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Stereocontrolled synthesis of enantiopure *cis*- and *trans*-3,4,4a,5,8,8a-hexahydro-1*H*-quinolin-2-ones

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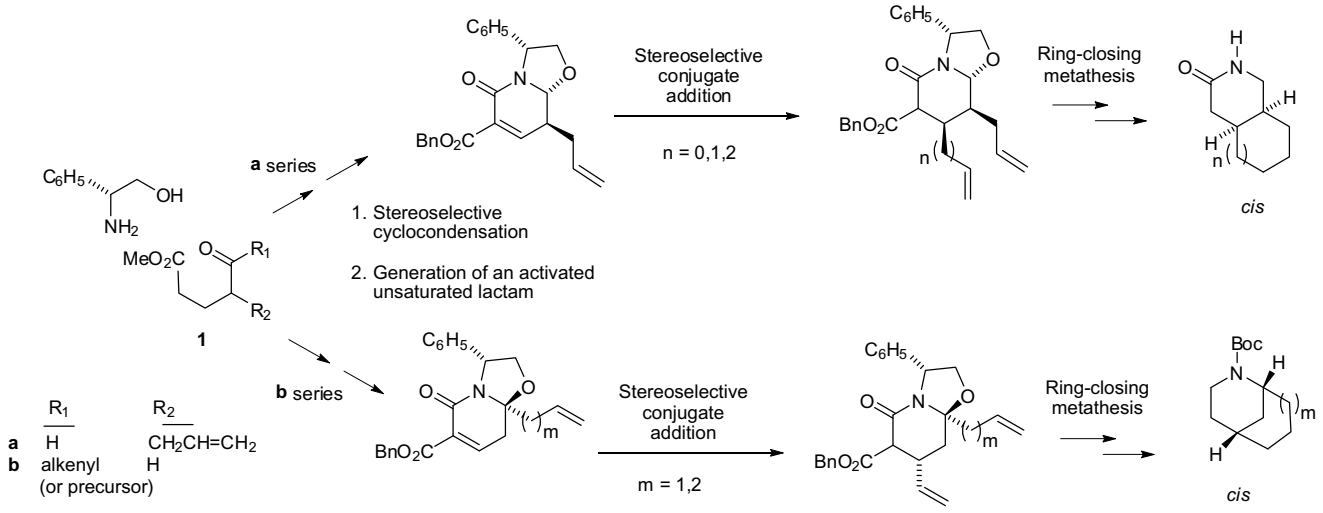
ABSTRACT

Starting from the 8-allyl substituted oxazolopiperidone lactam **2b**, which is easily accessible from (*R*)-phenylglycinol and racemic δ-oxoester **1a**, two-step sequences involving a stereoselective α-amidoalkylation reaction, either with inversion or retention of configuration, followed by a ring-closing metathesis, provide diastereodivergent routes to enantiopure *cis*- and *trans*-3,4,4a,5,8,8a-hexahydro-1*H*-quinolin-2-ones.

1. Introduction

Previous work has illustrated that phenylglycinol-derived oxazolopiperidone lactams are extremely useful building blocks that allow the preparation of a wide range of enantiopure piperidine derivatives bearing virtually any type of substitution pattern, including indolizidines, quinolizidines, decahydroquinolines, perhydroisoquinolines, and complex piperidine-containing indole alkaloids.[1–3]

In this context, starting from easily accessible unsaturated lactams bearing an appropriate alkenyl substituent, a stereoselective conjugate addition–ring-closing metathesis sequence has provided efficient and versatile routes to enantiopure piperidines *cis*-3,4-fused and *cis*-2,4-bridged to five-, six-, and seven-membered carbocyclic rings[4] (Scheme 1). A crucial aspect of the above approaches is the control of the *cis* relative stereochemistry of the substituents at the 3- (or 2-) and 4-positions of the piperidine ring, which is ensured by a stereoselective conjugate addition reaction.



Scheme 1. Enantioselective synthesis of *cis*-3,4-fused and *cis*-2,4-bridged piperidines.

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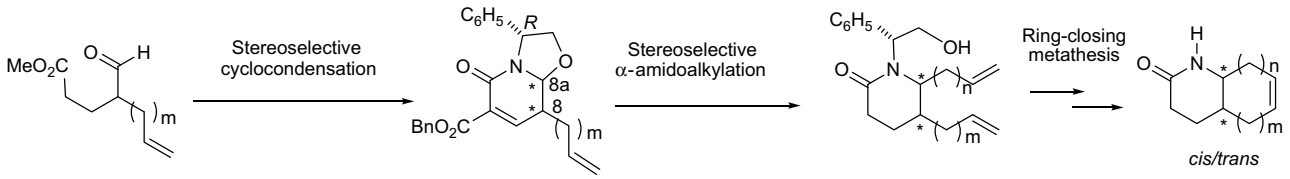


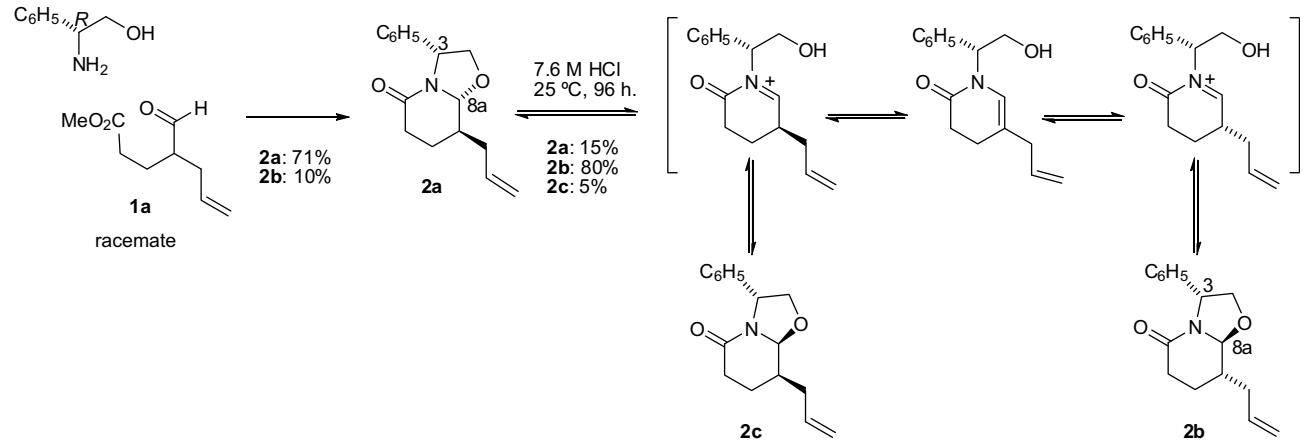
Scheme 2. Synthetic strategy for the enantioselective synthesis of *cis*- and *trans*-2,3-fused piperidines.

2. Results and discussion

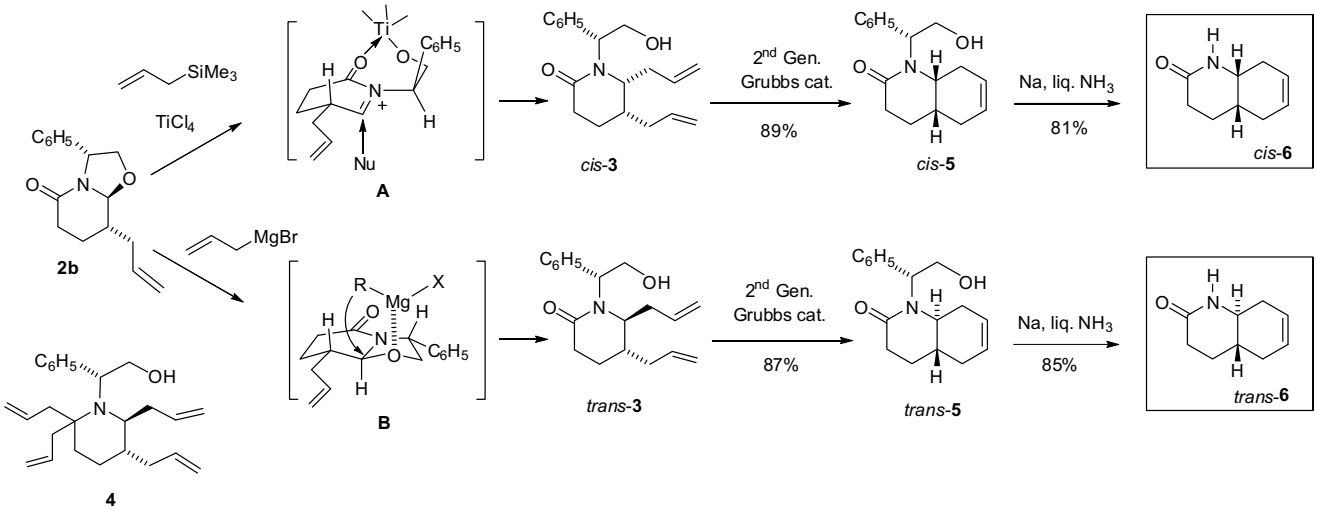
A similar ring-closing metathesis process from a piperidine bearing alkenyl substituents at the 2- and 3-positions would provide enantiopure piperidines 2,3-fused to a carbocyclic ring. Taking into account that phenylglycinol-derived oxazolopiperidone lactams allow the stereocontrolled introduction of substituents at the α-position of the piperidine ring (C-8a) by asymmetric α-amidoalkylation, either with retention or inversion of configuration of this stereocenter,[5] this approach could open access to fused bicyclic systems in both the *cis* and *trans* series starting from an appropriate 8-alkenyl lactam (Scheme 2).

Herein, we report the application of the above stereoselective α-amidoalkylation–ring-closing metathesis sequence to the diastereodivergent synthesis of *cis*- and *trans*-hexahydroquinoline derivatives (Scheme 2; $m = n = 1$).

The known[4a] 8-allyl lactam **2a** might seem *a priori* as the suitable starting material for our purpose. This lactam can be prepared in 71% yield by cyclocondensation of the γ-allyl-δ-oxoester **1a** with (*R*)-phenylglycinol, in a process that involves a dynamic kinetic resolution of the racemic substrate.[6] However, taking into account that earlier studies from related phenylglycinol-derived lactams indicate that the success of α-amidoalkylation reactions depends upon the H_3–H_{8a} relative stereochemistry, with the *trans* H_3–H_{8a} isomers being more efficient than the *cis* isomers in terms of chemical yield and stereoselectivity,[5c,d] we decided to use the isomeric H_3–H_{8a} *trans* lactam **2b**, which was prepared in 73% yield by equilibration of **2a** under acidic conditions. Minor amounts (4%) of lactam **2c**



Scheme 3. Equilibration of lactam **2a**.



Scheme 4. Diastereodivergent synthesis of enantiopure *cis*- and *trans*-hexahydroquinolones **6**.

were also formed. This isomerization to the most stable *trans* H_3–H_{8a} lactam **2b** can be rationalized as depicted in Scheme 3.[7]

The introduction of an allyl substituent at the piperidine α-position was accomplished in good yield (78%) using allyltrimethylsilane in the presence of $TiCl_4$. Under these conditions, α-amidoalkylation occurred with inversion of the configuration at the C-8a position to give the *cis*-2,3-derivative *cis*-**3** as the major product (*cis*-**3**/*trans*-**3** ratio, 4:1; Scheme 4).

The stereoselectivity of the α-amidoalkylation was reversed using allylmagnesium bromide as the nucleophile (*cis*-**3**/*trans*-**3** ratio, 1:4), although in this case the chemical yield was low (30%) due to the formation of the polyallylated piperidine **4** as the major product (34%), even at −78 °C. The different stereoselectivity of the above α-amidoalkylation reactions can be explained by considering either an attack of the nucleophile upon the less hindered face of an acyl iminium cation[8] **A** (inversion of configuration), or the intramolecular delivery of the nucleophile from the Grignard reagent, as depicted in **B** (retention of configuration).

The ring-closing metathesis of diallylpiperidones *cis*-**3** and *trans*-**3** catalyzed by a second generation Grubbs catalyst[9] resulted in the closure of the carbocyclic ring to give the respective hydroquinolones *cis*-**5** and *trans*-**5** in excellent yields.[10]

Finally, removal of the phenylethanol moiety from lactams **5** was accomplished with sodium in liquid ammonia to lead to the target enantiopure hexahydroquinolones *cis*-**6** and *trans*-**6**, also in good yields.

3. Conclusion

Through a two-step sequence involving a stereoselective α-amidoalkylation reaction and a ring-closing metathesis, phenylglycinol-derived oxazolopiperidone lactams open up short diastereodivergent routes to enantiopure *cis*- and *trans*-hydroquinolone derivatives. By an appropriate selection of the alkenyl substituents at the piperidine 2- and 3-positions, the above methodology could provide general access to enantiopure piperidines *cis*- and *trans*-2,3-fused to carbocyclic rings of different sizes. Taking into account that both enantiomers of phenylglycinol are commercially available, access to 2,3-fused piperidines in both enantiomeric series is assured.

4. Experimental

4.1. General procedures

All non-aqueous reactions were performed under an argon or nitrogen atmosphere with dry, freshly distilled solvents using standard procedures. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a rotatory evaporator. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located by UV and by either a 1% $KMnO_4$ solution or iodine. Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, 230–400 mesh). Melting points were determined in a capillary tube and are uncorrected. NMR spectra were recorded at 300 or 400 MHz (^{1}H) and 75.4 or 100.6 MHz (^{13}C), and chemical shifts are reported in δ values downfield from TMS or relative to residual chloroform (7.26, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, coupling constant (*J*) in hertz (Hz), integrated intensity, and assignment (when possible). Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; ap, apparent. Only noteworthy IR absorptions (cm^{-1}) are listed. Mass spectra (MS) data are reported as *m*/*z* (%).

4.2. Epimerization of 2a

4.2.1. (3*R*,8*S*,8a*S*)-8-Allyl-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine 2b

A solution of pure lactam **2a**[4a] (500 mg, 1.95 mmol) in MeOH–HCl (7.6 M, 12.5 mL) was stirred at 25 °C for 96 h. The resulting acidic solution was neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (1:1 EtOAc/hexane) to give pure **2b** (365 mg, 73%), **2a** (70 mg, 14%), and **2c** (20 mg, 4%). Compound **2b**: IR (NaCl) 1658 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.53 (m, 1H, H-7), 1.66 (m, 1H, H-8), 1.96 (m, 1H, H-7), 2.07 (dt, *J* = 16.5, 8.4, 8.4 Hz, 1H, CH_2 allyl), 2.35 (ddd, *J* = 18.6, 12.0, 6.6 Hz, 1H, H-6), 2.56 (m, 2H, H-6, CH_2 allyl), 3.76 (dd, *J* = 9.0, 7.8 Hz, 1H, H-2), 4.48 (dd, *J* = 9.0, 8.1 Hz, 1H, H-2), 4.71 (d, *J* = 8.4 Hz, 1H, H-8a), 5.13 (m, 2H, CH_2=), 5.25 (t, *J* = 7.8 Hz, 1H, H-3), 5.83 (dddd, *J* = 16.5, 10.2, 8.1, 6.0 Hz, 1H, CH=), 7.25–7.34 (m, 5H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 22.8 (C-7), 31.4 (CH_2 allyl), 35.9 (C-6), 39.6 (C-8), 58.3 (C-3), 72.4 (C-2), 92.0 (C-8a), 117.4 (CH_2=), 126.0, 128.6 (C-*o*, *m*), 127.5 (C-*p*), 134.6 (CH=), 139.4 (C-*i*), 168.6 (NCO); $[\alpha]_D^{22} = -59.9$ (*c* 1.06, EtOH). Anal. Calcd for $C_{16}H_{19}NO_2 \cdot 1/4H_2O$: C, 73.40; H, 7.51; N, 5.35. Found: C, 73.27; H, 7.25; N, 5.51. Compound **2c**: IR (NaCl) 1657 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, COSY, HETCOR) δ 1.72–1.96 (m, 3H, 2H-7, H-6), 2.32–2.48 (m, 4H, $2CH_2$ allyl, H-8, H-6), 3.79 (dd, *J* = 12.0, 10.0 Hz, 1H, H-2), 4.42 (dd, *J* = 12.0, 10.8 Hz, 1H, H-2), 5.05–5.09 (m, 2H, CH_2=), 5.13 (d, *J* = 5.2 Hz, 1H, H-8a), 5.26 (t, *J* = 10.4 Hz, 1H, H-3), 5.26 (m 1H, CH=), 7.20–7.38 (m, 5H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.2 (C-7), 27.5 (CH_2 allyl), 28.6 (C-6), 34.7 (C-8), 58.1 (C-3), 72.1 (C-2), 89.6 (C-8a), 116.9 (CH_2=), 126.0, 128.6 (C-*o*, *m*), 127.5 (C-*p*), 135.5 (CH=), 139.5 (C-*i*), 168.6 (NCO); $[\alpha]_D^{22} = -118.9$ (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.60; H, 7.52; N, 5.40.

4.3. α-Amidoalkylation reactions

4.3.1. (5*S*,6*R*)-5,6-Diallyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone *cis*-3

Allyltrimethylsilane (2.5 mL, 16.3 mmol) and $TiCl_4$ (0.6 mL, 5.4 mmol) were added to a solution of **2b** (700 mg, 2.7 mmol) in CH_2Cl_2 (22 mL). The resulting mixture was heated at reflux for 18 h. The reaction was quenched by the addition of saturated aqueous Na_2CO_3, and the mixture extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated, and the resulting residue was chromatographed (1:3 EtOAc/hexane to EtOAc) to give a mixture of compounds *cis*-**3**/*trans*-**3** (635 mg, 78% yield, ratio 4:1). *cis*-**3** (data from the above mixture): IR (NaCl) 1620, 3376 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, HETCOR) δ 1.65 (tt, *J* = 13.0, 8.5 Hz, 1H, H-4), 1.80–1.96 (m, 2H, H-4, H-5), 2.03 (m, 2H, CH_2 allyl), 2.17 (q, *J* = 7.6 Hz, 1H, CH_2 allyl), 2.36 (m, 1H, CH_2 allyl), 2.56–2.62 (m, 2H, H-3), 3.27 (dd, *J* = 9.2, 5.2 Hz, 1H, H-6), 4.04 (dd, *J* = 12.0, 3.3 Hz, 1H, H-2′), 4.17 (dd, *J* = 12.0, 7.2 Hz, 1H, H-2′), 4.66 (dd, *J* = 7.2, 3.3 Hz, 1H, H-1′), 4.95–5.09 (m, 4H, CH_2=), 5.60 (td, *J* = 17.1, 6,8 Hz, 1H, CH=), 5.73 (dddd, *J* = 16.8, 10.0, 6.8, 6.8 Hz, 1H, CH=), 7.21–7.40 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.0 (C-4), 31.0 (C-3), 34.3 (CH_2 allyl), 36.9 (CH_2 allyl), 38.9 (C-5), 60.9 (C-6), 64.2 (C-2′), 68.0 (C-1′), 116.9, 117.8 (CH_2=), 126.4–128.6 (C-*o*, *m*, *p*), 135.2, 135.5 (CH=), 137.3 (C-*i*), 172.2 (NCO); HMRS calcd for [$C_{19}H_{25}NO_2$ + H]: 300.1958, found: 300.1955.

4.3.2. (5*S*,6*S*)-5,6-Diallyl-1-[(1*R*)-2-hydroxy-1-phenylethyl]-2-piperidone *trans*-3

Allylmagnesium bromide (1 M in Et_2O, 23.3 mL) was added to a cooled (0 °C) solution of **2b** (1.1 g, 4.2 mmol) in THF (10 mL), and

the mixture was stirred at this temperature for 18 h. The reaction was quenched by the addition of saturated aqueous NaCl, and the mixture extracted with EtOAc. The organic extracts were dried and concentrated. Purification by column chromatography (1:3 EtOAc/hexane to EtOAc) gave compound **4** (516 mg, 34% yield) and a mixture of compounds *cis*-**3**/*trans*-**3** (378 mg, 30% yield, ratio 1:4). *trans*-**3** (data from the above mixture): ^{1}H NMR (400 MHz, $CDCl_3$, HETCOR) δ 1.53 (ddd, J = 14.0, 9.6, 5.2 Hz, 1H, H-4), 1.78 (m, 1H, CH_2 allyl), 1.85 (m, 1H, H-5), 1.90 (m, 1H, CH_2 allyl), 1.98 (ddd, J = 14.0, 8.8, 4.8 Hz, 1H, H-4), 2.27 (ddd, J = 14.4, 10.4, 8.4 Hz, 1H, CH_2 allyl), 2.44 (m, 3H, CH_2 allyl, 2H-3), 3.09 (d, J = 10.4 Hz, 1H, H-6), 4.14 (dd, J = 11.6, 4.8 Hz, 1H, H-2′), 4.26 (dd, J = 11.6, 8.4 Hz, 1H, H-2′), 5.00 (m, 4H, CH_2=), 4.28 (dd, J = 8.4, 4.8 Hz, 1H, H-1′), 5.50 (dddd, J = 16.8, 13.6, 6.8, 6.8 Hz, 1H, CH=), 5.57 (m, 1H, CH=), 7.20–7.35 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.2 (C-4), 28.4 (C-3), 33.4 (CH_2 allyl), 36.0 (CH_2 allyl), 39.3 (C-5), 59.6 (C-6), 63.6 (C-1′), 63.9 (C-2′), 116.9, 118.0 (CH_2=), 127.6–128.5 (C-*o*, *m*, *p*), 133.8, 135.7 (CH=), 136.9 (C-*i*), 172.5 (NCO). Compound **4**: IR (NaCl) 3397 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, HETCOR) δ 0.94 (td, J = 12.0, 12.0, 3.2 Hz, 1H, H-3), 1.14 (m, 1H, H-4), 1.20 (br, 1H, H-3), 1.25 (m, 1H, H-4), 1.33 (m, 1H, H-5), 1.93-2.25 (3m, 8H, CH_2 allyl), 2.58 (m, 1H, H-6), 3.50 (dd, J = 10.8, 8.8 Hz, 1H, H-2′), 3.63 (dd, J = 10.8, 4.6 Hz, 1H, H-2′), 3.78 (dd, J = 8.8, 4.8 Hz, 1H, H-1′), 4.94–5.11 (m, 8H, CH_2=), 5.58–5.82 (m, 4H, CH=), 5.57 (m, 1H, CH=), 7.10–7.20 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.8 (C-4), 34.5 (CH_2 allyl), 35.1 (CH_2 allyl), 37.0 (C-3), 41.0 (C-5), 43.4 (CH_2 allyl), 43.6 (CH_2 allyl), 56.7 (C-6), 62.6 (C-1′), 66.7 (C-2′), 73.3 (C-2), 115.8, 117.0, 118.4, 118.5 (CH_2=), 127.5–128.5 (C-*o*, *m*, *p*), 133.7, 136.2, 137.7 (CH=), 141.5 (C-*i*); $[\alpha]_D^{22} = +33.7$ (c 1.5, $CHCl_3$); HMRS calcd for [$C_{25}H_{35}NO$ + H]: 366.2791, found: 366.2777.

4.4. Ring-closing metathesis reactions

4.4.1. (4a*S*,8a*R*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-3,4,4a,5,8,8a-hexahydro-1*H*-quinolin-2-one *cis*-5

Second-generation Grubbs catalyst (71 mg) was added to a solution of lactams *cis*-**3**/*trans*-**3** (ratio 4:1, 343 mg, 1.1 mmol) in CH_2Cl_2 (163 mL). The mixture was stirred at rt for 3 h and concentrated. The resulting residue was purified by flash column chromatography (1:4 EtOAc/hexane to EtOAc and then 95:5 EtOAc/MeOH) to yield bicyclic lactams *cis*-**5** (220 mg) and *trans*-**5** (48 mg) (89% overall yield). *cis*-**5**: IR (NaCl) 1616, 3358 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, HETCOR) δ 1.61 (ddd, J = 9.2, 7.2, 3.2 Hz, 1H, H-4), 1.86–2.08 (m, 4H, H-4, H-8, 2H-5), 2.16 (ddd, J = 12.8, 9.2, 3.6 Hz, 1H, H-4a), 2.39 (dm, J = 18.0 Hz, 1H, H-8), 2.61 (m, 2H, H-3), 3.39 (q, J = 4.8 Hz, 1H, H-8a), 3.98 (m, 1H, OH), 4.07 (dd, J = 11.6, 2.8 Hz, 1H, H-2′), 4.25 (m,1H, H-2′), 4.93 (dd, J = 7.6, 3.6 Hz, 1H, H-1′), 5.45 (m, 1H, CH=), 5.53 (m, 1H, CH=), 7.28–7.38 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.9 (C-4), 28.7 (C-5), 30.9 (C-3), 31.4 (C-8), 32.2 (C-4a), 55.3 (C-8a), 63.9 (C-2′), 64.9 (C-1′), 123.0 (CH=), 124.6 (CH=), 127.7–128.6 (C-*o*, *m*, *p*), 137.4 (C-*i*), 171.6 (COO); $[\alpha]_D^{22} = -39.6$ (c 1.2, $CHCl_3$); HMRS calcd for [$C_{17}H_{21}NO_2$ + H]: 272.1645, found: 272.1638.

4.4.2. (4a*S*,8a*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]-3,4,4a,5,8,8a-hexahydro-1*H*-quinolin-2-one *trans*-5

Operating as above, from the mixture *cis*-**3**/*trans*-**3** (ratio 1:4, 53 mg, 0.17 mmol) and second generation Grubbs catalyst (11 mg) in CH_2Cl_2 (25 mL), bicyclic lactams *cis*-**5** (6 mg) and *trans*-**5** (34 mg) (87% overall yield) were obtained after column chromatography (3:7 EtOAc/hexane). *trans*-**5**: IR (NaCl) 1621, 3380 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.57 (td, J = 12.3, 12.3, 4.8 Hz, 1H, H-4), 1.76–1.91 (m, 4H, H-4, H-8, H-5, H-4a), 2.21 (dm, J = 16.4 Hz, 1H, H-5), 2.31 (dm, J = 16.0 Hz, 1H, H-8), 2.53 (ddd, J = 18.0, 12.6, 5.4 Hz, 1H, H-3), 2.64 (ddd, J = 18.0, 5.1, 1.8 Hz, 1H, H-3), 3.23 (td, J = 10.2, 10.2, 4.5 Hz, 1H, H-8a), 4.11 (dd, J = 11.8, 3.0 Hz, 1H, H-2′), 4.29 (m, 1H, H-2′), 4.90 (br, 1H, H-1′), 5.45 (m, 1H, CH=), 5.60 (m, 1H, CH=), 7.23–7.35 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 26.3 (C-4), 32.4 (C-5), 33.9 (C-8), 33.5 (C-3), 37.4 (C-4a), 61.7 (C-8a), 64.0 (C-2′), 64.7 (C-1′), 124.4 (CH=), 126.0 (CH=), 125.9–128.2 (C-*o*, *m*, *p*), 137.9 (C-*i*), 172.8 (COO); $[\alpha]_D^{22} = +256.0$ (c 0.8, $CHCl_3$); HMRS calcd for [$C_{17}H_{21}NO_2$ + H]: 272.1645, found: 272.1635.

4.5. Removal of the chiral inductor

4.5.1. (4a*S*,8a*R*)-3,4,4a,5,8,8a-Hexahydro-1*H*-quinolin-2-one *cis*-6

Into a three-necked, 100 mL round-bottomed flask equipped with a coldfinger condenser charged with dry ice–acetone was condensed 10 mL of NH_3 at −78 °C, and a solution of *cis*-**5** (50 mg, 0.15 mmol) in THF (4 mL) was added. The temperature was raised to −33 °C, and then sodium metal was added in small portions until the blue color persisted. The mixture was stirred at −33 °C for 1 min. The reaction was quenched by addition of solid NH_4Cl until the blue color disappeared, and then the mixture was stirred at rt for 4 h. The resulting residue was digested at rt with CH_2Cl_2, and the suspension was filtered through Celite® and concentrated. Flash chromatography (EtOAc to 95:5 EtOAc/MeOH) afforded *cis*-**6** (22 mg, 81% yield): IR (NaCl) 1663, 3205 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.69–1.76 (m, 1H, H-4), 1.85 (tt, J = 14.0, 8.0 Hz, 1H, H-4), 1.98–2.08 (m, 2H, H-8, H-5), 2.15 (ddd, J = 12.8, 9.2, 4.0 Hz, 1H, H-4a), 2.25 (dm, J = 17.6 Hz, 1H, H-5), 2.36–2.50 (m, 3H, 2H-3, H-8), 3.59 (m, 1H, H-8), 5.55, 5.64 (2m, 2H, 2CH=), 6.49 (br, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.7 (C-4), 27.4 (C-5), 29.2 (C-3), 30.0 (C-4a), 31.0 (C-8), 49.3 (C-8a), 122.2 (CH=), 125.4 (CH=), 172.5 (NCO); $[\alpha]_D^{22} = -33.9$ (c 0.9, $CHCl_3$); HMRS calcd for $C_9H_{13}NO$: 174.0889, found: 174.0884.

4.5.2. (4a*S*,8a*S*)-3,4,4a,5,8,8a-Hexahydro-1*H*-quinolin-2-one *trans*-6

Operating as described above in the preparation of *cis*-**6**, from *trans*-**5** (120 mg, 0.4 mmol) in THF (5 mL), sodium, and liquid NH_3 (15 mL), at −33 °C for 60 s, compound *trans*-**6** was obtained (52 mg, 85%) after flash chromatography (EtOAc to 95:5 EtOAc/MeOH): IR (NaCl) 1680, 3189 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, COSY, HETCOR) δ 1.52 (ddd, J = 17.9, 12.1, 6.3 Hz, 1H, H-4), 1.59–1.69 (m, 1H, H-4a), 1.79–1.93 (m, 2H, H-4, H-5), 2.05 (m, 1H, H-8), 2.24 (m, 1H, H-5), 2.32 (m, 1H, H-8), 2.42 (dt, J = 18.0, 6.4, 6.4 Hz, 1H, H-3), 2.48 (ddd, J = 18.0, 6.3, 2.0 Hz, 1H, H-3), 3.25 (td, J = 10.5, 10.5, 5.3 Hz, 1H, H-8a), 5.61–5.71 (2m, 2H, 2CH=), 6.65 (br, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.5 (C-4), 31.1 (C-5), 31.5 (C-3), 33.2 (C-8), 35.3 (C-4a), 54.1 (C-8a), 123.9 (CH=), 126.7 (CH=), 172.3 (NCO); $[\alpha]_D^{22} = +186.5$ (c 1.7, $CHCl_3$); HMRS calcd for $C_9H_{13}NO$: 174.0889, found: 174.0882.

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