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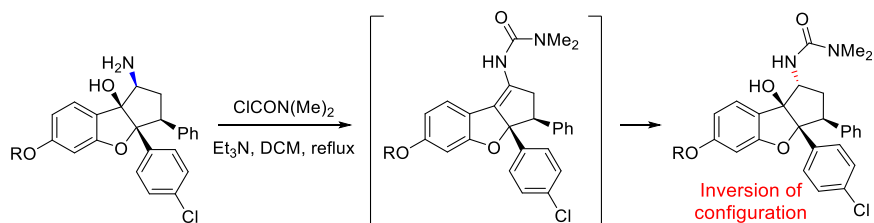
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Unexpected inversion of configuration during the carbamoylation of 1-azaflavaglines

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Abstract The acylation of 8-demethoxy-1-azaflavaglines by dimethylcarbonyl chloride was found to operate with an inversion of configuration, which is rationalized by the occurrence of styrylurea intermediate. The configuration-reversed products was not observed when the substrate was substituted by a methoxy in position 8, suggesting that an overstabilization of the carbocationic intermediate prevents this reaction to take place.

Key words inversion of configuration, aminoalcohol, flavaglines

Isolated from medicinal plants used in traditional Chinese medicine, flavaglines represent a promising class of anticancer, cardioprotectant and anti-inflammatory agents due to their combined action on the initiation factor of protein synthesis eIF4a and on the scaffold proteins called prohibitins¹. In the course of our medicinal program²⁻³, we aimed at introducing a 2-chloroethoxy moiety at the position 6 of the flavagline FL45 (**1**, Figure 1), which displays remarkable cardioprotectant and anti-KRAS activities⁴.

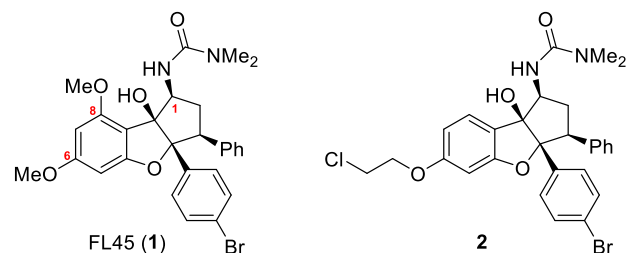
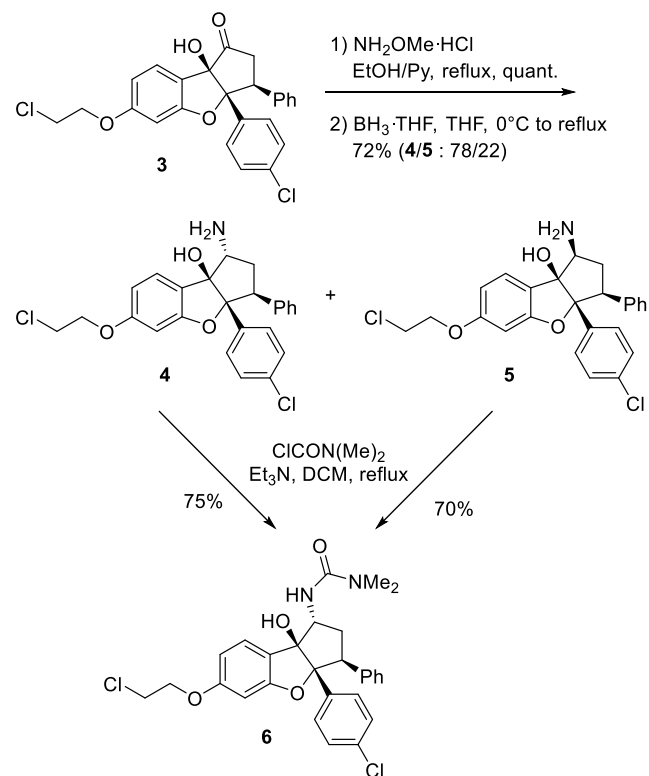


Figure 1 Structures of FL45 (**1**) and its 2-chloroethoxy derivative **2**

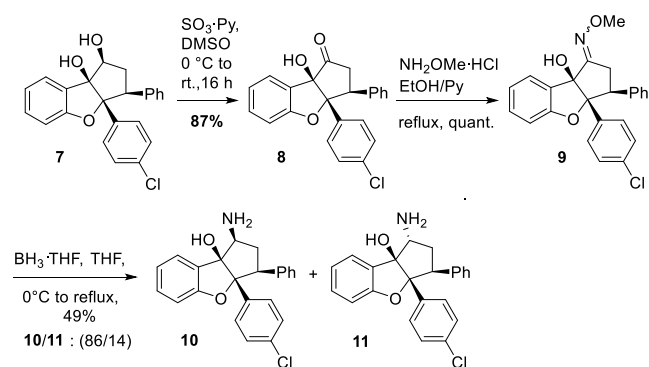
Our synthesis of flavagline **6** started with the conversion of the known ketone **3**⁵ into an oxime that was reduced with borane to afford amines **4** and **5** in a 78:22 ratio, which were separated by column chromatography (Scheme 1). Acylation of **4** with dimethylcarbonyl chloride at room temperature occurred with a low yield (12%), but at reflux in dichloromethane, the expected adduct was formed with a 75% yield. Surprisingly, reaction of diastereoisomer **5** under these conditions also afforded **6** as a sole adduct. As far as we know, this type of inversion of configuration of an aminoalcohol has

not been reported yet. The structure of **6** was confirmed by NOE correlations (Supplementary data).



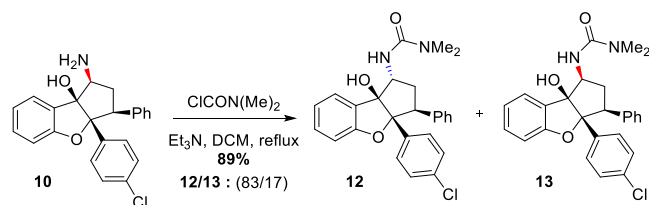
Scheme 1 Synthesis of flavagline **6** and unexpected inversion of configuration during the acylation of **5**

To explore the scope of this reaction, we prepared the α -hydroxyamines **10** and **11**, using a Parikh–Doering oxidation of the known diol **7**⁶ into hydroxyketone **8** (Scheme 2). This latter was coupled with *O*-methylhydroxylamine to give quantitatively oxime **9** that was reduced with borane to afford amines **10** and **11** in a 86:14 ratio.



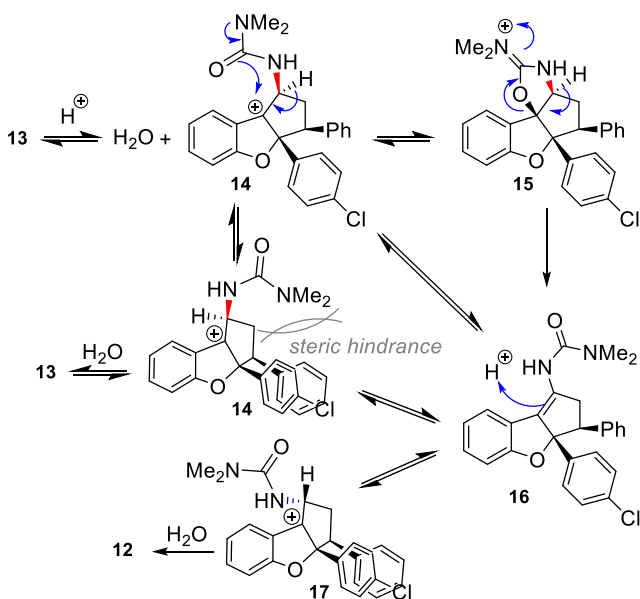
Scheme 2 Synthesis of flavaglines **10** and **11**

As previously, carbamoylation of flavagline **10** occurred principally with an inversion of configuration to afford the *trans*- α -hydroxyurea **12** as the major diastereoisomer (Scheme 3).



Scheme 3 Carbamoylation of flavagline **10**

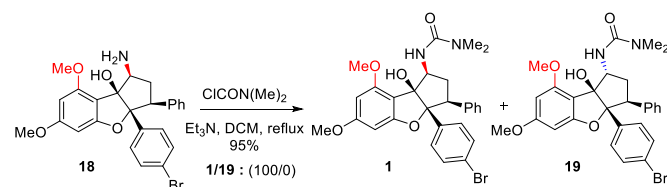
The source of this remarkable inversion of configuration is unclear. Yet, MM2 molecular modeling suggests that the *trans*-hydroxyurea **12** is more stable by 5.6 kcal mol⁻¹ than its *cis*-isomer **13**, which may explain the possible interconversion depicted in Scheme 4. Protonation of **13** may generate the benzylic carbocation **14** that may either generate the styrylurea **16** or undergo a ring closure due to the nucleophilic character of the urea to form the oxazolidinone dimethyliminium salt **15**. The latter may also undergo a rearrangement to form **16**, which upon protonation and hydration may generate the hydroxyurea **12** and **13** via the carbocations **17** and **14**, with a strong preference for the thermodynamically more stable isomer **12** (Scheme 4).



Scheme 4 Proposed mechanism accounting for the inversion of configuration during the carbamoylation of flavagline **10**

This selectivity may also be explained by the passage through favoured carbocation **17** in which cyclopentane moiety adopts an envelope conformation where both phenyl and urea bulky groups are anti to avoid steric interaction.

Interestingly, the carbamoylation of flavagline **18** afforded only the urea **1** without any trace of its *trans* isomer **19**, as previously described⁴ (Scheme 5). In that case, the protonation of **1** may generate a carbocation that is too stabilized to produce the cognate styrylurea.



Scheme 5 Carbamoylation of flavagline **18**

In summary, we report a most unusual thermodynamically driven inversion of configuration consecutive to the carbamoylation of 1-azafavaglines that possibly involves a reactive styrylurea as an intermediate.

Acknowledgment

We thank the "Ministère de l'Enseignement Supérieur et de l'Innovation" for a fellowship to H. A-H.

Supporting Information

YES (this text will be updated with links prior to publication)

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- (6) Diedrichs, N.; Ragot, J.; Thede, K.; Horvath, E. *Eur. J. Org. Chem.* **2005**, 1731-1735.
- (7) **General.** All commercial reagents were used without purification. All the anhydrous solvents are commercially available and were conserved on molecular sieves. All reactions sensitive to moisture or oxygen were carried out under argon atmosphere and in flasks dried at 110 °C. Reactions were stirred with a magnetic stirrer. Temperatures for the reactions refer to bath temperatures. Reactions were monitored by TLC (0.2 mm, Merck DC Platten Kieselgel 60 F254) with detection by UV light ($\lambda = 254$ nm) and treatment with anisaldehyde and potassium permanganate-stain. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were acquired on a Bruker DRX-400 spectrometer in CDCl₃ (referenced to 7.26 ppm for ¹H and 77.16 ppm for ¹³C) or (CD₃)₂SO (referenced to 2.50 ppm for ¹H and 39.5 ppm for ¹³C) as solvents. Coupling constants (*J*) are in Hz. Chemical shifts are reported in parts per million (ppm). The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet. High resolution mass spectra were recorded on a Bruker MicroTOF-Q (ESI Q-TOF) spectrometer.

- (8) **(3S,3aR,8bS)-1-Amino-6-(2-Chloroethoxy)-3a-(4-chlorophenyl)-3-phenyl-1,2,3,3a-tetrahydro-8bH-cyclopenta[b]benzofuran-8b-ol (4 & 5)**. Ketone **3** (390 mg, 0.86 mmol) and *O*-methylhydroxylamine hydrochloride (358 mg, 4.28 mmol) were diluted in absolute ethanol (15.6 ml) and distilled pyridine (15.6 ml). The reaction was heated up to reflux 3 h, and then the volatiles were removed, and the crude product was extracted with EtOAc. The organic phase was washed twice with HCl (1M), a saturated solution of Na₂CO₃, and brine. Then, the organic phase was dried over MgSO₄ and concentrated to dryness to give quantitatively the desired oxime ether (414 mg, mixture of two isomers) as a white solid, which was used in the next step without purification. To a stirred solution of methylether oxime (340 mg, 0.70 mmol) in dry THF (25 ml), BH₃-THF complex (9.8 ml, 1M) was added dropwise at 0 °C. After addition, the reaction was heated to 65 °C overnight. After cooling to room temperature, a solution of 3 M NaOH was added to stop the reaction, and the aqueous phase was extracted twice with EtOAc. The cumulated organic phase was washed with brine, dried over MgSO₄, and then purified by column chromatography on silica gel using DCM / MeOH (95 / 5) as eluent to give *trans*- α -hydroxy amine **4** (180 mg, 56%) and *cis*- α -hydroxy amine **5** (50 mg, 16%) as white solids. *trans*- α -hydroxy amine **4** is described (¹H & MS) in literature.⁵ **4**: mp = 102-105 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.83 (1H, brs), 2.28 (1H, m), 2.96 (1H, m), 3.42 (1H, brs), 3.83 (2H, t, *J* = 5.6 Hz), 3.88 (1H, dd, *J* = 6.4, 7.5 Hz), 4.08 (1H, m), 4.25 (2H, t, *J* = 5.6 Hz), 4.35 (1H, brs), 6.58-6.62 (2H, m), 6.94 (2H, d, *J* = 8.7 Hz), 6.95-6.98 (2H, m), 7.04 (2H, d, *J* = 8.7 Hz), 7.10-7.16 (3H, m), 7.20 (1H, d, *J* = 8.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 31.4, 41.7, 53.7, 67.7, 68.6, 91.5, 98.2, 103.3, 109.3, 118.0, 125.7, 127.0, 127.5, 128.3, 128.7, 129.2, 133.3, 133.9, 137.7, 160.5, 162.2; **5**: mp = 79-82 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.78 (2H, brs), 1.88 (1H, m), 2.60 (1H, m), 3.83 (2H, t, *J* = 5.8 Hz), 3.94 (2H, m), 4.24 (2H, t, *J* = 5.8 Hz), 6.55 (1H, dd, *J* = 2.1, 8.2 Hz), 6.58 (1H, d, *J* = 2.1 Hz), 6.96-7.13 (9H, m), 7.21 (1H, d, *J* = 8.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 36.6, 41.9, 53.7, 61.5, 68.4, 92.9, 97.3, 103.3, 108.3, 120.5, 126.5, 126.6, 127.2, 128.0, 128.6, 129.1, 133.1, 134.7, 139.2, 160.3, 161.1; HRMS (ESI-TOF) *m/z* [M+H]⁺ calcd for C₂₅H₂₄Cl₂NO₃ 456.1133, found 456.1119.
- (9) **3-((1R,3S,3aR,8bS)-6-(2-Chloroethoxy)-3a-(4-chlorophenyl)-8b-hydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-1-yl)-1,1-dimethylurea (6)**. To a stirred solution of *trans*- α -hydroxy amine **4** (50 mg, 0.11 mmol) in dry DCM (1.7 ml), was added triethylamine (50 μ L, 0.36 mmol) followed by dimethylcarbamoyl chloride (25 μ L, 0.27 mmol), at room temperature under argon atmosphere. The resulting reaction mixture was stirred at reflux over 40 h. After cooling to room temperature, the mixture was concentrated and then purified by column chromatography on silica gel using pentane / Et₂O (9 / 1 to 3 / 7) as eluent to give *trans*- α -hydroxy urea **6** (43 mg, 75%) as a white solid. mp = 171-174 °C; ¹H NMR (400 MHz, (CD₃)₂SO) δ 2.12 (1H, m), 2.36 (1H, m), 2.92 (6H, s), 3.81 (2H, t, *J* = 5.9 Hz), 3.99 (1H, dd, *J* = 3.1, 7.5 Hz), 4.21 (2H, t, *J* = 5.9 Hz), 4.35 (1H, d, *J* = 6.7 Hz), 4.94 (1H, m), 5.45 (1H, brs), 6.44 (1H, d, *J* = 2.3 Hz), 6.52 (1H, dd, *J* = 2.3, 8.3 Hz), 7.04 (2H, d, *J* = 8.7 Hz), 7.08 (1H, d, *J* = 8.3 Hz), 7.14-7.18 (7H, m); ¹³C NMR (100 MHz, (CD₃)₂SO) δ 30.5, 35.0, 36.6, 42.0, 53.3, 63.0, 68.4, 91.0, 96.9, 103.2, 108.1, 122.3, 126.0, 126.6, 127.3, 128.2, 129.2, 129.8, 133.4, 135.0, 140.1, 159.7, 159.8, 160.6; HRMS (ESI-TOF) *m/z* [M+Na]⁺ calcd for C₂₈H₂₈Cl₂N₂NaO₄ 549.1324, found 549.1346.
- (10) **(3S,3aR,8bR)-3a-(4-Chlorophenyl)-8b-hydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-1-one (8)**. To a solution of *cis*-diol **7b** (360 mg, 0.95 mmol) in dry DMSO (2.9 ml) at 0 °C under argon, a solution of SO₃.Py (454 mg, 2.85 mmol) in dry DMSO (1.7 ml) was added slowly. The mixture was stirred at room temperature overnight. The reaction was treated with a saturated cold solution of NH₄Cl and then liquid phase was eliminated by filtration. The obtained solid was diluted with DCM. The organic phase was washed with water, dried over anhydrous MgSO₄, filtered, concentrated, and purified by column chromatography on silica gel using pentane / DCM (3 / 7) as eluent to give ketone **8** (310 mg, 87%) as a white solid. mp = 88-91 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.80 (1H, s), 2.93-3.12 (2H, m), 3.80 (1H, dd, *J* = 9.4, 13.1 Hz), 6.93-6.96 (2H, m), 7.03-7.20 (9H, m), 7.43-7.47 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 40.1, 48.5, 77.4, 88.3, 100.2, 112.4, 122.6, 125.2, 126.7, 127.4, 127.9, 128.0, 128.3, 128.4, 132.5, 133.8, 136.4, 158.4, 210.9; HRMS (ESI-TOF) *m/z* [M+Na]⁺ calcd for C₂₃H₁₇ClNaO₃ 399.0764, found 399.0746.
- (11) **(3S,3aR,8bS)-1-Amino-3a-(4-chlorophenyl)-3-phenyl-1,2,3,3a-tetrahydro-8bH-cyclopenta[b]benzofuran-8b-ol (10 & 11)**. Ketone **8** (300 mg, 0.80 mmol) and *O*-methylhydroxylamine hydrochloride (333 mg, 4 mmol) were diluted in absolute ethanol (15 ml) and distilled pyridine (15 ml). The reaction was heated up to reflux overnight, and then the volatiles were removed, and the crude product was extracted with EtOAc. The organic phase was washed twice with HCl (1M), a saturated solution of Na₂CO₃, and brine. Then, the organic phase was dried over MgSO₄ and concentrated to dryness to give quantitatively the desired oxime ether **9** (320 mg, mixture of two isomers) as a white solid, which was used in the next step without purification. To a stirred solution of methylether oxime **9** (310 mg, 0.76 mmol) in dry THF (24 ml), BH₃-THF complex (10.7 ml, 1M) was added dropwise at 0 °C. After addition, the reaction was heated to 65 °C overnight. After cooling to room temperature, a solution of 3 M NaOH was added to stop the reaction, and the aqueous phase was extracted twice with EtOAc. The cumulated organic phase was washed with brine, dried over MgSO₄, and then purified by column chromatography on silica gel using DCM / MeOH (95 / 5) as eluent to give *cis*- α -hydroxy amine **10** (106 mg, 43%) and *trans*- α -hydroxy amine **11** (17 mg, 6%) as white solids. **10**: mp = 89-92 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.96 (1H, m), 2.67 (1H, m), 4.02 (2H, m), 6.96-7.15 (11H, m), 7.31-7.37 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 36.9, 53.9, 61.8, 93.4, 102.4, 110.7, 121.4, 126.0, 126.5, 127.3, 127.8, 128.0, 128.6, 129.2, 131.1, 133.2, 134.7, 139.3, 159.0; **11**: mp = 95-98 °C; ¹H NMR (400 MHz, CDCl₃) δ 1.81 (1H, brs), 2.31 (1H, m), 2.99 (1H, m), 3.36 (1H, m), 3.92 (1H, m), 4.12 (1H, m), 4.26 (1H, brs), 6.93-7.18 (11H, m), 7.28 (1H, d, *J* = 7.4 Hz), 7.41 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 31.4, 53.7, 67.8, 91.8, 102.4, 111.6, 122.4, 125.1, 125.4, 127.1, 127.5, 128.3, 128.7, 129.3, 132.5, 133.2, 133.9, 137.7, 159.0; HRMS (ESI-TOF) *m/z* [M+H]⁺ calcd for C₂₃H₂₁ClNO₂ 378.1261, found 378.1250.
- (12) **3-((3S,3aR,8bS)-3a-(4-Chlorophenyl)-8b-hydroxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-1-yl)-1,1-dimethylurea (12)**. To a stirred solution of *cis*- α -hydroxy amine **10** (120 mg, 0.32 mmol) in dry DCM (4.8 ml), was added triethylamine (0.12 ml, 0.82 mmol) followed by dimethylcarbamoyl chloride (59 μ L, 0.63 mmol), at room temperature under argon atmosphere. The resulting reaction mixture was stirred at reflux over 24 h. After cooling to room temperature, the mixture was concentrated and then purified by column chromatography on silica gel using DCM / AcOEt (95 / 5) as eluent to give an inseparable mixture of two diastereomers, *trans*- α -hydroxy urea **12** and *cis*- α -hydroxy urea **13** (**12**: 83 / **13**: 17) (126 mg, 89%) as a white solid. mp mixture = 191-194 °C; **12**: ¹H NMR (400 MHz, (CD₃)₂SO): δ 2.07 (1H, m), 2.53 (1H, m), 2.78 (6H, s), 3.98 (1H, t, *J* = 8.2 Hz), 4.85 (1H, dd, *J* = 7.5, 15.1 Hz), 6.11 (1H, s), 6.25 (1H, d, *J* = 7.4 Hz), 6.94-7.31 (13H, m); ¹³C NMR (100 MHz, (CD₃)₂SO): δ 33.6, 36.1, 52.8, 61.0, 91.7, 101.3, 109.9, 120.5, 126.1, 126.3, 126.5, 127.6, 128.2, 129.4, 129.7, 130.0, 131.2, 135.8, 139.6, 157.5, 159.0; HRMS (ESI-TOF) *m/z*: [M+Na]⁺ calcd for C₂₆H₂₅ClN₂NaO₃ 471.1451, found 471.1439.
- (13) **3-((1S,3S,3aR,8bS)-3a-(4-Bromophenyl)-8b-hydroxy-6,8-dimethoxy-3-phenyl-2,3,3a,8b-tetrahydro-1H-cyclopenta[b]benzofuran-1-yl)-1,1-dimethylurea (1)**. To a stirred solution of *cis*- α -hydroxy amine **18** (50 mg, 0.10 mmol) in dry DCM (1.5 ml), was added triethylamine (37 μ L, 0.27 mmol) followed by dimethylcarbamoyl chloride (19 μ L, 0.21 mmol), at

room temperature under argon atmosphere. The resulting reaction mixture was stirred at reflux over 24 h. After cooling to room temperature, the mixture was concentrated and then purified by column chromatography on silica gel using pentane / AcOEt (9 / 1) as eluent to give *cis*- α -hydroxy urea **1** (54 mg, 95%) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 2.31 (1H, m), 2.34 (1H, s), 2.76 (1H, m), 2.95 (6H, s), 3.67-3.75 (4H, m), 3.78 (3H, s), 4.52 (1H, m), 5.72 (1H, d, $J = 5.8$ Hz), 6.00 (1H, d, $J = 1.9$ Hz), 6.19 (1H, d, $J = 1.9$ Hz), 7.03-7.12 (7H, m), 7.21 (2H, d, $J = 8.7$ Hz); ^{13}C

NMR (100 MHz, CDCl_3) δ 30.4, 36.3, 36.8, 52.0, 55.5, 55.7; 57.6, 88.2, 88.9, 92.5, 102.4, 110.4, 121.3, 126.4, 127.9, 128.1, 129.4, 130.3, 135.3, 138.2, 157.8, 158.6, 159.9, 163.8; HRMS (ESI-TOF) m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{28}\text{H}_{29}\text{BrN}_2\text{NaO}_5$ 575.1158, found 575.1136.