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A Formal Asymmetric Synthesis of (−)-Epibatidine Using a Highly Diastereoselective Hetero Diels–Alder Reaction[1]

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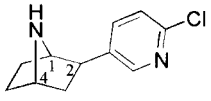
Abstract—A formal asymmetric synthesis of (−)-epibatidine is reported. The key step of the synthesis is a regio- and diastereoselective cycloaddition of silyloxycyclohexadiene with the acylnitroso dienophile derived from (+)-camphorsultam. The resulting cycloadduct was readily transformed into the *N*-protected-7-azabicyclo[2.2.1]heptan-2-one derivative which has previously been transformed into (−)-epibatidine.

Introduction

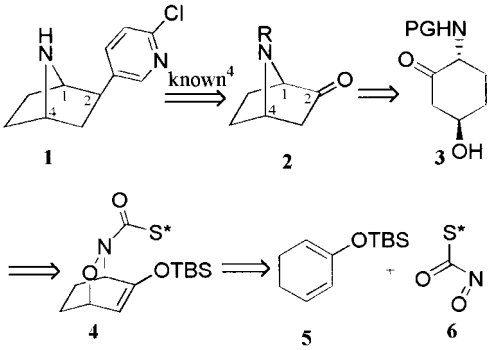
(−)-Epibatidine **1** was extracted in 1992 from the skin of the Ecuadorian frog *Epipedobates tricolor*.[2a,b] Because of its paucity in nature, its absolute stereochemistry was only established in 1994 as 1*R*,2*R*,4*S*[3](Fig. 1).

(−)-Epibatidine **1** is a powerful non-morphinic analgesic which acts as an agonist of the nicotinic acetylcholine receptor in the central and autonomic nervous system.[2] As a compound showing interesting pharmacological properties and being scarce in nature, (−)-epibatidine has attracted much interest from synthetic chemists.[4,5] Among the reported syntheses, however, only a few have furnished the natural non-racemic (−)-epibatidine **1** in an asymmetric way.[6] We were particularly interested by the asymmetric synthesis of (−)-epibatidine **1** reported by the group of Kibayashi in which the key step was a cycloaddition of 2-chloro-5-(1,5-cyclohexadienyl)-pyridine with an acylnitroso dienophile derived from (1*S*)-8-(2-naphtyl)-menthol.[6c,d] However the cycloaddition gave a 2:1 mixture of regioisomeric adducts. This report prompted us to disclose our own approach towards (−)-epibatidine **1**. It involves the development of an efficient synthesis of the enantiomerically pure bicyclic 7-azabicyclo[2.2.1]heptane-2-one **2** which had already been converted into **1** (Scheme 1).[4] Such an approach presents the advantage of being readily applicable to the synthesis of analogs of the natural product.



(-)-Epibatidine **1**

Figure 1.



Scheme 1.

Keywords: (−)-epibatidine; asymmetric synthesis; acylnitroso compounds; hetero Diels–Alder cycloaddition.
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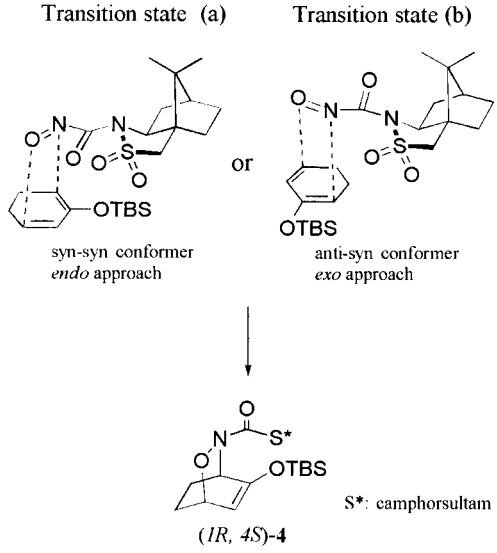


Scheme 2.

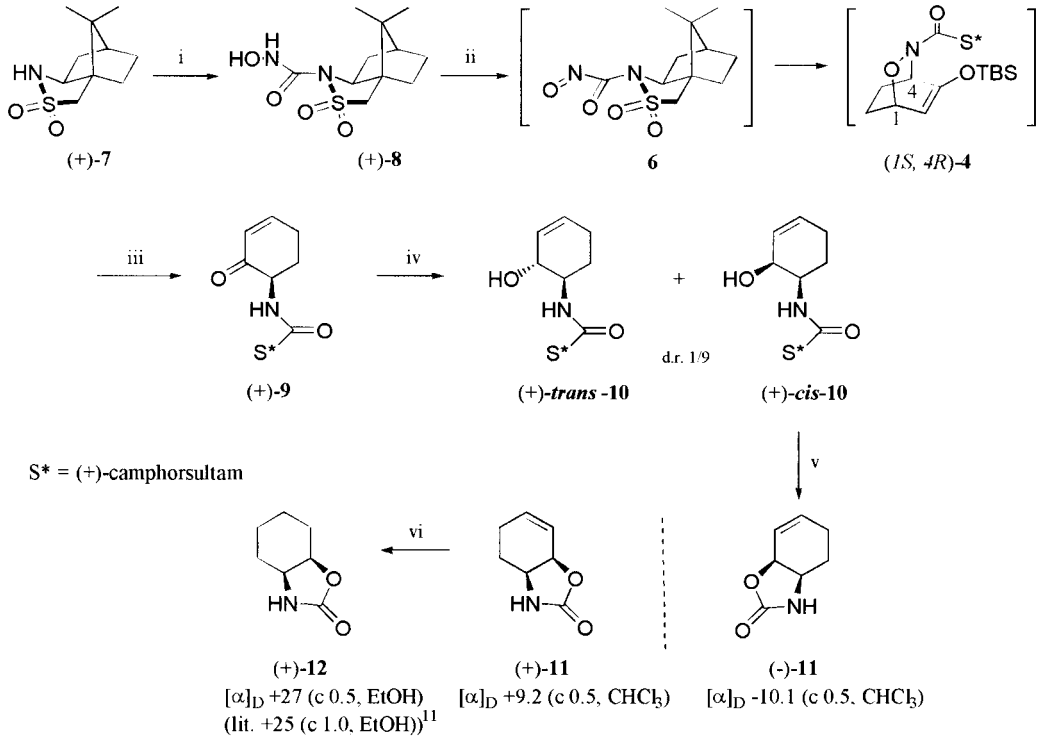
The key step of our synthetic route uses an asymmetric hetero Diels–Alder cycloaddition of silyloxycyclohexadiene **5** with an acylnitroso reagent **6** derived from camphorsultam. The latter had been reported to cycloadd to dienes with excellent regio- and diastereoselectivity.[7] We describe herein a practical asymmetric synthesis of the *N*-tosyl derivative of **2**.

Results and Discussion

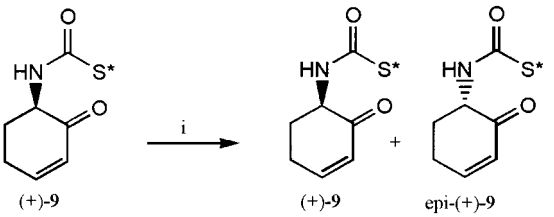
Earlier results on the cycloadditions of **6** to dienes had been rationalized on the basis of two possible transition states (Scheme 2) involving (a) an *endo*-approach of the diene from the less-hindered face of the dienophile in a *syn–syn* conformation or (b) an *exo*-approach of the diene from the less-hindered face of the dienophile in an *anti-syn* conformation.[7c] The model implied that the construction of the adduct (1*R*,4*S*)-**4** leading to natural (−)-epibatidine **1** required the use of an acylnitroso compound derived from (+)-camphorsultam.

(+)-Camphorsultam (+)-**7** was converted into the corresponding hydroxamic acid (+)-**8** by the method described earlier for the synthesis of (−)-**8** (Scheme 3).[7]

The corresponding acylnitroso compound **6** was generated by oxidation of (+)-**8** with tetraethylammonium periodate in the presence of excess 2-*t*-butyldimethylsilyloxycyclohexadiene **5**.[8] Flash chromatography yielded a single cycloadduct (1*S*,4*R*)-**4** as shown by ^{1}H NMR analysis. The regiochemistry of the cycloaddition was that expected from earlier cycloaddition of **6**.[7c] Compound **4** was somewhat unstable and could never be obtained in a satisfactory state of purity. We then converted the crude (1*S*,4*R*)-**4** into enone (+)-**9** by treatment with $Mo(CO)_6$.[9] Under these conditions the reductive cleavage of the N–O bond was accompanied by the hydrolysis of the silyl enol ether function and subsequent elimination of a molecule of water. Compound (+)-**9** was obtained in 63% total yield from hydroxamic acid (+)-**8** as a single diastereomer. The excellent stereo- and regioselectivities (>98%) of the cycloaddition were evidenced by extensive NMR studies of the crude mixture of adduct **4**. Only two sets of signals for the bridgehead protons H_1 and H_4 were observed. In the ^{1}H NMR spectrum the H_1 gave a signal at 4.9 ppm (ddd,



Scheme 3. Reagents: (i) triphosgene, i-Pr_2EtN, Et_2O then $NH_2OH{\cdot}HCl$, K_2CO_3, H_2O, 85%; (ii) $Et_4N^+IO_4^-$, CH_2Cl_2, diene **5**, −78°C to rt; (iii) $Mo(CO)_6$, CH_3CN, H_2O, Δ, 3.5 h, 63% (ii+iii); (iv) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 95%; (v) KOH, MeOH, rt, 95%; (vi) H_2, Rh/C, EtOAc, 3 h, rt, 95%.



Scheme 4. Reagents: (i) HCl 6N, rfx, 2 h.

J=1.6, 3.6 Hz (J–H_1/H_6) and J=5.7 Hz (J–H_1/H_2)) while H_4 gave a signal at 5.35 ppm (dd, J=2.7 Hz and J=6.6 Hz (J–H_4/H_5)). This was further confirmed by the conversion of crude **4** into aminocyclohexenone derivative (+)-**9**. None of the known epimer epi-(+)-**9** could be detected in the NMR spectrum. This epimer could be obtained by treatment of (+)-**9** with refluxing 6N HCl for 2 h, followed by recrystallization from hexane/dichloromethane (Scheme 4). The high facial and regio-selectivities are superior to those obtained in the work of Kibayashi,[6c] making our method highly competitive. Compound (+)-**9** was readily converted into oxazolidinone (−)-**11** (Scheme 3).

Reduction of the carbonyl functionality of cyclohexenone (+)-**9** following Luche's procedure,[10] gave a 9:1 mixture of diastereomers (95% yield). The major *cis*-diastereomer (+)-**10** was readily isolated by chromatography (86% yield). Treatment with base gave oxazolidinone (−)-**11**. Further experiments showed that the minor (+)-*trans*-**10** isomer did not cyclise under these conditions, making the chromatographic separation unnecessary. As anticipated (vide supra), oxazolidinone (−)-**11** was shown to have the (3a*S*,7a*R*) configuration by comparison of its optical rotation to its enantiomer (+)-**11**, which was reduced for chemical correlation purposes into the corresponding saturated known oxazolidinone (+)-**12**.[11]

Compound (−)-**11** was then converted into bicyclic ketone (−)-**17**, according to the sequence already described in the racemic series (Scheme 5).[12]

N-Tosylation of (−)-**11** gave (−)-**13** (97% yield), which upon treatment with aqueous bromine regioselectively yielded the corresponding bromohydrin (−)-**14** as two diastereomers (−)-**14a** and (−)-**14b** (**14a**/**14b**=80/20) easily separated by column chromatography. Reductive removal of bromine[13] from compound (−)-**14a** followed by hydrolysis of the oxazolidinone ring gave diol (+)-**15** in 80% yield. Cyclization under Mitsunobu's conditions,[14] yielded the bicyclic alcohol (−)-**16** (90%). Swern oxidation of (−)-**16** gave the target ketone (−)-(1*R*,4*S*)-**17** (88% yield), the racemate of which had earlier been converted into (±)-epibatidine **1**.[15]

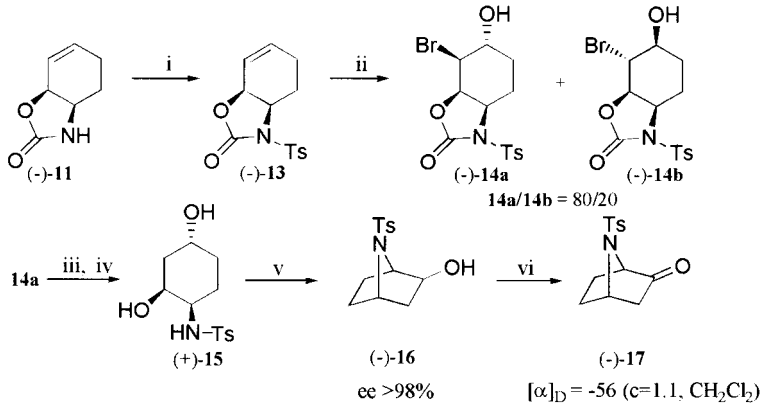
Optical purity was determined on amino-alcohol (−)-**16**. Comparison of NMR spectra of racemic (±)-**16** and (−)-**16** in the presence of an increasing amount of the chiral NMR shift reagent Eu(tfc)$_3$ allowed us to determine the enantiomeric excess to be greater than 98%.

Conclusion

We have thus achieved a formal synthesis of (−)-epibatidine **1**. Bicyclic ketone (−)-**17** has been prepared in high enantiomeric purity by a sequence of 8 steps. The total yield was 18%. The bicyclic ketone could be a useful intermediate for building combinatorial libraries of epibatidine analogs.

Experimental

IR spectra were recorded with a Genesis Matteson infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC 250 apparatus (250 MHz, δ=0 (TMS), in $CDCl_3$ if not specified otherwise, J in Hertz). ^{13}C NMR spectra were recorded at 62.5 MHz on a Bruker AC 300 apparatus (δ in ppm relative to internal TMS, J in Hertz). Samples were dissolved in $CDCl_3$ unless stated. Multiplicities in the ^{13}C spectra were determined by DEPT experiments. Elemental analyses were performed by the service of microanalyse, ICSN, CNRS, Gif-sur-Yvette. Mass spectra were recorded with a AEI MS-50 (Electronic Impact 50 eV) or AEI MS-9 (Chemical Ionisation with isobutane as ionising gas). Optical rotations were measured on polarimeter Perkin–Elmer 241 MC at a temperature around 20°C. Chromatographic solvents were distilled



Scheme 5. Reagents: (i) NaH, TsCl, THF, rt, 97%; (ii) Br_2, DME/H_2O, 75%; (iii) AIBN, Bu_3SnH, toluene 70°C, 1 h; (iv) LiOH, MeOH, rt 80% (iii+iv); (v) PPh_3, DEAD, THF, rt, 90%; (vi) $(COCl)_2$, DMSO, Et_3N, 88%.

before use. Flash chromatographies were performed on Merck 60 silica gel (230–400 mesh). TLC were performed on Merck 60 F254 aluminium plates. All dry solvents were distilled in vacuo. All the reactions were carried out under inert atmosphere unless water was used as the solvent. Solvents were distilled prior to use: CH_3CN and CH_2Cl_2 over CaH_2, THF and Et_2O over Na, benzophenone, toluene over P_2O_5. The other solvents were used in their commercial quality grades.

(7*S*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo-[5.2.1.0^{3,7}]decane-4-hydroxamic acid (+)-8.[7] To a solution of 10.21 g (47.49 mmol, 1 equiv.) of camphorsultam (+)-**7** and 24.8 mL (142.4 mmol, 3 equiv.) of *i*Pr_2EtN in 300 mL dry Et_2O was added very slowly 14.09 g (47.49 mmol, 1 equiv.) of triphosgene at 0°C. The cooling bath was removed and vigourous stirring was maintained for 18 h with the solution turning yellow. 16.5 g (237.4 mmol, 5 equiv.) of hydroxylamine hydrochloride and a solution of K_2CO_3 (6.5 g, 3 equiv. in 45 mL H_2O) were successively added. Stirring was continued for 6 h. The organic layer was separated and the aqueous layer was extracted 3 times with 200 mL CH_2Cl_2. The organic layers were joined, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Hydroxamic acid (+)-**8** was purified by flash chromatography (CH_2Cl_2/EtOAc 7/3); yield: 11 g, 85%; white solid; recrystallized from cyclohexane/CH_2Cl_2; mp 250°C; IR (film, cm^{-1}): 3260, 1658, 1360; ^1H NMR (300 MHz, $CDCl_3$): 8.30 (1H, bs), 6.75 (1H, bs), 3.85 (1H, dd, *J*=5.1, 7.8 Hz), 3.4 (2H, s), 2.1–2.1 (7H, m), 1.15 (3H, s), 0.95 (3H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$): 152.9, 64.2, 51.7, 49.5, 47.9, 44.3, 37.3, 32.1, 26.6, 20.2, 19.8; *m/z* (E.I.): 274 (M^+), 242; $[\alpha]_D$=+70.2 (*c*=1.1, $CHCl_3$). Starting from (−)-camphorsultam (−)-**7**, hydroxamic acid (−)-**8** was obtained in a similar way as (+)-**8**. $[\alpha]_D$=−71 (*c*=0.8, $CHCl_3$; lit.[11] −69 (*c*=1.05, $CHCl_3$).

(1*S*,4*R*)-[5-(*tert*-Butyl-dimethyl-silyloxy)-2-oxa-3-aza-bicyclo[2,2,2]oct-5-en-3-yl]-(3,3-dioxo-10,10-dimethyl-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]dec-4-yl)-methanone (1*S*,4*R*)-4. To a solution of 6.2 g (29.56 mmol, 1 equiv.) of 2-(*tert*-Butyl-dimethyl-silyloxy)-cyclohexadiene **5**[8] in 100 mL dry CH_2Cl_2 was added 9.91 g (30.85 mmol, 1.1 equiv.) of Et_4NIO_4 then the reaction was cooled to −78°C. A solution of 8.1 g (29.56 mmol, 1 equiv.) of hydroxamic acid (−)-**8** in 100 mL CH_2Cl_2 was slowly added to the mixture then the cooling bath was removed. After addition of 100 mL of a 10% aqueous solution of $Na_2S_2O_3$, the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2, the organic layers joined, dried over Na_2SO_4 and the solvents were evaporated under reduced pressure. The cycloadduct (1*S*,4*R*)-**4** was purified by flash chromatography (heptane/ethylacetate 7/3); yield: 13.73 g, 64%; light brown foam; IR (film, cm^{-1}): 1707, 1350. ^1H NMR (250 MHz, $CDCl_3$): 5.35 (1H, dd, *J*=2.7, 6.6 Hz), 4.9 (1H, ddd, *J*=1.6, 3.6, 5.7 Hz), 4.75 (1H, dd, *J*=2.9, 5.9 Hz), 4.00 (1H, dd, *J*=4.4, 7.4 Hz), 3.4 (2H, s), 2.4–2.1 (2H, m), 1.9–1.3 (9H, m), 1.25 (3H, s), 0.95 (3H, s), 0.90 (9H, s), 0.20 (3H, s), 0.15 (3H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$): 154.7, 152.8, 102.4, 72.9, 64.7, 60.0, 54.8, 48.5, 47.9, 44.6, 37.3, 32.5, 26.8, 25.6, 25.1, 20.5, 19.9, −4.4, −4.7. Starting from (−)-**8**, (1*R*,4*S*)-**4** was obtained in a similar way as (1*S*,4*R*)-**4**.

(1*R*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo-[5.2.1.0^{1,5}]decane-4-carboxylic acid-(2-oxo-cyclohex-3-enyl)-amide (+)-9. Cycloadduct **4** being unstable, with a significant loss of material during purification, enone (+)-**9** was prepared from crude product (1*S*,4*R*)-**4**. To a solution of crude cycloadduct (1*S*,4*R*)-**4** (29.56 mmol th.) in 270 mL of a 15/1 solution of CH_3CN/H_2O[9] was added 5.46 g (20.7 mmol, 0.7 equiv.) of $Mo(CO)_6$. The reaction was heated to 80°C and stirring was maintained until completion of reaction (12 h). The mixture was filtered through a plug of celite. After evaporation of the filtrate, the enone (+)-**9** was purified by flash chromatography (cyclohexane/EtOAc 6/4); yield: 6.42 g, 63%; colourless crystals; recrystallized from hexane/CH_2Cl_2; mp 144°C; IR (film, cm^{-1}): 3468, 1689, 1529, 1417; ^1H NMR (300 MHz, $CDCl_3$): 7.0–6.8 (2H, m), 6.1 (1H, dd, *J*=2.6, 10.0 Hz), 4.3 (1H, dt, *J*=4.8, 13.8 Hz), 3.8 (1H, dd, *J*=4.8, 7.8 Hz), 3.4 (2H, s), 2.85–1.15 (11H, m), 1.1 (3H, s), 0.95 (3H, s); ^{13}C NMR (62.5 MHz, $CDCl_3$): 195.2, 150.7, 150.6, 128.0, 64.2, 56.9, 51.8, 48.8, 47.8, 44.4, 37.7, 32.2, 30.2, 26.8, 25.8, 20.4, 19.9; *m/z* (C.I.): 381 (M+29), 353 (MH^+), 259, 216; $C_{17}H_{24}N_2O_4S$: Calculated: C, 57.93; H, 6.86; N, 7.94, Found: C, 57.66; H, 6.68; N, 7.86; $[\alpha]_D$=+71.2 (*c*=1.0, $CHCl_3$). Enone (−)-**9** was obtained from (−)-**8** in a similar way as (+)-**9**. $[\alpha]_D$=−69.3 (*c*=0.8, $CHCl_3$).

(1*S*)-10,10-Dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo-[5.2.1.0^{1,5}]decane-4-carboxylic acid-(2-oxo-cyclohex-3-enyl)-amide epi-(+)-9. A solution of 60 mg (0.19 mmol, 1 equiv.) of enone (+)-**9** in 0.570 mL of 6N HCl was heated to the reflux temperature, until complete solubilization of the enone. After 2 h stirring at 80°C, a saturated aqueous solution of $NaHCO_3$ was added to pH 8–9. The aqueous layer was extracted 3 times with 20 mL CH_2Cl_2, the organic layers were joined, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Enones **9** were purified by flash chromatography (cyclohexane/ethylacetate 7/3); yield: enone (+)-**9**, 25 mg (41 %); enone epi-(+)-**9**, 20 mg (33 %); white solid; recrystallized from hexane/CH_2Cl_2; mp 92°C; IR (film, cm^{-1}): 3400, 1693, 1510, 1335; ^1H NMR (300 MHz, $CDCl_3$): 7.0 (1H, m), 6.8 (1H, d, *J*=5.0 Hz), 6.1 (1H, dd, *J*=1.6, 10.0 Hz), 4.4 (1H, dt, *J*=5.0, 13.9 Hz), 3.8 (1H, dd, *J*=4.7, 7.8 Hz), 3.4 (2H, s), 2.6–2.4 (3H, m), 2.15–2.1 (8H, m), 1.1, 3H, s), 0.95 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): 195.4, 150.9, 127.9, 64.1, 56.4, 51.8, 48.7, 47.9, 44.4, 37.6, 32.2, 30.2, 26.7, 25.7, 20.3, 19.9; *m/z* (C.I.): 353 (MH^+), 259, 216; $[\alpha]_D$=+3.5 (*c*=0.9, $CHCl_3$).

(1*S*,2*R*)-10,10-Dimethyl-3,3-dioxo-3λ-thia-4-aza-tricyclo-[5.2.1.0^{1,5}]decane-4-carboxylic acid-(2-hydroxy-cyclohex-3-enyl)-amide (+)-*cis*-10 and (1*S*,2*S*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-aza-tricyclo[5.2.1.0^{1,5}]decane-4-carboxylic acid-(2-hydroxy-cyclohex-3-enyl)-amide (+)-*trans*-10. To a solution of 400 mg (1.13 mmol, 1 equiv.) of enone (+)-**9** in 4 mL MeOH were added 424 mg (1.13 mmol, 1 equiv.) of $CeCl_3{\cdot}7H_2O$[10] and the reaction was cooled to 0°C. A solution of 43 mg (1.13 mmol, 1 equiv.) of $NaBH_4$ in MeOH (2 mL) was slowly added to the mixture. After 30 min, the cooling bath was removed and stirring was maintained for 20 min. After pouring a 5% HCl aqueous solution (to pH 4–5), 15 mL of Et_2O and 15 mL of H_2O were successively added. The organic layer was decanted,

and the aqueous layer was extracted 3 times with 10 mL Et_2O portions. The organic layers were joined, dried over Na_2SO_4 and the solvents evaporated under reduced pressure. The allylic alcohols (+)-*cis*-**10** and (+)-*trans*-**10** were purified by flash chromatography (heptane/EtOAc 8/2); yield: (+)-*cis*-**10:** 345 mg, 86%; (+)-*trans*-**10**: 35 mg, 9%; white foam; IR (film, cm^{-1}): 3300, 1690; *m/z* (C.I.): 355 (MH^+), 337, 216; $C_{17}H_{26}N_2O_4S$: Calculated: C, 57.60; H, 7.39; N, 7.90, Found: C, 57.95; H, 7.12; N, 7.89.

Allylic alcohol (+)-cis-**10**: ^1H NMR (250 MHz, $CDCl_3$): 6.6 (1H, d, J=7.7 Hz), 5.75–5.65 (2H, m), 3.9 (1H, t, J=4.0 Hz), 3.6 (2H, m), 3.35 (1H, d, J=14.2 Hz), 3.30 (1H, d, J=14.2 Hz), 2.1–1.1 (11H, m), 1.05 (3H, s), 0.90 (3H s); ^{13}C NMR (75 MHz, $CDCl_3$): 152.6, 131.7, 128.4, 65.4, 64.9, 52.5, 52.1, 49.6, 48.9, 45.7, 38.7, 33.0, 27.5, 25.7, 24.4, 20.8, 20.1; $[\alpha]_D$=+119.5 (c=1.1, $CHCl_3$).

Allylic alcohol (+)-trans-**10**: ^1H NMR (250 MHz, $CDCl_3$): 5.8 (1H, d, J=8.3 Hz), 5.75 (1H, bs), 5.65 (1H, dd, J=5.6, 10.2 Hz), 4.1 (1H, d, J=7.1 Hz), 3.8 (2H, m), 3.4 (2H, s), 3.1 (1H, bs), 2.1–1.1 (11H, m), 1.1 (3H, s), 0.9 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): 151.2, 128.5, 128.3, 70.3, 64.1, 53.6, 51.6, 48.5, 47.8, 44.2, 37.4, 31.9, 26.5, 25.9, 23.8, 20.2, 19.7; $[\alpha]_D$=+53.6 (c=0.9, $CHCl_3$).

Allylic alcohols (−)-cis-**10**: ($[\alpha]_D$=−122 (c=1.1, $CHCl_3$)) and (−)-*trans*-**10** ($[\alpha]_D$=−52 (c=1.1, $CHCl_3$)) were obtained from (−)-**9** in a similar way as (+)-*cis*-**10** and (+)-*trans*-**10**.

(3a*R*,7a*S*)-3a,4,5,7a-Tetrahydrobenzoxazolin-2-one (−)-11. To a solution of 70 mg (0.197 mmol, 1 equiv.) of diastereomer (+)-*cis*-**10** in 2 mL MeOH were added 56 mg (1 mmol, 5 equiv.) of KOH. The reaction was stirred at rt until completion of reaction (1 h, TLC monitoring). After evaporation of the solvent under reduced pressure, addition of 15 mL CH_2Cl_2 and successive washing with 5 mL of H_2O, the organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The oxazolidinone (−)-**11** was purified by flash chromatography (heptane/EtOAc 1/1); yield 26 mg, 95%; colourless crystals; recrystallized from EtOAc/MeOH; mp 85°C; IR (KBr, cm^{-1}): 3250, 1750; ^1H NMR (300 MHz, CD_3OD): 6.1 (1H, dt, J=3.8, 10.1 Hz), 5.7 (1H, ddt, J=4.0, 10.1, 2.0 Hz), 4.95 (1H, dd, J=2.0, 3.9 Hz), 3.95 (1H, dt, J=4.0, 7.6 Hz), 2.25–2.10 (1H, m), 2.0–1.8 (2H, m), 1.7–1.5 (1H, m); ^{13}C NMR (75 MHz, CD_3OD): 172.9, 135.2, 123.8, 73.9, 52.3, 26.5, 21.5; *m/z* (C.I.): 140 (MH^+); $C_7H_9NO_2$: Calculated: C, 56.69; H, 6.75; N, 9.40, Found: C, 56.46; H, 6.68; N, 9.01; $[\alpha]_D$=−10.1 (c=0.5, $CHCl_3$). Oxazolidinone (+)-**11** was obtained from diastereomer (−)-*cis*-**10** in a similar way as (−)-**11**. $[\alpha]_D$=+9.2 (c=0.5, $CHCl_3$).

(3a*S*,7a*R*)-3a,4,5,6,7,7a-Hexahydrobenzoxazolin-2-one (+)-12. To a solution of 45 mg (0.32 mmol, 1 equiv.) of oxazolidinone (+)-**11** in 5 mL EtOAc was added 10 mg Rh/C and the reaction was stirred under H_2 atmosphere for 3 h at rt. The mixture was filtered and the solvent evaporated under reduced pressure. The oxazolidinone (+)-**12** was purified by filtration on silica gel (EtOAc); yield: 38 mg, 85%; colourless crystals; recrystallized from heptane/CH_2Cl_2; mp 90–92°C; IR (KBr, cm^{-1}): 3260, 1729; ^1H NMR (300 MHz, $CDCl_3$): 5.4 (1H, bs), 4.6 (1H, td, J=6.8, 4.8 Hz), 3.75 (1H, q, J=6.8 Hz), 2.10–1.10 (8H, m). ^{13}C NMR (75 MHz, $CDCl_3$): 76.2, 51.8, 28.9, 26.8, 19.9, 19.6; *m/z* (C.I.): 142 (MH^+); $C_7H_{11}NO_2$: Calculated: C, 59.56; H, 7.85; N, 9.92, Found: C, 59.18; H, 8.04; N, 9.79; $[\alpha]_D$=+27 (c=0.5, EtOH) lit.[17] +25 (c=1.0, EtOH).

(3a*R*,7a*S*)-3-Tosyl-3a,4,5,7a-tetrahydrobenzoxazolin-2-one (−)-13. To a solution of 200 mg (1.43 mmol, 1 equiv.) of oxazolidinone (−)-**11** in 5 mL THF were slowly added 85 mg (3.57 mmol, 2.5 equiv.) of NaH at 0°C. Stirring was maintained for 20 min and 300 mg (1.57 mmol, 1.1 equiv.) of freshly recrystallized tosylchloride were added. The cooling bath was removed and stirring was maintained for 1 h. The mixture was neutralized by addition of a 1 M aqueous solution of HCl (to pH 4–5). The aqueous layer was then extracted 3 times with 10 mL Et_2O portions. The organic layers were joined, dried over Na_2SO_4 and the solvents evaporated under reduced pressure. *N*-protected oxazolidinone (−)-**13** was obtained in excellent purity; yield: 420 mg, 97%; colourless crystals; recrystallized from Et_2O; mp 108–110°C; IR (KBr, cm^{-1}): 1785, 1370, 1173; ^1H NMR (250 MHz, $CDCl_3$): 8.0 (2H, d, J=7.9 Hz), 7.25 (2H, d, J=7.9 Hz), 6.2 (1H, m), 5.8 (1H, bs), 4.8 (1H, m), 4.45 (1H, ddd, J=4.5, 7.1, 11.7 Hz), 2.45 (3H, s), 2.3–2.1 (2H, m), 2.05–1.9 (1H, m), 1.6 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): 145.5, 135.5, 135.4, 129.8, 128.5, 121.2, 70.7, 56.9, 24.9, 21.8, 21.7; *m/z* (C.I.): 294 (MH^+), 157, 140, 96; $C_{14}H_{15}NO_4S$: Calculated: C, 57.32; H, 5.15; N, 4.77, Found: C, 57.59; H, 5.03; N, 4.61; $[\alpha]_D$=−8.0 (c=1.4, CH_2Cl_2).

(3a*R*,6*R*,7*S*,7a*S*)-3-Tosyl-3a,4,5,6,7,7a-6-hydroxy-7-bromo-hexahydrobenzoxazolin-2-one (−)-14a and **(3a*R*,6*S*,7*R*,7a*S*)-3-tosyl-3a,4,5,6,7,7a-6-hydroxy-7-bromo-hexahydrobenzoxazolin-2-one (−)-14b.** To a solution of 75 mg (0.25 mmol, 1 equiv.) of *N*-tosyloxazolidinone (−)-**13** in DME/H_2O (1/1, 5 mL) was added dropwise a solution of 26 μL (0.5 mmol, 2 equiv.) of Br_2 in 2 mL DME, at rt under vigourous stirring. After 15 min stirring, a 5% aqueous solution of $Na_2S_2O_3$ was added until the yellow colour disappeared. The solution was extracted 3 times with 10 mL CH_2Cl_2 portions. The organic layers were joined, dried over Na_2SO_4 and the solvents evaporated under reduced pressure. The bromhydrin (−)-**14** was purified by flash chromatography (heptane/EtOAc 1/1); yield: **14a** (60 mg, 60%), **14b** (15 mg, 15%); white solids.

Compound 14a. Recrystallized from heptane/EtOAc; mp 130–136°C; IR (film, cm^{-1}): 3300, 1785, 1370, 1173; ^1H NMR (200 MHz, $CDCl_3$): 7.95 (2H, d, J=8.3 Hz), 7.45 (2H, d, J=8.3 Hz), 5.60 (1H, d, J=5.5 Hz), 5.15 (1H, dd, J=3.7, 5.8 Hz), 4.75 (1H, td, J=5.9, 10.2 Hz), 4.35 (1H, dd, J=3.7, 10.0 Hz), 3.70 (1H, ddt, J=5.0, 5.3, 10.1 Hz), 2.50 (3H, s), 2.40–2.30 (1H, m), 1.90 (1H, m), 1.60–1.45 (1H, m), 1.45–1.30 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): 150.3, 145.5, 134.7, 129.8, 128.1, 78.8, 68.2, 57.2, 54.2, 29.4, 25.3, 21.1; *m/z* (C.I.): 392/390 (MH^+), 238/236;. $C_{14}H_{16}BrNO_5S$: Calculated: C, 43.09; H, 4.13; N, 3.59, Found: C,43.25; H, 4.22; N, 3.40; $[\alpha]_D$=−120 (c=0.5, $CHCl_3$).

Compound 14b. IR (Film, cm^{-1}): 3330, 1788, 1370, 1164; ^1H NMR (200 MHz, $CDCl_3$): 8.00 (2H, d, J=7.9 Hz), 7.60

(2H, d, J=7.9 Hz), 5.60 (1H, d, J=3.9 Hz), 5.05 (1H, t, J=7.3 Hz), 4.55 (1H, dt, J=4.5, 6.4 Hz), 4.20 (1H, t, J=7.6 Hz), 3.80 (1H, m), 2.55 (3H, s), 2.45–1.60 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$): 150.8, 145.0, 133.2, 129.3, 127.5, 77.8, 67.7, 56.8, 55.9, 26.4, 21.6, 20.5; *m/z* (C.I.): 450/448 (M+57), 392/390 (MH^+); $[\alpha]_D$=−52 (c=0.7, $CHCl_3$).

(1*S*,2*R*,5*R*)-1,5-Dihydroxy-2-tosylamino-cyclohexane (+)-15. To a solution of 120 mg (0.30 mmol, 1 equiv.) of bromhydrin (−)-**14** and 15 mg of AIBN in 10 mL of degassed toluene were added 100 μL (0.36 mmol, 1.2 equiv.) of Bu_3SnH at rt.[13] The mixture was heated rapidly to 70°C. Stirring was maintained for 1 h at this temperature then the heating bath was removed. Toluene was evaporated and the residue was dissolved in 20 mL of acetonitrile. After 3 times washing with 10 mL hexane portions, the acetonitrile phase was evaporated under reduced pressure and 110 mg of crude product were obtained, together with stannic salts. To a solution of this crude in 10 mL MeOH was then added 50 mg (0.9 mmol, 3 equiv.) of LiOH. After 20 min stirring the reaction was complete and 10 mL of a saturated aqueous solution of NH_4Cl were added. The organic layer was decanted and the aqueous layer was extracted 3 times with 10 mL CH_2Cl_2 portions. The organic layers were joined, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The diol (+)-**15** was purified by flash chromatography (EtOAc); yield: 69 mg, 80% overall); white solid; IR (film, cm^{-1}): 3330, 1164; ^{1}H NMR (250 MHz, $CDCl_3$): 7.8 (2H, d, J=8.2 Hz), 7.3 (2H, d, J=8.2 Hz), 4.8 (1H, bs), 4.0 (2H, m), 3.2 (1H, m), 2.5 (3H, s), 2.2–1.3 (6H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): 143.3, 137.7, 129.5, 126.6, 68.4, 64.3, 54.6, 39..8, 32.5, 24.8, 21.1; *m/z* (C.I.): 286 (MH^+); $C_{13}H_{19}NO_4S$: Calculated: C, 54.72; H, 6.71; N, 4.91, Found: C, 54.37; H, 6.57; N, 4.80; $[\alpha]_D$=+22 (c=1.3, EtOH).

(1*R*,2*S*,4*S*)-7-Tosyl-7-azabicyclo[2.2.1]heptane-2-ol (−)-16. To a solution of 90 mg (0.31 mmol, 1 equiv.) of diol (+)-**15** and 225 mg (0.77 mmol, 2.5 equiv.) of PPh_3 in 5 mL THF were added 125 μL (0.77 mmol, 2.5 equiv.) of DEAD at rt.[14] Stirring was maintained for 30 min and 5 mL of H_2O were then added. The aqueous layer was extracted 3 times with 10 mL CH_2Cl_2 portions. The organic layers were joined, dried over Na_2SO_4 and the solvents were evaporated under reduced pressure. Bicyclic compound (−)-**16** was purified by flash chromatography (heptane/EtOAc 8/2 then 7/3); yield: 75 mg, 90%; white crystals; recrystallized from heptane/CH_2Cl_2; mp 124–126°C; IR (film, cm^{-1}): 3400, 1317, 1151; ^{1}H NMR (300 MHz, $CDCl_3$): 7.8 (2H, d, J=8.0 Hz), 7.3 (2H, d, J=8.0 Hz), 4.25 (1H t, J=4.3 Hz), 4.0 (1H, d, J=4.1 Hz), 3.85 (1H ddd, J=2.5, 7.5, 10.1 Hz), 2.6 (1H, d, J=10.6 Hz), 2.5 (3H, s), 2.0–1.4 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$): 144.0, 129.7, 127.7, 74.2, 66.1, 74.2, 66.1, 58.6, 44.0, 28.4, 24.5, 21.6; *m/z* (C.I.): 268 (MH^+); $C_{13}H_{17}NO_3S$: Calculated: 58.41; H, 6.41; N, 5.24, Found: C, 58.34; H, 6.66; N, 5.44; $[\alpha]_D$=−13 (c=0.7, $CHCl_3$).

(1*R*,4*S*)-7-Tosyl-7-azabicyclo[2.2.1]heptane-2-one (−)-17. To a solution of 40 μL (0.54 mmol, 3 equiv.) of DMSO and 25 μl (0.27 mmol, 1.5 equiv.) of oxalyl chloride in 3 mL CH_2Cl_2 were added, after 15 min stirring at −78°C, 50 mg (0.18 mmol, 1 equiv.) of bicyclic compound (−)-**16**. Stirring was maintained for 30 min. 120 μL (0.81 mmol, 4.5 equiv.) of Et_3N were then added and the cooling bath was removed. After 1 h, the solution was treated with 5 mL H_2O and the aqueous layer was extracted 3 times with 5 mL CH_2Cl_2 portions. The organic layers were joined, dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Ketone (−)-**17** was purified by flash chromatography (heptane/EtOAc 7/3); yield: 42 mg, 88%; white crystals; recrystallized from CH_2Cl_2/MeOH; mp 133–135°C; IR (film, cm^{-1}): 1762, 1157; ^{1}H NMR (300 MHz, $CDCl_3$): 7.8 (2H, d, J=8.0 Hz), 7.4 (2H, d, J=8.0 Hz), 4.6 (1H, t, J=4.6 Hz), 4.2 (1H, d, J=5.1 Hz), 2.4 (3H, s), 2.3 (1H, m), 2.2 (1H, m), 2.1–1.8 (2H, m), 1.7–1.5 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) 133.7, 129.9, 65.3, 59.0, 44.5, 28.6, 24.3, 21.7; *m/z*: (C.I.): 266 (MH^+); $C_{13}H_{15}NO_3S$: Calculated: C, 58.85; H, 5.70; N, 5.28, Found: C, 58.73; H, 5.94; N, 5.06; $[\alpha]_D$=−56 (c=1.1, CH_2Cl_2).

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