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Solid-phase synthesis of biarylalanines via Suzuki cross-coupling and intramolecular *N*-acyliminium Pictet–Spengler reactions

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Abstract—Solid-supported masked peptide aldehydes containing 3- or 4-iodophenylalanine residues were subjected to Pd-catalyzed Suzuki cross-coupling reactions with arylboronic acids. The biarylalanines generated were applied in intramolecular *N*-acyliminium Pictet–Spengler reactions. In this way, a range of pharmacologically interesting aryl-substituted pyrroloisoquinolines was obtained in excellent purity (>95%).

The palladium-catalyzed Suzuki cross-coupling reaction of organic electrophiles with organoboron compounds has emerged as one of the most widely used reactions for the formation of carbon–carbon bonds,[1,2] in particular for the mild and reliable generation of biaryl compounds. Compared to alternative transition metal-catalyzed cross-coupling protocols, the Suzuki reaction offers several advantages. The related Stille reaction suffers from the use of inherently toxic organostannanes, whereas the Kumada (Grignard reagents) and Negishi (zinc reagents) reactions employ more reactive and nucleophilic coupling partners, which may be less selective and sensitive to heat, air and moisture.[3] Circumventing these drawbacks, the Suzuki reaction meets the need for readily available, shelf-stable and diverse building blocks for use in parallel synthesis and combinatorial chemistry. In addition, the Suzuki reaction has proved to be applicable to multikilogram-scale synthesis of pharmaceutical compounds.[4]

As part of an investigation on the solid-phase intramolecular *N*-acyliminium Pictet–Spengler reaction,[5–7] a range of arylalanine derivatives has recently been shown to react with cyclic *N*-acyliminium ions with the formation of pyrroloisoquinoline ring systems.[8] The scaffold is well suited for the generation of combinatorial libraries since the nature and pattern of substituents may be varied conveniently both on the reactive aromatic ring and the cyclic *N*-acyliminium intermediate. The introduction of aryl substituents on the scaffold is highly relevant because aryl–aryl bonds are widely present in natural products and constitute important structural elements for molecular recognition of pharmaceuticals with target receptors.[9] On the other hand, only a few aryl-substituted phenylalanines are available from commercial suppliers. Therefore, it was envisioned that a solid-phase decoration of the pyrroloisoquinoline scaffold via the Suzuki reaction[10] would emerge as a successful approach towards a series of pharmacologically interesting molecules.

In principle, the cross-coupling process could be carried out at different stages of the solid-phase synthesis sequence towards the target pyrroloisoquinoline. Bearing in mind the risk of Fmoc-deprotection under basic reaction conditions and how the rate of the Pictet–Spengler cyclization is expected to be enhanced by the introduction of aryl moieties in preference to electron-withdrawing iodo groups, it was decided to carry out the Suzuki reactions on iodo-substituted masked aldehyde substrates **3** and **4**. Starting with attachment of the base-labile 4-hydroxymethylbenzoic acid (HMBA) linker to the resin ($PEGA_{800}$),[11] substrates **3** and **4** were prepared by standard solid-phase synthesis protocols (Scheme 1), utilizing MSNT[12] and TBTU[13] as coupling

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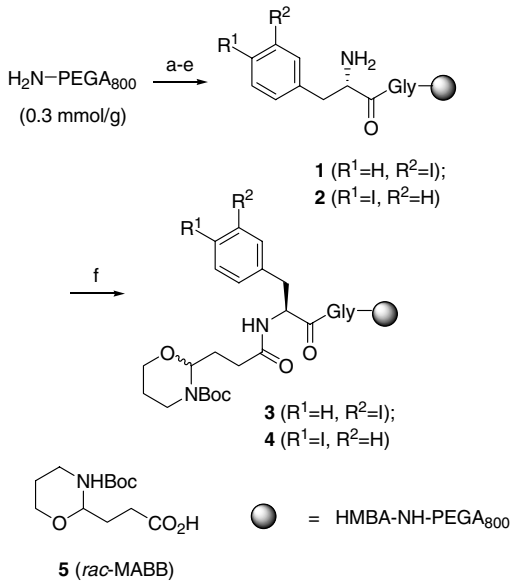


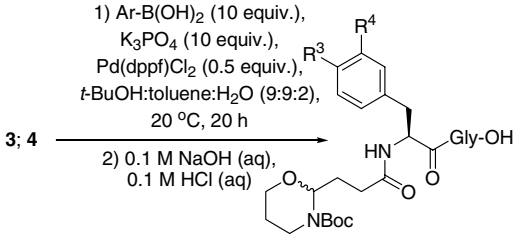
Scheme 1. Reagents and conditions: (a) HMBA, TBTU, NEM, DMF; (b) Fmoc-Gly-OH, MSNT, MeIm, CH_2Cl_2; (c) 20% piperidine (DMF); (d) Fmoc-(3-I)Phe-OH or Fmoc-(4-I)Phe-OH, TBTU, NEM, DMF; (e) 20% piperidine (DMF); (f) **5**, TBTU, NEM, DMF.

reagents for the attachment of Fmoc-amino acids and the readily available masked aldehyde building block **5**, with intermediate Fmoc deprotection using 20% piperidine (DMF).

With substrates **3** and **4** at hand, a range of reaction conditions (base/solvent/catalyst) was screened to determine the optimal coupling with phenylboronic acid. Although several synthetically useful combinations were found in these experiments, two findings seemed particularly important for quantitative conversion: water as co-solvent and $Pd(dppf)Cl_2$ as catalyst.[14a] Using generous amounts of phenyl boronic acid (10 equiv) and $Pd(dppf)Cl_2$ (0.5 equiv),[14b] two combinations of base (10 equiv) and solvent generally gave quantitative conversions at room temperature: CsF in THF/H_2O (4:1), and K_3PO_4 in *t*-BuOH/toluene/H_2O (9:9:2). The latter is illustrated in Table 1 for the coupling of 3- and 4-iodophenylalanine derivatives, **3** and **4**, respectively, with 15 different substituted arylboronic acids.[15] Except for the coupling with pentafluorophenylboronic acid (Table 1, entry 14), all couplings proceeded almost quantitatively towards the biarylalanine derivatives **6a**–**o** and **7a**–**o**. Notably, both electron-rich and electron-poor arylboronic acids coupled with the same high efficiency to the 3- and 4-iodophenylalanine derivatives **3** and **4**.

A recent study has demonstrated that phenylalanine derivatives with electron-rich substituents, such as methoxy and hydroxy groups, in the 3-position generally give rise to regioisomeric pyrroloisoquinolines via Pictet–Spengler cyclization at the 2- and 6-positions on the *N*-acyliminium intermediate.[8] Since 3-alkyl and 3-halophenylalanine derivatives only give rise to Pictet–Spengler cyclization at the 6-position, it was particularly interesting to observe the effect of an aryl-substituent in the 3-position. According to the standard reaction

Table 1. Suzuki cross-coupling reactions of solid-supported 3- and 4-iodophenylalanine derivatives **3** and **4**[a]



6a-o (R^3=H, R^4=Ar);
7a-o (R^3=Ar, R^4=H)

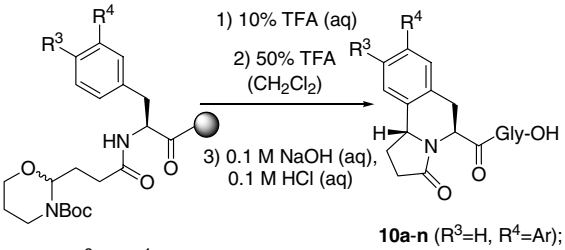
Entry	Ar	Product, purity (%)[b]
1	Ph	**6a**, >95; **7a**, >95
2	4-Me-C_6H_4	**6b**, >95; **7b**, >95
3	4-(CHO)-C_6H_4	**6c**, >95; **7c**, >95
4	2-MeO-C_6H_4	**6d**, >95; **7d**, >95
5	4-BuO-C_6H_4	**6e**, 89; **7e**, 90
6	4-MeS-C_6H_4	**6f**, >95; **7f**, >95
7	4-MeO-C_6H_4	**6g**, >95; **7g**, >95
8	4-MeO-3-Cl-C_6H_3	**6h**, >95; **7h**, >95
9	3-CF_3-C_6H_4	**6i**, >95; **7i**, >95
10	3,5-$(MeO)_2$-C_6H_3	**6j**, >95; **7j**, >95
11	4-Cl-C_6H_4	**6k**, >95; **7k**, >95
12	3,4-(OCH_2O)-C_6H_3	**6l**, >95; **7l**, >95
13	3-NO_2-C_6H_4	**6m**, >95; **7m**, >95
14	C_6F_5	**6n**, 0; **7n**, 0
15	3-(CHO)-4-MeO-C_6H_3	**6o**, >95; **7o**, >95

[a] All reactions were carried out at 20 °C.
[b] Crude product purity as determined by RP-HPLC (UV detection at 215 nm).

conditions,[8] the masked aldehyde substrates **8a**–**n** and **9a**–**n** were treated with 10% TFA (aq) to liberate the aldehyde and form the corresponding 5-hydroxylactams. Pictet–Spengler cyclization was then carried out by treatment with 50% TFA (CH_2Cl_2). With two exceptions (Table 2, entries 5 and 6),[16] the desired pyrroloisoquinolines **10a**–**n** and **11a**–**n** were formed quantitatively with excellent diastereoselectivity (Table 2), notably via attack at the 6-position of both the 3-aryl and 4-arylalanine derivatives on the corresponding *N*-acyliminium intermediates.[17]

In summary, a highly efficient protocol for the Pd-catalyzed Suzuki cross-coupling reaction has been utilized to generate biarylalanine derivatives on solid support. In this approach, masked peptide aldehydes protected as the corresponding *N*-Boc 1,3-oxazinanes, containing 3- or 4-iodophenylalanine residues, are coupled with arylboronic acids under the action of $Pd(dppf)Cl_2/K_3PO_4$ in an aqueous mixture of *t*-BuOH and toluene. A range of arylboronic acids, substituted with different electron-rich and electron-poor substituents, were within the scope of the reaction, and subsequent TFA-mediated intramolecular *N*-acyliminium Pictet–Spengler cyclization provided a series of pharmacologically interesting aryl-substituted pyrroloisoquinolines. Generally, the solid-phase events of peptide synthesis, Pd-catalyzed Suzuki cross-coupling, aldehyde unmasking (via *N*-Boc-1,3-oxazine hydrolysis), and intramolecular *N*-acyliminium Pictet–Spengler reaction occurred to

Table 2. Intramolecular *N*-acyliminium Pictet–Spengler cyclizations of solid-supported 3- and 4-arylphenylalanine derivatives **8a**–**n** and **9a**–**n**[a]



8a-n (R^3=H, R^4=Ar); **9a-n** (R^3=Ar, R^4=H)

10a-n (R^3=H, R^4=Ar); **11a-n** (R^3=Ar, R^4=H)

Entry	Ar	Product, purity (%)[b]
1	Ph	**10a**, >95; **11a**, >95
2	4-Me-C_6H_4	**10b**, >95; **11b**, >95
3	4-(CHO)-C_6H_4	**10c**, >95; **11c**, >95
4	2-MeO-C_6H_4	**10d**, >95; **11d**, >95
5	4-BuO-C_6H_4	**10e**, 89; **11e**, >95
6	4-MeS-C_6H_4	**10f**, 85; **11f**, 90
7	4-MeO-C_6H_4	**10g**, >95; **11g**, >95
8	4-MeO-3-Cl-C_6H_3	**10h**, >95; **11h**, >95
9	3-CF_3-C_6H_4	**10i**, >95; **11i**, >95
10	3,5-$(MeO)_2$-C_6H_3	**10j**, >95; **11j**, >95
11	4-Cl-C_6H_4	**10k**, >95; **11k**, >95
12	3,4-(OCH_2O)-C_6H_3	**10l**, >95; **11l**, >95
13	3-NO_2-C_6H_4	**10m**, >95; **11m**, >95
14	3-(CHO)-4-MeO-C_6H_3	**10n**, >95; **11n**, >95

[a] All reactions were carried out at 20 °C.

[b] Crude product purity as determined by RP-HPLC (UV detection at 215 nm); products were generally isolated in yields exceeding 65%.

provide the desired products in overall purities exceeding 95%, thereby rendering this chemistry well suited for the generation of combinatorial libraries.

Acknowledgements

The Danish National Research Foundation is gratefully acknowledged for financial support.

Supplementary data

RP-HPLC chromatograms and MS (ES) data for compounds **6a**–**o**, **7a**–**o**, **10a**–**n** and **11a**–**n**. ^1H and ^{13}C NMR spectra for **10j**, **10l**, **10n**, **11j**, **11l** and **11n**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.080.

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14. (a) It was noted that the presence of water was required for complete dissolution of the base. Generally, the use of $Pd(PPh_3)_4$ led to the formation of side-products, whereas $Pd(dppf)Cl_2$ gave clean conversions under a variety of reaction conditions (base/solvent/temperature); (b) If the cross-coupling step was repeated once, the catalyst loading could be lowered to 0.1 equiv in each run, still enabling the quantitative formation of biaryl compounds.
15. General procedure for Suzuki-cross coupling reactions on solid phase: The resin **3** or **4** (0.023 mmol, 75 mg) was swelled in degassed toluene/*t*-BuOH/H_2O (9:9:2, 1.5 mL), containing K_3PO_4 (0.23 mmol, 48 mg) and the arylboronic acid (0.23 mmol), followed by vigorous degassing for 1 h with a stream of Ar. $Pd(dppf)Cl_2$ (0.01 mmol, 8.2 mg) was then added to the reaction mixture under Ar, and the reaction vessel was sealed before shaking overnight at room temperature. Subsequently, the resin was washed with CH_2Cl_2 (×6), DMF (×6), water (×6), DMF (×3) and CH_2Cl_2 (×6) in a plastic syringe fitted with a Teflon filter. The resin was lyophilized to remove all traces of solvent. For the release of material **6a**–**o** and **7a**–**o** from the solid phase, beads were treated with 0.1 M NaOH (aq) for 2 h, then neutralized with an equimolar amount of 0.1 M HCl (aq), and finally diluted with CH_3CN. The resulting solution was filtered through a Teflon filter and analyzed by RP-HPLC and ESMS.
16. The purity of **11e** is higher than that of **7e**, indicating the presence of insoluble impurities resisting to be washed out of the solid-supported coupling product **8e** prior to cleavage from the resin.
17. Selected analytical data for pyrroloisoquinolines: {[(5*S*, 10b*R*)-8-(2,5-dimethoxyphenyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl]amino}acetic acid (**10j**). Yield: 8.98 mg (92%); purity: >95%; R_t =

14.05 min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.53 (br s, 1H), 8.39 (t, $J = 6$ Hz, 1H), 7.34 (dd, $J = 1$ Hz, $J = 8$ Hz, 1H), 7.24 (d, $J = 1$ Hz, 1H), 7.21 (d, $J = 8$ Hz, 1H), 7.02 (d, $J = 9$ Hz, 1H), 6.88 (dd, $J = 3$ Hz, $J = 9$ Hz, 1H), 6.82 (d, $J = 3$ Hz, 1H), 4.98 (t, $J = 8$ Hz, 1H), 4.79 (dd, $J = 3$ Hz, $J = 7$ Hz, 1H), 3.73 (s, 3H), 3.72 (d, $J = 6$ Hz, 1H), 3.68 (s, 3H), 3.23 (dd, $J = 3$ Hz, $J = 16$ Hz, 1H), 3.01 (dd, $J = 7$ Hz, $J = 16$ Hz, 1H), 2.77–2.46 (m, 2H), 2.28 (dd, $J = 8$ Hz, $J = 15$ Hz, 1H), 1.82 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 173.28, 170.87, 169.93, 153.16, 150.15, 136.28, 135.88, 131.32, 130.17, 129.16, 127.59, 124.11, 115.85, 113.28, 112.87, 55.93, 55.33, 54.04, 49.24, 40.35, 30.92, 29.89, 26.90; MS (ES) calcd for $C_{23}H_{23}N_2O_6$ $[M-H]^-$ 423.2, found 423.2.

[((5*S*,10b*R*)-8-1,3-Benzodioxol-5-yl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]acetic acid (**10l**). Yield: 6.39 mg (68%); purity: >95%; $R_t = 13.45$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.52 (s, 1H), 8.40 (t, $J = 6$ Hz, 1H), 7.45 (dd, $J = 1$ Hz, $J = 8.0$ Hz, 1H), 7.39 (d, $J = 1$ Hz, 1H), 7.23 (d, $J = 8$ Hz, 1H), 7.22 (d, $J = 2$ Hz, 1H), 7.12 (dd, $J = 2$ Hz, $J = 8$ Hz, 1H), 6.97 (d, $J = 8$ Hz, 1H), 6.05 (s, 2H), 4.98 (t, $J = 7.6$ Hz, 1H), 4.80 (dd, $J = 3$ Hz, $J = 7$ Hz, 1H), 3.71 (d, $J = 6$ Hz, 2H), 3.26 (dd, $J = 3$ Hz, $J = 16$ Hz, 1H), 3.00 (dd, $J = 7$ Hz, $J = 16$ Hz, 1H), 2.77–2.45 (m, 2H), 2.27 (dd, $J = 8$ Hz, $J = 15$ Hz, 1H), 1.78 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 173.29, 170.84, 169.88, 147.82, 146.68, 138.09, 135.91, 133.96, 132.13, 126.52, 125.09, 124.67, 119.99, 108.51, 106.90, 101.01, 54.01, 49.20, 40.64, 30.93, 29.99, 27.02; MS (ES) calcd for $C_{22}H_{19}N_2O_6[M-H]^-$ 407.1, found 407.1.

{[(5*S*,10b*R*)-8-(3-Formyl-4-methoxyphenyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl]-amino}acetic acid (**10n**). Yield: 9.62 mg (99%); purity: >95%; $R_t = 13.95$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.53 (s, 1H), 10.39 (s, 1H), 8.40 (t, $J = 6$ Hz, 1H), 7.97 (dd, $J = 2$ Hz, $J = 9$ Hz, 1H), 7.92 (d, $J = 2$ Hz, 1H), 7.52 (dd, $J = 1$ Hz, $J = 8$ Hz, 1H), 7.46 (d, $J = 1$ Hz, 1H), 7.33 (d, $J = 9$ Hz, 1H), 7.28 (d, $J = 8$ Hz, 1H), 5.00 (t, $J = 8$ Hz, 1H), 4.82 (dd, $J = 3$ Hz, $J = 7$ Hz, 1H), 3.96 (s, 3H), 3.71 (d, $J = 6$ Hz, 2H), 3.29 (dd, $J = 3$ Hz, $J = 16$ Hz, 1H), 3.03 (dd, $J = 7$ Hz, $J = 16$ Hz, 1H), 2.81–2.45 (m, 2H), 2.28 (dd, $J = 9$ Hz, $J = 16$ Hz, 1H), 1.79 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 189.03, 173.28, 170.85, 169.86, 160.84, 136.84, 136.30, 134.23, 132.41, 132.06, 126.36, 125.40, 125.34, 124.48, 124.20, 113.37, 56.09, 54.01, 49.18, 40.35, 30.95, 29.98, 27.05; MS (ES) calcd for $C_{23}H_{21}N_2O_6$ $[M-H]^-$ 421.1, found 421.1

{[(5*S*,10b*R*)-8-(2,5-Dimethoxyphenyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl]amino}-acetic acid (**11j**). Yield: 8.97 mg (92%); purity: >95%; $R_t = 14.09$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.54 (s, 1H), 8.40 (t, $J = 6$ Hz, 1H), 7.29 (dd, $J = 1$ Hz, $J = 8$ Hz, 1H), 7.27 (d, $J = 1$ Hz, 1H), 7.17 (d, $J = 8$ Hz, 1H), 7.02 (d, $J = 8$ Hz, 1H), 6.89 (dd, $J = 3$ Hz, $J = 9$ Hz, 1H), 6.84 (d, $J = 3$ Hz, 1H), 4.99 (t, $J = 8$ Hz, 1H), 4.81 (dd, $J = 3$ Hz, $J = 7$ Hz, 1H), 3.74 (s, 3H), 3.72 (d, $J = 6$ Hz, 2H), 3.69 (s, 3H), 3.22 (dd, $J = 3$ Hz, $J = 16$ Hz, 1H), 2.99 (dd, $J = 7$ Hz, $J = 16$ Hz, 1H), 2.77–2.46 (m, 2H), 2.28 (dd, $J = 9$ Hz, $J = 15$ Hz, 1H), 1.81 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 173.29, 170.88, 169.95, 153.20, 150.14, 136.80, 136.26, 130.36, 130.29, 128.16, 127.52, 125.20, 115.98, 113.14, 113.08, 112.93, 55.96,55.34, 54.19, 49.20, 30.94, 29.65, 26.97; MS (ES) calcd for $C_{23}H_{23}N_2O_6$ $[M-H]^-$ 423.2, found 423.2.

[((5*S*,10b*R*)-8-1,3-Benzodioxol-5-yl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl)amino]-acetic acid (**11l**). Yield: 6.38 mg (68%); purity: >95%; $R_t = 13.45$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.51 (s, 1H), 8.41 (t, $J = 6$ Hz, 1H), 7.41–7.38 (m, 2H), 7.24 (d, $J = 2$ Hz, 1H), 7.19 (d, $J = 9$ Hz, 1H), 7.13 (dd, $J = 2$ Hz, $J = 8$ Hz, 1H), 6.98 (d, $J = 8$ Hz, 1H), 6.05 (s, 2H), 5.00 (t, $J = 8$ Hz, 1H), 4.80 (dd, $J = 3$ Hz, $J = 7$ Hz, 1H), 3.70 (d, $J = 6$ Hz, 2H), 3.22 (dd, $J = 3$ Hz, $J = 16$ Hz, 1H), 2.97 (dd, $J = 7$ Hz, $J = 16$ Hz, 1H), 2.83–2.46 (m, 2H), 2.28 (dd, $J = 8$ Hz, $J = 16$ Hz, 1H), 1.82 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 173.34, 170.84, 169.87, 147.82, 146.66, 138.21, 137.60, 134.06, 130.40, 129.13, 124.61, 122.55, 120.01, 108.49, 106.97, 101.01, 54.29, 49.18, 40.34, 30.97, 29.60, 27.06; MS (ES) calcd for $C_{22}H_{19}N_2O_6$ $[M-H]^-$ 407.1, found 407.1.

{[(5*S*,10b*R*)-8-(3-Formyl-4-methoxyphenyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbonyl]-amino}acetic acid (**11n**). Yield: 7.68 mg (79%); purity: >95%; $R_t = 13.95$ min; ^{1}H NMR (250 MHz, DMSO-d_6) δ 10.40 (s, 1H), 8.39 (t, $J = 6$ Hz, 1H), 7.98 (dd, $J = 2$ Hz, $J = 9$ Hz, 1H), 7.92 (d, $J = 2$ Hz, 1H), 7.47 (s, 1H), 7.46 (d, $J = 7$ Hz, 1H), 7.33 (d, $J = 9$ Hz, 1H), 7.25 (d, $J = 9$ Hz, 1H), 5.03 (t, $J = 8$ Hz, 1H), 4.83 (dd, $J = 3$ Hz, $J = 7$ Hz, 1H), 3.97 (s, 3H), 3.71 (d, $J = 6$ Hz, 2H), 3.24 (dd, $J = 3$ Hz, $J = 16$ Hz, 1H), 2.99 (dd, $J = 7$ Hz, $J = 16$ Hz, 1H), 2.86-2.45 (m, 2H), 2.29 (dd, $J = 8$ Hz, $J = 16$ Hz, 1H), 1.83 (m, 1H); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 189.54, 173.81, 171.36, 170.34, 138.32, 137.52, 134.82, 132.70, 131.30, 129.88, 125.90, 125.04, 124.98, 124.69, 122.90, 113.84, 56.59, 54.76, 49.61, 41.12, 31.46, 30.09, 27.64; MS (ES) calcd for $C_{23}H_{21}N_2O_6$ $[M-H]^-$ 421.1, found 421.1.