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Synthesis of β- and γ-carbolines *via* ruthenium and rhodium catalysed [2 + 2 + 2] cycloadditions of yne-ynamides with methylcyanoformate†

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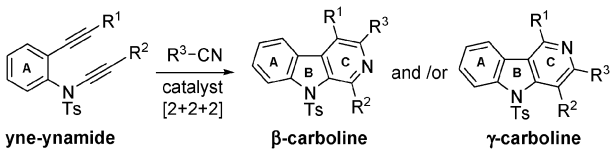
A flexible approach towards substituted β- and γ-carbolines based on transition metal catalysed [2 + 2 + 2] cycloaddition reactions between functionalised yne-ynamides and methylcyanoformate is described. The versatility of this new reaction sequence is demonstrated by its application in the total synthesis of the marine natural product eudistomin U.

Pyrido[3,4-*b*]indoles, commonly known as β-carbolines, are the key structural motif of a variety of biologically important alkaloids of natural and synthetic origin.[1] Natural products containing a β-carboline unit have been isolated from terrestrial plants and various marine invertebrates and their biological properties range from interactions with the benzodiazepine receptor to potent antitumor, antiviral and antimicrobial activities.[2] The occurrence of the pyrido[4,3-*b*]indole or γ-carboline motif in natural products is less well documented.[3] However, a number of reports have shown that γ-carbolines possess significant antitumor properties based on their structural similarity to the natural products ellipticine and olivacine.[4]

Due to their biological importance synthetic methodologies for the β- and the γ-carboline framework received considerable attention. The Pictet–Spengler reaction followed by a dehydrogenation reaction is the most widely studied method to access β-carbolines.[5] More recently, palladium catalysed cross-coupling and iminoannulation reactions,[6] as well as gold(III)-catalysed cycloisomerisation sequences were reported for the construction of β- and γ-carbolines.[7]

We disclose here an expedient method for the synthesis of β- and γ-carbolines that is based on an A → ABC ring formation strategy by transition metal catalysed [2 + 2 + 2] cycloaddition reactions of functionalised yne-ynamides with nitriles (Scheme 1).[8,9]

Such a straightforward assembly *via* a consecutive formation of three bonds in a single reaction step should allow diversity as well as target oriented syntheses of either β- or γ-carbolines. Furthermore, this approach should be relevant for applications

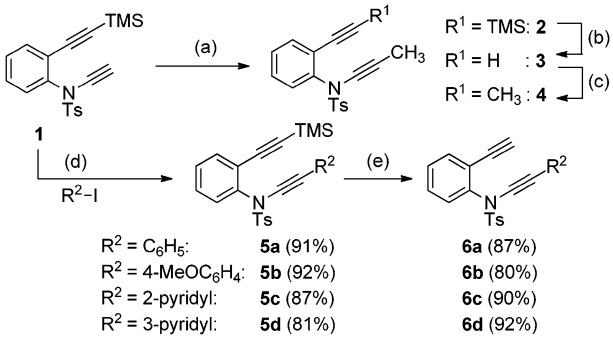


Scheme 1 The A → ABC ring formation strategy to β- and/or γ-carbolines.

in natural product syntheses when methylcyanoformate (R^3 = CO_2Me in Scheme 1) is used as the nitrile component.

The synthesis of a set of substituted diyne precursors needed for this study started with the readily available yne-ynamide **1** that was obtained through our previously reported method of the direct *N*-ethynylation of tosylanilides with ethynyliodonium triflate (Scheme 2).[8b,10] Methylation of the ynamide unit in **1** provided compound **2** (97% yield) and a subsequent desilylation with tetrabutylammonium fluoride (TBAF) afforded yne-ynamide **3** (90% yield). Thereafter, the bismethylated diyne **4** (92% yield) became available through a second methylation sequence starting from **3**.

A simple and flexible way to further functionalise yne-ynamide **1** was found in the Negishi reaction.[11] Palladium catalysed cross-couplings of **1** with various iodobenzenes and iodopyridines provided the yne-ynamides **5a–d** already at room temperature and their subsequent desilylation with TBAF afforded the desired yne-ynamides **6a–d** in a short overall synthetic sequence (Scheme 2).



Scheme 2 *Reagents and conditions*: (a) LiHMDS, THF, MeI, −40 °C to rt, 12 h (97% yield for **2**); (b) TBAF, THF, 0 °C, 15 min (90% yield for **3**); (c) LiHMDS, THF, MeI, −40 °C to rt, 12 h (92% yield for **4**); (d) LiHMDS, $ZnBr_2$, Pd_2dba_3 (5 mol%), PPh_3 (20 mol%), THF, rt, 12 h; (e) TBAF, THF, 0 °C.

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Next, [2+2+2] cycloaddition reactions of yne-ynamides with methylcyanoformate were investigated.[12,13] Catalysts for the co-cyclisation of tethered diynes with electron deficient nitriles to provide annelated pyridines were reported by Itoh and Tanaka utilising the Cp*RuCl(cod) complex or cationic rhodium complexes, respectively.[14,15] Therefore, co-cyclisations of yne-ynamides with methylcyanoformate as the electron deficient nitrile component were carried out with either Cp*RuCl(cod) at 35 °C (method A, Table 1) and 120 °C (method B, Table 1), or with a cationic rhodium catalyst generated from 3 mol% $[Rh(cod)_2]BF_4$ and 3 mol% BINAP at room temperature (method C, Table 1).

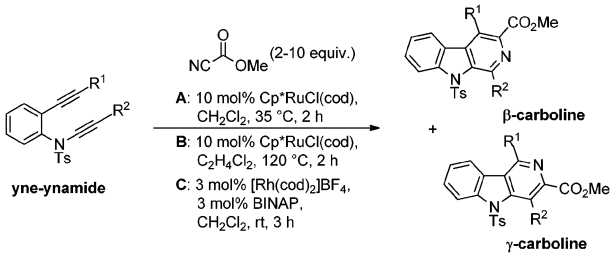
Gratifyingly, the [2+2+2] cycloaddition of yne-ynamides with an excess of methylcyanoformate led to the successful synthesis of either β- or γ-carbolines as the major products with the following details: compounds **3**, **6a**, and **6b** provided the β-carbolines **7**, **8a**, and **8b**, respectively, as single regioisomers when Cp*RuCl(cod) was used as a catalyst and β-carbolines were obtained as the major regioisomers, when the cationic rhodium catalyst generated by method C was applied (Table 1, entries 1–5). The 2-pyridyl substituted yne-ynamide **6c** and methylcyanoformate underwent a co-cyclisation neither in the presence of the Cp*RuCl(cod), nor in the presence of the cationic rhodium complex following method C. Presumably the bipyridyl moiety in product **8c** inhibits the catalytic cycle by complexation to the Rh- or Ru-based catalyst. In strong contrast, the β-carboline **8d** was obtained in 70% yield as a single regioisomer when Cp*RuCl(cod) mediated the co-cyclisation of the 3-pyridyl substituted yne-ynamide **6d** with methylcyanoformate (Table 1, entry 8), whereas the cationic rhodium catalyst was again unproductive (entry 9).

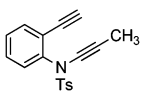
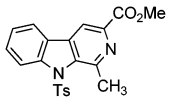
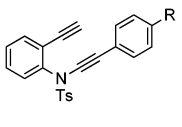
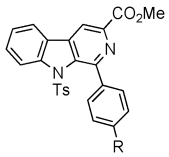
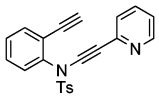
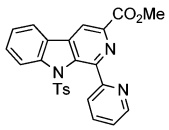
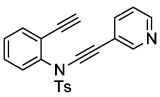
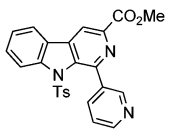
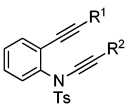
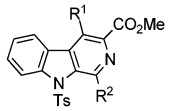
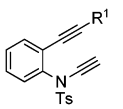
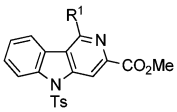
Mixtures of regioisomeric β- and γ-carbolines were obtained when symmetrically substituted yne-ynamides were subjected to the [2+2+2] cycloaddition reaction (Table 1, entries 10–13). These results strongly indicate that the regioselective outcome of the co-cyclisation is directed by the substitution pattern on the starting yne-ynamide. Indeed, with the cycloaddition precursors **12**, **14**, and **16** both catalysts now provided γ-carbolines. The Cp*RuCl(cod) complex afforded the γ-carbolines **13**, **15**, and **17** as a single isomer in 46%, 52% and 67% yield respectively (Table 1, entries 14, 16, and 17). Here, the cationic Rh-catalysts gave the corresponding γ-carbolines as the major products, and with a steric increase of the substituent on the alkyne moiety the ratio of regioisomers was significantly raised (Table 1, entries 15 and 18). These results are in agreement with other studies concerning the regioselective outcome of [2+2+2] cycloadditions of tethered diynes with nitriles.[16] In all examples studied within the carboline series reported here, the Cp*RuCl(cod) catalyst was less reactive but more selective than the cationic rhodium-based catalyst generated from $[Rh(cod)_2]BF_4$ and BINAP.

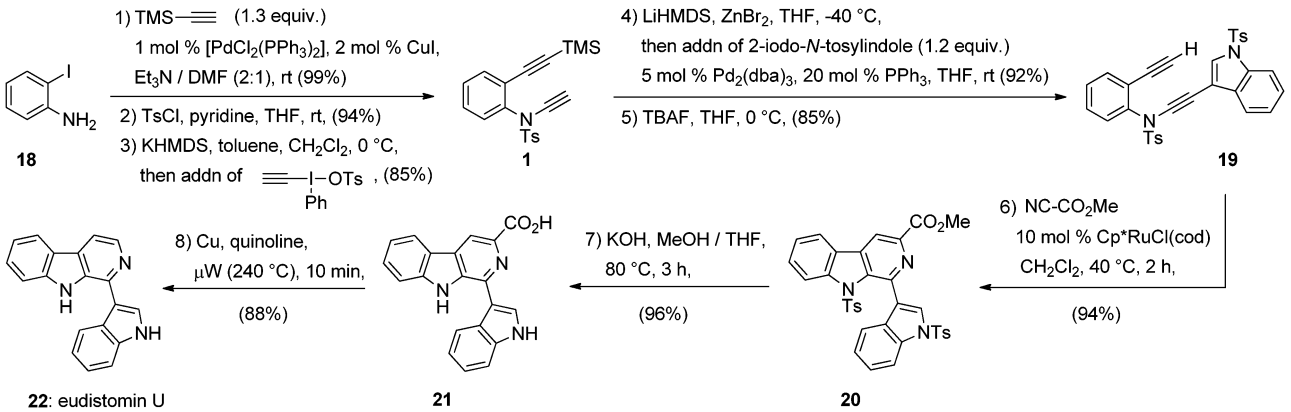
With the aim to underline the applicability of this new atom- and step economic approach towards either β- or γ-carbolines, the total synthesis of the β-carboline eudistomin U (**22**) was targeted (Scheme 3). Eudistomin U was isolated from the Caribbean ascidian *Lissoclinum fragile* and showed DNA binding and antimicrobial properties.[17,18]

Our synthesis commenced with commercially available 2-iodoaniline (**18**) that was transformed into the yne-ynamide **1** *via* three steps including a Sonogashira coupling with trimethylsilyl acetylene and the *N*-ethynylation of the tosylamide moiety with ethynyliodonium triflate (Scheme 3). The Negishi reaction of **1** with 3-iodo-*N*-tosylindole was followed

Table 1 Synthesis of β-carbolines and γ-carbolines



Entry	Yne-ynamide	Method	Product	Ratio β : γ	Yield (%)
					
1	**3**	**A**	**7**	100 : 0	92
2	**3**	**C**	**7**	75 : 25	84
					
3	**6a** R = H	**A**	**8a** R = H	100 : 0	61
4	**6a** R = H	**C**	**8a** R = H	92 : 8	95
5	**6b** R = OMe	**A**	**8b** R = OMe	100 : 0	60
					
6	**6c**	**A**	**8c**	—	0
7	**6c**	**C**	**8c**	—	0
					
8	**6d**	**A**	**8d**	100 : 0	70
9	**6d**	**C**	**8d**	—	0
					
10	**9** $R^1 = R^2 = H$	**A**	**10** $R^1 = R^2 = H$	30 : 70	70
11	**9** $R^1 = R^2 = H$	**C**	**10** $R^1 = R^2 = H$	40 : 60	40
12	**4** $R^1 = R^2 = CH_3$	**B**	**11** $R^1 = R^2 = CH_3$	50 : 50	87
13	**4** $R^1 = R^2 = CH_3$	**C**	**11** $R^1 = R^2 = CH_3$	60 : 40	84
					
14	**12** $R^1 = CH_3$	**B**	**13** $R^1 = CH_3$	0 : 100	46
15	**12** $R^1 = CH_3$	**C**	**13** $R^1 = CH_3$	40 : 60	83
16	**14** $R^1 = C_5H_{11}$	**B**	**15** $R^1 = C_5H_{11}$	0 : 100	52
17	**16** $R^1 = C_6H_5$	**B**	**17** $R^1 = C_6H_5$	0 : 100	67
18	**16** $R^1 = C_6H_5$	**C**	**17** $R^1 = C_6H_5$	7 : 93	65



Scheme 3 Application of this new β-carboline synthesis in the total synthesis of eudistomin U (**22**).

by a desilylation with TBAF to provide the yne-ynamide **19** (78% yield over two steps). The Cp*RuCl(cod) catalysed [2+2+2] cycloaddition of **19** with methylcyanoformate (7 equiv.) gave rise to the β-carboline ester **20** (94% yield) that was thereafter saponificated with simultaneous removal of the *N*-carboline and *N*-indolyl tosyl groups to provide the β-carboline carboxylic acid **21** (96% yield). Finally, decarboxylation of **21** with the help of copper powder under microwave irradiation afforded eudistomin U (**22**, 88% yield) whose spectroscopic data were identical to that of natural material.[17]

In conclusion an expedient method for the synthesis of either β- or γ-carbolines based on ruthenium or rhodium-catalysed [2+2+2] cycloaddition reactions was developed. This new method for the construction of the β-carboline framework was applied in the total synthesis of the marine natural product eudistomin U that was achieved within 8 steps and with 49% overall yield starting from commercially available 2-iodoaniline.

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