r.t. until TLC showed complete conversion. A sat. aq NH_4Cl solution (ca. 5.0 mL) was added dropwise until pH 6. After the most amount of DMF was removed by evaporation under reduced pressure, the reaction mixture was diluted with EtOAc (10.0 mL) and washed with H_2O (10 mL). The aqueous phase was then extracted with EtOAc (5 × 10 mL). The organic layers were combined and washed with brine (50.0 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo and chromatography (PE–EtOAc, 4:1) gave (–)-**12** (635 mg, 80% in 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.358–7.274 (5 H, m, PhH), 3.760 (1 H, m, C4-H), 3.692 (1 H, m, C5-H), 3.562 (1 H, d, *J* = 11.2 Hz, C6-H), 3.251 (1 H, d, *J* = 10.8 Hz, C6-H), 2.977 (1 H, m, C3-H), 2.920 (3 H, s, NMe), 2.535 (1 H, dd, *J* = 8.4, 15.6 Hz, C3-H), 0.842 (9 H, s, *t*-BuSi), –0.091 (3 H, s, CH_3Si), –0.121 (3 H, s, CH_3Si). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.718, 137.498, 128.493, 128.051, 127.803, 127.624, 126.755, 64.983, 59.452, 41.419, 35.213, 28.091, 25.404, 17.630, –6.151, –6.292. ESI-HRMS: *m/z* calcd for $[C_{18}H_{29}NO_2Si + H]^+$: 320.2040; found: 320.2038. $[\alpha]_D^{20}$ –21.3 (*c* 1.11, $CHCl_3$).

(15) **Data for (–)-3:**
^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.29 (3 H, s, NCH_3), 2.278 (1 H, d, *J* = 8.4 Hz, C3-H), 3.057 (1 H, t, *J* = 13.6 Hz, C3-H), 3.814 (1 H, dd, *J* = 8.4, 19.2 Hz, C4-H), 4.161 (1 H, s, C6-H), 5.348 (1 H, d, *J* = 4.0 Hz, OH), 7.458–7.185 (10 H, m, PhH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.351, 141.957, 137.607, 128.297, 127.930, 127.686, 126.862, 126.832, 124.725, 71.307, 70.025, 43.026, 34.586, 30.602. ESI-HRMS: *m/z* calcd for $[C_{18}H_{19}NO_2 + H]^+$: 282.14920; found: 282.14966. $[\alpha]_D^{20}$ –139.2 (*c* 0.50, MeOH).

(16) **Data for (+)-2:**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.623–7.375 (10 H, m, PhH), 5.366 (1 H, d, *J* = 10.4 Hz, C6-H), 4.639 (1 H, s, C5-H), 4.116 (1 H, d, *J* = 8.0 Hz, C3-H), 3.845 (1 H, t, *J* = 9.2 Hz, C4-H), 2.489 (3 H, s, NMe). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.913, 136.126, 128.936, 128.497, 128.127, 127.476, 125.047, 109.630, 70.550, 70.382, 68.319, 52.414, 31.534. ESI-HRMS: *m/z* calcd for $[C_{18}H_{19}NO_3 + H]^+$: 298.14432; found: 298.14426. $[\alpha]_D^{20}$ +205.3 (*c* 0.48, MeOH); lit.[3] $[\alpha]_D^{20}$ +201 (*c* 0.25, MeOH).

(17) Both (+)- and (–)-**3** gave a single diastereomer when converted into their respective ester form with (*S*)-*O*-acetylmandelic acid, as indicated by ^{1}HNMR (see Supporting Information). Both esters were then hydrolyzed, and the recovered samples of (+)- and (–)-**3** showed literally identical optical rotation on comparison to that of the original samples {(+)-**3**: $[\alpha]_D^{20}$ +137.0 (*c* 0.23, MeOH) vs. $[\alpha]_D^{20}$ +138.9 (*c* 0.62, MeOH); (–)-**3**: $[\alpha]_D^{20}$ –138.0 (*c* 0.45, MeOH) vs. $[\alpha]_D^{20}$ –139.2 (*c* 0.50, MeOH)}. Therefore, the possibility of epimerization during the process of synthesis, particularly the steps to (–)- and (+)-**8**, was precluded.

