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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of the spirocyclic core of the cylindricine-type alkaloids

Wolfgang Oppolzer† and Christian G. Bochet*

Department of Organic Chemistry, University of Geneva, 30 quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland

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Abstract

Marine alkaloids from the cylindricine and lepadiformine families possess an interesting spirotricyclic skeleton. An intramolecular nitrone/olefin 1,3-dipolar cycloaddition has been used to form their spirocyclic 1-azaspiro[4.5]decane core in a regio- and stereoselective fashion. The cyclization precursor can be easily accessed using the asymmetric electrophilic hydroxyamination of enolate.

1. Introduction

Nitrones are versatile intermediates for alkaloid synthesis, with an interesting dual reactivity as electrophiles[1] or 1,3-dipoles for cycloadditions.[2,3] The intramolecular 1,3-dipolar cycloaddition of nitrones and olefins is of particular interest, since it provides an efficient access to spirocyclic alkaloids.[4] Since 1994, several alkaloids have been isolated from ascidians (marine invertebrates), possessing an unusual perhydropyrrolo[2,1-*j*]quinoline skeleton and exhibiting cytotoxic activity against cancerous cells.[5,6] For example, the cylindricine C **1** was isolated from *Clavelina cylindrica* and showed moderate activity in the brine shrimp test.[5] A recent preliminary report on the assembly of the 1-azaspiro[4.5]decane skeleton of **1** by an intramolecular nitrone–olefin cycloaddition and the lack of regioselectivity in such a process prompts us to disclose our results on the diastereo- and regiocontrol in intramolecular 1,3-cycloadditions.[7]

In our retrosynthetic analysis (Scheme 1), the B ring is formed by a type IVa intramolecular cycloaddition.[4] The correct C5 stereocenter should arise from the facial control of C2, directing the reaction to the lower face, whereas the C10 center would be controlled by an expected *exo* transition state (Scheme 2).

* Corresponding author. E-mail: christian.bochet@chiorg.unige.ch

† Deceased March 15th, 1996.

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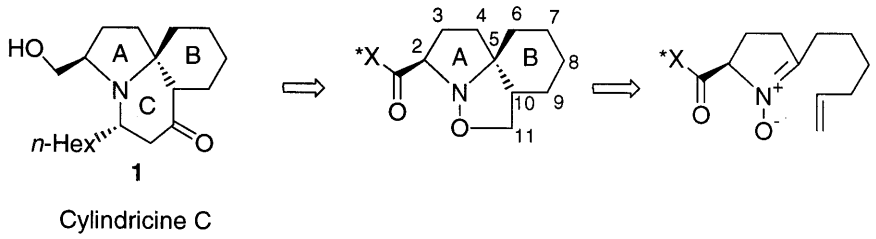
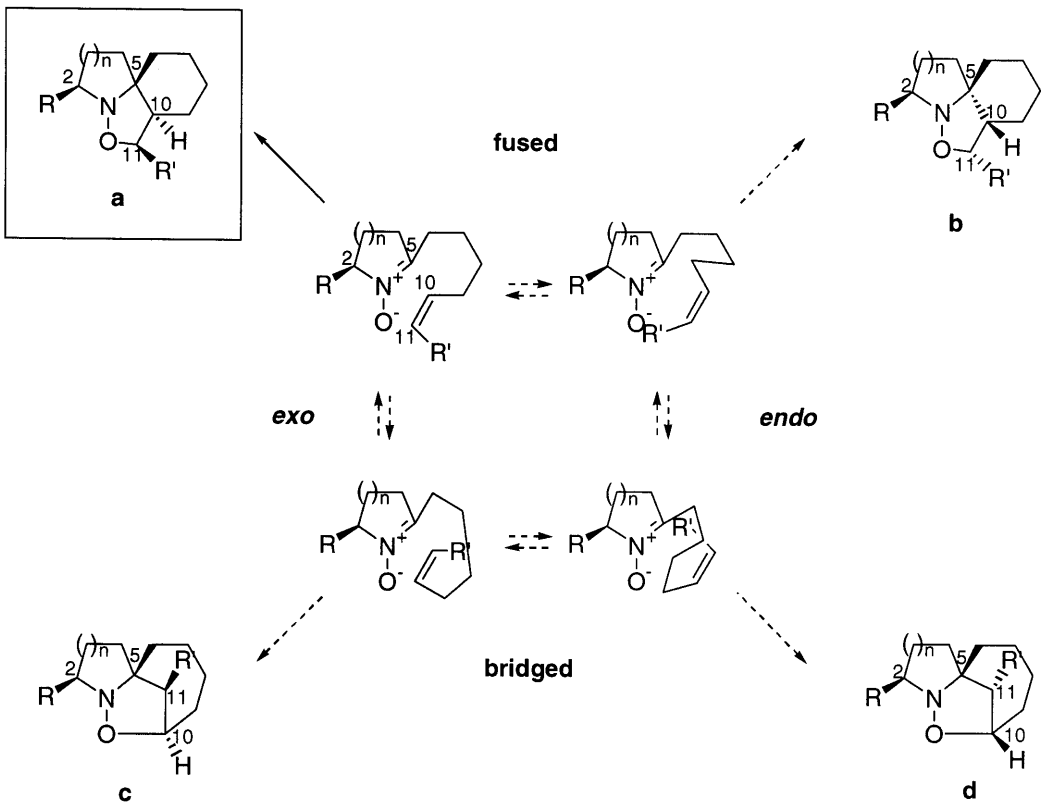


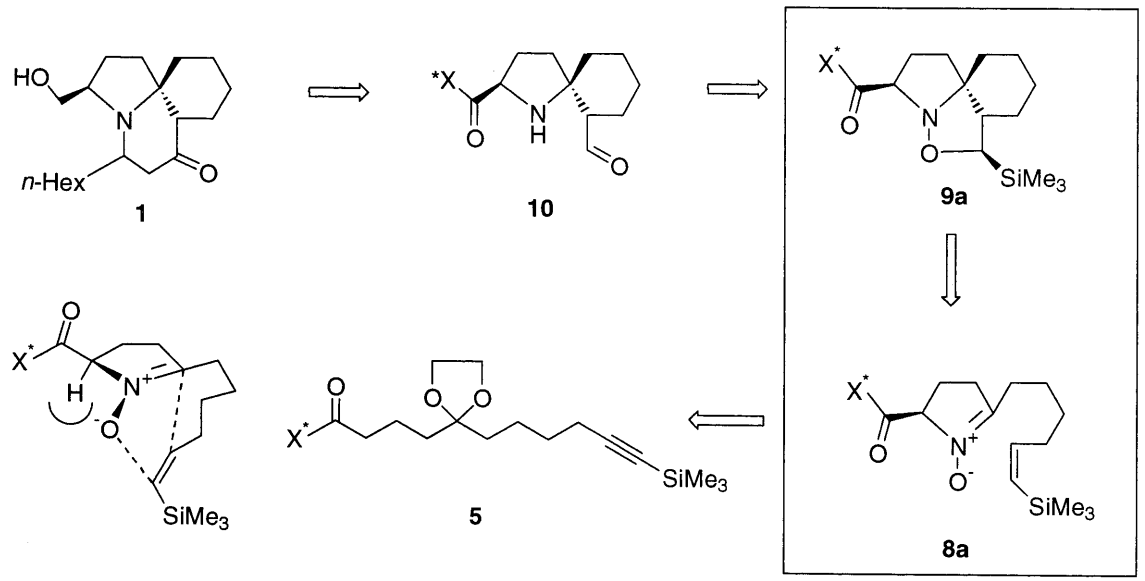
Scheme 1.



Scheme 2.

The fused/bridged mode of cycloaddition is a question of regiocontrol. Early work by Gössinger et al.[8] ($n=2$, R,R′=H) suggested that only the fused adduct **a** would be obtained, in clear contrast to the intermolecular version, where a 5-substituted isoxazolidine is normally obtained (i.e. the oxygen reacting with the most substituted carbon of the olefin). This efficient strategy was, however, rapidly jeopardized when reports by Grigg[9] and Weinreb,[6] independently confirmed in our laboratory,[7] showed that a slightly different cycloaddition ($n=1$, R′=H) led to the formation of both the bridged and fused isoxazolidines **a** and **c** in a ca. 1:1 ratio. The strain induced by the intramolecularity of the reaction obviously compensated only partially for the inherent electronic preference for the opposite regiochemistry.[4]

We reasoned that if both electronic and strain factors could work in the same direction, a selective reaction would occur. Vinylsilanes are known to add to nitrones with the oxygen on the silyl-bearing center; when 1,2-disubstituted vinylsilanes were used, mixtures were observed.[10] Since only a small bias in the electronic preference was needed, we hypothesized that the terminal olefin could be silylated to improve the regiochemical control. The *cis* vinylsilane was preferred over its *trans* isomer, to avoid a possible destabilizing interaction with the C2 hydrogen in the *exo* transition state. The retrosynthetic analysis was thus reformulated according to Scheme 3.

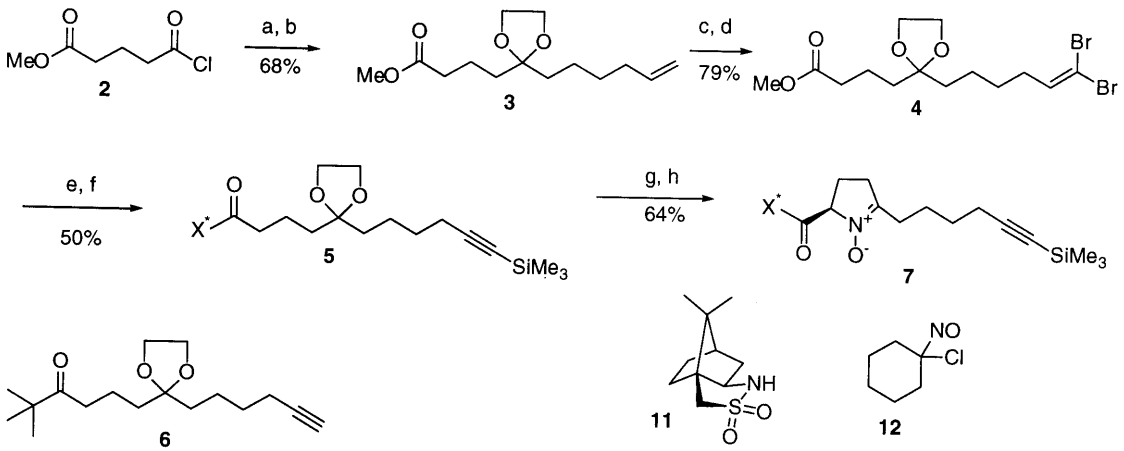


Scheme 3.

2. Results and discussion

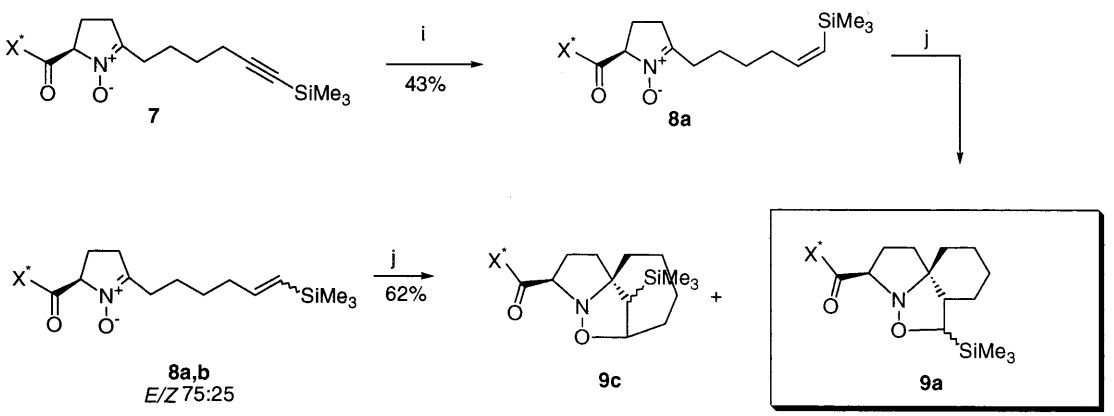
The precursor **3** was prepared by a similar route to the one previously published (Scheme 4).[11] A recent report by Meyers showed the monoaddition of a Grignard reagent to the glutaric acid chloride monoester **2**.[12] Indeed, the addition of 5-hexenylmagnesium bromide to **2** followed by the protection of the ketone as a dioxolane (ethylene glycol, PPTS, PhH) proceeded with an overall yield of 68%. The terminal olefin was then ozonized and converted to the *gem*-dibromide **4** by the Corey–Fuchs procedure,[13] with an overall yield of 79%. Hoping that the ester would be in situ protected as an enolate, we attempted to convert **4** directly into the terminal alkyne **5** by the addition of *t*-BuLi (THF, −78°C, 3 equiv.). No trace of the expected product was detected, but rather the *t*-butylketone **6**. Increasing the steric hindrance around the carbonyl group, while enhancing the acidity of the Cα protons was attempted by first coupling the bornane-10,2-sultam chiral auxiliary **11**, using our standard protocol ($AlMe_3$, PhMe, 60°C, 72 h).[11] This sequence inversion proved useful, and the alkynylsilane **7** was obtained in 50% yield upon addition of 3 equiv. of *t*-BuLi and quenching with TMSCl. Electrophilic hydroxyamination was performed by treating the amide enolate (NaHMDS, THF, −78°C) with the blue 1-chloro-1-nitrosocyclohex-

ane **12**.[14] Acidic hydrolysis in HCl (conc., 25°C, 90 min) provoked the hydrolysis of the initial cyclohexylnitrone and liberated the masked ketone, with concomitant cyclization to give a single diastereoisomer of the nitrone **7**.



Scheme 4. (a) $C_6H_{11}MgBr$, THF, −78°C. (b) $(CH_2OH)_2$, PPTS, PhH. (c) O_3, MeOH, Me_2S, −78°C. (d) CBr_4, PPh_3, Zn, CH_2Cl_2. (e) **11**, $AlMe_3$, PhMe, 70°C. (f) *t*-BuLi (3 equiv.), then Me_3SiCl. (g) $NaN(SiMe_3)_2$, THF, −78°C, then **12**. (h) Conc. HCl, rt

The partial reduction of the alkyne **7** into a *cis* vinylsilane was first attempted using deactivated palladium catalysts (Pd–$BaSO_4$, quinoline, MeOH or Pd–$CaCO_3$, PbO, MeOH or EtOAc) with moderate success,[15] giving rise to inseparable mixtures of *Z* and *E* olefins **8a**,**b** in ratios never better than 3:1 (Scheme 5). On the other hand, a recent protocol with nickel boride on a borohydride resin (Ni_2B–BER) led to a smooth and selective reduction (43%, unoptimized).[16] Exclusive formation of the cycloadduct **9a** was obtained by heating the nitrone **8a** in refluxing benzene for 144 hours. The relative configuration of the spirocyclic structure was confirmed by a strong NOESY cross peak between the hydrogens at C10 and C2. The



Scheme 5. (i) Ni_2–BER, H_2, MeOH, rt. (j) PhH, 80°C, 208 h

stereochemistry at C4 was assigned by the nature of the mechanism and the geometry of the initial olefin; this stereocenter is in any case lost in the next step. On the other hand, the cyclization of a 75:25 mixture of **8a** and **8b** led to the formation of a 63:12:25 mixture of the fused adduct **9a**, the bridged cycloadduct **9c**, and unreacted *E*-vinylsilane **8b** (88%). Clearly, the interaction between the hydrogen at C2 and the *E*-vinylsilane is severe and significantly slows down the cycloaddition. The bridged cycloadduct **9c** probably arises from **8b**, although experimental confirmation has not been carried out. The isoxazolidine **9a** was converted into the aldehyde **10** upon treatment with HF–pyridine.

3. Conclusion

In conclusion, we have shown that the spirocyclic skeleton of marine alkaloids, such as cylindricines or lepadiformine could be accessed by a stereo- and regioselective 1,3-dipolar cycloaddition. Careful tuning of the geometric and electronic properties of the dipolarophile was essential to achieve the required selectivity.

4. Experimental

4.1. General

All reactions were carried out under argon, with magnetic stirring, unless otherwise specified. Chemicals were purchased from Fluka and Aldrich, and were used without purification, unless otherwise specified. Solvents were dried by distillation from drying agents as follows: Et_2O, THF, toluene and benzene (Na/benzophenone); CH_2Cl_2 (CaH_2); MeOH ($Mg(OMe)_2$). Flash column chromatography (FC): SiO_2 (Merck 9385). $[\alpha]_D$: Perkin–Elmer-241 polarimeter. IR: Perkin–Elmer FT-1600, in $CHCl_3$ solutions, unless otherwise specified. ^1H NMR: Bruker AMX-400 in $CDCl_3$, unless otherwise specified; standard $CHCl_3$ ($\delta = 7.27$ ppm). ^{13}C NMR: standard $CDCl_3$ ($\delta = 77.0$ ppm). *J* in Hz. Multiplicities assigned with the DEPT sequence. MS: m/z (rel. %).

4.2. Methyl 5-oxo-10-undecenoate

The Grignard reagent was prepared according to standard protocols, from 6-bromo-1-hexene (6.69 ml, 50 mmol) and magnesium turnings (3.65 g, 150 mmol) in anhydrous THF (50 ml). The acid chloride **2** (9.55 ml, 69 mmol) was slowly added to the filtered solution of the Grignard reagent at −78°C, and the temperature was raised to 25°C over a period of 4 hours. The mixture was quenched by a saturated aqueous solution of ammonium chloride, and was extracted three times with ether. Drying the organic layer over $MgSO_4$, filtration and evaporation of the solvent gave a brown liquid (12.2 g) that was directly used in the next reaction without purification.

4.3. Methyl 5,5-ethylenedioxy-10-undecenoate *3*

The crude methyl 5-oxo-10-undecenoate (12.15 g), pyridinium 4-toluenesulfonate (2.32 g, 9.28 mmol) and ethylene glycol (9.31 g, 150 mmol) were dissolved in benzene (200 ml). The mixture

was refluxed for 15 hours, removing the water formed with a Dean–Stark trap. The benzene was evaporated, and ether was added (200 ml). The solution was washed with water, aqueous saturated bicarbonate solution and brine. Drying over $MgSO_4$, filtration and evaporation of the solvent gave a brown liquid (11.1 g, 87%). ^{1}H NMR (400 MHz): 5.88 (tdd, $J=17.2$, 10.2, 6.6, 1H); 5.1–4.8 (2H); 3.92 (s, 4H); 3.66 (s, 3H); 2.32 (t, $J=6.9$, 2H); 2.1–2.0 (2H); 1.8–1.2 (10H). ^{13}C NMR (100 MHz): 174.4 (s); 139.3 (d); 114.8 (t); 111.9 (s); 65.4 (t); 51.9 (q); 37.5 (t); 36.8 (t); 34.6 (t); 34.2 (t); 29.6 (t); 23.8 (t); 19.8 (t). Additional data are published elsewhere.[7]

4.4. Methyl 5,5-ethylenedioxy-10-oxodecanoate

The terminal olefin **3** (150 mg, 0.586 mmol) was dissolved in methanol (15 ml) and the solution was cooled to −78°C. A stream of ozone was bubbled through the solution until the persistence of a blue color. The excess ozone was then removed by bubbling nitrogen for 15 minutes. Dimethylsulfide (1 ml) was added, and the solution was warmed to 25°C over a period of 3 hours. The volatiles were evaporated, and ether was added (50 ml). The solution was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The aldehyde was obtained as a colorless oil (135 mg, 89%) and was used directly in the next reaction without further purifications. ^{1}H NMR (400 MHz): 9.75 (t, $J=1.8$, 1H); 3.92 (s, 4H); 3.66 (s, 3H); 2.43 (td, $J=7.1$, 2.8, 2H); 1.8–1.3 (10H). ^{13}C NMR (100 MHz): 203.0 (d); 174.4 (s); 111.6 (s); 65.4 (t); 51.9 (q); 44.3 (t); 37.3 (t); 36.8 (t); 34.5 (t); 23.8 (t); 22.8 (t); 19.8 (t).

4.5. 11,11-Dibromo-5,5-ethylenedioxy-10-undecenoate ***4***

A mixture of tetrabromomethane (586 mg, 1.77 mmol), triphenylphosphine (464 mg, 1.77 mmol) and zinc powder (116 mg, 1.77 mmol) was stirred in dichloromethane at room temperature for 15 hours. To this milky pink suspension was added the aldehyde **3** (135 mg, 0.523 mmol) and the mixture was stirred at room temperature for 1 hour. Water (20 ml) was added, and the mixture was extracted three times with dichloromethane (20 ml). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The pure dibromide **4** was obtained by FC (hexane/EtOAc 5:1) as a colorless oil (42 mg, 66%). IR ($CHCl_3$): 3016, 2952, 2889, 1732, 1458, 1348, 1365, 1267, 1227, 1198, 1170, 1140, 1069, 948. ^{1}H NMR (400 MHz): 6.39 (t, $J=7.4$, 1H); 3.94 (s, 4H); 3.67 (s, 3H); 2.32 (t, $J=7.3$, 2H); 2.10 (q, $J=7.2$, 2H); 1.8–1.5 (6H); 1.5–1.3 (4H). ^{13}C NMR (100 MHz): 173.9 (s); 138.6 (d); 111.2 (s); 88.7 (s); 65.0 (t); 51.5 (q); 36.8 (t); 36.3 (t), 34.0 (t); 32.9 (t); 28.0 (t); 23.2 (t); 19.3 (t). MS (EI): 385 (3), 383 (5), 381 (3), 315 (22), 313 (52), 311 (26), 227 (2), 225 (3), 223 (2), 201 (5), 199 (8), 197 (5), 173 (100). HR-MS: 384.9837 (calcd for $C_{13}H_{21}O_3{}^{79}Br^{81}Br$: 384.9832).

4.6. 2,2-Dimethyl-7,7-ethylenedioxy-12-tridecyn-3-one ***6***

The dibromide **4** (14 mg, 0.0338 mmol) was dissolved in anhydrous THF (2 ml) and the mixture was cooled to −78°C. A solution of *t*-butyllithium in pentane (1.7 M, 0.08 ml, 0.135 mmol) was added dropwise and the mixture was stirred for 1 hour at −78°C and 1 hour at −15°C. A saturated aqueous solution of ammonium chloride was added (2 ml), and the mixture was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by FC (hexane/EtOAc 5:1) to give a colorless oil (3 mg, 32%). IR ($CHCl_3$): 3307, 2975, 2868, 2115, 1702, 1600, 1478, 1458, 1382, 1355, 1100, 1066, 946, 902. ^{1}H

NMR (400 MHz): 3.93 (s, 4H); 2.50 (t, $J=6.8$, 2H); 2.19 (td, $J=7.2$, 2.6, 2H); 1.94 (t, $J=2.6$, 1H); 1.7–1.4 (10 H); 1.13 (s, 9H). ^{13}C NMR (100 MHz): 215.6 (s); 111.5 (s); 84.4 (d); 68.3 (s); 64.9 (t); 44.0 (s); 36.6 (t); 36.5 (t); 28.7 (t); 26.4 (q); 23.0 (t); 18.3 (t).

*4.7. (2*R*)-*N*-(11,11-Dibromo-5,5-ethylenedioxy-10-undecenoyl)bornane-10,2-sultam*

(2*R*)-Bornane-10,2-sultam **11** (225 mg, 1.05 mmol) was dissolved in anhydrous toluene (5 ml). A solution of trimethylaluminum in toluene (2 M, 0.524 ml, 1.05 mmol) was added and the mixture was stirred at room temperature for 1 hour. A solution of the ester **4** (289 mg, 0.698 mmol) in toluene (2.5 ml) was added and the mixture was heated at 60°C for 70 hours. An aqueous solution of ammonium chloride was added, and the mixture was extracted five times with ether. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. FC (hexane/EtOAc) furnished the sulfonamide as a thick colorless oil (283 mg, 68%) and unreacted bornane-10,2-sultam (101 mg, 67%). $[\alpha]_D^{22}=-53.2$, $[\alpha]_{578}^{22}=-54.8$, $[\alpha]_{546}^{22}=-61.1$, $[\alpha]_{436}^{22}=-107.3$, $[\alpha]_{365}^{22}=-175.4$ ($c=0.3$, $CHCl_3$). IR ($CHCl_3$): 3024, 2959, 2889, 1697, 1600, 1458, 1414, 1370, 1333, 1267, 1164, 1131, 1060, 989, 946, 532. ^{1}H NMR (400 MHz): 6.39 (t, $J=7.2$, 1H); 3.92 (s, 4H); 3.86 (dd, $J=7.3$, 5.2, 1H); 3.49 (d, $J=14$, 1H); 3.42 (d, $J=14$, 1H); 2.74 (t, $J=7.2$, 2H); 2.2–2.0 (4H); 2.0–1.8 (3H); 1.8–1.5 (7H); 1.5–1.3 (5H); 1.15 (s, 3H); 0.97 (s, 3H). ^{13}C NMR (100 MHz): 171.1 (s); 138.6 (d); 111.2 (s); 88.6 (s); 65.2 (d); 65.0 (t); 53.0 (t); 48.4 (s); 47.8 (s); 44.7 (d); 38.5 (t); 36.8 (t); 36.1 (t); 35.4 (t); 33.0 (t); 32.9 (t); 28.0 (t); 26.5 (t); 23.2 (t); 20.8 (q); 19.9 (q); 18.8 (t). MS (EI): 553 (1), 474 (0.5), 356 (6), 315 (24), 323 (55), 311 (40), 259 (44), 257 (44).

*4.8. (2*R*)-*N*-(11′-Trimethylsilyl-5′,5′-ethylenedioxy-10′-undecynoyl)bornane-10,2-sultam* ***5***

The sulfonamide described above (560 mg, 0.938 mmol) was dissolved in anhydrous THF (30 ml) and the solution was cooled down to −78°C. A solution of *t*-butyllithium in pentane (1.7 M, 1.66 ml, 2.81 mmol) was added dropwise, and the mixture was stirred at −78°C for 20 minutes. Freshly distilled trimethylchlorosilane (0.475 ml, 3.75 mmol) was added dropwise, and allowed to react for 90 minutes at this temperature. Aqueous HCl (1 M) was added, and the temperature was raised to 25°C over a period of 10 minutes. The mixture was partitioned between aqueous saturated bicarbonate and dichloromethane, and the aqueous phase was re-extracted twice with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The pure alkyne **5** was obtained by FC (hexane/EtOAc 3:1) as a colorless oil (300 mg, 63%). $[\alpha]_D^{23}=-56.7$, $[\alpha]_{578}^{23}=-59.8$, $[\alpha]_{546}^{23}=-66.8$, $[\alpha]_{436}^{23}=-115.4$, $[\alpha]_{365}^{23}=-187.4$ ($c=0.83$, $CHCl_3$). IR ($CHCl_3$): 3018, 2930, 2889, 2170, 1697, 1456, 1414, 1383, 1332, 1270, 1250, 1233, 1166, 1133, 1060, 985, 949, 844. ^{1}H NMR (400 MHz): 3.93 (s, 4H); 3.86 (dd, $J=7.4$, 6.0, 1H); 3.49 (d, $J=14$, 1H); 3.43 (d, $J=14$, 1H); 2.74 (t, $J=7.0$, 2H); 2.22 (t, $J=7.0$, 2H); 2.20–2.15 (2H); 2.0–1.8 (4H); 1.8–1.2 (11H); 1.16 (s, 3H); 0.97 (s, 3H); 0.15 (s, 9H). ^{13}C NMR (100 MHz): 171.7 (s); 113.3 (s); 107.4 (s); 84.4 (s); 65.2 (d); 64.9 (t); 52.9 (d); 48.4 (s); 47.7 (s); 44.7 (d); 38.5 (t); 36.6 (t); 36.1 (t); 35.4 (t); 32.8 (t); 28.9 (t); 26.4 (t); 23.0 (t); 20.8 (q); 19.9 (q); 19.8 (q); 18.8 (t); 0.2 (q). MS (EI): 493 (0.5), 450 (2), 428 (3), 356 (80), 225 (100), 153 (13), 99 (95), 73 (68).

*4.9. (2*R*,2′*R*)-*N*-(5′-(6″-Trimethylsilyl)-5″-hexyn-1″-yl)-1′-oxy-3′,4′-dihydro-2*H*-pyrrol-2′-carbonyl)bornane-10,2-sultam* ***7***

The alkyne **5** (140 mg, 0.275 mmol) was dissolved in anhydrous THF (20 ml) and cooled down to −78°C. A solution of sodium hexamethyldisilazide in THF (2 M, 0.165 ml, 0.330 mmol)

was added dropwise, and the mixture was stirred at −78°C for 1 hour. 1-Chloro-1-nitorosocyclohexane[17] **12** was added dropwise (42 μl, 0.330 mmol) and the mixture was allowed to react at −78°C for 1 hour. Concentrated hydrochloric acid was then added (1.5 ml) and the mixture was stirred at room temperature for 2.5 hours. The mixture was partitioned between aqueous saturated bicarbonate and dichloromethane, and the aqueous phase was re-extracted twice with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered, concentrated and purified by FC (EtOAc) to give the pure nitrone **7** as a colorless oil (82 mg, 62%). $[\alpha]_D^{22}=-42.5$, $[\alpha]_{578}^{22}=-48.6$, $[\alpha]_{546}^{22}=-54.2$, $[\alpha]_{436}^{22}=-101.4$, $[\alpha]_{365}^{22}=-171.5$ ($c=0.4$, $CHCl_3$). IR ($CHCl_3$): 2961, 2169, 1701, 1600, 1464, 1393, 1339, 1273, 1240, 1164, 1137, 848. ^{1}H NMR (400 MHz): 5.43 (t, $J=7.4$, 1H); 3.92 (dd, $J=7.7$, 4.8, 1H); 3.56 (d, $J=13.6$, 1H); 3.44 (d, $J=13.6$, 1H); 2.9–2.7 (2H); 2.56 (t, $J=7.7$, 4.8, 1H); 2.41 (*m*, 1H); 2.35–2.2 (4H); 2.2–2.0 (2H); 2.0–1.8 (3H); 1.7–1.5 (4H); 1.5–1.3 (2H); 1.15 (s, 3H); 0.97 (s, 3H); 0.13 (s, 9H). ^{13}C NMR (100 MHz): 167.7 (s); 106.8 (s); 84.9 (s); 74.1 (d); 65.4 (d); 53.0 (t); 49.0 (s); 47.9 (s); 44.6 (d); 38.1 (t); 32.8 (t); 30.5 (t); 28.3 (t); 26.5 (t); 26.0 (t); 24.2 (t); 21.9 (t); 20.9 (q); 19.9 (q); 19.5 (t); 0.15 (q).

*4.10. (2*R,*2′*R,*5″*Z*)*-N-*(5′-(6″-Trimethylsilyl)-5″-hexen-1″-yl)-1′-oxy-3′,4′-dihydro-2*H*-pyrrol-2′-carbonyl)bornane-10,2-sultam* ***8a***

The nitrone **7** (82 mg, 0.171 mmol) was dissolved in methanol (10 ml). Freshly distilled quinoline (10 μl, 0.084 mmol) was added, followed by 5% palladium on barium sulfate (6 mg). The atmosphere was purged five times with hydrogen, and the mixture was vigorously stirred under 1 bar hydrogen for 30 minutes. The solvent was evaporated and the residue was purified by FC (EtOAc) to give a 75:25 mixture of *Z* olefin **8a** and *E*-olefin **8b** (71 mg, 87%). A geometrically pure sample was obtained by an alternative method: BER-resin (660 mg, freshly prepared[16]) was added to a suspension of nickel acetate (50 mg) in methanol (10 ml). The atmosphere was purged with hydrogen, and the resin beads became slowly black. After 10 minutes, the nitrone **7** (30 mg, 0.063 mmol) was added as a solution in methanol (3 ml) and the mixture was stirred under 1 bar hydrogen for 1 hour. The pure *Z*-vinylsilane **8a** was obtained, after filtration and FC (EtOAc), as a colorless oil (13 mg, 43%). $[\alpha]_D^{21}=-48.4$, $[\alpha]_{578}^{21}=-51.0$, $[\alpha]_{546}^{21}=-58.4$, $[\alpha]_{436}^{21}=-105.1$, $[\alpha]_{365}^{21}=-187.9$ ($c=0.96$, $CHCl_3$). IR ($CHCl_3$): 2962, 1700, 1604, 1459, 1413, 1394, 1339, 1272, 1248, 1167, 1136, 1118, 1068, 978, 858, 839. ^{1}H NMR (400 MHz): 6.27 (dt, $J=14$, 7.4, 1H); 5.50 (d, $J=14$, 1H); 5.43 (t, $J=7.2$, 1H); 3.93 (dd, $J=7.7$, 4.8, 1H); 3.56 (d, $J=13.6$, 1H); 3.44 (d, $J=13.6$, 1H); 2.9–2.6 (2H); 2.54 (t, $J=7.9$, 2H); 2.40 (m, $J=9.6$, 5.5, 1H); 2.35–2.2 (2H); 2.14 (quint, $J=7.3$, 2H); 2.08 (dd, $J=14$, 7.7, 1H); 2.0–1.8 (3H); 1.7–1.3 (6H); 1.25 (s, 3H); 0.97 (s, 3H); 0.11 (s, 9H). ^{13}C NMR (100 MHz): 167.8 (s); 148.3 (d); 129.5 (d); 74.0 (d); 65.4 (d); 53.1 (t); 49.0 (s); 44.7 (d); 38.2 (t); 33.1 (t); 32.8 (t); 30.5 (t); 29.7 (t); 26.6 (t); 26.5 (t); 24.7 (t); 21.8 (t); 20.9 (q); 19.9 (q); 0.3 (q).

*4.11. (2*R,*2′*R,*6′*R*)*-N-*(5′-Trimethylsilyl-octahydro-4′-oxa-3′a-aza-cyclopenta[*c*]inden-3′-carbonyl)bornane-10,2-sultam* ***9a***

A 75:25 mixture of nitrones **8a** and **8b** (44.3 mg, 0.092 mmol) was dissolved in benzene (70 ml). The solution was degassed by five freeze–pump–thaw cycles, and heated to reflux for 208 hours. The solvent was evaporated and a 63:12:25 mixture of isoxazolidine **9a**, **9c**, and unreacted **8b** was obtained. FC (hexane/EtOAc 2:1) gave the individual components for characterization (39 mg, 88%). A similar experiment with pure *Z*-vinylsilane **8a** was performed, leading to

isoxazolidine **9a** without any trace of **9c**. ^{1}H NMR (400 MHz): 4.32 (dd, $J=10.2$, 6.2, 1H); 3.95 (bdd, $J=7.4$, 4.8, 1H); 3.69 (d, $J=4.4$, 1H); 3.51 (d, $J=13.7$, 1H); 3.41 (d, $J=13.7$, 1H); 2.3–1.1 (23H); 0.96 (s, 3H); 0.09 (s, 9H). ^{13}C NMR (100 MHz): 74.5 (s); 72.5 (s); 69.9 (d); 65.5 (d); 53.2 (t); 52.1 (d); 48.5 (s); 47.8 (s); 44.9 (d); 39.1 (t); 38.6 (t); 33.8 (t); 32.9 (t); 28.0 (t); 26.5 (t); 24.7 (t); 21.9 (t); 20.9 (q); 19.9 (q); 19.7 (t); –2.11 (q). NOESY correlation: 3.69–4.32 ppm.

*4.12. (2*R*,2′*R*,6′*R*)-*N*-(6′-Formyl-1′-aza-spiro[4,5]decan-2′-carbonyl)bornane-10,2-sultam* ***10***

The isoxazolidine **9a** (3.2 mg, 0.007 mmol) was dissolved in 1 ml CH_2Cl_2, and the HF–pyridine complex was added (0.2 ml). The mixture was stirred at room temperature for 1 hour, and an aqueous solution on sodium carbonate was added (1 M, 5 ml). The phases were separated and the aqueous phase was extracted again with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to give the pure aldehyde **10**. ^{1}H NMR: 9.87 (d, $J=3.1$, 1H); 4.28 (t, $J=6.6$, 1H); 3.89 (dd, $J=8$, 5.3, 1H); 3.51 (d, $J=14$, 1H); 3.44 (d, $J=14$, 1H); 2.3–1.8 (2H); 2.1–1.8 (6H); 1.8–1.7 (1H); 1.7–1.2 (12H); 1.16 (s, 3H); 0.98 (s, 3H). ^{13}C NMR (100 MHz): 207.2 (s); 174.3 (s); 65.5 (d); 63.3 (s); 60.6 (d); 56.5 (d); 53.0 (t); 48.8 (s); 47.8 (s); 44.5 (d); 38.4 (t); 37.8 (t); 37.3 (t); 32.8 (t); 29.4 (t); 26.5 (t); 24.3 (t); 23.2 (t); 23.1 (t); 20.8 (q); 19.9 (q).

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References

1. Denis, J. N.; Tchertchian, S.; Tomassini, A.; Vallée, Y. *Tetrahedron Lett*. **1997**, *38*, 5503.
2. Oppolzer, W.; Deerberg, J.; Tamura, O. *Helv. Chim. Acta* **1994**, *77*, 554.
3. Confalone, P. N.; Huie, E. M. *Org. React*. **1988**, 1; LeBel, N. A.; Post, M. E.; Whang, J. J. *J. Am. Chem. Soc*. **1964**, *86*, 3759; LeBel, N. A.; Banucci, E. G. *J. Org. Chem*. **1971**, *36*, 2440; Padwa, A.; Schoffstall, A. M. *Advances in Cycloadditions* **1990**, *2*, 1; Tufariello, J. J. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley, 1984; pp. 83–168.
4. Type **IV** for intramolecular with a C-tether, and **a** for a nitrone as 1,3-dipole. For reviews, see: Oppolzer, W. *Angew. Chem., Int. Ed. Engl*. **1977**, *16*, 10; Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497.
5. Li, C.; Blackman, A. J. *Aust. J. Chem*. **1994**, *47*, 1355; Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645; Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F., Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett*. **1994**, *35*, 2691.
6. For syntheses of lepadiformine, see: Abe, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett*. **2000**, *41*, 1205; Werner, K. M.; de los Santos, J. M.; Weinreb, S. M.; Shang, M. *J. Org. Chem*. **1999**, *64*, 686; Pearson, W. H.; Ren, Y. *J. Org. Chem*. **1999**, *64*, 688.
7. Bagley, M. C.; Oppolzer, W. *Tetrahedron*: *Asymmetry* **2000**, *11*, 2625.
8. Gössinger, E.; Imhof, R.; Wehrli, H. *Helv. Chim. Acta* **1975**, *58*, 96.
9. Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 10399.
10. DeShong, P.; Li, W.; Kennington, J. W.; Ammon, H. L.; Leginus, J. M. *J. Org. Chem*. **1991**, *56*, 1364; DeShong, P.; Leginus, J. M.; Lander Jr., S. W. *J. Org. Chem*. **1986**, *51*, 575; DeShong, P.; Leginus, J. M. *J. Org. Chem*. **1986**, *51*, 574.

11. Oppolzer, W.; Bochet, C. G.; Merifield, E. *Tetrahedron Lett*. **1994**, *35*, 7015.
12. Munchhof, M. J.; Meyers, A. I. *J. Org. Chem*. **1995**, *60*, 7084.
13. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett*. **1972**, *13*, 3769.
14. Oppozler, W.; Tamura, O. *Tetrahedron Lett*. **1990**, *31*, 991; Oppolzer, W.; Tamura, O.; Deerberg, J. *Helv. Chim. Acta* **1992**, *75*, 1965.
15. Overman, L. E.; Brown, M. J.; McCann, S. F. *Org. Synth*. **1990**, *68*, 182.
16. Choi, J.; Yoon, N. M. *Tetrahedron Lett*. **1996**, *37*, 1057.
17. Müller, E.; Metzger, H.; Fries, D. *Chem. Ber*. **1954**, *87*, 1449.