Tetrahedron 67 (2011) 7989–7999

Contents lists available at ScienceDirect

Tetrahedron

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

The enantioselective synthesis of tetracyclic methyllycaconitine analogues

Kevin Sparrow, David Barker, Margaret A. Brimble *

Department of Chemistry, University of Auckland, 23 Symonds St, Auckland, New Zealand

ARTICLE INFO

Article history:
Received 22 May 2011
Received in revised form 20 July 2011
Accepted 8 August 2011
Available online 16 August 2011

Keywords:
Methyllycaconitine
Diels–Alder reaction
Enantioselective
Semi-synthesis
Cobalt(III) salen catalyst

ABSTRACT

A new enantioselective synthesis of ABEF ring analogues of methyllycaconitine has been developed using a chiral cobalt(III) salen-catalyzed Diels–Alder reaction to form the B ring. Subsequent elaboration to form the A, E and F rings was achieved by sequential Dieckmann, Mannich and Wacker-type cyclizations to afford tetracyclic analogues in 97.5% ee.

1. Introduction

Methyllycaconitine **1** (MLA), a hexacyclic alkaloid isolated from *Delphinium* species, is a subtype-selective antagonist of the α7 neuronal acetylcholine receptor (nAChR) binding with nanomolar affinity (Fig. 1).[1] The α7 nAChR has been identified as a potential therapeutic target for cognitive impairment observed in diseases, such as schizophrenia and Alzheimer's disease.[2,3] Previous synthetic efforts have focused on the semi-synthesis of MLA fragments including E, AE, BE, ABE, ABDE and ABDF ring systems.[4–9] In an effort to develop new scaffolds for appendage of the methylsuccinimidoanthranilate pharmacophore, we were interested in extending the availability of suitable tetracyclic ring systems. We therefore report a new approach to the ABEF scaffold of MLA **1** using a Diels–Alder, Mannich, Wacker oxidative-cyclization strategy.

It was envisaged that tetracyclic ABEF ring analogue **2** of methyllycaconitine **1** can be synthesized from β-hydroxyester **3** using a Wacker-type palladium(II)-catalyzed intramolecular cyclization[10] followed by reduction of the ester and the olefin (Scheme 1). β-Hydroxyester **3** can be formed by the stereoselective reduction of ketone **4** that is formed from β-ketoester **5** by sequential Boc-deprotection and Mannich cyclization. Finally, β-ketoester **5** can be synthesized by Diels–Alder reaction of diene **6** with dienophile **7**.

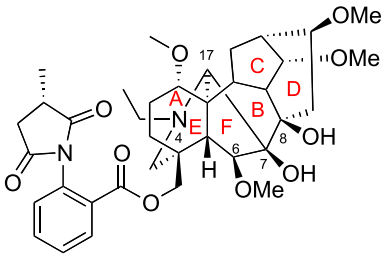
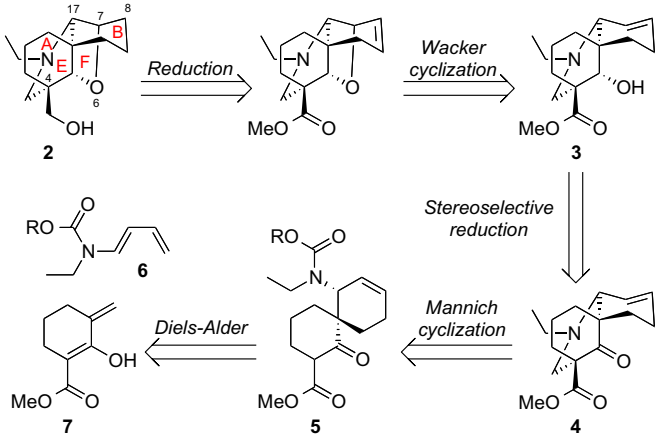


Fig. 1. Methyllycaconitine **1** (MLA).



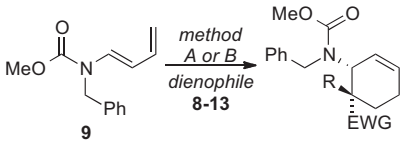
Scheme 1. Retrosynthesis of ABEF analogue.

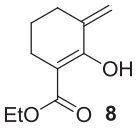
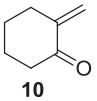
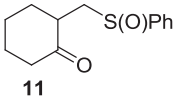
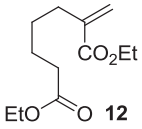
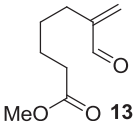
* Corresponding author. E-mail address: m.brimble@auckland.ac.nz (M.A. Brimble).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.08.026

Initial attempts focused on the Diels–Alder addition of dienophile **8**[11] to Moc-protected 1-aminodiene **9**.[12] Disappointingly, no Diels–Alder adducts were afforded under thermal or Lewis-acid promoted conditions (Table 1). It was suspected that the predominance of the enol form in dienophile **8** may have contributed to its lack of reactivity with diene **9**. Several cyclic (**10**, **11**) and acyclic dienophiles (**12**, **13**), in which the keto tautomer predominated, were next investigated.

Table 1
Reactivity of various dienophiles with 1-aminodiene **9**



Entry	Structure	Method A[a]	Method B[b]
1		n.r	n.r
2		Decomp.	Decomp.
3		Decomp.	Decomp.
4		n.r.	n.r.
5		56	66

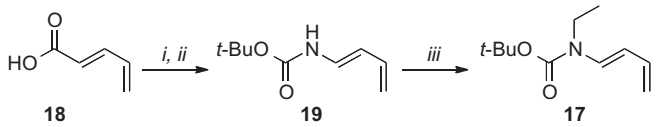
[a] Toluene, 150 °C, sealed tube, 2 h.
[b] $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 1 h.

Enone **10** and its sulfoxide precursor **11** were synthesized from ethyl 2-oxocyclohexanecarboxylate to test their reactivity in the Diels–Alder reaction. Unfortunately, use of enone **10** and γ-ketosulfoxide **11** (that forms enone **10** in situ by thermal or Lewis-acid promoted elimination of phenylsulfinic acid) only resulted in decomposition under the reaction conditions. The simple acyclic esters **12**[13,14] and **13** were next evaluated with the idea that subsequent Dieckmann-type cyclization of the adducts would afford the desired bicyclic ring system present in β-ketoester **5**. Pleasingly, although enoate **12** proved unreactive, enal **13** reacted rapidly with diene **9** under thermal and $BF_3{\cdot}OEt_2$-promoted conditions to afford the *endo* Diels–Alder adduct **14** in 56% and 66% yield, respectively.

Given the successful formation of Diels–Alder adduct **14**, attention turned to establishing effective conditions to promote subsequent Dieckmann-type cyclization to β-hydroxyester **15** (Scheme 2). Few examples of Dieckman-type cyclization of esters onto aldehydes exist in the literature. Following the example of Corey and co-workers,[15] treatment of ester **14** with sodium hexamethyldisilazide at low temperature was investigated. Unfortunately, further cyclization onto the methyl carbamate occurred forming a mixture of alcohol **15** and oxazolidinone **16** at −78 °C. Warming the reaction to 0 °C resulted in exclusive formation of oxazolidinone **16**. Pleasingly, treatment of **14** with lithium diisopropylamide (LDA) at −78 °C suppressed the formation of oxazolidinone **16** affording β-hydroxyester **15** in 57% yield. It next remained to switch from Moc-protected diene **9** to Boc-protected diene **17** to facilitate subsequent Mannich cyclization upon removal of the labile Boc group.

1.1. Synthesis of racemic ABE ring analogue 4

Boc-protected 1-aminodiene **17** was prepared from 2,4-pentadienoic acid **18** via Curtius rearrangement in the presence of *tert*-butanol to afford secondary carbamate **19** by a modified route[8] based on a method reported by Overman and co-workers (Scheme 3).[16] The sodium salt of carbamate **19** was subsequently alkylated with iodoethane.

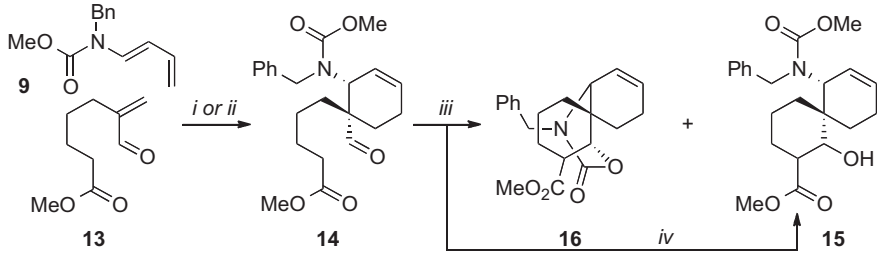


Scheme 3. Reagents and conditions: (i) DPPA; (ii) Δ, *t*-BuOH, BHT, toluene, 3 h, 76%; (iii) NaH, EtI, THF, 0 °C to rt, 18 h, 68%.

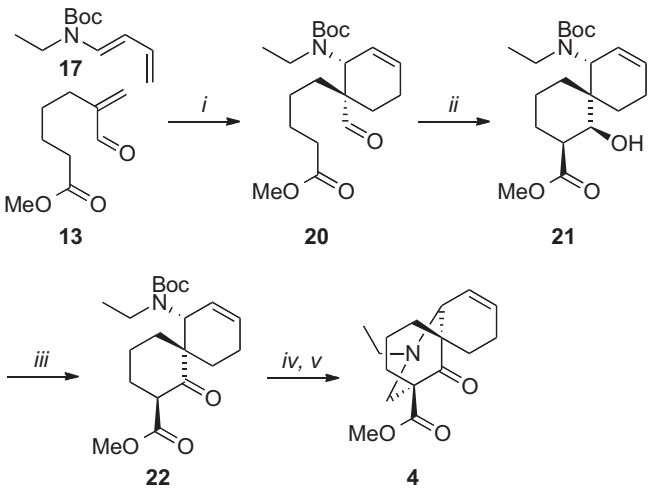
N-Ethyl diene **17** was progressed to investigate the Mannich cyclization chemistry required to form the E ring (Scheme 4). The $BF_3{\cdot}OEt_2$-catalyzed Diels–Alder reaction between enal **13** and diene **17** afforded cyclohexene **20** in 75% yield with >95% *endo* selectivity. LDA-promoted Dieckman cyclization then afforded β-hydroxyester **21** as a single diastereomer in 57% yield. Oxidation with Dess–Martin periodinane gave β-ketoester **22** in 90% yield. The Boc group was removed using trifluoroacetic acid with the resulting salt redissolved in methanol and treated with excess formalin and potassium carbonate to afford ABE ring analogue **4** in quantitative yield.

1.2. Asymmetric synthesis of ABEF ring analogue 2

With the racemic synthesis of an ABE ring analogue of MLA **4** successfully completed, an enantioselective route utilizing chiral

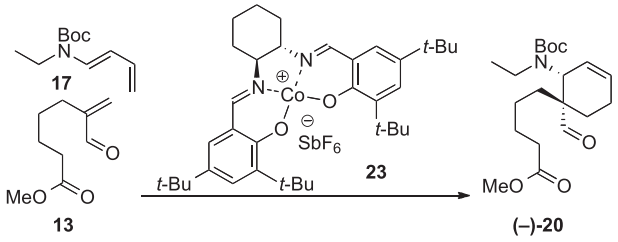


Scheme 2. Reagents and conditions: (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 2 h, 65%; (ii) Δ, toluene, 3 h, 56%; (iii) NaHMDS, THF, −78 °C, 1.5 h, **15** 28%, **16** 35%; (iv) LDA (2.2 equiv), THF, −78 °C, 1 h, **15** 57%.



Scheme 4. Reagents and conditions: (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 1 h, 75%; (ii) LDA (2.5 equiv), THF, −78 °C, 1.5 h, 57%; (iii) Dess–Martin Periodinane, py, CH_2Cl_2, 0 °C, 2 h, 90%; (iv) 1:1 TFA/CH_2Cl_2, 0–45 °C, 1 h; (v) 37% formalin, K_2CO_3, MeOH, 5 min, quantitative over two steps.

cobalt(III) salen catalyst **23** to promote the Diels–Alder reaction between enal **13** and diene **17** was investigated.[17] Catalyst **23** has been successfully used to effect the enantioselective Diels–Alder reaction of α-substituted acroleins with 1-carbamatobutadienes.[18] Use of cobalt(III) salen catalyst **23** to effect the Diels–Alder reaction of enal **13** and diene **17** afforded cyclohexene **20** in 81% yield with 80% ee as determined by chiral HPLC analysis (Scheme 5). The absolute stereochemistry of cyclohexene (−)**-20** was assigned by analogy with previously reported examples.[19,20]

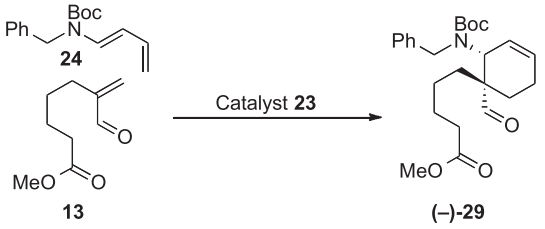


Scheme 5. Reagents and conditions: 2.5 mol % **23**, CH_2Cl_2, 4 h, 81%, 80% ee.

Attempts to improve the enantioselectivity by lowering of the temperature met with little success with the reaction proving to be very sluggish below 0 °C. In related Diels–Alder reactions, Rawal and co-workers reported that enantioselectivity improved with the increasing bulk of the *N*-alkyl substituent on the diene without significant loss of reactivity.[20] With this in mind, *N*-benzyl 1-carbamatobutadiene **24** was synthesized in four steps from *trans*-4-methoxy-buten-2-one **25** (Scheme 6).[21] The benzyl group could also be removed by hydrogenolysis to allow alternative *N*-alkyl derivatives to be synthesized.

Condensation of **25** with benzylamine, followed by removal of volatiles and condensation with di-*tert*-butyl pyrocarbonate afforded γ-keto ene-carbamate **26** that was reduced with sodium borohydride to alcohol **27**. Initial attempts to dehydrate alcohol **27** with trifluoroacetic anhydride (TFAA)[22] afforded a mixture of TFAA condensation product **28** and diene **24** that proved difficult-to-separate. By switching to methanesulfonyl chloride, *N*-benzyl-1-carbamatobutadiene **24** could be synthesized cleanly in 72% overall yield from enone **25**.

Diels–Alder reaction of enal **13** with *N*-benzyl diene **24** at room temperature afforded cyclohexene **29** in 83% yield with 95% ee (Scheme 7). No reaction was observed at −78 °C, however when left to warm slowly to room temperature overnight the reaction proceeded to completion resulting in a slightly higher 97.5% ee. Conducting the reaction at 0 °C for 3 h afforded the same enantioselectivity (97.5% ee).

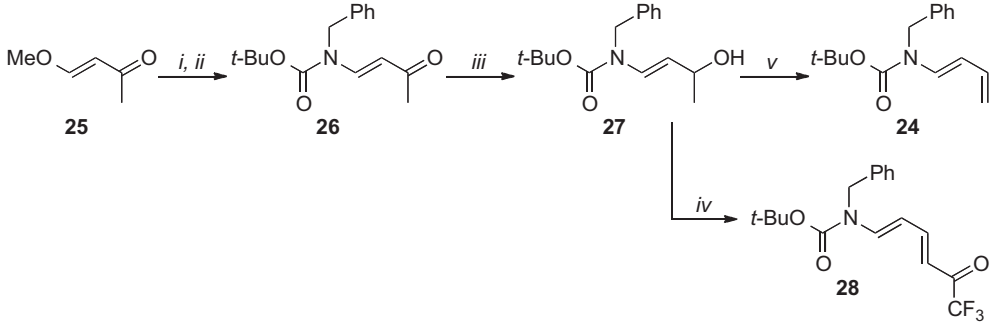


T (°C)	% e.e.
−78	n.r.
r.t.	95
−78 to 20	97.5
0	97.5

Scheme 7. Reagents and conditions: 2.5 mol % **23**, CH_2Cl_2, 0 °C, 3 h, 90%, 97.5% ee.

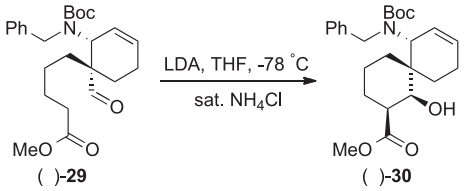
Attention next turned to the Dieckmann-type cyclization of (−)-**29** to (−)-**30** (Table 2). Enantioenriched aldehyde (−)-**29** was treated with variable quantities of LDA in dry THF at −78 °C in order to optimize the formation of β-hydroxyester (−)-**30**. The addition of 1 equiv of LDA to aldehyde (−)-**29** at −78 °C only afforded starting material, however using 1.5 equiv of LDA resulted in the rapid formation of the desired product (−)-**30** in 69% yield. Using 2 equiv of LDA at −78 °C gave an improved yield of 74% with further equivalents resulting in diminished yields.

Pleasingly, the same high-yielding reaction sequence used to convert alcohol **21** to *N*-ethyl ABE analogue **4** was used to convert bicyclic β-hydroxyester (−)-**30** to tricyclic β-ketoester (+)-**31** proceeding via β-ketoester (−)-**32** over three steps in 45% yield (Scheme 8).



Scheme 6. Reagents and conditions: (i) $BnNH_2$, CH_2Cl_2, 2 h; (ii) Boc_2O, 4-DMAP (1 mol %), CH_2Cl_2, 18 h, 93% over two steps; (iii) $NaBH_4$, MeOH, 0 °C, 3 h, quant.; (iv) TFAA, py, MeCN, NEt_3, Δ, 2 h, **24** 48%, **28** 42%; v) MsCl, py, MeCN, 4 Å MS, NEt_3, Δ, 2 h, 77%.

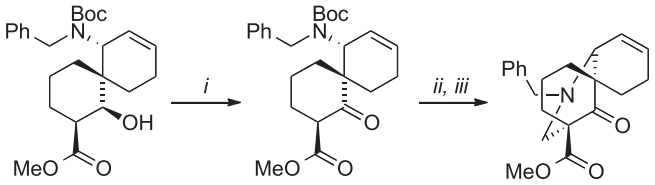
Table 2
Optimization of Dieckmann-type cyclization of (−)-**29** to (−)-**30**



( )-**29** ( )-**30**

LDA equiv	Reaction time (min)	Yield %
1.0	10	0[a]
1.5	3	69
2.0	2	74
3.0	5	72

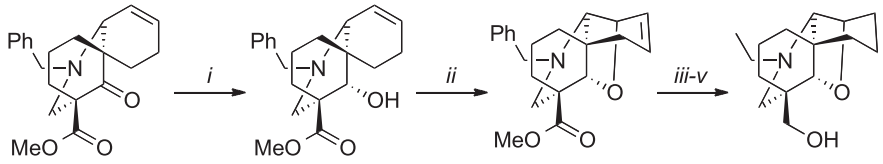
[a] 74% returned starting material.



(−)-**30** (−)-**32** (+)-**31**

Scheme 8. Reagents and conditions: (i) DMP (2.4 equiv), py (1.2 equiv), 0 °C to rt, 67%; (ii) 1:1 TFA/CH_2Cl_2, 0 °C, 1 h; (iii) 37% formalin, K_2CO_3, 5 min, 67%.

With the ABE ring skeleton of MLA **1** embedded in tricyclic ketone (+)-**31**, it remained to install the F ring using a Wacker-type oxidative cyclization. Ketone (+)-**31** underwent stereoselective reduction from the top face to afford alcohol (+)-**33** as a single diastereomer in 64% yield (Scheme 9). Wacker-type cyclization[10] of alcohol (+)-**33** onto the olefin took place using catalytic palladium(II) acetate, under an oxygen atmosphere at 50 °C for 18 h, to afford ABEF ring analogue (+)-**34** in 95% yield.



(+)-**31** (+)-**33** (+)-**34** (+)-**2**

Scheme 9. Reagents and conditions: (i) $NaBH_4$, MeOH, 0 °C to rt, 3 h, 64%; (ii) $Pd(OAc)_2$, O_2, DMSO, 50 °C, 18 h, 95%; (iii) Pd/C (10 wt %), concd HCl, H_2, 1:1 EtOAc/MeOH, 50 °C, 4 h; (iv) AcCl (10 equiv), $^iPr_2NEt$ (12 equiv), 4-DMAP (1 mol %) CH_2Cl_2, 72 h; (v) $LiAlH_4$, THF, Δ, 18 h, 72% over three steps.

Finally, the benzyl group and alkene were removed by hydrogenolysis over 10% palladium(0) on carbon under acidic conditions. The resulting secondary amine salt was acylated with excess acetyl chloride and the crude amide globally reduced with lithium aluminium hydride in THF under reflux to afford tetracyclic alcohol (+)-**2** in 72% yield over three steps.

2. Conclusion

A novel tetracyclic ABEF ring analogue of MLA has been prepared in 14 linear steps in 15% overall yield in 97.5% ee. The key step involved cobalt(III) salen-catalyzed Diels–Alder reaction[18] of enal **13** and 1-aminodiene **24**. The resulting enantio-enriched cyclohexene (−)-**29** served as a stereodirecting template for the diastereoselective formation of the A, E and F rings by Dieckmann cyclization, Mannich cyclization and Wacker-type cyclization, respectively. This synthetic route provides a convenient and high-yielding entry to the enantioselective synthesis of MLA analogues incorporating a B ring moiety.

3. Experimental section

3.1. General

All reactions were carried out in oven-dried glassware. HPLC-grade THF, MeCN, MeOH, diethyl ether, benzene, toluene and lab-grade DCM distilled from CaH_2 were dried over activated 3 Å molecular sieves.[23] DMF, DMSO, DIPA, DIPEA, TEA and pyridine were dried over CaH_2 and distilled onto activated 4 Å molecular sieves. A Fischer model 502 ozone generator was used for the production of ozone from dry oxygen. All other reagents were used as received. Thin layer chromatography (TLC) was carried out using E. Merck silica gel plates using UV light (254 nm) as the primary visualisation method with supplementary visualisation by staining with vanillin in 95% ethanol, iodine on silica gel or aqueous potassium permanganate. Flash column chromatography was performed using Davisil LC60A 40–63 μm amorphous silica. Melting points were measured on a Reichert™ stage apparatus, Electrothermal™ capillary apparatus or a Stuart Scientific SMP3 melting point apparatus, with the melting points uncorrected. Optical rotations were measured with a Perkin–Elmer 341 polarimeter using the sodium D line (589 nm), with the concentration measured in grams per 100 mL. Infrared (IR) spectra were recorded using a Perkin–Elmer Spectrum 1000 FT-IR spectrometer with the absorption peaks expressed in wavenumbers (cm^{-1}) and recorded between 450 cm^{-1} and 4000 cm^{-1}. NMR spectra were recorded on a Bruker Avance-300 or DRX400. High resolution mass spectra were recorded using a VG70-SE spectrometer or microTOF-Q mass spectrometer. Chiral stationary phase HPLC was carried out on a Daicel Chiralpak™ IC column using Dionex Ultimate 3000™ HPLC kit with Chromeleon software.

3.1.1. Ethyl 2-hydroxy-3-methylenecyclohex-1-enecarboxylate ***8***[11]. Ethyl 2-oxocyclohexane-1-carboxylate **23** (9.0 g, 52.9 mmol), formalin (7.3 g, 89.9 mmol), diethylamine (7.8 g, 106.6 mmol), *c*HCl (5.4 g, 54.8 mmol, 37%) and 1,4-dioxane (80 mL) were stirred together overnight under a N_2 atmosphere. The reaction mixture was diluted with EtOAc (160 mL), washed with 2 M HCl (80 mL), water (80 mL), satd $NaHCO_3$ (80 mL) and satd NaCl (80 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude oil was purified by flash column chromatography (8% Et_2O in *n*-hexanes) to afford the *title compound* as a colourless oil (3.0 g, 31%). The ^1H and ^{13}C NMR spectra were consistent with the literature.[24] δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.32 (3H, t, *J*=6.9 Hz, $-OCH_2CH_3$), 1.65–1.73 (2H, m), 2.37 (2H, t, *J*=6.3 Hz), 2.40–2.45 (2H, m), 4.24 (2H, q, *J*=6.9 Hz, $-OCH_2CH_3$), 5.18 (1H, d, *J*=1.5 Hz, C=H_2), 5.82 (1H, d, *J*=1.2 Hz, C=CH_2), 12.10 (1H, s, O*H*). δ_C (75 MHz, $CDCl_3$) 14.3 (CH_3, $-OCH_2CH_3$), 22.6 (CH_2, C-4), 23.5 (CH, C-3), 31.3 (CH_2, C-5), 60.5 (CH_2, $-OCH_2CH_3$), 100.2 (CH, C-2), 115.5 (CH_2, C=CH_2), 138.7 (C, C-6), 163.9 (CH, Ph), 173.0 (C, C=O).

3.1.2. (E)-Methyl benzyl(buta-1,3-dienyl)carbamate ***9***[17]. To a mixture of crotonaldehyde (8.3 mL, 100 mmol) and $MgSO_4$ (12.9 g, 100 mmol) in dry Et_2O (20 mL) at 0 °C was added benzylamine dropwise (10.9 mL, 100 mmol) over 10 min. In a separate flask filled with dry Et_2O (50 mL)

at −78 °C was placed dry DIPEA (18 mL, 103 mmol) followed by methyl chloroformate (7.8 mL, 101 mmol). The imine formed in the first solution was added to the second by syringe with the residual solids rinsed with dry ether (5×10 mL). The solution was stirred at −78 °C for 45 min then warmed to room temperature and stirred for a further 30 min. The mixture was filtered through Celite®, concentrated in vacuo and purified by flash column chromatography (5% Et_2O in *n*-pentane) to afford the *title compound* as a light-amber oil (4.8 g, 23%). δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.81 (3H, s (br), OCH_3), 4.79 (2H, s (br), $-CH_2Ph$), 4.86 (1H, dd, *J*=1.2, 10.2 Hz, H-4A), 4.95 (1H, d, *J*=16.8 Hz, H-4B), 5.55 (1H, dd, *J*=10.2, 14.1 Hz, H-3), 6.26 (1H, s (br), H-2), 7.18–7.32 (6H, m, H-1, Ph–H). δ_C (75 MHz, $CDCl_3$) 47.9 (CH_2, $-CH_2Ph$), 53.6 (CH_3, OMe), 111.8 (CH_2, C-4), 113.4 (CH, C-2), 126.4 (CH, Ph), 127.1 (CH, Ph), 128.6 (CH, Ph), 130.8 (CH, C-1), 135.1 (CH, C-3), 136.7 (C, Ph), carbamate C=O not observed. IR: ν_{max}(film)/cm^{-1}; 3089, 3034, 2956, 1709, 1642, 1606, 1497, 1439, 1424, 1372, 1321, 1255, 1208, 1172, 1112, 995, 970, 948, 929, 885, 858, 766, 735, 696. MS *m*/*z* (EI^+) 240 (MNa^+, 100), 218 (7), 160 (2), 130 (39), 91 (2). HRMS (EI^+) (MNa^+) found: 240.0999. Calculated: 240.0995.

3.1.3. (2-Oxocyclohexyl)methylacetate[25]. Ethyl 2-oxocyclohexane-1-carboxylate (5.6 g, 33.0 mmol), trimethyl *ortho*formate (9.1 g, 85.3 mmol) and *para*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) in dry MeOH (20 mL) were heated under reflux with a N_2 atmosphere overnight. The crude mixture was cooled to room temperature, quenched with solid Na_2CO_3, filtered and concentrated in vacuo to afford crude ethyl 2,2-dimethoxycyclohexanecarboxylate as a colourless oil (8.8 g, >100% yield). To a slurry of $LiAlH_4$ (2.5 g, 65.9 mmol) in dry Et_2O (80 mL) at 0 °C was added the crude acetal dissolved in dry Et_2O (10 mL). The reaction was warmed to room temperature, stirred for 1 h then quenched by the addition of 4 M NaOH (50 mL). The organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo to afford (2,2-dimethoxycyclohexyl) methanol as an amber oil (7.2 g, >100% yield). The crude alcohol and 4-DMAP (25 mg, 0.2 mmol) were dissolved in dry pyridine (15 mL, 186 mmol) under a nitrogen atmosphere. Ac_2O (4.2 mL, 44.4 mmol) was added dropwise (caution: exothermic) and the mixture left to stir for 3 h. The reaction was quenched with 2 M HCl (100 mL) and Et_2O (80 mL) with vigorous stirring for 5 min. The organic phase was separated and the aqueous phase extracted with Et_2O (3×100 mL). The combined organic extracts were neutralized with satd $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo to afford the *title compound* as a colourless oil (5.6 g, 99.7%). ^1H and ^{13}C NMR spectra were consistent with literature values.[25] δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.38 (1H, dt, *J*=3.9, 16.5 Hz), 1.56–1.67 (2H, m), 1.81–1.90 (1H, m), 1.96 (3H, s, CH_3), 1.99–2.06 (1H, m), 2.07–2.15 (1H, m), 2.21–2.39 (2H, m), 2.60 (1H, sext, *J*=6.2 Hz, H-1), 3.97 (1H, dd, *J*=4.8, 10.2 Hz, $-OCH_2-$), 4.30 (1H, dd, *J*=5.4, 11.1 Hz, $-OCH_2-$). δ_C (75 MHz, $CDCl_3$) 20.6 (CH_3), 24.4 (CH_2), 27.4 (CH_2), 30,7 (CH_2), 41.8 (CH_2), 49.2 (CH, C-1), 63.0 (CH_2, $-OCH_2-$), 170.2 (C, C=O), 210.0 (C, C-2).

3.1.4. 2-Methylenecyclohexanone **10**[26]. To a solution of (2-oxocyclohexyl)methylacetate (0.95 g, 5.6 mmol) in dry benzene (25 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.84 mL, 5.6 mmol). The reaction was stirred overnight then diluted with *n*-hexanes (200 mL). The organic layer was washed with water (200 mL), 2 M HCl (30 mL), H_2O (3×30 mL), satd NaCl (50 mL), dried over Na_2SO_4 and concentrated in vacuo to afford the *title compound* as a crude oil (0.61 g, 99%). The ^{13}C NMR spectra were consistent with literature values.[27] δ_C (100 MHz, $CDCl_3$), 24.2 (CH_2, C-4), 24.4 (CH_2, C-5), 32.9 (CH_2, C-3), 40.9 (CH_2, C-6), 120.1 (CH_2), 145.5 (C, C-2), 202.0 (C, C-1).

3.1.5. 2-(Phenylthiomethyl)cyclohexanone. To a solution of (2-oxocyclohexyl)methylacetate (0.95 g, 5.6 mmol) in dry benzene (25 mL) was added thiophenol (0.59 mL, 5.8 mmol) followed by DBU (0.84 mL, 5.6 mmol). The reaction was stirred overnight then diluted with *n*-hexanes (200 mL). The organic layer was washed with water (200 mL), 2 M HCl (30 mL), H_2O (3×30 mL), satd NaCl (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude oil afforded the *title compound* in circa 95% purity by as observed by ^1H NMR (1.22 g, 99%). The ^1H and ^{13}C NMR spectra were consistent with literature values.[28] δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.36–1.45 (1H, m, H-3), 1.61–1.68 (2H, m, H-4, H-5), 1.85–1.90 (1H, m, H-4), 2.04–2.09 (1H, m, H-5), 2.24–2.33 (1H, m, H-6), 2.38–2.44 (2H, m, H-3, H-6), 2.49–2.57 (1H, m, H-2), 2.72 (1H, dd, *J*=8.0, 16.0 Hz, $-CH_2SPh$), 3.47 (1H, dd, *J*=6.0, 12.0 Hz, $-CH_2SPh$), 7.14–7.18 (1H, m, Ph), 7.21–7.33 (4H, m, Ph). δ_C (100 MHz, $CDCl_3$) 24.9 (CH_2, C-4), 27.8 (CH_2, C-5), 33.2 (CH_2, $PhSCH_2-$), 33.4 (CH_2, C-3), 42.0 (CH_2, C-6), 50.3 (CH, C-2), 125.8 (CH, Ph), 128.9 (CH, Ph), 136.6 (C, Ph), 211.3 (C, C-1).

3.1.6. 2-(Phenylsulfinyl)cyclohexanone **11**. $NaIO_4$ (0.55 g, 2.6 mmol) was added to a solution of 2-(phenylthiomethyl)cyclohexanone (0.56 g, 2.5 mmol) in 9:1 MeOH/H_2O (50 mL) and stirred overnight. The crude reaction mixture was diluted with DCM (100 mL) and H_2O (100 mL), the organic layer was separated and the aqueous phase extracted with DCM (3×50 mL). The combined organic extracts were washed with satd NaCl (50 mL) and dried over Na_2SO_4 to afford the *title compound* as a colourless oil (0.60 g, 100%) as a 1:1 inseparable mixture of diastereomers. δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.38–1.61 (1H, m, H-6), 1.62–1.97 (2H, m, H-4, H-5), 1.87–1.94 (1H, m, H-4), 2.10–2.18 (2H, m, H-5, H-6), 2.28–2.37 (0.5H, m, H-3), 2.40–2.49 (1.5H, m, H-3, $-CH_2S(=O)Ph$), 2.57–2.64 (1H, m, H-6, $-CH_2S(=O)Ph$), 2.91–2.98 (0.5H, m, H-1), 3.08–3.15 (0.5H, m, H-1), 3.28–3.37 (1H, m, $CH_2S(=O)Ph$), 7.27–7.33 (1H, m, Ph), 7.47–7.55 (2H, m, Ph), 7.61–7.64 (1H, m, Ph), 7.69–7.71 (1H, m, Ph). δ_C (100 MHz, $CDCl_3$) 24.9, 25.2 (CH_2, C-4), 27.7, 27.9 (CH_2, C-5), 33.5, 35.1 (CH_2, C-6), 41.9, 41.9 (CH_2, C-3), 44.8, 45.3 (CH, C-1), 57.5, 58.4 (CH_2, $-CH_2S(=O)Ph$), 123.6, 123.9 (CH, Ph), 127.1, 127.4 (CH, Ph), 128.9, 129.0 (CH, Ph), 129.2 (CH, Ph), 130.8, 131.0 (CH, Ph), 143.8, 144.9 (C, Ph), 209.9, 210.2 (C, C-1). IR: ν_{max}(film)/cm^{-1}; 3054, 2933, 2861, 1706 (C=O), 1443. MS *m*/*z* (EI^+) 259 (MNa^+, 100), 237 (M^++1, 29), 173 (2), 133 (3), 111 (7). HRMS (EI^+) (MH^+) found: 237.0942. Calculated: 237.0944.

3.1.7. Diethyl 2-(diethoxyphosphoryl)heptanedioate[13]. To a slurry of 60 wt % NaH (0.45 g, 11.3 mmol) in dry THF (20 mL) was added triethyl phosphonoacetate (2.5 g, 11.2 mmol). The mixture was cooled to 0 °C and ethyl 5-bromovalerate (2.4g, 11.6 mmol) was added. The reaction was heated under reflux for 23 h, cooled to room temperature and quenched with satd NH_4Cl (20 mL). The organic layer was separated and the aqueous phase extracted with EtOAc (3×20 mL). The combined organic extracts were washed with H_2O (50 mL); satd NaCl (50 mL) then dried over $MgSO_4$. Concentration of the filtrate in vacuo afforded the *title compound* as a colourless oil (4.0 g, 97%). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.22–1.43 (14H, m, 4× OCH_2CH_3, H-4), 1.59–1.69 (2H, m, H-5), 1.76–2.08 (3H, m, H-3), 2.27–2.36 (2H, m, H-6), 2.86–3.00 (1H, m, H-2), 4.08–4.25 (8H, m, 4× OCH_2CH_3). δ_H (100 MHz; $CDCl_3$) 14.1 (CH_3, C(=O) OCH_2CH_3), 14.2 (CH_3, C(=O)OCH_2CH_3), 16.3 (CH_3, d, *J*=2.4 Hz, P(=O)OCH_2CH_3), 16.4 (CH_3, d, *J*=2.0 Hz, P(=O)CH_2CH_3), 24.4 (CH_2, C-5), 26.6 (CH_2, d, *J*=4.9 Hz, C-4), 27.8 (CH_2, d, *J*=15.0 Hz, C-3), 34.0 (CH_2, C-6), 45.7 (CH, d, *J*=131.2 Hz, C-2), 60.2 (CH_2, C(=O)OCH_2CH_3), 61.3 (CH_2, C(=O)OCH_2CH_3), 62.6 (CH_2, t, *J*=6.5 Hz, P(=O)OCH_2CH_3), 169.1 (C, C-1), 173.3 (C, C-7). δ_P (121 MHz; $CDCl_3$; 85% H_3PO_4) 22.6.

3.1.8. Diethyl 2-methyleneheptanedioate **12**[14]. Paraformaldehyde (0.9 g, 30.0 mmol), K_2CO_3 (1.4 g, 10.3 mmol) and diethyl 2-(diethoxyphosphoryl)heptanedioate (3.9 g, 11.2 mmol) in dry THF (40 mL) were heated under reflux with a N_2 atmosphere overnight. The crude mixture was diluted with Et_2O (40 mL), washed with H_2O (20 mL) and satd NaCl (20 mL), dried over $NaSO_4$ and concentrated

in vacuo. The crude oil was purified by flash chromatography on silica (9:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless oil (1.4 g, 55%). The ^{1}H NMR spectrum was in agreement with the literature.[14] δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.25 (3H, t, J=7.2 Hz, CH_3), 1.30 (3H, t, J=7.2 Hz, CH_3), 1.47–1.55 (2H, m, H-4), 1.62–1.70 (2H, m, H-5), 2.32, 2.32 (2×2H, t, J=7.2 Hz, H-3, H-6), 4.12 (2H, q, J=7.1 Hz, –OCH_2CH$_3$), 4.21 (2H, q, J=7.2 Hz, –OCH_2CH$_3$), 5.53 (1H, dq, J=1.5 Hz, –C=CH_2), 6.27 (1H, d, J=1.2 Hz, –C=CH_2). δ_C (100 MHz, $CDCl_3$) 14.1, 14.1 (2× CH_3, –OCH$_2$CH_3), 24.4 (CH_2, C-5), 27.8 (CH_2, C-4), 31.4 (CH_2, C-3), 34.0 (CH_2, C-6), 60.1 (CH_2, –OCH_2CH$_3$), 60.5 (CH_2, –OCH_2CH$_3$), 124.5 (CH_2, =CH_2), 140.4 (C, C-2), 167.1 (C, C-1), 173.5 (C, C-7).

3.1.9. Methyl 7-oxoheptanoate[29]. Cycloheptene (5.0 g, 90%, 52 mmol), anhydrous $NaHCO_3$ (1.3 g, 15.8 mmol), dry MeOH (35 mL) and dry DCM (120 mL) were combined in a three-necked round-bottom flask and cooled to −78 °C under a N_2 atmosphere. O_3 in a stream of dry O_2 was bubbled through the stirred mixture until a faint metallic blue colour appeared in the solution. The solution was purged of excess O_3 with dry O_2 followed by N_2 gas. The mixture was filtered, the filtrate diluted with benzene (50 mL) and concentrated in vacuo to circa 30 mL volume. The concentrated solution was diluted with DCM (120 mL) and cooled to 0 °C under a N_2 atmosphere. A mixture of dry TEA (10.7 mL, 76.8 mmol) and Ac_2O (14.2 mL, 150.5 mmol) was added and the reaction mixture was left to warm slowly to room temperature overnight. The reaction was quenched with 1 M HCl (80 mL), the organic layer was separated and washed with 1 M HCl (80 mL), H_2O (50 mL), satd $NaHCO_3$ (50 mL) and satd NaCl (50 mL). The organic extract was dried over $MgSO_4$ and concentrated in vacuo to afford the *title compound* as a colourless oil (6.7 g, 82%). The ^{1}H and ^{13}C NMR spectra were consistent with the literature.[29] δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.33–1.41 (2H, m, H-4), 1.61–1.69 (4H, m, H-3, H-5), 2.32 (2H, t, J=8.0 Hz, H-2), 2.46 (2H, dt, J=2.7, 8.0 Hz, H-3, H-6), 3.66 (3H, s, –OCH$_3$), 9.76 (1H, t, J=1.6 Hz, H-7). δ_C (100 MHz, $CDCl_3$) 21.3 (CH_2, C-4), 24.2 (CH_2, C-3), 28.2 (CH_2, C-5), 33.3 (CH_2, C-2), 43.2 (CH_2, C-6), 51.0 (CH_3, -OCH$_3$), 173.5 (C, C-1), 201.9 (CH, C-7).

3.1.10. Methyl 6-formyl-6-eneoate ***13***[30]. Methyl 7-oxoheptanoate (4.0 g, 25.5 mmol), formalin (2.2 g, 37%, 26.7 mmol), pyrrolidinium propionate (0.4 g, 2.7 mmol) and isopropanol (2.5 g) were combined and stirred overnight at circa 50 °C under a N_2 atmosphere. The reaction mixture was diluted with H_2O (50 mL), extracted with DCM (3×50 mL), dried over Na_2SO_4 and concentrated in vacuo to afford the *title compound* as a colourless oil (4.1 g, 94%). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.46–1.53 (2H, m, H-4), 1.61–1.69 (2H, m, H-3), 2.27 (2H, t, J=7.6 Hz, H-5), 2.33 (2H, t, J=7.2 Hz, H-2), 3.67 (3H, s, –OCH_3), 6.01 (1H, s, =CH_2), 6.27 (1H, s, =CH_2), 9.54 (1H, s, –HC=O). δ_C (100 MHz, $CDCl_3$) 24.4 (CH_2, C-3), 27.1 (CH_2, C-4), 27.4 (CH_2, C-5), 33.7 (CH_2, C-2), 51.5 (CH_3, –OCH_3), 134.2 (CH_2, =CH_2), 149.8 (C, C-6), 173.9 (C, C-1), 194.6 (CH, –HC=O). IR: ν_{max}(film)/cm^{-1}; 2950, 2866, 1733, 1686, 1436, 1361; MS m/z (EI$^+$) 193 (MNa$^+$, 100), 84 (10). HRMS (EI$^+$) [MNa$^+$] found: 193.0839. Calculated: 193.0835.

3.1.11. Methyl 5-((1′S,2′R*)-2-(benzyl(methoxycarbonyl)amino)-1′-formylcyclohex-3′-enyl)pentanoate* ***14***. *Method A*: Methyl 6-formyl-6-eneoate **13** (89 mg, 0.52 mmol) and (*E*) methyl benzyl(buta-1,3-dienyl)carbamate **9** (119 mg, 0.55 mmol) were placed in a sealed tube and heated to 150 °C for 3 h. The crude mixture was purified by flash column chromatography (4:1 *n*-hexanes/EtOAc) to afford an inseparable 9:1 mixture of *endo*/*exo* isomers as a colourless solid (114 mg, 56%). Mp: 51–52 °C.

Method B: Methyl 6-formyl-6-eneoate **13** (350 mg, 2.0 mmol) and (*E*)-methyl benzyl(buta-1,3-dienyl)carbamate **9** (590 mg, 2.7 mmol) were dissolved in DCM (25 mL) and cooled to −78 °C under a N_2 atmosphere. $BF_3{\cdot}OEt_2$ (0.52 mL, 4.1 mmol) was added dropwise and the reaction stirred for 40 min. Satd $NaHCO_3$ (20 mL) was added by syringe and the reaction mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous phase extracted with DCM (3×20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to yield a viscous oil. The crude mixture was purified by flash column chromatography (4:1 *n*-hexanes/EtOAc) to afford the *endo* isomer exclusively as a colourless solid (0.60 g, 75%). Mp: 71–72 °C. δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.90–1.18 (1H, m), 1.26–1.31 (1H, m), 1.59–1.67 (4H, m), 1.76–1.85 (2H, m), 1.89–2.00 (1H, m), 2.17–2.23 (1H, m), 2.31 (2H, t, J=7.4 Hz, H-2), 3.59 (3H, s (br), –NC(=O)OCH_3), 3.66 (3H, s, –CO$_2$CH_3), 4.36–4.50 (2H, m, –CH_2Ph), 4.82 (1H, s (br), H-2′), 5.47–5.51 (1H, m, H-4′), 5.92–5.96 (1H, m, H-3′), 7.09 (2H, s (br), *o*-PhH), 7.18–7.22 (1H, m, *p*-PhH), 7.26–7.29 (2H, m, *m*-PhH), 9.71 (1H, s (br), –HC=O). δ_C (100 MHz, $CDCl_3$) 20.0 (CH_2), 21.2 (CH_2), 23.7 (CH_2), 25.3 (CH_2), 32.2 (CH_2), 33.7 (CH_2, C-2), 48.4 (CH_2, –CH_2Ph), 51.5 (CH_3, –CO$_2$CH_3), 52.9 (CH_3, –NC(=O)OCH_3), 53.7 (C, C-1′), 56.4 (CH, C-2′), 123.3 (CH, C-4′), 126.3 (CH, *o*-Ph), 126.6 (CH, *p*-Ph), 128.2 (CH, *m*-Ph), 132.2 (CH, C-3′), 139.2 (C, Ph), 158.0 (C, –NC=O), 173.7 (C, –CO$_2$CH$_3$), 205.3 (CH, –HC=O). IR: ν_{max}(film)/cm^{-1}; 2945, 2721, 1722 (C=O), 1682 (C=O), 1604, 1496, 1460, 1450, 1423. MS m/z (EI$^+$) 410 (MNa$^+$, 100), 220 (35), 142 (3). HRMS (EI$^+$) (MNa$^+$) found: 410.1945. Calculated: 410.1938.

3.1.12. (1S,6S*)-Methyl 7-(benzyl(methoxycarbonyl)amino)-1-hydroxyspiro[5.5]undec-8-ene-2-carboxylate* ***15***. Methyl 5-((1′*S*,2′*S*)-2-(benzyl(methoxycarbonyl)amino)-1′-formylcyclohex-3′-enyl) pentanoate**14** (1.9 g, 5.2 mmol) was dissolved in dry THF (80 mL) under a N_2 atmosphere and cooled to −78 °C. An LDA solution [12.8 mmol; made from 1.8 mL DIPA (1.8 mL, 12.9 mmol) in dry THF (20 mL) and *n*-BuLi in hexanes (8.0 mL, 1.6 M, 12.8 mmol) at 0 °C] was added dropwise and the reaction stirred for 90 min. The reaction was quenched with satd $NaHCO_3$ (80 mL). EtOAc (80 mL) was added and the organic phase was separated. The aqueous phase was extracted with EtOAc (3×80 mL) with the combined organic extracts dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash column chromatography (3:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless solid (1.1 g, 57%). Mp=52 °C; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.42–1.56 (4H, m), 1.33–1.38 (1H, m), 1.62–1.69 (2H, m), 1.74–1.84 (2H, m), 2.05–2.12 (2H, m), 2.58 (1H, s (br), O*H*), 3.04 (1H, s (br), H-2), 3.55 (3H, s (br), N(C=O)OCH_3), 3.63 (3H, s, –CO$_2$CH_3), 3.77 (1H, s (br), H-1), 4.35 (1H, d, J=16.2 Hz, CH_2Ph), 5.04 (1H, d, J=16.2 Hz, CH_2Ph), 5.41–5.46 (1H, m, H-9), 5.82–5.85 (1H, m, H-8), 7.07–7.10 (2H, m, *o*-Ph), 7.11–7.14 (1H, m, *p*-Ph), 7.18–7.23 (2H, m, *m*-Ph). δ_C (100 MHz, $CDCl_3$) 20.3 (CH_2), 21.1 (CH_2), 21.9 (CH_2), 26.7 (CH_2), 27.4 (CH_2), 36.6 (CH_2, C-3), 40.0 (C, C-6), 43.1 (CH, C-2), 48.3 (CH_2, CH_2Ph), 51.7 (CH_3, C(C=O)OCH_3), 52.5 (CH, C-7), 52.8 (C, CH_3, N(C=O)OCH_3), 70.7 (CH, C-1), 124.2 (CH, C-9), 126.6 (CH, Ph), 128.1 (CH, Ph), 131.0 (CH, C-8), 139.2 (C, Ph), 156.8 (C, NC=O), 176.9 (C,CO$_2$CH$_3$). IR: ν_{max}(film)/cm^{-1}; 3486 (O–H), 2970, 2937, 2886, 1738 (C=O), 1659, 1542, 1468, 1456, 1436. HRMS (EI$^+$) found (M$^+$): 387.2045. Calculated: 387.2046.

3.1.13. (4aR,7aR*,11^{1}S*)-Methyl 7-benzyl-6-oxo-1,2,3,4,4a,6,7,7a,10,-11-decahydrodibenzo[d,e][1,3]oxazine-4-carboxylate* ***16***. Methyl 5-((1′*S*,2′*S*)-2-(benzyl(methoxycarbonyl)amino)-1′-formylcyclohex-3′-enyl)pentanoate**14** (0.48 g, 1.2 mmol) was dissolved in dry THF(15 mL) under a N_2 atmosphere and cooled to −78 °C. NaHMDS in THF (2.5 mL, 1.0 M, 2.5 mmol) was added dropwise and the reaction stirred for 10 min. The reaction was warmed to 0 °C for 1 h then quenched with satd $NaHCO_3$ (15 mL). DCM (50 mL) was added, the organic phase separated and the aqueous phase extracted with DCM (3×50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo with the crude material purified

by flash column chromatography (3:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless solid (0.13 g, 28%). Mp: 162–163 °C; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.89 (1H, dt (br), *J*=4.0, 13.2 Hz, H-1), 1.40–1.56 (2H, m, H-2, H-3), 1.57–1.63 (1H, m, H-2), 1.71–1.80 (3H, m, H-1, H-11), 1.96–2.05 (2H, m, H-3, H-10), 2.14–2.20 (1H, m, H-10), 2.80 (1H, dt, *J*=4.4, 11.6 Hz, H-4), 3.21 (1H, d, *J*=5.2 Hz, H-7a), 3.75 (3H, s, $-OCH_3$), 4.10 (1H, d, *J*=15.6 Hz, CH_2Ph), 4.26 (1H, d, *J*=10.8 Hz, H-4a), 5.30 (1H, d, *J*=15.2 Hz, CH_2Ph), 5.61–5.66 (1H, m, H-8), 5.92 (1H, ddd, *J*=2.4, 4.4, 10.0 Hz, H-9), 7.34–7.38 (3H, m, Ph), 7.26–7.30 (2H, m, Ph). δ_C (100 MHz, $CDCl_3$) 17.1 (CH_2, C-11), 19.5 (CH_2, C-2), 21.2 (CH_2, C-10), 28.6 (CH_2, C-3), 29.6 (CH_2, C-1), 33.9 (C, C-11[1]), 42.6 (CH, C-4), 48.2 (CH_2, CH_2Ph), 52.2 (CH_3, $-CO_2CH_3$), 57.9 (CH, C-7a), 80.0 (CH, C-4a), 121.9 (CH, H-8), 127.4 (CH, Ph), 127.7 (CH, Ph), 128.7 (CH, Ph), 132.4 (CH, H-9), 136.8 (C, Ph), 153.3 (−NC=O), 173.9 (C, $-CO_2CH_3$). IR: ν_{max} (film)/cm^{-1}; 3061, 3032, 2953, 2903, 2874, 2838, 1730, 1691 (C=O), 1605, 1495, 1460, 1444, 1423. MS *m*/*z* (EI^+) 356 (MH^+, 22), 324 (9), 312 (3), 280 (3), 233 (7), 205 (17), 191 (7), 173 (22), 145 (100). HRMS (EI^+) (MNa^+) found: 356.1863. Calculated: 356.1863.

3.1.14. (E)-tert-Butyl buta-1,3-dienylcarbamate ***19***[16]. To a solution of malonic acid (5.2 g, 50.3 mmol) in dry pyridine (7.7 mL, 95.6 mmol) heated to 80 °C under an atmosphere of N_2 was added 90% acrolein (4.2 mL, ~51.5 mmol). After 30 min, another aliquot of acrolein (0.3 mL, ~4.0 mmol) was added. The reaction was heated for a further 30 min then cooled to room temperature. The reaction was quenched by the addition of ice (33 g) followed by cH_2SO_4 (4.4 mL, 70 mmol) and the mixture extracted with $CHCl_3$ (3×60 mL). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo to afford (*E*)-penta-2,4-dienoic acid **18** as a light yellow solid (3.5 g, 72%). The crude material was used immediately in the next reaction without further purification. Crude acid **18** (3.5 g, ~35.7 mmol) was dissolved in dry Et_2O (40 mL) under a N_2 atmosphere, the solution cooled to 0 °C and dry TEA (5.5 mL, 39.5 mmol) was added. After 5 min, diphenylphosphoryl azide (8.6 mL, 40.2 mmol) was added and the reaction warmed to room temperature. The reaction was quenched after 1 h with a mixture of satd $NaHCO_3$ (40 mL) and Et_2O (40 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (3×50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The brown oil was passed through a short column of silica (15% EtOAc in *n*-hexanes to 50% EtOAc in *n*-hexanes) to afford crude (*E*)-penta-2,4-dienoyl azide as a bright yellow oil (5.3 g, >100%) that was used immediately without characterization. 3,5-Di-*tert*-butyl-4-hydroxytoluene (32 mg, 0.15 mmol); *tert*-butanol (2.8 mL, 37.4 mmol) and dry toluene (40 mL) were heated under reflux. Crude (*E*)-penta-2,4-dienoyl azide (5.3 g) in dry toluene (15 mL) was added by syringe pump over a 25 min period. The reaction was heated under reflux for 11 h then concentrated in vacuo. The crude oil was purified by flash column chromatography (9:1 *n*-hexanes/EtOAc) to yield the *title compound* as a colourless solid (4.1 g, 67% from (*E*)-penta-2,4-dienoic acid **18**). The ^1H NMR spectrum was in agreement with the literature.[16] Mp: 66–68 °C [lit.: 67–68 °C].[16]

3.1.15. (E)-tert-Butyl buta-1,3-dienyl(ethyl)carbamate ***17***. NaH (1.1 g, 26.5 mmol, 60 wt %) was washed with *n*-pentane (3×15 mL); suspended in dry THF (240 mL) and cooled to 0 °C under a N_2 atmosphere. (*E*)-*tert*-Butyl buta-1,3-dienylcarbamate **19** (3.3 g, 19.4 mmol) in dry THF (20 mL) was added dropwise to the slurry. After 1 h, iodoethane (4.6 mL, 29.7 mmol) was added and the reaction allowed to warm up to room temperature slowly overnight. The reaction was quenched with satd NH_4Cl (50 mL), the organic layer separated and the aqueous layer extracted with Et_2O (3×150 mL). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography (19:1 *n*-hexanes/EtOAc) to afford the *title compound* as a light-amber oil (2.6 g, 68%) and returned starting material (0.67 g, 20%). δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.09 (3H, t, *J*=7.2 Hz, $-NCH_2CH_3$), 1.45 (9H, s, $-C(CH_3)_3$), 3.50 (2H, d (br), *J*=6.6 Hz, $-NCH_2CH_3$), 4.81 (1H, dd, *J*=1.2, 10.2 Hz, H-4B), 4.97 (1H, dt, *J*=0.6, 16.8 Hz, H-4A), 5.49 (1H, dd, *J*=10.5, 14.4 Hz, H-2), 6.26 (1H, dt, *J*=10.2, 16.8 Hz, H-3), 7.01 (1H, s (br), H-1). δ_C (75 MHz, $CDCl_3$) 12.2 (CH_3, $-NCH_2CH_3$), 28.1 (CH_3, $-C(CH_3)_3$), 38.5 (CH_2, $-NCH_2CH_3$), 81.0 (C, $-C(CH_3)_3$), 109.2 (CH, C-2), 111.9 (CH_2, C-4), 130.7 (CH, C-3), 135.6 (CH, C-1), 152.4 (C, C=O). IR: ν_{max}(film)/cm^{-1}; 3042, 3088, 2978, 2936, 1703, 1640, 1605, 1472, 1457, 1425. MS *m*/*z* (EI^+) 220 (MNa^+, 100), 166 (3), 142 (10), 120 (2), 98 (1). HRMS (EI^+) found (MNa^+): 220.1313. Calculated: 220.1308.

3.1.16. (1R,2R)-(−)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt(III) hexafluoroantimonate ***23***[18]. (1*R*,2*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (154 mg, 0.26 mmol) was dissolved in dry DCM (5 mL) under N_2. The reaction vessel was covered in foil to exclude light and silver(I) hexafluoroantimonate was added in a single portion. After 18 h stirring, the dark green solution was passed through a pad of Celite® and the filtrate concentrated in vacuo to afford the *title compound* as a dark green powder (210 mg, 100%). Mp=196 °C (dec) (CH_2Cl_2); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.30 (18H, s, CH_3, 5-^{t}Bu), 1.59–1.68 (2H, m, H-4′, H-5′), 1.74 (18H, s CH_3, 3-^{t}Bu), 1.91 (2H, d (br), *J*=10.8 Hz, H-3′, H-6′), 2.01 (2H, d (br), *J*=7.6 Hz, H-4′, H-5′), 3.07 (2H, d (br), *J*=11.2 Hz, H-3′, H-6′), 3.61 (2H, d (br), *J*=8.0 Hz, H-1′, H-2′), 7.44 (2H, d, *J*=2.4 Hz, H-4), 7.47 (2H, d, *J*=2.8 Hz, H-6), 7.81 (2H, s, *H*C=N−). δ_C (100 MHz, $CDCl_3$) 24.2 (CH_2, C-4′, C-5′), 29.4 (CH_2, C-3′, C-6′), 30.3 (CH_3, 5-^{t}Bu), 31.4 (CH_3, 3-^{t}Bu), 54.8 (C, ^{t}Bu), 69.2 (CH, C-1′, C-2′), 118.5 (C, C-1), 128.7 (CH, C-4), 129.1 (CH, C-6), 135.8 (CH, C-3), 141.7 (C, C-5), 162.0 (C, C-2), 164.5 (C, HC=N−). IR: ν_{max} (film)/cm^{-1}; 2957, 2902, 1604, 1524, 1462, 1421. MS *m*/*z* (EI^+) 603 (M^+, 100), 547 (3), 274 (3). HRMS (EI^+) found (M^+): 603.3355. Calculated: 603.3355.

3.1.17. Methyl 5-((1′S,2′R)-2-(ethyl(tert-butoxycarbonyl)amino)-1′-formylcyclohex-3′-enyl)pentanoate ***20***. *Racemic method*: Methyl 6-formyl-6-eneoate **13** (2.1 g, 12.2 mmol) and (*E*)-*tert*-butyl-ethyl (buta-1,3-dienyl)carbamate**17** (2.9 g, 14.4 mmol) were dissolved in DCM (50 mL) and cooled to −78 °C under an Ar atmosphere. $BF_3{\cdot}OEt_2$ (1.5 mL, 11.5 mmol) was added dropwise and the reaction stirred for 1 h. Satd $NaHCO_3$ (20 mL) was added by syringe and the reaction mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous layer extracted with DCM (3×20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to yield a viscous oil. The crude mixture was purified by flash column chromatography (4:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless oil (3.3 g, 72%). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.02 (3H, t (br), *J*=6.8 Hz, $-NCH_2CH_3$), 1.22–1.31 (1H, m), 1.33–1.38 (1H, m), 1.45 (9H, s, ^{t}Bu), 1.51–1.63 (4H, m), 1.71–1.82 (2H, m), 1.85–1.99 (1H, m), 2.18–2.23 (1H, m), 2.30 (2H, q (br), *J*=7.3 Hz, NCH_2CH_3), 3.04–3.19 (2H, m, H-2), 3.64 (3H, s, $-CO_2CH_3$), 4.57 (0.16H, s (br), rotamer, H-2′), 4.72 (0.84H, s (br), rotamer, H-2′), 5.48–5.55 (1H, m, H-4′), 6.01–6.03 (1H, m, H-3′), 9.62 (1H, s, −*H*C=O). δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3, NCH_2CH_3), 21.0 (CH_2,), 23.5 (CH_2,), 25.1 (CH_2), 28.2 (CH_3), 31.8 (CH_2), 33.5 (CH_2, C-2), 39.3 (CH_2, NCH_2CH_3), 51.3 (CH_3, OCH_3), 52.5 (CH), 53.5 (C, C-1′), 55.3 (CH, C-2′), 79.9 (C, ^{t}Bu), 123.9 (CH,C-4′), 131.5 (CH, C-′), 156.4 (C, NC=O), 173.7 (C, $-CO_2CH_3$), 205.3 (CH, −HC=O). MS *m*/*z* (EI^+) 390 (MNa^+, 100), 368 (MH^+, 10), 312 (18), 276 (14). High resolution (EI^+) [MH^+] Found: 368.2445 Calculated: 368.2431.

Enantioselective method: (1*R*,2*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(III) hexafluoroantimonate **23** (17 mg, 20 μmol) was dissolved in dry DCM (0.5 mL) under N_2. Methyl 6-formyl-6-eneoate **13** (100 mg, 0.59 mmol) was added

and stirred for circa 10 min. Neat (*E*)-*tert*-butyl ethyl(buta-1,3-dienyl) carbamate **17** (144 mg, 0.73 mmol) was added dropwise and the reaction stirred for 3 h. The crude mixture was loaded directly onto a column of silica gel and purified by flash column chromatography (9:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless oil that solidified upon refrigeration (0.19 g, 87%). Enantiomeric excess was determined by HPLC with a chiralpak IC column (hexane/^{i}PrOH=80:20, 0.5 mL/min), t_R minor=16.59 min, t_R major=30.63 min; ee=80%. $[\alpha]_D^{20}$ −72.5 (*c* 1.1, $CHCl_3$).

3.1.18. (1S,2S*,6S*,7R*)-Methyl 7-(tert-butoxycarbonyl(ethyl)amino)-1-hydroxyspiro[5.5]undec-8-ene-2-carboxylate **21**.* Methyl 5-((1′*S**, 2′*R**)-2-(ethyl(*tert*-butoxycarbonyl)amino)-1′-formylcyclohex-3′-enyl)pentanoate **20** (1.9 g, 5.2 mmol) was dissolved in dry THF (80 mL) under a N_2 atmosphere and cooled to −78 °C. An LDA solution [12.8 mmol; made from DIPA (1.8 mL, 12.9 mmol) in dry THF (20 mL) and 1.6 M *n*-BuLi in hexanes (8.0 mL, 12.8 mmol) at 0 °C] was added dropwise and the reaction stirred for 90 min. The reaction was quenched with satd $NaHCO_3$ (80 mL). EtOAc (80 mL) was added, the organic phase was separated and the aqueous phase extracted with EtOAc (3×80 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash column chromatography (3:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless solid (1.1 g, 57%). Mp: 88–90 °C (*n*-hexanes/EtOAc); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.12 (3H, t, *J*=6.8 Hz, $-NCH_2CH_3$), 1.36–1.47 (2H, m), 1.46 (9H, s, ^{t}Bu), 1.51–1.61 (3H, m), 1.75–1.76 (2H, m), 1.87–1.92 (1H, m), 2.04–2.09 (2H, m), 2.88 (0.6H, s (br), −O*H*), 3.10–3.28 (3H, m, $-NCH_2CH_3$, H-2), 3.64 (3H, s (br), $-OCH_3$), 3.86 (1H, s (br), H-1), 4.65 (0.2H, s (br), H-7 rotamer), 4.89 (0.8H, s (br), H-7 rotamer), 5.46–5.50 (1H, m, H-9), 5.90–5.93 (1H, m, H-8). δ_C (100 MHz, $CDCl_3$) 15.1 (CH_3, $-NCH_2CH_3$), 20.2 (CH_2), 21.0 (CH_2), 21.9 (CH_2), 26.7 (CH_2), 27.3 (CH_2), 28.1 (CH_3, ^{t}Bu), 39.4 (CH_2, $-NCH_2CH_3$), 39.5 (C, C-6), 42.9 (CH, C-7), 50.7 (CH, C-2), 51.3 (CH_3, $-CO_2CH_3$), 70.5 (CH, C-1), 79.4 (C, ^{t}Bu), 124.8 (CH, C-9), 129.7 (CH, C-8), 156.5 ($-NCO_2^{t}Bu$), 177.1 (C, $-CO_2CH_3$). IR: ν_{max}(film)/cm^{-1}; 3481 (O–H), 2970, 2937, 2884, 1739 (C=O), 1654, 1547, 1468, 1454, 1436. MS *m*/*z* (EI$^+$) 278 (MH^+, 9), 246 (10), 221 (19), 189 (100), 161 (4), 133 (2). HRMS (EI$^+$) found (MH^+): 278.1746. Calculated: 278.1751.

3.1.19. (6S,7R*)-Methyl 7-(tert-butoxycarbonyl(ethyl)amino)-1-oxospiro[5.5]undec-8-ene-2-carboxylate **22**.* Dess–Martin periodinane (2.3 g, 5.5 mmol) was suspended in dry DCM (50 mL) under a N_2 atmosphere at 0 °C. Dry pyridine (0.25 mL, 3.1 mmol) was added, the mixture was warmed to room temperature and stirred for 30 min. The homogenous solution was cooled to 0 °C and a solution of (1S*,6S*,7R*)-methyl 7-(*tert*-butoxycarbonyl(ethyl) amino)-1-hydroxyspiro[5.5]undec-8-ene-2-carboxylate **21** (0.97 g, 2.6 mmol) in dry DCM (10 mL) was added dropwise. After 4 h, the reaction was quenched with satd $NaHCO_3$ (40 mL), filtered through Celite®, the organic layer separated and the aqueous layer extracted with DCM (3×40 mL). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatography (9:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless solid (0.87 g, 91%). Mp: 94–103 °C (*n*-hexanes/ethyl acetate); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.01 (3H, t, *J*=7.0 Hz, $-NCH_2CH_3$), 1.30–1.38 (1H, dt, *J*=4.4, 14.4 Hz), 1.42–1.48 (1H, m), 1.48 (9H, s (br), ^{t}Bu), 1.73–1.78 (1H, m), 1.90–2.05 (2H, m), 2.09–2.17 (3H, m), 2.19–2.25 (2H, m), 3.01–3.12 (2H, m, $-NCH_2CH_3$), 3.69 (3H, s, $-OCH_3$), 4.20 (1H, dd, *J*=5.0, 13.4 Hz, H-2), 5.30 (1H, s (br), H-7), 5.43–5.46 (1H, m, H-9), 5.92–5.96 (1H, m, H-8). δ_C (100 MHz, $CDCl_3$) 19.7 (CH_2,), 20.6 (CH_2,), 25.8 (CH_2,), 27.9 (CH_3, ^{t}Bu), 29.9 (CH_2,), 35.6 (CH_2,), 48.0 (CH_2, CH_2Ph), 51.6 (CH_3, $-OCH_3$), 51.7 (C, C-6), 52.1 (CH, C-7), 55.0 (CH, C-2), 80.5 (C, ^{t}Bu), 123.4 (CH, C-9), 126.1 (CH, *o*-Ph), 127.7 (CH ×2, Ph), 130.9 (CH, C-8), 140.1 (C, Ph), 156.5 (C, NC=O), 171.3 (C, $-CO_2CH_3$), 209.3 (CH, C=O). IR: ν_{max}(film)/cm^{-1}; 2981, 2937, 2868, 1749, 1703, 1678, 1641, 1548, 1479, 1452, 1431, 1405. MS *m*/*z* (EI$^+$) 388 (MNa^+, 5), 356 (3), 332 (72), 288 (28), 256 (15), 191 (100). HRMS (EI$^+$) found (MNa^+): 388.2105. Calculated: 388.2105.

3.1.20. (1R,4R*,9S*)-Methyl-3-ethyl-13-oxo-3-azatricyclotridec[8.3.1.0^{4,9}]-5-ene-1-carboxylate **4**.* To (6S*,7R*)-methyl 7-(*tert*-butoxycarbonyl(ethyl)amino)-1-oxospiro[5.5]undec-8-ene-2-carboxylate **22** (0.26 g, 0.7 mmol) dissolved in DCM (5 mL) at 0 °C was added TFA (5 mL). The reaction was stirred for 1 h then concentrated in vacuo (40 °C) to afford an amber gum that was used in the next step without further purification. The crude trifluoroacetate salt was dissolved in MeOH (4 mL) and formalin (0.1 mL, 37 % w/w, 1.4 mmol) and solid K_2CO_3 (0.30 g, 2.2 mmol) were added. TLC monitoring showed that the reaction was complete within 5 min. The reaction mixture was diluted with Et_2O (20 mL) and H_2O (20 mL), the organic layer was separated and the aqueous layer extracted with Et_2O (5×20 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated in vacuo to afford the *title compound* as a colourless solid (0.20 g, 100%). Mp: 65–66 °C (diethyl ether); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.12 (3H, t, *J*=7.2 Hz, $-NCH_2CH_3$), 1.21 (1H, ddd, *J*=7.2, 10.8, 17.6 Hz, H-10B), 1.48 (1H, qt, *J*=3.2, 6.4 Hz, H-11B), 1.71 (1H, dt, *J*=6.4, 12.4 Hz, H-10A), 1.87–1.93 (1H, m, H-7B), 1.93 (1H, qt, *J*=0.8, 6.4 Hz, H-8B), 2.06 (1H, ddt, *J*=1.2, 8.8, 13.6 Hz, H-10A), 2.20 (1H, ddt, *J*=1.6, 8.8 Hz, H-12B), 2.44–2.55 (2H, m, H-8, H-12A), 2.57–2.72 (2H, m, $-NCH_2CH_3$), 2.95 (1H, dd, *J*=1.4, 11.2 Hz, H-2B), 2.87–3.00 (1H, m, H-11A), 3.29 (1H, dd, *J*=2.0, 11.6 Hz, H-2A), 3.68 (4H, s (br), H-4, $-CO_2CH_3$), 5.66 (1H, dd, *J*=1.6, 10.4 Hz, H-6), 5.79–5.82 (1H, m, H-5). δ_C (100 MHz, $CDCl_3$) 13.3 (CH_3, $-NCH_2CH_3$), 21.3 (CH_2, C-11), 23.4 (CH_2, C-7), 30.3 (CH_2, C-8), 38.3 (CH_2, C-13), 43.9 (CH_2, C-10), 46.5 (CH_2, $-NCH_2CH_3$), 48.4 (C, C-1), 52.0 (CH_3, CO_2CH_3), 55.4 (CH_2, C-2), 59.3 (C, C-9), 65.6 (CH, C-4), 122.3 (CH, C-6), 132.0 (CH, C-5), 171.7 (C, -CO_2CH_3), 212.5 (C, C-13). IR: ν_{max}(film)/cm^{-1}; 3019, 2984, 2957, 2920, 2848, 2814, 1735, 1705, 1646, 1474, 1456, 1437. MS *m*/*z* (EI$^+$) 278 (M^++1, 9), 246 (10), 221 (19), 189 (100), 161 (4), 133 (2); HRMS (EI$^+$) found (M+1): 278.1746. Calculated: 278.1751.

*3.1.21. (E)-tert-Butyl benzyl(3-oxobut-1-enyl)carbamate **26**.* Benzy lamine (4.3 mL, 39 mmol) was added dropwise to (*E*)-4-methoxy-3-buten-2-one **25** (4.4 mL, 40 mmol) in dry DCM (40 mL) and stirred for 2 h under N_2. Volatiles were removed in vacuo and the resultant brown gum redissolved in dry DCM (40 mL). The solution was cooled to 0 °C and di-*tert*-butyl dicarbonate (9.0 g, 41 mmol) in dry DCM (20 mL) was added dropwise and the reaction was left to warm to room temperature overnight. The reaction was quenched with 0.5 M HCl (30 mL) and the organic phase washed with H_2O (30 mL), satd $NaHCO_3$ (30 mL), satd NaCl (30 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude oil was purified by flash column chromatography (9:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless oil that slowly solidified upon refrigeration (9.6 g, 89%). Mp: 46–48 °C (CH_2Cl_2); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.53 (9H, s, $-C(CH_3)_3$), 2.19 (3H, s, $-COCH_3$), 4.76 (2H, s, $-NCH_2Ph$), 5.52 (1H, d, *J*=14.8 Hz, H-2), 7.15–7.17 (2H, m, Ph), 7.23–7.26 (1H, m, Ph), 7.27–7.30 (2H, m, Ph), 8.25 (1H, d, *J*=14.4 Hz, H-1). δ_C (100 MHz, $CDCl_3$) 27.1 (CH_3, C-4), 27.9 (CH_3, $-C(CH_3)_3$), 47.9 (CH_2, $-CH_2Ph$), 83.7 (C, $-C(CH_3)_3$), 109.2 (CH, C-2), 126.3 (CH, Ph), 127.4 (CH, Ph), 128.7 (CH, Ph), 135.8 (C, Ph), 142.5 (CH, C-1), 152.4 (C, C=O), 197.2 (C, C-3). IR: ν_{max}(film)/cm^{-1}; 3061, 3035, 3010, 2940, 2974, 1720, 1681, 1626, 1583, 1496, 1456. MS *m*/*z* (EI$^+$) 298 (MNa^+, 85), 276 (MH^+, 100), 242 (13), 220 (88), 198 (8), 176 (48), 91 (11). HRMS (EI$^+$) found (MH^+): 276.1599. Calculated: 276.1594.

*3.1.22. (E)-tert-Butyl benzyl(3-hydroxybut-1-enyl)carbamate **27**.* Na BH_4 (1.4 g, 36 mmol) was added to a solution of (*E*)-*tert*-butyl benzyl (3-oxobut-1-enyl)carbamate **26** (5.5 g, 20 mmol) in MeOH at 0 °C in three portions over a 15 min period. The reaction was

warmed to room temperature and stirred for 1 h by which time effervescence had ceased. The reaction was quenched by addition of H_2O (15 mL) with 15 min stirring, followed by the removal of methanol in vacuo at 40 °C. The aqueous residue was extracted with DCM (3×50 mL) and the combined organic extracts were dried over $MgSO_4$. The filtrate was concentrated in vacuo to afford the *title compound* as a colourless oil (5.6 g, 100%). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.21 (3H, d, J=6.4 Hz, H-4), 1.46–1.52 (9H, m, $-C(CH_3)_3$), 4.28 (1H, s (br), H-3), 4.69 (2H, s (br), $-NCH_2Ph$), 4.87 (1H, s (br), H-2), 7.08–7.32 (6H, m, H-1, Ph). δ_C (100 MHz, $CDCl_3$) 23.9 (CH_3, C-4), 28.2 (CH_3, $-C(CH_3)_3$), 47.4, 48.0 (CH_2, $-CH_2Ph$, rotamers), 68.1 (CH, C-3), 81.7 (C, $-C(CH_3)_3$), 113.2 (CH, C-2), 126.4 (CH, Ph), 127.0 (CH, Ph), 128.5 (CH, Ph), 128.7 (CH, C-1), 137.3 (C, Ph), 153.4 (C, C=O). IR: ν_{max}(film)/cm^{-1}; 3426 (O–H), 3033, 2976, 2975, 1703 (C=C), 1658 (C=O), 1454. MS m/z (EI^+) 300 (MNa^+, 67), 260 (3), 244 (7), 204 (100), 180 (8), 160 (19), 91 (17). HRMS (EI^+) found (MNa^+): 300.1574. Calculated: 300.1570.

3.1.23. (E)-tert-Butyl benzyl(1,3-dienyl)carbamate ***24***[17]. To (*E*)-*tert*-butyl benzyl(3-hydroxybut-1-enyl)carbamate **27** (2.9 g, 10.6 mmol), 4 Å MS (300 mg), 4-DMAP (10 mg, 1 mol %) in dry MeCN (30 mL) at 0 °C was added dry pyridine (1.9 mL, 23.6 mmol) followed by methanesulfonyl chloride (1.4 mL, 18.1 mmol) The reaction was warmed slowly to room temperature over 1 h. Dry TEA (3.4 mL, 24.4 mmol) was added dropwise and the solution was heated under reflux for 1.5 h. The crude mixture was concentrated in vacuo and purified by flash column chromatography on silica gel (14:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless oil that slowly solidified upon refrigeration (2.1 g, 77%). Mp: 37 °C (CH_2Cl_2); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.35 (9H, s, $-C(CH_3)_3$), 4.55 (2H, s (br), $-NCH_2Ph$), 4.73 (1H, dd, J=1.2, 10.4 Hz, H-4B), 4.84 (1H, dd, J=1.2, 16.8 Hz, H-4A), 5.42 (1H, m, H-2), 6.17 (1H, m, H-3), 7.01–7.23 (5H, m, Ph) [H-1 not observed]. δ_C (100 MHz, $CDCl_3$) 28.2 (CH_3, $-C(CH_3)_3$), 48.0, 47.4 (CH_2, $-CH_2Ph$, rotamers), 81.8 (C, $-C(CH_3)_3$), 110.9 (CH, C-2), 112.8 (CH_2, C-4), 126.3 (CH, Ph), 127.0 (CH, Ph), 128.6 (CH, Ph), 131.4 (CH, C-3), 135.5 (CH, C-1), 137.3 (C, Ph), 153.1 (C, C=O). IR: ν_{max}(film)/cm^{-1}; 3087, 3061, 3032, 3009 (=C–H), 2984, 2971, 2931, 1689 (C=O), 1642 (C=C), 1606, 1497, 1455, 1427. MS m/z (EI^+) 282 (MNa^+, 23), 204 (100), 182 (4), 160 (25), 143 (3), 91 (37). HRMS (EI^+) found (MNa^+): 282.1472. Calculated: 282.1465.

3.1.24. (1E,3E)-tert-Butyl benzyl(6,6,6-trifluoro-5-oxohexa-1,3-dienyl)carbamate ***28*** *and (E)-tert-butyl benzyl(1,3-dienyl)carbamate* ***24***. To (*E*)-*tert*-butyl benzyl(3-hydroxybut-1-enyl)carbamate **27** (5.5 g, 20 mmol) in dry MeCN (100 mL) were added 4-DMAP (20 mg, 1 mol %), dry pyridine (3.6 mL, 45 mmol) and trifluoroacetic anhydride (5.0 mL, 35 mmol). The solution was stirred for 25 min, dry TEA (6.4 mL, 47 mmol) was added and the mixture heated under reflux for 2 h. The dark amber solution was concentrated in vacuo, the crude oil redissolved in DCM (40 mL) and quenched with satd $NaHCO_3$ (40 mL). The organic layer was separated and the aqueous phase extracted with DCM (40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude oil was purified by flash column chromatography (19:1 *n*-hexanes/EtOAc) to afford (*E*)-*tert*-butyl benzyl(1,3-dienyl)carbamate **24** (2.5 g, 48%) and the *title compound* **28** (2.2 g, 42%) as dark amber oils. R_f (**24**)=0.6 (4:1 *n*-hexanes/EtOAc); R_f (**28**)=0.55; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.53 (9H, m, $-C(CH_3)_3$), 4.82 (2H, s, $-NCH_2Ph$), 5.70 (1H, dd, J=11.2, 13.6 Hz, H-2), 6.23 (1H, d, J=15.2 Hz, H-4), 7.16–7.18 (2H, m, Ph), 7.24–7.30 (1H, m, Ph), 7.32–7.37 (2H, m, Ph), 7.63 (1H, dd, J=11.6, 15.2 Hz, H-3), 7.83 (1H, d, J=13.6 Hz, H-1). δ_C (100 MHz, $CDCl_3$) 28.2 (CH_3, $-C(CH_3)_3$), 48.0 (CH_2, $-CH_2Ph$), 84.0 (C, $-C(CH_3)_3$), 107.4 (CH, C-2), 115.0 (CH, C-4), 116.6 (C, q, J=291 Hz, C-6, $-CF_3$,), 126.2 (CH, Ph), 127.6 (CH, Ph), 128.9 (CH, Ph), 135.7 (C, Ph), 144.0 (CH, C-1), 151.0 (CH, C-3), 152.0 (C, C=O), 179.4 (C, q, J=179 Hz, C-5, C=O). IR: ν_{max}(film)/cm^{-1}; 2981, 1782, 1722, 1610, 1573, 1498, 1478. MS m/z (EI^+) 398 (MNa^+, 18), 356 (MH^+, 14), 300 (100), 256 (11), 206 (13), 149 (15), 91 (5). HRMS (EI^+) found (MH^+): 356.1462. Calculated: 356.1468.

3.1.25. Methyl 5-((1′S,2′R)-2′-(benzyl(tert-butoxycarbonyl)amino)-1′-formylcyclohex-3′-enyl)pentanoate ***29***. *Racemic method*: Methyl 6-formyl-6-eneoate **13** (50 mg, 0.29 mmol) and (*E*)-*tert*-butyl benzyl(buta-1,3-dienyl)carbamate**24** (104 mg, 0.40 mmol) were dissolved in DCM (50 mL) and cooled to −78 °C under N_2. $BF_3{\cdot}OEt_2$ (50 μL, 0.41 mmol) was added dropwise and the reaction stirred for 1 h. Satd $NaHCO_3$ (20 mL) was added by syringe and the reaction mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous layer extracted with dichloromethane (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to yield a viscous oil. The crude mixture was purified by flash column chromatography (9:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless oil (81 mg, 64%). δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.07–1.16 (1H, m), 1.23 (9H, s, ^tBu), 1.26–1.31 (1H, m), 1.56–1.68 (4H, m), 1.76–1.97 (3H, m), 2.17–2.21 (1H, m), 2.30–2.34 (2H, m, H-2), 3.65 (3H, s, $-CO_2CH_3$), 4.31–4.38 (2H, m, $-CH_2Ph$), 4.86 (1H, s (br), H-2′), 5.57 (1H, s (br), H-4′), 5.95–5.97 (1H, m, H-3′), 7.09–7.34 (5H, m, Ph), 9.73 (1H, s (br), $-HC$=O). δ_C (100 MHz, $CDCl_3$) 19.7 (CH_2), 21.1 (CH_2), 23.7 (CH_2), 25.3 (CH_2), 27.9 (CH_3, ^tBu), 32.1 (CH_2), 33.9 (CH_2, C-2), 48.6 (CH_2, $-CH_2Ph$), 51.5 (CH_3, $-CO_2CH_3$), 54.0 (C, C-1′), 56.5 (CH, C-2′), 80.4 (C, ^tBu), 123.5 (CH, C-4′), 125.3 (CH, Ph), 126.3 (CH, Ph), 128.2 (CH, Ph), 132.3 (CH, C-3′), 140.2 (C, Ph), 1579 (C, −NC=O), 173.8 (C, $-CO_2CH_3$), 205.5 (CH, −HC=O). IR: ν_{max}(film)/cm^{-1}; 2981, 1736, 1719, 1682, 1605, 1497, 1451. MS m/z (EI^+) 452 (MNa^+, 100), 434 (9), 374 (71), 346 (19), 334 (83), 330 (28), 300 (2), 267 (1), 223 (12), 205 (15), 173 (5). HRMS (EI^+) found (MNa^+): 452.2400. Calculated: 452.2407.

Enantioselective method: (1*R*,2*R*)-(−)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(III) hexafluoroantimonate **23** (115 mg, 0.14 mmol) was dissolved in dry DCM (4 mL) under a N_2 atmosphere. The solution was cooled to −78 °C, methyl 6-formyl-6-eneoate **13** (0.57 g, 3.3 mmol) was added and stirred for circa 10 min. (*E*)-*tert*-butyl benzyl(buta-1,3-dienyl)carbamate **24** (1.1 g, 4.2 mmol) in DCM (1.5 mL) was added dropwise and the reaction left to warm to room temperature overnight. The crude mixture was loaded directly onto a column of silica gel and purified by flash column chromatography (9:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless oil (1.3 g, 90%). Enantiomeric excess was determined by HPLC with a chiralpak IC column (hexane/^{i}PrOH=65:35, 0.5 mL/min), t_R (minor)=13.63 min, t_R (major)=26.17 min; ee=95%. $[\alpha]_D^{20}$ −131.2 (*c* 1.0, $CHCl_3$).

3.1.26. (1S,2S,6S,7R)-Methyl 7-(benzyl(tert-butoxycarbonyl)amino)-1-hydroxyspiro[5.5]undec-8-ene-2-carboxylate ***30***. To a solution of aldehyde **29** (2.3 g, 5.2 mmol) in dry THF (40 mL) at −78 °C was added an LDA solution dropwise [*n*-BuLi (6.5 mL, 1.6 M, 10.4 mmol) was added dropwise to a solution of dry DIPA (1.5 mL, 10.6 mmol) in dry THF (5 mL) at 0 °C under a N_2 atmosphere] under a N_2 atmosphere. After 1.5 equiv, the solution turned bright yellow and the reaction was stirred for a further 2 min then quenched with satd NH_4Cl (30 mL) and allowed to warm to room temperature. The organic phase was separated, the aqueous phase was extracted with EtOAc (4×40 mL), the combined organic extracts were washed with satd NaCl (40 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (4:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless solid (1.7 g, 74%). Mp=96–98 °C (CH_2Cl_2); $[\alpha]_D^{20}$ −156.6 (*c* 0.6, $CHCl_3$); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.18 (9H, s (br), ^tBu), 1.35–1.56 (2H, m), 1.60–1.64 (2H, m), 1.77–1.81 (2H, m), 1.85–1.89 (1H, m), 2.06–2.08 (2H, m), 2.84 (1H, s (br), O*H*), 3.23 (1H, s (br), H-2), 3.67 (3H, s, $-OCH_3$), 3.88 (1H, s (br), H-1), 4.32 (1H, dd, J=15.6 Hz, CH_2Ph), 4.48 (1H, dd (br), J=15.6 Hz, CH_2Ph), 5.09 (1H, s

(br), H-7), 5.62 (1H, s (br), H-9), 5.91 (1H, d (br), J=9.6 Hz, H-8), 7.15–7.20 (3H, m, Ph), 7.24–7.28 (2H, m, Ph). δ_C (100 MHz, $CDCl_3$) 20.5 (CH_2), 21.1 (CH_2), 22.1 (CH_2), 26.7 (CH_2), 27.9 (CH_3, ^{t}Bu), 40.1 (C, C-6), 43.1 (CH, C-2), 48.6 (CH_2, CH_2Ph), 51.0 (CH, C-7), 51.5 (CH_3, $-OCH_3$), 70.6 (CH, C-1), 80.1 (C, ^{t}Bu), 124.3 (CH, C-9), 126.3 (CH, Ph), 126.4 (CH, Ph), 127.9 (CH, Ph), 130.9 (CH, C-8), 140.3 (C, Ph), 156.6 (C, NC=O), 177.2 (C, $-CO_2CH_3$). IR: ν_{max}(film)/cm^{-1}; 3468 (O–H), 3032 (C=C), 2932, 1741 (C=O), 1663 (C=O), 1450, 1404. MS m/z (EI$^+$) 452 (MNa^+, 100), 430 (MH^+, 23), 330 (25), 223 (85), 173 (5), 152 (34). HRMS (EI$^+$) found (MNa^+): 452.2396. Calculated: 452.2407.

3.1.27. (2S,6S,7R)-Methyl 7-(benzyl(tert-butoxycarbonyl)amino)-1-oxospiro[5.5]undec-8-ene-2-carboxylate ***32***. Dess–Martin periodinane (4.6 g, 10.9 mmol) was suspended in dry DCM (60 mL) under a N_2 atmosphere at 0 °C. Dry pyridine (0.5 mL, 6.2 mmol) was added, the mixture was warmed to room temperature and stirred for 30 min. The homogenous solution was cooled to 0 °C and a solution of alcohol **30** (2.6 g, ~5.2 mmol) in dry DCM (20 mL) was added dropwise. After 2 h, the reaction was quenched with satd $NaHCO_3$ (40 mL), filtered through Celite® and the organic layer was separated. The aqueous layer was extracted with DCM (3×40 mL) and the combined organic extracts dried over $MgSO_4$. The filtrate was concentrated in vacuo and purified by flash column chromatography (9:1 *n*-hexanes/EtOAc) to afford the *title compound* as a colourless oil (1.5 g, 67%). $[\alpha]_D^{20}$ −81.8 (*c* 0.5, $CHCl_3$); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.20 (9H, s (br), ^{t}Bu), 1.33–1.47 (1H, m), 1.57–1.68 (1H, m), 1.75–1.84 (1H, m), 1.92–2.04 (2H, m), 2.08–2.19 (3H, m), 2.20–2.32 (2H, m), 3.72 (3H, s, $-OCH_3$), 4.22 (1H, dd, J=5.4, 13.3 Hz, H-2), 4.29 (2H, s (br), CH_2Ph), 5.45 (1H, s (br), H-7), 5.54–5.57 (1H, m, H-9), 5.86–5.91 (1H, m, H-8), 7.08–7.11 (2H, m, *o*-Ph), 7.15–7.19 (1H, m, *p*-Ph), 7.22–7.26 (2H, m, *m*-Ph). δ_C (100 MHz, $CDCl_3$) 19.7 (CH_2), 20.6 (CH_2), 25.8 (CH_2), 27.9 (CH_3, ^{t}Bu), 29.9 (CH_2), 35.6 (CH_2), 48.0 (CH_2, CH_2Ph), 51.6 (CH_3, $-OCH_3$), 51.7 (C, C-6), 52.1 (CH, C-7), 55.0 (CH, C-2), 80.5 (C, ^{t}Bu), 123.4 (CH, C-9), 126.1 (CH, *o*-Ph), 127.7 (CH ×2, Ph), 130.9 (CH, C-8), 140.1 (C, Ph), 156.5 (C, NC=O), 171.3 (C, $-CO_2CH_3$), 209.3 (CH, C=O). IR: ν_{max} (film)/cm^{-1}; 3021 (C=C), 2980, 2947, 2924, 2868, 1747 (C=O), 1707, 1676, 1668 (C=O), 1607, 1500, 1481, 1448, 1435, 1402. MS m/z (EI$^+$) 450 (MNa^+, 90), 428 (26), 372 (40), 328 (100), 296 (22), 221 (16), 189 (3). HRMS (EI$^+$) found (MNa^+): 450.2242. Calculated: 450.2251.

3.1.28. (1R,4R,9S)-Methyl-3-benzyl-13-oxo-3-azatricyclotridec[8.3.1.0^{4,9}]-5-ene-1-carboxylate ***31***. To (6*S*,7*R*)-methyl 7-(*tert*-butoxycarbonyl(benzyl)amino)-1-oxospiro[5.5]undec-8-ene-2-carboxylate **32** (59 mg, 0.14 mmol) dissolved in DCM (1 mL) at 0 °C was added TFA (1 mL). The reaction was stirred for 1 h then concentrated in vacuo (40 °C) to afford an amber gum that was used in the next step without further purification. The crude TFA salt was dissolved in methanol (1 mL). Formalin (0.1 mL, 37 % w/w, 1.4 mmol) was added followed by K_2CO_3 (48 mg, 0.35 mmol). TLC monitoring showed that the reaction was complete within 5 min. The reaction mixture was diluted with DCM (20 mL) and H_2O (5 mL), the organic layer was separated and the aqueous layer extracted with DCM (3×5 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo to afford the *title compound* as a colourless oil that solidified upon refrigeration (31 mg, 65%). Mp=75–80 °C (CH_2Cl_2); $[\alpha]_D^{20}$ +7.7 (*c* 0.7, $CHCl_3$); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.18–1.26 (1H, m, H-8), 1.53–1.61 (1H, m, H-11), 1.71 (1H, ddd, J=5.2, 12.0, 13.2 Hz, H-10), 1.89–1.94 (1H, m, H-7), 1.96 (1H, q, J=6.8 Hz, H-8), 2.09–2.20 (2H, H-11, H-12), 2.44–2.56 (2H, m, H-8, H-12), 2.90 (1H, dd, J=1.0, 11.2 Hz, H-2), 2.98–3.11 (1H, m, H-11), 3.38 (1H, dd, J=1.6, 11.6 Hz, H-2), 3.69 (3H, s, $-CO_2CH_3$), 3.71 (1H, d, J=13.2 Hz, $-CH_2$Ph), 3.71 (1H, s, H-4), 3.88 (1H, d, J=12.8 Hz, $-CH_2$Ph), 5.87 (1H, s, H-5), 5.88 (1H, t, J=13.0 Hz, H-6), 7.2–7.30 (1H, m, *p*-Ph), 7.33–7.40 (4H, m, Ph). δ_C (100 MHz, $CDCl_3$) 21.4 (CH_2, C-11), 23.4 (CH_2, C-7), 30.3 (CH_2, C-8), 38.0 (CH_2, C-12), 43.7 (CH_2, C-10), 48.6 (C, C-1), 52.1 (CH_3, CO_2CH_3), 55.3 (CH_2, C-2), 57.6 (CH_2, -CH_2Ph), 59.3 (C, C-9), 65.9 (CH, C-4), 121.6 (CH, C-6), 127.3 (CH, *p*-Ph), 128.4 (CH, Ph), 129.1 (CH, Ph), 132.5 (CH, C-5), 138.5 (C, Ph), 171.6 (C, $-CO_2CH_3$), 212.3 (C, C-13); IR: ν_{max} (film)/cm^{-1}; 3025 (C=C), 2982, 2914, 2844, 1738 (C=O), 1711, 1649, 1603, 1495, 1444. MS m/z (EI$^+$) 362 (MNa^+, 3), 340 (100), 308 (3), 221 (10), 189 (3), 120 (2). HRMS (EI$^+$) found (MH^+): 340.1902. Calculated: 340.1907.

3.1.29. (1R,4R,9S,13S)-Methyl 3-benzyl-13-hydroxy-3-azatricyclotridec[8.3.1.0^{4,9}]-5-ene-1-carboxylate ***33***. To a solution of ketone **31** (0.26 g, 0.77 mmol) in MeOH (10 mL) at 0 °C was added $NaBH_4$ flakes (100 mg, 2.6 mmol). After 1 h, a further portion of $NaBH_4$ (100 mg, 2.6 mmol) was added. After another hour, a third portion of $NaBH_4$ (100 mg, 2.6 mmol) was added and the reaction mixture was warmed to 13 °C. The reaction was quenched with 1:1 satd NH_4Cl/NaCl (30 mL) and the aqueous phase extracted with DCM (4×40 mL). The combine organic extracts were dried over $MgSO_4$, concentrated in vacuo and the crude product purified by flash column chromatography (9:1 *n*-hexanes/EtOAc) to afford the *title compound* as a light-blue oil that darkened on storage (0.17 g, 64%). The intensely blue-coloured impurity was not detectable by NMR spectroscopy.

$[\alpha]_D^{20}$ +7.0 (*c* 2.3, $CHCl_3$), δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.39 (1H, dt, J=13.2, 6.4 Hz, H-10A), 1.45–1.60 (3H, m, H-11A, H-8A, H-10B), 1.71 (1H, dd, J=13.2, 6.4 Hz, H-12A), 1.77 (1H, dd, J=14.0, 6.4 Hz, H-8B), 1.99 (1H, ddt, J=13.2, 6.8, 1.6 Hz, H-12B), 1.98–2.06 (1H, m, H-7A), 2.43–2.51 (1H, m, H-7B), 2.67 (1H, d, J=12.0 Hz, H-2), 2.74–2.87 (1H, m, H-11B), 3.08 (1H, dd, J=12.0, 1.2 Hz, H-2), 3.33–3.35 (1H, m, H-4), 3.61 (3H, s, $-OCH_3$), 3.76 (1H, d, J=13.2 Hz, $-CH_2$Ph), 3.80 (1H, s, H-13), 3.81 (1H, d, J=13.2 Hz, $-CH_2$Ph), 5.90 (1H, dq, J=10.4, 3.0 Hz, H-6), 6.10 (1H, dd, J=10.4, 1.6 Hz, H-5), 7.22–7.26 (1H, m, *p*-Ph), 7.28–7.36 (4H, m, Ph). δ_C (100 MHz, $CDCl_3$) 22.4 (CH_2, C-11), 26.2 (CH_2, C-7), 35.8 (CH_2, C-12), 36.0 (CH_2, C-8), 37.5 (C, C-9), 42.8 (CH_2, C-10), 49.5 (CH_2, C-2), 51.2 (C, C-1), 52.1 (CH_3, $-OCH_3$), 59.4 (CH_2, $-CH_2$Ph), 61.6 (CH, C-4), 79.8 (CH, C-13), 125.4 (CH, C-6), 128.0 (CH, C-5), 129.3 (CH, Ph), 130.1 (CH, Ph), 132.7 (CH, C-5), 140.6 (C, Ph), 177.6 (C, C=O); IR: ν_{max} (film)/cm^{-1}; 3550 (O–H), 3025 (C–H, Ph), 2915 (C–H), 2844, 1729 (C=O), 1451, 1433. HRMS (EI$^+$) found (MH^+): 342.2061. Calculated: 342.2064.

3.1.30. (+)-Ester ***34***. $Pd(OAc)_2$ (15 mg, 67 μmol) was added to a solution of alcohol **33** (98 mg, 287 μmol) in DMSO (8 mL) and heated at circa 50 °C under an O_2 atmosphere overnight (18 h). H_2O (80 mL) was added and the aqueous layer extracted with Et_2O (4×80 mL). The combined organic extracts were washed with satd NaCl (20 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by flash column chromatography (4:1 *n*-hexanes/EtOAc) to afford **34** as a colourless oil (95 mg, 97%). $[\alpha]_D^{20}$ +62.3 (*c* 1.9, $CHCl_3$); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.45–1.63 (3H, m, H-12, H-13, H14), 1.83–1.86 (1H, m, H-12), 1.99 (1H, dd, J=14.0, 5.6 Hz, H-14), 2.18–2.24 (1H, m, H-7), 2.25–2.31 (1H, m, H-7), 2.49–2.61 (1H, m, H-13), 2.79 (1H, d, J=11.2 Hz, H-11), 2.89 (1H, s, H-9), 2.91 (1H, dd, J=11.6, 1.6 Hz, H-11), 3.64 (2H, s, $-CH_2$Ph), 3.66 (3H, s, $-OCH_3$), 4.25 (1H, s, H-2), 4.41 (1H, d, J=5.6 Hz, H-4), 5.64–5.66 (1H, m, H-6), 6.04–6.08 (1H, m, H-5), 7.23–7.27 (1H, m, *p*-Ph), 7.31–7.32 (4H, m, Ph). δ_C (100 MHz, $CDCl_3$) 20.2 (CH_2, C-13), 32.7 (CH_2, C-14), 32.9 (CH_2, C-12), 41.1 (C, C-8), 43.9 (CH_2, C-7), 48.9 (C, C-1), 51.9 (CH_3, $-OCH_3$), 52.2 (CH_2, C-11), 59.9 (CH_2, $-CH_2$Ph), 68.3 (CH, C-9), 69.7 (CH, C-4), 85.8 (CH, C-2), 127.0 (CH, *p*-Ph), 128.3 (CH, Ph), 128.6 (CH, Ph), 130.9 (CH, C-6), 131.8 (CH, C-5), 138.9 (C, Ph), 175.8 (C, C=O). IR: ν_{max} (film)/cm^{-1}; 3031 (C–H, Ph), 2928 (C–H), 2862, 1729 (C=O), 1454, 1434. HRMS (EI$^+$) found (MH^+): 340.1914. Calculated: 340.1907.

3.1.31. (+)-Alcohol ***2***. Pd/C 10% (20 mg) was added to a solution of ester **34** (47 mg, 0.14 mmol) in 1:1 MeOH/EtOAc (10 mL) with *c*HCl (5 drops). The slurry was heated at circa 50 °C with vigorous stirring under a H_2 atmosphere for 4 h. The mixture was filtered through Celite© and the solids were washed with ethyl acetate. The filtrate

was concentrated in vacuo to afford a light amber gum. The crude material was dissolved in dry DCM (10 mL) under a N_2 atmosphere. Acetyl chloride (0.1 mL, 1.4 mmol), DIPEA (0.3 mL, 1.7 mmol) and 4-DMAP (2 mg, 16 μmol) were added at 0 °C. The reaction was warmed to room temperature and left to stir for three days. The reaction was quenched with satd $NaHCO_3$ (10 mL), the organic layer was separated and the aqueous layer extracted with DCM (3×20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo to afford the crude acetamide as a light amber gum. The crude material was redissolved in dry THF (30 mL), $LiAlH_4$ (110 mg, 2.9 mmol) was added and the slurry was heated under reflux overnight (19 h) under N_2. After cooling to room temperature, the reaction was quenched by the dropwise addition of 4 M NaOH (2 mL, 8 mmol). The organic phase was decanted and the white solid left in the flask washed with EtOAc (3×20 mL). The combined organic extracts were concentrated in vacuo and the crude product purified by flash column chromatography (2:1 EtOAc/*n*-hexanes) to afford amino alcohol **2** as a light-amber oil (26.2 mg, 75%). $[\alpha]_D^{20}$ +23.7 (*c* 0.6, $CHCl_3$); δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.06 (3H, t, *J*=7.2 Hz, $-NCH_2CH_3$), 1.12 (1H, td (br), *J*=13.4, 2.0 Hz, H-12), 1.20–1.35 (2H, m, H-6, H-10), 1.36–1.50 (5H, m, H-7, H-8×2, H-11, H-12), 1.72–1.85 (2H, m, H-6, H-7), 1.91 (1H, dd, *J*=14.0, 5.6 Hz, H-10), 2.27–2.39 (2H, m, H-11), 2.40–2.50 (3H, m, $-NCH_2CH_3$, H-2), 2.53–2.56 (1H, m, H-2), 2.58 (1H, s, H-4), 3.09 (1H, s (br), O*H*), 3.35 (1H, d, *J*=10.8 Hz, $-CH_2OH$), 3.44 (1H, d, *J*=10.4 Hz, $-CH_2OH$), 3.79 (1H, s, H-13), 4.33 (1H, d, *J*=5.2 Hz, H-5). δ_C (100 MHz, $CDCl_3$) 13.3 (CH_3, $-NCH_2CH_3$), 18.8 (CH_2, C-7), 20.6 (CH_2, C-11), 30.5 (CH_2, C-6), 31.8 (CH_2, C-12), 33.3 (CH_2, C-10), 38.7 (CH_2, C-8), 40.1 (C, C-1), 43.2 (C, C-9), 49.0 (C, -NCH_2CH_3), 52.5 (CH_2, C-2), 70.3 (CH_2, $-CH_2OH$), 72.2 (CH, C-4), 72.9 (CH, C-5), 85.8 (CH, C-13). IR: ν_{max}(film)/cm^{-1}; 3389 (C–OH), 2915 (C–H), 1445. HRMS (EI^+) found (MH^+): 252.1968. Calculated: 252.1958.

Acknowledgements

We are grateful for the financial support afforded by a University of Auckland doctoral scholarship.

References and notes

1. Aiyar, V. N.; Benn, M. H.; Hanna, T.; Jacyno, J.; Roth, S. H.; Wilkens, J. L. *Experientia* **1979**, *35*, 1367.
2. Malysz, J.; Gronlien, J. H.; Anderson, D. J.; Hakerud, M.; Thorin-Hagene, K.; Ween, H.; Wetterstrand, C.; Briggs, C. A.; Faghih, R.; Bunnelle, W. H.; Gopalakrishnan, M. *J. Pharmacol. Exp. Ther.* **2009**, *330*, 257.
3. Haydar, S. N.; Dunlop, J. *Curr. Top. Med. Chem.* **2010**, *10*, 144.
4. Goodall, K. J.; Barker, D.; Brimble, M. A. *Synlett* **2005**, 1809.
5. Huang, J.; Orac, C. M.; McKay, S.; McKay, D. B.; Bergmeier, S. C. *Bioorg. Med. Chem.* **2008**, *16*, 3816.
6. Chan, Y.; Balle, J.; Kevin, S. J.; Boyd, P. D. W.; Brimble, M. A.; Barker, D. *Tetrahedron* **2010**, *66*, 7179.
7. Guthmann, H.; Conole, D.; Wright, E.; Koerber, K.; Barker, D.; Brimble, M. A. *Eur. J. Org. Chem.* **2009**, 1944.
8. Huang, J.; Bergmeier, S. C. *Tetrahedron* **2008**, *64*, 6434.
9. Lehmann, A.; Brocke, C.; Barker, D.; Brimble, M. A. *Eur. J. Org. Chem.* **2006**, 3205.
10. Roenn, M.; Baeckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749.
11. Burn, D.; Butcher, F. K.; Cole, A.; Coombs, R. A.; Davies, M. T.; Green, M. J.; Petrow, V. *Tetrahedron* **1968**, *24*, 4033.
12. Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, 981.
13. Samarat, A.; Landais, Y.; Amri, H. *Tetrahedron Lett.* **2004**, *45*, 2049.
14. Stetter, H.; Marten, K. *Liebigs Ann. Chem.* **1982**, 240.
15. Hu, Q.-Y.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 13708.
16. Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164.
17. Huang, Y.; Iwama, T.; Rawal, V. H. *Org. Lett.* **2002**, *4*, 1163.
18. Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 5950.
19. Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628.
20. Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 7843.
21. Attempted alkylation of carbamate **19** with benzyl bromide afforded a difficult-to-separate mixture of *N*-benzyl carbamate **24** and benzyl bromide. Attempts to use this mixture in the Diels–Alder reaction with Co(III) salen catalyst **23** afforded no detectable product.
22. McAlonan, H.; Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J.; Thompson, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 69.
23. Williams, D. B. G.; Lawton, M. *J. Org. Chem.* **2010**, *75*, 8351.
24. Hon, Y.-S.; Hsu, T.-R.; Chen, C.-Y.; Lin, Y.-H.; Chang, F.-J.; Hsieh, C.-H.; Szu, P.-H. *Tetrahedron* **2003**, *59*, 1509.
25. Rubottom, G. M.; Beedle, E. C.; Kim, C. W.; Mott, R. C. *J. Am. Chem. Soc.* **1985**, *107*, 4230.
26. Ono, N.; Miyake, H.; Fujii, M.; Kaji, A. *Tetrahedron Lett.* **1983**, *24*, 3477.
27. Nakahira, H.; Ryu, I.; Ikebe, M.; Oku, Y.; Ogawa, A.; Kambe, N.; Sonoda, N.; Murai, S. *J. Org. Chem.* **1992**, *57*, 17.
28. Tamura, R.; Kusama, Y.; Oda, D. *J. Org. Chem.* **1990**, *55*, 595.
29. Duffy, M. G.; Grayson, D. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1555.
30. Erkkila, A.; Pihko, P. M. *J. Org. Chem.* **2006**, *71*, 2538.