Synthesis of Nuevamine Aza-Analogues by a Sequence: I-MCR–Aza-Diels–Alder–Pictet–Spengler

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Abstract: A series of nuevamine aza-analogues were prepared in moderate to good yields in two reaction steps. The synthetic strategy involves an isonitrile-based multicomponent reaction, including an aza-Diels–Alder cycloaddition and Pictet–Spengler reaction as postcondensation.

Key words: nuevamine aza-analogue, I-MCR, aza-Diels–Alder, S-oxidation, Pictet–Spengler cyclization

Heterocyclic compounds of type tetrahydroisoindolo[1,2-*a*]isoquinoline amides are an important class of tetracyclic lactams with a relatively high occurrence in nature.[1] (±)-Nuevamine (**1**)[2] is an alkaloid isolated from *Berberis Darwinii* Hook, which occupies a special place in natural product chemistry, since it was the first recognized tetrahydroisoindolo[1,2-*a*]isoquinoline amide reported from natural sources (Scheme 1).

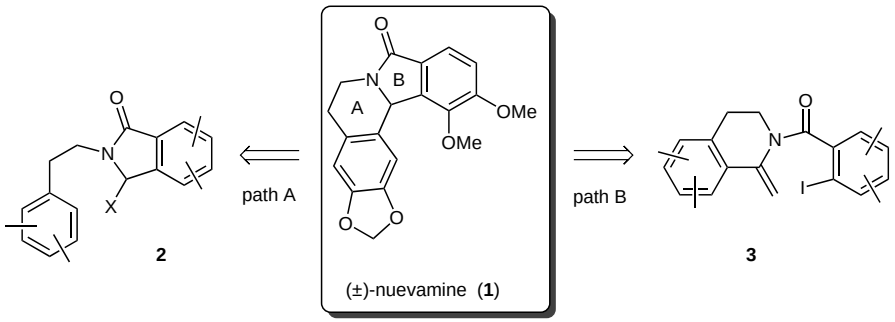
Two main general approaches for the synthesis of tetrahydroisoindolo[1,2-*a*]isoquinoline amides have been reported.[3] They differ in the type of annulation process and in the hetero-ring unit embedded in the alkaloid skeleton formed in the last step. Thus, ring A (Scheme 1, path A) of the tetrahydroisoquinoline unit, in molecules fused with the isoindolinone moiety, has generally been built either through a Parham cyclization or a Pomeranz–Fritsch–Bobbitt, Pictet–Spengler, or Bischler–Napieralski reaction. Other sophisticated methods have also been employed, these involving either harsh conditions, sensitive reagents, or multiple steps.[4]

The formation of ring B has been performed by an intramolecular Heck cyclization of aromatic enamides **3**,[5] (Scheme 1, path B). There are few reports in the literature about the preparation of nuevamine aza-analogues.[6]

During the annulation process to prepare the lennoxamine aza-analogues **5** by a Pummerer cyclization of *S*-oxides **4**, the tetrahydroazaisoindolo[1,2-*a*]isoquinoline amides **6** were unexpectedly isolated in moderate to good yields (Scheme 2).

The use of a combination of isocyanide-based multicomponent reactions (I-MCR)[7] with other postcondensation processes is a powerful tool to prepare numerous highly functionalized heterocyclic molecules and compounds with high molecular complexity, in a minimum of steps, from either commercially available or readily isolable starting materials.

As a part of our own efforts to develop short and versatile routes for the preparation of novel nitrogen heterocyclic



Scheme 1 General approaches for the synthesis of tetrahydroisoindolo[1,2-*a*]isoquinoline amides

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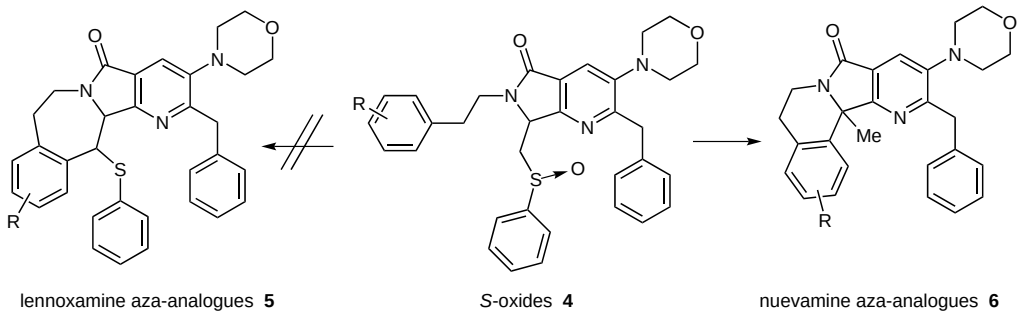
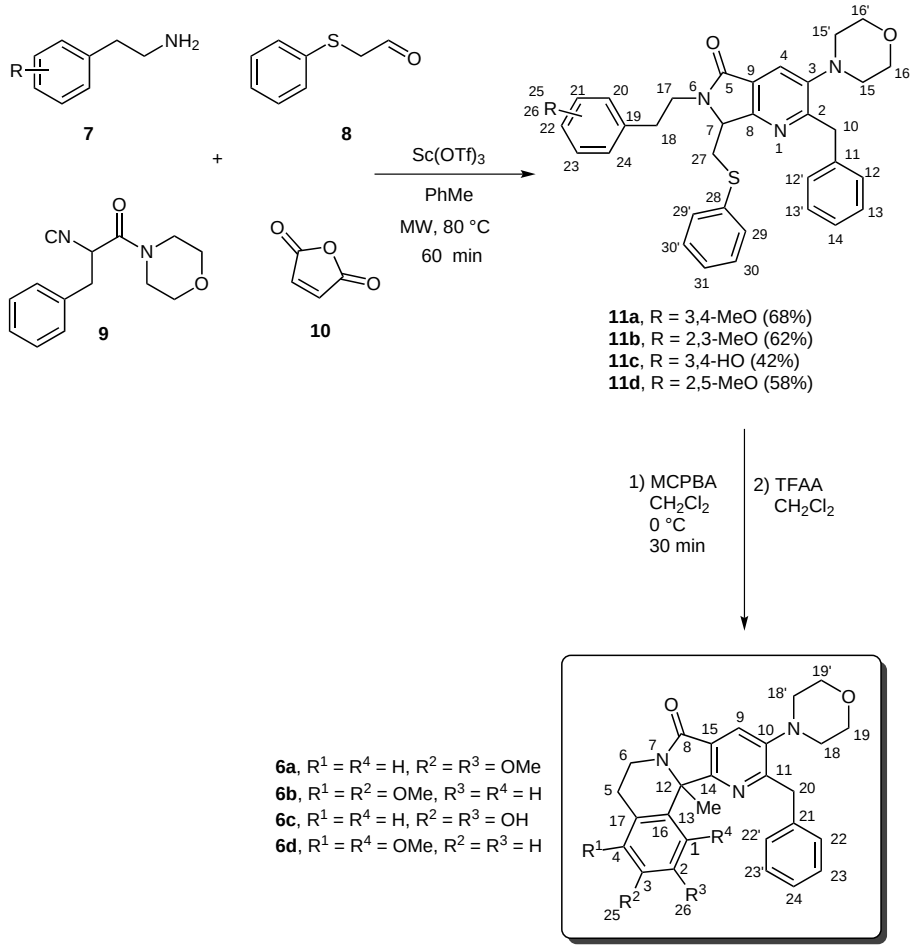


Scheme 2 Unexpected nuevamine aza-analogue formation

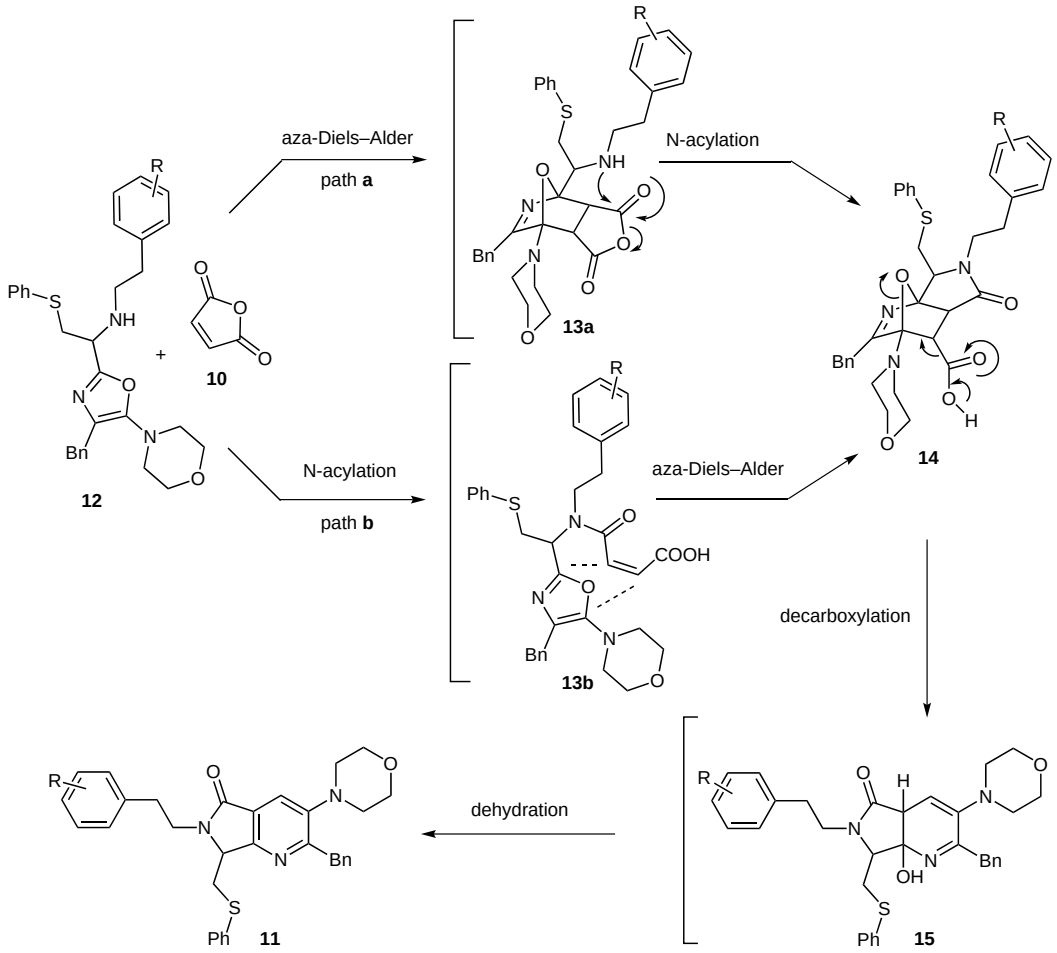
structures,[8] we herein describe the synthesis of an aza-analogue series of tetrahydroisoindolo[1,2-*a*]isoquinoline amides. Our strategy (Scheme 3) involved six processes in two steps: (1) I-MCR; (2) aza-Diels–Alder; (3) aromatization; (4) S-oxidation; (5) acyloxysulfonium β-elimination; and (6) Pictet–Splenger cyclization. This strategy is based on the preparation of pyrrolo[3,4-*b*]pyridin-5-ones **11** and their use as key intermediates in the Pictet–Spengler reaction.

In the first step, the pyrrolo[3,4-*b*]pyridin-5-one series **11a–d** was prepared in moderate to good yields applying the protocol recently reported by our group,[6d,9,10] which involves a consecutive process Ugi-3CR/aza-Diels–Alder, followed by aromatization (Scheme 3).

It is likely that the mechanism of formation pyrrolo[3,4-*b*]pyridin-5-ones **11** starts from 5-aminooxazoles **12** (Ugi-3CR adducts), which reacts with maleic anhydride (**10**) by an aza-Diels–Alder cycloaddition to obtain cycloadduct **13a** (Scheme 4). Then, an intramolecular N-acylation occurs to give intermediate **14** (path a). However, an alternative cyclization mechanism may be considered,[11] which take place from 5-aminooxazoles **12** involving first intermolecular transamidation to lead amide **13b** (path b), followed by the intramolecular Diels–Alder reaction to give



Scheme 3 Synthesis of nuevamine aza-analogues **6a–d**



Scheme 4 Mechanism for the formation of pyrrolo[3,4-*b*]pyridine-5-ones **11**

intermediate **14**. Aromatization process from **14** to **11** can be explained by decarboxylation of the β-keto acid function of **14**, followed by an intermolecular base-assisted dehydration process of compound **15** favored by the temperature that was used.[12]

In the second step, compounds **11a**–**d** were S-oxidized to obtain the corresponding *S*-oxide series **4a**–**d** employing the typical oxidation conditions (MCPBA, CH_2Cl_2, 0 °C).[13] As part of our interest in obtaining compounds containing the lennoxamine skeleton from the sulfoxides **4a**–**d** via a Pummerer-type cyclization,[14] we used the conditions reported by Ishibashi et al.,[15] which employs trifluoroacetic anhydride (TFAA) as the *S*-oxide activator to promote the final cyclization process. To our surprise, the unexpected nuevamine aza-analogue **6a** was isolated in moderate yield.[16]

After the characterization of novel compound **6a**, we assumed that the reaction was carried out by a Pictet–Spengler cyclization.[17] Table 1 (entry 2) shows that compound **6a** was isolated at a yield of 89% when the reaction was carried out at 0 °C, and of 92% at room temperature (Table 1, entry 3). The latter conditions were employed for the preparation of nuevamine aza-analogues **6b**,**c** (Table 1, entries 4 and 5). When the attempt was made to obtain compound **6d** under the same conditions (Table 1, entry 6), only the starting material was observed. Compound **6d** was first isolated at 20% of yield under heating at reflux (Table 1, entry 7). We tried to improve the result by using microwaves as a heat source, with a slight increase in the yield (Table 1, entry 8). Finally, with the idea of increasing the temperature, we changed the solvent from dichloromethane to ethanol raising the yield to 38% (Table 1, entry 9). The lowest yield obtained for derivative **6d** is probably due to the hindrance effect of the methoxy group as R^4 during the final cyclization. One important feature of this process is that the starting materials (corresponding to *S*-oxides **4**) were ever recovered, and for this reason additional trials were carried out to increase the yield of **6d**, even using higher temperatures. However, decomposition of both the final product and starting material was observed.

The structure of these novel compounds **6a**–**d** was established by spectroscopic analysis (^1H, ^{13}C, DEPT, COSY, HSQC, HMBC, IR, and HRMS).

A reasonable reaction mechanism that can account for the conversion of the *S*-oxides **4** into the corresponding nuevamine aza-analogues **6** is depicted in Scheme 5. Condensation of **4** with TFAA gives the acyloxysulfonium salts

Table 1 Results for Nuevamine Aza-Analogues **3a–d**

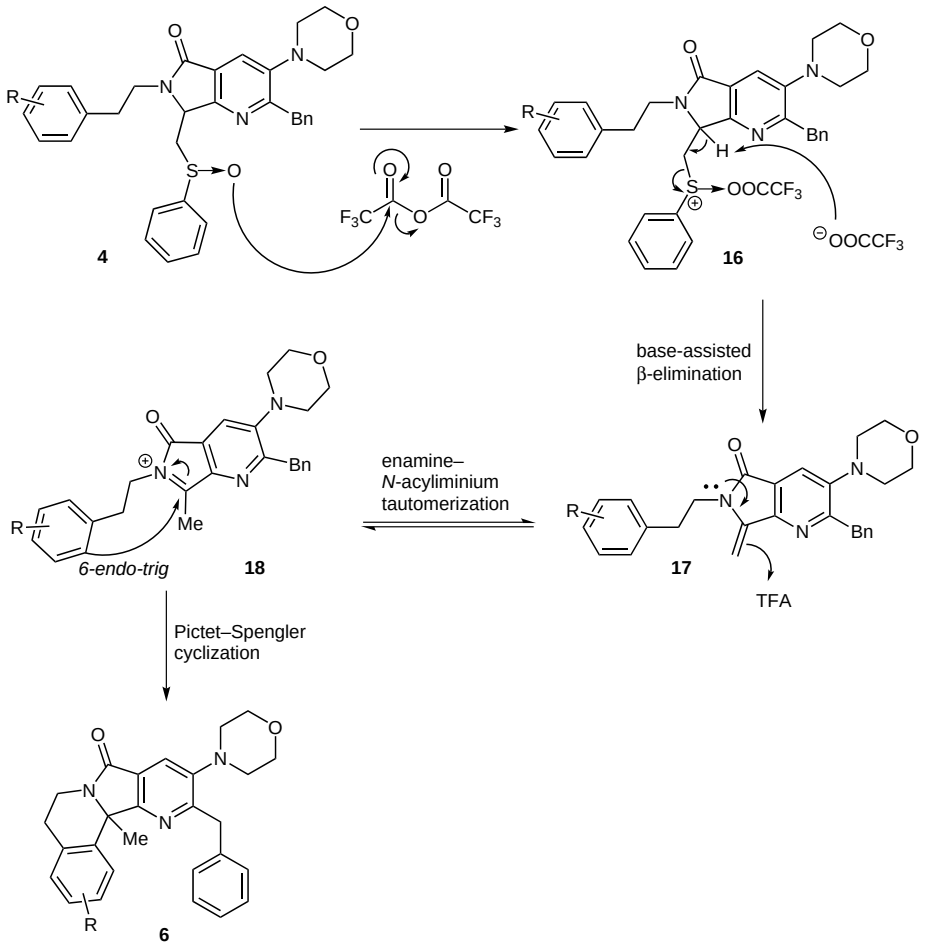
Entry	Conditions	Time (h)	Yield (%)	Product
1	CH_2Cl_2, –45 °C	16	60	**6a**
2	CH_2Cl_2, 0 °C	8	89	**6a**
3	CH_2Cl_2, 25 °C	3	92	**6a**
4	CH_2Cl_2, 25 °C	3	87	**6b**
5	CH_2Cl_2, 25 °C	3	60	**6c**
6	CH_2Cl_2, 25 °C	24	n.r.	**6d**
7	CH_2Cl_2, reflux	36	20	**6d**
8	CH_2Cl_2, MW, 52 °C	3	24	**6d**
9	EtOH, MW, 75 °C	1.5	38	**6d**

16, which by a subsequent trifluoroacetate ion assisted β-elimination process provides the enamide intermediate **17**. Tautomerization of the latter gives the reactive *N*-acyliminium ion intermediates **18**. Then, a TFA-promoted Pictet–Spengler cyclization furnishes **6**. The highly favored 6-*endo*-trig cyclization gave the novel nitrogen polyheterocycles **6** under mild protic conditions.

One possible rationalization for the observed behavior of the *S*-oxide group is the acidity of proton H-7 and the stability of the resulting enamide moiety in **17**. Both effects promote the elimination of the leaving group in intermediate **16**.[18]

The generation of the *N*-acyliminium ions from enamides is facilitated by the acidic reagent, the solvent, and the substrate structure.[19] Although the role of *S*-oxides as precursors of *N*-acyliminium ions in a Pummerer–Mannich cascade process has been reported by Padwa et al.,[20] the Pictet–Spengler reaction observed in this work appears to be a new contribution in these closely related transformations.

In summary, this methodology represents a powerful tool for the preparation of nuevamine aza-analogues and shows the potential of the Pictet–Spengler cyclization as an Ugi postcondensation.[21] In contrast to the conventional methodologies for the preparation of tetrahydroisoindoloisoquinoline amides, which require strong conditions; the present methodology uses mild conditions. This synthetic strategy is an example of a sustainable annulation process in which only one step is required for the preparation of the key precursor. The asymmetric version of this methodology is currently in process, and it will be reported in due course.



Scheme 5 Plausible reaction mechanism for the transformation of **4** to **6**

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(10) **Procedure for the Synthesis of Pyrrolo[3,4-*b*]pyridin-5-ones 11a–d: Selected Compound 6-(3,4-Dimethoxyphenethyl)-2-benzyl-6,7-dihydro-3-morpholino-7-[(phenylthio)methyl]pyrrolo[3,4-*b*]pyridin-5-one (11a)**

3,4-Dimethoxyphenethylamine (0.671 mmol, 1.0 equiv) and 2-thiophenylacetaldehyde (0.603 mmol, 0.9 equiv) were placed in a 10 mL sealed CEM Discover™ microwave reaction tube and diluted in 1.0 mL of dry toluene. Then, the mixture was irradiated (MW, 80 °C, 25 W) for 10 min and $Sc(OTf)_3$ (0.0211 mmol, 0.03 equiv) was added. The mixture was irradiated (MW, 80 °C, 25 W) for 10 min, and 2-isocyano-1-morpholino-3-phenylpropan-1-one (0.805 mmol, 1.2 equiv) was added. The mixture was again irradiated (MW, 80 °C, 25 W), this time for 15 min, and maleic anhydride (0.805 mmol, 1.2 equiv) was added. Finally, this reaction mixture was irradiated (MW, 80 °C, 25 W) for 15 min, and the solvent was removed under reduced pressure. The crude was dissolved in CH_2Cl_2 (5.0 mL) and washed with a concentrated aq solution of $NaHCO_3$ (3 × 25 mL) and with brine (3 × 25 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was immediately purified using a silica gel chromatoflash (hexane–EtOAc = 2:1) to afford compound **11a** (68%) as a pale yellow powder; mp 58–59 °C; R_f = 0.25 (hexane–EtOAc = 1:1).

Spectral Data for Compound 11a

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79 (s, 1 H, H-4), 7.25–7.13 (m, 10 H, HAr), 6.76–6.69 (m, 3 H, HAr), 4.51 (m, 1 H, H-7), 4.27 (d, *J* = 14.2 Hz, 1 H, H-10), 4.19 (d, *J* = 14.2 Hz, 1 H, H-10), 4.21–4.13 (m, 1 H, H-17), 3.83 (s, 3 H, H-25), 3.83–3.79 (m, 4 H, H-16), 3.78 (s, 3 H, H-26), 3.56 (dd, *J* = 14.1, 3.8 Hz, 2 H, H-27), 3.25–3.19 (m, 1 H, H-17), 2.96–2.89 (m, 1 H, H-18), 2.88–2.82 (m, 1 H, H-18), 2.82–2.80 (m, 4 H, H-15). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.0 (C-5), 161.1 (C-2), 158.3 (C-8), 148.9 (C-23), 147.8 (C-3), 147.6 (C-22), 139.2 (C-11), 135.2 (C-28), 131.0 (C-19), 130.7 (C-12), 128.8 (C-13), 128.8 (C-29), 128.3 (C-30), 126.7 (C-14), 126.2 (C-31), 125.1 (C-9), 123.2 (C-4), 120.5 (C-20), 111.8 (C-21), 111.2 (C-19), 67.1 (C-16), 60.1 (C-7), 55.9 (C-25, C-26), 52.9 (C-15), 41.7 (C-17), 39.8 (C-10), 35.6 (C-27), 34.0 (C-18). FT-IR (film in CH_2Cl_2): 1691 (C=O) cm^{-1}. HRMS: *m/z* calcd for $C_{33}H_{31}N_3O_4S$: 595.2505; found: 595.2507.

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(16) **Procedure for the Synthesis of Nuevamine Aza-Analogues 6a–d: Selected Compound 6a**

To a stirred solution of *S*-oxide **4a** (0.034 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL) at 0 °C, drops of TFAA (0.172 mmol, 5.0 equiv) were added. After stirring at r.t. for 3 h, the solvent was removed under reduced pressure, and the crude was

dissolved in CH_2Cl_2 (1.0 mL), and washed with an aq solution of $NaHCO_3$ (3 × 10 mL) and with brine (3 × 10 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed under vacuum. The residue was immediately purified using a silica gel chromatoflash (hexane–EtOAc = 1:1) to afford compound **6a** (92%) as a pale pink powder; mp 72–74 °C; R_f = 0.15 (hexane–EtOAc = 1:1).

Spectral Data for Compound 6a

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (s, 1 H, H-9), 7.67 (s, 1 H, H-4), 7.27–7.16 (m, 5 H, HAr), 6.55 (s, 1 H, H-1), 4.67–4.63 (m, 1 H, H-6), 4.50 (d, *J* = 14.5 Hz, 1 H, H-20), 4.32 (d, *J* = 14.5 Hz, 1 H, H-20), 3.83–3.79 (m, 7 H, H-19, H-25), 3.67 (s, 3 H, H-26), 3.42–3.26 (m, 1 H, H-6), 3.06–2.99 (m, 1 H, H-5), 2.84–2.82 (m, 4 H, H-18), 2.76–2.72 (m, 1 H, H-5), 1.81 (s, 3 H, H-13). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7 (C-8), 163.5 (C-16), 161.0 (C-11), 148.0 (C-3), 147.7 (C-10), 147.5 (C-2), 139.6 (C-21), 129.6 (C-16), 128.9 (C-22), 128.3 (C-23), 126.2 (C-24), 124.6 (C-17), 123.7 (C-9), 123.1 (C-15), 111.2 (C-1), 109.9 (C-4), 67.2 (C-19), 63.1 (C-12), 55.9 (C-25), 55.8 (C-26), 53.0 (C-18), 40.0 (C-20), 34.7 (C-6), 29.0 (C-5), 27.9 (C-13). FT-IR (film in CH_2Cl_2): 1693 (C=O) cm^{-1}. HRMS: *m/z* calcd for $C_{33}H_{29}N_3O_4S$: 485.2315; found: 485.2314.

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