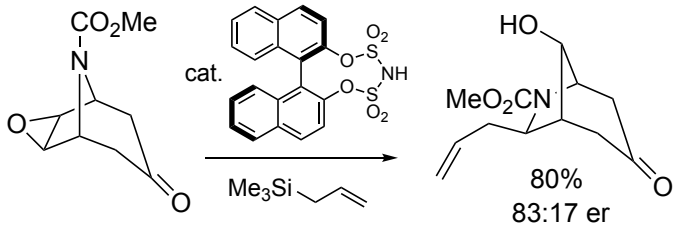
CO2Me
N
O
O
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O2
S
NH
O
S
O2
Me3Si
HO
MeO2CN
80%
83:17 er
O

Enantioselective desymmetrisation of an epoxytropinone for peduncularine synthesis

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Dedicated to the Achievements of Professor Jonathan Williams.

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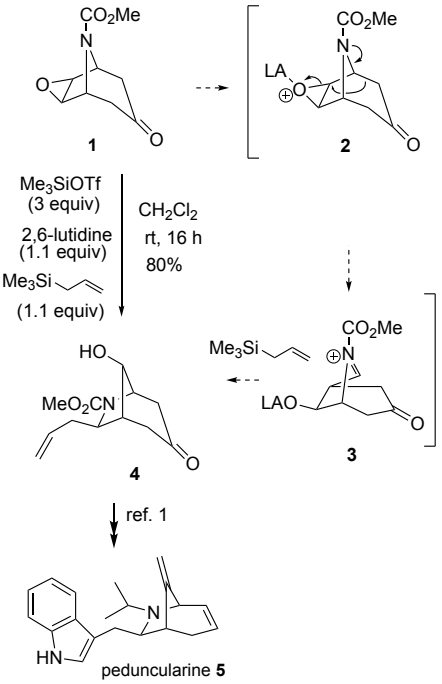
Abstract
A key 7-allyl-8-hydroxy-6-azabicyclo[3.2.1]octan-3-one intermediate in a synthesis of the alkaloid peduncularine is obtained enantioenriched, by desymmetrisation of an achiral 6,7-epoxy-8-azabicyclo[3.2.1]octan-3-one (epoxytropinone). Chiral lithium amide-assisted enantioselective silyl enol ether formation then TMSOTf/allyltrimethylsilane/2,6-lutidine-induced rearrangement–allylation proceeded in up to 80:20 er, but modest overall yield. Chiral amines or (thio)ureas replacing 2,6-lutidine gave up to 76:24 er directly from epoxytropinone. A direct, simplified (base-free) process using a BINOL-derived bis(sulfuryl)imide catalyst and allyltrimethylsilane proved the most promising (80%, 83:17 er).

Keywords: Desymmetrisation, Enantioselective, Epoxide, Organocatalysis, Iminium, Sulfonimide

1. Introduction

In 2010 we reported a synthesis of the *Aristotelia* alkaloid (±)-peduncularine (**5**) (Scheme 1).[1] The key transformation was an efficient Lewis acid-induced nitrogen-driven rearrangement iminium-trapping cascade (most straightforwardly envisaged via **2** and **3**) from an easily accessible epoxytropinone **1**, which gave the more unusual 6-azabicyclo[3.2.1]octane system

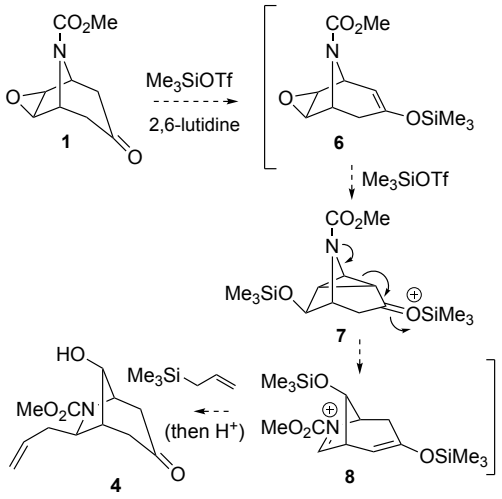
4 present in the natural product. The current work describes our studies on enabling the rearrangement to proceed in an enantioselective manner, thereby providing an asymmetric entry to peduncularine (**5**).



Scheme 1. Rearrangement–allylation approach to peduncularine.

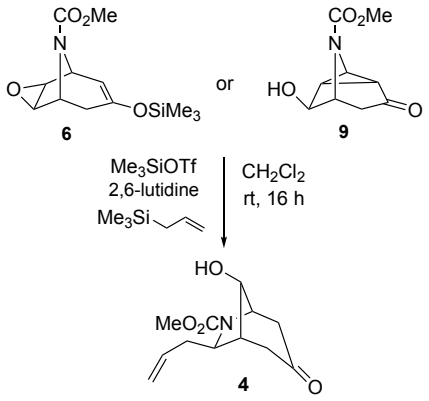
2. Results and discussion

We first investigated a strategy based on enantioselective silyl enol ether formation through ketone α-deprotonation with a chiral lithium amide. This approach was based on mechanistic conjecture that the rearrangement could be preceded by formation of the silyl enol ether **6** from the ketone functionality in epoxytropinone **1** (Scheme 2). In this scenario, silylated epoxide (oxonium) opening would then likely occur with assistance of the proximal electron rich C=C bond, passing through the tricyclic species **7** to iminium **8**.



Scheme 2. Silyl enol ether approach to ketone **4**.

Three observations in support of the above pathway were the following. Firstly, TMSOTf and 2,6-lutidine (1.1 equiv each) in CH_2Cl_2 at rt with 4-*tert*-butylcyclohexanone gave complete conversion to the corresponding silyl enol ether[2] within 1 h by GCMS (93% isolated). Secondly, the hydrolytically sensitive silyl enol ether **6** (Scheme 3) of epoxytropinone **3** (via LDA, TMSCl in situ, HMPA, THF, −78 °C, then evaporative removal of THF and ice-cold pentane/dilute aq. HCl work-up, ~65% crude) gave yields, albeit modest, of 7-allylated 6-azabicyclo[3.2.1]octan-3-one **4** using TMSOTf and allyltrimethylsilane, with 2,6-lutidinium triflate or 2,6-lutidine or no further additive (20%, 25% and 28%, respectively, all reagents 1.1 equiv). Finally, chromatographically sensitive tricyclic ketone **9** (Scheme 3), available (38%) from NaO*t*Bu-induced cyclisation of epoxytropinone **1**, also generated 7-allylated 6-azabicyclo[3.2.1]octan-3-one **4** under the rearrangement reaction conditions, albeit in 27% yield. While the yields for these (unoptimised) transformations are much lower than the 80% yield reported for 6-azabicyclo[3.2.1]octane **4** from epoxytropinone **1**, the latter refers to reaction on large scale (39 mmol of **1**) with lower yields being observed on smaller scales (67% from 12 mmol, 55% from 0.5 mmol).



Scheme 3. Ketone **4** from silyl enol ether **6** or tricyclic ketone **9**.

The above findings provided encouragement to examine chiral lithium amide-assisted enantioselective enol ether formation and rearrangement. Furthermore, there are several examples of achiral 3-oxo-8-azabicyclo[3.2.1]octanes related to epoxytropinone **1** being successfully converted from the ketone to the corresponding silyl enol ether in good er using a chiral lithium amide.[3,4] A variety of structurally diverse chiral lithium amides **10a-d** were screened with the current substrate (Fig. 1).

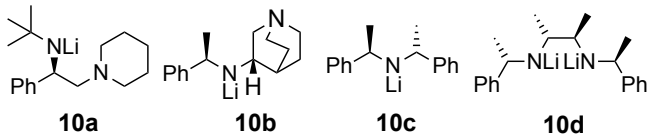
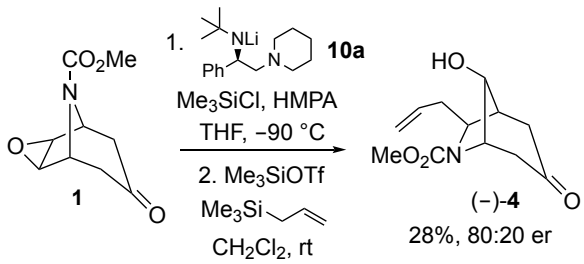


Fig. 1. Chiral lithium amides examined with epoxytropinone **1**.

Similar to our ibogamine synthesis,[4] where the substrate for enantioselective deprotonation–silylation differed from epoxytropinone **1** by having alkene instead of epoxide functionality, it was found that Koga-type lithium amide **10a** showed the best selectivity. This provided ketone (–)-**4** in up to 80:20 er (by Mosher's ester analysis) at –90 °C (78.5:21.5 er at –78 °C), through enol silane formation (~60% crude) leading to 28% yield over the two steps (Scheme 4). The predominant sense of asymmetric induction was tentatively assigned by analogy with that seen in our ibogamine synthesis. Lithium amides **10b-d**, where enolate formation was carried out in the presence of LiCl (THF, –78 °C, 1 h) before addition of TMSCl, gave similar two-step yields with lower ers for ketone **4** (75.5:24.5, 29.5:70.5 and 52.5:47.5, respectively). It was therefore decided to explore alternative potentially more efficient routes to enantioenriched ketone **4**.



Scheme 4. Ketone **4** via enantioselective enolisation.

A direct (one-step) way to make the rearrangement asymmetric could be to replace 2,6-lutidine with a chiral, enantiopure analogue. Using chiral pyridines **11a-c**[5,6] (Fig. 2) instead of 2,6-lutidine under the otherwise original conditions (cf, Scheme 1) all produced ketone **4** (57%, 64%, 59%, respectively) and with enantioenrichment, although none of the ers (64.5:35.5, 36: 64, 70:30, respectively) were higher than that obtained with the best chiral lithium amide **10a**. Unlike 2,6-lutidine, 2,6-di-*tert*-butylpyridine and the chiral pyridines **11a,b** with TMSOTf all failed to generate any of the silyl enol ether of 4-*tert*-butylcyclohexanone. This suggests that sterically hindered pyridines could assist the rearrangement in a different manner to that indicated in Scheme 2.

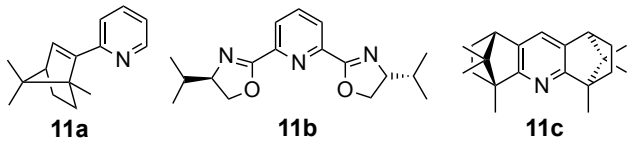


Fig. 2. Chiral pyridines examined with epoxytropinone **1**.

The asymmetric induction seen with chiral pyridines **11a-c** led us also to consider applying chiral tertiary amines in the desymmetrisation process. In 2009, Jørgensen and co-workers reported that cinchona alkaloid-based catalysts are able to exert stereocontrol over the β-fragmentation of achiral cyclic ketones through an α-deprotonation process, although the catalysts were very substrate specific.[7] Epoxytropinone **1** was first examined under Jørgensen's conditions with quinine (**12a**, Fig. 3) (10 mol%, CH_2Cl_2, rt, 4 h) to see if any 'fragmentation' occurred (eg, formation of tricycle **9**), but no reaction was observed. However, when quinine (**12a**) was used stoichiometrically as a direct replacement for 2,6-lutidine in the rearrangement, this enabled conversion to rearranged ketone **4** in 65% yield, albeit in a racemic manner. While benzylated quinine **12b**[8] also gave racemic ketone **4**, use of urea **12c** and thiourea **12d**, catalysts more successful in Jørgensen's study, delivered modest asymmetric induction (58.5:41.5 and

62.5:37.5, respectively). The slightly better er for thiourea **12d** led to two other, commercially available thioureas bearing tertiary amine functionality **12e,f** being studied (giving 24:76 and 54.5:45.5 ers, respectively). It is tempting to speculate that, by analogy with the postulated mechanism in Jørgensen's work, these amines induce reaction and enantioselectivity through ketone α-deprotonation (and, in the case of the (thio)ureas by prior bidentate hydrogen bonding through this group to the ketone); however, thiourea **12g** which lacks basic tertiary amine functionality, also induced rearrangement with some enantioselectivity (67.5:32.5 er).

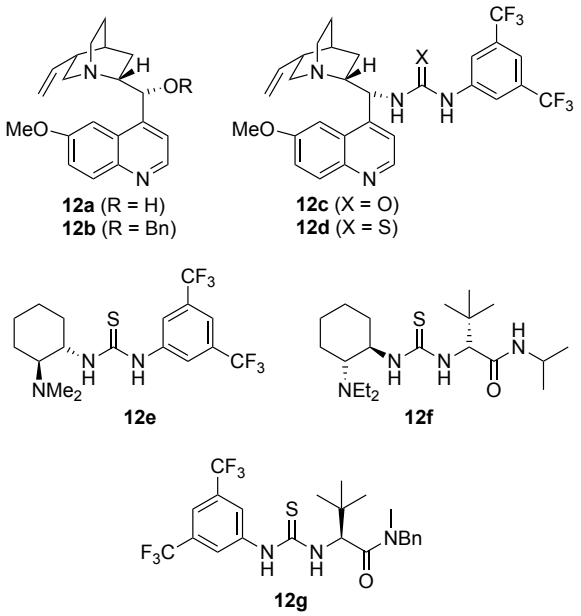
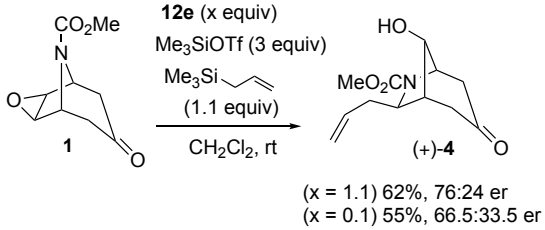


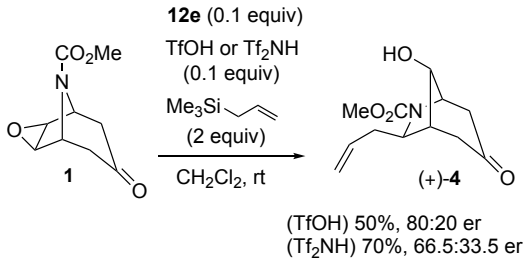
Fig. 3. Chiral amines/thioureas examined with epoxytropinone **1**.

The tertiary amine which gave the best asymmetric induction above (Takemoto's catalyst[9] **12e**, giving ketone (+)-**4** in 62% yield and 76:24 er, Scheme 5) was also studied for its ability to act catalytically in the rearrangement of epoxytropinone **1**. With 10 mol% **12e**, in the absence of any other base (conditions otherwise as Scheme 1), ketone (+)-**4** was obtained in 55% yield and 66.5:33.5 er (the presence of TMSOTf was essential to observe any conversion of epoxytropinone **1**). This result, together with the observation that thiourea **12g** induced conversion to ketone **4**, prompted an examination of the presence of any base at all being necessary in the original racemic rearrangement (Scheme 1). Although no reaction was observed with 1.1 equiv each of TMSOTf and allyltrimethylsilane, reaction did proceed with a larger excess of these reagents (3 equiv and 1.6 equiv, respectively), to give 60% yield of ketone **4** after 22 h (43% after 20 min).



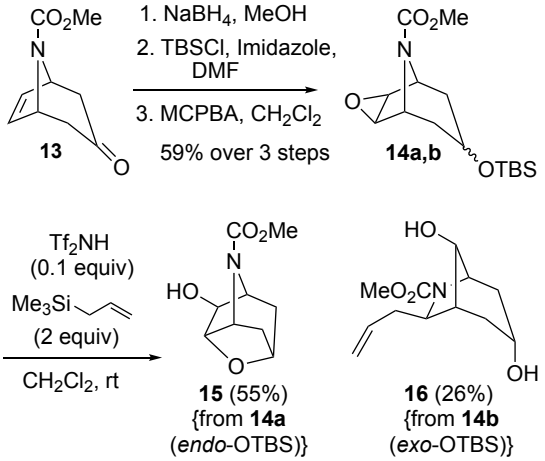
Scheme 5. Enantioselective rearrangement–allylation using Takemoto's catalyst and TMSOTf.

Due to its moisture sensitivity, TMSOTf requires careful handling for reproducibility in the above reactions. Triflic acid is known to conveniently and readily generate TMSOTf from allyltrimethylsilane,[10] and the rearrangement to ketone **4** was found to proceed in 50% yield using TfOH (0.2 equiv) and allyltrimethylsilane (2 equiv); using more TfOH (0.4 equiv) led to decomposition. Trifluoromethanesulfonimide (Tf_2NH, 0.1 equiv) with allyltrimethylsilane (2 equiv) proved more efficient, giving ketone **4** in 75% yield. With added thiourea **12e** (10 mol%), both these Brønsted acids led to ketone **4** with enantioenrichment (80:20 and 66.5:33.5 ers, Scheme 6).



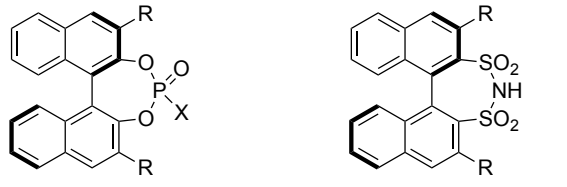
Scheme 6. Triflic acid or triflimide in the asymmetric synthesis of ketone **4**.

As the rearrangement had now been shown to proceed in the absence of a base, it suggested that, in those cases, enol silane formation/participation (cf, Scheme 2) was unlikely. To ascertain whether the ketone functional group was necessary for the rearrangement, silyl ethers **14a,b** were efficiently prepared in three standard steps from alkene **13**[1] and individually reacted with Tf_2NH and allyltrimethylsilane (Scheme 7). *Endo*-silyl ether **14a** gave the tricyclic alcohol **15**, a rearrangement similar to that seen in Mann and de Almeida Barbosa's synthesis of scopoline.[11] However, *exo*-silyl ether **14b** did give the corresponding known[1] diol **16** (26%), indicating rearrangement can proceed by C–C σ-bond participation.



Scheme 7. Preparation and reactions of silyl ethers **14a,b**.

Finally, a simplified way to induce rearrangement of epoxytropinone **1** in an enantioselective manner was considered: use of a chiral Brønsted acid with allyltrimethylsilane. 10 mol% (*R*)-binol-phosphoric acid **17a** (Fig. 4), its more hindered and CH_2Cl_2-soluble 3,3′-bis(triphenylsilyl) analogue **17b**, *N*-triflylphosphoramide **17c**,[12] or List's disulfonimide catalyst **18**[13] all failed to catalyse any useful reaction. However, the more acidic[14] (*R*)-bis(sulfuryl)imide **19-H**, readily prepared in one step from BINOL and imidobis(sulfuryl chloride)[15], induced efficient conversion at 10 mol% loading to give ketone (+)-**4** (70%, 73:27 er) after 2 h at rt. The highest er in the current study (83:17) was observed with this catalyst at 0 °C (Scheme 8), the reaction now taking 15 h; no reaction was observed at −58 °C.



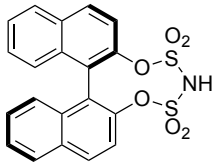
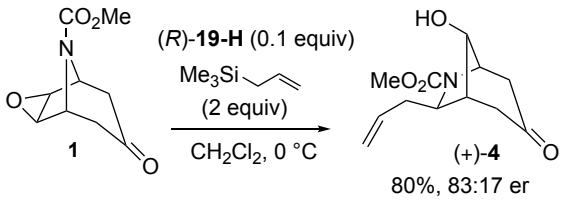
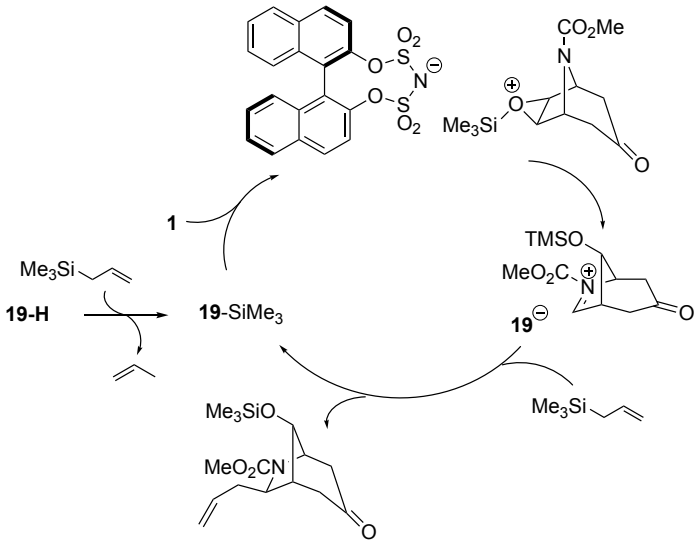


Fig. 4. BINOL-derived catalysts examined with epoxytropinone **1**.



Scheme 8. Bis(sulfuryl)imide catalysed asymmetric synthesis of ketone **4**.

A suggested catalytic cycle for the rearrangement–allylation with bis(sulfuryl)imide **19-H** is shown in Scheme 9. Enantioselectivity may arise from the silylated epoxide (oxonium) opening involving σ-bond participation (synartetic acceleration[16]), with bias for which C–O bond is lengthened/broken (and hence which σ-bond migrates) being due to the asymmetric environment created by the associated chiral counteranion **19**$^{-}$.



Scheme 9. Possible catalytic cycle for rearrangement–allylation with bis(sulfuryl)imide **19-H**.

Enantioselective desymmetrisation of achiral epoxides is an attractive strategy for asymmetric synthesis[17] and organocatalytic variants are increasing.[18,19] However skeletal rearrangements combined with C–C bond formation from an external nucleophile are rare. The present work provides an example of this in the context of an intermediate for alkaloid synthesis, with the most efficient catalyst **19-H** providing a promising lead for further improvements through structural variation.

4. Experimental Section

4.1. General

Reactions were performed in flame-dried glassware under an atmosphere of dry argon or nitrogen. CH_2Cl_2, Et_2O, THF and MeOH were degassed and dried *via* activated alumina column chromatography under N_2.[20] HMPA and 2,6-lutidine were distilled from CaH_2. Me_3SiCl was distilled from K_2CO_3. All other reagents were used as received unless otherwise stated. Petroleum ether refers to the fraction that boils at 30– 40 °C. Reactions were monitored by TLC using silica 60, gel aluminium-backed plates or (where stated) aluminium oxide 150 F_{254} neutral aluminium-backed plates. The plates were visualised using ultraviolet light and developed in basic potassium permanganate or phosphomolybdic acid solution and then heated. Column chromatography was performed using the solvent systems indicated. The stationary phase used was silica gel 60. Infra-red spectra were recorded on a 1750 Perkin-Elmer FT-IR spectrophotometer, neat or as a film, as indicated. Peak intensities are reported as: s, strong; m, medium; w, weak; br, broad. ^1H, and ^{13}C NMR spectra were recorded on Brüker DPX400, AV400 or AV500 spectrometers at 27 °C. Data are expressed as chemical shifts in parts per million (ppm) relative to residual chloroform or $CDCl_3$ (^1H δ 7.26, ^{13}C δ 77.1, respectively) as internal standards on the δ scale. The multiplicity of each signal is designated by the following abbreviations: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; ddt, doublet of doublet of triplets; t, triplet; sept, septuplet; br, broad; m, multiplet. Coupling constants *J* are given in Hz and are reported to ±0.5 Hz. Doubling of signals was often observed due to carbamate rotamers; in ^1H spectra the double peaks are assigned, where appropriate, as separate peaks or the word 'and' is used to specifically signify extra peaks arising from rotamers. In ^{13}C spectra the word 'and' is used to specifically signify extra peaks arising from rotamers. ^1H and ^{13}C NMR peak assignments were established on the basis of COSY, APT, DEPT and HMQC correlations. High-resolution mass spectra were obtained using chemical ionization (CI) or electrospray ionization (ESI) techniques (H^+, NH_4^+, Na^+), electron impact (EI) techniques (M^+) or by gas chromatography analysis with a BPX5 column-HP 6890 (dimethylsilicone capillary column, 30m, 0.25 mm internal diameter) equipped with a reflectron TOF mass spectrometer operating at 60 eV (flow rate (He) = 1 mL/min).

4.2. Experimental procedures and data for synthetic compounds

*4.2.1 Methyl 7-allyl-8-hydroxy-3-oxo-6-azabicyclo[3.2.1]octane-6-carboxylate (**4**)*

4.2.1.1 From tricyclic ketone **9**. 2,6-Lutidine (8 μL, 0.07 mmol) and allyltrimethylsilane (8 μL, 0.07 mmol) were added to a solution of tricyclic ketone **9** (12 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) at rt. After 5 min, TMSOTf (33 μL, 0.18 mmol) was added. After 16 h, the reaction mixture was washed with sat. aq. NH_4Cl (2 mL) and brine (2 mL). The combined aq. layers were extracted with CH_2Cl_2 (2 × 2 mL) and the combined organic layers dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (60% EtOAc in petroleum ether) gave ketone **4** as a colourless oil (4 mg, 27%). Data as previously reported.[1]

4.2.1.2 From epoxytropinone **1** using chiral lithium amide (*R*)-**10a**. HMPA (1.28 mL) was added to chiral lithium amide (*R*)-**10a** [generated by the dropwise addition of *n*BuLi (2.3 mL, 1.6 M in hexane, 3.7 mmol) to a solution of the corresponding amine (962 mg, 3.90 mmol) in THF (7.5 mL) at −78 °C] and the resulting solution was allowed to warm to rt for 30 min. After cooling to −90 °C, TMSCl (892 μL, 7.04 mmol) was added dropwise, followed by the dropwise addition of a solution of epoxytropinone **1** (694 mg, 3.52 mmol) in THF (4 mL). After stirring at −90 °C for 3 h, the reaction mixture was evaporated under reduced pressure. The residue was diluted with ice-cold pentane (10 mL) and washed with ice-cold aq. HCl (2 × 5 mL, 0.2 N). The combined aq. layers were extracted with cold pentane (2 × 10 mL) and the combined organic layers dried ($MgSO_4$) and evaporated under reduced pressure, to give the crude silyl enol ether **6**. R_f 0.35 (20% EtOAc in petroleum ether). Indicative signal in crude ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05-5.03 (1H, m, HC=); *m/z* (ESI) 312.3 ($[M+H]^+$, 100%); HRMS ($[M+Na]^+$) 334.1445, $C_{15}H_{25}NNaO_4Si$ requires 334.1445. TMSOTf (419 μL 2.32 mmol) was added dropwise to a solution of the crude silyl enol ether **6** (2.11 mmol, from 3.52 mmol **1**) and allyltrimethylsilane (367 μL, 2.32 mmol) in CH_2Cl_2 (10 mL) at rt. After 2 h, the reaction was diluted with CH_2Cl_2 (20 mL) and washed with sat. aq. NH_4Cl (20 mL). The aq layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (60% EtOAc in petroleum ether) gave ketone **4** as a pale-yellow oil (235 mg, 28% from epoxytropinone **1**). $[\alpha]_D^{24}$ −1.4 (*c* = 1.9, CH_2Cl_2; 80:20 er from Mosher's ester derivatisation, see below; all other data as previously reported.[1]

4.2.1.3 From epoxytropinone **1** by chiral amine **12e**-mediated rearrangement. TMSOTf (119 μL, 0.66 mmol) was added dropwise to a solution of epoxytropinone **1** (43 mg, 0.22 mmol), Takamoto's catalyst **12e** (100 mg, 0.24 mmol) and allyltrimethylsilane (38 μL, 0.24 mmol) in CH_2Cl_2 (1.5 mL) at rt. The solution was stirred for 16 h then washed with sat. aq. NH_4Cl (2 mL) and brine (2 mL). The combined aqueous layers were extracted with CH_2Cl_2 (2 x 3 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (60% EtOAc in petroleum ether) gave ketone **4** as a yellow oil (33 mg, 62%). $[\alpha]_D^{24}$ +0.6 (*c* 0.7, CH_2Cl_2); 76:24 er from Mosher's ester derivatisation; all other data as previously reported.[1]

4.2.1.4 From epoxytropinone **1** using chiral disulfonimide catalyst **19-H**. Disulfonimide **19-H** (5.3 mg, 0.0124 mmol) was added to a stirred solution of epoxytropinone **1** (24.6 mg, 0.125 mmol, 0.06 M in CH_2Cl_2) and allyltrimethylsilane (39.5 μL, 0.25 mmol) at 0 °C. After 15 h, the reaction mixture was evaporated under reduced pressure and the residue dissolved in THF (2 mL) and 2N HCl (1 mL). After 4 h, Et_2O (3 mL) was added and the mixture was washed with sat. aq. $NaHCO_3$ (1 mL). The aq. layer was extracted with Et_2O (3 x 3 mL) and CH_2Cl_2 (1 × 2 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (60% EtOAc

in petroleum ether) gave ketone **4** as a yellow oil (24 mg, 80%). $[\alpha]_D^{24}$ +2.5 (*c* 1.0, MeOH); 83:17 er from Mosher's ester derivatisation; all other data as previously reported.[1]

4.2.2 Mosher's ester derivatisation: (1R,5R,7R,8S)-Methyl 7-allyl-3-oxo-8-((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)-6-azabicyclo[3.2.1]octane-6-carboxylate and (1S,5S,7S,8R)-Methyl 7-allyl-3-oxo-8-((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)-6-azabicyclo[3.2.1]octane-6-carboxylate

Ketone **4** (39 mg, 0.16 mmol) in CH_2Cl_2 (300 μL) was added to a solution of (*R*)-Mosher's acid chloride (43 μL, 0.23 mmol) in pyridine (300 μL). After 16 h, 3-dimethylamino-1-propylamine (41 μL, 0.33 mmol) was added, then after 5 min the reaction was diluted with Et_2O (5 mL) and washed with ice-cold aq. HCl (5 mL, 0.2 M), followed by ice-cold sat. aq. $NaHCO_3$ (5 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure, to give the crude Mosher esters as a yellow oil (41 mg, 4:1 mixture of diastereomers by ^{19}F NMR analysis). The residue was purified by column chromatography (50% Et_2O in petroleum ether) to give the Mosher esters as a colourless oil (33 mg, 46%, 4:1 mixture of diastereomers by ^{19}F NMR analysis). R_f 0.24 (50% Et_2O in petroleum ether); $[\alpha]_D^{24}$ −16.2 (*c* = 1.0, CH_2Cl_2); IR (film, cm^{-1}) 2958br, 1753s (C=O ester), 1703s (C=O ketone), 1641s (C=O carbamate), 1513m, 1379m, 1274w, 1171m, 1029w; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 and 7.49 (2H, 2 × HCAr rotamers), 7.44-7.36 (3H, m, 3 × HCAr rotamers), 5.67-5.51 (1H, m, HC= rotamers), 5.44-5.37 (1H, m, CHO rotamers), 5.04-4.97 (0.8H, m, 0.8H HH′C= rotamers), 4.95-4.86 (1H, m, HH′C= rotamers), 4.76-4.64 (0.2H, m, 0.2H HH′C= rotamers), 4.48-4.35 (0.6H, m, 0.6H CHN bridge rotamers), 4.29-4.25 (0.4H, m, 0.4H CHN bridge rotamers), 3.72-3.51 (7H, m, OMe, CO_2Me, CHN rotamers), 3.05-2.42 (6H, m, CHH′ allylic, 2 × CH_2, CH bridge rotamers), 2.03-1.84 (1H, m, CHH′ allylic rotamers); ^{13}C NMR (100 MHz, $CDCl_3$, discernible data for major diastereomer) δ 205.8 and 205.5 (C=O ketone), 166.4 and 166.3 (C=O ester), 154.9 and 154.5 (C=O carbamate), 134.8 and 134.6 (HC=), 131.7 (CAr, quat), 130.0 and 129.9 (HCAr), 128.8 and 128.7 (HCAr), 127.3 and 127.2 (HCAr), 124.7 (CF_3), 118.0 and 117.9 (H_2C=), 80.5 and 79.7 (CHO), 63.5 and 62.9 (CHN), 59.0 and 58.6 (CHN bridge), 55.7 (OMe), 52.8 and 52.7 (OMe carbamate), 47.3 and 47.2 (CH_2), 45.7 and 44.7 (CH_2), 40.6 and 39.5 (CH bridge), 36.7 and 35.8 (CH_2 allylic); ^{19}F NMR (377 MHz, $CDCl_3$) δ −70.8 and −70.9 (CF_3), −71.3 and −71.4 (CF_3); *m/z* (CI) 473.2 ($[M+NH_4]^+$, 90%), 456.1 (100), 261.2 (15); HRMS ($[M+Na]^+$) 478.1444, $C_{22}H_{24}F_3NNaO_6$ requires 478.1448.

*4.2.3 Methyl 8-hydroxy-3-oxo-6-azatricyclo[3.2.1.0^{2,7}]octane-6-carboxylate (**9**)*

NaO*t*Bu (65 mg, 0.68 mmol) was added to epoxytropinone **1** (121 mg, 0.61 mmol) in THF (5 mL) at –20 °C. After 4 h, the reaction mixture was warmed to rt and diluted with EtOAc (15 mL), washed with sat. aq. NH_4Cl (2 × 15 mL) and the combined organic layers dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography (1% Et_3N in EtOAc) gave tricyclic ketone **9** as a colourless oil (45 mg, 38%). R_f 0.31 (EtOAc); IR (film, cm^{-1}) 3386br (OH), 1690s, 1592s, 1461m, 1416m, 1461m, 1416m, 1194m, 1121m; ^1H NMR (400 MHz, $CDCl_3$) δ 4.38 (1H, br s, H-1), 4.19 (2H, br s, CHN, CH(OH)), 3.75 (3H, s, OMe), 2.77 (1H, br s, OH), 2.47-2.42 (1H, br m, CHH′), 2.38-2.32 (1H, m, H-7), 2.13-2.12 (1H, m, CHH′), 2.06-2.01 (H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0 (C=O ketone), 155.6 (C=O carbamate), 72.1 (CH(OH)), 56.1 (CHN), 53.6 and 53.2 (OMe), 41.3 (CH_2), 39.3 (C-1), 32.5 (C-2), 27.0 (C-7); m/z (CI) 198.1 ($[M+H]^+$, 100%); HRMS ($[M+H]^+$) 198.0762, $C_9H_{12}NO_4$ requires 198.0766.

*4.2.4 Methyl 7-((tert-butyldimethylsilyl)oxy)-3-oxa-9-azatricyclo[3.3.1.0^{2,4}]nonane-9-carboxylates (**14a**) and (**14b**)*

Alkene **13**[1] (544 mg, 3.0 mmol) and $NaBH_4$ (227 mg, 6.0 mmol) were stirred in MeOH (30 mL) at rt. After 4 h, sat. aq. $NaHCO_3$ (10 mL) and CH_2Cl_2 (20 mL) were added, and the mixture was stirred at rt for 5 min. The organic layer was separated, and the aq. layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give an inseparable mixture of *endo*- and *exo*-alcohols (63:37, 540 mg, quant.) as a colourless liquid. R_f 0.26 (EtOAc); IR (film, cm^{-1}); 3429br, 2953w, 2360w, 1678s, 1454s, 1395s, 1315s, 1189m, 1104s, 1059s, 1018m, 947w, 887w, 807m, 762s, 723s, 682m; HRMS (ESI$^+$): ([M+Na]$^+$) 206.0789, $C_9H_{13}NNaO_3$ requires 206.0788. Discernible data for *endo*-alcohol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (d, *J* 7.5, 2H, 2 x HC=), 4.65-4.56 (m, 2H, 2 x CHN, overlapped with $CH_{endo}N$), 4.00-3.86 (m, 1H, CH(OH), overlapped with CH_{endo}(OH)), 3.71 (s, 3H, OMe), 2.35-2.08 (m, 2H, 2 x CHH′ with rotamer), 1.77 (d, *J* 15, 2H, 2 x CHH′ with rotamer); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3 (carbamate), 136.0 and 135.7 (2 x HC=), 65.7 (CH(OH)), 57.2 (2 x CHN), 52.4 (OMe), 35.9 and 35.1 (2 x CH_2). Discernible data for *exo*-alcohol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, *J* 7.5, 2H, 2 x HC=), 4.65-4.56 (m, 2H, 2 x CHN, overlapped with $CH_{exo}N$), 4.00-3.86 (m, 1H, CH(OH), overlapped with CH_{exo}(OH)), 3.69 (s, 3H, OMe), 2.01-1.92 (m, 2H, 2 x CHH′ with rotamer), 1.53 (dt, *J* 21, 10, 2H, 2 x CHH′ with rotamer);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0 (carbamate), 131.1 and 130.8 (2 x HC=), 64.8 (CH(OH)), 57.2 (2 x CHN), 52.4 (OMe), 34.7 and 34.0 (2 x CH_2).

A mixture of the above *endo*- and *exo*-alcohols (460 mg, 2.51 mmol) was added to a solution of TBDMSCl (577 mg, 3.83 mmol) and imidazole (434 mg, 6.38 mmol) in DMF (2 mL) at rt. After16 h, the reaction mixture was partitioned between Et_2O (6 mL) and H_2O (3 mL). The layers were separated, the organic layer was diluted with Et_2O (12 mL), washed with H_2O (6 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (8% EtOAc in petroleum ether) gave an inseparable mixture of unsaturated *endo*- and *exo*-silyl ethers (63:37, 520 mg, 70%) as a colourless liquid. R_f 0.42 (8% EtOAc in petroleum ether); IR (film, cm^{-1}) 2953m, 2856w, 2360w, 2341w, 1708s, 1451m, 1395m, 1255w, 1073s, 1024s, 1004w, 806m, 773w; HRMS (ESI$^+$): ([M+H]$^+$) 298.1830, $C_{15}H_{28}NO_3Si$ requires 298.1833. Discernible data for unsaturated *endo*-silyl ether: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (d, *J* 11.5, 2H, 2 x HC=), 4.63-4.41(m, 2H, 2 x CHN, overlapped with $CH_{endo}N$), 3.99-3.94 (m, 1H, CHOTBS), 3.68 (bs, 3H, OMe, overlapped with $_{exo}$OMe), 2.14 (d, *J* 13, 1H, 0.5 x 2 CHH′, rotamer), 2.03 (d, *J* 14, 1H, 0.5 x 2 CHH′, rotamer), 1.53 (d, *J* 14, 2H, 2 x CHH′, with rotamer), 0.83 (s, 4.5H, $SiCMe_3$, rotamer), 0.82 (s, 4.5H, $SiCMe_3$, rotamer), -0.06 (s, 3H, $SiMe_2$, rotamer), -0.07 (s, 3H, $SiMe_2$, rotamer). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3 (C=O), 134.0 and 133.5 (2 x HC=), 65.0 (CHOTBS), 57.2 (2 x CHN), 52.2 (OMe), 35.9 and 35.1 (2 x CH_2), 25.7 ($SiCMe_3$), 17.8 ($SiCMe_3$), -4.9 ($SiMe_2$). Discernible data for unsaturated *exo*-silyl ether: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (d, *J* 10, 2H, 2 x HC=), 4.63-4.41(m, 2H, 2 x CHN, overlapped with $CH_{exo}N$), 3.94-3.81 (m, 1H, CHOTBS), 3.68 (bs, 3H, OMe, overlapped with $_{endo}$OMe), 1.78 (dd, *J* 13, 6.5 Hz, 2H, 2 x CHH′, with rotamer), 1.62 (t, *J* 11, 1H, 0.5 x 2 CHH′, rotamer), 1.51-1.45 (m, 1H, 0.5 x 2 CHH′, rotamer), 0.81 (s, 9H, $SiCMe_3$), -0.03 (s, 3H, $SiMe_2$, rotamer), -0.04 (s, 3H, $SiMe_2$, rotamer). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9 (C=O), 131.1 and 130.8 (2 x HC=), 65.4 (CHOTBS), 57.2 (2 x CHN), 52.2 (OMe), 34.0 and 34.2 (2 x CH_2), 25.8 ($SiCMe_3$), 18.1 ($SiCMe_3$), -4.6 ($SiMe_2$).

A solution of MCPBA (70%, 862 mg, 3.5 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a solution of the above unsaturated *endo*- and *exo*-silyl ethers (520 mg, 1.75 mmol) in CH_2Cl_2

(15 mL) at 0–5 °C (ice-bath). After 2 h, the reaction mixture was allowed to warm to rt. After a further 14 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and the organic layer washed successively with sat. aq. $Na_2S_2O_3$ (2x10 mL), aq. NaOH (1 M, 10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by column chromatography (20% EtOAc in petroleum ether) gave a separable mixture of *endo*-silyl ether **14a** and *exo*-silyl ether **14b** (462 mg, 84% total yield) as a colourless liquid. IR (film, cm^{-1}) 2928w, 2856w, 1702s, 1446m, 1386m, 1293m, 1251m, 1098s, 971w, 833s, 770s, 673m; HRMS (ESI^+): ($[M+Na]^+$) 336.1588, $C_{15}H_{27}NNaO_4Si$ requires 336.1602. Data for *endo*-silyl ether **14a**: R_f 0.45 (20% EtOAc in petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (bs, 1H, CHN, rotamer), 4.29 (bs, 1H, CHN, rotamer), 3.97 (t, *J* 4, 1H, CHOTBS), 3.67 (s, 3H, OMe), 3.49 (dd, *J* 9, 3, 2H, CHO), 2.10-1.95 (m, 2H, 2 x CHH′), 1.68-1.54 (m, 2H, 2 x CHH′), 0.86 (s, 9H, $SiCMe_3$), 0.02 (s, 6H, $SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5 (C=O), 63.8 (CHOTBS), 53.8 (2 x CHN), 53.5 and 53.3 (2 x CHO), 52.6 (OMe), 35.0 and 34.8 (2 x CH_2), 25.8 ($SiCMe_3$), 17.8 ($SiCMe_3$), -4.9 and -4.9 ($SiMe_2$). Data for *exo*-silyl ether **14b**: R_f 0.31 (20% EtOAc in petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (bs, 1H, CHN, rotamer), 4.32 (bs, 1H, CHN, rotamer), 4.15-4.05 (m, 1H, CHOTBS), 3.67 (s, 3H, OMe), 3.39-3.35 (m, 2H, 2 x CHO, with rotamer), 2.00-1.88 (m, 2H, 2 x CHH′), 1.75-1.61 (m, 2H, 2 x CHH′), 0.84 (s, 9H, $SiCMe_3$), 0.01 (s, 6H, $SiMe_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9 (C=O), 64.2 (CHOTBS), 53.8 and 53.4 (2 x CHN), 52.6 (OMe), 52.1 and 51.8 (2 x CHO), 35.8 and 35.5 (2 x CH_2), 25.7 ($SiCMe_3$), 18.1 ($SiCMe_3$), -4.6 and -4.6 ($SiMe_2$).

*4.2.5 Methyl 6-hydroxyhexahydro-4H-2,5-methanofuro[3,2-b]pyrrole-4-carboxylate (**15**)*

Tf_2NH (3.3 mg, 0.0118 mmol) was added to a solution of *endo*-silyl ether **14a** (37 mg, 0.118 and allyltrimethylsilane (37 μL 0.236 mmol) in CH_2Cl_2 (2.36 mL) at rt. After 15 min, the reaction mixture was concentrated under reduced pressure, then redissolved in THF (2 mL) and 2N HCl (1 mL). After 4 h, Et_2O (3 mL) was added and the mixture was washed with saturated aq. $NaHCO_3$ (1 mL). The aq. layer was extracted with Et_2O (3 x 3 mL) and CH_2Cl_2 (1 × 2 mL). The combined organic layers were washed with brine (1 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (EtOAc) gave tricyclic alcohol **15** (13 mg, 55%) as a white solid. R_f 0.32 (EtOAc); IR (film, cm^{-1}) 3411br, 2957w, 1677s, 1342s, 1309s 1278s, 1161m, 1012m, 842m, 791m; ^1H NMR (500 MHz, $CDCl_3$) δ 4.64-4.53 (m, 2H, 2 x CHN, overlapped with CHO), 4.38 (broad s, 1H, CHO)), 4.31 (broad s, 0.5H, CH(OH) rotamer), 4.22 (broad d, 0.5H, CH(OH) rotamer), 4.07 (broad s, 1H, CHN), 3.73 (broad d, 3H OMe), 2.22-1.99 (m, 2H, CHH′CO, overlapped with OH), 1.81-1.73 (m, 3H, CH_2CH overlapped with CHH′CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8 and 155.6 (carbamate), 82.9 and 82.3 (CHN), 76.0 and 75.7 (CHO), 74.4 and 74.3 (CHO), 61.0 and 60.7 (CH(OH)), 58.3 and 58.2 (CHN), 52.9 and 52.8 (OMe), 40.6 and 40.2 (CH_2CO), 33.5 and 33.0 (CH_2CH); HRMS ($[M+Na]^+$) 222.0739, $C_9H_{13}NNaO_4$ requires 222.0737.

*4.2.6 Methyl 7-allyl-3,8-dihydroxy-6-azabicyclo[3.2.1]octane-6-carboxylate (**16**)*

Tf_2NH (0.28 mL, 0.059 M in toluene, 0.0167 mmol) was added to a solution of *exo*-silyl ether **14b** (52.5 mg, 0.167 mmol) and allyltrimethylsilane (53 μL 0.33 mmol) in CH_2Cl_2 (1.67 mL) at rt. After 15 min, the reaction mixture was concentrated under reduced pressure, then re-dissolved in THF (4 mL) and 2N HCl (2 mL). After 4 h, Et_2O (6 mL) was added and the mixture was washed with saturated aq. $NaHCO_3$ (2 mL) and brine (2 mL). The aq. layer was extracted with Et_2O (3 x 3 mL) and the combined organic layers washed with brine (2 mL), dried ($MgSO_4$) and evaporated under reduced pressure. TBAF (0.14 mL, 1 M in THF, 0.14 mmol) was added to a solution of the residue (25 mg) in THF (0.2 mL) at 0 °C. After 1 h, water (0.5

mL) was added and the reaction mixture extracted with CH_2Cl_2 (2 x 2 mL). The combined organic layers were washed with brine (1 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by column chromatography (EtOAc) gave diol **16** (10.6 mg, 26%) as a colourless oil. Data as previously reported.[1]

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Appendix A. Supplementary data

Supplementary data to this article can be found online at xx.

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