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Direct and Selective Functionalization of a Tetrahydro-β-carboline at Position 4

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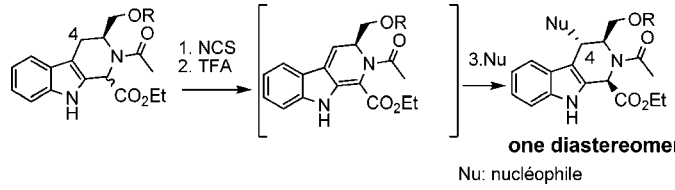
ABSTRACT



The first example of direct functionalization of a tetrahydro-β-carboline (THBC) at position 4 is presented. Nucleophiles with various reactivity add to a transient intermediate generated in situ from this THBC. This reaction proceeds with a total control of the two created stereogenic centers.

Tetrahydro-β-carbolines (THBCs) are widespread skeletons frequently encountered in indole alkaloids (as neonaucleoside C[1] (**1**) and jadiffine[2] (**2**)) and in a large number of synthetic compounds that often display various and important biological activities[3] (Figure 1). For example, fumitremorgine C (**3**) and demethoxyfumitremorgine C (**4**), both isolated from *Aspergillus fumigatus*, reverse multidrug resistance and increase cytotoxicity of several anticancer agents in vitro.[4]

THBCs are also common precursors of β-carbolines, well-known to possess activity in the central nervous system at serotonin receptors (like ZK 93423 (**5**)).[5]

While C1- and C3-functionalized THBCs can be easily prepared by a Pictet−Spengler condensation between appropriate reactants, the direct elaboration of 4-substituted THBCs is, however, still challenging, and multistep procedures are required. Typically, synthesis of such compounds involves introduction of the 4-substituent prior to the Pictet−Spengler cyclization.[6] As an alternative to this conventional strategy, Bandini and co-workers have described an interesting method to prepare 4-functionalized THBCs by an intramolecular indium-catalyzed Michael

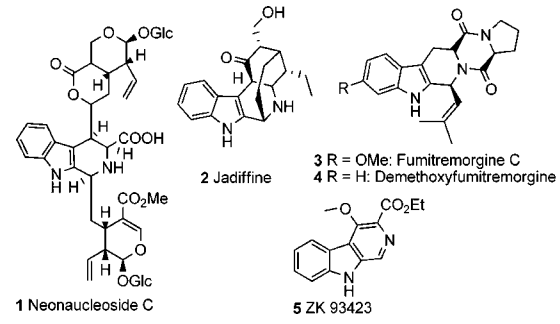


Figure 1. Structures of molecules containing the THBC skeleton.

(1) Itoh, A.; Tanahashi, T.; Nagakura, N.; Nishi, T. *Phytochemistry* **2003**, *62*, 359–369.

(2) Garnier, J.; Mahuteau, J.; Plat, M.; Merienne, C. *Phytochemistry* **1989**, *28*, 308–309.

(3) Trujillo, J. I.; Meyers, M. J.; Anderson, D. R.; Hedge, S.; Mahoney, M. W.; Vernier, W. F.; Buchler, I. P.; Wu, K. K.; Yang, S.; Hartmann, S. J.; Reitz, D. B. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4657–4663.

(4) (a) Kodato, S.; Nakagawa, M.; Hongu, M.; Kawate, T.; Tohru, H. *Tetrahedron* **1988**, *44*, 359–377. (b) Limbach, M.; Surayakanta, D.; Janssen, A.; Es-Sayed, M.; Magull, J. M.; de Meijere, A. *Eur. J. Org. Chem.* **2005**, 610–617.

(5) Hollinshead, S. P.; Trudell, M. L.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1990**, *33*, 1062–1069.

(6) (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842. (b) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608–9645.

(7) Agnusdei, M.; Bandini, M.; Melloni, A.; Umani-Ronchi, A. *J. Org. Chem.* **2003**, *68*, 7126–7129.

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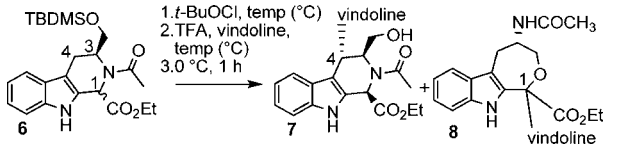
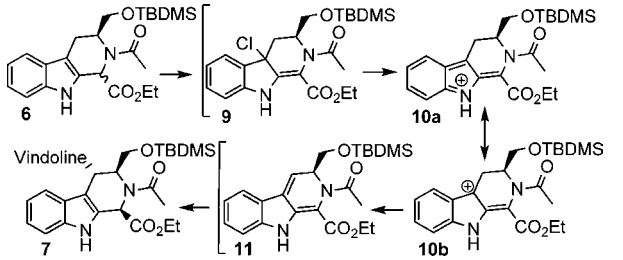
Table 1. Effect of the Temperature on the Regiochemistry of the Functionalization of THBCs[a]



		ratio[b]	
entry	temp (°C)	**7** (%)	**8** (%)
1	−30	28	72
2	0	100	0

[a] Reaction conditions: **6** (1 equiv) and *t*-BuOCl (1.1 equiv) in CH_2Cl_2 under argon at reaction temperature (°C) for 10 min, then addition of TFA (10 equiv) and vindoline (1 equiv) and stirring during 1 h at 0 °C. [b] Ratios calculated on the ^{1}H NMR spectra of the crude mixture.

Scheme 1. Proposed Mechanism



addition as the final key step.[7] More recently, the group has prepared 4-vinyl-THBCs via a Pd-catalyzed intramolecular allylic alkylation.[8] While these new approaches are very elegant and efficient in terms of yield, they require the preparation of the appropriate reactant for each targeted 4-functionalized THBC and do not permit the elaboration of a common intermediate in a library format.

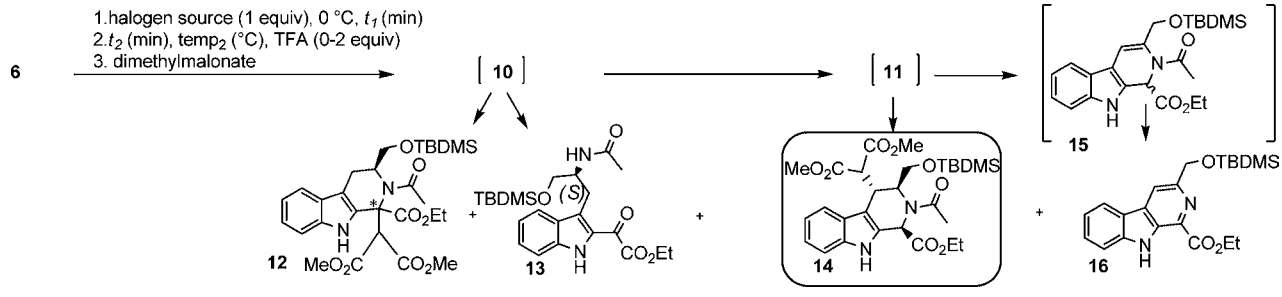
In the course of our study of vinblastine−phomospine hybrids,[9] we intended to functionalize THBC **6**[10] at the C1 position via a chloroindolenine intermediate.[11] We noticed that varying the temperature of the reaction produced a change in the regioselectivity of the nucleophilic attack.

When THBC **6** was treated with *t*-BuOCl at −30 °C and with vindoline as a nucleophile, the major product was the rearranged compound **8** arising from the unstable 1-substituted THBC,[12] whereas at 0 °C the unexpected 4-functionalized THBC **7** was solely isolated (Table 1).

The proposed mechanism for the formation of **7** is described in Scheme 1. First, the chloroindolenine **9** generated from **6** could lead, in the presence of TFA, to a cationic intermediate **10**.[13] Then spontaneous elimination of the adjacent proton on **10b** could give product **11**. Transient **11** behaves like a super-reactive Michael acceptor and thus could be trapped quickly by the electron-rich vindoline to form the 4-functionalized THBC **7**. This intermediate is similar to reactive indolenines generated from gramine or 3-substituted indoles by departure of a good leaving group or C−H activation.[6b,14] Its formation depends on the temperature of the reaction, as illustrated by the formation of **7** at 0 °C versus formation of **8** at −30 °C.

To improve the scope of this reaction, it was necessary to optimize the experimental conditions, and the highly reactive deprotonated dimethylmalonate was chosen as a nucleophile for that purpose. In fact, in order to be able to functionalize THBC (**6**) with any kind of nucleophiles (even charged ones),

Table 2. Optimization of the Reaction Conditions for the Selective C4 Functionalization of THBC **6**[a]

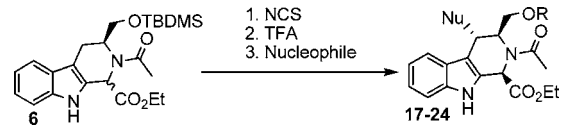


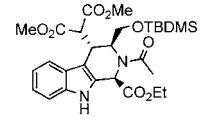
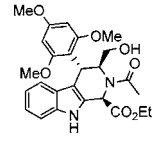
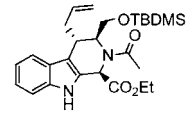
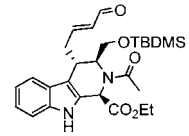
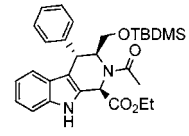
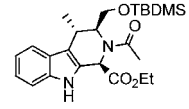
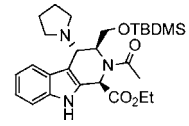
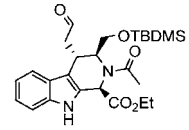
						products[b] (%)			
entry	halogen source	stirring time t_1 (min)	TFA (equiv)	stirring time t_2 (min)	strirring temp$_2$ (°C)	**12**	**13**	**14**	**16**
1	*t*-BuOCl	10	0	15	20	40	0	60	0
2	*t*-BuOCl	10	0	25	20	30	0	35	35
3	*t*-BuOCl	10	1	5	0	33	24	43	0
4	*t*-BuOCl	10	1	15	20	16	33	16	33
5	*t*-BuOCl	10	2	5	0	0	31	69	0
7	NCS	15	1	5	0	0	0	100	0
8	NCS	15	0	15	20	0	33	77	0

[a] Reaction conditions: THBC **6** (1 equiv) and halogen source (1 equiv) in CH_2Cl_2 under argon at 0 °C, stirring for t_1, then addition of TFA and stirring for t_2 at temp$_2$, and finally addition of deprotonated dimethyl malonate (3 equiv) and stirring at −20 °C for 30 min. [b] Ratios calculated on ^{1}H NMR spectra of the crude mixture.

it was necessary to generate first selectively the transient intermediate **11** and to decrease the amount of TFA. Five main factors that influence reaction efficiency and regioselectivity were identified: (1) halogen source, (2) stirring time to form the haloindolenine t_1, (3) addition of TFA, (4) temperature $temp_2$, and (5) stirring time t_2 before addition of dimethyl malonate. Table 2 summarizes the observed results. When *t*-BuOCl was used as a chlorine source (entries 1−5), THBC (**6**) was completely converted to the chloroindolenine **9** in 10 min. Without TFA, when the reaction mixture was stirred for 15 min at 0 °C before the addition of dimethyl malonate, a mixture of the desired 4-functionalized THBC **14** and the 1-functionalized THBC **12** was obtained in a 6/4 ratio respectively (entry 1). The conversion of the cationic intermediate **10** to compound **11** was not total in these conditions. When t_2 was increased in order to promote the selective formation of **14**, a mixture of **12**, **14**, and **16** was observed (entry 2). Carboline **16** should come from an aromatization of intermediate **15**.[15] This latest product may arise from a 1,5 sigmatropic rearrangement of **11**[15] that occurred even though the cationic intermediate **10** was not totally converted to **11**, as indicated by the formation of **12**. As the 1,5 sigmatropic rearrangement of **11** is faster than its formation, these conditions are neither suitable nor improvable. We then studied the reaction in the presence of TFA (entries 3−5). With 1 equiv of TFA at 0 °C, a mixture of **12**, **14**, and a new compound **13** was obtained (entry 3).[16] Increasing t_2 and $temp_2$ (entry 4) or the quantity of TFA (entry 5) did not improve the amount of the desired **14**. Since the results obtained with *t*-BuOCl were not completely satisfactory, and as it was necessary to prepare fresh *t*-BuOCl prior to use for reproductible results, we investigated others halogen sources. When the reaction was carried out with NBS, a complex mixture of unidentified compounds was obtained. Finally, NCS gave the best results and led selectively to the desired 4-functionalized THBC **14** (entry 7). Experimental conditions were smooth, and the reaction was very fast and efficient. The role of TFA was essential as it allowed the formation of the Michael acceptor in a very short and reproductible time thus avoiding the formation of side products (entry 8).

Table 3. Scope of the Reaction of Functionalization of THBCs at Position 4



entry	nucleophile	product[a]	yield [b](%)	configuration
1	MeO_2C CO_2Me	 **17**	55	(1*R*,4*S*)
2	MeO, OMe, OMe	 **18**	46[c]	(1*R*,4*R*)
3	$SiMe_3$	 **19**	75	(1*R*,4*S*)
4	$OSiMe_3$	 **20**	79	(1*R*,4*S*)
5	Ph_2CuLi	 **21**	75	(1*R*,4*S*)
6	Me_2CuLi	 **22**	75	(1*R*,4*S*)
7		 **23**	46[d]	(1*R*,4*S*)
8	EtO	 **24**	41	(1*R*,4*S*)

[a] Reaction conditions: THBC **6** (1 equiv) and NCS (1.2 equiv) in CH_2Cl_2 under argon at 0 °C, stirring for 15 min, then addition of TFA (1 equiv) and stirring for 5 min at 0 °C, and finally addition of the nucleophile and stirring for 20−60 min. [b] Isolated yields after alumina or silica gel chromatography. [c] 10 equiv of TFA was added at the end of the reaction to achieve total deprotection of the alcohol that occurred partially spontaneously. [d] Compound **23** was unstable: fast departure of the pyrrolidine group regenerates the Michael acceptor **11**.

Having established an optimal set of conditions, we applied this reaction to various nucleophiles (Table 3). Each time, the crude mixture only contained the expected 4-functionalized THBC. The reaction proceeded efficiently with a wide

(8) Bandini, M.; Alfonso, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2003**, *128*, 1424–1425.

(9) Ngo, Q. A.; Roussi, F.; Cornier, A.; Thoret, S.; Knossow, M.; Guénard, D.; Guéritte, F. *J. Med. Chem.* **2009**, *52*, 134–142.

(10) THBC **6** was obtained in four steps from L-tryptophane (50% yield). For more details, see the Supporting Information.

(11) For a general review on haloindolenines, see: (a) Ikeda, M.; Tamura, Y. *Heterocycles* **1980**, *14*, 867–888. (b) For an example of the use of choroindolenine in synthesis, see: Miyazaki, T.; Yokoshima, S.; Simizu, S.; Osada, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 4737–4740.

(12) For a similar rearrangement, see: Pouillhès, A.; Kouklovsky, C.; Langlois, Y.; Baltaze, J. P.; Vispe, S.; Annereau, J. P.; Barett, J. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1212–1216, and references cited therein.

(13) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *Tetrahedron* **1980**, *36*, 3053–3060.

(14) (a) Colombo, F.; Cravotto, G.; Palmisano, G.; Penoni, A.; Sisti, M. *Eur. J. Org. Chem.* **2008**, 2801–2807. (b) Palmieri, A.; Petrini, M. *J. Org. Chem.* **2007**, *72*, 1863–1866. (c) De la Herrán, G.; Segura, A.; Csákÿ, A. G. *Org. Lett.* **2007**, *9*, 961–964. (d) Matsuo, J.; Tanaki, Y.; Ishibashi, H. *Tetrahedron* **2008**, *64*, 5262–5267. (e) For a similar intermediate, see also: Nicolaou, K. C.; Lee, S.; Estrada, A. A.; Zak, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3736–3740.

(15) For a similar rearrangement, see: Irikawa, H.; Mutoh, S.; Uehara, M.; Okumura, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3031–3033.

(16) Compound **13** should come from the hydrolysis of an imminium, mesomeric form of **10**. For a similar example, see: Pouilhès, A.; Langlois, Y.; Chiaroni, A. *Synlett* **2003**, *10*, 1488–1490.

range of nucleophiles; electron-rich aromatics (entry 2), allyl silanes (entry 3), silyl enol ether (entry 4), cuprates (entries 5 and 6), and heterocycles (entry 7). Finally, the in situ formed Michael acceptor could even react with ethyl vinyl ether to form the aldehyde **24** by mild deprotection of the ethoxy group (entry 8). Yields of purified compounds ranged between 46% and 79%. Some of these values seem low compared to the crude mixture which suggests that the final products are not stable on silica gel or alumina.

In this reaction, the formation of the two new stereogenic centers C1 and C4 was totally controlled, and only one out of the four possible diastereomers was obtained each time. The relative configuration of desilylated compound **17** was established by X-ray crystallography analysis (Figure 2). The

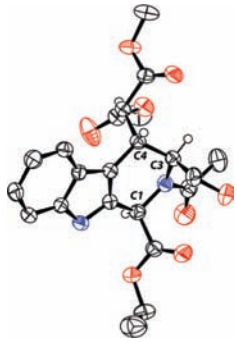
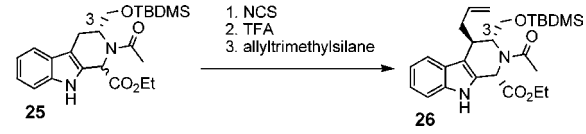


Figure 2. X-ray structure of desilylated compound **17**.

(1*R*,4*S*) configuration was deduced from the known absolute configuration of the C3 center. The carbethoxy group and the lateral chain are *syn* to each other, *anti* to the malonate moiety. The value of the dihedral angle between the planes H4−C4−C3 and C4−C3−H3 is around 90° which is reflected by an absence of coupling between H3 and H4 in the COSY spectrum. The same observation could be made for all the other compounds which allowed us to deduce by analogy their absolute configurations (Table 3). The configuration at C4 could be explained by an attack of the nucleophiles *anti* to the hindered lateral chain at C3. As for C1, the observed diastereomers may arise from a keto−enol ester equilibrium leading to the thermodynamic compounds.

Starting from **25** with an opposite configuration at C3 compared to **6** and using allyltrimethylsilane as a nucleophile, we obtained exclusively the functionalized THBC **26**, the enantiomer of **19** (Scheme 2). This clearly indicates that the

Scheme 2. Influence of the C3 Configuration on the Diastereoselectivity of the Reaction



C-4 functionalization is enantiospecific and that the lateral chain at C3 governs the selectivity of the reaction.

In summary, we have developed a convenient, one-pot, highly selective functionalization of compound **6** at position 4 with various nucleophiles. This is the first example of a direct functionalization of THBCs at C4. We are currently investigating the application of this methodology to the synthesis of 4-substituted analogues of active THBCs.

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Supporting Information Available: Experimental procedures, characterization data for all new compounds, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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