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Total Synthesis of Natural (-)-205B Alkaloid and its Activity Toward $\alpha 7$ nAChR.

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

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A new approach to alkaloid (-)-205B is first 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 reaction of the highly selective iridium catalyzed partial reduction of lactam coupled with an acid promoted aza-Prins reaction, and an almost complete stereochemical control in the Shenvi's radical hydrogen atom transfer on an exocyclic methylene. The second part of this work demonstrate a positive allosteric behavior of this natural alkaloid toward $\alpha 7$ nAChR, in contrast to the reported inhibitory effect of the unnatural enantiomer.

Introduction

The Alkaloid (-)-205B (**1**) has been isolated more than three decades ago in low yield from the skin of amphibians *Dendrobate pumilio*.^[1] These frogs are used by local population to poison their blow darts, inflicting severe neurological effects to 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 the $\alpha 7$ nicotinic acetylcholine receptors (nAChR).^[4] The importance of these receptors have drastically increased with the recognition of their high affinity with the A β peptide and of their involvement in the internalization of this peptide.^[5] Thus local high concentration will favor peptide aggregation that will potentially leads to the formation of the characteristic amyloid plaques of the Alzheimer disease. In this context, the behavior of the natural enantiomer of this alkaloid towards $\alpha 7$ nAChR is of primary importance.

Results and discussion

We recently reported an efficient approach to the tricyclic 8b-azaacenaphthylene ring system which characterize 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 by the formation

of an hydroxy-indolizidinone intermediate **3** through a vinylogous Mannich reaction^[9] and finally by a cyclization through an aza-Prins reaction.^[10] Unfortunately, this approach then suffered 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**, figure 1).

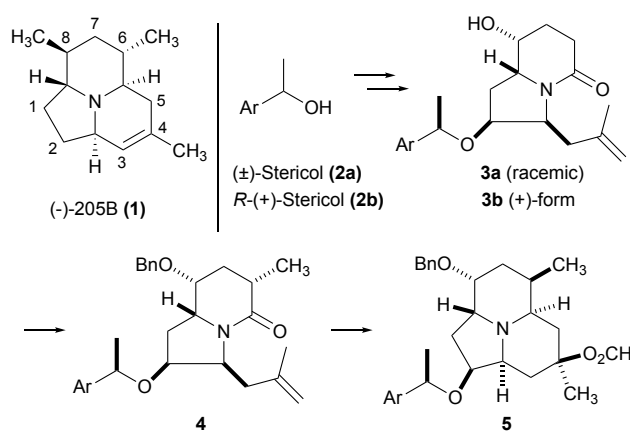


Figure 1. Alkaloid (-)-205B and our first approach to the 8b-azaacenaphthylene ring system. Ar = 2,4,6-triisopropylphenyl.

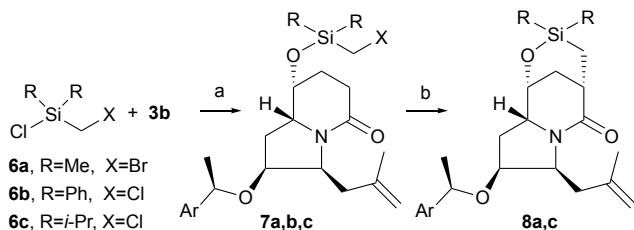
In order to overcome this major difficulty, we wondered if it would be possible to lock the configuration of this center by the addition of a transient bridged cycle. This scenario was particularly attractive since the transient cycle would be accessible from the hydroxy-indolizidinone intermediates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

^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.

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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 enantiomeric pure form by the 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 5g of **3b**. The secondary hydroxyl group was then silylated with the commercially available dimethylchlorosilane **6a** (Scheme 1 and Table 1). Efficient conversion was achieved only under uncommon high temperature (50°C) that reveals the intrinsic steric strain nature 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 not negligible amount of the starting hydroxy-indolizidinone **3b** was also obtained due to basic hydrolysis of the silyl ether intermediate. The use of commercial or freshly prepared solution of base didn't change drastically the situation. In order to slowdown this hydrolysis, the corresponding more crowded diphenylsilyl ether was also tested due to the facile access of the corresponding chlorosilane reagent **6b**.^[14]



Scheme 1. Transfer of chirality by silyl tethered alkylation. a) DCM, Et₃N, 50°C, 2.5h; b) LiHMDS, THF, -78°C to -15°C, 1h. Ar = 2,4,6-triisopropylphenyl

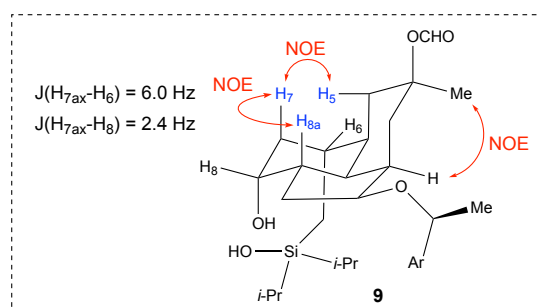
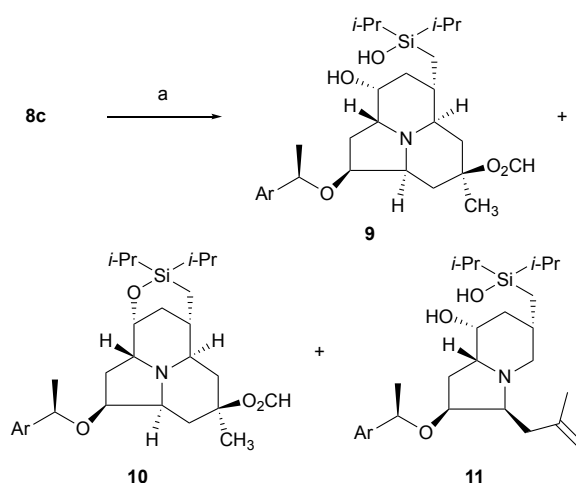
Entry	6	R	X	7 (%)	8 (%)
1	a	Me	Br	95	50-62 ^[a]
2	b	Ph	Cl	66	-
3	c	<i>i</i> -Pr	Cl	85	91

Table 1. Development of a reliable chirality transfer. [a] Variable amounts of **3b** are also obtained.

Silylation proceeded with a satisfactory yield, however only the hydrolyzed product could be isolated on cyclisation attempts from silyl ether **7b**. By comparison to the known resistance toward 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 high yield^[17] and, more rewarding, 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 of the newly formed stereogenic center could be obtained by extraction 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 worthy to note that this particularly efficient intramolecular alkylation reaction is in a 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 works are in progress in order to evaluate the scope and limitations of this chirality transfer by intramolecular alkylation through a silyl link.

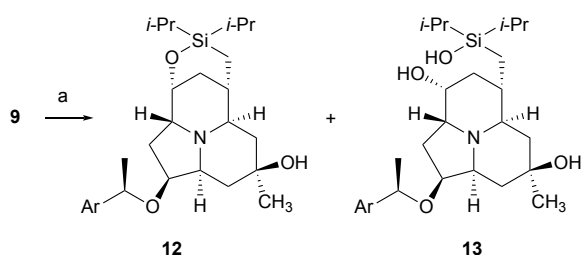
The crucial formation of the last ring was then investigated by partial reduction of the lactam followed by acid treatment to generate the corresponding iminium and trigger the aza-Prins reaction. Reduction with a standardized solution of LAH followed by quenching with formic acid lead to an encouraging mixture of cyclized products **9** and **10** in 68%, 14% yield respectively and some over-reduced amine **11** (scheme 2).



Scheme 2. Cyclization through aza-Prins reaction. a) LiAlH₄, Et₂O, -10°C, then HCOOH -10°C and representative NMR data for compound **9**. Ar = 2,4,6-triisopropylphenyl.

To ensure that the silyl ether hydrolysis in **9** appeared in the last event of this cascade, the stereo integrity of C6 was assessed by extracting the *J* coupling constants values for both C7 hydrogen. The fact that all these *J* values were below 10 Hz (except for the ²*J* coupling constant), was consistent with an

equatorial orientation for both hydrogens on C6 and C8. Furthermore, the chair conformation of this ring was ensued by the observation of NOE signals between C7-Hax/C5-Hax and C7-Hax/C8a-H. As an additional proof, the saponification of the isolated formate **9** gave a mixture of corresponding tertiary alcohols **12** and **13** where the silyl ether linkage has been 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 to the 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 lactam partial reduction.

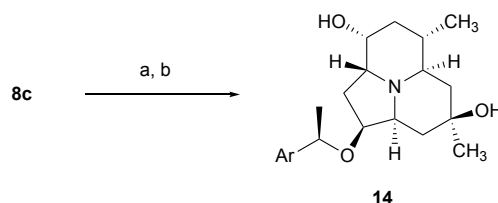


Scheme 3. Saponification of formate **9**. a) K_2CO_3 , MeOH, 1 h. Ar = 2,4,6-triisopropylphenyl.

Recently, Dixon^[19] demonstrated in nitro-Mannich cyclizations 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 reproducible almost quantitative yield in an enough pure form to be engaged in the next step. In addition, no over-reduced amine **11** or at least not higher than 2% (from 1H NMR on crude material) was formed in that transformation.

The following task was to unmask the C6 methyl group. Efficient protodesilylation of unactivated C(sp³)-Si bond or sterically hindered silicon moiety were reported using tBuOK, TBAF/THF solution in DMF at elevated temperature.^[23] However, during optimization of the reaction conditions we have noticed erratic results depending on the age and/or on the source of the TBAF solution. Furthermore, the importance of the optimal amount of residual water in TBAF/THF solution has been reported in the literature.^[24] Finally, we found that using CsF as 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

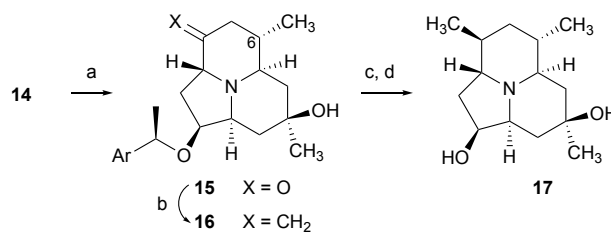
46% overall yield for this two steps, four transformations sequence.



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

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, Dess-Martin oxidation gave a complex mixture whereas Swern oxidation provided not 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 Stal^[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). Albeit suffering some degradation, pure analytical sample of **16** could be separated from the excess of 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.

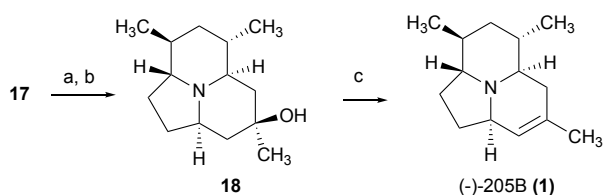
Based on the shape of this tricyclic system and by comparison with results described by Smith on related structure,^[26] catalytic hydrogenation was expected to occur on the α -face of the exo-methylene of **16** in order to furnish the expected equatorial oriented methyl substituent. Unfortunately, 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 steric bias between the two faces of the olefin.



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

To set-up the required thermodynamically favored equatorial methyl substituent, the radical hydrogen atom transfer (HAT) developed by Shenvi appeared promising.^[27] To our great satisfaction, these conditions allowed the formation of only *one stereoisomer*, as judged on the ¹H NMR of the crude mixture. This high selectivity certainly reflects the high steric 1,3-diaxial interaction between the two methyl substituents in the undesired epimer. From pure sample of **16**, hydrogenated product could be isolated in high yield (85%), however for synthetic purpose and due to difficult purifications of intermediates **15** and **16**, the methylation and the HAT reaction was performed on crude material and led to tricyclic amino alcohol **17** after 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, thus tributyltin hydride was precluded. We were please to observe that under conventional radical conditions,^[28] tris(trimethylsilyl)silane was a very powerful hydrogen donor^[29] and allows neat conversion to the corresponding amino alcohol **18**. Finally, dehydration performed in 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** (4 steps).^[30]



Scheme 6. Completion of the synthesis of the alkaloid (-)-205B. a) PhO(CS)Cl, DMAP, DCM; b) TMS₃SiH, AIBN, benzene, reflux; c) *p*-TsOH, benzene, reflux, (38% from **17**)

With the natural form of the (-)-205B alkaloid in hand, we turned our attention toward its effect on $\alpha 7$ nAChR. The gene coding for the human $\alpha 7$ nAChR 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/oocyte). The heterologous expression in the plasma membrane is sufficient after 2 to 3 days of incubation at 19°C. The functional characterization of (-)-205B was performed electrophysiologically by 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 was an initial incubation with the natural agonist acetylcholine (ACh) at 100 μ M, then with the alkaloid (-)-205B at 1, 10 and 100 μ M 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 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 μ M) (Figure 2). However, lower concentrations (1 and 10 μ M) of this alkaloid significantly increased the current amplitude compared to the control.

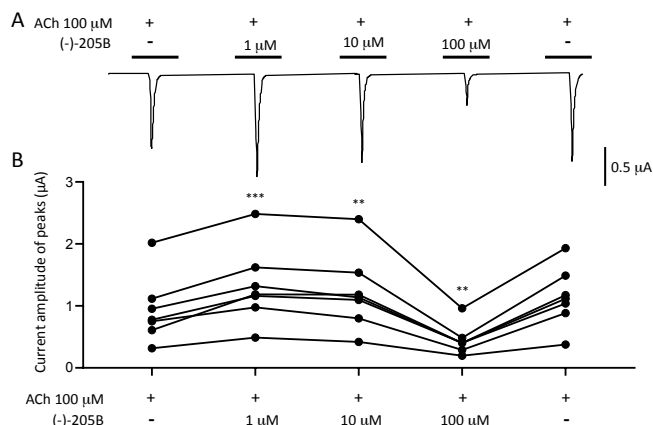


Figure 2. Effects of alkaloid (-)-205B on ACh-induced currents in *Xenopus oocytes* expressing $\alpha 7$ nAChR. A) Representative TEVC recording of response $\alpha 7$ nAChR-expressing oocytes to ACh and (-)-205B. B) Statistical analysis of 6 recordings based on paired *t*-test with the first application of ACh 100 μ M as reference.

To evaluate if the alkaloid had an agonist effect on the $\alpha 7$ -nAChRs, the oocytes were incubated with the alkaloid at 1, 10 and 100 μ M without ACh and no current was observed (Figure 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 μ M) and an antagonist effect at high concentrations (100 μ M).

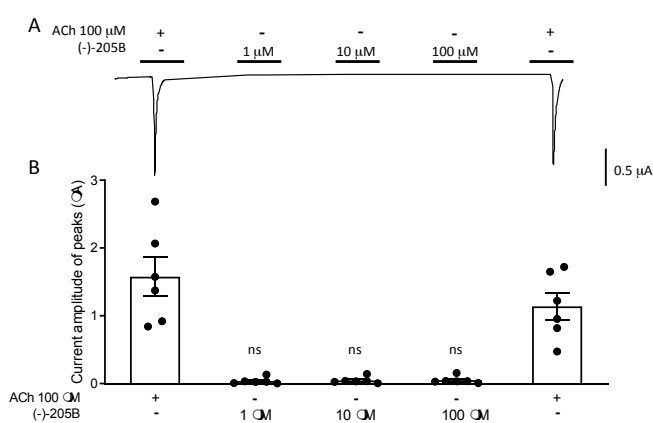


Figure 3. Effects of alkaloid (-)-205B on $\alpha 7$ nAChR expressed in *Xenopus oocytes*. A) Representative TEVC recording of responses to ACh and (-)-205B applied separately. B) Dot plots of 6 recordings showing means of normalized current amplitudes in bars +/- SEM. ns: not significant (one sample *t*-test with 0 as reference).

Conclusions

In this paper, we have described the total synthesis of alkaloid (-)-205B in its natural optical 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 serve as an efficient configurationnal 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 has been observed in the radical HAT favoring the thermodynamic isomer. Furthermore, by opposition to the previously published results for the unnatural antipode, this natural form of the alkaloid (-)-205B has shown a modest positive allosteric behavior toward $\alpha 7$ nAChR at a concentration as low as 1 μ M and an antagonist effect at 100 μ M.

Author Contributions

S. Mazeh: chemical synthesis; M. D. Garcia-Fernandez, 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.

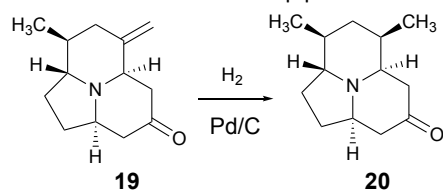
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References

- 1 T. Tokuyama, N. Nishimori, A. Shimada, H. W. Edwards and J. W. Daly, *Tetrahedron* 1986, **43**, 643.
- 2 J. W. Daly, H. M. Garraffo, T. F. Spande In *Alkaloids: Chemical and Biological Perspectives*, Vol. 13 (Ed.: S. W. Pelletier), Elsevier Science 1999, 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. Majirek and S. M. Weinreb, *J. Org. Chem.* 2014, **79**, 7.
- 13 Both enantiomers of Stericol are commercially available, it 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 tetraisopropylidisiloxane derivative is also isolated in low amount (7%) coming from the partially hydrolyzed starting material in the preparation of the diisopropylchlorosilane, (see Supporting Information).
- 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.* 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. Almealmadi, K. Yamazaki and D. J. Dixon, *ACS Catalysis* 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 3c), the catalytic hydrogenation of olefin **20** gave the hydrogenated product **21** as the major isomer. Hydrogenation occurs on the exo-methylene face, opposite to the *cis* substituted 4-piperidinone ring moiety.



- 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. Vázquez-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. Chatgililoglu, C. Ferreri, Y. Landais and V. I. Timokhin, *Chem. Rev.* 2018, **118**, 6516.
- 30 Analytical data are in agreement with previous reported synthetic and natural samples. However, the obtained rotation value was $[\alpha]_{\text{D}}^{25} = +2.5^\circ \pm 0.1$ (compared to $[\alpha]_{\text{D}}^{25} = -8.5^\circ$ for the isolated sample, ref 1). We are confident that our synthetic sample fall in the natural stereogenic serie 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 induce the *S*- configuration of the benzylic ether carbon of the pyrrolidine moiety, like in the chiral intermediate **3b**, as been unambiguously established in previous synthesis (see ref 7).