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Neat total synthesis of six monoterpenic alkaloids of the actinidine series

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Abstract—A concise enantiopure synthesis of six monoterpenic alkaloids of the actinidine series possessing a cyclopenta[*c*]pyridine skeleton, (+)-deoxyrhexifoline (**4**), (+)-boschniakinic acid (**5**), (+)-boschniakine (**6**), (−)-plantagonine (**7**), (−)-indicaine (**8**) and (−)-tecostidine (**9**) is reported starting with the chiral precursor 3-bromo-5-((4*R*)-phenyloxazolin-2-yl)pyridine (**10**). It involves a C-4 regioselective connection of a butene appendice and an intramolecular 5-*exo-trig* Heck annulation sequence followed by hydrogenation of the exocyclic alkene. Mixture of (3*R*)- and (3*S*)-7-((4*R*)-phenyloxazolin-2-yl)cyclopenta[*c*]pyridines was separated by HPLC before being transformed into enantiopure natural products (**4**–**9**) by modification of the oxazoline group.

1. Introduction

A number of monoterpenic alkaloids containing the cyclopenta[*c*]pyridine system have been isolated from various plants, most of them being used in traditional local medicines. The great interest of the synthetic community for these natural products stems mainly from their unique biological activities. For instance, (−)-actinidine (**1**) shows a cat-exciting action[1a] and a significant antifungal activity,[1b] lousianines A–D (**2**) produced in the cultured broth of *Streptomyces* sp. WK-4028[2a] shows a high growth inhibition of testosterone-responsive Shionogi carcinoma.[2b] (−)-Oxerine (**3**) is isolated from the arial part of *Oxera morieri*,[3a] a species related to *Oxera robsta*, the bark extract of which is known for its abortive activity.[3b] To date few synthetic studies have been devoted to the actinidine-type alkaloids possessing the 3-methylcyclopenta[*c*]pyridine skeleton (**4**–**9**) depicted in Figure 1. (+)-Deoxyrhexifoline (**4**) was extracted in very few quantities from the seed of *Castilleja rhexifolia aff. Miniata*,[4] a natural hybrid of *Castilleja rhexifolia* from which (+)-rhexifoline was isolated. (+)-Boschniakinic acid (**5**) and (+)-boshniakine (**6**) were both isolated and characterized from a red-bracted species *Castilleja miniata* (Indian paint brush)[5] closely related to *C. rhexifolia.* (+)-Boschniakine (**6**) was also isolated from many other plants, *Boschniakia rossica*,[6] *Penstemon whippleanus*,[8] *Plantago sempervirens*,[7] and *Tecoma stans*,[8] a bush common in Latin America used in Mexico for the control of diabetes. However, Costantino and co-workers recently showed that (+)-boschniakine (**6**) is not directly

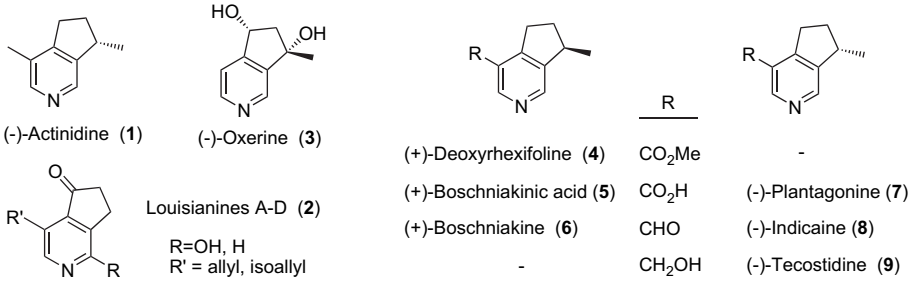

Figure 1.

Keywords: Nucleophilic addition; Intramolecular Heck reaction; Oxazoline; Pyridine alkaloid; Pyridoterpene.
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responsible for the hypoglycaemic action.[8] The corresponding enantiomers of the (+)-boschniakinic acid and (+)-boschniakine, (−)-plantagonine (**7**) and (−)-indicaine (**8**) are also natural products isolated and characterized, respectively, from *Pedicularis olgae* and *Plantago indica*,[9] which are curiously different from those previously described. (−)-Tecostidine (**9**) was isolated from the leaves of *Tecama stans Juss*.[10]

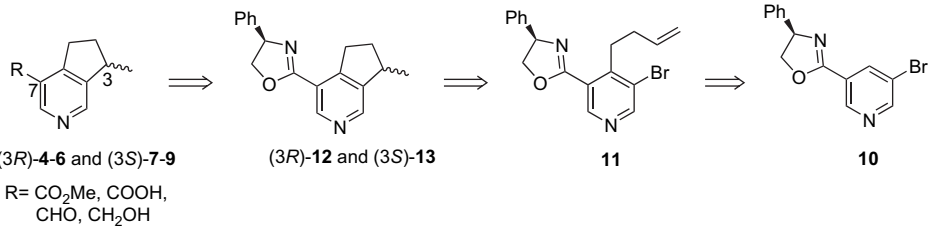
In 1967, Sakan and co-workers reported the first and unique total synthesis of (+)-boschniakine (**6**) from (+)-pulegone through a five-steps route in a moderate 5% overall yield.[6] In 1990, Tillequin documented an efficient biomimetic synthesis of (−)-tecostidine (**9**) from loganin in three-step synthesis and a 36% overall yield.[11] No literature precedent gives sound of total synthesis of (−)-plantagonine (**7**) and (−)-indicaine (**8**).

Almost all synthetic routes to the cyclopenta[*c*]pyridine skeleton reported during the last decade have been secured by exploring diverse annulation techniques starting from commercially available functionalized pyridines. The pyridine radical-olefin condensation,[12] the intramolecular Heck ring closure,[13] the fluorine-induced desilylation–cyclation of aldehyde and recently a Dieckmann-type condensation[14] have been successively envisaged for construction of the cyclopenta[*c*]pyridine framework. Thus, the development of general versatile routes to cyclopenta[*c*]pyridine skeleton mainly relies on the judicious choice of a parent pyridine, which could be easily alkylated and equipped with suitable functions for the cyclopentane ring formation by annulation. In this context, we specifically selected the 3-bromo-5-((4*R*)-phenyl-oxazolin-2-yl)pyridine (**10**) as a valuable precursor to access to the six monoterpenic alkaloids **4**–**9**. Our retrosynthetic analysis is depicted in Scheme 1. The presence of the oxazoline should allow the tailored C-4 alkylation of **10** via the regioselective addition of a Grignard reagent, avoiding a preliminary N-activation step of the pyridine nucleus, before oxidation of the resulting 1,4-dihydro intermediate to **11**. The construction of the 3-methylcyclopentane ring should then be secured by a 5-*exo-trig* intramolecular Heck reaction followed by a reduction step affording both key diastereoisomers (3*R*)-**12** and (3*S*)-**13**. This technique was successfully used recently by Zhaï and co-workers for the construction of the methylcyclopenta[*c*]pyridine skeleton.[13] Thus, separation of diastereoisomers (3*R*)-**12** and (3*S*)-**13** and chemical modulation of the oxazoline function would later lead to natural (3*R*)-**4**–**6** and (3*S*)-**7**–**9**.

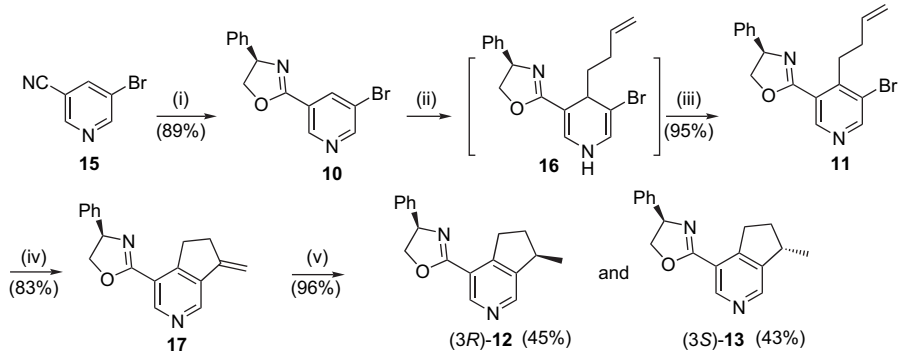
2. Results and discussion

The 3-bromo-5-((4*R*)-phenyloxazolin-2-yl)pyridine (**10**) was prepared in a multi-grams scale in 89% yield from the commercially available 3-cyano-5-bromo-pyridine (**15**) by treatment with (*R*)-phenylglycinol in the presence of catalytic amounts of zinc chloride. Regioselective introduction of the butene chain at the C-4 position of **10** was achieved by reaction with freshly prepared 4-but-1-enyl magnesium bromide (Scheme 2). The quantitatively formed 1,4-dihydropyridine intermediate was then subjected to oxidation and different oxidants were checked. Chloranil allowed clean oxidation of the dihydropyridine system but surprisingly the (4′-phenyl)oxazoline ring was also completely aromatized to the corresponding phenyloxazole.

We then turned our mind to oxygen and we found that bubbling O_2 into a solution of the crude dihydropyridine in ethyl acetate provided a clean access to the expected 4-but-1-enyl-pyridine (**11**) in a 95% overall yield from **10**.



Scheme 1. Retrosynthetic analysis.

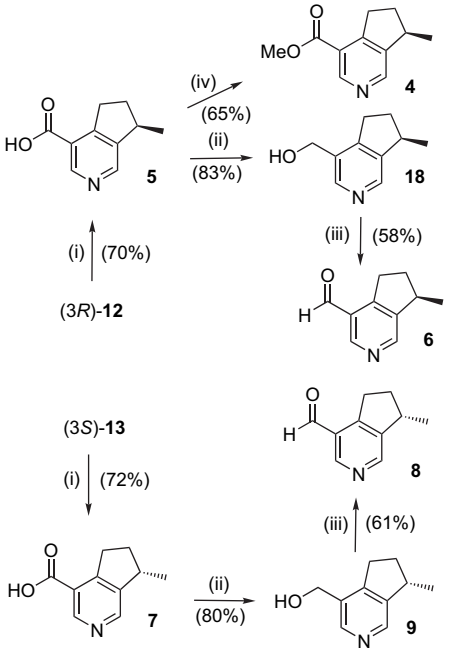


Scheme 2. Reagents and conditions: (i) (*R*)-phenylglycinol, $ZnCl_2$ (10%), PhCl, reflux, 48 h; (ii) (a) freshly prepared solution of 4-but-1-enyl magnesium bromide in Et_2O (4 ml, *c*=0.66 M), **10**, THF, rt, 1 h; (iii) O_2, ethyl acetate, 48 h; (iv) $Pd(OAc)_2$ (0.1 mol %), dppp (25 mol %), Ag_2CO_3 (1 equiv), CH_3CN, 80 °C, 2 h; (v) H_2 (1 bar), Pd/C (5 mol %), MeOH, rt, 3 h.

The 5-*exo-trig* ring closure via an intermolecular Heck reaction and subsequent reduction for elaboration of the 3-methylcyclopenta[*c*]pyridine system were then investigated. Among the possible 5-*exo-trig* intramolecular Heck ring closure[15] we first applied the Zhai's procedure[13] to the *ortho*-bromobutenylpyridine (**11**) using $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), NEt_3 (2 equiv) in refluxing CH_3CN for 4 h. The expected cyclopentene[*c*]pyridine **16** could be obtained but in a modest 43% yield. Optimization of the ring closure under the Boger's conditions[16a] using $Pd(OAc)_2$ (5 mol %), dppf (10 mol %), NEt_3 (2 equiv) and Ag_2CO_3 (1 equiv) allowed the clean conversion of **11** to **17** in an excellent 83% yield with a reaction time of only 2 h (GC–MS monitoring). The benefit of silver salts as additives for internal Heck coupling reaction has been often reported.[16] In our case, we found that the ring closure is much slower without Ag_2CO_3 giving a full conversion of **11** in 18 h (GC–MS monitoring) with a 79% yield of **16**. Subsequent reduction of **16** was then smoothly carried out with H_2 and Pd/C as catalyst at room temperature in MeOH for 48 h providing the corresponding 3-methylcyclopenta[*c*]pyridines (3*R*)-**12** and (3*S*)-**13** as a 1:1 diastereomeric mixture in 96% yield.

However, preparative HPLC separation on silica gel (Lichrosorb 10 μm) of the latter diastereoisomers furnished diastereopure isomers (3*R*)-**12** and (3*S*)-**13**, respectively, in 45% and 43% yields.

At this stage we focused our attention on the target natural products by chemical transformations of the oxazoline group into ester, aldehyde and hydroxymethyl functions. Hydrolysis of (3*R*)-**12** and (3*S*)-**13** to (+)-bocshniakinic acid (**5**) and (−)-plantagonine (**7**) (Scheme 3) was achieved by treatment with concentrated hydrochloric acid for 18 h under reflux leading to the expected compounds, respectively, in 70% and 72% yields.[17] Complete reduction of (+)-boschniakinic acid (**5**) using $LiAlH_4$ in THF followed by Swern oxidation afforded (+)-boschniakine (**6**) in 48% overall yield (Scheme 3). Similar reduction of (−)-plantagonine (**7**) led first to (−)-tecostidine (**9**) in 80% yield before subsequent Swern oxidation to (−)-indicaine (**8**) in 61% yield. Esterification of (+)-boschniakinic acid (**5**) to (+)-deoxyrhexifoline (**4**) was finally achieved by sequential treatment with oxalyl chloride and MeOH in 65% overall yield.



Scheme 3. Reagents and conditions: (i) HCl (4 M), reflux, 18 h; (ii) $LiAlH_4$ (2 equiv), THF, rt, 24 h; (iii) Swern oxidation; (iv) (a) $(COCl)_2$, cat. DMF, reflux, 1 h, (b) MeOH, rt, 2 h.

3. Conclusion

In conclusion, an efficient enantiopure synthesis of six monoterpenic alkaloids of the actinidine series have been accomplished in five to seven steps from the chiral 3-bromo-5-((4*R*)-phenyloxazolin-2-yl)pyridine precursor (**10**). The construction of the 7-methylcyclopenta[*c*]pyridine skeleton involves sequential C-4 regioselective connection of a butenyl appendice and 5-*exo-trig* intramolecular Heck annelation. The subsequent reduction of the exocyclic methylenecyclopenta[*c*]pyridines produced a 1:1 diastereoisomeric mixture of 3-methylcyclopenta[*c*]pyridines, which were readily separated by HPLC on silica gel. The latter both diastereopure isomers were used to prepare the enantiopure target natural products by chemical transformation of the oxazoline group. (+)-Deoxyrhexifoline (**4**), (+)-boschniakinic acid (**5**), (+)-boschniakine (**6**), (−)-plantagonine (**7**), (−)-indicaine (**8**) and (−)-tecostidine (**9**) were thus selectively prepared in 14%, 21%, 10%, 20%, 10% and 16% overall yields, respectively.

4. Experimental

4.1. General

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were pre-dried with pellets of KOH and distilled over sodium benzophenone ketyl under Ar before use. CH_2Cl_2, NEt_3 and toluene were distilled from CaH_2. Methanol and ethanol were distilled from magnesium turning. Dimethylacetamide was stored over 4 Å molecular sieves before distillation. Flash chromatography separations were done on Merck silica gel (70–230 mesh). The melting points were measured on a Kofler melting points apparatus and were not corrected. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300 spectrometer operating at 300 MHz. Infrared spectra were recorded on a Perkin–Elmer FTIR 1650 spectrophotometer. Elemental analyses were carried out on a Carlo Erba 1160. Optical rotations were measured at 20 °C on a Perkin–Elmer 341 polarimeter. Commercially available starting materials were used without further purification. The starting compound **15** is commercially available.

4.2. Synthesis of the 3-bromo-5-((4*R*)-phenyloxazolin-2-yl)pyridine (10)

In a 100 ml round bottom flask, commercial zinc chloride (75 mg, 0.55 mmol) was melted three times under high vacuum and cooled under nitrogen. A solution of 5-bromonicotinonitrile **15** (1.0 g, 5.52 mmol) and (*R*)-phenylglycinol (1.13 g, 8.2 mmol) in chlorobenzene (10 ml) was added and the resulting mixture was refluxed under nitrogen for

48 h and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (30 ml) and water was added (20 ml). The separated aqueous solution was extracted with CH_2Cl_2 (3×10 ml) and the combined organic phases were dried ($MgSO_4$) and concentrated under vacuum. The crude product was chromatographed on a silica gel using ethyl acetate as an eluent to afford **10** (1.48 g, 89%, $[\alpha]_D^{20}$ +28.0 (*c* 1.20, CH_2Cl_2)) as an oil. ^{1}H NMR ($CDCl_3$) δ 4.26 (dd, 1H, *J*=8.7, 8.7 Hz, 1H), 4.77 (dd, 1H, *J*=10.2, 8.7 Hz, 1H), 5.35 (dd, 1H, *J*=10.2, 8.7 Hz, 1H), 7.20–7.26 (m, 5H), 8.41 (s, 1H), 8.73 (s, 1H), 9.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 70.5, 75.5, 120.9, 125.5, 127.0, 129.3, 138.7, 141.9, 147.9, 153.6, 161.9; IR (KBr) ν 3039, 1651, 1418, 1354; Anal. Calcd for $C_{14}H_{11}BrN_2O$ (303.10): C, 55.47; H, 3.66; N, 9.24. Found: C, 55.61; H, 3.72; N, 9.12%.

4.3. Synthesis of the cyclopenta[*c*]pyridines ((3*R*)-12 and (3*S*)-13)

4.3.1. Synthesis of the 3-bromo-4-(but-3-enyl)-5-((4*R*)-phenyloxazolin-2-yl)pyridine (11). The 4-bromobutene (1 ml, 10 mmol) was added dropwise at a rate fast enough to maintain reflux to a mixture of Mg turnings (239 mg, 10 mmol) in anhydrous Et_2O (10 ml) containing an iodine crystal. After complete addition, the mixture was refluxed for 1 h. The concentration of the Grignard reagent was then measured at 0 °C using menthol and phenanthroline as indicator (*C*=0.66 M). To a solution of **10** (750 mg, 2.5 mmol) in anhydrous THF (20 ml) was added the above prepared Grignard solution (3.93 ml, 2.6 mmol, *c*=0.66 M) at room temperature under nitrogen. After stirring 1 h, satd aq NH_4Cl (10 ml) was added and the product was extracted with CH_2Cl_2 (3×20 ml). The combined organic phases were dried ($MgSO_4$) and concentrated under vacuum to give the crude dihydropyridine **16**, which was dissolved in ethyl acetate (50 ml). The resulted solution was flushed by O_2 for 48 h. The solvent was then evaporated under vacuum and the residue was chromatographed on silica gel using ethyl acetate as an eluent to afford **11** (846 mg, 95%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.29 (m, 2H), 3.26 (m, 2H), 4.19 (dd, *J*=8.7, 8.7 Hz, 1H), 4.74 (dd, *J*=10.2, 8.7 Hz, 1H), 4.88–4.96 (m, 2H), 5.39 (dd, *J*=10.2, 8.7 Hz, 1H), 5.75–5.84 (m, 1H), 7.24–7.28 (m, 5H), 8.68 (s, 1H), 8.85 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 33.1, 33.3, 70.9, 74.8, 115.8, 124.8, 125.4, 126.9, 128.2, 129.2, 137.5, 142.1, 150.0, 151.0, 154.1, 162.5; IR (KBr) ν 953, 1089, 1352, 1643, 2361, 2896–2934; Anal. Calcd for $C_{18}H_{17}BrN_2O$ (357.2): C, 60.52; H, 4.80; N, 7.84. Found: C, 60.55; H, 4.94; N, 7.66%.

4.3.2. Synthesis of the 7-methylene-3-((4*R*)-phenyloxazolin-2-yl)cyclopenta[*c*]pyridine (17). A degassed mixture of **11** (200 mg, 0.56 mmol), $Pd(OAc)_2$ (15 mg, 0.067 mmol), dppp (55 mg, 0.13 mmol), Et_3N (160 µl, 1.1 mmol) and Ag_2CO_3 (154 mg, 0.56 mmol) in CH_3CN (10 ml) was heated in a sealed tube at 80 °C for 2 h. After filtration through a short pad of Celite washed with AcOEt and concentrated under vacuum, the residue was chromatographed on silica gel using ethyl acetate/petrol 40:60 as an eluent to afford **17** (120 mg, 83%) as a beige oil. ^{1}H NMR ($CDCl_3$) δ 2.74–2.78 (m, 2H), 3.26–3.32 (m, 2H), 4.15 (dd, *J*=8.7, 8.7 Hz, 1H), 4.70 (dd, *J*=10.2, 8.7 Hz, 1H), 5.10 (d, *J*=2.1 Hz, 1H), 5.35 (dd, *J*=10.2, 8.7 Hz, 1H), 5.50 (d, *J*=2.1 Hz, 1H), 7.30–7.34 (m, 5H), 8.73 (s, 1H), 8.87 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 31.1, 32.1, 70.6, 74.7, 106.0, 121.3, 126.9, 128.0, 129.1, 138.1, 142.6, 145.1, 147.6, 149.2, 156.7, 163.1; IR (KBr) ν 1545, 1644, 2894–2969, 3076; Anal. Calcd for $C_{18}H_{16}N_2O$ (276.1): C, 78.24; H, 5.84; N, 5.79. Found: C, 78.12; H, 5.69; N, 5.67%.

4.3.3. Synthesis of the (3*R*)- and (3*S*)-methyl-7-((4*R*)-phenyloxazolin-2-yl)cyclopenta[*c*]pyridine ((3*R*)-12 and (3*S*)-13). A suspension of palladium (124 mg, 10% on charcoal, 0.12 mmol) in a solution of **17** (320 mg, 1.2 mmol) in MeOH (13 ml) was vigorously stirred for 3 h at room temperature under hydrogen. The mixture was then filtered though a short pad of Celite washed with ethyl acetate (20 ml) and the solvent was evaporated under vacuum. The residue was chromatographed on silica gel using ethyl acetate as an eluent to afford a mixture of diastereomers (3*R*)-**12** and (3*S*)-**13** (310 mg, 96%) as a yellow oil, which was then separately isolated by preparative high-performance liquid chromatography (HPLC) on silica gel (LiChrosorb Alox T 10 µm) using heptane/isopropanol 97:3 (UV 254 nm) as an eluent to provide (3*R*)-**12** (139.5 mg, 45%) and (3*S*)-**13** (133 mg, 43%). ^{1}H NMR ($CDCl_3$) δ 1.29 (d, *J*=6.8 Hz, 3H), 1.56–1.63 (m, 1H), 2.28–2.31 (m, 1H), 3.03–3.14 (m, 1H), 3.22–3.35 (m, 2H), 4.17 (dd, *J*=8.7, 8.7 Hz, 1H), 4.72 (dd, *J*=10.2, 8.7 Hz, 1H), 5.36 (dd, *J*=10.2, 8.7 Hz, 1H), 8.45 (s, 1H), 8.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.8, 31.7, 32.9, 36.5, 69.2, 73.3, 119.2, 125.6, 126.6, 127.7, 141.3, 143.9, 145.8, 146.8, 153.3, 162.1; Anal. Calcd for $C_{18}H_{18}N_2O$ (278.3): C, 77.67; H, 6.52; N, 10.06. Found for (3*R*)-**12**: C, 77.56; H, 6.54; N, 9.98%. Found for (3*S*)-**13**: C, 77.63; H, 6.57; N, 10.01%.

4.4. Synthesis of the pyridoterpenes alkaloids (4–9)

4.4.1. Synthesis of (+)-boschniakinic acid (5) and (−)-plantagonine (7). The solution of (3*R*)-**12** (respectively (3*S*)-**13**) (120 mg, 0.43 mmol) in aq HCl (4 M, 4 ml) was refluxed for 18 h. After cooling, the pH was adjusted to 4 by adding K_2CO_3 and the product was extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and evaporated under vacuum to give (+)-boschniakinic acid (**5**) (53.5 mg, 70%, $[\alpha]_D^{20}$ +28.0 (*c* 1.05, MeOH), $[\alpha]_D^{20}$ +31.4[17b] (*c* 0.35, MeOH)) and (−)-plantagonine (**7**) (53.5 mg, 72%, $[\alpha]_D^{20}$ −27.0 (*c* 0.96, MeOH), $[\alpha]_D^{20}$ −30.8[17c] (*c* 1.00, MeOH)). Mp=238–239 °C. ^{1}H NMR (DMSO) δ 1.28 (d, 3H, *J*=6.8 Hz), 1.56 (m, 1H), 2.29 (m, 1H), 3.04 (m, 1H), 3.25 (m, 2H), 8.60 (s, 1H), 8.82 (s, 1H); ^{13}C NMR (DMSO) δ 19.9, 31.8, 33.4, 36.8, 123.2, 145.1, 147.9, 148.6, 154.8, 166.9; IR (KBr) ν 3449, 2960, 2379, 1713, 1606, 1450; Anal. Calcd for $C_{14}H_{18}N_2O$ (177.2): C, 67.78; H, 6.26; N, 7.90. Found for **5**: C, 67.94; H, 6.39; N, 7.99%. Found for **7**: C, 67.82; H, 6.29; N, 7.69%.

4.4.2. Synthesis of (+)-tecostidine (18) and (−)-tecostidine (9). Lithium aluminium hydride (22.0 mg, 0.56 mmol) was added portionwise to a solution of boschniakinic acid (**5**) (50 mg, 0.28 mmol) (respectively (−)-plantagonine (**7**)) in THF (2 ml) under nitrogen. The resulting mixture was then refluxed for 24 h. After cooling, water (1 ml), NaOH (1 M, 1 ml) and water (1 ml) were successively added in order to precipitate the aluminium salts. The aluminium salts were removed by filtration and washed with ethyl acetate. The separated organic phase was dried ($MgSO_4$)

and concentrated under vacuum to give non-natural (+)-tecostidine (**18**) (37.9 mg, 83%, $[\alpha]_D^{20}$ +4.0 (*c* 1.10, CH_2Cl_2), $[\alpha]_D^{20}$ +3.0[18] (*c* 1.10, CH_2Cl_2)) and (−)-tecostidine (**9**) (36.5 mg, 80%, $[\alpha]_D^{20}$ −3.0 (*c* 0.95, CH_2Cl_2), $[\alpha]_D^{20}$ −4.0[19] (*c* 1.22, $CHCl_3$)) as yellow oils. ^{1}H NMR ($CDCl_3$) δ 1.28 (d, *J*=7.0 Hz, 3H), 1.59–1.63 (m, 1H), 2.31–2.37 (m, 1H), 2.80–2.84 (m, 1H), 2.91–2.97 (m, 1H), 3.21–3.27 (m, 1H), 4.67 (s, 2H), 8.26 (s, 1H), 8.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.2, 29.5, 34.2, 37.8, 60.9, 132.7, 143.5, 144.7, 145.6, 152.6; IR (KBr) ν 3361, 2958, 2867, 1740, 1596, 1455, 1024; Anal. Calcd for $C_{10}H_{13}NO$ (163.2): C, 73.59; H, 8.03; N, 8.58. Found for **9**: C, 73.59; H, 8.03; N, 8.58. Found for **18**: C, 73.10; H, 8.10; N, 8.63.

4.4.3. Synthesis of (+)-boschniakine (6) and (−)-indicaine (8). DMSO (21 µl, 0.30 mmol) was slowly added to a solution of oxalyl chloride (11 µl, 0.13 mmol) in CH_2Cl_2 (2 ml) and the resulted solution was stirred at −78 °C for 30 min. A second addition of DMSO (11 µl, 0.13 mmol) was done and the resulting mixture was stirred at the same temperature for 30 min. A solution of the non-natural (+)-tecostidine (**18**) (20 mg, 0.12 mmol) (respectively (−)-tecostidine (**9**)) in CH_2Cl_2 (2 ml) was then added and the solution was stirred at −78 °C for 30 min. Triethylamine (87 µl, 0.60 mmol) was added and stirring was continued for 30 min at the same temperature. Water (2 ml) and CH_2Cl_2 (5 ml) were added and the separated organic layer was washed with $NaHCO_3$ (2×5 ml), dried ($MgSO_4$) and concentrated under vacuum. The residue was chromatographed on silica gel using ethyl acetate as an eluent to afford (+)-boschniakine (**6**) (11.5 mg, 58%, $[\alpha]_D^{20}$ +20.0 (*c* 0.90, CH_2Cl_2), $[\alpha]_D^{20}$ +21.0[6] (*c* 0.99, $CHCl_3$)) and (−)-indicaine (**8**) (12.0 mg, 61%, $[\alpha]_D^{20}$ −22.0 (*c* 1.05, CH_2Cl_2)) as oils. ^{1}H NMR ($CDCl_3$) δ 1.35 (d, *J*=6.8 Hz, 3H), 1.70 (m, 2H), 2.43 (m, 1H), 3.13 (m, 1H), 3.35 (m, 2H), 8.69 (s, 1H), 8.81 (s, 1H), 10.2 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.6, 27.3, 30.5, 33.9, 36.9, 127.7, 145.7, 148.9, 150.9, 154.5, 191.4; IR (KBr) ν 3435, 1637, 1456, 1124; Anal. Calcd for $C_{10}H_{11}NO$ (161.2): C, 74.51; H, 6.88; N, 8.69. Found for **6**: C, 74.55; H, 6.91; N, 8.71. Found for **8**: C, 74.59; H, 6.74; N, 8.76.

4.4.4. Synthesis of (+)-deoxyrhexifoline (4). Oxalyl chloride (2 ml, 20 mmol) was added to a stirred solution of (+)-boschniakinic acid **5** (15 mg, 0.08 mmol) in dry CH_2Cl_2 (2 ml) and DMF (0.1 ml) at 0 °C. The resulting mixture was stirred at room temperature for 1 h and the solvents were removed under vacuum. MeOH (4 ml) was slowly added to the crude acyl chloride at 0 °C and the resulted solution was stirred at room temperature for 2 h. After evaporation of the excess of MeOH under vacuum, CH_2Cl_2 (5 ml) was added and the organic phase was washed with aq K_2CO_3 (2 M), water (5 ml), brine (5 ml), dried ($MgSO_4$) and concentrated under vacuum. The crude oil was chromatographed on silica gel using ethyl acetate as an eluent to afford (+)-deoxyrhexifoline (**4**) as an oil (10.5 mg, 65%, $[\alpha]_D^{20}$ +21 (*c* 0.95, CH_2Cl_2).

References and notes

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