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Synthesis of the tetracyclic core skeleton of the lundurines by a gold-catalyzed cyclization

Catalina Ferrer, Ana Escribano-Cuesta, Antonio M. Echavarren *

Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans, 16, 43007 Tarragona, Spain

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ABSTRACT

The 1*H*-azocino[5,4-*b*]indole skeleton of the lundurines has been prepared by the 8-*endo*-*dig* cyclization of an alkynylindole using $AuCl_3$ or other gold complexes as catalysts.

1. Introduction

Plants of the genus *Kopsia*, growing in South and Southeast Asia, are a rich source of novel alkaloids with intriguing carbon skeletons that display a wide variety of biological activities.[1,2] Prominent examples are the lundurines A–D (**1**–**4**) (Fig. 1),[3] which are characterized by a cyclopropyl moiety embedded within a hexacyclic ring system that includes an 1*H*-azocino[5,4-*b*]indole ring unit. Lundurines B (**2**) and D (**4**) display significant cytotoxicity in vitro toward B16 melanoma cells. Structurally related are the alkaloids lapidilectine B (**5**) and isolapidilectine (**6**).[4]

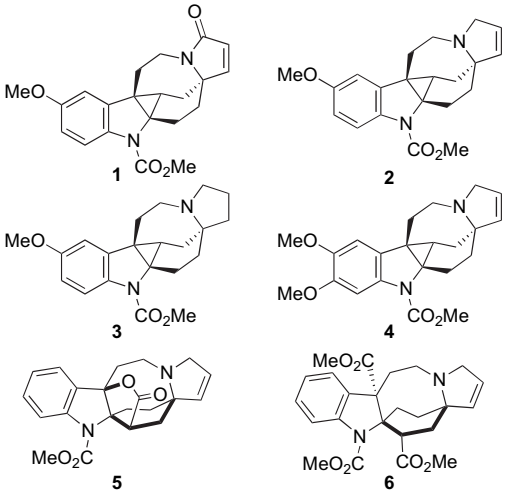
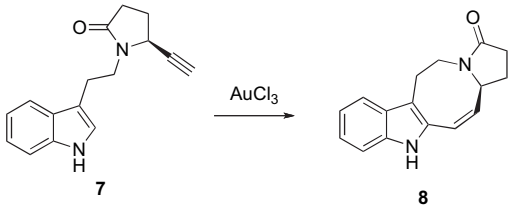


Figure 1. Lundurines A–D (**1**–**4**), lapidilectine B (**5**), and isolapidilectine (**6**).

No synthesis of the lundurines has been reported, although the group of Pearson had completed the synthesis of lapidilectine B (**5**).[1] As a first step toward the synthesis of **1**–**4** we decided to study the potential of the gold-catalyzed cyclization of indoles with alkynes[5–8] for the ready construction of the 1*H*-azocino[5,4-*b*]indole skeleton of these alkaloids. Here we report the synthesis of the tetracyclic ring compound **8** by the 8-*endo*-*dig* cyclization of **7** with $AuCl_3$ or other gold catalysts (Scheme 1).



Scheme 1. Gold(III)-catalyzed cyclization of alkynylindole **7** to give azocino[5,4-*b*]-indole derivative **8**.

2. Results and discussion

2.1. Synthesis of alkynylindole 7

For the synthesis of a suitable enantiomerically pure precursor for the synthesis of the lundurines, we first tried to follow the procedure described by Germanas and co-workers for the enantioselective alkylation of proline.[9,10] This procedure was based on a method originally reported by Seebach,[11] forms more stable oxazolidinone **9** replacing pivalaldehyde by chloral in the condensation with proline (Scheme 2). Alkylation of **9** using LDA and commercially available ((2-bromoethoxy)methyl)benzene led only to decomposition products. However, alkylation of the lithium enolate of **9** with ((2-iodoethoxy)methyl)benzene gave the desired derivative **10**, albeit in only 33% yield, while 60% of the alkylating

* Corresponding author.
E-mail address: aechavarren@iciq.es (A. M. Echavarren).

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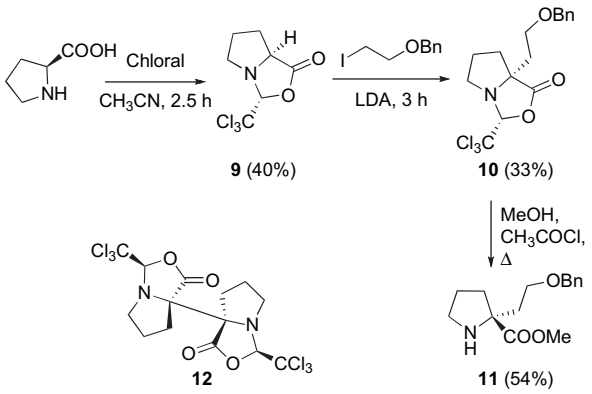


Scheme 2. Synthesis of alkylated proline derivative **11**.

agent was recovered. Cleavage of the *N*,*O*-acetal function was performed under the acidic conditions described by Germanas[9] to give **11** in 54% yield. Interestingly, **10** was accompanied by small amounts of dimeric compound **12**, whose structure was confirmed by X-ray crystallography (Fig. 2). A similar dimeric structure was described by Johnson and co-workers in the alkylation of Seebach oxazolidinone with dibromoethane.[12]

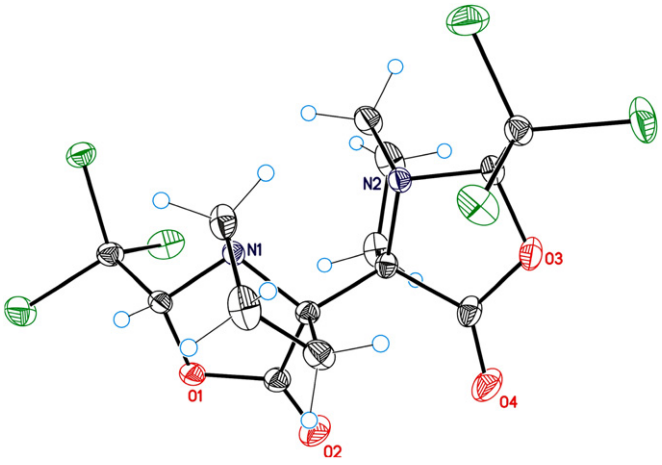
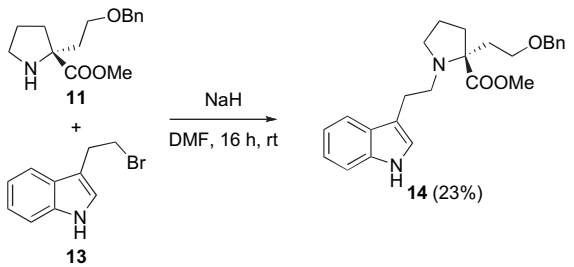


Figure 2. X-ray crystal structure of **12**.

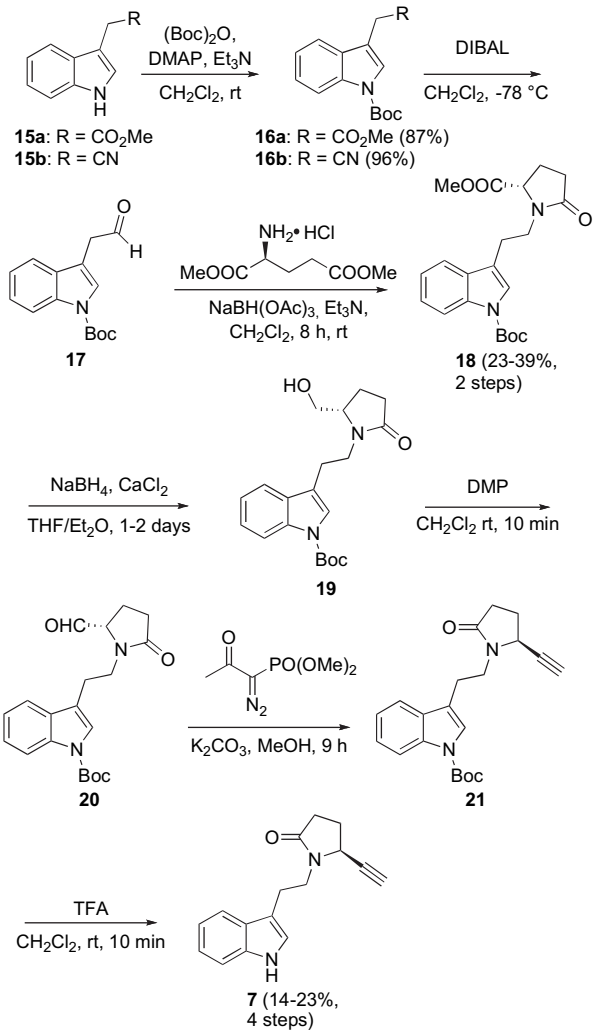
Alkylation of proline derivative **11** with 3-(2-bromoethyl)-1*H*-indole under the conditions developed by Rapoport afforded **14** in 23% yield (Scheme 3).[13] Although it was described that $NaHCO_3$ led to a more efficient alkylation,[13] in our case, using this base only unchanged starting material was recovered. Using *N*-Boc protected indole derivative[14] for the alkylation was also unsuccessful. Similarly ineffective was the alkylation of *N*-(trimethylsilyl)pyroglutamate with 3-(2-bromoethyl)-1*H*-indole.

Since most of the steps in the synthetic route toward **14** were low yielding, we sought alternative ways for the preparation of



Scheme 3. Alkylation of proline **11** with 3-(2-bromoethyl)-1*H*-indole **13**.

a related substrate. Thus, methyl 2-(1*H*-indol-3-yl)acetate (**15a**) was protected as a Boc-carbamate using $(Boc)_2O$ to give known **16a**,[15] which was reduced with DIBAL to give aldehyde **17** (Scheme 4). Reductive amination of aldehyde **17** with dimethyl (*S*)-glutamate in the presence of sodium triacetoxyborohydride gave lactam **18** in moderate yield. Alternatively, aldehyde **17** could also be prepared from nitrile **16b**.[16]



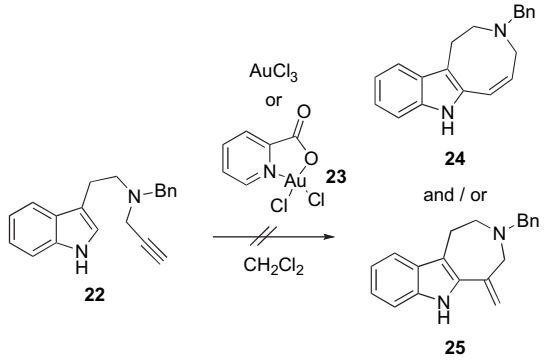
Scheme 4. Synthesis of alkynylindole **7**.

Ester **18** was reduced to alcohol **19** in 90% yield using $NaBH_4$ and $CaCl_2$[17] (Scheme 4). Routinely this alcohol was submitted to the subsequent transformation without purification. When lithium aluminum hydride was used, competitive reduction of the lactam was also observed, even at low temperature. Dess–Martin oxidation of alcohol **19** gave aldehyde **20**, which was used in the next step without further purification. Aldehyde **20** reacted with the Bestmann–Ohira reagent[18] to give **21**, from which alkynyl derivative **7** was obtained by Boc cleavage after brief exposure to trifluoroacetic acid. This four-step procedure can be routinely carried out without purification of any intermediate in 14–23% overall yield. Alternatively, alkyne **21** could be prepared from aldehyde **20** by the Corey–Fuchs procedure,[19] although the overall yield was lower.

2.2. Gold-catalyzed cyclization of alkynylindole 7

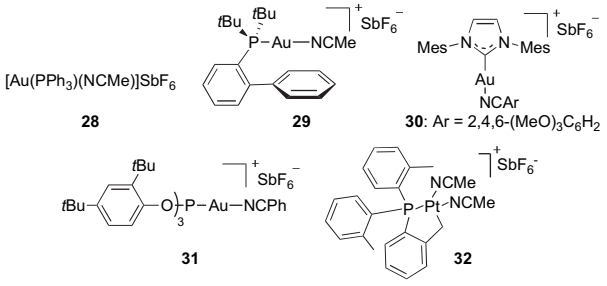
In our previous work, we have shown that protection of the basic amine function as a sulfonamide was required for the success

of the gold-catalyzed cyclization.[5] Thus, not surprisingly, treatment of *N*-benzyl-*N*-propargyltryptamine (**22**) with $AuCl_3$ or Au(III) complex **23**[20,21] (5 mol %) in CH_2Cl_2 solution failed to give cyclized compound **24** or **25** (Scheme 5), presumably a result of the coordination of the amine to Au(III). In situ protonation of the amine **22** using trifluoroacetic acid prior to the addition of the catalyst was not effective.



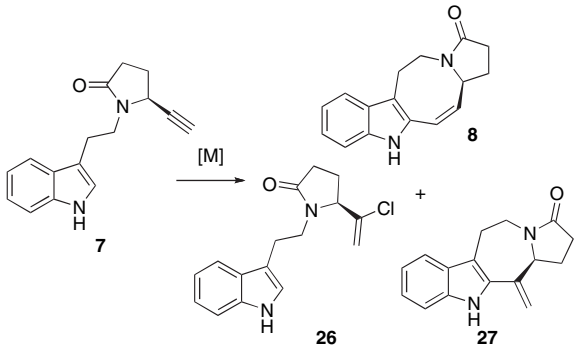
Scheme 5. Unsuccessful cyclization of *N*-benzyl-*N*-propargyltryptamine **22**.

On the other hand, cyclization of substrate **7** using 5 mol % $AuCl_3$ as catalyst in CH_2Cl_2 at room temperature afforded the desired indoloazocine **8** in 55% isolated yield (Table 1, entry 1). Traces of **26**, the product of Markovnikov gold-catalyzed hydrochlorination of the alkyne were also isolated in this reaction.[22] Vinyl chloride **26** was only observed in the presence of $AuCl_3$. The cyclization was less efficient with Au(III) complex **23** or $HAuCl_4$ as catalysts (Table 1, entries 2 and 3), whereas $NaAuCl_4$ salt was not effective (Table 1, entry 4). Interestingly, cationic Au(I) complex **28**[23] favored the 8-*exo*-*dig* cyclization leading to **8** as the major product, whereas related complex **29**[24] with a bulkier phosphine favored the formation of **27** (Table 1, compare entries 5 and 6). Similar selectivity was observed using cationic catalysts **30** and **31**,[25] although lower reactivity was observed using complex **30** with a more donating NHC ligand. AuCl was also a catalyst for the formation of **8** (Table 1, entry 9). A low conversion was achieved with cationic platinacycle **32**[26] (Table 1, entry 10). Low yields of **8** were obtained using Ag(I) salts such as $AgSbF_6$ or AgOTf[27] whereas, $GaCl_3$, $InCl_3$, and Brönsted acid TfOH were not effective in this cyclization (Table 1, entries 11–15).



The fact that very similar results were obtained using $AuCl_3$ and AuCl (compare entries 1 and 9 in Table 1) suggests that Au(III) might be reduced to Au(I) under the reaction conditions. However, factors that control the *exo* versus *endo* selectivity in this cyclization are not easy to rationalize since electronically similar Au(I) complexes **28** and **29** give different results, whereas almost identical regioselectivities were obtained using complexes **29**–**31** with very different ligands.

Table 1
Gold-catalyzed cyclization of substrate **7**[a]



Entry	[M]	Conversion (%)	Products (ratio)	Yield (%)
1	$AuCl_3$	100	**8**+**26** (ca. 95:5)	55
2	**23**	66	**8**	34[b]
3	$HAuCl_4$	100	**8**	30[b]
4	$NaAuCl_4$	100	—[c]	—
5	**28**	100	**8**+**27** (78:22)	—
6	**29**	80	**8**+**27** (27:73)	—
7	**30**	54	**8**+**27** (27:73)	—
8	**31**	100	**8**+**27** (13:87)	—
9	AuCl	82	**8**	42[b]
10	**32**	13	**8**	—
11	$AgSbF_6$	100	**8**	17
12	AgOTf	29	**8**	—
13	$GaCl_3$	—[d]	—	—
14	$InCl_3$	—[d]	—[e]	—
15	TfOH	—[d]	—	—

[a] Reactions carried out with 5 mol % [M] in CH_2Cl_2 at room temperature for 24 h.
[b] Determined by NMR using 1,3,5-trimethoxybenzene as standard.
[c] Complex mixture.
[d] Conversion <5%.
[e] Traces of **8** were observed.

3. Conclusion

The 1*H*-azocino[5,4-*b*]indole skeleton of the lundurines can be readily obtained by using $AuCl_3$ or other gold complexes as catalysts by the 8-*endo*-*dig* cyclization of an alkynylindole substrate. Progress toward the synthesis of **1**–**4** using this type of gold-catalyzed cyclization is in progress.

4. Experimental

4.1. General methods

All preparations and manipulations were carried out under an oxygen-free nitrogen atmosphere using conventional Schlenk techniques. NMR experiments were run in a Bruker Avance 400 Ultrashield spectrometer. HPLC chromatography was performed on an Agilent Technologies Series 1100 chromatograph with UV detector. Mass spectra were recorded on Waters LCT Premier (ESI) and Waters GCT (EI, CI) spectrometers. Elemental analyses were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid. Melting points were determined using a Büchi melting point apparatus. Optical rotations were recorded on a P-1030 polarimeter from Jasco at the sodium D line.

*4.1.1. (R)-Methyl 2-(2-(benzyloxy)ethyl)pyrrolidine-2-carboxylate (**11**).* An ice cold solution of LDA (0.86 mL diisopropylamine/2.45 mL *n*-BuLi, 6.13 mmol) was added dropwise to a solution of **9**[9] (1.00 g, 4.09 mmol) in THF (20 mL) at −78 °C. After 30 min, ((2-iodoethoxy)methyl)benzene (1.18 g, 4.5 mmol) was added and it was stirred at this temperature for 3 h. Then, the reaction was quenched with MeOH and it was allowed to warm up to room temperature. The resulting mixture was portioned between chloroform and water, the organic layer dried over $MgSO_4$, and

evaporated under reduced pressure. The residue was purified by silica gel chromatography (10:1, hexane/EtOAc) to give **10** (510 mg, 33%) as an oil. Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 4.96 (s, 1H), 4.49 (s, 2H), 3.81–3.75 (m, 1H), 3.72–3.67 (m, 1H), 3.43–3.39 (m, 1H), 3.21 (dd, *J*=8.6, 4.4 Hz, 2H), 2.30–2.16 (m, 3H), 2.11 (dt, *J*=12.3, 6.2 Hz, 1H), 1.94–1.86 (m, 1H), 1.71–1.61 (m, 1H). (3*R*,3′*R*,7a*R*)-3,3′-Bis(trichloromethyl) tetrahydro-1*H*,1′*H*-7a,7′a-bipyrrolo[1,2-*c*]oxazole-1,1′(3*H*,3′*H*,5*H*,5′*H*)-dione (**12**) was also formed as formed in variable amounts as a secondary product, which could not be separated by chromatography, although a single crystal could be obtained from an EtOAc solution, which allowed for its structural characterization. The crystal structure of **12** has been deposited at the Cambridge Crystallographic Data Centre (deposition number CCDC 743970). Compound **12** (from a 1:5 mixture with **10**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (s, 2H), 2.40 (dd, *J*=13.7, 10.6 Hz, 2H), 2.30–2.16 (m, 2H), 2.02–1.97 (m, 2H), 1.94–1.86 (m, 2H), 1.79 (dd, *J*=13.3, 10.1 Hz, 2H), 1.71–1.61 (m, 2H).

To a solution of **10** (1.42 g, 3.75 mmol) in MeOH (16 mL) was added a solution of acetyl chloride (0.60 mL, 8.36 mmol) in MeOH (8 mL). The mixture was heated at reflux for 12 h. Then, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 and washed with water. The aqueous phase was made basic and then it was extracted again with CH_2Cl_2. The residue was purified by silica gel chromatography eluting with EtOAc to give **11** as a colorless oil (540 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 4.42 (s, 2H), 3.60 (s, 3H), 3.53 (dd, *J*=6.8, 5.3 Hz, 2H), 3.04–2.93 (m, 2H), 2.27 (dd, *J*=13.9, 6.9 Hz, 1H), 2.17–2.10 (m, 1H), 1.84–1.63 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 177.6 (C), 138.3 (C), 128.3 (CH, 2C), 127.8 (CH, 2C), 127.5 (CH), 73.2 (CH_2), 67.4 (C), 67.2 (CH_2), 52.1 (CH_3), 46.6 (CH_2), 39.6 (CH_2), 36.8 (CH_2), 24.9 (CH_2). Anal. Calcd for $C_{15}H_{21}NO_3\cdot 1/2H_2O$: C, 66.15; H, 8.14; N, 5.14. Found: C, 66.59; H, 7.87; N, 5.74. HRMS-ESI *m*/*z* calcd for $C_{15}H_{22}NO_3$: 264.1600; found: 264.1600 [M^++H].

*4.1.2. Methyl 1-(2-(1H-indol-3-yl)acetyl)-2-(2-(benzyloxy)ethyl)pyrrolidine-2-carboxylate (**14**).* To a solution of NaH (60% in mineral oil, 8 mg, 0.79 mmol) in DMF (1 mL) was added **11** (50 mg, 0.79 mmol) at 0 °C, the mixture was allowed to stir for 15 min. Then, 3-(2-bromoethyl)-1*H*-indole (**13**) (43 mg, 0.79 mmol) was added and the reaction was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with water. The organic layer was dried with Na_2SO_4, filtered, and evaporated. The residue was purified by chromatography (4:1, hexane/EtOAc) to give **14** as a colorless oil (18 mg, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.57 (d, *J*=7.7 Hz, 1H), 7.35–7.27 (m, 6H), 7.17 (t, *J*=7.4 Hz, 1H), 7.10 (t, *J*=7.6 Hz, 1H), 6.98 (d, *J*=2.0 Hz, 1H), 4.39 (s, 2H), 3.59 (s, 3H), 3.50 (ddd, *J*=9.4, 8.2, 6.3 Hz, 1H), 3.43 (ddd, *J*=9.3, 7.9, 5.6 Hz, 1H), 3.32–3.27 (m, 1H), 3.03–2.97 (m, 1H), 2.93 (dd, *J*=9.7, 4.2 Hz, 1H), 2.86–2.79 (m, 1H), 2.71–2.66 (m, 1H), 2.60–2.55 (m, 1H), 2.25 (ddd, *J*=14.0, 7.7, 6.4 Hz, 1H), 2.19–2.14 (m, 1H), 1.94–1.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.5 (C), 138.6 (C), 136.2 (C), 128.3 (CH, 2C), 127.6 (C), 127.6 (CH, 2C), 127.4 (CH), 121.9 (CH), 121.5 (CH), 119.2 (CH), 118.9 (CH), 111.0 (CH), 103.5 (C), 72.9 (CH_2), 69.4 (C), 67.0 (CH_2), 51.3 (CH_2), 51.0 (CH_3), 50.1 (CH_2), 34.4 (CH_2), 34.0 (CH_2), 25.5 (CH_2), 22.0 (CH_2). HRMS-ESI *m*/*z* calcd for $C_{25}H_{31}N_2O_3$: 407.2335; found: 407.2316 [M^++H].

*4.1.3. tert-Butyl 3-(cyanomethyl)-1H-indole-1-carboxylate (**16b**).* To a mixture of 3-indoleacetonitrile (**15b**) (11.68 g, 74.80 mmol), Boc_2O (17.14 g, 79.00 mmol), and DMAP (457 mg, 3.74 mmol) in CH_2Cl_2 (250 mL) was added Et_3N (20.85 mL, 3.74 mmol). The reaction was allowed to stir at room temperature for 2 h then it was diluted with CH_2Cl_2. The organic phase was washed with 10% HCl solution, brine and dried over Na_2SO_4, the solvent was removed under reduced pressure. The residue was purified by chromatography (10:1, hexane/EtOAc) to give **16b**[16] as a white solid (18.39 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br d, *J*=8,1 Hz, 1H), 7.64 (s, 1H), 7.52 (d, *J*=7.7 Hz, 1H), 7.38 (t, *J*=7.8 Hz, 1H), 7.29 (t, *J*=7.2 Hz, 1H), 3.77 (d, *J*=1.63 Hz, 2H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 149.3 (C), 135.58 (C), 128.5 (C), 125.2 (CH), 124.3 (CH), 123.0 (CH), 118.2 (CH), 117.1 (C), 115.6 (CH), 109.5 (C), 84.3 (C), 28.2 (CH_3, 3C), 14.3 (CH_2). HRMS-ESI *m*/*z* calcd for $C_{15}H_{16}N_2O_2Na$: 279.1109; found: 279.111 [M^++Na].

*4.1.4. tert-Butyl 3-(2-oxoethyl)-1H-indole-1-carboxylate (**17**).*

4.1.4.1. Procedure A. To a solution of *tert*-butyl 3-(2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (**16a**) (7.10 g, 24.54 mmol) in CH_2Cl_2 (300 mL) at −78 °C was added DIBAL (1 M solution in CH_2Cl_2, 49.1 mL, 49.10 mmol). The solution was allowed to stir for 1.5 h at this temperature and then it was quenched with MeOH at −78 °C and warmed up to room temperature for 2 h. The mixture was diluted with EtOAc and washed with a Na/K tartrate saturated solution, the organic layer dried over $MgSO_4$, and the solvent evaporated under reduced pressure. The residue was purified by chromatography (10:1, hexane/EtOAc) to give **17** as a yellow oil (2.20 g, 37%).

4.1.4.2. Procedure B. To a solution of *tert*-butyl 3-(cyanomethyl)-1*H*-indole-1-carboxylate (**16b**) (1.96 g, 7.64 mmol) in CH_2Cl_2 (76 mL) at −78 °C was added DIBAL (1 M solution in toluene, 11.46 mL, 11.46 mmol) during 30 min. The solution was allowed to stir for 30 min at this temperature and then it was quenched with EtOH (1.5 mL) at −78 °C and warmed up to room temperature. The reaction was treated with satd NH_4Cl solution (30 mL) and 3 M H_2SO_4 solution (100 mL). The aqueous phase was washed with CH_2Cl_2, then the organic layer dried over $MgSO_4$, and the solvent evaporated under reduced pressure to afford aldehyde **17** as a yellow oil, which was used immediately without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J*=2.3 Hz, 1H), 8.16 (br d, *J*=8.6 Hz, 1H), 7.57 (s, 1H), 7.45 (d, *J*=7.8 Hz, 1H), 7.35 (td, *J*=7.2, 1.2 Hz, 1H), 7.26 (td, *J*=7.6, 1.0 Hz, 1H), 3.76 (dd, *J*=2.1, 1.0 Hz, 2H), 1.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 198.5 (CH), 149.5 (C), 135.5 (C), 130.1 (C), 124.8 (CH), 124.8 (CH), 122.8 (CH), 118.7 (CH), 115.4 (CH), 110.9 (C), 83.9 (C), 40.0 (CH_2), 28.2 (CH_3, 3C). HRMS-ESI *m*/*z* calcd for $C_{16}H_{21}NO_4Na$: 314.1368; found: 314.1369 [M^++MeOH+Na].

*4.1.5. (S)-tert-Butyl 3-(2-(2-(methoxycarbonyl)-5-oxopyrrolidin-1-yl)-ethyl)-1H-indole-1-carboxylate (**18**).* To a solution of crude **17** (3.82 mmol) and L-glutamic acid methyl ester hydrochloride (889 mg, 4.20 mmol) in CH_2Cl_2 (39 mL), was added Et_3N (0.798 mL, 5.73 mmol). After 15 min triacetoxyborohydride (1.21 g, 5.73 mmol) was added. The mixture was stirred at room temperature for 12 h and after extractive workup (EtOAc/$NaHCO_3$ saturated solution) it was purified by chromatography (1:1–1:2, hexane/EtOAc) to give **18** as a yellow oil (1.14 g, 39% over 2 steps): $[\alpha]_D$ −6.61 (*c* 1.16, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (br d, *J*=7.5 Hz, 1H), 7.54 (d, *J*=7.7 Hz, 1H), 7.41 (s, 1H), 7.31 (td, *J*=7.4, 1.2 Hz, 1H), 7.24 (td, *J*=7.3, 1.0 Hz, 1H), 4.08 (dd, *J*=9.0, 3.1 Hz, 1H), 4.00 (ddd, *J*=13.9, 9.0, 5.6 Hz, 1H), 3.73 (s, 3H), 3.24 (ddd, *J*=13.9, 8.6, 6.7 Hz, 1H), 3.00 (dddd, *J*=14.5, 9.0, 6.6, 0.8 Hz, 1H), 2.87 (dddd, *J*=14.5, 8.7, 5.8, 0.9 Hz, 1H), 2.51 (ddd, *J*=16.8, 9.3, 9.2 Hz, 1H), 2.36 (ddd, *J*=16.7, 9.6, 3.8 Hz, 1H), 2.26–2.16 (m, 1H), 2.08–2.01 (m, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 175.3 (C), 172.5 (C), 149.7 (C), 135.5 (C), 130.3 (C), 124.5 (CH), 123.0 (CH), 122.5 (CH), 118.8 (CH), 117.5 (C), 115.3 (CH), 83.6 (C), 60.2 (CH), 52.5 (CH_3), 42.1 (CH_2), 29.5 (CH_2), 28.2 (CH_3, 3C), 23.1 (CH_2, 2C). HRMS-ESI *m*/*z* calcd for $C_{21}H_{26}N_2O_5Na$: 409.1739; found: 409.1741 [M^++Na].

*4.1.6. (S)-tert-Butyl 3-(2-(2-(hydroxymethyl)-5-oxopyrrolidin-1-yl)-ethyl)-1H-indole-1-carboxylate (**19**).* To a solution of **18** (1.10 g, 2.83 mmol) and calcium chloride (649 mg, 5.67 mmol) in a mixture of THF (38 mL) and Et_2O (28 mL) was added sodium borohydride (447 mg, 11.34 mmol) at 0 °C. The reaction was allowed to warm up

to room temperature and it was left to stir for 1 day. Then the equivalents of water necessary to react with the $NaBH_4$ were added and also $MgSO_4 \cdot 7H_2O$, the mixture was stirred until the evolution of gas ceased and then it was filtered through a path of Celite. After evaporation of the solvent, **19** was obtained as a colorless oil: $[\alpha]_D$ 13.40 (*c* 1.03, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (br d, *J*=7.8 Hz, 1H), 7.58 (d, *J*=7.5 Hz, 1H), 7.42 (s, 1H), 7.31 (td, *J*=7.8, 1.1 Hz, 1H), 7.23 (td, *J*=7.2, 0.9 Hz, 1H), 3.91 (ddd, *J*=13.8, 9.2, 5.8 Hz, 1H), 3.77–3.73 (m, 1H), 3.62–3.55 (m, 2H), 3.36 (ddd, *J*=13.8, 9.0, 6.2 Hz, 1H), 3.03 (ddd, *J*=14.3, 9.1, 6.1 Hz, 1H), 2.90 (ddd, *J*=14.3, 8.9, 5.9 Hz, 1H), 2.45 (ddd, *J*=17.0, 9.9, 7.3 Hz, 1H), 2.33 (ddd, *J*=17.0, 10.1, 5.3 Hz, 1H), 2.08–1.98 (m, 1H), 1.91–1.83 (m, 1H), 1.66 (s, 9H), 1.63 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 176.0 (C), 149.7 (C), 135.5 (C), 130.4 (C), 124.5 (CH), 123.1 (CH), 122.5 (CH), 118.9 (CH), 117.7 (C), 115.3 (CH), 83.6 (C), 63.5 (CH_2), 59.6 (CH), 41.3 (CH_2), 30.4 (CH_2), 28.2 (CH_3, 3C), 23.3 (CH_2), 21.3 (CH_2). HRMS-ESI *m*/*z* calcd for $C_{20}H_{26}N_2O_4Na$: 381.1790; found: 381.1773 [M^++Na].

*4.1.7. (S)-tert-Butyl 3-(2-(2-formyl-5-oxopyrrolidin-1-yl)ethyl)-1H-indole-1-carboxylate (**20**).* To a solution of **19** (0.77 g, 2.14 mmol) in CH_2Cl_2 (24 mL) was added the Dess–Martin periodinane (1.00 g, 2.35 mmol). The reaction mixture was stirred at room temperature for 20 min and then saturated aqueous $Na_2S_2O_3$ was slowly added. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuum to afford aldehyde **20** as a yellow oil, which was used immediately without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, *J*=2.3 Hz, 1H), 8.12 (br d, *J*=7.8 Hz, 1H), 7.53 (d, *J*=7.7 Hz, 1H), 7.41 (s, 1H), 7.31 (td, *J*=7.8, 1.1 Hz, 1H), 7.24 (td, *J*=7.6, 1.0 Hz, 1H), 4.01–3.94 (m, 2H), 3.34 (ddd, *J*=13.9, 8.5, 7.0 Hz, 1H), 3.01 (ddd, *J*=14.4, 8.9, 6.8 Hz, 1H), 2.88 (dddd, *J*=14.5, 8.5, 5.8, 0.8 Hz, 1H), 2.44–2.40 (m, 2H), 2.22–2.11 (m, 1H), 2.05–1.97 (m, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 198.6 (CH), 175.3 (C), 149.6 (C), 136.1 (C), 135.5 (C), 124.6 (CH), 123.2 (CH), 122.6 (CH), 118.8 (CH), 117.2 (C), 115.3 (CH), 83.7 (C), 66.1 (CH), 42.6 (CH_2), 29.3 (CH_2), 28.2 (CH_3, 3C), 23.3 (CH_2), 19.4 (CH_2).

*4.1.8. (S)-tert-Butyl 3-(2-(2-ethynyl-5-oxopyrrolidin-1-yl)ethyl)-1H-indole-1-carboxylate (**21**).*

4.1.8.1. Procedure A. (i) (*S*)-*tert*-Butyl 3-(2-(2-(2,2-dibromovinyl)-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate. Triphenylphosphine (1.91 g, 7.29 mmol) was added at 0 °C to a solution of CBr_4 (1.21 g, 3.65 mmol) in CH_2Cl_2 (30 mL). At the same temperature, aldehyde **20** (650 mg, 1.82 mmol) dissolved in CH_2Cl_2 (10 mL) was dropped slowly into the reaction mixture and then it was stirred at room temperature for 10 min. After extractive workup (CH_2Cl_2) and chromatography (2:1, hexane/EtOAc) the title compound was obtained as a light yellow oil (420 mg, 45%): $[\alpha]_D$ 37.49 (*c* 1.15, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (br d, *J*=7.7 Hz, 1H), 7.57 (d, *J*=7.6 Hz, 1H), 7.44 (s, 1H), 7.31 (td, *J*=7.6, 1.3 Hz, 1H), 7.27–7.23 (m, 1H), 6.22 (d, *J*=8.9 Hz, 1H), 4.26 (ddd, *J*=8.9, 8.0, 5.3 Hz, 1H), 3.81 (ddd, *J*=13.9, 8.9, 6.1 Hz, 1H), 3.23 (ddd, *J*=13.8, 8.6, 6.2 Hz, 1H), 3.00 (dddd, *J*=14.3, 8.9, 6.1, 0.8 Hz, 1H), 2.88 (dddd, *J*=14.3, 8.7, 6.1, 0.8 Hz, 1H), 2.48–2.33 (m, 2H), 2.26–2.16 (m, 1H), 1.76–1.69 (m, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.7 (C), 149.7 (C), 137.6 (CH), 135.5 (C), 130.4 (C), 124.5 (CH), 123.3 (CH), 122.6 (CH), 118.9 (CH), 117.4 (C), 115.3 (CH), 93.0 (C), 83.6 (C), 60.7 (CH), 41.7 (CH_2), 29.9 (CH_2), 28.2 (CH_3, 3C), 24.2 (CH_2), 23.3 (CH_2). HRMS-ESI *m*/*z* calcd for $C_{21}H_{24}N_2O_3NaBr_2$: 533.0051; found: 533.0070 [M^++Na]. (ii) To a solution of the dibromide (100 mg, 0.19 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (0.41 mmol). The reaction was kept at this temperature for 1 h, then it was quenched with MeOH and it was allowed to warm up to room temperature overnight. After extractive workup (EtOAc), the residue was purified by chromatography (2:1, hexane/EtOAc) to give **21** as a colorless oil.

4.1.8.2. Procedure B. To a stirring solution of **20** (765 mg, 2.15 mmol) and dimethyldiazo-2-oxopropylphosphonate (495 mg, 2.580 mmol) in MeOH (12 mL) was added potassium carbonate (614 mg, 4.44 mmol). The resulting solution was allowed to stir for 12 h and then it was quenched with water (0.34 mL) and extracted with CH_2Cl_2. The combined organic phases were washed with satd $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford the alkyne **21** as a brown oil, which was used without further purification (25 mg, 36%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (br d, *J*=8.0 Hz, 1H), 7.59 (d, *J*=7.5 Hz, 1H), 7.44 (s, 1H), 7.31 (td, *J*=7.6, 1.3 Hz, 1H), 7.24 (td, *J*=7.2, 1.0 Hz, 1H), 4.25 (ddd, *J*=7.4, 5.1, 2.2 Hz, 1H), 3.93 (ddd, *J*=13.8, 9.3, 5.9 Hz, 1H), 3.46 (ddd, *J*=13.6, 9.1, 6.2 Hz, 1H), 3.06–2.90 (m, 2H), 2.56–2.48 (m, 1H), 2.41 (d, *J*=2.2 Hz, 1H), 2.40–2.24 (m, 2H), 2.12–2.04 (m, 1H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.2 (C), 149.7 (C), 135.5 (C), 130.4 (C), 124.5 (CH), 123.1 (CH), 122.5 (CH), 118.9 (CH), 117.5 (C), 115.3 (CH), 83.5 (C), 81.6 (CH), 73.5 (C), 49.5 (CH), 41.1 (CH_2), 29.9 (CH_2), 28.2 (CH_3, 3C), 26.3 (CH_2), 23.1 (CH_2). HRMS-ESI *m*/*z* calcd for $C_{21}H_{24}N_2O_3Na$: 375.1685; found: 375.1686 [M^++Na].

*4.1.9. (S)-1-(2-(1H-Indol-3-yl)ethyl)-5-ethynylpyrrolidin-2-one (**7**).* A solution of **21** (626 mg, 1.78 mmol) in TFA/CH_2Cl_2 (18:5 mL) was stirred at room temperature for 10 min. Then the solvent was evaporated and the residue was diluted in EtOAc and washed with $NaHCO_3$, the aqueous phase was extracted with EtOAc several times, and then the solvent was evaporated. Compound **7** was obtained as a colorless oil (243 mg, 23% over four steps): $[\alpha]_D$ −20.22 (*c* 0.93, $CHCl_3$). IR thin film ν 3218.3 (s), 3053.3 (m), 2925.0 (s), 2853.8 (m), 2115.3 (w), 1654.3 (vs), 1455.9 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.65 (d, *J*=7.8 Hz, 1H), 7.35 (d, *J*=7.8 Hz, 1H), 7.19 (t, *J*=7.6 Hz, 1H), 7.12 (t, *J*=7.4 Hz, 1H), 7.08 (s, 1H), 4.19 (ddd, *J*=7.6, 5.1, 2.1 Hz, 1H), 4.05–3.98 (m, 1H), 3.48–3.41 (m, 1H), 3.12–2.99 (m, 2H), 2.51 (ddd, *J*=16.6, 9.6, 6.6 Hz, 1H), 2.40 (d, *J*=2.2 Hz, 1H), 2.33 (ddd, *J*=16.4, 9.2, 6.3 Hz, 1H), 2.27–2.17 (m, 1H), 2.09–2.01 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.3 (C), 136.2 (C), 127.5 (C), 122.1 (CH), 121.8 (CH), 119.4 (CH), 118.7 (CH), 112.9 (C), 111.2 (CH), 81.6 (C), 73.4 (CH), 49.3 (CH), 41.4 (CH_2), 30.0 (CH_2), 26.2 (CH_2), 23.1 (CH_2). HRMS-ESI *m*/*z* calcd for $C_{16}H_{16}N_2ONa$: 275.1160; found: 275.1168 [M^++Na].

*4.1.10. N-(2-(1H-Indol-3-yl)ethyl)-N-benzylprop-2-yn-1-amine (**22**).* To a solution of NaH (60% in mineral oil, 186 mg, 4.65 mmol) in THF (10 mL) was added *N*-benzyl-2-(1*H*-indol-3-yl)ethanamine (970 mg, 3.87 mmol) at 0 °C. The mixture was allowed to stir for 15 min and propargyl bromide (0.41 mL, 4.65 mmol) was added. The reaction was stirred at room temperature for 24 h. Then, the mixture was washed with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by chromatography (10:1, hexane/EtOAc) to give **22** as a colorless oil (163 mg, 15%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.59 (d, *J*=7.8 Hz, 1H), 7.38–7.27 (m, 6H), 7.19 (td, *J*=7.6, 1.1 Hz, 1H), 7.10 (td, *J*=7.3, 1.0 Hz, 1H), 7.05 (d, *J*=2.3 Hz, 1H), 3.73 (s, 2H), 3.44 (d, *J*=2.3 Hz, 2H), 3.02–2.98 (m, 2H), 2.95–2.90 (m, 2H), 2.26 (t, *J*=2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 138.7 (C), 136.2 (C), 129.2 (CH, 2C), 128.4 (C), 128.3 (CH, 2C), 127.1 (CH), 121.9 (CH), 121.6 (CH), 119.2 (CH), 118.9 (CH), 114.4 (C), 111.1 (CH), 78.7 (C), 73.2 (CH), 58.0 (CH_2), 53.9 (CH_2), 41.5 (CH_2), 23.7 (CH_2). Anal. Calcd for $C_{20}H_{20}N_2 \cdot 1/3H_2O$: C, 81.60; H, 7.08; N, 9.52. Found: C, 81.52; H, 7.68; N, 10.10. HRMS-ESI *m*/*z* calcd for $C_{20}H_{21}N_2$: 289.1705; found: 289.1693 [M^++H].

*4.1.11. Tetracyclic compound **8**.* To a solution of **7** (45 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was added $AuCl_3$ (3 mg, 0.008 mmol) and the mixture was stirred at room temperature for 16 h. The residue was purified by chromatography (1:2, hexane/EtOAc) to

give compound **8** (25 mg, 55%): $[\alpha]_D$ 478.5 (*c* 0.46, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.50 (d, *J*=7.9 Hz, 1H), 7.29 (d, *J*=8.1 Hz, 1H), 7.20 (t, *J*=8.1 Hz, 1H), 7.12 (t, *J*=7.5 Hz, 1H), 6.68 (d, *J*=10.9 Hz, 1H), 5.65 (dd, *J*=10.7, 7.1 Hz, 1H), 4.52–4.47 (m, 1H), 3.90 (dt, *J*=14.0, 4.6 Hz, 1H), 3.83–3.76 (m, 1H), 3.09 (dd, *J*=5.9, 4.8 Hz, 2H), 2.50 (ddd, *J*=16.3, 9.2, 6.6 Hz, 1H), 2.42–2.24 (m, 2H), 1.90–1.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.1 (C), 136.1 (C), 131.1 (CH), 129.7 (C), 128.6 (C), 124.6 (CH), 123.1 (CH), 119.8 (CH), 118.6 (CH), 113.6 (C), 110.6 (CH), 56.7 (CH), 37.8 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 26.3 (CH_2). HRMS-ESI *m*/*z* calcd for $C_{16}H_{16}N_2ONa$: 275.1160; found: 275.1164 [M^++Na].

*4.1.12. (S)-1-(2-(1H-Indol-3-yl)ethyl)-5-(1-chlorovinyl)pyrrolidin-2-one (**26**).* ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.61 (d, *J*=7.9 Hz, 1H), 7.39 (d, *J*=8.1 Hz, 1H), 7.22 (td, *J*=7.9, 0.8 Hz, 1H), 7.14 (td, *J*=7.7, 0.7 Hz, 1H), 7.07 (d, *J*=2.0 Hz, 1H), 5.33 (d, *J*=1.5 Hz, 1H), 5.18 (d, *J*=1.5 Hz, 1H), 4.07–3.96 (m, 2H), 3.18–2.95 (m, 3H), 2.55 (ddd, *J*=17.3, 10.1, 7.6 Hz, 1H), 2.35 (ddd, *J*=17.0, 10.1, 5.2 Hz, 1H), 2.12–1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.4 (C), 142.0 (C), 136.4 (C), 127.7 (C), 122.3 (CH), 122.0 (CH), 119.6 (CH), 118.9 (CH), 115.6 (CH_2), 113.3 (C), 111.3 (CH), 64.2 (CH), 41.6 (CH_2), 30.2 (CH_2), 26.4 (CH_2), 23.3 (CH_2). LRMS *m*/*z* 287 [M^+]. HRMS-ESI *m*/*z* calcd for $C_{16}H_{17}N_2O_{35}ClNa$: 311.0927; found: 311.0919 [M^++Na].

*4.1.13. Tetracyclic compound **27**.* Mixture of **8** and **27** was separated by HPLC chromatography using a NH_2 column (95:5, hexane/ethanol), flow=1.5 mL/min, λ=254 nm. Retention times: 14.24 min, compound **8**; 16.35 min, compound **27**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.49 (d, *J*=8.0 Hz, 1H), 7.31 (d, *J*=8.2 Hz, 1H), 7.22 (t, *J*=7.5 Hz, 1H), 7.11 (t, *J*=7.6 Hz, 1H), 5.38 (s, 1H), 5.32 (s, 1H), 4.68 (d, *J*=7.7 Hz, 1H), 4.20–4.15 (m, 1H), 3.43–3.30 (m, 2H), 2.94–2.89 (m, 1H), 2.47–2.24 (m, 3H), 1.92–1.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, DEPT) δ 174.3 (C), 160.9 (C), 142.2 (C), 135.8 (C), 128.8 (C), 123.3 (CH), 119.9 (CH), 119.1 (CH_2), 113.2 (C), 112.8 (CH), 110.5 (CH), 65.1 (CH), 39.8 (CH_2), 30.9 (CH_2), 27.9 (CH_2), 25.1 (CH_2). HRMS-ESI *m*/*z* calcd for $C_{16}H_{16}N_2ONa$: 275.1160; found: 275.1156 [M^++Na]. The $[\alpha]_D$ of pure compound **27** could not be obtained because of its partial isomerization to the endocyclic olefin.

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