Highly diastereoselective desymmetrisation of cyclic *meso*-anhydrides and derivatisation for use in natural product synthesis†

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A new and efficient desymmetrisation of succinic and glutaric cyclic *meso*-anhydrides is described, providing excellent yields and diastereoselectivities in most cases. Derivatisation of the desymmetrised products is demonstrated by their conversion into mono-protected 1,4-diols. General synthetic utility of the method is established by its application towards a key fragment in the total synthesis of the immunosuppressant antitumour natural product, rapamycin.

Introduction

The rapidly increasing need to generate intricate chiral molecular structures in a robust and efficient manner demands the development of new strategies for the direct assembly of complex molecular architectures. In order to be synthetically useful reaction processes, such methods are expected to be high yielding, durable and readily scalable, generating the desired molecular complexity in a minimum number of chemical steps and, most importantly, facilitating the production of multiple stereogenic centres in a highly selective manner. Desymmetrisation of an achiral or *meso*-compound using a chiral species (either a catalyst or an auxiliary) serves as an efficient means for generating usefully functionalised chiral building blocks with potential application in the asymmetric synthesis of biologically active products, allowing multiple stereocentres to be created in a single symmetry-breaking transformation. This field has attracted a large amount of interest over the years and a number of powerful methods for the desymmetrisation of anhydrides, epoxides, diols, dienes, ketones and dialdehydes have been developed, among others.[1–4] More specifically, the desymmetrisation of cyclic *meso*-anhydrides is a particularly useful transformation, facilitating the production of one or more stereocentres in a single step and simultaneously producing two chemically differentiated carbonyl groups that can be synthetically elaborated further in a number of ways, thus rapidly and efficiently increasing molecular complexity.

There are two commonly used types of cyclic *meso*-anhydrides: five-membered succinic and six-membered glutaric anhydrides (**1** and **2**, Fig. 1). Both provide unique precursor frameworks with potential for application in natural product synthesis (Fig. 2).

A considerable body of work has been devoted to the development of diastereo- and enantioselective non-enzymatic desymmetrisations of *meso*-anhydrides. Chiral auxiliaries[5–7] and chiral catalysts[8] have both been employed to differentiate the

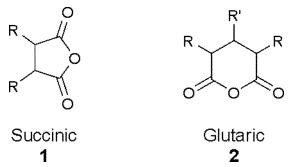

Fig. 1 Examples of cyclic *meso*-anhydrides.

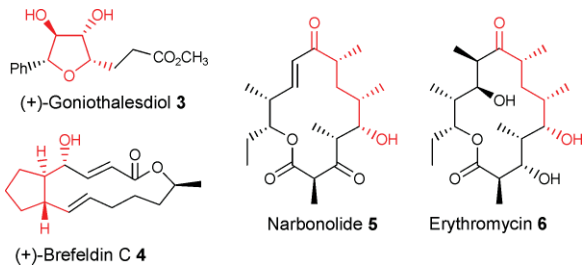

Fig. 2 Examples of natural products incorporating desymmetrised anhydride frameworks.

enantiotopic carbonyl groups present in the cyclic anhydride structure, facilitating diastereo- and enantioselective desymmetrisation, respectively. Diastereoselective desymmetrisation in particular is a practical means for employing cyclic anhydrides in synthesis, permitting the immediate physical isolation and characterisation of diastereomerically pure materials by chromatography or crystallisation; the appended chiral auxiliaries can then provide flexibility for further chemical differentiation *via* cleavage.

A number of nucleophilic chiral auxiliaries have been studied over the years for the desymmetrisation of cyclic *meso*-anhydrides, including chiral alcohols,[5] chiral amines,[6] and chiral oxazolines and oxazolidinones.[7] However, despite the indisputable advances that have been made, existing desymmetrisation methodologies utilising chiral auxiliaries frequently suffer from one or more of the following problems: difficulties with auxiliary cleavage and recovery, extended reaction times at reduced temperature, low enantio- or diastereoselectivities and/or a limited substrate scope. Given the experimental precedent for high selectivity induced by benzopyranoisoxazolidines as asymmetric alkylation auxiliaries and their facile Weinreb-amide-like cleavage as demonstrated by Abiko *et. al.*,[9–16] it was recognised that (+)- and (–)-**7** might also

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have potential application as chiral auxiliaries in the desymmetrisation of cyclic *meso*-anhydrides (Fig. 3).

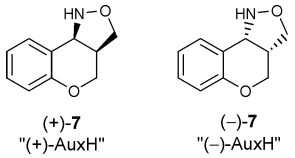


Fig. 3 Benzopyranoisoxazolidine chiral auxiliaries (+)- and (–)-**7**.

Results and discussion

A multi-gram synthesis of racemic auxiliary **7** proved to be straightforward and isolation of each of the (+)- and (–)-enantiomers from the racemic reaction mixture was possible using a simple kinetic resolution using a precedented reciprocal recrystallisation with (+)-10-camphorsulfonic acid ((+)-CSA).[10] Due to the highly crystalline nature of the (+)-**7**·(+)-CSA salt and the known absolute stereochemical configuration of (+)-CSA, X-ray diffraction analysis was performed in order to confirm which enantiomer of the auxiliary was isolated from each reciprocal recrystallisation. Abiko had previously assigned an (*R*,*S*)-configuration to the (+)-**7**·(+)-CSA salt and an (*S*,*R*)-configuration to the (–)-**7**·(+)-CSA salt;[10] however we believe this assignment to be incorrect, based on our X-ray diffraction analysis of the (+)-**7**·(+)-CSA salt‡, and upon analysis of the original published structure as deposited at the Cambridge Crystallographic Data Centre (CCDC) by Abiko *et al.* Indeed we would assign the (*S*,*R*)-configuration to the (+)-**7**·(+)-CSA salt and the (*R*,*S*)-configuration to the (–)-**7**·(+)-CSA salt (Fig. 4). This assignment has been rigorously corroborated by optical rotation analysis, ^{1}H- and ^{13}C-NMR spectra, and X-ray diffraction analysis. Having established the correct configurations of auxiliaries (+)- and (–)-**7**, we then proceeded with our investigation of the application of **7** as a desymmetrisation agent.§

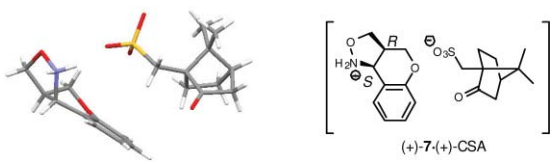
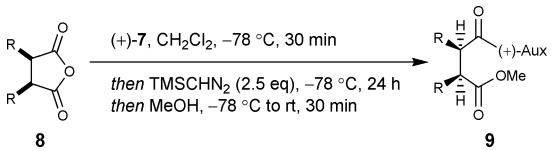


Fig. 4 X-ray diffraction analysis of (+)-**7** (+)-CSA.

‡ Crystal Data for (+)-**7**·(+)-CSA: $C_{20}H_{27}NO_6S$, M = 409.49, orthorhombic, a = 6.53530(10) Å, α= 90°, b = 9.87590(10) Å, β= 90°, c = 30.2519(5) Å, γ = 90°, 120(2) K, wavelength 0.71073 Å, P2(1)2(1)2(1), U = 1952.52(5) Å, Z = 4, 1.393 Mg/m^3, μ(Mo-Kα) = 0.204 mm^{-1}, F(000), crystal size: 0.46 × 0.23 × 0.16 mm^3, –8<=h<= 8, –12<=k<= 12, –34<=l<= 39, 12106 reflections collected, 4392 unique, [R(int) = 0.0295], completeness to theta = 27.46°, 98.7%, max. and min. transmission: 0.969 and 0.904, data/restraints/parameters: 4392/0/255, final R indices [I>2sigma(I)]: R1 = 0.0282, wR2 = 0.0700, R indices (all data): R1 = 0.0297, wR2 = 0.0713, absolute structure parameter: –0.02(5), largest diff. peak and hole: 0.232 and –0.352 e.Å^{-3}.

§ It should be noted that our initial communication[17] concerning the use of **7** as a desymmetrising agent was published prior to our re-evaluation of the X-ray diffraction analysis structure as reported by Abiko *et al.*[10] Therefore all structures depicted therein are the enantiomers of the actual products obtained.

Initial investigations using **7** as a chiral auxiliary in the desymmetrisation of cyclic *meso*-anhydrides required some optimisation of reaction conditions, but pleasingly the reaction of succinic *meso*-anhydride **8a** (Table 1) with (+)-auxiliary **7** at –8 °C in dichloromethane and subsequent trapping of the carboxylic acid thus formed with TMS-diazomethane was found to produce only one diastereomeric product (Scheme 1), as determined by ^{1}H-NMR and chiral HPLC.[17]



Scheme 1 Desymmetrisation of succinic *meso*-anhydrides.

Upon examination of the scope of this one-pot desymmetrisation-methylation reaction process, it was found that the protocol works extremely well on a broad range of substrates under the standard conditions (Table 1, entry 1). The majority of bi- (entries 1–5) and tri-cyclic (entries 7–9) succinic anhydrides screened were generally desymmetrised and methylated with excellent yields and diastereoselectivities. Indeed, in most cases a single diastereoisomer was produced, and the only instance in which the observed diastereoselectivity was less than optimal, for anhydride **8f** (entry 6), the major diastereoisomer was easily separable from the minor one by standard column chromatography. In addition, many of the desymmetrised products were crystalline, thus allowing the determination of relative stereochemistry by X-ray diffraction analysis. A representative example of this is the methyl ester product **9a**, the result of desymmetrisation of anhydride **8a** with auxiliary (+)-**7** (Fig. 5).¶[17]

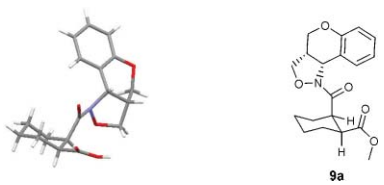
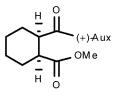
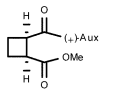
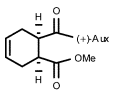
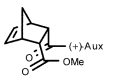
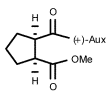
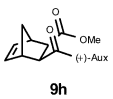
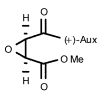
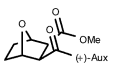
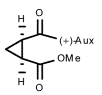


Fig. 5 X-ray diffraction analysis of **9a**.

The excellent results obtained using the one pot desymmetrisation/TMS-diazomethane methylation of succinic anhydride examples were unfortunately not reproducible when applied to glutaric anhydrides and resulted in lower conversion and only moderate stereoselection. Following further investigation, it became apparent that use of TMS-diazomethane as the methylating agent was the problem: the intermediate carboxylate

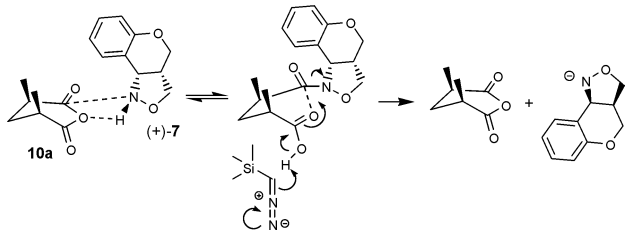
¶ Crystal Data for **9a**: $C_{18}H_{21}NO_5$, M = 331.36, monoclinic, a = 9.0302(3) Å, α= 90°, b = 8.0096(3) Å, β= 109.7370(10)°, c = 12.1640(4) Å, γ = 90°, 180(2) K, wavelength 0.71073 Å, P2(1), U = 828.12(5) Å^3, Z = 2, 1.329 Mg/m^3, μ(Mo-Kα) = 0.097 mm^{-1}, F(000)352, crystal size: 0.46 × 0.46 × 0.07 mm^3, theta range for data collection: 3.56 to 27.48°, 4767 reflections collected, 2025 unique, [R(int) = 0.0285], completeness to theta = 27.48°, 99.2%, max. and min. transmission: 0.994 and 0.954, data/restraints/parameters: 2025/2/220, 1.091, final R indices [I>2sigma(I)]R1 = 0.0385, wR2 = 0.0866, R indices (all data): R1 = 0.0453, wR2 = 0.0913, absolute structure parameter: 0.4(13), largest diff. peak and hole: 0.160 and –0.171 e.Å^{-3}.

Table 1 Desymmetrisation of succinic *meso*-anhydrides using (+)-**7**

Entry	Anhydride	Yield (%)[a,b]	de (%)[c]	Product	Entry	Anhydride	Yield (%)[a,b]	de (%)[c]	Product
1	 **8a**	96[d]	> 95	 **9a**	**6**	 **8f**	100[e]	60	 **MAJOR 9f** (and **MINOR 9f**)
2	 **8b**	90[d]	> 95	 **9b**	**7**	 **8g**	98[e]	> 95	 **9g**
3	 **8c**	74[d]	92	 **9c**	**8**	 **8h**	93[e]	> 95	 **9h**
4	 **8d**	98[e]	> 95	 **9d**	**9**	 **8i**	98[e]	> 95	 **9i**
5	 **8e**	99[e]	> 95	 **9e**					

[a] Isolated yield. [b] All examples were desymmetrised using (+)-**7**. [c] Determined by ^{1}H-NMR spectroscopy and LC-MS. [d] Desymmetrised using both (+)-**7** and (–)-**7**, with matching yields and diastereoselectivities. [e] Desymmetrised using (+)-**7**.

anion formed after deprotonation can readily substitute into the auxiliary amide carbonyl and force the auxiliary to leave, resulting in generation of the anhydride and a negatively charged auxiliary (Scheme 2).‖ This charged auxiliary would be much more nucleophilic than the neutral species, and therefore less likely to discriminate selectively between the two anhydride carbonyl groups upon further reaction. Hence, it became clear

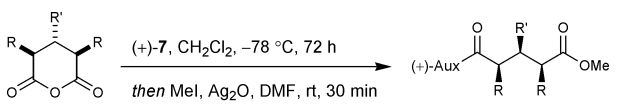


Scheme 2 Postulated mechanism for the reduced desymmetrisation diastereoselectivities of glutaric *meso*-anhydride **10**.

‖ This does not occur with the succinic anhydrides as the systems undergoing desymmetrisation are bicyclic in nature and the regenerated anhydride would be a five-membered ring attached to another ring system: assuming this reformation occurs more slowly than methylation due to strain factors, the initial diastereoselectivity generated by the auxiliary should be preserved, as was the observed result. Given the lower degree of strain in six-membered ring glutaric anhydrides, if ring closure occurs more rapidly than methylation, an overall lower diastereoselectivity would result, as was observed.

that a methylation protocol that did not involve carboxylate anion formation would be required.

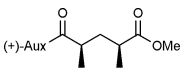
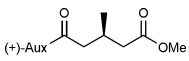
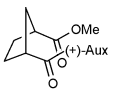
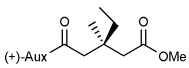
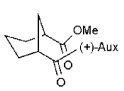
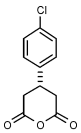
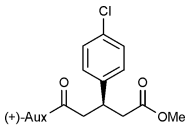
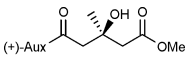
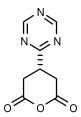
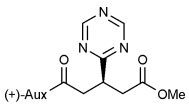
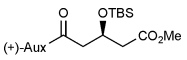
Indeed, the use of methyl iodide with silver oxide in dimethyl formamide gave such a good result (91%, 86% de, Table 2, entry 1) that these conditions were then taken and applied directly to a range of other glutaric anhydride examples (Scheme 3, Table 2).



Scheme 3 Desymmetrisation of glutaric *meso*-anhydrides.

Pleasingly, all subsequent glutaric anhydride examples evaluated provided desymmetrised products in good to excellent yields; however, the diastereoselectivity of desymmetrisation proved to be highly dependent upon anhydride structure. Glutaric anhydrides with substituents alpha to the carbonyl groups afforded good yields and high diastereoselectivities (entries 1–3), as did glutaric anhydrides substituted in the 3-position with groups such as –OH and –OTBS (entries 4, 5). In contrast, the glutaric anhydrides substituted in the 3-position with only small alkyl substituents or aromatic groups that can lie flat and effectively perpendicular to the anhydride ring provided excellent yields but no diastereoselectivity (entries 6–9), as auxiliary **7** could no longer differentiate between the two diastereotopic carbonyl centers of attack for these examples. All diastereoisomers were easily

Table 2 Desymmetrisation of glutaric *meso*-anhydrides using (+)- and (−)-**7**

Entry	Anhydride	Yield (%)[a,b]	de (%)[c]	Product	Entry	Anhydride	Yield (%)[a,b]	de (%)[c]	Product
1	 **10a**	91	86	 **MAJOR 11a** (and **MINOR 11a**)	**6**	 **10f**	100	0	 **MAJOR 11f** (and **MINOR 11f**)
2	 **10b**	87	70	 **MAJOR 11b** (and **MINOR 11b**)	**7**	 **10g**	100	0	 **MAJOR 11g** (and **MINOR 11g**)
3	 **10c**	85	75	 **MAJOR 11c** (and **MINOR 11c**)	**8**	 **10h**	100	0	 **MAJOR 11h** (and **MINOR 11h**)
4	 **10d**	75	70	 **MAJOR 11d** (and **MINOR 11d**)	**9**	 **10i**	95	0	 **MAJOR 11i** (and **MINOR 11i**)
5	 **10e**	99	80	 **MAJOR 11e** (and **MINOR 11e**)					

[a] Isolated yield. [b] All examples were desymmetrised using both (+)-**7** and (−)-**7**, with matching yields and diastereoselectivities. [c] Determined by ^{1}H-NMR spectroscopy and LC-MS.

separable by chromatography, and isolated yields were found to reflect the diastereomeric excess observed analytically for all crude reaction mixtures. In addition, the majority of diastereomeric products isolated were again crystalline, allowing the use of X-ray diffraction analysis for determination of relative stereochemistry. A representative example of this is the methyl ester product **11a**, the result of the desymmetrisation of anhydride **10a** using auxiliary (+)-**7** (Fig. 6).**

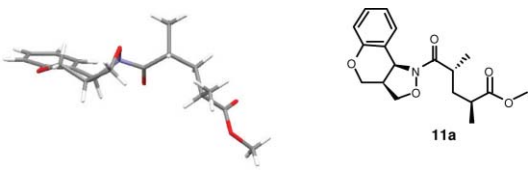
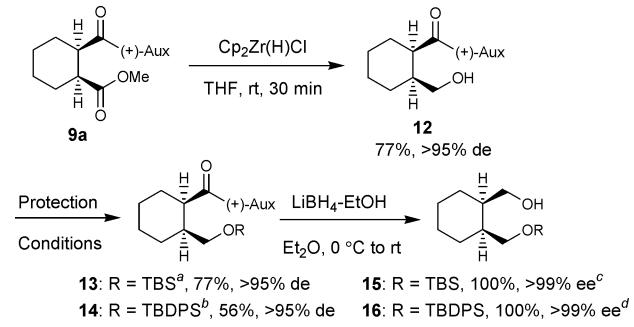


Fig. 6 X-ray diffraction analysis of **11a**.

With the successful desymmetrisation of both succinic and glutaric *meso*-anhydrides now accomplished, their derivatisation and subsequent application in a total synthesis programme was initiated. At this stage, it was necessary to first investigate whether the amide and ester moieties present in the desymmetrised products could definitively be successfully differentiated. In theory, the Weinreb-type amide and ester functionalities should have differing reactivities: thus it was anticipated that *via* selective manipulation of these, chiral mono-protected diols might be generated. Chemodifferentiation between the ester and the Weinreb-type amide in **9a** was indeed successfully achieved using Schwartz reagent under relatively mild conditions (Scheme 4),[18,19] which selectively reduced the methyl ester moiety in **9a** to alcohol **12** at room temperature in 30 minutes. This reaction was found to be reproducible on scale in high yield without erosion of diastereomeric excess, and left the auxiliary portion of the molecule intact.

Protection of the primary alcohol **12** as a TBS- or TBDPS-ether also proceeded smoothly, and subsequent borohydride reduction facilitated cleavage of the auxiliary to give 1,4-mono-protected diols **15** and **16** in quantitative yields and with complete retention of stereochemistry. The diastereoselectivity of the

** Crystal Data for **11a**: $C_{18}H_{23}NO_5$, M = 333.37, monoclinic, a = 7.6843(2) Å, α= 90°. b = 10.9358(3) Å, β= 100.974(2)°, c = 10.2015(3) Å, γ = 90°, 180(2) K, wavelength: 0.71073 Å, P2(1), U = 841.60(4) Å^3, Z 2, 1.316 Mg/m^3, μ(Mo-Kα) = 0.096 mm^{-1}, F(000)356, crystal size: 0.46 × 0.46 × 0.42 mm^3, theta range for data collection: 3.58 to 27.49°, 5141 reflections collected, 2004 unique, [R(int) = 0.0195], completeness to theta = 27.49°, 99.0%, max. and min. transmission: 0.968 and 0.922, data/restraints/parameters: 2004/1/220, final R indices [I>2sigma(I)]R1 = 0.0420, wR2 = 0.1141, R indices (all data): R1 = 0.0596, wR2 = 0.1424, absolute structure parameter: –0.4(11), largest diff. peak and hole: 0.973 and –0.971 e.Å^{-3}.



Scheme 4 Chemoselective reduction, protection and reductive auxiliary cleavage for succinic anhydrides. *Protection conditions:* [a]TBS-OTf, 2,6-lutidine, CH_2Cl_2, 1 h, 0 °C to rt. [b]TBDPS-Cl, imidazole, DMAP, TBAI, CH_2Cl_2, 16 h, 0 °C to rt. [c]Determined by Mosher ester formation. [d]Determined by chiral HPLC.

original desymmetrisation step was thus maintained throughout the derivatisation process, as monitored by ^{1}H-NMR. Indeed, the diastereoselectivity of the original anhydride desymmetrisation ultimately translated into excellent enantioselectivity upon auxiliary cleavage, as determined by derivatisation *via* Mosher ester formation and subsequent ^{1}H-NMR and/or chiral HPLC analysis.

Selective manipulation and derivatisation of glutaric *meso*-anhydride product **11a** was next attempted. This particular substrate was of interest because the *syn*-deoxypolypropionate moiety **17** (Fig. 7) is a structural feature found in many natural products.[20] A new method for the stereoselective formation of this motif would therefore have significant potential application.

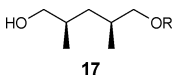
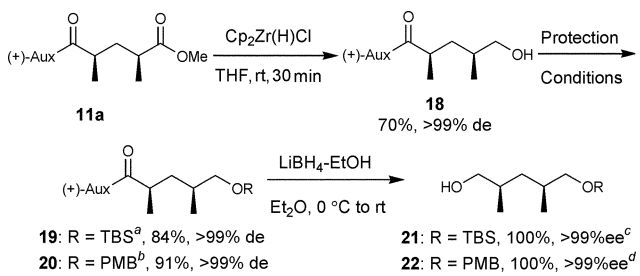


Fig. 7 *Syn*-deoxypolypropionate moiety **17**.

Using the same conditions as had been applied to derivatisation of the succinic substrate **9a**, reduction of ester **11a** was now attempted (Scheme 5). Pleasingly, under these conditions the ester moiety was indeed reduced to give alcohol **18** in high yield without any erosion of diastereoselectivity. Alcohol **18** was then protected as TBS- and PMB-ethers in high yields and with complete retention of diastereomeric excess. Reduction of ethers **19** and **20** to mono-protected diols **21** and **22** also proved to be highly successful (100% yield, >99% ee), thus demonstrating the general

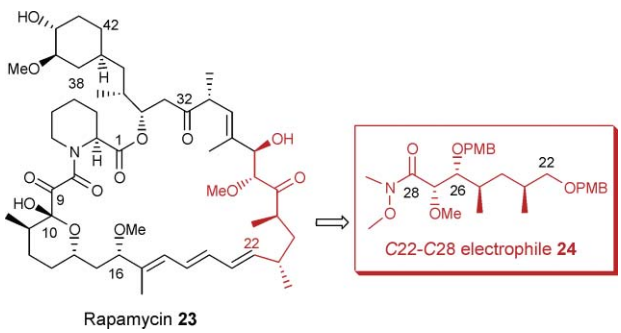


Scheme 5 Chemoselective reduction, protection and auxiliary cleavage for glutaric anhydrides. *Conditions*: [a]TBS-OTf, 2,6-lutidine, CH_2Cl_2, 1 h, 0 °C to rt. [b]PMB-TCA, La(OTf)$_3$, toluene, 20 min, rt. [c]Detemined by Mosher ester formation. [d]Determined by chiral HPLC.

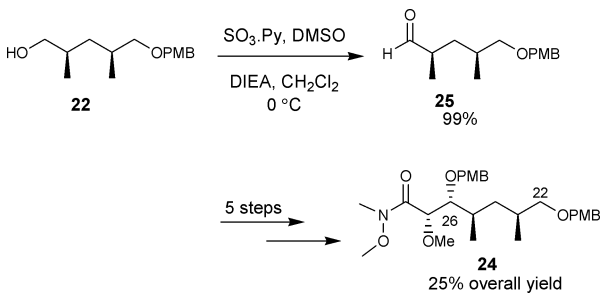
utility of this desymmetrisation and derivatisation methodology for both succinic and glutaric anhydrides.

In addition, the desymmetrisation method combined with the derivatisation sequence of **11a** has now been shown to provide a highly robust and scaleable route to mono-protected diol **22**.

This compound, originally synthesised by alternative means, has recently been utilised as a key fragment in our group's total synthesis of rapamycin **23**,[21] a powerful immunosuppressant[22] and antitumour agent:[23] the *syn*-deoxypolypropionate moiety **22** was used to construct key intermediate *C*22-*C*28 electrophile **24** (Scheme 6).[21] In the original publication,[21] oxidation of **22** using Parikh-Doering conditions provided aldehyde **25** in excellent yield (99%) and in just five subsequent steps the *C*22–*C*28 electrophile **24** was obtained in 25% overall yield (Scheme 7), which was then incorporated into the total synthesis of rapamycin. One advantage of using the desymmetrisation method outlined here to obtain alcohol precursor **22** is that, not only can the mono-protected diol be accessed in high yields and with excellent stereocontrol, but its enantiomer can also be easily obtained with the same degree of efficiency and enantiopurity, thus providing a readily available route for analogue synthesis.



Scheme 6 Rapamycin **23** and *C*22-*C*28 electrophile fragment **24**.



Scheme 7 Oxidation of diol **25** and formation *C*22–*C*28 electrophile fragment **22**.[21]

Conclusion

A general synthetically useful method for the desymmetrisation of cyclic *meso*-anhydrides using benzopyranoisoxazolidines as chiral auxiliaries has thus been developed and successfully applied to a wide range of both succinic and glutaric anhydrides. Facile access to both enantiomers of the chiral auxiliary **7** facilitates the formation of all possible diastereomers, and the highly crystalline nature of many of the desymmetrised products permits straightforward isolation of the desired products in excellent yields and diastereoselectivities. Additionally, the desymmetrised

products have been effectively derivatised to 1,4-mono-protected alcohols, which are precursors to key intermediates in natural product synthesis. An example of this is alcohol **22**, which has been shown to be a useful component in our group strategy towards the total synthesis of the biologically active natural product rapamycin **23**.

Experimental

General methods

When anhydrous conditions were required, reactions were carried out under an atmosphere of argon and in oven-dried glassware. Synthetic intermediates were dried *in vacuo* before use in non-aqueous reactions. Molecular sieves were dried at 200 °C before use.

Petroleum ether was distilled between 40 and 60 °C. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled over calcium hydride and lithium aluminium hydride. Dichloromethane (CH_2Cl_2), toluene, acetonitrile (MeCN) and methanol (MeOH) were distilled over calcium hydride. Triethylamine was distilled from calcium hydride and stored over potassium hydride. Other reagents and solvents were used as supplied or purified using standard procedures as required. Aqueous solutions are saturated unless otherwise specified.

Flash column chromatography was carried out using Merck BDH F_{254} Kieselgel 60 (230–400 mesh) as the stationary phase and eluted with positive pressure of compressed air.

Analytical thin layer chromatography was performed using pre-coated Merck glass-backed silica gel plates (Merck Kieselel 60 F_{254}) and visualised by ultraviolet light (254 nm) and treatment with acidic potassium permanganate, acidic ammonium molybdate (IV), Schlittler, or anisaldehyde stains followed by heating as appropriate.

Mass spectra and accurate mass data were obtained on Micromass Platform HP1050 LC/MS, Waters Alliance HT2795 LC/MS, Kratos QTOF or Bruker BIOAPEX 4.7 FTICR spectrometers by electrospray ionization (+ESI) or electron impact (EI) at the Department of Chemistry, University of Cambridge.

Chiral HPLC was performed on Agilent 1100 using Chiralcel columns, HPLC grade solvents and UV detection (λ = 215, 254, 280 nm) at room temperature.

Infra-red spectra were recorded on Perkin Elmer Spectrum One FT-IR 1620 Universal ATR sampling accessory from 4000–600 cm^{-1}. All samples were run as thin films on a diamond/Se plate. Absorption maxima are reported in wavenumbers (cm^{-1}).

Optical rotations were measured on a Perkin Elmer Model 343 polarimeter using a sodium lamp (λ 589 nm, D-line); $[\alpha]_D$ values are reported in units of 10^{-1} deg cm^2 g^{-1}. All optical rotations were measured using $CHCl_3$ as solvent and were measured at 25 °C; concentration (*c*) is reported in g/(100 mL).

Melting points were measured on a Reichert hot stage apparatus, and are uncorrected.

Nuclear magnetic resonance (NMR) spectra were recorded at 27 °C in deuterated chloroform ($CDCl_3$) unless otherwise stated. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded using a Bruker DPX 400 Fourier transform spectrometer at 400 MHz with residual protic solvent as the internal standard ($CHCl_3$, δ_H = 7.26, s). Spectra are reported as follows: chemical shift δ (parts per million, ppm) (multiplicity, number of protons, coupling constant *J*, in Hertz, Hz, assignment). Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br) or combinations of the preceding.

Carbon nuclear magnetic resonance spectra (^{13}C-NMR) were recorded on a Bruker DPX 400 spectrometer at 100 MHz using the central resonance of $CDCl_3$ as the internal standard (δ_C = 77.0, t). Spectra are reported as follows: chemical shift δ (parts per million, ppm), (assignment).

COSY, HMQC, HMBC and DEPT-135 experiments were used to aid in the assignment of ^{1}H- and ^{13}C-NMR signals.

All X-ray diffraction analyses were performed by Dr. John Davies at the Department of Chemistry, University of Cambridge.

Formation of chiral auxiliary

1,3a,4,9b-Tetrahydro-3*H*-[1]benzopyrano[4,3-*c*]isoxazole ((±)-7). *Prepared by the literature procedure.*[9–16] A mixture of 2-allylhydroxybenzaldehyde (0.50 g, 3.08 mmol), 5-hydroxypentanal oxime (0.38 g, 3.24 mmol), dibutyl tin oxide (0.08 g, 0.31 mmol), and toluene (40 mL) was heated under reflux with Dean-Stark apparatus for 12 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the resulting crude product (±)-**7** was taken up in ethanol (14 mL) and aqueous hydrochloric acid (3 N, 7 mL) solution. This mixture was stirred at room temperature for 15 h, at which point the solvent was removed *in vacuo* and the remaining aqueous phase was washed with diethyl ether (2 × 20 mL), neutralized with ammonium hydroxide (50 mL, 15%), and extracted with dichloromethane (5 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil. This oil was dissolved in acetone (1.2 L) and left to stand at ambient temperature, generating yellowish crystals of (±)-**7** (0.49 g, 2.74 mmol, 89%). mp 95–96 °C (lit.,[9–16] 95–96 °C); IR ν_{max} (film)/cm^{-1} 3187 (NH), 1607 (aromatic), 1582 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41 (d, 1H, *J* = 7.4 Hz), 7.22 (t, 1H, *J* = 8.3 Hz), 6.98 (t, 1H, *J* = 7.4 Hz), 6.94 (d, 1H, *J* = 8.3 Hz), 5.03 (s, 1H), 4.35–4.31 (m, 2H), 4.23 (m, 1H), 3.76–3.72 (m, 2H), 3.11–3.07 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.5, 131.3, 129.4, 121.6, 118.5, 117.3, 72.8, 65.2, 57.3, 40.7; MS (+ESI) = Calcd. for $C_{10}H_{11}NO_2$ $(M + Na)^+$: 200.0691, Found $(M + Na)^+$: 200.0690.

(+)-1,3a,4,9b-Tetrahydro-3*H*-[1]benzopyrano[4,3-*c*]isoxazole ((+)-7) and (–)-1,3a,4,9b-tetrahydro-3*H*-[1]benzopyrano[4,3-*c*]isoxazole ((–)-7). *Prepared by the literature procedure.*[9–16] A mixture of crude (±)-**7** (130 g, 0.73 mol) and (+)-camphorsulfonic acid ((+)-CSA) (194 g, 0.78 mmol) in acetone (1.3 L) was heated until everything was dissolved and then allowed to cool to room temperature. After being allowed to stand overnight, the first crop of (+)-**7**·(+)-CSA (56 g, 0.13 mol, 18%) was collected. The mother liquor was concentrated to 2/3 of its original volume (800 mL) and left to stand overnight, yielding the first crop of (–)-**7**·(+)-CSA (43 g, 0.10 mol, 14%). This protocol was repeated twice to yield a second crop of (+)-**7**·(+)-CSA (40 g, 0.09 mol, 13%) and (–)-**7**·(+)-CSA (34 g, 0.08 mol, 12%), respectively. After enantiomeric purities were determined to be >99% ee by chiral HPLC (Chiralcel OD-H, 1.0 mL/min, 30 min, hexane:isopropanol, 95:5; retention time for (–)-**7** = 13.2 min, retention time for (+)-**7** = 22.7 min), matching crystalline crops were combined, neutralised by treatment with aqueous sodium hydroxide (1 N, 40 mL), extracted twice with

dichloromethane (2 × 30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford white crystals: (+)-**7** (96 g, 0.23 mol, 31%) and (−)-**7** (81 g, 0.20 mol, 26%).

(+)-7·(+)-CSA. mp 185–187 °C (lit.,[9] 185–187); $[\alpha]_D^{25} = +63$ ($c = 1.12$, $CHCl_3$) (lit.,[9]: $[\alpha]_D^{25} = +61.5$ ($c = 1.10$, CH_3OH)); IR ν_{max} (film)/cm^{-1} 2954 (CH), 1739 (CO), 1586 (aromatic); ^{1}H-NMR ($CDCl_3$): δ 7.41 (d, 1H, $J = 7.5$ Hz), 7.38 (t, 1H, $J = 8.3$ Hz), 7.09 (t, 1 H, $J = 7.5$ Hz), 7.02 (d, 1H, $J = 8.3$ Hz), 5.19 (d, 1H, $J =$ 7.2 Hz), 4.62 (s, 2H), 4.40–4.35 (m, 1H), 3.90–3.75 (m, 3H), 3.22–3.17 (m, 1H), 2.79–2.74 (m, 1H), 2.68–2.64 (m, 1H), 2.35–2.31 (m, 1H), 2.06–2.01 (m, 2H), 1.93–1.88 (m, 1H), 1.62–1.58 (m, 1H), 1.15 (s, 3H), 1.13 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 218.8, 157.6, 133.1, 132.8, 123.7, 119.5, 115.1, 75.3, 65.3, 60.0, 58.9, 48.8, 43.2, 40.5, 29.6, 28.2, 26.8, 26.2, 20.8, 20.6; MS (+ESI) = Calcd. for $C_{20}H_{28}NO_6S$ $(M + H)^+$: 410.1637, Found $(M + H)^+$: 410.1642.

(−)-7·(+)-CSA. mp 186–189 °C (lit.,[9] 186–188); $[\alpha]_D^{25} = -11$ (c = 1.05, $CHCl_3$) (lit.,[9] $[\alpha]_D^{25} = -12$ ($c = 1.15$, CH_3OH)); IR ν_{max} (film)/cm^{-1} 2954 (CH), 1739 (CO), 1586 (aromatic); ^{1}H-NMR ($CDCl_3$): δ 7.40 (d, 1H, $J = 7.5$ Hz), 7.38 (t, 1H, $J = 8.3$ Hz), 7.08 (t, 1 H, $J = 7.5$ Hz), 7.02 (d, 1H, $J = 8.3$ Hz), 5.19 (d, 1H, $J =$ 7.2 Hz), 4.60 (s, 2H), 4.42–4.35 (m, 1H), 3.90–3.76 (m, 3H), 3.22–3.15 (m, 1H), 2.80–2.74 (m, 1H), 2.68–2.63 (m, 1H), 2.35–2.30 (m, 1H), 2.07–2.00 (m, 2H), 1.93–1.88 (m, 1H), 1.62–1.58 (m, 1H), 1.15 (s, 3H), 1.10 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 218.7, 157.6, 133.0, 132.8, 123.7, 119.3, 115.2, 75.3, 65.5, 60.0, 59.0, 48.8, 43.0, 40.5, 29.5, 28.2, 26.8, 26.1, 20.8, 20.6; MS (+ESI) = Calcd. for $C_{20}H_{28}NO_6S$ $(M + H)^+$: 410.1637, Found $(M + H)^+$: 410.1645.

(+)-1,3a,4,9b-Tetrahydro-3*H*-[1]benzopyrano[4,3-*c*]isoxazole ((+)-7). mp 95–96 °C (lit.,[9] 95–96); $[\alpha]_D^{25} = +62$ ($c = 1.20$, $CHCl_3$) (lit.,[9] $[\alpha]_D^{25} = +62.4$ ($c = 1.11$, $CHCl_3$)); IR ν_{max} (film)/cm^{-1} 3187 (CH), 1607 (aromatic), 1582 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41 (d, 1H, $J = 7.4$ Hz), 7.22 (t, 1H, $J = 8.3$ Hz), 6.98 (t, 1H, $J = 7.4$ Hz), 6.94 (d, 1H, $J = 8.3$ Hz), 5.03 (s, 1H), 4.33 (m, 2H), 4.26–4.19 (m, 1H), 3.75–3.71 (m, 2H), 3.12–3.08 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.5, 131.3, 129.4, 121.6, 118.5, 117.3, 72.8, 65.2, 57.3, 40.7; MS (+ESI) = Calcd. for $C_{10}H_{11}NO_2$ $(M + H)^+$: 178.1296, Found $(M + H)^+$: 178.1298.

(−)-1,3a,4,9b-Tetrahydro-3*H*-[1]benzopyrano[4,3-*c*]isoxazole ((−)-7). $[\alpha]_D^{25} = -59$ ($c = 0.92$, $CHCl_3$) (lit.,[9] $[\alpha]_D^{25} = -62.4$ ($c =$ 1.11, $CHCl_3$)).

General protocol for desymmetrisation of succinic anhydrides

To a stirred solution of cyclic *meso*-anhydride (0.55 mmol) in dichloromethane (1.5 mL) at −78 °C was added a solution of (+)- or (−)-**7** (89 mg, 0.5 mmol) in dichloromethane (0.5 mL) dropwise *via* syringe. The reaction was stirred at −78 °C for 30 min, and trimethylsilyldiazomethane (2.0 M in hexanes, 0.5 mL, 1.0 mmol) was added dropwise *via* syringe. The resulting yellow solution was allowed to stir at −78 °C for 24 h, at which point the reaction was quenched with methanol (4 mL). The reaction mixture was allowed to stir for 30 min while warming to room temperature and was then concentrated *in vacuo.* Crude product was purified by flash column chromatography (petroleum ether:diethyl ether, 1:1). All diastereomeric excesses were evaluated by ^{1}H-NMR spectroscopy of crude reaction mixtures prior to purification; all yields are isolated yields.

All desymmetrisations were performed using (+)-**7**; in some cases (−)-**7** was also used, as is noted where appropriate.

(+)-(1′*S*,2′*R*,3a*R*,9b*S*)-Methyl-2′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-c]isoxazole-1′-yl)cyclohexanecarboxylate (9a). Isolated as a white powder, 166 mg total yield (96%, >95% de). mp = 151–152 °C; $[\alpha]_D^{25} = +69$ ($c = 1.17$, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2229 (CH), 2857 (CH), 1711 (CO-ester), 1664 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 1H, $J = 7.9$ Hz), 7.18 (t, 1H, $J = 7.8$ Hz), 6.98 (t, 1H, $J = 7.6$ Hz), 6.87 (d, 1H, $J = 7.8$ Hz), 5.40 (d, 1H, $J = 7.9$ Hz), 4.30 (dd, 1H, $J = 11.2$ and 4.4 Hz), 3.85–3.75 (m, 1H), 3.62 (dd, 1H, $J = 7.3$ and 3.7 Hz), 3.37 (dd, 1H, $J = 11.2$ and 9.4 Hz), 3.68 (s, 3H), 3.54–3.49 (m, 1H), 3.19–3.08 (m, 1H), 2.57–2.53 (m, 1H), 2.35–2.25 (m, 1H), 2.11–2.06 (m, 1H), 1.98–1.91 (m, 1H), 1.84–1.79 (m, 1H), 1.66–1.57 (m, 1H), 1.51–1.38 (m, 2H), 1.31–1.27 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 179.8, 175.4, 155.4, 131.9, 129.2, 122.5, 122.4, 117.2, 71.9, 65.8, 52.7, 52.0, 43.5, 40.5, 38.9, 28.8, 25.4, 25.2, 22.4; MS (+ESI) = Calcd. for $C_{19}H_{23}NO_5$ $(M + H)^+$: 346.1954, Found $(M + H)^+$: 346.1957. **Ent 9a**: $[\alpha]_D^{25} = -81$ ($c = 1.25$, $CHCl_3$).

(+)-(1′*S*,3a*R*,6′*R*,9b*S*)-Methyl-6′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1′-yl)cyclohex-3′-enecarboxylate (9b). Isolated as a white powder, 154 mg total yield (90%, >95% de). mp = 152–153 °C; $[\alpha]_D^{25} = +98$ ($c = 0.85$, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2950 (CH), 1729 (CO-ester), 1668 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 1H, $J = 7.6$ Hz), 7.15 (t, 1H, $J = 8.0$ Hz), 6.98 (t, 1H, $J = 7.5$ Hz), 6.88 (d, 1H, $J =$ 8.0 Hz), 5.80–5.70 (m, 1H), 5.70–5.60 (m, 1H), 5.43 (d, 1H, $J =$ 8.0 Hz), 4.30 (dd, 1H, $J = 11.4$ and 4.4 Hz), 4.19–4.15 (m, 1H), 4.10 (dd, 1H, $J = 7.3$ and 3.7 Hz), 3.93 (dd, 1H, $J = 11.4$ and 8.0), 3.68 (s, 3H), 3.59–3.53 (m, 1H), 3.22–3.17 (m, 1H), 2.90–2.78 (m, 2H), 2.48–2.39 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 179.0, 175.1, 155.4, 132.0, 129.2, 125.9, 124.3, 122.5, 122.2, 117.2, 72.1, 65.7, 52.9, 52.2, 40.6, 39.8, 36.2, 27.7, 25.9. MS (+ESI) = Calcd. for $C_{19}H_{21}NO_5$ $(M + H)^+$: 344.1423, Found $(M + H)^+$: 344.1419. **Ent 9b**: $[\alpha]_D^{25} = -104$ ($c = 0.95$, $CHCl_3$).

(+)-(1′*S*,2′*R*,3a*R*,9b*S*)-Methyl-2′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1′-yl)cyclopentanecarboxylate(9c). Isolated as a white powder, 123 mg total yield (74%, 92% de). mp = 197–200 °C; $[\alpha]_D^{25} = +170$ ($c = 1.10$, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 3074 (CH), 2956 (CH), 1717 (CO-ester), 1669 (CO-amide), 1585 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (d, 1H, $J =$ 7.4 Hz), 7.17 (t, 1H, $J = 8.1$ Hz), 6.98 (t, 1H, $J = 7.4$ Hz), 6.81 (d, 1H, $J = 8.1$ Hz), 5.45 (d, 1H, $J = 8.1$ Hz), 4.28–4.17 (m, 2H), 4.05–4.00 (m, 1H), 3.99–3.93 (m, 1H), 3.68 (s, 3H), 3.64–3.59 (m, 1H), 3.23–3.18 (m, 1H), 3.11–3.06 (m, 1H), 2.24 – 2.16 (m, 1H), 2.05–1.94 (m, 4H), 1.76–1.73 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.2, 173.0, 155.1, 131.3, 128.8, 122.9, 119.9, 117.3, 71.9, 66.1, 53.2, 52.2, 40.8, 39.5, 33.6, 29.9, 28.6, 22.4; MS (+ESI) = Calcd. for $C_{18}H_{21}NO_5$ $(M + H)^+$: 332.2015, Found $(M + H)^+$: 332.2011. **Ent 9c**: $[\alpha]_D^{25} = -164$ ($c = 1.00$, $CHCl_3$).

(+)-(1′*S*,2′*R*,3a*R*,9b*S*)-Methyl-2′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1′-yl)cyclobutanecarboxylate (MAJOR 9d) and (+)-(1′*R*,2′*S*,3a*R*,9b*S*)-methyl-2′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1′-yl)cyclobutanecarboxylate (MINOR 9d). Isolated as major (126 mg, 80%) and minor (31 mg, 20%) diastereoisomers, as clear oils, 157 mg total yield (100%, 60% de). **MAJOR 9d:** $[\alpha]_D^{25} = +234$ ($c = 1.02$, $CHCl_3$); IR ν_{max}

(film)/cm^{-1} 3074 (CH), 2956 (CH), 1715 (CO-ester), 1668 (CO-amide), 1585 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70 (d, 1H, J = 7.4 Hz), 7.17 (t, 1H, J = 8.1 Hz), 6.98 (t, 1H, J = 7.4 Hz), 6.85 (d, 1H, J = 8.1 Hz), 5.48 (d, 1H, J = 8.1 Hz), 4.25 (dd, 1H, J = 11.4 and 4.4 Hz), 4.23–4.16 (m, 1H), 3.94–3.88 (m, 3H), 3.68 (s, 3H), 3.52–3.48 (m, 1H), 3.20–3.16 (m, 1H), 2.54–2.48 (m, 2H), 2.33–2.27 (m, 1H), 2.22–2.18 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 176.1, 174.4, 155.2, 132.2, 129.4, 122.4, 121.1, 117.3, 71.3, 65.4, 53.1, 52.1, 41.6, 40.5, 39.0, 23.2, 22.2; MS (+ESI) = Calcd. for $C_{17}H_{19}NO_5$ (M + H)$^+$: 318.3309, Found (M + H)$^+$: 318.3312. **MINOR 9d:** $[\alpha]_D^{25}$ = + 225 (c = 1.04, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 3074 (CH), 2956 (CH), 1715 (CO-ester), 1668 (CO-amide), 1585 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70 (d, 1H, J = 7.4 Hz), 7.17 (t, 1H, J = 7.3 Hz), 6.98 (t, 1H, J = 7.1 Hz), 6.85 (d, 1H, J = 8.1 Hz), 5.46 (d, 1H, J = 8.1 Hz), 4.25 (dd, 1H, J = 11.4 and 4.4 Hz), 4.23–4.16 (m, 1H), 3.94–3.88 (m, 3H), 3.68 (s, 3H), 3.52–3.48 (m, 1H), 3.20–3.16 (m, 1H), 2.54–2.48 (m, 2H), 2.33–2.27 (m, 1H), 2.22–2.18 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 176.0, 174.3), 155.1, 132.1, 129.4, 122.3, 121, 117.3, 71.3, 65.3, 53.0, 52.0, 41.4, 40.5, 39.0, 23.1, 22.1. MS (+ESI) = Calcd. for $C_{17}H_{19}NO_5$ (M + H)$^+$: 318.3424, Found (M + H)$^+$: 318.3428.

(+)-(1′*S*,2′*R*y,3a*R*,9b*S*)-Methyl-2′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1′-yl)cyclopropanecarboxylate (9e). Isolated as a white powder, 150 mg total yield (99%, >95% de). mp = 221–222 °C; $[\alpha]_D^{25}$ = + 270 (c = 1.10, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2953 (CH), 1709 (CO-ester), 1665 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 (dd, 1H, J = 7.1 Hz), 7.16 (t, 1H, J = 8.1 Hz), 6.93 (t, 1H, J = 7.1 Hz), 6.85 (d, 1H, J = 8.1 Hz), 5.47 (d, 1H, J = 8.0 Hz), 4.29–4.23 (m, 3H), 3.95 (dd, 1H, J = 8.1 and 1.5 Hz), 3.65 (s, 3H), 3.13–3.08 (m, 1H), 2.46–2.41 (m, 1H), 2.16–2.12 (m, 1H), 1.78–1.71 (m, 1H), 1.30–1.25 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.0, 171.5, 155.3, 132.0, 129.4, 122.5, 121.8, 117.3, 71.7, 65.5, 53.3, 52.5, 40.6, 22.2, 21.0, 11.4; MS (+ESI) = Calcd. for $C_{16}H_{17}NO_5$ (M + H)$^+$: 304.3151, Found (M + H)$^+$: 304.3147.

(+)-(2′*R*,3′*S*,3a*R*,9b*S*)-Methyl-3′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1′-yl)bicyclo[2.2.1]hept-5′-ene-2′-carboxylate (9f). Isolated as a white powder, 174 mg total yield (98%, >95% de). mp = 152–154 °C; $[\alpha]_D^{25}$ = + 164 (c = 1.05, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2975 (CH), 1713 (CO-ester), 1666 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73 (d, 1H, J = 7.4 Hz), 7.15 (t, 1H, J = 8.1 Hz), 6.93 (t, 1H, J = 7.4 Hz), 6.85 (d, 1H, J = 8.1 Hz), 6.52 (dd, 1H, J = 5.2 Hz and 2.8 Hz), 6.10 (dd, 1H, J = 5.2 Hz and 2.8 Hz), 5.43 (d, 1H, J = 7.9 Hz), 4.25 (dd, 1H, J = 11.2 and 4.7 Hz), 4.03–4.00 (m, 1H), 3.94–3.88 (m, 2H), 3.65 (s, 3H), 3.57–3.53 (m, 1H), 3.40–3.36 (m, 1H), 3.18–3.06 (m, 3H), 1.45 (d, 1H, J = 8.2 Hz), 1.36 (d, 1H, J = 8.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 176.2, 173.8, 155.0, 137.6, 133.3, 132.5, 131.6, 129.8, 122.3, 117.7, 70.5, 65.0, 57.7, 53.2, 49.2, 47.2, 47.2, 47.0, 46.9, 40.3; MS (+ESI) = Calcd. for $C_{20}H_{21}NO_5$ (M + H)$^+$: 356.3126, Found (M + H)$^+$: 356.3125.

(+)-(2′*S*,3′*R*,3a*R*,9b*S*)-Methyl-3′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1-carbonyl)bicyclo[2.2.1]hept-5′-ene-2′-carboxylate (9g). Isolated as a white solid, 178 mg total yield (93%, >95% de). mp = 151–154 °C; $[\alpha]_D^{25}$ = + 183 (c = 1.00, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2975 (CH), 1710 (CO-ester), 1659 (CO-amide), 1584 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.72 (d, 1H, J = 6.9 Hz), 7.17 (t, 1H, J = 8.2 Hz), 6.98 (t, 1H, J = 6.9 Hz), 6.87 (d, 1H, J = 8.2 Hz), 6.23 (s, 2H), 5.45 (d, 1H, J = 7.9 Hz), 4.33 (dd, 1H, J = 11.2 and 4.7 Hz), 4.18–4.14 (m, 1H), 3.99–3.88 (m, 2H), 3.68 (s, 3H), 3.15–3.07 (m, 4H), 2.71–2.68 (m, 1H), 2.19–2.16 (m, 1H), 1.54–1.51 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 177.1, 174.5, 155.1, 139.0, 138.1, 132.3, 129.4, 122.5, 122.0, 117.2, 70.9, 65.2, 53.1, 52.2, 48.3, 46.8, 46.1, 46.0, 44.1, 40.5; MS (+ESI) = Calcd. for $C_{20}H_{21}NO_5$ (M + H)$^+$: 356.3213, Found (M + H)$^+$: 356.3210.

(+)-(2′*S*,3′*R*,3a*R*,9b*S*)-Methyl-3′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1-carbonyl)oxirane-2′-carboxylate (9h). Isolated as a clear oil, 150 mg total yield (98%, >95% de). $[\alpha]_D^{25}$ = + 246 (c = 1.10, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2955 (CH), 1719 (CO-ester), 1677 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, J = 7.6 Hz), 7.22 (t, 1H, J = 8.3 Hz), 6.96 (t, 1H, J = 7.6 Hz), 6.82 (d, 1H, J = 8.3 Hz), 5.44 (d, 1H, J = 8.0 Hz), 4.31–4.28 (m, 1H), 4.09–4.05 (m, 2H), 3.95–3.90 (m, 1H), 3.83–3.76 (m, 4H), 3.73–3.70 (m, 1H), 3.23–3.17 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.3, 166.5, 155.3, 131.9, 129.7, 122.6, 120.8, 117.5, 72.2, 65.2, 53.3, 52.9, 52.5, 52.2, 40.4; MS (+ESI) = Calcd. for $C_{15}H_{15}NO_6$ (M + H)$^+$: 306.3550, Found (M + H)$^+$: 306.3554.

(+)-(2′*S*,3′*R*,3a*R*,9b*S*)-Methyl-3′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1-yl)-7′-oxabicyclo[2.2.1]heptane-2′-carboxylate (9i). Isolated as a clear oil, 180 mg total yield (98%, >95% de). $[\alpha]_D^{25}$ = + 217 (c = 1.10, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2951 (CH), 1708 (CO-ester), 1610 (CO-amide), 1584 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70 (d, 1H, J = 6.9 Hz), 7.15 (t, 1H, J = 7.5 Hz), 6.92 (t, 1H, J = 6.9 Hz), 6.85 (d, 1H, J = 7.5 Hz), 5.45 (d, 1H, J = 7.9 Hz), 4.98–4.93 (m, 1H), 4.88–4.84 (m, 1H), 4.22 (dd, 1H, J = 11.2 and 4.7 Hz), 4.18–4.13 (m, 1H), 3.96–3.92 (m, 2H), 3.68 (s, 3H), 3.34–3.28 (m, 1H), 3.15–3.09 (m, 1H), 3.04–3.00 (m, 1H), 1.84–1.75 (m, 2H), 1.55–1.49 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.6, 172.1, 155.1, 132.4, 129.4, 122.4, 121.8, 117.1, 79.1, 78.2, 70.9, 65.1, 53.1, 52.7, 52.0, 49.0, 40.0, 29.3, 28.9; MS (+ESI) = Calcd. for $C_{19}H_{21}NO_6$ (M + H)$^+$: 360.6581, Found (M + H)$^+$: 360.6587.

General protocol for desymmetrisation of glutaric anhydrides

To a stirred solution of cyclic *meso*-anhydride (0.55 mmol) in dichloromethane (1.5 mL) at −78 °C was added a solution of (+)- or (−)-**7** (89 mg, 0.5 mmol) in dichloromethane (0.5 mL) dropwise *via* syringe. The reaction mixture was stirred at −78 °C for 72 h, at which point the solvent was removed *in vacuo*. The resulting crude product was dissolved in *N*,*N*-dimethylformamide (2 mL) and the flask covered with aluminium foil. Methyl iodide (62 μL, 1.0 mmol) and freshly prepared silver oxide†† (232 mg, 1.0 mmol) were added and the resulting mixture was stirred at room temperature for 30 min. The suspension was then filtered through celite and washed four times with diethyl ether. The resulting filtrate was washed with lithium bromide (5 mL, 4% aqueous) and brine (5 mL),

†† **Preparation of silver oxide** Ag_2OA solution of sodium hydroxide (345 mg, 8.6 mmol) in water (10 mL) was heated to 85 °C and added to a stirred solution of silver nitrate (1.5 g, 8.8 mmol) in water (10 mL) at 85 °C. The resulting brown precipitate was filtered and washed with water (10 mL) at 85 °C, then with ethanol (2 × 10 mL) at rt. The solid thus generated was dried *in vacuo* and kept in the freezer, protected from light with aluminium foil.

dried ($MgSO_4$) and concentrated *in vacuo*. Crude product was then purified by flash column chromatography (petroleum ether:diethyl ether, 1:1). All diastereomeric excesses were evaluated by ^{1}H-NMR spectroscopy of crude reaction mixtures prior to purification; all yields are isolated yields.

All desymmetrisations were performed using (+)-**7** and (−)-**7**.

(+)-(2′*S*,3a*R*,4′*R*,9b*S*)-Methyl-2′,4′-dimethyl-5′-oxo-5′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)pentanoate (MAJOR 11a) and (+)-(2′*R*,3a*R*,4′*S*,9b*S*)-methyl-2′,4′-dimethyl-5′-oxo-5′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]yisoxazol-1-yl)pentanoate (MINOR 11a). Isolated as major (141 mg, 85%) and minor (11 mg, 6%) diastereoisomers, both as white powders, 152 mg total yield (91%, 86% de). **MAJOR 11a:** mp = 110–113 °C; $[\alpha]_D^{25}$ = + 192 (*c* = 1.10, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2965 (CH), 1706 (CO-ester), 1663 (CO-amide), 1504 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 8.2 Hz), 6.98 (t, 1H, *J* = 7.4 Hz), 6.88 (d, 1H, *J* = 8.2 Hz), 5.45 (d, 1H, *J* = 8.1 Hz), 4.29 (dd, 1H, *J* = 11.3 and 4.6 Hz), 4.12–4.03 (m, 2H), 3.88 (dd, 1H, *J* = 11.3 and 8.6 Hz), 3.65 (s, 3H), 3.20–3.12 (m, 1H), 3.10–3.02 (m, 1H), 2.59–2.52 (m, 1H), 2.18–2.09 (m, 1H), 1.62–1.51 (m, 1H), 1.18 (d, 3H, *J* = 6.7 Hz), 1.14 (d, 3H, *J* = 6.7 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.9, 173.6, 155.4, 131.8, 129.5, 122.6, 122.1, 117.5, 72.1, 65.9, 52.4, 52.0, 40.6, 35.8, 34.4, 30.5, 17.8, 16.2; MS (+ESI) = Calcd. for $C_{18}H_{23}NO_5$ (M + Na)$^+$: 356.1240, Found (M + Na)$^+$: 356.1242. **Ent MAJOR 11a**: $[\alpha]_D^{25}$ = − 187 (*c* = 1.02, $CHCl_3$). **MINOR 11a:** mp = 114–118 °C; $[\alpha]_D^{25}$ = + 206 (*c* = 0.97, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2965 (CH), 1706 (CO-ester), 1663 (CO-amide), 1504 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 8.2 Hz), 6.98 (t, 1H, *J* = 7.4 Hz), 6.88 (d, 1H, *J* = 8.2 Hz), 5.42 (d, 1H, *J* = 8.1 Hz), 4.29 (dd, 1H, *J* = 11.3 and 4.6 Hz), 4.12–4.03 (m, 2H), 3.88 (dd, 1H, *J* = 11.3 and 8.6 Hz), 3.63 (s, 3H), 3.20–3.12 (m, 1H), 3.10–3.02 (m, 1H), 2.59–2.52 (m, 1H), 2.18–2.09 (m, 1H), 1.62–1.51 (m, 1H), 1.18 (d, 3H, *J* = 6.7 Hz), 1.14 (d, 3H, *J* = 6.7 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.1, 173.4, 155.4, 131.9, 129.3, 122.6, 122.0, 117.3, 71.9, 65.6, 52.6, 52.2, 40.5, 35.8, 34.4, 30.4, 17.7, 16.1; MS (+ESI) = Calcd. for $C_{18}H_{23}NO_5$ (M + Na)$^+$: 356.1240, Found (M + Na)$^+$: 356.1238. **Ent MINOR 11a**: $[\alpha]_D^{25}$ = − 208 (*c* = 1.00, $CHCl_3$).

(+)-(1′*R*,3′*S*,3a*R*,9b*S*)-Methyl-3′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1-yl)cyclopentanecarboxylate (MAJOR 11b) and (+)-(1′*S*,3′*R*,3a*R*,9b*S*)-methyl-3′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1-yl)cyclopentanecarboxylate (MINOR 11b). Isolated as major (122 mg, 74%) and minor (22 mg, 13%) diastereoisomers, both as white powders, 144 mg total yield (87%, 70% de). **MAJOR 11b:** mp = 125–129 °C; $[\alpha]_D^{25}$ = + 147 (*c* = 1.02, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2965 (CH), 1715 (CO-ester), 1665 (CO-amide), 1510 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 8.2 Hz), 6.98 (t, 1H, *J* = 7.4 Hz), 6.88 (d, 1H, *J* = 8.2 Hz), 5.47 (d, 1H, *J* = 8.1 Hz), 4.29 (dd, 1H, *J* = 11.2 and 4.6 Hz), 4.13–4.08 (m, 2H), 3.88 (dd, 1H, *J* = 11.2 and 8.6 Hz), 3.69 (s, 3H), 3.23–3.18 (m, 2H), 2.88–2.84 (m, 1H), 2.25–2.18 (m, 2H), 2.10–1.97 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.4, 173.2, 155.2, 131.4, 129.0, 122.3, 121.9, 117.5, 72.1, 65.4, 52.1, 51.9, 44.2, 40.6, 39.8, 35.4, 29.5, 28.5; MS (+ESI) = Calcd. for $C_{18}H_{21}NO_5$ (M + Na)$^+$: 354.2349, Found (M + Na)$^+$: 354.2347. **Ent MAJOR 11b**: $[\alpha]_D^{25}$ = − 140 (*c* = 0.98, $CHCl_3$). **MINOR 11b:** mp = 118–122 °C; $[\alpha]_D^{25}$ =+ 146 (*c* = 0.87, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2965 (CH), 1715 (CO-ester), 1665 (CO-amide), 1511 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 8.2 Hz), 6.98 (t, 1H, *J* = 7.4 Hz), 6.88 (d, 1H, *J* = 8.2 Hz), 5.45 (d, 1H, *J* = 8.1 Hz), 4.29 (dd, 1H, *J* = 11.3 and 4.6 Hz), 4.13–4.08 (m, 2H), 3.88 (dd, 1H, *J* = 11.2 and 8.6 Hz), 3.66 (s, 3H), 3.23–3.18 (m, 2H), 2.88–2.84 (m, 1H), 2.25–2.18 (m, 2H), 2.10–1.97 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.3, 173.1, 155.1, 131.3, 129.0, 122.2, 121.9, 117.5, 72.2, 65.3, 52.1, 51.8, 44.1, 40.6, 39.7, 35.3, 29.6, 28.4; MS (+ESI) = Calcd. for $C_{18}H_{21}NO_5$ (M + Na)$^+$: 354.2349, Found (M + Na)$^+$: 354.2351. **Ent MINOR 11b**: $[\alpha]_D^{25}$ = − 138 (*c* = 0.80, $CHCl_3$).

(+)-(1′*R*,3′*S*,3a*R*,9b*S*)-Methyl-3′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1-yl)cyclohexanecarboxylate (MAJOR 11c) and (+)-(1′*S*,3′*R*,3a*R*,9b*S*)-methyl-3′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1-yl)cyclohexanecarboxylate (MINOR 11c). Isolated as major (129 mg, 75%) and minor (18 mg, 10%) diastereoisomers, both as white powders, 147 mg total yield (85%, 75% de). **MAJOR 11c:** mp = 122–126 °C; $[\alpha]_D^{25}$ = + 129 (*c* = 1.00, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2965 (CH), 1702 (CO-ester), 1663 (CO-amide), 1510 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 8.2 Hz), 6.98 (t, 1H, *J* = 7.4 Hz), 6.88 (d, 1H, *J* = 8.2 Hz), 5.47 (d, 1H, *J* = 8.1 Hz), 4.29 (dd, 1H, *J* = 11.2 and 4.6 Hz), 4.09–4.00 (m, 2H), 3.88 (dd, 1H, *J* = 11.2 and 8.6 Hz), 3.65 (s, 3H), 3.21–3.15 (m, 1H), 2.92–2.82 (m, 1H), 2.48–2.35 (m, 1H), 2.04–1.99 (m, 2H), 1.92–1.88 (m, 2H), 1.78–1.71 (m, 1H), 1.51–1.41 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.6, 173.4, 155.3, 131.5, 129.2, 122.3, 121.7, 116.9, 71.2, 65.3, 52.2, 52.0, 42.2, 40.2, 35.2, 31.4, 29.5, 28.5, 13.6; MS (+ESI) = Calcd. for $C_{19}H_{23}NO_5$ (M + Na)$^+$: 368.4539, Found (M + Na)$^+$: 368.4542. **Ent MAJOR 11c**: $[\alpha]_D^{25}$ = − 120 (*c* = 0.76, $CHCl_3$). **MINOR 11c:** mp = 110–114 °C; $[\alpha]_D^{25}$ = + 144 (*c* = 0.85, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2965 (CH), 1702 (CO-ester), 1658 (CO-amide), 1510 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 8.2 Hz), 6.98 (t, 1H, *J* = 7.4 Hz), 6.88 (d, 1H, *J* = 8.2 Hz), 5.45 (d, 1H, *J* = 8.1 Hz), 4.29 (dd, 1H, *J* = 11.2 and 4.6 Hz), 4.09–4.00 (m, 2H), 3.88 (dd, 1H, *J* = 11.2 and 8.6 Hz), 3.62 (s, 3H), 3.21–3.15 (m, 1H), 2.92–2.82 (m, 1H), 2.48–2.35 (m, 1H), 2.04–1.99 (m, 2H), 1.92–1.88 (m, 2H), 1.78–1.71 (m, 1H), 1.51–1.41 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.5, 173.3, 155.2, 131.4, 129.2, 122.2, 121.7, 116.9, 71.1, 65.2, 52.0, 51.8, 42.1, 40.2, 35.1, 31.3, 29.4, 28.4, 13.5; MS (+ESI) = Calcd. for $C_{19}H_{23}NO_5$ (M + Na)$^+$: 368.4539, Found (M + Na)$^+$: 368.4538. **Ent MINOR 11c**: $[\alpha]_D^{25}$ = − 127 (*c* = 0.70, $CHCl_3$).

(+)-(3′*S*,3a*R*,9b*S*)-3′-Hydroxy-3′-methyl-5′-oxo-5′y-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)pentanoate (MAJOR 11d) and (+)-(3′*R*,3a*R*,9b*S*)-3′-hydroxy-3′-methyl-5′-oxo-5′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*cy*]isoxazol-1-yl)pentanoate (MINOR 11d). Isolated as major (107 mg, 64%) and minor (20 mg, 11%) diastereoisomers, both as white powders, 126 mg total yield (75%, 70% de). **MAJOR 11d:** mp = 89–92 °C; $[\alpha]_D^{25}$ = + 195 (*c* = 1.05, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 3311 (OH), 2965 (CH), 1709 (CO-ester), 1665 (CO-amide), 1519 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 8.2 Hz), 6.98 (t, 1H, *J* = 7.4 Hz), 6.88 (d, 1H, *J* = 8.2 Hz), 5.48 (d, 1H, *J* = 8.1 Hz), 4.29 (dd, 1H, *J* = 11.2 and 4.6 Hz), 4.25 (m, 2H), 3.88 (dd, 1H, *J* = 11.2 and 8.6 Hz),

3.68 (s, 3H), 3.22–3.16 (m, 1H), 2.65–2.25 (m, 4H), 1.28 (s, 3H, C*H*$_3$); ^{13}C-NMR ($CDCl_3$): δ 175.2, 173.4, 155.4, 131.8, 129.5, 122.6, 122.0, 117.3, 71.9, 70.1, 65.6, 52.6, 52.2, 41.2, 40.7, 39.7, 25.5; MS (+ESI) = Calcd. for $C_{17}H_{21}NO_6$ (M + Na)$^+$: 358.3531, Found (M + Na)$^+$: 358.3528. **Ent MAJOR 11d**: $[\alpha]_D^{25}$ = − 185 (*c* = 1.00, $CHCl_3$). **MINOR 11d:** mp = 97–101 °C; $[\alpha]_D^{25}$ = + 213 (*c* = 0.98, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 3311 (OH), 2965 (CH), 1709 (CO-ester), 1665 (CO-amide), 1519 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 8.2 Hz), 6.98 (t, 1H, *J* = 7.4 Hz), 6.88 (d, 1H, *J* = 8.2 Hz), 5.48 (d, 1H, *J* = 8.1 Hz), 4.29 (dd, 1H, *J* = 11.2 and 4.6 Hz), 4.25 (m, 2H), 3.88 (dd, 1H, *J* = 11.2 and 8.6 Hz), 3.66 (s, 3H), 3.22–3.16 (m, 1H), 2.65–2.25 (m, 4H), 1.26 (s, 3H, C*H*$_3$); ^{13}C-NMR ($CDCl_3$): δ 175.1, 173.3, 155.3, 131.7, 129.6, 122.5, 122.0, 117.3, 71.8, 70.0, 65.5, 52.5, 52.2, 41.2, 40.7, 39.8, 25.5; MS (+ESI) = Calcd. for $C_{17}H_{21}NO_6$ (M + Na)$^+$: 358.3531, Found (M + Na)$^+$: 358.3530. **Ent MINOR 11d**: $[\alpha]_D^{25}$ = − 207 (*c* = 0.93, $CHCl_3$).

(+)-(3′*S*,3a*R*,9b*S*)-Methyl-3′-(*tert*-butyldimethylsilyloxy)-5′-oxo-5′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)pentanoate (MAJOR 11e) and (+)-(3′*R*,3a*R*,9b*S*)-methyl-3′-(*tert*-butyldimethylsilyloxy)-5′-oxo-5′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)pentanoate (MINOR 11e). Isolated as major (185 mg, 89%) and minor (33 mg, 10%) diastereoisomers, both as yellow oils, 218 mg total yield (99%, 80% de). **MAJOR 11e:** $[\alpha]_D^{25}$ = + 178 (*c* = 1.00, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2929 (CH), 2857 (CH), 1711 (CO-ester), 1664 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.7 Hz), 7.19 (t, 1H, *J* = 8.0 Hz), 6.98 (t, 1H, *J* = 7.7 Hz), 6.87 (d, 1H, *J* = 8.0 Hz), 5.49–5.45 (m, 1H), 4.62–4.58 (m, 1H), 4.26 (dd, 1H, *J* = 11.5 and 4.1 Hz), 4.12–4.08 (m, 2H), 3.99–2.94 (m, 1H), 3.66 (s, 3H), 3.19–3.15 (m, 1H), 2.95–2.91 (m, 2H), 2.64–2.60 (m, 2H), 0.85 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.2, 172.8, 155.0, 131.5, 129.1, 122.2, 121.2, 116.9, 71.5, 65.9, 65.4, 52.4, 52.2, 42.2, 40.2, 39.8, 25.6, 18.4, –4.7, –4.8; MS (+ESI) = Calcd. for $C_{22}H_{33}NO_6Si$ (M + Na)$^+$: 458.5935, Found (M + Na)$^+$: 458.5933. **Ent MAJOR 11e**: $[\alpha]_D^{25}$ = − 169 (*c* = 0.90, $CHCl_3$). **MINOR 11e:** $[\alpha]_D^{25}$ = + 190 (*c* = 1.08, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2929 (CH), 2857 (CH), 1711 (CO-ester), 1664 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.7 Hz), 7.19 (t, 1H, *J* = 8.0 Hz), 6.98 (t, 1H, *J* = 7.7 Hz), 6.87 (d, 1H, *J* = 8.0 Hz), 5.49–5.45 (m, 1H), 4.62–4.58 (m, 1H), 4.26 (dd, 1H, *J* = 11.5 and 4.1 Hz), 4.12–4.08 (m, 2H), 3.99–2.94 (m, 1H), 3.64 (s, 3H), 3.19–3.15 (m, 1H), 2.95–2.91 (m, 2H), 2.64–2.60 (m, 2H), 0.83 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.1, 172.7, 155.1, 131.4, 129.1, 122.1, 121.2, 116.9, 71.4, 65.8, 65.3, 52.3, 52.1, 42.1, 40.2, 39.7, 25.5, 18.3, –4.6, –4.8; MS (+ESI) = Calcd. for $C_{22}H_{33}NO_6Si$ (M + Na)$^+$: 458.5935, Found (M + Na)$^+$: 458.5934. **Ent MINOR 11e**: $[\alpha]_D^{25}$ = − 195 (*c* = 1.20, $CHCl_3$).

(+)-(3′*S*,3a*R*,9b*S*)-3′-Methyl-5′-oxo-5′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)pentanoate (MAJOR 11f) and (+)-(3′*R*,3a*R*,9b*S*)-3′-methyl-5′-oxo-5′y-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)pentanoate (MINOR 11f). Isolated as major (80 mg, 50%) and minor (80 mg, 50%) diastereoisomers, both as clear oils, 160 mg total yield (100%, 0% de). **MAJOR 11f:** $[\alpha]_D^{25}$ = + 221 (*c* = 1.01, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2965 (CH), 1706 (CO-ester), 1663 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 8.2 Hz), 6.98 (t, 1H, *J* = 7.4 Hz), 6.88 (d, 1H, *J* = 8.2 Hz), 5.45 (d, 1H, *J* = 8.1 Hz), 4.29 (dd, 1H, *J* = 11.2 and 4.6 Hz), 4.05–3.97 (m, 2H), 3.88 (dd, 1H, *J* = 11.2 and 8.6 Hz), 3.65 (s, 3H), 3.19–3.14 (m, 1H), 2.65–2.25 (m, 5H), 1.08 (d, 3H, *J* = 5.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.3, 173.4, 155.4, 131.8, 129.4, 122.6, 122.0, 117.3, 71.9, 65.6, 52.6, 52.2, 41.2, 40.7, 39.7, 27.4, 20.5; MS (+ESI) Calcd. for $C_{17}H_{21}NO_5$ (M + H)$^+$: 320.2939, Found (M + H)$^+$: 320.2941. **Ent MAJOR 11f**: $[\alpha]_D^{25}$ = − 222 (*c* = 1.10, $CHCl_3$). **MINOR 11f:** $[\alpha]_D^{25}$ = + 193 (*c* = 1.00, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2965 (CH), 1706 (CO-ester), 1663 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 8.2 Hz), 6.98 (t, 1H, *J* = 7.4 Hz), 6.88 (d, 1H, *J* = 8.2 Hz), 5.43 (d, 1H, *J* = 8.1 Hz), 4.29 (dd, 1H, *J* = 11.2 and 4.6 Hz), 4.05–3.97 (m, 2H), 3.88 (dd, 1H, *J* = 11.2 and 8.6 Hz), 3.63 (s, 3H), 3.19–3.14 (m, 1H), 2.65–2.25 (m, 5H), 1.08 (d, 3H, *J* = 5.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.2, 173.3, 155.3, 131.7, 129.4, 122.5, 122.0, 117.3, 71.8, 65.5, 52.5, 52.1, 41.1, 40.7, 39.7, 27.3, 20.4; MS (+ESI) = Calcd. for $C_{17}H_{21}NO_5$ (M + H)$^+$: 320.2939, Found (M + H)$^+$: 319.3144. **Ent MINOR 11f**: $[\alpha]_D^{25}$ =− 188 (*c* = 1.10, $CHCl_3$).

(+)-(3′*S*,3a*R*,9b*S*)-3′-Ethyl-3′-methyl-5′-oxo-5′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)pentanoate (MAJOR 11g) and (+)-(3′*R*,3a*R*,9b*S*)-3′-ethyl-3′-methyl-5′-oxo-5′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)pentanoate (MINOR 11g). Isolated as major (87 mg, 50%) and minor (87 mg, 50%) diastereoisomers, both as yellow oils, 174 mg total yield (100%, 0% de). **MAJOR 11g:** $[\alpha]_D^{25}$ = + 189 (*c* = 1.00, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2936 (CH), 1715 (CO-ester), 1643 (CO-amide), 1584 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.5 Hz), 7.25 (t, 1H, *J* = 8.0 Hz), 6.98 (t, 1H, *J* = 7.5 Hz), 6.87 (d, 1H, *J* = 8.0 Hz), 5.48–5.44 (m, 1H), 4.31 (dd, 1H, *J* = 11.5 and 4.1 Hz), 4.13–4.04 (m, 2H), 3.97–3.88 (m, 1H), 3.70 (s, 3H), 3.22–3.16 (m, 1H), 2.82–2.78 (m, 1H), 2.54–2.34 (m, 3H), 1.47 (q, 2H, *J* = 7.5 Hz), 1.06 (s, 3H), 0.91 (t, 3H, *J* = 7.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.1, 173.6, 155.4, 131.8, 129.5, 122.6, 122.0, 117.3, 71.9, 65.6, 52.7, 52.2, 41.7, 40.3, 39.7, 27.4, 33.1, 23.6, 6.6; MS (+ESI) = Calcd. for $C_{18}H_{23}NO_5$ (M + Na)$^+$: 356.1496, Found (M + Na)$^+$: 356.1491; **Ent MAJOR 11g**: $[\alpha]_D^{25}$ = − 191 (*c* = 1.01, $CHCl_3$). **MINOR 11g:** $[\alpha]_D^{25}$ = + 211 (*c* = 1.05, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2936 (CH), 1715 (CO-ester), 1643 (CO-amide), 1583 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, *J* = 7.5 Hz), 7.25 (t, 1H, *J* = 8.0 Hz), 6.98 (t, 1H, *J* = 7.5 Hz), 6.87 (d, 1H, *J* = 8.0 Hz), 5.45–5.42 (m, 1H), 4.31 (dd, 1H, *J* = 11.5 and 4.1 Hz), 4.13–4.04 (m, 2H), 3.97–3.88 (m, 1H), 3.68 (s, 3H), 3.22–3.16 (m, 1H), 2.82–2.78 (m, 1H), 2.54–2.34 (m, 3H), 1.47 (q, 2H, *J* = 7.5 Hz), 1.06 (s, 3H), 0.91 (t, 3H, *J* = 7.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.0, 173.5, 155.3, 131.7, 129.5, 122.5, 121.9, 117.3, 71.8, 65.5, 52.6, 52.1, 41.6, 40.3, 39.6, 27.3, 33.1, 23.6, 6.6; MS (+ESI) = Calcd. for $C_{19}H_{25}NO_5$ (M + H)$^+$: 348.3285, Found (M + H)$^+$: 348.3283. **Ent MINOR 11g**: $[\alpha]_D^{25}$ = − 224 (*c* = 1.10, $CHCl_3$).

(+)-(3′*S*,3a*R*,9b*S*)-Methyl-3′-(4″-chlorophenyl)-5′-oxo-5′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)pentanoate (MAJOR 11h) and (+)-(3′*R*,3a*S*,9b*R*)-methyl-3′-(4″-chlorophenyl)-5′-oxo-5′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)pentanoate (MINOR 11h). Isolated as major (103 mg, 50%) and minor (103 mg, 50%) diastereoisomers, both as a yellow oil, 206 mg total yield (100%, 0% de). **MAJOR 11h:** $[\alpha]_D^{25}$ = + 156 (*c* = 1.10, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2965 (CH), 1706 (CO-ester), 1663 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H,

J = 7.4 Hz), 7.26–7.22 (m, 2H), 7.20–7.14 (m, 3H), 6.98 (t, 1H, J = 7.4 Hz), 6.88 (d, 1H, J = 8.2 Hz), 5.48 (d, 1H, J = 8.1 Hz), 4.29 (dd, 1H, J = 11.3 and 4.6 Hz), 4.03–3.90 (m, 2H), 3.88 (dd, 1H, J = 11.2 and 8.6 Hz), 3.80–3.72 (m, 1H), 3.68 (s, 3H), 3.20–3.15 (m, 1H), 2.90–2.70 (m, 3H), 2.65–2.62 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.6, 173.2, 155.4, 141.0, 131.8, 130.5, 129.5, 128.5, 127.5, 122.6, 122.0, 117.3, 71.9, 65.6, 52.6, 52.2, 41.2, 39.7, 38.0, 29.8; MS (+ESI) = Calcd. for $C_{22}H_{22}ClNO_5$ (M + Na)$^+$: 438.1595, Found (M + Na)$^+$: 438.1598. **Ent MAJOR 11h**: $[\alpha]_D^{25} = -149$ (c = 1.00, $CHCl_3$). **MINOR 11h:** $[\alpha]_D^{25} = +177$ (c = 1.04, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2965 (CH), 1707 (CO-ester), 1663 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, J = 7.4 Hz), 7.26–7.22 (m, 2H), 7.20–7.14 (m, 3H), 6.98 (t, 1H, J = 7.4 Hz), 6.88 (d, 1H, J = 8.2 Hz), 5.44 (d, 1H, J = 8.1 Hz), 4.29 (dd, 1H, J = 11.3 and 4.6 Hz), 4.03–3.90 (m, 2H), 3.88 (dd, 1H, J = 11.2 and 8.6 Hz), 3.80–3.72 (m, 1H), 3.67 (s, 3H), 3.20–3.15 (m, 1H), 2.90–2.70 (m, 3H), 2.65–2.62 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.5, 173.1, 155.1, 141.0, 131.7, 130.3, 129.5, 128.4, 127.4, 122.5, 122.0, 117.3, 71.8, 65.5, 52.5, 52.1, 41.1, 39.7, 38.0, 29.7; MS (+ESI) = Calcd. for $C_{22}H_{22}ClNO_5$ (M + Na)$^+$: 438.1595, Found (M + Na)$^+$: 438.1598. **Ent MINOR 11h**: $[\alpha]_D^{25} = -174$ (c = 1.00, $CHCl_3$).

(+)-(3′*S*,3a*R*,9b*S*)-3′-(1″,3″,5″-Triazin-2″-yl)-methyl-5′y-oxo-5′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)pentanoate (MAJOR 11i) and (+)-(3′*S*,3a*R*,9b*S*)-3′-(1″,3″,5″-triazin-2″-yl)-methyl-5′-oxo-5′-(3,3a,4,9b-tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)pentanoate (MINOR 11i). Isolated as major (96 mg, 48%) and minor (95 mg, 47%) diastereoisomers, both as clear oils, 191 mg total yield (95%, 0% de). **MAJOR 11i:** $[\alpha]_D^{25}$ = + 182 (c = 1.14, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2965 (CH), 1712 (CO-ester), 1670 (CO-amide), 1517 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 2H), 7.65 (d, 1H, J = 7.4 Hz), 7.19 (t, 1H, J = 8.2 Hz), 6.98 (t, 1H, J = 7.4 Hz), 6.88 (d, 1H, J = 8.2 Hz), 5.48 (d, 1H, J = 8.1 Hz), 4.29 (dd, 1H, J = 11.2 and 4.6 Hz), 4.28–4.22 (m, 2H), 3.88 (dd, 1H, J = 11.2 and 8.6 Hz), 3.69 (s, 3H), 3.35–3.31 (m, 1H), 3.19–3.14 (m, 1H), 2.65–2.25 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 181.0, 175.4, 173.2, 165.9, 155.4, 131.8, 129.5, 122.6, 122.0, 117.3, 71.9, 65.6, 52.6, 52.2, 41.3, 39.8, 30.1, 29.8; MS (+ESI) = Calcd. for $C_{19}H_{20}N_4O_5$ (M + Na)$^+$: 407.1225, Found (M + Na)$^+$: 407.1226. **Ent MAJOR 11i**: $[\alpha]_D^{25} = -169$ (c = 0.99, $CHCl_3$). **MINOR 11i:** $[\alpha]_D^{25} = +164$ (c = 1.07, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2965 (CH), 1712 (CO-ester), 1670 (CO-amide), 1518 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 2H), 7.65 (d, 1H, J = 7.4 Hz), 7.19 (t, 1H, J = 8.2 Hz), 6.98 (t, 1H, J = 7.4 Hz), 6.88 (d, 1H, J = 8.2 Hz), 5.46 (d, 1H, J = 8.1 Hz), 4.29 (dd, 1H, J = 11.2 and 4.6 Hz), 4.28–4.22 (m, 2H), 3.88 (dd, 1H, J = 11.2 and 8.6 Hz), 3.67 (s, 3H), 3.35–3.31 (m, 1H), 3.19–3.14 (m, 1H), 2.65–2.25 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 180.9, 175.3, 173.1, 165.8, 155.3, 131.7, 129.5, 122.5, 122.0, 117.3, 71.8, 65.5, 52.5, 52.1, 41.1, 39.7, 30.0, 29.7; MS (+ESI) = Calcd. for $C_{19}H_{20}N_4O_5$ (M + Na)$^+$: 407.1225, Found (M + Na)$^+$: 407.1228. **Ent MINOR 11i**: $[\alpha]_D^{25} = -166$ (c = 1.05, $CHCl_3$).

((1′*R*,2′*S*,3a*R*,9b*S*)-((3,3a,4,9b-Tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)-2′-(hydroxymethyl)cyclohexyl)methanone (12). A solution of ester **9a** (50 mg, 0.14 mmol) in tetrahydrofuran (1 mL) was added dropwise *via* cannula to a flask containing Schwartz reagent (75 mg, 0.29 mmol) at 0 °C. The resulting mixture was allowed to stir at 0 °C for 40 min, at which point the reaction was quenched with aqueous Rochelle's salt (5 mL). The organic layer was separated, washed with brine (2 × 5 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash column chromatography (dichloromethane:methanol, 99:1) to afford **12** as a clear oil (34 mg, 0.11 mmol, 77%). $[\alpha]_D^{25}$ = + 94 (c = 1.22, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 3361 (OH), 2925 (CH), 2864 (CH), 1663 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.63 (d, 1H, J = 6.9 Hz), 7.14 (t, 1H, J = 8.2 Hz), 6.98 (t, 1H, J = 6.9 Hz), 6.87 (d, 1H, J = 8.2 Hz), 5.40 (d, 1H, J = 7.9 Hz), 4.29 (dd, 1H, J = 11.2 and 4.7 Hz), 4.18–4.13 (m, 1H), 3.99–3.96 (m, 1H), 3.83–3.77 (m, 1H), 3.53–3.47 (m, 1H), 3.22–3.14 (m, 2H), 2.90 (br s, 1H), 2.13–2.07 (m, 1H), 2.03–1.97 (m, 1H), 1.86–1.77 (m, 3H), 1.70–1.30 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 179.4, 155.3, 131.9, 129.4, 122.5, 122.1, 117.3, 72.0, 65.6, 64.4, 52.1, 41.1, 40.5, 39.8, 26.5, 24.8, 23.3, 22.8; MS (+ESI) = Calcd. for $C_{18}H_{23}NO_4$ (M + H)$^+$: 318.1422, Found (M + H)$^+$: 318.1419.

((1′*R*,2′*S*,3a*R*,9b*S*)-((3,3a,4,9b-Tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1-yl)-2′-((*tert*-butyldimethylsilyloxy)methyl)cyclohexyl)methanone (13). To a solution of alcohol **12** (43.0 mg, 0.14 mmol) in dichloromethane (2 mL) was added 2,6-lutidine (24 μL, 0.21 mmol). This mixture was cooled to 0 °C in an ice bath and *tert*-butyldimethylsilyl trifluoromethansulfonate (41 μL, 0.18 mmol) was added dropwise *via* syringe. The resulting solution was allowed to stir at 0 °C for 1.5 h, at which point the reaction was quenched with aqueous ammonium chloride (2 mL). The organic layer was separated, washed with dichloromethane (2 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash column chromatography (petroleum ether:diethyl ether, 5:1) to afford **13** as a clear oil (46 mg, 0.11 mmol, 77%). $[\alpha]_D^{25}$ = + 68 (c = 1.00, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2930 (CH), 2857 (CH), 1664 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, J = 6.9 Hz), 7.15 (t, 1H, J = 8.2 Hz), 6.98 (t, 1H, J = 6.9 Hz), 6.81 (d, 1H, J = 8.2 Hz), 5.40 (d, 1H, J = 7.9 Hz), 4.31 (dd, 1H, J = 11.2 and 4.7 Hz), 4.06–4.00 (m, 1H), 3.96–3.91 (dd, 1H, J = 7.3 and 3.7 Hz), 3.83 (dd, 1H, J = 11.2 and 9.4 Hz), 3.76–3.72 (m, 1H), 3.58–3.54 (m, 1H), 3.26–3.21 (m, 1H), 3.12–3.07 (m, 1H), 2.02–1.86 (m, 3H), 1.66–1.59 (m, 2H), 1.53–1.38 (m, 4H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 176.8, 155.1, 131.7, 129.4, 123.0, 121.9, 117.1, 71.8, 65.4, 55.3, 52.2, 41.3, 40.2, 37.8, 27.3, 25.9, 25.4, 25.1, 22.6, 18.1, −5.7, −5.8; MS (+ESI) = Calcd. for $C_{24}H_{37}NO_4Si$ (M + H)$^+$: 432.2516, Found (M + H)$^+$: 432.2513.

((1′*R*,2′*S*,3a*R*,9b*S*)-((3,3a,4,9b-Tetrahydro-1*H*y-chromeno[4,3-*c*]isoxazole-1-yl)-2′-((*tert*-butyldiphenylsilyloxy)methyl)cyclohexyl)methanone (14). A solution of alcohol **12** (87 mg, 0.27 mmol) in dichloromethane (1 mL) was added dropwise *via* cannula. to a cooled (0 °C) solution of *tert*-butyldiphenylsilyl chloride (73 μL, 0.28 mmol) and imidazole (38 mg, 0.55 mmol) in dichloromethane (2 mL). Catalytic amounts of 4-dimethylaminopyridine and tetrabutylammonium iodide were added, and the resulting mixture was allowed to warm to room temperature over 10 h. The reaction was then diluted with dichloromethane (2 mL), filtered, washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash column chromatography (petroleum ether:diethyl ether, 9:1) to afford **14** as a clear oil (84 mg, 0.15 mmol, 56%). $[\alpha]_D^{25}$ = + 53 (c = 1.05, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2955 (CH), 2849 (CH), 1659 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.70–7.58 (m, 6H), 7.37–7.32 (m,

5H), 6.96 (t, 1H, J = 8.2 Hz), 6.94 (t, 1H, J = 6.9 Hz), 6.85 (d, 1H, J = 8.2 Hz), 5.35 (d, 1H, J = 7.9 Hz), 4.18 (dd, 1H, J = 11.2 and 4.7 Hz), 3.85–3.65 (m, 5H), 3.34–3.30 (m, 1H), 2.84–2.79 (m, 1H), 2.10–1.88 (m, 3H), 1.70–1.57 (m, 3H), 1.50–1.39 (m, 3H), 1.08 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 178.1, 155.3, 135.9, 135.2, 132.0, 129.5, 128.1, 128.0, 122.6, 122.4, 117.2, 71.8, 65.7, 65.6, 52.1, 40.9, 40.5, 27.4, 27.0, 25.7, 23.6, 25.1, 23.6, 19.8; MS (+ESI) = Calcd. for $C_{34}H_{41}NO_4Si$ (M + H)$^+$: 556.2180, Found (M + H)$^+$: 556.2177.

((1′*R*,2′*S*)-2′-((*tert*-Butyldimethylsilyloxy)methyl)cyclohexyl)-methanol (15). Ethanol (17.3 μL, 0.3 mmol) and lithium borohydride (2 M in THF, 150 μL, 0.3 mmol) were added dropwise *via* syringe to a cooled solution (0 °C) of mono-protected alcohol **13** (42.5 mg, 0.10 mmol) in diethyl ether (2 mL). The resulting mixture was allowed to warm to room temperature over 10 h, at which point the reaction was quenched with aqueous Rochelle's salt (2 mL). The organic layer was separated, washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash column chromatography (petroleum ether:diethyl ether, 9:1) and afforded **15** as a clear oil (26 mg, 0.10 mmol, 100%, >99% ee—evaluated by Mosher ester formation). $[\alpha]_D^{25}$ = − 25 (c = 1.02, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 3303 (OH), 2929 (CH), 2857 (CH); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.85–3.80 (m, 1H), 3.68–3.61 (m, 1H), 3.58–3.53 (m, 1H), 3.45–3.41 (m, 1H), 3.28–3.24 (m, 1H), 1.94–1.83 (m, 2H), 1.55–1.32 (m, 8H), 0.91 (s, 9H), 0.11 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 64.9, 64.1, 40.9, 39.9, 27.5, 27.0, 26.1, 25.3, 25.9, 18.1, −5.6; MS (+ESI) = Calcd. for $C_{14}H_{30}O_2Si$ (M + H)$^+$: 259.1340, Found (M + H)$^+$: 259.1342.

((1*R*,2*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)cyclohexyl)-methanol (16). Ethanol (16 μL, 0.27 mmol) and lithium borohydride (2 M in THF, 135 μL, 0.27 mmol) were added dropwise *via* syringe to a cooled solution (0 °C) of mono-protected alcohol **14** (49.0 mg, 0.09 mmol) in diethyl ether (2 mL). The resulting solution was allowed to warm slowly to room temperature over 10 h, at which point the reaction was quenched with aqueous Rochelle's salt (2 mL). The organic layer was separated, washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash column chromatography (petroleum ether:diethyl ether, 9:1) to afford **16** as a clear oil (34 mg, 0.09 mmol, 100%, >99% ee). $[\alpha]_D^{25}$ = −34 (c = 0.96, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 3300 (OH), 2941 (CH), 2857 (CH); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68–7.62 (m, 4H), 7.40–7.33 (m, 6H), 3.86–3.81 (m, 1H), 3.78–3.74 (m, 1H), 3.54–3.50 (m, 2H), 2.87–2.84 (m, 1H), 2.04–1.96 (m, 2H), 1.49–1.44 (m, 4H), 1.35–1.29 (m, 4H), 1.07 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 134.0, 130.0, 128.5, 122.4, 64.9, 64.1, 40.9, 39.9, 27.5, 27.0, 26.8, 25.1, 23.5, 19.2; MS (+ESI) = Calcd. for $C_{24}H_{34}O_2Si$ (M + H)$^+$: 383.2317, Found (M + H)$^+$: 383.2314. Chiralcel ODH: 1 mL/min, 30 min, hexanes:*iso*-propanol (90:10), retention time = 9.3 min.

(2′*R*,4′*S*,3a*R*,9b*S*)-1′-(3,3a,4,9b-Tetrahydro-1*H*-chromeno[4,3-*c*]isoxazol-1-yl)-2′,4′-dimethyl-5′-hydroxypentan-1′-one (18). A solution of ester **11a** (438 mg, 1.32 mmol) in tetrahydrofuran (13 mL) was added dropwise *via* cannula to a flask containing Schwartz reagent (680 mg, 2.63 mmol) at 0 °C. The resulting mixture was allowed to stir at 0 °C for 40 min, at which point the reaction was quenched with aqueous Rochelle's salt (20 mL). The organic layer was separated, washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash column chromatography (dichloromethane:methanol, 99:1), affording **18** as a clear oil (282 mg, 0.92 mmol, 70%). $[\alpha]_D^{25}$ = + 83 (c = 1.20, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 3345 (OH), 2963 (CH), 1663 (CO-amide), 1509 (aromatic); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, J = 7.4 Hz), 7.19 (t, 1H, J = 8.2 Hz), 6.98 (t, 1H, J = 7.4 Hz), 6.88 (d, 1H, J = 8.2 Hz), 5.48 (d, 1H, J = 8.1 Hz), 4.29 (dd, 1H, J = 11.3 and 4.6 Hz), 3.95–3.82 (m, 2H), 3.80 (dd, 1H, J = 11.2 and 8.6 Hz), 3.47–3.39 (m, 2H), 3.10–3.05 (m, 1H), 2.99–2.91 (m, 1H), 1.97 (br s, 1H), 1.88–1.79 (m, 1H), 1.51–1.45 (m, 1H), 1.22–1.18 (m, 1H), 1.11 (d, 3H, J = 6.7 Hz), 0.85 (d, 3H, J = 6.7 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.1, 155.4, 131.8, 129.4, 122.6, 121.9, 117.3, 72.1, 67.4, 65.6, 52.6, 41.2, 35.4, 33.6, 31.1, 17.8, 16.2; MS (+ESI) = Calcd. for $C_{17}H_{23}NO_4$ (M + Na)$^+$: 328.1292, Found (M + Na)$^+$: 328.1289.

(2′*R*,4′*S*,3a*R*,9b*S*)-1′-(3,3a,4,9b-Tetrahydro-1*H*-chromeno-[4,3*c*]isoxazol-1-yl)-2′,4′–dimethyl-5′y-(*tert*–butyldimethylsilyl-oxy)-pentan-1′-one (19). To a solution of alcohol **18** (0.60 mmol, 198 mg) in dichloromethane (9 mL) was added 2,6-lutidine (126 μL, 1.08 mmol). This mixture was cooled to 0 °C in an ice bath and *tert*-butyldimethylsilyl trifluoromethansulfonate (216 μL, 0.93 mmol) was added dropwise *via* syringe. The resulting solution was allowed to stir at 0 °C for 1.5 h, at which point the reaction was quenched with aqueous ammonium chloride (2 mL). The organic layer was separated, washed with dichloromethane (2 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash column chromatography (petroleum ether:diethyl ether, 3:1) to afford **19** as a clear oil (252 mg, 0.60 mmol, 100% yield). $[\alpha]_D^{25}$ = + 33 (c = 1.00, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2959 (CH), 1670 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.65 (d, 1H, J = 7.4 Hz), 7.19 (t, 1H, J = 8.2 Hz), 6.98 (t, 1H, J = 7.4 Hz), 6.88 (d, 1H, J = 8.2 Hz), 5.48 (d, 1H, J = 8.1 Hz), 4.29 (dd, 1H, J = 11.3 and 4.6 Hz), 4.03–3.97 (m, 2H), 3.88 (dd, 1H, J = 11.2 and 8.6 Hz), 3.54–5.48 (m, 1H), 3.39–3.33 (m, 1H), 3.16–3.11 (m, 2H), 1.83–1.79 (m, 1H), 1.61–1.57 (m, 1H), 1.23–1.16 (m, 4H), 0.98–0.85 (m, 12H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 179.8, 155.3, 131.9, 129.3, 122.5, 122.3, 117.2, 71.9, 68.6, 65.6, 52.3, 40.6, 37.0, 34.3, 34.2, 26.3, 19.2, 18.7, 17.6, −5.0; MS (+ESI) = Calcd. for $C_{23}H_{37}NO_4Si$ (M + Na)$^+$: 442.6312, Found (M + Na)$^+$: 442.6311.

(2*R*,4*S*,3a*R*,9b*S*)-1′-(3,3a,4,9b-Tetrahydro-1*H*-chromeno[4,3-*c*]isoxazole-1-yl)-2′,4′-dimethyl-5′-(4-methoxybenzyloxy)pentan-1-one (20). To a solution of alcohol **18** (106 mg, 0.35 mmol) in toluene (4 mL) at room temperature was added *p*-methoxybenzyl trichloroacetimidate (147 mg, 0.52 mmol) and lanthanum trifluoromethansulfonate (5 mol%, 10 mg, 0.017 mmol), and the resulting solution was allowed to stir at room temperature for 20 min. Aqueous ammonium chloride (10 mL) was then added, and the separated organic phase was washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was then purified by flash column chromatography (petroleum ether:diethyl ether, 1:1) providing **20** as a white powder (135 mg, 0.31 mmol, 91%). mp = 59–61 °C; $[\alpha]_D^{25}$ = + 55 (c = 0.97, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 2980 (CH), 1663 (CO-amide); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.69 (d, 1H, J = 7.4 Hz), 7.35–7.28 (m, 2H), 7.17 (t, 1H, J = 8.2 Hz), 6.98 (t, 1H, J = 7.4 Hz), 6.92–6.88 (m, 3H), 5.48 (d, 1H, J = 8.1 Hz), 4.43 (s, 2H), 4.26 (dd, 1H, J = 11.3 and 4.6 Hz),

3.99–3.83 (m, 3H), 3.80 (s, 3H), 3.36–3.31 (m, 1H), 3.23–3.19 (m, 1H), 3.10–2.99 (m, 2H), 1.92–1.88 (m, 1H), 1.78–1.74 (m, 1H), 1.22–1.18 (m, 4H), 0.96 (d, 3H, $J = 6.7$ Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 179.6, 159.5, 155.3, 131.9, 131.1, 129.5, 122.5, 122.2, 122.6, 117.3, 115.3, 77.5, 73.1, 71.9, 65.6, 55.7, 52.3, 40.5, 37.6, 34.4, 32.3, 19.4, 18.0; MS (+ESI) = Calcd. for $C_{25}H_{31}NO_5$ (M + Na)$^+$: 448.2350, Found (M + Na)$^+$: 448.2351.

(2*R*,4*S*)-2,4-Dimethyl-5-(*tert*-butyldimethylsilyloxy)-pentan-1-ol (21). Ethanol (3 μL, 0.4 mmol) and lithium borohydride (2 M in THF, 200 μL, 0.4 mmol) were added dropwise *via* syringe to a cooled solution (0 °C) of mono-protected alcohol **19** (56.6 mg, 0.13 mmol) in diethyl ether (3 mL). The resulting solution was allowed to warm slowly to room temperature over 10 h, at which point the reaction was quenched with aqueous Rochelle's salt (2 mL). The organic layer was separated, washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash column chromatography (petroleum ether:diethyl ether, 3:1) to afford **21** as a clear oil (32 mg, 0.13 mmol, 100%, >99% ee—evaluated by Mosher ester formation). $[\alpha]_D^{25} = -25$ ($c = 1.25$, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 3415 (OH), 2875 (CH); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.52–3.30 (m, 4H), 1.77–1.69 (m, 2H), 1.47–1.42 (m, 2H), 1.02–0.95 (m, 15H), 0.11–0.07 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 68.1, 65.2, 35.4, 33.6, 33.0, 26.1, 18.7, 18.5, 17.3, −5.4; MS (+ESI) = Calcd. for $C_{13}H_{30}O_2Si$ (M + Na)$^+$: 269.1319, Found (M + Na)$^+$: 269.1322.

(2*R*,4*S*y)-2,4-Dimethyl-5-(*p*-methoxybenzyloxy)-pentan-1-ol (22). Ethanol (18 μL, 0.30 mmol) and lithium borohydride (2 M in THF, 150 μL, 0.30 mmol) were added dropwise *via* syringe to a solution of mono-protected alcohol **20** (43.5 mg, 0.10 mmol) in diethyl ether (1 mL) at 0 °C. The resulting mixture was allowed to warm slowly to room temperature over 10 h, at which point the reaction was quenched with aqueous Rochelle's salt (3 mL). The organic layer was separated, washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash column chromatography (petroleum ether:diethyl ether, 3:1), affording **22** as a clear oil (25 mg, 0.10 mmol, 100%, >99% ee—evaluated by chiral HPLC). mp 64–67 °C; $[\alpha]_D^{25} = +10$ ($c = 0.85$, $CHCl_3$); IR ν_{max} (film)/cm^{-1} 3315 (OH), 2980 (CH); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26–7.23 (m, 2H), 6.92–6.89 (m, 2H), 4.41 (s, 2H), 3.80 (s, 3H), 3.51–3.41 (m, 2H), 3.27–3.22 (m, 2H), 1.88–1.80 (m, 1H), 1.74–1.69 (m, 1H), 1.50 (br s, 1H), 1.45–1.40 (m, 2H), 0.98–0.92 (m, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.5, 131.1, 129.5, 114.2, 76.0, 73.1, 68.4, 55.6, 38.1, 33.7, 31.4, 18.6, 18.0; MS (+ESI) = Calcd. for $C_{15}H_{24}O_3$ (M + Na)$^+$: 275.1673, Found (M + Na)$^+$: 275.1672.

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