HETEROCYCLES, Vol. 105, No. , 2022, pp. -. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 17th March, 2022, Accepted, 30th March, 2022, Published online, 12th April, 2022
DOI: 10.3987/COM-22-S(R)21

OXIDATIVE FRAGMENTATION OF CYTISINE AS AN ENTRY TO THE BIS(PIPERIDINE) SCAFFOLD OF VIRGIDIVARINE

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This paper is dedicated to Professor Somsak Ruchirawat, an old and dear friend, as he turns 80 years young.

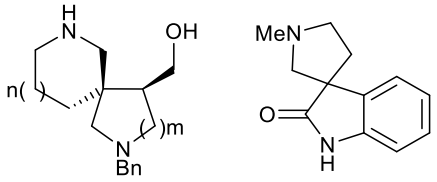
Abstract – Using virgidivarine as a focus, we have extended the oxidative fragmentation of (-)-cytisine as a source of functionalized heterocyclic fragments to provide a novel bis(piperidine) 2′-epivirgidivarine. This stereochemically-defined scaffold offers synthetic versatility within an "sp^3-rich" environment that makes it amenable to further manipulation and development within the context of de novo drug design.

INTRODUCTION

The ability of chemical synthesis to explore novel "chemical space" and expand and build on molecular diversity underpins much of contemporary "small molecule" drug discovery and various strategies are available for this.[1,2] These encompass "de novo" in silico approaches based on understanding the structural requirements of a drug target and "evolving" a core fragment or fragments and are exemplified by widely available commercial products such as SPOUT,[3a] SPARK[3b] and LigBuilder 2[3c] (and others), and well-established combinatorial methodologies and, more recently, diversity-oriented and chemical genetics approaches.[4] These approaches often rely on use of a molecular scaffold as a starting point, where that scaffold is *(i)* known to be synthetically accessible and *(ii)* well-positioned in terms of its downstream versatility; so readily manipulated at a variety of different sites within the scaffold. In that regard, natural products have long inspired drug discovery efforts, either directly or indirectly serving as a guide to crucial structure-activity profiles. Clearly, natural products offer a huge structural diversity but as starting points for drug discovery, also offer major stereochemical advantages as the basis of "privileged scaffolds",[5a] of which piperidines are a significant grouping.[5b-d] Relevant natural products are almost

invariably available as single enantiomers, often heterocyclic in nature, frequently contain multiple stereogenic centers and, linked to that, provide a high proportion of sp^3-centers. The proportion of sp^3 C vs total carbon (measured as Fsp^3) has been recognized as important for key properties associated with clinical success, such as solubility.[6]

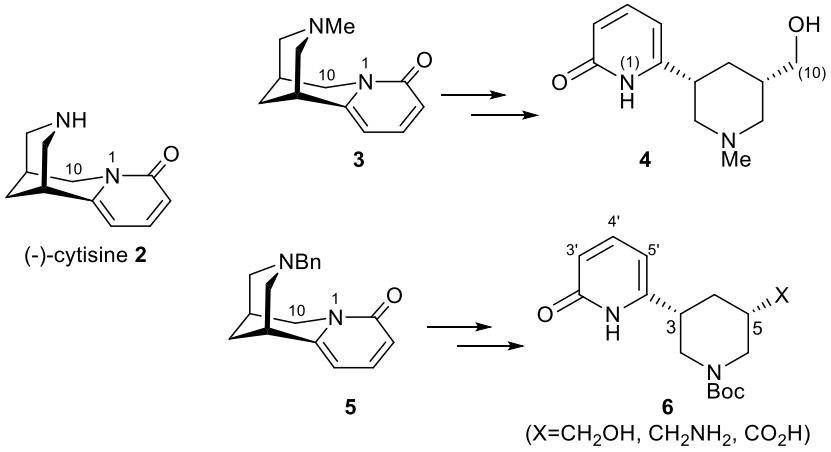
We had previously developed the chemistry of cyclic sulfamidates for a range of chiral heterocyclic scaffolds.[7] This includes the stereochemically-defined spirocyclic bis(azacycles) **1a/b** that offer discrete, differentiated and extendable functionality (two distinguishable secondary amines and a primary alcohol) based on the spiro-oxindole core of coerulescine.[8]



1a m= 0; n= 0 and 1
1b m= 1; n= 0 and 1

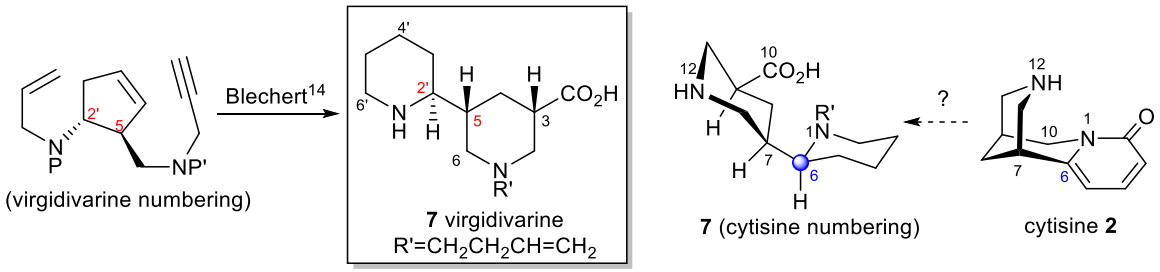
coerulescine

More recently, we have sought to develop the chemistry of (-)-cytisine **2**,[9] a lupin alkaloid that is both readily available and has an established biological profile as an effective smoking cessation agent.[10] An attractive feature of cytisine is an embedded piperidine moiety (a recognized "privileged" unit[5] in medicinal chemistry) and we have reported on the fragmentation of N-methylcytisine **3** (via directed metalation at C10, see below) to provide (+)-kuramamine **4**.[11] The utility of the core *cis*-3,5-disubstituted piperidine in terms of further scaffold elaboration was illustrated further using N-benzylcytisine **5** which allows access to a range of variants (**6**) with functionality available at a number of different sites: the piperidine amine, pyridone N, introduction of a carboxylic acid and exploiting the intrinsic reactivity of the 2-pyridone unit at C3′/C5′ (via electrophilic bromination) and at C4′ (via Ir-mediated CH activation) (**Scheme 1**).[4,12]



Scheme 1. Scaffold elaboration via fragmentation of (-)-cytisine

In this paper, this chemistry is further developed to provide a fully-reduced, stereochemically defined bis(piperidine) that was prompted by the structure of virgidivarine **7**,[13] which is structurally related to cytisine and fully reduced lupin alkaloid sparteine. In elegant synthetic work, Blechert and co-workers[14] prepared virgidivarine using an enzymatic desymmeterisation of a meso diacetate (so providing an enantioselective entry) followed by a double Ru-mediated metathesis sequence (RCM/ROM and enyne-RCM) to construct the two piperidine rings. Critically, the stereochemistry between the two heterocyclic moieties (C5-C2′) was set at the outset and C3 was established later using a diastereoselective alkene reduction (**Scheme 2**).



Scheme 2. Blechert's approach to virgidivarine **7**; stereochemical relationship of **7** to C6-reduction of **2**

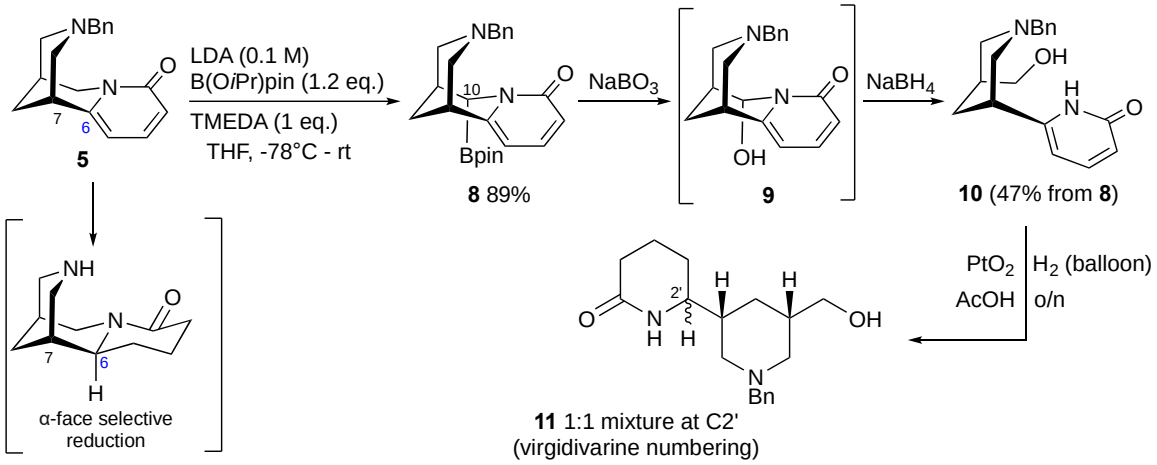
We envisaged an approach to the bis(piperidine) scaffold associated with virgidivarine **7** based on fragmentation of cytisine (which houses the two latent piperidine units) followed by pyridone reduction to set the stereochemistry required at C5-C2′ (corresponding to C6-C7 of cytisine). The challenge this presented was with pyridone reduction and in this paper we report on two approaches to achieve that transformation, one of which proved to be nonselective and the alternative which led smoothly to a diastereomer of virgidivarine **7**, the 2′-epivirgidivarine **16**. While the natural product is often seen as an attractive goal, in a wider sense and seen together with Blechert's approach, these provide two novel piperidine-based scaffolds (**7** and **16**) representing stereochemically-defined, functionally-flexible and sp^3-rich heterocyclic fragments available for integration with a de novo drug design strategy.

RESULTS AND DISCUSSION

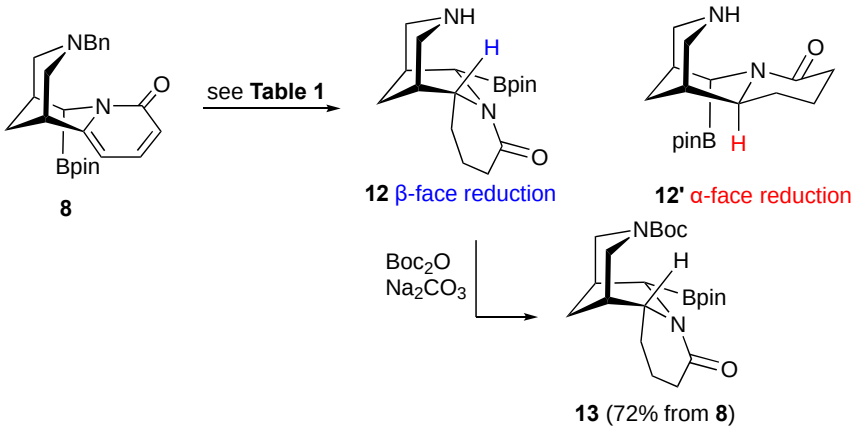
The lithiation of N-alkylcytisine (first reported by Rouden[15]) is achieved under remarkably mild conditions using LDA and trapping of the resulting C10-lithiated intermediate with a boron (or silyl) electrophile provides an effective vehicle for subsequent oxidative cleavage of the C10-N1 bond. Details have been reported previously[4,8] but C10 metalation does require use of an N-alkyl (Me or Bn) derivative; in our hands cytisine itself fails to lithiate and use of N-Boc cytisine leads preferentially to α-lithiation (at C11/C13) adjacent to the piperidine N.

Lithiation of N-benzylcytisine **5** and trapping with a borate ester provided the 10-Bpin adduct **8** as a single diastereomer (**Scheme 3**). Given that 2-pyridone reduction of N-benzylcytisine **5** (and also cytisine itself[16]) is highly selective at the α-face (opposite to the piperidine NBn residue and can be coupled to concomitant N-debenzylation), this would provide the stereochemical outcome (at C6-C7; see above) required for virgidivarine **7**. However, given the presence and proximity of the Bpin moiety, we selected to carry out oxidative cleavage prior to pyridone reduction. Perborate oxidation of **8** followed by hydride reduction of the intermediate hemiaminal **9** provided the fragmented 3,5-disubstituted pyridone **10** in 47% overall yield. Hydrogenation of **10** using Adams' catalyst allowed pyridone reduction, however, this was nonselective and a 1:1 mixture of diastereomers **11** was observed by ^{1}H NMR. This process was further compromised by our inability to separate these isomers by HPLC which made any further optimization more difficult. We also subjected hemiaminal **9** to the same hydrogenation conditions, but no reaction was observed.

These observations forced a more detailed evaluation of the reduction of the Bpin adduct **8**. As anticipated, the presence (at C10) of the bulky borate ester led to significant decrease in reactivity and a variety of reduction conditions were evaluated (**Scheme 4** and **Table 1**).



Scheme 3. Metalation of **5**, oxidative fragmentation followed by 2-pyridone reduction



Scheme 4. Diastereoselective reduction of pyridone **8** to give **12** (and **13**)

An effective reduction (Entry 7, **Table 1**) was achieved in the presence of acid and while the N-debenzylated product **12** was observable (by ^{1}H NMR), conversion of this intermediate directly to the corresponding N-Boc adduct **13** (in 72% overall yield from **8**) facilitated isolation and purification. When reduction occurred, we only observed β-face selective reduction (leading to **12**) and no trace of the α-face diastereomer **12′** was detected.

Table 1. Conditions evaluated for diastereoselective reduction of pyridone **8**

Entry	Catalyst (amount)	Solvent	Pressure (bar)	Temp	Conversion (%)[a]
1	PtO_2 (25% w/w)	MeOH	1	rt	-
2	PtO_2 (25% w/w)	AcOH	1	rt	-
3	PtO_2 (25% w/w)	AcOH	1	60 °C	-[b]
4	PtO_2 (25% w/w)	AcOH	50	rt	60% but <5% product recovery
5	Rh/C (20 mol%)	AcOH	1[c]	40 °C	-
6	Rh/Al_2O_3 (20 mol%)	*i*-PrOH	1[b,c]	60 °C	n.d.[d]
7	PtO_2 (25% w/w) + aq. HCl (1.6 eq.)	EtOH	1	rt	>99% (2 days) (**12**; Scheme 4)

[a] Conversion of **8** was determined by ^{1}H NMR analysis of the crude product
[b] Only N-debenzylation was observed
[c] H_2 was bubbled continuously through the reaction mixture
[d] The desired product plus *N*-isopropyl/*N*-cyclohexylmethyl derivatives were observed.

The stereochemical course of the reduction of **8** was such that the N-Boc derivative **13** was isolated as a single isomer, the structure of which was established by n.O.e. (**Figure 1**). Key was irradiation of H_6 which showed enhancement of H_{13} which allowed us to assign the structure of **13** as shown in **Scheme 4** (see additional nOe data in the Supporting Information).

Reduction took place exclusively for the β(top) face and presumably this is a consequence of the steric bulk of the Bpin residue shielding the α-face. Interesting, this outcome is also consistent with the ^{11}B NMR shift observed for **13**. Generally, boronate esters have shifts in the region of 22-42 ppm whereas for **13**, we observed this at 12 ppm. This decrease in chemical shift suggests additional coordination is taking place and, given the essentially enforced "boat" conformation of the central ring (**Figure 1**), this most reasonably points to an interaction of B with the lactam oxygen.

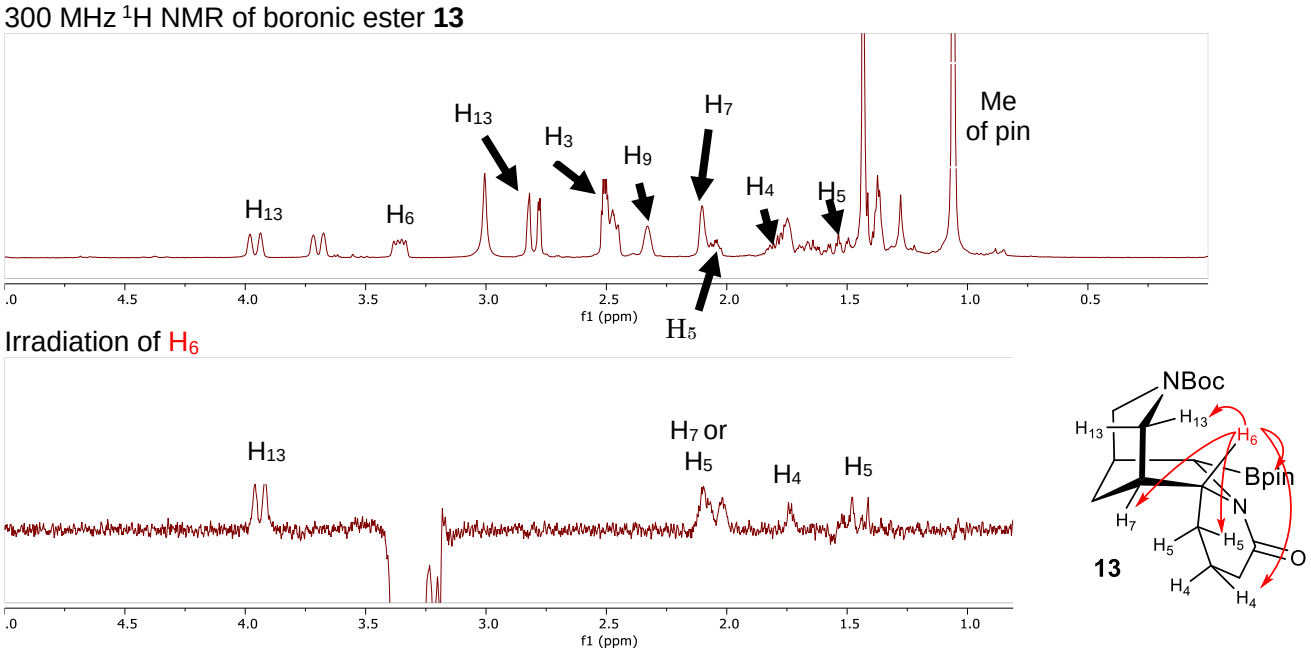
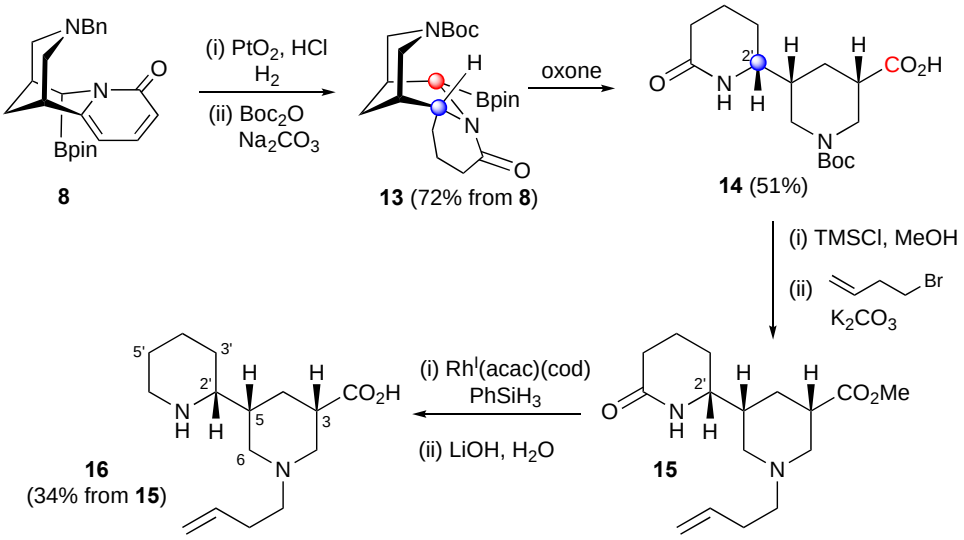


Figure 1. N.O.E of boronate ester **13** (further details are available in Supporting Information)

Further, boronate **13** was also significantly more resistant to oxidation; again, indicative of additional coordination. More forcing conditions (oxone) were required but this also provided us directly with the target carboxylic acid **14**. (**Scheme 5**). In order to allow a comparison with the Blechert approach,[14] acid **14** was esterified with N-Boc cleavage, and site-selective N-alkylation using 4-bromobut-1-ene gave **15**. Chemoselective lactam reduction[17] (in the presence of the ester moiety) was achieved with a silane reductant under Rh^I-catalyzed conditions to provide, after saponification, 2′-epivirgidivarine **16**.



Scheme 5. Synthesis of 2′-epivirgidivarine **16**

Comparison of the ^{1}H NMR data for **16** with that reported by Blechert for **7** was also carried out and it was clear (see Supporting Information) that the key differences observed were in the C5/2′ region, providing further support for the earlier stereochemical assignment of the reduction of boronate **13**.

In summary, the chemistry shown in **Scheme 5** provides a novel bis(piperidine) fragment that is a diastereomer of virgidivarine. The chemistry presented here has not been optimized, but the essential transformations (diastereoselective reduction, oxidative fragmentation as well as site-selective N-alkylation and chemoselective lactam reduction as in (**14→16**) have been demonstrated. Importantly, and alongside the earlier work of Blechert, there are now two stereochemically distinct and defined and complementary bis(piperidine) units available that offer attractive and flexible templates for exploring chemical space and we are currently exploring the potential of these scaffolds as (in silico) starting points for new subtype selective ligands for therapeutically important nicotinic acetylcholine receptors.

EXPERIMENTAL

General. All reactions involving air- or moisture-sensitive compounds were carried out under argon in oven-dried glassware. All reagents and solvents were purchased as reagent grade from commercial suppliers and used without purification. All reactions were monitored by TLC silica gel 60 F254 aluminium sheets unless otherwise stated. Flash column chromatography was carried out by using silica gel 40-63 μm (230-400 mesh) and silica gel 60 (70-230 mesh) for sensitive products. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer. NMR spectra were recorded on a Bruker AVANCE III HD 300 MHz or Bruker; AVANCE 600 MHz spectrometer. High resolution mass spectra (HRMS) were measured by electrospray ionization (ESI) techniques. Optical rotations were measured on a Jasco P-1020 at 589 nm.

***tert*-Butyl (*6S*, 11a*S*)-8-oxo-6-(4, 4, 5, 5-tetramethyl-1, 3, 2-dioxaborolan-2-yl)octahydro-2*H*-1, 5-methanopyrido[1, 2-*a*][1,5]diazocine-3(4*H*)-carboxylate (13):** A solution of **8**[4,18] (406 mg, 1.0 mmol), PtO_2 (81 mg, 20% w/w) and HCl (0.27 mL, 6.0 M (aq.), 1.6 mmol) in EtOH (1.7 mL) was hydrogenated (1 atm) at room temperature for 2 days, after which time ^{1}H NMR showed the absence of **8** in the reaction mixture. The mixture was filtered through Celite and the solvent was removed *in vacuo*. The resulting oil was dissolved in THF (4.0 mL) and water (0.30 mL). Na_2CO_3 (1.06 g, 10.0 mmol) and Boc_2O (0.95 mL, 2.0 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 18 h. DCM (25 mL) and water (25 mL) were added. The aqueous layer was extracted with DCM (25 mL x 3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by column chromatography [NH_4OH:MeOH:DCM (0.25:2.5:97.75 to 0.5:5:94.5)] gave **13** (303 mg, 72%) as a colorless solid. $[\alpha]_D^{25.0}$ –11.1° (*c* 0.50, $CHCl_3$); R_f = 0.27 [MeOH:DCM

(5:95)]; mp 201 – 203 °C (DCM); IR (neat, ν/cm^{-1}) 2961, 2932, 1685, 1590, 1423, 1116, 1022; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.96 (d, *J* = 13.0 Hz, 1H), 3.70 (d, *J* = 12.5 Hz, 1H), 3.36 (dd, *J* = 10.0, 5.0 Hz, 1H), 2.87 – 2.73 (m, 2H), 2.51 – 2.42 (m, 1H), 2.33 (s, 1H), 2.16 – 1.99 (m, 2H), 1.86 – 1.72 (m, 2H), 1.72 – 1.60 (m, 1H), 1.59 – 1.48 (m, 1H), 1.43 (s, 9H), 1.40 – 1.34 (m, 1H), 1.06 (s, 12H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.0, 155.7, 79.4, 79.2, 57.8, 50.2, 48.5, 34.8, 30.1, 28.6, 28.1, 26.5, 25.7, 25.6, 25.1, 18.5; ^{11}B NMR (96 MHz, $CDCl_3$) δ 12.3; HRMS calcd for $C_{22}H_{38}BN_2O_3$ $[M+H]^+$: 421.2868, found 421.2847.

(2*S*,3'*R*,5'*S*)-1'-(*tert*-Butoxycarbonyl)-6-oxo-[2,3'-bipiperidine]-5'-carboxylic acid (14): To a solution of **13** (44 mg, 0.10 mmol) in acetone (1.2 mL) and water (1.2 mL), was added oxone (124 mg, 0.40 mmol). The reaction mixture was stirred at room temperature for 18 h, and concentrated *in vacuo*. DCM (25 mL) and water (25 mL) were added. The aqueous layer was extracted with DCM (25 mL x 3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by column chromatography [MeOH:DCM (5:95 to 10:90)] gave **14** (17 mg, 51%) as a colorless solid. $[\alpha]_D^{25.3}$ +19.3° (*c* 0.50, $CHCl_3$); R_f = 0.22 [MeOH:DCM (5:95)]; mp 149 – 150 °C (DCM); IR (neat, ν/cm^{-1}) 2922, 2870, 1677 (br), 1619, 1417, 1267, 1148; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 4.45 – 3.91 (m, 2H), 3.38 – 3.08 (m, 1H), 2.87 – 2.66 (m, 1H), 2.64 – 2.12 (m, 5H), 2.02 – 1.80 (m, 2H), 1.76 – 1.53 (m, 3H), 1.53 – 1.36 (m, 10H), 1.37 – 1.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 175.2, 154.6, 80.2, 55.3, 45.9, 45.5, 40.8, 40.0, 30.7, 29.0, 28.4, 26.1, 19.1; HRMS calcd for $C_{16}H_{27}O_5N_2$ $[M+H]^+$: 327.1914, found 327.1909.

Methyl (2*S*,3'*R*,5'*S*)-1'-(but-3-en-1-yl)-6-oxo-[2,3'-bipiperidine]-5'-carboxylate (15): To a solution of **14** (98 mg, 0.30 mmol) in MeOH (42 mL) at room temperature, was added TMSCl (0.57 mL, 4.50 mmol) dropwise. The reaction mixture was heated to 50 °C and stirred for 18 h. After being cooled to room temperature, the solvent was removed *in vacuo*. Using a sealed tube, the resulting crude product was dissolved in MeCN (3.0 mL), followed by the addition of K_2CO_3 (830 mg, 6.0 mmol) and 4-bromo-1-butene (0.21 mL, 2.1 mmol). The reaction mixture was stirred at 80 °C for 18 h. After being cooled to room temperature, DCM (25 mL) and water (25 mL) were added. The aqueous layer was extracted with DCM (25 mL x 3). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by column chromatography [NH_4OH:MeOH:DCM (0.5:5:94.5 to 0.75:7.5:92.25)] gave **15** (30 mg, 34%) as a colorless oil. $[\alpha]_D^{26.9}$ +46.6° (*c* 0.05, MeOH); R_f = 0.41 [MeOH:DCM (95:5)]; IR (neat, ν/cm^{-1}) 3217, 2947, 2850, 1731, 1645, 1326, 1265, 1159; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (s, 1H), 5.79 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 5.12 – 4.99 (m, 2H), 3.69 (s, 3H), 3.38 – 3.26 (m, 1H), 3.25 – 3.16 (m, 1H), 2.99 – 2.88 (m, 1H), 2.69 (tt, *J* = 12.0, 4.0 Hz, 1H), 2.58 – 2.47

(m, 2H), 2.40 – 2.34 (m, 1H), 2.34 – 2.24 (m, 3H), 2.14 – 2.00 (m, 1H), 1.98 – 1.59 (m, 8H), 1.56 – 1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 172.6, 135.9, 116.1, 57.9, 56.0, 55.0, 54.8, 51.9, 41.3, 40.2, 31.4, 31.0, 28.9, 25.3, 19.9; HRMS calcd for $C_{16}H_{27}O_3N_2$ $[M+H]^+$: 295.2016, found 295.2013.

Methyl (2*S*,3'*R*,5'*S*)-1'-(but-3-en-1-yl)-[2,3'-bipiperidine]-5'-carboxylate: To a solution of **15** (19 mg, 65 μmol) and (acetylacetonato)(1,5-cyclooctadiene)rhodium(I) (0.4 mg, 2 mol%) in THF (0.3 mL), was added $PhSiH_3$ (32 μL, 0.26 mmol). The reaction mixture stirred for 18 h at room temperature. Saturated aqueous NH_4F (1 mL) was added and the resulting mixture was stirred at room temperature overnight. Solvent was removed *in vacuo*. Purification by column chromatography [NH_4OH:MeOH:DCM (1:10:89 to 2:20:78)] gave the title *methyl ester* (6 mg, 33%) as a colorless oil. $[\alpha]_D^{26.8}$ +46.6° (*c* 0.05, MeOH); R_f = 0.19 [MeOH:DCM (90:10)]; IR (neat, ν/cm^{-1}) 2927, 1733, 1431, 1130, 910; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H), 5.15 – 4.94 (m, 2H), 3.69 (s, 3H), 3.23 – 2.99 (m, 3H), 2.73 – 2.59 (m, 2H), 2.52 – 2.39 (m, 3H), 2.35 – 2.22 (m, 2H), 2.22 – 2.08 (m, 1H), 2.07 – 1.98 (m, 1H), 1.90 – 1.56 (m, 7H), 1.54 – 1.43 (m, 1H), 1.36 – 1.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 136.4, 115.7, 60.0, 58.1, 55.9, 55.1, 51.8, 47.1, 41.6, 40.4, 31.3, 29.7, 29.0, 24.5; HRMS calcd for $C_{16}H_{29}O_2N_2$ $[M+H]^+$: 281.2224, found 281.2223.

(2*S*,3'*R*,5'*S*)-1'-(But-3-en-1-yl)-[2,3'-bipiperidine]-5'-carboxylic acid (2'-Epivirgidivarine) (16): To a solution of **15** (19 mg, 65 μmol) and (acetylacetonato)(1,5-cyclooctadiene)rhodium(I) (0.4 mg, 2 mol%) in THF (0.3 mL), was added $PhSiH_3$ (32 μL, 0.26 mmol). The reaction mixture stirred for 18 h at room temperature. Saturated aqueous NH_4F (1 mL) was added and the resulting mixture was stirred at room temperature overnight and solvent was removed *in vacuo*. The resulting crude product (*methyl ester, see previous procedure*) was dissolved with THF (0.5 mL) and water (0.5 mL) followed by the addition of $LiOH{\cdot}H_2O$ (4.7 mg, 195 μmol). The reaction mixture was stirred at room temperature for 3 days. Solvent was removed *in vacuo*. 10% EtOH/DCM (5 mL) was added and the mixture was filtered by syringe filter (0.45 μm pore size). Solvent was removed *in vacuo* to give **16** (6 mg, 34%) as a colorless oil. $[\alpha]_D^{27.1}$ +34.2° (*c* 0.11, MeOH); IR (neat, ν/cm^{-1}) 3370, 2920, 2851, 2359, 1652, 1457, 1259, 1019, 799; ^{1}H NMR (600 MHz, CD_3OD) δ 5.83 (ddt, *J* = 17.2, 10.0, 7.2, 6.6 Hz, 1H), 5.08 – 5.02 (m, 1H), 5.00 – 4.96 (m, 1H), 4.57 – 4.52 (m, 1H), 3.70 – 3.58 (m, 1H), 2.92 – 2.71 (m, 3H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.39 – 2.32 (m, 2H), 2.29 – 2.21 (m, 2H), 2.20 – 2.06 (m, 3H), 2.00 – 1.93 (m, 1H), 1.85 – 1.67 (m, 3H), 1.67 – 1.58 (m, 1H), 1.56 – 1.50 (m, 1H), 1.36 – 1.30 (m, 1H); ^{13}C NMR (151 MHz, CD_3OD) δ 173.5, 138.2, 115.8, 59.8, 59.6, 59.2, 58.5, 45.4, 37.4, 33.2, 32.7, 30.7, 28.5, 26.4, 20.5; HRMS calcd for $C_{15}H_{27}O_2N_2$ $[M+H]^+$: 267.2067, found 267.2069.

ACKNOWLEDGEMENTS

We thank the Chulabhorn Graduate Institute for financial support, the Development and Promotion of Science and Technology (DPST) Thailand for a research scholarship (to WN) and Dr Hugo Rego Campello for helpful discussions and support.

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