EurJOC
European Journal of Organic Chemistry

Research Article
doi.org/10.1002/ejoc.202400035

Chemistry Europe
European Chemical Societies Publishing

www.eurjoc.org

A Short Synthesis of (−)-6,7-Secoagroclavine via Metal-Free Reductive Coupling

Francesca Diotallevi,[a] Francesca Bartoccini,*[a] and Giovanni Piersanti*[a]

A concise, convergent, and enantioselective synthesis of (−)-6,7-secoagroclavine, a pivotal intermediate in the synthesis of both clavine and ergot alkaloids, was accomplished from a derivative of the renowned Uhle's ketone. The synthesis is centered on metal-free reductive coupling of the tosylhydrazone derivative of protected 4-amino Uhle's ketone and commercially available 2,2-dimethylethenylboronic acid, which is used as a four-carbon building block. This novel approach directly sets the stereochemistry on the difficult-to-access aryl vinyl methane carbon stereogenic center of (−)-6,7-secoagroclavine.

Introduction

Clavine alkaloids belong to a subclass of the ergot family and are produced from L-tryptophan and dimethylallylpyrophosphate by several fungal families; they have aroused much interest due to their promising biological properties, fascinating chemical structures, and food safety concerns.[1] They differ from the ergot alkaloids produced by *Claviceps* in that they lack the extensive peptide/amide chain modifications occurring in lysergic acid-derived ergot alkaloids; therefore, they are considered simpler ergot alkaloids.[2] They can be classified into three subclasses based on their distinguishing structures: tricyclic clavines (also known as secoergolines), tetracyclic clavines (also known as ergolines), or rearranged clavines (Figure 1).[2a] Whereas the latter are considered biosynthetic derailment products of clavine biosynthesis, the first two subclass are believed to originate from the single, chiral, enantiopure progenitor tricyclic compound called (−)-6,7-secoagroclavine (**1 a**) via a series of selective oxidation, reduction, and annulation reactions.[3] The distinguishing structural features of (−)-6,7-secoagroclavine (**1 a**) are as follows: 1) the 3,4-fused tricyclic indole scaffold, also called an indole-based peri-annulated system; 2) the two vicinal stereogenic centers C4 and C5; 3) the methylamine group on C4; and 4) two π-systems separated by a saturated carbon atom on C5, i.e. an allyl-substituted arene. It is considered a lipophilic prenyl-containing constrained tryptamine analog and has attracted the interest of synthetic chemists since Horwell and co-workers reported the isolation and identification of its structure from *Claviceps purpurea*.[4] Ever since, many racemic total syntheses of (±)-6,7-secoagroclavine have been reported,[5] while the asymmetric synthesis of the natural compound (−)-6,7-secoagroclavine (**1 a**) still remains a stimulating synthetic target.[6]

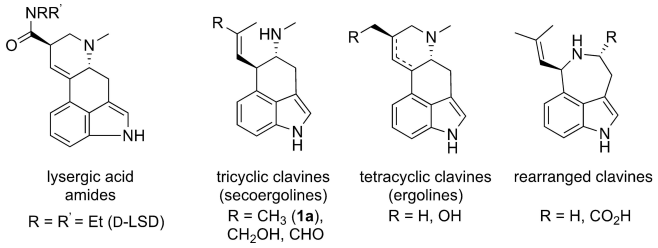


Figure 1. Structures of ergot and clavine alkaloids.

The first synthesis of optically active (−)-6,7-secoagroclavine (**1 a**) was disclosed by Nakagawa and Somei[6a] in 1991. Their procedure employed an optical resolution by applying preparative chiral column chromatography to an advanced intermediate of the total synthesis. In particular, the key racemic tricyclic nitro compound, which was later resolved, was obtained by the Lewis acid-mediated intramolecular allylic S_N2' alkylation of a 3,4-disubstituted indole. Finally, the optically pure tricyclic nitro compound was converted to the final natural product by treatment with an excess amount of methyl magnesium iodide, followed by reduction with zinc in methanolic hydrochloric acid at reflux. The absolute configuration was determined by X-ray crystallographic analysis of an amide derivative (Figure 2a). In 2015, Bernardi and co-workers reported a formal asymmetric synthesis of (−)-6,7-secoagroclavine (**1 a**).[6b] They developed an elegant asymmetric domino Friedel-Crafts/nitro-Michael reaction between a suitable 4-substituted indole and nitroethene, catalyzed by a BINOL-derived phosphoric acid catalyst. Such a domino process directly led to the corresponding 3,4-ring-fused indole, with very good results in terms of yield and diastereo- and enantioselectivity, as well as having the nitro group at the strategic C4 position and the ester-containing alkyl chain at C5 to be converted into (−)-6,7-secoagroclavine (**1 a**) (Figure 2b).[5e] Furthermore, this approach provided convenient general access to all four optically active stereoisomers of 6,7-secoagroclavine. A few years later, Bisai and co-workers[6c] implemented a similar intramolecular organocatalytic enantioselective nitro-Michael

[a] *F. Diotallevi, F. Bartoccini, G. Piersanti*
Department of Biomolecular Sciences, University of Urbino Carlo Bo Piazza Rinascimento 6, 61029 Urbino, PU, Italy
E-mail: francesca.bartoccini@uniurb.it
giovanni.piersanti@uniurb.it
Homepage: https://sites.google.com/uniurb.it/giovannipiersanti

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202400035

Research Article
doi.org/10.1002/ejoc.202400035

Chemistry Europe
European Chemical Societies Publishing

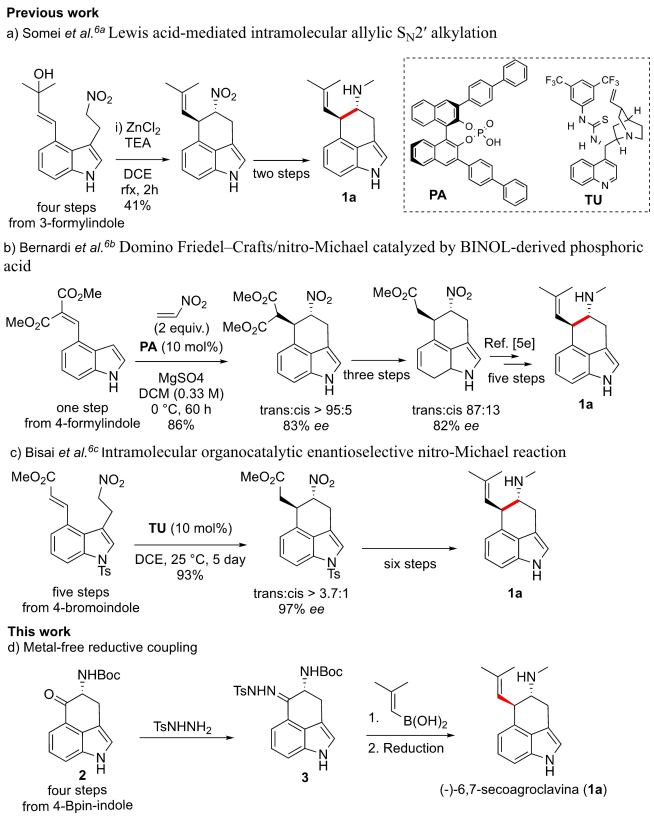


Figure 2. Synthesis of (−)-6,7-secoagroclavine (**1 a**) (a, b, c = previous work, d = this work).

reaction onto the α,β-unsaturated ester to construct the *N*-tosyl-protected tricyclic γ-nitroester derivative; however, they used cinchona alkaloid-derived catalysts. By simply changing the chirality of the catalyst with the basic selective epimerization at the α-nitro stereogenic center, favoring the *cis* stereoisomer of the nitro compound (high acidity of the nitro-group α-proton), all four optically active stereoisomers of (−)-6,7-secoagroclavine (**1 a**) were obtained. Nevertheless, to complete the total synthesis of natural (−)-6,7-secoagroclavine (**1 a**), six additional steps were needed: 1) reduction of the nitro functionality in the presence of Zn–AcOH; 2) *N*-Boc protection; 3) *N*-methylation; 4) reaction with MeLi to furnish the tertiary alcohol; 5) dehydration and *N*-Boc deprotection using triflic acid; and 6) tosyl deprotection with Mg in MeOH (Figure 2c). Nearly all of the previous racemic and asymmetric synthetic pathways share a common scheme, which involves the construction of the tricyclic ring system by the intentional intramolecular alkylation cyclization at the α-position of the nitro group promoted by a Brønsted and/or Lewis acid. These syntheses afforded the desired product, but intensive functional group manipulations consisting of many classical synthetic procedures were indispensable to arrange the key nitro intermediate and the following reactions to provide the natural product.

To explore innovative synthetic strategies permitted by the development of novel methods as well as new biological applications, we have recently established a program for the concise asymmetric total synthesis of clavine alkaloids, including (*R*)-4-amino Uhle's ketone, an enantiopure tricyclic framework shared by most of these alkaloids.[7] Motivated by our group's achievements in the field of preparation, reactivity, and related cross-coupling Csp^2–Csp^3 bond-forming reactions of boronic compounds,[8] we set out to develop a straightforward, convergent, and strategically distinct approach to **1 a**, compared to past asymmetric reports. The combination of D-tryptophan-derived *N*-carbamoyl (*R*)-4-amino Uhle's ketone **2**[9] and isobutenyl boronic acid provides the necessary skeletal features of (−)-6,7-secoagroclavine (**1 a**) (Figure 2d), while the stereochemical details can arise from the selectivities of the reactions involved.

We envisioned a regio- and diastereoselective metal-free Barluenga-Valdés cross-coupling reaction[10] between enantiopure sulfonylhydrazone **3** of the α-amino ketone derivative **2** and commercially available 2,2-dimethylethenylboronic acid to introduce the remaining four carbons of the pendant unconjugated trisubstituted olefinic chain. As the required tosylhydrazone is easily generated from the carbonyl compound, it can be seen as a reductive alkenylation coupling of Uhle's ketone, a process of high synthetic relevance requiring several steps using other methodologies. The sensitive α-chiral ketone, *N*-Boc tricyclic Uhle's ketone **2**, is accessible through a known four-step sequence from inexpensive D-serine, as reported by us recently.[7c] Furthermore, while the use of an *N*-protecting group is deemed necessary for the stability of this cyclic α-amino ketone, we chose simple *tert*-butyl carbamate, which can be readily reduced to the corresponding *N*-methyl species present in (−)-6,7-secoagroclavine (**1 a**), further increasing the step economy of our approach.

We herein wish to report the successful realization of the above-outlined design.

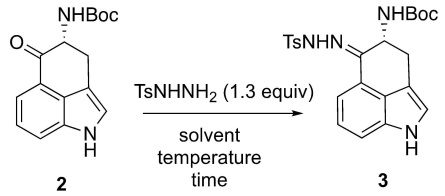
Results and Discussion

To initiate our investigation, we needed to prepare sulfonylhydrazone-derived **3** from cyclic ketone **2**. In our initial study, 4-methylbenzenesulfonohydrazide ($TsNHNH_2$) was selected to test the tosylhydrazone formation of **2**. The tosylhydrazone synthesis constituted the critical step for the enantioselectivity of the overall synthetic procedure since chiral (endo)cyclic α-amino ketone **2** undergoes facile keto-enol tautomerization, base-mediated racemization, and irreversible isomerization to the more stable naphthalenoid structure than that of indole.[11] In addition, according to its structure, compound **2** is a vinylogous acid amide that significantly contributes to the low reactivity of the carbonyl moiety towards ordinary neutral nucleophiles; therefore, more stringent reaction conditions are required. As shown in Table 1, six solvents (CH_3CN, CH_3OH, EtOAc, toluene, $CHCl_3$, and dioxane) were tested at room temperature for 40 h, and $CHCl_3$ afforded the highest yield (Table 1, entry 5). Next, with $CHCl_3$ as the solvent, we investigated the effect of the reaction temperature. It was found that the yield increased significantly when the reactants were refluxed in $CHCl_3$ for 6 h (Table 1, entry 7). In refluxing $CHCl_3$ without the presence of an acid or base catalyst, tosylhydrazone

Research Article
doi.org/10.1002/ejoc.202400035

Chemistry Europe
European Chemical Societies Publishing

Table 1. Synthesis of tosylhydrazone **3**[a].



2 **3**

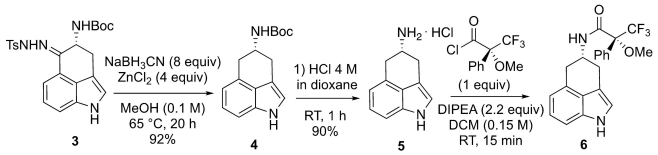
Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	CH_3CN	RT	40	22
2	CH_3OH	RT	40	15
3	EtOAc	RT	40	24
4	toluene	RT	40	12
5	$CHCl_3$	RT	40	43
6	dioxane	RT	40	31
7	$CHCl_3$	65	6	90

[a] Reaction conditions: **2** (0.2 mmol), $TsNHNH_2$ (0.26 mmol), solvent (0.07 M). [b] Isolated yields.

3 was obtained in excellent yield as a single stereoisomer and, even more important, with a specific optical rotation of $[\alpha]_D^{25} = -115$ ($c = 0.1$, $CHCl_3$).

The optical purity of **3** was determined to be greater than 99% by HPLC and NMR diastereomeric analysis of the Mosher amide obtained by the reduction of tosylhydrazone **3** to the expected indolylalkane **4** in high yield (92%) using $NaBH_3CN$/$ZnCl_2$, followed by acidic cleavage of the *N*-Boc protecting group and amidation with Mosher's acid chloride (Scheme 1).[12] The low basicity and high nucleophilicity features of the hydrazine reagent were indispensable to performing the enantioretentive condensation reaction of the reluctant and highly sensitive Uhle's ketone derivative **2**, even in the presence of two relatively acidic NH groups. Notably, enantiopure compound **5** has been recently studied as a simplified and potentially safer derivative of ergoline compounds, which can be useful to gain further insight into the features necessary for the activity and selectivity of the serotonin 5-HT_{2A} receptor agonism important for promoting neural plasticity and increasing the dendritic spine density of neuronal cells.[13]

Having established suitable conditions for the *N*-tosylhydrazone reaction, we turned our attention to investigating its reaction with 2,2-dimethylethenylboronic acid, an alkenyl boronic acid, to develop reaction conditions that might lead to a single regioisomer of the reductive alkenylation derivative. Indeed, it has been reported that this type of reaction proceeds very efficiently with aryl and alkylboronic acids,[14] whereas

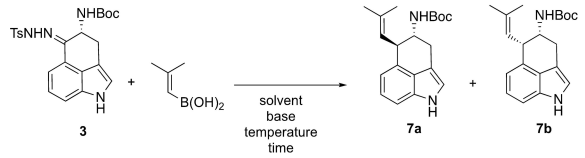


Scheme 1. Synthesis of the Mosher amide (**6**).

reactions with alkenylboronic acids provide more ambiguous results because of the formation of a mixture of isomers arising from the position of the double bond, which depends on the nature of both coupling partners.[15]

We observed that the formation of **7a** occurred in the presence of various bases (Table 2). Remarkably, the reactions proceeded simply by heating both reagents in dioxane in the presence of a base, and only the correct alkene regioisomer (no borotropic rearrangement), with the double bond in the original position, was observed.[15] After screening several reaction conditions and bases, the optimal conditions for the C–C bond-forming reaction were identified as dioxane at 110 °C, with inexpensive KO*t*Bu as the base (Table 2, entry 3). The reaction also occurred with Cs_2CO_3, NaH and CsF, with similar yields but with a switching of diastereoselectivity (Table 2, entries 2 and 4,5). The reaction proceeded at a lower temperature (Table 2, entry 6), but with a substantial decrease in the percentage conversion. To facilitate the purification process, we found that the addition of a large excess of boronic acid (3–5 equivalents) led to complete consumption of the starting material and avoided the formation of side products. However, the mixture of diastereoisomers (~1:1) was inseparable, despite testing different eluents and combinations.

Table 2. Optimization of metal-free reductive coupling.[a]



3 **7a** **7b**

Entry	Solvent	Base (equiv)	T (°C)	Yield[b](%)	d.r. (*trans*:*cis*)[c]
1	1,4-dioxane	K_2CO_3	110	NR	–
2	1,4-dioxane	Cs_2CO_3	110	40	1:2
3	1,4-dioxane	KO*t*Bu	110	40	1.6:1
4	1,4-dioxane	NaH	110	31	1:3
5	1,4-dioxane	CsF	110	36	1:2.5
6	1,4-dioxane	KO*t*Bu	70	22	1:1
7	clorobenzene	KO*t*Bu	120	15	1.6:1
9	trifluoromethyl benzene	KO*t*Bu	120	47	1:1.7
10	CF_3CH_2OH	KO*t*Bu	120	NR	–
11	THF	KO*t*Bu	70	43	1:1.4
12	DME	KO*t*Bu	110	30	1:1.3
13[d,e]	1,4-dioxane	KO*t*Bu	160	50	1:1.8
14[d,f]	1,4-dioxane	KO*t*Bu	160	60	1:1
15[d,g]	1,4-dioxane	KO*t*Bu	160	88 (65)[h]	1:1
16[d,g,i]	1,4-dioxane	KO*t*Bu	160	50	1:1

[a] Reaction conditions: **3** (0.1 mmol), boronic acid (0.5 mmol), base (0.3 mmol), solvent (0.05 M) for 16 h. [b] Yields were determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as the internal standard. [c] The diastereomeric ratio was determined by ^{1}H NMR of the crude product. [d] The reaction was performed under microwave irradiation. [e] 1 h. [f] 20 min. [g] 5 min. [h] Isolated yield. [i] 0.3 mmol of boronic acid was used.

Research Article
doi.org/10.1002/ejoc.202400035

During the study, we found that the use of microwave heating under similar reaction conditions (KO*t*Bu, 1,4-dioxane) not only dramatically reduced the reaction time (16 h to 5 min) (Table 2, entry 15) but also increased the yield.

As depicted in Figure 3, the proposed mechanism for this reaction comprises the following steps: 1) thermolysis of the tosylhydrazone in the presence of a base to form the diazo compounds **II** and **III**; 2) formation of the boronate intermediates **IV** and **V** by the interaction of the boronic acid with the diazo compound; 3) Csp^3–Csp^2 bond formation by migration of the dimethylvinyl group with the loss of nitrogen to give the sterically hindered benzylic-allylic boronic acids **7a,b**; and 4) Csp^3–H bond formation via protodeboronation to give the final allyl-substituted arene. Very poor diastereoselectivity was observed in the reactions with different solvents, bases, and reaction conditions (see Table 2). This is quite surprising considering the asynchronous concerted transition state that leads to the intermediate allyl-benzylboronic acid, which is notoriously favored through an equatorial trajectory.[15b]

The rationale for the poor stereoselectivity observed is based on the following assumptions: 1) the approach of the boronic acid to the diazocyclohexane on its most stable chair conformation through an equatorial trajectory; and 2) the presence of a mixture of the two chair conformations **II** (the NHCOOtBu substituent is pseudoequatorial) and **III** (the NHCOOtBu substituent is pseudoaxial) inverting rapidly at the reaction temperature. Likely, there is no a preferred stable conformation among **II** and **III** that can be ascribed to the absence of 1,3-diaxial interactions of the NHCOOtBu group with the pseudoaxial hydrogens.

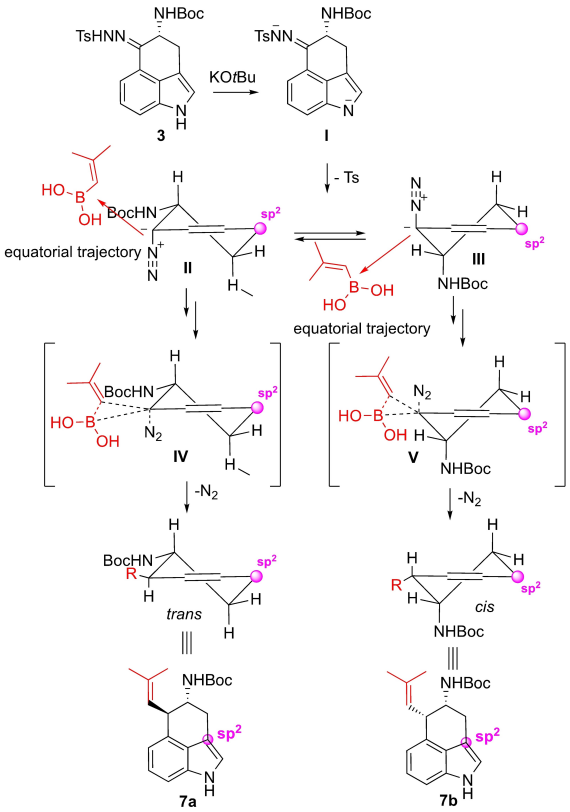


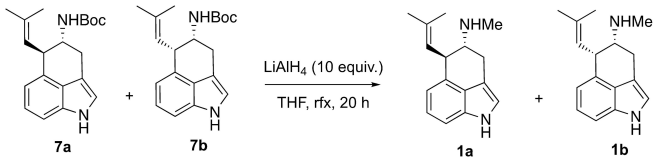
Figure 3. Proposed mechanism for metal-free reductive coupling.

At this point, we decided to subject the inseparable diastereomeric mixture of carbamates **7a,b** to reduction conditions, with the intent to obtain polar, separable secondary amines (Scheme 2). As mentioned previously, full reduction of the carbamate functionality with $LiAlH_4$ gave rise to *N*-methylated products that turned out, after separation, to be the natural *trans* product (−)-6,7-secoagroclavine (**1a**) and (+)-5-epi-6,7-secogroclavine (**1b**). Importantly, all ^1H and ^{13}C NMR spectra and mass spectra of **1a** and **1b** were in excellent agreement with those reported by Somei and co-workers.[5d] The optical rotations of **1a** and **1b** (**1a**: $[\alpha]_D^{25} = -121$ (c = 0.05, EtOH) and **1b**: $[\alpha]_D^{25} = +130$ (c = 0.05, EtOH)) in this work, however, differed only in magnitude from their reported values (**1a**: $[\alpha]_D^{25} = -121$ (c = 0.05, EtOH); Lit. $[\alpha]_D^{25} = -212.6$ (c = 0.35, EtOH) and **1b**: $[\alpha]_D^{25} = +130$ (c = 0.05, EtOH); Lit. $[\alpha]_D^{25} = +211.3$ (c = 0.35, EtOH)). The enantiomeric ratio (er) of **1a,b** was estimated to be approximately 4:1 by comparing the empirical and literature optical rotation values. Diastereomeric analysis of separated (−)-6,7-secoagroclavine (**1a**) and (+)-5-epi-6,7-secogroclavine (**1b**) transformed to amides with Mosher's acid chloride corroborated these chiral ratios. This finding is quite surprising since it has been elegantly reported that the formation of the *N*-tosyl hydrazone prevents epimerization at the α-center in configurationally unstable α-chiral ketones, such as **2**, under similar reductive coupling reaction conditions.[16]

Unfortunately, reinvestigation of solvent, base equivalents, and concentration effects did not ameliorate this issue.[15] Alternatively, and more likely, the discrepancy reflects the fact that 6,7-secoagroclavine proved to be unstable in long-term storage. Nonetheless, it can be purified as a single diastereomer with silica gel chromatography. The reaction between tosylhydrazone **3** and 2,2-dimethylethenylboronic acid could be performed at 1 mmol scale without issue.

Conclusions

In summary, we have accomplished a novel, convergent, and asymmetric total synthesis of the natural product (−)-6,7-secoagroclavine (**1a**) and its unnatural epimer (**1b**) through the powerful reductive alkenylation of enantiopure 4-amino carbamate-protected Uhle's ketone (**2**), by its tosyl hydrazone (**3**), utilizing 2,2-dimethylethenylboronic acid as a C4 synthon. From a synthetic point of view, the innovative approach introduced herein represents a very powerful tool for the



Scheme 2. Synthesis of (−)-6,7-secoagroclavine and (+)-5-epi-6,7-secoagroclavine (**1a,b**).

modification of reluctant and sensitive chiral α-amino Uhle's ketones with the simultaneous and regioselective formation of Csp^2–Csp^3 and Csp^3–H bonds from the benzylic ketone group and giving rise to two adjacent stereocenters. This new procedure offers significant advantages over previous synthetic approaches for (−)-6,7-secoagroclavine (**1 a**), the key intermediate in the synthesis of both secoergolines and ergoline clavines, embracing brevity, convergency, and modularity as well as avoiding the use of stoichiometric amounts of strongly basic/organometallic reagents. The application of this chemistry to the synthesis of other clavines, not available in nature, is underway.

Supporting Information

The data that support the findings of this study are available in the supplementary material of this article.

Acknowledgements

This work was supported by the Italian Ministry for University and Research (MUR, PRIN 2020, 2020AEX4TA project) and University of Urbino grants (DISB_PIERSANTI_PROG_SIC_ALIMENTARE).

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: asymmetric synthesis · boronic acid · chiral ketone · alkaloids · reductive coupling

[1] a) C. L. Schardl, D. G. Panaccione, P. Tudzynski, *Alkaloids Chem. Biol.* **2006**, *63*, 45–86; b) M. Somei, Y. Yokoyama, Y. Murakami, I. Ninomiya, T. Kiguchi, T. Naito in *The Alkaloids, Vol. 54* (Eds.: G. A. Cordell), Academic Press: San Diego, **2000**, pp 191–257; c) L. V. Boichenko, D. M. Boichenko, N. G. Vinokurova, T. A. Reshetilova, M. U. Arinbasarov, *Microbiology* **2001**, *70*, 306–310; d) J. F. Martín, R. Álvarez-Álvarez, P. Liras, *Genes* **2017**, *8*, 342; e) P. L. Schiff *Am. J. Pharm. Educ.* **2006**, *70*, 98; f) Y. Doi, D. Wakana, S. Kitaoka, F. Sato, E. Tanaka, H. Takeda, T. Hosoe *J. Nat. Med.* **2023**, *77*, 306–314; g) N. R. Tasker, E. J. Pazur, P. Wipf, *Front. Psychiatry* **2023**, *14*, 1286941.

[2] a) N. R. Tasker, P. Wipf, in *The Alkaloids: Chemistry and Biology*, Vol. 85 (Eds: H.-J. Knölker), Academic Press **2021**, pp 1–112; b) H. Liu, Y. Jia, *Nat. Prod. Rep.* **2017**, *34*, 411–432; c) B. Milde, M. Pawliczek, P. G. Jones, D. B. Werz *Org. Lett.* **2017**, *19*, 1914–1917; d) S. Bhunia, S. Chaudhuri, A. Bisai, *Chem. – Eur. J.* **2017**, 11234–11238.

[3] a) S. R. McCabe, P. Wipf, *Org. Biomol. Chem.* **2016**, *14*, 5894–5913; b) N. Gerhards, L. Neubauer, P. Tudzynski, S.-M. Li, *Toxin Rev.* **2014**, *6*, 3281–3295.

[4] D. C. Horwell, J. P. Verge, *Phytochemistry* **1979**, *18*, 519.

[5] a) M. Somei, F. Yamada, Y. Karasawa, C. Kaneko, *Chem. Lett.* **1981**, *5*, 615–618; b) W. Oppolzer, J. I. Grayson, H. Wegmann, M. Urrea, *Tetrahedron* **1983**, *39*, 369–375; c) M. Somei, F. Yamada, *Chem. Pharm. Bull.* **1984**, *32*, 5064–5065; d) M. Somei, F. Yamada, H. Ohnishi, Y. Makita, M. Kuriki, *Heterocycles* **1987**, *26*, 2823–2828; e) F. Yamada, Y. Makita, M. Somei, *Heterocycles* **2007**, *72*, 599–620.

[6] a) K. Nakagawa, M. Somei, *Heterocycles* **1991**, *32*, 873–878; b) S. Romanini, E. Galletti, L. Caruana, A. Mazzanti, F. Himo, S. Santoro, M. Fochi, L. Bernardi, *Chem. Eur. J.* **2015**, *21*, 17578–17582; c) S. Chaudhuri, S. Bhunia, A. Roy, M. K. Das, A. Bisai, *Org. Lett.* **2018**, *20*, 288–291.

[7] a) A. Regni, F. Bartoccini, G. Piersanti, *Beilstein J. Org. Chem.* **2023**, *19*, 918–927; b) F. Bartoccini, A. Regni, M. Retini, G. Piersanti, *Eur. J. Org. Chem.* **2022**, *2022*, e202200315; c) F. Bartoccini, A. Regni, M. Retini, G. Piersanti, *Org. Biomol. Chem.* **2021**, *19*, 2932–2940; d) F. Bartoccini, S. Venturi, M. Retini, M. Mari, G. Piersanti, *J. Org. Chem.* **2019**, *84*, 8027–8034; e) F. Bartoccini, M. Casoli, M. Mari, G. Piersanti, *J. Org. Chem.* **2014**, *79*, 3255–3259; f) G. Leoni, F. Bartoccini, G. Piersanti, *Adv. Synth. Catal.* **2024**, https://doi.org/10.1002/adsc.202301422.

[8] a) F. Bartoccini, G. Piersanti, S. Armaroli, A. Cerri, W. Cabri, *Tetrahedron Lett.* **2014**, *55*, 1376–1378; b) F. Bartoccini, W. Cabri, D. Celona, P. Minetti, G. Piersanti, G. Tarzia, *J. Org. Chem.* **2010**, *75*, 5398–5401.

[9] F. Bartoccini, G. Piersanti, *Synthesis* **2021**, *53*, 1396–1408.

[10] Seminal work, see: a) J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Nat. Chem.* **2009**, *1*, 494–499. For a related reactions of boroxines with α-diazocarbonyl compounds, see: b) C. Peng, W. Zhang, G. Yan, J. Wang, *Org. Lett.* **2009**, *11*, 1667–1670. For reviews, see: c) J. Barluenga, C. Valdés, *Angew. Chem. Int. Ed.* **2011**, *50*, 7486–7500; d) M. Paraja, M. Plaza, C. Valdes, *Synlett* **2017**, 2373–2389; e) H. Wang, Y.-H. Deng, Z. Shao, *Synthesis* **2018**, *50*, 2281–2306; f) D. Arunprasath, B. Devi Bala, G. Sekar, *Adv. Synth. Catal.* **2019**, *361*, 1172–1207; g) Y. Xia, J. Wang, *J. Am. Chem. Soc.* **2020**, *142*, 10592–10605; h) C. Valdés in *Homologation Reactions, Vol. 2*, (Eds. V. Pace), **2023**, pp 467–511.

[11] The greater stability of naphthalenoid isomers was based on the fact that the resonance energy of naphthalene is much greater than that of indole, see: a) C. A. Grob, J. Voltz, *Helv. Chim. Acta* **1950**, *33*, 1796–1808; b) C. A. Grob, B. Hofer, *Helv. Chim. Acta* **1952**, *35*, 2095–2105; c) C. Grob, P. Payot, *Helv. Chim. Acta* **1953**, *36*, 839–846.

[12] J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543–2549.

[13] D. E.; Olson, L. Dunlap, F. Wagner, M. Chytil, Milan; N. A. Powell, Patent WO2021076572, 2021.

[14] a) Y. Yang, J. Tsien, A. Ben David, J. M. E. Hughes, R. R. Merchant, T. Qin, *J. Am. Chem. Soc.* **2021**, *143*, 471–480; b) R. R. Merchant, J. A. Lopez, *Org. Lett.* **2020**, *22*, 2271–2275.

[15] a) M. C. Pérez-Aguilar, C. Valdés, *Angew. Chem. Int. Ed.* **2012**, *51*, 5953–5957; b) M. Plaza, M. C. Perez-Aguilar, C. Valdes, *Chem. – Eur. J.* **2016**, *22*, 6253–6257.

[16] a) J. Barluenga, M. Escribano, F. Aznar, C. Valdés, *Angew. Chem. Int. Ed.* **2010**, *49*, 6856–6859; b) J. Barluenga, N. Quiñones, M.-P. Cabal, F. Aznar, C. Valdés, *Angew. Chem. Int. Ed.* **2011**, *50*, 2350–2353; c) R. Barroso, M. Escribano, M.-P. Cabal, C. Valdes, *Eur. J. Org. Chem.* **2014**, *16*, 1672–1675; d) M. C. Pérez-Aguilar, C. Valdés, *Angew. Chem. Int. Ed.* **2015**, *54*, 13729–13733; Although the optical rotation value for synthetic **1 a**,**b** differs in magnitude, such discrepancies are not uncommon, and they can arise from diverse factors. For some examples of total syntheses where differences in optical rotation values arise, see: e) S. Edmondson, S. J. Danishefsky, L. Sepp-Lorenzino, N. Rosen, *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155; f) S. Ribe, R. K. Kondru, D. N. Beratan, P. Wipf, *J. Am. Chem. Soc.* **2000**, *122*, 4608–4616; particularly in compounds containing basic nitrogens: g) J. H. Almquist, D. M. Greenberg, *J. Biol. Chem.* **1934**, *105*, 519–522; h) W. Guschlbaur, Y. Courtois, *FEBS Lett.* **1968**, *1*, 183–186.

Manuscript received: January 12, 2024
Revised manuscript received: February 14, 2024
Accepted manuscript online: February 16, 2024
Version of record online: March 4, 2024