HETEROCYCLES, Vol. 71, No. 2, 2007, pp. 245 – 252. © The Japan Institute of Heterocyclic Chemistry
Received, 6th November, 2006, Accepted, 22nd December, 2006, Published online, 26th December, 2006. COM-06-10937

AN IMPROVED PICTET-SPENGLER CONDENSATION: A CONVENIENT SYNTHETIC ROUTE TO BIOACTIVE MANZAMINE DERIVATIVES

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Abstract - An improved Pictet-Spengler method for the construction of a modified β-carboline moiety from an α,β-unsaturated aldehyde is described. The Pictet-Spengler reactions between ircinal A (**1**) and tryptamine derivatives under milder conditions have resulted in shorter reaction times and higher product yields (70 to 89%) with control of stereochemistry. The Pictet-Spengler products (**9** and **11**) are two new manzamine alkaloids, which display strong activities against *Mycobacterium intracellulare* with IC_{50} values of 0.2 and 0.06 μg/mL, respectively.

The first manzamine alkaloid, manzamine A was isolated in 1986 by Higa and coworkers from an Okinawan sponge.[1] The manzamine alkaloids have been to date isolated from more than 17 species of marine sponges from 5 different family groups.[2,3] This group of alkaloids has attracted considerable attention due to its biological activity as a novel family of antiparasitic-antibiotics with significant in vivo activity against malaria and Mtb.[4,5] The manzamines have an unusual polycyclic skeleton characterized by a β-carboline group attached to a pentacyclic moiety, which comprises an eight- and thirteen-membered ring on a pyrrolo[2,3-*i*]isoquinoline framework. Both the β-carboline and the eight-membered ring have been linked to the compounds significant antimalarial activity.

The formation of diverse libraries at the β-carboline moiety of manzamine starting with the readily available natural compound, ircinal A (**1**) is now possible. The Pictet-Spengler reaction has been extensively studied especially in the preparation of β-carbolines and tetrahydroisoquinolines by the synthetic community.[6-13] However, most of the reported results involve the use of an aldehyde or activated ketone as a starting material, while reactions using α,β-unsaturated aldehydes receive much less attention. The reported yields from the Pictet-Spengler reaction involving α,β-unsaturated aldehydes

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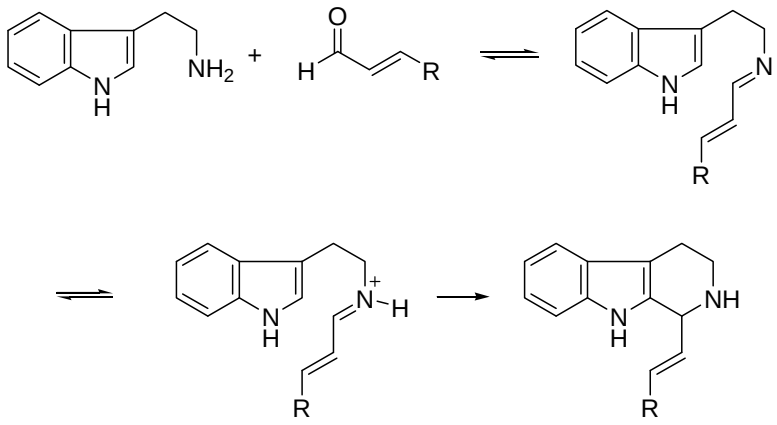
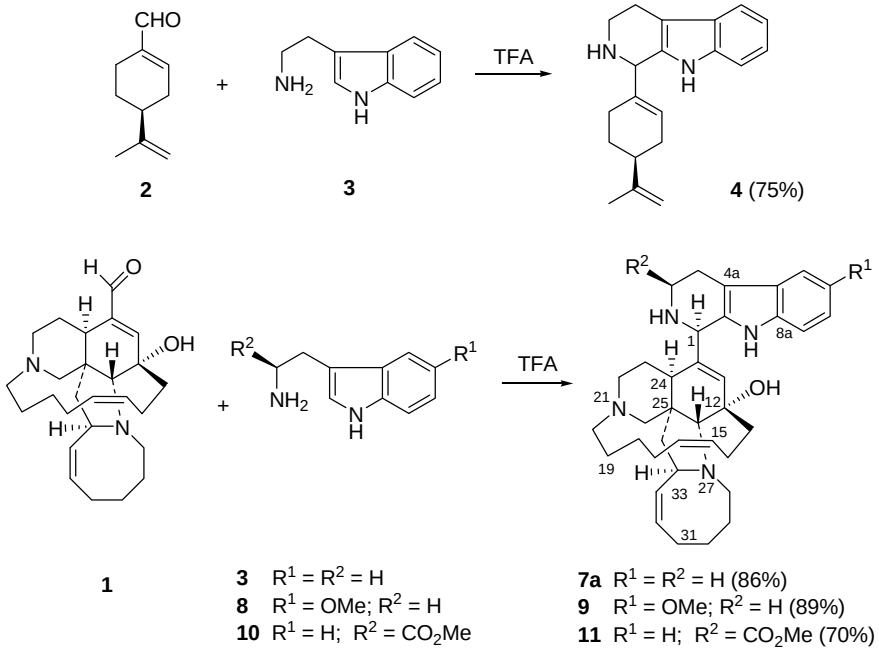
ranges from poor to moderate (17-58%).[14-16] Lower reaction yields associated with α,β-unsaturated aldehydes is due to the lower reactivity of the intermediate involved. The lower reactivity of the protonated α,β-unsaturated imine is caused by two factors, which include greater delocalization of the positive charge of the conjugate acid (Scheme 1), and the lower electrophilicity of the imine double bond.[6,16]

We were able to show that utilizing improved Pictet-Spengler reaction conditions, it is possible to increase the yield substantially (70 to 89%).[17,18,31,32] A conventional Pictet-Spengler reaction involves prolonged stirring of a mixture of an amine, ketone or aldehyde with trifluoroacetic acid (TFA) in an organic solvent (such as benzene or dioxane).[5] High temperatures are often employed to facilitate the reaction. These improved milder reaction conditions required shorter reaction times and lower temperatures while providing control of stereochemistry.

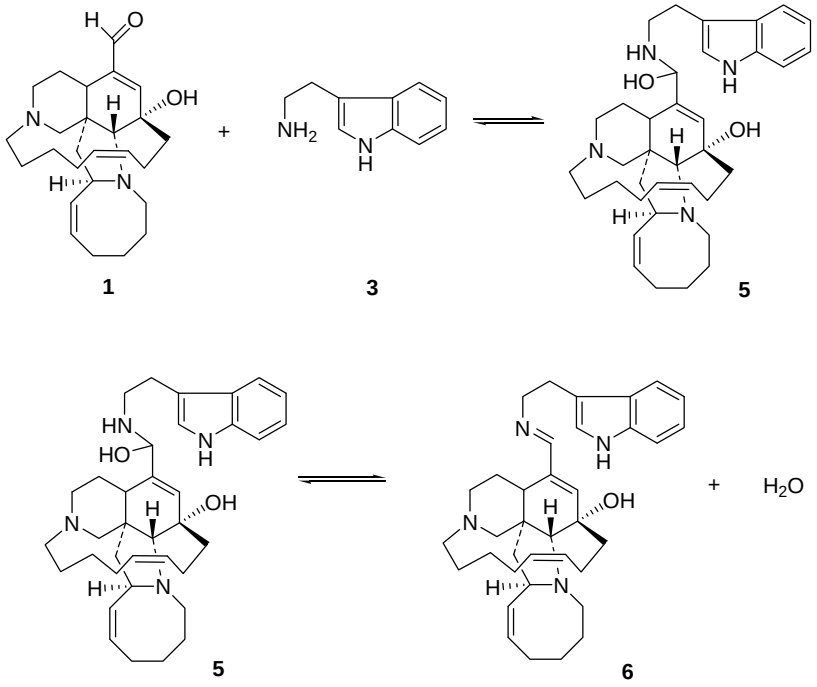


Scheme 1



Scheme 2

Perillaldehyde (**2**), which possesses a similar α,β-unsaturated aldehyde function was chosen as a model compound for the optimization of the reaction conditions in order to establish the broader utility of the reaction to this functional group. In general an α,β-unsaturated aldehyde (perillaldehyde (**2**) or ircinal A (**1**)), tryptamine (**3**), and molecular sieves were stirred at room temperature for 2 hours. TFA was then added to the reaction mixture and stirred for an additional 3 hours to complete the reaction with 75 and 86% yields, respectively (Scheme 2).[17,18] The inclusion of a time interval prior to the addition of TFA is crucial as this interval allows sufficient formation of the imine intermediate (**6**), which then cyclizes to form the Pictet-Spengler product. The imine intermediate is an obligatory intermediate in the Pictet-Spengler reaction. The formation of the imine proceeds in two steps, which are reversible with each having a rate-determining step at a different pH (Scheme 3).[19,20] At neutral pH, the amine reacts with the carbonyl compound to form the addition compound, carbinolamine (**5**) (step 1), which then undergoes a slow, acid-catalyzed dehydration to form the imine (**3**) (step 2).[20] The addition of TFA together with other substrates at the beginning of the reaction without a time interval as in the conventional Pictet-Spengler reaction decreased the formation of the imine due to limited attack of the free nitrogen base on the carbonyl compound, and therefore produced a lower yield. Although isolation of the imine intermediate proved unsuccessful the time interval for each step could be successfully optimized. The modified reaction conditions reported here allowed sufficient time for the formation of the imine intermediate (**6**) (or carbinolamine (**5**)) at neutral pH. The addition of TFA after a short time interval completes the cyclization to give the β-carboline. The NMR data (^{1}H and ^{13}C) obtained for semisynthetic manzamine D is identical to that of the reported data of the natural product (**7a**).[14,15,21,22]



Scheme 3

The Pictet-Spengler reaction generally produces both *R* and *S* isomers.[6] However, in the solution phase synthesis beginning with ircinal A to generate manzamine D, only one isomer (*R*) was observed, indicating the control of stereochemistry in the present reaction. Although the energy calculated for minimized structures of both *R* and *S* isomers are comparable (91.76 kcal/mol for *R*-isomer and 91.48 kcal/mol for *S*-isomer), the conformations for these isomers are significantly different.[23] The energy minimized structure indicates the presence of unfavorable proximity between the H(1) and the bulky ircinal moiety in the *S*-isomer. In the case of *R*-isomer, H(1) is directed away from the bulky ircinal moiety. The distance from H(1) to H(24) and H_2(23) are 2.36, 3.84 and 3.24 Å in the *R*-isomer. In the case of *S*-isomer, the distance between these hydrogens are 2.51, 3.21 and 2.62 Å, respectively (Figure 1). The X-ray data of manzamine A hydrochloride showed that *N*(9)-H, *N*(27), and OH are hydrogen bonded to HCl, while molecular modeling indicated that solution phase manzamine A possesses a similar conformation with its HCl crystal structure.[1,4] The energy minimized structure of the *R*-isomer indicated that it possesses similar conformation as manzamine A, while the S-isomer adopts a significantly different conformation. The main difference between both isomers lies in the conformation of the indole moiety. In the *R*-isomer, the indolic-*N* is in close proximity with *N*(27) and 12-OH, while the indolic-*N* is located far away from *N*(27) and 12-OH in the case of the *S*-isomer. These heteroatoms are able to hydrogen-bond, which hold the intermediate in a suitable position for the stereo-controlled cyclization to take place. The observation obtained from the study of the energy minimized structures gave an insight in the preponderance of one isomer over the other although the actual control of steoreochemistry depends on the difference in activation energy between the transition states.

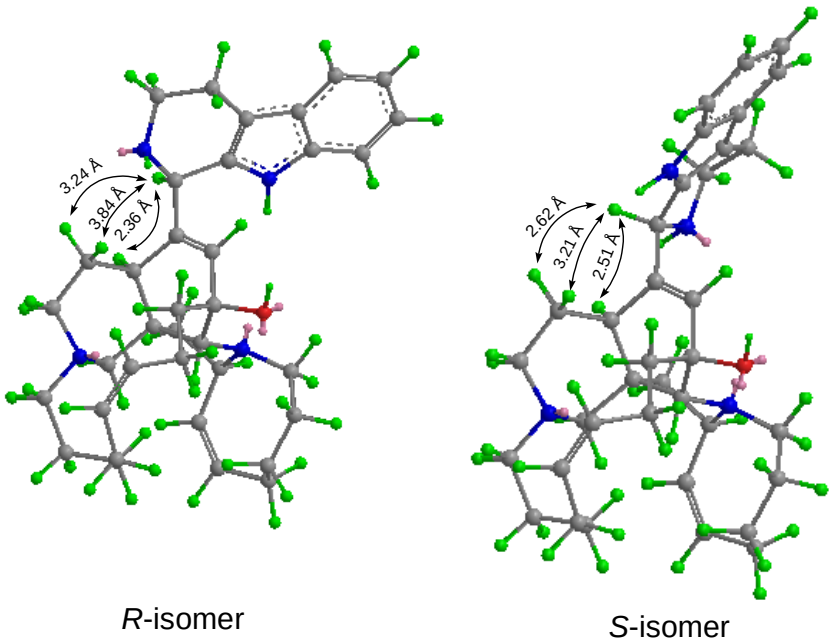
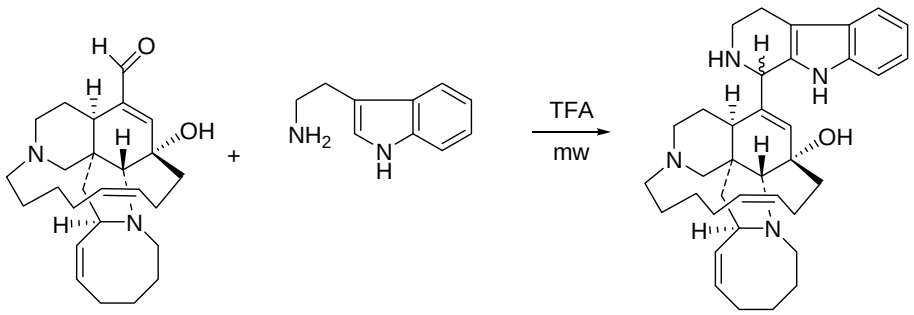


Figure 1

A solvent-free microwave-assisted Pictet-Spengler reaction from an α,β-unsaturated aldehyde has also been successfully carried out. It has been demonstrated previously that microwave irradiation often improves the reaction significantly in terms of reaction time and product yield.[24,25] However, previous reports on microwave-assisted Pictet-Spengler reaction were limited to aldehydes or activated ketones as starting materials.[8,26] The microwave-assisted Pictet-Spengler reaction between ircinal A (**1**) and tryptamine (**3**) in the presence of trifluoroacetic acid (TFA) gave manzamine D (**7a**, *R* isomer) and *epi*-manzamine D (**7b**, *S* isomer) (Scheme 4).[21,22,27,28] The reaction mixture was irradiated for 10 min at 390 W under solvent-free conditions, which yielded both the *R* and *S* isomers with a ratio of 1:1.1, respectively and total yield of 42%.[29] The reaction time for a microwave-assisted Pictet-Spengler reaction was improved tremendously, while total product yields are comparable to that of previous reported yield utilizing conventional Pictet-Spengler reaction conditions (e.g. without time interval).[1,15]



1 **3** **7a** H = α **7b** H = β

Scheme 4

Manzamine D (**7a**) was then treated with DDQ to give manzamine A (**12**) in a 50% yield.[30] In conclusion, we increased the production yields starting from a less reactive α,β-unsaturated aldehyde in a conventional Pictet-Spengler reaction using improved reaction conditions. We have also successfully carried out a microwave-assisted Pictet-Spengler reaction under solvent-free conditions utilizing the same α,β-unsaturated aldehyde as starting material. This is the first report to our knowledge of a microwave-assisted Pictet-Spengler reaction using an α,β-unsaturated aldehyde as a starting material. Our results indicate that the solution phase Pictet-Spengler reaction using improved conditions provide higher yield with control of stereochemistry when compared to that of the microwave-assisted solid phase reactions and will have significant utility in the lead optimization of the manzamine class of drug leads starting with the natural product ircinal A.

Applying this reaction methodology, ircinal A was reacted with other tryptamine derivatives (Scheme 2).[31,32] The Pictet-Spengler reaction between ircinal A (**1**) and 5-methoxytryptamine (**8**) yielded a product, ircinal C (**9**) with no trace of starting material in 89% yield. A similar reaction between ircinal A (**1**) with D-tryptophan methyl ester hydrochloride (**10**) gave ircinal D (**11**) in 70% yield. Both compounds (**9** and

11) have not been reported before as natural or synthetic products. The IC_{50} values for the inhibition of *Mycobacterium intracellulare* of **9** and **11** are 0.2 and 0.06 μg/ml, respectively, and have been improved significantly when compared to that of manzamine A (0.35 μg/mL)[2] and these compounds also showed reduced toxicity against vero cell lines with IC_{50} values of 210 and 950 ng/mL for **9** and **11**, respectively, *versus* 120 ng/mL for manzamine A. The complete results regarding bioactivities and SAR of a series of ircinal analogs shall be reported in a full paper in due course.

ACKNOWLEDGMENTS

Jiangnan Peng and Subagus Wahyuono are gratefully acknowledged for providing ircinal A. We thank F. T. Wiggers and C. D. Dunbar, the National Center for Natural Products Research, for the spectral data. Financial support was provided by NIH (1R01A136598) and The Medicines for Malaria Venture.

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17. Ircinal A (**1**, 43 mg), tryptamine (**3**, 31 mg), and molecular sieves were stirred at room temperature in CH_2Cl_2 (3 mL) for 2 h. TFA (50 μL) was then added to the reaction mixture and further stirred for another 3 h at 50°C. The reaction mixture was chromatographed over silica gel immediately to give manzamine D (**7a**, 52.7 mg, 86%).
18. Perillaldehyde (**2**, 72 mg), tryptamine (**3**, 149 mg), and molecular sieves were stirred at room temperature in CH_2Cl_2 (3 mL) for 2 h. TFA (50 μL) was then added to the reaction mixture and further stirred for another 3 h at 50°C. The reaction mixture was chromatographed over silica gel immediately to give the Pictet-Spengler product (**4**, 104.1 mg, 75%).
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22. 7.78 (IH, br s), 7.51 (1H, d, *J* = 7.5 Hz), 7.35 (1H, br d, *J* = 7.5 Hz), 7.17 (1H, t, *J* = 7.5 Hz), 7.12 (1H, t, *J* = 7.5 Hz), 5.95 (1H, dd, *J* = 18, 7 Hz), 5.77 (1H, br s), 5.67 (1H, q, *J* = 9 Hz), 5.55 (1H, td, *J* = 10, 5 Hz), 5.30 (1H, t, *J* = 10 Hz), 4.60 (1H, s), 4.17 (1H, t, *J* = 7 Hz), 3.42 (1H, s), 3.35 (1H, m), 3.04 (2H, m), 2.83 (1H, m), 2.75 (2H, m), 2.51 (2H, m), and 1.20-2.40 (complex); ^{13}C NMR ($CDCl_3$) δ 141.2, 136.8, 135.6, 134.5, 133.9, 132.2, 129.9, 128.8, 127.8, 121.4, 119.2, 118.0, 111.0, 109.4, 75.3, 69.6, 68.5, 59.7, 54.9, 53.4, 50.8, 49.7, 47.3, 44.6, 43.2, 40.7, 37.8, 33.0, 31.8, 28.2, 26.9, 26.0, 25.7, 22.4, and 21.7; ESI-MS *m/z* 553 ($C_{36}H_{48}N_4O$ + H).
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28. 7.78 (IH, br s), 7.51 (1H, d, *J* = 7.5 Hz), 7.34 (1H, br d, *J* = 7.5 Hz), 7.17 (1H, t, *J* = 7.5 Hz), 7.11 (1H, t, *J* = 7.5 Hz), 5.92 (1H, dd, *J* = 18, 7 Hz), 5.62 (1H, q, *J* = 9 Hz), 5.53 (1H, td, *J* = 10, 5 Hz), 5.43 (1H, br s), 5.24 (1H, t, *J* = 10 Hz), 4.51 (1H, s), 4.14 (1H, t, *J* = 7 Hz), 3.40 (1H, s), 3.30 (1H, dt, *J* = 13, 5 Hz), 3.02 (2H, m), 2.83 (1H, m), 2.75 (2H, m), 2.51 (2H, m), and 1.20-2.40 (complex); ^{13}C

NMR ($CDCl_3$) δ 140.9, 135.8, 135.0, 134.5, 133.4, 131.8, 129.7, 128.9, 127.6, 121.6, 119.2, 118.0, 110.9, 110.8, 75.1, 69.2, 68.5, 56.7, 55.1, 53.6, 50.9, 49.7, 46.9, 44.4, 41.8, 40.8, 39.5, 32.9, 31.8, 28.1, 27.0, 26.1, 25.7, 22.8, and 21.6; ESI-MS *m/z* 553 ($C_{36}H_{48}N_4O$ + H).

29. Ircinal A (**1**, 50.9 mg) and tryptamine (**3**, 30.8 mg) in 1 mL anhydrous EtOH were added to 0.2 mL of TFA. The mixture was then absorded onto 1.5 g of silica gel. The silica mixture was placed in a glass vessel and was irradiated in a microwave oven (Panasonic NN-S543BFR-1300W) at 390 W for 10 min. The crude mixture was then eluted from the silica gel using acetone, concentrated, and chromatographed over silica gel to furnish manzamine D (**7a**, 15.3 mg, 23 %), *epi*-manzamine D (**7b**, 12.6 mg, 19%), and unreacted ircinal A (**1**, 16.3 mg).
30. A solution of manzamine D (**7a**, 10.9 mg) in CH_2Cl_2 (2 mL) at room temperature was added to DDQ (2,3-dichloro-5,6-dicyanobenzoquinone, 16.4 mg) in benzene (2 mL) and the mixture was stirred for 1 h. The mixture was then washed with saturated $NaHCO_3$ (5 ml), extracted with CH_2Cl_2 (2 x 5mL), dried ($MgSO_4$), and evaporated to give brownish oil. Chromatography of the crude over silica gel afforded manzamine A (**12**, 5.6 mg, 50 %) and unreacted manzamine D (**7a**, 5.1 mg, 50%). The 1H NMR and ESI-MS data of **12** were identical with the reported data of manzamine A (ref. 1).
31. Ircinal A (**1**, 38.8 mg) and 5-methoxytryptamine (**8**, 56.1 mg) in CH_2Cl_2 were reacted as described in ref. 17 to give ircinal C (**9**, 48.6 mg, 89%). Ircinal C (**9**; 6-methoxy-manzamine D): white amorphous; ^{1}H NMR ($CDCl_3$) δ 7.52 (1H, br s), 7.21 (1H, d, *J* = 8.8 Hz), 6.93 (1H, d, *J* = 1.6 Hz), 6.79 (1H, dd, *J* = 8.8, 1.6 Hz), 5.90 (1H, q, *J* = 8.3 Hz), 5.73 (1H, br s), 5.62 (1H, q, *J* = 8.5 Hz), 5.50 (1H, td, *J* = 10.4, 4.4 Hz), 5.22 (1H, t, *J* = 9.2 Hz), 4.14 (1H, br s), 3.85 (3H, s), 3.33 (2H, m), and 1.00-3.20 (complex); ^{13}C NMR ($CDCl_3$) δ 153.4, 141.1, 136.8, 134.8, 134.5, 132.2, 130.6, 129.9, 128.7, 128.2, 111.6, 111.1, 109.2, 100.4, 75.3, 69.5, 68.5, 59.8, 55.9, 54.8, 53.4, 50.7, 49.6, 47.3, 44.5, 43.2, 40.6, 37.7, 33.0, 31.8, 28.5, 26.8, 25.9, 25.7, 22.5, and 21.7; ESI-MS *m/z* 583 ($C_{37}H_{50}N_4O_2$ + H).
32. Ircinal A (**1**, 83.2 mg) and D-tryptophan methyl ester HCl (**10**, 67.1 mg) in EtOH were reacted as described in ref. 17 to give ircinal D (**11**, 87.6 mg, 70%). Ircinal D (**11**; 3-methoxycarbonyl-manzamine D): white amorphous; ^{1}H NMR ($CDCl_3$) δ 7.60 (1H, br s), 7.48 (1H, d, *J* = 7 Hz), 7.35 (1H, d, *J* = 7 Hz), 7.16 (1H, td, *J* = 7, 1 Hz), 7.10 (1H, t, *J* = 7 Hz), 5.9 (1H, q, *J* = 10 Hz), 5.86 (1H, br s), 5.64 (1H, q, *J* = 8 Hz), 5.52 (1H, td, *J* = 10, 4 Hz), 5.22 (1H, t, *J* = 9 Hz), 4.75 (1H, br s), 4.17 (1H, t, *J* = 6 Hz), 3.82 (3H, s), 3.37 (1H, br s), 3.12 (1H, br d, *J* = 15 Hz), 3.02 (1H, m), 2.88 (1H, br t, *J* = 12 Hz), 2.65 (1H, d, *J* = 11 Hz), and 1.20-2.55 (complex); ^{13}C NMR ($CDCl_3$) δ 173.4, 171.1, 142.8, 136.2, 132.7, 132.6, 127.5, 127.1, 121.7, 119.3, 117.8, 111.4, 108.7, 70.5, 70.1, 60.4, 59.7, 56.8, 56.2, 53.4, 52.5, 52.1, 49.3, 47.1, 44.2, 40.0, 37.7, 32.9, 28.3, 26.5, 25.7, 25.1, 24.8, 24.6, 21.0, 21.0, and 14.2; ESI-MS *m/z* 610 ($C_{38}H_{50}N_4O_3$ + H).