A Synthesis of Jaspamide Based on 1,2-Metallate Rearrangements of α-Heteroalkenylmetal Derivatives

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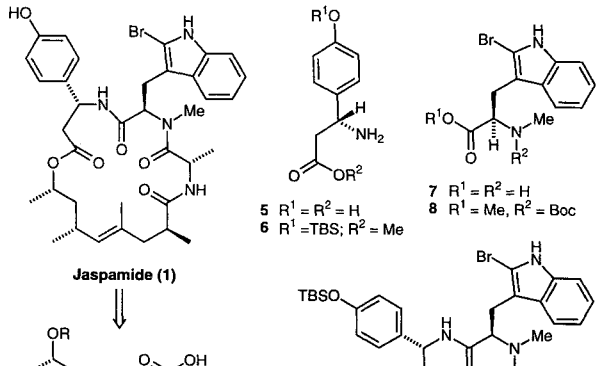
Jaspamide (Jasplakinolide), a marine cyclodepsipeptide, was synthesised from tripeptide fragment **4** and (2*S*,4*E*,6*R*,8*S*)-8-benzoyloxy-2,4,6-trimethylnon-4-enoic acid (**3**). The tripeptide fragment was prepared from β-tyrosine derivative **6**, Boc-2-bromoabrine (**8**), and alanine. β-Tyrosine derivative **6** was prepared by asymmetric conjugate amination of methyl *p*-hydroxycinnamate. Bromabrine derivative **8** was prepared from tryptophan. Key steps in the synthesis of the polyketide fragment **3** include 1,2-metallate rearrangement of a metallated dihydropyran and a metallated enol carbamate derivative.

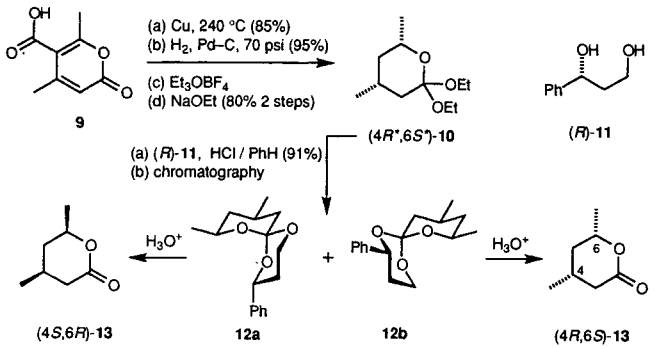
Jaspamide (**1**) is a marine cyclodepsipeptide with antifungal, antihelminthic, insecticidal, and ichthyotoxic activity (Note 1).[1,2] A combination of NMR spectroscopy, X-ray crystallographic analysis and chemical degradation revealed a 19-membered macrolide ring composed of a tripeptide unit spanned by a polyketide chain [(2*S*,4*E*,6*R*,8*S*)-8-hydroxy-2,4,6-trimethylnon-4-enoic acid (**2**)].[3,4] The tripeptide unit harbours two rare amino acids, (*R*)-2-bromoabrine (**7**) and (*R*)-β-tyrosine (**5**), along with the common amino acid (*S*)-alanine. To date four syntheses of Jaspamide have been recorded[5-8] as well as syntheses of the polyketide fragment[9,10] (Note 2). We now give details of our synthesis of Jaspamide which features two variants of a copper catalysed 1,2-metallate rearrangement of metallated enol ether intermediates as a key step.



Scheme 1

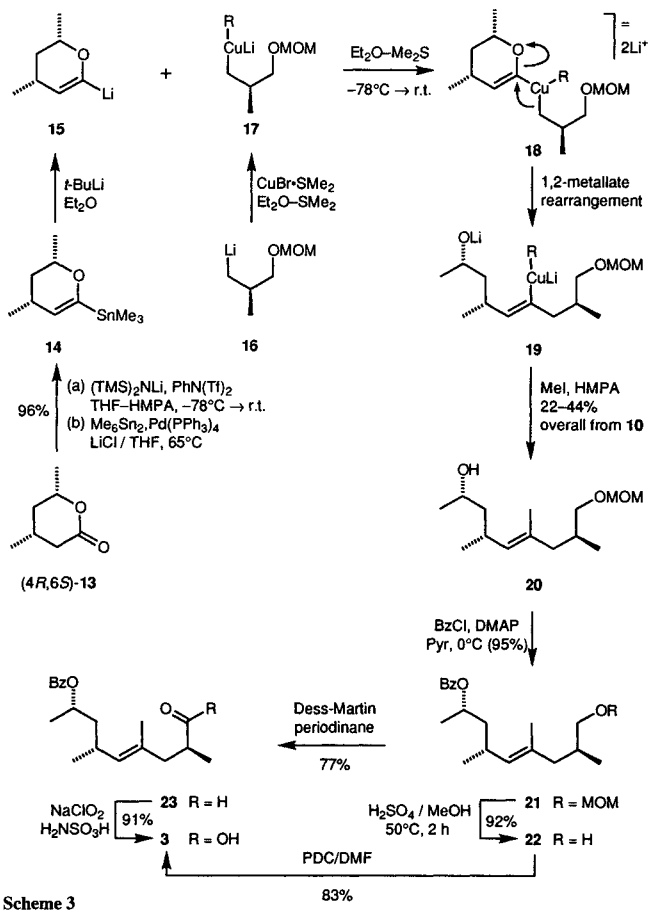
(4*R*,6*S*)-4,6-Dimethyloxan-2-one [(4*R*,6*S*)-**13**], harbouring two of the three stereogenic centres required for the polyketide fragment **3**, was prepared using a chromatographic resolution as shown in Scheme 2.[11] Racemic lactone (4*R**,6*S**)-**13**, prepared from 4,6-dimethylcoumalic acid (**9**) by decarboxylation followed by catalytic hydrogenation,[12,13] was converted to its ortholactone derivative (4*R**,6*S**)-**10** using standard procedures. Reaction of (4*R**,6*S**)-**10** with (*R*)-1-phenylpropan-1,3-diol (**11**)[14] in benzene in the presence of a trace of hydrogen chloride gave a mixture of two spirocyclic ortholactones **12a** and **12b** (ca 1:1) which were easily separated by column chromatography on silica gel (R_f = 0.51 and 0.27 respectively, 5% diethyl ether in benzene). Hydrolysis of **12b** then gave the desired enantiomer (4*R*,6*S*)-**13** having an optical rotation comparable to that previously reported.[15]

In 1989 we reported the first example of a connective synthesis of alkenyllithiums and alkenylcuprates by reaction of lower order homocuprates with metallated dihydrofurans and dihydropyrans.[16,17] The reaction was applied to the synthesis of the trisubstituted alkene moiety of polyketide fragment **3** as shown in Scheme 3. Thus metallated dihydropyran **15**, prepared in three steps from (4*R*,6*S*)-**13**,[18] was added to two equivalents of the homocuprate **17** at –78°C to give the putative higher order cuprate intermediate **18** which then underwent 1,2-metallate rearrangement with clean inversion of configuration on warming to r.t.



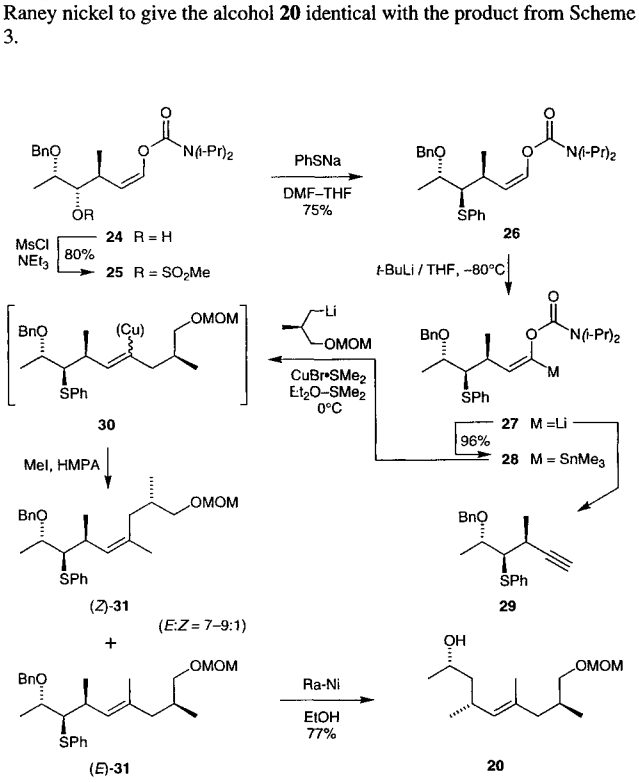
Scheme 2

Alkylation of the resultant alkenylcuprate **19** with MeI gave the trisubstituted alkene fragment **20** as a single stereoisomer in 22–44% yield overall from (4*R*,6*S*)-**13**. Protection of the secondary alcohol as its benzoate ester **21** followed by methanolysis of the methoxymethyl (MOM) protecting group released a primary alcohol **22** whose two-stage oxidation[19,20] furnished the desired carboxylic acid fragment **3** in 73% overall yield from **22**. Oxidation of the alcohol **22** to acid **3** could also be accomplished in a single step (83%) using pyridinium dichromate (PDC) in DMF[21] but the two stage procedure was more reliable on a larger (i.e. > 2 mmol) scale.



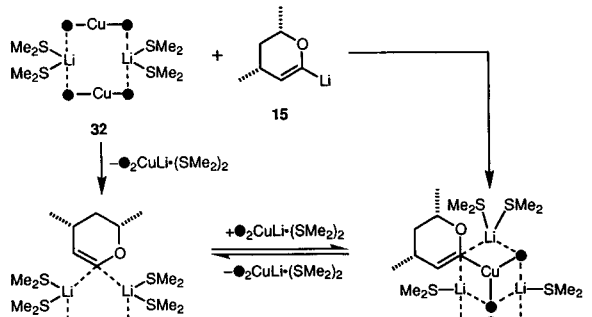
Scheme 3

In order to circumvent the low efficiency of the metallate rearrangement described in Scheme 3 (Note 3), we sought an α-heteroalkenylmetal substrate with a better leaving group in the hope of cleaner reactions at lower temperatures. Hoppe's (*Z*)-anti enol carbamate **24**[22] was selected because it is readily available in homochiral form from cheap reagents (Note 4) on a 0.2 mole scale; furthermore, by embedding the oxygen atom in a highly hindered diisopropyl carbamate moiety, we hoped to enjoy the twin benefits of improved nucleofugacity through resonance and stability towards powerful lithium bases. The first two steps (Scheme 4) of a three sequence used to remove the surplus homoallylic hydroxyl from the Hoppe intermediate **24** (Note 5) involved methanesulfonation followed by displacement with sodium thiophenoxide. Lithiation of the resultant enol carbamate **26** with *tert*-butyllithium at –80°C afforded the lithiated species **27** in quantitative yield with complete retention of double bond configuration. Unfortunately, the anticipated improvement in nucleofugacity now exacted its toll: the lithio derivative **27** underwent slow Fritsch-Buttenberg-Wiechell rearrangement[23] to the alkyne **29** even at –70°C; at –40°C alkyne formation competed with the desired metallate rearrangement which did not occur at an appreciable rate until the temperature reached –20°C.[24] However, the corresponding alkenylstannane **28**, prepared in 95% yield by reaction with trimethyltin chloride at –85°C, transmetallated with alkyllithium reagent **16** in diethyl ether–dimethyl sulphide at 0°C in the presence of the lower order cuprate **17** to give alkenylcuprate intermediate **30** whose alkylation with iodomethane furnished the trisubstituted alkene **31** in 50% yield as a mixture of double bond isomers (*E*/*Z*, 7–9:1) (Notes 6 and 7). To complete the synthesis of the polyketide fragment (Scheme 6), the mixture of alkenes **31** were separated by column chromatography and the phenylthio and benzyl groups removed simultaneously from the *E* isomer by reduction with Raney nickel to give the alcohol **20** identical with the product from Scheme 3.



Scheme 4

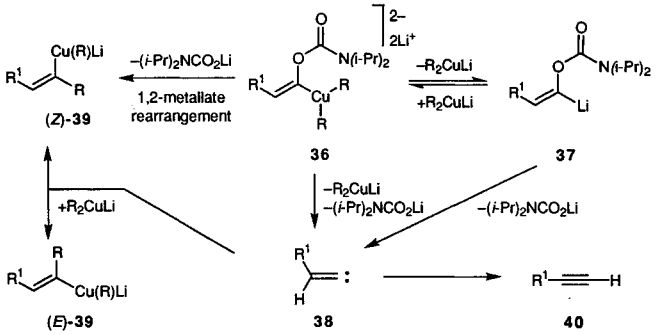
We would now like to speculate on some of the possible mechanisms for the 1,2-metallate rearrangements described in Schemes 3 and 4 beginning with the α-alkoxyalkenyl cuprate derived from metallated dihydropyran **15**. In our original communication,[16] we proposed that higher order cuprates are crucial intermediates in the 1,2-metallate rearrangement and two pieces of evidence reconcile our proposal with new evidence regarding the stability of higher order cuprates. First, we noted that dimethyl sulphide has a beneficial effect on the efficiency of the rearrangement;[25] secondly, Olmstead and Power[26,27] have obtained single crystal X-ray structures of higher order cuprates *which incorporate Me_2S as stabilising ligands*. Taken together, this information suggests that lithiated enol ether **15** reacts with lower order cuprate **32** (Scheme 5) to generate higher order cuprate **33b** in which the alkenyl carbon is bound to copper as well as two bridging lithiums. A 1,2-alkyl shift with inversion of configuration then converts **33b** directly to the product **35** — a transformation which is easily explicable in molecular orbital terms (Note 8). If, on the other hand, the alkene bond of intermediate **33b** is highly nucleophilic (as observed with the corresponding borates[28,29] and aluminates[30]), then the rearrangement may proceed through intermediate **34** in which a lithium cation serves as the electrophilic trigger. Collapse of intermediate **34** with its antiperiplanar relation between the Li and O atoms would then account for the formation of alkenylcuprate **35**.



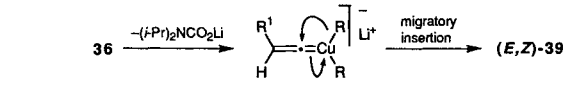
Scheme 5

Another possible mechanism (Scheme 5) which avoids the tricoordinate Cu(I) dianion **33b** involves the aggregate **33a** consisting of a lower order Gilman cuprate and the α-alkoxyalkenyllithium **11**. A 1,2-metallate rearrangement of **18a** followed by aggregation with a Gilman cuprate also accounts for the formation of **35**. Although the balance of current opinion seems to be weighted against the existence of higher order cuprates and cyanocuprates as stable entities *in ethereal solvents*,[31-35] their implication in organic reactions as fleeting intermediates remains a possibility.

In the case of the rearrangement featured in Scheme 4, the diminished stereoselectivity in the formation of **31** and the attendant formation of alkyne **29** may unite both products by a common intermediate reflecting the intrinsic instability of α-(carbamoyloxy)alkenyl cuprates or their lithium precursor. Thus, in the generalized Scheme 6, α-elimination of **36** or **37** to the vinylidene carbene **38** provides a junction which leads either to a mixture of alkenylcuprates (*E*)-**39** and (*Z*)-**39** by insertion into the C–Cu bond of a lower order cuprate (Note 9) or to alkyne **40** by a Fritsch-Buttenberg-Wiechell rearrangement. Alternatively, a 1,2-metallate rearrangement with clean inversion of configuration leading to (*Z*)-**39** (like

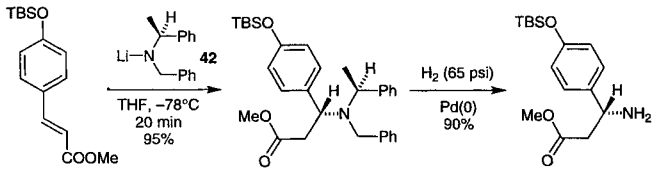


Scheme 6



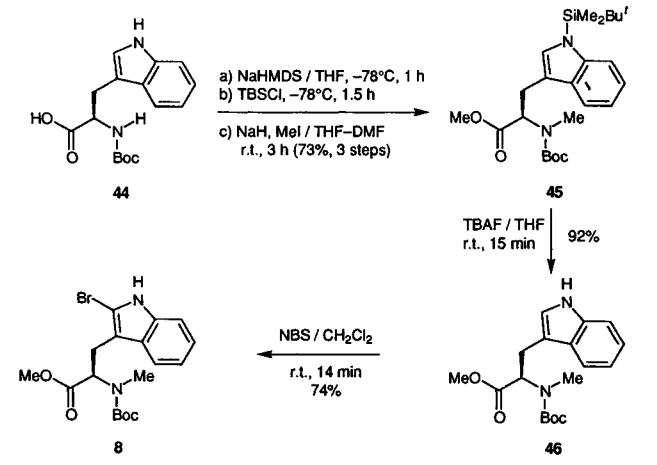
that described in Scheme 3) may be accompanied by competing α-elimination leading to a carbene which is then trapped with an alkyllithium, thereby accounting for the loss of stereochemistry at the double bond.

The two unusual amino acid derivatives of (*R*)-β-tyrosine and (*R*)-bromoabrine required for the synthesis of the tripeptide fragment **4**, were prepared by short routes from readily available commercial starting materials. Thus, the synthesis of β-tyrosine derivative **6** (Scheme 7) began with protection of methyl *p*-hydroxycinnamate as its *tert*-butyldimethylsilyl (TBS) ether. Asymmetric conjugate amination was then accomplished by addition of ester **41** to a solution of lithium (*S*)-*N*-benzyl-1-phenylethanamide (**42**)[36] in tetrahydrofuran at −78°C to give adduct **43** in 95% yield (d.e. >95%). Finally, palladium-catalysed hydrogenolysis of the *N*-benzyl and *N*-phenethyl groups in tetrahydrofuran–acetic acid (1:2) at room temperature gave the desired amine **6** as a solid in 90% yield. This three-step sequence (82% overall), adapted from the procedure of Davies and coworkers, is probably the most efficient and economical synthesis of β-tyrosine derivatives reported to date.[37]



Scheme 7

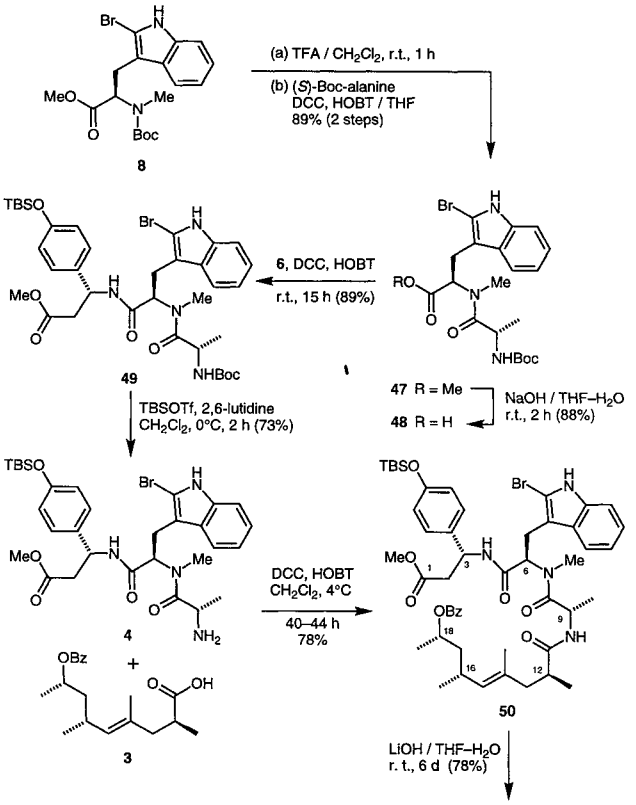
Our four-step synthesis of the protected (*R*)-bromoabrine derivative **8**, summarised in Scheme 8, is a modification of the route used by Grieco and coworkers[5] in their pioneering synthesis of Jaspamide. Protection of the indole nitrogen in (*R*)-Boc-tryptophan (**44**) as its labile TBS derivative followed by methylation of the Nα and carboxyl groups gave **45** in 73% yield. Removal of the TBS group from **45** with tetrabutylammonium fluoroborate (TBAF) (Note 10) followed by bromination at the 2-position of the indole with *N*-bromosuccinimide[38] (Note 11) furnished the desired methyl ester **8** as a crystalline solid in 50% overall yield from **44**.



Scheme 8

Construction of the tripeptide fragment **4** from the two synthetic amino acid derivatives **6** and **8** and (*S*)-Boc-alanine was achieved efficiently using conventional deprotection-peptide coupling techniques as outlined in Scheme 9. The only step in the sequence requiring comment is the deprotection of the Boc group in **49** using TBSOTf[39] because the usual protonolytic methods caused premature removal of the phenolic TBS group as well.[40]

To complete the synthesis of Jaspamide, an amide bond between the polyketide fragment **3** and the tripeptide fragment **4** was created in the usual way using hydroxybenzotriazole-assisted activation with



Scheme 9

dicyclohexylcarbodiimide (DCC). Although the reaction was slow, a good yield (78%) of the diester derivative **50** was obtained. Hydrolysis of all three protecting groups with lithium hydroxide in aqueous tetrahydrofuran gave *seco*-acid **51** which underwent cyclodehydration with CMC [1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate] according to the procedure of Boden and Keck[41] to furnish Jaspamide in 28% yield (Notes 12 and 13).

In conclusion, our synthesis of Jaspamide has served as a useful vehicle for understanding the scope and limitations of 1,2-metallate rearrangements in the construction of polyketide chains. Although α-alkoxyalkenylcuprates rearrange with clean inversion of configuration, the regrettable loss of stereoselectivity in the rearrangement of enol carbamate derivatives indicates a mechanistic diversity in metallate rearrangements which has yet to be fully understood and explored. Nevertheless, the very fact that heteroatoms bound to sp^2 carbon can be displaced by C-nucleophiles, whatever the precise details of the mechanism, underscores the potential of α-heteroalkenylmetals (alkenylidene carbenoids) in organic synthesis.[17,42,43]

Notes

1. The name Jaspamide was given to **1** by Ireland and Faulkner,[3] but Crews,[4] in a simultaneous and independent study, assigned the name Jasplakinolide.

2. The Geodiamolides are antifungal marine cyclodepsipeptides which have the polyketide fragment **2** in common with Jaspamide.[44] Total syntheses of the Geodiamolides have been reported.[7,8,45-48]

3. The principal source of irreproducibility appears to be temperature. Each 1,2-metallate rearrangement we have examined has a temperature window which must be reached at the right time after mixing the reagents in order to achieve optimum results.

4. The development of Hoppe's homoaldol reaction has been reviewed.[49,50]

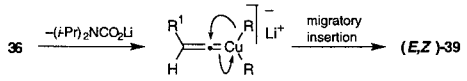
5. Attempts to remove the hydroxy group by reduction of the xanthate ester with Bu_3SnH or methanesulfonate **25** with $LiHBEt_3$ gave low yields or messy reactions.

6. The loss of stereochemistry was not the result of isomerization during the slow alkylation step since protonation of **30** at low temperature gave a mixture of disubstituted alkenes in the same ratio.

7. Similar reactions of stannane **28** with the higher order cyanocuprates derived from BuLi, *s*-BuLi, *t*-BuLi, and MeLi also gave good yields of the coupling product; however, contrary to our earlier report [51] with the exception of *t*-BuLi, all the coupling reactions gave mixtures of alkenes (*E*:*Z* = 4–6:1).

8. Recent calculations suggest that direct displacement with inversion at sp^2 centres is a low energy process.[52] X-ray structures of a number of α-heteroalkenylmetals show significant lengthening of the C–heteroatom bond.[34,53,54]

9. Another possible mechanism for the rearrangement is that the alkenylcuprate (*E,Z*)-**39** stems from migratory insertion of a vinylidene copper carbenoid:



10. Attempts to accomplish the simultaneous bromination and desilylation using pyridinium hydrobromide perbromide as described previously[5] returned the desired product in only 24% yield.

11. The use of NBS adsorbed onto silica as originally reported by Smith and co-workers[38] was not necessary to facilitate the reaction, although an induction period of 5 minutes was required if the silica were omitted.

12. Jaspamide could not be completely separated from dicyclohexylurea when DCC was used in the cyclodehydration.

13. The appalling yield in the macrocyclisation can be blamed on the free phenolic hydroxyl since the corresponding *O*-methyl ether cyclized under identical conditions in 83% yield. Unfortunately, the methyl ether could not be cleaved from the macrocycle or its *seco*-acid precursor with BBr_3[55] or $AlBr_3$–EtSH.[56]

All reactions requiring anhydrous conditions were conducted in flame-dried apparatus. Where appropriate, solvents and reagents were dried by standard methods, *i.e.* by distillation from the usual drying agent prior to use: tetrahydrofuran from sodium and benzophenone; pyridine, triethylamine, dichloromethane, dimethylformamide and hexamethylphosphoric triamide from calcium hydride. Chloroform was distilled from phosphorus pentoxide. Diethyl ether, benzene and toluene were stored over sodium wire. Copper(I) bromide-dimethyl sulfide complex was purified by recrystallization from anhydrous dimethyl sulfide and anhydrous pentane. (–)-Sparteine was isolated from its sulfate by treatment with solid sodium hydroxide followed by distillation twice. All reactions were magnetically stirred unless otherwise stated. Organic extracts were dried over $MgSO_4$ and concentrated at aspirator pressure using a Büchi rotary evaporator. All reactions were monitored by TLC with Macherey-Nagel Duren Alugram Sil G/UV_{254} precoated aluminium foil sheets, layer thickness 0.25 mm. Compounds were visualised with UV light, followed by ceric sulfate/ethanolic sulfuric acid. Column chromatography was performed on Merck kiesel gel 60 (0.04-0.063 mm, 230-400 mesh).

IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrophotometer, using a thin film supported on NaCl plates or as a liquid phase. Details are reported as ν_{max} (cm^{-1}), followed by a description using the following abbreviations: s = strong, m = medium, w = weak or br = broad. ^1H NMR spectra were recorded in Fourier Transform mode on Jeol FX-90 (90 MHz), Jeol GX-270 (270 MHz) or Bruker AM 360 (360 MHz) spectrometers. All spectra were obtained in $CDCl_3$ solution as stated and the chemical shift values are reported as values in ppm relative to residual chloroform (δ = 7.27) as internal standard unless otherwise stated. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, app = apparent and br = broad. Coupling constants (*J*) are reported in Hz. ^{13}C NMR spectra were recorded on a Jeol GX-270 (67.5 MHz), or a Bruker AM 360 (90 MHz) spectrometer. All spectra were obtained in $CDCl_3$ solution and the chemical shift values are reported as values in ppm relative to residual chloroform (δ = 77.2) as internal standard. The multiplicities refer to the signals in the off-resonance spectra and were elucidated using the Distortionless Enhancement by Polarisation Transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Multiplicities are described using the following abbreviations: 0 = singlet (due to quarternary carbon), 1 = doublet (methyne), 2 = triplet (methylene), 3 = quartet (methyl). Numbers encased in brackets indicates signals arising from rotamers.Mass spectra were run on a VG 70-250-SE spectrometer. Ion mass (*m/z*) signals, are reported as values in atomic mass units followed, in parentheses, by the peak intensity relative to the base peak (100%). Satisfactory microanalyses were obtained for **8**: C -0.34, H +0.10, N +0.03, and **25**: C -0.10, H +0.13, N +0.18, Br +0.01.

(4*R*,6*S*)-4,6-Dimethyl-2-(trimethylstannyl)-2-oxene (14):
To a solution of hexamethyldisilazane (542 mg, 3.25 mmol) in THF (6 mL) was added BuLi (2 mL of 1.63 M solution in hexane, 3.25 mmol) at 0°C under Ar. After 30 min the solution was cooled to –80°C and a solution of (4*R*,6*S*)-4,6-dimethyloxan-2-one (**13**)[18] (320 mg, 2.5 mmol) in THF (1 mL) was added followed by HMPA (672 mg, 3.75 mmol). The solution was stirred for 3 h at –80°C before the addition of *N*-phenyltriflamide (1.07 g, 3.75 mmol). Stirring was continued for a further 30 min at –80°C and the mixture allowed to warm to 22°C and stirred for 2 h. The mixture was concentrated to a volume of 2 mL which was then added to a mixture of hexamethyldistannane (0.9 g, 2.75 mmol), $Pd(PPh_3)_4$ (144 mg, 0.13 mmol) and LiCl (800 mg, 18 mmol) in THF (5 mL). The mixture was then heated at 60°C for 12 h. The resultant black suspension was poured into sat. $NaHCO_3$, extracted with Et_2O (2 x 25 mL) and dried. The residue obtained after concentration was purified by column chromatography (neutral alumina, Et_2O–hexanes, 1:10) followed by Kugelrohr distillation to give **14** (662 mg, 2.4 mmol, 96%) as a colourless oil: bp 50°C (bath)/12 mmHg.

IR (film): ν = 1604 (m), 1454 (m), 1434 (m), 1312 (m), 1270 (m), 1058 (s), 770 (s), 743 (s), 696 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 4.56 (1H, br s), 3.94–3.86 (1H, m), 2.44–2.28 (1H, m), 1.89–1.76 (1H, m), 1.26–1.19 (1H, m), 1.21 (3H, d, *J* = 6.2 Hz), 0.95 (3H, d, *J* = 6.6 Hz), 0.01 (9H, s).

^{13}C NMR (67.5 MHz): δ = 164.4 (0), 118.1 (1), 73.2 (1), 40.1 (2), 28.5 (1), 22.1 (3), 22.1 (3), –9.1 (3C, 3).

(2*S*,4*E*,6*S*,8*S*)-8-Hydroxy-1-(methoxymethoxy)-2,4,6-trimethylnon-4-ene (20):
To a stirred solution of stannane **14** (2.22 g, 8.1 mmol) in Et_2O (10 mL) was added *t*-BuLi (1.7 M in pentane, 5.0 mL, 8.5 mmol) at –78°C. Stirring at –78°C was continued for 30 min whereupon the cooling bath was removed and the mixture allowed to warm to 0°C over 100 min and then stirred at 0°C for 1 h. The resultant yellow solution of lithiated enol ether **15** was used immediately in the next step.

To a solution of (*R*)-3-(methoxymethoxy)-2-methyl-1-iodopropane[57] (8.80 g, 32 mmol) in Et_2O (100 mL) was added *t*-BuLi (1.7 M in pentane, 34.0 mL, 57.6 mmol) dropwise at –78°C. After addition was complete, the mixture was allowed to stir at –78°C for 30 min whereupon the cooling bath was replaced by an ice bath and the mixture allowed to stir for a further 30 min. To the resultant organolithium reagent **16** was then added slowly under Ar pressure via cannula a solution of CuBr•Me_2S (1.74 g, 8.5 mmol) in Me_2S (10 mL). The resultant yellow solution was allowed to warm to 10°C over 45 min to give a colourless solution to which was added rapidly the lithiated enol ether **15** solution prepared as described above. The resultant orange solution was stirred at 20°C for 4 h. After cooling to –80°C, MeI (2 mL) and HMPA (2 mL) were added and and the mixture allowed to warm gradually to r.t. over 16 h whereupon a solution of NH_4OH (15 M), in sat. NH_4Cl (1:10, 30 mL) was added with vigorous stirring. The layers were separated and the organic layer thoroughly washed with NH_4OH-NH_4Cl until the aqueous extracts were colourless. The organic layer was washed with brine, dried and concentrated to a pale yellow oil which was purified by column chromatography (silica gel; hexanes/Et_2O, 2:1) to give alcohol **20** (0.87 g, 3.6 mmol, 44%) as a viscous oil; $[\alpha]_D$ = –17.9° (*c* = 1.04, MeOH).

IR (film): ν = 3421 (br s), 1638 (w), 1047 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 4.97 (1H, d, *J* = 9.7 Hz, C5H), 4.58 (2H, s, OCH_2O), 3.78 (1H, dt, *J* = 6.8, 6.2 Hz, C8H), 3.34 (1H, dd, *J* = 10.4, 6.0 Hz, $C1H_B$), 3.33 (3H, s, OMe), 3.26 (1H, dd, *J* = 9.8, 6.6 Hz, $C1H_A$), 2.48 (1H, m, C6H), 2.11 (1H, dd, *J* = 12.9, 5.8 Hz, $C3H_B$), 1.98-1.82 (2H, m, OH & C2H), 1.72 (1H, ddd, *J* = 8.6, 12.9, 0.8 Hz, $C3H_A$), 1.60 (3H, d, *J* = 1.3 Hz, C4–Me), 1.39-1.32 (2H, m, $C7H_2$), 1.13 (3H, d, *J* = 6.0 Hz, C9–Me), 0.92 (3H, d, *J* = 6.6 Hz, C6–Me), 0.85 (3H, d, *J* = 6.6 Hz, C2–Me).

^{13}C NMR (67.5 MHz): δ = 132.9 (1), 132.1 (0), 96.5 (2), 73.0 (2), 67.7 (1), 55.0 (3), 47.3 (2), 44.1 (2), 31.4 (1), 30.0 (1), 23.4 (3), 21.4 (3), 16.8 (3), 16.0 (3).

LRMS (CI): *m/z* (%) = 262 [$(M+NH_4)^{+\bullet}$, 15], 245 [$(M+H)^{+\bullet}$, 100], 213 (40), 183 (25).

(2*S*,4*E*,6*S*,8*S*)-8-Benzoyloxy-1-(methoxymethoxy)-2,4,6-trimethylnon-4-ene (21):
To a solution of alcohol **20** (500 mg, 2.04 mmol) and DMAP (10 mg) in pyridine (3 mL) and CH_2Cl_2 (10 mL) under Ar was slowly added benzoyl chloride (480 µL, 4.1 mmol), before pouring into dil. HCl (45 mL) and extracting the aqueous layer with Et_2O (4 x 20 mL). The combined organic extracts were dried and concentrated prior to purification by column chromatography (silica gel; hexanes/Et_2O, 2:1) to give ester **21** (680 mg, 1.95 mmol, 95%) as a viscous oil: $[\alpha]_D$ = +15.0° (*c* = 1.68, MeOH).

IR (film): ν = 2928 (s), 1710 (s), 1451 (m), 1277 (s), 1111 (s), 1047 (s), 712 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 8.05–8.11 (2H, m), 7.67–7.57 (1H, m), 7.54–7.45 (2H, m), 5.17 (1H, m, C8H), 5.00 (1H, dq, *J* = 8.9, 1.0 Hz, C5H), 4.61 (2H, s, OCH_2O), 3.40-3.33 (1H, dd, *J* = 9.3, 5.8, $C1H_B$), 3.36 (3H, s, OMe), 3.28 (1H, dd, *J* = 9.3, 6.6 Hz, $C1H_A$), 2.52 (1H, m, C6H), 2.10 (1H, dd, *J* = 12.9, 6.0 Hz, $C3H_B$), 2.04-1.65 (3H, m, C2H, $C3H_A$, $C7H_B$), 1.60 (3H, d, *J* = 1.4 Hz, C4–Me), 1.54 (1H, dd, *J* = 13.3, 6.7 Hz, $C7H_A$), 1.33 (3H, d, *J* = 6.2 Hz, C9–Me), 0.98 (3H, d, *J* = 6.6 Hz, C6–Me), 0.9 (3H, d, *J* = 6.6 Hz, C2–Me).

^{13}C NMR (67.5 MHz): δ = 166.0 (0), 132.7 (1), 132.2 (1), 132.0 (0), 130.9 (0), 129.5 (1), 128.3 (1), 96.6 (2), 73.9 (2), 70.3 (1), 55.0 (3), 44.0 (2), 43.7 (2), 31.4 (1), 29.3 (1), 21.2 (3), 20.2 (3), 17.0 (3), 16.0 (3).

LRMS (CI): *m/z* (%) = 366 [$(M+NH_4)^{+\bullet}$, 100], 349 [$(M+H)^{+\bullet}$, 5], 317 (90), 195 (45), 183 (55), 109 (20).

(2*S*,4*E*,6*S*,8*S*)-8-Benzoyloxy-2,4,6-trimethylnon-4-en-1-ol (22):
To a solution of ester **21** (680 mg, 1.95 mmol) in MeOH (7 mL) at 50°C was added conc. H_2SO_4 (8 drops) and the reaction maintained at reflux until completion (TLC). The reaction mixture was then cooled and solid $NaHCO_3$ added until effervescence ceased. The reaction solution was filtered and concentrated and the gelatinous residue dissolved in a small amount of MeOH and sufficient silica gel added to give a free flowing powder upon removal of the MeOH: Purification by column chromatography (silica gel; hexanes/Et_2O, 3:1) gave alcohol **21** [419 mg, 1.37 mmol, 70% (92% based on recovered **20** , 145 mg)] as a clear oil: $[\alpha]_D$ = +15.4° (*c* = 2.08, MeOH).

IR (film) ν = 3400 (br), 1716 (s), 1451 (m), 1278 (s), 1112 (m), 1026 (m), 712 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 8.11–8.05 (2H, m), 7.67–7.57 (1H, m), 7.54–7.45 (2H, m), 5.22–5.10 (1H, m, C8H), 5.04 (1H, dd, *J* = 9.5, 0.8 Hz, C5H), 3.49 (1H, dd, *J* = 10.6, 5.6 Hz, $C1H_B$), 3.40 (1H, dd, *J* = 10.6, 6.0 Hz, $C1H_A$), 2.50 (1H, m, C6H), 2.01 (1H, dd, *J* = 12.9, 6.0 Hz, $C3H_B$), 1.90-1.65 (3H, m, $C3H_A$, C2H, $C7H_B$), 1.61 (3H, d, *J* =

1.4 Hz, C4–Me), 1.60-1.50 (1H, m, C7H$_A$), 1.32 (3H, d, J = 6.4, C9–Me), 0.97 (3H, d, J = 6.8 Hz, C6–Me), 0.88 (3H, d, J = 6.4 Hz, C2–Me).

^{13}C NMR (67.5 MHz): δ = 166.8 (0), 132.7 (1), 132.5 (0), 131.9 (1), 130.8 (0), 129.4 (1), 128.2 (1), 70.3 (1), 68.0 (2), 43.9 (2), 43.6 (2), 33.8 (1), 29.3 (1), 21.1 (3), 20.1 (3), 16.7 (3), 16.0 (3).

LRMS (CI, NH_3): m/z (%) = 322 [$(M+NH_4)^{+\bullet}$, 10], 305 [$(M+H)^{+\bullet}$, 35], 201 (35), 183 (100), 109 (10), 99 (15).

(2*S*,4*E*,6*S*,8*S*)-8-Benzoyloxy-2,4,6-trimethylnon-4-en-1-al (23):

To a stirred solution of alcohol **22** (525 mg, 1.72 mmol) in CH_2Cl_2 (30 mL) under Ar was added Dess-Martin periodinane[19,58] (1.67 g, 3.94 mmol) at r.t. and the resulting solution stirred for 1 h. The reaction solution was then diluted with CH_2Cl_2 (50 mL) and washed with sat. aq $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 x 25 mL) and the combined organic extracts were dried and concentrated prior to purification by column chromatography (silica gel; hexanes/Et_2O, 3:1) to give aldehyde **23** (400 mg, 1.32 mmol, 77%) as a clear oil: $[\alpha]_D$ = +10.8° (c = 1.95, MeOH).

IR (film): ν = 1715 (s), 1452 (m), 1278 (s), 1112 (s), 1070 (m), 713 (s) cm^{-1}.

^{1}H NMR (270 MHz): δ = 9.59 (1H, d, J = 2.1 Hz, CHO), 8.11–8.04 (2H, m), 7.67–7.57 (1H, m), 7.54–7.45 (2H, m), 5.15 (1H, ddq, J = 6.8, 6.8, 6.2 Hz, C8H), 5.05 (1H, dq, J = 9.5, 1.3 Hz, C5H), 2.50 (1H, m, C2H), 2.36 (1H, ddd, J = 8.3, 13.8, 1.2 Hz, C3H$_B$), 1.93 (1H, ddd, J = 6.8, 13.7, 1.0 Hz, C3H$_A$), 1.75 (1H, ddd, J = 13.7, 7.7, 6.2 Hz, C7H$_B$) 1.74 (1H, m, C6H), 1.61 (3H, d, J = 1.4 Hz, C4–Me), 1.55 (1H, ddd, J = 13.5, 7.0, 6.6 Hz, C7H$_A$), 1.32 (3H, d, J = 6.2 Hz, C9–Me), 1.03 (3H, d, J = 6.7 Hz, C6–Me), 0.96 (3H, d, J = 6.6 Hz, C2–Me).

^{13}C NMR (67.5 MHz): δ = 205.0 (1), 166.2 (0), 133.6 (1), 132.8 (1), 130.9 (0), 130.4 (0), 129.6 (1), 128.5 (1), 128.4 (1), 70.3 (1), 44.4 (1), 43.7 (2), 40.9 (2), 29.6 (1), 21.2 (3), 20.4 (3), 16.2 (3), 13.3 (3).

LRMS (CI, NH_3): m/z = 320 [$(M+NH_4)^{+\bullet}$, 100%], 303 [$(M+H)^{+\bullet}$, 26], 245 (12, 181 (30).

(2*S*,4*E*,6*S*,8*S*)-8-Benzoyloxy-2,4,6-trimethylnon-4-enoic acid (3):

The method of Lindgren and Nilsson[20] was used to oxidise aldehyde **23** to the acid **3**. To a vigorously stirred solution of aldehyde **23** (575 mg, 1.90 mmol) and 1-methylcyclohexene (1.3 mL, 11.0 mmol) in CH_2Cl_2 (8 mL) and H_2O (4 mL) at 4°C was added sulfamic acid (275 mg, 2.85 mmol) and sodium chlorite (602 mg, 6.65 mmol) and the resultant yellow solution was stirred for 2 h whilst being allowed to warm to r.t. The reaction mixture was then poured into sat. aq $NaHCO_3$ and extracted with EtOAc (3 x 30 mL). The organic extracts were combined, dried and concentrated prior to purification by column chromatography (silica gel; hexanes/Et_2O, 2:1) to give acid **3** (550 mg, 1.76 mmol, 91%) as a viscous oil.

Alternatively, reaction of alcohol **35** (330 mg, 1.08 mmol) in DMF (6 mL) at r.t. with pyridinium dichromate (2.03 g, 5.4 mmol) for 9 h followed by standard extractive workup with Et_2O and purification by column chromatography gave acid **3** (284 mg, 0.90 mmol, 83%): $[\alpha]_D$ = +15.0° (c = 2.1, MeOH).

IR (film): ν = 3417 (br s), 1713 (s), 1277 (s), 1111 (m), 712 (s) cm^{-1}.

^{1}H NMR (270 MHz): δ = 11.10 (1H, br s, CO_2H), 8.11–8.05 (2H, m), 7.67-7.57 (1H, m), 7.54–7.45 (2H, m), 5.16 (1H, ddq, J = 6.6, 6.6, 6.2 Hz, C8H), 5.06 (1H, d, J = 9.5 Hz, C5H), 2.61 (1H, ddq, J = 7.6, 7.0, 7.0 Hz, C2H), 2.58-2.42 (1H, m, C6H), 2.31 (1H, dd, J = 13.5, 7.5 Hz, C3H$_B$), 2.00 (1H, dd, J = 13.5, 7.5 Hz, C3H$_A$), 1.72 (1H, ddd, J = 13.5, 7.7, 7.3 Hz, C7H$_A$, C7H$_B$), 1.61 (3H, s, C4–Me), 1.53 (1H, ddd, J = 13.5, 6.6, 6.6 Hz, C7H$_A$), 1.32 (3H, d, J = 6.1 Hz, C9–Me), 1.14 (3H, d, J = 6.8 Hz, C6–Me), 0.95 (3H, d, J = 6.7 Hz, C2–Me).

^{13}C NMR (67.5 MHz): δ = 182.8 (0), 166.3 (0), 133.4 (1), 132.9 (1), 130.9 (0), 130.8 (0), 129.6 (1), 128.4 (1), 70.4 (1), 43.8 (2), 43.7 (2), 38.1 (1), 29.5 (1), 21.1 (3), 20.4 (3), 16.5 (3), 16.0 (3).

HRMS (CI, NH_3): found $(M+NH_4)^{+\bullet}$ = 336.2175. $C_{19}H_{30}NO_4$ requires M = 336.2180.

(3*S*,4*S*,5*S*)-5-Benzyloxy-1-(*N*,*N*-diisopropylcarbamoyloxy)-3-methylhex-1-en-4-ol (24):

The title compound was prepared in 65% yield on a 33 mmol scale by the method of Hoppe and coworkers.[22]

(3*S*,4*R*,5*S*)-5-Benzyloxy-1-(*N*,*N*-diisopropylcarbamoyloxy)-4-methanesulfonyloxy-3-methylhex-1-ene (25):

Methanesulfonyl chloride (3.0 mL, 38.6 mmol) was slowly added to a stirred solution of alcohol **24** (12.2 g, 33.6 mmol) and Et_3N (11.3 mL, 80.6 mmol) in CH_2Cl_2 (100 mL) at –30°C. The reaction solution was stirred for 2 h at –30°C before quenching with H_2O (100 mL) and extracting with CH_2Cl_2 (5 x 50 mL). The organic extracts were combined, dried and concentrated to yield a residue which was then purified by column chromatography (silica gel; hexanes/Et_2O, 1:3, Rf = 0.20) to give **25** [10.7 g, 24.2 mmol, 72% (80% based on recovered starting material)] as a white crystalline solid: mp 71–73°C (pentane/Et_2O); $[\alpha]_D$ = +35.8° (c = 1.80, MeOH).

IR (KBr): ν = 1703 (s), 1673 (m), 1440 (m), 1165 (s), 1062 (s), 851 (m), 755 (m) cm^{-1}.

^{1}H NMR (360 MHz): δ = 7.35 (5H, m, Ar), 7.08 (1H, d, J = 6.5 Hz, C1H), 4.79 (1H, dd, J = 10.1, 6.5 Hz, C2H), 4.65 and 4.41 (1H each, d, J = 11.4 Hz, PhCH$_2$), 4.54 (1H, dd, J = 7.5, 3.8 Hz, C4H), 4.15 and 3.85 (1H each, br s, Me$_2$C**H**), 3.71 (1H, dq, J = 7.4, 6.2 Hz, C5H), 3.10 (1H, ddq, J = 10.1, 6.6, 3.75 Hz, C3H), 2.89 (3H, s, MeSO$_2$), 1.25 and 1.24 (6H each, d, J = 6.8 Hz, *i*-Pr), 1.22 (3H, d, J = 6.5 Hz, C6H$_3$), 1.16 (3H, d, J = 7.0 Hz, C3–Me).

^{13}C NMR (90 MHz): δ = 152.5 (0), 137.9 (0), 136.0 (1), 128.5 (1), 127.9 (1), 129.7 (1), 110.0 (1), 89.4 (1), 75.6 (1), 71.2 (2), 47.0 (1), 46.0 (1), 38.9 (3), 31.5 (1), 21.6 (3), 20.5 (3), 18.5 (3), 15.5 (3).

LRMS (CI): m/z (%) = 459 [$(M+NH_4)^{+\bullet}$, 55], 442 [$(M+H)^{+\bullet}$, 100], 346 (5), 236 (35), 128 (75).

(3*S*,4*R*,5*S*)-5-Benzyloxy-1-(*N*,*N*-diisopropylcarbamoyloxy)-3-methyl-4-phenylthiohex-1-ene (26):

To a vigorously stirred solution of methanesulfonate **25** (11.95 g, 27.0 mmol) in THF (40 mL) and DMF (40 mL) was added sodium thiophenoxide (17.9 g, 135.3 mmol). The reaction solution was heated for 8 h at 60°C before quenching with aq NaOH (2 M, 250 mL) and extracting with Et_2O (4 x 100 mL). The organic extracts were combined, dried and then concentrated prior to purification by column chromatography (silica gel; hexanes/Et_2O, 20:1) to give **26** (9.27 g, 20.3 mmol, 75%) as a clear colourless oil; $[\alpha]_D$ = +49.1° (c = 2.04, MeOH).

IR (film): ν = 1713 (s), 1435 (s), 1307 (s), 1067 (s), 735 (m), 696 (m) cm^{-1}.

^{1}H NMR (270 MHz): δ = 7.44–7.50 (2H, dd, J = 8.1, 1.5 Hz), 7.14–7.40 (8H, m), 7.03 (1H, dd, J = 6.4, 1.0 Hz, C1H), 4.89 (1H, dd, J = 9.6, 6.5, C2H), 4.59 and 4.42 (1H each, d, J = 11.6, PhCH$_2$), 4.04 and 3.82 (1H each , br s, Me$_2$C**H**), 3.77 (1H, dq, J = 6.5, 6.5 Hz), 3.38 (1H, ddq, J = 9.5, 6.8, 6.5 Hz), 3.17 (1H, dd, J = 7.0, 5.9 Hz), 1.30 (3H, d, J = 6.0 Hz, C6–Me), 1.23 (12H, m, *i*-Pr), 1.14 (3H, d, J = 7.0 Hz, C3–Me).

^{13}C NMR (67.5 MHz): δ = 152.7 (0), 138.7 (0), 137.9 (0), 134.3 (1), 131.0 (1), 128.9 (1), 128.3 (1), 127.8 (1), 127.5 (1), 126.3 (1), 114.9 (1), 76.7 (1), 70.9 (2), 62.1 (1), 46.7 (1), 45.9 (1), 31.3 (1), 21.5 (3), 20.5 (3), 17.4 (3), 17.0 (3).

LRMS (CI): m/z (%) = 473 [$(M+NH_4)^{+\bullet}$, 5], 456 [$(M+H)^{+\bullet}$, 10], 348 (65), 256 (20), 240 (40), 128 (60).

(3*S*,4*R*,5*S*)-5-Benzyloxy-1-(*N*,*N*-diisopropylcarbamoyloxy)-3-methyl-4-phenylthio-1-(trimethylstannyl)hex-1-ene (28):

To a stirred solution of **26** (10.1 g, 22.2 mmol) in THF (70 mL) at –80°C under Ar was slowly added *t*-BuLi (1.5 M in pentane, 16.2 mL, 24.3 mmol) whilst maintaining the temperature below –75°C. After 30 min at –80°C, trimethyltin chloride (5.76 g, 28.9 mmol) in THF (20 mL) was slowly added and the resulting reaction solution stirred at –80°C for 2 h, before adding sat. NH_4Cl (100 mL). The layers were separated and the aqueous phase extracted with Et_2O (4 x 100 mL). The organic extracts were then combined, dried (Na_2SO_4), and concentrated prior to purification by column chromatography (silica gel; hexanes/Et_2O 25:1) to give **28** (13.2 g, 21.4 mmol, 96%) as a viscous oil; $[\alpha]_D$ = –30.6° (c = 2.52, MeOH).

IR (film): ν = 2969 (m), 1668 (s), 1435 (m), 1057 (s), 733 (s), 697 (m) cm^{-1}.

^{1}H NMR (270 MHz): δ = 7.44–7.49 (2H, m), 7.36-7.10 (8H, m), 5.00 (1H, dt, J = 8.7 , $J_{H,Sn}$ = 34.1 Hz, C2H), 4.58 and 4.40 (1H each, d, J = 11.8 Hz, PhCH$_2$), 3.91 (2H, m, 2 x Me$_2$C**H**), 3.72 (1H, dq, J = 7.5, 6.2 Hz, C5H), 3.50 (1H, ddd, J = 8.7, 6.8, 5.5 Hz, C3H), 3.19 (1H, dd, J = 7.5, 5.6 Hz, C4H), 1.06–1.30 (12H, 4 overlapping d, *i*-Pr), 1.13 (3H, d, J = 6.0 Hz, C6–Me), 1.10 (3H, d, J = 6.8 Hz, C3–Me), 0.15 (9H, t, $J_{H,Sn}$ = 61.0 Hz, SnMe$_3$).

^{13}C NMR (67.5 MHz): δ = 154.5 (0), 153.9 (0), 138.8 (0), 138.3 (0), 131.0 (1), 128.9 (1), 128.7 (1), 127.8 (1), 127.6 (1), 126.6 (1), 76.6 (1), 71.0 (2), 62.6 (1), 46.0 (1), 32.1 (1), 21.3 (3), 20.5 (3), 17.3 (3), 16.9 (3), –6.0 (3).

LRMS (CI): m/z (%) = 637 [$(M+NH_4)^{+\bullet}$, 5], 620 [$(M+H)^{+\bullet}$, 100%)], 602 (20), 512 (15), 340 (40), 182 (20), 128 (30).

(2*S*,4*E*,6*S*,7*R*,8*S*)-8-Benzyloxy-1-(methoxymethoxy)-7-phenylthio-2,4,6-trimethylnon-4-ene [(*E*)-31]:

To a magnetically stirred solution of (*R*)-3-(methoxymethoxy)-2-methyl-1-iodopropane[57] (976 mg, 4.0 mmol) in dry Et_2O (5.5 mL) at –80°C under Ar was slowly added *t*-BuLi (1.52 M in pentanes, 4.6 mL, 6.92 mmol) and the resulting suspension was stirred for 45 min. The reaction mixture was warmed quickly to 0°C *via* an ice bath, whereupon dry THF (0.8 mL) was added and the reaction solution stirred at ice bath temperature for a further 30 min. The clear solution was cooled to –50°C with vigorous stirring, and to the resultant opaque solution was added slowly CuBr•Me$_2$S (216 mg, 1.05 mmol) in dry Me$_2$S (2.3 mL). The clear solution was warmed to r.t. over 1.5 h and maintained at r.t. for 30 min before cooling the cuprate solution to –28°C. Stannane **28** (620 mg, 1.00 mmol) in dry Et_2O (2.3 mL) was added quickly causing the temperature to rise –24°C. The resulting clear pale yellow solution was allowed to warm gradually to 0°C over 2 h, whereupon it was placed in an ice bath at +4°C. To the clear solution was added more stannane **28** (20 mg) in dry Et_2O (0.5 mL) and the resulting solution maintained at 4°C for 2.5 h. The black reaction mixture was cooled to –60°C and MeI (0.8 mL, 13.2 mmol) was added followed by HMPA (0.4 mL, 2.22 mmol). The reaction mixture was warmed to r.t. over 4 h, and sat. NH_4Cl containing 10% ammonia (25 mL) was added. The solution was extracted with Et_2O (3 x 25 mL), the Et_2O extracts were combined, dried, and concentrated to an oil which was then purified by column chromatography (silica gel; Et_2O/hexanes, 1:10) to yield **31** (222 mg, 0.50 mmol, 50%) as a mixture of isomers (*E*:*Z* = 7:1) according to ^{1}H NMR (270 MHz) resonances of the alkenyl proton at δ 5.20 (*E* isomer) and δ 5.34 (*Z* isomer). When the same reaction described above was performed on an 8.09 mmol scale (stannane), the alkenes were obtained in 39% yield with an isomeric ratio of 9:1 in favour of the (*E*)-isomer. The isomers could be separated by careful column chromatography on silica gel (Et_2O/hexanes, 1:20) to give pure (*E*)-**28**: $[\alpha]_D$ = +0.9° (c = 2.1, MeOH).

IR (film): ν = 1454 (s), 1373 (m), 1109 (s), 1046 (s), 917 (s), 734 (s), 696 (s) cm^{-1}.

^{1}H NMR (270 MHz): δ = 7.46–7.54 (2H, m), 7.40-7.20 (8H, m), 5.19 (1H, d, J = 9.5 Hz, C5H), 4.64 (2H, s, OCH$_2$O), 4.59 and 4.45 (1H each, d, J = 11.8 Hz, PhCH$_2$O), 3.82 (1H, dq, J = 6.0, 6.0 Hz, C8H), 3.39 (3H, s, OMe), 3.39 (1H, dd, J = 10.6, 6.4 Hz, C1H$_B$), 3.32 (1H, dd, J = 10.6, 6.4 Hz, C1H$_A$), 2.93 (1H, ddq, J = 9.5, 6.75, 6.5 Hz, C6H), 2.18 (1H, dd, J = 12.9, 6.7 Hz, C3H$_B$), 1.95 and 1.75 (1H each, m, C2H, C3H$_A$), 1.65 (3H, d, J = 1.2 Hz, C4–Me), 1.31 (3H, d, J = 6.2 Hz, C9–Me), 1.14 (3H, d, J = 6.8 Hz, C6–Me), 0.83 (3H, d, J = 6.8 Hz, C2–Me).

^{13}C NMR (67.5 MHz): δ = 138.8 (0), 138.3 (0), 132.8 (0), 131.2 (1), 130.9 (1), 128.8 (1), 128.4 (1), 127.7 (1), 127.6 (1), 126.2 (1), 96.7 (2), 76.4 (1), 73.2 (2), 70.8 (2), 62.4 (1), 55.2 (3), 44.3 (2), 34.4 (1), 31.6 (1), 18.4 (3), 16.9 (3), 16.6 (3), 16.2 (3).

LRMS (EI): *m/z* (%) = 442 ($M^{+\bullet}$, 5), 319 (5), 257 (10), 153 (10), 91 (100), 45 (40).

(2*S*,4*E*,6*S*,8*S*)-8-Hydroxy-1-(methoxymethoxy)-2,4,6-trimethylnon-4-ene (20):
To a stirred solution of alkene (*E*)-**31** (1.20 g, 2.7 mmol) in EtOH (5 mL) at reflux under Ar was slowly added sufficient Raney nickel (EtOH slurry) to remove both the benzyl ether and phenylthio ether (as determined by TLC). The reaction mixture was cooled and filtered through celite, washing well with EtOH. The filtrate was concentrated (bath temperature ≤ 30°C), prior to purification by column chromatography (silica gel; hexanes/Et_2O, 2:1) to give alcohol **20** (509 mg, 2.08 mmol, 77%) as a viscous oil having spectroscopic data identical to those reported above.

Methyl 4-(*tert*-Butyldimethylsiloxy)cinnamate (41):
To a solution of methyl *p*-hydroxycinnamate (4.0 g, 22.4 mmol) and imidazole (3.82 g, 56.1 mmol) in freshly distilled DMF (30 mL) at 0°C was added a solution of TBSCl in DMF (10 mL) under Ar. The reaction mixture was maintained at 0°C for 1 h, before warming to r.t. Upon completion (TLC) the reaction mixture was poured into H_2O (100 mL) and the layers separated. The aqueous phase was then extracted with Et_2O (4 x 50 mL) and the combined extracts were washed with H_2O (50 mL). The organic phase was dried (Na_2SO_4), and concentrated prior to purification by column chromatography (silica gel; hexanes/Et_2O, 2:1) to give **41** (6.29 g, 21.5 mmol, 96%) as a white waxy solid: mp 32–34°C.

IR (film): ν = 1721 (s), 1634 (m), 1601 (s), 1510 (s), 1260 (s), 912 (s), 839 (s) cm^{-1}.

^{1}H NMR (270 MHz): δ = 7.85 (1H, d, *J* = 16.0 Hz, CH=C), 7.42 and 6.84 (4H, m, AA'BB' system), 6.31 (1H, d, *J* = 15.8 Hz, C=CH), 3.79 (3H, s, CO_2Me), 0.99 (9H, s, *t*-Bu), 0.22 (6H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 167.8 (0), 157.9 (0), 144.7 (1), 129.8 (1), 127.8 (0), 120.6 (1), 115.6 (1), 51.6 (3), 25.8 (3), 18.4 (1), –4.3 (3).

LRMS (CI): *m/z* (%) = 310 [$(M+NH_4)^{+\bullet}$, 10], 293 [$(M+H)^{+\bullet}$, 100%)].

Methyl (3*R*,5*S*)-5-Phenyl-4-benzyl-3-[4-(*tert*-butyldimethylsiloxy)phenyl]-4-azahexanoate (43):
To a solution of (*S*)-*N*-benzyl-1-phenylethanamine[36] (3.23 g, 15.4 mmol) in THF (70 mL) at 0°C was added BuLi (2.5 M in hexanes, 6.2 mL, 15.4 mmol), the resulting dark red solution of amide **42** was maintained at 0°C for 15 min before cooling to –78°C. A solution of the ester **41** (3.0 g, 10.3 mmol) in THF (20 mL) was slowly added to the lithium amide solution. The reaction mixture was maintained at –78°C for 20 min before quenching with sat. aq NH_4Cl (60 mL). Brine (40 mL) was added and the layers separated. The aqueous layer was extracted with Et_2O (4 x 50 mL) and the organic extracts were combined, dried and concentrated prior to purification by column chromatography (silica gel; hexanes/EtOAc, 5:1) to give **43** (4.90 g, 9.74 mmol, 95%) as a pale yellow viscous oil: $[\alpha]_D$ = +1.9° (*c* = 1.61, $CHCl_3$).

IR (film): ν = 1739 (s), 1605 (m), 1509 (s), 1260 (s), 915 (m), 839 (s), 780 (m) cm^{-1}.

^{1}H NMR (270 MHz): δ = 7.42-7.20 (12H, m), 6.83 (2H, m, AA' portion of AA'BB' system), 4.38 (1H, dd, *J* = 9.1, 6.0 Hz, C3H), 4.01 (1H, q, *J* = 7.0 Hz, NC$\underline{H}$$CH_3$), 3.73 and 3.64 (1H each, d, *J* = 14.6 Hz, $PhCH_2$), 3.47 (3H, s, COOMe), 2.69 (1H, dd, *J* = 14.6, 5.9, $C2H_B$), 2.53 (1H, dd, *J* = 14.6, 9.2 Hz, $C2H_A$), 1.22 (3H, d, *J* = 6.6 Hz, NCHC$\underline{H}_3$), 0.97 (9H, s, *t*-Bu), 0.20 (6H, s, $SiMe_2$).

^{13}C NMR (75 MHz): δ = 172.5 (0), 154.9 (0), 144.5 (0), 141.7 (0), 134.6 (0), 129.2 (1), 128.3 (1), 128.0 (1), 127.0 (1), 126.8 (1), 120.0 (1), 59.0 (1), 56.8 (1), 51.6 (3), 50.8 (2), 37.9 (2), 25.9 (3), 18.4 (0), 16.0 (3), –4.2 (3).

LRMS (EI): *m/z* (%) = 503 ($M^{+\bullet}$, 10), 470 (100), 326 (65), 293 (50), 251 (30).

Methyl (*R*)-3-Amino-3-[4-(*tert*-butyldimethylsiloxy)phenyl]propanoate (6):
To a solution of **43** (2.10 g, 4.2 mmol) in acetic acid (20 mL) and THF (10 mL) was added 5% Pd/C (2.0 g). The reaction mixture was then agitated under a hydrogen atmosphere (44.8 kbar) for 21 h. The catalyst was removed by filtration through celite, washed with MeOH, and the filtrate concentrated. The residue was dissolved in toluene (10 mL) and evaporated (4 x) prior to purification by column chromatography (silica gel; EtOAc) to yield **6** (1.16 g, 90% , 3.75 mmol) as a white waxy solid: mp 80–82°C; $[\alpha]_D$ = +7.1° (*c* = 1.0, $CHCl_3$).

IR (film): ν = 1737 (s), 1512 (s), 1258 (s), 1173 (m), 914 (s), 840 (s) cm^{-1}.

^{1}H NMR (270 MHz): δ = 7.21 and 6.88 (4H, m, AA'BB' system), 5.55 (2H, br s, NH_2), 4.39 (1H, dd, *J* = 7.9, 5.4 Hz, C3H), 3.65 (3H, s, COOMe), 2.80 (1H, dd, *J* = 16.2, 8.5 Hz, $C2H_B$), 2.69 (1H, dd, *J* = 16.1, 5.3 Hz, $C2H_A$), 0.97 (9H, s, *t*-Bu), 0.18 (6H, s, $SiMe_2$).

^{13}C NMR (67.5 MHz): δ = 172.2 (0), 155.4 (0), 135.3 (0), 127.7 (1), 120.4 (1), 51.9 (1), 51.9 (3), 42.6 (2), 25.8 (3), 18.3 (0), –4.3 (3).

LRMS (EI): *m/z* (%) = 309 ($M^{+\bullet}$, 6), 237 (29), 236 (100), 210 (6), 178 (11), 151 (5), 122 (12), 73 (8).

HRMS: Found $M^{+\bullet}$ = 309.1744. $C_{16}H_{27}O_3NSi$ requires M = 309.1760.

Methyl (*R*)-3-[1-(*tert*-Butyldimethylsilyl)indol-3-yl]-2-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)propanoate (45):
To a stirred solution of Boc-(*R*)-tryptophan **44** (3.0 g, 9.86 mmol) in THF (100 mL) at –78°C under N_2 was slowly added sodium hexamethyldisilylazide solution (1 M in THF, 30 mL, 30 mmol). The resulting yellow solution was stirred for 1 h before the addition of TBSCl (1.64 g, 10.84 mmol) in THF (20 mL) at –78°C. The resulting solution was stirred for 1.5 h at –78°C, before quenching with H_2O (100 mL) and extracting with EtOAc (3 x 70 mL). The combined extracts were washed with H_2O (3 x 50 mL), dried and concentrated to afford a stable yellow foam (4.25 g) which was used in the next step without further purification.

To a stirring slurry of sodium hydride (946 mg, 39.4 mmol) in THF (110 mL) and DMF (11 mL) at 0°C under N_2 was slowly added a solution of crude silyl derivative prepared above. The reaction mixture was stirred for 3 h at r.t. before the addition of MeI (3.7 mL, 59.2 mmol). The resulting solution was then stirred at r.t. for a further 15 h. The reaction mixture was quenched with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine (50 mL), dried and concentrated prior to purification by column chromatography (silica gel; EtOAc/hexanes, 1:5, R_f = 0.48) to yield **45** (3.18 g, 7.14 mmol, 73% over 2 steps) as a pale yellow, viscous oil: $[\alpha]_D$ = +35.35° (c = 1.23, $CHCl_3$); lit.[5] $[\alpha]_D$ =+39.0° (*c* = 1.27, $CHCl_3$).

IR (film): ν = 1744 (s), 1695 (s), 1452 (s), 1142 (s), 788 (s), 737 (s) cm^{-1}.

UV (EtOH): λ = 290.2 nm (ε 12,940), 280 (12,510), 273 (12,180), 225 (31,620).

^{1}H NMR (270 MHz): δ = 7.60 (1H, d, *J* = 7.9 Hz), 7.48 (1H, d, *J* = 7.1 Hz), 7.24-7.10 (2H, m), 6.97 [7.02] (1H, s), 4.99 [4.79] (1H, dd, *J* = 10.4, 5.4 Hz, C2H), 3.77 [3.75] (3H, s, COOMe), 3.44 and 3.18 (1H each, m, $C3H_2$), 2.77 [2.71] (3H, s, NMe), 1.43 (3H, s, O-*t*-Bu), 1.23 (6H, s, O-*t*-Bu), 0.92 (9H, s, Si-*t*-Bu), 0.60 and 0.58 (3H each, s, $SiMe_2$).

^{13}C NMR (67.5 MHz): δ = 172.1 [172.3] (0), 155.1 [155.8] (0), 141.5 (0), 130.6 [130.9] (0), 129.5 (1), 128.9 (1), 121.6 (1), 119.6 (1), 118.5 (1), 114.1 [113.9] (1), 113.4 [113.6] (0), 80.0 [79.9] (0), 59.9 (1), 58.7 (1), 52.2 (3), 32.1 [32.9] (3), 28.4 [28.1] (3), 26.4 (3), 25.8 [25.5] (3), 19.5 (0), –3.8 [–3.4] (3).

LRMS (CI): *m/z* (%) = 464 [$(M+NH_4)^{+\bullet}$, 3], 447 [$(M+H)^{+\bullet}$, 80)], 391 (100), 347 (30), 244 (45).

HRMS: Found $(M+H)^{+\bullet}$ = 447.2651. $C_{24}H_{39}O_4N_2Si$ requires M = 447.2679.

Methyl (*R*)-3-(1*H*-Indol-3-yl)-2-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)propanoate (46):
Tetrabutylammonium fluoride (TBAF) (1 M THF, 7.2 mL, 7.2 mmol) was slowly added to a stirred solution of **45** (2.3 g, 5.15 mmol) in THF (20 mL) at r.t. and stirred for 15 min. The resulting solution was quenched with H_2O (20 mL), extracted with EtOAc (3 x 20 mL), dried, and concentrated prior to purification by column chromatography (silica gel; EtOAc/hexanes, 1:5, R_f = 0.15) to give **46** (1.58 g, 4.77 mmol, 92%) as a pale yellow foam: $[\alpha]_D$ = +88.0° (c = 1.1, MeOH); lit.[59] $[\alpha]_D$ = +133.1° (*c* = 1.1, MeOH).

IR ($CHBr_3$): ν = 1736 (s), 1682 (s) cm^{-1}.

UV (EtOH): λ = 290 nm (ε 9,630), 281 (9,330), 276 (5, 950), 222 (7,370).

^{1}H NMR (270 MHz): δ = 8.42 (1H, s, N_1H), 7.61 (1H, d, *J* = 7.5 Hz), 7.36 (1H, d, *J* = 7.7 Hz), 7.26-7.08 (2H, m), 6.98 [7.04] (1H, s, indole C2H), 5.05 (0.5H, dd, *J* = 10.1, 5.1 Hz, C2H), 4.79 (0.5H, dd, *J* = 10.3, 4.3 Hz, C2H), 3.78 [3.74] (3H, s, COOMe), 3.47 and 3.16 (1H each, m, $C3H_2$), 2.79 [2.75] (3H, s, NMe), 1.22 [1.43] (9H, s, O-*t*-Bu).

^{13}C NMR (90 MHz): δ = 171.9 [172.2] (0), 155.4 [155.9] (0), 136.3 [136.2] (0), 127.0 [127.3] (0), 122.9 [122.4] (1), 121.7 (1), 119.0 (1), 118.1 (1), 111.4 [111.2] (1), 110.8 [110.6] (0), 80.2 [80.0] (0), 60.6 [59.1] (1), 52.0 (3), 31.8 (3), 27.8 [28.2] (3), 25.3 [24.7] (2).

LRMS (EI): *m/z* (%) = 332 ($M^{+\bullet}$, 20), 276 (5), 259 (5), 201 (30), 130 (100).

Methyl (*R*)-3-(2-Bromo-1*H*-indol-3-yl)-2-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)-propanoate (8):
N-Bromosuccinimide (NBS) (1.12 g, 6.3 mmol) was added to a stirred solution of **46** (1.9 g, 5.7 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred for 15 min and then concentrated and absorbed onto silica gel prior to purification by column chromatography (silica gel; hexanes/EtOAc, 5:1, R_f = 0.3) to give a white powder which was recrystallized (EtOAc/hexanes) to give pure **8** (2.03 g, 4.9 mmol, 87%): mp 143–144°C; lit.[5]mp 146–147°C; $[\alpha]_D$ = +91.8° (*c* = 1.20, $CHCl_3$).

IR (KBr): ν = 3218 (s br), 1736 (s), 1667 (s), 1138 (s), 1002 (s), 746 (m) cm^{-1}.

UV (EtOH): λ = 290 nm (ε 7,260), 282 (8,570), 276 (8,160), 222 (36,650).

^{1}H NMR (270 MHz): δ = 8.4 (1H, br s, N_1H), 7.52 (1H, d, *J* = 7.3 Hz), 7.27 (1H, m), 7.19-7.08 (2H, m), 4.68 (1H, dd, *J* = 10.6, 4.2 Hz, C2H), 3.78 [3.74] (3H, s, COOMe), 3.42 (1H, dd, *J* = 14.9, 4.3 Hz, $C3H_B$), 3.20 (1H, dd, *J* = 14.8, 10.7 Hz, $C3H_A$), 2.76 [2.71] (3H, s, NMe), 1.23 [1.37] (9H, s, *t*-Bu).

^{13}C NMR (90 MHz): δ = 172.1 [171.8] (0), 155.2 (0), 136.3 (0), 127.5 (0), 122.3 91), 120.1 (1), 117.9 [118.3] (1), 111.3 [111.1] (0), 110.9 [110.6] (1), 109.5 [109.2] (0), 80.6 [80.1] (0), 60.2 [60.0] (1), 52.4 (3), 33.6 [34.1] (3), 28.4 [28.2] (3), 25.4 [25.0] (3).

LRMS (CI): *m/z* (%) = 428 [$(M+NH_4)^{+\bullet}$, 5], 411 [$(M+H)^{+\bullet}$, 60], 372 (100), 357 (75), 311 (80), 233 (35), 208 (25).

Methyl (2*R*,5*S*)-5-(*tert*-Butoxycarbonylamino)-3-methyl-2-[(2-bromo-1*H*-indol-3-yl)methyl]-4-oxo-3-azahexanoate (47):
To a stirred solution of **8** (1.07 g, 2.61 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (TFA) (2.98 g, 2.0 mL, 26.1 mmol) and the solution stirred for 1 h. The reaction mixture was concentrated, taken up in EtOAc (20 mL), and washed with H_2O (2 x 10 mL) and sat. $NaHCO_3$ (2 x 10 mL). The organic layer was then dried and concentrated to a white foam (820 mg) which was used without further purification.

To a stirred solution of crude amine **43** (820 mg) in THF (40 mL) was added sequentially Boc-(*S*)-alanine (494 mg, 2.61 mmol), 1-hydroxybenzotriazole hydrate (HOBT) (35 mg, 26.0 mmol), and dicyclohexylcarbodiimide (DCC) (539 mg, 2.61 mmol). The reaction mixture was stirred at 0°C for 24 h, before filtration to remove dicyclohexyl urea (DCU). The DCU was washed with cold Et_2O (5 mL). Concentration

of the filtrate and purification of the residue by column chromatography (silica gel; hexanes/EtOAc, 2:1) gave **47** (1.11 g, 2.31 mmol, 89%) as a white foam. Treatment of this foam with Et_2O gave **47** (620 mg, 1.29 mmol) as a white powder (mp 152–154°C); concentration of the Et_2O supernatant gave **47** (480 mg, 1.0 mmol) as a white foam indistinguishable from the powder by ^1H and ^{13}C NMR spectroscopy: $[\alpha]_D$ = +55.9° (*c* = 1.0, MeOH); lit.[6] $[\alpha]_D$ = +65.9° (*c* = 1.0, MeOH).

IR ($CHBr_3$): ν = 1737 (m), 1699 (m), 1486 (m), 1150 (s), 1132.(s) cm^{-1}.

^1H NMR (360 MHz): δ = 8.55 (1H, br s, N_iH), 7.51 (1H, d, *J* = 7.4 Hz), 7.26 (1H, d, *J* = 8.1 Hz), 7.15 (1H, td, *J* = 7.6, 1.4 Hz), 7.10 (1H, td, *J* = 7.4, 1.3 Hz), 5.46 (1H, d, *J* = 8.0 Hz, NH), 5.14 (1H, dd, *J* = 10.7, 5.2 Hz, C2H), 4.44 (1H, dq, *J* = 7.8, 6.9, Hz, C5H), 3.75 (3H, s, COOMe), 3.42 (1H, dd, *J* = 15.1, 5.3 Hz, indoleCH$_A$H$_B$), 3.33 (1H, dd, *J* = 15.0, 10. 8 Hz, indoleCH$_A$H$_B$), 2.84 (3H, s, NMe), 1.41 (9H, s, *t*-Bu), 0.79 (3H, d, *J* = 6.8 Hz, C6H$_3$).

^{13}C NMR (90 MHz): δ = 173.3 (0), 171.0 (0), 155.1 (0), 136.2 (0), 127.6 (0), 122.7 (1), 120.4 (1), 118.1 (1), 110.8 (0), 110.7 (1), 109.1 (0), 79.5 (0), 58.5 (1), 52.5 (3), 46.6 (1), 34.2 (3), 28.5 (3), 24.6 (2), 18.3 (3).

LRMS (EI): *m/z* (%) = 481 ($M^{+\bullet}$, 20), 408 (25), 279 (15), 208 (60), 200 (100).

HRMS: Found $M^{+\bullet}$ = 481.1209. $C_{21}H_{28}O_5N_3Br$ requires M = 481.1212.

(2*R*,5*S*)-5-(*tert*-Butoxycarbonylamino)-3-methyl-2-[(2-bromo-1*H*-indol-3-yl)methyl]-4-oxo-3-azahexanoic Acid (48):

NaOH (64 mg) in H_2O (4 mL) was added to a stirred solution of ester **47** (650 mg, 1.35 mmol) in THF (8 mL). The reaction mixture was stirred for 2 h at r.t. before being poured into sat. $NaHCO_3$ (20 mL) and extracted with Et_2O (3 x 10 mL). The aqueous layer was acidified to pH 3 with dil. HCl and extracted with EtOAc (3 x 15 mL). The organic extracts were combined and dried prior to purification by column chromatography (silica gel; hexanes/EtOAc, 1:1, 0.2% acetic acid) to yield acid **48** (555 mg, 1.19 mmol, 88%) as a white foam. Treatment of this foam with Et_2O gave **48** (431 mg, 0.92 mmol) as a white powder: mp 178–180°C (decomp); lit.[6] mp 184-185°C; $[\alpha]_D$ = +48.1° (*c* = 1.35, MeOH). Concentration of the filtrate gave **48** (100 mg, 0.21 mmol) as a white foam indistinguishable from the solid by ^1H and ^{13}C NMR spectroscopy.

IR (nujol): ν = 3253 (br s), 1742 (s), 1682 (s), 1637 (s), 1453 (s), 1164 (m) cm^{-1}.

^1H NMR (360 MHz, DMSO-d_6): δ = 12.90 (1H, br s, CO_2H), 11.70 (1H, s, N_iH), 7.58 (1H, d, *J* = 7.7 Hz), 7.32 (1H, d, *J* = 7.9 Hz), 7.13 (1H, td, *J* = 7.7, 1.1 Hz), 7.08 (1H, td, *J* = 7.7, 1.0 Hz), 6.42 (1H, d, *J* = 7.6 Hz, NH), 5.25 (1H, dd, *J* = 10.7, 4.7 Hz, C2H), 4.36 (1H, dq, *J* = 7.9, 6.7 Hz, C5H), 3.34 (1H, dd, *J* = 14.9, 4.8 Hz, indoleCH$_A$H$_B$), 3.24 (1H, dd, *J* = 14.8, 10.8 Hz, indoleCH$_A$H$_B$), 2.98 (3H, s, NMe), 1.43 (9H, s, *t*-Bu), 0.75 (3H, d, *J* = 6.9 Hz, C6–Me).

^{13}C NMR (90 MHz, DMSO-d_6): δ =171.6 (0), 170.9 (0), 152.9 (0), 134.4 (0), 125.5 (0), 119.6 (1), 117.6 (1), 116.0 (1), 108.9 (1), 107.8 (0), 107.5 (0), 76.2 (0), 55.4 (1), 44.2 (1), 31.0 (3), 26.5 (3), 22.3 (2), 15.2 (3).

LRMS (EI): *m/z* (%) = 467 ($M^{+\bullet}$, 25), 449 (65), 349 (55), 208 (100)

Methyl (3*R*,6*R*,9*S*)-9-(*tert*-Butoxycarbonylamino)-7-methyl-6-[(2-bromo-1*H*-indol-3-yl)methyl]-3-[4-(*tert*-butyldimethylsilyloxy)phenyl]-5,8-dioxo-4,7-diazadecanoate (49):

To a stirred solution of acid **48** (1.40 g, 2.99 mmol) and **6** (925 mg, 2.99 mmol) in THF (25 mL) at r.t. was added hydroxybenzotriazole hydrate (404 mg, 2.99 mmol). After 15 min a solution of freshly distilled DCC (620 mg, 2.99 mmol) in THF (5 mL) was added and the reaction mixture stirred for 15 h at r.t. The DCU was filtered off, washed with cold Et_2O, and the filtrate concentrated prior to purification by column chromatography (silica gel; hexanes/EtOAc, 1:2) to yield tripeptide **49** (2.03 g, 2.67 mmol, 89%) as a white foam contaminated with 1-3% DCU: $[\alpha]_D$ = +35.5° (*c* = 1.56, $CHCl_3$).

IR ($CHCl_3$): ν = 1735 (m), 1689 (m), 1661 (m), 1255 (s), 1170 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 8.27 (1H, s, N_iH), 7.52 (1H, d, *J* = 7.0 Hz), 7.22 (1H, d, *J* = 7.1 Hz), 7.09 (4H, m), 6.90 (1H, d, *J* = 8.5 Hz, N4H), 6.76 (2H, m, AA′ portion of AA′BB′ system), 5.68 (1H, dd, *J* = 10.8, 5.6 Hz), 5.40 (1H, ddd, *J* = 8.5, 7.7, 6.8 Hz, C3H), 5.10 (1H, d, *J* = 7.0 Hz, NHBoc), 4.29 (1H, dq, *J* = 7.0, 6.7 Hz, C9H), 3.61 (3H, s, COOMe), 3.40 (1H, dd, *J* = 15.5, 5.5 Hz, indoleCH$_A$H$_B$), 3.21 (1H, dd, *J* = 15.2, 10.9 Hz, indoleCH$_A$H$_B$), 2.97 (3H, s, NMe), 2.88 (1H, dd *J* = 15.3, 7.6 Hz, C2H$_B$), 2.76 (1H, dd, *J* = 15.2, 6.3 Hz, C2H$_A$), 1.37 (9H, s, O-*t*-Bu), 0.98 (9H, s, Si-*t*-Bu), 0.65 (3H, d, *J* = 6.7 Hz, C10–Me), 0.19 (6H, s, $SiMe_2$).

^{13}C NMR (67.5 MHz): δ =174.4 (0), 171.3 (0), 169.4 (0), 155.7 (0), 155.2 (0), 136.3 (0), 133.3 (0), 127.6 (1), 122.3 (1), 120.3 (1), 120.0 (1), 118.4 (1), 110.6 (1), 110.5 (0), 109.3 (0), 79.8 (0), 56.3 (1), 51.9 (3), 49.7 (1), 46.6 (1), 40.7 (2), 34.1 (2), 31.7 (3), 28.4 (3), 25.8 (3), 13.3 (0), 16.9 (3), –4.3 (3).

LRMS (FAB): *m/z* (%) = 783 [(M+ Na)$^{+\bullet}$, 8), 759 ($M^{+\bullet}$, 20), 679 (40), 588 (10), 477 (55), 450 (35), 394 (70), 350 (20), 293 (100), 251 (50)

HRMS (Ar FAB, MNOBA matrix): Found = $(M+H)^{+\bullet}$, 759.2738. $C_{36}H_{51}N_4O_7BrSi$+H requires M = 759.2788.

Methyl (3*R*,6*R*,9*S*)-9-Amino-7-methyl-6-[(2-bromo-1*H*-indol-3-yl)methyl]-3-[4-(*tert*-butyldimethylsilyloxy)phenyl]-5,8-dioxo-4,7-diazadecanoate (4):

TBSOTf (1.15 mL, 4.9 mmol) was slowly added to a solution of tripeptide **49** (815 mg, 1.07 mmol) and 2,6-lutidine (0.75 mL, 6.44 mmol) in CH_2Cl_2 (15 mL) at 0°C under Ar. The reaction mixture was stirred for 2 h at 0°C before adding H_2O (20 mL) and extracting the resulting aqueous phase with Et_2O (3 x 40 mL). The organic extracts were combined, dried and concentrated to a viscous yellow oil. The crude oil was placed on a silica gel column prepared using CH_2Cl_2. After 1 h the column was eluted with CH_2Cl_2 (700 mL), followed by elution with CH_2Cl_2/MeOH [99:1 (250 mL), 9:1 (700 mL)] to give amine **4** (513 mg, 0.78 mmol, 73%) as a pale yellow foam: $[\alpha]_D$ = +49.1° (*c* = 1.50, $CHCl_3$).

IR ($CHCl_3$): ν = 3018 (m), 1732 (s), 1676 (s), 1660 (s), 1510 (s), 914 (s), 842 (s) cm^{-1}.

^1H NMR (270 MHz): δ = 9.07 (1H, br s, N_iH), 7.53 (1H, d *J* = 6.8 Hz), 7.22 (1H, d *J* = 7.1 Hz), 7.15-7.02 (4H, m), 6.78 (1H, d, *J* = 8.3 Hz, N4H), 6.75 (2H, m, AA′ portion of AA′BB′ system), 5.64 (1H, dd, *J* = 9.6, 6.5 Hz, C6H), 5.35 (1H, dt, *J* = 8.3, 6.5 Hz, C3H), 3.67 (1H, m, C9H), 3.58 (3H, s, COOMe), 3.34 (1H, dd, *J* = 15.7, 6.8 Hz, indoleCH$_A$H$_B$), 3.24 (1H, dd, *J* = 15.7, 10.0 Hz, indoleCH$_A$H$_B$), 2.93 (3H, s, NMe), 2.74 (2H, app d, *J* = 6.4 Hz, C2H$_2$), 2.00 (2H, br s, NH_2), 0.97 (9H, s, *t*-Bu), 0.70 (3H, d, *J* = 6.8 Hz, C10–Me), 0.18 (6H, s, $SiMe_2$).

^{13}C NMR (90 MHz): δ = 177.5 (0), 171.7 (0), 169.5 (0), 155.2 (0), 136.3 (0), 133.1 (0), 127.7 (1), 127.5 (1), 122.4 (1), 120.3 (1), 120.2 (1), 118.4 (1), 110.7 (1), 110.5 (0), 109.3 (0), 56.5 (1), 51.9 (3), 49.5 (1), 47.2 (1), 40.6 (2), 31.5 (3), 25.8 (3), 23.7 (2), 19.9 (3), 18.3 (0), –4.2 (3)

HRMS (Ar FAB, MNOBA matrix): Found $(M+H)^{+\bullet}$ = 659.2278. $C_{31}H_{43}N_4O_5BrSi$+H requires M = 659.2264.

Methyl (3*R*,6*R*,9*S*,12*S*,14*E*,16*R*,18*S*)-6-[(2-Bromo-1*H*-indol-3-yl)methyl]-18-benzoyloxy-3-[4-(*tert*-butyldimethylsilyloxy)phenyl]-7,9,12,14,16-pentamethyl-5,8,11-trioxo-4,7,10-triazanonadeca-14-enoate (50):

To a solution of amine **4** (320 mg, 0.49 mmol) and HOBT (67 mg, 0.49 mmol) in dry CH_2Cl_2 (7 mL) at –20°C under Ar was added acid **3** (157 mg, 0.49 mmol). To the reaction mixture at –20°C was slowly added a solution of freshly distilled DCC (102 mg, 0.49 mmol) in CH_2Cl_2 (3 mL).The reaction mixture was stirred at –20°C for 30 min and 4°C for 40 h. The precipitate was removed *via* filtration, washing with cold Et_2O, and the filtrate concentrated to a yield a foam. Purification of the crude foam by column chromatography (silica gel; EtOAc/hexanes, 1:1, R_f = 0.35) gave **50** (371 mg, 0.39 mmol, 78%) as a white foam: $[\alpha]_D$ = +32.95° (*c* = 1.22, $CHCl_3$).

IR (KBr): ν = 3312 (br m), 1741 (s), 1716 (s), 1644 (s), 1511 (m), 1275 (s), 1109 (m), 914 (m), 840 (m), 713 (m) cm^{-1}.

^1H NMR (360 MHz): δ = 9.13 (1H, s, N_iH), 8.02 (2H, m, $PhCO_2$), 7.60-7.35 (4H, m), 7.24-7.00 (5H, m), 6.74 (2H, m, AA′ portion of AA′BB′ system), 6.33 (1H, d, *J* = 5.8 Hz, N4H), 5.62 (1H, dd, *J* = 11.1, 5.5 Hz, C6H), 5.41 (1H, m, C3H), 5.13 (1H, m, C18H), 4.98 (1H, d with fine splitting, *J* = 8.8 Hz, C15H), 4.44 (1H, dq, *J* = 6.9, 5.5 Hz, C9H), 3.60 (3H, s, COOMe), 3.43 (1H, dd, *J* = 15.4, 5.2 Hz, indoleCH$_A$H$_B$), 3.20 (1H, dd, *J* = 15.0, 11.1 Hz, indoleCH$_A$H$_B$, 2.95 (3H, s, NMe), 2.92 (1H, dd, *J* = 15.5, 7.9 Hz, C2H$_B$), 2.81 (1H, dd, *J* = 15.5, 5.9 Hz, C2H$_A$), 2.48-2.18 (3H, m), 1.92 (1H, dd, *J* = 15.1, 7.5 Hz, C12H), 1.75-1.56 (2H, m), 1.50 (3H, d, *J* = 1.15 Hz, C14Me), 1.29 (3H, d, *J* = 6.8 Hz, C19–Me), 1.02 (3H, d, *J* = 6.8 Hz, C12–Me), 0.97 (9H, s, *t*-Bu), 0.92 (3H, d, *J* = 6.6 Hz, C16–Me), 0.66 (3H, d, *J* = 6.9 Hz, C9–Me), 0.18 (6H, s, $SiMe_2$).

^{13}C NMR (90 MHz): δ = 176.7 (0), 174.0 (0), 171.4 (0), 169.2 (0), 166.3 (0), 155.1 (0), 136.1 (0), 133.6 (0), 133.3 (1), 132.9 (0), 131.4 (0), 130.9 (0), 129.6 (1), 128.4 (1), 127.8 (1), 122.2 (1), 120.2 (1), 120.0 (1), 110.7 (1), 110.6 (0), 109.1 (0), 70.5 (1), 56.7 (1), 51.8 (3), 49.7 (1), 45.8 (1), 43.8 (2), 43.8 (2), 40.8 (2), 39.3 (1), 32.0 (3), 29.4 (1), 25.8 (3), 23.5 (2), 21.1 (3), 20.3 (3), 18.3 (0), 17.1 (3), 16.3 (3), 16.1 (3), –4.3 (3).
HRMS (Ar FAB, MNOBA matrix): Found $(M+H)^{+\bullet}$ = 959.3922. $C_{50}H_{67}N_4O_8BrSi$+H requires M = 959.3989.

(4*R*,7*R*,10*S*,13*S*,15*E*,17*R*,19*S*)-7-[(2-Bromo-1*H*-indol-3-yl)methyl]-4-(4-hydroxyphenyl)-8,10,13,15,17,19-hexamethyl-1-oxa-5,8,11-triazacyclononadec-15-ene-2,6,9,12-tetrone (Jaspamide, 1):

LiOH (18 mg) in H_2O (5 mL) was added to a stirred solution of siloxy ester **50** (400 mg, 0.42 mmol) in THF (10 mL) and MeOH (50 mL). The reaction mixture was stirred for 6 d at r.t. before being poured into dil HCl (20 mL) and extracted with EtOAc (3 x 25 mL). The organic extracts were combined, dried and concentrated to yield a pale yellow foam. Purification by column chromatography (silica gel; $CHCl_3$/MeOH, 10:1, 0.2% acetic acid) gave *seco*-acid **51** (235 mg, 0.32 mmol, 78%) as a white foam.

To a gently refluxing solution of DMAP (22 mg, 0.18 mmol), 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (CMC) (51 mg, 0.12 mmol) and DMAP•TFA (28 mg, 0.12 mmol) in freshly distilled $CHCl_3$ (EtOH free, 40 mL) was slowly added *seco*-acid **51** (35 mg, 0.048 mmol) in $CHCl_3$ (17 mL) and THF (3 mL) *via* syringe pump over 20 h. After addition was complete, the reaction mixture was refluxed for 1 h and then allowed to cool before concentrating. The residue was taken up into EtOAc (20 mL), washed with H_2O (2 x 10 mL) and brine (10 mL) before drying. Concentration and purification by column chromatography (silica gel; EtOAc/hexanes, 1:1, R_f = 0.15) gave **1** (9.7 mg, 0.014 mmol, 28%) as a white amorphous solid. Further purification by reverse phase HPLC (Zorbax ODS 9.6 x 250 mm) using MeCN/H_2O (7:3, flow rate 2 mL/min, UV detector set at 290 nm, retention time 10.7 min) gave an analytical sample [mp 140°C (dec)] having spectroscopic data comparable to those reported for the natural product.[3,4]: $[\alpha]_D$ = +33.8° (*c* = 1.4, MeOH); lit.[4] $[\alpha]_D$ = +35° (*c* = 3.62, MeOH).

IR (KBr): ν = 3395 (br s), 1722 (m), 1659 (s), 1639 (s), 1630 (s), 1516 (s) cm^{-1}.

^1H NMR (500 MHz): δ = 8.95 (1H, s, N27H), 7.67 (1H, d, *J* = 8.9 Hz, N5H), 7.55 (2H, d, *J* = 7.8 Hz, C34H), 7.23 (1H, d, *J* = 8.0 Hz, C31H), 7.12 (1H, t, *J* = 7.4 Hz, C32H), 7.09 (1H, t, *J* = 7.4 Hz, C33H), 6.94 and 6.67 (2H each, AA′BB′ system, C21H, C22H, C24H, C25H), 5.86 (1H, dd, *J* = 10.3, 6.4 Hz, C7H), 5.28 (1H, ddd, *J* = 8.9, 5.0, 5.0 Hz, C4H), 4.78 (1H, d, *J* = 9.6 Hz, C16H), 4.75 (1H, dq, *J* = 6.9, 6.9 Hz, C10H), 4.63 (1H, m, C19H), 3.38 (1H, dd, *J* = 15.3, 6.4 Hz, C26H$_B$), 3.24 (1H, dd, *J* = 15.5, 10.5 Hz, C26H$_A$), 2.95 (3H, s, N8–Me), 2.69 (1H, dd, 15.0, 4.7 Hz, C3H$_B$), 2.62 (1H, dd, *J* = 15.0, 5.7 Hz, C3H$_A$), 2.51 (1H, m, C13H), 2.38 (1H, dd, *J* = 16.0, 11.2 Hz, C14H$_B$), 2.23 (1H, m, C17H), 2.00 (2H, app d, C14H$_A$), 1.38–1.22 (2H, m, C18H$_2$), 1.55 (3H, s, C4–Me), 1.12 (3H, d, *J* = 7.1 Hz, C13–Me), 1.06 (3H, d, *J* = 6.4 Hz, C19–Me), 0.81 (3H, d, *J* = 6.6 Hz, C17–Me), 0.69 (3H, d, *J* = 6.6 Hz, C10–Me).

^{13}C NMR (67.5 MHz): δ = 175.1 (0, C12), 174.6 (0, C2), 171.1 (0, C6), 169.2 (0, C9), 156.1 (0, C23), 136.4 (0, C35), 133.7 (0, C20), 131.3 (2C, 0, C30, C15), 128.0 (1, C16), 127.3 (2C, 1, C21, C25), 122.5 (1, C32), 120.3 (1, C33), 118.3 (1, C31), 115.8 (2C, 1, C22, C24), 110.8 (1, C34), 110.0 (0, C29), 109.3 (0, C28), 71.0 (1, C19), 55.7 (1, C7), 49.2 (1, C4), 46.2 (1, C10), 43.5 (2, C18), 40.9 (2, C14), 40.3 (2, C3), 39.9 (1, C13), 31.0 (3, N8–Me), 29.4 (1, C17), 23.5 (2, C26), 22.1 (3, C17–Me), 20.5 (3, C13–Me), 19.2 (3, C19–Me), 18.7 (3, C15–Me), 17.9 (3, C10–Me).

HRMS (FAB): Found $(M+H)^{+\bullet}$ = 709.2602. $C_{36}H_{45}N_4O_6Br+H$ requires 709.2600.

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(1) Inman, W.; Crews, P. *J. Am. Chem. Soc.* **1989**, *111*, 2822.
(2) Braekman, J. C.; Daloze, D.; Moussiaux, B. *J. Nat. Prod.* **1987**, *50*, 994.
(3) Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3123.
(4) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2979.
(5) Grieco, P. A.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.* **1989**, *110*, 1630.
(6) Chu, K. S.; Negrete, G. R.; Konopelski, J. P. *J. Org. Chem.* **1991**, *56*, 5196.
(7) Imaeda, T.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1994**, *35*, 591.
(8) Rama Rao, A. V.; Gurjar, M. K.; Nallaganchu, B. R.; Bhandari, A. *Tetrahedron Lett.* **1993**, *34*, 7085.
(9) Schmidt, U.; Siegel, W.; Mundinger, K. *Tetrahedron Lett.* **1989**, *29*, 1269.
(10) Kang, S.-K.; Lee, D.-H. *Synlett* **1991**, 175.
(11) Ashworth, P.; Belagali, S. L.; Casson, S.; Marczak, A.; Kocienski, P. *Tetrahedron* **1991**, *47*, 9939.
(12) Smith, N. R.; Wiley, R. H. *Org. Synth. Coll. Vol. IV* **1963**, 337.
(13) McKelvey, R. D.; Kawada, Y.; Sugawara, T.; Iwamura, H. *J. Org. Chem.* **1981**, *46*, 4948.
(14) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B. *J. Org. Chem.* **1982**, *47*, 1378.
(15) Carroll, F. I.; Mitchell, G. N.; Blackwell, J. T.; Sobti, A.; Meck, R. *J. Org. Chem.* **1974**, *39*, 3890.
(16) Kocienski, P.; Wadman, S. J.; Cooper, K. *J. Am. Chem. Soc.* **1989**, *111*, 2363.
(17) Kocienski, P.; Barber, C. *Pure Appl. Chem.* **1990**, *62*, 1933.
(18) Barber, C.; Jarowicki, K.; Kocienski, P. *Synlett* **1991**, 197.
(19) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(20) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *23*, 888.
(21) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(22) Hoppe, D.; Tarara, G.; Wilckens, M. *Synthesis* **1989**, 83.
(23) Köbrich, E. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 49.
(24) Pimm, A.; Kocienski, P.; Street, S. D. A. *Synlett* **1992**, 886.
(25) Lenders, B.; Grove, D. M.; Smeets, W. J. J.; van der Sluis, P.; Spek, A. L.; van Koten, G. *Organometallics* **1991**, *10*, 786.
(26) Olmstead, M. M.; Power, P. P. *J. Am. Chem. Soc.* **1990**, *112*, 8008.
(27) Power, P. P. In *Progress in Inorg. Chem.*; S. J. Lippard, Ed.; Wiley Interscience: New York, 1991; Vol. 39; pp 75-112.
(28) Birkinshaw, S.; Kocienski, P. *Tetrahedron Lett.* **1991**, *32*, 6961.
(29) Soderquist, J. A.; Rivera, I. *Tetrahedron Lett.* **1989**, *30*, 3919.
(30) Alexakis, A.; Hanaizi, J.; Jachiet, D.; Normant, J.-F.; Toupet, L. *Tetrahedron Lett.* **1990**, *31*, 1271.
(31) Bertz, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 4031.
(32) Lipshutz, B. H. *J. Am. Chem. Soc.* **1990**, *112*, 4032.
(33) Snyder, J. P.; Tipsword, G. E.; Spangler, D. P. *J. Am. Chem. Soc.* **1992**, *114*, 1507.
(34) Stemmler, T.; Penner-Hahn, J. E.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 348.
(35) Snyder, J. P.; Spangler, D. P.; Behling, J. R.; Rossiter, B. E. *J. Org. Chem.* **1994**, *59*, 2665.
(36) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523.
(37) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.
(38) Mistry, A.; Smith, K.; Bye, M. R. *Tetrahedron Lett.* **1986**, *27*, 1051.
(39) Ohfune, Y.; Sakaitani, M. *Tetrahedron Lett.* **1985**, *26*, 5543.
(40) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994, pp 33-38.
(41) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.
(42) Stocks, M.; Kocienski, P.; Donald, D. K. *Tetrahedron Lett.* **1990**, *31*, 1637.
(43) Barber, C.; Bury, P.; Kocienski, P.; O'Shea, M. *J. Chem. Soc., Chem. Commun.* **1991**, 1595.
(44) Chan, W. R.; Tinto, W. F.; Manchand, P. S.; Todaro, L. J. *J. Org. Chem.* **1987**, *52*, 3091.
(45) Grieco, P. A.; Perez-Medrano, A. *Tetrahedron Lett.* **1988**, *29*, 4225.
(46) White, J. D.; Amedio, J. C. *J. Org. Chem.* **1989**, *54*, 736.
(47) Hirai, Y.; Yokota, K.; Sakai, H.; Yamazaki, T.; Momose, T. *Heterocycles* **1989**, *29*, 1865.
(48) Hirai, Y.; Yokota, K.; Yamazaki, T.; Momose, T. *Heterocycles* **1990**, *30*, 1101.
(49) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932.
(50) Hoppe, D.; Krämer, T.; Schwark, J.-R.; Zschage, O. *Pure Appl. Chem.* **1990**, *37*, 1999.
(51) Kocienski, P.; Dixon, N. J. *Synlett* **1989**, 52.
(52) Glukhovtsev, M. N.; Pross, A.; Radom, L. *J. Am. Chem. Soc.* **1994**, *16*, 5961.
(53) Bosold, F.; Zulauf, P.; Marsch, M.; Harms, K.; Lohrenz, J.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1497.
(54) Boche, G.; Marsch, M.; Müller, A.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1032.
(55) Vickery, E. H.; Pahler, L. F.; Eisenbraun, E. J. *J. Org. Chem.* **1979**, *44*, 4444.
(56) Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275.
(57) O'Connor, S. J.; Williard, P. G. *Tetrahedron Lett.* **1989**, *30*, 4637.
(58) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(59) Kato, S.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1985**, *29*, 6465.