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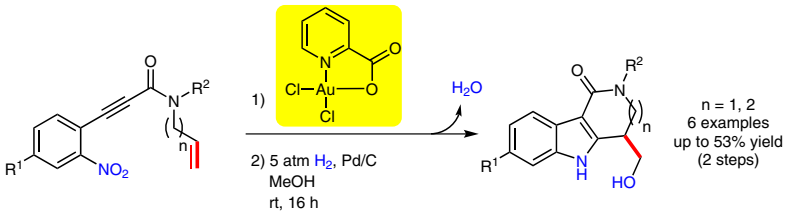
Synthesis of Piperidinone and Azepanone Fused Indoles via a Wagner–Meerwein Type 1,2-Amide Migration of 2-Spiropseudoindoxyls

Niels Marien
Ting Luo
Guido Verniest*

Research Group of Organic Chemistry, Department of Chemistry and Department of Bio-engineering Sciences, Faculty of Science and Bio-engineering Sciences, Vrije Universiteit Brussel (VUB), Pleinlaan 2, 1050 Brussels, Belgium
guido.verniest@vub.ac.be

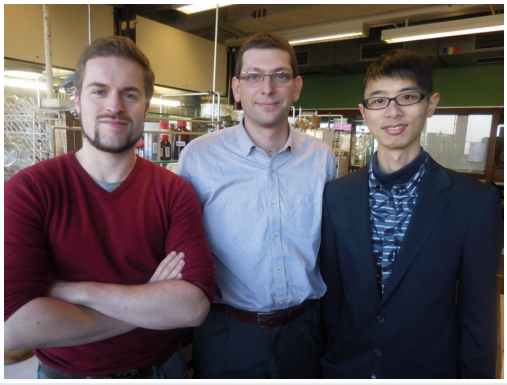


Received: 18.11.2016
Accepted after revision: 09.01.2017
Published online: 02.02.2017
DOI: 10.1055/s-0036-1588138; Art ID: st-2016-b0779-l

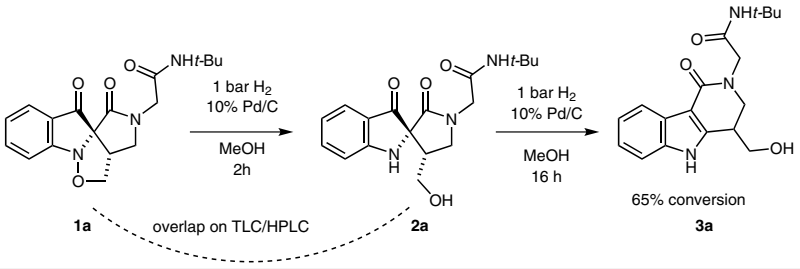
Abstract Spiropseudoindoxyls were synthesized by using a gold(III)-catalyzed intramolecular nitroalkyne redox–dipolar cycloaddition cascade. These compounds were then transformed into novel piperidinone and azepanone fused indoles via a straightforward hydrogenation. The reaction mechanism of this ring expansion is believed to proceed through a rare Wagner–Meerwein type 1,2-amide migration.

Key words dihydro-γ-carbolinone, Wagner–Meerwein, indoles, 1,2-acyl shift, spirocycles

Indoles are common motifs that are found in many natural products and biologically active molecules,[1] and a large variety of syntheses towards these structures are well documented. Strategies towards 2,3-disubstituted indoles include direct cyclizations to form the five-membered ring, direct derivatizations of the indole core and rearrangement reactions of indolone or indolenine derivatives.[2] Regarding the latter strategy, numerous examples have been described that proceed through C-3 to C-2 migratory aryl or alkyl 1,2-shifts. As an example, the Pictet–Spengler reaction is believed to proceed via a spiroindolenine intermediate, which subsequently rearranges through a 1,2-alkyl shift;[3] such shifts are also known to proceed under gold catalysis.[4] 3,3-Disubstituted 3*H*-indolinium species are known to give 2,3-disubstituted indoles through the Ciamician–Plancher rearrangement.[5] When the C-2 of the indolinium salt bears an alkyl substituent, this rearrangement is reversible and proceeds through both C-2 to C-3 and C-3 to C-2 alkyl migrations.[6] Remarkably, such Wagner–Meerwein type migratory 1,2-shifts from C-2 to C-3 to give 2,3-disubstituted indoles have barely been described. This rearrangement can occur for example when 3-hydroxy-2,2-disubstituted indolines are treated with acid to give the cationic C-3 intermediate. This reaction was reported in 1951 by Witkop and Patrick[7] and has only been described in a few examples since then, including a recent approach towards polycyclic indolines and indolenines starting from spiropseudoindoxyls (2-spiroindol-3-ones).[8]



Guido Verniest (born 1976) obtained his bio-engineering degree in chemistry from Ghent University, Belgium in 2000 and started PhD work on cyclobutanone and heterocyclic chemistry at the Department of Organic Chemistry at Ghent University under the guidance of Norbert De Kimpe. He obtained a PhD degree in 2004 and continued research in organofluorine chemistry as a FWO Postdoctoral Fellow also at Ghent University. In 2007, he undertook postdoctoral research in the laboratory of Albert Padwa at Emory University, Atlanta, Georgia (USA) where he worked on alkyne transformations towards heterocyclic compounds using gold and platinum catalysis. In 2008, he returned to Belgium to continue his work on organofluorine chemistry and, in 2010, he was appointed as Lecturer at the Faculty of Science and Bio-Engineering Sciences at the Vrije Universiteit Brussel (VUB) where he started his independent career. His main research focus involves synthetic methodology in heterocyclic organic chemistry, alkyne transformations and more applied research towards the synthesis of novel sugar and peptide derivatives.

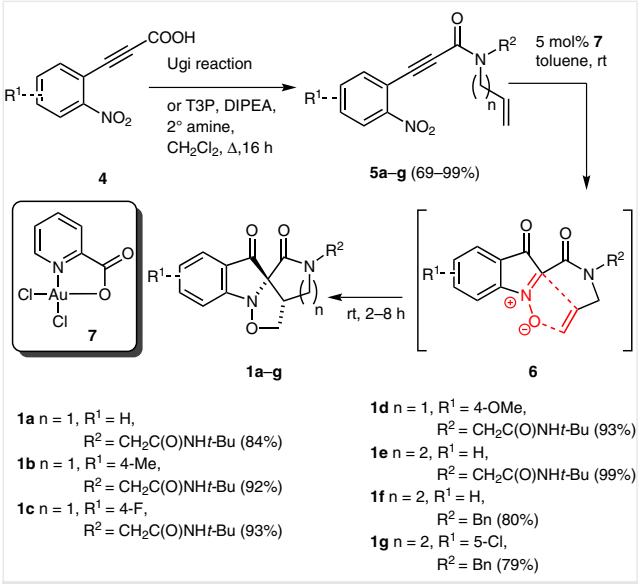


Scheme 1 Serendipitous over-reduction of **1a** towards fused indole **3a**

In a previous study by our group regarding the synthesis of 2-spiropseudoindoxyls, the selective N–O cleavage of **1a** towards **2a** was investigated.[9] For most examples, the reaction reached completion in two hours and afforded near-quantitative yields. However, in one case (Scheme 1), the 'closed' **1a** and 'open' pseudoindoxyl **2a** gave completely overlapping signals on both TLC and HPLC, suggesting at first sight that no conversion took place. After a prolonged reaction time (ca. 16 h), a significant conversion was observed towards dihydro-γ-carbolinone **3a** rather than the envisioned spiropseudoindoxyl **2a**. Compounds containing this dihydro-γ-carbolinone core are known to display interesting bioactivities (e.g., Alosteron, a 5-HT_3 serotonin receptor antagonist).[10] Although this transformation was an unexpected discovery, the conditions that were used appeared to be too mild to obtain full conversion. A further optimization towards the synthesis of **3** was therefore necessary.

The starting materials **1** for this optimization study and for the subsequent exploration of the scope of the reaction were synthesized from carboxylic acids **4** in a simple two-step approach (Scheme 2). Both the Ugi reaction and amide bond formation through activation of **4** with T3P (*n*-propanephosphonic acid anhydride) gave amides **5** in good yields. Treatment of **5** with catalytic amounts of gold catalyst **7**[11] at room temperature resulted in cycloisomerization towards isatogen **6**, followed by spontaneous [3+2]-cycloaddition to afford pseudoindoxyls **1** in excellent yields.[9]

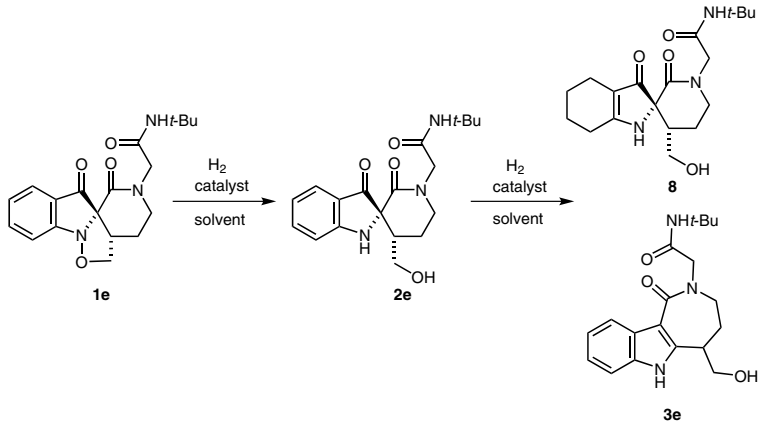
Given our group's ongoing interest in azepinone containing polyheterocycles,[12] substrate **1e** was chosen as a model substrate for the screening of hydrogenation conditions, expecting that the ring expansion of a six-membered to a seven-membered ring would be more difficult than conversion of **1a** into **3a**. The original 1 bar hydrogenation was chosen as a benchmark and resulted in ca. 45% conversion of **2e** after 16 hours at room temperature (Table 1). However, conversion stagnated afterwards, and even prolonged reaction times (up to 7 days) did not drive the reaction further towards completion. This difficulty in hydrogenation probably arises from the steric hindrance caused by the adjacent spirocyclic lactam. A simple increase in hydrogen pressure was attempted while keeping solvent and catalyst the same. This already led to a significant increase in conversion, while also giving rise to the formation of side product **8** through partial hydrogenation of the benzene ring of intermediate **2e**.[13]



Scheme 2 Synthesis of spiropseudoindoxyls **1** from carboxylic acids **4**

Either increasing or lowering the reaction temperature (entries 3 and 4) was largely inefficient because this resulted in either a loss of hydrogenation chemoselectivity or conversion, respectively. A solvent switch to ethanol also had a detrimental effect on the formation of **3e**. Other hydrogenation catalysts were also screened (entries 6 and 7) but in these cases no indole formation was observed. However, the use of PtO_2 as a catalyst facilitated a clean conversion of **1e** into **8**, providing a facile entry to these fused spiropyrrolinones **8**. Finally, generation of a catalytic amount of HCl in situ through hydrogenation of chlorobenzene was evaluated (entry 8)[14] but this also did not lead to an increased formation of indoles **3e**. After this limited optimization study, it was decided to use the conditions described in entry 2 (Table 1) to evaluate the scope of the reaction.

Table 1 Evaluation of Reaction Conditions for the Synthesis of **3e** from **1e**

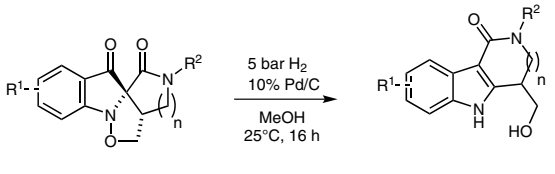


Entry	Conditions	Ratio **2e**/**3e**/**8**[a]
1	1 bar H_2, 10 mol% Pd/C, MeOH, r.t.	56:41:3
2	5 bar H_2, 10 mol% Pd/C, MeOH, r.t.	23:59:18
3	5 bar H_2, 10 mol% Pd/C, MeOH, 10 °C	60:16:24
4	5 bar H_2, 10 mol% Pd/C, MeOH, 70 °C	complex mixture
5	5 bar H_2, 10 mol% Pd/C, EtOH, r.t.	16:7:77
6	5 bar H_2, 10 mol% Pt/C, MeOH, r.t.	93:0:7
7	5 bar H_2, 10 mol%PtO_2, MeOH, r.t.	36:0:64
8	5 bar H_2, 10 mol% Pd/C, MeOH, r.t., 10 mol% PhCl	44:28:28

[a] Ratios based on HPLC analysis; reactions were performed on 50 mg scale (0.025 mM); full conversion of **1e** into **2e**, **8** and/or **3e** was observed in all cases (HPLC).

While conversion of **1e** into **3e** was deemed acceptable, isolation of **3** from the reaction mixture proved to be challenging. Indoles **3** displayed very poor solubility in most organic solvents, except for dimethyl sulfoxide (DMSO) and warm AcOH. Considering the need to remove the heterogeneous Pd/C catalyst either by filtration or centrifugation, this lack of solubility was unfortunate. A minor washing step with DMSO after filtration was therefore introduced during workup to circumvent this issue as much as possible. After evaporation of the methanol, the crude reaction mixture in DMSO was purified further by direct reverse-phase (C18) flash chromatography.

To evaluate the scope of this reaction, a number of spiropseudoindoxyls **1** were subjected to the optimized reaction conditions (Scheme 3). In the case of five-membered rings **1a–d**, no side product **8** formation was observed and conversions were in general quite clean. Both electron-donating and electron-withdrawing groups were tolerated and the desired dihydro-γ-carbolinones **3a–d** could be isolated. For six-membered rings **1e–f**, we expected yields to be lower due to byproduct **8** formation and therefore a more difficult chromatographic purification. This was largely consistent with experimental observations, as indoloazepinones **3e–f** were isolated in relatively low yields. When a chlorine atom was used as a substituent in **1g**, hydrogenative dechlorination and indole formation occurred equally fast, resulting in the formation of **3f** rather than **3g**.



1

3a n = 1, R^1 = H, R^2 = $CH_2C(O)NHt$-Bu (55%)
3b n = 1, R^1 = 4-Me, R^2 = $CH_2C(O)NHt$-Bu (51%)
3c n = 1, R^1 = 4-F, R^2 = $CH_2C(O)NHt$-Bu (57%)

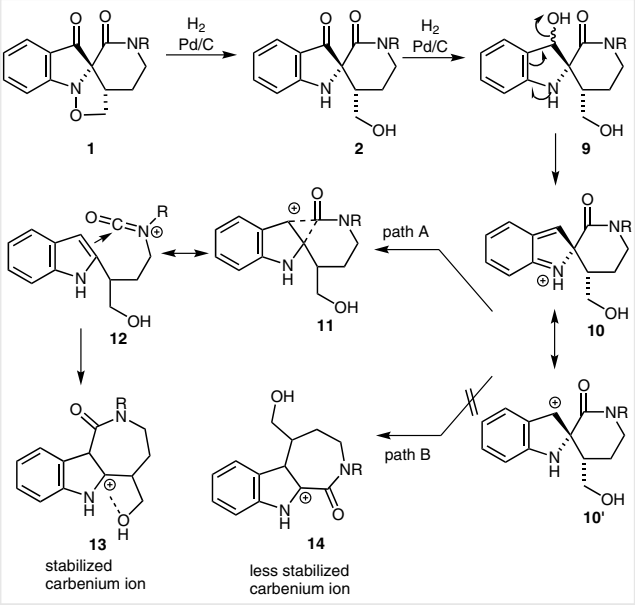
3

3d n = 1, R^1 = 4-OMe, R^2 = $CH_2C(O)NHt$-Bu (35%)
3e n = 2, R^1 = H, R^2 = $CH_2C(O)NHt$-Bu (31%)
3f n = 2, R^1 = H, R^2 = Bn (17%)
3g n = 2, R^1 = 5-Cl, R^2 = Bn (0%)

Scheme 3 Scope evaluation using the optimized conditions

Concerning the reaction mechanism, it is noteworthy that only migration of the amide carbonyl was observed (Scheme 4, path A), because alkyl groups are also known to migrate after acid treatment of 3-hydroxy-2,2-dialkylindolines.[15] The 1,2-shift of an amide functionality in indolines

of type **2** (spirocyclic or not) has not been described previously. It has been shown that in azapinacol-type migrations, substituents that stabilize a cationic center have larger migratory aptitude because of the proposed 3-center-2-electron transition state (cf. **11**).[16] Next to these electronic properties of the migrating groups, the stability of the cationic intermediate also needs to be taken into account. In our case, the migrating carbonyl group can stabilize the generated positive charge at C through delocalization from the amide N-atom (cf. **12**). In addition, this migration leads to a stabilized intermediate **13**, whereas in the case of an alkyl migration the generated positive charge is destabilized by the electron-withdrawing amide carbonyl group (cf. **14**). This result is consistent with the migration of ester groups over alkyl groups in related Wagner–Meerwein type rearrangements.[15–17] We were able to identify only one paper in which a 1,2-acyl shift was observed in substituted 3-hydroxyindolines;[8f] in that case, the reduction of duocarmycin induced the C-2 to C-3 migration of an ester carbonyl group.



Scheme 4 Mechanistic proposal

In conclusion, we synthesized piperidinone and azepanone fused indoles through a Wagner–Meerwein type 1,2-amide migration of 2-spiroindolinones. The proposed amide migration is unprecedented in indolines and offers a simple procedure that facilitates access to these interesting polyheterocycles.[18–21]

Acknowledgment

The authors acknowledge the Vrije Universiteit Brussel (starting grant for G.V. and AAP-PhD Fellowship for N.M.) and the Research Fund-Flanders (FWO-KN249) for financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588138.

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(18) **Synthesis of carboxylic acids 4; Typical procedure for 4a.** A flame-dried, three-necked, flat-bottom flask was charged with DMSO (35 mL). CO_2 was dried by sublimating dry ice and bubbled through two wash bottles containing concentrated sulfuric acid, similar to Vogel's procedure. The dried CO_2 was bubbled through the DMSO solution for 5 min before adding the reagents. Caesium fluoride (3.12 g, 20.5 mmol) was dissolved in the stirring mixture and 1-(2-nitrophenyl)-2-trimethylsilylacetylene (3.00 g, 13.7 mmol) was added subsequently by using a syringe. After reaction for 2 h at room temperature, the mixture was acidified with 2 M aq HCl and extracted with ethyl acetate (5 × 75 mL). The combined organic phases were concentrated to a total volume of ca. 150 mL, washed with brine (5 × 150 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to afford the desired carboxylic acid **4a** (90%, 2.36 g, 12.3 mmol) as a pale-pink solid. ^{1}H NMR (250 MHz, DMSO-d_6): δ = 14.22 (br s, 1 H), 8.23 (dd, *J* = 7.5, 1.5 Hz), 7.75–7.95 (m, 3 H). ^{13}C NMR (63 MHz, DMSO-d_6): δ = 153.9, 149.5, 135.5, 134.1, 131.8, 125.2, 124.8, 87.3, 79.1.
(19) **Synthesis of amides 5; Typical procedure for 5a.** A round-bottom flask was charged with carboxylic acid **4a** (250 mg, 1.3 mmol) dissolved in methanol (0.1 M). Subsequently, formaldehyde (37% in water; 97 µL, 1.3 mmol) and allylamine (98 µL, 1.3 mmol) were added and the resulting mixture was stirred for 15 min at room temperature. *tert*-Butyl isocyanide (148 µL, 1.3 mmol) was added and the reaction was heated to 50 °C and stirred overnight. Upon completion, the reaction mixture was concentrated in vacuo, dissolved in EtOAc (25 mL), and washed with aqueous saturated $NaHCO_3$ (25 mL), 1 M aq HCl (25 mL) and brine (25 mL). The organic phase was dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting crude mixture was purified by silica gel column chromatography (EtOAc/hexanes, 50%) to afford the desired amide **5a** (75%, 0.34 g, 0.98 mmol) as a red oil. R_f 0.27 (EtOAc/hexanes, 50%). IR (neat): 3325, 3088, 3064, 2974, 2224, 1684, 1648, 1567, 1341 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.08 (m, 1 H), 7.73 (m, 1 H), 7.60 (m, 2 H), 6.09 and 5.84* (br s, 1 H), 5.88–5.63 (m, 1 H), 5.20 (m, 2 H), 4.36 and 4.11* (d, *J* = 6.0 Hz, 2 H), 4.17 and 3.90* (s, 2 H), 1.27 and 1.25* (s, 9 H). ^{13}C NMR (63 MHz, $CDCl_3$): δ = 167.0 and 168.8*, 154.7 and 154.3*, 149.4, 136.3 and 136.1*, 133.7 and 133.6*, 132.0 and 131.6, 131.0, 125.2, 119.1, 115.9, 87.5 and 87.2*, 85.3 and 84.5*, 52.9 and 51.63*, 51.8 and 51.56*, 49.7 and 48.6*, 28.7. HRMS: *m*/*z* [M + H]$^+$ calcd: 344.1605; found: 344.1612. * Double signals due to rotamers across the C–N bond of the amide as well as the carbamate.
(20) **Gold-catalyzed cycloisomerization towards spiropseudoindoxyls 1; Typical procedure for 1a.** A round-bottom flask was charged with amide **5a** (200 mg, 0.58 mmol) and dissolved in toluene (6 mL; 0.1 M relative to **1a**). To this solution was added dichloro(2-pyridinecarboxylato)gold (11.4 mg, 0.029 mmol) in one portion. The resulting mixture was stirred at room temperature for 4 h. Subsequently, the reaction was concentrated in vacuo, followed by the addition of ethyl acetate (6 mL, 0.1 M relative to **1a**). This resulted in the formation of a gray precipitate, which was separated by decantation. The decanted organic phase was filtered through a silica plug, washed with additional EtOAc and concentrated in vacuo. Both the precipitate and the solid obtained from the EtOAc fraction were deemed pure based on HPLC and NMR analysis and combined to afford the desired spiropseudoindoxyl **1a** (84%, 0.17 g, 0.5 mmol) as a gray solid. Mp 206–207 °C (decomp.). IR (neat): 3332, 2970, 2933, 1682 (br), 1606, 909, 727 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (m, 2 H), 7.49 (d, *J* = 8.1 Hz, 1 H), 7.33 (t, *J* = 7.5 Hz; 1 H), 5.94 (br s, 1 H), 4.03–3.86 (m, 4 H), 3.83 (dd, *J* = 9.5, 5.2 Hz, 1 H), 3.50 (dd, *J* = 10.0, 4.9 Hz), 3.41 (m, 1 H), 1.38 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.1, 168.6, 166.2, 162.9, 137.8, 126.9, 126.1, 124.3, 119.0, 83.0, 73.3, 51.9, 51.2, 48.7, 44.6, 28.9. HRMS: *m*/*z* [M + H]$^+$ calcd: 344.1605; found: 344.1606.
(21) **Hydrogenation towards indoles 3; Typical procedure for 3a.** A Teflon insert for a Parr hydrogenation vessel was flushed with argon and charged with spiropseudoindoxyl **1a** (240 mg, 0.70 mmol). After dissolving this solid in methanol (10 mL; ca. 0.05 M), the resulting solution was flushed again with argon. Palladium on carbon (74 mg, 10wt%, 0.07 mmol.) was added in one portion, followed by rinsing of the insert walls with methanol if necessary. The reaction mixture was then subjected to 5 bar of hydrogen in a Parr series 4793 high-pressure vessel and stirred for 16 h at room temperature. Subsequently, the reaction mixture was transferred to a vial of appropriate size and centrifuged to afford a semiclear solution, which was filtered through a plug of Celite. The precipitated solid was washed with MeOH (2 × 5 mL) and DMSO (1 mL) in MeOH (5 mL) and the centrifugation/filtration steps were repeated. The resulting solution was concentrated in vacuo until only the DMSO (ca. 1 mL) remained. This crude mixture was purified by reverse-phase column chromatography with liquid loading and using Milli-Q water+0.1% TFA / acetonitrile+0.1% TFA as eluents (see the Supporting Information for gradient details). Acetonitrile and trifluoroacetic acid were evaporated and the remaining water was removed by freeze-drying to afford the desired fused indole **3a** (55%, 126 mg, 0.38 mmol) as a white solid. Mp 241–242 °C. IR (neat): δ = 1660, 1623, 1489, 1454, 1218, 1177, 785, 741 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.60 (br s, 1 H), 7.91 (d, *J* = 7.5 Hz, 1 H), 7.53 (br s, 1 H), 7.41 (d, *J* = 7.5 Hz, 1 H), 7.11 (m, 2 H), 5.00 (br s, 1 H), 4.08 (d, *J* = 15.4 Hz, 1 H), 3.94 (d, *J* = 15.4 Hz, 1 H), 3.77 (m, 2 H), 3.66 (dd, *J* = 9.2, 8.5 Hz, 1 H), 3.57 (dd, *J* = 12.2, 6.4 Hz, 1 H), 3.24 (qt, *J* = 5.7 Hz, 1 H), 1.28 (s, 9 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.4, 164.1, 144.6, 136.2, 125.2, 121.6, 120.6, 119.6, 111.7, 105.2, 61.6, 50.2, 49.8, 48.8, 36.3, 28.6. HRMS: *m*/*z* [M + H]$^+$ calcd: 330.1812; found: 330.1810.