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Catalytic Asymmetric 1,3-Dipolar Cycloaddition/hydroamination Sequence: Expeditious Access to Enantioenriched Pyrroloisoquinoline Derivatives

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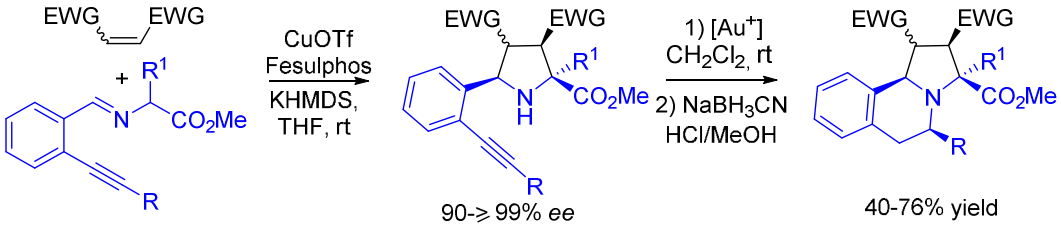
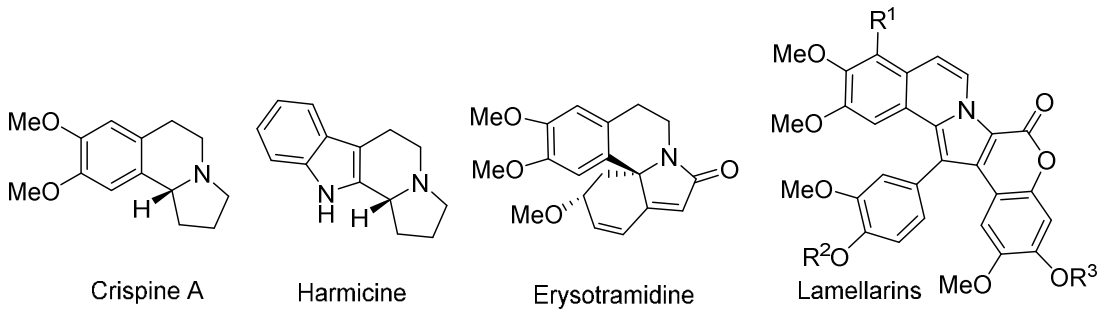


ABSTRACT: A three step reaction sequence has been developed to prepare a variety of enantioenriched pyrroloisoquinoline derivatives. The process involves a catalytic asymmetric azomethine ylide 1,3-dipolar cycloaddition followed by an intramolecular Au^{I} catalyzed alkyne hydroamination and enamine reduction.

Nitrogen containing heterocycles are present in countless natural products and have been used as privileged structures in the search of novel therapeutic agents based in small molecules.[1] Consequently, the development of processes that allow the concise construction of structurally diverse aza-heterocycles is a central synthetic goal that is currently intensively investigated. The pyrroloisoquinoline unit is an important motif, present in a family of natural occurring alkaloids with relevant biological activities. For example, Crispine A[2], displays important cytotoxic properties, Harmicine[3] shows strong anti-leishmania activity, Erysotramidine[4] exhibits hypotensive, sedative and anticonvulsive properties, and Lamellarins, a family of marine natural products,[5] possess promising antitumor activities (Figure 1). Furthermore, some unnatural derivatives containing this heterocyclic system also display potential pharmacological properties.[6]

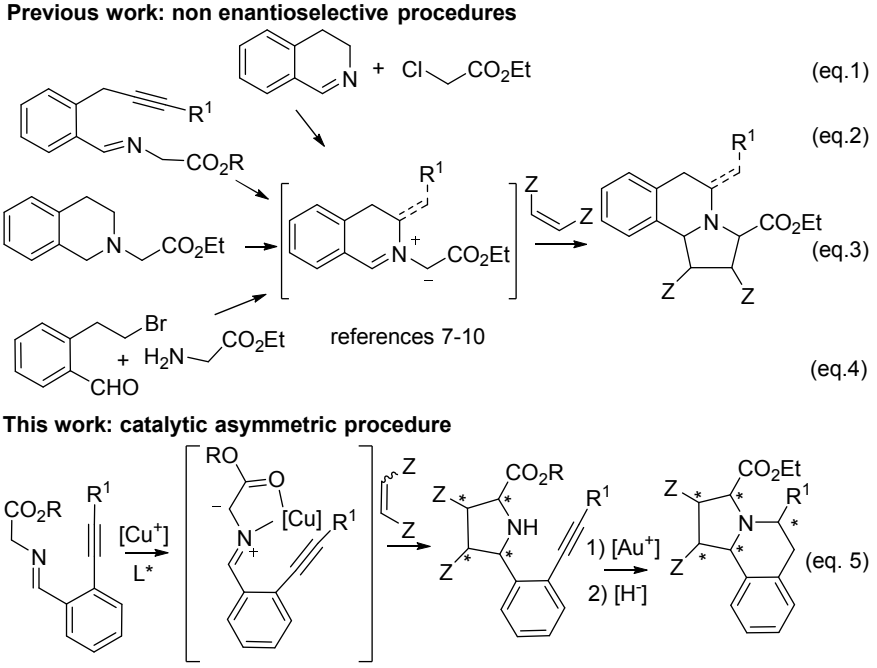
Figure 1. Selected natural products containing the pyrroloisoquinoline scaffold



The interest of this kind of compounds has encouraged the search of effective approaches for the construction of this skeleton, and several powerful methods for their synthesis have been established. Among them, the 1,3-dipolar cycloaddition has played a prevalent role due to its versatility and high atom economy. More specifically, several efficient procedures for the synthesis of racemic pyrrolidinoisoquinoline derivatives by cycloaddition of cyclic azomethine ylides and activated alkenes have been reported. These approaches involve different methods for the formation of the required isoquinoline derived dipole, which can be generated by inter[7] or intramolecular[8] N-alkylation of imines (Scheme 1, eq. 1 and eq. 2), via metal catalyzed 6-*exo* cyclization of alkynyliminoesters[9] (Scheme 1, eq. 3) or by metal or photocatalyzed oxidation of the corresponding tetrahydroisoquinoline precursor (Scheme 1, eq. 4).[10]

However, to the best of our knowledge, catalytic asymmetric procedures to the synthesis of enantioenriched pyrroloisoquinolines have not been yet developed using this general cycloaddition approach, despite of the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides is one of the most straightforward methods for the preparation of enantioenriched pyrrolidines.[11]

Scheme 1. Synthesis of pyrroisoquinoline derivatives by 1,3-dipolar cycloaddition of azomethine ylides.

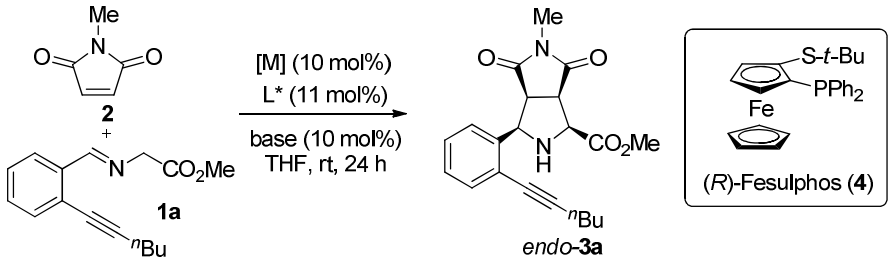


In connection with our previous work in metal-catalyzed asymmetric [3+2] cycloadditions of azomethine ylides,[12] we set out to explore the application of this methodology to the enantioselective synthesis of pyrroloisoquinolines. Taking into account that the excellent enantioinduction obtained in this reaction relays on the formation of a five membered metallacycle by coordination of the oxygen and nitrogen atoms of the iminoester to the chiral metal complex, we postulated that a catalytic asymmetric 1,3-dipolar cycloaddition/hydroamination sequence from an *ortho*-alkynylaryl α-iminoester (Scheme 1, eq. 5) may enable the enantioselective preparation of the challenging pyrroloisoquinoline motif. We report herein the development of this approach by means of an asymmetric Cu^{I} catalyzed 1,3-dipolar cycloaddition followed by Au^{I} catalyzed intramolecular alkyne hydroamination as key steps.

To explore the viability of this strategy, we selected as model reaction the cycloaddition between the iminoester **1a** (prepared by Sonogashira reaction of 2-bromobenzaldehyde with 1-hexyne followed by

condensation with methyl glycinate) and *N*-methylmaleimide (**2**) (Table 1). As starting point we used the conditions previously reported by our research group [$Cu(CH_3CN)_4PF_6$ as metal source, (*R*)-Fesulphos as ligand, Et_3N as base and THF as solvent].[13] This reaction afforded the expected adduct *endo*-**3a** with nearly complete diastereoselectivity (*endo*/*exo* = >20/1) and excellent enantiocontrol[14] (98% *ee*) albeit modest isolated yield (56%, Table 1, Entry 1). The use of AgOAc as metal source improved the yield but at the expense of the enantioselectivity (Entry 2). Other combinations of chiral ligands, solvents and bases were also tested in the reaction although with less satisfactory results (see Supporting Information for details). Kobayashi and co-workers have recently described a highly reactive catalyst system for a related 1,3-dipolar cycloaddition based on the generation of a chiral copper amide/Fesulphos complex.[15] Gratifyingly, using Kobayashi´s conditions the yield increased to 77% as well as preserving an excellent enantioselectivity (Entry 3). The reaction can be also performed using a lower catalyst loading (5 mol% instead of 10 mol%) albeit with lower chemical efficiency and enantiocontrol (Entry 4).

Table 1: Optimization experiments for the model 1,3-dipolar cycloaddition with (*R*)-Fesulphos as ligand.



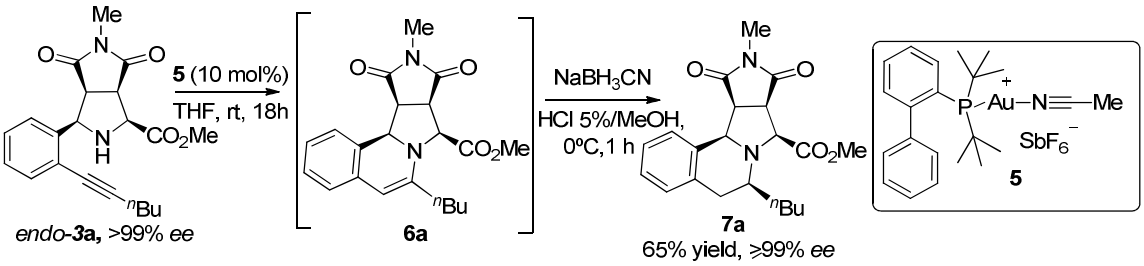
Entry	[M]	Base	Yield (%)[a,b]	*ee* (%)[c]
1	$CuPF_6$[d]	Et_3N	56	98
2	AgOAc	Et_3N	70	88
3	CuOTf[e]	KHMDS	77	≥ 99
4[f]	CuOTf[e]	KHMDS	52	90

[a]Isolated yield after chromatographic purification. [b]Only the *endo* adduct was observed by ^{1}H-NMR in the crude mixtures. [c]*ee* determined by HPLC. [d]$Cu(CH_3CN)_4PF_6$. [e]CuOTf = CuOTf. 0.5 toluene complex. [f]5 mol% of catalyst.

Next, we focus our attention to the subsequent intramolecular alkyne hydroamination. This process has been widely applied for the construction of nitrogen containing heterocycles and many metal

catalysts has showed activity in this reaction.[16] After a survey of metal salts and ligands, we found that the desired enamine product **6a** was cleanly formed using commercialy available cationic gold complex JohnPhosAu **5** as catalyst.[17] However, the silica-gel chromatographic purification of this tetracyclic enamine **6a** was problematic due to its instability. Thus, it was stereoselectively transformed into the corresponding tetrahydroisoquinoline **7a** by "in situ" reduction of the enamine moiety with $NaBH_3CN$ under acid conditions (HCl 5%, MeOH), providing **7a** in 65% isolated overall yield, preserving as expected the high enantioselectivity (≥99 % *ee*, Scheme 2).

Scheme 2. Hidroamination/enamine reduction sequence.



With this optimal reaction conditions in hands, we studied the scope of the process with regard to the substitution at the azomethine precursor. As summarized in Scheme 3, iminoesters **1b-j** with different substituents at the alkyne and the aromatic ring were investigated. The cyclohexylethynyl and phenylethynyl derivatives **1b** and **1c** furnished the corresponding pyrrolidines (*endo*-**3b** and *endo*-**3c**) in high yield and excellent enantioselectivity. The cycloaddition of iminoesters (**1d-e**) bearing electron rich aromatic alkyne substituents proceeded similarly giving rise the desired *endo*-pyrrolidines **3d** and **3e** as the only detectable isomers with excellent enantiocontrol (96% and -≥99% *ee*, respectively). The presence of a heteroaromatic substituent such as thiophenyl unit is also well tolerated albeit with incomplete *endo*-selectivity (adduct **3f**, *endo/exo* 88/12).[18]

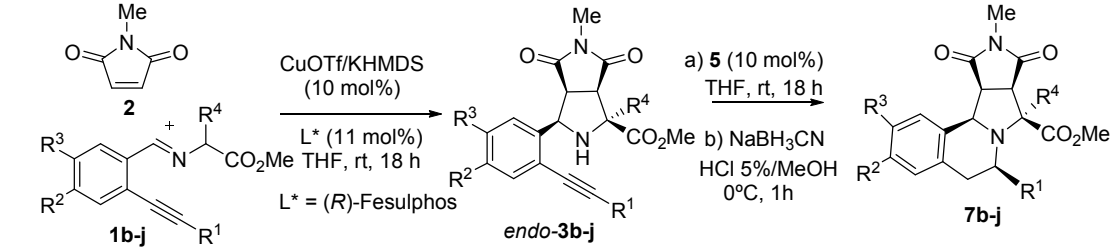
Electronically diverse substrates having different substituents at the aromatic ring such as Me, OMe or F also provided the corresponding adducts (**3g-i**) with good enantioselectivity under the reaction conditions. The procedure can be also applied to alanine-based dipoles (R^4= Me, *endo*-**3j**) with good enantioselectivity (89% *ee*).

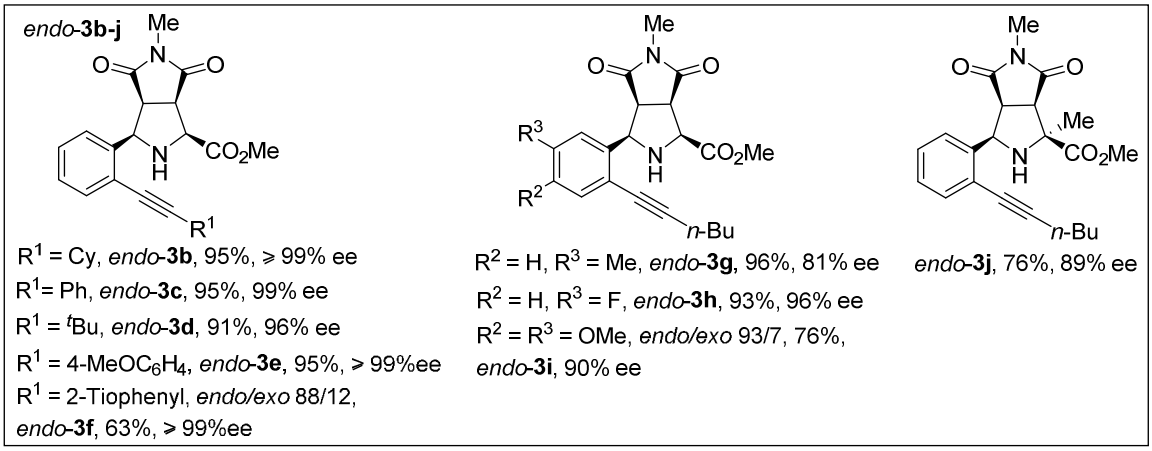
The subsequent intramolecular one pot gold-catalyzed hydroamination/reduction reaction sequence

took place generally with reasonable yields (45-76% yield) providing the desired highly enantioenriched pyrroloisoquinoline derivatives (**7b-i**) with very high *cis*-diastereoselectivities. On the other hand, the reaction of pyrrolidine **3j** with a quaternary stereocenter at C-2 proved less diastereoselective.[19]

The relative and absolute configuration of the adducts *endo*-**3** was established based on the results previously obtained by our research group using the Cu^{I}/(*R*)-Fesulphos catalytic system,[13,14] while the relative configuration of products **7** having five stereogenic centres was unequivocally established by X-ray diffraction analysis of **7d**.[20]

Scheme 3. Scope of the cycloaddition/hydroamination/reduction sequence. [a,b]

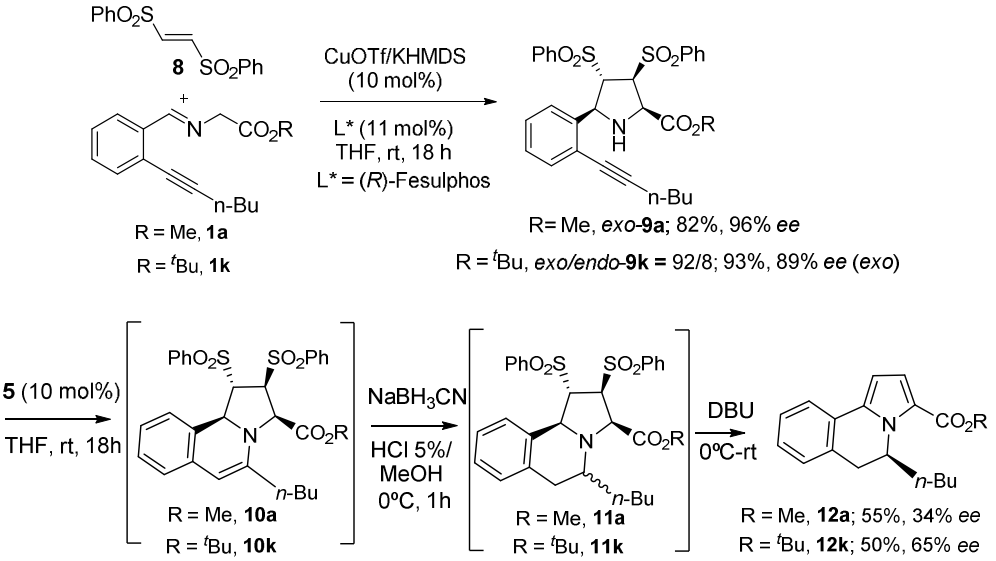




[a]Isolated yield after chromatographic purification. [b]*ee* determined by HPLC for adducts **3** (products **7** are assumed to have the same *ee* than the corresponding precursor **3**).

Next, we extended the scope of this asymmetric [3+2] cycloaddition/hydroamination sequence to the use of *trans*-bissulfonylethylene **8** as dipolarophile. The reaction of iminoester **1a** (R= Me) or **1k** (R= ^{t}Bu) under the optimized conditions afforded efficiently the corresponding bissulfonyl pyrrolidine **9** with high *exo*-diastereoselectivity[13b] and enantioselectivity (96% and 89% *ee*, respectively, Scheme 4). However, the intramolecular one pot hydroamination/reduction sequence did not afford the desired pyrroloisoquinolines due to the formation of a complex mixture of products after isolation and analysis by ^{1}H-NMR. Assuming a low stability of the expected pyrroloisoquinoline **11**, DBU was added to the reaction mixture after the reduction step in order to promote the *in situ* basic elimination of the sulfonyl groups. Under these conditions the pyrroloisoquinoline **12a** was obtained in 55% yield but with low enantioselectivity (34% *ee*, Scheme 4), showing that the reduction of the enamine moiety in intermediate **10a** was much less *cis*-diatereoselctive than in the case of the maleimide adducts. Replacing the methyl ester with the more sterically demanding *t*-butyl ester resulted in a significant improvement in the enantioselectivity (product **12k**, 65% *ee*).

Scheme 4. Reactions with *trans*-bissulfonylethylene.



In conclusion, a practical procedure for the enantioselective synthesis of pyrroloisoquinoline derivatives has been developed using the catalytic asymmetric 1,3-dipolar cycloaddition of alkynyl substituted azomethine ylides as key step. In the presence of Cu^I/(*R*)-Fesulphos as catalyst system the pyrrolidine

adducts were obtained with very high diastereoselectivity and excellent enantioselectivity. The subsequent one pot gold catalyzed hydroamination/reduction sequence provided the desired enantioenriched pyrroisoquinoline scaffolds in a straightforward manner.

Experimental Section

General procedures.

All air- and moisture-sensitive manipulations were carried out in anhydrous solvents and under argon atmosphere. Dichloromethane, toluene, tetrahydrofuran and acetonitrile were dried over the *PureSolv MD* purification system. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (230-400 mesh). Flash column chromatographies were performed using silica gel (230-400 mesh). NMR spectra were recorded on 300 or 500 MHz spectrometers and calibrated using residual undeuterated solvent ($CDCl_3$) as internal reference (δ_H = 7.26 ppm, δ_C = 77.16 ppm). HRMS spectra were measured on a TOF mass spectrometer with electrospray ionization (ESI) as the ionization source. α-Iminoesters **1a-k** were prepared by condensation of methyl glycinate hydrochloride and the corresponding aldehydes.[13] Aldehydes were prepared by Sonogashira coupling between 2-bromobenzaldehyde and the corresponding alkyne, according to literature procedures.[21] Due to their lability, all α-iminoesters once isolated were immediately used in the 1,3-dipolar cycloaddition without further purification.

2-(Hex-1-yn-1-yl)-4,5-dimethoxybenzaldehyde: To a solution of $Pd(CH_3CN)_2Cl_2$ (19.45 mg, 0.15 mmol), PPh_3 (39.3 mg, 0.30 mmol), CuI (23.8 mg, 0.25 mmol) and 6-bromoveratraldehyde (1.23 g, 5.0 mmol) in THF (6 mL) under nitrogen atmosphere, 1-hexyne (0.48 mL, 246 mg, 6.0 mmol) and Et_3N (1.4 ml, 1.0 g, 10.0 mmol) were added and the resulting mixture was stirred for 12h at 50ºC. The solution was filtered over Celite® and purified by silica gel flash chromatography (cyclohexane-EtOAc 100:1) to afford 2-(hex-1-yn-1-yl)-4,5-dimethoxybenzaldehyde (900.6 mg, 73%, brown oil,) which was isolated together with 5% of the starting aldehyde. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 10.17 (s, 1H), 7.13 (s, 1H), 6.71 (s, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.28 (t, *J* = 7.0 Hz, 2H), 1.50 – 1.36 (m, 2H), 1.36 – 1.23

(m, 2H), 0.77 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 190.5, 153.5, 149.0, 130.0, 122.5, 114.3, 107.8, 96.3, 76.0, 56.0, 55.82, 30.5, 22.0, 19.1, 13.5. **HRMS** (FB+): Calculated for $C_{15}H_{19}O_3$, 247.1334; found, 247.1342 ([M+H], 20).

Typical procedure for the synthesis of α-iminoesters. Methyl (*E*)-*N*-[(2-(hex-1-yn-1-yl)phenyl)methylene]glycinate (1a): A suspension of methyl glycinate hydrochloride (1.60 g, 18.0 mmol), $MgSO_4$ (2.17 g, 18.0 mmol) and Et_3N (2.5 mL, 18.0 mmol) in dry dichloromethane (8 mL) was stirred at room temperature for 30 minutes and 2-(hex-1-yn-1-yl)benzaldehyde (1.78 g, 9.0 mmol) in dichloromethane (2 mL) was added. After stirring 12h at room temperature the mixture was filtered and water (10 mL) was added. The organic layer was separated and the aqueous phase was extracted with dichloromethane (15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford **1a** (1.49 g, 64%, brown oil), used without further purification in the next reaction step. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.70 (s, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.41 – 7.23 (m, 3H), 4.41 (s, 2H), 3.72 (s, 3H), 2.44 (t, J = 6.9 Hz, 2H), 1.62 – 1.49 (m, 2H), 1.49 – 1.37 (m, 2H), 0.97 – 0.85 (m, 3H).

Methyl (*E*)-*N*-[(2-(cyclohexylethynyl)phenyl)methylene]glycinate (1b): Following the typical procedure, the reaction of methyl glycinate hydrochloride (239 mg, 1.9 mmol), $MgSO_4$ (228 mg, 1.9 mmol), Et_3N (0.26 mL, 1.9 mmol) and 2-(cyclohexylethynyl)benzaldehyde (201.9 mg, 0.95 mmol) in dry dichloromethane (3 mL) afforded **1b** (262 mg, 93%, yellow oil). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.45 – 7.27 (m, 3H), 4.45 (s, 2H), 3.79 (s, 3H), 2.72 – 2.58 (m, 1H), 1.97 – 1.83 (m, 2H), 1.82 – 1.69 (m, 2H), 1.64 – 1.49 (m, 3H), 1.45 – 1.31 (m, 3H).

Methyl (*E*)-*N*-[(2-(phenylethynyl)phenyl)methylene]glycinate (1c): Following the typical procedure, the reaction of methyl glycinate hydrochloride (258 mg, 2.90 mmol), $MgSO_4$ (349 mg, 2.90 mmol), Et_3N (404 μL, 2.90 mmol) and 2-(phenylethynyl)benzaldehyde (300 mg, 1.45 mmol) in dry dichloromethane (3 mL) afforded **1c** (242 mg, 87%, brown oil). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.19 (d, J = 7.0 Hz, 1H), 7.68 – 7.59 (m, 3H), 7.52 – 7.37 (m, 5H), 4.56 (s, 2H), 3.83 (s, 3H).

Methyl (*E*)-*N*-[(2-(4-*tert*-butylphenylethynyl)phenyl)methylene]glycinate (1d): Following the typical procedure, the reaction of methyl glycinate hydrochloride (445 mg, 5.0 mmol), $MgSO_4$ (601 mg, 5.0 mmol), Et_3N (0.7 mL, 5.0 mmol) and 2-(4-*tert*-butylphenylethynyl)benzaldehyde (656 mg, 2.5 mmol) in dry dichloromethane (5 mL) afforded **1d** (805 mg, 97%, brown oil). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.65 – 7.38 (m, 7H), 4.55 (s, 2H), 3.84 (s, 3H), 1.39 (s, 9H).

Methyl (*E*)-*N*-[(2-(4-methoxyphenylethynyl)phenyl)methylene]glycinate (1e): Following the typical procedure, the reaction of methyl glycinate hydrochloride (39.2 mg, 0.44 mmol), $MgSO_4$ (53.0 mg, 0.44 mmol), Et_3N (61.3μL, 0.44 mmol) and 2-(4-methoxyphenylethynyl)benzaldehyde (52.0 mg, 0.22 mmol) in dry dichloromethane (1 mL) afforded **1e** (60.8 mg, 90%, brown oil). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.23 – 8.12 (m, 1H), 7.62 – 7.37 (m, 5H), 6.99 – 6.92 (m, 2H), 4.53 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H).

Methyl (*E*)-*N*-[(2-(tiofen-2-ylethynyl)phenyl)methylene]glycinate (1f): Following the typical procedure, the reaction of methyl glycinate hydrochloride (89.1 mg, 1.0 mmol), $MgSO_4$ (120.3 mg, 1.0 mmol), Et_3N (139 μL, 1.0 mmol) and 2-(tiofen-2-ylethynyl)benzaldehyde (106 mg, 0.5 mmol) in dry dichloromethane (3 mL) afforded **1f** (122 mg, 86%, brown oil). **^{1}H NMR** (300 MHz, CDCl3): δ 8.75 (s, 1H), 8.05 (d, *J* = 6.8 Hz, 1H), 7.57 – 7.24 (m, 5H), 7.03 – 6.93 (m, 1H), 4.43 (s, 2H), 3.72 (s, 3H).

Methyl (*E*)-*N*-[(2-(hex-1-yn-1-yl)-5-methylphenyl)methylene]glycinate (1g): Following the typical procedure, the reaction of methyl glycinate hydrochloride (57.0 mg, 0.64 mmol), $MgSO_4$ (77.0 mg, 0.64 mmol), Et_3N (89 μL, 0.64 mmol) and 2-(hex-1-yn-1-yl)-5-methylbenzaldehyde (64.0 mg, 0.32 mmol) in dry dichloromethane (1 mL) afforded **1g** (72.4 mg, 83%, brown oil). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.66 (s, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.19 – 7.08 (m, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), 4.35 (s, 2H), 3.69 (s, 3H), 2.43 – 2.33 (m, 2H), 2.24 (s, 3H), 1.59 – 1.30 (m, 4H), 0.87 (t, *J* = 7.2 Hz, 3H).

Methyl (*E*)-*N*-[(5-fluoro-2-(hex-1-yn-1-yl)phenyl)methylene]glycinate (1h): Following the typical

procedure, the reaction of methyl glycinate hydrochloride (133.6 mg, 1.5 mmol), $MgSO_4$ (210 mg, 1.8 mmol), Et_3N (209 μL, 1.5 mmol) and 5-fluoro-2-(hex-1-yn-1-yl)benzaldehyde (204 mg, 1.0 mmol) in dry dichloromethane (3 mL) afforded **1h** (274 mg, 99%, brown oil). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.71 (s, 1H), 7.74 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.42 – 7.38 (m, 1H), 7.05 (td, *J* = 8.3, 2.6 Hz, 1H), 4.45 (s, 2H), 3.78 (s, 3H), 2.55 – 2.40 (m, 2H), 1.67 – 1.36 (m, 4H), 1.01 – 0.86 (m, 3H).

Methyl (*E*)-*N*-[(2-(hex-1-yn-1-yl)-4,5-dimethoxyphenyl)methylene]glycinate (1i): Following the general procedure, the reaction of methyl glycinate hydrochloride (0.4 g, 5.0 mmol), $MgSO_4$ (0.60 g, 5.0 mmol), Et_3N (0.7 mL, 5.0 mmol) and 2-(hex-1-yn-1-yl)-4,5-dimethoxybenzaldehyde (0.6 g, 2.5 mmol) in dry dichloromethane (5 mL) afforded **1i** (0.7 g, 91%, brown oil). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.53 (s, 1H), 6.85 (s, 1H), 4.41 (s, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.76 (s, 3H), 2.43 (t, *J* = 7.0 Hz, 2H), 1.65 – 1.40 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H).

Methyl (*E*)-*N*-[(2-(hex-1-yn-1-yl)phenyl)methylene]alaninate (1j): Following the typical procedure, the reaction of methyl alaninate hydrochloride (0.30 g, 2.2 mmol), $MgSO_4$ (0.26 g, 2.2 mmol), Et_3N (0.3 mL, 2.2 mmol) and 2-(hex-1-yn-1-yl)-benzaldehyde (0.20 g, 1.1 mmol) in dry dichloromethane (5 mL) afforded **1j** (0.27 g, 92%, brown oil). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.21 – 7.94 (m, 1H), 7.47 – 7.39 (m, 1H), 7.40 – 7.28 (m, 2H), 4.23 (q, *J* = 6.8 Hz, 1H), 3.78 (s, 3H), 2.50 (t, *J* = 6.9 Hz, 2H), 1.74 – 1.44 (m, 7H), 0.99 (t, *J* = 7.2 Hz, 3H).

***tert*-Butyl (*E*)-*N*-[(2-(hex-1-yn-1-yl)phenyl)methylene]glycinate (1k):** Following the typical procedure, the reaction of *tert*-butyl glycinate hydrochloride (0.36 g, 2.2 mmol), $MgSO_4$ (0.26 g, 2.2 mmol), Et_3N (0.3 mL, 2.2 mmol) and 2-(hex-1-yn-1-yl)-benzaldehyde (0.2 g, 1.1 mmol) in dry dichloromethane (5 mL) afforded **1k** (0.27 g, 89%, brown oil). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.08 (d, *J* = 7.1 Hz, 1H), 7.41 (d, *J* = 7.0 Hz, 1H), 7.37 – 7.24 (m, 2H), 4.35 (s, 2H), 2.46 (t, *J* = 6.9 Hz, 2H), 1.70 – 1.52 (m, 4H), 1.50 (s, 9H), 0.96 (t, *J* = 7.2 Hz, 3H).

Typical procedure for the asymmetric [3+2] cycloaddition of azomethine ylides with *N*-

methylmaleimide. (1*S*,3*R*,3a*S*,6a*R*)- Methyl 3-(2-(hex-1-yn-1-yl)phenyl)-5-methyl-4,6-dioxooctahydropyrrolo [3,4-*c*]pyrrole-1-carboxylate (*endo*-3a): A suspension of (*R*)-Fesulphos (5.04 mg, 0.011 mmol), CuOTf. 0.5 toluene complex (5.17 mg, 0.01 mmol) and KHMDS (1.99 mg, 0.01 mmol) in THF (1 mL) under argon atmosphere was heated at 40ºC for 1h (Kobayashi´s conditions[15]). The resulting mixture was cooled to room temperature and solutions of **1a** (33.5 mg, 0.13 mmol) in THF (1 mL) and *N*-methylmaleimide (11.1 mg, 0.10 mmol) in THF (1 mL) were successively added. After 18h at room temperature, the mixture was diluted with dichloromethane and filtered over Celite®. The crude was concentrated under reduced pressure and purified by silica gel flash chromatography (cyclohexane-EtOAc 3:1) to afford *endo*-**3a** (28.7 mg, 77%, brown oil). **$[\alpha]_D^{20}$: -** 65.7 (c = 0.10, $CHCl_3$), ≥ 99% *ee*. **HPLC:** Daicel Chiralpak AS-H, hexane-isopropanol 80-20, flow rate 0.7 mL/min (λ = 254 nm), t_R: 18.6 min (1*S*,3*R*,3a*S*,6a*R*)-**3a** and 28.9 min (1*R*,3*S*,3a*R*,6a*S*)-**3a**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.52 – 7.48 (m, 1H), 7.48 – 7.43 (m, 1H), 7.33 – 7.27 (m, 2H), 4.89 (d, *J* = 8.2 Hz, 1H), 4.12 (d, *J* = 6.7 Hz, 1H), 3.93 (s, 3H), 3.72 (t, *J* = 8.0 Hz, 1H), 3.62 (t, *J* = 7.3 Hz, 1H), 2.89 (s, 3H), 2.51 (t, *J* = 6.9 Hz, 2H), 1.73 – 1.46 (m, 4H), 1.01 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl3): δ 176.2, 174.6, 170.3, 138.4, 132.4, 127.9, 127.8, 125.7, 123.1, 95.7, 78.7, 62.2, 61.8, 52.4, 48.2, 47.7, 31.0, 25.1, 22.2, 19.4, 13.7. **HRMS** (ESI+): Calculated for $C_{21}H_{25}N_2O_4$, 369.1808; found, 369.1798 ([M+H], 100).

(1*S*,3*R*,3a*S*,6a*R*)- Methyl 3-(2-(cyclohexylethynyl)phenyl)-5-methyl-4,6-dioxooctahydro pyrrolo [3,4-*c*]pyrrole-1-carboxylate (*endo*-3b): Following the typical procedure, the reaction of *N*-methylmaleimide (11.1 mg, 0.10 mmol) and **1b** (36.8 mg, 0.13 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 4:1), the cycloadduct *endo*-**3b** (37.5 mg, 95%, brown oil). **$[\alpha]_D^{20}$**:+8.4 (c=0.89, $CHCl_3$), ≥ 99% *ee.* **HPLC:** Daicel Chiralpak IB, hexane-isopropanol 80-20, flow rate 0.7 mL/min (λ = 254 nm), t_R:17.8 min (1*R*,3*S*,3a*R*,6a*S*)-**3b** and 19.9 min (1*S*,3*R*,3a*S*,6a*R*)-**3b**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.49 – 7.34 (m, 2H), 7.29 – 7.18 (m, 2H), 4.85 (dd, *J* = 7.6, 5.2 Hz, 1H), 4.12 – 3.96 (m, 1H), 3.87 (s, 3H), 3.68 (t, *J* = 8.0 Hz, 1H), 3.56 (t, *J* = 7.3 Hz, 1H), 2.83 (s, 3H), 2.72 – 2.56 (m, 1H), 2.47 – 2.30 (m, 1H), 2.00 – 1.83 (m, 2H), 1.82 – 1.73 (m, 2H), 1.59 –

1.50 (m, 3H), 1.41 – 1.30 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.1, 174.5, 170.3, 138.4, 132.2, 127.8, 127.7, 125.6, 123.1, 99.6, 78.6, 62.1, 61.7, 52.3, 48.0, 47.5, 32.9, 32.8, 29.9, 25.9, 25.0. **HRMS** (ESI+): Calculated for $C_{23}H_{27}N_2O_4$, 395.1965; found, 395.1948 ([M+H], 100).

(1*S*,3*R*,3a*S*,6a*R*)- Methyl 3-(2-(phenylethynyl)phenyl)-5-methyl-4,6-dioxooctahydropyrrolo [3,4-*c*]pyrrole-1-carboxylate (*endo*-3c): Following the typical procedure, the reaction of *N*-methylmaleimide (11.1 mg, 0.10 mmol) and **1c** (36.1 mg, 0.13 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), the cycloadduct *endo*-**3c** (36.9 mg, 95%, brown oil). **$[\alpha]_D^{20}$**:+18.7 (c=1.03, $CHCl_3$), 99% *ee*. **HPLC:** Daicel Chiralpak AS-H, hexane-isopropanol 80-20, flow rate 0.7 mL/min (λ = 254 nm), t_R: 31.2 min (1*S*,3*R*,3a*S*,6a*R*)-**3c** and 41.9 min (1*R*,3*S*,3a*R*,6a*S*)-**3c**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.61 – 7.56 (m, 1H), 7.55 – 7.46 (m, 3H), 7.40 – 7.29 (m, 5H), 4.93 (d, *J* = 8.3 Hz, 1H), 4.09 (d, *J* = 6.8 Hz, 1H), 3.88 (s, 3H), 3.73 (t, *J* = 8.0 Hz, 1H), 3.57 (t, *J* = 7.3 Hz, 1H), 2.83 (s, 3H), 2.47 (bs, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.7, 174.2, 169.9, 138.4, 132.0, 131.2, 128.4, 128.3, 128.2, 127.5, 125.5, 122.7, 121.8, 93.9, 86.9, 61.7, 61.3, 52.0, 47.6, 47.3, 24.7. **HRMS** (ESI+): Calculated for $C_{23}H_{21}N_2O_4$, 389.1495; found, 389.1478 ([M+H], 100).

(1*S*,3*R*,3a*S*,6a*R*)- Methyl 3-(2-(4-*tert*-butylphenylethynyl)phenyl)-5-methyl-4,6-dioxo octahydropyrrolo [3,4-*c*]pyrrole-1-carboxylate (*endo*-3d): Following the typical procedure, the reaction of *N*-methylmaleimide (11.1 mg, 0.10 mmol) and **1d** (43.3 mg, 0.13 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 4:1), the cycloadduct *endo*-**3d** (40.5 mg, 91%, brown solid). **$[\alpha]_D^{20}$**:+46.9 (c=0.22, $CHCl_3$), 96% *ee*. **Mp** 117-119 ºC. **HPLC:** Daicel Chiralpak IA, hexane-isopropanol 80-20, flow rate 0.7 mL/min (λ = 254 nm), t_R: 36.8 min (1*S*,3*R*,3a*S*,6a*R*)-**3d** and 54.7 min (1*R*,3*S*,3a*R*,6a*S*)-**3d**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.60 – 7.54 (m, 1H), 7.49 – 7.43 (m, 3H), 7.42 – 7.35 (m, 2H), 7.32 – 7.27 (m, 2H), 4.92 (d, *J* = 8.4 Hz, 1H), 4.07 (d, *J* = 7.0 Hz, 1H), 3.87 (s, 3H), 3.73 (t, *J* = 8.1 Hz, 1H), 3.55 (t, *J* = 7.4 Hz, 1H), 2.83 (s, 3H), 1.34 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.1, 174.6, 170.3, 152.1, 138.8, 132.3, 131.3, 128.6, 127.9, 125.9, 125.6, 122.4, 120.1, 94.5, 86.7, 62.2, 61.7, 52.4, 48.1, 47.7, 34.9, 31.3, 25.1. **HRMS** (ESI+): Calculated

for $C_{27}H_{29}N_2O_4$, 445.2121; found, 445.2117 ([M+H], 100).

(1*S*,3*R*,3a*S*,6a*R*)- Methyl 3-(2-(4-methoxyphenylethynyl)phenyl)-5-methyl-4,6-dioxo octahydropyrrolo [3,4-*c*]pyrrole-1-carboxylate (*endo*-3e): Following the typical procedure, the reaction of *N*-methylmaleimide (11.1 mg, 0.10 mmol) and **1e** (40.0 mg, 0.13 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), the cycloadduct *endo*-**3e** (39.8 mg, 95%, brown oil). $[\alpha]_D^{20}$:+53.3 (c=0.17, $CHCl_3$), ≥99% *ee.* **HPLC:** Daicel Chiralpak IB, hexane-isopropanol 70-30, flow rate 0.7 mL/min (λ = 254 nm), t_R: 36.8 min (1*R*,3*S*,3a*R*,6a*S*)-**3e** and 54.7min (1*S*,3*R*,3a*S*,6a*R*)-**3e**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.65 – 7.50 (m, 1H), 7.51 – 7.41 (m, 3H), 7.35 – 7.06 (m, 2H), 7.01 – 6.69 (m, 2H), 4.90 (d, *J* = 8.5 Hz, 1H), 4.08 (d, *J* = 7.0 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.72 (t, *J* = 8.1 Hz, 1H), 3.57 (t, *J* = 7.3 Hz, 1H), 2.82 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.1, 174.6, 170.3, 159.9, 138.5, 133.0, 132.2, 128.4, 127.8, 125.9, 122.5, 115.1, 114.2, 94.4, 86.0, 62.1, 61.7, 55.4, 52.3, 48.0, 47.7, 25.0. **HRMS** (ESI+): Calculated for $C_{24}H_{23}N_2O_5$, 419.1601; found, 419.1583 ([M+H], 100).

(1*S*,3*R*,3a*S*,6a*R*)- Methyl 3-(2-(tiophen-2-ylethynyl)phenyl)-5-methyl-4,6-dioxooctahydro pyrrolo [3,4-*c*]pyrrole-1-carboxylate (*endo*-3f): Following the typical procedure, the reaction of *N*-methylmaleimide (11.1 mg, 0.10 mmol) and **1f** (36.8 mg, 0.13 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), the cycloadduct *endo*-**3f** (24.9 mg, 63%, brown oil). $[\alpha]_D^{20}$:+3.3 (c=0.12, $CHCl_3$), ≥99% *ee.* **HPLC:** Daicel Chiralpak IB, hexane-isopropanol 70-30, flow rate 0.7 mL/min (λ = 254 nm), t_R: 36.8 min (1*R*,3*S*,3a*R*,6a*S*)-**3f** and 54.7min (1*S*,3*R*,3a*S*,6a*R*)-**3f**. **^{1}H NMR** (300 MHz, $CDCl_3$): 7.58 – 7.53 (m, 1H), 7.51 – 7.45 (m, 1H), 7.34 – 7.27 (m, 4H), 7.03 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.89 (d, *J* = 8.1 Hz, 1H), 4.11 (d, *J* = 7.0 Hz, 1H), 3.88 (s, 3H), 3.76 – 3.67 (m, 1H), 3.64 – 3.55 (m, 1H), 2.83 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.1, 174.6, 170.3, 138.8, 132.3, 132.1, 129.1, 128.0, 127.8, 127.4, 126.0, 123.1, 122.0, 91.1, 87.6, 62.1, 61.8, 52.5, 48.1, 47.8, 25.2. **HRMS** (ESI+): Calculated for $C_{21}H_{17}N_2O_5S$, 409.0852; found, 409.0850 ([M+H], 70).

(1*S*,3*R*,3a*S*,6a*R*)- Methyl 3-(2-(hex-1-yn-1-yl)-5-methylphenyl)-5-methyl-4,6-dioxo

octahydropyrrolo [3,4-*c*]pyrrole-1-carboxylate (*endo*-3g): Following the typical procedure, the reaction of *N*-methylmaleimide (11.1 mg, 0.10 mmol) and **1g** (35.3 mg, 0.13 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 4:1), the cycloadduct *endo*-**3g** (36.7 mg, 96%, yellow oil). **Mp** 88-90 ºC. $[\alpha]_D^{20}$:+85.5 (c=0.8, $CHCl_3$), 81% *ee*. **HPLC:** Daicel Chiralpak IB, hexane-isopropanol 80-20, flow rate 0.7 mL/min (λ = 210 nm), t_R: 44.0 min (1*R*,3*S*,3a*R*,6a*S*)-**3g** and 59.2 min (1*S*,3*R*,3a*S*,6a*R*)-**3g**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37 – 7.16 (m, 2H), 7.14 – 6.97 (m, 1H), 4.80 (d, *J* = 7.7 Hz, 1H), 4.07 (d, *J* = 6.6 Hz, 1H), 3.89 (s, 3H), 3.76 – 3.42 (m, 2H), 2.85 (s, 3H), 2.46 (t, *J* = 6.8 Hz, 2H), 2.30 (s, 3H), 1.66 – 1.39 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.3, 174.8, 170.4, 137.4, 135.2, 133.1, 128.9, 125.7, 122.8, 95.2, 78.7, 62.8, 61.8, 52.4, 48.2, 47.8, 31.0, 25.1, 22.2, 21.1, 19.4, 13.8. **HRMS** (ESI+): Calculated for $C_{22}H_{27}N_2O_4$, 383.1965; found, 383.1963 ([M+H], 100).

(1*S*,3*R*,3a*S*,6a*R*)- Methyl 3-(5-fluoro-2-(hex-1-yn-1-yl)phenyl)-5-methyl-4,6-dioxo octahydropyrrolo [3,4-*c*]pyrrole-1-carboxylate (*endo*-3h): Following the typical procedure, the reaction of *N*-methylmaleimide (11.1 mg, 0.10 mmol) and **1h** (35.8 mg, 0.13 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 4:1), the cycloadduct *endo*-**3h** (26.6 mg, 93%, yellow oil). $[\alpha]_D^{20}$:+40.9 (c=0.10, $CHCl_3$), 96% *ee*. **HPLC:** Daicel Chiralpak AS-H, hexane-isopropanol 80-20, flow rate 0.7 mL/min (λ = 254 nm), t_R: 18.7 min (1*S*,3*R*,3a*S*,6a*R*)-**3h** and 31.7min (1*R*,3*S*,3a*R*,6a*S*)-**3h**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 8.4, 5.6 Hz, 1H), 7.16 (dd, *J* = 9.8, 2.6 Hz, 1H), 6.97 – 6.83 (m, 1H), 4.78 (d, *J* = 8.2 Hz, 1H), 4.05 (d, *J* = 6.8 Hz, 1H), 3.86 (s, 3H), 3.65 (t, *J* = 8.0 Hz, 1H), 3.55 (t, *J* = 7.3 Hz, 1H), 2.83 (s, 3H), 2.43 (t, *J* = 7.0 Hz, 2H), 1.71 – 1.37 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.0, 174.4, 170.1, 162.3 (d, *J* = 248.7 Hz), 141.5 (d, *J* = 7.7 Hz), 134.0 (d, *J* = 8.2 Hz), 119.1 (d, *J* = 3.3 Hz), 114.9 (d, *J* = 22.0 Hz), 113.2 (d, *J* = 24.0 Hz), 95.2, 77.7, 77.4, 77.2, 61.6, 61.6, 52.4, 47.7, 47.3, 30.9, 25.1, 22.2, 19.4, 13.7. **^{19}F NMR** (282 MHz, $CDCl_3$): δ -110.85. **HRMS** (ESI+): Calculated for $C_{21}H_{24}FN_2O_4$, 387.1714; found, 387.1699 ([M+H], 100).

(1*S*,3*R*,3a*S*,6a*R*)- Methyl 3-(2-(hex-1-yn-1-yl)-4,5-dimethoxyphenyl)-5-methyl-4,6-dioxo octahydropyrrolo [3,4-*c*]pyrrole-1-carboxylate (*endo*-3i): Following the typical procedure, the reaction of *N*-methylmaleimide (11.1 mg, 0.10 mmol) and **1i** (41.3 mg, 0.13 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 2:1) an inseparable mixture (93:7) of the cycloadducts *endo*-**3i** and *exo*-**3i**. (32.6 mg, 76%, brown oil) $[\alpha]_D^{20}$:+94.7 (c=0.80, $CHCl_3$), 90% *ee* (*endo*). **HPLC:** Daicel Chiralpak IA, hexane-isopropanol 70-30, flow rate 0.7 mL/min (λ = 254 nm), t_R: 24.3 min (1*R*,3*S*,3a*R*,6a*S*)-**3i** and 35.5min (1*S*,3*R*,3a*S*,6a*R*)-**3i**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.92 (s, 1H), 6.86 (s, 1H), 4.79 (dd, *J* = 7.4, 4.1 Hz, 1H), 4.07 – 4.01 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.62 – 3.50 (m, 2H), 2.84 (s, 3H), 2.44 (t, *J* = 7.0 Hz, 3H), 1.68 – 1.38 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.1, 174.5, 170.1, 148.8, 147.9, 131.4, 114.96, 114.5, 108.6, 93.9, 78.2, 61.7, 61.4, 56.0, 55.7, 52.1, 47.7, 47.3, 30.9, 24.6, 22.1, 19.2, 13.56. **HRMS** (ESI+): Calculated for $C_{23}H_{29}N_2O_6$, 429.2020; found, 429.2016 ([M+H], 100).

(1*S*,3*R*,3*aS*,6*aR*)- Methyl 3-(2-(hex-1-yn-1-yl)phenyl)-1,5-dimethyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (3j): Following the typical procedure, the reaction of *N*-methylmaleimide (11.1 mg, 0.10 mmol) and **1j** (32.6 mg, 0.13 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 4:1), the cycloadduct *endo*-**3j** (23.6 mg, 63%, brown oil).**$[\alpha]_D^{20}$:** +39.3 (c = 0.06, $CHCl_3$), 89% *ee*. **HPLC:** Daicel Chiralpak AD, hexane-isopropanol 80-20, flow rate 0.7 mL/min (λ = 254 nm), t_R: 18.6 min (1*R*,3*S*,3a*R*,6a*S*)-**3j** and 12.60 min (1*S*,3*R*,3*aS*,6*aR*)-**3j**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48 – 7.42 (m, 1H), 7.40 – 7.28 (m, 1H), 7.28 – 7.19 (m, 2H), 5.24 – 5.02 (m, 1H), 3.87 (s, 3H), 3.73 (t, *J* = 8.2 Hz, 1H), 3.26 (d, *J* = 7.5 Hz, 1H), 2.78 (s, 3H), 2.67 (bs, 1H), 2.48 (t, *J* = 6.8 Hz, 2H), 1.63 (s, 3H), 1.60 – 1.44 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.0, 174.5, 172.9, 138.4, 132.4, 127.9, 127.7, 125.3, 123.4, 95.7, 78.7, 67.3, 60.2, 55.5, 52.7, 48.6, 30.9, 24.9, 23.8, 22.2, 19.4, 13.7. **HRMS** (FB+): Calculated for $C_{22}H_{27}N_2O_4$, 383.1971; found, 383.1976 ([M+H], 100).

Typical procedure for catalytic asymmetric [3+2] cycloaddition of azomethine ylides with

bis(phenylsulfonyl)ethylene (2*R*,3*S*,4*S*,5*S*)- Methyl 5-(2-(hex-1-yn-1-yl)phenyl)-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate (*exo*-9a): A suspension of (*R*)-Fesulphos (5.04 mg, 0.011 mmol), CuOTf 0.5 toluene complex (5.17 mg, 0.01 mmol) and KHMDS (1.99 mg, 0.01 mmol) in THF (1 mL) under argon atmosphere was heated at 40ºC for 1h. The resulting mixture was cooled to room temperature and solutions of **1a** (33.5 mg, 0.13 mmol) in THF (1 mL) and *trans*-1,2-bis(phenylsulfonyl)ethylene (30.1 mg, 0.10 mmol) in THF (1 mL) were successively added. After 18h at room temperature, the mixture was diluted with dichloromethane and filtered over Celite®. The crude was concentrated under reduced pressure and purified by silica gel flash chromatography (cyclohexane-EtOAc 3:1) to afford *exo*-**9a** (60.3 mg, 82%, brown oil).**[α]$_D^{20}$:** +17.6 (c = 0.15, $CHCl_3$), 96% *ee*. **HPLC:** Daicel Chiralpak IB, hexane-isopropanol 80-20, flow rate 0.7 mL/min (λ = 254 nm), t_R: 17.4 min (2*S*,3*R*,4*R*,5*R*)-**9a** and 20.8 min (2*R*,3*S*,4*S*,5*S*)-**9a**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.9 Hz, 2H), 7.75 – 7.56 (m, 5H), 7.54 – 7.40 (m, 2H), 7.35 – 7.04 (m, 5H), 5.20 (d, *J* = 7.2 Hz, 1H), 4.62 (dd, *J* = 6.2, 3.0 Hz, 1H), 4.53 (dd, *J* = 7.2, 3.0 Hz, 1H), 4.26 (d, *J* = 6.2 Hz, 1H), 3.66 (s, 3H), 2.49 (t, *J* = 7.0 Hz, 2H), 1.73 – 1.42 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.6, 138.7, 138.6, 137.2, 134.5, 134.1, 132.5, 129.5, 129.2, 128.7, 128.5, 128.5, 128.2, 126.5, 124.8, 96.2, 78.3, 71.0, 67.6, 64.7, 61.6, 52.7, 30.8, 22.2, 19.5, 13.8. **HRMS** (ESI+): Calculated for $C_{30}H_{32}NO_6S_2$, 566.1665; found, 566.1646 ([M+H], 100).

(2*R*,3*S*,4*S*,5*S*)-*tert*-Butyl 5-(2-(hept-1-yn-1-yl)phenyl)-3,4-bis(phenylsulfonyl)pyrrolidine-2-carboxylate (*exo*-9k): Following the typical procedure, the reaction of *trans*-1,2-bis(phenylsulfonyl)ethylene (30.8 mg, 0.10 mmol) and **1k** (44.9 mg, 0.15 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), a 92:8 mixture of *exo*-**9k** and *endo*-**9k** (56.5 mg, 93%, yellow oil). **[α]$_D^{20}$:** +22.4 (c = 0.98, $CHCl_3$), 89% *ee* (*exo*). **HPLC:** Daicel Chiralpak AD, hexane-isopropanol 80-20, flow rate 0.7 mL/min (λ = 254 nm), t_R: 14.2 min (2*R*,3*S*,4*S*,5*S*)-**9k** and 17.8 min (2*S*,3*R*,4*R*,5*R*)-**9k**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.90 – 7.84 (m, 2H), 7.74 – 7.66 (m, 1H), 7.62 – 7.53 (m, 3H), 7.50 – 7.38 (m, 2H), 7.34 – 7.03 (m, 6H), 5.16 (d, *J* = 7.4 Hz,

1H), 4.61 (dd, *J* = 6.4, 3.1 Hz, 1H), 4.45 (dd, *J* = 7.3, 3.1 Hz, 1H), 4.22 (d, *J* = 6.3 Hz, 1H), 2.49 (t, *J* = 7.1 Hz, 2H), 1.73 – 1.41 (m, 13H), 0.97 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.1, 139.0, 137.2, 134.4, 134.0, 132.6, 129.5, 129.1, 128.7, 128.5, 128.3, 128.2, 127.8, 126.6, 124.6, 83.4, 78.4, 71.5, 67.4, 66.0, 61.6, 30.8, 28.1, 22.3, 19.6, 13.8. **HRMS** (FAB+): Calculated for $C_{33}H_{38}NO_6S_2$, 608.2141; found, 608.2155 ([M+H], 85).

Typical procedure for the hydroamination/reduction sequence.

(6*S*,8*S*,8a*R*,11a*S*,11b*R*)- Methyl 6-butyl-10-methyl-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (7a): A solution of *endo*-**3a** (31.8 mg, 0.08 mmol) in dichloromethane (1 mL) was added to a solution of JohnPhosAuMeCN SbF_6 (6.7 mg, $8\cdot10^{-3}$ mmol) in dichloromethane (1 mL) under argon atmosphere at room temperature. After 18h the solution was cooled to 0ºC and MeOH (0.4 mL), HCl 5% (0.17 mL) and $NaBH_3CN$ (10.6 mg) were successively added. The mixture was stirred for 1h at 0ºC, diluted with dichloromethane (5 mL) and washed with 5 mL of saturated $NaHCO_3$ solution, water (2 x 5 mL) and brine (2 x 5 mL). The organic layer was separated, dried (Mg_2SO_4), concentrated under reduced pressure and purified by silica gel flash chromatography (cyclohexane-EtOAc 3:1) to afford **7a** (20.0 mg, 65%, white solid), ≥99% *ee*. **HPLC:** Daicel Chiralpak IB, hexane-isopropanol 70-30, flow rate 0.7 mL/min (λ = 254 nm), t_R: 23.5 min (6*S*,8*S*,8a*R*,11a*S*,11b*R*)-**7a** and 34.2 min (6*R*,8*R*,8a*S*,11a*R*,11b*S*)-**7a**. **Mp** 157-159 ºC. **$[\alpha]_D^{20}$:** +6.1 (c=0.54, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.51 – 7.42 (m, 1H), 7.25 – 7.15 (m, 2H), 7.12 – 7.03 (m, 1H), 3.95 (d, *J* = 6.2 Hz, 1H), 3.75 (s, 3H), 3.71 (d, *J* = 6.7 Hz, 1H), 3.60 – 3.48 (m, 2H), 2.96 – 2.70 (m, 5H), 2.52 (dd, *J* = 12.0, 8.1 Hz, 1H), 1.53 – 1.11 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.1, 174.9, 171.6, 134.8, 132.1, 128.5, 127.3, 127.2, 125.1, 68.5, 67.5, 62.0, 52.5, 46.8, 45.5, 35.9, 33.7, 28.4, 25.2, 22.9, 14.0. **HRMS** (ESI+): Calculated for $C_{21}H_{27}N_2O_4$, 371.1965; found, 371.1967 ([M+H], 100).

(6*R*,8*S*,8a*R*,11a*S*,11b*R*)- Methyl 6-cyclohexyl-10-methyl-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (7b): Following the

typical procedure, the hydroamination/reduction of *endo*-**3b** (43.6 mg, 0.11 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), **7b** (19.5 mg, 45%, white solid). **Mp** 212-214 ºC. $[\alpha]_D^{20}$:+187.2 (c=0.20, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.55 – 7.36 (m, 1H), 7.25 – 7.16 (m, Hz, 2H), 7.16 – 7.01 (m, 1H), 3.90 (d, *J* = 7.3 Hz, 1H), 3.78 – 3.68 (m, 4H), 3.63 – 3.43 (m, 2H), 3.16 – 2.95 (m, 1H), 2.90 (s, 3H), 2.69 – 2.60 (m, 1H), 2.51 – 2.36 (m, 1H), 1.97 – 1.55 (m, 6H), 1.53 – 1.38 (m, 2H), 1.06 – 0.77 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.3, 175.1, 170.8, 135.0, 132.0, 128.4, 127.2, 126.9, 125.1, 69.4, 68.4, 68.3, 52.4, 46.8, 45.5, 41.1, 32.5, 30.9, 27.4, 27.3, 26.8, 26.5, 25.1. **HRMS** (ESI+): Calculated for $C_{23}H_{29}N_2O_4$, 397.2121; found, 397.2118 ([M+H], 100).

(6*R*,8*S*,8a*R*,11a*S*,11b*R*)- Methyl 10-methyl-6-phenyl-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (7c): Following the typical procedure, the hydroamination/reduction of *endo*-**3c** (20.1 mg, 0.05 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), **7c** (11.0 mg, 56%, yellow solid). **Mp** 157-159 ºC. $[\alpha]_D^{20}$:+6.1 (c=0.54, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.57 – 7.51 (m, 1H), 7.39 – 7.20 (m, 7H), 7.16 – 7.10 (m, 1H), 4.07 (d, *J* = 6.0 Hz, 1H), 3.83 – 3.72 (m, 1H), 3.64 – 3.54 (m, 2H), 3.53 – 3.38 (m, 2H), 3.11 (s, 3H), 3.00 – 2.83 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.9, 175.0, 169.5, 138.6, 134.8, 131.9, 130.3, 128.8, 128.3, 128.1, 127.4, 127.2, 125.4, 69.0, 68.6, 67.4, 51.6, 46.6, 45.5, 37.8, 25.1. **HRMS** (ESI+): Calculated for $C_{23}H_{23}N_2O_4$, 391.1652; found, 391.1647 ([M+H], 100).

(6*R*,8*S*,8a*R*,11a*S*,11b*R*)-Methyl 6-(4-*tert*-butylphenyl)-10-methyl-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (7d): Following the typical procedure, the hydroamination/reduction of *endo*-**3d** (53.5 mg, 0.12 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), **7d** (27.3 mg, 51%, white solid). **Mp** 238-240 ºC. $[\alpha]_D^{20}$:+118.9 (c=0.35, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.60 – 7.49 (m, 1H), 7.40 – 7.22 (m, 6H), 7.19 – 7.10 (m, 1H), 4.09 (d, *J* = 6.0 Hz, 1H), 3.83 – 3.74 (m, 1H), 3.66 – 3.54 (m, 2H), 3.52 – 3.39 (m, 2H), 3.11 (s, 3H), 2.99 – 2.80 (m, 4H), 1.34 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.0, 175.1, 169.6, 151.7, 135.5, 135.0, 131.9, 130.0, 128.4, 127.3, 127.2, 125.4, 124.9,

68.9, 68.4, 66.9, 51.6, 46.6, 45.5, 37.6, 34.7, 31.4, 25.1. **HRMS** (ESI+): Calculated for $C_{27}H_{31}N_2O_4$, 447.2278; found, 447.2261 ([M+H], 100).

(6*R*,8*S*,8a*R*,11a*S*,11b*R*)-Methyl 6-(4-methoxyphenyl)-10-methyl-9,11-dioxo-5,8,8a,9,10,11, 11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (7e): Following the typical procedure, the hydroamination/reduction of *endo*-**3e** (53.6 mg, 0.13 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), **7e** (28.8 mg, 53%, brown solid). **Mp** 250-252 ºC. **$[\alpha]_D^{20}$**:+90.7 (c=0.17, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.2 Hz, 1H), 7.35 – 7.18 (m, 4H), 7.13 (d, *J* = 7.1 Hz, 1H), 6.82 (t, *J* = 5.6 Hz, 2H), 4.05 (d, *J* = 5.9 Hz, 1H), 3.75 – 3.85 (m, 4H), 3.56 – 3.53 (m, 2H), 3.44 (d, *J* = 3.7 Hz, 2H), 3.16 (s, 3H), 2.93 – 2.84 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.0, 175.1, 169.6, 159.9, 135.0, 131.9, 131.4, 130.8, 128.4, 127.3, 127.2, 125.4, 113.4, 69.0, 68.6, 66.6, 55.4, 51.7, 46.6, 45.6, 37.9, 25.1. **HRMS** (ESI+): Calculated for $C_{24}H_{25}N_2O_5$, 421.1757; found, 421.1755 ([M+H], 100).

(6*R*,8*S*,8a*R*,11a*S*,11b*R*)-Methyl 6-(tiophen-2-yl)-10-methyl-9,11-dioxo-5,8,8a,9,10,11,11a, 11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (7f): Following the typical procedure, the hydroamination/reduction of *endo*-**3f** (36.8 mg, 0.10 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), **7f** (28.32 mg, 76%, white solid). **Mp** 180-182 ºC. **$[\alpha]_D^{20}$**:+102.8 (c=0.48, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.58 – 7.46 (m, 1H), 7.34 – 7.20 (m, 3H), 7.19 – 7.10 (m, 1H), 7.06 – 7.01 (m, 1H), 6.94 (dd, *J* = 5.0, 3.6 Hz, 1H), 4.10 (d, *J* = 6.5 Hz, 1H), 3.93 (dd, *J* = 11.6, 3.4 Hz, 1H), 3.83 – 3.72 (m, 1H), 3.67 – 3.53 (m, 2H), 3.54 – 3.43 (m, 1H), 3.27 (s, 3H), 3.07 (dd, *J* = 16.1, 3.1 Hz, 1H), 2.87 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.7, 174.9, 169.2, 142.4, 134.4, 131.7, 128.8, 128.3, 127.4, 127.3, 126.4, 126.2, 125.6, 68.7, 68.3, 61.0, 51.9, 46.5, 45.5, 38.9, 25.2. **HRMS** (ESI+): Calculated for $C_{21}H_{21}N_2O_4S$, 397.1216; found, 397.1212 ([M+H], 100).

(6*S*,8*S*,8a*R*,11a*S*,11b*R*)-Methyl 6-butyl-2,10-dimethyl-9,11-dioxo-5,8,8a,9,10,11,11a,11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (7g): Following the

typical procedure, the hydroamination/reduction of *endo*-**3g** (34.4 mg, 0.09 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), **7g** (20.7 mg, 60%, brown oil). **[α]$_D^{20}$**:+118.9 (c=0.35, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.91 (s, 1H), 3.95 (d, *J* = 6.2 Hz, 1H), 3.75 (s, 3H), 3.71 (d, *J* = 6.7 Hz, 1H), 3.60 – 3.48 (m, 2H), 2.88 (s, 3H), 2.82 – 2.74 (m, 2H), 2.51 – 2.47 (m, 1H), 2.30 (s, 3H), 1.53 – 1.11 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.1, 175.0, 171.7, 136.7, 134.6, 129.1, 129.0, 127.1, 126.0, 68.3, 67.5, 62.0, 52.4, 46.8, 45.6, 35.8, 33.6, 28.4, 25.2, 22.8, 21.3, 14.0. **HRMS** (ESI+): Calculated for $C_{22}H_{29}N_2O_4$, 385.2121; found, 385.2113 ([M+H], 100).

(6*S*,8*S*,8a*R*,11a*S*,11b*R*)-Methyl 6-butyl-2-fluoro-10-methyl-9,11-dioxo-5,8,8a,9,10,11,11a, 11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (7h): Following the typical procedure, the hydroamination/reduction of *endo*-**3h** (26.3 mg, 0.07 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), **7h** (17.67 mg, 65%, orange solid). **Mp** 185-187 ºC. **[α]$_D^{20}$**:+173.2 (c=0.87, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.17 (dd, *J* = 9.7, 2.3 Hz, 1H), 7.12 – 7.00 (m, 1H), 6.90 (m, 1H), 3.96 – 3.86 (m, 1H), 3.75 (s, 3H), 3.67 (t, *J* = 6.4 Hz, 1H), 3.61 – 3.50 (m, 2H), 2.90 (s, 3H), 2.87 – 2.81 (m, 1H), 2.78 – 2.66 (m, 1H), 2.57 – 2.44 (m, 1H), 1.52 – 1.11 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.9, 174.7, 171.5, 160.4 (d, *J* = 243.2 Hz), 133.8 (d, *J* = 7.5 Hz), 130.3 (d, *J* = 3.1 Hz), 129.8 (d, *J* = 7.9 Hz), 114.5 (d, *J* = 21.4 Hz), 114.0 (d, *J* = 22.5 Hz), 68.2, 67.4, 62.0, 52.5, 46.6, 45.4, 35.2, 33.6, 28.4, 25.3, 22.9, 14.0. **HRMS** (ESI+): Calculated for $C_{21}H_{26}N_2O_4F$, 389.1871; found, 389.1871 ([M+H], 100).

(6*S*,8*S*,8a*R*,11a*S*,11b*R*)-Methyl 10-methyl-2,3-dimethoxy-6-(hex-1-yn-1-yl)-9,11-dioxo-5,8,8a,9,10,11,11a, 11b-octahydro-6*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (7i): Following the typical procedure, the hydroamination/reduction of *endo*-**3i** (40.3 mg, 0.09 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 2:1), **7i** (24.4 mg, 63%, yellow solid). **Mp** 90-92 ºC. **[α]$_D^{20}$**:+70.2 (c=0.13, $CHCl_3$). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.96 (s, 1H), 6.57 (s, 1H), 3.91 (s, 3H), 3.88 (d, *J* = 6.9 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.68 (t, *J* = 6.8

Hz, 1H), 3.61 – 3.46 (m, 2H), 2.89 (s, 3H), 2.85 – 2.64 (m, 2H), 2.54 – 2.42 (m, 1H), 1.50 – 1.39 (m, 2H), 1.34 – 1.14 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.0, 174.9, 171.6, 148.3, 146.6, 127.0, 124.2, 110.9, 110.8, 68.3, 67.5, 62.2, 56.3, 55.9, 52.4, 46.8, 45.7, 35.5, 33.6, 28.4, 25.3, 22.9, 14.1. **HRMS** (ESI+): Calculated for $C_{23}H_{31}N_2O_6$, 431.2176; found, 431.2167 ([M+H], 100).

Methyl 6-butyl-8,10-dimethyl-9,11-dioxo-6,8,8a,9,10,11,11a,11b-octahydro-5*H*-pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline-8-carboxylate (7j): Following the typical procedure, the hydroamination/reduction of *endo*-**3j** (47.2 mg, 0.12 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), the adduct *cis*-**7j** (18.2 mg, 40%, yellow oil) and *trans*-**7j** (9.8 mg, 23%, yellow oil).

(6*S*,8*S*,8*aR*,11*aS*,11*bR*)-*cis*-7j: $[\alpha]_D^{20}$: +25.7 (c = 0.31, $CHCl_3$), 90% *ee*. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44 – 7.37 (m, 1H), 7.32 – 7.21 (m, 2H), 7.12 (d, *J* = 6.5 Hz, 1H), 5.00 (d, *J* = 3.6 Hz, 1H), 4.45 (s, 1H), 3.70 (s, 3H), 3.34 – 3.20 (m, 2H), 2.98 (s, 3H), 1.83 – 1.63 (m, 2H), 1.41 (s, 3H), 1.31 – 1.05 (m, 6H), 0.82 (t, *J* = 6.5 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 177.6, 176.2, 172.4, 143.1, 141.8, 127.8, 127.7, 122.3, 122.1, 71.7, 71.1, 63.5, 56.9, 52.3, 52.0, 36.3, 31.9, 25.1, 24.1, 22.5, 20.9, 14.0.**HRMS** (FB+): Calculated for $C_{22}H_{29}N_2O_4$, 385.2121; found, 385.2127 ([M+H], 25).

(6*S*,8*S*,8*aR*,11*aS*,11*bR*)-*trans*-7j: $[\alpha]_D^{20}$: -20.0 (c = 0.02, $CHCl_3$), 99% *ee*. **^{1}H NMR** (300 MHz, $CDCl_3$ δ 7.51 – 7.45 (m, 1H), 7.33 – 7.18 (m, 2H), 7.15 – 7.09 (m, 1H), 4.40 (d, *J* = 5.9 Hz, 1H), 3.77 – 3.64 (m, 4H), 3.13 – 3.06 (m, 1H), 2.99 – 2.86 (m, Hz, 4H), 2.82 – 2.66 (m, 2H), 1.57 (s, 3H), 1.52 – 1.13 (m, 6H), 0.92 (t, *J* = 6.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.2, 175.2, 174.0, 134.2, 132.5, 128.3, 127.4, 126.7, 124.9, 69.6, 63.2 56.0, 55.3, 52.3, 45.6, 36.2, 32.7, 28.5, 25.0, 22.7, 15.5, 14.0. **HRMS** (ESI+): Calculated for $C_{22}H_{29}N_2O_4$, 385.2121; found, 385.2098 ([M+H], 20).

Typical procedure for the hydroamination/reduction/desulfonylation sequence.

(*S*)-Methyl 5-butyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (12a): A solution of *exo*-**9a** (50.0 mg, 0.088 mmol) in dichloromethane (1 mL) was added to a solution of JohnPhosAuMeCN SbF_6

(6.8 mg, $8.8 \cdot 10^{-3}$ mmol) in dichloromethane (0.5 mL) under argon atmosphere at room temperature. After 18h at room temperature, the solution was cooled to 0ºC and MeOH (0.5 mL), HCl 5% (0.25 mL) and $NaBH_3CN$ (11.2 mg, 0.18 mmol) were successively added. The mixture was stirred for 1h at 0ºC and DBU was added to pH=8. Then, the reaction mixture was warmed to rt, diluted with dichloromethane (5 ml) and washed with water (2 x 5 mL) and brine (2 x 5 mL). The organic layer was separated, dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by silica gel flash chromatography (cyclohexane-EtOAc 3:1) to afford **12a** (13.7 mg, 55%, yellow oil). **$[\alpha]_D^{20}$:** -9.7 (c = 1.10, $CHCl_3$), 34% *ee*. **HPLC:** Daicel Chiralpak IA, CO_2-methanol 99-1, flow rate 1 mL/min (λ = 230 nm), t_R: 18.6 min (*S*)-**12a** and 28.9 min (*R*)-**12a**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.60 (d, J = 7.2 Hz, 1H), 7.34 – 7.23 (m, 2H), 7.05 (d, *J* = 4.1 Hz, 1H), 6.56 (d, *J* = 4.1 Hz, 1H), 5.58 – 5.37 (m, 1H), 3.88 (s, 3H), 3.33 (dd, *J* = 15.9, 6.0 Hz, 1H), 3.00 (d, *J* = 15.9 Hz, 1H), 1.70 – 1.21 (m, 6H), 0.86 (t, *J* = 6.4 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 161.7, 135.2, 130.3, 128.9, 128.3, 127.7, 127.1, 123.5, 121.3, 118.6, 104.7, 52.3, 51.2, 33.5, 32.4, 28.5, 22.6, 14.1. **HRMS** (FB+): Calculated for $C_{18}H_{21}NO_2$, 283.1572; found, 283.1573 ([M], 100).

(*S*)-*tert*-Butyl 5-butyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (12k): Following the typical procedure, the hydroamination/reduction/desulfonylation secuence of *exo*-**9k** (38.1 mg, 0.06 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane-EtOAc 3:1), **12k** (10.2 mg, 50%, yellow oil). Compound characterization should be performed immediately after purification in order to minimize the formation of decomposition products. **$[\alpha]_D^{20}$:** +11 (c = 1.30, $CHCl_3$), 65% *ee*. **HPLC:** Daicel Chiralpak IA, CO_2-methanol 99-1, flow rate 1 mL/min (λ = 230 nm), t_R: 16.9 min (*S*)-**12k** and 18.5 min (*R*)-**12k**. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.70 – 7.56 (m, 1H), 7.36 – 7.21 (m, 3H), 6.99 (d, *J* = 4.0 Hz, 1H), 6.56 (d, *J* = 4.1 Hz, 1H), 5.74 – 5.24 (m, 1H), 3.43 – 3.22 (m, 1H), 2.98 (d, *J* = 16.1 Hz, 1H), 1.64 (s, 9H), 1.45 – 1.24 (m, 6H), 0.87 (t, *J* = 6.5 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 160.5, 134.1, 129.8, 128.4, 128.1, 127.0, 126.6, 122.9, 117.82, 104.0, 79.9, 77.2, 51.8, 33.3, 32.3, 28.2, 22.3, 13.7. **HRMS** (FB+): Calculated for $C_{21}H_{27}NO_2$, 325.2035; found, 325.2042 ([M],

70).

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds, copies of HPLC chromatograms used to determine the enantiomeric purity and X-ray crystallographic data of compound *endo*-**7d** in CIF format are available free of charge via the Internet at http://pubs.acs.org

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