Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2023, **21**, 817

Total synthesis of the natural (–)-205B alkaloid and its activity toward α7 nAChRs†

Sara Mazeh,[a] M. Dolores Garcia-Fernandez,[b] Barbara Pelletier,[b] Christophe Moreau[b] and Philippe Delair *[a]

Received 21st September 2022,
Accepted 20th December 2022

DOI: 10.1039/d2ob01723g

rsc.li/obc

A new approach to the synthesis of the (–)-205B alkaloid is described in this paper. This work is characterised by the development of an efficient chirality transfer through a silyl tethered intramolecular alkylation reaction, an unprecedented tandem highly selective iridium catalyzed partial reduction of lactam coupled with an acid promoted aza-Prins reaction, and an almost complete stereochemical control in Shenvi's radical hydrogen atom transfer on an exocyclic methylene. The second part of this work demonstrates the positive allosteric behavior of this natural alkaloid toward α7 nAChRs, in contrast to the reported inhibitory effect of the unnatural enantiomer.

Introduction

The alkaloid (–)-205B (**1**) was isolated more than three decades ago in low yield from the skin of the amphibian *Dendrobate pumilio*.[1] These frogs are used by the local population to poison their blow darts, inflicting severe neurological effects on their preys.[2] To the best of our knowledge, the biological activity of this uncommon tricyclic lipophilic alkaloid has not been evaluated, despite several synthetic approaches reported to date.[3] However, the unnatural enantiomer has been shown to selectively inhibit α7 nicotinic acetylcholine receptors (nAChRs).[4] The importance of these receptors has drastically increased with the recognition of their high affinity for the Aβ peptide and of their involvement in the internalization of this peptide.[5] Thus local high concentration will favor peptide aggregation that will potentially lead to the formation of the characteristic amyloid plaques of Alzheimer's disease. In this context, the behavior of the natural enantiomer of this alkaloid towards α7 nAChRs is of primary importance.

Results and discussion

We recently reported an efficient approach to the synthesis of the tricyclic 8b-azaacenaphthylene ring system which is characteristic of the targeted alkaloid.[6] This approach is based first on the well-established methodology[7] developed by Greene involving a highly stereoselective 2 + 2 cycloaddition,[8] second, on the formation of a hydroxy-indolizidinone intermediate **3** through a vinylogous Mannich reaction[9] and finally on a cyclization through an aza-Prins reaction.[10] Unfortunately, this approach suffers from a difficult stereoselective introduction of a methyl group and from an unexpectedly easy epimerization of this chiral center during the aza-Prins formation of the last ring (**4** to **5**, Fig. 1).

In order to overcome this major difficulty, we wondered if it would be possible to lock the configuration of this center by the addition of a transient bridged cycle. This scenario was particularly attractive since the transient cycle would be accessible from the hydroxy-indolizidinone intermediates **3a,b**

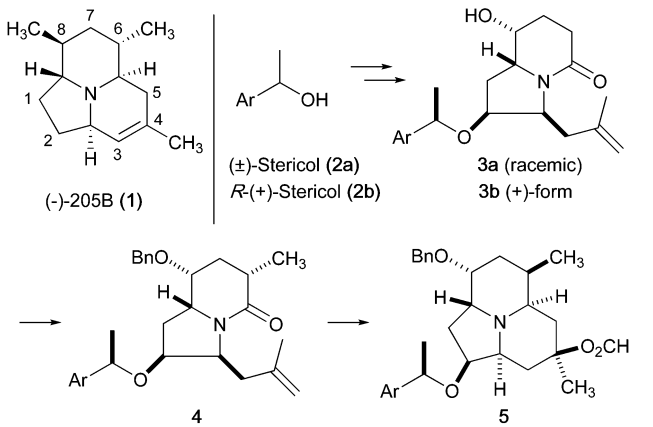


Fig. 1 Alkaloid (–)-205B and our first approach to the synthesis of the 8b-azaacenaphthylene ring system. Ar = 2,4,6-triisopropylphenyl.

[a]*Département de Pharmacochimie Moléculaire, Univ. Grenoble Alpes, ICMG FR-2607, CNRS, UMR-5063, F-38041 Grenoble, France.*
E-mail: philippe.delair@univ-grenoble-alpes.fr
[b]*Univ. Grenoble Alpes, CNRS, CEA, IBS, F-38000 Grenoble, France*

†Electronic supplementary information (ESI) available: Experimental procedures, analytical data and copies of NMR data. See DOI: https://doi.org/10.1039/d2ob01723g

through an intramolecular chirality transfer from the axially oriented C8 hydroxyl substituent to the new stereogenic center on C6 (target compound numbering). The nature of this transient cycle should also allow the generation of the required methyl group. A silyl tether seemed to be promising due to its simple introduction from a secondary hydroxyl group and to the possible generation of the requested methyl substituent by the known proto-desilylation.[11] To the best of our knowledge, similar chirality transfer through a silicon tethered intramolecular alkylation has been mentioned only scarcely in the literature.[12] Inspired by these reports, we decided to test this hypothesis. The chiral intermediate **3b** was first prepared in the enantiomerically pure form using a previously reported procedure[6] starting from optically active (*R*)-Stericol® (**2b**), an efficient and readily available chiral auxiliary.[13] This well-established procedure allowed the preparation of almost 5 g of **3b**. The secondary hydroxyl group was then silylated with the commercially available dimethylbromosilane **6a** (Scheme 1 and Table 1). An efficient conversion was achieved only at an uncommonly high temperature (50 °C) that revealed the intrinsic steric strain of the substrate. After some experimentation, we found that treating the corresponding silylated ether **7a** with a strong base allows the formation of the expected intramolecular alkylation product **8a** in moderate yield. However, variable and non-negligible amount of the starting hydroxy-indolizidinone **3b** was also obtained due to basic hydrolysis of the silyl ether intermediate. The use of a commercial or freshly prepared solution of a base did not drastically change the situation. In order to slow down this hydrolysis, the corresponding more crowded diphenylsilyl ether was also tested due to the facile access of the corresponding chlorosilane reagent **6b**.[14] The silylation proceeded with a satisfactory yield; however, only the hydrolyzed product could be isolated upon cyclisation attempts from silyl ether **7b**.

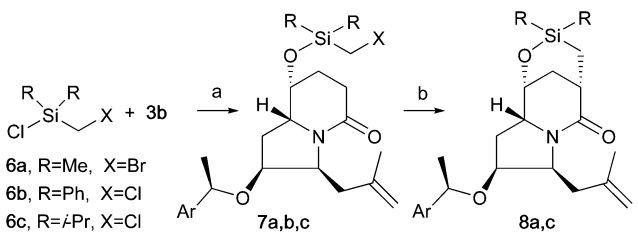
By comparison to the known resistance toward the basic hydrolysis of TIPS ether,[15] we prepared the corresponding diisopropylchlorosilane **6c** using the procedure described by Gevorgyan.[16] Pleasingly, the silylation of chiral hydroxy-indolizidinone **3b** gave the corresponding silyl ether **7c** in a high yield,[17] and more rewardingly, the basic treatment of this silyl ether furnished the expected cyclized product **8c** in 91% yield without the detection of any hydrolyzed material. Stereochemical insight into the newly formed stereogenic center could be obtained by the determination of the *J* coupling constants for C6–H. All these values being below 10 Hz indicated an equatorial orientation of this hydrogen, which is consistent with the bridgehead nature of this position. At this stage, it is noteworthy that this particularly efficient intramolecular alkylation reaction is in sharp contrast to the difficulties encountered in our previously published intermolecular version.[6] More generally, this effective under-developed strategy can further increase the arsenal of silyl tethered transformations.[18] Thus, current studies are in progress to evaluate the scope and limitations of this chirality transfer by intramolecular alkylation through a silyl link.

The crucial formation of the final ring was then investigated by partial reduction of the lactam followed by acid treatment to generate the corresponding iminium and trigger the aza-Prins reaction. Reduction with a standardized solution of LAH

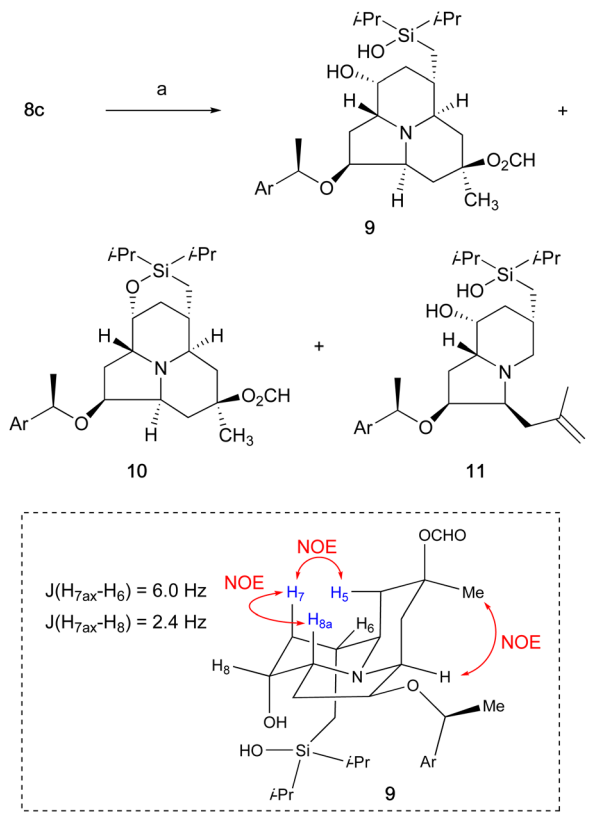
Table 1 Development of a reliable chirality transfer

Entry	6	R	X	7 (%)	8 (%)
1	**a**	Me	Br	95	50–62[a]
2	**b**	Ph	Cl	66	—
3	**c**	i-Pr	Cl	85	91

[a] Variable amounts of **3b** were also obtained.



Scheme 1 Transfer of chirality by silyl tethered alkylation. (a) DCM, Et_3N, 50 °C, 2.5 h; (b) LiHMDS, THF, −78 °C to −15 °C, 1 h. Ar = 2,4,6-triisopropylphenyl.



Scheme 2 Cyclization through the aza-Prins reaction. (a) $LiAlH_4$, Et_2O, −10 °C, then HCOOH −10 °C and representative NMR data for compound **9**. Ar = 2,4,6-triisopropylphenyl.

followed by quenching with formic acid led to an encouraging mixture of cyclized products **9** and **10** in 68% and 14% yield, respectively, and some over-reduced amine **11** (Scheme 2).

To ensure that the silyl ether hydrolysis of **9** appeared in the final event of this cascade, the stereo integrity of C6 was assessed by determining the *J* coupling constant values for both C7 hydrogens. The fact that all these *J* values were below 10 Hz (except for the ^2J coupling constant) was consistent with an equatorial orientation for both hydrogens on C6 and C8. Furthermore, the chair conformation of this ring was confirmed by the observation of NOE signals between C7–H_{ax}/C5–H_{ax} and C7–H_{ax}/C8a–H. As additional proof, the saponification of the isolated formate **9** gave a mixture of the corresponding tertiary alcohols **12** and **13** where the silyl ether linkage was partially restored (Scheme 3). This observation is an indirect confirmation of the C6 stereo-integrity in this process. At this stage, we were able to completely preclude the facile epimerization of this center observed in our previous approach.[6] However, we rapidly faced low reproducibility of this tandem process. In the events, the proportion of the over-reduced amine **11** was difficult to control, which could be as high as 30% when increasing the scale. It was thus necessary to identify more robust conditions for partial lactam reduction.

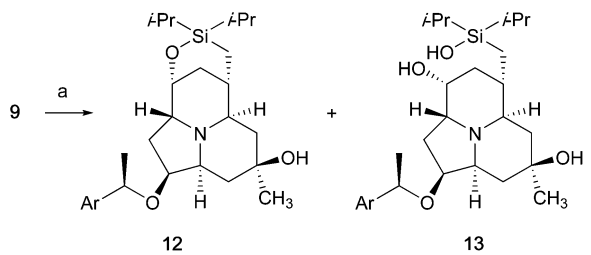
Recently, Dixon[19] demonstrated in nitro-Mannich cyclization that the partial reduction of lactams by silanes is more efficient when the reaction is catalyzed by an iridium complex as developed by Nagashima,[20] instead of the original Buchwald titanium catalyst.[21] Application of this iridium catalyzed partial reduction of lactams to elegant tandem transformations emerged right after and is still a particularly growing field of interest.[22] In this context, we were able to show that these conditions are also perfectly suitable to combine a lactam partial reduction with an aza-Prins cyclization. In our case, we were pleased to obtain formate **9** in a reproducible almost quantitative yield in sufficient purity to be engaged in the next step. In addition, no over-reduced amine **11** or at least not higher than 2% (from ^{1}H NMR analysis of the crude material) was formed in that transformation.

The following task was to unmask the C6 methyl group. An efficient protodesilylation of the unactivated C(sp^3)–Si bond or sterically hindered silicon moiety was reported using KO*t*-Bu and TBAF/THF solution in DMF at elevated temperature.[23] However, during the optimization of the reaction conditions we noticed erratic results depending on the age and/or the source of the TBAF solution. Furthermore, the importance of the optimal amount of residual water in TBAF/THF solution is reported in the literature.[24] Finally, we found that using CsF as the fluoride source together with the addition of 3% of water in dry DMSO was more reliable. Applying these conditions directly to the crude mixture of the aza-Prins cyclization led to the isolation of the tricyclic structure **14** in 46% overall yield from this two step, four transformation sequence (Scheme 4).

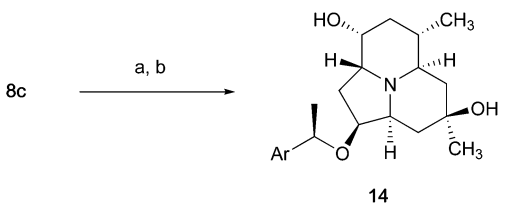
We next turned our attention to the introduction of the second methyl group, which was planned to be performed through the classic sequence of oxidation of the secondary alcohol, methylenation and hydrogenation. However, the oxidation of amino alcohol **14** was more difficult than expected since the corresponding amino ketone appeared to be highly unstable. For example, the Dess–Martin oxidation gave a complex mixture whereas the Swern oxidation provided non-reproducible results from which the expected amino ketone could be isolated in low yield from various byproducts. Fortunately, applying the Iwabuchi modification of nitroxyl/copper catalyzed aerobic oxidation developed by Stahl[25] allowed the efficient formation of the expected amino ketone. Due to its moderate stability, this ketone was immediately engaged in the subsequent Wittig reaction to provide the exocyclic methylene product **16** (Scheme 5). Although suffering some degradation, a pure sample of **16** could be separated from the excess Wittig reagent. The conservation of the stereochemistry of C8a was confirmed by the observation of NOE interactions between C8a–H and the two axially oriented hydrogens at C3 and C5.

Based on the shape of this tricyclic system and by comparison with the results described by Smith on a related structure,[26] catalytic hydrogenation was expected to occur on the α-face of the *exo*-methylene of **16** in order to furnish the expected equatorially oriented methyl substituent. Unfortunately, we observed that the hydrogenation of **16** first needed medium pressure to occur, and second, gave a disappointing 1 : 1 mixture of the two epimers. This low stereoselectivity is certainly due to the presence of the axial methyl group on C6 that brings enough interaction to reduce the difference of the steric bias between the two faces of the olefin.

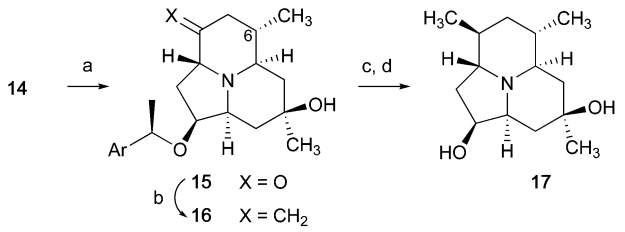
To set up the required thermodynamically favored equatorial methyl substituent, the radical hydrogen atom transfer



Scheme 3 Saponification of formate **9**. (a) K_2CO_3, MeOH, 1 h. Ar = 2,4,6-triisopropylphenyl.



Scheme 4 Formation of the 8b-azaacenaphthylene core by unmasking the methyl substituent. (a) $IrCl(CO)(PPh_3)_2$, $(Me_2SiH)_2O$, then HCOOH; (b) CsF, KO*t*-Bu, DMSO, H_2O 3%, 120 °C. Ar = 2,4,6-triisopropylphenyl.



Scheme 5 Exo-methylene installation. (a) AZADO, CuCl, DMAP, bpy, MeCN, air; (b) $MePPh_3Br$, NaHMDS, THF, −78 °C to RT; (c) $Mn(dpm)_3$, $PhSiH_3$, TBHP, i-PrOH, RT; (d) TFA, DCM, 0 °C. Ar = 2,4,6-triisopropylphenyl.

(HAT) developed by Shenvi appeared promising.[27] To our great satisfaction, these conditions allowed the formation of only one stereoisomer, as concluded from the ^{1}H NMR of the crude mixture. This high selectivity certainly reflects the highly steric 1,3-diaxial interaction between the two methyl substituents in the undesired epimer. From a previously purified sample of **16**, the hydrogenated product could be isolated in high yield (85%); however, for synthetic purposes and due to the difficult purification of intermediates **15** and **16**, the methylenation and the HAT reaction were performed using the crude material which led to tricyclic amino alcohol **17** after the cleavage of the chiral auxiliary under acidic conditions in 43% overall yield from **14**.

To complete the synthesis, a selective Barton deoxygenation of the secondary hydroxyl group of **17** was achieved through its phenyl thiono-carbonate derivative. Radical reduction was evaluated with the aim of future biological evaluations of the final product, and thus tributyltin hydride was precluded. We were pleased to observe that under conventional radical conditions,[28] tris(trimethylsilyl)silane was a very powerful hydrogen donor[29] and allowed neat conversion into the corresponding amino alcohol **18**. Finally, dehydration performed under the acidic conditions described in the last step of the synthesis reported by Toyooka[3a] gave the same 6 : 1 mixture of olefin, from which the natural product was isolated in 38% overall yield from **17** (3 steps) (Scheme 6).[30]

With the natural form of the (−)-205B alkaloid in hand, we turned our attention toward its effect on α7 nAChRs. The gene coding for the human α7 nAChRs was subcloned in a specific vector (pGEMHE-derivative) for overexpression in *Xenopus laevis* oocytes. The related mRNA was synthesized *in vitro* and micro-injected in *Xenopus* oocytes (2.7 ng per oocyte). The heterologous expression in the plasma membrane was sufficient after 2 to 3 days of incubation at 19 °C. The functional characterization of (−)-205B was performed electrophysiologically using the two-electrode voltage-clamp technique with a HiClamp robot (Multichannel Systems). The buffer was the standard ND96 buffer and the membrane voltage was clamped at −60 mV. The protocol of recordings involved an initial incubation with the natural agonist acetylcholine (ACh) at 100 μM, and then with the alkaloid (−)-205B at 1, 10 and 100 μM for 5 seconds. The oocytes were washed for 90 seconds between each application. A total of 6 oocytes were tested for each condition. In sharp contrast to the results published by Toyooka[4] with the unnatural enantiomer, the natural form of this alkaloid induced a significant inhibitory effect only at a high concentration (100 μM) (Fig. 2). However, lower concentrations (1

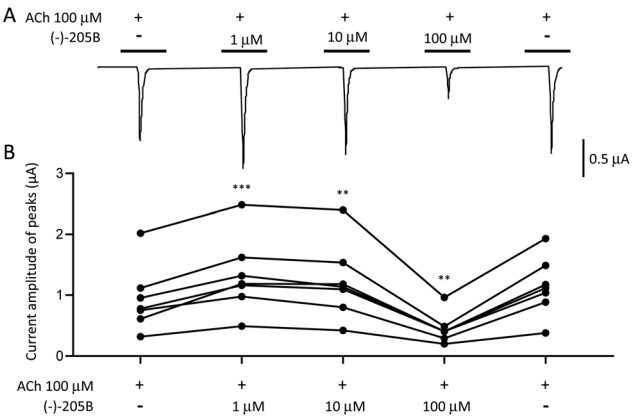
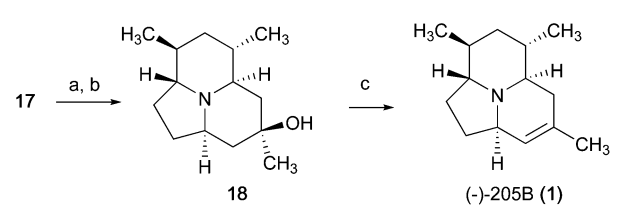


Fig. 2 Effects of the (−)-205B alkaloid on ACh-induced currents in *Xenopus* oocytes expressing α7 nAChRs. (A) Representative TEVC recording of the response of α7 nAChR-expressing oocytes to ACh and (−)-205B. (B) Statistical analysis of 6 recordings based on the paired *t*-test with the first application of 100 μM ACh as the reference.



Scheme 6 Completion of the synthesis of the alkaloid (−)-205B. (a) PhO(CS)Cl, DMAP, DCM; (b) TMS_3SiH, AIBN, benzene, reflux; (c) *p*-TsOH, benzene, reflux, (38% from **17**).

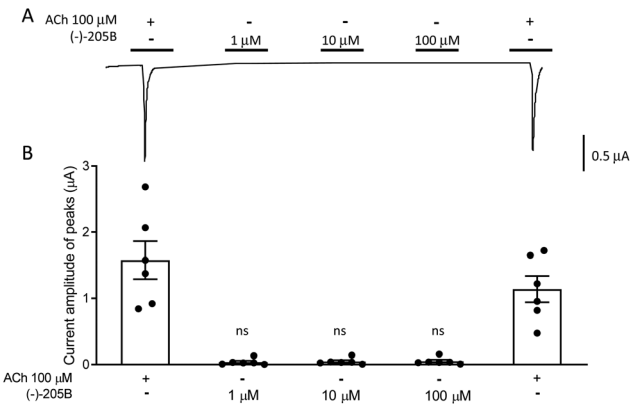


Fig. 3 Effects of the (−)-205B alkaloid on α7 nAChRs expressed in *Xenopus* oocytes. (A) Representative TEVC recording of responses to ACh and (−)-205B applied separately. (B) Dot plots of 6 recordings showing the means of normalized current amplitudes in bars, ±SEM. ns: not significant (one sample *t*-test with 0 as the reference).

and 10 μM) of this alkaloid significantly increased the current amplitude compared to the control.

To evaluate if the alkaloid had an agonist effect on α7-nAChRs, the oocytes were incubated with the alkaloid at 1, 10 and 100 μM without ACh and no current was observed (Fig. 3), meaning that this alkaloid cannot open the channel by itself. These data suggest a positive allosteric modulator role of this alkaloid at low concentrations (1 and 10 μM) and an antagonist effect at high concentrations (100 μM).

Conclusions

In this paper, we have described the total synthesis of the (−)-205B alkaloid in its natural enantiomeric form with high control of the different stereogenic centers. In this work, a reliable chirality transfer by intramolecular enolate alkylation through a silyl link has been exploited. The transient bridged cycle thus created served as an efficient configurational lock of a potentially epimerizable chiral center. In addition, the highly selective iridium catalyzed partial reduction of lactam was efficiently coupled with an intramolecular aza-Prins reaction, and a particularly high stereoselectivity was observed in the radical HAT favoring the thermodynamic isomer. Furthermore, in contrast to the previously published results for the unnatural antipode, this natural form of the (−)-205B alkaloid has shown a modest positive allosteric behavior toward α7 nAChRs at a concentration as low as 1 μM and an antagonist effect at 100 μM.

Author contributions

S. Mazeh: chemical synthesis; M. D. Garcia-Fernandez and B. Pelletier: biological experiments; C. Moreau: biological supervision and writing; P. Delair: chemical supervision and writing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Professor Ahcène Boumendgel and Doctor Yung-Sing Wong for their interest and support in this work. Financial support from NeuroCoG IDEX UGA in the framework of the "Investissements d'avenir" program (ANR-15-IDEX-02), the Labex Arcane CBH-EUR-GS (ANR-17-EURE-0003) from CNRS and Université Grenoble Alpes, and a doctoral fellowship (to S. M.) from the French Ministry are gratefully acknowledged. We also thank Justine Magnat for the technical support of this study and Hervé Pointu, Soumalamaya Bama Toupet and Charlène Caloud for the management and the maintenance of *Xenopus* and acknowledge the platform supported by GRAL, financed within the University Grenoble Alpes graduate school (Ecoles Universitaires de Recherche) CBH-EUR-GS (ANR-17-EURE-0003). IBS acknowledges integration into the Interdisciplinary Research Institute of Grenoble (IRIG, CEA). This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (Grant Agreement No. 682286). The NanoBio ICMG (UAR 2607) is also acknowledged for providing facilities for mass spectrometry analyses (A. Durand, L. Fort, and R. Gueret).

References

1 T. Tokuyama, N. Nishimori, A. Shimada, H. W. Edwards and J. W. Daly, *Tetrahedron*, 1987, **43**, 643.
2 J. W. Daly, H. M. Garraffo and T. F. Spande, in *Alkaloids: Chemical and Biological Perspectives*, ed. S. W. Pelletier, Elsevier Science, 1999, vol. 13, pp. 1–161.
3 (*a*) N. Toyooka, A. Fukutome, H. Shinoda and H. Nemoto, *Angew. Chem., Int. Ed.*, 2003, **42**, 3808; (*b*) A. B. Smith and D.-S. Kim, *Org. Lett.*, 2005, **7**, 3247; (*c*) A. B. Smith and D.-S. Kim, *J. Org. Chem.*, 2006, **71**, 2547; (*d*) S. V. Tsukanov and D. L. Comins, *Angew. Chem., Int. Ed.*, 2011, **50**, 8626; (*e*) S. V. Tsukanov and D. L. Comins, *J. Org. Chem.*, 2014, **79**, 9074; (*f*) D. Yang and G. C. Micalizio, *J. Am. Chem. Soc.*, 2012, **134**, 15237; (*g*) N. N. Rao and J. K. Cha, *J. Am. Chem. Soc.*, 2015, **137**, 2243.
4 N. Toyooka, H. Tsuneki, S. Kobayashi, Z. Dejun, M. Kawasaki, I. Kimura, T. Sasaoka and H. Nemoto, *Curr. Chem. Biol.*, 2007, 97.
5 (*a*) H. Y. Wang, D. H. Lee, M. R. D'Andrea, P. A. Peterson, R. P. Shank and A. B. Reitz, *J. Biol. Chem.*, 2000, **275**, 5626; (*b*) S. I. Deutsch, J. A. Burket and A. D. Benson, *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 2014, **54**, 131.
6 A. Kamath, C.-H. Fabritius, C. Philouze and P. Delair, *Org. Biomol. Chem.*, 2015, **13**, 9834.
7 J.-P. Deprés, P. Delair, J.-F. Poisson, A. Kanazawa and A. E. Greene, *Acc. Chem. Res.*, 2016, **49**, 252.
8 A. E. Greene and F. Charbonnier, *Tetrahedron Lett.*, 1985, **26**, 5525.
9 (*a*) S. F. Martin, *Acc. Chem. Res.*, 2002, **35**, 895; (*b*) M. S. Roselló, C. del Pozo and S. Fustero, *Synthesis*, 2016, **48**, 2553.
10 (*a*) C. Olier, M. Kaafarani, S. Gastaldi and M. Bertrand, *Tetrahedron*, 2010, **66**, 413; (*b*) B. V. S. Reddy, P. N. Nair, A. Antony, C. Lalli and R. Grée, *Eur. J. Org. Chem.*, 2017, 1805.
11 P. F. Hudrlik, P. E. Holmes and A. M. Hudrlik, *Tetrahedron Lett.*, 1988, **29**, 6395–6398.
12 (*a*) M. Iwamoto, M. Miyano, M. Utsugi, H. Kawada and M. Nakada, *Tetrahedron Lett.*, 2004, **45**, 8647; (*b*) Y. Feng, M. M. Majireck and S. M. Weinreb, *J. Org. Chem.*, 2014, **79**, 7.
13 Both enantiomers of Stericol are commercially available, and they also can be prepared according to the described

procedure: P. Delair, A. M. Kanazawa, M. B. M. de Azevedo and A. E. Greene, *Tetrahedron: Asymmetry*, 1996, 7, 2707.

14 J. M. Allen, S. L. Aprahamian, E. A. Sans and H. Shechter, *J. Org. Chem.*, 2002, **67**, 3561.

15 (*a*) C. Rücker, *Chem. Rev.*, 1995, **95**, 1009; (*b*) T. D. Nelson and R. D. Crouch, *Synthesis*, 1996, 1031.

16 M. Parasram, V. O. Iaroshenko and V. Gevorgyan, *J. Am. Chem. Soc.*, 2014, **136**, 17926.

17 A tetraisopropyldisiloxane derivative was also isolated in low amount (7%) from the partially hydrolyzed starting material in the preparation of diisopropylchlorosilane (see the ESI†).

18 (*a*) M. Bols and T. Skrydstrup, *Chem. Rev.*, 1995, **95**, 1253; (*b*) L. Fensterbank, M. Malacria and S. McN. Sieburth, *Synthesis*, 1997, 813; (*c*) D. R. Gauthier, K. S. Zandi and K. J. Shea, *Tetrahedron*, 1998, **54**, 2289; (*d*) S. Bracegirdle and E. A. Anderson, *Chem. Soc. Rev.*, 2010, **39**, 4114; (*e*) A. Čusak, *Chem. – Eur. J.*, 2012, **18**, 5800; (*f*) M. Parasram and V. Gevorgyan, *Acc. Chem. Res.*, 2017, **50**, 2038.

19 A. W. Gregory, A. Chambers, A. Hawkins, P. Jakubec and D. J. Dixon, *Chem. – Eur. J.*, 2015, **21**, 111.

20 (*a*) Y. Motoyama, M. Aoki, N. Takaoka, R. Aoto and H. Nagashima, *Chem. Commun.*, 2009, 1574; (*b*) A. Tahara, Y. Miyamoto, R. Aoto, K. Shigeta, Y. Une, Y. Sunada, Y. Motoyama and H. Nagashima, *Organometallics*, 2015, **34**, 4895.

21 (*a*) S. Bower, K. A. Kreutzer and S. L. Buchwald, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1515; (*b*) P. Jakubec, A. Hawkins, W. Felzmann and D. J. Dixon, *J. Am. Chem. Soc.*, 2012, **134**, 17482.

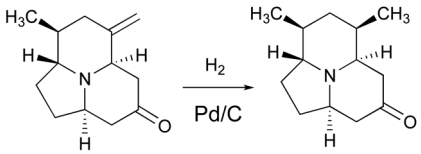
22 (*a*) M. Nakajima, T. Sato and N. Chida, *Org. Lett.*, 2015, **17**, 1696; (*b*) P. W. Tan, J. Seayad and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2016, **55**, 13436; (*c*) S. Katahara, S. Kobayashi, K. Fujita, T. Matsumoto, T. Sato and N. Chida, *J. Am. Chem. Soc.*, 2016, **138**, 5246; (*d*) Á. L. Fuentes de Arriba, E. Lenci, M. Sonawane, O. Formery and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2017, **56**, 3655; (*e*) X.-N. Hu, T.-L. Shen, D.-C. Cai, J.-F. Zheng and P.-Q. Huang, *Org. Chem. Front.*, 2018, **5**, 2051; (*f*) P. Gabriel, A. W. Gregory and D. J. Dixon, *Org. Lett.*, 2019, **21**, 6658. For selective reduction to enamino-ester, see: (*g*) Z.-P. Yang, Q. He, J.-L. Ye and P.-Q. Huang, *Org. Lett.*, 2018, **20**, 4200. For recent reviews see: (*h*) A. Chardon, E. Morisset, J. Rouden and J. Blanchet, *Synthesis*, 2018, **50**, 984; (*i*) Y. Takahashi, T. Sato and N. Chida, *Chem. Lett.*, 2019, **48**, 1138; (*j*) D. Matheau-Raven, P. Gabriel, J. A. Leitch, Y. A. Almehmadi, K. Yamazaki and D. J. Dixon, *ACS Catal.*, 2020, **10**, 8880.

23 (*a*) C. L. Heitzman, W. T. Lambert, E. Mertz, J. B. Shotwell, J. M. Tinsley, P. Va and W. R. Roush, *Org. Lett.*, 2005, **7**, 2405; (*b*) L. L. Anderson and K. A. Woerpel, *Org. Lett.*, 2009, **11**, 425.

24 R. I. Hogrefe, A. P. McCaffrey, L. U. Borozdina, E. S. McCampbell and M. M. Vaghefi, *Nucleic Acids Res.*, 1993, **21**, 4739.

25 (*a*) J. M. Hoover and S. S. Stahl, *J. Am. Chem. Soc.*, 2011, **133**, 16901; (*b*) Y. Sasano, S. Nagasawa, M. Yamazaki, M. Shibuya, J. Park and Y. Iwabuchi, *Angew. Chem., Int. Ed.*, 2014, **53**, 3236.

26 In the Smith's synthesis (ref. 3*c*), the catalytic hydrogenation of olefin **19** gave the hydrogenated product **20** as the major isomer. Hydrogenation occurs on the exo-methylene face, opposite to the cis substituted 4-piperidinone ring moiety.



19 **20**

27 (*a*) K. Iwasaki, K. K. Wan, A. Oppedisano, S. W. M. Crossley and R. A. Shenvi, *J. Am. Chem. Soc.*, 2014, **136**, 1300; (*b*) C. Obradors, R. M. Martinez and R. A. Shenvi, *J. Am. Chem. Soc.*, 2016, **138**, 4962; (*c*) S. A. Green, S. W. M. Crossley, J. L. M. Matos, S. Vásquez-Céspedes, S. L. Shevick and R. A. Shenvi, *Acc. Chem. Res.*, 2018, **51**, 2628.

28 P. Kraft, C. Weymuth and C. Nussbaumer, *Eur. J. Org. Chem.*, 2006, 1403.

29 C. Chatgilialoglu, C. Ferreri, Y. Landais and V. I. Timokhin, *Chem. Rev.*, 2018, **118**, 6516.

30 Analytical data are in agreement with previously reported synthetic and natural samples. However, the obtained rotation value was $[\alpha]_{25}^{D}$ = +2.5° ± 0.1 (compared to $[\alpha]_{25}^{D}$ = −8.5° for the isolated sample, ref. 1). We are confident that our synthetic sample falls in the natural stereogenic series because (1) the relative stereochemistry of the PMB protected racemic alcohol **3a** was unambiguously confirmed by X-ray analysis (see ref. 6) and (2) the fact that the *R*-(+)-Stericol isomer induces the *S*-configuration of the benzylic ether carbon of the pyrrolidine moiety, as in the chiral intermediate **3b**, has been unambiguously established in previous syntheses (see ref. 7). A 1% overall yield of this natural alkaloid was obtained from the starting chiral secondary alcohol (see a summary of previous syntheses in the ESI†).