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FULL-LENGTH PAPER

Traceless synthesis of diketopiperazine fused tetrahydro-β-carbolines on soluble polymer support

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Abstract The Pictet–Spengler reaction, using polyethylene glycol immobilized tryptophan ester with a variety of ketones, was achieved by refluxing condition in acidic chloroform. The linear as well as cyclic ketones were employed. All the ketones were reacted within 6–8 h to furnish soluble polymer-supported tetrahydro-β-carboline in good yields. Further expansion at N-terminus of tetrahydro-β-carbolines was achieved through a reaction with chloroacetyl chloride. Finally, the 2,5-diketopiperazine skeleton was constructed over a β-carboline by amination of the resulting N-chloroacetamides and subsequent intramolecular cyclization leading to cleavage of the polymer; constitutes a traceless synthesis of tetracyclic molecular architecture. Significantly, this strategy affords a straightforward and efficient approach for the construction of biological promising molecules with high purity and good yields.

Keywords Pictet–Spengler reaction · Soluble polymer-supported synthesis · Polyethylene glycol · Diketopiperazine · Tetrahydro-β-carbolines

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Introduction

Traditional drug discovery used natural products isolated from plants, animals, and fermentation processes as conventional sources of biologically active compounds. However, in modern drug discovery this resource has been replaced with the synthesis and screening of a large number of molecules in the laboratory, looking for plausible biological activities. The recent advent of high-throughput automated techniques has facilitated screening compounds faster, which combined with the increasing number of therapeutic targets emerging from molecular biology and genome sequencing, have made it possible to rapidly and efficiently synthesize large collections of diverse molecules for novel bioactivities. To accelerate the process of compound synthesis, combinatorial chemistry has emerged to access structurally diverse libraries and also to discover novel modulators [1,2].

Solid-supported synthesis is an important technique to accelerate organic chemistry. The application of solid phase synthesis for the preparation of heterocycles continues to be an area of great interest [3–5]. Since the inception of Merrifield's landmark contribution to solid phase peptide synthesis [6,7], much emphasis has been placed on the development of solid phase methods to synthesize small molecules [8–10]. Despite remarkable achievements in solid phase synthesis, soluble polymer support has been investigated due to some disadvantages associated with insoluble polymer supports such as heterogeneous reaction conditions and the difficulty to characterize the intermediates. The use of various soluble polymer supports in combinatorial synthesis facilitates the preparation of library of small molecules and overcomes the drawbacks of solid phase reactions. Soluble polymer support serves as a chemically robust macromolecular protecting group and is carried along with molecular modifications in multi-step synthesis until the intentional

cleavage at an appropriate stage. Additionally, soluble polymer conjugated intermediates dissolve in many organic solvents and the reaction progress can be directly monitored by proton NMR spectroscopy as well as other conventional analytical methods. Additionally, the cleavage of the desired product from the polymer support during the final step via intramolecular cyclization (traceless cleavage) eliminates post-cleavage workup. The product cleaved from the polymer is released into solution with high purity levels and it is easily isolated by filtering out the polymer support [11–13]. Inexpensive and readily available polyethylene glycol (PEG), a family of long chain polymers link through covalent attachment (PEGylation) with a substrate, is commonly used to synthesize and modify a variety of drug molecules.

In continuation of our interest in the generation of biologically interesting heterocycles on PEG support, we have already demonstrated the synthesis of diverse nitrogen heterocycles [14–17]. Recently the alkaloids containing β-carbolines skeleton such as Reserpine and Yohimibine, represents important lead structures in view of their wide range of biological activities. Several tetracyclic β-carbolines **1** which have either been isolated from natural sources or synthetically manipulated in the laboratory depict anti-aggregation, antimalarial, and anticonvulsant properties [18–21]. Additionally, compounds with the 2,5-diketopiperazine skeleton **2** have also attracted attention because of their broad biological activities [22–24]. However, the less explored tetracyclic ring system **3** has been derived by unification of pharmacophores **1** and **2** (Fig. 1). These compounds were designed with contemplation of the promising biological activities like inhibiting the cyclic guanosine monophosphate (cGMP) type 5 specific phosphodiesterase (PDE 5) (a), topoisomerase II inhibitors (b), and oral anti-thrombotic agents (c) (Fig. 2) [25–27]. These diketopiperazine fused tetrahydro-β-carboline derivatives **3** dominates the formation of lymphatic vessels and the proliferation of lymphatic

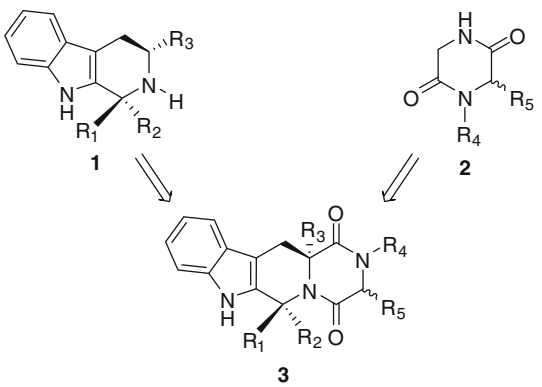


Fig. 1 Rational design of new scaffold

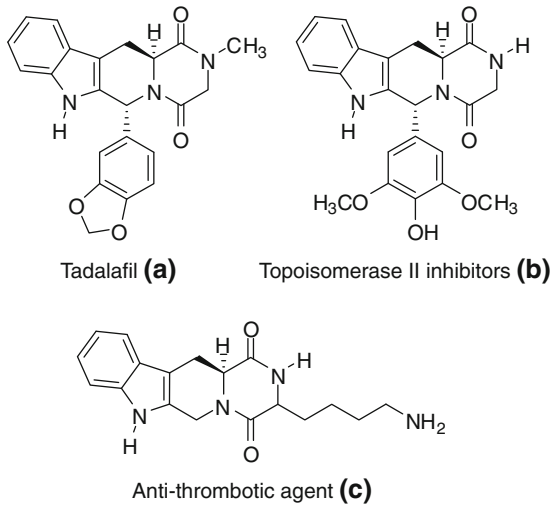


Fig. 2 Structurally related biologically active compounds

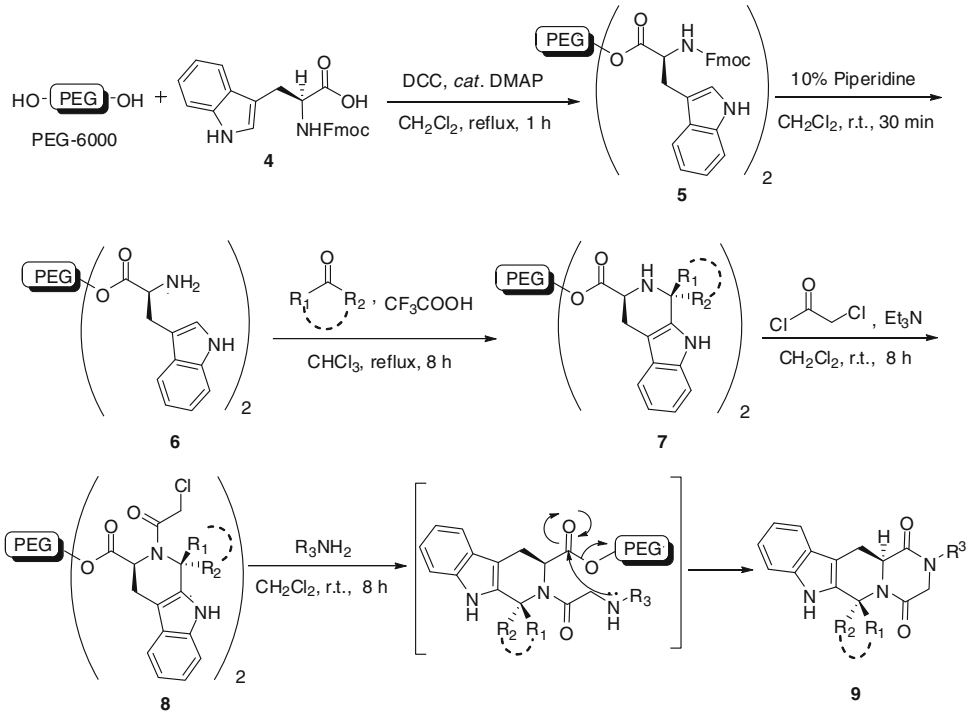
endothelial cells [28–30] are also interesting to investigate for the inhibition of VEGFR-3. To date only few cases of small molecule targeting VEGFR-3 have been reported [31,32]. Hence further development of a combined tetracyclic skeleton comprising tetrahydro β-carboline and diketopiperazine for potential anti-cancer therapeutics is warranted.

Although the Pictet–Spengler reaction with aldehydes for the synthesis of tetrahydro-β-carboline derivatives is well-established, the corresponding reaction with ketones is less well explored [33–37]. This could be attributed to (i) the lower reactivity of ketones thus resulting in a slow imine formation, and (ii) the steric congestion at the C1 carbon of tetrahydro-β-carbolines. By exploring new synthetic strategies to prepare libraries of novel molecules for drug discovery research, we report a traceless synthesis of diketopiperazine fused tetrahydro-β-carbolines using Pictet–Spengler reaction with various ketones.

Results and discussion

For the investigation of the proposed Pictet–Spengler reaction with ketones for the synthesis of β-carboline fused target compounds, *N*-protected L-tryptophan was chosen as a starting substrate. *N*-Fmoc-protected L-tryptophan **4** was immobilized on a polyethylene glycol (PEG-6000) via *O*-acylation with DCC (Scheme 1). The reaction was carried out in refluxing conditions for 1 h to allow complete conversion to the PEG bound tryptophan ester **5**. The removal of the Fmoc protecting group from polymer conjugate **5** was achieved with 10% piperidine in dichloromethane at room temperature within 30 min. The reaction mixture was precipitated by the addition of ice-cold ether and the PEG bound amine **6** was filtered and washed thoroughly to remove the traces of piper-

Scheme 1 PEG supported synthesis of diketopiperazines fused tetrahydro-β-carbolines



idine and other side products. The Fmoc group removal was confirmed by the ^{1}H NMR spectrum of **6** (Fig. 3, spectrum a).

With the proper precursor in hand, the stage was set for the investigation of the Pictet–Spengler reaction on ketones. The polymer conjugate **6** was subjected to the Pictet–Spengler reaction conditions with acetone as a model reaction. Based on our earlier experience on Pictet–Spengler reaction, chloroform was chosen as solvent for this investigation. The PEG conjugate **6** was dissolved in chloroform and allowed to react with acetone under mild acidic conditions using 10% TFA. The iminium ion was generated in situ from the protonation of carbonyl group of ketones and the subsequent nucleophilic attack on the carbonyl carbon underwent C–C bond formation with the C-2 of the indole ring to furnish the tetrahydro-β-carboline skeleton [38,39]. The reaction was monitored by ^{1}H NMR spectroscopy and was found to be completed after refluxing for 8 h. The work-up and purification process is simple due to polymer support. The reaction mixture was precipitated by the addition of ice-cold ether and then filtered to furnish the polymer immobilized tetrahydro-β-carboline **7** with good yields. To introduce diversity in the targeted skeleton and to demonstrate the versatility of this reaction, symmetric, asymmetric, and cyclic ketones were investigated. All the ketones examined underwent Pictet–Spengler reaction with conjugate **6** in 6–8 h under refluxing condition to afford the corresponding immobilized tetrahydro-β-carbolines **7** in good to excellent yields. By using cyclic ketones, a spiro moiety was also introduced onto the tetrahydro-β-carboline skeleton, thus increasing the structural diversity of the compounds. However, the use of unsymmetrical ketones under the same reaction condition led to a mixture of *cis* and *trans* diastereomers.

The next critical step was the construction of a terminal diketopiperazine ring across the *N*-2/C-3 bond on this skeleton. The functionalized β-carbolines **7** were reacted with chloroacetyl chloride in the presence of triethylamine to generate the *N*-chloroacetyl conjugates **8**. The formation of *N*-chloroacetyl conjugates **8** were achieved at room temperature in 8 h. To create a target framework with maximum diversity, the immobilized *N*-chloroacetamides **8** were further reacted with various primary amines. Initial study of this particular reaction was done at room temperature in dichloromethane and the progress of the reaction was carefully monitored which indicated that the desired compounds were completely released from the support after 8 h. The nitrogen in the transient α-aminoacetamides is located in a favorable position for an intramolecular nucleophilic attack on the PEG-ester carbonyl leading to a traceless synthesis of final compounds **9** by an acyl-polymer oxygen bond cleavage. The reaction mixtures were precipitated with ice-cold ether, the polymer was removed by filtration and the filtrates were purified by column chromatography to furnish diketopiperazine functionalized β-carbolines **9** with excellent yield. Different types of aliphatic, aromatic, and heteroaromatic primary amines were used for the final cyclization and all of them reacted with no substantial difference in reactivity. It is worth noting that a facile and high yielding ring closure reaction at room temperature is quite distinct compared to the regular synthetic approach toward the amino acid functionalized, diketopiperazine fused

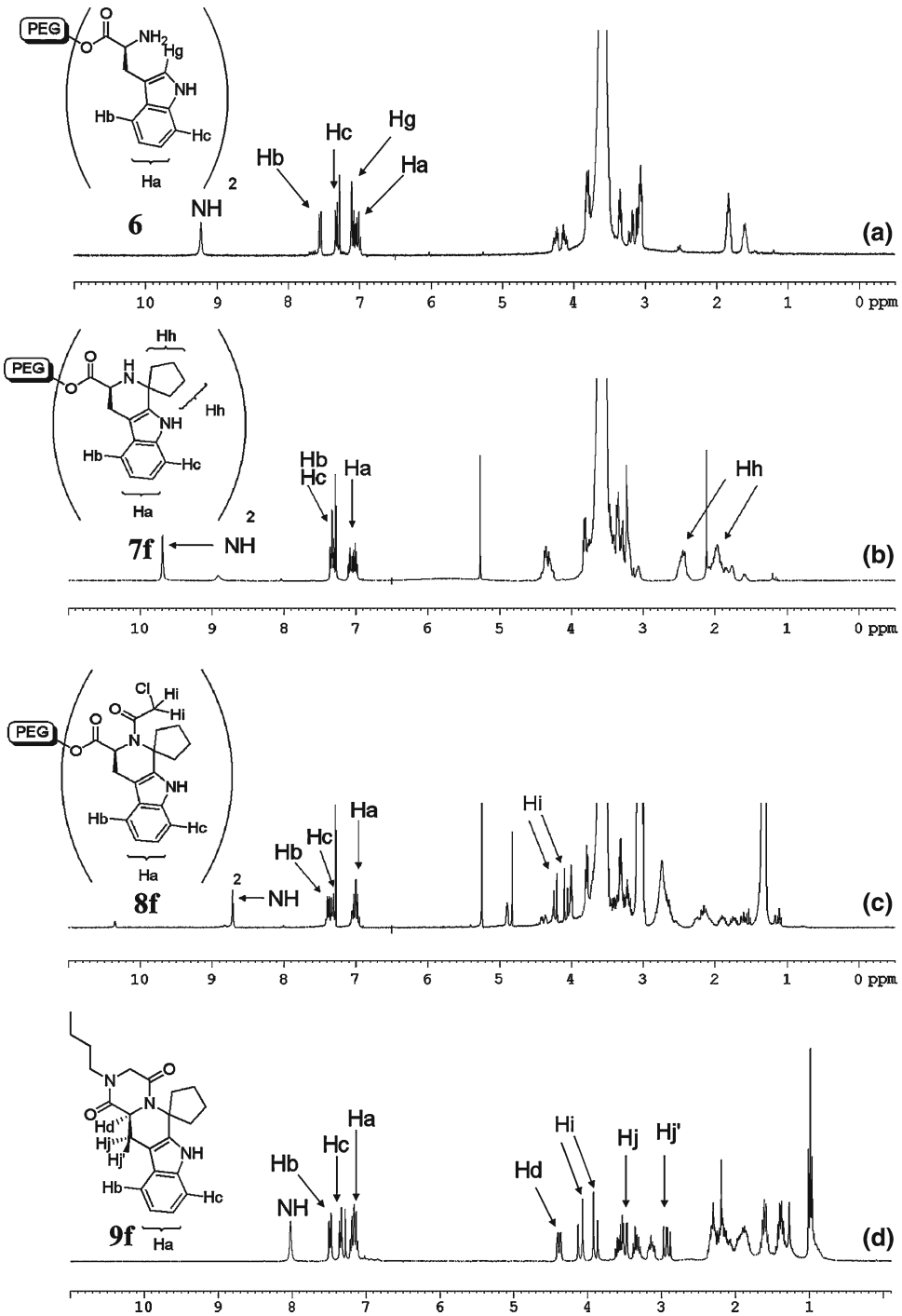
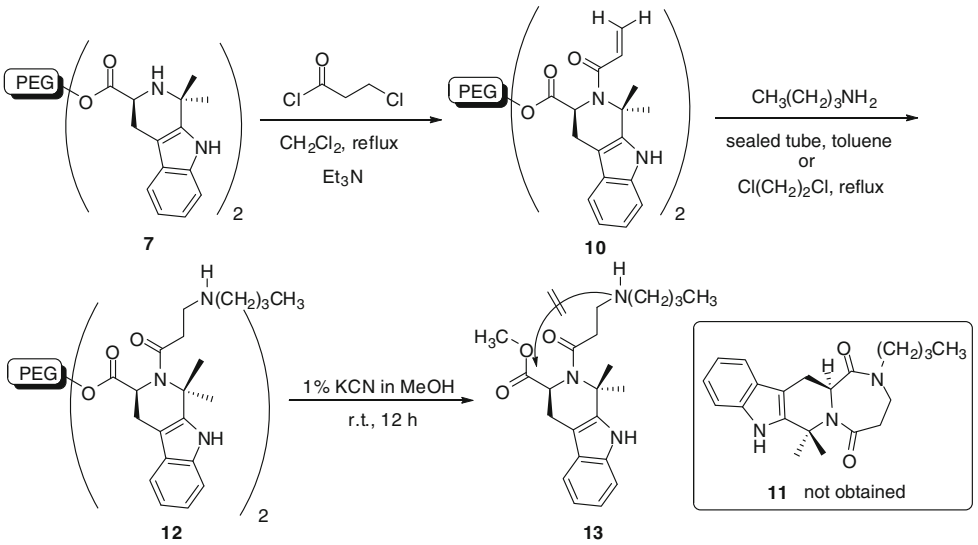


Fig. 3 Stepwise ^{1}H NMR monitoring of reaction progress toward the formation of tetracyclic 2,5-diketopiperazine

β-carbolines which required refluxing in dimethylformamide [18–21].

In order to expand the substrate types and scope of this methodology, we turned our attention to synthesize seven-membered 2,6-diazepinediones rings over β-carboline **11**. Consequently polymer-supported tetrahydro-β-carboline **7** was treated with 3-chloropropionyl chloride for the generation of *N*-chloropropionyl conjugates; as a precursor for 2,6-diazepinediones ring system. However, instead of the expected *N*-chloropropionyl conjugates, we obtained the *N*-acrolyl conjugates **10** (Scheme 2). To achieve the desired seven-member cyclized product, *N*-acrolyl conjugate **10** was reacted with *n*-butyl amines under refluxing condition in 1,2-dichloroethane. However, this condition failed to provide the desired compound **11**. Attempts to perform the same reaction in a sealed tube at high temperature

Scheme 2 Attempted synthesis of 2,6-diazepinediones on the polymer support



(160 °C) using toluene as a solvent resulted in the decomposition of the starting material. The primary amine underwent nucleophilic addition with conjugates **10** to produce the compound **12** which was further confirmed after cleavage from the support to deliver **13** (see Supporting information). The low reactivity of substrate **12** could be attributed to the large steric strain inside the fused β-carboline ring and the di-substitution at C1 carbon.

The progress of the total reaction sequence was monitored by regular proton NMR spectroscopy directly on the polymer support (Fig. 3). Formation of the tetrahydro β-carboline skeleton **7f** from **6** via Pictet–Spengler reaction was confirmed by the disappearance of a characteristic singlet of C_2–Hg proton at 7.15 ppm (Fig. 3, spectrum b) and the appearance of a NH proton peak of β-carboline around 9.7 ppm. Reaction of **7f** with chloroacetyl chloride was observed from the emergence of two signals of Hi protons around 3.90–4.15 ppm and disappearance of NH proton signal (Fig. 3, spectrum c). Cyclization toward the diketopiperazine conjugate **9f** was seen after reaction of **8f** with *n*-butyl amine. Disconnection of the final product from the polymeric support was directly observed by the absence of signals at 4.4 ppm which corresponds to PEG absorbance. In the ^{1}H NMR spectrum, other characteristic signals of different protons are in agreement with structure **9f** (Fig. 3, spectrum d).

By using this traceless synthetic route, various 2,5 -diketopiperazine fused tetrahydro β-carboline derivatives were synthesized from PEG-supported Fmoc-protected L-tryptophan **4**, appropriate ketones (R_1COR_2) and primary amines (R_3NH_2) (Table 1). Unsymmetrical ketones gave a mixture of *cis* and*trans* diastereomers which were separated and characterized (Table 1 entries **9m**–**9q**).

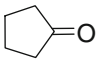
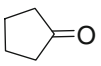
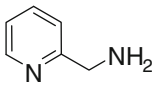
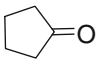
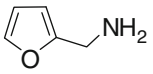
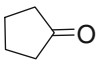
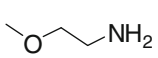
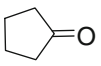
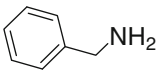
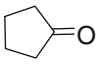
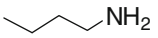
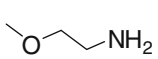
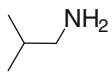
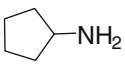
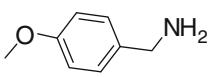
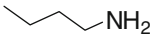
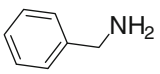
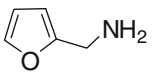
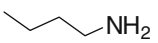
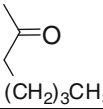
The stereochemistry of the products obtained from the reactions with asymmetric ketones was determined by comparing the spectral data of the compounds with those reported by Cook [40]. In our investigation, we have further confirmed the *cis/trans* stereochemistry of target compounds using 1D NOE analysis of compound **9o** (Fig. 4). The irradiation of proton Ha in *trans* isomer of compound **9o** enhanced the signal of Hc protons by 1.74% and the signal for Hd proton by 2.07%. However, signal of Hb protons does not show any enhancement. In the same way, the irradiation of Ha protons in cis isomer of compound **9o** enhanced the signals of Hb protons by 1.91%, while no enhancement effect in the signal of Hc protons. These observations verified the *cis* and *trans* isomers of **9o**.

Furthermore, the structures of 2,5-diketopiperazine fused tetrahydro-β-carbolines **9** was unambiguously confirmed by the single crystal X-ray analysis of compound **9l** (see Supporting information for crystallographic data). The ORTEP diagram for compound **9l** is presented in Fig. 5. The single crystal X-ray analysis of compound **9l** indicates that two rings of diketopiperazine and carboline moiety are in antiperiplanar orientation.

Conclusions

In summary, we have developed a traceless and diversity-oriented synthesis of diketopiperazines fused tetrahydro-β-carbolines. The key reaction employed was the Pictet–Spengler reaction of various ketones in refluxing condition. A unique spiro element similar to drug-like skeleton was also achieved along with the two sets of diversities. Finally the target compounds were released from the support in a traceless manner and purification was done by simple precipitation and filtration. The reaction progress of all the synthetic steps carried out on the soluble polymer support was directly monitored by conventional proton NMR. Thus, the traceless synthetic strategy represents a well-defined tool for the rapid library generation of diverse target compounds

Table 1 Soluble polymer supported synthesis of 2,5-diketopiperazine fused tetrahydro β-carboline derivatives (**9a**–**9q**)

Entry	R_1COR_2	R_3NH_2	LRMS	Yield
9a			351	72
9b			400	58
9c			389	75
9d			367	61
9e			399	80
9f			365	81
9g			341	67
9h			339	82
9i			325	74
9j			351	69
9k			403	74
9l			339	81
9m			387	75 (45/30)
9n			377	67 (40/27)
9o			339	74 (44/30)
9p			353	72 (42/30)
9q			381	68 (45/23)

LRMS are detected with EI ionization source
Yields are based on loading of soluble support. Parentheses denote the isolated yield of two diastereomers (*trans* + *cis*)

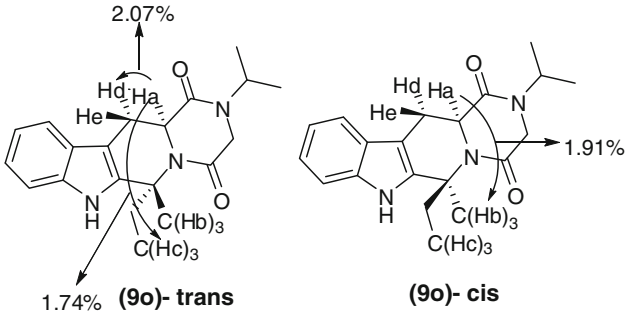


Fig. 4 Key NOE interactions of **9o**-*trans* and **9o**-*cis*

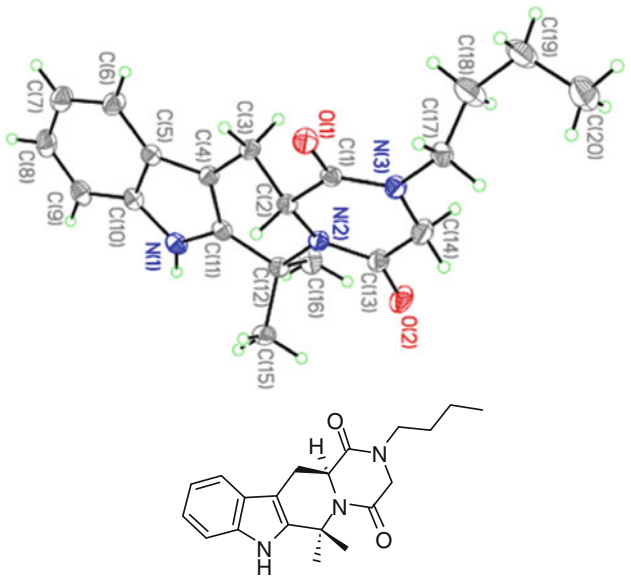


Fig. 5 ORTEP diagram of compound **9l**

with readily available building blocks such as ketones and primary amines.

Experimental section

General methods

All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel coated Kiselgel 60 F254 plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230–400 mesh). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker DX-300

spectrometer. Chemical shifts are reported in parts per million (ppm) on the scale from an internal standard. Mass spectra were recorded on a time-of-flight mass spectrometer (Quattro Micro, Waters), samples being introduced by infusion method using the electrospray ionization technique. High-resolution mass spectra (HRMS) were recorded on a JEOL TMS-HX 110 mass spectrometer. IR spectra were recorded with a HORIBA FREEXACT-II FT-720 spectrometer. PEG was purchased from SHOWA and Fmoc-protected L-tryptophan was purchased from Advanced ChemTech.

General procedure for the preparation of diketopiperazine fused tetrahydro-β-carbolines (9)

The soluble polymer support (HO-PEG-OH, MW 6000) (1 g, 0.16 mmol, 1.0 equiv.) was esterified with Fmoc-L-tryptophan **4** (0.170 g, 0.39 mmol, 2.4 equiv) in dichloromethane (10 mL) in the presence of *N*,*N*′-dicyclohexyl carbodiimide (DCC) (0.082 g, 0.39 mmol, 2.4 equiv) and *N*,*N*′-dimethylamino pyridine (DMAP) (0.002 g). The reaction mixture was refluxed for 1 h to obtain the polymer-bound Fmoc-L-tryptophan **5**. During the reaction, the suspended dicyclohexylurea (DCU) which formed as byproduct was filtered off and the reaction mixture was precipitated with ice-cold ether (100 mL). The precipitated polymer-bound Fmoc-L-tryptophan **5** was filtered through a fritted funnel and thoroughly washed with ether (50 mL×3) and dried under vacuum. The removal of the Fmoc group on polymer-bound Fmoc-L-tryptophan **5** was achieved by treating the compound with 10% piperidine in dichloromethane (10 mL) for 30 min. The amines **6** which were produced after Fmoc deprotection further reacted with various ketones (5.0 equiv) by refluxing 8 h in 10% trifluoroacetic acid and chloroform (10 mL). After completion of the reaction, ice-cold ether (100 mL) was added to precipitate the polymer-bound β-carbolines **7**. The precipitated solid **7** was washed with ether (50 mL×3) to remove the unreacted ketones and the solid was dried under vacuum for the next step. The tricyclic polymer conjugates **7** were dissolved in dichloromethane (10 mL), treated with chloroacetyl chloride (5.0 equiv) and triethylamine (3.0 equiv) and stirred for 8 h at room temperature. After completion, ice-cold ether (100 mL) was added for precipitation to provide the polymer-bound *N*-chloroacetyl product **8**. The precipitated solid **8** was washed with ether (50 mL×3) to remove the unreacted reagents and dried under vacuum to obtain the compound **8** in quantitative yield. Immobilized *N*-chloroacetyl product **8** was dissolved in dichloromethane (10 mL), and was further reacted with various primary amines (5.0 equiv) for 8 h at room temperature to trigger the traceless release of the target compound from the polymeric support as judged by TLC. Addition of excess of ice cold ether (50 mL) resulted in the precipitation of the polymer support which was filtered off and washed with ether (20 mL×3). The combined extracts were subjected to evaporation to afford crude, polymer free compounds **9**. These crude products were further purified by using column chromatography and eluted with ethyl acetate/hexane mixtures (1:1) to obtain diketo piperazinones **9** in good to excellent yields.

*(12a′S)-2′-(1-Methylethyl)-12′,12a′-dihydro-2′ H-spiro [cyclopentane-1,6′-pyrazino[1′,2′:1,6] pyrido [3,4-b]indole]-1′,4′(3′H,7′H)-dione (***9a***)*

Yield 0.197 g, 72%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.40$ (s, 1 H, N-H), 7.48 (d, $J = 7.8$ Hz, 1 H, 8-H), 7.33 (d, $J = 7.5$ Hz, 1 H, 11-H), 7.10–7.19 (m, 2 H, Ar), 4.87 (sept, $J = 6.8$ Hz, 1 H, *i*Pr), 4.41 (dd, $J = 11.7$, 3.5 Hz, 1 H, 12a′-H), 3.96 (d, $J = 17.3$ Hz, 1 H, 3-H), 3.87 (d, $J = 17.3$Hz, 1 H, 3-H), 3.48 (dd, $J = 15.4$, 3.7 Hz, 1 H, 12′-H), 3.18 (m, 1 H, 6-H), 2.95 (dd, $J = 15.4$, 11.7 Hz, 1 H, 12′-H), 2.36-1.82 (m, 7 H, 6-H), 1.22 (d, $J = 6.8$Hz, 6 H, *i*Pr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 165.9$, 164.9, 139.0, 136.4, 126.7, 122.5, 120.3, 118.6, 111.4, 106.4, 69.8, 58.4, 45.1, 44.6, 41.4, 38.5, 27.3, 26.4, 26.1, 19.4, 19.2 ppm. MS (EI)$m/z = 351$ (M^+). HRMS (EI): calcd. for $C_{21}H_{25}N_3O_2$ (M^+) 351.1947; found351.1943. $[\alpha]_D^{25} = -108.9$ ($c = 0.2$, CH_2Cl_2). IR (neat): $\tilde{\nu} = 3313$, 2964, 1660, 1652, 1452 cm^{-1}.

*(12a′S)-2′-(Pyridin-2-ylmethyl)-12′,12a′-dihydro-2′ H-spiro[cyclopentane-1,6′-pyrazino [1′,2′:1,6]pyrido [3,4-b]indole]-1′,4′(3′H,7′H)-dione (***9b***)*

Yield 0.182 g, 58%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.59$ (dd, $J = 5.0$, 0.7 Hz, 1 H, py), 8.17 (s, 1 H, NH), 7.72 (dd, $J = 7.7$, 1.7 Hz, 1 H, py), 7.49 (d, $J = 7.7$ Hz, 1 H, 8-H), 7.34 (t, $J = 8.2$ Hz, 2 H, Ar), 7.25 (d, $J = 7.6$ Hz, 1 H, Ar), 7.19–7.10 (m, 2 H, Ar), 4.87 (d, $J = 15.0$ Hz, 1 H, –*C*H_2Py), 4.66 (d, $J = 15.0$ Hz, 1 H, –*C*H_2Py), 4.65 (dd, $J = 11.7$, 3.8 Hz, 1 H, 12a′-H), 4.22 (d, $J = 17.5$ Hz, 1 H, 3-H), 4.04 (d, $J = 17.5$ Hz, 1 H, 3-H), 3.53 (dd, $J = 15.4$, 3.8 Hz, 1 H, 12′-H), 3.13 (m, 1 H, 6-H), 2.96 (dd, $J = 15.4$, 11.7 Hz, 1 H, 12′-H), 2.40–1.79 (m, 7 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.7$, 164.5, 155.5, 150.0, 139.2, 137.6, 136.4, 126.7, 123.3, 123.0, 122.6, 120.4, 118.6, 111.4, 106.4, 69.7, 58.2, 51.6, 51.2, 41.2, 38.7, 27.5, 26.5, 26.3 ppm. MS (EI)$m/z = 400$ (M^+). HRMS (EI): calcd. for $C_{24}H_{24}N_4O_2$ (M^+) 400.1899; found 400.1899. $[\alpha]_D^{25} = -89.2$ ($c = 0.266$, CH_2Cl_2). IR (neat): $\tilde{\nu} = 3314$, 2955, 1664, 1592, 1437 cm^{-1}.

*(12a′S)-2′-(Furan-2-ylmethyl)-12′,12a′-dihydro-2′ H-spiro[cyclopentane-1,6′-pyrazino [1′,2′:1,6]pyrido [3,4-b]indole]-1′,4′(3′H,7′H)-dione (***9c***)*

Yield 0.228 g, 75%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.03$ (s, 1 H, NH), 7.50 (d, $J = 7.6$ Hz, 1 H, 8-H), 7.43 (s, 1 H, Ar), 7.34 (d, $J = 7.6$ Hz, 1 H, 11-H), 7.21–7.11 (m, 2 H, Ar), 6.39 (s, 2 H, furan), 4.72 (d, $J = 15.2$, Hz, 1 H, $-CH_2$furan), 4.60 (d, $J = 15.2$, Hz, 1 H, $-CH_2$furan), 4.43 (dd, $J = 11.8$, 3.4 Hz, 1 H, 12a′-H), 4.07 (d, $J = 17.4$ Hz, 1 H, 3-H), 3.95 (d, $J = 17.4$ Hz, 1 H, 3-H), 3.53 (dd, $J = 15.4$, 3.4 Hz, 1 H, 12′-H), 3.11 (m, 1 H, 6-H), 2.95 (dd, $J = 15.4$, 11.8 Hz, 1 H, 12′-H), 2.41–1.80 (m, 7 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.2$, 164.3, 149.0, 143.5, 139.1, 136.3, 126.6, 122.6, 120.4, 118.6, 111.4, 111.0, 110.3, 106.4, 69.6, 58.2, 50.6, 42.1, 41.1, 38.8, 27.5, 26.5, 26.4 ppm. MS (EI) $m/z = 389$ (M^+).HRMS (EI): calcd. for $C_{23}H_{23}N_3O_3$ (M^+) 389.1739; found 389.1739. $[\alpha]_D^{25} = -96.6$ ($c = 0.17$, CH_2Cl_2). IR (neat): $\tilde{\nu} = 3323$, 2957, 1668, 1661, 1447 cm^{-1}.

*(12a′S)-2′-(2-Methoxyethyl)-12′,12a′-dihydro-2′ H-spiro[cyclopentane-1,6′-pyrazino [1′,2′:1,6]pyrido [3,4-b]indole]-1′,4′(3′H,7′H)-dione (***9d***)*

Yield 0.175 g, 65%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.36$ (s, 1 H, NH), 7.47 (d, $J = 7.9$ Hz, 1 H, 8-H), 7.32 (d, $J = 7.2$ Hz, 1 H, 11-H), 7.19–7.09 (m, 2 H, Ar), 4.40 (dd, $J = 11.7$, 3.7 Hz, 1 H, 12a′-H), 4.25 (d, $J = 17.7$ Hz, 1 H, 3-H), 4.08 (d, $J = 17.7$ Hz, 1 H, 3-H), 3.73 (m, 1 H, 12′-H), 3.63 (t, $J = 4.6$ Hz, 2 H, 2-H), 3.57–3.46 (m, 2 H, 2-H), 3.37 (s, 3 H, OMe), 3.15 (m, 1 H, 6-H), 2.96 (dd, $J = 15.4$, 11.7 Hz, 1 H, 12′-H), 2.33–1.83 (m, 7 H, 6-H) ppm. ^{13}C NMR(75 MHz, $CDCl_3$): $\delta = 166.5$, 164.8, 139.2, 136.4, 126.7, 122.5, 120.3, 118.5, 111.4, 106.4, 70.8, 69.7, 59.3, 58.2, 52.8, 46.3, 41.2, 38.7, 27.4, 26.4, 26.3. MS (EI) $m/z = 367$ (M^+). HRMS (EI): calcd. for $C_{21}H_{25}N_3O_3$ (M^+) 367.1896; found 367.1896. $[\alpha]_D^{25} = -100.3$ ($c = 0.2$, CH_2Cl_2). IR (neat): $\tilde{\nu} = 3307$, 2943, 1658, 1452 cm^{-1}.

*(12a′S)-2′-Benzyl-12′,12a′-dihydro-2′H-spiro[cyclopentane-1,6′-pyrazino[1′,2′:1,6]pyrido [3,4-b]indole]-1′,4′(3′H,7′H)-dione (***9e***)*

Yield 0.250 g, 80%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.37$ (s, 1 H, NH), 7.51 (d, $J = 7.5$ Hz, 1 H, 8-H), 7.44–7.33 (m, 6 H, Ar), 7.20–7.15 (m, 2 H, Ar), 4.80 (d, $J = 14.4$ Hz, 1 H, $-CH_2$Ph), 4.52 (d, $J = 14.4$ Hz, 1 H, $-CH_2$Ph), 4.48 (dd, $J = 11.8$, 3.7 Hz, 1 H, 12a′-H), 3.97 (d, $J = 17.4$ Hz, 1 H, 3-H), 3.83 (d, $J = 17.4$ Hz, 1 H, 3-H), 3.57 (dd, $J = 15.3$, 3.7 Hz, 1 H, 12′-H), 3.15 (m, 1 H, 6-H), 2.98 (dd, $J = 15.3$, 11.8 Hz, 1 H, 12′-H), 2.33–1.70 (m, 7 H, 6-H) ppm. ^{13}C NMR(75 MHz, $CDCl_3$): $\delta = 166.4$, 164.4, 139.1, 136.4, 135.4, 129.5, 128.9, 128.6, 126.5, 122.6, 120.4, 118.6, 111.5, 106.3, 69.8, 58.3, 50.5, 49.6, 41.3, 38.7, 27.7, 26.4, 26.2 ppm. MS (EI)$m/z = 399$ (M^+). HRMS (EI): calcd. for $C_{25}H_{25}N_3O_2$ (M^+) 399.1947; found 399.1938. $[\alpha]_D^{25} = -84.9$ ($c = 0.2$, CH_2Cl_2). IR (neat): $\tilde{\nu} = 3319$, 2954, 1663, 1452 cm^{-1}.

*(12a′S)-2′-Butyl-12′,12a′-dihydro-2′H-spiro[cyclopentane-1,6′-pyrazino[1′,2′:1,6]pyrido [3,4-b]indole]-1′,4′(3′H,7′H)-dione (***9f***)*

Yield 0.233 g, 81%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.02$ (s, 1 H, NH), 7.49 (d, $J = 7.8$Hz, 1 H, 8-H), 7.37 (d, $J = 8.4$ Hz, 1 H, 11-H), 7.21–7.02 (m, 2 H, Ar), 4.39 (dd, $J = 11.8$, 3.6 Hz, 1 H, 12a′-H), 4.10 (d, $J = 17.4$ Hz, 1 H, 3-H), 3.90 (d, $J = 17.4$ Hz, 1 H, 3-H), 3.58 (m, 1 H, *n*Bu), 3.50 (dd, $J = 15.4$, 3.6 Hz, 1 H, 12′-H), 3.34 (m, 1 H, *n*Bu), 3.14 (m, 1 H, 6-H), 2.93 (dd, $J = 15.4$, 11.8 Hz, 1 H, 12′-H), 2.35–1.84 (m, 7 H, 6-H), 1.62 (quint, $J = 7.5$Hz, 2 H, *n*Bu), 1.39 (m, 2 H, *n*Bu), 0.99(t, $J = 7.2$ Hz, 3H, *n*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.1$, 164.5, 139.1, 136.3, 126.7, 122.6, 120.4, 118.6, 111.4, 106.6, 69.6, 58.3, 51.1, 46.0, 41.2, 38.7, 29.0, 27.5, 26.5, 26.3, 20.4, 14.2 ppm. MS (EI)$m/z = 365$ (M^+). HRMS (EI): calcd. for (M^+)$C_{22}H_{27}N_3O_2$ 365.2103; found 365.2106. $[\alpha]_D^{25} = -117.1$ ($c = 0.114$, CH_2Cl_2). IR (neat): $\tilde{\nu} = 3311$, 2958, 1655, 1452 cm^{-1}.

*(12aS)-2-(2-Methoxyethyl)-6,6-dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido [3,4-b]indole-1,4-dione (***9g***)*

Yield 0.179 g, 67%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.03$ (s, 1 H, NH), 7.54 (d, $J = 7.6$Hz, 1 H, 8-H), 7.37 (d, $J = 7.7$ Hz, 1 H, 11-H), 7.24–7.13 (m, 2 H, Ar), 4.29 (d, $J = 17.3$ Hz, 1 H, 3-H), 4.19 (d, $J = 17.3$ Hz, 1 H, 3-H), 4.12 (m, 1 H, 12a-H), 3.70 (m, 1 H, 12-H), 3.65–3.61 (m, 4 H, $-CH_2CH_2$OMe), 3.38 (s, 3 H, OMe), 2.91 (dd, $J = 15.4$, 11.3 Hz, 1 H, 12-H), 2.06 (s, 3 H, 6-CH_3), 1.86 (s, 3 H, 6-CH_3) ppm.^{13}C NMR(75 MHz, $CDCl_3$): $\delta = 165.5$, 164.2, 138.6, 136.4, 126.6, 122.7, 120.4, 118.9, 111.3, 107.1, 70.9, 60.1, 59.3, 56.7, 52.7, 46.5, 30.2, 27.8, 24.6 ppm. MS (EI)$m/z = 341$ (M^+). HRMS (EI): calcd. for $C_{19}H_{23}N_3O_3$(M^+)341.1739; found 341.1766. $[\alpha]_D^{25} = -164.8$ ($c = 0.03$, CH_2Cl_2). IR (neat): $\tilde{\nu} = 3283$, 2925, 1654, 1449 cm^{-1}.

*(12aS)-6,6-Dimethyl-2-(2-methylpropyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido [3,4-b]indole-1,4-dione (***9h***)*

Yield 0.218 g, 82%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.28$ (s, 1 H, NH), 7.53 (d, $J = 7.5$Hz, 1 H, 8-H), 7.37 (d, $J =$

7.7 Hz, 1 H, 11-H), 7.24-7.11 (m, 2 H, Ar), 4.24 (dd, J = 11.4, 3.2 Hz, 1 H, 12a-H), 4.15 (dd, J = 17.2, 1.1 Hz, 1 H, 3-H), 3.92 (dd, J = 17.2, 1.1 Hz, 1 H, 3-H), 3.67 (dd, J = 15.4, 3.2 Hz, 1 H, 12-H), 3.53 (dd, J = 13.4, 7.0 Hz, 1 H, *i*Bu), 3.07 (dd, J = 13.4, 7.0 Hz, 1 H, *i*Bu), 2.90 (dd, J = 15.4, 11.4 Hz, 1 H, 12-H), 2.07 (s, 3 H, 6-CH_3), 2.06 (m, 1 H, *i*Bu), 1.85 (s, 3 H, 6-CH_3), 0.99 (d, J = 6.6 Hz, 6 H, *i*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 164.0, 138.5, 136.4, 126.6, 122.7, 120.4, 118.9, 111.3, 107.2, 60.1, 56.9, 53.5, 51.7, 30.1, 28.1, 26.3, 24.7, 20.5, 20.3 ppm. MS (EI)m/z = 339 (M^+) HRMS (EI): calcd. for $C_{20}H_{25}N_3O_2$ (M^+) 339.1947; found339.1942; $[\alpha]_D^{25}$ = −151.9 (c = 0.054, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3284, 2925, 1655, 1452 cm^{-1}.

*(12aS)-6,6-Dimethyl-2-(1-methylethyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido [3,4-b]indole-1,4-dione (***9i***)*

Yield 0.188 g, 74%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (s, 1 H, NH), 7.54 (d, J = 7.5Hz, 1 H, 8-H), 7.37 (d, J = 7.7 Hz, 1 H, 11-H), 7.24–7.13 (m, 2 H, Ar), 4.88 (sept, J = 6.8 Hz, 1 H, *i*Pr), 4.21 (dd, J = 11.4, 3.3 Hz, 1 H, 12a-H), 4.04 (dd, J = 17.1, 1.5 Hz, 1 H, 3-H), 3.87 (dd, J = 17.1, 1.5 Hz, 1 H, 3-H), 3.67 (dd, J = 15.4, 3.3 Hz, 1 H, 12-H), 2.89 (dd, J = 15.4, 11.4 Hz, 1 H, 12-H), 2.06 (s, 3 H, 6-CH_3), 1.85 (s, 3 H, 6-CH_3), 1.24 (d, J = 6.8 Hz, 6 H, *i*Pr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.1, 163.9, 138.1, 135.9, 126.2, 122.3, 120.0, 118.4, 110.9, 106.8, 59.6, 56.6, 44.6, 44.4, 29.7, 27.4, 24.2, 18.9, 18.6 ppm. MS (EI)m/z = 325 (M^+). HRMS (EI): calcd. for $C_{19}H_{23}N_3O_2$ (M^+) 325.1790; found325.1790; $[\alpha]_D^{25}$ = −59.3 (c = 0.315, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3292, 2975, 1649, 1441 cm^{-1}.

*(12aS)-2-Cyclopentyl-6,6-dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-b] indole-1,4-dione (***9j***)*

Yield 0.275 g, 69%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (s, 1 H, NH), 7.54 (d, J = 7.5Hz, 1 H, 8-H), 7.36 (d, J = 7.9 Hz, 1 H, 11-H), 7.23–7.13 (m, 2 H, Ar), 4.94 (quint, J = 8.3 Hz, 1 H, *cy*Pentyl), 4.22 (dd, J = 11.4, 3.2 Hz, 1 H, 12a-H), 4.08 (d, J = 17.1 Hz, 1 H, 3-H), 3.89 (d, J = 17.1 Hz, 1 H, 3-H), 3.67 (dd, J = 15.4, 3.2 Hz, 1 H, 12-H), 2.91 (dd, J = 15.4, 11.4 Hz, 1 H, 12-H), 2.07 (s, 3 H, 6-CH_3), 1.86 (s, 3 H, 6-CH_3), 1.98-1.52 (m, 8 H, 2-H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 164.3, 138.5, 136.4, 126.6, 122.7, 120.3, 118.9, 111.3, 107.1, 60.1, 57.1, 54.7, 46.2, 30.1, 28.1, 28.0, 27.9, 24.6, 24.5 ppm. MS (EI)m/z = 351 (M^+). HRMS (EI): calcd. for $C_{21}H_{25}N_3O_2$ (M^+) 351.1947; found 351.1945. $[\alpha]_D^{25}$ = −210.8 (c = 0.09, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3299, 2957, 1649, 1440 cm^{-1}.

*(12aS)-2-(4-Methoxybenzyl)-6,6-dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6] pyrido[3,4-b]indole-1,4-dione (***9k***)*

Yield 0.234 g, 74%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.46 (s, 1 H, NH), 7.55 (d, J = 7.7 Hz, 1 H, 8-H), 7.35–7.28 (m, 3 H, Ar), 7.23–7.15 (m, 2 H, Ar), 6.92 (d, J = 8.7 Hz, 2 H, Ar), 4.66 (d, J = 14.2Hz, 1 H, -PMB), 4.55 (d, J = 14.2 Hz, 1 H, -PMB), 4.27 (dd, J = 11.4, 3.2 Hz, 1 H, 12a-H), 4.03 (d, J = 17.3Hz, 1 H, 3-H), 3.85 (d, J = 17.3 Hz, 1 H, 3-H), 3.83 (s, 3 H, OMe), 3.74 (dd, J = 15.4, 3.2 Hz, 1 H, 12-H), 2.94 (dd, J = 15.4, 11.4 Hz, 1 H, 12-H), 2.04 (s, 3 H, 6-CH_3), 1.84 (s, 3 H, 6-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 164.0, 160.0, 138.6, 136.4, 130.6, 127.4, 126.6, 122.6, 120.3, 118.9, 114.8, 111.3, 106.9, 60.3, 56.9, 55.8, 50.2, 49.2, 30.1, 28.0, 24.5 ppm. MS (EI)m/z = 403 (M^+). HRMS (EI): calcd. for $C_{24}H_{25}N_3O_3$ (M^+) 403.1896; found 403.1895; $[\alpha]_D^{25}$ = −186.9 (c = 0.23, CH_2Cl_2); IR(neat): $\tilde{\nu}$ = 3300, 2932, 1659, 1652, 1440 cm^{-1}.

*(12aS)-2-Butyl-6,6-dimethyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-b]indole -1,4-dione (***9l***)*

Yield 0.215 g, 81%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40 (s, 1 H, NH), 7.53 (d, J = 7.5 Hz, 1 H, 8-H), 7.36 (d, J = 7.8 Hz, 1 H, 11-H), 7.23–7.12 (m, 2 H, Ar), 4.23 (dd, J = 11.3, 3.2 Hz, 1 H, 12a-H), 4.16 (d, J = 17.1 Hz, 1 H, 3-H), 3.96 (d, J = 17.1Hz, 1 H, 3-H), 3.68 (dd, J = 15.4, 3.2 Hz, 1 H, 12-H), 3.57 (m, 1 H, *n*Bu), 3.38 (m, 1 H, *n*Bu), 2.91 (dd, J = 15.4, 11.3 Hz, 1 H, 12-H), 2.08 (s, 3 H, 6-CH_3), 1.86 (s, 3 H, 6-CH_3), 1.68-1.58 (m, 2 H, *n*Bu), 1.46-1.34 (m, 2 H, *n*Bu), 0.99 (t, J = 7.3 Hz, 3 H, *n*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 164.0, 138.6, 136.4, 126.6, 122.6, 120.3, 118.9, 111.3, 107.0, 60.2, 56.9, 51.0, 46.2, 30.1, 28.8, 28.0, 24.6, 20.4, 14.2. MS (EI)m/z = 339 (M^+). HRMS (EI): calcd. for $C_{20}H_{25}N_3O_2$ (M^+) 339.1947; found 339.1939; $[\alpha]_D^{25}$ = −249.4 (c = 0.1, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3299, 2930, 1654, 1439 cm^{-1}.

*trans-(6R,12aS)-2-Benzyl-6-ethyl-6-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6] pyrido[3,4-b]indole-1,4-dione (***9m***-trans)*

Yield 0.136 g, 45%. ^{1}H NMR (300 MHz, $CDCl_3$): δ =8.20 (s, 1 H, NH), 7.58 (d, J = 7.3 Hz, 1 H, 8-H), 7.46–7.30 (m, 6 H, Ar), 7.24–7.13 (m, 2 H, Ar), 4.76 (d, J = 14.4 Hz, 1 H, –CH_2Ph), 4.60 (d, J = 14.4 Hz, 1 H, –CH_2Ph), 4.35

(dd, J = 11.4, 3.2 Hz, 1 H, 12a-H), 4.01 (dd, J = 17.2, 1.5 Hz, 1 H, 3-H), 3.93 (dd, J = 17.2, 1.5 Hz, 1 H, 3-H), 3.80 (dd, J = 15.4, 3.2 Hz, 1 H, 12-H), 3.00–2.89 (m, 2 H, 12-H, 6-Et), 2.37 (m, 1 H, 6-Et), 1.95 (s, 3 H, 6-CH_3), 0.87 (t, J = 7.3 Hz, 3 H, 6-Et) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 163.9, 137.0, 136.5, 135.3, 129.4, 129.1, 128.7, 126.5, 122.6, 120.3, 118.7, 111.4, 108.7, 64.4, 58.9, 50.3, 49.8, 30.6, 29.7, 27.5, 10.1 ppm. MS (EI)m/z = 387 (M^+). HRMS (EI): calcd. for $C_{24}H_{25}N_3O_2$ (M^+) 387.1947; found 387.1951. $[\alpha]_D^{25} = -129.6$ (c = 0.114, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3290, 2928, 1659, 1453 cm^{-1}.

*cis-(6S,12aS)-2-Benzyl-6-ethyl-6-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido [3,4-b]indole-1,4-dione (***9m***-cis)*

Yield 0.091 g, 30%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (s, 1 H, NH), 7.58 (d, J = 7.0 Hz, 1 H, 8-H), 7.44–7.35 (m, 6 H, Ar), 7.25–7.14 (m, 2 H, Ar), 4.70 (d, J = 15.0 Hz, 1 H, –CH_2Ph), 4.65 (d, J = 15.0 Hz, 1 H, –CH_2Ph), 4.26 (dd, J = 11.4, 3.2 Hz, 1 H, 12a-H), 4.03 (dd, J = 17.2, 1.4 Hz, 1 H, 3-H), 3.86 (dd, J = 17.2, 1.4 Hz, 1 H, 3-H), 3.74 (dd, J = 15.4, 3.2 Hz, 1 H, 12-H), 3.38 (m, 1 H, 6-H), 2.91 (dd, J = 15.4, 11.4 Hz, 1 H, 12-H), 1.83 (s, 3 H, 6-CH_3), 1.67 (m, 1 H, 6-H), 0.54 (t, J = 7.3 Hz, 3H, 6-CH_3) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 163.6, 136.6, 136.5, 135.4, 129.4, 129.1, 128.7, 126.4, 122.7, 120.3, 118.8, 111.3, 109.6, 64.2, 56.8, 50.1, 49.8, 34.0, 28.0, 24.4, 8.7 ppm. MS (EI)m/z = 387 (M^+). HRMS (EI): calcd. for $C_{24}H_{25}N_3O_2$ (M^+) 387.1947; found 387.1917; $[\alpha]_D^{25} = -128.7$ (c = 0.14, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3310, 2929, 1660, 1652, 1453 cm^{-1}.

*trans-(6R,12aS)-6-Ethyl-2-(furan-2-ylmethyl)-6-methyl-2,3,6,7,12,12a-hexahydropyrazino [1′,2′:1,6]pyrido[3,4-b] indole-1,4-dione (***9n***-trans)*

Yield 0.118 g, 40%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (s, 1 H, NH), 7.56 (d, J = 7.6 Hz, 1 H, 8-H), 7.43 (s, 1 H, Ar), 7.37 (d, J = 7.6 Hz, 1 H, 11-H), 7.25-7.14 (m, 2 H, Ar), 6.40 (s, 2 H, furan), 4.66 (d, J = 7.2 Hz, 2 H, –CH_2furan), 4.30 (d, J = 11.2 Hz, 1 H, 12a-H), 4.11 (d, J = 17.2 Hz, 1 H, 3-H), 4.03 (d, J = 17.2 Hz, 1 H, 3-H), 3.75 (dd, J = 15.5, 3.2 Hz, 1 H, 12-H), 2.95 (m, 1 H, 6-Et), 2.90 (dd, J = 15.5, 11.2 Hz, 1 H, 12-H), 1.95 (s, 3 H, 6-CH_3), 1.87 (m, 1 H, 6-Et), 0.87 (t, J = 7.3 Hz, 3 H, 6-Et) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 163.9, 149.0, 143.5, 136.9, 136.4, 126.7, 122.7, 120.4, 118.8, 111.3, 111.0, 110.3, 108.9, 64.3, 58.8, 50.5, 42.3, 30.6, 29.8, 27.3, 10.1 ppm. MS (EI)m/z = 377 (M^+); HRMS (EI): calcd. for $C_{22}H_{23}N_3O_3$ (M^+) 377.1739; found 377.1747. $[\alpha]_D^{25} = -145.6$ (c = 0.137, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3313, 2926, 1659, 1440 cm^{-1}.

*cis-(6S,12aS)-6-Ethyl-2-(furan-2-ylmethyl)-6-methyl-2,3,6,7,12,12a-hexahydropyrazino [1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione (***9n***-cis)*

Yield 0.79 g, 27%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (s, 1 H, NH), 7.55 (d, J = 7.5 Hz, 1 H, 8-H), 7.44 (s, 1 H, Ar), 7.36 (d, J = 7.8 Hz, 1 H, Ar), 7.24-7.13 (m, 2 H, Ar), 6.40 (s, 2 H, furan), 4.75 (d, J = 15.2 Hz, 1 H, –CH_2furan), 4.60 (d, J= 15.2 Hz, 1 H, –CH_2furan), 4.23 (d, J = 11.5 Hz, 1 H, 12a-H), 4.13 (d, J = 17.7 Hz, 1 H, 3-H), 3.97 (d, J = 17.7 Hz, 1 H, 3-H), 3.69 (dd, J = 15.5, 3.0 Hz, 1 H, 12-H), 3.38 (m, 1 H, 6-Et), 2.89 (dd, J = 15.5, 11.5 Hz, 1 H, 12-H), 1.83 (s, 3 H, 6-CH_3), 1.68 (m, 1 H, 6-Et), 0.55 (t, J = 7.3 Hz, 3 H, 6-Et) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 163.5, 149.0, 143.5, 136.4, 136.2, 126.4, 122.7, 120.3, 118.8, 111.3, 111.0, 110.4, 109.6, 64.2, 56.7, 50.3, 42.3, 34.0, 27.8, 24.4, 8.7 ppm. MS (EI)m/z = 377 (M^+); HRMS (EI): calcd. for $C_{22}H_{23}N_3O_3$ (M^+) 377.1739; found 377.1745; $[\alpha]_D^{25} = -158.3$ (c = 0.11, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3310, 2929, 1655, 1440 cm^{-1}.

*trans-(6R,12aS)-6-Ethyl-6-methyl-2-(1-methylethyl)-2,3,6,7, 12,12a-hexahydropyrazino [1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione (***9o***-trans)*

Yield 0.117 g, 44%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (s, 1 H, NH), 7.55 (d, J = 7.8 Hz, 1 H, 8-H), 7.37 (d, J = 7.6 Hz, 1 H, 11-H), 7.24–7.13 (m, 2 H, Ar), 4.88 (sept, J = 6.8Hz, 1 H, iPr), 4.20 (dd, J = 11.4, 3.2 Hz, 1 H, 12a-H), 4.02 (d, J = 17.1 Hz, 1 H, 3-H), 3.93 (d, J = 17.1 Hz, 1 H, 3-H), 3.71 (dd, J = 15.3, 3.2 Hz, 1 H, 12-H), 2.96 (m, 1 H, 6-Et), 2.88 (dd, J = 15.3, 11.4 Hz, 1 H, 12-H), 2.07 (s, 3 H, 6-CH_3), 1.93 (m, 1 H, 6-Et), 1.24 (d, J = 6.8 Hz, 6 H, iPr), 0.88 (t, J = 7.2 Hz, 3 H, 6-Et) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 164.5, 137.0, 136.4, 126.7, 122.6, 120.3, 118.8, 111.4, 108.8, 64.2, 58.9, 44.9, 44.8, 30.6, 29.7, 27.2, 19.3, 19.2, 10.1 ppm. MS (EI)m/z = 339 (M^+); HRMS (EI): calcd. for $C_{20}H_{25}N_3O_2$ (M^+) 339.1947; found 339.1957. $[\alpha]_D^{25} = -130.4$ (c = 0.163, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3316, 2972, 1652, 1443 cm^{-1}.

*cis-(6S,12aS)-6-Ethyl-6-methyl-2-(1-methylethyl)-2,3,6,7, 12,12a-hexahydropyrazino [1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione (***9o***-cis)*

Yield 0.79 g, 30%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (s, 1 H, NH), 7.54 (d, J = 7.8 Hz, 1 H, 8-H), 7.36 (d, J = 7.6 Hz, 1 H, 11-H), 7.23–7.13 (m, 2 H, Ar), 4.88 (sept, J = 6.8 Hz, 1 H, iPr), 4.20 (dd, J = 11.4, 3.2 Hz, 1 H, 12a-H), 4.04 (d, J = 17.1 Hz, 1 H, 3-H), 3.86 (d, J = 17.1 Hz, 1 H, 3-H), 3.67 (dd, J = 15.3, 3.2 Hz, 1 H,

12-H), 3.41 (m, 1 H, 6-Et), 2.86 (dd, J = 15.3, 11.4 Hz, 1 H, 12-H), 1.85 (s, 3 H, 6-CH_3), 1.69 (m, 1 H, 6-Et),1.24 (d, J = 6.8 Hz, 6 H, iPr), 0.57 (t, J = 7.2 Hz, 3 H, 6-Et). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 164.0, 136.4, 136.2, 126.4, 122.7, 120.3, 118.8, 111.3, 109.7, 64.1, 57.0, 44.8, 44.7, 34.0, 27.8, 24.5, 19.3, 19.0, 8.8. MS (EI)m/z = 339 (M^+); HRMS (EI): calcd. for $C_{20}H_{25}N_3O_2$ (M^+) 339.1947; found 339.1914. $[\alpha]_D^{25}$ = −157.7 (c = 0.073, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3271, 2971, 1672, 1644, 1442 cm^{-1}.

*trans-(6R,12aS)-2-Butyl-6-ethyl-6-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido [3,4-b]indole-1,4-dione (***9p***-trans)*

Yield 0.116 g, 42%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (s, 1 H, NH), 7.54 (d, J = 7.5 Hz, 1 H, 8-H), 7.36 (d, J = 7.5 Hz, 1 H, 11-H), 7.24-7.21 (m, 2 H, Ar), 4.20 (dd, J = 11.3, 3.2 Hz, 1 H, 12a-H), 4.10 (d, J = 17.1 Hz, 1 H, 3-H), 4.03 (d, J = 17.1 Hz, 1 H, 3-H), 3.73 (dd, J = 15.4, 3.2 Hz, 1 H, 12-H), 3.55 (m, 1 H, nBu), 3.37 (m, 1 H, nBu), 2.96 (m, 1 H, 6-Et), 2.87 (dd, J = 15.4, 11.3 Hz, 1 H, 12-H), 1.97 (s, 6-Me), 1.94 (m, 1 H, 6-Et), 1.63 (quint, J = 8.1 Hz, 2 H, nBu), 1.39 (sept, J = 7.8 Hz, 2 H, nBu), 0.99 (t, J = 7.2 Hz, 3 H, nBu), 0.88 (t, J = 7.2Hz, 3 H, 6-Et). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 164.1, 137.0, 136.5, 126.7, 122.6, 120.2, 118.7, 111.4, 108.8, 64.3, 58.8, 50.9, 46.2, 30.0, 29.7, 28.9, 27.3, 20.4, 14.2, 10.1 ppm. MS (EI)m/z = 353 (M^+). HRMS (EI): calcd. for $C_{21}H_{27}N_3O_2$ (M^+) 353.2103; found 353.2109. $[\alpha]_D^{25}$ = −182.8 (c = 0.13, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3300, 2960, 1655, 1649, 1439 cm^{-1}.

*cis-(6S,12aS)-2-Butyl-6-ethyl-6-methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido [3,4-b]indole-1,4-dione (***9p***-cis)*

Yield 0.83 g, 30%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (s, 1 H, NH), 7.54 (d, J = 7.5 Hz, 1 H, 8-H), 7.36 (d, J = 7.5 Hz, 1 H, 11-H), 7.24-7.13 (m, 2 H, Ar), 4.20 (dd, J = 11.3, 3.2 Hz, 1 H, 12a-H), 4.14 (d, J = 17.1 Hz, 1 H, 3-H), 3.95 (d, J = 17.1 Hz, 1 H, 3-H), 3.67 (dd, J = 15.4, 3.2 Hz, 1 H, 12-H), 3.58-3.36 (m, 2 H, nBu), 2.85 (dd, J = 15.4, 11.3 Hz, 1 H, 12-H), 1.85 (s, 3 H, 6-CH_3), 1.76-1.58 (m, 4 H, nBu, 6-Et), 1.40 (m, 2 H, nBu), 0.99 (t, J = 7.2Hz, 3 H, 6-Et), 0.57 (t, J = 7.2 Hz, 3 H, nBu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 163.7, 136.4, 136.2, 126.4, 122.7, 120.3, 118.8, 111.3, 109.7, 64.2, 56.8, 50.7, 46.2, 34.0, 28.8, 27.9, 24.4, 20.4, 14.2, 8.7 ppm. MS (EI)m/z = 353 (M^+); HRMS (EI): calcd. for $C_{21}H_{27}N_3O_2$ (M^+) 353.2103; found 353.2109; $[\alpha]_D^{25}$ = −180.4 (c = 0.08, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3288, 2931, 1654, 1443 cm^{-1}.

*trans-(6R,12aS)-6-Methyl-2-(1-methylethyl)-6-pentyl-2,3,6,7,12,12a-hexahydropyrazino [1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione (***9q***-trans)*

Yield 0.135 g, 45%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (s, 1 H, NH), 7.56 (d, J = 7.4 Hz, 1 H, 8-H), 7.38 (d, J = 7.7 Hz, 1 H, 11-H), 7.25–7.13 (m, 2 H, Ar), 4.88 (sept, J = 6.9 Hz, 1 H, iPr), 4.25 (dd, J = 11.4, 3.4 Hz, 1 H, 12a-H), 4.01 (d, J = 17.1 Hz, 1 H, 3-H), 3.92 (d, J = 17.1 Hz, 1 H, 3-H), 3.72 (dd, J = 15.5, 3.4 Hz, 1 H, 12-H), 2.94 (m, 1 H, nPentyl), 2.87 (dd, J = 15.5, 11.4 Hz, 1 H, 12-H), 1.96 (s, 3 H, 6-CH_3), 1.80 (m, 1 H, nPentyl), 1.27–1.23 (m, 12 H, nPentyl, iPr),0.84 (t, J = 6.8 Hz, 3 H, nPentyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 164.4, 137.2, 136.4, 126.8, 122.7, 120.3, 118.8, 111.3, 108.6, 63.3, 58.8, 44.9, 44.8, 37.9, 32.4, 29.9, 27.3, 25.4, 22.9, 19.3, 19.1, 14.4 ppm. MS (EI)m/z = 381 (M^+). HRMS (EI): calcd. for $C_{23}H_{31}N_3O_2$ (M^+) 381.2416; found 381.2401; $[\alpha]_D^{25}$ = −37.7 (c = 0.075, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3321, 2926, 1647, 1456 cm^{-1}.

*cis-(6S,12aS)-6-Methyl-2-(1-methylethyl)-6-pentyl-2,3,6,7,12,12a-hexahydropyrazino [1′,2′:1,6]pyrido[3,4-b]indole-1,4-dione (***9q***-cis)*

Yield 0.068 g, 23%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (s, 1 H, NH), 7.55 (d, J = 7.6 Hz, 1 H, 8-H), 7.37 (d, J = 7.1 Hz, 1 H, 11-H), 7.25–7.13 (m, 2 H, Ar), 4.87 (sept, J = 6.9 Hz, 1 H, iPr), 4.22 (dd, J = 11.4, 3.2 Hz, 1 H, 12a-H), 4.02 (d, J = 17.1 Hz, 1 H, 3-H), 3.85 (d, J = 17.1 Hz, 1 H, 3-H), 3.66 (dd, J = 15.4, 3.2 Hz, 1 H, 12-H), 3.38 (m, 1 H, nPentyl), 2.85 (dd, J = 15.4, 11.4 Hz, 1 H, 12-H), 1.83 (s, 3 H, 6-CH_3), 1.60 (m, 1 H, nPentyl), 1.27–1.22 (m, 12 H, nPentyl, iPr),0.76 (t, J = 6.8 Hz, 3 H, nPentyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 164.1, 136.6, 136.3, 126.6, 122.6, 120.3, 118.8, 111.3, 109.4, 63.5, 57.0, 44.8, 41.0, 32.0, 30.1, 27.8, 24.7, 23.9, 22.8, 19.3, 19.0, 14.4 ppm. MS (EI)m/z = 381(M^+). HRMS (EI): calcd. for $C_{23}H_{31}N_3O_2$ (M^+) 381.2416; found 381.2419. $[\alpha]_D^{25}$ = −237.0 (c = 0.004, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3359, 2923, 1658, 1632 cm^{-1}.

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