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Authors: Jiří Mikušek, Petr Jansa, Pratap R. Jagtap, Tomáš Vašíček, Ivana Císařová, and Eliška Matoušová

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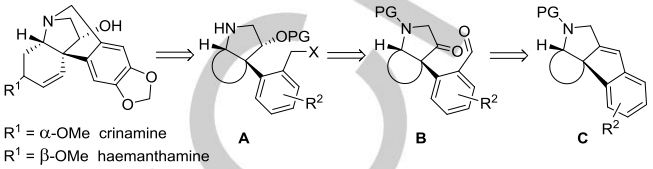
Enantioselective Synthesis of All-Carbon Quaternary Centers Structurally Related to Amaryllidaceae Alkaloids

Jiří Mikušek, Petr Jansa, Pratap R. Jagtap, Tomáš Vašíček, Ivana Císařová, and Eliška Matoušová*

Abstract: Enantioselective synthesis of all-carbon quaternary centers remains a considerable challenge for synthetic organic chemists. Here, we report a two-step protocol to synthesize such centers including tandem cyclization/Suzuki cross-coupling followed by halocarbocyclization. During this process, two rings, three new C-C bonds and a stereochemically defined all-carbon quaternary center are formed. The absolute configuration of this center is controlled by the stereochemistry of the adjacent stereocenter, which derives from an appropriate enantioenriched starting material. Using this method, we synthesized polycyclic compounds structurally similar to *Amaryllidaceae* alkaloids in high enantiomeric excesses. Because these products resemble naturally occurring compounds, our protocol can be used to synthesize various potentially bioactive compounds.

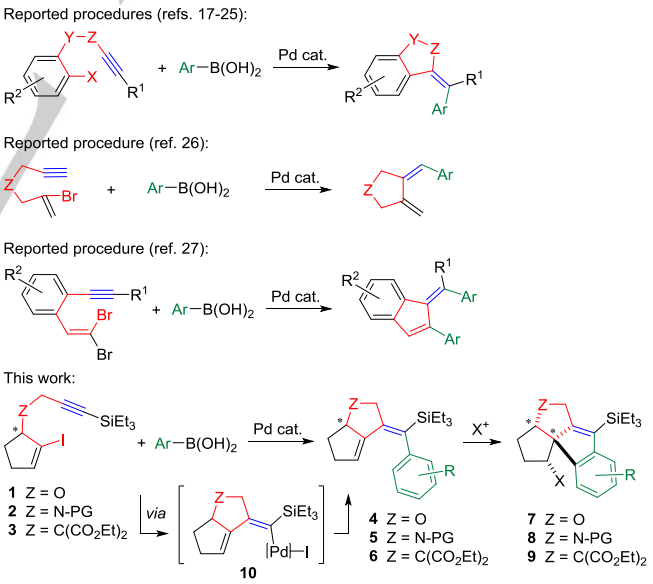
Alkaloids with a crinane skeleton are an important subclass of *Amaryllidaceae* alkaloids containing all-carbon quaternary centers. These alkaloids have valuable biological effects, including cytotoxic,[1] antimalarial[2] or antiinflammatory[3] activities. Crinamine and haemanthamine, for example, are potent and selective cytotoxic agents (Scheme 1).[4,5] However, the synthesis of such natural products requires the enantioselective formation of an all-carbon quaternary center. Although many research groups have developed methods for the enantioselective synthesis of all-carbon quaternary centers,[6–12] this remains a challenging task requiring further investigation.

Considering our interest in the synthesis of biologically active alkaloids and their analogues, we sought to develop an approach that would allow us to form all-carbon quaternary centers with good stereocontrol. Our proposed retrosynthetic analysis of the target alkaloids (Scheme 1) shows that they could be derived from **A** by intramolecular nucleophilic substitution forming the methylene bridge. In turn, compound **A** could be made from dicarbonyl **B**, which would be the product of oxidative cleavage of a double bond in tetracycle **C**. The stereochemistry of the all-carbon quaternary center in **C** would remain unaffected by this process.



Scheme 1. Retrosynthetic analysis of crinane-type *Amaryllidaceae* alkaloids.

Hence, our attention turned to the enantioselective synthesis of **C**-like compounds. We decided to start with the five-membered analogues of our target alkaloids because we expected a preferential *cis*-fusion between the two rings, which would increase the stereoselectivity. The formation of a tetracyclic skeleton similar to that of compound **C** has been previously described in only three reports.[13–15] However, in contrast to our targets, the reported products were carbocyclic (angular triquinanes), their syntheses were based on acid-promoted rearrangements and lacked enantiocontrol.



Scheme 2. Tandem reaction – comparison between reported procedures and our approach.

In order to develop an efficient method, we explored the possibility of including tandem reactions in our sequence. We envisioned that palladium-catalyzed tandem cyclization/Suzuki cross-coupling followed by halocarbocyclization could be a convenient approach to the synthesis of all-carbon quaternary centers. The tandem reaction consisting of cyclic carbopalladation[16] and subsequent Suzuki cross-coupling with

[*] Dr. J. Mikušek, P. Jansa, Dr. P. R. Jagtap, T. Vašíček, Dr. E. Matoušová
Department of Organic Chemistry
Faculty of Science, Charles University
Praha, 128 43 (Czech Republic)
E-mail: eliska.matousova@natur.cuni.cz
Dr. I. Císařová
Department of Inorganic Chemistry
Faculty of Science, Charles University
Praha, 128 43 (Czech Republic)

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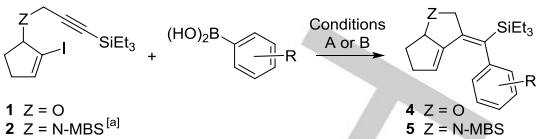
aryl halides as starting materials[17–21] has been previously applied to the synthesis of natural products and bioactive compounds.[22–25] However, to our knowledge, only two methods have been reported using alkenyl halides,[26] and alkenyl dihalides[27] as starting compounds. Moreover, the reported procedures prevented further cyclization of the products to form an all-carbon quaternary center (Scheme 2, refs. 17-25) or they lacked any form of stereocontrol (refs. 26 and 27).

In this study, we selected alkenyl iodides **1-3** as starting materials to transform the products of the tandem reaction **4-6** into the polycyclic compounds **7-9**, respectively, by halocarbocyclization[28] (Scheme 2). In the second step, the all-carbon quaternary center of the defined configuration is formed. In fact, *cis*-fusion between the two five-membered rings should be the only possible stereochemical outcome of cyclization because the energy difference between *cis*- and *trans*-fused bicyclo[3.3.0]octanes is sufficiently high for any *trans*-fused compound to equilibrate to the *cis*-isomer immediately.[29] Thus, we should be able to control the absolute configuration of the quaternary center when the corresponding enantioenriched starting material **1**, **2** or **3** is employed. Notably, halocarbocyclization has been used before to prepare spirocycles,[30–32] and also in total synthesis[33–35] but not to synthesize quaternary centers.

To test our method, we subjected compound **1** to a reaction with methylenedioxyphenylboronic acid under Suzuki cross-coupling conditions ($Pd(PPh_3)_4$ (4 mol%), Na_2CO_3, refluxing benzene). Fortunately, we were able to isolate the desired product **4a** with an 80% yield in this initial experiment. The yield was further improved, up to 98%, by changing the solvent and the base. We then used these modified conditions to explore the scope of the tandem reaction (Table 1). Starting compounds **1** and **2** were converted into products **4** and **5**, respectively, with high yields and good *Z*/*E* ratios with all tested arylboronic acids, regardless of their electronic properties. Generally, the *Z*/*E* ratios were better for nitrogen-containing products **5** (entries 7–12) than for their oxygen congeners (entries 1–6) and always yielding the desired *Z* isomer as the main product, which is the only product that undergoes subsequent halocyclization (see Table S1 in the Supporting Information for additional experiments). The minor *E* isomer was presumably formed by isomerization of intermediate **10** (Scheme 2). Such isomerization was previously described for 1-silyl-1-metalloalkenes.[36] In addition to the aforementioned heteroatom-containing substrates, we performed an experiment with carbocyclic substrate **3**, generating product **6b** with a good yield and with an excellent *E*/*Z* ratio (Entry 13).

The presence of triethylsilyl group in our starting compounds was necessary to ensure the high yield of the reaction. We also tested different capping groups. However, in these cases, the following side reactions were observed, depending on the capping group: isomerization of the product, when using the methyl group; partial desilylation in the following step, when using trimethylsilyl; low yield and isomerization of the product, when using uncapped substrate. Moreover, in the subsequent halocarbocyclization the triethylsilyl group hindered the attack of electrophile on the adjacent double bond.

Table 1. Scope of the tandem cyclization/Suzuki cross-coupling reaction.



1 Z = O
2 Z = N-MBS[a]
3 Z = $C(CO_2Et)_2$

4 Z = O
5 Z = N-MBS
6 Z = $C(CO_2Et)_2$

Entry	**1-3**	R	Conditions[b]	Time [h]	Product	Yield[c] [%]	Ratio *Z* / *E*
1	**1**	3,4-OCH_2O	A	4	**4a**	98	73 / 27
2	**1**	4-OCH_3	A	4	**4b**	98	75 / 25
3	**1**	4-CH_3	A	3	**4c**	89	87 / 13
4	**1**	H	A	3	**4d**	98	74 / 26
5	**1**	4-CF_3	B[d]	25	**4e**	74	77 / 23
6	**1**	2,4-diF	B[d,e]	19	**4f**	67	91 / 9
7	**2**	3,4-OCH_2O	B	23	**5a**	94	93 / 7
8	**2**	4-OCH_3	B	45	**5b**	96	92 / 8
9	**2**	4-CH_3	A	3	**5c**	98	88 / 12
10	**2**	H	A	3.5	**5d**	90	90 / 10
11	**2**	4-CF_3	B	19	**5e**	98	90 / 10
12	**2**	2,4-diF	B	17.5	**5f**	94	93 / 7
13	**3**	4-OCH_3	B	16	**6b**	83	1 / 99

[a] MBS = 4-methoxybenzenesulfonyl. [b] A: $Pd(PPh_3)_4$ (4 mol%), K_2CO_3 (4 eq), and boronic acid (1.6 eq) at 80 °C in toluene/H_2O (4:1). B: $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (2 eq) and boronic acid (1.6 eq) in THF/H_2O (10:1). [c] Isolated yield. [d] 2.6 eq of Cs_2CO_3 was used. [e] 1.3 eq of boronic acid was used.

Halocarbocyclization of compounds **4-6** was first attempted using *N*-bromosuccinimide (NBS), albeit with unsatisfactory results. Further reagent screening showed that *N*-iodosuccinimide (NIS) provided the best yields in the cyclizations of **4a** and **5a** (Table 2, entries 1, 8), whereas Snyder's BDSB[37] was more suitable for all other starting compounds (compare entries 5 vs. 6, and 10 vs. 11). The reaction proceeded well when using substrates containing electron-donating groups on the aromatic ring (entries 3, 10, 11, 12). Conversely, no compound with electron-poor aromatics was involved in halocarbocyclization; accordingly, we observed only traces or no product formation in such instances (entries 7, 14, 15). Nitrogen-containing products **8** were formed with higher yields (entries 8–13), especially after changing the solvent to DCM, than oxygen derivatives **7** (entries 1–6). This result may be attributed to the lower stability of compounds **4**, both during storage and under the reaction conditions tested. Carbocyclic compound **6b** was also subjected to halocyclization with BDSB, and the corresponding product **9bb** was generated with a 68% yield (Entry 16).

To gather solid evidence on the stereochemistry of this reaction, we prepared a crystal of product **7ai** suitable for X-ray analysis. The resulting data[38] confirmed the expected relative configuration of **7ai** and that the two saturated five-membered rings are *cis*-fused, as predicted. This result prompted us to explore an enantioselective version of our synthesis.

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Table 2. Scope of halocarbocyclization.

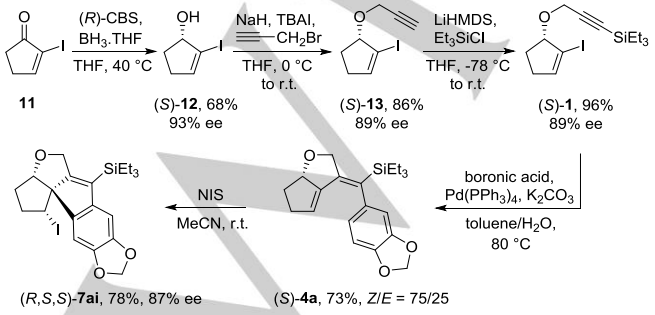
4 Z = O
5 Z = N-MBS[a]
6 Z = $C(CO_2Et)_2$

7 Z = O
8 Z = N-MBS
9 Z = $C(CO_2Et)_2$

Entry	4-6	R	Reagent[b]	Time [h]	Solvent	Product	Yield[c]
1	**4a**	3,4-OCH_2O	NIS	1	MeCN	**7ai**	82
2	**4a**	3,4-OCH_2O	BDSB[d]	0.5	MeCN	**7ab**	26
3	**4b**	4-OCH_3	BDSB	1	DCM	**7bb**	50
4	**4c**	4-CH_3	BDSB	0.3	MeCN	**7cb**	32
5	**4d**	H	NIS	15	MeCN	**7di**	0
6	**4d**	H	BDSB	0.6	MeCN	**7db**	37
7	**4e**	4-CF_3	BDSB	0.6	MeCN	**7eb**	traces
8	**5a**	3,4-OCH_2O	NIS	1	MeCN	**8ai**	98
9	**5a**	3,4-OCH_2O	BDSB	0.5	DCM	**8ab**	59
10	**5b**	4-OCH_3	NIS	1.3	MeCN	**8bi**	60
11	**5b**	4-OCH_3	BDSB	0.6	MeCN	**8bb**	77
12	**5c**	4-CH_3	BDSB	0.5	DCM	**8cb**	80
13	**5d**	H	BDSB	1.3	DCM	**8db**	74
14	**5e**	4-CF_3	BDSB	0.6	DCM	**8eb**	traces
15	**5f**	2,4-diF	BDSB	1.5	DCM	**8fb**	0
16	**6b**	4-OCH_3	BDSB	0.2	MeCN	**9bb**	68

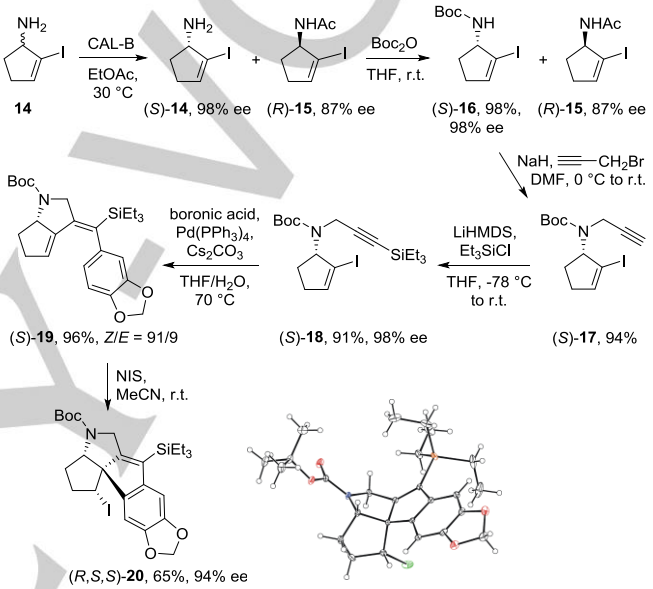
[a] MBS = 4-methoxybenzenesulfonyl. [b] Reactions were performed with 1.2 eq. of NIS or 1.05 eq. of BDSB. [c] Isolated yield based on the *Z* isomer of the starting material. [d] Bromodiethylsulfonium bromopentachloroantimonate (see ref. 34).

To prepare enantioenriched compounds **1** and **2**, we used asymmetric Corey-Bakshi-Shibata reduction of ketone **11**,[39] yielding alcohol (*S*)-**12** with high enantiomeric excess (up to 99% ee after recrystallization). The proof-of-concept synthesis of oxygen-containing compound (*R*,*S*,*S*)-**7ai** was performed using alcohol (*S*)-**12** with 93% ee (Scheme 3). The alcohol was alkylated, and the resulting terminal alkyne (*S*)-**13** was protected with triethylsilyl group to give (*S*)-**1**. Then, (*S*)-**1** was subjected to the tandem reaction with methylenedioxyphenylboronic acid followed by halocarbocyclization under standard conditions, and the final pentacyclic product, (*R*,*S*,*S*)-**7ai**, was formed with an 87% ee. Notably, the overall loss of optical purity was only 6% in the entire reaction sequence.



Scheme 3. Enantioselective synthesis of the oxygen-containing (*R*,*S*,*S*)-**7ai**.

Encouraged by these results, we proceeded with the enantioselective synthesis of the nitrogen-containing compound **8ai**. Our original reaction sequence was based on the Mitsunobu reaction of the enantioenriched alcohol (*S*)-**12** with a protected propargylamine (Section 5.2 in the Supporting Information). Unfortunately, the anticipated inversion of configuration did not occur in this step, and the ee value decreased from 99% to 72%. This result was attributed to the competing S_N2' mechanism, which has been previously reported for allylic alcohols.[40] Importantly, the enantiomeric excess did not decrease in the following reactions, and the final product (*S*,*R*,*R*)-**8ai** was isolated with a 76% ee.



Scheme 4. Chemoenzymatic synthesis of the nitrogen-containing (*R*,*S*,*S*)-**20**.

These results showed that our method is suitable for enantioselective formation of all-carbon quaternary centers but only if the substrate can be prepared with higher enantioselectivity. To this end, we decided to use a commercially available *Candida antarctica* lipase B (CAL-B), which has been shown to be an effective catalyst to prepare chiral amines and amides,[41] for enzymatic kinetic resolution. The enzymatic reaction was performed with the racemic primary amine **14**, prepared from alcohol **12** by Gabriel synthesis, and generated a mixture of amine (*S*)-**14** and amide (*R*)-**15** in high enantiomeric excesses (Scheme 4). Due to difficulties in isolating the amine, the mixture was directly treated with Boc anhydride to yield carbamate (*S*)-**16** and amide (*R*)-**15**, easily separable from each other by column chromatography. The isolated carbamate (*S*)-**16** was then alkylated with propargyl bromide, providing alkyne (*S*)-**17** in 94% yield, albeit only when replacing the solvent by DMF. Subsequent capping with Et_3SiCl yielded compound (*S*)-**18**, which was then subjected to the tandem reaction/halocarbocyclization sequence under standard conditions. We observed no significant decrease in enantiomeric excess throughout the reaction sequence, and the final product

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(*R*,*S*,*S*)-**20** was isolated with a 65% yield and 94% ee. A single-crystal X-ray analysis of the final product provided an unequivocal confirmation of its absolute configuration.[42]

In summary, we showed that our method is as an efficient tool for the enantioselective synthesis of polycyclic compounds containing all-carbon quaternary centers. The method is particularly suitable for substrates bearing electron-rich aromatic rings. Because methylenedioxy-substituted phenyl rings occur widely in natural alkaloids, such as those depicted in Scheme 1, we designed our targeted compounds to have this substitution. We successfully synthesized products (*R*,*S*,*S*)-**7ai** and (*R*,*S*,*S*)-**20** with high yield and enantioselectivity (87 and 97% ee, respectively). The proposed absolute configuration of compound (*R*,*S*,*S*)-**20** and the relative configuration of compound **7ai** were unambiguously confirmed by a single-crystal X-ray analysis. Furthermore, we are currently applying this method to synthesize crinane-type *Amaryllidaceae* alkaloids and their derivatives.

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Keywords: alkaloids • all-carbon quaternary centers • cyclization • enantioselectivity • synthetic methods

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[42] See the Supporting Information for details. CCDC 1837916 (**20**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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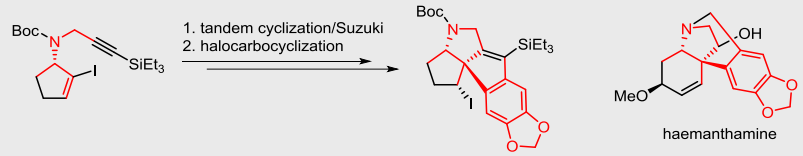

62% yield in two steps, 94% ee

A two-step protocol for an enantioselective synthesis of all-carbon quaternary centers is reported. Using this method, we synthesized polycyclic compounds structurally similar to *Amaryllidaceae* alkaloids in high yield and enantioselectivity.

*Jiří Mikušek, Petr Jansa, Pratap R. Jagtap, Tomáš Vašíček, Ivana Císařová, and Eliška Matoušová**

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Enantioselective Synthesis of All-Carbon Quaternary Centers Structurally Related to Amaryllidaceae Alkaloids

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