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Asymmetric synthesis of 1-azaspiro[4.5]decanes via intramolecular dipolar cycloaddition of nitrones containing the bornane-10,2-sultam chiral auxiliary

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Abstract

The intramolecular 1,3-dipolar cycloaddition of a cyclic nitrone, prepared by an asymmetric electrophilic enolate hydroxyamination using the (2*R*)-bornane-10,2-sultam chiral auxiliary, proceeds to give bridged and fused cycloadducts with total diastereocontrol. Reduction of the fused isoxazolidine provides a 1-azaspiro[4.5]-decane as a potential intermediate in the asymmetric synthesis of the cylindricine alkaloids.

1. Introduction

Spirocyclic alkaloids exhibiting the perhydropyrrolo- and perhydropyrido[2,1-*j*]quinoline framework, such as cylindricine A **1**, C **2**, D **3**, E **4** and F **5**,[1] the putative structure of lepadiformine **6**,[2] and fasicularin **7**,[3] isolated from the ascidians *Clavelina cylindrica*, *Clavelina lepadiformis* and *Nephteis fasicularis*, respectively, have been attracting increasing attention. Many of these spirocyclic alkaloids exhibit interesting biological properties, with equilibrium mixtures of cylindricine A **1** and B **8** causing mortality in a brine shrimp assay and fasicularin displaying cytotoxicity and functioning as a DNA damaging agent. Consequently, there has been considerable synthetic interest in the perhydropyrrolo[2,1-*j*]quinoline skeleton of these alkaloids. Not only has the preparation of (±)-cylindricine A, D and E been addressed by Snider,[4] but an enantioselective synthesis of (–)-cylindricine C has been reported by Molander,[5] and the challenge of establishing the spirocyclic stereogenic centre with control of relative stereochemistry has been addressed by Pearson,[6] Kibayashi[7] and Weinreb.[8] In these studies it was shown that the intriguing structure proposed for lepadiformine, on the basis of NMR spectroscopic measurements, was incorrect.

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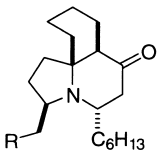
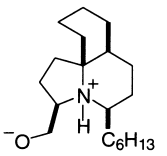
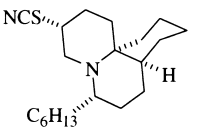
This recent revelation, and the success of Weinreb's synthesis, has prompted us to report on our asymmetric dipolar cycloaddition approach to the cylindricine spirocyclic framework using the (2*R*)-bornane-10,2-sultam chiral auxiliary.



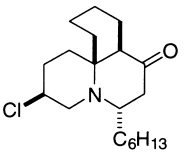
1 R=Cl, cylindricine A
2 R=OH, cylindricine C
3 R=OMe, cylindricine D
4 R=OAc, cylindricine E
5 R=SCN, cylindricine F



putative structure of lepadiformine, **6**

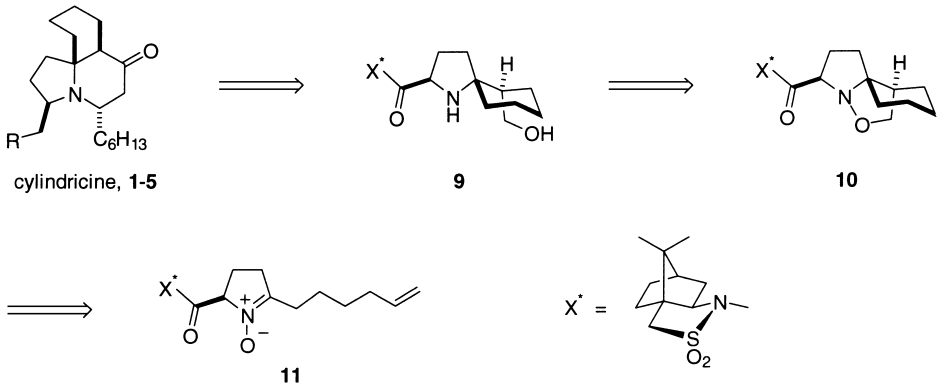


fasicularin, **7**



cylindricine B, **8**

Based on the ready availability of chiral nitrones,[9] from the asymmetric electrophilic α-hydroxyamination of *N*-(δ-ketoacyl)sultam acetals,[10] and to continue our interest in the synthesis of spirocyclic natural products,[11] we investigated an intramolecular 1,3-dipolar cycloaddition approach to 1-azaspiro[4.5]decane **9**. It was hoped that the (2*R*)-bornane-10,2-sultam chiral auxiliary would specify the stereochemistry of the α-centre in cyclic nitrone **11** and thus dictate the facial stereoselectivity of the cycloaddition to establish fused cycloadduct **10** (Scheme 1). This isoxazolidine would be an ideal intermediate in the synthesis of cylindricine natural products as N–O reductions would provide functionality for subsequent assembly of the indolizidine skeleton.



cylindricine, **1-5** **9** **10**

11

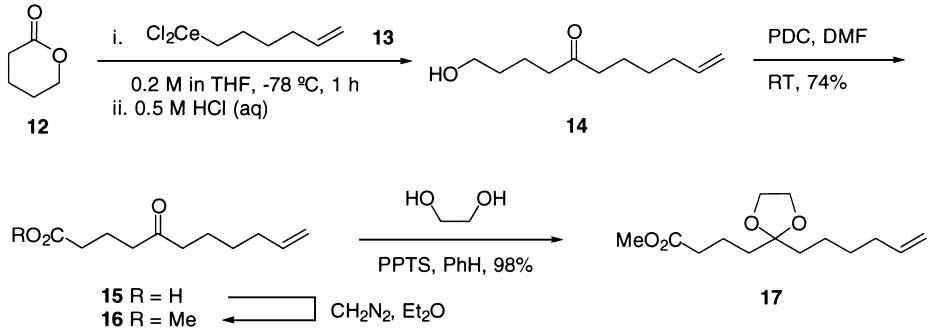
Scheme 1.

2. Results and discussion

In the light of previous studies within the group,[12] it was proposed that nitrone **11** could be prepared from methyl ester **17**, generated by the mono-addition of a hexenyl organometallic reagent to δ-valerolactone **12**. In view of literature precedent,[13] 6-hex-1-enylcerium dichloride **13** was prepared by the treatment of 6-hex-1-enylmagnesium bromide with cerium(III) chloride,[14] sonicated prior to reaction according to the procedure of Grieves,[15] and reacted with δ-valerolactone **12** in tetrahydrofuran at –78°C. Providing the lactone **12** was freed from polymeric contamination immediately prior to reaction by distillation, undecenol **14** was formed in excellent yield. Alcohol **14** was not purified but was oxidised directly with pyridinium dichromate in

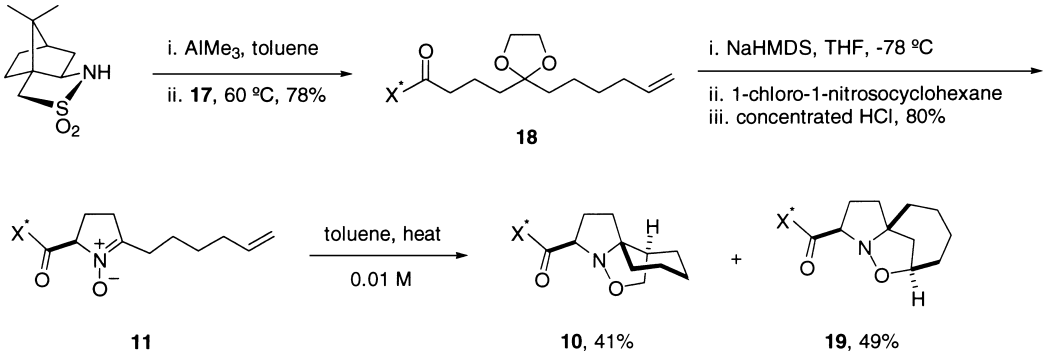
DMF[16] to give undecenoic acid **15** in 74% yield. Treatment with diazomethane, formed in situ by the basification of *N*-methyl-*N*-nitrosourea,[17] and reaction with ethylene glycol under acid-catalysed conditions, according to the procedure of Sterzycki,[18] gave acetal **17** in 73% yield as a substrate suitable for coupling with the (2*R*)-bornane-10,2-sultam chiral auxiliary (Scheme 2).

The amide linkage of (undecenoyl)bornane-10,2-sultam **18** was established by Weinreb's pro-



Scheme 2.

tocol[19] which had met with success in previous studies within the group.[9,10] The trimethylaluminium mediated acylation of (2*R*)-bornane-10,2-sultam with methyl undecenoate **17** at 60°C produced acylsultam **18** in 78% yield (Scheme 3). Deprotonation with sodium hexamethyldisilazide at –78°C, trapping the (*Z*)-enolate with the electrophilic hydroxyaminating agent 1-chloro-1-nitrosocyclohexane,[20] followed by the acid-catalysed hydrolysis of the acetal protecting group resulted in spontaneous cyclodehydration to form nitrone **11** in 80% yield as a single diastereoisomer. It was found that the action of concentrated hydrochloric acid at room temperature provided the optimum results for the hydrolysis–cyclisation sequence in preference to the previously reported procedure.[9,10] Subjecting chiral nitrone **11** to conditions known to favour intramolecular cycloaddition,[21] namely heating a highly dilute solution at reflux in benzene for 16 h, liberated none of the desired cycloadduct **10** and afforded only a quantitative return of unreacted starting material **11**. However, repeating the procedure in a higher boiling solvent, such as toluene or mesitylene, overcame this difficulty and resulted in the isolation of two new products. These were separated by flash chromatography and were identified as fused **10** and bridged **19** cycloadducts, isolated in 41 and 47% yield, respectively.



Scheme 3.

Structural identification of the cycloadducts **10** and **19** was elucidated by 400 MHz ^{1}H, COSY, 100 MHz ^{13}C and $^{1}H/^{13}C$ heteronuclear correlation NMR spectroscopic studies. The stereochemistry of fused cycloadduct **10** was established by a NOESY irradiation experiment that indicated a significant enhancement of the signal at 4.41 ppm. arrising from the methine adjacent to the acylsultam upon irradiation of the bridgehead methine resonance at 2.45 ppm. or the methylene isoxazolidine α-proton resonance at 4.23 ppm. (Fig. 1). Similarly, irradiation of the isoxazolidine methine resonance at 4.72 ppm enhanced the methine signal at 4.31 ppm. in bridged cycloadduct **19**.

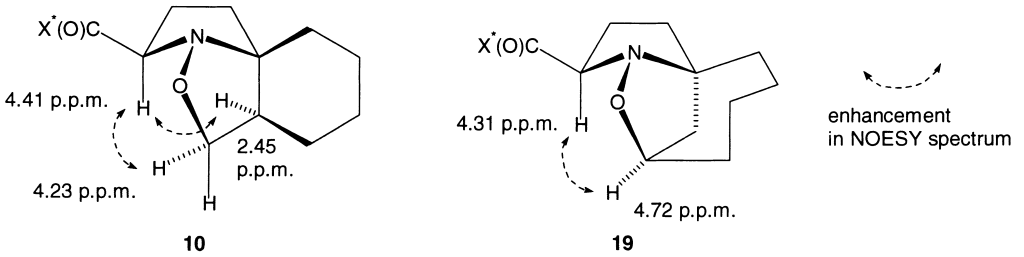


Figure 1.

Evidently, the (2*R*)-bornane-10,2-sultam had been successful in specifying the stereochemistry of the spirocyclic and bridgehead stereogenic centres, the dipolarophilic tether approaching the α-face of the 1,3-dipole in an *exo*-cycloaddition. However, the problem in the regiochemistry of cycloaddition severely limits the efficiency of this route for the synthesis of natural products. The formation of bridged and fused adducts in the intramolecular cycloaddition of cyclic nitrones has been reported in the literature.[22] LeBel succeeded in the isomerisation of bridged to fused cycloadducts by heating the mixture to 280°C.[23] Unfortunately all attempts (Carius tube/neat or in mesitylene/200–250°C) to affect this transformation on bridged cycloadduct **19** resulted only in either complete recovery of starting material or decomposition. However, N–O bond cleavage of fused cycloadduct **10** by heating in acetic acid:water (1:1) in the presence of activated zinc did provide 1-azaspiro[4.5]decane **9** in 53% yield, an intermediate with potential for elaboration to cylindricine or lepadiformine natural products.

3. Conclusions

While the poor regioselectivity of this approach was disappointing, this investigation has validated the potential of this methodology for the asymmetric synthesis of 1-azaspiro[4.5]decanes. The bornane-10,2-sultam auxiliary specified the stereochemistry of the nitrone α-centre and thus controlled the stereochemistry of the intramolecular dipolar cycloaddition that established the spirocyclic stereogenic centre. Subsequent efforts have been underway to control the regiochemistry of the nitrone cycloaddition by introducing extra substituents into the dipolarophilic tether and these results should be reported in due course.

4. Experimental

4.1. General methods and materials

All reactions were carried out under Ar with magnetic stirring unless otherwise specified. Solvents and commercially available reagents were dried and purified according to standard procedures; diethyl ether, toluene and tetrahydrofuran (THF) were distilled over sodium; dichloromethane was distilled from calcium hydride; hexane, ethyl acetate and δ-valerolactone were distilled before use; other chemicals were purchased from Fluka and were used without further purification. Melting points were recorded on a Kofler hot stage and are uncorrected. ^{1}H nuclear magnetic resonance (δ_H) spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise specified. Coupling constants (J) are reported in hertz, chemical shifts are quoted in ppm. downfield from TMS and the following abreviations are used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad; app, apparent. ^{13}C nuclear magnetic resonance (δ_C) spectra were recorded at 100 MHz in $CDCl_3$ unless otherwise specified and multiplicities were assigned using DEPT sequence. Optical rotations were measured on a Perkin–Elmer 241 polarimeter as solutions in chloroform at 20°C. Infra-red (ν_{max}) spectra were recorded as solutions in $CHCl_3$ on a Perkin–Elmer 1600 spectrometer unless otherwise specified. Mass spectra were recorded on a Varian CH-4 or Finnigan 4023 spectrometer using electron impact (EI) unless otherwise stated. Flash chromatography was carried out on Merck silica gel (grade 60, 230–240 mesh).

4.2. 6-Hex-1-enylcerium dichloride **13**

6-Bromohexene (4.0 ml, 30 mmol) was added dropwise to a stirred suspension of magnesium turnings (0.73 g, 30 mmol) (pre-dried in oven at 130°C overnight) in dry THF (10 ml) in the presence of iodine (5 mg, 0.02 mmol) at a rate able to maintain a gentle heat at reflux. Once addition was complete the mixture was heated at reflux for 45 min, allowed to cool and diluted with dry THF (60 ml) to give a solution of 6-hex-1-enylmagnesium bromide in THF. Finely ground cerium(III) chloride heptahydrate (11.2 g, 30 mmol) was dried in vacuo (oil pump) at 140°C overnight, allowed to cool and flushed with Ar. Dry THF (80 ml) was added, the suspension sonicated in an ultrasonic bath at room temperature for 1 h and then cooled to –78°C. A solution of 6-hex-1-enylmagnesium bromide in THF (70 ml, 30 mmol) was added dropwise and the mixture stirred for 1 h to give 6-hex-1-enylcerium dichloride **13** which was used directly.

4.3. 5-Oxoundec-10-enoic acid **15**

Freshly distilled δ-valerolactone (2.0 ml, 21.6 mmol) was added dropwise to 6-hex-1-enyl cerium dichloride **13** in THF (150 ml, 30 mmol) at –78°C. The mixture was stirred for 1 h, quenched at –78°C by the addition of 0.5 M aqueous HCl (60 ml) and partitioned between water (25 ml) and dichloromethane (200 ml). The aqueous phase was further extracted with dichloromethane (3×75 ml) and the organic extracts were combined, dried ($MgSO_4$) and evaporated in vacuo to give crude 5-oxoundec-10-en-1-ol **14** as a pale yellow oil (4.27 g). Ketoalcohol **14** was dissolved in DMF (25 ml) and added to a solution of pyridinium dichromate (28.4 g, 75.6 mmol) in DMF (60 ml) at room temperature. The mixture was stirred overnight and partitioned between water (200 ml) and diethyl ether (200 ml). The aqueous phase was further extracted with diethyl ether (4×200 ml)

and the organic extracts were combined, dried ($MgSO_4$) and evaporated in vacuo to give 5-oxoundec-10-enoic acid **15** (3.18 g, 74%) as a colourless solid. A small portion was further purified by recrystallisation (chloroform–hexane) to give the title compound as colourless prisms, m.p. 39.5–40.0°C (found: C, 66.59; H, 9.19%. $C_{11}H_{18}O_3$ requires: C, 66.64; H, 9.15%) (Found: M^+, 198.1260. $C_{11}H_{18}O_3$ requires: 198.1251); ν_{max} (film)/cm^{-1} 3078, 3027, 2936, 2856, 1712, 1638, 1412, 1371, 1233, 994, 916; δ_H (400 MHz, $CDCl_3$) 5.79 (1H, ddt, $J=17.2$, 10.2, 7, CH), 5.00 (1H, m, C*H*H), 4.95 (1H, m, CH*H*), 2.50 (2H, t, $J=7$, CH_2), 2.41 (2H, t, $J=7$, CH_2), 2.39 (2H, t, $J=7$, CH_2), 2.06 (2H, dt, $J=7$, 7, CHCH_2), 1.90 (2H, app qn, $J=7$, $CH_2CH_2CH_2$), 1.59 (2H, app qn, $J=7$, $CH_2CH_2CH_2$) and 1.38 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 210.1 (C), 178.9 (C), 138.4 (CH), 114.7 (CH_2), 42.7 (CH_2), 41.3 (CH_2), 33.5 (CH_2), 32.9 (CH_2), 28.4 (CH_2), 23.2 (CH_2) and 18.5 (CH_2); *m*/*z* (EI) 198 (M^+, 3%), 181 (10), 143 (12), 130 (44), 112 (62), 87 (65) and 55 (100).

4.4. Methyl 5-oxoundec-10-enoate **16**

N-Methyl-*N*-nitrosourea (0.5 g, 5.5 mmol) was added portionwise to a biphasic solution of 40% aqueous potassium hydroxide (1.5 ml, 12.5 mmol) and diethyl ether (5 ml) at room temperature. The deep yellow ethereal layer was decanted using a pasteur pipette (flame treated to round sharp edges) and added to a solution of 5-oxoundec-10-enoic acid **15** (0.40 g, 2.0 mmol) in diethyl ether (5 ml) at 0°C until a yellow colour persisted. The reaction was warmed to room temperature, stirred for 1.5 h and evaporated in vacuo to give methyl 5-oxoundec-10-enoate **16** (0.44 g, quant) as a colourless oil that was used without further purification (found: M^+, 212.1442. $C_{12}H_{20}O_3$ requires: 212.1407); ν_{max}/cm^{-1} 3026, 2936, 2859, 1737, 1710, 1641, 1437, 1415, 1376, 1231, 1202, 1173, 1098, 996 and 912; δ_H (400 MHz, $CDCl_3$) 5.79 (1H, ddt, $J=17$, 10.3, 7, CH), 5.00 (1H, ddt, $J=17$, 2, 2, C*H*H), 4.95 (1H, m, CH*H*), 3.67 (3H, s, MeO), 2.47 (2H, t, $J=7$, CH_2), 2.40 (2H, t, $J=7$, CH_2), 2.34 (2H, t, $J=7$, CH_2), 2.05 (2H, dt, $J=7$, 7, CHCH_2), 1.89 (2H, app qn, $J=7$, $CH_2CH_2CH_2$), 1.58 (2H, app qn, $J=7$, $CH_2CH_2CH_2$) and 1.38 (2H, m, CH_2); δ_C (100 MHz, $CDCl_3$) 210.1 (C), 173.6 (C), 138.4 (CH), 114.6 (CH_2), 51.5 (Me), 42.6 (CH_2), 41.4 (CH_2), 33.5 (CH_2), 33.0 (CH_2), 28.4 (CH_2), 23.2 (CH_2) and 18.9 (CH_2); *m*/*z* (EI) 212 (M^+, 2%), 181 (9), 144 (71), 129 (55), 112 (72), 101 (70), 83 (48), 67 (26) and 55 (100).

4.5. Methyl 5-ethylenedioxyundec-10-enoate **17**

A mixture of methyl 5-oxoundec-10-enoate **16** (0.44 g, 2.0 mmol), ethylene glycol (0.35 ml, 6.37 mmol) and pyridinium *p*-toluenesulphonate (0.15 g, 0.58 mmol) in benzene (50 ml) was heated to reflux overnight with the azeotropic removal of water using Dean–Stark apparatus. The mixture was concentrated, allowed to cool and partitioned between diethyl ether (100 ml) and saturated aqueous sodium hydrogen carbonate solution (50 ml). The organic extract was washed with brine (75 ml), dried ($MgSO_4$) and evaporated in vacuo to give methyl 5-ethylenedioxyundec-10-enoate **17** (0.50 g, 98%) as a pale yellow oil (found: M^+, 256.1660. $C_{14}H_{24}O_4$ requires: 256.1668); ν_{max}/cm^{-1} 3026, 2950, 2885, 1731, 1636, 1438, 1373, 1232, 1174, 1068, 995, 948 and 912; δ_H (400 MHz, $CDCl_3$) 5.80 (1H, ddt, $J=17$, 10, 7, CH), 5.01 (1H, ddt, $J=17$, 2, 2, C*H*H), 4.94 (1H, m, CH*H*), 3.93 (4H, s, OCH_2CH_2O), 3.67 (3H, s, MeO), 2.33 (2H, t, $J=7$, CH_2), 2.05 (2H, m, CH_2), 1.75–1.57 (6 H) and 1.44–1.33 (4 H); δ_C (100 MHz, $CDCl_3$) 173.9 (C), 138.9 (CH), 114.3 (CH_2), 111.4 (C), 64.9 (CH_2), 51.4 (Me), 37.0 (CH_2), 36.3 (CH_2), 34.1 (CH_2), 33.7 (CH_2), 29.2 (CH_2), 23.3 (CH_2) and 19.4 (CH_2); *m*/*z* (EI) 256 (M^+, 0.5%), 225 (10), 173 (100), 155 (85), 129 (13), 112 (19), 99 (55), 83 (16), 67 (26) and 55 (37).

4.6. (2R)-N-(5-Ethylenedioxyundec-10-enoyl)bornane-10,2-sultam **18**

A 2.0 M solution of trimethylaluminium in toluene (0.95 ml, 1.90 mmol) was added dropwise to a stirred solution of (2*R*)-bornane-10,2-sultam (0.40 g, 1.90 mmol) in dry toluene (10 ml) at room temperature under Ar and the mixture was stirred for 2 h. A solution of methyl 5-ethylenedioxyundec-10-enoate **17** (0.48 g, 1.90 mmol) in dry toluene (5 ml) was added, the reaction was stirred at 60°C for 2 days and partitioned between ethyl acetate (100 ml) and semi-saturated aqueous ammonium chloride solution (100 ml). The aqueous phase was further extracted with ethyl acetate (3×100 ml) and the organic extracts were combined, dried ($MgSO_4$), evaporated in vacuo and purified by column chromatography on silica (ethyl acetate:hexane, 1:4) to give (2*R*)-*N*-(5-ethylenedioxyundec-10-enoyl)bornane-10,2-sultam **18** (0.22 g, 77%) as a colourless oil (found: $[M–C_6H_{11}]^+$, 356.1523. $C_{17}H_{26}NO_5S$ requires: 356.1525); $[\alpha]_D$ –69.3 (*c* 1.05, $CHCl_3$); ν_{max}/cm^{-1} 3030, 2960, 2878, 1697, 1640, 1438, 1332, 1273, 1229, 1210, 1134, 1055, 990, 946 and 911; δ_H (400 MHz, $CDCl_3$) 5.80 (1H, ddt, $J=17$, 10, 7, CH), 4.99 (1H, m, C*H*H), 4.93 (1H, m, CH*H*), 3.92 (4H, s, OCH_2CH_2O), 3.86 (1H, dd, $J=7.3$, 5.2, CHN), 3.49 (1H, d, $J=13.6$, C*H*HSO_2), 3.42 (1H, d, $J=13.6$, CH*H*SO_2), 2.73 (2H, dt, $J=2$, 7), 2.07 (4H), 1.88 (3H), 1.74 (2H, m), 1.63 (4H), 1.37 (6H), 1.15 (3H, s, Me) and 0.97 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 171.7 (C), 138.9 (CH), 114.3 (CH_2), 111.4 (C), 65.2 (CH), 64.9 (CH_2), 53.0 (CH_2), 48.4 (C), 47.8 (C), 44.7 (CH), 38.5 (CH_2), 37.0 (CH_2), 36.0 (CH_2), 35.4 (CH_2), 33.7 (CH_2), 32.9 (CH_2), 29.2 (CH_2), 26.5 (CH_2), 23.3 (CH_2), 20.8 (Me), 19.9 (Me) and 18.8 (CH_2); *m*/*z* (EI) 356 (40%), 225 (12), 155 (100), 173 (100) and 99 (79).

4.7. (2R,2′R)-N-(5-[Hex-5-en-1-yl]-3,4-dihydro-2H-pyrrole-1-oxide-2-carbonyl)bornane-10,2-sultam **11**

A 1.0 M solution of sodium hexamethyldisilazide (0.33 ml, 0.33 mmol) was added dropwise to a stirred solution of (2*R*)-*N*-(5-ethylenedioxyundec-10-enoyl)bornane-10,2-sultam **18** (0.17 g, 0.27 mmol) in dry THF (4 ml) at –78°C under Ar. The reaction was stirred for 45 min, a 2.0 M solution of 1-chloro-1-nitrosocyclohexane[20] in toluene (0.14 ml, 0.28 mmol) was added dropwise until a blue–green colour persisted and the mixture was stirred for 1.5 h. Tetrahydrofuran (40 ml) and concentrated hydrochloric acid (37%, 2.5 ml) were added, the mixture was warmed to room temperature, stirred overnight and partitioned between saturated aqueous sodium hydrogen carbonate solution (100 ml) and dichloromethane (100 ml). The aqueous phase was further extracted with dichloromethane (75 ml) and the organic extracts were combined, dried (Na_2SO_4), evaporated in vacuo and purified by column chromatography on silica (ethyl acetate) to give (2*R*,2′*R*)-*N*-(5-[hex-5-en-1-yl]-3,4-dihydro-2*H*-pyrrole-1-oxide-2-carbonyl)bornane-10,2-sultam **11** (87 mg, 80%) as a colourless oil (found: M^+, 408.2079. $C_{21}H_{32}N_2O_4S$ requires: 408.2075); $[\alpha]_D$ –55.5 (*c* 1.10, $CHCl_3$); ν_{max}/cm^{-1} 3030, 2963, 2921, 2845, 1700, 1638, 1603, 1339, 1272, 1239, 1167, 1136 and 916; δ_H (400 MHz, $CDCl_3$) 5.78 (1H, ddt, $J=17$, 10, 7, CH), 5.42 (1H, t, $J=7$, CHNO), 5.01 (1H, ddt, $J=17$, 2, 2, C*H*H), 4.95 (1H, m, CH*H*), 3.92 (1H, dd, $J=7.7$, 4.8, CHN), 3.56 (1H, d, $J=13.6$, C*H*HSO_2), 3.44 (1H, d, $J=13.6$, CH*H*SO_2), 2.82 (1H, m), 2.70 (1H, m), 2.53 (2H, t, $J=7.5$), 2.40 (2H, m), 2.29 (2H, m), 2.12–1.84 (5H), 1.64–1.30 (6H), 1.26 (3H, s, Me) and 0.98 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 167.8 (C), 149.9 (C), 138.3 (CH), 114.8 (CH_2), 74.0 (CH), 65.4 (CH), 53.0 (CH_2), 48.9 (C), 47.9 (C), 44.6 (CH), 38.1 (CH_2), 33.3 (CH_2), 32.8 (CH_2), 30.5 (CH_2), 28.8 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 24.5 (CH_2), 21.8 (CH_2), 20.9 (Me) and 19.9 (Me); *m*/*z* (EI) 408 (M^+, 1%), 340 (10), 166 (100) and 98 (73).

4.8. Fused cycloadduct **10** and bridged cycloadduct **19**

A solution of (2*R*,2′*R*)-*N*-(5-[hex-5-en-1-yl]-3,4-dihydro-2*H*-pyrrole-1-oxide-2-carbonyl)bornane-10,2-sultam **18** (50 mg, 0.12 mmol) in dry toluene (12 ml) was heated to reflux for 16 h under Ar. The reaction was allowed to cool, evaporated in vacuo by forming an azeotrope with methanol and purified by flash chromatography on silica (ethyl acetate:hexane, 1:4) to give bridged cycloadduct **19** (23 mg, 47%) and fused cycloadduct **10** (20 mg, 41%). Bridged cycloadduct **19** was formed as a colourless oil (found: M^+, 408.2067. $C_{21}H_{32}N_2O_4S$ requires: 408.2075); $[\alpha]_D$ +12.3 (*c* 0.95, $CHCl_3$); ν_{max}/cm^{-1} 3027, 2994, 2963, 2928, 2885, 2861, 1702, 1600, 1450, 1413, 1334, 1268, 1236, 1166, 1134, 1114, 1083, 1064 and 1000; δ_H (400 MHz, $CDCl_3$) 4.72 (1H, app d, $J=8.8$, OCH), 4.31 (1H, t, $J=8$, CHNO), 3.93 (1H, dd, $J=7.7$, 4.8, CHN), 3.50 (1H, d, $J=13.6$, C*H*HSO$_2$), 3.41 (1H, d, $J=13.6$, CH*H*SO$_2$), 2.33–1.27 (21H), 1.20 (3H, s, Me) and 0.96 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 172.1 (C), 79.8 (CH), 74.0 (C), 69.9 (CH), 65.5 (CH), 53.2 (CH_2), 48.5 (C), 47.8 (C), 44.8 (CH), 40.5 (CH_2), 40.4 (CH_2), 38.7 (CH_2), 34.4 (CH_2), 33.3 (CH_2), 32.9 (CH_2), 26.4 (CH_2), 25.6 (CH_2), 23.7 (CH_2), 23.2 (CH_2), 21.0 (Me) and 19.9 (Me); *m*/*z* (EI) 408 (M^+, 1%) and 166 (100). Fused cycloadduct **10** was formed as a colourless oil (found: M^+, 408.2132. $C_{21}H_{32}N_2O_4S$ requires: 408.2075); $[\alpha]_D$ +20.8 (*c* 1.02, $CHCl_3$); ν_{max}/cm^{-1} 3031, 2992, 2963, 2938, 2882, 2859, 1702, 1600, 1451, 1414, 1334, 1269, 1236, 1162, 1134, 1114, 1066 and 907; δ_H (400 MHz, $CDCl_3$) 4.41 (1H, t, $J=8$, CHNO), 4.23 (1H, app t, $J=8$, OC*H*H), 3.93 (1H, dd, $J=7.7$, 4.8, CHN), 3.75 (1H, app t, $J=8$, OCH*H*), 3.51 (1H, d, $J=14$, C*H*HSO$_2$), 3.41 (1H, d, $J=14$, CH*H*SO$_2$), 2.45 (1H, m, OCH$_2$C*H*), 2.34–1.30 (19 H), 1.20 (3H, s, Me) and 0.96 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 172.0 (C), 72.6 (C), 71.9 (CH_2), 68.4 (CH), 65.5 (CH), 53.2 (CH_2), 48.5 (C), 47.8 (C), 45.3 (CH), 44.8 (CH), 38.6 (CH_2), 33.8 (CH_2), 33.6 (CH_2), 32.9 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 23.5 (CH_2), 23.0 (CH_2), 21.2 (CH_2), 21.0 (Me) and 19.9 (Me); *m*/*z* (EI) 408 (M^+, 1%), 390 (1) and 166 (100).

4.9. (2R,2′R,5′R,6′R)-(6-Hydroxymethyl-1-azaspiro[4.5]decane-2-carbonyl)bornane-10,2-sultam **9**

Activated zinc dust (0.59 g, 9.00 mmol) was added to a stirred solution of fused cycloadduct **10** (74 mg, 0.18 mmol) in glacial acetic acid:water (1:1) (3 ml) at room temperature. The mixture was warmed rapidly to 40°C, stirred for 4 h, allowed to cool and partitioned between dichloromethane (50 ml) and saturated aqueous sodium hydrogen carbonate solution (50 ml). The aqueous phase was further extracted with dichloromethane (3×50 ml) and the organic extracts were combined, dried (Na_2SO_4), evaporated in vacuo and purified by flash chromatography on silica (ethyl acetate:hexane, 3:2) to give the title compound (40 mg, 53%) as a colourless oil (found: M^+, 411.2311. $C_{21}H_{35}N_2O_4S$ requires: 411.2309); $[\alpha]_D$ –28.7 (*c* 1.08, $CHCl_3$); ν_{max}/cm^{-1} 3286, 3026, 2995, 2961, 2936, 2884, 2862, 1685, 1451, 1413, 1376, 1338, 1269, 1236, 1166, 1136 and 1054; δ_H (400 MHz, $CDCl_3$) 4.31 (1H, t, $J=7$, C*H*NH), 3.91 (1H, m, OC*H*H), 3.88 (1H, dd, $J=7.7$, 5.2, CHN), 3.76 (1H, m, OCH*H*), 3.51 (1H, d, $J=13.6$, C*H*HSO$_2$), 3.43 (1H, d, $J=13.6$, CH*H*SO$_2$), 2.36 (1H, m, OCH$_2$C*H*), 2.17–1.15 (19 H), 1.14 (3H, s, Me) and 0.97 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 173.8 (C), 66.3 (C), 65.6 (CH), 65.3 (CH_2), 59.9 (CH), 52.9 (CH_2), 48.9 (C), 47.9 (C), 44.5 (CH), 43.4 (CH), 38.4 (CH_2), 37.0 (CH_2), 32.8 (CH_2), 32.8 (CH_2), 30.6 (CH_2), 29.7 (CH_2), 27.2 (CH_2), 26.5 (CH_2), 24.0 (CH_2), 20.8 (Me) and 19.9 (Me); *m*/*z* 411 (MH^+, 33%), 168 (100) and 150 (6).

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