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Enantioselective total synthesis of pyrroloquinolone as a potent PDE5 inhibitor

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ABSTRACT

A concise enantioselective strategy for the synthesis of key PDE5 inhibitor **2** was developed in **5** and **6** steps using asymmetric hydrogenation and one-pot chiral auxiliary approaches, respectively. The synthesis features the use of imine **6** obtained through Bischler–Napieralsky reaction from amide **5**. Absolute *R* configuration was introduced in (+)-**7** by asymmetric transfer-hydrogenation reaction with Ru(II) catalyst followed by establishing the tricyclic pyrroloquinalone core using the Winterfeldt oxidation. Another alternative synthetic approach for the introduction of chirality in the molecule employed imine **6** and chloroformates of different chiral auxiliaries, which achieved *N*-acyliminium ion intermediates that were reduced in situ using $PdCl_2/Et_3SiH$ protocol. These synthetic routes were applied in the total synthesis of promising male erectile dysfunction (MED) PDE5 inhibitor **1**.

Nowadays, Sildenafil is the main drug employed for male erectile dysfunction (MED). Through several mechanistic considerations about the mode of action of these classes of compounds, Sildenafil and its analogues showed inhibition of the phosphodiesterase type 5 (PDE5) enzyme but not in a specific manner.[1] This class of compounds was initially studied for the treatment of angina, and then it showned its effectiveness in treating erectile dysfunction (ED).[2] Although its success, accumulation of clinical data suggested that several side effects were observed when sildenafil was used, which are headache, nausea, cutaneous flushing, and visual disturbances.[3] Herein, sildenafil and other PDE5 inhibitors are contraindicated for patients taking nitrates or NO^- donors due to abrupt synergistic decrease of blood pressure observed after co-administration of these agents.[4] Recently, a wide variety of PDE5 inhibitors were synthesized by Jiang group and evaluated for their biological profiles, which included the lead compound RWJ387273 (**1**)[5] as shown in Figure 1.

Chirality in molecules plays an enormous role in areas ranging from medicine to material science. However, after great developments in synthetic organic chemistry, there are still few methodologies that allow the stereoselective construction of predetermined moieties in some classes of compounds. In this context, particular attention in efficient synthetic routes for novel chemotypes is already pursued when stereoselectivity is required.

As part of our efforts in the field of biologically relevant β-carbolines, we turned our attention toward an alternative synthetic route for PDE5 inhibitors, figured out through key intermediate (−)-**2**. Recently, we reported an enantioselective total syntheses of arborescidine alkaloids and (−)-quinolactacin B antibiotic.[6] Structurally, **1** comprises a tricyclic framework attributing a common pyrroloquinolone core. The retrosynthetic analysis for the basic framework of **2** was depicted in Figure 2, and features the Noyori asymmetric hydrogen-transfer reaction and chiral-auxiliary

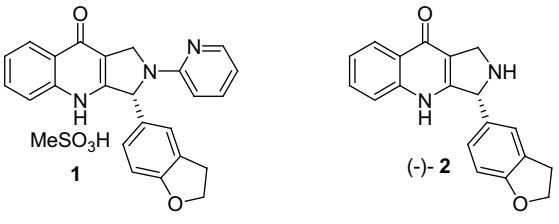

Figure 1. Optically active potential PDE5 inhibitor **1** (RWJ387273) and its important intermediate (−)-**2**.

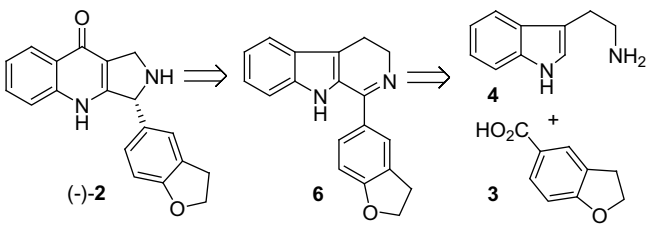

Figure 2. Retrosynthetic analysis of key pyrroloquinolone (PDE5) inhibitor intermediate **2**.

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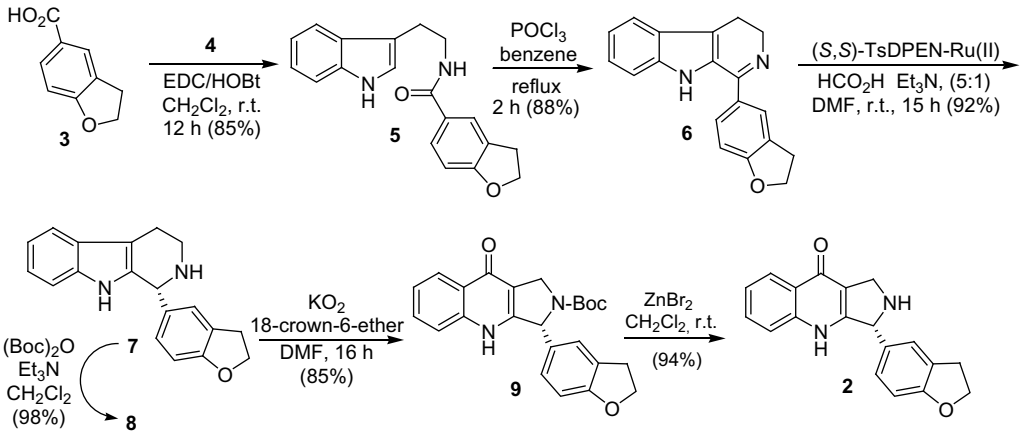


Scheme 1. Asymmetric hydrogen-transfer with (*S*,*S*)-TsDPEN-Ru(II) followed by Winterfeldt reaction for key PDE5 inhibitor **2** intermediate.

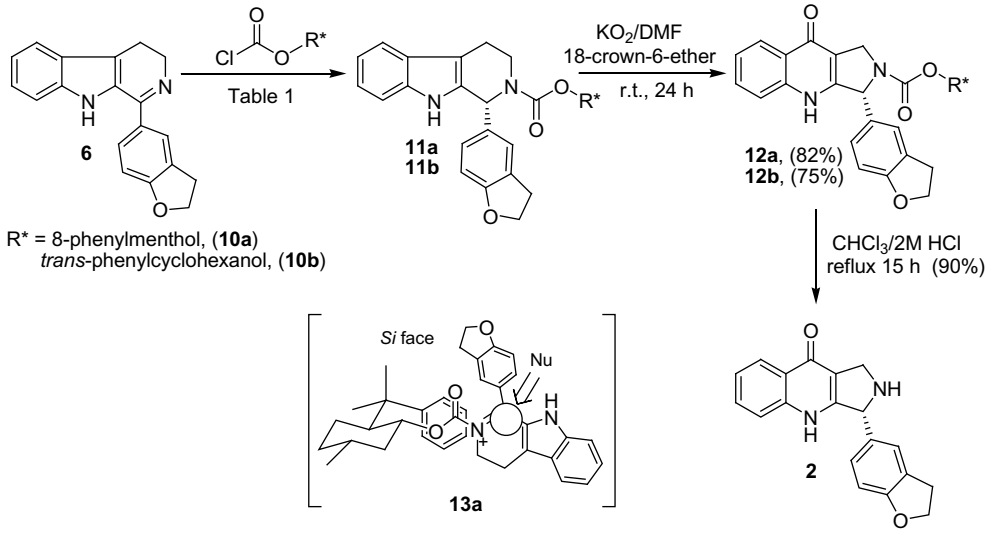
mediated reductions (**6** to **7**/**11**) as key steps. Although demonstrated as a useful synthetic method, these asymmetric reductions remain to be fully explored in the arena of total syntheses of alkaloid natural products.[7,8]

We first explored the Noyori asymmetric hydrogenation (NAH) reaction of the preformed imine **6**. Imine **6** was obtained in 75% overall yield from dihydrobenzo[*b*]furan-5-carboxylic acid (**3**) and tryptamine (**4**) by coupling with EDC/HOBt in CH_2Cl_2 at room temperature, which afforded the corresponding amide **5**. The amide was subjected to Bischler–Napieralsky cyclization affording imine **6**. Having prepared imine **6**, the next stage was set to introduce the required asymmetry through the Noyori asymmetric hydrogen-transfer reaction.[7] In nature, oxidoreductases catalyze remarkably selective transfer hydrogenations of carbonyl compounds to alcohols using co-factors such as NADH or NADPH.[9] Noyori and co-workers have shown that *p*-cymene–Ru(II) complexes of certain chiral 1,2-diamines are highly effective as catalysts for the asymmetric reduction of imines. This method uses a $HCO_2H{-}Et_3N$ azeotropic mixture as the hydrogen source and provides a convenient, general route to natural and unnatural β-carboline alkaloids.

The Noyori hydrogenation of imine **6** was accomplished using the preformed (*S*,*S*)-TsDPEN–Ru(II) complex in DMF, and a $HCO_2H{-}Et_3N$ mixture that afforded amine **7** in 92% yield and >90% ee, as determined by HPLC analysis using a ChiralPack OD column. On the basis of the examples that have been reported by Noyori, the absolute stereochemistry of **7** is expected to be *R*. When it is used (*S*,*S*)-TsDPEN-Ru(II) complex is used in in the hydrogen-transfer, the *Si*-face of imine **6** is expected to be selected for hydrogenation providing (*R*)-**7**. This outcome is consistent with the general model that Noyori had proposed for the asymmetric hydrogen transfer reactions with TsDPEN–Ru(II) complexes,[7] and it was probed by comparing the optical rotation of **7** that agreed in signal to previously described (*R*)-(+)-**7**.[10,11]

Then, amine **7** was protected with Boc using $(Boc)_2O$ and Et_3N in CH_2Cl_2 giving (+)-**8** in 98% yield. A viable method was anticipated to oxidize dihydro-β-carbolines bearing amide functionality into the pyrroloquinolones, the Winterfeldt reaction. It is known that KO_2 is an alternative useful oxygen source for Winterfeldt oxidation reactions.[12,13] Thus, Winterfeldt reaction of (+)-**8** using KO_2 and 18-crown-6-ether gave quinolone (+)-**9** in 85% yield (>90% ee) after 16 h.[6b,14] The enantiomeric excesses were determined by HPLC to assure that no epimerization occurred in the reaction due to basic conditions. The target compound **2** was obtained by treatment of $ZnBr_2$ in 94% yield, as depicted in Scheme 1.

Next, we investigated the scope of reduction of imine **6** mediated by chiral auxiliaries in an one-pot manner. The tested chiral auxiliaries were chloroformate of 8-phenylmenthol (**10a**), and *trans*-phenylcyclohexanol (**10b**), as depicted in Scheme 2. In situ formation of corresponding *N*-acyliminium ions **13a**,**b** from chloro-



Scheme 2. Asymmetric synthesis of PDE5 inhibitor by using chiral auxiliaries followed by Winterfeldt oxidation.

Table 1
Reduction of imine **6** by using chloroformates of 8-phenylmenthyl (**10a**) and *trans*-phenylcyclohexyl (**10b**) as chiral auxiliaries, and reducing agents

Entry	Chiral auxiliaries	Reaction conditions[c]	Yield[a] (%)	dr[b] (%)
1	**10a**	A	85	13:1 (*R*,*S*)
2	**10b**	A	78	7:1 (*R*,*S*)
3	**10a**	B	88	9:1 (*R*,*S*)
4	**10b**	B	79	7:1 (*R*,*S*)
5	**10a**	C	92	5:1 (*R*,*S*)
6	**10b**	C	80	4:1 (*R*,*S*)

[a] Isolated yields.
[b] Diastereomeric ratio (dr%) calculated based on HPLC.
[c] **A**: chiral auxiliary, CH_2Cl_2, rt, 30 min, then $PdCl_2/Et_3SiH$, Et_3N, −78 °C, 1 h; **B**: chiral auxiliary, CH_2Cl_2, rt, 30 min, then $NaCNBH_3$/THF, −78 °C, 1 h; **C**: chiral auxiliary, CH_2Cl_2, rt, 30 min, $NaBH_4$/THF, 0 °C−rt, 1 h.

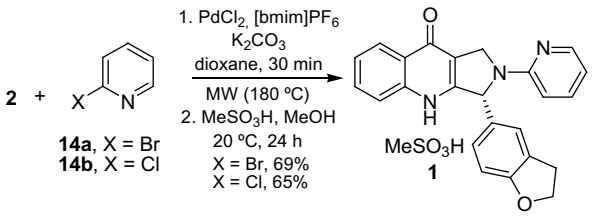
formates of chiral auxiliaries **10a**,**b** and imine **6**, followed by reduction afforded **11a**,**b** in moderate to good yields (Table 1). Pd–H reductions of **13** were carried out using $PdCl_2/Et_3SiH$ protocol[15] at −78 °C, and compounds **11a**,**b** were obtained in 85% and 78% yield, respectively (Table 1, entries 1 and 2). The diastereomeric ratio obtained employing palladium protocol was 13:1 for **11a** (Table 1, entry 1) and 7:1 for **11b** (Table 1, entry 2).

It also employed $NaCNBH_3$ as reducing agent in a CH_2Cl_2/THF (2:1)[16] mixture as a solvent at −78 °C. Using $NaCNBH_3$, **11a** was obtained in 88% yield and 80% dr (9:1 *R*/*S*, entry 3), and **11b** in 79% yield and 75% dr (7:1 *R*/*S*, entry 4), respectively. Herein, $NaBH_4$ was also tested giving **11a** in 92% yield and 66% dr (entry 5), and **11b** in 80% yield and 60% dr (entry 6), when CH_2Cl_2/THF (2:1) was used as solvent at 0 °C to 25 °C. The absolute configuration of the major compounds was determined to be (*R*) after chiral auxiliaries removal using $CHCl_3$/HCl (2.0 M) and reflux, which gave (+)-**7** in yields around 85–89%. The enantiomeric excesses of (*R*)-(+)-**7** obtained from **11a**,**b** were >99% ee, as determined by HPLC analysis, and it is in accordance with pure (*R*)-(+)-**7** data.

Table 1 shows that these one-pot reduction reactions are proceeding efficiently by using CH_2Cl_2/THF (2:1) as solvent, when boranes are employed. The yields increased when the reaction was performed using $NaBH_4$ at ambient temperature, but with lower%dr. Chiral auxiliaries were recovered in 95% yield with no decrease of its optical rotations. Selectivity and the chiral auxiliary mediated reduction of **6** was rationalized by transition state as depicted in Scheme 2, which is in accordance with the reduction of the *N*-acyliminium ion **13** through its *Si*-face when **10a** is used. The same model depicted in Scheme 2 can be applied using **10b** as chiral auxiliary.

Then, Winterfeldt oxidation was analyzed using the chiral auxiliaries as protecting groups in **11**. According to the mechanism proposed by Speier[17] for the oxidation of indole derivatives, it is conceivable that **11a**,**b** might produce **12a**,**b** under oxidation conditions. Initially, **11a**, and 4 equiv of KO_2 with 1 equiv of 18-crown-6-ether were used at room temperature. However, the reaction did not produce any product as indicated by TLC analysis, and any change of color in the reaction mixture.

Generally, it is observed that oxidation proceeds when the reaction mixture turned yellow to reddish color. Thus, we decided to increase the amount of KO_2 up to 16 equiv, 18-crown-6-ether to 4 equiv, and the reaction was monitored by TLC until disappearance of starting material. Using the higher amount of oxidizing agent, (+)-**12a** was obtained in 82% yield, and (+)-**12b** in 75% yield. Finally, the key intermediate **2** was obtained in yields reaching 90% by acidic treatment (2.0 M HCl in $CHCl_3$) and >99%ee. Synthetic compound **2** displayed the same spectroscopic data of the compound obtained from NAH. The optical rotation of **2** was $[\alpha]_D$ −34.4 (*c* 1.0, MeOH), and it is in accordance to reported one, $[\alpha]_D$ −37.9 (*c* 1.0, MeOH).[5a]



Scheme 3. Buchwald–Hartwig coupling reaction of **2** and **14** for the synthesis of potential PDE5 inhibitor RWJ387273 (**1**).

Finally, compound RWJ387273 (**1**) was obtained by using Buchwald–Hartwig reaction[18] and microwave-assisted (MWA) irradiation co-catalyzed by the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate, [bmim] PF_6.[19] The concept of performing microwave-assisted synthesis using nonpolar solvents and ionic liquids as 'doping agents' is becoming increasingly popular, as demonstrated by Ley[20a] and others.[20] Ionic liquids interact very efficiently with microwaves through ionic conduction mechanism and are rapidly heated at rates easily exceeding 10 °C s^{-1} without any significant pressure build-up.[20b] Recently, Markó described the use of $Pd(dba)_2$ and BINAP ligand to couple intermediate **2** and **14a** affording the desired compound after 9 h in 90% yield.[10] Thus, we figured out the use of cheaper palladium reagents and no ligands by using [bmim]PF_6 ionic liquid, and microwave irradiation to reduce reaction time and costs, a green chemistry approach. The coupling of **2** and **14a** using $PdCl_2$ (5.0 mol %), [bmim]PF_6 (20 mol %), K_2CO_3 as base, in dioxane, and microwave irradiation by 15 min gave the desired product in 85% yield. Furthermore, using the inexpensive pyridine derivative **14b**, and the same conditions described above, the desired product was obtained in 80% yield after 30 min of MWA irradiation (Scheme 3).[21] Simple crystallization of the methanesulfonate salt of **1** from methanol achieved the final product in 80% yield, as described previously.[10]

In conclusion, we have completed an alternative and efficient route for the synthesis of key pyrroloquinolone (PDE5) inhibitor **2**. The developed method features the use of Noyori catalytic asymmetric hydrogen-transfer reaction or chiral auxiliary mediated reduction reactions to introduce the chirality in dihydro-β-carboline **6**. The reductions were performed using the (*S*,*S*)-TsDPEN-Ru(II) catalyst and menthyl-based chiral auxiliaries, which, on the basis of the ample precedent from NAH and these kind of auxiliaries, produced chiral dihydro-β-carbolines and ultimately the products possessing the *R* absolute configuration. The optical rotations of our synthetic intermediates, as well as the final product **1**, were in accordance in sign with described ones.[22–25]

Acknowledgments

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21. All the microwave reactions were performed in a CEM Discover LabMate equipment in a closed vessel (built-in infrared sensor) with cooling system.
22. *Analytical data for key intermediates*: Compound **5**: mp: 130–131 °C. FT-IR, (KBr film, cm^{-1}): 3488, 3220, 3058, 2963, 2924, 2855, 1777, 1681, 1634, 1609, 1538, 1488, 1456, 1444, 1329, 1246, 1095, 1011, 982, 938, 814, 744. ^{1}H NMR (400 MHz, *d*-$CDCl_3$): δ 8.38 (br s, 1H), 7.65 (d, 1H, *J* 8.08 Hz), 7.61 (s, 1H), 7.44 (d, 1H, *J* 6.56 Hz), 7.38 (d, 1H, *J* 8.08 Hz), 7.23 (t, 1H, *J* 8.08 Hz), 7.14 (t, 1H, *J* 7.07, 8.08 Hz), 7.06 (s, 1H), 6.74 (d, 1H, *J* 8.58 Hz), 6.22 (br s, 1H), 4.61 (t, 2H, *J* 8.58, 9.09 Hz), 3.77–3.82 (q, 2H, *J* 6.06, 6.56 Hz), 3.19 (t, 2H, *J* 8.58, 9.09 Hz), 3.10 (t, 2H, *J* 6.56 Hz). ^{13}C NMR (50 MHz, *d*-$CDCl_3$): δ 167.4, 162.9, 138.2, 136.6, 127.5, 127.4, 127.2, 124.4, 122.2, 119.5, 118.8, 113.1, 111.4, 108.9, 71.8, 40.3, 29.2, 25.3. HRMS (70 eV): calcd for $C_{19}H_{18}N_2O_2$ 306.3632, found 306.3641. Compound **6**: mp: 138–140 °C. FT-IR, (KBr film, cm^{-1}): 3408, 2924, 2899, 2833, 1612, 1533, 1443, 1371, 1306, 1217, 1161, 1115, 1043, 766. ^{1}H NMR (400 MHz, *d*-$CDCl_3$): δ 8.46 (br s, 1H), 7.68 (d, 1H, *J* 8.08 Hz), 7.63 (s, 1H), 7.50 (d, 1H, *J* 8.08 Hz), 7.37 (d, 1H, *J* 8.58 Hz), 7.30 (t, 1H, *J* 8.08, 6.06 Hz), 7.19 (t, 1H, *J* 7.07, 7.57 Hz), 6.86 (d, 1H, *J* 8.08 Hz), 4.63 (t, 2H, *J* 8.58, 9.09 Hz), 4.00 (t, 2H, *J* 8.58, 9.09 Hz), 3.24 (t, 2H, *J* 8.08 Hz), 2.97 (t, 2H, *J* 8.08 Hz). ^{13}C NMR (50 MHz, *d*-$CDCl_3$): δ 161.7, 159.0, 136.5, 130.3, 128.3, 128.0, 127.9, 125.6, 124.7, 124.4, 120.3, 119.9, 117.8, 112.0, 109.2, 71.7, 48.6, 29.4, 19.3. HRMS (70 eV): calcd for $C_{19}H_{16}N_2O$ 288.3484, found 288.3497.
23. Compound **7**: mp: 112–114 °C. $[\alpha]_D$ +21.5 (*c* 1.0, MeOH). FT-IR, (KBr film, cm^{-1}): 3454, 3384, 3054, 2921, 2838, 1610, 1492, 1449, 1303, 1245, 1099, 982, 946, 813. ^{1}H NMR (400 MHz, *d*-$CDCl_3$): δ 7.77 (br s, 1H), 7.45 (d, 1H, *J* 8.80 Hz), 7.10 (d, 1H, *J* 6.35 Hz), 7.01–7.11 (m, 2H), 6.99 (s, 1H), 6.91 (d, 1H, *J* 7.82 Hz), 6.62 (d, 1H, *J* 7.82 Hz), 4.94 (s, 1H), 4.44 (t, 2H, *J* 8.31, 8.80 Hz), 3.22–3.27 (m, 2H), 3.01 (t, 2H, *J* 8.31, 8.80 Hz), 2.69–2.85 (m, 2H), 1.78 (br s, 1H). ^{13}C NMR (50 MHz, *d*-$CDCl_3$): δ 159.9, 135.8, 134.9, 133.9, 128.3, 127.6, 127.3, 124.9, 121.5, 119.2, 118.1, 110.7, 109.9, 109.0, 71.3, 57.6, 42.8, 29.5, 22.4. HRMS (70 eV): calcd for $C_{19}H_{18}N_2O$ 290.3642, found 290.3638.
24. Typical procedure for compound **11a**: The chloroformate **10a** (0.077 g, 0.260 mmol) was added to an anhydrous solution of imine **6** (0.050 g, 0.173 mmol) in CH_2Cl_2 (2.0 mL). The reaction mixture was stirred at room temperature for 30 min. After this period, the reaction temperature was brought to −78 °C, and then a solution of $NaCNBH_3$ (0.033 g, 0.520 mmol) in dry THF (1.0 mL) was added dropwise to the reaction mixture. The mixture was stirred at −78 °C for 1 h. Then, the reaction mixture was brought to room temperature, and 10 mL of H_2O added, extracted with CH_2Cl_2 (3 × 10 mL), dried in Na_2SO_4, and evaporated. The crude product was purified by flash chromatography through silica gel (100–200 mesh) using EtOAc–hexane (2:8) as eluent, which gave compound **11a** in 88% yield as a white solid. Mp: 160–161 °C. $[\alpha]_D$ −99.8 (*c* 1.0, $CHCl_3$). FT-IR, (KBr film, cm^{-1}): 3409, 3322, 3057, 3008, 2956, 2916, 2860, 2850, 1666, 1629, 1491, 1468, 1425, 1230, 1092, 982, 760. ^{1}H NMR (400 MHz, *d*-$CDCl_3$): δ 7.84 (br s, 1H), 7.53 (d, 1H, *J* 7.31 Hz), 7.40 (d, 1H, *J* 7.68 Hz), 7.19–7.24 (m, 2H), 7.02–7.15 (m, 3H), 6.97 (d, 1H, *J* 8.05 Hz), 6.87 (t, 1H, *J* 7.31, 7.68 Hz), 6.67 (d, 1H, *J* 8.05 Hz), 6.56 (d, 1H, *J* 8.05 Hz), 6.47 (t, 1H, *J* 6.95, 7.31 Hz), 6.31 (s, 1H), 4.81 (ddd, 1H, *J* 3.65, 4.02, 6.95 Hz), 4.47 (tt, 2H, *J* 8.78, 13.90 Hz), 4.33 (m, 1H), 2.88–3.14 (m, 3H), 2.77 (m, 2H), 2.31–2.53 (m, 2H), 2.11–2.19 (m, 1H), 1.56–1.69 (m, 2H), 1.44 (m, 2H), 1.26 (d, 3H, *J* 12.07 Hz), 1.11 (s, 3H), 0.88–0.93 (m, 1H), 0,79–0.83 (m, 3H). ^{13}C NMR (50 MHz, *d*-$CDCl_3$): δ 164.1, 155.7, 152.0, 136.1, 132.2, 131.9, 131.6, 128.1, 127.9, 127.6, 126.4, 126.0, 125.3, 124.6, 122.7, 121.2, 120.6, 114.0, 111.8, 109.2, 76.9, 74.6, 72.1, 57.3, 51.0, 42.2, 41.6, 39.6, 34.6, 31.2, 29.1, 27.5, 26.5, 25.5, 25.0, 21.7. HRMS (ESI(+)): calcd for $[C_{36}H_{40}N_2O_3 + H]^+$ 549.7230, found 549.7244. Compound **11b**: $[\alpha]_D$ −50.6 (*c* 1.0, $CHCl_3$). FT-IR, (KBr film, cm^{-1}): 3394, 3322, 3051, 3028, 2928, 2856, 1668, 1489, 1449, 1421, 1230, 1087, 983, 943, 752. ^{1}H NMR (400 MHz, *d*-$CDCl_3$): δ 7.79 (br s, 1H), 7.49 (d, 1H, *J* 7.57 Hz), 7.30–7.34 (m, 5H), 7.08–7.15 (m, 3H, *J* 7.82 Hz), 6.93 (s, 1H), 6.63 (d, 1H, *J* 4.54 Hz), 6.22 (s, 1H), 4.92–4.97 (m, 1H), 4.49 (p, 2H, *J* 8.58, 8.08, 7.07 Hz), 3.98–4.14 (m, 1H), 3.63–3.68 (m, 1H), 2.91–3.09 (m, 1H), 2.62–2.75 (m, 1H), 2.42 (t, 2H, *J* 9.60 Hz), 2.31 (d, 1H, *J* 10.61 Hz), 2.25 (s, 1H), 2.10 (d, 2H, *J* 9.60 Hz), 1.75–1.96 (m, 2H), 1.46–1.60 (m, 2H), 1.28–1.42 (m, 2H). ^{13}C NMR (50 MHz, *d*-$CDCl_3$): δ 160.1, 143.2, 136.0, 135.1, 133.8, 128.5, 127.9, 127.4, 125.0, 124.4, 121.7, 119.4, 118.2, 110.9, 110.0, 109.2, 108.5, 77.0, 71.5, 57.8, 43.8, 31.0, 27.9, 22.6. HRMS (ESI(+)): calcd for $[C_{32}H_{32}N_2O_3 + H]^+$ 493.6158, found 493.6179.
25. Compound **12a**: mp: 182–184 °C. $[\alpha]_D$ −142 (*c* 1.0, $CHCl_3$). FT-IR, (KBr film, cm^{-1}): 3259, 3222, 3079, 3055, 2949, 2919, 2861, 1693, 1625, 1567, 1509, 1495, 1475, 1403, 1236, 1110, 981, 933, 872, 821. ^{1}H NMR (400 MHz, *d*-$CDCl_3$): δ 9.73 (s, 1H), 9.05 (s, 1H), 8.29 (t, 1H, *J* 5.86, 6.84 Hz), 7.47–7.53 (m, 1H), 7.26–7.32 (m, 5H), 7.14 (t, 1H, *J* 7.33, 7.82 Hz), 7.06 (d, 1H, *J* 3.42 Hz), 6.84–6.93 (m, 1H), 6.64 (t, 1H, *J* 8.31, 10.27 Hz), 6.51 (dd, 1H, *J* 7.82, 5.86 Hz), 5.61 (d, 1H, *J* 2.93 Hz), 5.23 (s, 1H), 4.51–4.67 (m, 2H), 4.36–4.43 (m, 2H), 4.20 (d, 1H, *J* 13.69 Hz), 3.95 (d, 1H, *J* 2.44 Hz), 3.84 (dd, 1H, *J* 3.42, 2.93 Hz), 2.88–2.98 (m, 2H), 1.78–1.90 (m, 2H), 1.48–1.65 (m, 2H), 1.05–1.29 (m, 6H), 0.78 (s, 3H). ^{13}C NMR (50 MHz, *d*-$CDCl_3$): δ 174.6, 160.1, 153.6, 153.1, 151.4, 149.6, 131.8, 131.4, 128.0, 127.8, 127.7, 126.0, 125.6, 123.7, 114.6, 113.9, 110.1, 108.5, 71.4, 64.6, 49.6, 49.3, 41.6, 39.6, 39.3, 34.5, 31.6, 30.9, 29.6, 26.1, 21.7. HRMS (ESI(+)) calcd for $C_{36}H_{38}N_2O_4$ 563.7062, found 563.7081.