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Copper Carbenoid, Reactant and Catalyst for One-Pot Diazo Ester Coupling Cascade Rearrangement of Enediynes: Formation of Two Contiguous Tetrasubstituted Stereocenters

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Abstract: The copper-catalyzed reaction of enediynes with diazo esters leads to cyclic amino esters bearing two contiguous tetrasubstituted stereogenic centers through a one-pot, five-step cascade. Copper iodide catalyzes the formation of an intermediate 3-alkynoate and copper carbenoid promotes its reversible isomerization to the corresponding allenoate. The alkynoate-allenoate equilibrium is completely shifted to the right by the rapid consumption of the allenoate by Myers–Saito cyclization. This is followed by 1,5-H atom transfer and recombination of the resulting biradical. Memory of chirality phenomenon explains the high enantioselectivity.

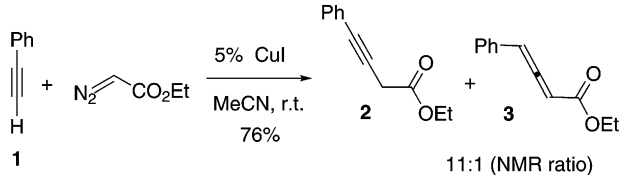
Keywords: allenes; carbenoids; diazo compounds; enediyne rearrangement; memory of chirality; radical reactions

Introduction

Interest in the chemistry of enediynes and enyne-allenes has dramatically increased since the discovery of the antitumor activity of natural enediynes.[1] The bioactivity of enediyne-connected amino esters, notably the evaluation of enediyne peptide conjugates as DNA damaging and protein cleavage agents, has been the subject of recent interest.[2] However, their chemical reactivity has hardly been explored.[3–6]

Investigations of the enantioselective rearrangement of this type of enediynes were recently started in our group.[7,8] The Myers–Saito cycloaromatization of substrates where the formation of the key allenic motive is activated by a base-catalyzed 1,3-proton shift from a propargylic sulfone was investigated first.[7] These reactions were shown to lead to cyclic amino esters bearing a tetrasubstituted stereogenic center adjacent to a tertiary one, in good yields and with a high level of enantioselectivity based on memory of chirality phenomenon.[9] The Crabbé homologation of related terminal enediynes leads directly through a one-pot procedure to polycyclic amino esters with a very high stereocontrol of the unique tetrasubstituted center.[8]

Searching to devise a one-pot route to potentially bioactive analogues[10] bearing two contiguous tetrasubstituted stereocenters, we were interested in applying the strategy published in 2004 by Fu for the preparation of 3-alkynoates.[11a] As exemplified in Scheme 1, in this very simple procedure alkyne **1**, 1 equivalent of ethyl diazoacetate (Figure 1), and



Scheme 1. Cu-catalyzed coupling of phenylacetylene with ethyl diazo ester.

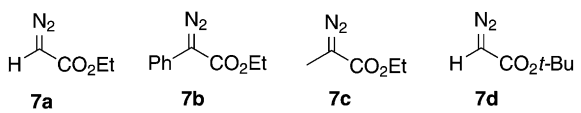
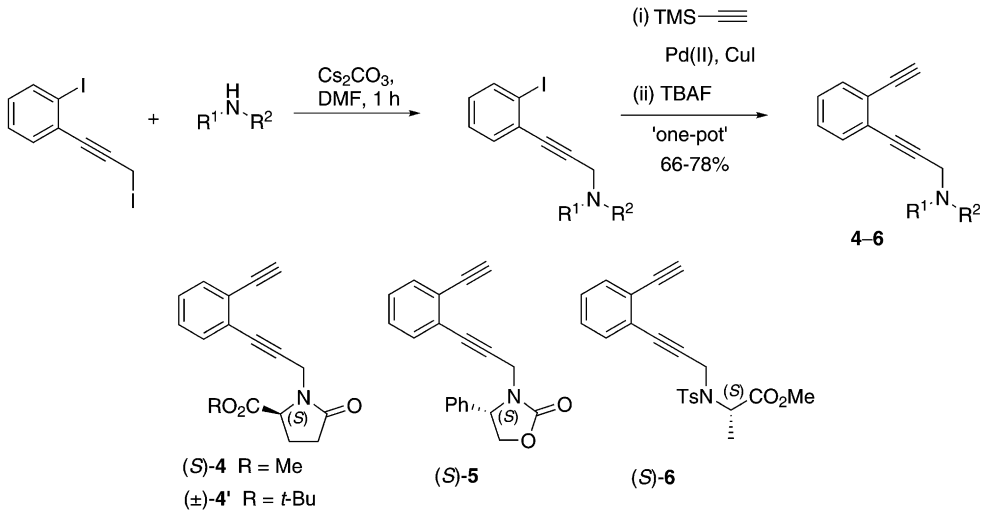


Figure 1. Structures of diazo esters **7**.



Scheme 2. Synthesis of substrates.

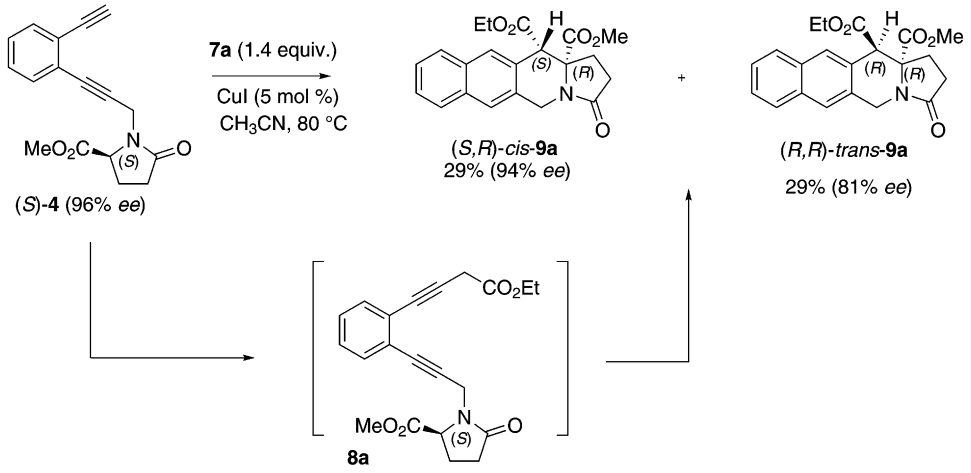
5 mol% of CuI in acetonitrile, were the only reactants. Alkynoate **2** was isolated in 76% yield together with atrace amount of the isomeric allene **3**. While we were applying this protocol to amino ester-connected terminal enediynes (**4–6**) (Scheme 2), another procedure, designed to give directly the allenoates was reported by Fox and co-workers.[12]

In this new protocol, the reaction was conducted in the presence of a ligand, and 2 equivalents of potassium carbonate in addition to the copper catalyst. A mechanism involving the insertion of a copper carbenoid in the alkyne C–H bond followed by reductive elimination and base-induced proton migration was proposed. In closely related studies, Wang and coworkers proposed a slightly different, alternative mechanism, in which, a copper acetylide intermediate was involved in the formation of trisubstituted allenes.[13]

Results and Discussion

As depicted in Scheme 2, the enantiopure substrates **4–6** (Figure 1) were readily available from nucleophilic substitution of 1-iodo-2-(3-iodoprop-1-ynyl)benzene by nitrogen-centered nucleophiles, derived from the chiral pool, followed by a one-pot Sonogashira-TBAF deprotection .

Under Fu's conditions, that is, at room temperature in the presence of 1 equivalent of diazo ester **7a** (Figure 1) in acetonitrile, **8a** was isolated in 42% yield from (*S*)-**4** (Scheme 3). Trace amounts of tetracyclic ester **9a** were simultaneously detected. Much to our satisfaction, in the absence of any base or ligand, the yield of **9a** increased up to 58%, when the reaction was performed in the presence of 1.4 equivalents of ethyl diazoacetate (**7a**) at 80 °C. Ester **9a** was isolated as 1:1 mixture of diastereoisomers with 94 and 81% *ee*, for the *cis* and *trans* isomers, respectively. The rela-



Scheme 3. Rearrangement of (*S*)-**4**.

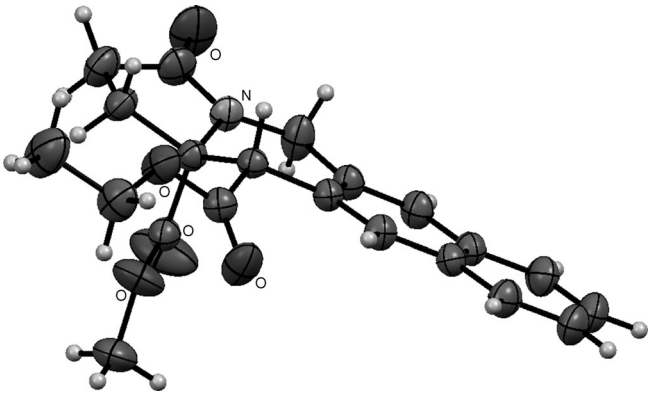


Figure 2. X-ray structure of *cis*-**9a**.

tive stereochemistry was confirmed by X-ray data (Figure 2).[14] A larger excess of diazo ester (2 equiv.) did not improve the overall yield. Like in all the reactions described in the following, the well-known dimerization of the diazo ester (to fumaric and maleic diesters) occurred which justifies the necessity of using **7** in excess.

Similar results were obtained when (*S*)-**4** (Table 1, entry 1) was allowed to react with diazo ester **7b** (Figure 1). At 80 °C, the overall yield was lowered by the competitive formation of the tetrayne resulting from a Glaser–Hay homocoupling reaction.[15]

Lowering the temperature to 50 °C (entry 2), allowed the tetracyclic product **9b** (Figure 3 and Figure 4) to be isolated in 65% yield in only 0.5 h, as a 1:1 mixture of diastereomers. At room temperature, the cascade process not only remained efficient, but it led to improved yields (Table 1, entry 3). Nearly total retention of configuration[16] (95 and 94% *ee* for the *trans* and the *cis* isomers, respectively) was observed. The synthesis of such compounds bearing two contiguous tetrasubstituted stereogenic centers is still a challenge for organic chemists.[17]

Tetracyclic compound *cis*-**9c** (Figure 3) was isolated in 30% and 93% *ee* (Table 1, entry 4) when (*S*)-**4** was reacted with **7c** (Figure 1). Competitive formation of

Table 1. Tandem alkynoate formation/cascade rearrangement of compounds **4**, **5** and **6**.

Entry	Substrate (*ee* [%])	**7**	Time [h]	Temperature [°C]	Product (*ee* [%])[a]	Yield [%][b]	Overall yield
1	(*S*)-**4** (96)	**7b**	0.5	80	*cis*-**9b** (92) *trans*-**9b** (94)	–	41[c]
2	(*S*)-**4** (96)	**7b**	0.5	50	*cis*-**9b** (92) *trans*-**9b** (94)	–	65
3	(*S*)-**4** (96)	**7b**	2	r.t.	*cis*-**9b** (94) *trans*-**9b** (95)	35 35	70
4	(*S*)-**4** (96)	**7c**	2	80	*cis*-**9c** (93) *trans*-**9c** (91) (*S*)-**11** (93)	30 13[d] 30	73
5	(*S*)-**4** (96)	**7d**	2	80	*cis*-**9d** (91) *trans*-**9d** (79)	28 35	63
6	(±)-**4′**	**7d**	2	80	(±)-*cis*-**9′d** (±)-*trans*-**9′d**	37 37	74
7	(*S*)-**5** (99)	**7b**	2	r.t.	*cis*-**10b** (95) *trans*-**10b** (91)	32 46	78
8	(*R*)-**5** (>99.5)	**7b**	2	r.t.	*ent-cis*-**10b** (97) *ent-trans*-**10b** (89)	39 45	83
9	(*S*)-**5** (99)	**7b**	2	r.t.	*cis*-**10b** (95) *trans*-**10b** (91)	28 40	68[e]
10	(*S*)-**5** (99)	**7c**	1	80	(*S,R*)-**10c** (97) **12**	34[f] 9[d]	44
11	(*S*)-**6** (99)	**7a**	2	80	*cis*-**13a** (80) *trans*-**13a** (88) **14a**	30 24 9	63
12	(*S*)-**6** (99)	**7b**	2	rt	*cis*-**13b** (94) *trans*-**13b** (92) **14b**	30 30 13	73

[a] The *ee* was determined by chiral HPLC.
[b] Isolated yield of the two diastereoisomers, unless otherwise stated.
[c] At 80 °C, the Glaser–Hay homocoupling product was formed in 40% yield.
[d] NMR yield (*trans*-**9c** and **12** could not be isolated as pure samples, their yield was determined from the crude mixture).
[e] 1 equiv. of **7b** was used
[f] The second diastereomer was detected in a trace amount.

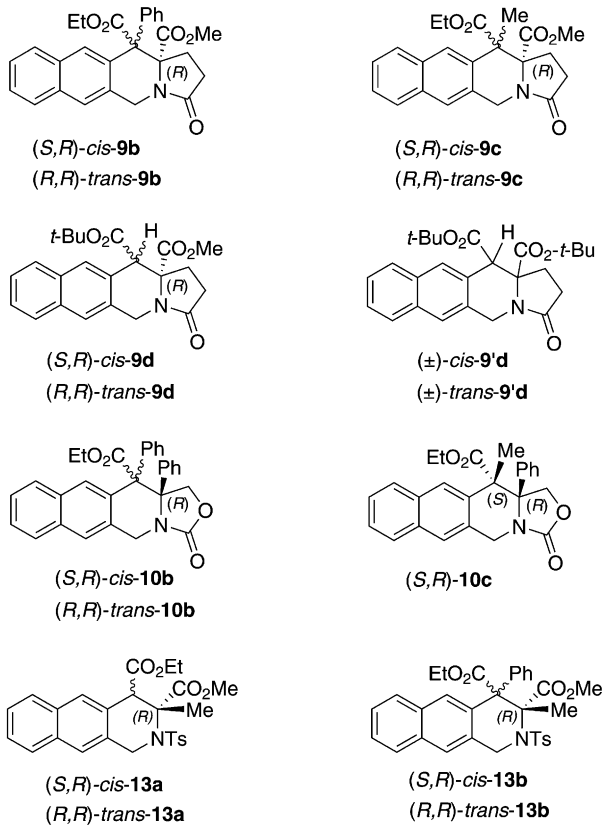


Figure 3. Structures of rearranged products **9**–**13**.

(*S*)-**11** (Figure 5) accounted for the 30% yield. It is interesting to note that the later was isolated in 93% *ee*.

Attempts to enhance the diastereoselectivity of the process by replacing the ethyl ester on the diazo ester by a bulkier ester group **7d** (Figure 1, namely, a *tert*-butyl ester) did not lead to the expected result. No significant effect was recorded either on the diastereoselectivity or on the enantioselectivity (entry 5). The introduction of two bulky *tert*-butyl esters, that is, reaction of (±)-**4′** with **7d**, did not improve the diastereomeric ratio of (±)-**9′d** either (Figure 3, Table 1, entry 6).

This rearrangement was then extended to substrates **5** and **6** with diazo esters **7a–c**.[18] An overall yield, as high as 83%, in isolated **10b** (Figure 3) was obtained from oxazolidinone (*R*)-**5** and diazo ester **7b** with a very high level of memory of chirality. The reaction performed on (*S*)-**5** led to the enantiomeric products (Table 1, entries 7 and 8).

As already observed for the reaction of (*S*)-**4** with **7c**, (*S*)-**5** led to **12** (Figure 5) in 9% NMR yield. A closely related behaviour was observed when alkyne (*S*)-**6** was submitted to the above described protocol and allowed to react with either **7a** or **7b**. Two diastereomers of **13a** were formed in 30% (80% *ee*) and 24% (88% *ee*) yields, respectively, (Table 1, entry 11), together with **14a**, isolated in 9% yield (Figure 3 and Figure 5).

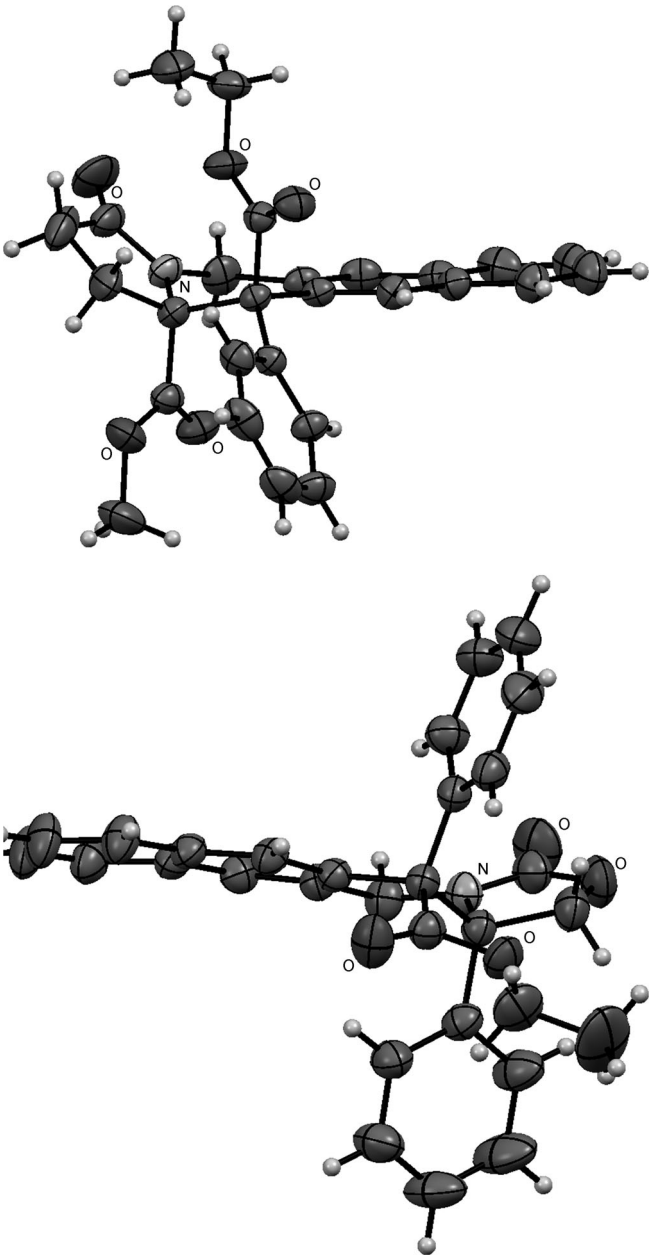


Figure 4. X-ray structures of *trans*-**9b** and *trans*-**10b**.

Very similar data were obtained from the reaction of (*S*)-**6** with **7b**. Tetrahydrobenzoisoquinolines (*R*,*R*)-**13b**[16] (Figure 3 and Figure 6) and (*S*,*R*)-**13b**, bearing also two contiguous tetrasubstituted stereocenters, were obtained in a 1:1 ratio (60% yield) with 94 and 92% *ee* for the *cis* and the *trans* isomers, respectively (Table 1, entry 12). Alkene **14b** (Figure 5) was formed in 13% yield.

Mechanistic Investigations

The involvement of a Myers–Saito cyclization in the rearrangement process made it obvious that, in the

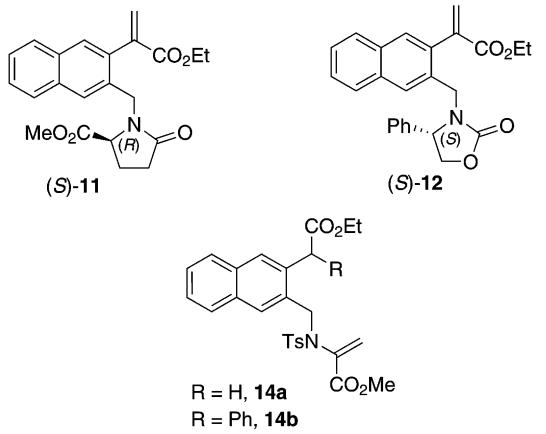


Figure 5. Alkenes **11**, **12** and **14**.

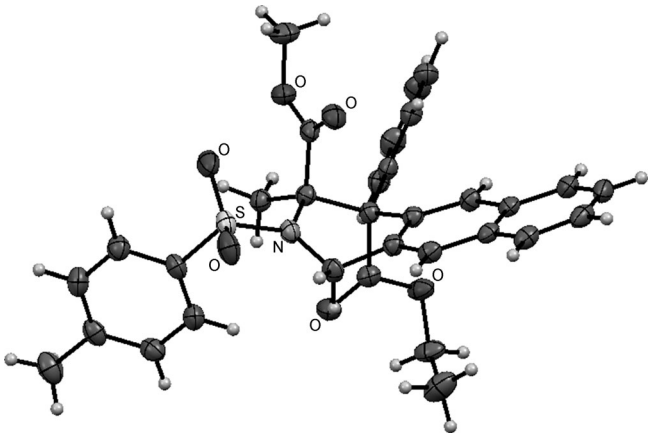


Figure 6. Determination of absolute configuration of (*R,R*)-*trans*-**13b** by X-ray analysis.

presence of the copper catalyst and the diazo ester, and in the absence of any additional base, an equilibrium was established between the alkynoate and the isomeric allenoate. The base-catalyzed isomerization of 3-alkynoates to allenoates is known to be reversible.[19] Furthermore, complexation could increase either the propargylic proton acidity or the stability of the allenoate.[20] The fact that reactions involving **7b** could be promoted at room temperature is consistent with both proposals.

In the case of the enediyne substrates, the equilibrium would be completely shifted to the right by the rapid consumption of the allenoate by Myers–Saito cyclization.

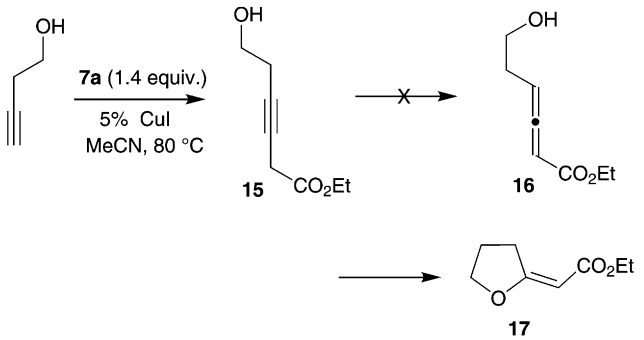
When strictly 1 equivalent of diazo ester was used, the overall yield was decreased by only 10% (substrate (*S*)-**5**, Table 1, entry 9). This led us to propose that the copper carbenoid intermediate would play a double role. This was confirmed by the following experiments: (i) **8a** was shown to be an intermediate in the cascade reaction. An isolated sample of **8a** led to **9a** when it was allowed to react with mesoporous silica grafted with a tertiary amino group (GA-SBA15) as the base. (ii) No reaction occurred when **8a** was submitted to the action of either diazo ester **7a** alone, or to the action of copper iodide alone. Both reagents are necessary for the rearrangement to proceed. (iii) A catalytic amount of diazo ester (40%) and copper iodide (5%) led to the complete conversion of alkynoate **8a** into **9a**.

Therefore in this process, the copper carbenoid[21] would play at the same time the role of reagent and that of 1,3-proton shift catalyst.

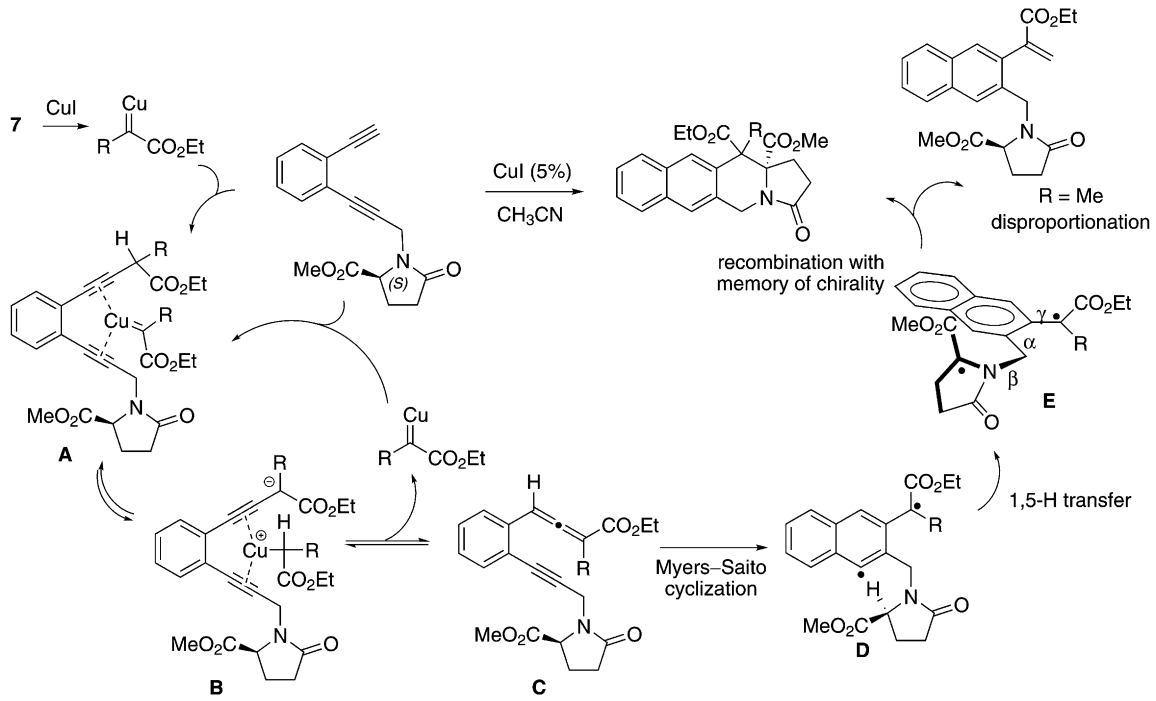
In order to validate this hypothesis we have applied the same procedure to compound **15**. Tan has recently reported that the isomeric allenoate **16** could be trapped intramolecularly to afford 2-alkylidenetetrahydrofuran **17** through Michael addition.[22] Surprisingly, when 3-butyn-1-ol was submitted to the action of 1.4 equivalents of **7a** at 80 °C, the cyclized product was not observed (Scheme 4). Only alkynoate **15** was formed.

From these observations, it can be postulated that chelation of the copper carbenoid by the *ortho*-diyne is required to activate the alkyne-allene isomerization *via* 1,3-proton migration. The mechanism proposed for the overall five-step rearrangement is detailed in Scheme 5, taking the reaction of enediyne **4** as a prototype. The necessity of an additional ligand is in agreement with the observations made by Fox[12] and Wang.[13] In our protocol, the only difference resides in the absence of any base.

As shown in Scheme 5, once formed, the enyne-allene **C** undergoes fast Myers–Saito cycloaromatization to give biradical **D**. The latter rearranges according to a 1,5-H atom transfer. Subsequent recombination of the newly formed biradical **E** gives the constrained heterocyclic targets. This last step is crucial for the memory of chirality. The recombination of radicals should be faster than the rates of rotations around the α and β bonds that would racemize the conformationally chiral captodative radical center in **E**.[7,8]



Scheme 4. Tentative tandem Cu-catalyzed coupling of 3-butynol with **7a**/Michael cyclization.



Scheme 5. Proposed mechanism.

Competitive disproportionation occurs when a methyl group is linked to one of the radical centers in intermediate **E**. This disproportionation had previously been observed with substrates bearing a sulfone group in the alanine series.[7,8] Alkene side products were also isolated in the case where the methyl group is attached to the benzylic radical center. In this case, the formal 1,7-hydrogen atom transfer occurs with memory of chirality (formation of **11** in 93% *ee*).

Conclusions

The copper-catalyzed reaction of terminal enediynes **4–6** with diazo esters **7a–d** leads directly through a five-step cascade rearrangement to the formation of heterocyclic analogues of aspartic esters bearing contiguous tetrasubstituted stereogenic centers. The phenomenon of memory of chirality explains the high enantioselectivity of the process. This reaction proceeds *via* a copper carbenoid, which acts both as reactant and as a catalyst by promoting the isomerization the intermediate 3-alkynoates to the transient allenoates.

Experimental Section

All reactions were performed under an argon atmosphere. CH_3CN (Teflon-sealed) was HPLC grade. THF was distilled over sodium benzophenone ketyl prior to use. Purifications were performed on silica gel 60 Å (70–230 mesh). Analytical thin layer chromatography was performed on pre-coated silica gel plates. Visualization was accomplished by UV (254 nm) and with phosphomolybdic acid in ethanol. Optical rotations were measured on a polarimeter at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm and are reported relative to internal $CHCl_3$ (^{1}H, $\delta = 7.26$) and $CDCl_3$ (^{13}C, $\delta = 77.16$). Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Coupling constants (*J*) are listed in the order of the multiplicity assignment and are reported in Hertz (Hz). APT was used for the assignment of ^{13}C spectra. All melting points were uncorrected.

Purified compounds were analyzed by chiral HPLC with double detection, with UV and circular dichroïsm (CD) detectors. The solvents for chiral chromatography (*n*-hexane, 2-PrOH, ethanol) were HPLC grade, they were degassed and filtered on a 0.45 μm membrane before use. The columns used are Chiralpak IA, AD-H, Chiralpak IB, OD-3, Chiralpak IC and Lux-Cellulose-4. Enantiomeric excesses were determined by integration of the peaks on the chromatograms obtained by UV detection at 230, 240 or 254 nm, and confirmed by circular dichroïsm detection at 254 nm. The sign given by the on-line circular dichroïsm detector for one enantiomer is the sign in the solvent used for the chromatographic separation. Retention times Rt (in minutes), retention factors $k_i = (Rt_i - Rt_0)/Rt_0$, enantioselectivity factor $\alpha = k_2/k_1$, and resolution are given. Rt_0 was determined by injection of tris-*tert*-butylbenzene.

(*S*)-Methyl 1-[3-(2-ethynylphenyl)prop-2-ynyl]-5-oxopyrrolidine-2-carboxylate (4)

To (*S*)-methyl 1-[3-(2-iodophenyl)prop-2-ynyl]-5-oxopyrrolidine-2-carboxylate[7a] (3 g, 7.83 mmol) in THF (75 mL), Et_3N (15 mL) was added and the reaction mixture was degassed with argon bubbling for 15 min. Then the catalyst, $Pd(PPh_3)_2Cl_2$ (110 mg, 2 mol%), and the co-catalyst, CuI (60 mg, 4 mol%), were added to the reaction mixture. After stirring for 10 min trimethylsilylacetylene (1.66 mL, 11.74 mmol) was added and the reaction mixture was stirred for additional 2 h at room temperature. The conversion of the starting material was monitored by TLC. A solution of TBAF (12 mL of 1 M in THF, 12 mmol) was then added and the reaction mixture stirred further for 30 min. The reaction mixture was then passed through a small celite bed, concentrated and the residue was purified by column chromatography on silica gel, using ethyl acetate/pentane (3:7) as eluent, to afford compound **4** as a brown liquid: yield: 1.72 g (78% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.48$–7.45 (1 H, m, CH_{ar}), 7.40–7.38 (1 H, m, CH_{ar}), 7.29–7.25 (2 H, m, CH_{ar}), 4.89 (1 H, d, $J = 17.8$ Hz, CH_2N, A part of an AB pattern), 4.65–4.62 (1 H, m, $CHCO_2Me$), 4.02 (1 H, d, $J = 17.8$ Hz, CH_2N, B part of an AB pattern), 3.75 (3 H, s, CO_2CH_3), 3.31 (1 H, s, C≡CH), 2.49–2.36 (3 H, m, CH_2), 2.13–2.10 (1 H, m, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 174.5 (CO), 172.2 (CO), 132.6 (CH_{ar}), 132.1 (CH_{ar}), 128.6 (CH_{ar}), 128.3 (CH_{ar}), 125.4 (C_{ar}), 124.7 (C_{ar}), 86.7 ($C_{C\equiv C}$), 83.3 ($C_{C\equiv C}$), 82.2 ($C_{C\equiv C}$), 81.1 ($C_{\equiv CH}$), 58.4 (CH), 52.6 (OCH_3), 32.3 (CH_2N), 29.6 (CH_2), 22.9 (CH_2); HR-MS (ESI): $m/z = 282.1125$, calcd for $[M+H]^+$ $C_{17}H_{16}NO_3$: 282.1125. Chiral HPLC separation of enantiomers (Chiralpak IC, hexane/ethanol 8/2, 1 mL min^{-1}, detection UV and CD 254 nm): Rt(*S*) = 13.41, Rt(*R*) = 14.78, k(*S*) = 3.47, k(*R*) = 3.93, $\alpha = 1.13$ and Rs = 1.95; *ee* = 96%; $[\alpha]_D^{25}$: +12.4 (c 0.78, CH_2Cl_2).

tert-Butyl 1-[3-(2-Iodophenyl)prop-2-ynyl)-5-oxopyrrolidine-2-carboxylate [(±)-1′]

This compound was synthesized with slight modification according to a known methodology.[23] 1-Iodo-2-(3-iodoprop-1-ynyl)benzene[7a] (2.3 g, 6.25 mmol) was dissolved in DMF (15 mL) and Cs_2CO_3 (3.1 g, 9.38 mmol) was added followed by *tert*-butyl oxopyrrolidine-2-carboxylate[24] (1.4 g, 7.5 mmol), the reaction mixture was stirred for 1 h under argon, poured into water (30 mL), and then extracted with EtOAc (3 × 30 mL). The organic layer was washed with water (2 × 30 mL) and brine (30 mL) and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified over a short pad of silica gel (pentane/EtOAc, 90/10) to afford (±)-**1′** as brown oil; yield: 2.26 g (85% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.81$ (1 H, dd, $J = 8.0$ and 1.0 Hz, CH_{ar}), 7.40 (1 H, dd, $J = 7.8$ and 1.8 Hz, CH_{ar}), 7.28 (1 H, td, $J = 7.5$ and 1.0 Hz, CH_{ar}), 7.00 (1 H, td, $J = 8.0$ and 1.8 Hz, CH_{ar}), 4.93 (1 H, d, $J = 17.8$ Hz, CH_2N, A part of an AB pattern), 4.57–4.54 (1 H, m, CH), 3.99 (1 H, d, $J = 17.8$ Hz, CH_2N, B part of an AB pattern), 2.53–2.33 (3 H, m), 2.12–2.03 (1 H, m), 1.47 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.7$ (CO), 170.9 (CO), 138.8 (CH_{ar}), 132.9 (CH_{ar}), 129.8 (CH_{ar}), 129.2 (C_{ar}), 128.0 (CH_{ar}), 100.8 (C_{ar}), 86.8 ($C_{C\equiv C}$), 86.7 ($C_{C\equiv C}$), 82.5 (C), 59.5 (CH), 32.3 (CH_2N), 29.7 (CH_2), 28.2 ($3\,CH_3$), 22.9 (CH_2); HR-MS (ESI): $m/z = 426.0563$, calcd. for $[M+H]^+$ $C_{18}H_{21}NO_3I$: 426.0561.

tert-Butyl 1-[3-(2-Ethynylphenyl)prop-2-ynyl]-5-oxopyrrolidine-2-carboxylate (±)-4′

Enediyne **4′** was prepared as described above for **4** from (±)-*tert*-butyl 1-[3-(2-iodophenyl)prop-2-ynyl]-5-oxopyrrolidine-2-carboxylate (700 mg, 1.65 mmol), $Pd(PPh_3)_2Cl_2$ (23 mg, 2 mol%), CuI (12.5 mg, 4 mol%), trimethylsilylacetylene (0.46 mL, 3.29 mmol), Et_3N (4 mL) in THF (10 mL). The reaction mixture was stirred for 2 h. The deprotection was carried out with TBAF solution (1 M in THF) (5 mL, 5 mmol). The product was purified by column chromatography (20% ethyl acetate/pentane) to afford compound **4** as a brown liquid; yield: 400 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.48$–7.46 (1 H, m, CH_{ar}), 7.41–7.38 (1 H, m, CH_{ar}), 7.27–7.25 (2 H, m, CH_{ar}), 4.92 (1 H, d, $J = 17.6$ Hz, CH_2N, A part of an AB pattern), 4.52–4.49 (1 H, m, CH), 3.98 (1 H, d, $J = 17.8$ Hz, CH_2N, B part of an AB pattern), 3.28 (1 H, s, -C≡CH), 2.48–2.32 (3 H, m), 2.11–2.02 (1 H, m), 1.45 (9 H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.5$ (CO), 170.8 (CO), 132.6 (CH_{ar}), 132.0 (CH_{ar}), 128.6 (CH_{ar}), 128.2 (CH_{ar}), 125.5 (C_{ar}), 124.7 (C_{ar}), 86.8 (C), 83.1 ($C_{C\equiv C}$), 82.4 ($C_{C\equiv}$), 82.2 ($C_{C\equiv C}$), 81.0 ($C_{\equiv H}$), 59.2 (CH), 32.2 (CH_2N), 29.6 (CH_2), 28.0 ($3\,CH_3$), 22.9 (CH_2); HR-MS (ESI): $m/z =$ 324.1593, calcd. for $[M+H]^+$ $C_{20}H_{22}NO_3$: 324.1594.

(*S*)-3-[3-(2-Ethynylphenyl)prop-2-ynyl]-4-phenyloxazolidin-2-one (5)

Enediyne **5** was prepared, as described above, from (*S*)-3-[3-(2-iodophenyl)prop-2-ynyl]-4-phenyloxazolidin-2-one[7a] (3.20 g, 7.94 mmol), $Pd(PPh_3)_2Cl_2$ (111.4 mg, 2 mol%), CuI (60.5 mg, 4 mol%), trimethylsilylacetylene (1.68 mL, 11.90 mmol), Et_3N (16 mL) in THF (80 mL). The reaction mixture was stirred for 12 h. The deprotection was carried out with TBAF solution (1 M in THF) (12 mL, 12 mmol). The product was purified by column chromatography (20% ethyl acetate/pentane) to yield compound **5** as a brown liquid; yield: 1.57 g (66% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$–7.36 (1 H, m, CH_{ar}), 7.29–7.25 (5 H, m, CH_{ar}), 7.17–7.12 (3 H, m, CH_{ar}), 5.01 (1 H, t, $J = 8.3$ Hz), 4.55 (1 H, d, $J = 17.8$ Hz, CH_2N, A part of an AB pattern), 4.53 (1 H, t, $J = 8.8$ Hz), 4.05 (1 H, t, $J = 8.0$ Hz), 3.51 (1 H, d, $J = 17.8$ Hz, CH_2N, B part of an AB pattern), 3.15 (1 H, s, -C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 157.9$ (CO), 136.9 (C_{ar}), 132.7 (CH_{ar}), 132.2 (CH_{ar}), 129.4 ($2\,CH_{ar}$), 129.3 (CH_{ar}), 128.7 (CH_{ar}), 128.4 (CH_{ar}), 127.5 ($2\,CH_{ar}$), 125.4 (C_{ar}), 124.8 (C_{ar}), 86.2 ($C_{C\equiv C}$), 83.5 ($C_{C\equiv C}$), 82.4 ($C_{C\equiv C}$), 81.2 ($C_{\equiv CH}$), 70.0 (OCH_2), 59.0 (CH), 33.1 (CH_2N); HR-MS (ESI): $m/z = 302.1176$, calcd. for $[M+H]^+$ $C_{20}H_{16}NO_2$: 302.1176. Chiral HPLC separation of enantiomers (Chiralpak IB, hexane/ethanol 9/1, 1 mL min^{-1}, detection UV 230 nm and CD 254 nm): Rt(*R*) = 9.63, Rt(*S*) = 10.61, k(*R*) = 2.21, k(*S*) = 2.54, $\alpha = 1.15$; *ee* = 99%; $[\alpha]_D^{25}$: +169.7 (*c* 0.67, CH_2Cl_2).

(*S*)-Methyl-2-{*N*-[3-(2-ethynylphenyl)prop-2-ynyl]-4-methylphenylsulfonamido}propanoate (6)

Enediyne **6** was prepared from (*S*)-methyl 2-{*N*-[3-(2-iodophenyl)prop-2-ynyl]-4-methylphenylsulfonamido}propano-

ate[7a] (4.00 g, 8.04 mmol), $Pd(PPh_3)_2Cl_2$ (113 mg, 2 mol%), CuI (61.3 mg, 4 mol%), trimethylsilylacetylene (1.7 mL, 12.06 mmol), Et_3N (20 mL) in THF (100 mL). The reaction mixture was stirred for 2 h. Deprotection was carried out with TBAF solution (1 M in THF) (12.5 mL, 12.5 mmol). The product was purified by column chromatography (20% ethyl acetate/pentane) to afford compound **6** as a brown liquid; yield: 2.45 g (77% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (2H, d, J = 8.3 Hz, CH_{ar}), 7.48 (1H, m, CH_{ar}), 7.29–7.23 (5H, m, CH_{ar}), 4.71 (1H, q, J = 7.3 Hz, $CHCH_3$), 4.64 (1H, d, J = 18.8 Hz, CH_2N, A part of an AB pattern), 4.41 (1H, d, J = 18.8 Hz, CH_2N, B part of an AB pattern), 3.65 (3H, s, CO_2CH_3), 3.24 (1H, s, -C≡CH), 2.36 (3H, s, CH_3), 1.57 (3H, d, J = 7.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0 (CO), 143.6 (C_{ar}), 137.3 (C_{ar}), 132.7 (CH_{ar}), 132.2 (CH_{ar}), 129.6 (2CH_{ar}), 128.5 (CH_{ar}), 128.3 (CH_{ar}), 127.7 (2CH_{ar}), 125.5 (C_{ar}), 124.6 (C_{ar}), 88.6 ($C_{C\equiv C}$), 83.0 ($C_{C\equiv C}$), 82.0 ($C_{C\equiv C}$), 81.1 ($C_{\equiv CH}$), 55.1 ($CHCH_3$), 52.4 (OCH_3), 35.2 (CH_2N), 21.6 (CH_3 of Ts), 16.5 ($CHCH_3$); HR-MS (ESI): m/z = 396.1264, calcd. for $[M+H]^+$ $C_{22}H_{22}NO_4S$: 396.1264. Chiral HPLC separation of enantiomers (Chiralcel OD-3, hexane/2-propanol 8/2, 1 mL min^{-1}, detection UV and CD 254 nm): Rt(S) = 12.04, Rt(R) = 13.00, k(S) = 3.01, k(R) = 3.33, α = 1.11 and Rs = 1.22; ee = 99%. $[\alpha]_D^{25}$: −35.8 (c 0.5, CH_2Cl_2).

General Protocol for the One-Pot Copper-Catalyzed Reaction of Diazoesters 7 with Terminal Alkynes and Cascade Rearrangement

Coupling of (S)-4 with 7a: Argon gas was bubbled through a solution of enediyne (*S*)-**4** (200 mg, 0.71 mmol) and diazo ester **7a** (113 mg, 1 mmol) in dry acetonitrile (500 μL) for 10 min. Then CuI (7 mg, 5 mol%) was added, and the reaction mixture was heated for 2 h at 80 °C. Then the reaction mixture was evaporated under vacuum and the residue redissolved in DCM. After filtration through a celite bed, the filtrate was concentrated under vacuum and the crude product was purified by column chromatography on silica gel using 3:7 ethyl acetate:pentane as eluent. This led to the isolation of (12*S*,12a*R*)-**9a** (yield: 75 mg, 29%, ee = 94%) and (12*R*,12a*R*)-**9a** (yield: 75 mg, 29%, ee = 81%).

(12S,12aR)-12-Ethyl 12a-methyl 3-oxo-1,2,3,5,12,12a-hexahydrobenzo[g]pyrrolo[1,2-b]isoquinoline-12,12a-dicarboxylate (cis-9a): White solid; mp 160.4 °C (CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (1H, s, CH_{ar}), 7.80–7.77 (2H, m, CH_{ar}), 7.67 (1H, s, CH_{ar}), 7.49–7.45 (2H, m, CH_{ar}), 5.16 (1H, d, J = 16.1 Hz, CH_2N, A part of an AB pattern), 4.60 (1H, d, J = 15.8 Hz, CH_2N, B part of an AB pattern), 4.23 (1H, s, CH), 4.26–4.12 (2H, AB part of an ABX_3 pattern, OCH_2), 3.70 (3H, s, OCH_3), 2.75 (1H, ddd, J = 1.5, 8.3 and 12.8 Hz), 2.57–2.51 (1H, m), 2.32 (1H, ddd, J = 1.5, 9.0 and 16.6 Hz), 2.11 (1H, m), 1.27 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6 (CO), 172.2 (CO), 170.8 (CO), 132.7 (C_{ar}), 132.6 (C_{ar}), 132.0 (C_{ar}), 128.4 (CH_{ar}), 128.1 (C_{ar}), 127.8 (CH_{ar}), 127.6 (CH_{ar}), 126.9 (CH_{ar}), 126.2 (CH_{ar}), 125.3 (CH_{ar}), 67.2 (C-12a), 61.9 (OCH_2), 54.9 (CH), 52.9 (OCH_3), 41.9 (CH_2N), 32.9 (CH_2), 30.0 (CH_2), 14.2 (CH_3); HR-MS (ESI): m/z = 368.1499, calcd. for $[M+H]^+$ $C_{21}H_{22}NO_5$: 368.1492. Chiral HPLC separation of enantiomers (Chiralpak IC, hexane/ethanol 7/3, 1 mL min^{-1}, detection UV 230 nm and CD 254 nm): Rt(12*S*,12a*R*) = 23.95, Rt(12*R*,12a*S*) = 31.23, k(12*S*,12a*R*) = 6.98, k(12*R*,12a*S*) = 9.41, α = 1.35 and Rs = 4.32; ee = 94%; $[\alpha]_D^{30}$: −71.4 (c 0.63, CH_2Cl_2). The structure was confirmed by X-ray crystallography.

(12R,12aR)-12-Ethyl 12a-methyl 3-oxo-1,2,3,5,12,12a-hexahydrobenzo[g]pyrrolo[1,2-b]isoquinoline-12,12a-dicarboxylate (trans-9a): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (2H, m, CH_{ar}), 7.74 (1H, s, CH_{ar}), 7.70 (1H, s, CH_{ar}), 7.49–7.43 (2H, m, CH_{ar}), 5.15 (1H, d, J = 17.3 Hz, CH_2N, A part of an AB pattern), 4.68 (1H, d, J = 17.1 Hz, CH_2N, B part of an AB pattern), 4.63 (1H, s, CH), 4.16–4.00 (2H, AB part of an ABX_3 pattern, OCH_2), 3.54 (3H, s, OCH_3), 2.64–2.54 (1H, m), 2.52–2.36 (3H, m), 1.17 (3H, t, J = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7 (CO), 172.6 (CO), 170.0 (CO), 133.2(C_{ar}), 132.2 (C_{ar}), 129.4 (C_{ar}), 128.5 (CH_{ar}), 128.0 (C_{ar}), 127.7 (CH_{ar}), 127.5 (CH_{ar}), 126.8 (CH_{ar}), 126.3 (CH_{ar}), 126.2 (CH_{ar}), 67.2 (C-12a), 61.8 (OCH_2), 53.3 (CH), 52.1 (OCH_3), 43.0 (CH_2N), 29.5 (CH_2), 27.8 (CH_2), 14.1 (CH_3); HR-MS (ESI): m/z = 368.1494, calcd. for $[M+H]^+$ $C_{21}H_{22}NO_5$: 368.1492. Chiral HPLC separation of enantiomers (Chiralpak IC, hexane/ethanol 7/3, 1 mL min^{-1}, detection UV 230 nm and CD 254 nm): Rt(12*S*,12a*S*) = 14.21, Rt(12*R*,12a*R*) = 15.99, k(12*S*,12a*S*) = 3.74, k(12*R*,12a*R*) = 4.33, α = 1.16 and Rs = 2.20; ee = 81%; $[\alpha]_D^{30}$: −34.9 (c 0.91, CH_2Cl_2).

Coupling of (S)-4 with 7b: Enediyne (*S*)-**4** (200 mg, 0.71 mmol), diazo ester **7b**[25] (190 mg, 1.00 mmol) and CuI (7 mg, 5 mol%) in dry acetonitrile (500 μL) were allowed to react for 2 h at room temperature. The products were purified by column chromatography (30% ethyl acetate/pentane) to afford (12*R*,12a*R*)-9b (yield: 109 mg, 35%, ee = 94%) and (12*S*,12a*R*)-**9b** (yield: 109 mg, 35%, ee = 95%).

(12R,12aR)-12-Ethyl 12a-methyl 3-oxo-12-phenyl-1,2,3,5,12,12a-hexahydrobenzo[g]pyrrolo[1,2-b]isoquinoline-12,12a-dicarboxylate (cis-9b): Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (1H, s, CH_{ar}), 7.76 (1H, d, J = 8.0 Hz, CH_{ar}), 7.71 (1H, d, J = 8.0 Hz, CH_{ar}), 7.68 (1H, s, CH_{ar}), 7.43 (1H, td, J = 6.8 and 1.2 Hz, CH_{ar}), 7.37 (1H, td, J = 6.8 and 1.2 Hz, CH_{ar}), 7.30 (3H, m, CH_{ar}), 6.91–6.89 (2H, m, CH_{ar}), 5.41 (1H, d, J = 17.8 Hz, CH_2N, A part of an AB pattern), 4.44 (2H, q, J = 7.0 Hz, OCH_2), 4.30 (1H, d, J = 17.6 Hz, CH_2N, B part of an AB pattern), 3.65 (3H, s, OCH_3), 2.87–2.79 (1H, m), 2.33–2.20 (2H, m), 1.4 (3H, t, J = 7.0, CH_3), 1.37–1.30 (1H, superimposed m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3 (CO), 172.2 (CO), 172.1 (CO), 141.3 (C_{ar}), 134.8(C_{ar}), 132.5 (C_{ar}), 132.0 (C_{ar}), 130.7 (CH_{ar}), 129.0 (2CH_{ar}), 128.7 (CH_{ar}), 128.6 (C_{ar}), 128.4 (2CH_{ar}), 127.7 (CH_{ar}), 126.8 (CH_{ar}), 126.6 (CH_{ar}), 125.7 (CH_{ar}), 124.3 (CH_{ar}), 71.4 (C-12a), 62.0 (OCH_2), 60.9 (C_{12}), 53.0 (OCH_3), 41.7 (CH_2N), 29.1 (CH_2), 26.9 (CH_2), 14.2 (CH_3); HR-MS (ESI): m/z = 444.1803, calcd. for $[M+H]^+$ $C_{27}H_{26}NO_5$: 444.1805. Chiral HPLC separation of enantiomers (Chiralpak IC, hexane/ethanol 8/2, 1 mL min^{-1}, detection UV 230 nm and CD 254 nm): Rt(12*R*,12a*R*) = 18.44, Rt(12*S*,12a*S*) = 20.22, k(12*R*,12a*R*) = 5.15, k(12*S*,12a*S*) = 5.74, α = 1.12 and Rs = 1.74; ee = 94%; $[\alpha]_D^{30}$: +2 (c 4.47, CH_2Cl_2).

(12S,12aR)-12-Ethyl 12a-methyl 3-oxo-12-phenyl-1,2,3,5,12,12a-hexahydrobenzo[g]pyrrolo[1,2-b]isoquinoline-12,12a-dicarboxylate (trans-9b): Yellowish solid; mp 181.2 °C (CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (1H, s, CH_{ar}), 7.71 (1H, d, J = 8.3 Hz, CH_{ar}), 7.66 (1H, s, CH_{ar}), 7.57 (1H, d, J = 8.3 Hz, CH_{ar}), 7.38 (1H, pseudo t, J =

7.3 Hz, CH_{ar}), 7.30 (1H, pseudo t, $J=7.3$ Hz, CH_{ar}), 7.31–7.26 (5H, m, CH_{ar}), 5.18 (1H, d, $J=17.6$ Hz, CH_2N, A part of an AB pattern), 4.73 (1H, d, $J=17.6$ Hz, CH_2N, B part of an AB pattern), 3.98–3.86 (2H, AB part of an ABX_3 pattern, OCH_2), 3.14 (3H, s, OCH_3), 2.79–2.76 (1H, m), 2.46–2.37 (3H, m), 0.89 (3H, t, $J=7.0$ Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.6$ (CO), 171.4 (CO), 169.7 (CO), 136.9 (C_{ar}), 132.7 (C_{ar}), 131.7 (C_{ar}), 131.6 (C_{ar}), 131.2 (C_{ar}), 130.6 (CH_{ar}), 130.0 (CH_{ar}), 128.3 (CH_{ar}), 128.0 ($2\,CH_{ar}$), 127.9 ($2\,CH_{ar}$), 127.1 (CH_{ar}), 126.8 (CH_{ar}), 125.7 (CH_{ar}), 124.7 (CH_{ar}), 70.9 (C-12a), 62.7 (C-12), 61.9 (OCH_2), 52.3 (OCH_3), 42.9 (CH_2N), 29.5 (CH_2), 26.4 (CH_2), 13.7 (CH_3); HR-MS (ESI): $m/z=444.1803$, calcd. for $[M+H]^+$ $C_{27}H_{26}NO_5$: 444.1805. Chiral HPLC separation of enantiomers (Chiralpak IC, hexane/ethanol 5/5, 1 mL min^{-1}, detection UV 230 nm and CD 254 nm): Rt(12*S*,12a*R*) = 13.83, Rt(12*R*,12a*S*) = 26.05, k(12*S*,12a*R*) = 3.61, k(12*R*,12a*S*) = 7.68, $\alpha=2.12$ and Rs = 9.40; *ee* = 95%; $[\alpha]_D^{30}$: −13.4 (*c* 3.57, CH_2Cl_2). The structure was confirmed by X-ray crystallography.

Coupling of (S)-4 with 7c: Enediyne (*S*)-**4** (100 mg, 0.35 mmol) was allowed to react with diazo ester **7c**[26] (64 mg, 0.49 mmol) and CuI (3.5 mg, 5 mol%) in dry acetonitrile (250 μL) for 1 h at 80 °C. The products were purified by column chromatography (DCM) to yield (12*R*,12a*R*)-**9c** (yield: 40 mg, 30%, *ee* = 91%) and olefin (*S*)-**11** (yield: 40 mg, 30%, *ee* = 93%). The *cis* diastereomer, detected in the crude mixture (13% NMR yield, 93% ee) could not be isolated as a pure sample.

(12R, 12aR)-12-Ethyl 12a-methyl 12-methyl-3-oxo-1,2,3,5,12,12a-hexahydrobenzo[g]pyrrolo[1,2-b]isoquinoline-12,12a-dicarboxylate (trans-9c): Colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.94$ (1H, s, CH_{ar}), 7.77 (2H, t, $J=8.5$ Hz, CH_{ar}), 7.63 (1H, s, CH_{ar}), 7.48–7.41 (2H, m, CH_{ar}), 5.12 (1H, d, $J=17.3$ Hz, CH_2N, A part of an AB pattern), 4.66 (1H, d, $J=17.0$ Hz, CH_2N, B part of an AB pattern), 4.39–4.20 (2H, AB part of an ABX_3 pattern, OCH_2), 3.55 (3H, s, OCH_3), 2.77–2.70 (1H, m), 2.63–2.54 (1H, m), 2.49–2.39 (2H, m), 1.62 (3H, s, CH_3), 1.31 (3H, t, $J=7.0$ Hz, CH_3). The stereochemical assignment was supported by a 2D NOESY spectrum, which showed correlation cross-peaks between the protons of the singlet Me group at 1.62 ppm and those of the OMe group at 3.55 ppm.

The characteristic ^1H NMR signals of the minor *cis* diastereomer are: $\delta=5.06$ (1H, d, $J=16.8$ Hz), 4.74 (1H, d, $J=16.8$ Hz), 3.44 (3H, s), 2.81–2.73 (1H, m), 1.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.9$ (CO), 172.3 (CO), 171.9 (CO), 135.4 (C_{ar}), 132.4 (C_{ar}), 132.3 (C_{ar}), 129.1 (C_{ar}), 128.1 (CH_{ar}), 127.1 (CH_{ar}), 126.6 (CH_{ar}), 126.3 (CH_{ar}), 125.9 (CH_{ar}), 125.0 (CH_{ar}), 70.3 (C-12a), 61.9 (OCH_2), 53.8 (C_{12}), 52.7 (OCH_3), 42.7 (CH_2N), 29.9 (CH_2), 26.6 (CH_2), 24.3 (CH_3), 14.2 (CH_3); HR-MS (ESI): $m/z=382.1649$, calcd. for $[M+H]^+$ $C_{22}H_{24}NO_5$: 382.1649. Chiral HPLC separation of enantiomers (Chiralpak IC, hexane/ethanol 7/3, 1 mL min^{-1}, detection UV 230 nm): Rt(12*R*,12a*R*) = 20.05, Rt(12*S*,12a*S*) = 24.05, k(12*R*,12a*R*) = 5.68, k(12*S*,12a*S*) = 7.02, $\alpha=1.24$; *ee* = 91%; $[\alpha]_D^{30}$: −33.9 (*c* 0.28, CH_2Cl_2).

(S)-Methyl 1-{[3-(3-ethoxy-3-oxoprop-1-en-2-yl)naphthalen-2-yl]methyl}-5-oxopyrrolidine-2-carboxylate (S-11): Yellowish oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.81$–7.78 (2H, m, CH_{ar}), 7.64 (2H, s, CH_{ar}), 7.50–7.47 (2H, m, CH_{ar}), 6.58 (1H, d, $J=1.5$ Hz, H_a of $=CH_aH_b$), 5.82 (1H, d, $J=1.5$ Hz, H_b of $=CH_aH_b$), 5.24 (1H, d, $J=15.3$ Hz, CH_2N, A part of an AB pattern), 4.28–4.20 (2H, AB part of an ABX_3 pattern, OCH_2CH_3), 4.03 (1H, d, $J=15.3$ Hz, CH_2N, B part of an AB pattern), 3.90 (1H, dd, $J=9.3$ and 2.8 Hz, CH), 3.65 (3H, s, OCH_3), 2.52 (1H, pseudo dt, $J=16.8$ and 9.5 Hz), 2.38 (1H, ddd, $J=3.5$, 9.5, and 16.8 Hz), 2.22 (1H, dtt, $J=13.0$, 9.5, and 9.3 Hz), 2.02 (1H, ddt, $J=12.8$, 9.5, and 3.3 Hz), 1.30 (3H, t, $J=7.0$ Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.0$ (CO), 172.4 (CO), 166.3 (CO), 140.9 (C_{ar}), 135.4 (C_{ar}), 133.1 (C_{ar}), 132.8 (C_{ar}), 132.1 (C), 129.7 (CH_{ar}), 129.3 ($=CH_2$), 128.2 (CH_{ar}), 127.8 (CH_{ar}), 127.6 (CH_{ar}), 126.7 (CH_{ar}), 126.6 (CH_{ar}), 61.5 (OCH_2), 58.5 (CH), 52.4 (OCH_3), 43.9 (CH_2N), 29.6 (CH_2), 22.9 (CH_2), 14.3 (CH_3); HR-MS (ESI): $m/z=382.1649$, calcd for $[M+H]^+$ $C_{22}H_{24}NO_5$: 382.1649. Chiral HPLC separation of enantiomers (Chiralpak IC, hexane/ethanol 7/3, 1 mL min^{-1}, detection UV 230 nm and CD 254 nm): Rt(*R*) = 15.98, Rt(*S*) = 17.78, k(*R*) = 4.33, k(*S*) = 4.93, $\alpha=1.14$ and Rs = 1.98; *ee* = 93%; $[\alpha]_D^{30}$: +3.8 (*c* 0.42, CH_2Cl_2).

Coupling of (S)-4 with 7d: Enediyne (*S*)-**4** (200 mg, 0.71 mmol), was allowed to react with diazo ester **7d** (142 mg, 0.99 mmol) and CuI (7 mg, 5 mol%) in dry acetonitrile (500 μL) for 2 h at 80 °C. The products was purified by column chromatography (30% ethyl acetate/pentane) to yield (12*S*,12a*R*)-9d (yield: 80 mg, 28%, *ee* = 91%) and (12*R*,12a*R*)-**9d** (yield: 97 mg, 35%, *ee* = 79%).

(12S,12aR)-12-tert-Butyl 12a-methyl 3-oxo-1,2,3,5,12,12a-hexahydrobenzo[g]pyrrolo[1,2-b]isoquinoline-12,12a-dicarboxylate (cis-9d): Yellowish oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.80$ (1H, s, CH_{ar}), 7.80–7.78 (2H, m, CH_{ar}), 7.66 (1H, s, CH_{ar}), 7.50–7.43 (2H, m, CH_{ar}), 5.14 (1H, d, $J=16.0$ Hz, CH_2N, A part of an AB pattern), 4.58 (1H, d, $J=15.8$ Hz, CH_2N, B part of an AB pattern), 4.17 (1H, s, CH), 3.69 (3H, s, OCH_3), 2.76 (1H, ddd, $J=1.5$, 8.5 and 12.8 Hz), 2.59–2.51 (1H, dddd, $J=1.0$, 8.5, 11.3, and 16.6 Hz), 2.31 (1H, ddd, $J=1.2$, 9.0 and 16.6 Hz), 2.07 (1H, ddd, $J=9.0$, 11.5 and 12.6 Hz), 1.42 (9H, s, CH_3 *t*-Bu). The stereochemical assignment was supported by a 2D NOESY spectrum, which showed correlations cross-peaks between the protons of the OMe and the *tert*-butyl groups. No detectable significant cross-peak was detected from the NOESY spectrum of the second diastereoisomer. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.6$ (CO), 172.1 (CO), 169.8 (CO), 132.6 (C_{ar}), 132.5 (C_{ar}), 132.0 (C_{ar}), 128.6 (C_{ar}), 128.1 (CH_{ar}), 127.8 (CH_{ar}), 127.5 (CH_{ar}), 126.7 (CH_{ar}), 126.1 (CH_{ar}), 125.2 (CH_{ar}), 82.7 [$OC(CH_3)_3$], 67.1 (C-12a), 55.9 (CH), 52.7 (OCH_3), 41.9 (CH_2N), 32.8 (CH_2), 30.1 (CH_2), 28 ($3\,CH_3$); HR-MS (ESI): $m/z=396.1805$, calcd. for $[M+H]^+$ $C_{23}H_{26}NO_5$: 396.1805. Chiral HPLC separation of enantiomers (Chiralpak IA, hexane/ethanol/chloroform 8/1/1, 1 mL min^{-1}, detection UV 230 nm and CD 254 nm): Rt(12*S*,12a*R*) = 6.20, Rt(12*R*,12a*S*) = 9.35, k(12*S*,12a*R*) = 1.07, k(12*R*,12a*S*) = 2.12, $\alpha=1.98$ and Rs = 5.10; *ee* = 91%; $[\alpha]_D^{30}$: −58.6 (*c* 1.41, CH_2Cl_2).

(12R,12aR)-12-tert-Butyl 12a-methyl 3-oxo-1,2,3,5,12,12a-hexahydrobenzo[g]pyrrolo[1,2-b]isoquinoline-12,12a-dicarboxylate (trans-9d): Yellowish oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.80$ (2H, m, CH_{ar}), 7.72 (1H, s, CH_{ar}), 7.69 (1H, s, CH_{ar}), 7.49–7.42 (2H, m, CH_{ar}), 5.12 (1H, d, $J=17.3$ Hz, CH_2N, A part of an AB pattern), 4.66 (1H, d, $J=17.3$ Hz, CH_2N, B part of an AB pattern), 4.49 (1H, s, CH), 3.52 (3H, s, OCH_3), 2.64–2.53 (1H, m),

2.52–2.36 (3H, m), 1.32 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6 (CO), 172.7 (CO), 169.2 (CO), 133.2 (C_{ar}), 132.2 (C_{ar}), 129.4 (Car), 128.5 (C_{ar}), 128.1 (CH_{ar}), 127.7 (CH_{ar}), 127.5 (CH_{ar}), 126.7 (CH_{ar}), 126.2 (CH_{ar}), 126.0 (CH_{ar}), 82.6 [$OC(CH_3)_3$], 67.2 (C-12a), 53.4 (CH), 53.2 (OCH_3), 43.1 (CH_2N), 29.5 (CH_2), 27.9 (3CH_3), 27.6 (CH_2); HR-MS (ESI): *m*/*z* = 396.1804, calcd. for $[M+H]^+$ $C_{23}H_{26}NO_5$: 396.1805. Chiral HPLC separation of enantiomers (Chiralpak IC, hexane/ethanol 7/3, 1 mL min^{-1}, detection UV 240 nm and CD 254 nm): Rt(12*S*,12a*S*) = 9.25, Rt(12*R*,12a*R*) = 11.58, k(12*S*,12a*S*) = 2.05, k(12*R*,12a*R*) = 2.86, α = 1.39 and Rs = 2.95; *ee* = 79%; $[\alpha]_D^{30}$: −30.1 (*c* 2.58, CH_2Cl_2).

Coupling of (±)-4′ with 7d: Enediyne (±)-4′ (100 mg, 0.31 mmol), diazo ester **7d** (61.5 mg, 0.43 mmol) and CuI (3 mg, 5 mol%) in dry acetonitrile (250 μL) for 2 h at 80 °C. The mixture was purified by column chromatography (30% ethyl acetate/pentane) to afford (±)-*cis*-**9′d** (yield: 50 mg, 37%) and (±)-*trans*-**9′d** (yield: 50 mg, 37%).

(±)-Di-tert-butyl 3-oxo-1,2,3,5,12,12a-hexahydrobenzo[g]pyrrolo[1,2-b]isoquinoline-12,12a-dicarboxylate (cis-9′d): Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (1H, s, CH_{ar}), 7.80–7.75 (2H, m, CH_{ar}), 7.64 (1H, s, CH_{ar}), 7.49–7.42 (2H, m, CH_{ar}), 5.11 (1H, d, *J* = 16.3 Hz, CH_2N, A part of an AB pattern), 4.58 (1H, d, *J* = 16.3 Hz, CH_2N, B part of an AB pattern), 4.10 (1H, s, CH), 2.78 (1H, ddd, *J* = 1.2, 8.5 and 12.6 Hz), 2.62–2.53 (1H, m), 2.32 (1H, ddd, *J* = 1.3, 9.3 and 16.6 Hz), 2.09–2.01 (1H, m), 1.47 (9H, s, *t*-Bu), 1.30 (9H, s, *t*-Bu). The assignment follows from the analogy with the spectrum of *cis*-**9d**. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.7 (CO), 170.2 (CO), 169.5 (CO), 132.5 (C_{ar}), 132.4 (C_{ar}), 131.8 (C_{ar}), 129.2 (C_{ar}), 127.9 (CH_{ar}), 127.6 (CH_{ar}), 127.4 (CH_{ar}), 126.5 (CH_{ar}), 126.0 (CH_{ar}), 124.9 (CH_{ar}), 82.9 (C), 82.5 (C), 67.4 (C), 55.6 (CH), 42.3 (CH_2N), 32.5 (CH_2), 30.2 (CH_2), 28.2 (3 CH_3), 27.9 (3CH_3); HR-MS (ESI): *m*/*z* = 438.2272, calcd. for $[M+H]^+$ $C_{26}H_{32}NO_5$: 438.2275.

(±)-Di-tert-butyl 3-oxo-1,2,3,5,12,12a-hexahydrobenzo[g]pyrrolo[1,2-b]isoquinoline-12,12a-dicarboxylate (trans-9′d): White solid; mp 142.0 °C (CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.77 (2H, m, CH_{ar}), 7.69 (2H, s, CH_{ar}), 7.49–7.42 (2H, m, CH_{ar}), 5.07 (1H, d, *J* = 17.1 Hz, CH_2N, A part of an AB pattern), 4.66 (1H, d, *J* = 17.0 Hz, CH_2N, B part of an AB pattern), 4.40 (1H, s, CH), 2.61–2.53 (1H, m), 2.49–2.37 (3H, m), 1.32 (9H, s, *t*-Bu), 1.11 (9H, s, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.6 (CO), 171.2 (CO), 169.3 (CO), 133.1 (C_{ar}), 132.1 (C_{ar}), 130.0 (C_{ar}), 129.0 (C_{ar}), 128.0 (CH_{ar}), 127.7 (CH_{ar}), 127.5 (CH_{ar}), 126.6 (CH_{ar}), 126.1 (CH_{ar}), 125.8 (CH_{ar}), 83.0 (C), 82.5 (C), 67.8 (C), 54.1 (CH), 43.6 (CH_2N), 29.7 (CH_2), 27.9 (3CH_3), 27.6 (3CH_3), 27.2 (CH_2); HR-MS (ESI): *m*/*z* = 438.2276, calcd. for $[M+H]^+$ $C_{26}H_{32}NO_5$: 438.2275.

Coupling of (S)-5 with 7b: Enediyne (*S*)-**5** (50 mg, 0.166 mmol) was allowed to react with diazo ester **7b** (44.2 mg, 0.23 mmol) and CuI (1.6 mg, 5 mol%) in dry acetonitrile (125 μL) for 2 h at room temperature. The products was purified by column chromatography (30% ethyl acetate/pentane) to afford compounds 12*S*,12a*R*)-**10b** (yield: 25 mg, 32%, *ee* = 95%) and (12*R*,12a*R*)-**10b** (35 mg, 46%, *ee* = 91%).

(12S,12aR)-Ethyl 3-oxo-12,12a-diphenyl-3,5,12,12a-tetrahydro-1H-benzo[g]oxazolo[3,4-b]isoquinoline-12-carboxylate (cis-10b): Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (1H, s, CH_{ar}), 7.84 (1H, s, CH_{ar}), 7.83 (1H, superimposed d, *J* = 7.5 Hz, CH_{ar}), 7.64 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.49 (1H, td, *J* = 6.8 and 1.3 Hz, CH_{ar}), 7.41 (2H, 2 superimposed td, *J* = 7.0 and 1.0 Hz, CH_{ar}), 7.27 (2H, t, *J* = 8.0 Hz, CH_{ar}), 7.01 (1H, tt, *J* = 7.3 and 1.0 Hz, CH_{ar}), 6.95–6.93 (2H, m, CH_{ar}), 6.88 (2H, t, *J* = 8.3 Hz, CH_{ar}), 6.44 (2H, br d, *J* = 7.5 Hz, CH_{ar}), 5.31 (1H, d, *J* = 8.8 Hz, CH_2O, A part of an AB pattern), 5.18 (1H, d, *J* = 17.3 Hz, CH_2N, A part of an AB pattern), 5.06 (1H, d, *J* = 16.8 Hz, CH_2N, B part of an AB pattern), 4.62 (1H, d, *J* = 8.8 Hz, CH_2O, B part of an AB pattern), 4.18–4.07 (2H, A part of an ABX_3 pattern, OCH_2), 1.04 (3H, t, *J* = 7.0 Hz, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7 (CO), 158.9 (CO), 142.9 (C_{ar}), 135.6 (C_{ar}), 132.6 (C_{ar}), 132.2 (C_{ar}), 131.7 (C_{ar}), 131.5 (2CH_{ar}), 130.7 (CH_{ar}), 130.2 (C_{ar}), 128.6 (2CH_{ar}), 128.4 (CH_{ar}), 128.2 (CH_{ar}), 127.6 (2CH_{ar}), 127.5 (CH_{ar}), 127.1 (CH_{ar}), 127.0 (2CH_{ar}), 126.1 (CH_{ar}), 125.2 (CH_{ar}), 74.6 (OCH_2), 67.2 (C-12a), 64.8 (C-12), 62.3 (OCH_2), 46.1 (CH_2N), 13.8 (CH_3); HR-MS (ESI): *m*/*z* = 464.1855, calcd. for $[M+H]^+$ $C_{30}H_{26}NO_4$: 464.1856. Chiral HPLC separation of enantiomers (Chiralpak IB, hexane/ethanol 7/3, 1 mL min^{-1}, detection UV 230 nm and CD 254 nm): Rt(12*S*,12a*R*) = 6.72, Rt(12*R*,12a*S*) = 8.23, k(12*S*,12a*R*) = 1.24, k(12*R*,12a*S*) = 1.74, α = 1.40; *ee* = 95%; $[\alpha]_D^{30}$: +21.4 (*c* 0.41, CH_2Cl_2).

(12R, 12aR)-Ethyl 3-oxo-12,12a-diphenyl-3,5,12,12a-tetrahydro-1H-benzo[g]oxazolo [3,4-b]isoquinoline-12-carboxylate (trans-10b): White solid; mp 90.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (1H, s, CH_{ar}), 7.80 (1H, d, *J* = 8.8 Hz, CH_{ar}), 7.73 (1H, d, *J* = 7.8 Hz, CH_{ar}), 7.59 (1H, s, CH_{ar}), 7.46–7.42 (2H, m, CH_{ar}), 7.29–7.24 (5H, m, CH_{ar}), 7.19–7.16 (3H, m, CH_{ar}), 7.03 (2H, 2 superimposed dt, *J* = 6.7 and 1.8 Hz, CH_{ar}), 5.05 (1H, d, *J* = 17.3 Hz, CH_2N, B of an AB pattern), 4.87 (1H, d, *J* = 10.3 Hz, CH_2O, A part of an AB pattern), 4.68 (1H, d, *J* = 10.6 Hz, CH_2O, B part of an AB pattern), 4.29–4.20 (2H, AB part of an ABX_3 pattern, OCH_2), 4.02 (1H, d, *J* = 17.1 Hz, CH_2N, B part of an AB pattern), 1.02 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (CO), 156.2 (CO), 141.6 (C_{ar}), 141.5 (C_{ar}), 134.8 (C_{ar}), 132.6 (C_{ar}), 131.9 (C_{ar}), 130.7 (CH_{ar}), 128.8 (2CH_{ar}), 128.7 (CH_{ar}), 128.66 (2CH_{ar}), 128.60 (2CH_{ar}), 128.5 (C_{ar}), 128.0 (CH_{ar}), 127.9 (CH_{ar}), 126.9 (CH_{ar}), 126.8 (CH_{ar}), 126.7 (2CH_{ar}), 126.0 (CH_{ar}), 124.8 (CH_{ar}), 75.0 (OCH_2), 66.9 (C_{12a}), 61.9 (OCH_2), 60.5 (C-12), 41.6 (CH_2N), 13.6 (CH_3); HR-MS (ESI): *m*/*z* = 464.1848, calcd. for $[M+H]^+$ $C_{30}H_{26}NO_4$: 464.1856. Chiral HPLC separation of enantiomers (Chiralpak IC, hexane/ethanol 9/1, 1 mL min^{-1}, detection UV 230 nm and CD 254 nm): Rt(12*S*,12a*S*) = 17.37, Rt(12*R*,12a*R*) = 19.41, k(12*S*,12a*S*) = 4.79, k(12*R*,12a*R*) = 5.47, α = 1.14; *ee* = 91%. $[\alpha]_D^{30}$: +123.7 (*c* 1.46, CH_2Cl_2). The structure was confirmed by X-ray crystallography.

Coupling of (R)-5 with 7b: Enediyne (*R*)-**5** (200 mg, 0.66 mmol, >99.5% *ee*) was allowed to react with diazo ester **7b** (177 mg, 0.93 mmol) and CuI (6 mg, 5 mol%) in dry acetonitrile (500 μL) for 2 h at room temperature. The products was purified by column chromatography (30% ethyl acetate/pentane) to afford compounds (12*R*,12a*S*)-**10b** (yield: 118.5 mg, 39%, *ee* = 97%) and (12*S*,12a*S*)-**10b** (yield: 138 mg, 45%, *ee* = 89%).

(12*R*,12a*S*)-10b: $[\alpha]_D^{30}$: −21.1 (*c* 2.18, CH_2Cl_2).

(12*S*,12a*S*)-10b: $[\alpha]_D^{30}$: −117.3 (*c* 2.48, CH_2Cl_2).

Coupling of (S)-5 with 7c: Enediyne (*S*)-**5** (100 mg, 0.33 mmol) was allowed to react with diazo ester **7c** (59.5 mg, 0.46 mmol) and CuI (3.2 mg, 5 mol%) in dry acetonitrile (250 μL) for 1 h at 80 °C. The products were purified by column chromatography (DCM) to afford compounds (12*S*, 12a*R*)-**10c** (yield: 45 mg, 34%, *ee* = 97.5%) and olefin ***S*-12** (yield: 15 mg, 9% (corrected yield. Compound **12** could not be isolated as a pure sample as it was contaminated by 10% of **10c**).

(12S,12aR)-Ethyl 12-methyl-3-oxo-12a-phenyl-3,5,12,12a-tetrahydro-1H-benzo[g]oxazolo[3,4-b]isoquinoline-12-carboxylate (10c): Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.90 (1H, s, CH_{ar}), 8.00 (1H, m, CH_{ar}), 7.81 (1H, m, CH_{ar}), 7.60 (1H, s, CH_{ar}), 7.58 (2H, m, CH_{ar}), 7.31–7.29 (2H, m, CH_{ar}), 7.26–7.24 (3H, m, CH_{ar}), 5.28 (1H, d, *J* = 10.3 Hz, CH_2O, A part of an AB pattern), 5.09 (1H, d, *J* = 17.6 Hz, CH_2N, A part of an AB pattern), 4.92 (1H, d, *J* = 10.3 Hz, CH_2O, B part of an AB pattern), 4.35 (1H, d, *J* = 17.1 Hz, CH_2N, B part of an AB pattern), 4.35–4.27 (2H, superimposed AB part of an ABX_3 pattern, OCH_2), 1.93 (3H, s, CH_3), 1.25 (3H, t, *J* = 7.0, CH_2CH_3). The stereochemical assignment follows from the observation of a cross-peak between the signal of protons of the methyl group at 1.93 ppm and that of one the protons in position α relative to nitrogen atom (5.28 ppm). This correlation is in agreement with the Chem-3D model. Such a spatial proximity does not exist in the other diastereomer. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2 (CO), 157.1 (CO), 141.0 (C_{ar}), 135.7 (C_{ar}), 132.5 (C_{ar}), 131.9 (C_{ar}), 128.5 (CH_{ar}), 128.4 (2 CH_{ar}), 128.0 (CH_{ar}), 127.8 (C_{ar}), 127.4 (CH_{ar}), 127.1 (2 CH_{ar}), 126.9 (CH_{ar}), 126.7 (CH_{ar}), 126.1 (CH_{ar}), 125.4 (CH_{ar}), 74.6 (OCH_2), 66.3 (C-12a), 61.7 (OCH_2), 52.2 (C-12), 42.4 (CH_2N), 27.6 (CH_3), 13.9 (CH_3); HR-MS (ESI): *m*/*z* = 402.1699, calcd. for $[M+H]^+$ $C_{25}H_{24}NO_4$: 402.1700. Chiral HPLC separation of enantiomers (Chiralpak IA, hexane/ethanol 1/1, 1 mL min^{-1}, detection UV and CD 254 nm): Rt(12*R*,12a*S*) = 5.57, Rt(12*S*,12a*R*) = 6.50, k(12*R*,12a*S*) = 0.86, k(12*S*,12a*R*) = 1.17, α = 1.36 and Rs = 2.97; *ee* = 97%; $[\alpha]_D^{30}$: +145.4 (*c* 1.46, CH_2Cl_2).

(S)-Ethyl 2-{3-[(2-oxo-4-phenyloxazolidin-3-yl)methyl]-napthalen-2-yl}acrylate (S-12): sample contaminated with **10c;** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.79 (1H, m, CH_{ar}), 7.74–7.71 (1H, m, CH_{ar}), 7.64 (1H, s, CH_{ar}), 7.50–7.48 (1H, m, CH_{ar}), 7.49 (1H, superimposed d, *J* = 9.5 Hz, CH_{ar}), 7.42 (1H, s, CH_{ar}), 7.37–7.35 (2H, m, CH_{ar}), 7.11–7.09 (3H, m, CH_{ar}), 6.52 (1H, d, *J* = 1.5 Hz, $=CH_aH_b$), 5.68 (1H, d, *J* = 1.5 Hz, $=CH_aH_b$), 5.02 (1H, d, *J* = 15.0 Hz, CH_2N, A part of an AB pattern), 4.54 (1H, pseudo t, *J* = 8.8 Hz, CH), 4.44 (1H, dd, *J* = 9.0 and 5.2 Hz, CH_2O), 4.21–4.18 (2H, AB part of an ABX_3 pattern, OCH_2), 4.10 (1H, dd, *J* = 8.3 and 5.2 Hz, CH_2O), 3.78 (1H, d, *J* = 15.0 Hz, CH_2N, B part of an AB pattern), 1.27 (3H, t, *J* = 7.3 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4 (CO), 158.0 (CO), 140.5 (C_{ar}), 138.2 (C_{ar}), 135.5 (C_{ar}), 132.9 (C_{ar}), 132.8 (C_{ar}), 131.4 (C_{ar}), 129.7 (CH_{ar}), 129.3 (2 CH_{ar}), 129.3 ($=CH_2$), 129.1 (CH_{ar}), 128.6 (CH_{ar}), 127.8 (CH_{ar}), 127.7 (CH_{ar}), 127.2 (2 CH_{ar}), 126.7 (CH_{ar}), 126.6 (CH_{ar}), 70.1 (OCH_2), 61.5 (OCH_2), 58.6 (CH), 44.5 (CH_2N), 14.3 (CH_3); HR-MS (ESI): *m*/*z* = 402.1699, calcd. for $[M+H]^+$ $C_{25}H_{24}NO_4$: 402.1700.

Coupling of (S)-6 with 7a: Enediyne (*S*)-**6** (100 mg, 0.25 mmol) was allowed to react with diazo ester **7a** (40.4 mg, 0.35 mmol) and CuI (2.5 mg, 5 mol%) in dry acetonitrile (250 μL) for 2 h at 80 °C. The products were purified by column chromatography (DCM) to afford (3*R*,4*S*)-**13a** (yield: 36 mg, 30%, *ee* = 80%), (3*R*,4*R*)-**13a** (yield: 28.5 mg, 24%, *ee* = 88%). The presence of alkene **14** was inferred from the analysis of the ^{1}H NMR spectrum of the crude reaction mixture. No pure sample could be isolated. An approximate 10% yield was calculated from this spectrum. The characteristic signals were obtained from an enriched intermediate chromatographic fraction.

(3R,4S)-4-Ethyl 3-methyl 3-methyl-2-tosyl-1,2,3,4-tetrahydrobenzo[g]isoquinoline-3,4-dicarboxylate (cis-13a): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (2H, d, *J* = 8.3, CH_{ar}), 7.78–7.65 (2H, m, CH_{ar}), 7.75 (1H, s, CH_{ar}), 7.61 (1H, s, CH_{ar}), 7.50–7.45 (2H, m, CH_{ar}), 7.28 (2H, d, *J* = 8.3 Hz, CH_{ar}), 4.90 (1H, d, *J* = 15.0 Hz, CH_2N, A part of an AB pattern), 4.79 (1H, d, *J* = 14.8 Hz, CH_2N, B part of an AB pattern), 4.38 (1H, s, CH), 4.19 (2H, q, *J* = 7.3 Hz, OCH_2), 3.63 (3H, s, OCH_3), 2.41 (3H, s, CH_3), 1.74 (3H, s, CH_3), 1.26 (3H, t, *J* = 7.3 Hz, CH_3). The stereochemical assignment follows from the presence of a cross-peak between the signals of the protons of the methoxy group at 3.63 ppm and those of the methyl group of CO_2Et (t at 1.26 ppm) and another cross-peak between the signal of the proton at 4.38 ppm and the protons of methyl (s at 1.74 ppm). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1 (CO), 169.3 (CO), 143.4 (C_{ar}), 138.8 (C_{ar}), 132.8 (C_{ar}), 132.7 (C_{ar}), 131.3 (C_{ar}), 129.7 (2 CH_{ar}), 129.1 (C_{ar}), 127.9 (CH_{ar}), 127.6 (CH_{ar}), 127.3 (2 CH_{ar}), 126.7 (CH_{ar}), 126.7 (CH_{ar}), 126.3 (CH_{ar}), 124.8 (CH_{ar}), 65.3 (C), 61.6 (OCH_2), 54.7 (CH), 53.0 (OCH_3), 47.8 (CH_2N), 21.6 (2 CH_3), 14.2 (CH_3); HR-MS (ESI): *m*/*z* = 482.1630, calcd. for $[M+H]^+$ $C_{26}H_{28}NO_6S$: 482.1632. Chiral HPLC separation of enantiomers (Chiralpak IB, hexane/2-propanol 95/5, 1 mL min^{-1}, detection UV 230 nm and CD 254 nm): Rt(3*S*,4*R*) = 23.61, Rt(3*R*,4*S*) = 28.81, k(3*S*,4*R*) = 6.87, k(3*R*,4*S*) = 8.60, α = 1.25 and Rs = 2.83; *ee* = 80%; $[\alpha]_D^{30}$: +7.4 (*c* 0.60, CH_2Cl_2).

(3R,4R)-4-Ethyl 3-methyl 3-methyl-2-tosyl-1,2,3,4-tetrahydrobenzo[g]isoquinoline-3,4-dicarboxylate (trans-13a): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (2H, d, *J* = 8.3 Hz, CH_{ar}), 7.80–7.76 (2H, m, CH_{ar}), 7.67 (1H, s, CH_{ar}), 7.58 (1H, s, CH_{ar}), 7.49–7.47 (2H, m, CH_{ar}), 7.28 (2H, d, *J* = 8.0 Hz, CH_{ar}), 4.76 (1H, d, *J* = 14.3 Hz, CH_2N, A part of an AB pattern), 4.60 (1H, d, *J* = 14.6 Hz, CH_2N, B part of an AB pattern), 4.18–4.09 (2H, AB part of an ABX_3 pattern, OCH_2), 4.05 (1H, s, CH), 3.81 (3H, s, OCH_3), 2.41 (3H, s, CH_3), 1.70 (3H, s, CH_3), 1.22 (3H, t, *J* = 7.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (CO), 169.8 (CO), 143.6 (C_{ar}), 137.6 (C_{ar}), 133.1 (C_{ar}), 132.8 (C_{ar}), 131.5 (C_{ar}), 129.7 (2 CH_{ar}), 129.0 (C_{ar}), 128.0 (2 CH_{ar}), 127.8 (CH_{ar}), 127.7 (CH_{ar}), 127.5 (CH_{ar}), 126.8 (CH_{ar}), 126.5 (CH_{ar}), 125.4 (CH_{ar}), 65.7 (C), 61.8 (OCH_2), 57.7 (CH), 52.9 (OCH_3), 47.1 (CH_2N), 26.3 (CH_3), 21.7 (CH_3), 14.1 (CH_3). The deshielding of the carbon of the methyl group at 26.3 ppm in *trans* isomer/21.6 ppm in the *cis* isomer (where there is an additional *gauche* interaction) confirms the stereochemical assignment. HR-MS (ESI): *m*/*z* = 482.1627, calcd. for $[M+H]^+$ $C_{26}H_{28}NO_6S$: 482.1632. Chiral HPLC

separation of enantiomers (Chiralpak IC, hexane/ethanol 1/1, 1 mL min^{-1}, detection UV 230 nm and CD 254 nm): Rt(3*R*,4*R*) = 9.14, Rt(3*S*,4*S*) = 12.73, k(3*R*,4*R*) = 2.05, k(3*S*,4*S*) = 3.24, α = 1.58 and Rs = 3.93; *ee* = 88%; $[\alpha]_D^{30}$: +49.5 (*c* = 0.22, CH_2Cl_2).

Characteristic signals of 14a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.17 (1H, s, =CH_aH_b), 5.61 (1H, s, =CH_aH_b), 4.83 (2H, s, CH_2N), 4.10 (2H, s, CH_2O), 3.58 (3H, s, CH_3O), 1.27 (3H, t, *J* = 7.3, CH_3).

Coupling of (S)-6 with 7b: Enediyne (*S*)-**6** (100 mg, 0.25 mmol) was allowed to react with diazo ester **7b** (67.3 mg, 0.35 mmol) and CuI (2.4 mg, 5 mol%) in dry acetonitrile (250 µL) for 2 h at room temperature. The products were purified by preparative HPLC [the product was dissolved in a mixture of ethanol and chloroform and separated under the following conditions: Chiralpak IA (250 × 10 mm), eluent hexane/2-propanol (80/20), 5 mL min^{-1}, UV detector at 254 nm] to afford (3*R*,4*S*)-**13b** (yield: 42 mg, 30%, *ee* = 94%), (3*R*,4*R*)-**13b** (yield: 42 mg, 30%, *ee* = 92%) and alkene **14b** (yield: 18 mg, 13%). The chiral column was used to separate the diastereomers, which did not affect the *ee*s.

(3R,4S)-4-Ethyl 3-methyl 3-methyl-4-phenyl-2-tosyl-1,2,3,4-tetrahydrobenzo[g]isoquinoline-3,4-dicarboxylate (cis-13b): Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (2H, d, *J* = 8.3 Hz, CH_{ar}), 7.80 (1H, s, CH_{ar}), 7.77 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.68 (1H, s, CH_{ar}), 7.64 (1H, d, *J* = 8.3 Hz, CH_{ar}), 7.45 (1H, td, *J* = 7.8 and 1.0 Hz, CH_{ar}), 7.38 (1H, td, *J* = 8.0 and 1.0 Hz, CH_{ar}), 7.30–7.26 (7H, m, CH_{ar}), 5.08 (1H, d, *J* = 16.0 Hz, CH_2N, A part of an AB pattern), 4.68 (1H, d, *J* = 16.0 Hz, CH_2N, B part of an AB pattern), 4.17–4.10 (1H, m, OCH_2), 3.96–3.88 (1H, m, OCH_2), 3.62 (3H, s, OCH_3), 2.42 (3H, s, CH_3), 1.43 (3H, s, CH_3), 0.87 (3H, t, *J* = 7.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7 (CO), 170.8 (CO), 143.6 (C_{ar}), 138.5 (C_{ar}), 137.7 (C_{ar}), 133.1 (C_{ar}), 132.3 (C_{ar}), 132.1 (C_{ar}), 132.0 (CH_{ar}), 130.8 (C_{ar}), 129.8 (CH_{ar}), 129.5 (2CH_{ar}), 128.2 (CH_{ar}), 127.9 (2CH_{ar}), 127.8 (CH_{ar}), 127.1 (2CH_{ar}), 127.0 (CH_{ar}), 126.8 (CH_{ar}), 125.9 (CH_{ar}), 124.3 (CH_{ar}), 68.8 (C), 64.4 (C), 61.7 (OCH_2), 52.6 (OCH_3), 46.9 (CH_2N), 22.0 (CH_3), 21.7 (CH_3), 13.6 (CH_3); HR-MS (ESI): *m*/*z* = 558.1947, calcd. for $[M+H]^+$ $C_{32}H_{32}NO_6S$: 558.1945. Chiral HPLC separation of enantiomers (Chiralpak AD-H, hexane/2-propanol 8/2, 1 mL min^{-1}, detection UV and CD 254 nm): Rt(3*S*,4*S*) = 25.45, Rt(3*R*,4*R*) = 28.43, k(3*S*,4*S*) = 7.48, k(3*R*,4*R*) = 8.48, α = 1.13 and Rs = 1.62; *ee* = 94%; $[\alpha]_D^{30}$: +41.5 (*c* 0.55, CH_2Cl_2).

(3R,4R)-4-Ethyl 3-methyl 3-methyl-4-phenyl-2-tosyl-1,2,3,4-tetrahydrobenzo[g]isoquinoline-3,4-dicarboxylate (trans-13b): White solid; mp 167.0 °C (CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (2H, d, *J* = 8.3 Hz, CH_{ar}), 7.81 (1H, d, *J* = 8.3 Hz, CH_{ar}), 7.76 (1H, s, CH_{ar}), 7.70 (1H, s, CH_{ar}), 7.67 (1H, d, *J* = 8.0, CH_{ar}), 7.47 (1H, t, *J* = 7.0 Hz, CH_{ar}), 7.40 (1H, t, *J* = 7.3 Hz, CH_{ar}), 7.37–7.28 (7H, m, CH_{ar}), 5.37 (1H, d, *J* = 15.3 Hz, CH_2N, A part of an AB pattern), 4.86 (1H, d, *J* = 14.8 Hz, CH_2N, B part of an AB pattern), 4.06–3.97 (2H, m, OCH_2), 3.22 (3H, s, OCH_3), 2.43 (3H, s, CH_3), 1.88 (3H, s, CH_3), 0.93 (3H, t, *J* = 7.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ) = 172.0 (CO), 170.5 (CO), 143.2 (C_{ar}), 140.0 (C_{ar}), 136.5 (C_{ar}), 133.2 (C_{ar}), 133.0 (C_{ar}), 132.7 (C_{ar}), 132.4 (C_{ar}), 131.9 (2CH_{ar}), 129.6 (2CH_{ar}), 129.5 (CH_{ar}), 128.3 (CH_{ar}), 128.2 (CH_{ar}), 127.4 (2CH_{ar}), 127.3 (CH_{ar}), 127.1 (2CH_{ar}), 126.7 (CH_{ar}), 125.8 (CH_{ar}), 124.0 (CH_{ar}), 68.7 (C), 65.6 (C), 61.8 (OCH_2), 52.1 (OCH_3), 48.2 (CH_2N), 21.7 (CH_3), 19.9 (CH_3), 13.7 (CH_3); HR-MS (ESI): *m*/*z* = 558.1942, calcd. for $[M+H]^+$ $C_{32}H_{32}NO_6S$: 558.1945. Chiral HPLC separation of enantiomers (Lux-Cellulose-4, hexane/ethanol 1/1, 1 mL min^{-1}, detection UV and CD 254 nm): Rt(3*R*,4*S*) = 12.45, Rt(3*S*,4*R*) = 25.37, k(3*R*,4*S*) = 3.15, k(3*S*,4*R*) = 7.46, α = 2.36 and Rs = 11.49; *ee* = 92%; $[\alpha]_D^{30}$: −8.3 (*c* = 0.30, CH_2Cl_2). The absolute configuration could be determined from X-ray cyrstallographic (Cu-irradiation) data.

Methyl 2-{*N*-[(3-(2-ethoxy-2-oxo-1-phenylethyl)naphthalen-2-yl]methyl}-4-methylphenylsulfonamido)acrylate (14b): Colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (1H, s, CH_{ar}), 7.80 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.69 (2H, d, *J* = 8.0 Hz, CH_{ar}), 7.66 (1H, d, *J* = 7.8 Hz, CH_{ar}), 7.55 (1H, s, CH_{ar}), 7.49–7.41 (3H, m, CH_{ar}), 7.32–7.30 (6H, m, CH_{ar}), 6.10 (1H, s, CH), 5.70 (1H, s, =CH_aH_b), 5.57 (1H, s, =CH_aH_b), 4.83 (1H, d, *J* = 13.6, CH_2N, A part of an AB pattern), 4.59 (1H, d, *J* = 13.6, CH_2N, B part of an AB pattern), 4.25 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.54 (3H, s, OCH_3), 2.45 (3H, s, CH_3), 1.27 (3H, t, *J* = 7.0 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8 (CO), 164.0 (CO), 144.0 (C_{ar}), 137.8 (C_{ar}), 135.5 (C_{ar}), 134.7 (C_{ar}), 133.2 (C_{ar}), 132.4 (C_{ar}), 131.0 (CH_{ar}), 130.9 (C_{ar}), 130.3 (C), 129.6 (3CH_{ar}), 129.4 (2CH_{ar}), 128.6 (2CH_{ar}), 128.1 (2CH_{ar}), 128.0 (CH_{ar}), 127.9 (CH_{ar}), 127.5 (CH_{ar}), 127.4 (CH_{ar}), 126.8 (CH_{ar}), 126.5 (=CH_2), 61.5 (OCH_2), 52.5 (CH), 52.3 (OCH_3), 50.7 (CH_2N), 21.8 (CH_3), 14.1 (CH_3); HR-MS (ESI): *m*/*z* = 482.1627, calcd. for $[M+H]^+$ $C_{26}H_{28}NO_6S$: 482.1632.

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[15] This would be consistent with the formation of an intermediate copper acetylide at this temperature.

[16] Retention of configuration in *trans*-**13b** was probed by the X-ray crystal structure [anomalous scattering effect measured with 1023 Bijvoet pairs at copper wavelength. Flack parameter: −0.006 (0.0153)]. CCDC 860530 contains the supplementary crystallographic data for *trans*-**13b**.These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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