Tetrahedron: *Asymmetry* 20 (2009) 961–969

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Favorskii rearrangement of a highly functionalized *meso*-dihaloketone

Paula M. Tomlin [b], David J. Davies [c], Martin D. Smith [a,b,*]

[a] *Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, UK*
[b] *Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK*
[c] *GlaxoSmithKline, Ion Channel Group, Discovery Medicinal Chemistry, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK*

ARTICLE INFO

Article history:
Received 2 March 2009
Accepted 11 March 2009
Available online 22 April 2009

Dedicated to GWJF—a great scientist and advisor—on the occasion of his 65th birthday

ABSTRACT

This paper describes studies on the feasibility of an asymmetric Favorskii rearrangement of a *meso*-dihaloketone substrate. In the racemic series, metal amide bases in the presence of amines give poor to reasonable yields of ring-contracted unsaturated cyclopentyl amides, whilst amines in aqueous solvent mixtures afford cyclopentyl amides in good to excellent yields. A range of chiral non-racemic amines are screened, a tiny diastereo-bias is observed and a tentative mechanistic rationale for the diastereoselective process is proposed.

1. Introduction

Since its disclosure in 1894,[1] the Favorskii rearrangement of α-haloketones has developed into a powerful synthetic tool[2–4] for the preparation of functionalized cyclopentyl units[5] and natural products.[6–8] It has found application in the generation of polycyclic cage structures[9,10] and alkenes,[11] and has been implicated in certain polyketide biosynthetic pathways.[12] The mechanism of this transformation has been investigated extensively,[13,14] and it has been demonstrated that substrates with an acidic α-hydrogen rearrange via a cyclopropanone intermediate.[15,16] The initial step in this process is deprotonation at the α′ carbon to generate an enolate, and two pathways have been proposed for the subsequent cyclopropanone formation (Fig. 1).

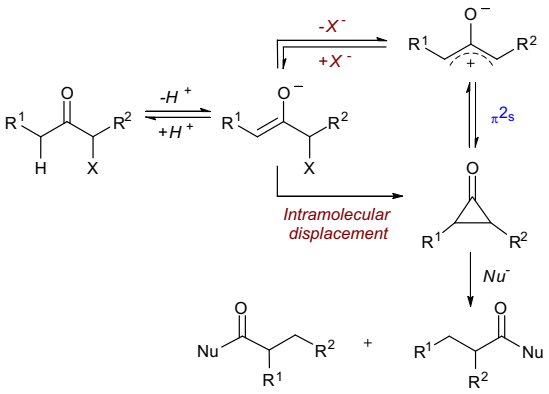


Figure 1. Mechanistic pathways in the Favorskii rearrangement.

The cyclopropanone may be formed in a single step through intramolecular displacement of the leaving group by the enolate carbanion[16] (in an analogous manner to the generally accepted mechanism of the Ramberg–Bäcklund reaction)[17] but this is disfavoured on stereoelectronic grounds.[18] An alternative mechanism for cyclopropanone formation involving loss of the leaving group from the enolate to form a delocalized zwitterion that undergoes a reversible 2π-electron disrotatory electrocyclization has also been proposed.[19–21] According to the zwitterion pathway, the stereochemistry of the Favorskii rearrangement is determined after halide elimination, since the planar zwitterion may close in one of two directions. Factors such as solvent choice, substitution and ring strain will affect the relative rates of direct displacement of the halide and zwitterion formation, and hence determine how the cyclopropanone may be formed. Products consistent with a direct displacement mechanism have occasionally been reported in aprotic solvent systems,[22] but this stereoselectivity is lost when the transformation is performed in polar protic solvents,[23] presumably due to reversible zwitterion electrocyclization.

Although chiral haloketones have been demonstrated to undergo the Favorskii rearrangement with high diastereoselectivity, to the best of our knowledge there are no examples of enantio- or diastereoselective Favorskii rearrangements of achiral haloketones; such a process would have significant utility in the synthesis of highly functionalized chiral building blocks. Accordingly, we initiated investigations into a transformation by which a *meso*-dihaloketone such as **1** could undergo a Favorskii rearrangement to afford chiral cyclopentenes such as **3** (Fig. 2).

Loss of *HX* to form an intermediate cyclopropanone **2** can occur by the two mechanisms described previously. Subsequently, an enantioenriched cyclopropanone **2** may be opened by a nucleophile via two distinct pathways, resulting in a mixture of enantiomers. Stepwise cleavage to place the resulting anion adjacent to the

* Corresponding author. Tel.: +44 1865 285103; fax: +44 1865 285002.
E-mail address: martin.smith@chem.ox.ac.uk (M.D. Smith).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.03.020

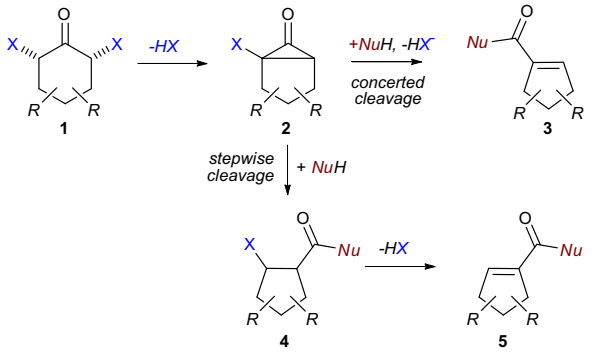
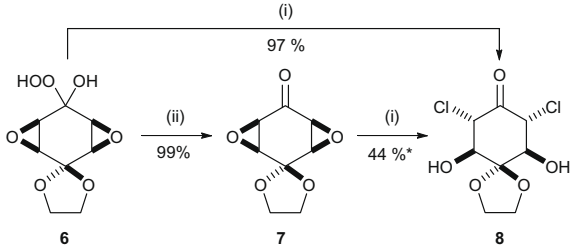


Figure 2. Desymmetrization of a *meso*-dihaloketone (X = leaving group; Nu = nucleophile).

electronegative halide, followed by β-elimination, would yield **5**, whilst concerted cyclopropanone cleavage and halide elimination would produce its enantiomer **3**. In general, both steric factors and carbanion stability determine the direction of cyclopropanone cleavage.[24] Thus an enantioselective Favorskii rearrangement requires formation of an enantioenriched cyclopropanone intermediate, and also discrimination between the stepwise and concerted mechanisms of cleavage. Concerted cyclopropanone cleavage and stepwise cyclopropanone cleavage have been known to compete during the Favorskii rearrangement of acyclic dichloroketones, despite the absence of a strictly antiperiplanar relationship between the σ* orbitals of the breaking C–C and C–Cl bonds in the cyclopropanone.[25]

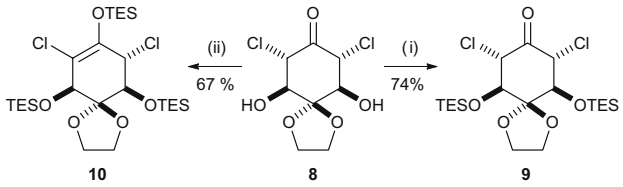
2. Results and discussion

We planned to investigate the Favorskii rearrangement of a highly substituted *meso*-dihaloketone in the generation of functionalized cyclopentenes. The *syn*-bis epoxide **7** and the hydroperoxide hemiacetal **6** are readily available in two high-yielding steps from 4-methoxyphenol,[26] and we had envisaged that regioselective opening of this epoxide with a halide anion could afford a highly functionalized *meso*-haloketone. This was achieved through treatment of peroxide **6** with anhydrous cerium trichloride in acetonitrile[27] to give *meso*-chlorohydrin **8** as the sole product in 97% yield; no trace of the C-3 chloride regioisomer was detected (Scheme 1).



Scheme 1. Reagents and conditions: (i) $CeCl_3$, MeCN, rt (ii) Na_2SO_3 (aq), MeOH. *Estimated conversion based on ^{1}H NMR spectroscopy.

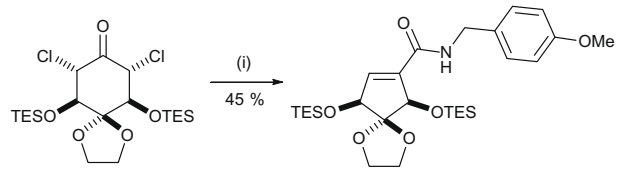
The chloride **8** may be stored for extended periods of time at 0 °C, but cannot be purified by chromatography, and it was isolated as an analytically pure solid by filtration through Celite™. Epoxyketone **7** was also treated with cerium trichloride to yield **8** but the reaction was significantly less efficient (and hence hydroperoxide **6** was used preferentially). It is unlikely that the hydroperoxide **6** would directly undergo such regioselective opening, so it is proposed that the carbonyl derivative **7** is regenerated in situ before the epoxide is opened. Protection of the hydroxyl groups in **8** required mild conditions to prevent β-elimination, and a variety of methods were attempted for installing a range of protecting groups. Protection with triethylsilyl chloride (TESCl) and imidazole in DMF proceeded smoothly with 1.85 equiv of TESCl to afford **9** in 74% yield; the use of an excess of TESCl resulted in formation of silylenol ether **10** that could be isolated in 67% yield (Scheme 2).



Scheme 2. Reagents and conditions: (i) 1.8 equiv TESCl, imidazole, DMF; (ii) 6 equiv TESCl, imidazole, DMF.

2.1. Initial investigations: metal hydride and amide bases

With a practical and scalable route to the protected chloroketone **9** in hand, our initial approach considered whether an appropriate enantioenriched base[28] in an aprotic solvent could, through the selective and essentially irreversible deprotonation of one of the axial hydrogens, facilitate the formation of an enantioenriched cyclopropanone. This requires cyclopropanone formation to be faster than equilibration between the enantiomeric enolates. With this tenet in mind, it was decided to explore the use of metal amide bases in the presence of a nucleophilic amine, and 4-methoxybenzylamine was initially chosen as the nucleophile (as its incorporation could easily be observed by the distinctive signals in the ^{1}H NMR spectra). In a typical experiment, a solution of the amide base and substrate **9** was stirred at −78 °C and was allowed to warm to room temperature before adding the nucleophile.[29] No products derived through β-elimination were observed under these conditions. The best results were obtained with NaHMDS in dichloromethane; however, only a 45% yield of amide **11** was obtained (Scheme 3).

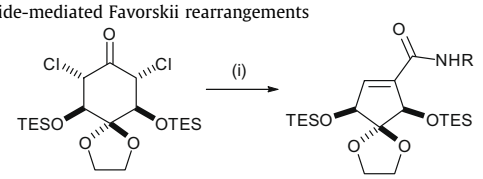


Scheme 3. Reagents and conditions: (i) NaHMDS, DCM, −78 °C to rt; then $PMBNH_2$.

Lithium amide bases were also explored but these gave only traces of the desired product as components of complex mixtures of materials. Enantioenriched enolates formed using enantiopure lithium amide bases are often trapped at low temperature, before exposure to electrophiles;[30] such procedures are known to improve the enantioselectivity of these reactions.[31] However, attempting to initiate Favorskii rearrangements at such low temperatures led to low conversions, and attempts to facilitate the rearrangement of enol ethers such as **10** were unproductive. In further attempts to attain synthetically useful yields in the Favorskii rearrangement of **9**, sodium and potassium hydrides were screened using 4-methoxybenzylamine ($PMBNH_2$) as the nucleophile with a range of solvents, stoichiometries and temperatures.[29] The most effective combination was sodium hydride in dichloromethane (47% yield), and a range of amines were employed under

these conditions (Table 1). Unhindered primary amines such as hexylamine **12** (21% yield), generally give poor to moderate yields under these conditions, whilst respectable yields are achieved with more hindered amines such as *tert*-butylamine (to afford **14**) and pyrrolidine (to yield **15**). Unhindered primary amines have previously been reported to result in low yields in Favorskii rearrangements, presumably due to the reactivity of haloketones towards more nucleophilic species.[32] Diisopropylamine gave only 11% of the required cyclopentene **18**, suggesting that this nucleophile is approaching the limit of steric bulk that may be accommodated in this reaction. Alcohols such as methanol **19** and isopropanol (compound **20**) may also be utilized, with more hindered alcohols affording the product in a higher yield, consistent with similar observations in the amine series.

Table 1
Metal hydride-mediated Favorskii rearrangements



9

Compound	Nucleophile (RH)	Yield (%)
11	4-Methoxybenzylamine	47
12	Hexylamine	21
13	(*S*)-α-Methylbenzylamine	26 (dr 1:1)
14	*tert*-Butylamine	67
15	Pyrrolidine	70
16	Piperidine	61
17	Morpholine	56
18	Diisopropylamine	11
19	Methanol	36
20	Isopropanol	45

Reagents and conditions: (i) NaH (2.6 equiv), DCM, 0 °C to rt; then nucleophile (1.2 equiv).

2.2. Mechanistic implications

In an attempt to ascertain the nature of the rearrangement process, direct detection of the enolate **21** by ^{1}H NMR spectroscopy was attempted. At first, NaHMDS was added to a solution of **9** in deuterated chloroform that contained 1,3-dinitrobenzene as an internal standard. Within 4 min at 27 °C, a new species consistent with enolate **21** was observed. Enolization appeared to be effectively complete within 10 min, at which point acetic acid was added, effecting regeneration of substrate **9** at the expense of the new species within 3 min. These observations are consistent with the formation of an intermediate enolate **21** under these conditions, demonstrating that deprotonation of **9** occurs readily at room temperature under the reaction conditions (Fig. 3).

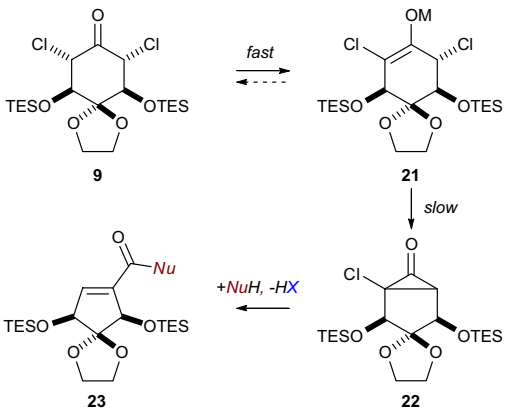


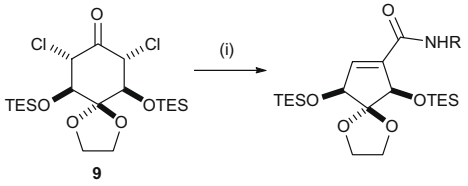
Figure 3. Enolization is faster than Favorskii rearrangement in the presence of metal amide bases (M = metal, Nu = nucleophile).

The experiment was repeated, by replacing the acetic acid with 4-methoxybenzylamine.[33] However, upon treatment with $PMBNH_2$ the enolate **21** was still visible as the Favorskii amide **11** was formed. Complete conversion of enolate **21** into amide **11** required more than 1.5 h at 27 °C, which is significantly longer than the 10 min required for enolization to occur. This indicates that Favorskii rearrangement of enolate **21** is markedly slower than deprotonation of ketone **9**. A corollary implication of this is that in the presence of a proton source, reversible enolization is likely to occur prior to Favorskii rearrangement. As a consequence, this approach is unlikely to facilitate an asymmetric Favorskii rearrangement.

2.3. An amine-induced Favorskii rearrangement

The moderate yields of Favorskii products obtained when sodium bases were used with primary amines or alcohols were not satisfactory, so a more general and high-yielding method was pursued. There are several examples in the literature in which the Favorskii rearrangement is induced through treatment with primary[34,35] or secondary amines.[36–38] Treatment of **9** with a range of primary and secondary amines in an acetonitrile/water mixture gave the desired products in good to excellent yields (Table 2).

Table 2
Amine-induced Favorskii rearrangements



9

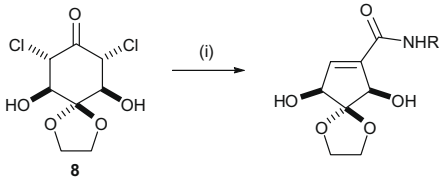
Compound	Amine (RH)	Yield (%)
11	4-Methoxybenzylamine	45
12	Hexylamine	72
13	(*S*)-α-Methylbenzylamine	92 (dr 1:1)
14	*tert*-Butylamine	67
15	Pyrrolidine	85
16	Piperidine	85
17	Morpholine	79
18	Diisopropylamine	0
24	*N*,*O*-Dimethylhydroxylamine[a]	71
25	*N*-Methyl piperazine	75

Reagents and conditions: (i) Amine (1.5 equiv), MeCN:H_2O (1:1), 0 °C to rt.
[a] *N*,*O*-Dimethylhydroxylamine. HCl (2.5 equiv) and Et_3N (4.5 equiv) were used.

Both secondary and primary amines were well tolerated, and chiral amines such as (*S*)-α-methylbenzylamine could be used to give diastereoisomeric products that may be separated to give enantiopure material **13**. This method requires aqueous solvent mixtures; switching to organic solvents led to significantly less efficient transformations. In general the yields are superior to those obtained in the metal-mediated process described earlier, with cyclic amines giving good to excellent yields of ring-contracted amide products. Synthetically useful morpholine and Weinreb amides may also be produced in this process **17** and **24**, respectively, allowing controlled access to a range of carbonyl oxidation levels. However, diisopropylamine was unsuccessful in this transformation **18**, anecdotally suggesting that the reaction proceeds

via an alternative mechanistic pathway. The mild nature of this process also permits the transformation to be employed with the unprotected dihydroxydihaloketone **8** as a substrate (Table 3).

Table 3
Amine-induced Favorskii rearrangements on unprotected substrates



8

Compound	Amine (RH)	Yield (%)
26	Hexylamine	70
27	Pyrrolidine	67
28	Morpholine	72
29	*N*-Methyl piperazine	67

Reagents and conditions: Amine (1.5 equiv), MeCN:H_2O (1:1), 0 °C to rt.

Cyclic **27**–**29** and primary amines **26** are successful under these conditions, giving access to hydroxylated cyclopentene amides in good overall yields. It is remarkable that these transformations proceed with such efficiency on this reactive substrate, and that no evidence of β-elimination is observed. The metal-mediated conditions described earlier were unsurprisingly unsuccessful in this regard.

2.4. Mechanistic implications II

The differences in reactivity and selectivity observed between the metal- and amine-mediated Favorskii rearrangements (e.g., in the preparation of diisopropylamide **18**) are consistent with alternative mechanisms for these two processes. A postulated mechanism for the amine-mediated Favorskii rearrangement is depicted below (Fig. 4).

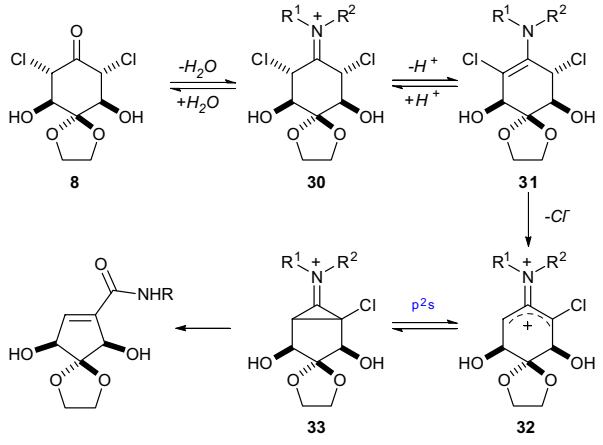


Figure 4. Postulated amine-mediated Favorskii rearrangement mechanism.

It is proposed that this reaction proceeds via loss of chloride from an enamine intermediate **31** to form a zwitterion **32** that will close to generate a cyclopropyliminium species **33**. Reaction of this with another mole of the nucleophilic amine and elimination of halide generate the finally observed cyclopentenyl amide. Mechanisms of this nature are not unprecedented; there are examples of Favorskii rearrangements induced by piperidine where sodium methoxide is ineffective, and it has been hypothesized that these reactions proceed by such pathways.[39] The rate-determining step for the Favorskii rearrangement has been shown to be either halide loss or deprotonation, depending on the substrates and conditions employed. It has been postulated that for reactions proceeding via cyclopropyliminium species, deprotonation of the iminium cation, and not halide loss is the rate-determining step.[40,41]

2.5. Studies using chiral non-racemic amines: a diastereoselective Favorskii rearrangement

It was hoped that the amine-induced Favorskii rearrangement could be rendered enantio- or diastereoselective through selective deprotonation of the imine or iminium cation intermediate. If the rate-determining step were loss of a proton to form the enamine such as **31**,[36] then the amine would require a functional group on the side chain that is capable of intramolecular deprotonation (Fig. 5A). If chloride loss, and not deprotonation, were the rate-determining step, then it is possible that an amine derivative with a functional group capable of stabilizing a developing positive charge could induce some diastereoselectivity (Fig. 5B).

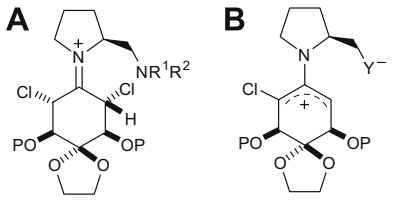
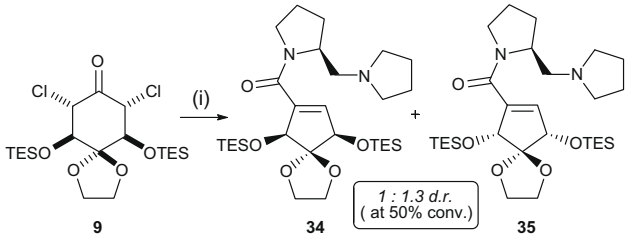


Figure 5. Rationale for screening chiral proline-derived amines.

It was therefore decided to also screen a range of amines bearing a negatively charged side chain. L-Proline derivatives were utilized, as the pyrrolidine ring has superior nucleophilic properties than other cyclic amines,[42,43] and its side chain can be easily modified to bear both amino and other functional groups.

With these concerns in mind, dichloroketone **9** was treated with 1.5 equiv of several L-proline derivatives in a 1:1 solution of acetonitrile and water, and the crude reaction mixtures of the resulting Favorskii amides were analyzed by ^{1}H NMR spectroscopy. The only promising result was obtained when dichloroketone **9** was stirred for 114 h with 1.5 equiv of *(S)*-1-(2-pyrrolidinylmethyl) pyrrolidine to afford amides **34** and **35**. The crude ^{1}H NMR spectrum in DMSO at 90 °C revealed a modest 1.3:1 d.r. at 50% conversion (Scheme 4).[44]



Scheme 4. Reagents and conditions: (i) *(S)*-1-(2-pyrrolidinylmethyl) pyrrolidine (1.5 equiv), MeCN:H_2O (1:1), 0 °C to rt.

Complete conversion could be achieved through the use of 3.5 equiv of the chiral pyrrolidine at the expense of the modest selectivity (complete conversion in 18 h, 1:1 d.r.). Alternatively, 1.5 equiv of the chiral pyrrolidine plus 3.5 equiv of another tertiary amine base (presumably to buffer the 2 equiv of HCl that is generated during the reaction) could be employed. Bases such as triethylamine, diisopropylethylamine and 1,2,2,6,6-pentamethylpiperidine gave complete conversion but no diastereoselectivity, but more hindered bases such as 2,6-lutidine (25% conversion in 42 h, 1.3:1 d.r.) and 2,6-di-*tert*-butylpyridine (70% conversion in 65 h, 1.3:1 d.r.) were more

promising. These results were consistent with the hypothesis that competing intermolecular deprotonation was a contributing factor to the low diastereoselectivity obtained. Our subsequent attempts to improve the selectivity in this transformation were all based around this tenet. Unfortunately, a wide range of experiments to elucidate the effects of dilution and solvent changes led only to erosion of the tiny observed diastereoselectivity.

3. Conclusions

The Favorskii rearrangement is a mechanistically complex multi-stage transformation that may be exploited to generate highly functionalized cyclopentanes, which are important synthetic intermediates. This study outlines two distinct and moderately efficient methods for this rearrangement by which chiral cyclopentene derivatives may be obtained from a *meso*-dihaloketone. Our attempts to induce a truly asymmetric Favorskii rearrangement were ultimately unsuccessful. Although some diastereoselectivity was obtained through the use of a proline-derived chiral non-racemic amine, we were unable to develop this into a reaction with genuine synthetic utility. However, this small diastereo-bias (which is probably the only example of a diastereoselective Favorskii rearrangement of an achiral haloketone) augurs well for future endeavours concerning this multifaceted, yet ultimately frustrating reaction.

4. Experimental

4.1. General

4.1.1. Solvents

Dichloromethane, methanol, toluene, hexane and acetonitrile were distilled from calcium hydride. Tetrahydrofuran was distilled from lithium aluminium hydride and calcium hydride in the presence of triphenylmethane, or from sodium in the presence of benzophenone. All other anhydrous solvents were used as supplied (Sureseal®). Petroleum ether refers to 40:60 petroleum ether.

4.1.2. Reagents

Except as otherwise indicated, reactions were carried out under nitrogen. Anhydrous cerium trichloride was obtained by heating cerium trichloride heptahydrate at 150 °C under high vacuum for 8 h. Buffer solution, pH 7, contained KH_2PO_4 (212.5 g) and NaOH (36.25 g) in distilled water (2375 mL). All other reagents were purified in accordance with common procedures or were used as obtained from commercial sources.

4.1.3. Chromatography

Flash Column chromatography was performed using Merck or Breckland Kieselgel (230–400 mesh) under pressure. Analytical layer chromatography (TLC) was performed using glass plates precoated with Merck silica gel 60 F_{254}. Visualization was done by ultra-violet radiation (254 nm) or by staining with ceric ammonium molybdate or aqueous potassium permanganate.

4.1.4. Data collection

Except as otherwise indicated, yields refer to chromatographically and spectroscopically pure compounds. Melting points were obtained using a Reichert hot plate microscope with a digital thermometer attachment and are uncorrected. Infrared spectra were recorded neat on a Perkin–Elmer Spectrum One FT-IR spectrometer equipped with an attenuated total reflectance accessory. Absorption maxima (ν_{max}) are reported in wave numbers (cm^{-1}). ^1H NMR spectra were recorded on Bruker AM-400 and DRX-600 spectrometers at 400 and 600 MHz, respectively. Proton assignments are supported by ^1H–^1H correlation spectra where necessary. Chemical shifts (δ_H) are quoted to the nearest 0.01 ppm and are referenced to the residual non-deuterated solvent peak. Coupling constants (J) are reported in hertz to the nearest 0.5 Hz and are not averaged. Data are reported as follows: chemical shift, multiplicity, [b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; or as a combination of these (e.g., dd and dt)], integration, coupling constant(s) and assignment (Hn). Equatorial and axial protons are assigned as Hn*eq* and Hn*ax*, respectively. Where the observed multiplicity differs from the coupling observed in a COSY spectrum the suffix a- (apparent) is used (e.g., a-t, apparent triplet). Diastereotopic protons are assigned as Hn and Hn′, where the ′ indicates the higher field proton. ^{13}C NMR spectra were recorded at 100 MHz and 150 MHz on Bruker AM-400 and DRX-600 spectrometers, respectively. Carbon assignments are supported by DEPT editing and where necessary by ^{13}C–^1H (HMQC and HMBC) correlations. Chemical shifts (δ_C) are quoted in ppm to the nearest 0.1 ppm, and are referenced to the residual solvent peak. High-resolution mass measurements were performed by the University of Cambridge and the EPSRC mass spectrometry service at the University of Wales, Swansea, using electrospray ionization (ES^+) or electron impact (EI^+) techniques.

4.1.4.1. *meso*-(6*S*,7*R*,9*S*,10*R*)-7,9-Dichloro-6,10-dihydroxy-1,4-dioxa-spiro[4.5]decan-8-one 8. A solution of **6** (1.97 g, 9.27 mmol) in acetonitrile (90 mL) was added with vigorous stirring to anhydrous cerium trichloride (7.25 g, 29.4 mmol) at rt under N_2. The resulting mustard-coloured suspension was stirred for 67 h before being filtered through Celite® and was washed with acetonitrile. The filtrate was concentrated in vacuo to afford **8** as a white solid that was used without further purification (2.43 g, 9.46 mmol, 97% yield). IR ν_{max} (neat) 3399 (b, O–H), 1755, (C=O), 1420, 1343, 1248, 1224, 1173, 1133, 1117, 1030, 1000, 953, 851 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 5.86 (d, 2H, *J* 7.0 Hz, O*H*), 4.92 (d, 2H, *J* 11.0 Hz, H2), 4.16–4.08 (m, 4H, OCH_2CH_2O), 3.68 (d, 2H, *J* 11.0, 7.0 Hz, H3); δ_C (100 MHz, DMSO-d_6) 191.3 (C1), 109.0 (C4), 73.3 (C3), 68.3 (C2), 68.2 (OCH_2CH_2O), 67.0 (OCH$_2CH_2$O); HRMS (EI^+) calcd for $C_8H_{10}{}^{35}Cl_2O_5$ $[M]^+$ 255.9905, found 255.9917; mp = 165–167 °C (acetonitrile).

4.1.4.2. *meso*-(6*S*,7*R*,9*S*,10*R*)-7,9-Dichloro-6,10-bis-(triethyl-silanyloxy)-1,4-dioxa-spiro[4.5]decan-8-one 9. Triethylsilyl chloride (1.22 mL, 7.29 mmol) was added dropwise to a stirred solution of **8** (1.17 g, 4.56 mmol) and imidazole (1.24 g, 18.2 mmol) in *N*,*N*-dimethylformamide (15 mL) at 0 °C under N_2. The reaction mixture was stirred at rt for 19 h before being diluted with 10% $MgSO_4$ solution (50 mL) and extracted with petroleum ether (4 × 50 mL). The organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo to leave **9** as a white crystalline solid (1.64 g, 3.39 mmol, 74% yield). IR ν_{max} (neat) 2957, 2909, 2878, 1753 (C=O), 1459, 1416, 1265, 1247, 1144, 1046, 1006, 953, 856 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.77 (d, 2H, *J* 10.5 Hz, H2), 4.21 (t, 2H, *J* 6.0 Hz, OCH_2CH$_2$O), 4.14 (t, 2H, *J* 6.0 Hz, OCH$_2CH_2$O), 3.68 (d, 2H, *J* 10.5 Hz, H3), 0.98 (t, 18H, *J* 8.0 Hz, SiCH$_2CH_3$), 0.70 (q, 12H, *J* 8.0 Hz, SiCH_2CH$_3$); δ_C (100 MHz, $CDCl_3$) 191.2 (C1), 109.0 (C4), 76.0 (C3), 68.4 (OCH_2CH_2O), 68.0 (C2), 67.8 (OCH$_2$-CH_2O), 7.2 (CH_2CH_3), 5.5 (SiCH_2); HRMS (ES^+) calcd for $C_{20}H_{38}{}^{35}Cl_2NaO_5Si_2$ $[MNa]^+$ 507.1533, found 507.1538; mp = 63–64 °C (petroleum ether).

4.1.4.3. *rac*-(6*S*,9*S*,10*R*)-7,9-Dichloro-6,8,10-tris-(triethyl-silanyloxy)-1,4-dioxa-spiro[4.5]dec-7-ene 10. Triethylsilyl chloride (0.27 mL, 1.59 mmol) was added dropwise to a stirred solution of **8** (68 mg, 0.27 mmol) and imidazole (145 mg, 2.12 mmol) in *N*,*N*-dimethylformamide (0.2 mL) at 0 °C under N_2. The reaction mixture was stirred at rt for 7 h before being diluted with 10% $MgSO_4$

solution (10 mL) and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with 10% $MgSO_4$ solution, dried over $MgSO_4$, filtered and concentrated in vacuo to leave an orange oil. Purification over silica gel (40:1 petroleum ether:ethyl acetate) gave **10** as a clear oil (107 mg, 0.18 mmol, 67% yield). IR ν_{max} (neat) 2954, 2911, 2877, 1645 (C=C), 1458, 1413, 1380, 1287, 1238, 1221, 1172, 1140, 1116, 1063, 1003, 831 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.43 (dd, 1H, *J* 8.0, 2.5 Hz, H5), 4.35 (d, 1H, *J* 2.5 Hz, H3), 4.12–4.03 (m, 4H, OCH_2CH_2O), 3.85 (d 1H, *J* 8.0 Hz, H6) 1.02–0.98 (m, 27H, $SiCH_2CH_3$), 0.75–0.68 (m, 18H, $SiCH_2CH_3$); δ_C (100 MHz, $CDCl_3$) 142.6 (C1), 116.7 (C2/4), 109.2 (C2/4), 77.6 (C3/5), 72.9 (C3/5), 67.6 (OCH_2CH_2O), 67.2 (OCH_2CH_2O), 65.0 (C6), 7.3, 7.2, 7.1, 7.0, 6.8, 6.0, 5.53, 5.47 ($SiCH_2CH_3$); HRMS (ES^+) calcd for $C_{26}H_{52}{}^{35}Cl_2NaO_5Si_3$ $[MNa]^+$ 621.2397, found 621.2379.

4.1.4.4. General procedures for Favorskii rearrangements. *Method A*: Sodium hydride (60% dispersion in mineral oils) was added to a solution of chloroketone in dichloromethane at −78 °C under N_2. The reaction mixture was warmed to rt over 1 h before the nucleophile was added. The reaction mixture was stirred until TLC analysis (4:1 petroleum ether:ethyl acetate) indicated consumption of the substrate. Buffer, pH 7, was added and the mixture was extracted with chloroform:isopropanol (4:1). The organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to leave a crude product that was purified over silica gel.

Method B: Nucleophilic amine was added to a mixture of chloroketone in acetonitrile and water at 0 °C. The reaction mixture was stirred until TLC analysis (4:1 petroleum ether:ethyl acetate) indicated consumption of the substrate. Buffer, pH 7, was added and the mixture was extracted with chloroform:isopropanol (4:1). The organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to leave a crude product that was purified over silica gel.

Method C: Nucleophilic amine was added to a mixture of chloroketone in acetonitrile and water at 0 °C. The reaction mixture was stirred until TLC analysis (4:1 petroleum ether:ethyl acetate) indicated consumption of the substrate. The reaction mixture was concentrated in vacuo to leave a crude product that was purified over silica gel.

Method D: Amine hydrochloride was added to a mixture of chloroketone in acetonitrile and water at 0 °C. Triethylamine was added and the reaction mixture was stirred until TLC analysis (4:1 petroleum ether:ethyl acetate) indicated consumption of the substrate. Buffer, pH 7, was added and the mixture was extracted with chloroform:isopropanol (4:1). The organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to leave a crude product that was purified over silica gel.

4.1.4.5. *rac*-(6*S*,9*R*)-6,9-Bis-(triethyl-silanyloxy)-1,4-dioxa-spiro-[4.4]non-7-ene-7-carboxylic acid 4-methoxy-benzylamide 11. *Method A:* A solution of **9** (88 mg, 0.18 mmol), sodium hydride (19 mg, 0.47 mmol) and 4-methoxybenzylamine (28 μL, 0.22 mmol) in dichloromethane (5 mL) was stirred for 30 h. Purification over silica gel (5:1 petroleum ether:ethyl acetate) gave **11** as a clear oil (47 mg, 0.09 mmol, 47% yield).

Method C: A mixture of **9** (52 mg, 0.11 mmol) and 4-methoxybenzylamine (25 μL, 0.19 mmol) in acetonitrile (1.5 mL) and water (1.5 mL) was stirred for 19 h. Purification over silica gel (6:1 petroleum ether:ethyl acetate) gave **11** as a clear oil (27 mg, 0.05 mmol, 46% yield). IR ν_{max} (neat) 3370, 2954, 2876, 1667 (C=O), 1615, 1513, 1463, 1416, 1354, 1243, 1175, 1140, 1099, 1036, 1003, 951, 888, 816 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 7.27 (br s, 1H, NH), 7.20 (d, 2H, *J* 8.5 Hz, H9), 6.84 (d, 2H, *J* 8.5 Hz, H10), 6.58 (a-t, 1H, *J* 1.5 Hz, H3), 4.76 (a-t, 1H, *J* 1.5 Hz, H4), 4.51 (a-t, 1H, *J* 1.5 Hz, H6), 4.40 (m, 2H, H7), 4.21 (m, 1H, OCH_2CHHO), 4.08 (m, 1H, OCH_2CHHO), 4.06–4.00 (m, 2H, OCH_2CH_2O), 3.79 (s, 3H, OCH_3), 0.97 (t, 9H, *J* 8.0 Hz, CH_2CH_3), 0.86 (t, 9H, *J* 8.0 Hz, CH_2CH_3), 0.64 (m, 6H, $SiCH_2$) 0.50 (m, 6H, $SiCH_2$); δ_C (100 MHz, $CDCl_3$) 164.1 (C1), 159.5 (C11), 139.0 (C3), 137.9 (C8/2), 130.4 (C8/2), 130.0 (C9), 119.8 (C5), 114.4 (C10), 77.5 (C6), 75.0 (C4), 66.2 (OCH_2CH_2O), 66.0 (OCH_2CH_2O), 55.7 (OCH_3), 43.3 (C7), 7.1 (CH_2CH_3), 7.0 (CH_2CH_3), 5.3 ($SiCH_2$), 5.0 ($SiCH_2$); HRMS (ES^+) calcd for $C_{28}H_{48}NO_6Si_2$ $[MH]^+$ 550.3020, found 550.3030.

4.1.4.6. *rac*-(6*S*,9*R*)-6,9-Bis-(triethyl-silanyloxy)-1,4-dioxa-spiro[4.4]non-7-ene-7-carboxylic acid hexylamide 12. *Method A*: A solution of **9** (64 mg, 0.13 mmol), sodium hydride (14 mg, 0.55 mmol) and hexylamine (25 μL, 0.19 mmol) in dichloromethane (5 mL) was stirred for 52 h. Purification over silica gel (6:1 petroleum ether:ethyl acetate) gave **12** as a clear oil (14 mg, 0.03 mmol, 21% yield).

Method C: A mixture of **9** (51 mg, 0.11 mmol) and hexylamine (25 μL, 0.19 mmol) in acetonitrile (1.5 mL) and water (1.5 mL) was stirred for 47 h. Purification over silica gel (6:1 petroleum ether:ethyl acetate) gave **12** as a clear oil (39 mg, 0.08 mmol, 72% yield). IR ν_{max} (neat) 3365, 1659 (C=O), 1516, 1456, 1415, 1238, 1003 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.00 (br s, 1H, N*H*), 6.50 (a-t, 1H, *J* 1.5 Hz, H3), 4.79 (a-t, 1H, *J* 1.5 Hz, H4), 4.51 (a-s, 1H, H6), 4.25–4.20 (m, 1H, OCH_2CHHO), 4.13–4.03 (m, 3H, OCH_2CHHO), 3.38–3.18 (m, 2H, H7), 1.55–1.47 (m, 2H, H8), 1.36–1.27 (m, 6H, H9–H11), 0.99 (a-q, *J* 8.0 Hz, 18H, $SiCH_2CH_3$), 0.93–0.82 (m, 3H, H12), 0.77–0.60 (m, 12H, $SiCH_2$); δ_C (100 MHz, $CDCl_3$) 164.5 (C1), 138.4 (C3), 138.3 (C2), 119.7 (C5), 77.4 (C6), 75.1 (C4), 66.2 (OCH_2CH_2O), 66.0 (OCH_2CH_2O), 39.6 (C7), 31.9 (C8), 30.0 (C9), 27.1 (C10), 22.9 (C11), 14.4 (C12), 7.1 ($SiCH_2CH_3$), 7.1 ($SiCH_2CH_3$), 5.3 ($SiCH_2$), 5.2 ($SiCH_2$); HRMS (ES^+) calcd for $C_{26}H_{51}NNaO_5Si_2$ $[MNa]^+$ 536.3203, found 536.3198.

4.1.4.7. (6*R*,9*S*)-6,9-Bis-(triethyl-silanyloxy)-1,4-dioxa-spiro[4.4]-non-7-ene-7-carboxylic acid ((1*S*)-1-phenyl-ethyl)-amide 13a and (6*S*,9*R*)-6,9-bis-(triethyl-silanyloxy)-1,4-dioxa-spiro[4.4]non-7-ene-7-carboxylic acid ((1*S*)-1-phenyl-ethyl)-amide 13b[†]. *Method A:* A solution of **9** (130 mg, 0.27 mmol), sodium hydride (28 mg, 0.40 mmol) and (*S*)-α-methylbenzylamine (40 μL, 0.32 mmol) in dichloromethane (4.4 mL) was stirred for 22 h. Purification over silica gel (6:1 petroleum ether:ethyl acetate) gave a 1:1 mixture of diastereoisomers **13a** and **13b** as a clear oil (37 mg, 0.07 mmol, 26% yield).

Method C: A mixture of **9** (62 mg, 0.13 mmol) and (*S*)-α-methylbenzylamine (25 μL, 0.19 mmol) in acetonitrile (1.9 mL) and water (1.9 mL) was stirred for 80 h. Purification over silica gel (10:1 petroleum ether:ethyl acetate) gave a 1:1 mixture of **13a** and **13b** as a clear oil (63 mg, 0.12 mmol, 92% yield). IR ν_{max} (neat) 3374, 2955, 2876, 1659 (C=O), 1633, 1516, 1456, 1415, 1355, 1238, 1140, 1064, 1004, 887, 812 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.31–7.17 (m, 12H, ArH′, ArH, NH′, NH), 6.54 (a-t, 1H, *J* 1.5 Hz, H3′), 6.48 (a-t, 1H, *J* 1.5 Hz, H3), 5.21–5.14 (m, 2H, H7′, H7), 4.78 (a-s, 1H, H4), 4.72 (a-d, 1H, *J* 1.5 Hz, H4′), 4.47 (a-d, 2H, *J* 1.5 Hz, H6′, H6), 4.21–4.17 and 4.07–3.98 (m, 8H, OCH_2CH_2O), 1.49 (dd, 6H, *J* 6.9, 1.0 Hz, CH_3', CH_3), 0.98–0.78 (m, 36H, CH_2CH_3', CH_2CH_3), 0.66–0.38 (m, 24H, $SiCH_2$′, $SiCH_2$); δ_C (100 MHz, $CDCl_3$) 163.6 (C1′), 163.5 (C1), 143.4 (C8′, C8), 139.0 (C3′), 138.8 (C3), 138.4 (C2′), 138.1 (C2), 128.9 (ArC′), 128.9 (ArC), 127.7 (ArC′), 127.7 (ArC), 127.1 (ArC′), 126.7 (ArC), 119.8 (C5′), 119.6 (C5), 77.6 (C6′, C6), 75.0 (C4′), 74.9 (C4), 66.2, 66.2, 65.9, 65.9 (OCH_2CH_2O′, OCH_2CH_2O), 48.8 (C7′), 48.8 (C7), 21.8 (CH_3'), 21.0 (CH_3), 7.1, 7.1, 7.0, 7.0 (CH_2CH_3', CH_2CH_3), 5.3, 5.2, 5.1, 5.0 ($SiCH_2$′, $SiCH_2$); HRMS (ES^+) calcd for $C_{28}H_{48}NO_5Si_2$ $[MH]^+$ 534.3071, found 534.3061.

[†] The relative configurations of **13a** and **13b** were not determined.

4.1.4.8. *rac*-(6*S*,9*R*)-6,9-Bis-triethylsilanyloxy-1,4-dioxa-spiro[4.4]-non-7-ene-7-carboxylic acid tert-butylamide 14. *Method A:* A solution of **9** (64 mg, 0.13 mmol), sodium hydride (14 mg, 0.34 mmol) and *tert*-butylamine (25 μL, 0.24 mmol) in dichloromethane (5 mL) was stirred for 15 h 30 min. Purification over silica gel (6:1 petroleum ether:ethyl acetate) gave **14** as a clear oil (43 mg, 0,09 mmol, 67% yield).

Method C: A mixture of **9** (39 mg, 0.08 mmol) and *tert*-butylamine (13 μL, 0.12 mmol) in acetonitrile (2 mL) and water (2 mL) was stirred for 23 h. Purification over silica gel (10:1 petroleum ether:ethyl acetate) gave **14** as a clear oil (26 mg, 0.05 mmol, 67% yield). IR ν_{max} (neat) 3316, 2966, 2914, 2159, 2032, 1651 (C═O), 1628 (C═C), 1542, 1456, 1392, 1365, 1215, 1131, 1059, 1016, 988, 952, 889, 803, 758 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.68 (s, 1H, N*H*), 6.43 (a-t, 1H, *J* 1.5 Hz, H3), 4.76 (a-s, 1H, H4/6), 4.48 (a-s, 1H, H4/6), 4.24–4.18 (m, 1H, OC*H*HCH$_2$O), 4.12–4.01 (m, 3H, OCH*HC*H$_2$O), 1.37 (s, 9H, H8), 1.01–0.95 (m, 18H, CH$_2$C*H*$_3$), 0.81–0.58 (m, 12H, SiC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 163.9 (C1), 139.9 (C2), 137.5 (C3), 119.6 (C5), 77.3 (C4/6), 74.9 (C4/6), 66.2 (O*C*H$_2$CH$_2$O), 65.9 (OCH$_2$*C*H$_2$O), 51.6 (C7), 29.1 (C8), 7.1 (CH$_2$*C*H$_3$), 7.1 (CH$_2$*C*H$_3$), 5.2 (Si*C*H$_2$), 5.1 (Si*C*H$_2$); HRMS (ES^+) calcd for $C_{24}H_{48}NO_5Si_2$ $[MH]^+$ 486.3066, found 486.3067.

4.1.4.9. *rac*-(6*S*,9*R*)-(6,9-Bis-triethylsilanyloxy-1,4-dioxa-spiro[4.4]non-7-en-7-yl)-pyrrolidin-1-yl-methanone 15. *Method A*: A solution of **9** (80 mg, 0.16 mmol), sodium hydride (17 mg, 0.45 mmol) and pyrrolidine (20 μL, 0.24 mmol) in dichloromethane (6 mL) was stirred for 24 h. Purification over silica gel (4:1 petroleum ether:ethyl acetate) gave **15** as a clear oil (56 mg, 0.12 mmol, 70% yield).

Method B: A mixture of **9** (100 mg, 0.21 mmol) and pyrrolidine (30 μL, 0.36 mmol) in acetonitrile (3 mL) and water (3 mL) was stirred for 8 h. Purification over silica gel (6:1 petroleum ether:-ethyl acetate) gave **15** as a clear oil (85 mg, 0.18 mmol, 85% yield). IR ν_{max} (neat) 2963, 2876, 1650 (C═O), 1615 (C═C), 1434, 1343, 1275, 1235, 1146, 1119, 1099, 1064, 1041, 1003, 973, 951, 860, 819, 728, 691 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.74 (a-t, 1H, *J* 1.5 Hz, H3), 4.85 (d, 1H, *J* 1.5 Hz, H4/6), 4.53 (d, 1H, *J* 1.5 Hz, H4/6), 4.19–4.01 (m, 4H, OC*H*$_2$C*H*$_2$O), 3.81- 3.76 and 3.49–3.35 (m, 1H and 3H, H7, H10), 1.93–1.69 (m, 4H, H8, H9), 0.99–0.92 (m, 18H, CH$_2$C*H*$_3$), 0.66–0.59 (m, 12H, SiC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 165.8 (C1), 142.6 (C2), 130.5 (C3), 118.8 (C5), 76.9 (C4/6), 76.5 (C4/6), 66.5 (O*C*H$_2$CH$_2$O), 66.2 (OCH$_2$*C*H$_2$O), 48.9 (C7/10), 45.6 (C7/10), 26.2 (C8/9), 24.9 (C8/9), 7.1 (CH$_2$*C*H$_3$), 7.0 (CH$_2$*C*H$_3$), 5.1 (Si*C*H$_2$), 5.1 (Si*C*H$_2$); HRMS (ES^+) calcd for $C_{24}H_{46}NO_5Si_2$ $[MH]^+$ 484.2909, found 484.2908.

4.1.4.10. *rac*-(6*S*,9*R*)-(6,9-Bis-triethylsilanyloxy-1,4-dioxa-spiro[4.4]-non-7-en-7-yl)-piperidin-1-yl-methanone 16. *Method A*: A solution of **9** (59 mg, 0.12 mmol), sodium hydride (13 mg, 0.32 mmol) and piperidine (20 μL, 0.18 mmol) in dichloromethane (5 mL) was stirred for 16 h. Purification over silica gel (6:1 petroleum ether:ethyl acetate) gave **16** as a clear oil (37 mg, 0.07 mmol, 61% yield).

Method B: A mixture of **9** (90 mg, 0.19 mmol) and piperidine (30 μL, 0.30 mmol) in acetonitrile (2.8 mL) and water (2.8 mL) was stirred for 29 h. Purification over silica gel (6:1 petroleum ether:ethyl acetate) gave **16** as a clear oil (69 mg, 0.14 mmol, 75% yield).

Method D: A 0.02 M solution of **9** (49 mg, 0.10 mmol), piperidine hydrochloride (18 mg, 0.15 mmol) and triethylamine (0.05 mL, 0.35 mmol) in acetonitrile (2.5 mL) and water (2.5 mL) was stirred for 14 h. Purification over silica gel (6:1 petroleum ether:ethyl acetate) gave **16** as a clear oil (43 mg, 0.09 mmol, 85% yield). IR ν_{max} (neat) 2952, 2876, 1647 (C═O), 1619 (C═C), 1442, 1353, 1282, 1265, 1234, 1152, 1136, 1086, 1064, 1040, 1002, 952, 896, 875, 854, 811, 724 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.66 (dd, 1H, *J* 2.0, 1.0 Hz, H3), 4.84 (a-s, 1H, H4/6), 4.52 (a-s, 1H, H4/6), 4.19–4.00 (m, 4H, OC*H*$_2$C*H*$_2$O), 3.67–3.59 and 3.48–3.43 (m, 4H, H7, H11), 1.64–1.49 (m, 6H, H8, H9, H10), 0.98–0.93 (m, 18H, CH$_2$C*H*$_3$), 0.67–0.58 (m, 12H, SiC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 166.1 (C1), 141.8 (C2), 129.7 (C3), 119.0 (C5), 76.9 (C4/6), 76.5 (C4/6), 66.5 (OCH$_2$-CH$_2$O), 66.2 (OCH$_2$*C*H$_2$O), 48.6 (C7/11), 42.6 (C7/11), 26.8 (C8/10), 25.9 (C8/10), 25.0 (C9), 7.1 (CH$_2$*C*H$_3$), 7.0 (CH$_2$*C*H$_3$), 5.2 (Si*C*H$_2$), 5.2 (Si*C*H$_2$); HRMS (ES^+) calcd for $C_{25}H_{48}NO_5Si_2$ $[MH]^+$ 498.3066, found 498.3060.

4.1.4.11. (*rac*)-(6*S*,9*R*)-(6,9-Bis-triethylsilanyloxy-1,4-dioxa-spiro-[4.4]non-7-en-7-yl)-morpholin-4-yl-methanone (17). *Method A:* A solution of **9** (66 mg, 0.14 mmol), sodium hydride (14 mg, 0.35 mmol) and morpholine (20 μL, 0.23 mmol) in dichloromethane (3.8 mL) was stirred for 24 h. Purification over silica gel (4:1 petroleum ether:ethyl acetate) gave **17** as a clear oil (38 mg, 0.08 mmol, 56% yield).

Method C: A mixture of **9** (47 mg, 0.09 mmol) and morpholine (40 μL, 0.46 mmol) in acetonitrile (1 mL) and water (1 mL) was stirred for 46 h. Purification over silica gel (4:1 petroleum ether:-ethyl acetate) gave **17** as a clear oil (38 mg, 0.08 mmol, 79% yield). IR ν_{max} (neat) 2956, 2877, 1653 (C═O), 1624 (C═C), 1459, 1435, 1360, 1278, 1237, 1148, 1116, 1066, 1042, 1005, 909, 877, 848, 819, 744 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.70 (a-t, 1H, *J* 1.5 Hz, H3), 4.84 (a-s, 1H, H4/6), 4.53 (a-s, 1H, H4/6), 4.18–4.01 (m, 4H, OC*H*$_2$-C*H*$_2$O), 3.71–3.57 (m, 8H, H7, H8, H9, H10), 0.99–0.94 (m, 18H, CH$_2$C*H*$_3$), 0.65–0.61 (m, 12H, SiC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 166.4 (C1), 141.0 (C2), 130.8 (C3), 119.1 (C5), 76.7 (C4/6), 76.4 (C4/6), 67.5 (C8/9), 67.0 (C8/9), 66.5 (O*C*H$_2$CH$_2$O), 66.3 (OCH$_2$*C*H$_2$O), 47.9 (C7/10), 42.1 (C7/10), 7.1 (CH$_2$*C*H$_3$), 7.0 (CH$_2$*C*H$_3$), 5.2 (Si*C*H$_2$), 5.1 (Si*C*H$_2$); HRMS (ES^+) calcd for $C_{24}H_{46}NO_6Si_2$ $[MH]^+$ 517.3124, found 517.3127.

4.1.4.12. *rac*-(6*S*,9*R*)-6,9-Bis-triethylsilanyloxy-1,4-dioxa-spiro[4.4]-non-7-ene-7-carboxylic acid diisopropylamide 18. *Method A:* A solution of **9** (50 mg, 0.10 mmol), sodium hydride (11 mg, 0.27 mmol) and diisopropylamine (20 μL, 0.15 mmol) in dichloromethane (4.5 mL) was stirred for 16 h. Purification over silica gel (12:1 petroleum ether:ethyl acetate) gave **18** as a clear oil (6 mg, 0.01 mmol, 11% yield). IR ν_{max} (neat) 2968, 2911, 1729 (C═O), 1638 (C═C), 1603, 1448, 1418, 1381, 1368, 1351, 1266, 1211, 1138, 1118, 1059, 1037, 1019, 1006, 954, 865 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.55 (a-t, 1H, *J* 1.5 Hz, H3), 4.87 (a-t, 1H, *J* 1.5 Hz, H4/6), 4.51 (a-t, 1H, *J* 1.5 Hz, H4/6), 4.43–4.37 (m, 1H, H7/8), 4.21–3.99 (m, 4H, OC*H*$_2$C*H*$_2$O), 3.47–3.40 (m, 1H, H7/8), 1.46–1.43 (m, 6H, 2 × C(N)HC*H*$_3$), 1.16–1.10 (m, 6H, 2 × C(N)HC*H*$_3$), 1.00–0.94 (m, 18H, CH$_2$C*H*$_3$), 0.68–0.60 (m, 12H, SiC*H*$_2$); δ_C (100 MHz, $CDCl_3$) 166.6 (C1), 142.7 (C2), 127.4 (C3), 118.0 (C5), 77.3 (C4/6), 76.2 (C4/6), 66.1 (O*C*H$_2$CH$_2$O), 65.6 (OCH$_2$*C*H$_2$O), 50.2 (C7/8), 45.6 (C7/8), 20.8 (C(N)H*C*H$_3$), 20.7 (2 × C(N)H*C*H$_3$), 20.4 (C(N)H*C*H$_3$), 6.7 (CH$_2$*C*H$_3$), 6.7 (CH$_2$*C*H$_3$), 4.8 (Si*C*H$_2$), 4.8 (Si*C*H$_2$); HRMS (ES^+) calcd for $C_{26}H_{52}NO_5Si_2$ $[MH]^+$ 514.3379, found 514.3379.

4.1.4.13. *rac*-(6*S*,9*R*)-6,9-Bis-(triethyl-silanyloxy)-1,4-dioxa-spiro[4.4]non-7-ene-7-carboxylic acid methyl ester 19. *Method A:* A solution of **9** (63 mg, 0.13 mmol), sodium hydride (13 mg, 0.33 mmol) and methanol (5 μL, 0.2 mmol) in dichloromethane (2.1 mL) was stirred for 18 h. Purification over silica gel (8:1 petroleum ether:ethyl acetate) gave **19** as a clear oil (21 mg, 0.05 mmol, 36% yield).

Method B: A solution of **9** (53 mg, 0.11 mmol), in acetonitrile (2 mL) and methanol (0.1 mL) was stirred at 0 °C under N_2. DBU (0.16 mL, 1.07 mmol) was added and the reaction mixture was stirred for 2.5 h. Buffer having a pH 7 (10 mL) was added and the

mixture was extracted with diethyl ether (5 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to leave an amber oil. Purification over silica gel (8:1 petroleum ether:ethyl acetate) gave **19** as a clear oil (17 mg, 0.04 mmol, 35% yield). IR ν_{max} (neat) 2954, 2877, 1728 (C=O), 1632, 1458, 1437, 1414, 1360, 1268, 1233, 1142, 1066, 1040, 1004, 971, 815 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 6.65 (a-t, 1H, *J* 1.5 Hz, H3), 4.67 (a-s, 1H, H4), 4.43 (a-d, 1H *J* 1.0 Hz, H6), 4.13 (m, 1H, OCH_2CHHO), 4.08 (m, 1H, OCH_2CHHO), 4.02–3.99 (m, 2H, OCH_2CH_2O), 3.73 (s, 3H, OCH_3), 0.98 (m, 18H, CH_2CH_3), 0.66 (m, 12H, $SiCH_2$); δ_C (150 MHz, $CDCl_3$) 164.2 (C1), 142.7 (C3), 137.5 (C2), 116.7 (C5), 76.8 (C6), 75.0 (C4), 66.1 (OCH_2CH_2O), 65.4 (OCH_2CH_2O), 51.3 (OCH_3), 6.72 (CH_2CH_3), 6.64 (CH_2CH_3), 4.91 ($SiCH_2$), 4.83 ($SiCH_2$); HRMS (ES^+) calcd for $C_{21}H_{40}NaO_6Si_2$ $[MNa]^+$ 467.2261, found 467.2279.

4.1.4.14. *rac*-(6*S*,9*R*)-6,9-Bis-(triethyl-silanyloxy)-1,4-dioxa-spiro[4.4]non-7-ene-7-carboxylic acid isopropyl ester 20. *Method A:* A solution of **9** (69 mg, 0.14 mmol), sodium hydride (15 mg, 0.36 mmol) and 2-propanol (50 μL, 0.65 mmol) in dichloromethane (2.0 mL) was stirred for 18 h. Purification over silica gel (8:1 petroleum ether:ethyl acetate) gave **20** as a clear oil (30 mg, 0.06 mmol, 45% yield).

A solution of **9** (60 mg, 0.12 mmol), in acetonitrile (2.3 mL) and 2-propanol (0.12 mL) was stirred at 0 °C under N_2. DBU (0.18 mL, 1.20 mmol) was added and the reaction mixture was stirred for 2 h 30 min. Buffer having a pH 7 (10 mL) was added and the mixture was extracted with diethyl ether (5 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to leave an amber oil. Purification over silica gel (8:1 petroleum ether:ethyl acetate) gave **20** as a clear oil (28 mg, 0.06 mmol, 48% yield). IR ν_{max} (neat) 2953, 2876, 1747, 1717 (C=O), 1631 (C=C), 1458, 1413, 1372, 1318, 1270, 1234, 1143, 1109, 1065, 1005, 973, 950, 928, 888, 819 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.56 (a-t, 1H, *J* 1.0 Hz, H3), 5.06 (septet, 1H, *J* 6.0 Hz, H7), 4.65 (a-s, 1H, H4/6), 4.41 (a-d, 1H *J* 1.0 Hz, H4/6), 4.15–3.96 (m, 4H, OCH_2CH_2O), 1.27 (3H, d, *J* 6.0 Hz, H8/9), 1.26 (3H, d, *J* 6.0 Hz, H8/9), 0.97 (t, 18H, *J* 8.0 Hz, CH_2CH_3), 0.70–0.60 (m, 12H, $SiCH_2$); δ_C (100 MHz, $CDCl_3$) 163.8 (C1), 142.2 (C3), 138.9 (C2), 116.7 (C5), 77.3 (C4/6), 75.5 (C4/6), 68.3 (C7), 66.5 (OCH_2CH_2O), 65.7 (OCH_2CH_2O), 22.2 (C8/9), 22.2 (C8/9), 7.2 (CH_2CH_3), 7.1 (CH_2CH_3), 5.4 ($SiCH_2$), 5.3 ($SiCH_2$); HRMS (ES^+) calcd for $C_{23}H_{45}O_6Si_2$ $[MH]^+$ 473.2749, found 473.2749.

4.1.4.15. *rac*-(6*S*,9*R*)-6,9-Bis-triethylsilanyloxy-1,4-dioxa-spiro[4.4]non-7-ene-7-carboxylic acid methoxy-methyl-amide 24. *Method D:* A solution of **9** (65 mg, 0.13 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (17 mg, 0.17 mmol) and triethylamine (0.06 mL, 0.44 mmol) in acetonitrile (3.3 mL) and water (3.3 mL) was stirred for 19 h. Purification over silica gel (6:1 petroleum ether:ethyl acetate) gave **24** as a clear oil (45 mg, 0.095 mmol, 71% yield). IR ν_{max} (neat) 2954, 2877, 1662 (C=O), 1621 (C=C), 1459, 1417, 132, 1276, 1236, 1152, 1122, 1061, 1038, 1003, 878, 851, 819, 725 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.96 (br s, 1H, H3), 4.84 (a-s, 1H, H4/6), 4.51 (a-s, 1H, H4/6), 4.19–4.00 (m, 4H, OCH_2CH_2O), 3.71 (s, 3H, OCH_3), 3.26 (s, 3H, NCH_3), 0.99–0.93 (m, 18H, CH_2CH_3), 0.67–0.61 (m, 12H, $SiCH_2$); δ_C (100 MHz, $CDCl_3$)[‡] 165.3 (C1), 139.3 (C2), 137.6 (C3), 115.7 (C5), 77.4 (C4/6), 76.7 C4/6), 66.6 (OCH_2CH_2O), 66.0 (OCH_2CH_2O), 61.4 (OCH_3), 32.6 (NCH_3); HRMS (ES^+) calcd for $C_{22}H_{44}NO_6Si_2$ $[MH]^+$ 474.2702, found 474.2704.

[‡] This compound was rotameric, as observed in the ^{13}C NMR spectrum at 27 °C. C1, C2 and C3, were weak and broad, while NCH_3 and OCH_3 were not observed, and high temperatures resulted in partial removal of the TES groups. The data quoted is therefore at 27 °C after removal of the TES groups.

4.1.4.16. *rac*-(6*S*,9*R*)-(6,9-Bis-triethylsilanyloxy-1,4-dioxa-spiro[4.4]non-7-en-7-yl)-(4-methyl-piperazin-1-yl)-methanone 25. A 0.02 M solution of **9** (59 mg, 0.12 mmol) in acetonitrile (4 mL) and water (2 mL) was stirred at 0 °C. Triethylamine (60 μL, 0.42 mmol) was added, followed by *N*-methylpiperazine (16 μL, 0.15 mmol). The reaction mixture was stirred overnight, and allowed to warm to room temperature, until TLC analysis (4:1 petroleum ether:ethyl acetate) indicated consumption of the substrate. 5% Triethylamine in water (10 mL) was added and the reaction mixture was extracted with diethyl ether (4 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to leave a clear residue. Purification over silica gel (1:1:0.1 petroleum ether:ethyl acetate:methanol) gave **25** as a clear oil (47 mg, 0.092 mmol, 75% yield). IR ν_{max} (neat) 2954, 2877, 2794, 1652 (C=O), 1623 (C=C), 1459, 1437, 1370, 1292, 1236, 1139, 1102, 1042, 1002, 876, 856, 819, 742 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.68 (a-t, 1H, *J* 1.5 Hz, H3), 4.83 (a-s, 1H, H4/6), 4.52 (a-s, 1H, H6/4), 4.17–4.00 (m, 4H, OCH_2CH_2O), 3.70–3.55 (m, 4H, H7, H9), 2.42–2.26 (m, 4H, H8, H10), 2.29 (s, 3H, H11), 0.98–0.92 (m, 18H, CH_2CH_3), 0.66–0.58 (m, 12H, $SiCH_2$); δ_C (100 MHz, $CDCl_3$) 165.8 (C1), 140.9 (C2), 130.1 (C3), 118.7 (C5), 76.5 (C6/4), 76.0 (C4/6), 66.1 (OCH_2CH_2O), 65.9 (OCH_2CH_2O), 55.3 (C7/9), 54.5 (C7/9), 46.9 (C8/10), 46.0 (C11), 41.1 (C8/10) 6.7 (CH_2CH_3), 6.7 (CH_2CH_3), 4.8 ($SiCH_2$), 4.7 ($SiCH_2$); HRMS (ES^+) calcd for $C_{25}H_{49}N_2O_5Si_2$ $[MH]^+$ 513.3175, found 513.3179.

4.1.4.17. *rac*-(6*S*,9*R*)-6,9-Dihydroxy-1,4-dioxa-spiro[4.4]non-7-ene-7-carboxylic acid hexylamide 26. *Method C*: A mixture of **8** (40 mg, 0.16 mmol) and hexylamine (30 μL, 0.23 mmol) in acetonitrile (3.8 mL) and water (3.8 mL) was stirred for 1 h 30 min. Purification over silica gel (15:1 dichloromethane:methanol) gave **26** as a white solid (31 mg, 0.11 mmol, 70% yield). IR ν_{max} (neat) 3430 (N-H), 3281 (b, O-H), 2955, 2925, 2858, 1652 (C=O), 1629 (C=C), 1615, 1546, 1455, 1419, 1400, 1380, 1292, 1208, 1144, 1126, 1089, 1059, 1028, 988, 959, 912, 872, 820, 806, 770, 723, 670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.12 (br s, 1H, N*H*), 6.69 (a-t, 1H, *J* 1.5 Hz, H3), 4.62 (a-s, 1H, H4/6), 4.52 (a-s, 1H, H4/6), 4.20–4.10 (m, 4H, OCH_2CH_2O), 3.31 (q, 2H, *J* 6.5 Hz, H7), 3.26–3.05 (br s, 1H, O*H*), 2.56–2.52 (br s, 1H, O*H*), 1.57–1.50 (m, 2H, H8), 1.37–1.24 (m, 6H, H9–H11), 1.18 (t, 3H, *J* 6.5 Hz, H12); δ_C (100 MHz, $CDCl_3$) 163.5 (C1), 140.1 (C3), 138.6 (C2), 116.9 (C5), 76.4 (C4/6), 76.0 (C4/6), 67.1 (OCH_2CH_2O), 66.5 (OCH_2CH_2O), 39.7 (C7), 31.8 (C8), 29.7 (C9), 27.0 (C10), 22.9 (C11), 14.4 (C12); HRMS (ES^+) calcd for $C_{14}H_{24}NO_5$ $[MH]^+$ 286.1649, found 286.1652; mp = 119–120 °C (dichloromethane, methanol).

4.1.4.18. *rac*-(6*S*,9*R*)-(6,9-Dihydroxy-1,4-dioxa-spiro[4.4]non-7-en-7-yl)-pyrrolidin-1-yl-methanone 27. *Method C*: A mixture of **8** (70 mg, 0.27 mmol) and pyrrolidine (34 μL, 0.41 mmol) in acetonitrile (3 mL) and water (3 mL) was stirred for 2 h 45 min. Purification over silica gel (10:1 ethyl acetate:methanol) gave **27** as a cream solid (43 mg, 0.17 mmol, 62% yield). IR ν_{max} (neat) 3359 (b, O-H), 1640 (C=O), 1582, 1456, 1343, 1217, 1132, 1059, 1022, 992, 953 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.13 (a-t, 1H, *J* 1.5 Hz, H3), 4.79 (a-d, 1H, *J* 1.0 Hz, H4/6), 4.53 (a-s, 1H, H4/6), 4.20–4.08 (m, 4H, OCH_2CH_2O), 3.59–3.49 (m, 4H, H7, H10), 2.79–2.44 (br s, 1H, O*H*), 1.97–1.86 (m, 4H, H8, H9), 1.73–1.42 (br s, 1H, O*H*); δ_C (100 MHz, $CDCl_3$) 164.9 (C1), 141.1 (C2), 135.6 (C3), 116.0 (C5), 77.5 (C4/6), 76.4 (C4/6), 67.0 (OCH_2CH_2O), 66.3 (OCH_2CH_2O), 48.5 (C7/10), 46.6 (C7/10), 26.6 (C8/9), 24.4 (C8/9); HRMS (ES^+) calcd for $C_{12}H_{18}NO_5$ $[MH]^+$ 256.1179, found 256.1180; mp = 133–135 °C (dichloromethane, methanol).

4.1.4.19. *rac*-(6*S*,9*R*)-(6,9-Dihydroxy-1,4-dioxa-spiro[4.4]non-7-en-7-yl)-morpholin-4-yl-methanone 28. *Method C*: A mixture of **8** (266 mg, 1.04 mmol) and morpholine (0.19 mL, 2.17 mmol) in acetonitrile (11 mL) and water (11 mL) was stirred for 21 h

30 min. Purification over silica gel (10:1 ethyl acetate:methanol) gave **28** as a cream solid (203 mg, 0.75 mmol, 72% yield). IR ν_{max} (neat) 3364 (b, O-H), 2898, 1645 (C=O), 1595 (C=C), 1459, 1426, 1290, 1273, 1235, 1210, 1159, 1110, 1064, 1030, 1009, 987, 952, 907, 868, 819, 797, 757 cm^{-1}; δ_H (400 MHz, D_2O) 6.05 (a-s, 1H, H3), 4.72 (a-s, 1H, H4/6), 4.56 (a-s, 1H, H4/6), 4.10–4.06 (m, 4H, OCH_2CH_2O), 3.78–3.50 (m, 8H, H7, H8, H9, H10), δ_C (100 MHz, D_2O) 167.3 (C1), 138.9 (C2), 134.5 (C3), 116.5 (C5), 76.3 (C4/6), 75.7 (C4/6), 67.0 (C8, C9), 66.7 (OCH_2CH_2O), 66.4 (OCH_2CH_2O), 47.8 (C7/10), 42.7 (C7/10); HRMS (ES^+) calcd for $C_{12}H_{17}NO_6$ $[MH]^+$ 272.1129 found 272.1134; mp = 204–206 °C (ethyl acetate, methanol).

4.1.4.20. *rac*-(6*S*,9*R*)-(6,9-Dihydroxy-1,4-dioxa-spiro[4.4]non-7-en-7-yl)-(4-methyl-piperazin-1-yl)–methanone 29. A mixture of **8** (19 mg, 0.07 mmol) and *N*-methylpiperazine (25 μL, 0.23 mmol) in acetonitrile (1.8 mL) and water (1.8 mL) was stirred for 1 h. Purification over silica gel (10:1:0.2 ethyl acetate:methanol:triethylamine) gave **29** as a white solid (14 mg, 0.05 mmol, 67% yield). IR ν_{max} (neat) 3364 (b, O-H), 2952, 2901, 2806, 1641 (C=O), 1595, 1465, 1446, 1368, 1288, 1267, 1215, 1172, 1133, 1057, 996, 951, 912, 875, 824 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.90 (a-t, 1H, *J* 1.5 Hz, H3), 4.74 (a-t, 1H, *J* 1.0 Hz, H4/6), 4.52 (dd, 1H, *J* 2.0, 1.0 Hz, H4/6), 4.18–4.10 (m, 4H, OCH_2CH_2O), 3.79–3.51 (br m, 4H, H7, H9), 2.60–2.35 (br m, 4H, H8, H10), 2.30 (s, 3H, H11); δ_C (100 MHz, $CDCl_3$) 165.1 (C1), 140.2 (C2), 132.9 (C3), 115.6 (C5), 77.5 (C4/6), 76.1 (C4/6), 66.6 (OCH_2CH_2O), 66.0 (OCH_2CH_2O), 55.2 (C7/9), 54.5 (C7/9), 46.7 (C8/10), 45.9 (C11), 41.5 (C8/10); HRMS (ES^+) calcd for $C_{13}H_{21}N_2O_5$ $[MH]^+$ 285.1450, found 285.1442.

4.1.4.21. (6*S*,9*R*)-(6,9-Bis-triethylsilanyloxy-1,4-dioxa-spiro[4.4]-non-7-en-7-yl)-((*S*)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone 34 and (6*R*,9*S*)-(6,9-bis-triethylsilanyloxy-1,4-dioxa-spiro[4.4]non-7-en-7-yl)-((*S*)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-methanone 35. A solution of **9** (481 mg, 0.99 mmol), (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine (0.245 M in acetonitrile, 4.85 mL) and triethylamine (0.30 mL) in acetonitrile (20 mL) and water (25 mL) was stirred for 15 h 30 min. Purification over silica gel (10:1:0.1 ethyl acetate:methanol:triethylamine) gave a 1:1 mixture of **34** and **35** as a clear oil (332 mg, 0.59 mmol, 59% yield). A sample was taken and the diastereomers were separated by preparative TLC (3 elutions, 15:1:0.1 ethyl acetate:methanol:triethylamine). **34** or **35**; IR ν_{max} (neat) 2956, 2877, 1652 (C=O), 1616 (C=C), 1416, 1236, 1148, 1046, 1007, 822, 743 cm^{-1}; δ_H (400 MHz, DMSO-d_6, 100 °C) 5.87 (br s, 1H, H3), 4.67 (br s, 1H, H4/6), 4.46 (br s, 1H, H4/6), 4.26–4.13, 4.07–3.92 (m, 7H, H7, H10, OCH_2CH_2O), 3.64–3.36 (br m, 6H, H11, H12, H15), 2.03–1.68 (br m, 8H, H8, H9, H13, H14), 1.00–0.87 (m, 18H, CH_2CH_3), 0.68–0.48 (m, 12H, $SiCH_2$); HRMS (ES^+) calcd for $C_{29}H_{55}N_2O_5Si_2$ $[MH]^+$ 567.3644, found 567.3640. **34** or **35**; IR ν_{max} (neat) 2940, 2878, 2739, 2676, 2492, 1651 (C=O), 1619 (C=C), 1432, 1274, 1236, 1146, 1104, 1065, 1038, 1005, 857, 823, 745 cm^{-1}; δ_H (400 MHz, DMSO-d_6, 100 °C) 5.83 (br s, 1H, H3), 4.65 (t, 1H, *J* 1.5 Hz, H4/6), 4.44 (br s, 1H, H4/6), 4.24–3.92 (m, 7H, H7, H10, OCH_2CH_2O), 3.58–3.39 (br m, 6H, H11, H12, H15), 2.04–1.75 (br m, 8H, H8, H9, H13, H14), 0.98–0.89 (m, 18H, CH_2CH_3), 0.63–0.53 (m, 12H, $SiCH_2$); HRMS (ES^+) calcd for $C_{29}H_{55}N_2O_5Si_2$ $[MH]^+$ 567.3644, found 567.3641. **34** and **35**; δ_C (100 MHz, $CDCl_3$) 166.2,[§] 166.6, 165.1, 164.9, 142.4, 142.4, 141.8, 141.6, 130.5, 129.9, 129.5, 129.5, 118.5, 118.5, 118.0, 117.8, 77.1, 76.8, 76.7, 76.6, 75.9, 75.8, 75.8, 75.6, 66.1, 66.0, 65.7, 65.7, 66.7, 65.6, 59.1, 58.2, 58.0, 57.6, 57.1, 65.2, 56.0, 54.7, 54.5, 54.3, 48.8, 48.7, 46.8, 46.5, 45.5, 44.5, 29.8, 29.4, 29.0, 28.5, 28.2, 28.0, 24.2, 23.5, 23.5, 23.5, 21.9, 21.6, 21.4, 6.8, 6.7, 6.7, 6.6, 6.6, 6.6, 6.6, 4.9, 4.9, 4.9, 4.9, 4.8, 4.8, 4.8, 4.7, 4.7.

[§] High temperature ^{13}C NMR (toluene-d_6, 100 °C) did not resolve the peaks. Attempts to reduce the amide group to an amine were unsuccessful. The data quoted are from an 8-h ^{13}C acquisition of a 1:1 mixture of **34** and **35** at 27 °C.

Acknowledgements

The authors would like to thank the EPSRC and GlaxoSmithKline (for a CASE award to PT), the Royal Society for a URF (to MDS), AstraZeneca (for a Research Support Grant) and the EPSRC National Mass Spectrometry Service (Swansea).

References

1. Favorskii, A. E. *J. Russ. Phys. Chem. Soc.* **1894**, *26*, 590.
2. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon Press, 1991; Vol. 3, p 839.
3. Kende, A. S. *Org. React.* **1960**, *11*, 264.
4. Guijarro, D.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 1713.
5. Silva, L. F. *Tetrahedron* **2002**, *58*, 9137; Lee, E.; Yoon, C. H. *Chem. Commun.* **1994**, 479.
6. Andrews, S. P.; Ball, M.; Wierschem, F.; Cleator, E.; Oliver, S.; Högenauer, K.; Simic, O.; Antonello, A.; Hünger, U.; Smith, M. D.; Ley, S. V. *Chem. Eur. J.* **2007**, *13*, 5688.
7. Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353.
8. Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602.
9. Cole, T. W.; Eaton, P. E. *J. Am. Chem. Soc.* **1964**, *86*, 3157.
10. Sommer, L. H.; Webster, O. W. *J. Org. Chem.* **1964**, *29*, 3103.
11. Schamp, N.; De Kimpe, N.; Coppens, W. *Tetrahedron* **1975**, *31*, 2081.
12. Xiang, L.; Kalaitzis, J. A.; Moore, B. S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 15609.
13. Baretta, A.; Waegell, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1982; Vol. 2, p 527.
14. Hamblin, G. D.; Jimenez, R. P.; Sorensen, T. S. *J. Org. Chem.* **2007**, *72*, 8033.
15. McPhee, W. D.; Klinsberg, E. *J. Am. Chem. Soc.* **1944**, *66*, 1132.
16. Loftfield, R. B. *J. Am. Chem. Soc.* **1950**, *72*, 632; Loftfield, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 4707.
17. Bordwell, F. G.; Williams, J. M., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 43.
18. Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *38*, 2939.
19. Aston, J. G.; Newkirk, J. D. *J. Am. Chem. Soc.* **1951**, *73*, 3900.
20. Burr, J. G. J.; Dewar, M. J. S. *J. Chem. Soc.* **1954**, 1201.
21. Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.
22. Stork, G.; Borowitz, I. J. *J. Am. Chem. Soc.* **1960**, *82*, 4307.
23. House, H. O.; Gilmore, W. F. *J. Am. Chem. Soc.* **1961**, *83*, 3980.
24. Rappe, C.; Knutsson, L.; Turro, N. J.; Gagosian, R. B. *J. Am. Chem. Soc.* **1970**, *92*, 2032.
25. Schamp, N.; Coppens, W. *Tetrahedron Lett.* **1967**, *8*, 2697.
26. R. Keller, Ger. Offen. DE 304.5680; *Chem. Abstr.* **1982**, *98* 34904m.; McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Chem. Commun.* **1992**, 1589.
27. Montalban, A. G.; Wittenberg, L.-O.; McKillop, A. *Tetrahedron. Lett.* **1999**, *40*, 5893.
28. For a review see: O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439.
29. A wide range of experimental conditions were explored.
30. Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.
31. Bunn, B. J.; Simpkins, N. S.; Spavold, Z.; Crimmin, M. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3113.
32. Satoh, T.; Oguro, K.; Shishikura, J.; Kanetaka, N.; Okada, R.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2339.
33. Due to the difficulty in eliminating all proton sources from the NMR sample, only 80% enolization was observed.
34. Brik, M. E. *Synth. Commun.* **1990**, *20*, 1487.
35. De Kimpe, N.; D'Hondt, L.; Moens, L. *Tetrahedron* **1992**, *48*, 3183.
36. Makarova, N. V.; Moiseev, I. K.; Zemtsova, M. N. *Russ. J. Gen. Chem.* **2002**, *72*, 95.
37. Sato, K.; Inoue, S.; Kuranami, S.-I. *J. Chem. Soc., Perkin Trans 1* **1977**, 1666.
38. Sato, K.; Ohashi, M.; Aoki, E.; Murai, Y. *J. Org. Chem.* **1977**, *42*, 3713.
39. Bordwell, F. G.; Almy, J. *J. Org. Chem.* **1973**, *33*, 571.
40. R. P. Bell; O. M. Lidwell, *Proc. Roy. Soc. (London)*, **1940**, *A176*, 88.
41. The RDS for α,α′-dihaloketones may be different, as deprotonation of haloketones has been demonstrated to be faster than their non-halogenated counterparts (see Ref. 39).
42. Bunnett, J. F.; Sekiguchi, S.; Smith, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 4865.
43. Castro, E. A.; Peña, S. A.; Santos, J. G.; Vega, J. C. *J. Org. Chem.* **1984**, *49*, 863.
44. The relative configuration of the two diastereoisomers **34** and **35** was not determined.