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Synthesis and reactivity of pelletierine-derived building blocks and pelletierine analogs

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ABSTRACT

Lycopodium alkaloids are unique (and often impressive in terms of structures) polycyclic alkaloids that attract great interest from a biological point of view and that also provide ideal targets for total synthesis. Propylpiperidine units closely related to pelletierine are involved in the biosynthesis of these alkaloids. Therefore, stable pelletierine-like compounds, especially a (*R*)-phenylglycinol-based oxazolopiperidine analog, were prepared and their reactivity investigated. The compounds described in this work expand the tool-box of small building blocks in the piperidine series and pelletierine analogs and could be suitable for the synthesis of *Lycopodium* alkaloids following biosynthetically inspired strategies.

1. Introduction

Pelletierine, named in honor of Joseph Pelletier, is probably one of the most renowned alkaloid and one the most simple in terms of chemical structure. Isolated by Charles Tanret in 1878 from the bark of pomegranate tree (*Punica granatum* L., Lythraceae), which was traditionally used as an anti-helminthic drug, pelletierine has a long history of chemical controversies.[1] From the initial aldehydic (3-(2-piperidinyl)propionaldehyde) structure proposed by Hess and Eichel in 1917 (Fig. 1) to the final conclusions with the work of Gilman and Marion, several critical points, especially regarding terminology, have been debated. It is now accepted that (−)-pelletierine refers to (−)-1-(2-piperidinyl)propan-2-one and isopelletierine to (±)-pelletierine. Finally, the absolute configuration, as well as the biogenetic origin, was revealed in the 1960s.[1e]

The implication of pelletierine (**1**), or at least analogous C_5N–C_3 units, in the biosynthesis of complex alkaloids of the genus *Lycopodium* (Lycopodiaceae) is a matter of particular significance.[2] Indeed, with more than 250 known structures and a permanently enriched list,[3] *Lycopodium* alkaloids have attracted a great deal of interest thanks to promising biological activities (huperzine A is a potent inhibitor of acetylcholinesterase, nankakurine A[4] shows neurotrophic properties to cite two examples among many others) but also, in some cases, because their highly intricate structures designate them as beautiful targets for total synthesis featuring state-of-the-art methodology.[5]

In terms of biosynthesis, *Lycopodium* alkaloids were shown to derive from C_5N–C_3 units as beautifully demonstrated some years ago by Spenser with the revealing of lycopodine (**2**) biosynthesis by feeding experiments.[6] The studies clearly demonstrated the incorporation of lysine in combination with a polyketide derivative (**3**) as the precursor of the three side-chain carbons (Scheme 1).[7] Whether pelletierine (**1**) *sensu stricto* is incorporated cannot be

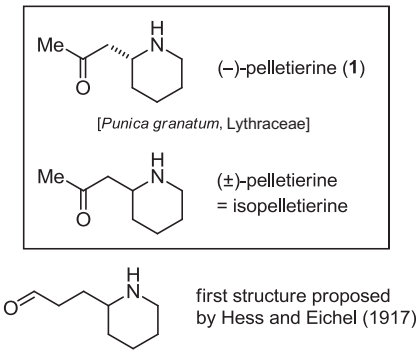

Fig. 1. Structures related to pelletierine.

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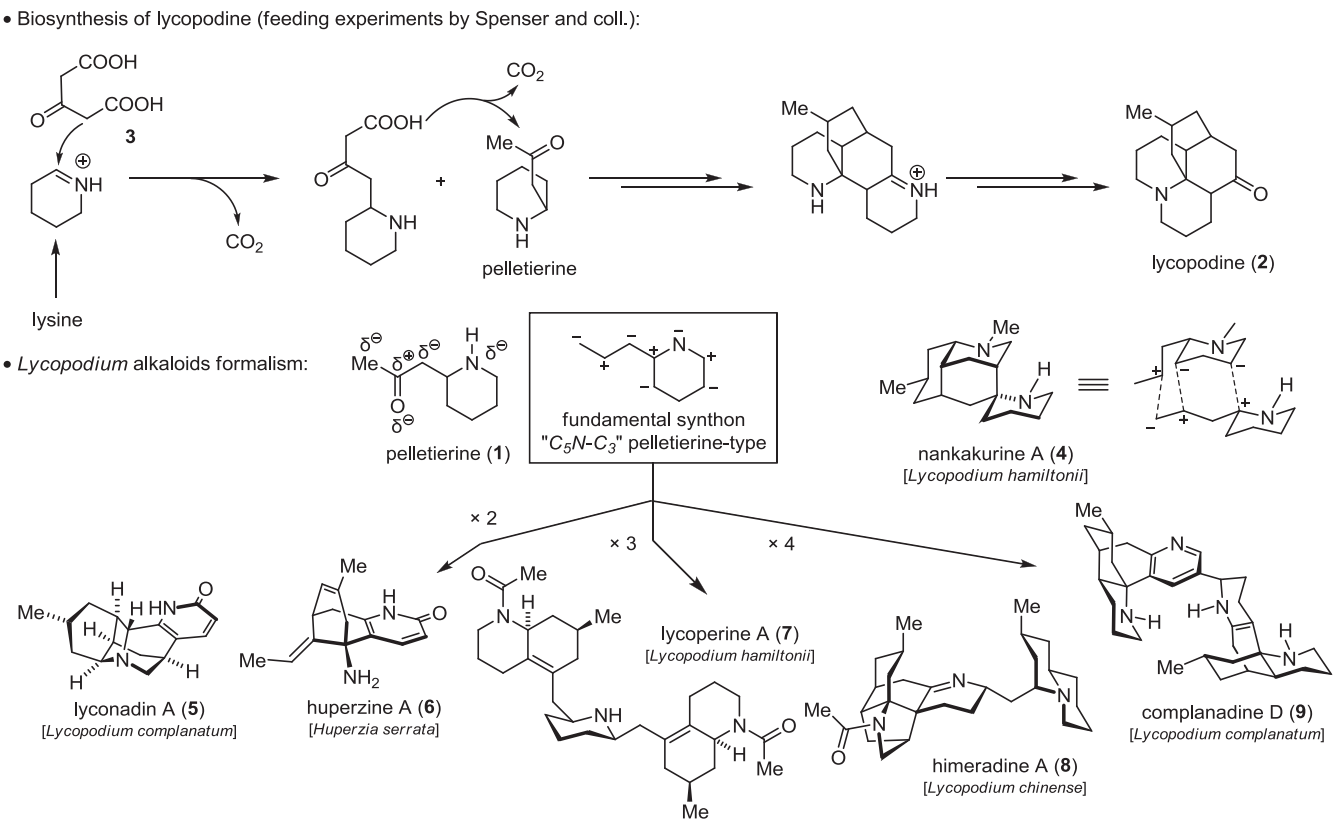


Scheme 1. *Lycopodium* alkaloids: diversity and biosynthesis.

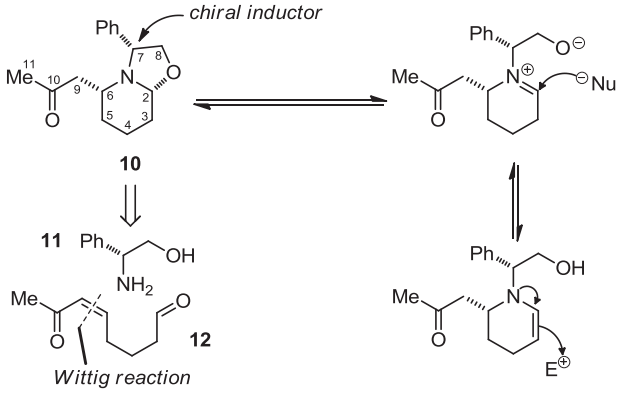
ascertained, but synthons with the same latent polarities may be, at least, commonly traced in *Lycopodium* alkaloids as depicted in Scheme 1 with the example of nankakurine A (**4**). Thus the *Lycopodium* class of alkaloids may be divided in several groups according to the number of pelletierine-like molecules incorporated in the final structure.[8] Indeed, from two up to four C_5N–C_3 units can be found in these alkaloids as exemplified on Scheme 1 with lyconadin A (**5**), above mentioned huperzine A (**6**), lycoperine A (**7**), himeradine A (**8**) and complanadine D (**9**).[9]

Puzzled by Nature's diversification of skeletons within *Lycopodium* alkaloids starting from C_5N–C_3 units analogous to pelletierine (**1**), we were interested in the synthesis of pelletierine-derived building blocks. Such compounds may display different latent or masked reactivities in different oxidation states enabling further functionalization through biomimetic strategies. The present work describes the first results toward this aim with the synthesis of several stable pelletierine analogs (in fact (−)-pelletierine (**1**) is known to be prone to both racemization and degradation along with displaying an inconvenient volatility),[10] from which at least two may be considered as building blocks *sensu stricto*.

2. Results and discussion

2.1. Conception, synthesis of 'phenyloxazolopelletierine' (10): (*R*)-(−)-phenylglycinol as the nitrogen source

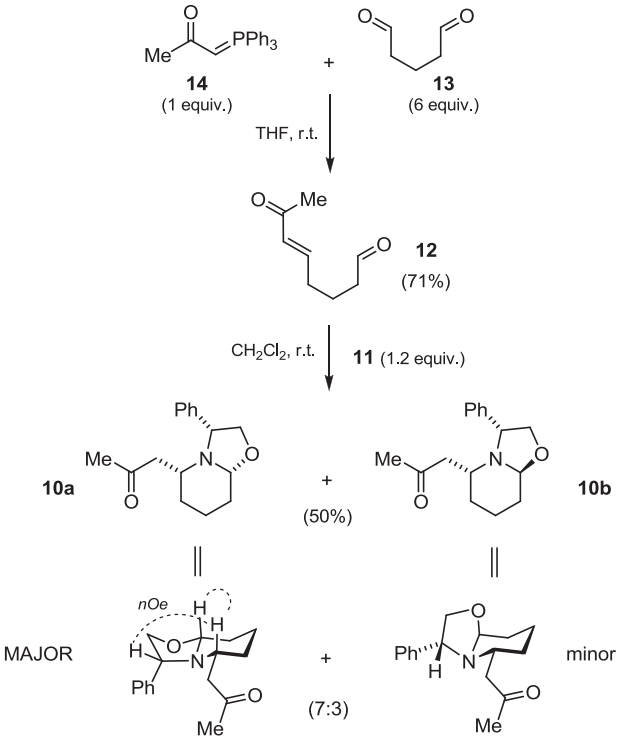
We thought of designing a stable analog of pelletierine, such as compound **10**, which can be seen as a stable equivalent of dehydropelletierine. It features a protected nitrogen atom with a phenylethanol moiety provided by (−)-phenylglycinol (**11**) (used as the nitrogen source and chirality inducer).[11] The primary alcohol also permits the stabilization of a potential iminium by forming an oxazolidine ring.[12] The piperidine ring and the propanone side chain could retrosynthetically come from Michael acceptor **12** bearing a free aldehyde function (Scheme 2).



Scheme 2. Retrosynthesis and potential reactivities of phenyloxazolopelletierine (**10**).

Glutaraldehyde (**13**) and 1-(triphenylphosphoranylidene)-2-propanone (**14**) were engaged to afford Michael acceptor **12** by a Wittig reaction in 71% yield. Several experiments were then conducted in order to investigate the best conditions for the condensation of **12** with (*R*)-(−)-phenylglycinol (**11**) (See Scheme 3). A satisfactory yield of 50% is observed when reacting **12** and **11** in dichloromethane at room temperature (the yield drops to 11% when the reaction was conducted in methanol). The so-called 'phenyloxazolopelletierine' (**10**) appears by NMR as a mixture of two diastereoisomers that are not separable by chromatography column.[13]

Careful analysis of NMR spectra permitted to establish the relative stereochemistry of both stereomers (see selected NMR data on Scheme 3).



Scheme 3. Synthesis of phenyloxazolopelletierine (**10**).

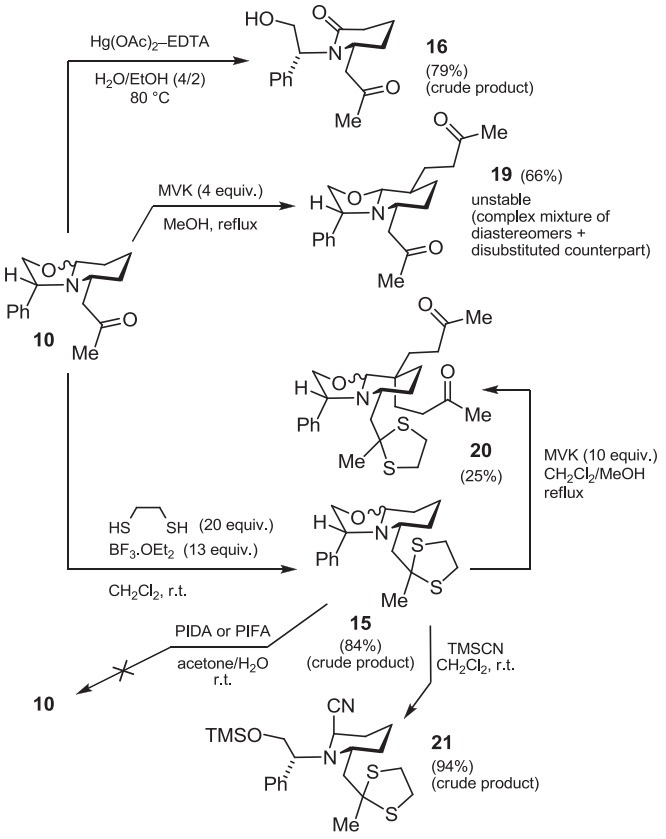
2.2. Reactivity of 'phenyloxazolopelletierine' (10)

Reactivity studies were conducted on compound **10** in order to evaluate the dual iminium/enamine reactivity, (which could permit access to substituted piperidines at the C-2 or C-3 positions) as well as the reactivity of the side chain.[14] Moreover, it was anticipated that diastereoselective transformations might be expected with the presence of the chiral appendage.

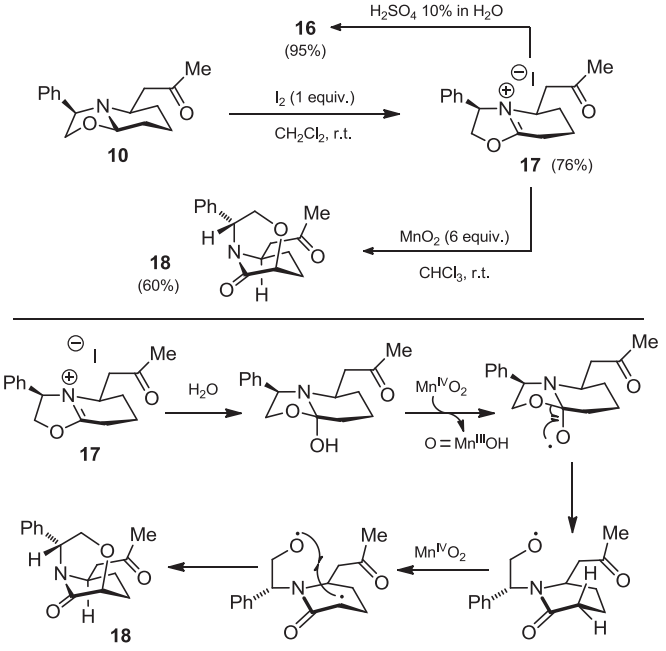
2.2.1. Protection of the carbonyl group. Various conditions were evaluated so as to protect the carbonyl of the propanone side chain as a cyclic diketal but were all unsuccessful. Conversely, the protection as a dithioketal **15** (2:1 mixture of diastereomers)[15] was easy using a large excess of 1,2-ethanedithiol and $BF_3{\cdot}Et_2O$ in dichloromethane at room temperature. Unfortunately, deprotection under the few conditions tested (diacetoxyiodobenzene (PIDA) and [bis(trifluoroacetoxy)]iodobenzene (PIFA)) did not permit to regenerate **10** as depicted on Scheme 4.

2.2.2. Oxidative conditions. Oxidation under classical mercuric acetate and EDTA conditions led to the formation of lactam **16** in good yields (9:1 mixture of diastereomers resulting from partial epimerization at C-6)[16] without further purification.[17,18]

An interesting reaction was observed when **10** was treated with iodine. Whereas a lactam, such as **16** could be expected, the iminium form **17** was obtained in useful yields and appeared to be stable. Such an iminium is believed to be an intermediate toward lactams in the phenyloxazolopiperidine series. In fact, when treated with an aqueous solution of H_2SO_4, **17** cleanly gave lactam **16** in high yield. A complex rearrangement was then observed when treating **17** with manganese dioxide resulting in the formation of bicyclic lactam **18** (in 60% yield, obtained as a single diastereomer) featuring a novel C–O bond at the β-position of the piperidine ring (Scheme 5). This outcome was surprisingly welcome as it provided another interesting pelletierine-like building block. Such a reaction probably takes place through radical intermediates and is, to the best of our knowledge, seldom described in the literature. A similar result was observed in the morphinane series in the late 1960[s] by the Kitano group.[19]



Scheme 4. Reactivity of phenyloxazolopelletierine (**10**).



Scheme 5. Particular reactivity of phenyloxazolopelletierine (**10**) under oxidizing conditions.

2.2.3. Reaction with nucleophiles and electrophiles. The enamine reactivity was tested with methylvinylketone (MVK) as a simple Michael acceptor (Scheme 4). Although a monoalkylation of

compound **10** was possible albeit in moderate yield, the diastereoselectivity of this reaction was difficult to evaluate because of an additional instability in NMR tube that rapidly resulted in an epimerization leading to a complex mixture of diastereomers. A rapid NMR analysis of chromatography fractions accounts for the formation of tentative structure **19** as the major diastereomer (~66%, indicative yield) as depicted on Scheme 4, along with hardly separable small amounts of its disubstituted counterpart confirmed by the observation of a *m*/*z* $[M+Na]^+$ 422 peak on the mass spectrum when 4 equiv were employed.

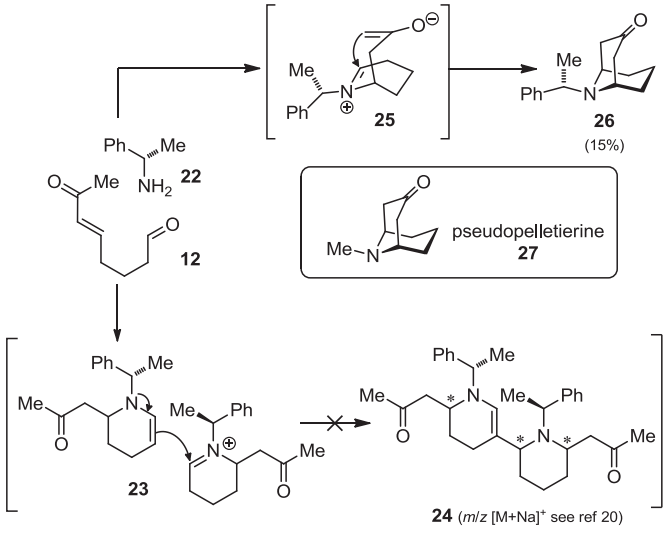
When protected analog **15** was treated with an excess of MVK, double adduct **20** was obtained in 25% yield (8:2 mixture of diastereomers).

The oxazolidine ring opening and the following trapping of the iminium by a cyanide ion leading to α-aminonitrile **21** was possible by treatment of **15** with trimethylsilyl cyanide in dichloromethane at room temperature. All subsequent reagents investigated ($AgBF_4$, $LiBF_4$, TBAF, SiO_2…) systematically gave back **15**.

2.3. Use of (*S*)-1-phenylethylamine and benzylamine as nitrogen sources

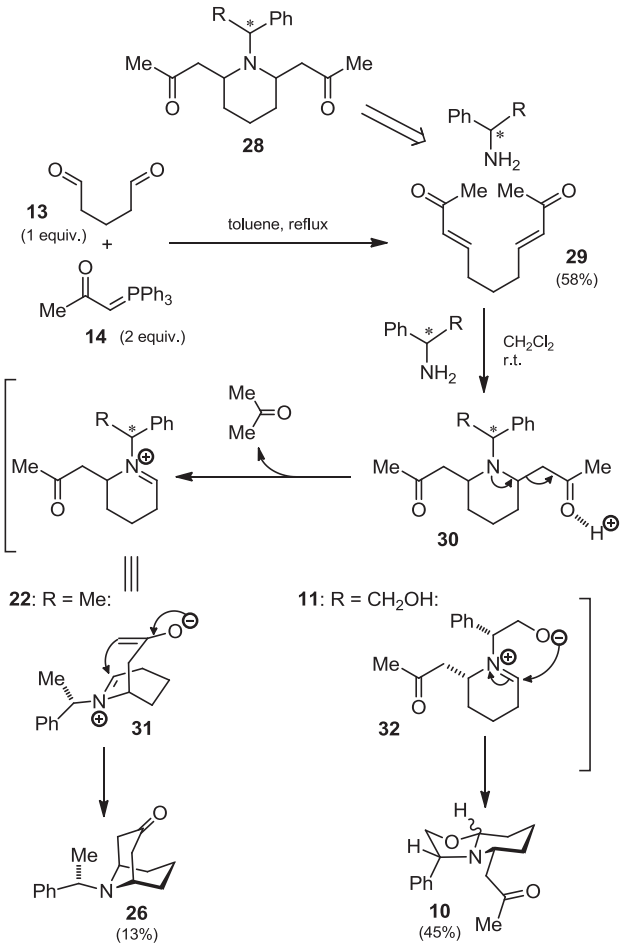
The use of chirality inductors devoid of any iminium stabilization ability was then investigated. Such an approach should permit a biosynthetically inspired dimerization as witnessed in the course of the biosynthesis of *Lycopodium* alkaloids, such as complanadine D (**9**). Reaction of Michael acceptor **12** with (*S*)-phenylethylamine (**22**) in dichloromethane at room temperature led to a mixture of compounds, in which no dimerization compound **24** could be isolated by column chromatography. The only compound that could be characterized was **26**, logically resulting from an intramolecular Mannich reaction to give a pseudopelletierine analog (Scheme 6).[20]

When targeting α,α′-disubstituted compounds of type **28** (See Scheme 7) to mimick the assembly of alkaloids, such as lycoperine A (**7**), an unexpected result was observed and further studied. Bis-Michael acceptor **29** was prepared by a double Wittig reaction on glutaraldehyde (**13**).



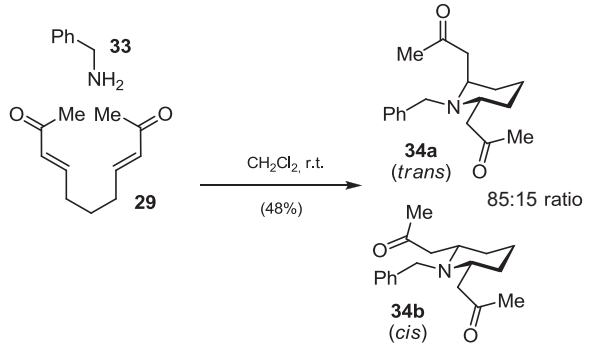
Scheme 6. Reaction with (*S*)-1-phenylethylamine (**22**).

Condensation of bis-Michael acceptor **29** was studied first with (*S*)-1-phenylethylamine (**22**) and surprisingly only the pseudopelletierine analog **26** could be isolated in low yield. Even more striking was the isolation of phenyloxazolopelletierine **10** in 45% yield when (*R*)-(−)-phenylglycinol (**11**) was employed. In both cases, expected α,α′-disubstituted piperidines were not isolated.



Scheme 7. Particular reactivity with a double Michael acceptor.

The loss of one side chain could be explained by a plausible retro-Mannich reaction mechanism providing reactive iminium intermediates **31** and **32** as depicted on Scheme 7.[21] Only the recourse to benzylamine (**33**) permitted the isolation of α,α′-disubstituted piperidine **34** as an 85:15 mixture of diastereoisomers with predominant *trans* configuration (Scheme 8).[22]



Scheme 8. Reactivity with a double Michael acceptor and benzylamine.

3. Conclusion

The described chemistry provides an entry to new and stable equivalents of pelletierine that are currently being studied. At least two of them can be considered as building blocks and are currently being studied for the biomimetic assembly of *Lycopodium* alkaloid skeletons. The main results of the present work include the

synthesis of phenyloxazolopelletierine (**10**), the reactivity of which was investigated especially in oxidative conditions (where an original rearrangement leading to **18** was observed). The access to α,α′-disubstituted piperidines was also studied and permitted the observation of unusual *retro*-Mannich reactions.

4. Experimental section

4.1. General methods

General: Reactions were monitored by thin-layer chromatography carried out on silica gel plates (Merck TLC Silicagel 60 $_{F254}$) using UV light as visualizing agent and sulfuric vanillin/heat and Draggendorff reagent/heat as developing agents. Merck Silicagel Geduran® Si 60 (particle size 40–63 μm) was used for flash chromatography. NMR spectra were recorded in deuterated chloroform on AM-300 (300 MHz) or AM-400 (400 MHz) Bruker spectrometers and calibrated using undeuterated chloroform as an internal reference. The following abbreviations are used to explain the multiplicities: s=singlet; d=doublet, t=triplet; q=quartet; qu=quintet; m=multiplet; br=broad. IR spectra were recorded on Vector 22 Bruker spectrometer and values are reported in cm^{-1} units. Mass spectra were recorded at the 'Service d'Analyse des Médicaments et des Métabolites' (Université Paris-Sud). Optical rotation measurements were conducted using an Optical Activity polAAR 32 polarimeter.

4.2. Procedures for the synthesis of compounds

*4.2.1. Michael acceptor **12**.* A mixture of glutaraldehyde (17.2 mL of a 50% aqueous solution, 94.3 mmol) and 1-(triphenylphosphoranylidene)-2-propanone (5 g, 15.7 mmol) in THF (75 mL) was stirred at room temperature for 23 h, after which water (75 mL) was added. The mixture was then extracted by Et_2O (3×70 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The oily residue was then purified by flash chromatography on silica gel with a gradient solvent system: cyclohexane/EtOAc (8:2 to 5:5) to afford compound **12** (1.57 g, 71%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.76 (s, 1H, CHO), 6.75 (dt, $^3J_{H,H}$=16 Hz, 7.0 Hz, 1H,=*CH*–CH_2), 6.07 (d, $^3J_{H,H}$=16 Hz, 1H,=*CH*–CO), 2.48 (t, $^3J_{H,H}$=7.0 Hz, 2H, *CH*$_2$–CHO), 2.25 (q, $^3J_{H,H}$=7.0 Hz, 2H, *CH*$_2$–CH=), 2.22 (s, 3H, CH_3), 1.80 (qu, $^3J_{H,H}$=7.0 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.5 (CHO), 198.5 (CO), 147.0 (CH), 131.9 (CH), 43.0 (CH_2), 31.7 (CH_2), 27.0 (CH_3), 20.3 (CH_2). IR ν_{max}: 1707, 1670, 1625 cm^{-1}. HRMS (ESI) calcd for $C_8H_{12}NaO_2$ 163.0732 $[M+Na]^+$ found 163.0730. R_f=0.33 (cyclohexane/EtOAc 1:1).

*4.2.2. Phenyloxazolopelletierine **10**.* A mixture of compound **12** (500 mg, 3.57 mmol) and (*R*)-phenylglycinol (587 mg, 4.28 mmol) in CH_2Cl_2 (10 mL) was stirred for 4 days at room temperature. The reaction mixture was concentrated under reduced pressure and then purified by flash chromatography on silica gel with cyclohexane/Et_2O (8:2) as eluent. A mixture of inseparable diastereoisomers **10** (463 mg, 50%) was obtained in a 7:3 ratio in favor of **10a** as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.37–7.21 (m, 5H, Ph), 4.13 (t, $^2J_{H,H}$=$^3J_{H,H}$=7.2 Hz, 1H, CH_2), 3.83 (dd, $^3J_{H,H}$=9.6 Hz, $^3J_{H,H}$=2.4 Hz, 1H, N–CH–O), 3.73 (t, $^3J_{H,H}$=7.2 Hz, 1H, *CH*–Ph), 3.55 (t, $^2J_{H,H}$=$^3J_{H,H}$=7.2 Hz, 1H, CH_2), 3.04 (m, 1H, N–CH–CH_2), 2.41 (dd, $^2J_{H,H}$=18 Hz, $^3J_{H,H}$=7.2 Hz, 1H, CH_2), 2.03 (dd, $^2J_{H,H}$=13.6 Hz, $^3J_{H,H}$=2.4 Hz, 1H, CH_2), 1.97 (dd, $^2J_{H,H}$=18 Hz, $^3J_{H,H}$=7.2 Hz, 1H, CH_2), 1.83 (m, 1H, CH_2), 1.52–1.66 (m, 2H, CH_2), 1.48 (s, 3H, CH_3), 1.45 (m, 1H, CH_2), 1.25–1.35 (m, 1H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ=206.7 (CO), 143.1 (C_{IV} Ph), 128.5 (2 CH Ph), 127.8 (2 CH Ph), 127.3 (CH Ph), 95.5 (CH), 74.5 (CH_2), 65.0 (*CH*–Ph), 55.3 (CH), 49.2 (CH_2), 32.9 (CH_2), 30.1 (CH_2), 29.8 (CH_3), 22.3 (CH_2). IR ν_{max}: 1714 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{22}NO_2$ 260.1651 $[M+H]^+$ found 260.1639. R_f=0.56 (cyclohexane/EtOAc 1:1).

*4.2.3. Dithioketal **15**.* To a solution of phenyloxazolopelletierine **10** (200 mg, 0.77 mmol) in CH_2Cl_2 (8 mL) were successively added 1,2-ethanedithiol (1.29 mL, 15.4 mmol) and boron trifluoride (1.27 mL, 10.0 mmol). The reaction mixture was stirred overnight at room temperature and then washed with a 2 M aqueous solution of NaOH (5×25 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give compound **15** (216 mg, 84%) as a yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.22–7.43 (m, 5H, Ph), 4.76 (dd, $^3J_{H,H}$=7.2, 4.4 Hz, 1H, *CH*–Ph), 4.55 (t, $^3J_{H,H}$=2.8, 2.0 Hz, 1H, N–CH–O), 4.39 (dd, $^2J_{H,H}$=7.6 Hz, $^3J_{H,H}$=7.2 Hz, 1H, CH_2–O), 3.81 (dd, $^2J_{H,H}$=7.6 Hz, $^3J_{H,H}$=4.4 Hz, 1H, CH_2–O), 3.27–3.33 (m, 4H, 2 CH_2–S), 2.76 (td, $^3J_{H,H}$=7.6, 2.4 Hz, 1H, N–*CH*), 2.31 (d, $^2J_{H,H}$=15.2 Hz, 1H, CH_2), 2.18 (m, 1H, CH_2), 2.07 (dd, $^2J_{H,H}$=15.2 Hz, $^3J_{H,H}$=7.6 Hz, 1H, CH_2), 1.99 (m, 1H, CH_2), 1.73 (s, 3H, CH_3), 1.52–1.66 (m, 2H, CH_2), 1.36 (m, 1H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ=142.7 (C_{IV} Ph), 128.4 (2 CH Ph), 127.7 (2 CH Ph), 126.9 (CH Ph), 89.0 (N–CH–O), 69.3 (CH_2–O), 65.7 (C), 64.9 (*CH*–Ph), 55.7 (N–*CH*), 50.5 (CH_2), 39.8 (CH_2), 39.6 (CH_2), 33.9 (CH_3), 32.6 (CH_2), 26.8 (CH_2), 18.4 (CH_2). HRMS (ESI) calcd for $C_{18}H_{26}NOS_2$ 336.1456 $[M+H]^+$ found 336.1460. R_f=0.73 (cyclohexane/Et_2O 1:1).

*4.2.4. Lactam **16**.* To a solution of phenyloxazolopelletierine **10** (50 mg, 0.193 mmol) in a minimum of EtOH was added a solution of mercury acetate (65 mg, 0.203 mmol) and sodium salt of ethylenediaminetetraacetic acid (68 mg, 0.203 mmol) in a mixture water/EtOH (6 mL, 2:1). The reaction mixture was stirred at 80 °C for 4 h, cooled to room temperature and filtered through a pad of Celite®. CH_2Cl_2 (5 mL) was added to the filtrate followed by saturated solution of ammonium chloride (5 mL). After separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to afford compound **16** (42 mg, 79%) as orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.21–7.32 (m, 5H, Ph), 5.18 (t, $^3J_{H,H}$=6.6 Hz, 1H, *CH*–Ph), 4.09 (d, $^3J_{H,H}$=6.6 Hz, 2H, CH_2–OH), 3.99 (m, 1H, N–*CH*), 2.80 (dd, $^3J_{H,H}$=3.9 Hz, $^2J_{H,H}$=18.0 Hz, 1H, CH_2), 2.68 (dd, $^3J_{H,H}$=8.4 Hz, $^2J_{H,H}$=18.0 Hz, 1H, CH_2), 2.52 (m, 2H, CH_2–CO), 1.95 (s, 3H, CH_3), 1.73–1.85 (m, 2H, CH_2), 1.61–1.70 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ=205.8 (CO), 172.5 (N–CO), 137.2 (C_{IV} Ph), 128.6 (2 CH Ph), 127.6 (2 CH Ph), 126.1 (CH Ph), 63.6 (*CH*–Ph), 63.3 (CH_2–OH), 51.7 (C–CH), 47.4 (CH_2), 31.6 (CH_2), 30.3 (CH_3), 27.7 (CH_2), 16.4 (CH_2). IR ν_{max}: 3290, 1711, 1615 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{21}NNaO_3$ 298.1414 $[M+Na]^+$ found 298.1412. R_f=0.54 (CH_2Cl_2/MeOH 9:1).
$[\alpha]_{546}^{27°C}$=−7.38 (*c*=0.4, $CHCl_3$).

*4.2.5. Iminium **17**.* A mixture of phenyloxazolopelletierine **10** (500 mg, 1.93 mmol) and iodine (490 mg, 1.93 mmol) in CH_2Cl_2 (11 mL) was stirred at room temperature for 4 days, after which the solvent was removed under vacuum. The residue was then purified by flash chromatography on silica gel with a gradient solvent system: CH_2Cl_2/MeOH (100:09 to 90:10) to afford compound **17** (563 mg, 76%) as a yellow oil. ^{1}H NMR (300 and 400 MHz, $CDCl_3$): δ=7.43–7.56 (m, 5H, Ph), 5.82 (dd, $^3J_{H,H}$=10, 8.8 Hz, 1H, CH–Ph), 5.59 (ddd, $^2J_{H,H}$=10.8 Hz, $^3J_{H,H}$=10 Hz, $^5J_{H,H}$=3.0 Hz, O–CH_2), 4.77 (ddd, $^2J_{H,H}$=10.8 Hz, $^3J_{H,H}$=8.8 Hz, $^5J_{H,H}$=3.0 Hz, O–CH_2), 4.59 (m, 1H, N–CH), 3.26 (dt, $^3J_{H,H}$=10.8, 5.4 Hz, 1H, CH_2), 3.02 (dt, $^3J_{H,H}$=13.8, 5.4 Hz, 1H, CH_2), 2.55 (dd, $^2J_{H,H}$=19.2 Hz, $^3J_{H,H}$=6.8 Hz, 1H, CH_2), 2.39 (m, 1H, CH_2), 2.32 (dd, $^2J_{H,H}$=19.2 Hz, $^3J_{H,H}$=3.6 Hz, 1H, CH_2), 2.15–2.17 (m, 2H, CH_2), 1.89–1.92 (m, 1H, CH_2), 1.58 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=204.0 (CO), 178.2 (C), 133.7 (C_{IV} Ph), 130.5 (2 CH Ph), 129.8 (2 CH Ph), 128.9 (CH Ph), 78.5 (O–CH_2), 67.4 (*CH*–Ph), 53.5 (N–CH), 45.2 (CH_2), 29.6 (CH_3), 27.2 (CH_2), 25.3 (CH_2), 15.6 (CH_2). IR ν_{max}: 1714, 1644 cm^{-1}. HRMS (ESI) calcd

for $C_{16}H_{20}NO_2$ 258.1489 $[M]^+$ found 258.1489. R_f=0.35 (CH_2Cl_2/MeOH 9:1).

*4.2.6. Bicyclic lactam **18**.* A mixture of iminium **17** (176 mg, 0.457 mmol) and manganese dioxide (238 mg, 2.74 mmol) in $CHCl_3$ (4 mL) was stirred at room temperature for 6 h. The reaction mixture was then filtered through a pad of silica gel and rinsed with dichloromethane. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel with CH_2Cl_2 as the eluent to afford **18** (75 mg, 60%).^{1}H NMR (300 MHz, C_6D_6): δ=7.08–7.19 (m, 5H, Ph), 3.72 (m, 3H, *CH*–O–*CH*$_2$), 3.62 (t, $^3J_{H,H}$=7.6 Hz, 1H, *CH*–Ph), 3.17 (m, 1H, N–CH), 2.48 (m, 1H, O–CH–*CH*$_2$), 2.01 (dd, $^2J_{H,H}$=16.8, $^3J_{H,H}$=4.8 Hz, 1H, O–CH–*CH*$_2$ and N–CH–*CH*$_2$), 1.85–1.92 (m, 2H, 2 CH_2), 1.76–1.84 (m, 1H, CH_2–CO), 1.28 (s, 3H, CH_3), 1.19–1.23 (m, 1H, N–CH–*CH*$_2$). ^{13}C NMR (75 MHz, C_6D_6): δ=204.8 (CO), 171.9 (CO), 139.6 (C_{IV} Ph), 128.8 (2 CH Ph), 128.0 (2 CH Ph), 127.7 (CH Ph), 70.6 (CH_2–O), 63.2 (*CH*–Ph), 62.1 (N–CH), 59.1 (O–CH), 49.0 (CH_2), 30.5 (CH_2), 29.7 (CH_3), 25.4 (CH_2). IR ν_{max}: 1748, 1708, 1150 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{19}NNaO_3$ 296.1257 $[M+Na]^+$ found 296.1252. R_f=0.8 (CH_2Cl_2/MeOH 9:1). $[\alpha]_{589}^{27^\circ C}$=+10.3 (*c*=0.14, $CHCl_3$).

*4.2.7. MVK-adduct **19**.* A mixture of phenyloxazolopelletierine **10** (100 mg, 0.39 mmol) and methylvinylketone (0.032 mL, 0.39 mmol) in MeOH (3 mL) was stirred at reflux for 6 h and at room temperature overnight. Methylvinylketone (0.094 mL, 1.16 mmol) was added again and the reaction mixture was stirred at reflux for 6 h. The solvent was removed under vacuum. The oily residue was then purified by flash chromatography on silica gel with a gradient solvent system: cyclohexane/Et_2O (85:15 to 8:2) to afford compound **19** (84 mg, 66%, indicative yield, unstable compound contaminated with traces of disubstituted adduct) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.15–7.28 (m, 5H, Ph), 4.03 (t, $^2J_{H,H}$=$^3J_{H,H}$=8 Hz, 1H, O–CH_2), 3.63 (t, $^3J_{H,H}$=8 Hz, 1H, CH–Ph), 3.62 (d, $^3J_{H,H}$=10 Hz, O–CH–N), 3.45 (t, $^2J_{H,H}$=$^3J_{H,H}$=8 Hz, 1H, O–CH_2), 2.99–3.01 (m, 1H, N–CH), 2.49–2.56 (m, 1H, CH), 2.28–2.40 (m, 1H, CH_2), 2.07 (s, 3H, CH_3), 1.91–1.96 (m, 1H, CH_2), 1.50–1.88 (m, 4H, 2 CH_2), 1.35 (s, 3H, CH_3), 0.80–1.30 (m, 4H, 2 CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ=209.2 (CO), 207.0 (CO), 143.2 (C_{IV} Ph), 128.5 (CH Ph), 127.3 (CH Ph), 126.3 (CH Ph), 99.8 (O–CH–N), 74.3 (O–CH_2), 64.8 (CH–Ph), 54.9 (N–CH), 49.0 (CH_2), 41.4 (CH_2), 34.1 (CH_2), 30.0 (CH_2), 29.7 (2 CH_3), 29.0 (CH), 26.4 (CH_2). IR ν_{max}: 1714 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{27}NNaO_3$ 352.1882 $[M+Na]^+$ found 352.1870. R_f=0.45 (cyclohexane/EtOAc 1:1).

*4.2.8. Double MVK-adduct **20**.* To a solution of compound **15** (38.2 mg, 0.114 mmol) in a mixture CH_2Cl_2/MeOH (2 mL, 1:1) was added methylvinylketone (92 μL, 1.14 mmol). The reaction mixture was stirred at room temperature for 4 h then heated at reflux for 24 h, cooled to room temperature and concentrated under vacuum. The oily residue was then purified by flash chromatography on silica gel with a gradient solvent system: cyclohexane/Et_2O (5:5 to 4:6) to afford compound **20** (13.5 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.22–7.38 (m, 5H, Ph), 4.08 (dd, $^2J_{H,H}$=8 Hz, $^3J_{H,H}$=8.8 Hz, 1H, O–CH_2), 3.95 (dd, $^3J_{H,H}$=8.8, 5.6 Hz, 1H, CH–Ph), 3.64 (s, 1H, O–CH–N), 3.56 (dd, $^2J_{H,H}$=8 Hz, $^3J_{H,H}$=5.6 Hz, O–CH_2), 3.18–3.34 (m, 4H, 2 CH_2–S), 3.01 (m, 1H, CH_2), 2.69–2.78 (m, 2H, CH_2), 2.64–2.66 (m, 1H, N–CH), 2.41–2.57 (m, 2H, CH_2), 2.31–2.39 (m, 2H, 2 CH_2), 2.19 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.04–2.10 (m, 2H, 2 CH_2), 1.83–1.87 (m, 2H, CH_2), 1.66–1.70 (m, 2H, CH_2), 1.55 (s, 3H, CH_3), 1.45–1.53 (m, 1H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ=209.6 (CO), 209.1 (CO), 145.2 (C_{IV} Ph), 128.6 (2 CH Ph), 127.1 (2 CH Ph), 126.2 (CH Ph), 102.3 (O–CH–N), 74.3 (O–CH_2), 65.6 (C), 64.2 (*CH*–Ph), 61.3 (N–CH), 46.9 (CH_2), 39.8 (CH_2–S), 39.2 (CH_2–S), 38.3 (CH_2), 37.6 (CH_2), 34.0 (CH_3), 33.0 (CH_2), 31.2 (CH_2), 30.5 (CH_2), 30.2 (CH_3), 30.1 (CH_3), 26.9 (CH_2), 21.8 (CH_2). IR ν_{max}: 1715 cm^{-1}. HRMS (ESI) calcd for $C_{26}H_{38}NO_3S_2$ 476.2288 $[M+H]^+$ found 476.2273. R_f=0.19 (cyclohexane/Et_2O 1:1).

*4.2.9. α-Aminonitrile **21**.* To a solution of compound **15** (54 mg, 0.16 mmol) in dry CH_2Cl_2 (5 mL) was added trimethylsilyl cyanide (33 μL, 0.25 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for two days, after which trimethylsilyl cyanide (33 μL, 0.25 mmol) and dry CH_2Cl_2 (5 mL) were added again. After 24 h of stirring, the mixture was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure to give compound **21** (65.9 mg, 94%) as an orange viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.29–7.39 (m, 5H, Ph), 4.03 (dd, $^2J_{H,H}$=10.0 Hz, $^3J_{H,H}$=4.2 Hz, 1H, *CH*$_2$–OTMS), 3.96 (dd, $^3J_{H,H}$=5.4, 4.2 Hz, 1H, *CH*–Ph), 3.86 (dd, $^2J_{H,H}$=10.0 Hz, $^3J_{H,H}$=5.4 Hz, 1H, *CH*$_2$–OTMS), 3.60 (dd, $^3J_{H,H}$=5.1, 2.1 Hz, 1H, NC–CH–N), 3.31–3.39 (m, 4H, 2 CH_2–S), 2.73 (dd, $^3J_{H,H}$=15, 10.8 Hz, 1H, N–CH), 2.51 (br d, $^2J_{H,H}$=14 Hz, 1H, CH_2), 2.22 (br d, $^2J_{H,H}$=14 Hz, 1H, CH_2), 1.82 (s, 3H, CH_3), 1.66–1.75 (m, 4H, 2 CH_2), 0.86 (m, 2H, CH_2), −0.04 (s, 9H, $OSi(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ=140.5 (C_{IV} Ph), 128.5 (2 CH Ph), 127.6 (2 CH Ph), 126.9 (CH Ph), 121.2 (CN), 66.1 (CH–Ph), 65.6 (O–CH_2), 64.3 (C), 52.5 (N–CH), 46.0 (NC–CH–N), 40.2 (CH_2), 39.8 (CH_2), 38.6 (CH_2), 34.4 (CH_3), 29.2 (CH_2), 28.4 (CH_2), 15.8 (CH_2), −0.6 ($OSi(CH_3)_3$). IR ν_{max}: 2141, 1250, 1107, 840 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{34}NOS_2Si$ 408.1851 $[M-CN]^+$ found 408.1853. R_f=0.65 (cyclohexane/Et_2O 7:3).

*4.2.10. Pseudopelletierine analog **26**.* A mixture of compound **12** (200 mg, 1.43 mmol) and (*S*)-phenylethylamine (0.22 mL, 1.71 mmol) in CH_2Cl_2 (5 mL) was stirred for 6 days at room temperature, after which the reaction mixture was concentrated under reduced pressure. The oily residue was then purified by flash chromatography on silica gel with a gradient solvent system: hexane/EtOAc (95:5) to CH_2Cl_2/MeOH (98:2 to 97:3) to afford compound **26** (51 mg, 15%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.35–7.19 (m, 5H, Ph), 3.93 (q, $^3J_{H,H}$=6.4 Hz, 1H, *CH*–Ph), 3.52 (br m, 1H, N–*CH*), 3.28 (br m, 1H, N–*CH*), 2.64 (dd, $^2J_{H,H}$=16.4 Hz, $^4J_{H,H}$=6.8 Hz, 1H, *CH*$_2$–CO), 2.55 (dd, $^2J_{H,H}$=16.4 Hz, $^4J_{H,H}$=6.8 Hz, 1H, *CH*$_2$–CO), 2.16 (d, $^2J_{H,H}$=16.4 Hz, 1H, *CH*$_2$–CO), 2.10 (d, $^2J_{H,H}$=16.4 Hz, 1H, *CH*$_2$–CO), 1.91 (m, 1H, CH_2), 1.72 (m, 1H, CH_2), 1.46–1.51 (m, 2H, CH_2), 1.39 (m, 1H, CH_2), 1.35 (m, 1H, CH_2), 1.29 (d, $^3J_{H,H}$=6.4 Hz, 1H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ=212.1 (CO), 146.1 (C_{IV} Ph), 128.6 (2 CH Ph), 127.1 (2 CH Ph), 126.9 (CH Ph), 58.3 (*CH*–Ph), 51.1 (N–*CH*), 50.3 (N–*CH*), 42.7 (CH_2), 42.5 (CH_2), 29.6 (2 CH_2), 22.6 (CH_3), 16.7 (CH_2). IR ν_{max}: 1716 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{22}NO$ 244.1696 $[M+H]^+$ found 244.1697. R_f=0.63 (cyclohexane/EtOAc 1:1).

*4.2.11. Double Michael acceptor **29**.* A mixture of glutaraldehyde (0.9 mL of a 50% aqueous solution, 5 mmol) and 1-(triphenylphosphoranylidene)-2-propanone (3.18 g, 10 mmol) in toluene (10 mL) was stirred at reflux for 3 h. The reaction mixture was cooled with an ice bath, filtered to remove triphenylphosphine oxide and the filtrate was concentrated. The oily residue was then purified by flash chromatography on silica gel with cyclohexane/EtOAc (6:4) as eluent to afford compound **29** (521 mg, 58%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.77 (dt, $^3J_{H,H}$=16.0, 7.0 Hz, 2H, 2 CH_2–*CH*=), 6.09 (d, $^3J_{H,H}$=16.0 Hz, 2H, 2 CO–*CH*=), 2.27 (q, $^3J_{H,H}$=7.0 Hz, 4H, 2 CH_2), 2.24 (s, 6H, 2 CH_3), 1.67 (qu, $^3J_{H,H}$=7.0 Hz, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ=198.4 (2 CO), 146.9 (2 CH), 131.7 (2 CH), 31.7 (2 CH_2), 27.0 (2 CH_3), 26.4 (CH_2). IR ν_{max}: 1672, 1626 cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{16}NaO_2$ 203.1044 $[M+Na]^+$ found 203.1042. R_f=0.34 (cyclohexane/ethyl acetate 1:1).

*4.2.12. α,α′-disubstituted piperidine **34**.* A mixture of compound **29** (100 mg, 0.556 mmol) and benzylamine (0.091 mL, 0.833 mmol) in CH_2Cl_2 (2 mL) was stirred for 21 h at room temperature. The reaction mixture was concentrated under reduced pressure and the oily residue was then purified by flash chromatography on silica gel

with a gradient solvent system: CH_2Cl_2/MeOH (100:0 to 98:2). A mixture of inseparable diastereoisomers **34** (77 mg, 48%) was obtained in an 85:15 ratio in favor of the *trans* isomer **34a** (determined by integration of signals in the ^1H NMR spectrum) as a viscous orange oil: ^1H NMR (400 MHz, $CDCl_3$): δ=7.20–7.32 (m, 5H, Ph), 3.70 (d, $^2J_{H,H}$=14.4 Hz, 1H, CH_2), 3.59 (d, $^2J_{H,H}$=14.4 Hz, 1H, CH_2), 3.37–3.42 (m, 1H, N–*CH*), 3.27–3.34 (m, 1H, N–*CH*), 2.73 (dd, $^2J_{H,H}$=15.4 Hz, $^3J_{H,H}$=6.8 Hz, 1H, CH_2), 2.59 (dd, $^2J_{H,H}$=16.4 Hz, $^3J_{H,H}$=4.8 Hz, 1H, CH_2), 2.46 (dd, $^2J_{H,H}$=15.4 Hz, $^3J_{H,H}$=7.2 Hz, 1H, CH_2), 2.27 (dd, $^2J_{H,H}$=16.4 Hz, $^3J_{H,H}$=8 Hz, 1H, CH_2), 1.98 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 1.67 (br m, 4H, 3 CH_2), 1.31–1.36 (m, 2H, 2 CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ=207.9 (2 CO), 140.2 (C_{IV} Ph), 128.5 (2 CH Ph), 128.3 (2 CH Ph), 128.2 (CH Ph), 57.9 (CH), 51.6 (CH), 51.3 (CH_2), 48.8 (CH_2), 46.6 (CH_2), 29.9 (2 CH_3), 25.4 (2 CH_2), 20.0 (CH_2). IR ν_{max}: 1707 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{26}NO_2$ 288.1958 $[M+H]^+$ found 288.1954. R_f=0.20 (cyclohexane/EtOAc 1:1).

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Supplementary data

NMR spectra (^1H, ^{13}C) of compounds **10**, **12**, **15**–**21**, **26**, **29** and **34**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.05.051.

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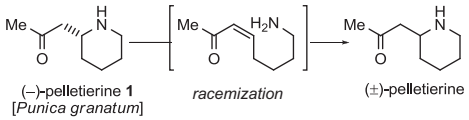

(–)-pelletierine **1** [*Punica granatum*] — *racemization* — (±)-pelletierine

11. For selected recent applications (2010, 2011, and early 2012) of (–)-phenylglycinol in nitrogen-containing heterocyclic chemistry, see: (a) Amat, M.; Subrizi, F.; Elias, V.; Llor, N.; Molins, E.; Bosch, J. *Eur. J. Org. Chem.* **2012**, 1835–1842; (b) Amat, M.; Arróniz, C.; Molins, E.; Escolano, C.; Bosch, J. *Org. Biomol. Chem.* **2011**, *9*, 2175–2184; (c) Arena, G.; Zill, N.; Salvadori, J.; Girard, N.; Mann, A.; Taddei, M. *Org. Lett.* **2011**, *13*, 2294–2297; (d) Amat, M.; Pérez, M.; Proto, S.; Gatti, T.; Bosch, J. *Chem.—Eur. J.* **2010**, *16*, 9438–9441; (e) Amat, M.; Elias, V.; Llor, N.; Subrizi, F.; Molins, E.; Bosch, J. *Eur. J. Org. Chem.* **2010**, 4017–4026; (f) Jida, M.; Deprez-Poulain, R.; Malaquin, S.; Roussel, P.; Agbossou-Niedercorn, F.; Deprez, B.; Laconde, G. *Green. Chem.* **2010**, *12*, 961–964; (g) Salvadori, J.; Airiau, E.; Girard, N.; Mann, A.; Taddei, M. *Tetrahedron* **2010**, *66*, 3749–3753.
12. For the particular use of (–)-phenylglycinol involved in: (a) *N*-Cyanomethyloxazolidine systems, see Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383–394; (b) Oxazolopiperidone lactams: Amat, M.; Pérez, M.; Bosch, J. *Synlett* **2011**, 143–160; (c) Amat, M.; Pérez, M.; Bosch, J. *Chem.—Eur. J.* **2011**, *17*, 7724–7732; (e) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198–8207.
13. In order to favour thermodynamically stable *cis*-oxazolidine, the use of Lewis acids is common especially with related cyano-phenyloxazolopiperidine (see structure **A** below), see: (a) Guz, N. R.; Pfeiffer, M.; Dickman, D. *Org. Process Res. Dev.* **2010**, *14*, 1476–1478 and references cited therein). In our case, treatment of **10** with a catalytic amount (10 mol %) of zinc bromide in dichloromethane did not permit the conversion of *trans*-**10** into *cis*-**10**, therefore rising questions concerning the occurrence of such a phenomenon with **10**. As the oxazolidine is the masked form of the corresponding iminium or enamine, this phenomenon of epimerization has usually no consequences on reactivity. The diastereocontrol of the oxazolidine ring formation of phenyloxazolopiperidine (see structure **B** below) is admirally studied in a recent paper; see: (b) Zill, N.; Schoenfelder, A.; Girard, N.; Taddei, M.; Mann, A. *J. Org. Chem.* **2012**, *77*, 2246–2253; For the first synthesis of building block A, see: (c) Guerrier, L.; Royer, J.; Grierson, D.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754–7755 .

14. Enamine reactivity of (–)-phenyloxazolopiperidine, see: (a) Poupon, E.; François, D.; Kunesch, N.; Husson, H.-P. *J. Org. Chem.* **2004**, *69*, 3836–3841; (b) François, D.; Poupon, E.; Lallemand, M.-C.; Kunesch, N.; Husson, H.-P. *J. Org. Chem.* **2000**, *65*, 3209–3212.
15. Such an epimerization of the oxazolidine probably occurs through ring opening/ring closure and has already been observed in similar series (see Ref. 13a and Ref. 13c for examples).
16. A partial epimerization at C-6 is observed and might be explained by a similar mechanism as the one depicted in Ref. 10.
17. For mercuric acetate oxidation of tertiary amines, see: (a) Leonard, N. J.; Morrow, D. F. *J. Am. Chem. Soc.* **1958**, *80*, 371–375; (b) Leonard, N. J.; Musker, W. K. *J. Am. Chem. Soc.* **1960**, *82*, 5148–5155 and for tertiary amine conversion into lactams, see: (c) Möhrle, H. *Arch. Pharmacol.* **1964**, *297*, 474–487.

18. For conversions of oxazolopiperidines into lactams: (a) With potassium permanganate François, D.; Poupon, E.; Kunesch, N.; Husson, H.-P. *Eur. J. Org. Chem.* **2004**, 4823–4829; (b) With bromine under alkaline conditions Liénard, P.; Varea, T.; Quirion, J.-C.; Husson, H.-P. *Synlett* **1994**, 143–144.
19. Ibuka, T.; Kitano, M. *Chem. Pharm. Bull.* **1967**, *15*, 1809–1810.
20. We also believe that this phenomenon mostly occurs during purification by chromatography in contact with silica gel. Expected dimeric compound **24** may in fact be present in crude mixture (m/z 509 $[M+Na]^+$).
21. Selected examples of retro-Mannich reactions: (a) Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 4831–4832; (b) Ragains, J. R.; Winkler, J. D. *Org. Lett.* **2006**, *8*, 4437–4440; (c) Winkler, J. D.; Fitzgerald, M. E. *Synlett* **2009**, 562–564; (d) Cramer, N.; Juretschke, J.; Laschat, S.; Baro, A.; Frey, W. *Eur. J. Org. Chem.* **2004**, 1397–1400.
22. The stereochemical outcome is consistent with literature. See for example, in the Lobeline series: (a) Compère, D.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 4528–4532 and also: (b) Felpin, F.-X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192–9199.