Toward an Asymmetric General Access to Azabicyclo[*n*.2.1]alkanes According to the CN(*R*,*S*) Method

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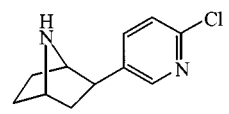
According to the CN(*R*,*S*) strategy, a general method for the synthesis of azabicyclo[*n*.2.1]alkanes of type **4** was described starting from the 2-cyano-5-oxazolopyrrolidine **5**. A Mannich-type cyclization allowed an asymmetric access to potent nicotinic acetylcholine receptor agonists like epibatidine **1**, ferruginine **2** and anatoxine-a **3**.

Introduction

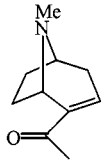
Natural aza-bicyclo derivatives have been reported to exhibit agonist activity for nicotinic receptors. (−)-Epibatidine **1**, a 7-azanorbornane analogue of nicotine isolated from the skin of the Ecuadorian poison frog *Epipedobates tricolour*, has been reported to be an extraordinary non-opioid analgesic and a very potent nicotinic acetylcholine receptor (nAChR) agonist.[1,2] Likewise, (+)-ferruginine **2**, an 8-azabicyclo[3.2.1]octane extracted from the arboreal species *Darlingiana ferruginea* and *D. darlingiana*, has been used as an nAChR agonist for the treatment of neurodegenerative diseases.[3,4]

Another well-known toxin, (+)-anatoxine-a **3**, possessing the 9-azabicyclo[4.2.1]nonane skeleton, produced by the fresh water cyanobacterium *Anabaena Flos aquae*, has been subjected to numerous chemical and biological studies due to its remarkable activity as an nAChR agonist.[5,6]

The biological activity of these compounds emerges from their structural similarity with nicotine, namely a nitrogen atom and a π system (aromatic or conjugated ketone group) together with an appropriate spatial arrangement. For all of them, the rigid bicyclic skeleton forces the nitrogen atom to be at a precise distance from the π electron system. This distance can be varied by varying *n* in the general structure **4** (see figure above). It therefore appeared interesting to design a general access to azabicyclo[*n*.2.1]alkanes **4** that could also be valuable for the synthesis of alkaloids **1**−**3** and some of their analogues. A strategy for the construction of bicyclic compounds of type **4** was envisaged starting from 2-cyano-5-oxazolopyrrolidine **5**. The synthetic interest



(–)-epibatidine **(1)**



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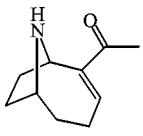
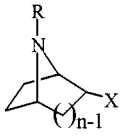


(+)-anatoxine-a **(3)**



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of this chiral nonracemic starting material has already been shown in many applications.[7] According to the CN(*R*,*S*) method,[7] our plan consisted of the alkylation of **5** at the position α to the nitrile function by an alkyl chain containing a nucleophilic group that would be able to add onto the potential iminium ion **6**[8a] and more precisely through a Mannich reaction as depicted in Scheme 1. It was anticipated that this intramolecular cyclization leading to the desired azabicyclic compound **4** would be governed by the empirical rules established by Baldwin.[8b] Nevertheless, attempts to cyclize by 5-, 6- and 7-*endo-trig* reactions were also undertaken.

Results and Discussion

The synthesis of the azabicyclo[n.2.1]skeleton started with the preparation of precursors **10a**−**c** following the general sequence depicted in Scheme 2. Alkylation of the lithiated anion of 2-cyano-5-oxazolopyrrolidine **5** (LDA 2.6

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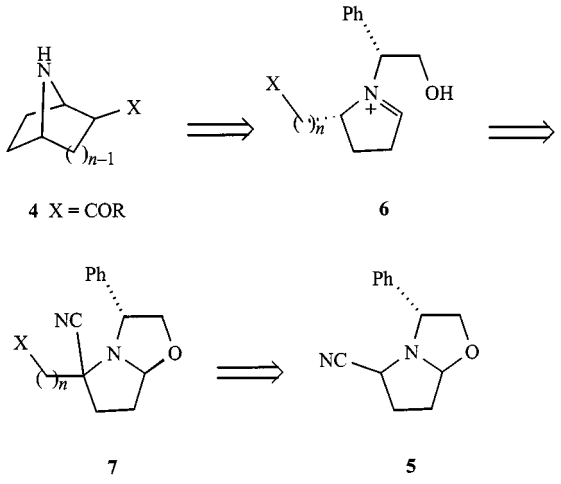
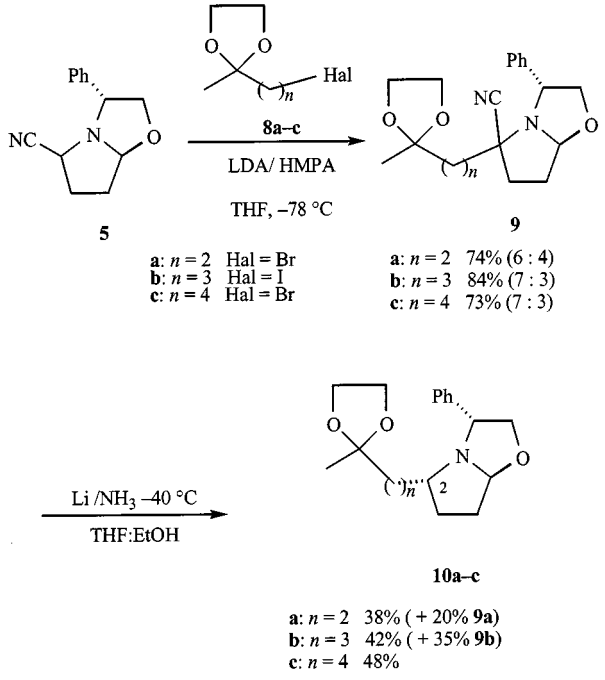


Scheme 1

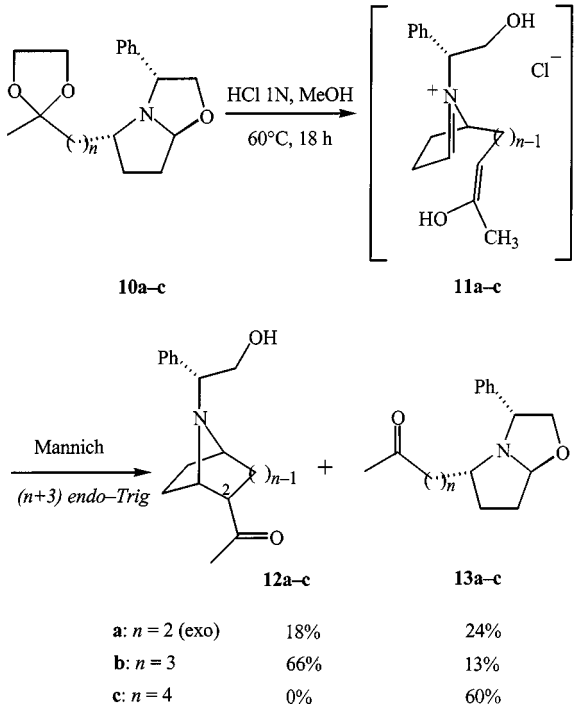
equiv. THF, −78 °C) in the presence of HMPA (4.2 equiv.) with haloketals **8a−c** afforded the amino nitriles **9a−c** as diastereomeric mixtures in good yield (Scheme 2).[9]



Scheme 2

Diastereoselective decyanation of **9a−c**[4,11] was achieved using Li/NH_3 in the presence of ethanol ($THF/NH_3/EtOH$ 100:10:1) to give compounds **10a−c** as single stereoisomers along with unreacted **9**. The use of ethanol in this reaction precluded the formation of by-products.[11] A 2*R*-configuration could be assigned for the pyrrolidine **10** in analogy to previous results in this series. This was the desired configuration for the C-1 carbon in the target bicyclic compounds of type **4**. Some attempts were made to improve the yield of this decyanation step by using sodium metal or by varying the reaction temperature, without success.

The next step consisted of the opening of the oxazolidine ring of compound **10** under acidic conditions to generate the iminium ion **11**, which should be able to undergo the planned intramolecular Mannich-type cyclization (Scheme 3). Indeed, treatment of **10a,b** with methanolic hydrochloric acid produced the desired bicyclic derivatives **12a,b** in varying yields together with the deprotected ketones **13a,b**; **10c** failed to undergo the cyclization reaction (Scheme 3).

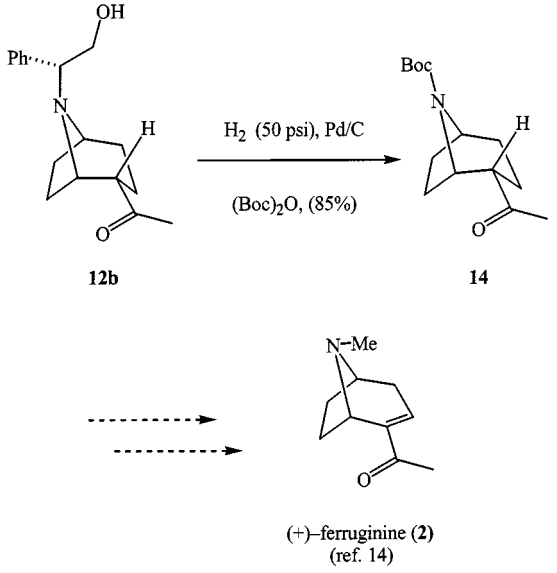


Scheme 3

The 7-azabicyclo[2.2.1] skeleton **12a** was isolated in 18% yield as a unique stereoisomer as proved by ^1H and ^{13}C NMR spectroscopy and chromatographic analyses. The *exo* configuration of the acetyl group was deduced in the ^1H NMR spectrum from the pattern of the H-2 signal, which appeared as a doublet of doublets at $\delta = 2.47$ ($J = 5.1$, 9.8 Hz) corresponding to a coupling with both H-3 protons, and the apparent absence of coupling with the bridgehead proton H-1. This observation was found to be in agreement with the signal pattern of very similar 7-azabicyclo[2.2.1]heptane systems.[12] Although the elaboration of the azanorbornane skeleton was accomplished with success, the low yield of the disfavoured 5-*endo-trig* cyclization was unfortunately incompatible with a multistep synthesis. For similar work in this field, Rapoport reported better results by applying the intramolecular Mannich-type cyclisation onto a more electrophilic acyliminium ion.[13]

Using the same strategy as above, the 8-azabicyclo[3.2.1] skeleton **12b** was successfully isolated in 66% yield. This transformation was totally stereoselective: only one stereoisomer was present in the crude mixture as indicated by ^1H and ^{13}C NMR spectrosopcy. The *endo* configuration of the acetyl group was deduced from the ^1H NMR spectrum

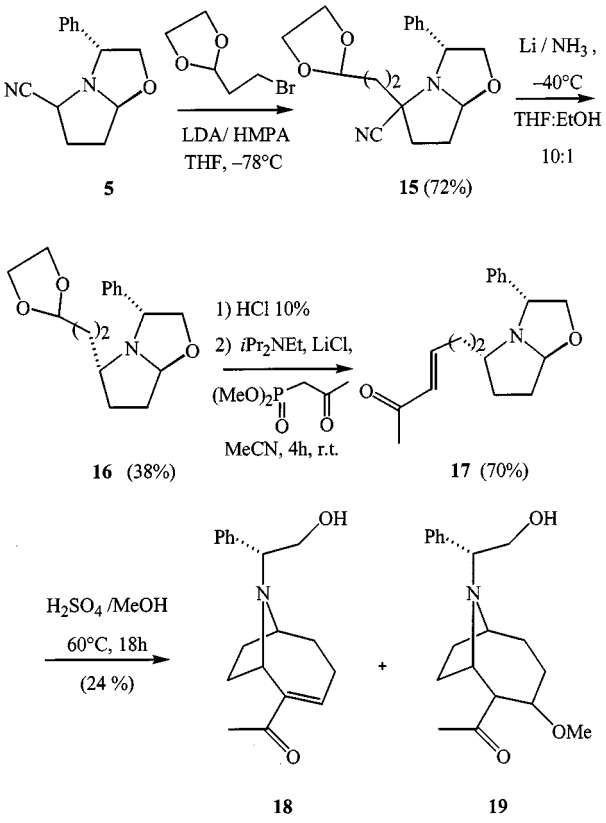
and thermodynamic stability hypotheses: in the ^{1}H NMR spectrum, the diagnostic H-2 proton exhibited coupling constants of 2.1 Hz with H-1 and 5.6 Hz and 11.5 Hz with H-3, which clearly indicated that H-2 occupied an axial position. The reaction conditions (MeOH, HCl 1 N, 60 °C) of the intramolecular cyclization of the iminium ion **11b** led to the formation of the thermodynamically more stable tropane **12b** in which the acetyl group occupies an equatorial position on the six-membered ring.[14] Removal of the chiral appendage of **12b** by hydrogenolysis and reprotection of the secondary amine as *tert*-butylcarbamate afforded the *N*-BOC bicyclic compound **14** in 85% yield in a one-pot reaction (Scheme 4). A formal diastereoselective synthesis of (+)-ferruginine could thus be achieved, since Rapoport et al. have described the conversion of **14** into the target alkaloid.[15] This short synthesis also appears very interesting for the synthesis of tropane analogues of epibatidine which could also be easily accessible in this manner.



Scheme 4

The 7-*endo-trig* type cyclization required for the construction of the 9-azabicyclo[4.2.1] skeleton was more difficult than would be expected from Baldwin's empirical rules. Indeed, the methanolic hydrochloric acid treatment of the amino ether **10c** was ineffective for the desired cyclization: no trace of cyclization product could be found and only deprotected ketone **13c** (60% yield), together with decomposition products, were isolated. Since reactions of iminium ion species with nucleophiles can generally be conducted with improved yields under anhydrous conditions, or, in some cases, even better with polar nonprotic solvents, we examined these alternatives. Nevertheless, all attempts to promote the 7-*endo-trig* cyclization failed, even in the presence of Lewis acid catalysts.

Our attention then turned to the intramolecular cyclization of an α,β-unsaturated ketone onto an iminium ion on the basis of our previous published total synthesis of (+)-ferruginine.[4] 2-Cyano-5-oxazolidine (**5**) was diastereospecifically converted into the oxazolidine **16** in two steps in 28% overall yield (Scheme 5). The presence of a single stereoisomer was proved by NMR spectroscopy and chromatography; some aminonitrile **15** was also recovered (20% yield). Treatment of the acetal function of compound **16** with dilute hydrochloric acid provided the crude aldehyde, which was immediately submitted to Horner–Wadsworth–Emmons conditions (iPr$_2$NEt, LiCl, MeCN)[16] to afford the enone **17** in 70% overall yield. The 7-*endo-trig* cyclization step carried out with methanolic sulfuric acid provided the two bicyclic derivatives **18** and **19**, which were isolated as an inseparable mixture in approximately 24% yield. These nonoptimized results potentially provide an easy access to *N*-methylanatoxine.



Scheme 5

Conclusion

By following the CN(*R,S*) method we have developed a short and original access to compounds possessing the azabicyclo[n.2.1] skeleton. The key step of our strategy, which is based on an intramolecular cyclization of a nucleophile group onto an alkyliminium ion, allowed us to achieve a formal synthesis of (+)-ferruginine.[4] Our general method has potential for the synthesis of various analogues of natural bicyclic alkaloids.

Experimental Section

General: Tetrahydrofuran was distilled from sodium/benzophenone ketyl immediately prior to use. Diisopropylamine was distilled from and stored over KOH. Acetonitrile was distilled from CaH_2 and methanol and ethanol from magnesium turnings. Flash chromatography was carried out using 230−400 mesh silica gel. Optical rotations were carried out at 20 °C in a 1 dm cell. Microanalyses were carried out at the "Service de Microanalyse" at the "Institut de Chimie des Substances Naturelles".

General Alkylation Procedure of Amino Nitrile (5): A solution of **5** (3 g, 14.0 mmol) in THF (24 mL) at −78 °C was added dropwise to a stirred solution of LDA [prepared from diisopropylamine (5.1 mL, 36.4 mmol) and 1.6 M *n*BuLi (22.8 mL, 36.4 mmol) in hexane] in THF (12 mL) and HMPA (10.3 mL, 58.8 mmol). After 30 min, a solution of **8** (16.8 mmol) in THF (5 mL) was added. After stirring for 4 hours at −78 °C, the mixture was quenched by saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layers were combined, dried and concentrated under vacuum. The crude oil was then purified by flash chromatography

5-{2-(2-Methyl-[1,3]dioxolan-2-yl)ethyl}-3-phenylhexahydropyrrolo-[2,1-*b*]oxazole-5-carbonitrile (9a): The general alkylation procedure was applied to **5** (3 g, 14 mmol) and **8a** (3.3 mL, 16.8 mmol) to give **9a** (3.41 g, 74% yield) as a 6:4 mixture of diastereomers and as a colourless oil after flash chromatography (heptane/EtOAc 7:3). (more polar diastereomer) $[\alpha]_D = -57$ ($CHCl_3$, $c = 1.0$). IR (neat): $\tilde{\nu}$ = 2979, 2950, 2880, 2235, 1449, 1379, 1065 cm^{-1}. MS (CI): *m*/*z* = 329 [MH^+], 302, 188. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5 H), 5.04 (dd, *J* = 3.7 Hz, 1 H), 4.54 (t, *J* = 7.4 Hz, 1 H), 4.28 (t, *J* = 7.7 Hz, 1 H), 3.70−3.90 (m, 4 H), 3.48 (t, *J* = 8.0 Hz, 1 H), 1.80−2.30 (m, 8 H), 1.24 (s, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.9, 28.5, 29.1, 35.4, 35.6, 61.1, 64.7, 65.4, 74.2, 97.9, 108.9, 122.0, 126.2, 127.3, 128.6, 141.4. HRMS (CI) calcd. for $C_{19}H_{24}N_2O_3 + H^+$ 329.1865; found 329.1846.

5-{3-(2-Methyl-[1,3]dioxolan-2-yl)propyl}-3-phenylhexahydropyrrolo[2,1-*b*]oxazole-5-carbonitrile (9b): The general alkylation procedure was applied to **5** (1.5 g, 6.9 mmol) and **8b** (2 mL, 8.4 mmol) to give **9b** (1.83 g, 84% yield) as a 7:3 mixture of diastereomers and as a colourless oil after flash chromatography (heptane/EtOAc 7:3). (more polar diastereomer) $[\alpha]_D = -60$ ($CHCl_3$, c = 0.28). IR (neat): $\tilde{\nu}$ = 2947, 2880, 2231, 1604, 1492, 1453, 1380, 1066 cm^{-1}. MS (CI): *m*/*z* = 343 [MH^+], 316, 195, 188. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5 H), 5.04 (dd, *J* = 1.9, 3.6 Hz, 1 H), 4.52 (t, *J* = 7.4 Hz, 1 H), 4.27 (dd, *J* = 7.3, 8.3 Hz, 1 H), 3.79−3.92 (m, 4 H), 3.47 (t, *J* = 8.1 Hz, 1 H), 1.20−2.29 (m, 10 H), 1.23 (s, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.7, 23.8, 29.2, 34.2, 35.5, 38.9, 61.2, 64.6, 65.8, 74.2, 97.9, 109.5, 122.2, 126.2, 127.4, 128.7, 141.3. $C_{20}H_{26}N_2O_3$ (342.4): calcd. C 70.15, H 7.65, N 8.18; found C 69.85, H 7.52, N 7.59.

5-{4-(2-Methyl-[1,3]dioxolan-2-yl)butyl}-3-phenylhexahydropyrrolo-[2,1-*b*]oxazole-5-carbonitrile (9c): The general alkylation procedure was applied to **5** (2.9 g, 13.5 mmol) and **8c** (2.9 mL) to give **9c** (3.51 g, 73% yield) as a 7:3 mixture of diastereomers and as a colourless oil after flash chromatography (heptane/EtOAc 7:3). (more polar diastereomer) $[\alpha]_D = -54$ ($CHCl_3$, $c = 6.6$). IR (neat): $\tilde{\nu}$ = 2950, 2870, 2230, 1149, 1375, 1080 cm^{-1}. MS (CI): *m*/*z* = 357 [MH^+], 330. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.24−7.41(m, 5 H), 5.03 (d, *J* = 3.5 Hz, 1 H), 4.54 (t, *J* = 7.3 Hz, 1 H), 4.27 (t, *J* = 8.3 Hz, 1 H), 3.88 (m, 4 H), 3.48 (t, *J* = 7.9 Hz, 1 H), 1.29−2.28 (m, 12 H), 1.26 (s, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.7, 24.1, 26.3, 29.1, 34.1, 35.4, 38.7, 61.1, 64.5, 65.7, 74.1, 97.8, 109.7, 122.2, 126.1, 127.3, 128.6, 141.3. $C_{21}H_{28}N_2O_3$ (356.5): calcd. C 70.76, H 7.96, N 7.86; found C 70.34, H 7.69, N 8.12.

General Reductive Decyanation Procedure for Compounds 9: A solution of the oxazolopyrrolidine **9** (10.4 mmol) in THF (39 mL) was added to liquid ammonia (360 mL) at −40 °C, followed by dry ethanol (3.6 mL). After stirring for 5 min lithium metal (174 mg, 25.0 mmol) was introduced. Stirring was continued at −78° C for 30 min, and then the ammonia was evaporated before the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, the combined organic phases were dried and concentrated under vacuum and purified by flash chromatography (heptane/EtOAc 8:2).

5-{2-(2-Methyl-[1,3]dioxolan-2-yl)ethyl}-3-phenylhexahydropyrrolo-[2,1-*b*]oxazole (10a): The general decyanation procedure was applied to **9a** (3.4 g, 10.4 mmol) to give **10a** (1.20 g, 38% yield) as a colourless oil (accompanied by starting material **9a** isolated in 20% yield). $[\alpha]_D = -35$ ($CHCl_3$, $c = 1.1$). IR (neat): $\tilde{\nu}$ = 2947, 2850, 1600, 1445, 1365, 1210, 1100 cm^{-1}. MS (EI): *m*/*z* = 304 (100), 273 (10), 260 (42), 188 (78) [MH^+]. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.21−7.40 (m, 5 H), 5.00 (dd, *J* = 2.2, 5.3 Hz, 1 H), 4.35 (t, *J* = 7.6 Hz, 1 H), 4.18 (t, *J* = 6.6 Hz, 1 H), 3.64−3.90 (m, 4 H), 3.61 (dd, *J* = 6.2, 8.2 Hz, 1 H), 2.90 (m, 1 H), 1.37−2.20 (m, 8 H), 1.22 (s, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.6, 29.9, 30.0, 30.1, 35.4, 64.4, 66.4, 67.9, 72.8, 98.8, 109.8, 126.5, 126.7, 128.3, 143.0. HRMS (CI) calcd. for $C_{18}H_{25}NO_3 + H^+$ 304.1912; found 304.1913.

5-{3-(2-Methyl-[1,3]dioxolan-2-yl)propyl}-3-phenylhexahydropyrrolo[2,1-*b*]oxazole (10b): The general decyanation procedure was applied to **9b** (2 g, 5.9 mmol) to give **10b** (795 mg, 42% yield) as a colourless oil [accompanied by starting material **9b** (35%)]: $[\alpha]_D = -42$ ($CHCl_3$, $c = 1.6$). IR (neat): $\tilde{\nu}$ = 2944, 2875, 1600, 1491, 1456, 1375, 1068 cm^{-1}. MS (CI): *m*/*z* = 318 [MH^+], 198. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.21−7.39 (m, 5 H), 5.00 (dd, *J* = 2.3, 5.3 Hz, 1 H), 4.35 (t, *J* = 7.7 Hz, 1 H), 4.14 (t, *J* = 6.8 Hz, 1 H), 3.80−3.93 (m, 4 H), 3.60 (dd, *J* = 6.5, 8.3 Hz, 1 H), 2.88 (m, 1 H), 1.25−2.20 (m, 10 H), 1.22 (s, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.1, 23.7, 30.1, 30.5, 36.3, 39.4, 64.6, 66.9, 68.4, 73.1, 98.9, 110.1, 126.6, 126.9, 128.2, 143.2. $C_{19}H_{27}NO_3$ (317.4): calcd. C 71.89, H 8.57, N 4.41; found C 71.59, H 8.28, N 4.29.

5-{4-(2-Methyl-[1,3]dioxolan-2-yl)butyl}-3-phenyl-exahydropyrrolo-[2,1-*b*]oxazole (10c): The general decyanation procedure was applied to oxazolopyrrolidine **9c** (1.5 g, 4.2 mmol) to give **10c** (667 mg, 48% yield) as a colourless oil: $[\alpha]_D = -34$ ($CHCl_3$, c = 1.1) {ref.:[9] $[\alpha]_D = -34$ ($CHCl_3$, $c = 2.1$)}. IR (neat): $\tilde{\nu}$ = 2947, 2873, 1453, 1144, 1030 cm-1. MS (CI): *m*/*z* = 332 [MH^+]. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5 H), 5.01 (dd, *J* = 2.3, 5.3 Hz, 1 H), 4.36 (dd, *J* = 7.1, 8.1 Hz, 1 H), 4.16 (t, *J* = 6.7 Hz, 1 H), 3.91 (m, 4 H), 3.63 (dd, *J* = 6.2, 8.2 Hz, 1 H), 2.88 (m, 1 H), 1.16−2.21 (m, 12 H), 1.22 (s, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.8, 24.4, 26.8, 30.2, 30.6, 36.1, 39.3, 64.7, 66.8, 68.2, 73.0, 99.0, 110.2, 126.7, 126.9, 128.5, 143.3. $C_{20}H_{29}NO_3$ (331.5): calcd. C 72.47, H 8.82, N 4.23; found C 72.10, H 8.48, N 4.55.

General Cyclization Procedure for Compounds 10: A solution of **10** (0.33 mmol) and 1 N HCl (2.2 mL) in MeOH (10 mL) was refluxed at 60 °C for 18 hours. The mixture was then cooled, poured into saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried and the solvents evaporated under vacuum. The residue was purified by flash chromatography (heptane/EtOAc 7:3 and 2:8).

1-{7-(2-Hydroxy-1-phenylethyl)-7-azabicyclo[2.2.1]hept-2-yl}-ethanone (12a): The general cyclization procedure was applied to **10a** (100 mg, 0.33 mmol) to afford, after purification, the deprotected product **13a** (20.5 mg, 24%) and the bicycle **12a** (15.4 mg, 18%) as a colourless oil.

12a: IR (neat): $\tilde{\nu}$ = 3430, 2958, 2875, 1704, 1450, 1370 cm^{-1}. MS (CI): *m*/*z* = 260 [MH^+]. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.26−7.40 (m, 5 H), 3.97 (*J* = 4.5, 11.0 Hz, 1 H), 3.90 (d, *J* = 4.6 Hz, 1 H), 3.59 (m, 1 H), 3.36 (m, 1 H), 3.15 (m, 1 H), 2.47 (dd, *J* = 5.1, 9.8 Hz, 1 H), 2.12 (s, 3 H), 1.33−2.15 (m, 7 H). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 26.3, 26.9, 29.8, 33.4, 55.6, 57.7, 58.4, 60.9, 65.8, 127.5, 128.2, 128.4, 140.3, 215.0. HRMS (CI) calcd. for $C_{16}H_{21}NO_2$ + H^+ 260.1650; found 260.1656.

13a: IR (neat): $\tilde{\nu}$ = 2933, 2868, 1715, 1666, 1454, 1367, 1030 cm^{-1}. MS (CI): *m*/*z* = 260 [MH^+], 188. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.23−7.39 (m, 5 H), 5.01 (dd, *J* = 1.8, 2.5 Hz, 1 H), 4.32 (dd, *J* = 7.2, 8.2 Hz, 1 H), 4.09 (t, *J* = 6.9 Hz, 1 H), 3.57 (dd, *J* = 7.0, 8.3 Hz, 1 H), 2.93 (quint, *J* = 6.5 Hz, 1 H), 2.32−2.41 (m, 2 H), 1.50−2.16 (m, 6 H), 1.93 (s, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 29.4, 29.8, 30.2, 40.2, 66.2, 69.1, 73.5, 99.1, 126.8, 127.1, 128.6, 142.9, 208.9.

1-{8-(2-Hydroxy-1-phenylethyl)-8-azabicyclo[3.2.1]oct-2-yl}-ethanone (12b): The general cyclization procedure was applied to **10b** (778 mg, 2.5 mmol) to afford, after purification, the deprotected product **13b** (87 mg, 13%) and the bicycle **12b** (401 mg, 66%) as a colourless oil.

12b: $[\alpha]_D$ = +21 ($CHCl_3$, *c* = 0.45). IR (neat): $\tilde{\nu}$ = 3443, 2952, 2878, 1705, 1453, 1355 cm^{-1}. MS (CI): *m*/*z* = 274 [MH^+], 256, 242. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.25−7.45 (m, 5 H), 3.88 (m, 1 H), 3.68−3.78 (m, 2 H), 3.59 (m, 1 H), 3.23 (m, 1 H), 2.85 (dd, *J* = 2.3, 10.2 Hz, 1 H), 1.87 (s, 3 H), 1.30−1.87 (m, 9 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 18.7, 24.3, 27.3, 28.1, 28.3, 51.9, 55.6, 58.1, 63.8, 64.5, 127.8, 128.4, 128.6, 140.7, 209.9. $C_{17}H_{23}NO_2$ (273.4): calcd. C 74.69, H 8.48, N 5.12; found C 74.32, H 7.87, N 4.84.

13b: $[\alpha]_D$ = −51 ($CHCl_3$, *c* = 1.25). IR (neat): $\tilde{\nu}$ = 2938, 2860, 1712, 1448, 1364, 1035 cm^{-1}. MS (CI): *m*/*z* = 274 [MH^+], 230, 188. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5 H), 5.00 (dd, *J* = 2.3, 5.3 Hz, 1 H), 4.35 (dd, *J* = 7.2, 8.2 Hz, 1 H), 4.13 (t, *J* = 6.8 Hz, 1 H), 3.59 (dd, *J* = 6.6, 8.3 Hz, 1 H), 2.89 (m, 1 H), 1.25−2.46 (m, 10 H), 2.03 (s, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.7, 29.8, 30.1, 30.3, 35.5, 43.8, 66.6, 68.4, 73.2, 98.9, 126.6, 127.0, 128.5, 143.1, 209.1. $C_{17}H_{23}NO_2$ (273.4): calcd. C 74.69, H 8.49, N 5.12; found C 74.39, H 8.55, N 5.24.

6-(3-Phenylhexahydropyrrolo[2,1-*b*]oxazol-5-yl)hexan-2-one (13c): The general cyclization procedure was applied to **10c** (200 mg, 0.61 mmol) to afford, after purification, the deprotected product **13c** (105 mg, 60%) as a colourless oil: IR (neat): $\tilde{\nu}$ = 2935, 2862, 1716, 1452, 1373, 1036 cm^{-1}. MS (CI): *m*/*z* = 288 [MH^+], 244, 215, 188. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5 H), 5.00 (dd, *J* = 2.0, 6.0 Hz, 1 H), 4.35 (dd, *J* = 7.0, 8.0 Hz, 1 H), 4.13 (t, *J* = 6.7 Hz, 1 H), 3.60 (dd, *J* = 6.5, 8.2 Hz, 1 H), 2.87 (m, 1 H), 1.85−2.35 (m, 6 H), 2.06 (s, 3 H), 1.18−1.55 (m, 6 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 23.9, 25.9, 29.8, 30.1, 30.4, 35.7, 43.6, 66.6, 68.3, 73.1, 98.9, 126.6, 126.9, 128.4, 143.1, 209.2.

2-Acetyl-8-azabicyclo[3.2.1]octane-8-carboxylic Acid *tert*-Butyl Ester (14): $(BOC)_2O$ (1.27 g) was added to a solution of **12b** (401 mg, 1.5 mmol) in MeOH (18 mL) followed by 10% Pd/C (95 mg), and the resulting suspension was hydrogenated (50 psi, room temp.) for 3 hours. The reaction mixture was filtered, and the filtrate was evaporated. The crude oil was purified by flash chromatography (heptane/EtOAc 8:2) to give the carbamate **14** (316 mg, 85%) as a white solid: m.p. 62 °C. $[\alpha]_D$ = +115 ($CHCl_3$, *c* = 0.86) {ref.:[14] $[\alpha]_D$ = +112 ($CHCl_3$, *c* = 1)}. IR (neat): $\tilde{\nu}$ = 2975, 2881, 1697, 1680, 1404, 1171 cm^{-1}. MS (CI): *m*/*z* = 254 [MH^+], 198, 154. ^1H NMR (400 MHz, $CDCl_3$ at 0 °C): δ (two rotamers) = 4.37 (br. d, *J* = 6.2 Hz, 1 H), 4.28 (br. d, *J* = 4.8 Hz, 1 H), 4.15 (br. s, 1 H), 4.05 (br. d, *J* = 5.9 Hz, 1 H), 2.82 (br. d, *J* = 11.8 Hz, 1 H), 2.68 (br. d, *J* = 10.6 Hz, 1 H), 2.09 (s, 3 H), 2.08 (s, 3 H), 1.20−1.91 (m, 16 H), 1.41 (s, 9 H), 1.40 (s, 9 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (two rotamers) = 18.0, 18.3, 24.5, 25.3, 27.3, 27.9, 28.2, 28.4, 28.6, 29.1, 29.7, 51.9, 53.0, 53.7, 54.2, 54.7, 79.4, 152.9, 153.3, 208.9, 209.2. $C_{14}H_{23}NO_3$ (253.3): calcd. C 66.37, H 9.15, N 5.53; found C 66.31, H 9.06, N 5.41.

5-(2-[1,3]-Dioxolan-2-ylethyl)-3-phenylhexahydropyrrolo[2,1-*b*]-oxazole-5-carbonitrile (15): The general alkylation procedure was applied to **5** (2.1 g, 9.7 mmol) and 2-bromoethyl[1,3]dioxolane (1.2 mL, 10.6 mmol) to afford, after purification, **15** (2.19 g, 72% yield) as a 7:3 mixture of diastereomers and as a colourless oil. These isomers could be separated to furnish analytical sample of each epimer.

Major compound (more polar): $[\alpha]_D$ = −41 ($CHCl_3$, *c* = 0.11). IR (neat): $\tilde{\nu}$ = 2950, 2881, 2225, 1606, 1450, 1137, 1044 cm^{-1}. MS (CI): *m*/*z* = 315 [MH^+]. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.27−7.41 (m, 5 H), 5.04 (d, *J* = 3.6 Hz, 1 H), 4.85 (t, *J* = 3.9 Hz, 1 H), 4.59 (t, *J* = 7.3 Hz, 1 H), 4.29 (t, *J* = 7.8 Hz, 1 H), 3.79−3.90 (m, 4 H), 3.49 (t, *J* = 7.9 Hz, 1 H), 1.79−2.31 (m, 8 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 28.0, 28.9, 30.5, 35.7, 61.0, 64.9, 65.3, 74.2, 97.9, 103.1, 121.9, 126.2, 127.3, 128.7, 141.4. $C_{18}H_{22}N_2O_3$ (314.4): calcd. C 68.77, H 7.05, N 8.91; found C 68.74, H 7.16, N 8.53.

Minor compound (less polar): ^1H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5 H), 5.06 (dd, *J* = 3.5, 5.6 Hz, 1 H), 4.75 (t, *J* = 3.8 Hz, 1 H), 4.67 (t, *J* = 7.9 Hz, 1 H), 4.56 (t, *J* = 7.1 Hz, 1 H), 3.80 (m, 4 H), 3.59 (dd, *J* = 6.7, 8.2 Hz, 1 H), 1.00−2.50 (m, 8 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 28.9, 29.1, 33.4, 37.3, 63.8, 64.7, 65.8, 75.5, 98.3, 103.4, 120.9, 126.2, 127.3, 128.7, 141.9.

5-(2-[1,3]-Dioxolan-2-ylethyl)-3-phenylhexahydropyrrolo[2,1-*b*]-oxazole (16): The general decyanation procedure was applied to oxazolopyrrolidine **15** (1.03 g, 5.8 mmol) to give **16** (636 mg, 38% yield), after flash chromatography (heptane/EtOAc 8:2), as a colourless oil accompanied by starting material **15** (20%): $[\alpha]_D$ = −67 ($CHCl_3$, *c* = 0.81). IR (neat): $\tilde{\nu}$ = 2950, 2867, 1606, 1450, 1375, 1137, 1044 cm^{-1}. MS (CI): *m*/*z* = 290 [MH^+], 188. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.20−7.40 (m, 5 H), 4.98 (dd, *J* = 2.2, 5.6 Hz, 1 H), 4.76 (t, *J* = 4.6 Hz, 1 H), 4.33 (dd, *J* = 7.2, 8.1 Hz, 1 H), 4.17 (t, *J* = 6.6 Hz, 1 H), 3.63−3.90 (m, 4 H), 3.60 (dd, *J* = 6.2, 8.2 Hz, 1 H), 2.91 (m, 1 H), 1.38−1.67 (m, 8 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 30.0, 30.1, 30.2, 30.7, 64.8, 66.3, 68.0, 72.9, 98.8, 104.5, 126.5, 126.8, 128.4, 143.1.

6-(5-Phenylhexahydropyrrolizin-3-yl)hex-3-en-2-one (17): A solution of **16** (641 mg, 2.2 mmol) in 5% aqueous HCl (19 mL) was stirred at room temperature for 15 hours. The mixture was then quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phases were dried and the solvents evaporated under vacuum to give a yellow oil. Dimethyl (2-oxopropyl)phosphonate (0.41 mL, 2.0 mmol), DIPEA (0.485 mL, 5.1 mmol) and the crude aldehyde in CH_3CN (16 mL) were added to a stirred suspension of LiCl (125 mg, 2.9 mmol) (stored with P_2O_5) in dry acetonitrile (12 mL) under nitrogen at room temperature,. After stirring for 4 hours, the mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organics layers were combined, dried and concentrated under vacuum. The crude oil was purified by flash chromatography (heptane/ EtOAc 7:3) to pro-

vide **17** (440 mg, 70% overall yield) as a colourless oil: $[\alpha]_D = -29$ ($CHCl_3$, $c = 1.78$). IR (neat): $\tilde{\nu}$ = 2936, 2865, 1699, 1675, 1627, 1452, 1362 cm^{-1}. MS (CI): *m*/*z* = 286 [MH^+], 244, 215, 188. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.19−7.38 (m, 5 H), 6.68 (dt, *J* = 15.9, 6.9 Hz, 1 H), 5.91 (d, *J* = 15.9 Hz, 1 H), 5.00 (dd, *J* = 2.1, 5.1 Hz, 1 H), 4.34 (t, *J* = 7.7 Hz, 1 H), 4.11 (t, *J* = 6.9 Hz, 1 H), 3.57 (t, *J* = 7.4 Hz, 1 H), 2.93 (m, 1 H), 1.44−2.22 (m, 8 H), 2.16 (s, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 26.8, 29.1, 30.0, 34.2, 66.2, 68.6, 73.4, 98.8, 126.2, 127.0, 128.4, 131.1, 142.7, 148.1, 198.6.

1-{9-(2-Hydroxy-1-phenylethyl)-3-methoxy-9-azabicyclo[4.2.1]non-2-yl}ethanone (18): A solution of enone **17** (100 mg, 0.35 mmol) and sulfuric acid (0.250 mL) in MeOH (10 mL) was heated to 60 °C for 15 h. The cooled mixture was treated with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. After drying and evaporation of the solvent, the product was purified by flash chromatography (heptane/ EtOAc 5:5 and 2:8) to afford a 45:55 mixture of the bicycle **18** and **19** (25 mg, 24% yield) which could not be completely separated.

18: IR (neat): $\tilde{\nu}$ = 3430, 2950, 2876, 1708, 1451, 1094 cm^{-1}. MS (CI): *m*/*z* = 318 [MH^+]. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.2−7.5 (m, 5 H), 4.7 (m, 1 H), 4.5 (m, 1 H), 3.65−3.9 (m, 2 H), 3.51 (m, 1 H), 3.28 (s, 3 H), 3.25 (m, 1 H), 3.05 (dd, *J* = 2.5, 10 Hz, 1 H), 2.51 (br. s, 1 H), 1.88−2.05 (m, 2 H), 1.80 (s, 3 H), 1.25−1.8 (m, 4 H).

19: IR (neat): $\tilde{\nu}$ = 3429, 2950, 2880, 1660, 1631, 1377, 1250 cm^{-1}. MS (CI): *m*/*z* = 286 [MH^+]. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.3−7.5 (m, 5 H), 6.91 (br. t, *J* = 6.0 Hz, 1 H), 5.1 (m, 1 H), 3.7−4.2 (m, 3 H), 3.43−3.57 (m, 2 H), 2.3−2.7 (m, 2 H), 2.16 (s, 3 H), 1.3−2.04 (m, 6 H).

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