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Synthesis of the Revised Structure of Acortatarin A

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A novel Maillard-type condensation between a primary amine derived from D-mannitol and a dihydropyranone, was used as a key step to access the unusual morpholine-spiroketal acortatarin A. The synthetic approach also enabled access to a C-2 analogue of acortatarin A, and can be used for the synthesis of related 2-formylpyrrole natural products.

Introduction

The rhizome of *Acorus tatarinowii* is widely used as a traditional Chinese medicine for the treatment of central nervous system disorders such as epilepsy, and also used as an aid to improve learning and memory.[1] In 2010, Cheng et al. reported the isolation of acortatarins A (**1**) and B (**2**) from the rhizome of *Acorus tatarinowii*.[2] The X-ray structure of **1** established the presence of a unique morpholine 6,5-spiroketal ring system and the relative configuration of the chiral centres (Figure 1). The same year, Guo et al. and Wang et al. independently reported the isolation of related spiroketals, the pollenopyrrosides A (**4**) and B (**3**) and capparisines A (**1**) and B (**5**), from bee-collected *Brassica campestris* pollen and *Capparis spinosa* fruit, respectively.[3] Guo et al. deduced that pollenopyrroside B was enantiomeric to the initially reported structure of acortatarin A (**1**), based on single-crystal X-ray analysis using the Flack parameter method. Capparisine A, on the other hand, was reported as having the same configuration as **1**, based on an X-ray crystal structure.

The absolute stereochemistry of acortatarin A was originally determined via Mosher ester analysis, giving rise to structure **1**. Similarly, the structure of acortatarin B was determined by COSY and HMBC analysis, and the relative stereochemistry via ROESY NMR spectroscopy. It was assumed that acortatarin B would arise biosynthetically from the same source as **1**, and thus the absolute stereochemistry of acortatarin B (**2**) was assigned accordingly.

However, in 2011 Sudhakar and co-workers found that the absolute configuration of the acortatarins **1** and **2** had been mistakenly assigned, and proposed the revised structure of acortatarin A (**3**) based on a synthetic study.[4] Borrero and Aponick later further confirmed that the revised structure of acortatarin A (**3**) was identical to that assigned for pollenopyrroside B.[5] Total syntheses of the revised structure of acortatarin A (**3**) were later reported by three independent research groups.[5,6] To date the absolute stereochemistry of capparisine A has yet to be confirmed; while the optical rotation reported is of the same sign, it is significantly lower in magnitude than that of acortatarin A.

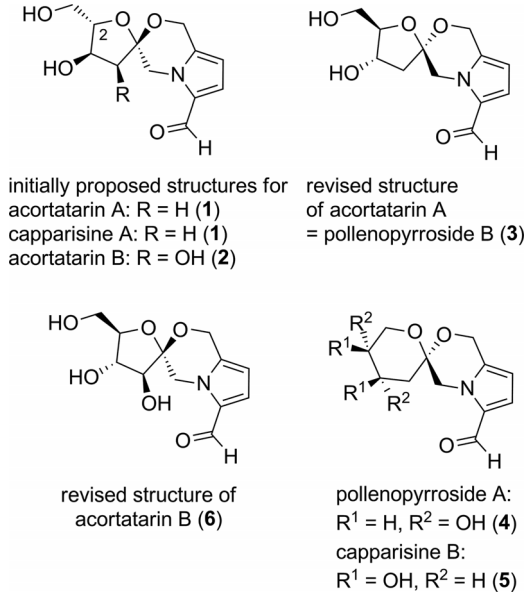

Figure 1. Initially proposed and revised structures of acortatarins A and B, pollenopyrrosides A and B, and capparisines A and B.

Both acortatarins A (**3**) and B (**6**) were examined for their antioxidant effects in high-glucose-induced mesangial cells in a dose- and time-dependent manner, with acortatarin A showing significant activity against the production of reactive oxygen species.[3a] Bee-collected *Brassica campestris* pollen is often used in China as a herbal medicine to

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strengthen the body's resistance to diseases. It has already been found to possess a wide range of biological activity, including antioxidant activity, antitumor activity, regulation of serum lipids, and treatment of prostatitis.[3a]

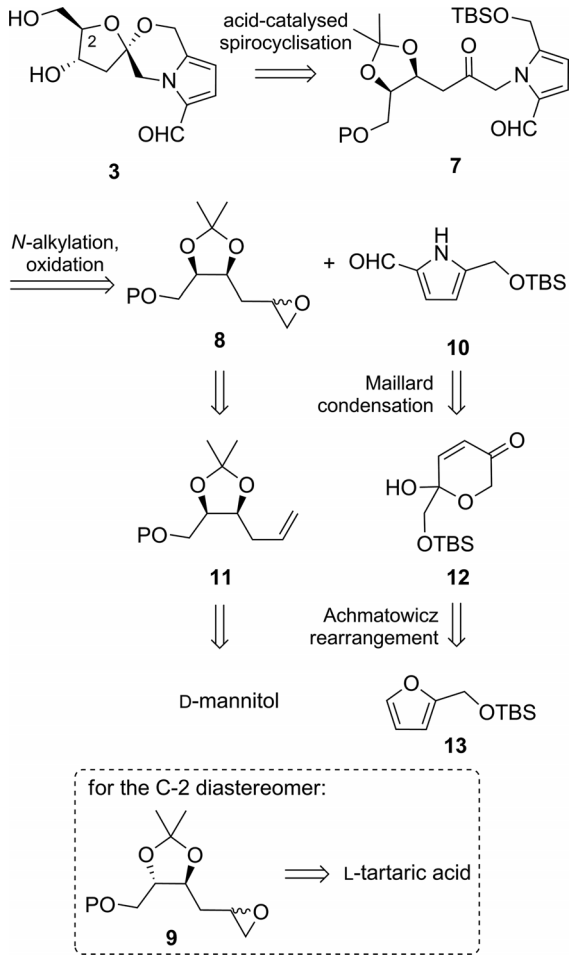
These spiroketal alkaloids possess a unique tricyclic structure containing a 2-formylpyrrole and a spiro-fused sugar-morpholine spiroketal subunit. The morpholine pharmacophore, in particular, is present in a number of important enzyme inhibitors, including phosphoinositide-3 kinases,[7] TNF-R converting enzyme,[8] matrix metalloproteinases and tumour necrosis factor.[9] A practical asymmetric synthesis of acortatarin A would allow evaluation of this new heterocyclic scaffold for drug discovery directed towards therapeutic intervention in diabetic nephropathy (DN).[10]

The synthesis of 2,5-disubstituted pyrrole ring systems is often tedious, requiring functionalisation of the pyrrole ring via formylation at both C-2 and C-5. Initially, we aimed to develop an enantioselective synthesis of the proposed structure of acortatarin A (**3**) via an efficient, modular strategy that would be amenable to the synthesis of analogues in order to probe the biological activity of this interesting structural scaffold, and also facilitate the preparation of other 2-formylpyrrole natural products. We herein report the full details of our synthetic approaches that led to the successful total synthesis of the revised structure of acortatarin A (**3**). We also provide full synthetic details for the synthesis of the C-2 diastereomer of acortatarin A that hitherto has not been reported.[11] All three previously reported synthetic approaches towards **3** have involved *N*-alkylation of a fully assembled pyrrole unit.[5,6] Both our initial and revised synthetic strategies focused on assembly of the pyrrole ring using Maillard-type condensation chemistry. Full details of our initial unsuccessful synthetic work are included herein.

Results and Discussion

Synthetic Strategy I

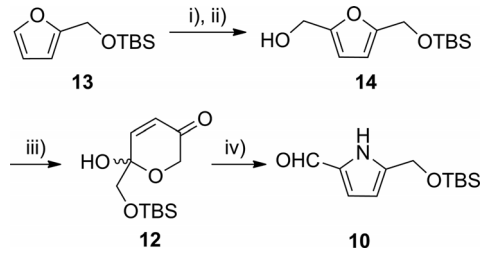
Initial attention focused on the synthesis of acortatarin A (**3**) via acid-catalysed cyclisation of a protected dihydroxy ketone **7** (Scheme 1). Ketone **7** was envisaged to be prepared via *N*-alkylation of 2,5-disubstituted pyrrole **10** with epoxide **8**. Epoxide **8** would be available from epoxidation of olefin **11**. In turn, the generation of 2-formylpyrrole **10** involved Maillard-type condensation[12] of ammonia with dihydropyranone **12**. Dihydropyranone **12** would be accessed with an Achmatowicz oxidation/rearrangement of furfuryl alcohol derivative **13**.[13] In the interest of preparing an array of spiroketal stereoisomers for biological evaluation, epoxides **8** and **9** would both be prepared, from D-mannitol and L-tartaric acid, respectively.



Scheme 1. Retrosynthetic analysis of acortatarin A (**3**) and its C-2 diastereomer.

Implementation of Initial Strategy

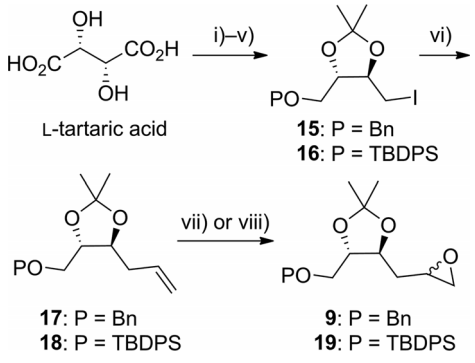
Synthesis of key pyrrole **10** started from TBS ether **13**, derived from commercially available furfuryl alcohol (Scheme 2). Regioselective lithiation, followed by formylation and reduction of the resulting aldehyde afforded **14** in 67% yield over two steps.[14] Subsequent Achmatowicz oxidative rearrangement using *m*-CPBA gave dihydropyranone **12** in quantitative yield. Initially, the Maillard condensation was attempted with aqueous ammonia. Thus,



Scheme 2. Synthesis of pyrrole **10**. *Reagents and conditions:* i) *n*BuLi, DMF, THF, –78 °C→room temp., 1.5 h; ii) $NaBH_4$, MeOH, 0 °C, 1 h, 67% over 2 steps; iii) *m*-CPBA, CH_2Cl_2, 0 °C→room temp., 4 h, quant.; iv) satd. aq. NH_3 solution, 1,4-dioxane, Et_3N, room temp., 2 h, 35%.

treatment of dihydropyranone **12** with aqueous ammonia in 1,4-dioxane in the presence of triethylamine afforded 2,5-disubstituted pyrrole **10** in 35% yield.

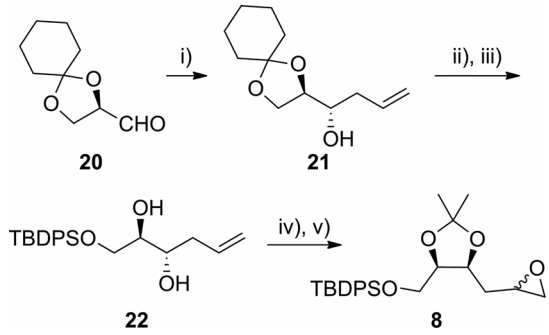
With pyrrole **10** in hand, attention then turned to synthesis of the other *N*-alkylation substrates, epoxides **8** and **9**. Synthesis of epoxide **9** began with esterification of L-tartaric acid (Scheme 3). The diester was then elaborated to known iodide **15** in a four-step sequence following Davies' protocol, involving diol protection as the acetonide, reduction of the diester, and monoprotection of the resultant diol as either a benzyl or TBDPS-ether in moderate yield.[15] A modified Appel reaction using I_2, PPh_3, and imidazole in toluene provided the unstable iodides **15** and **16**.



Scheme 3. Synthesis of epoxides **9** and **19**. *Reagents and conditions:* i) MeOH, concd. HCl, reflux, 12 h; ii) 2,2-dimethoxypropane, PTSA, PhMe, 50 °C, 6 h; iii) $LiAlH_4$, THF, reflux, 4 h; iv) NaH, BnBr, THF, 0 °C→room temp., 2 h, or TBDPSCl, THF, 0 °C→room temp., 4 h, **15** 70%, **16** 52% over 4 steps; v) I_2, PPh_3, imid., PhMe, reflux, 2 h; vi) vinylmagnesium bromide, CuI, DMPU/THF (1:1), –35 °C, 2 h, **17** 56%, **18** 50% over 2 steps; vii) CF_3COCH_3, Oxone®, MeCN/H_2O (3:2), 0 °C→room temp., 12 h, **9** 85%; viii) *m*-CPBA, CH_2Cl_2, room temp., 12 h, **19** 90%.

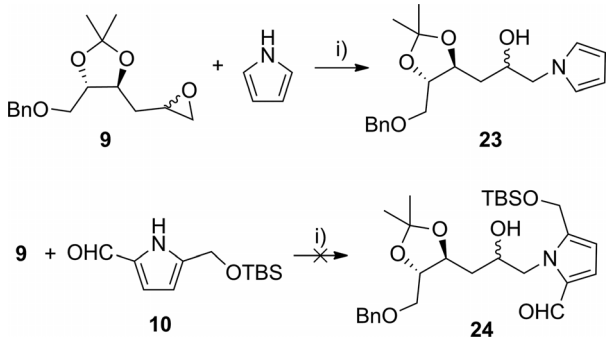
Grignard displacement of the unstable iodide **15** with vinylmagnesium bromide in THF at first failed to deliver any of the desired product, even using a large excess of vinylmagnesium bromide. After further investigation, the use of DMPU as co-solvent (DMPU/THF, 1:1) and the addition of CuI as a catalyst were found to facilitate the reaction, providing alkenes **17** and **18** in 56% and 50% yield, respectively.[16] Alkene **18** was smoothly converted into the corresponding epoxide **19** with *m*-CPBA in 90% yield. Treatment of alkene **17** with *m*-CPBA, however, was problematic, resulting only in recovery of starting material. Gratifyingly, it was found that exposure of **17** to Oxone® with catalytic trifluoroacetone in aqueous acetonitrile afforded the desired epoxide **9** in a reproducible 85% yield.[17]

Synthesis of epoxide **8** started from (*R*)-cyclohexylidene glyceraldehyde **20**, prepared from D-mannitol (Scheme 4).[18] Allylation according to Chattopadhyay's protocol using allyl bromide and zinc dust proceeded with excellent diastereoselectivity to afford *anti*-homoallylic alcohol **21** in good yield (88%, *dr* 97:3).[19] The selectivity of the allylation of **20** was substantially better than that obtained using the more widely used acetonide-protected glyceraldehyde equivalent.[20] Additionally, this method was amenable to multigram scale synthesis, and the undesired minor diastereomer readily removed via chromatography. Cleavage of the cyclohexylidene acetal was effected with methanolic HCl and the primary alcohol protected as the TBDPS ether **22** in 82% yield over two steps. Treatment of *anti*-diol **22** with 2,2-dimethoxypropane and catalytic PPTS, followed by epoxidation of the olefin with *m*-CPBA, gave epoxide **8** in 93% yield over two steps as an inconsequential 1.5:1 mixture of diastereomers.



Scheme 4. Synthesis of epoxide **8**. *Reagents and conditions:* i) Zn dust, allyl bromide, satd. aq. NH_4Cl, THF, 0 °C→room temp., 2 h, 88% (*dr* 97:3); ii) concd. HCl, MeOH, room temp., 24 h; iii) TBDPSCl, NaH, THF, 0 °C→r.t, 2 h, 82% over 2 steps; iv) PPTS, 2,2-dimethoxypropane, CH_2Cl_2, room temp., 2 h; v) *m*-CPBA, CH_2Cl_2, room temp., 12 h, 93% over 2 steps.

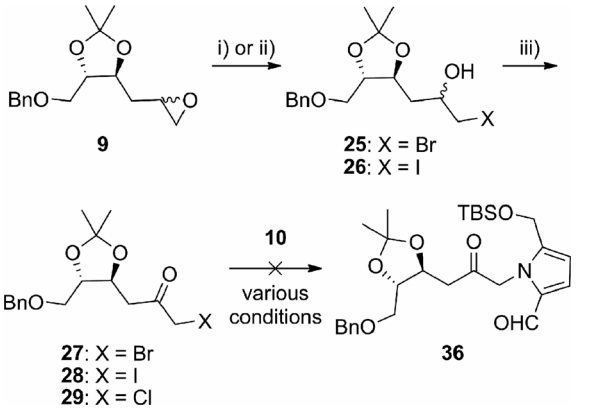
With both coupling partners for the key *N*-alkylation in hand, a model reaction was first conducted using epoxide **9** and unsubstituted pyrrole (Scheme 5). Pleasingly, deprotonation of pyrrole with NaH in DMF, followed by addition of **9** afforded the *N*-alkylation product **23** in 80% yield. These conditions were then applied to the *N*-alkylation of 2,5-disubstituted pyrrole **10** with epoxide **9**. Disappointingly, none of the desired product **24** was obtained despite investigating many reaction conditions, including the use of Lewis acids (LiCl, $BF_3{\cdot}Et_2O$), stronger bases (*n*BuLi), and elevated temperatures; only starting material was recovered in all cases.



Scheme 5. Model study of the *N*-alkylation of pyrrole using epoxide **9**, and attempted *N*-alkylation of pyrrole **10** using epoxide **9**. *Reagents and conditions:* i) NaH, DMF, 0 °C, 4 h, **23** 80%.

Postulating that this disappointing outcome was due to the poor electrophilicity of epoxide **9**, α-halo ketones **27**–**29** were also prepared as alternative electrophiles for the *N*-alkylation step (Scheme 6). Epoxide **9** was treated with either NaBr or NaI in a mixture of acetic and propionic

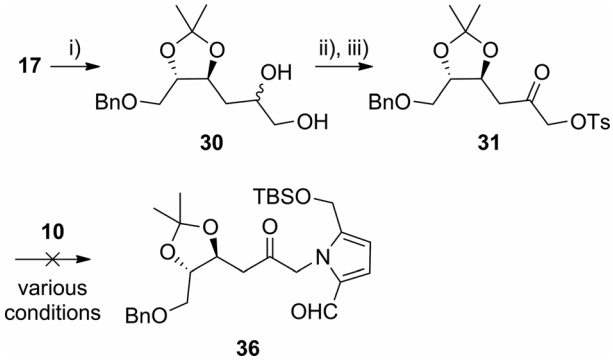
acids at –20 °C for 0.5 h, furnishing both the C-1 substituted bromohydrin **25** in 85% yield, and iodohydrin **26** in 87% yield. Oxidation of the halohydrins with excess PCC in the presence of molecular sieves (4 Å) in anhydrous CH_2Cl_2 at room temperature then afforded α-bromo ketone **27** in 70% yield, and α-iodo ketone **28** in 65% yield in addition to 32% of the corresponding α-chloro ketone **29**.



Scheme 6. Synthesis of α-halo ketones **27**–**29** and their attempted use in the *N*-alkylation of pyrrole **10**. *Reagents and conditions:* i) NaBr, $CH_3CO_2H/CH_3CH_2CO_2H$ (1:2), –20 °C, 0.5 h, **25** 85%; ii) NaI, $CH_3CO_2H/CH_3CH_2CO_2H$ (1:2), –20 °C, 0.5 h, **26** 87%; iii) PCC, 4 Å mol. sieves, CH_2Cl_2, room temp., 12 h, **27** 70% from **25**; **28** 65% and **29** 32% from **26**.

Again, attempts to alkylate pyrrole **10** with any of the α-halo ketones **27**–**29** were unsuccessful, despite using a variety of bases (NaH, Cs_2CO_3, K_2CO_3, KOH, LiHMDS). Only pyrrole **10** was recovered from the reaction mixture, and decomposition of the α-halo ketones was observed.

In order to circumvent decomposition of the electrophilic alkylation partner, use of a more robust tosylate **31** was employed (Scheme 7). Thus, alkene **17** was converted to diol **30** via Upjohn dihydroxylation in quantitative yield. Sequential tosylation and oxidation of the remaining secondary hydroxy group afforded tosylate **31** in 40% yield over two steps. Unfortunately, use of tosylate **31** in the attempted



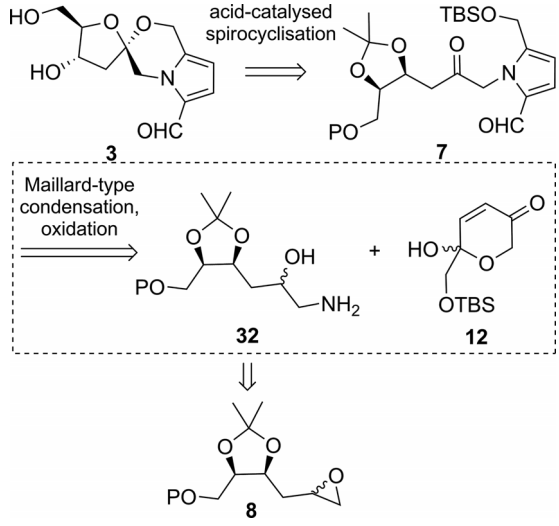
Scheme 7. Synthesis of tosylate **31** for attempted *N*-alkylation of pyrrole **10**. *Reagents and conditions:* i) OsO_4, NMO, *t*BuOH, acetone/H_2O (1:1), pH 7 buffer, room temp., 10 h, quant.; ii) TsCl, Et_3N, CH_2Cl_2, room temp., 3 h; iii) IBX, DMSO, 50 °C, 3 h, 50% over two steps.

N-alkylation of pyrrole **10** again only led to the recovery of starting materials.

In order to investigate the reason behind the unsuccessful *N*-alkylation, deuterium exchange experiments were conducted where a range of pyrroles were deprotonated with sodium hydride in DMF at 0 °C and then quenched with D_2O. The results revealed that while deuteration occurred with both pyrrole and 2-formylpyrrole, the corresponding exchange did not take place when 2,5-disubstituted pyrrole **10** was subjected to the same deprotonation conditions. This was potentially due to either the steric hindrance of the neighbouring silyl protecting group, or the ability of the benzyl ether to act as a leaving group, and therefore a modified approach to ketone **7** was required. Unfortunately, attempts to alkylate deprotected **10** were also unproductive.

Revision of Synthetic Strategy

Given the unsuccessful nature of our initial synthetic strategy, an alternative approach was devised (Scheme 8). Ketone **7** would now be constructed via Maillard-type condensation of dihydropyranone **12** with primary amine **32**, in which the *N*-alkyl substituent is pre-installed. Amine **32** was anticipated to be available by regioselective ring opening of epoxide **8**, available from our earlier synthetic route.

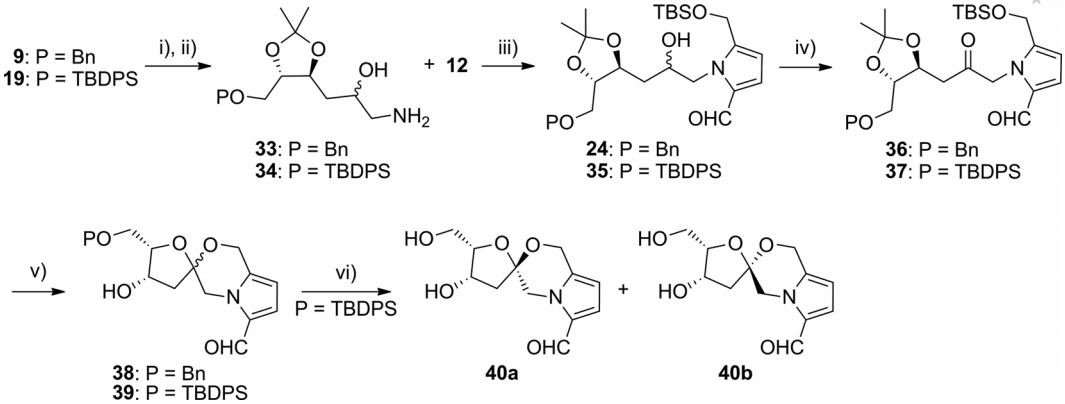


Scheme 8. Revised retrosynthetic analysis of acortatarin A (**3**).

Implementation of Revised Strategy

Our revised strategy began with the regioselective ring-opening of epoxides **9** and **19** with sodium azide, giving the azido alcohols that were then reduced to the corresponding amino alcohols **33** and **34** with trimethylphosphine, in good to excellent yield (Scheme 9).

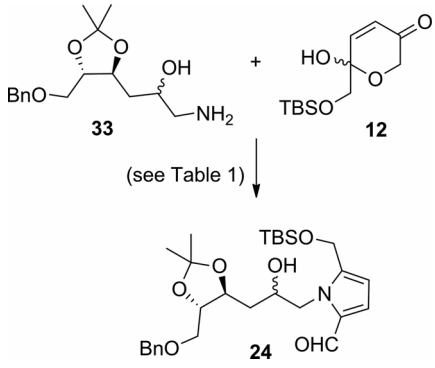
Initially, investigation of the Maillard-type condensation of amino alcohol **33** with dihydropyranone **12** gave disappointing results (Table 1). Use of anhydrous dioxane as solvent did not afford any of the desired product (entry 1), while undistilled dioxane afforded alcohol **24** in 10% yield.



Scheme 9. Synthesis of amino alcohols **33** and **34** and their use towards the synthesis of acortatarin A epimers **40a** and **40b**. *Reagents and conditions:* i) NaN_3, satd. aq. NH_4Cl, DMF/H_2O (8:1), 100 °C, 2 h; ii) PMe_3, THF/H_2O (5:1), 50 °C, 2 h, **33** 85%, **34** 64% over 2 steps; iii) Et_3N, 1,4-dioxane, room temp., 2–6 h, **24** 60%, **35** 54% (*dr* 1.6:1); iv) TPAP, NMO, CH_2Cl_2, 0 °C, 0.25 h, quant; v) 4 M HCl in 1,4-dioxane, THF/H_2O (1:1), room temp., 0.5–2.5 h, **38** 90% (*dr* 1:1), **39** 61% (*dr* 3.4:1); vi) TBAF, THF, room temp., 2 h, **40a** 30%, **40b** 50%.

Increasing the ratio of amino alcohol **33** to dihydropyranone **12** and the reaction temperature offered modest improvements in yield (entries 2–5). The addition of triethylamine, however, afforded alcohol **24** in 60% yield together with recovery of unreacted amino alcohol **33** (entry 6).

Table 1. Maillard-type condensation of amino alcohol **33** with dihydropyranone **12**.



Entry	Ratio **33**:**12**	Additive (equiv.)	Temperature [°C]	Yield [%]
1	1:1	–	r.t.	0[a]
2	1:1	–	r.t.	10
3	2:1	–	r.t.	25
4	3:1	–	r.t.	20
5	2:1	–	50	25
6	2:1	Et_3N (3.0)	r.t.	60

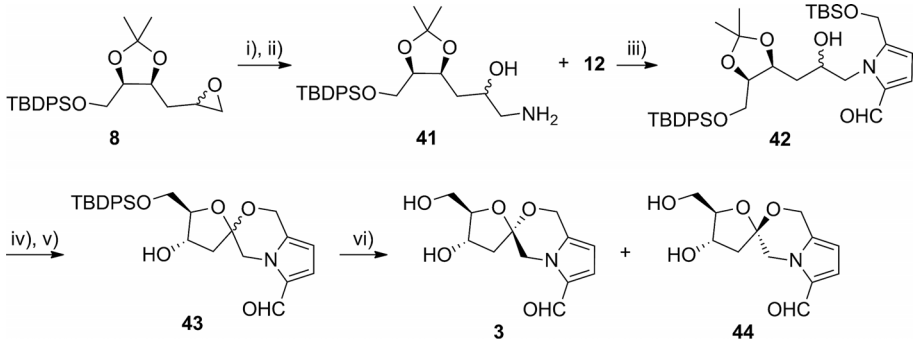
[a] Anhydrous dioxane was used. All other reactions were performed in undistilled dioxane for 3 h.

With condensation product **24** in hand, the stage was set to probe the final deprotection/cyclisation step to form the spiroketal (Scheme 9). A screen of several oxidants (PCC, PDC, IBX, DMP, TPAP/NMO) established that TPAP/NMO in CH_2Cl_2 most effectively oxidised the secondary alcohol, affording key ketone **36** in excellent yield. While exposure of **36** to a variety of mildly acidic conditions at room temperature (PPTS, PTSA, dil. aq. HCl, CSA) successfully removed the TBS group, the acetonide failed to deprotect under these conditions and only the hemiacetal was isolated. Use of harsher acidic reagents was therefore evaluated, with 4 M aq. HCl in THF proving the most effective, furnishing the desired spiroketals **38** as a separable 1:1 mixture in 90% yield.

Having formed the spiroketal, attention turned to removal of the final benzyl protecting group. Several methods were screened [H_2/Pd, H_2/Pd(OH)$_2$, BCl_3, LiDBB, BF_3·Et_2O/DMS, TMSCl/NaI], but none were effective, mirroring the difficulties observed by Sudhakar and co-workers in their synthesis of acortatarins A and B.[4] To overcome this, the synthesis was modified, replacing the benzyl ether with a TBDPS-ether. Removal of the TBDPS group, unlike the benzyl group, was envisaged to be straightforward using TBAF. Thus, epoxide **19** was taken through the same synthetic sequence as **9**, affording the TBDPS-protected Maillard condensation product **35** (Scheme 9). Oxidation of the alcohol, deprotection of the TBS-ether, and spirocyclisation occurred under the same conditions as used for **24** to give spiroketal **39** in 61% yield as a 3.4:1 mixture of isomers. As anticipated, final deprotection of the TBDPS-ether occurred smoothly upon treatment with TBAF to give the separable spiroketals 3-*epi*-*ent*-acortatarin A (**40a**) and 2-*epi*-acortatarin A (**40b**) in 30% and 50% yield, respectively.

Synthesis of Acortatarin A (3)

With synthesis of C-2 analogues **40a** and **40b** successfully completed, attention turned to synthesis of acortatarin A (**3**) from epoxide **8** (Scheme 10). Ring opening of the epoxide **8** with sodium azide and subsequent reduction with trimethylphosphine in THF provided the desired amino alcohol **41** in excellent yield. Amino alcohol **41** was then elaborated to acortatarin A (**3**) using the same strategy as developed earlier in our synthesis. Thus, Maillard-type condensation of **41** with dihydropyranone **12** in the presence of triethylamine in 1,4-dioxane afforded pyrrole **42** in 51–60% yield. Oxidation of the secondary alcohol with TPAP/NMO



Scheme 10. Synthesis of the revised structure of acortatarin A (**3**). *Reagents and conditions:* i) NaN_3, satd. aq. NH_4Cl, EtOH, reflux, 10 h; ii) PMe_3, THF/H_2O (5:1), 50 °C, 2 h, **41a** 48%, **41b** 37% over 2 steps; iii) Et_3N, 1,4-dioxane, room temp., 2 h, 51–60%; iv) TPAP, NMO, CH_2Cl_2, 0 °C, 0.25 h, 90%; v) 4 M HCl in 1,4-dioxane, THF/H_2O (1:1), room temp., 2 h, 82%; vi) TBAF, THF, room temp., 2.5 h, **3** 40%, **42** 27%.

afforded the spirocyclisation precursor in excellent yield. Subsequent treatment of the ketone with 2 M HCl in THF provided the TBDPS-protected spiroketals **43a** and **43b** in high yield, as an inseparable 1.5:1 mixture. Gratifyingly, final deprotection of the TBDPS ether with TBAF successfully afforded the revised structure of acortatarin A (**3**), along with its 5-epimer (**44**) in 67% combined yield as a separable 1.5:1 mixture.

The spectroscopic data (^1H, ^{13}C NMR and HRMS analysis) obtained for **3** was in good agreement with the literature. Comparison of the optical rotation data of the synthetic sample [$[\alpha]_D^{20}$ = +194.8 (*c* = 0.15, MeOH)] with that of the natural product [$[\alpha]_D^{20}$ = +178.4 (*c* = 0.4, MeOH)][2] and that of the synthetic sample prepared by Sudhakar et al. [$[\alpha]_D^{20}$ = +191.4 (*c* = 0.27, MeOH)][4] confirmed the stereorevision of the absolute configuration of acortatarin A.

Conclusions

In summary, a convergent synthetic strategy to construct the acortatarin family of natural products in described. The key Maillard-type condensation of chiral amino alcohol **39** with dihydropyranone building block **12** demonstrated herein is amenable to the efficient synthesis of a focused library of morpholine spiroketals to further probe their potential as agents to treat diabetic nephropathy. Dihydropyranone **12** has since been demonstrated to provide wider utility in the synthesis of related 2-formylpyrrole systems.[21]

Experimental Section

General: Unless stated otherwise, all reactions were carried out in flame- or oven-dried glassware under a dry nitrogen atmosphere. All solvents and reagents were used as supplied from commercial sources. Tetrahydrofuran was freshly distilled from sodium/benzophenone. Dichloromethane, diisopropylethylamine and dimethyl sulfoxide were freshly distilled from calcium hydride. Lithium chloride was dried for at least 24 h under vacuum (about 1 Torr) at 70 °C prior to use. Analytical thin-layer chromatography (TLC) was performed using Kieselgel F254 0.2 mm (Merck) silica plates with visualisation by ultraviolet irradiation (254 nm) followed by staining with potassium permanganate or vanillin. Flash column chromatography was performed using Kieselgel S 63–100 μm (Riedel-de-Hahn) silica gel. Preparatory TLC was carried out on 500 μm Uniplate™ (Analtech) silica gel (20 × 20 cm) thin layer chromatography plates. Melting points were determined on a Kofler hot-stage apparatus. Optical rotations were measured on a Perkin–Elmer 341 polarimeter at wavelength 589 nm and are given in units of 10^{-1} deg cm^2 g^{-1}. Infrared (IR) spectra were recorded on a Perkin–Elmer Spectrum 100 FT-IR spectrometer using a diamond ATR sampling accessory. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DRX400 spectrophotometer at ambient temperature. Unless stated, diastereomeric ratio (*dr*) was determined based on the ^1H NMR spectrum analysis after work-up. The exact *dr* for some diastereomers was not obtained due to overlapping resonances. All chemical shifts were referenced to δ = 7.26 for ^1H ($CHCl_3$), and δ = 77.0 for ^{13}C ($CDCl_3$), respectively. The multiplicities of ^1H signals are designated by the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. All ^{13}C NMR spectra were acquired using broadband decoupled mode and assignments were determined using DEPT sequences. Mass spectra were recorded on a Bruker microTOF QII (electrospray ionisation ESI$^+$, or chemical ionization CI) mass spectrometer.

Furan 14: *n*BuLi (1.6 M in hexanes, 15.5 mL, 15.5 mmol) was added dropwise to a solution of 1-(*tert*-butyldimethylsiloxymethyl)-4-methylfuran (3.00 g, 14.1 mmol) in THF (30 mL) at –78 °C, and the mixture allowed to stir at this temperature for 1.5 h, then warmed to 0 °C and stirred for 0.5 h. The mixture was then re-cooled to –78 °C, and DMF (2.2 mL, 28.4 mmol) added dropwise. The mixture was allowed to stir at –78 °C for 1 h, then warmed to room temp. and stirred for an additional 0.5 h. Water (75 mL) was added, and the mixture extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo to give the crude material. The crude was purified via flash chromatography (silica gel, ethyl acetate/hexanes, 1:20 as eluent) to give the 2-formylfuran (2.30 g, 68%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.48 (s, 1 H), 7.10 (d, *J* = 3.6 Hz, 1 H), 6.36 (d, *J* = 3.6 Hz, 1 H), 4.63 (s, 2 H), 0.81 (s, 9 H), 0.00 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5 (CH), 161.5 (C), 152.2 (C), 122.5 (CH), 109.4 (CH), 58.6 (CH_2), 25.8 (3 × CH_3), 18.3 (C), –5.4 (2 × CH_3) ppm. Spectral data were in agreement with literature values.[22]

Sodium borohydride (0.721 g, 19.1 mmol) was added portionwise to a solution of the above furan (2.30 g, 9.57 mmol) in methanol (50 mL) at 0 °C, and the mixture allowed to stir at this temperature

for 0.25 h. Water (2 mL) was added, and the methanol removed in vacuo. The residue was partitioned with water (40 mL) and ethyl acetate (50 mL). The organic layer was removed, and the aqueous further extracted with ethyl acetate (2× 50 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo to give crude **14** (2.3 g, 99%) as a colourless oil that was carried forward without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.21 (d, J = 3.6 Hz, 1 H), 6.18 (d, J = 3.6 Hz, 1 H), 4.62 (s, 2 H), 4.57 (s, 2 H), 1.84 (br. s, 1 H), 0.90 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.4 (C), 153.3 (C), 108.4 (CH), 107.9 (CH), 58.2 (CH_2), 57.6 (CH_2), 25.8 (3×CH_3), 18.4 (C), –5.2 (2×CH_3) ppm. Spectral data were in agreement with literature values.[22]

Dihydropyranone 12: *m*-CPBA (0.700 g, 77% purity, 3.2 mmol) was added to a solution of crude alcohol **14** (0.6 g, 2.5 mmol) in dichloromethane (20 mL) at 0 °C and the mixture allowed to stir at this temperature for 0.5 h, then warmed to room temp. and stirred for an additional 4 h. The reaction was quenched with satd. aq. Na_2SO_3 (20 mL), followed by neutralisation to pH 7–8 with 1 M NaOH solution. The mixture was extracted with dichloromethane (2× 20 mL) and the combined organic extracts were concentrated in vacuo to give the crude **12** (0.63 g, 92%) as a white solid that was carried forward without further purification, m.p. 54–55 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (d, J = 10.0 Hz, 1 H), 6.08 (d, J = 10.0 Hz, 1 H), 4.54 (d, J = 16.8 Hz, 1 H), 4.11 (d, J = 16.8 Hz, 1 H), 3.97 (br. s, 1 H), 3.73 (d, J = 10.4 Hz, 1 H), 3.65 (d, J = 10.4 Hz, 1 H), 0.88 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.3 (C), 146.3 (CH), 128.2 (CH), 92.6 (C), 67.9 (CH_2), 66.5 (CH_2), 25.7 (3×CH_3), 18.3 (C), –5.3 (2×CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3242, 295, 2929, 2857, 1677, 1244, 1114, 1061, 830, 773 cm^{-1}. HRMS (ESI$^+$): m/z 259.2365 [M + H]$^+$ (calcd. for $C_{12}H_{23}O_4Si$ 259.1360).

2-Formylpyrrole 10: Satd. aq. ammonia (0.1 mL, 4.6 mmol) was added to a solution of dihydropyranone **12** (0.200 g, 0.78 mmol) in undistilled 1,4-dioxane (4 mL) at room temp., and the mixture allowed to stir for 2 h before concentrating in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:8 as eluent) to give **10** (0.065 g, 35%) as a colourless solid, m.p. 55–57.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.21 (br. s, 1 H), 9.42 (s, 1 H), 6.90 (t, J = 3.0 Hz, 1 H), 6.15 (dd, J = 3.0, 1.0 Hz, 1 H), 4.76 (s, 2 H), 0.90 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (CH), 141.3 (C), 132.0 (C), 122.3 (CH), 108.0 (CH), 58.5 (CH_2), 25.8 (3×CH_3), 18.2 (C), –5.5 (2×CH_3) ppm. Spectral data were in agreement with literature values.[4]

Alkene 17: CuI (0.084 g, 0.44 mmol) was added to a solution of iodide **15**[15](0.800 g, 2.2 mmol) in THF/DMPU (1:1, 8.8 mL) at room temp. under argon. The resulting mixture was cooled to –35 °C, and vinylmagnesium bromide (1 M in THF, 4.4 mL, 4.4 mmol) added dropwise. The mixture was allowed to stir at –20 °C for 0.5 h, then an additional portion of vinylmagnesium bromide (1 M in THF, 1.4 mL, 1.4 mmol) added. The mixture was allowed to stir at –20 °C for an additional 2 h, then quenched with satd. aq. NH_4Cl (15 mL). The mixture was extracted with ethyl acetate (3× 30 mL), and the combined organic extracts washed with brine (90 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:10 as eluent) to give **17** (0.458 g, 85%) as a pale yellow oil. $[\alpha]_D^{20}$ = –12.8 (c = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H), 5.88–5.78 (m, 1 H), 5.16–5.07 (m, 2 H), 4.60 (s, 2 H), 3.92–3.89 (m, 2 H), 3.59 (d, J = 4.0 Hz, 2 H), 2.41–2.38 (m, 2 H), 1.44 (s, 3 H), 1.42 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0 (C), 133.8 (CH), 128.3 (2×CH), 127.6 (3×CH), 117.5 (CH_2), 108.9 (C), 79.5 (CH), 77.3 (CH), 73.4 (CH_2), 70.4 (CH_2), 37.4 (CH_2), 27.2 (CH_3), 27.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2985, 2864, 1642, 1454, 1077, 995, 914, 735, 697 cm^{-1}. HRMS (ESI$^+$): m/z 263.1638 [M + H]$^+$ (calcd. for $C_{16}H_{23}O_3$ 263.1642).

Epoxide 9: Using a precooled syringe, trifluoroacetone (0.10 mL, 0.11 mmol) was added to a solution of alkene **17** (0.200 g, 0.76 mmol) and $NaHCO_3$ (0.530 g, 6.31 mmol) in water/acetonitrile (2:3, 10 mL) at 0 °C. Oxone® (2.44 g, 4.0 mmol) was then added to the mixture in four portions over 1 h at 0 °C. The reaction was allowed to stir at room temp. for 12 h, then recooled to 0 °C and quenched by portionwise addition of satd. aq. Na_2SO_3 (20 mL). The mixture was extracted with ethyl acetate (3× 50 mL), and the combined organic extracts washed with brine (100 mL), dried with $MgSO_4$, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:5 as eluent) to give **9** (0.175 g, 85%) as a colourless oil and an inseparable mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 5 H), 4.58 (s, 2 H), 4.04–3.86 (m, 2 H), 3.65–3.55 (m, 2 H), 3.09–3.05 (m, 1 H), 2.80–2.49 (m, 2 H), 1.84–1.69 (m, 2 H), 1.43–1.41 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes minor isomer): δ = 137.9 (C), 128.4 (2×CH), 127.7 (3×CH), 109.1 (C), 109.0* (C), 79.9 (CH), 79.3* (CH), 76.1 (CH), 75.7* (CH), 73.59 (CH_2), 73.58* (CH_2), 70.2 (CH_2), 70.1* (CH_2), 49.5 (CH), 49.2* (CH), 47.5 (CH_2), 46.7* (CH_2), 36.8 (CH_2), 35.3* (CH_2), 27.3 (CH_3), 27.2* (CH_3), 27.0 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2989, 2942, 1515, 1376, 1261, 1081, 1020, 856, 821 cm^{-1}. HRMS (ESI$^+$): m/z 301.1408 [M + Na]$^+$ (calcd. for $C_{16}H_{22}NaO_4$ 301.1410).

Homoallylic Alcohol 21: A solution of allyl bromide (9.0 mL, 104 mmol) in THF (100 mL) was added dropwise to a mixture of aldehyde **20** (4.50 g, 26.4 mmol), zinc dust (6.70 g, 102 mmol), and satd. aq. NH_4Cl (10 mL) in THF (150 mL) at 0 °C over 10 min. The mixture was allowed to stir at room temp. for 2 h, then satd. aq. NH_4Cl (50 mL) added dropwise until no further effervescence was observed. The resulting mixture was allowed to stir for another 1 h, then filtered through a plug of silica. The filter cake was washed with ethyl acetate (200 mL), and the organic layer of the combined filtrates separated. The aqueous was further extracted with ethyl acetate (2× 75 mL), and the combined organic extracts dried with Na_2SO_4 and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:7 as eluent) to give **21** (4.94 g, 88%) as a colourless oil. $[\alpha]_D^{20}$ = +10.1 (c = 1.0, $CHCl_3$, ref.[19] $[\alpha]_D^{20}$ = +10.2, c = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.85–5.81 (m, 1 H), 5.18–5.13 (m, 2 H), 4.02–3.98 (m, 2 H), 3.95–3.89 (m, 1 H), 3.81–3.76 (m, 1 H), 2.37–2.29 (m, 1 H), 2.25–2.16 (m, 1 H), 1.65–1.56 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.0 (CH), 118.2 (CH_2), 109.6 (C), 77.7 (CH), 70.4 (CH), 64.8 (CH_2), 37.6 (CH_2), 36.2 (CH_2), 34.8 (CH_2), 25.1 (CH_2), 24.0 (CH_2), 23.8 (CH_2) ppm. Spectral data were in agreement with literature values.[19]

Diol 22: Conc. HCl (10 mL) was added dropwise to a solution of olefin **21** (4.00 g, 18.8 mmol) in methanol (20 mL) and the mixture allowed to stir at room temp. for 24 h. The reaction was neutralised to pH 7–8 with satd. aq. $NaHCO_3$, and the organic layer separated. The aqueous was further extracted with ethyl acetate (3× 50 mL), and the combined organic extracts washed with brine (100 mL), dried with $MgSO_4$, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 9:1 as eluent) to give the triol

(2.30 g, 90%) as a white solid, m.p. 52.5–54 °C (ref.[23] 54–55 °C). $[\alpha]_D^{20}$ = +10.0 (*c* = 1.1, H_2O, ref.[23] $[\alpha]_D^{20}$ = +9.2, *c* = 5.2, D_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90–5.80 (m, 1 H), 5.21–5.15 (m, 2 H), 3.82–3.75 (m, 3 H), 3.66–3.60 (m, 1 H), 3.03 (d, *J* = 4.0 Hz, 1 H), 2.66–2.60 (m, 1 H), 2.55 (d, *J* = 4.0 Hz, 1 H), 2.43–2.23 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.2 (CH), 118.6 (CH_2), 73.4 (CH), 72.5 (CH), 63.3 (CH_2), 37.7 (CH_2) ppm. Spectral data were in agreement with literature values.[23]

Sodium hydride (60% in mineral oil, 0.400 g, 10.0 mmol) was added slowly to a solution of the above triol (1.60 g, 12.1 mmol) in THF (40 mL) at 0 °C, and the mixture allowed to stir at this temperature for 10 min, before allowing to warm to room temp. and stirred for a further 10 min. TBDPSCl (3.50 g, 12.7 mmol) was then added, and the mixture allowed to stir at room temp. for 2 h. Water (40 mL) was then added carefully, and the mixture extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with brine (100 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:5 as eluent) to give **22** (4.00 g, 90%) as a pale yellow oil. $[\alpha]_D^{20}$ = +0.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.65 (m, 4 H), 7.47–7.38 (m, 6 H), 5.89–5.77 (m, 1 H), 5.14–5.08 (m, 2 H), 3.84–3.78 (m, 2 H), 3.78–3.72 (m, 2 H), 2.39–2.20 (m, 2 H), 1.08 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6 (4 × CH), 134.5 (CH), 132.9 (2 × C), 132.8 (2 × CH), 127.9 (4 × CH), 123.0 (CH_2), 73.3 (CH), 71.6 (CH), 64.7 (CH_2), 37.5 (CH_2), 26.9 (3 × CH_3), 19.3 (C) ppm. Spectral data were in agreement with literature values.[24]

Epoxide 8: PPTS (0.220 g, 0.88 mmol) was added to a solution of diol **22** (3.30 g, 8.91 mmol) in dichloromethane (60 mL), followed by 2,2-dimethoxypropane (30 mL, 244 mmol), and the mixture allowed to stir at room temp. for 2 h. The reaction was quenched with satd. aq. $NaHCO_3$ (40 mL), and the organic layer separated. The aqueous was further extracted with dichloromethane (2 × 60 mL), and the combined organic extracts washed with brine (100 mL), dried with $MgSO_4$, and concentrated in vacuo to give the crude alkene (3.60 g, quant.) as a colourless oil. The crude material was carried forward without further purification.

$[\alpha]_D^{20}$ = –6.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.67 (m, 4 H), 7.44–7.37 (m, 6 H), 5.93–5.86 (m, 1 H), 5.13–5.07 (m, 2 H), 4.26–4.20 (m, 2 H), 3.78–3.67 (m, 2 H), 2.46–2.36 (m, 2 H), 1.40 (s, 3 H), 1.34 (s, 3 H), 1.07 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.62 (2 × CH), 135.60 (2 × CH), 135.2 (CH), 133.4 (C), 133.3 (C), 129.7 (2 × CH), 127.7 (4 × CH), 116.8 (CH_2), 108.0 (C), 77.7 (CH), 77.0 (CH), 62.6 (CH_2), 34.0 (CH_2), 28.1 (CH_3), 26.9 (3 × CH_3), 25.5 (CH_3), 19.2 (C) ppm. IR (neat): $\tilde{\nu}$ = 3072, 2931, 2858, 1740, 1642, 1472, 1427, 1244, 1216, 1075, 823, 702 cm^{-1}. HRMS (ESI$^+$): *m*/*z* 433.2168 $[M + Na]^+$ (calcd. for $C_{25}H_{34}NaO_3Si$ 433.2169).

m-CPBA (1.70 g, 77% purity, 7.59 mmol) was added portionwise to a solution of the above crude alkene (2.40 g, 5.84 mmol) in dichloromethane (100 mL) at 0 °C. The mixture was warmed to room temp. and stirred for 12 h, then quenched with satd. aq. Na_2SO_3 (100 mL). The organic layer was separated, and the aqueous further extracted with dichloromethane (2 × 150 mL). The combined organic extracts were washed with satd. aq. $NaHCO_3$ (200 mL), dried with $MgSO_4$, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:15 as eluent) to give **8** (2.50 g, 93%, *dr* 1.5:1) as a pale yellow oil and an inseparable mixture of two diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$, * denotes minor isomer): δ = 7.67–7.63 (m, 4 H), 7.45–7.35 (m, 6 H), 4.46–4.29 (m, 1 H), 4.24–4.18 (m, 1 H), 3.74–3.63 (m, 2 H), 3.15–3.10 (m, 1 H), 2.83 (dd, *J* = 4.0, 1.0 Hz, 1 H), 2.77–2.75* (m, 1 H), 2.55* (dd, *J* = 2.9, 2.0 Hz, 1 H), 2.49 (dd, *J* = 4.0, 2.6 Hz, 1 H), 2.00–1.70 (m, 2 H), 1.39–1.32 (m, 6 H), 1.04 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes minor isomer): δ = 135.6 (4 × CH), 133.25 (C), 133.17* (C), 133.14 (C), 133.08* (C), 129.82* (2 × CH), 129.78 (2 × CH), 127.8 (4 × CH), 108.3 (C), 77.4 (CH), 74.71 (CH), 74.67* (CH), 62.5 (CH_2), 50.2 (CH), 47.8 (CH_2), 46.7* (CH_2), 33.2 (CH_2), 32.2* (CH_2), 28.1 (CH_3), 26.9 (3 × CH_3), 25.5 (CH_3), 19.2 (C) ppm. IR (neat): $\tilde{\nu}$ = 2930, 2858, 1472, 1379, 1427, 1216, 1105, 823, 702 cm^{-1}. HRMS (ESI$^+$): *m*/*z* 449.2119 $[M + Na]^+$ (calcd. for $C_{25}H_{34}NaO_4Si$ 449.2122).

Bromohydrin 25: NaBr (133 mg, 1.29 mmol) was added to a solution of epoxide **9** (0.300 g, 1.08 mmol) in acetic acid/propanoic acid (1:2, 6 mL) at –20 °C. The mixture was allowed to stir at –20 °C for 0.5 h, then warmed to room temperature and neutralised with satd. aq. $NaHCO_3$ (30 mL) to pH 7–8. The mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts washed with brine (50 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:4 as eluent) to give **25** (0.335 mg, 85%, *dr* 3.5:1) as a colourless oil and an inseparable mixture of two diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$, * denotes the minor isomer): δ = 7.34–7.28 (m, 5 H), 4.58 (s, 2 H), 4.12–3.96 (m, 2 H), 3.92–3.86 (m, 1 H), 3.66–3.53 (m, 2 H), 3.52–3.38 (m, 2 H), 2.00–1.96* (m, 2 H), 1.93–1.72 (m, 2 H), 1.42–1.38 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes minor isomer): δ = 137.75 (C), 137.71* (C), 128.45* (3 × CH), 128.43 (2 × CH), 127.8* (CH), 127.7 (3 × CH), 109.5* (C), 109.2 (C), 79.9* (CH), 79.7 (CH), 77.5* (CH), 75.6 (CH), 73.64* (CH_2), 73.60 (CH_2), 70.2 (CH_2), 70.0* (CH_2), 69.9* (CH), 68.7 (CH), 39.1* (CH_2), 38.1 (CH_2), 27.4 (CH_3), 27.3* (CH_3), 27.1* (CH_3), 26.9 (CH_3), 8.9 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3436, 2985, 2864, 2862, 1717, 1370, 1073 cm^{-1}. HRMS (ESI$^+$): *m*/*z* $[M + Na]^+$ 381.0667, 383.0646 (calcd. for $C_{16}H_{23}{}^{79}BrNaO_4$ 381.0677. $C_{16}H_{23}{}^{81}BrNaO_4$ 383.0657).

Iodohydrin 26: Prepared in an analogous manner to bromohydrin **25** using NaI from epoxide **9** (0.301 g, 1.08 mmol), to give **26** (0.386 g, 87%, *dr* 3.7:1) as a colourless oil and an inseparable mixture of two diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$, * denotes the minor isomer): δ = 7.35–7.29 (m, 5 H), 4.56 (s, 2 H), 4.08–3.98 (m, 1 H), 3.93–3.86 (m, 1 H), 3.86–3.75 (m, 1 H), 3.67–3.53 (m, 2 H), 3.37–3.22 (m, 2 H), 2.00–1.94* (m, 2 H), 1.94–1.70 (m, 2 H), 1.43–1.39 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes the minor isomer): δ = 137.68 (C), 137.65* (C), 128.41* (2 × CH), 128.39 (2 × CH), 127.77* (CH), 127.69* (2 × CH), 127.77 (3 × CH), 109.6* (C), 109.2 (C), 79.9* (CH), 79.5 (CH), 77.6* (CH), 75.8 (CH), 73.62* (CH_2), 73.58 (CH_2), 70.2 (CH_2), 70.0* (CH_2), 69.9* (CH), 68.6 (CH), 39.6* (CH_2), 39.1 (CH_2), 27.2 (CH_3), 27.1* (CH_3), 27.0* (CH_3), 26.9 (CH_3), 14.6 (CH_2), 13.6* (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3447, 2951, 2866, 1730, 1454, 1370, 1086 cm^{-1}. HRMS (ESI$^+$): *m*/*z* 429.0533 $[M + Na]^+$ (calcd. for $C_{16}H_{23}INaO_4$ 429.0540).

α-Bromo Ketone 27: PCC (0.065 g, 0.31 mmol) was added to a mixture of bromohydrin **25** (0.100 g, 0.28 mmol) and activated powdered molecular sieves (4 Å) (0.050 g) in dichloromethane (5 mL) at room temp. The mixture was allowed to stir at room temp. for 12 h, then concentrated in vacuo to ca. 1 mL. The resulting mixture was filtered through a plug of silica and the filter cake washed with ethyl acetate (3 × 10 mL). The combined filtrates were concentrated

in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:5 as eluent) to give **27** (0.070 g, 70%) as a brown oil. $[\alpha]_D^{20}$ = –53.2 (*c* = 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 5 H), 4.54 (s, 2 H), 4.26–4.21 (m, 1 H), 3.93 (s, 2 H), 3.90–3.85 (m, 1 H), 3.67–3.52 (m, 2 H), 2.91 (d, *J* = 5.6 Hz, 2 H), 1.39 (s, 3 H), 1.38 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.0 (C), 137.6 (C), 128.3 (2×CH), 127.6 (3×CH), 109.3 (C), 79.0 (CH), 74.8 (CH), 73.5 (CH_2), 70.0 (CH_2), 43.2 (CH_2), 35.0 (CH_2), 27.0 (CH_3), 26.8 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2979, 2864, 2859, 1712, 1690, 1368, 1075 cm^{-1}. HRMS (ESI^+): *m/z* $[M + Na]^+$ 381.0497 (calcd. for $C_{16}H_{21}{}^{81}BrNaO_4$ 381.0500).

α-Iodo Ketone 28: Prepared in an analogous manner to α-bromo ketone **27** from iodohydrin **26** (0.100 g, 0.25 mmol) to give **28** (0.068 g, 65%) and the corresponding α-chloro ketone **29** (0.025 g, 32%) as pale brown oils.

28: $[\alpha]_D^{20}$ = –31.5 (*c* = 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 5 H), 4.56 (s, 2 H), 4.27–4.22 (m, 1 H), 3.90–3.81 (m, 3 H), 3.68–3.63 (dd, *J* = 9.0, 5.4 Hz, 1 H), 3.56–3.53 (dd, *J* = 9.0, 5.4 Hz, 1 H), 3.03–2.93 (m, 2 H), 1.40 (s, 3 H), 1.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.3 (C), 137.8 (C), 128.5 (2×CH), 127.8 (3×CH), 109.5 (C), 79.3 (CH), 75.5 (CH), 73.7 (CH_2), 70.2 (CH_2), 42.8 (CH_2), 27.2 (CH_3), 27.0 (CH_3), 7.2 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 2983, 2934, 1690 1594, 1454, 1370, 1086 cm^{-1}. HRMS (ESI^+): *m/z* 427.0379 $[M + Na]^+$ (calcd. for $C_{16}H_{21}INaO_4$ 427.0377).

29: $[\alpha]_D^{20}$ = –63.5 (*c* = 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 4.55 (s, 2 H), 4.28–4.22 (m, 1 H), 4.14 (s, 2 H), 3.90–3.85 (m, 1 H), 3.68–3.65 (dd, *J* = 10.0, 5.4 Hz, 1 H), 3.56–3.52 (dd, *J* = 10.0, 5.0 Hz, 1 H), 2.85 (d, *J* = 5.4 Hz, 2 H), 1.39 (s, 3 H), 1.38 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.8 (C), 137.7 (C), 128.5 (2×CH), 127.8 (3×CH), 109.6 (C), 79.2 (CH), 74.9 (CH), 73.7 (CH_2), 70.2 (CH_2), 49.0 (CH_2), 43.1 (CH_2), 27.2 (CH_3), 26.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2979, 2917, 1675 1587, 1453, 1370, 1081 cm^{-1}. HRMS (ESI^+): *m/z* 335.1021 $[M + Na]^+$ (calcd. for $C_{16}H_{21}ClNaO_4$ 335.1016).

Diol 30: A solution of OsO_4 in *t*BuOH (2.5% w/v, 3 mL, 0.075 mmol) was added to a solution of olefin **17** (0.400 g, 1.5 mmol) in acetone/H_2O (1:1, 1.5 mL) in the presence of a pH 7 buffer (2 mL) at room temp., followed by NMO (0.210 g, 1.79 mmol). The mixture was allowed to stir at room temp. for 10 h, then satd. aq. Na_2SO_3 (15 mL) added. The acetone was removed in vacuo and the resulting mixture extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine (50 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude material **30** (0.440 g, quant.) as a pale yellow oil and as an inseparable mixture of diastereomers. The *dr* was unable to be determined due to overlapping signals in the ^1H NMR spectrum. The crude material was carried forward to the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 4.57 (s, 2 H), 4.07–3.97 (m, 1 H), 3.91–3.86 (m, 2 H), 3.62–3.48 (m, 4 H), 2.26–2.05 (m, 2 H), 1.85–1.66 (m, 2 H), 1.43–1.39 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes minor isomer): δ = 137.6 (C), 128.3 (2×CH), 127.6 (3×CH), 109.2* (C), 108.9 (C), 80.0* (CH), 79.7 (CH), 77.1* (CH), 75.6 (CH), 73.5 (CH_2), 70.6* (CH), 70.2 (CH_2), 69.9* (CH_2), 69.3 (CH), 66.6 (CH_2), 66.1* (CH_2), 36.4 (CH_2), 36.2* (CH_2), 27.2 (CH_3), 27.1* (CH_3), 27.0* (CH_3), 26.9 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3481, 2986, 2936, 2872, 1370, 1213, 1070, 738 cm^{-1}. HRMS (ESI^+): *m/z* 319.1519 $[M + Na]^+$ (calcd. for $C_{16}H_{24}NaO_5$ 319.1516).

Tosylate 31: Tosyl chloride (0.210 g, 1.10 mmol) and triethylamine (0.3 mL, 2.15 mmol) were added to a solution of crude diol **30** (0.300 g, 1.01 mmol) in dichloromethane (15 mL) at 0 °C. The mixture was allowed to stir at room temp. for 3 h, then water (20 mL) added. The organic layer was removed and the aqueous extracted with dichloromethane (2×20 mL). The combined organic extracts were washed with brine (50 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:3 as eluent) to give the tosylate (0.361 g, 80%, *dr* 3.2:1) as a colourless oil and as a mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$, * denotes the minor isomer): δ = 7.81–7.78 (m, 2 H); 7.38–7.27 (m, 7 H), 4.58–4.56 (m, 2 H), 4.13–3.92 (m, 4 H), 3.89–3.83 (m, 1 H), 3.63–3.50 (m, 2 H), 3.15* (d, *J* = 2.0 Hz, 1 H), 2.74 (m, 1 H), 2.45 (s, 3 H), 1.89–1.84* (m, 2 H), 1.83–1.63 (m, 2 H), 1.38–1.36 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes the minor isomer): δ = 145.02 (C), 144.97* (C), 137.8 (C), 137.7* (C), 132.78* (C), 132.75 (C), 129.93 (2×CH), 129.91* (2×CH), 128.5* (2×CH), 128.47 (2×CH), 128.0 (2×CH), 127.85* (CH), 127.80 (CH), 127.7 (2×CH), 109.5* (C), 109.2 (C), 79.9* (CH), 79.5 (CH), 77.3* (CH), 75.6 (CH), 73.7* (CH_2), 73.6 (CH_2, C-1), 73.4 (CH_2, C-1), 72.9*(CH_2, C-1), 70.2 (CH_2), 69.9* (CH_2), 68.4* (CH), 67.0 (CH), 36.1* (CH_2), 35.9 (CH_2), 27.2 (CH_3), 27.1* (CH_3), 27.0* (CH_3), 26.9 (CH_3), 21.6 (CH_3), 21.0* (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3453, 2989, 2922, 2869, 1598, 1454, 1395, 1175, 1095, 814, 667 cm^{-1}. HRMS (ESI^+): *m/z* 451.1781 $[M + H]^+$ (calcd. for $C_{23}H_{31}O_7S$ 451.1785).

IBX (0.149 g, 0.53 mmol) was added to a solution of the above tosylate (0.200 g, 0.44 mmol) in DMSO (10 mL) at room temp. The mixture was then heated at 50 °C for 3 h, cooled to room temp., and quenched by addition of satd. aq. Na_2SO_3 (10 mL). The mixture was extracted with ethyl acetate (3×10 mL), and the combined organic extracts washed with brine (40 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:4 as eluent) to give **31** (0.124 g, 63%) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.82–7.79 (m, 2 H), 7.36–7.28 (m, 7 H), 4.55 (s, 2 H), 4.54 (s, 2 H), 4.22–4.17 (m, 1 H), 3.86–3.82 (m, 1 H), 3.63 (dd, *J* = 4.0, 8.0 Hz, 1 H), 3.52 (dd, *J* = 8.0, 12 Hz, 1 H) 2.78 (d, *J* = 1.0 Hz, 1 H), 2.76 (s, 1 H), 2.45 (s, 3 H), 1.38–1.36 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.3 (C), 145.4 (C), 137.7 (C), 132.3 (C), 129.9 (2×CH), 128.4 (2×CH), 128.1 (2×CH), 127.8 (CH), 127.7 (2×CH), 109.5 (C) 79.1 (CH), 74.2 (CH), 73.6 (CH_2), 72.2 (CH_2), 70.0 (CH_2), 42.6 (CH_2), 27.0 (CH_3), 26.9 (CH_3), 21.6 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2978, 2924, 2845, 1708, 1451, 1392, 1168, 1094, 814, 667 cm^{-1}.

Amino Alcohol 33: Sodium azide (0.077 g, 1.18 mmol) was added to a solution of epoxide **9** (0.157 g, 0.56 mmol) and NH_4Cl (0.063 g, 1.18 mmol) in DMF/water (8:1, 3.6 mL) at room temp. The mixture was heated at 80 °C for 2 h, then cooled to room temp. and quenched with satd. aq. NH_4Cl (15 mL). The mixture was extracted with ethyl acetate (20 mL), and the organic layer washed with brine (3×10 mL), dried with $MgSO_4$, and concentrated in vacuo to give the crude azide (0.170 g, 95%) as a colourless oil and an inseparable mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 5 H), 4.58 (s, 2 H), 4.04–4.00 (m, 2 H), 3.92–3.87 (m, 1 H), 3.66–3.53 (m, 2 H), 3.38–3.27 (m, 2 H), 1.89–1.69 (m, 2 H), 1.43–1.41 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes minor isomer): δ = 137.7 (C), 128.46 (2×CH), 127.86* (2×CH), 127.83* (2×CH), 127.75 (2×CH), 127.74 (CH), 109.6* (C), 109.2 (C), 80.0* (CH), 79.5 (CH), 78.1* (CH), 77.9 (CH), 73.68* (CH_2), 73.65 (CH_2), 70.3* (CH_2), 70.1* (CH), 70.0 (CH_2), 68.3 (CH), 56.9 (CH_2), 56.3* (CH_2), 37.2* (CH_2), 37.1 (CH_2) 27.06 (CH_3), 27.01* (CH_3), 26.80* (CH_3), 26.75 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3681, 3442, 2920, 2848, 2100, 1454, 1257, 1055, 735,

697 cm^{-1}. HRMS (ESI^+): *m/z* 344.1586 $[M + Na]^+$ (calcd. for $C_{16}H_{23}N_3NaO_4$ 344.1581).

Trimethylphosphine (1 M in THF, 0.5 mL, 0.50 mmol) was added to a solution of the above crude azide (0.050 g, 0.16 mmol) in THF/water (5:1, 3 mL) at room temp. The mixture was heated at reflux for 1 h, then cooled to room temp. and aq. NaOCl (42 $g\,L^{-1}$, 5 mL) added. The THF was removed in vacuo and the residue partitioned with ethyl acetate (10 mL) and water (10 mL). The organic layer was removed, and the aqueous further extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, CH_2Cl_2/MeOH, 8:1 saturated with NH_3 as eluent) to give **33** (0.043 g, 90%) as a colourless oil and an inseparable mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 5 H), 4.58 (s, 2 H), 4.08–3.96 (m, 2 H), 3.91–3.84 (m, 1 H), 3.65–3.52 (m, 2 H), 3.34–3.22 (m, 2 H), 1.80–1.65 (m, 2 H), 1.43–1.37 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes the minor isomer): δ = 137.2 (C), 131.6 (CH), 131.5* (CH), 127.9 (2 × CH), 127.3* (2 × CH), 127.29* (2 × CH), 127.23 (2 × CH), 109.0* (C), 108.6 (C), 79.5* (CH), 79.0 (CH), 76.3* (CH), 75.4 (CH), 73.15* (CH_2), 73.12 (CH_2), 69.8 (CH_2), 69.50* (CH_2), 69.46* (CH), 67.8 (CH), 56.4 (CH_2), 55.8* (CH_2), 36.8 (CH_2), 26.71 (CH_3), 26.66* (CH_3), 26.45* (CH_3), 26.41 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3372, 2983, 2934, 2862, 1594, 1454, 1370, 1086 cm^{-1}. HRMS (ESI^+): *m/z* 296.1851 $[M + H]^+$ (calcd. for $C_{16}H_{26}NO_4$ 296.1856).

Maillard Condensation Product 24: A solution of amine **33** (0.024 g, 0.081 mmol) and triethylamine (14 µL, 0.10 mmol) in undistilled 1,4-dioxane (2.5 mL) was added to a solution of dihydropyranone **12** (0.008 g, 0.031 mmol) in undistilled 1,4-dioxane (0.5 mL) at room temp. The mixture was allowed to stir at room temp. for 6 h, then concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:6 as eluent) to give **24** (0.010 g, 60%) as a yellow oil and an inseparable mixture of diastereomers. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.46 (s, 1 H), 7.34–7.27 (m, 5 H), 6.91–6.89 (m, 1 H), 6.21–6.19 (m, 1 H), 4.84–4.67 (m, 2 H), 4.62–4.54 (m, 3 H), 4.25–4.18 (m, 1 H), 4.15–4.08 (m, 2 H), 3.96–3.88 (m, 1 H), 3.64–3.54 (m, 2 H), 1.95–1.80 (m, 2 H), 1.42–1.37 (m, 6 H), 0.90 (s, 9 H), 0.10–0.08 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes the minor isomer): δ = 179.9 (CH), 179.6* (CH), 143.4* (C), 142.9 (C), 137.9 (C), 137.6* (C), 133.6 (C), 133.3* (C), 128.4 (2 × CH), 127.7 (3 × CH), 125.1 (CH), 110.3 (CH), 110.0* (CH), 109.3* (C), 109.0 (C), 80.2* (CH), 79.8 (CH), 77.3* (CH), 75.8 (CH), 73.61* (CH_2), 73.56 (CH_2), 70.9* (CH), 70.4 (CH), 70.2* (CH_2), 69.6 (CH_2), 57.6* (CH_2), 57.5 (CH_2), 51.6 (CH_2), 51.4* (CH_2), 38.3 (CH_2), 37.6* (CH_2), 27.3 (CH_3), 27.2* (CH_3), 26.96* (CH_3), 26.93 (CH_3), 25.9 (3 × CH_3), 18.3 (C), –5.30 (CH_3), –5.34 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3459, 2954, 2929, 1659, 1462, 1369, 1252, 1071, 836, 778 cm^{-1}. HRMS (ESI^+): *m/z* 540.2732 $[M + Na]^+$ (calcd. for $C_{28}H_{43}NNaO_6Si$ 540.2752).

Ketopyrrole 36: Powdered activated molecular sieves (4 Å) (0.020 g), TPAP (0.001 g, 0.002 mmol), and NMO (0.013 g, 0.11 mmol) were added to a solution of alcohol **24** (0.020 g, 0.039 mmol) in dichloromethane (2 mL) at 0 °C and the mixture allowed to stir at this temperature for 0.25 h. The mixture was then filtered through a plug of silica and the filter cake washed with ethyl acetate (2 × 10 mL). The combined filtrates were concentrated in vacuo to give crude **36** (0.020 g, quant.) as a colourless oil that was carried forward without further purification. $[\alpha]_D^{20}$ = +8.3 (*c* = 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.46 (s, 1 H), 7.34–7.27 (m, 5 H), 6.85 (d, *J* = 4.0 Hz, 1 H), 6.14 (d, *J* = 4.0 Hz, 1 H), 5.25 (s, 2 H), 4.52 (s, 2 H), 4.53 (s, 2 H), 4.25–4.20 (m, 1 H), 3.90–3.84 (m, 1 H), 3.61–3.53 (m, 2 H), 2.76 (d, *J* = 6.0 Hz, 2 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 0.83 (s, 9 H), 0.00 (s, 3 H), –0.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.7 (C), 179.8 (CH), 142.0 (C), 137.9 (C), 132.3 (C), 128.4 (2 × CH), 127.71 (2 × CH), 127.66 (CH), 124.0 (CH), 110.1 (CH), 109.5 (C), 79.8 (CH), 74.2 (CH), 73.6 (CH_2), 70.2 (CH_2), 57.5 (CH_2), 55.3 (CH_2), 43.7 (CH_2), 27.2 (CH_3), 27.0 (CH_3), 25.8 (3 × CH_3), 18.2 (C), –5.4 (2 × CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2925, 2854, 1735, 1658, 1463, 1364, 1253, 1075, 779 cm^{-1}. HRMS (ESI^+): *m/z* 538.2577 $[M + Na]^+$ (calcd. for $C_{28}H_{41}NNaO_6Si$ 538.2595).

Bn-Protected Spiroketal 38: HCl (4 M in 1,4-dioxane, 0.5 mL, 2.00 mmol) was added to a solution of crude ketone **36** (0.010 g, 0.019 mmol) in THF/water (1:1, 4 mL) at room temp., and the mixture allowed to stir for 0.5 h. The reaction was quenched with satd. aq. $NaHCO_3$ (5 mL) and the mixture extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 2:3 as eluent) to give two diastereomers: **38a** (2*S*,4*S*,5*S*, 3 mg, 45%) as a yellow oil, and **38b** (2*R*,4*S*,5*S*, 3 mg, 45%) as a colourless oil.

38a: $[\alpha]_D^{20}$ = –6.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.47 (s, 1 H), 7.38–7.29 (m, 5 H), 6.91 (d, *J* = 4.0 Hz, 1 H), 5.99 (d, *J* = 4.0 Hz, 1 H), 4.94 (d, *J* = 15.5 Hz, 1 H), 4.78 (d, *J* = 15.5 Hz, 1 H), 4.74 (d, *J* = 4.0 Hz, 1 H), 4.71–4.64 (m, 1 H), 4.56 (d, *J* = 4.0 Hz, 2 H), 4.31–4.21 (m, 2 H), 3.78 (d, *J* = 5.0 Hz, 2 H), 2.80 (d, *J* = 6.4 Hz, 1 H), 2.55 (dd, *J* = 14.0, 7.3 Hz, 1 H), 2.06 (dd, *J* = 14.0, 5.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7 (CH), 137.3 (C), 134.7 (C), 130.9 (C), 128.6 (2 × CH), 128.1 (CH), 127.9 (2 × CH), 124.0 (CH), 104.7 (CH), 102.2 (C), 80.1 (CH), 73.9 (CH_2), 72.0 (CH), 68.6 (CH_2), 58.2 (CH_2), 51.2 (CH_2), 46.1 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 2925, 2854, 1735, 1658, 1463, 1364, 1253, 1075, 779 cm^{-1}. HRMS (ESI^+): *m/z* 366.1301 $[M + Na]^+$ (calcd. for $C_{19}H_{21}NNaO_5$ 366.1385).

38b: $[\alpha]_D^{20}$ = –12.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.45 (s, 1 H), 7.34–7.29 (m, 5 H), 6.90 (d, *J* = 4.0 Hz, 1 H), 5.99 (d, *J* = 4.0 Hz, 1 H), 5.00 (d, *J* = 15.5 Hz, 1 H), 4.74 (d, *J* = 15.5 Hz, 1 H), 4.64 (d, *J* = 14.0 Hz, 1 H), 4.59 (dd, *J* = 18.4, 12.0 Hz, 2 H), 4.47–4.41 (m, 1 H), 4.40–4.35 (m, 1 H), 4.30 (d, *J* = 14.0 Hz, 1 H), 3.89 (dd, *J* = 11.0, 4.4 Hz, 1 H), 3.70 (dd, *J* = 11.0, 4.4 Hz, 1 H), 2.96 (d, *J* = 10.0 Hz, 1 H), 2.36 (d, *J* = 14.0 Hz, 1 H), 2.25 (dd, *J* = 14.0, 2.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8 (CH), 137.8 (C), 134.5 (C), 131.2 (C), 128.6 (2 × CH), 127.9 (2 × CH), 127.8 (CH), 124.0 (CH), 104.8 (CH), 103.6 (C), 84.6 (CH), 73.5 (CH_2), 72.1 (CH), 69.3 (CH_2), 58.1 (CH_2), 50.8 (CH_2), 44.8 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 2925, 2854, 1735, 1658, 1463, 1364, 1253, 1075, 779 cm^{-1}. HRMS (ESI^+): *m/z* 366.1300 $[M + Na]^+$ (calcd. for $C_{19}H_{21}NNaO_5$ 366.1285).

Iodide 16: Sodium hydride (60% in mineral oil, 0.44 g, 11.0 mmol) was added slowly to a solution of [(*S*,*S*)-5-hydroxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]methanol[15] (1.60 g, 9.87 mmol) in THF (40 mL) at 0 °C, and the resulting suspension allowed to stir at this temperature for 10 min, then warmed to room temp. and stirred for a further 10 min. TBDPSCl (3.70 g, 13.5 mmol) was then added and the mixture allowed to stir at room temp. for 2 h. Water (40 mL) was added, and the mixture extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with brine (120 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:5 as eluent) to give the alcohol (3.60 g, 90%) as a pale yellow oil. $[\alpha]_D^{20}$ = –0.9 (*c*

= 2.1, $CHCl_3$), ref.[25] $[\alpha]_D^{20}$ = –1.5 (*c* = 14.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.64 (m, 4 H), 7.46–7.36 (m, 6 H), 4.10–4.05 (m, 1 H), 3.99–3.94 (m, 1 H), 3.85–3.78 (m, 2 H), 3.77–3.63 (m, 2 H), 2.12 (br. s, 1 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6 (4 × CH), 132.94 (C), 132.88 (C), 129.90 (CH), 129.89 (CH), 129.6 (CH), 127.8 (3 × CH), 109.2 (C), 79.5 (CH), 77.5 (CH), 64.2 (CH_2), 62.6 (CH_2), 27.1 (CH_3), 27.0 (CH_3), 26.8 (3 × CH_3), 19.2 (C) ppm. Spectral data were in agreement with literature values.[25]

Triphenylphosphine (2.40 g, 9.15 mmol), imidazole (1.30 g, 19.1 mmol), and iodine (3.20 g, 12.6 mmol) were added to a solution of the above alcohol (2.50 g, 6.24 mmol) in toluene (60 mL) at room temp. The mixture was then heated at reflux for 6 h, cooled to room temperature, and quenched with satd. aq. Na_2SO_3 (50 mL). The mixture was extracted with ethyl acetate (3 × 40 mL), and the combined organic extracts were washed with brine (100 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:20 as eluent) to give **16** (2.50 g, 80%) as a yellow oil. $[\alpha]_D^{20}$ = –6.0 (*c* = 2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.65 (m, 4 H), 7.47–7.38 (m, 6 H), 3.99–3.94 (m, 1 H), 3.90–3.86 (m, 1 H), 3.86–3.81 (m, 1 H), 3.80–3.76 (m, 1 H), 3.39 (dd, *J* = 10.6, 4.6 Hz, 1 H), 3.29 (dd, *J* = 10.6, 4.6 Hz, 1 H), 1.46 (s, 3 H), 1.39 (s, 3 H), 1.07 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6 (4 × CH), 133.02 (C), 132.97 (C), 129.88 (2 × CH), 129.84 (CH), 127.8 (3 × CH), 109.6 (C), 81.2 (CH), 77.6 (CH), 64.2 (CH_2), 27.5 (CH_3), 27.3 (CH_3), 26.9 (3 × CH_3), 19.2 (C), 6.8 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3071, 2986, 2931, 2858, 1472, 1427, 1379, 1370, 1236, 1111, 1072, 998, 937, 859, 822, 794, 738, 699 cm^{-1}. HRMS (ESI^+): *m*/*z* 533.1001 $[M + Na]^+$ (calcd. for $C_{23}H_{31}INaO_3Si$ 533.0979).

Alkene 18: Vinylmagnesium bromide (1 M in THF, 8.0 mL, 8.00 mmol) was added dropwise to a mixture of copper(I) iodide (0.070 g, 0.37 mmol) and iodide **16** (2.00 g, 3.92 mmol) in THF/DMPU (1:1, 40 mL) at –35 °C under an argon atmosphere. The mixture was allowed to stir at –35 °C for 0.5 h, then another portion of vinylmagnesium bromide (1 M in THF, 4.0 mL, 4.00 mmol) added. The mixture was allowed to stir at –30 °C for 0.5 h, then warmed to room temp. and stirred for an additional 2 h. The reaction was quenched with satd. aq. NH_4Cl (80 mL), and the mixture extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:20 as eluent) to give **18** (1.10 g, 65%) as a pale yellow oil. $[\alpha]_D^{20}$ = –16.9 (*c* = 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.68 (m, 4 H), 7.47–7.36 (m, 6 H), 5.91–5.83 (m, 1 H), 5.17–5.09 (m, 2 H), 4.17–4.08 (m, 1 H), 3.82–3.78 (m, 3 H), 2.49–2.36 (m, 2 H), 1.45 (s, 3 H), 1.43 (s, 3 H), 1.11 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6 (4 × CH), 134.0 (CH), 133.24 (C), 133.21 (C), 129.76 (CH), 129.73 (CH), 127.7 (4 × CH), 117.3 (CH_2), 108.6 (C), 80.5 (CH), 77.5 (CH), 64.1 (CH_2), 37.5 (CH_2), 27.3 (CH_3), 27.0 (CH_3), 26.8 (3 × CH_3), 19.2 (C) ppm. IR (neat): $\tilde{\nu}$ = 3072, 2930, 2857, 1643, 1590, 1472, 1428, 1216, 1078, 1111, 702 cm^{-1}. HRMS (ESI^+): *m*/*z* 433.2126 $[M + Na]^+$ (calcd. for $C_{25}H_{34}NaO_3Si$ 433.2169).

Epoxide 19: Using a pre-cooled syringe, trifluoroacetone (0.2 mL, 2.23 mmol) was added to a solution of olefin **18** (0.525 g, 1.28 mmol) in MeCN/water (3:2, 25 mL) at 0 °C. A mixture of Oxone® (4.30 g, 14.0 mmol) and $NaHCO_3$ (0.940 g, 11.1 mmol) was then added in four portions over 1 h. The mixture was stirred at 0 °C for 2 h, then warmed to room temp. and stirred for an additional 12 h. The reaction was quenched with satd. aq. Na_2SO_3 (50 mL), and the mixture extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were washed with brine (100 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:5 as eluent) to give **19** (0.520 g, 90%, *dr* 1.3:1) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$, * denotes minor isomer): δ = 7.70–7.65 (m, 4 H), 7.44–7.35 (m, 6 H), 4.21–4.08 (m, 1 H), 3.90–3.79 (m, 1 H), 3.78–3.73 (m, 2 H), 3.11–3.02 (m, 1 H), 2.80 (dd, *J* = 4.0, 1.0 Hz, 1 H), 2.75* (dd, *J* = 4.0, 1.0 Hz, 1 H), 2.52–2.48 (m, 1 H), 1.89–1.72 (m, 2 H), 1.42–1.40 (m, 6 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes minor isomer): δ = 135.6 (4 × CH), 133.13 (C), 133.09 (C), 129.7 (2 × CH), 127.7 (4 × CH), 108.87 (C), 108 ppm. 83* (C), 82.5 (CH), 80.6* (CH), 76.7 (CH), 74.7* (CH), 64.1 (CH_2), 63.9* (CH_2), 49.5 (CH), 49.1* (CH), 47.4 (CH_2), 46.5* (CH_2), 37.5 (CH_2), 35.5* (CH_2), 27.3 (CH_3), 27.2* (CH_3), 26.95* (CH_3), 26.93 (CH_3), 26.8 (3 × CH_3), 19.2 (C), 18.2* (C) ppm. IR (neat): $\tilde{\nu}$ = 2926, 2860, 1474, 1379, 1427, 1217, 1103, 823, 702 cm^{-1}. HRMS (ESI^+): *m*/*z* 449.2078 $[M + Na]^+$ (calcd. for $C_{25}H_{34}NaO_4Si$ 449.2119).

Amino Alcohol 34: Sodium azide (0.162 g, 2.49 mmol) was added slowly to a mixture of epoxide **19** (0.510 g, 1.20 mmol) and satd. aq. NH_4Cl (5 mL) in DMF/water (1:9, 20 mL) at room temp. The mixture was heated at 100 °C for 2 h, then cooled to room temp. and partitioned between water (70 mL) and ethyl acetate (30 mL). The organic layer was removed, and the aqueous further extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:8 as eluent) to give the azide (0.375 g, 65%) as a colourless oil and as an inseparable mixture of two diastereomers. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.64 (m, 4 H), 7.47–7.36 (m, 6 H), 4.23–4.05 (m, 1 H), 4.05–3.95 (m, 1 H), 3.85–3.71 (m, 3 H), 3.39–3.25 (m, 2 H), 2.75 (d, *J* = 4.0 Hz, 1 H), 1.93–1.65 (m, 2 H), 1.42–1.36 (m, 6 H), 1.07 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes minor isomer): δ = 135.6 (4 × CH), 133.0 (2 × C), 129.9 (2 × CH), 127.8 (4 × CH), 110.0 (C), 109.0* (C), 81.3* (CH), 80.4 (CH), 78.3* (CH), 76.0 (CH), 70.6* (CH), 68.5 (CH), 64.0 (CH_2), 63.7* (CH_2), 56.8 (CH_2), 56.3* (CH_2), 37.4* (CH_2), 36.6 (CH_2), 27.3 (CH_3), 27.2* (CH_3), 27.0 (3 × CH_3), 26.8 (CH_3), 19.2 (C) ppm. IR (neat): $\tilde{\nu}$ = 3443, 2931, 2858, 2099, 1736, 1674, 1472, 1427, 1295, 1246, 1218, 1144, 1111, 942, 823, 704 cm^{-1}. HRMS (ESI^+): *m*/*z* 492.2249 $[M + Na]^+$ (calcd. for $C_{25}H_{35}N_3NaO_4Si$ 492.2289).

Trimethylphosphine (1 M in THF, 3.0 mL, 3.00 mmol) was added dropwise to a solution of the above azide (0.375 g, 0.80 mmol) in THF/water (5:1, 12 mL). The mixture was heated at 50 °C for 2 h, then cooled to room temp. and quenched with aq. NaOCl (42 g L^{-1}, 2 mL). The volatiles were removed in vacuo and the residue partitioned between water (15 mL) and ethyl acetate (20 mL). The organic layer was removed, and the aqueous further extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, dichloromethane/methanol, 6:1 saturated with ammonia, as eluent) to give **34** (0.310 g, 99%) as a pale yellow oil and an inseparable mixture of two diastereomers. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.64 (m, 4 H), 7.43–7.36 (m, 6 H), 4.22–4.09 (m, 1 H), 3.82–3.73 (m, 4 H), 2.81–2.58 (m, 2 H), 2.20–2.00 (br. s, 2 H), 1.82–1.60 (m, 2 H), 1.40–1.37 (m, 6 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes minor isomer): δ = 135.62 (4 × CH), 135.60* (4 × CH), 133.13

(2×C), 133.07* (C), 133.04* (C), 129.82* (CH), 129.79* (CH), 129.76 (CH), 129.73 (CH), 127.7 (4×CH), 109.2* (C), 108.7 (C), 81.4* (CH), 80.8 (CH), 78.0* (CH), 76.0 (CH), 71.7* (CH), 69.6 (CH), 64.0 (CH_2), 63.8* (CH_2), 47.7 (CH_2), 37.7* (CH_2), 37.4 (CH_2), 27.34 (CH_3), 27.26* (CH_3), 26.95* (CH_3), 27.0 (CH_3), 26.8 (3×CH_3), 19.2 (C) ppm. IR (neat): $\tilde{\nu}$ = 3452, 2930, 2857, 1674, 1427, 1295, 1145, 1112, 942, 858, 824, 704, 613 cm^{-1}. HRMS (ESI^+): *m/z* 444.2525 $[M + H]^+$ (calcd. for $C_{25}H_{38}NO_4Si$ 444.2565).

Maillard Condensation Product 35: A solution of amine **34** (0.027 g, 0.61 mmol) in undistilled 1,4-dioxane (1 mL) was added dropwise to a solution of dihydropyranone **12** (0.060 g, 0.23 mmol) and triethylamine (0.05 mL, 0.36 mmol) in undistilled 1,4-dioxane (1 mL) over 5 min at room temp. The mixture was allowed to stir at room temp. for 2 h, then concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:8 as eluent) to give the product as the two separable diastereomers **35a** (0.018 g, 21%) and **35b** (0.028 g, 33%) as colourless oils.

35a: $[\alpha]_D^{20}$ = –10.0 (*c* = 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.47 (s, 1 H), 7.71–7.67 (m, 4 H), 7.42–7.37 (m, 6 H), 6.90 (d, *J* = 4.0 Hz, 1 H), 6.19 (d, *J* = 4.0 Hz, 1 H), 4.78 (d, *J* = 12.0 Hz, 1 H), 4.71 (d, *J* = 12.0 Hz, 1 H), 4.58 (dd, *J* = 13.2, 2.4 Hz, 1 H), 4.31–4.27 (m, 1 H), 4.26–4.20 (m, 1 H), 4.19–4.12 (m, 1 H), 3.84–3.70 (m, 3 H), 3.20 (d, *J* = 4.0 Hz, 1 H), 1.85–1.81 (m, 2 H), 1.41 (s, 3 H), 1.37 (s, 3 H), 1.06 (s, 9 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.9 (CH), 142.6 (C), 135.6 (4×CH), 133.14 (C), 133.09 (C), 132.7 (C), 129.74 (CH), 129.71 (CH), 127.7 (4×CH), 124.9 (CH), 110.3 (CH), 108.0 (C), 77.6 (CH), 73.9 (CH), 69.8 (CH), 62.6 (CH_2), 57.4 (CH_2), 51.8 (CH_2), 34.6 (CH_2), 28.1 (CH_3), 26.9 (CH_3), 25.8 (3×CH_3), 25.6 (3×CH_3), 19.2 (C), 18.3 (C), –5.3 (2×CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3671, 3465, 2956, 2930, 2857, 1739, 1660, 1462, 1428, 1137, 1250, 1112, 1073, 837, 779, 703, 613 cm^{-1}. HRMS (CI): *m/z* 688.3379 $[M + Na]^+$ (calcd. for $C_{37}H_{55}NNaO_6Si_2$ 688.3462).

35b: $[\alpha]_D^{20}$ = –7.0 (*c* = 1.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.47 (s, 1 H), 7.69–7.65 (m, 4 H), 7.43–7.37 (m, 6 H), 6.89 (d, *J* = 4.0 Hz, 1 H), 6.19 (d, *J* = 4.0 Hz, 1 H), 4.83 (d, *J* = 12.0 Hz, 1 H), 4.72 (d, *J* = 16.0 Hz, 1 H), 4.58 (dd, *J* = 14.0, 2.4 Hz, 1 H), 4.31–4.28 (m, 1 H), 4.22 (d, *J* = 12.0 Hz, 1 H), 4.19–4.12 (m, 1 H), 3.81–3.74 (m, 3 H), 3.47 (d, *J* = 2.4 Hz, 1 H), 1.96–1.92 (m, 1 H), 1.74–1.66 (m, 1 H), 1.44 (s, 3 H), 1.36 (s, 3 H), 1.04 (s, 9 H), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.5 (CH), 143.3 (C), 135.6 (4×CH), 133.14 (C), 133.09 (C), 132.6 (C), 129.74 (CH), 129.71 (CH), 127.7 (4×CH), 124.9 (CH), 109.9 (CH), 108.5 (C), 77.8 (CH), 77.3 (CH), 71.9 (CH), 62.5 (CH_2), 57.7 (CH_2), 51.4 (CH_2), 33.6 (CH_2), 27.9 (CH_3), 26.9 (3×CH_3), 25.8 (3×CH_3), 25.5 (CH_3), 19.2 (C), 18.3 (C), –5.30 (CH_3), –5.33 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3671, 3465, 2956, 2930, 2857, 1739, 1660, 1462, 1428, 1137, 1250, 1112, 1073, 837, 779, 703, 613 cm^{-1}. HRMS (CI): *m/z* 688.3379 $[M + Na]^+$ (calcd. for $C_{37}H_{55}NNaO_6Si_2$ 688.3460).

Ketopyrrole 37: NMO (3.9 mg, 0.33 mmol) and TPAP (1 mg, 0.002 mmol) were added to a mixture of alcohols **35a** and **35b** (0.030 g, 0.045 mmol) and activated molecular sieves (4 Å) (0.010 g) in dichloromethane (2 mL). The mixture was allowed to stir at room temp. for 0.5 h, then filtered through a plug of silica. The filter cake was further washed with THF (3×10 mL), and the combined filtrates concentrated in vacuo to give the crude **37** (0.029 g, 97%) as a pale brown oil that was carried forward without further purification. $[\alpha]_D^{20}$ = +16.0 (*c* = 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.44 (s, 1 H), 7.70–7.66 (m, 4 H), 7.43–7.36 (m, 6 H), 6.89 (d, *J* = 4.0 Hz, 1 H), 6.19 (d, *J* = 4.0 Hz, 1 H), 5.40 (d, *J* = 18.0 Hz, 1 H), 5.29 (d, *J* = 18.0 Hz, 1 H), 4.59 (s, 2 H), 4.42–4.40 (m, 1 H), 3.89–3.87 (m, 1 H), 3.83–3.75 (m, 2 H), 2.80–2.78 (m, 2 H), 1.41 (s, 3 H), 1.38 (s, 3 H), 1.05 (s, 9 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.7 (C), 179.7 (CH), 142.0 (C), 135.6 (4×CH), 133.04 (C), 133.00 (C), 132.3 (C), 129.74 (CH), 129.71 (CH), 127.7 (4×CH), 123.9 (CH), 110.0 (CH), 109.2 (C), 80.8 (CH), 74.2 (CH), 63.7 (CH_2), 57.2 (CH_2), 55.4 (CH_2), 43.9 (CH_2), 27.2 (CH_3), 26.9 (CH_3) 26.8 (3×CH_3), 25.8 (3×CH_3), 19.1 (C), 18.2 (C), –5.4 (2×CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3674, 2929, 2856, 1765, 1670, 1462, 1427, 1362, 1251, 1216, 1112, 1076, 836, 702 cm^{-1}. HRMS (CI): *m/z* 686.3471 $[M + Na]^+$ (calcd. for $C_{37}H_{53}NNaO_6Si_2$ 686.3304).

TBDPS-Spiroketal 39: HCl (4 M in 1,4-dioxane, 1.0 mL, 4.00 mmol) was added to a solution of crude ketone **37** (0.027 g, 0.041 mmol) in THF/water (1:1, 2 mL), and the mixture allowed to stir at room temp. for 2.5 h. The reaction was neutralised with satd. aq. $NaHCO_3$ to pH 7, and the mixture extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:3 as eluent) to give **39** (0.012 g, 61%, *dr* 3.4:1) as a yellow oil and an inseparable mixture of two diastereomers. ^1H NMR (400 MHz, $CDCl_3$, * denotes minor isomer): δ = 9.47 (s, 1 H), 9.45* (s, 1 H), 7.67–7.62 (m, 4 H), 7.43–7.35 (m, 6 H), 6.93* (d, *J* = 4.0 Hz, 1 H), 6.92 (d, *J* = 4.0 Hz, 1 H), 5.99 (d, *J* = 4.0 Hz, 1 H), 5.97* (d, *J* = 4.0 Hz, 1 H), 5.13–3.70 (m, 8 H), 3.03 (d, *J* = 7.2 Hz, 1 H), 2.79* (d, *J* = 7.2 Hz, 1 H), 2.57 (dd, *J* = 13.9, 6.6 Hz, 1 H), 2.38* (d, *J* = 14.0 Hz, 1 H), 2.25* (dd, *J* = 13.9, 5.2 Hz, 1 H), 2.14 (dd, *J* = 13.9, 3.9 Hz, 1 H), 1.04 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes minor isomer): δ = 179.8* (CH), 178.6 (CH), 135.6 (4×CH), 135.54* (4×CH), 135.46* (2×CH), 134.7 (C), 134.6 (C), 133.04* (C), 133.00* (C), 132.6 (C), 132.1 (C), 131.2 (C), 131.1* (C), 129.98 (CH), 129.96 (CH), 129.8* (2×CH), 127.84* (2×CH), 127.76 (2×CH), 124.1* (CH), 123.9 (CH), 104.8* (CH), 104.6 (CH), 103.5* (C), 102.3 (C), 85.6* (CH), 80.8 (CH), 72.6 (CH), 72.0* (CH), 63.0* (CH_2), 62.8 (CH_2), 58.5 (CH_2), 58.2* (CH_2), 51.4 (CH_2), 51.0* (CH_2), 46.3 (CH_2), 44.6* (CH_2), 26.78* (3×CH_3), 26.73 (3×CH_3), 19.14* (C), 19.07 (C) ppm. IR (neat): $\tilde{\nu}$ = 3674, 2929, 2856, 1765, 1670, 1462, 1427, 1362, 1251, 1216, 1112, 1076, 836, 702 cm^{-1}. HRMS (ESI^+): *m/z* 514.2003 $[M + Na]^+$ (calcd. for $C_{28}H_{33}NNaO_5Si$ 514.2020).

Spiroketals 40a and 40b: TBAF (1 M in THF, 0.1 mL, 0.10 mmol) was added to a solution of spiroketal **37** (6 mg, 0.012 mmol) in THF (0.5 mL), and the mixture allowed to stir at room temp. for 2 h. The mixture was then concentrated in vacuo to remove most of the solvent and filtered through a pad of silica. The filter cake was washed with ethyl acetate (10 mL), and the combined filtrates concentrated in vacuo to give the crude material. The crude was purified via preparative TLC (ethyl acetate/hexanes, 5:1 as eluent) to give **40a** (0.9 mg, 30%) and **40b** (1.5 mg, 50%) as yellow oils.

40a: ^1H NMR (400 MHz, CD_3COCD_3): δ = 9.47 (s, 1 H), 6.98 (d, *J* = 4.0 Hz, 1 H), 6.04 (d, *J* = 4.0 Hz, 1 H), 4.94 (d, *J* = 15.5 Hz, 1 H), 4.81 (d, *J* = 15.5 Hz, 1 H), 4.69 (d, *J* = 14.0 Hz, 1 H), 4.61–4.56 (m, 1 H), 4.23 (d, *J* = 13.9 Hz, 1 H), 4.14 (ddd, *J* = 5.1, 9.8, 9.8 Hz, 1 H), 3.87–3.75 (m, 2 H), 2.53 (dd, *J* = 6.6, 14.6 Hz, 1 H), 2.12 (dd, *J* = 3.3, 14.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 179.0 (CH), 135.8 (C), 132.3 (C), 124.2 (CH), 105.3 (CH), 103.1 (C), 84.0 (CH), 72.1 (CH), 61.5 (CH_2), 58.8 (CH_2), 52.4 (CH_2), 47.5 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3321, 2929, 2845, 1725, 1410, 1251, 1051, 788 cm^{-1}. HRMS (ESI^+): *m/z* 276.0848 $[M + Na]^+$ (calcd. for $C_{12}H_{15}NNaO_5$ 276.0842).

40b: $[\alpha]_D^{24}$ = –121.3 (*c* = 0.08, MeOH). ^1H NMR (400 MHz, CD_3COCD_3): δ = 9.47 (s, 1 H), 6.98 (d, *J* = 4.0 Hz, 1 H), 6.04 (d,

J = 4.0 Hz, 1 H), 5.14 (dd, J = 15.6, 0.8 Hz, 1 H), 4.83 (d, J = 16.0 Hz, 1 H), 4.54–4.51 (m, 2 H), 4.27 (dd, J = 10.8, 5.0 Hz, 1 H), 4.19 (d, J = 13.9 Hz, 1 H), 3.86 (dd, J = 11.7, 5.0 Hz, 1 H), 3.80 (dd, J = 11.7, 6.0 Hz, 1 H), 2.43 (dd, J = 14.0, 6.0 Hz, 1 H), 2.28 (dd, J = 14.0, 1.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 179.0 (CH), 136.0 (C), 132.2 (C), 124.2 (CH), 105.3 (CH), 104.0 (C), 86.7 (CH), 72.3 (CH), 62.2 (CH_2), 58.7 (CH_2), 52.0 (CH_2), 45.8 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3330, 2929, 2847, 1730, 1412, 1251, 1033, 796 cm^{-1}. HRMS (ESI$^+$): m/z 276.0850 [M + Na]$^+$ (calcd. for $C_{12}H_{15}NNaO_5$ 276.0842).

Amino Alcohol 41: Sodium azide (0.185 g, 2.85 mmol) was added slowly to a mixture of epoxide **8** (1.00 g, 2.34 mmol) and satd. aq. NH_4Cl (10 mL) in ethanol (125 mL). The mixture was heated at reflux for 10 h, then cooled to room temp. and the volatiles removed in vacuo. The residue was partitioned between ethyl acetate (100 mL) and water (50 mL). The organic layer was separated, and the aqueous further extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:8 as eluent) to give the diastereomeric alcohols **45a** (0.560 g, 51%) as a yellow oil, and **45b** (0.430 g, 38%) as colourless oil.

45a: $[\alpha]_D^{20}$ = +1.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68–7.64 (m, 4 H), 7.46–7.37 (m, 6 H), 4.44–4.39 (m, 1 H), 4.26–4.22 (m, 1 H), 4.06–4.00 (m, 1 H), 3.71 (d, J = 6.0 Hz, 2 H), 3.47 (s, 1 H), 3.33–3.25 (m, 2 H), 1.91–1.79 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.07 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6 (4 × CH), 133.1 (C), 133.0 (C), 129.9 (2 × CH), 127.8 (4 × CH), 108.1 (C), 77.5 (CH), 74.0 (CH), 68.5 (CH), 62.5 (CH_2), 57.2 (CH_2), 33.5 (CH_2), 28.1 (CH_3), 26.9 (3 × CH_3), 25.5 (CH_3), 19.2 (C) ppm. IR (neat): $\tilde{\nu}$ = 3443, 3071, 2931, 2858, 2099, 1589, 1472, 1427, 1218, 1111, 823, 702 cm^{-1}. HRMS (ESI$^+$): m/z 492.2283 [M + Na]$^+$ (calcd. for $C_{25}H_{35}N_3NaO_4Si$ 492.2289).

45b: $[\alpha]_D^{20}$ = –5.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 4 H), 7.45–7.38 (m, 6 H), 4.43–4.38 (m, 1 H), 4.25–4.21 (m, 1 H), 4.04–4.01 (m, 1 H), 3.71 (d, J = 8.0 Hz, 2 H), 3.47 (s, 1 H), 3.28 (d, J = 4.0 Hz, 2 H), 1.90–1.77 (m, 2 H), 1.40 (s, 3 H), 1.34 (s, 3 H), 1.06 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.60 (CH), 135.54 (3 × CH), 133.02 (C), 133.00 (C), 129.9 (2 × CH), 127.78 (2 × CH), 127.76 (2 × CH), 108.8 (C), 77.6 (CH), 77.2 (CH), 71.0 (CH), 62.2 (CH_2), 56.3 (CH_2), 33.4 (CH_2), 27.9 (CH_3), 26.8 (3 × CH_3), 25.5 (CH_3), 19.2 (C) ppm. IR (neat): $\tilde{\nu}$ = 3481, 3058, 2927, 2858, 2091, 1586, 1473, 1424, 1216, 1105, 823, 702 cm^{-1}. HRMS (ESI$^+$): m/z 492.2283 [M + Na]$^+$ (calcd. for $C_{25}H_{35}N_3NaO_4Si$ 492.2289).

Trimethylphosphine (1 M in THF, 2.7 mL, 2.70 mmol) was added dropwise to a solution of alcohol **45a** (0.400 g, 0.85 mmol) in THF/water (5:1, 24 mL). The mixture was heated at 50 °C for 2 h, then quenched with aq. NaOCl (42 g L^{-1}, 5 mL). Water (10 mL) and ethyl acetate (20 mL) were added, and the organic layer separated. The aqueous was further extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts washed with brine (30 mL), dried with Na_2SO_4, and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, dichloromethane/methanol saturated with ammonia 6:1 as eluent) to give the corresponding product **41a** (0.381 g, 95%) as a pale yellow oil.

The reduction of **45b** (0.400 g, 0.85 mmol) was carried out under the same conditions to give **41b** (0.392 g, 98%) as a pale yellow oil.

41a: $[\alpha]_D^{20}$ = +7.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.62 (m, 4 H), 7.44–7.33 (m, 6 H), 4.51–4.49 (m, 1 H), 4.24–4.22 (m, 1 H), 3.77–3.73 (m, 1 H), 3.72–3.63 (m, 2 H), 2.80 (dd, J = 12.8, 3.2 Hz, 1 H), 2.60–2.55 (m, 4 H), 1.73–1.67 (m, 2 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.03 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.53 (2 × CH), 135.50 (2 × CH), 133.2 (C), 133.0 (C), 129.7 (2 × CH), 127.7 (4 × CH), 107.8 (C), 77.6 (CH), 74.1 (CH), 70.5 (CH), 62.6 (CH_2), 47.8 (CH_2), 34.0 (CH_2), 28.0 (CH_3), 26.8 (3 × CH_3), 25.5 (CH_3), 19.1 (C) ppm. IR (neat): $\tilde{\nu}$ = 3451, 2930, 2857, 1674, 1427, 1295, 1145, 1112, 942, 858, 824, 704, 613 cm^{-1}. HRMS (ESI$^+$): m/z 444.2525 [M + Na]$^+$ (calcd. for $C_{25}H_{37}NNaO_4Si$ 444.2565).

41b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.63 (m, 4 H), 7.42–7.33 (m, 6 H), 4.41–4.36 (m, 1 H), 4.22–4.06 (m, 1 H), 3.79–3.64 (m, 3 H), 2.85–2.70 (m, 4 H), 1.82–1.66 (m, 2 H), 1.36 (s, 3 H), 1.31 (s, 3 H), 1.03 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.45 (CH), 135.40 (CH), 135.37 (2 × CH) 133.0 (C), 132.9 (C), 129.7 (2 × CH), 127.6 (4 × CH), 108.2 (C), 77.7 (CH), 76.5 (CH), 71.4 (CH), 62.3 (CH_2), 47.7 (CH_2), 33.6 (CH_2), 27.8 (CH_3), 26.9 (3 × CH_3), 25.4 (CH_3), 19.2 (C) ppm. IR (neat): $\tilde{\nu}$ = 3451, 2930, 2857, 1674, 1427, 1295, 1145, 1112, 942, 858, 824, 704, 613 cm^{-1}. HRMS (ESI$^+$): m/z 444.2525 [M + Na]$^+$ (calcd. for $C_{25}H_{37}NNaO_4Si$ 444.2565).

Maillard Condensation Product 42: Amino alcohol **41a** (0.103 g, 0.23 mmol) and triethylamine (0.02 mL, 0.14 mmol) were added to a solution of dihydropyranone **12** (0.030 g, 0.12 mmol) in undistilled 1,4-dioxane (2 mL), and the mixture allowed to stir at room temp. for 2 h. The volatiles were removed in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:8 as eluent) to give the corresponding product **42a** (0.044 g, 60%) as a yellow oil.

Amino alcohol **41b** underwent Maillard-type condensation under the same conditions to give pyrrole **42b** (0.041 g, 51%) as a yellow oil.

42a: $[\alpha]_D^{20}$ = +3.8 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.47 (s, 1 H), 7.72–7.67 (m, 4 H), 7.45–7.38 (m, 6 H), 6.90 (d, J = 4.0 Hz, 1 H), 6.20 (d, J = 4.0 Hz, 1 H), 4.73 (d, J = 13.2 Hz, 1 H), 4.68 (d, J = 13.2 Hz, 1 H), 4.61 (m, 1 H), 4.56–4.51 (m, 1 H), 4.26–4.19 (m, 2 H), 4.17–4.10 (m, 1 H), 3.78–3.68 (m, 2 H), 3.14 (d, J = 8.0 Hz, 1 H), 1.90–1.77 (m, 2 H), 1.38 (s, 3 H), 1.34 (s, 3 H), 1.08 (s, 9 H), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.9 (CH), 142.6 (C), 135.63 (3 × CH), 135.59 (CH), 133.2 (C), 133.1 (C), 132.2 (C), 129.7 (2 × CH), 127.75 (2 × CH), 127.74 (2 × CH), 124.9 (CH), 110.3 (CH), 108.5 (C), 77.8 (CH), 71.9 (CH), 69.8 (CH), 62.6 (CH_2), 57.4 (CH_2), 51.8 (CH_2), 34.5 (CH_2), 29.6 (CH_3), 28.1 (2 × CH_3), 26.9 (2 × CH_3), 25.8 (CH_3), 25.6 (2 × CH_3), 19.2 (C), 18.3 (C), –5.3 (CH_3), –5.4 (CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3658, 2931, 2857, 1658, 1438, 1421, 1362, 1246, 1216, 1112, 1066, 836, 702 cm^{-1}. HRMS (ESI$^+$): m/z 688.3465 [M + Na]$^+$ (calcd. for $C_{37}H_{55}NNaO_6Si_2$ 688.3460).

42b: $[\alpha]_D^{20}$ = +3.2 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.46 (s, 1 H), 7.69–7.65 (m, 4 H), 7.45–7.37 (m, 6 H), 6.88 (d, J = 4.1 Hz, 1 H), 6.19 (d, J = 4.1 Hz, 1 H), 4.86 (d, J = 13.2 Hz, 1 H), 4.69 (d, J = 13.2 Hz, 1 H), 4.60–4.57 (m, 1 H), 4.47–4.43 (m, 1 H), 4.25–4.13 (m, 3 H), 3.75–3.64 (m, 2 H), 3.56 (br. s, 1 H), 2.00–1.73 (m, 2 H), 1.38 (s, 3 H), 1.31 (s, 3 H), 1.06 (s, 9 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.01 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.5 (CH), 143.6 (C), 135.64 (2 × CH), 135.59 (2 × CH), 133.2 (C), 133.1 (C), 132.2 (C), 129.7 (2 × CH), 127.75 (2 × CH), 127.74 (2 × CH), 124.9 (CH), 109.9 (CH), 108.5 (C), 77.9 (CH), 77.3 (CH), 71.9 (CH), 62.5 (CH_2), 57.7 (CH_2), 51.4 (CH_2), 33.6 (CH_2), 27.9 (CH_3), 26.9 (3 × CH_3), 25.8 (3 × CH_3), 25.5 (CH_3),

19.2 (C), 18.3 (C), –5.29 (CH_3), –5.32 (CH_3) ppm. HRMS (ESI^+): *m/z* 688.3461 $[M + Na]^+$ (calcd. for $C_{37}H_{55}NNaO_6Si_2$ 688.3460).

TBDPS-Protected Spiroketal 43: NMO (0.026 g, 0.22 mmol) and TPAP (0.002 g, 0.004 mmol) were added to a mixture of alcohols **42a** and **42b** (0.040 g, 0.060 mmol) and activated molecular sieves (4 Å) (0.040 g) in dichloromethane (4 mL) at 0 °C. The mixture was warmed to room temp. and stirred for 0.25 h, then filtered through a plug of silica. The filter cake was washed with ethyl acetate (2 × 20 mL), and the combined filtrate concentrated in vacuo to give the crude ketone (0.032 g, 90%) as a colourless oil. $[\alpha]_D^{20}$ = –2.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 9.44 (s, 1 H), 7.70–7.65 (m, 4 H), 7.45–7.37 (m, 6 H), 6.88 (d, *J* = 4.1 Hz, 1 H), 6.19 (d, *J* = 4.0 Hz, 1 H), 5.37 (d, *J* = 16.0 Hz, 1 H), 5.26 (d, *J* = 16.0 Hz, 1 H), 4.69–4.66 (m, 1 H), 4.57 (s, 2 H), 4.26–4.21 (m, 1 H), 3.68 (d, *J* = 6.0 Hz, 2 H), 2.86–2.84 (m, 2 H), 1.40 (s, 3 H), 1.33 (s, 3 H), 1.07 (s, 9 H), 0.87 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.3 (C), 179.7 (CH), 142.0 (C), 135.6 (4 × CH), 133.12 (C), 133.07 (C), 132.3 (C), 129.8 (2 × CH), 127.78 (2 × CH), 127.77 (2 × CH), 123.9 (CH), 110.0 (CH), 108.5 (C), 77.1 (CH), 73.0 (CH), 62.5 (CH_2), 57.2 (CH_2), 55.3 (CH_2), 40.4 (CH_2), 27.9 (CH_3), 26.9 (3 × CH_3), 25.8 (3 × CH_3), 25.3 (CH_3), 19.2 (C), 18.0 (C), –5.4 (2 × CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3674, 2929, 2856, 1731, 1658, 1462, 1427, 1362, 1251, 1216, 1112, 1067, 836, 702 cm^{-1}. HRMS (ESI^+): *m/z* 664.3471 $[M + H]^+$ (calcd. for $C_{37}H_{54}NO_6Si_2$ 664.3484).

HCl (4 M in 1,4-dioxane, 0.2 mL, 0.80 mmol) was added to a solution of the above crude ketone (0.030 g, 0.046 mmol) in THF/water (1:1. 2 mL), and the mixture allowed to stir at room temp. for 2.5 h. The reaction was then neutralised to pH 7 with satd. aq. $NaHCO_3$, and the mixture extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo to give the crude material. The crude was purified via flash column chromatography (silica gel, ethyl acetate/hexanes, 1:5 as eluent) to give **43** (0.018 g, 82%, *dr* 3:2) as a yellow oil and an inseparable mixture of two diastereomers. ^1H NMR (400 MHz, $CDCl_3$, * denotes minor isomer): δ = 9.48 (s, 1 H), 9.44* (s, 1 H), 7.67–7.61 (m, 4 H), 7.45–7.32 (m, 6 H), 6.93 (d, *J* = 4.0 Hz, 1 H), 6.90* (d, *J* = 4.0 Hz, 1 H), 6.02 (d, *J* = 4.0 Hz, 1 H), 5.94* (d, *J* = 4.0 Hz, 1 H), 5.03 (d, *J* = 15.2 Hz, 1 H), 4.92* (d, *J* = 16.0 Hz, 1 H), 4.84 (d, *J* = 16.0 Hz, 1 H), 4.72 (d, *J* = 16.1 Hz, 1 H), 4.68* (d, *J* = 8.0 Hz, 1 H), 4.68–4.66* (m, 2 H), 4.65* (d, *J* = 16.0 Hz, 1 H), 4.46–4.41 (m, 1 H), 4.34 (d, *J* = 16.0 Hz, 1 H), 4.26–4.24 (m, 1 H), 4.22* (d, *J* = 8.0 Hz, 1 H), 4.05–4.00* (d, *J* = 5.6 Hz, 1 H), 3.84–3.81 (dd, *J* = 10.5, 5.6 Hz, 1 H), 3.70–3.60* (m, 2 H), 2.80 (dd, *J* = 10.8, 4.8 Hz, 1 H), 2.51* (dd, *J* = 13.0, 6.0 Hz, 1 H), 2.35 (dd, *J* = 13.0, 6.0 Hz, 1 H), 2.22 (dd, *J* = 13.2, 1.2 Hz, 1 H), 2.12* (dd, *J* = 12.0, 8.0 Hz, 1 H), 1.08 (s, 9 H), 1.06* (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, * denotes minor isomer): δ = 178.7 (CH), 135.62 (CH), 135.57 (2 × CH), 135.52 (CH), 132.8 (2 × C), 134.5 (C), 133.1 (4 × CH), 132.8* (4 × CH), 131.2 (CH), 131.1* (CH), 130.0 (2 × CH), 127.9* (CH), 127.9* (CH), 124.2 (CH), 123.9* (CH), 104.9 (C), 104.7* (C), 104.2 (C), 102.8* (C), 89.8 (CH), 86.6* (CH), 73.3 (CH), 72.3* (CH), 64.4 (CH_2), 64.1* (CH_2), 58.3 (CH_2), 58.1* (CH_2), 51.7 (CH_2), 50.4* (CH_2), 44.4 (CH_2), 44.3* (CH_2), 29.8* (3 × CH_3), 26.9 (3 × CH_3), 19.3 (C) ppm. IR (neat): $\tilde{\nu}$ = 3407, 2929, 2857, 1737, 1643, 1498, 1471, 1427, 1408, 1373, 1255, 1104, 1037, 701 cm^{-1}. HRMS (ESI^+): *m/z* 514.2003 $[M + Na]^+$ (calcd. for $C_{28}H_{33}NNaO_5Si$ 514.2020).

Spiroketals 3 and 44: TBAF (1 M in THF, 0.5 mL, 0.50 mmol) was added to a solution of spiroketal **43** (0.020 g, 0.041 mmol) in THF (0.5 mL), and the mixture allowed to stir at room temp. for 2.5 h. The reaction mixture was concentrated in vacuo to remove most of the solvent and the residue then filtered through a pad of silica. The filter cake was washed with THF (10 mL), and the combined filtrates concentrated in vacuo to give the crude material. The crude was purified via preparative TLC (silica plate, ethyl acetate/hexanes, 5:1 as eluent) to give **3** (4 mg, 40%) as a white solid, and **44** (2.7 mg, 27%) as a yellow oil.

Acortatarin A (3): M.p. 163–165 °C, ref.[3a] 159–160 °C. $[\alpha]_D^{20}$ = +194.8 (*c* = 0.15, $CHCl_3$), ref.[2] $[\alpha]_D^{20}$ = +178.4 (*c* = 0.4, MeOH). ^1H NMR (400 MHz, CD_3OD): δ = 9.32 (s, 1 H), 6.98 (d, *J* = 4.4 Hz, 1 H), 6.03 (d, *J* = 4.4 Hz, 1 H), 4.97 (d, *J* = 15.8 Hz, 1 H), 4.81 (d, *J* = 15.8 Hz, 1 H), 4.55 (d, *J* = 14.0 Hz, 1 H), 4.24 (ddd, *J* = 8.3, 4.9, 2.9 Hz, 1 H), 4.18 (d, *J* = 14.0 Hz, 1 H), 4.02 (ddd, *J* = 4.7, 4.7, 2.9 Hz, 1 H), 3.67 (dd, *J* = 12.1, 3.5 Hz, 1 H), 3.58 (dd, *J* = 12.2, 4.9 Hz, 1 H), 2.30 (dd, *J* = 14.0, 8.4 Hz, 1 H), 2.10 (dd, *J* = 14.0, 2.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 180.2 (CH), 137.6 (C), 132.4 (C), 125.9 (CH), 106.1 (CH), 104.5 (C), 89.4 (CH), 72.2 (CH), 63.0 (CH_2), 58.7 (CH_2), 52.0 (CH_2), 45.9 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3360, 2921, 2851, 1736, 1659, 1412, 1260, 1036, 796 cm^{-1}. HRMS (ESI^+): *m/z* 276.0843 $[M + Na]^+$ (calcd. for $C_{12}H_{15}NNaO_5$ 276.0842). Spectral data were in agreement with literature values.[4]

5-*epi*-Acortatarin A (44): $[\alpha]_D^{24}$ = –19.4 (*c* = 0.067, MeOH); ref.[6a] $[\alpha]_D^{19}$ = –111.3 (*c* = 1.0, MeOH). ^1H = NMR (400 MHz, CD_3OD): 9.33 (s, 1 H), 6.98 (d, *J* = 4.1 Hz, 1 H), 6.01 (d, *J* = 4.1 Hz, 1 H), 5.05 (d, *J* = 15.3 Hz, 1 H), 4.75 (d, *J* = 16.8 Hz, 1 H), 4.63 (d, *J* = 13.8 Hz, 1 H), 4.33 (td, *J* = 6.8, 4.8 Hz, 1 H), 4.18 (d, *J* = 13.8 Hz, 1 H), 3.96 (td, *J* = 6.8, 4.8 Hz, 1 H), 3.66 (dd, *J* = 12.1, 4.8 Hz, 1 H), 3.64 (dd, *J* = 11.8, 6.8 Hz, 1 H), 2.45 (dd, *J* = 13.2, 6.8 Hz, 1 H), 2.04 (dd, *J* = 13.3, 6.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 180.2 (CH), 137.5 (C), 132.4 (C), 126.1 (CH), 106.1 (CH), 104.2 (C), 89.5 (CH), 72.1 (CH), 64.3 (CH_2), 59.2 (CH_2), 52.8 (CH_2), 45.7 (CH_2) ppm. IR (neat): $\tilde{\nu}$ = 3351, 2910, 2837, 1733, 1645, 1412, 1260, 1038, 796 cm^{-1}. HRMS (ESI^+): *m/z* 276.0850 $[M + Na]^+$ (calcd. for $C_{12}H_{15}NNaO_5$ 276.0842). Spectral data were in agreement with literature values.[6a]

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra.

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[1] T. H. Pennington, *J. Infect.* **1995**, *30*, 63–65.
[2] X.-G. Tong, L.-L. Zhou, Y.-H. Wang, C. Xia, Y. Wang, M. Liang, F.-F. Hou, Y.-X. Cheng, *Org. Lett.* **2010**, *12*, 1844–1847.
[3] a) J. L. Guo, Z. M. Feng, Y. J. Yang, Z. W. Zhang, P. C. Zhang, *Chem. Pharm. Bull.* **2010**, *58*, 983–985; b) T. Yang, C.-h. Wang, G.-x. Chou, T. Wu, X.-m. Cheng, Z.-t. Wang, *Food Chem.* **2010**, *123*, 705–710.
[4] G. Sudhakar, V. D. Kadam, S. Bayya, G. Pranitha, B. Jagadeesh, *Org. Lett.* **2011**, *13*, 5452–5455.
[5] N. V. Borrero, A. Aponick, *J. Org. Chem.* **2012**, *77*, 8410–8416.
[6] a) J. M. Wurst, A. L. Verano, D. S. Tan, *Org. Lett.* **2012**, *14*, 4442–4445; b) T. Teranishi, M. Kageyama, S. Kuwahara, *Biosci. Biotechnol. Biochem.* **2013**, *77*, 676–678.
[7] J. C. Verheijen, A. Zask, *Drugs Future* **2007**, *32*, 537–547.
[8] J. I. Levin, J. M. Chen, L. M. Laakso, M. Du, X. Du, A. M. Venkatesan, V. Sandanayaka, A. Zask, J. Xu, W. Xu, Y. Zhang, J. S. Skotnicki, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4345–4349.

[9] N. G. Almstead, R. S. Bradley, S. Pikul, B. De, M. G. Natchus, Y. O. Taiwo, F. Gu, L. E. Williams, B. A. Hynd, M. J. Janusz, C. M. Dunaway, G. E. Mieling, *J. Med. Chem.* **1999**, *42*, 4547–4562.

[10] a) P. Rosen, P. P. Nawroth, G. King, W. Moller, H. J. Tritschler, L. Packer, *Diabetes Metab. Res. Rev.* **2001**, *17*, 189–212; b) H. J. Ha, H. B. Lee, *Kidney Int.* **2000**, *58*, S19–S25; c) J.-i. Matsuo, S. Sasaki, H. Tanaka, H. Ishibashi, *J. Am. Chem. Soc.* **2008**, *130*, 11600–11601; d) H. B. Lee, M. R. Yu, Y. Q. Yang, Z. P. Jiang, H. Ha, *J. Am. Soc. Nephrol.* **2003**, *14*, S241–S245.

[11] H. M. Geng, J. L. Y. Chen, D. P. Furkert, S. D. Jiang, M. A. Brimble, *Synlett* **2012**, *23*, 855–858.

[12] F. Ledl, E. Schleicher, *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 565–594; *Angew. Chem.* **1990**, *102*, 597.

[13] O. Achmatowicz, M. H. Burzynska, *Carbohydr. Res.* **1985**, *141*, 67–76.

[14] S. Celanire, F. Marlin, J. E. Baldwin, R. M. Adlington, *Tetrahedron* **2005**, *61*, 3025–3032.

[15] S. G. Davies, E. M. Foster, A. B. Frost, J. A. Lee, P. M. Roberts, J. E. Thomson, *Org. Biomol. Chem.* **2012**, *10*, 6186–6200.

[16] T. Mukhopadhyay, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 385–391.

[17] L. Shu, Y. Shi, *J. Org. Chem.* **2000**, *65*, 8807–8810.

[18] H. Yin, R. W. Franck, S. L. Chen, G. J. Quigley, L. Todaro, *J. Org. Chem.* **1992**, *57*, 644–651.

[19] A. Chattopadhyay, *J. Org. Chem.* **1996**, *61*, 6104–6107.

[20] J. Mulzer, A. Angermann, *Tetrahedron Lett.* **1983**, *24*, 2843–2846.

[21] a) T. M. Woods, M. Kamalov, P. W. R. Harris, G. J. S. Cooper, M. Brimble, *Org. Lett.* **2012**, *14*, 5740–5743; b) T.-Y. Yuen, S. E. Eaton, T. M. Woods, D. P. Furkert, K. W. Choi, M. A. Brimble, *Eur. J. Org. Chem.* **2014**, 1431–1437.

[22] B. J. McNelis, D. D. Sternbach, A. T. MacPhail, *Tetrahedron* **1994**, *50*, 6767–6782.

[23] R. W. Hoffmann, A. Endesfelder, H.-J. Zeiss, *Carbohydr. Res.* **1983**, *123*, 320–325.

[24] M. Arthuis, R. Beaud, V. Gandon, E. Roulland, *Angew. Chem. Int. Ed.* **2012**, *51*, 10510–10514.

[25] F.-F. Gan, S.-B. Yang, Y.-C. Luo, W.-B. Yang, P.-F. Xu, *J. Org. Chem.* **2010**, *75*, 2737–2740.

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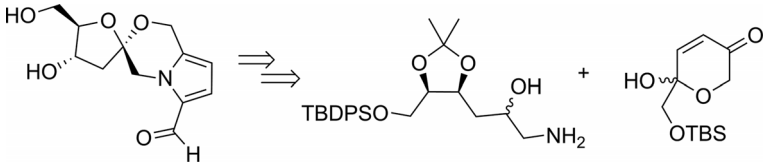
Maillard-Type Condensation



The use of a novel Maillard-type condensation between a primary amine derived from D-mannitol and a dihydropyranone as a key step to access the unusual morpholine-spiroketal acortatarin A is reported. The approach also allows access to a C-2 analogue, and can be used for synthesis of related 2-formylpyrrole natural products.

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Synthesis of the Revised Structure of Acortatarin A

Keywords: Natural products / Spiro compounds / Nitrogen heterocycles / Maillard condensation / Medicinal chemistry

