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Zinca-ene-allene cyclizations: A way to substituted tetrahydrofurans or pyrrolidines†

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Summary — Polysubstituted enynes have been lithiated on the propargylic position, and transmetalation to the corresponding zinc reagents promotes an easy cyclization reaction leading to polysubstituted tetrahydrofurans and pyrrolidines of definite geometry via the zinca-ene-allene reaction.

carbocyclization / allenyl zinc / tetrahydrofuran / pyrrolidine / zinca-ene-allene

Résumé — Cyclisation de type zinca-ène-allène. Nouvel accès à des tétrahydrofurannes et des pyrrolidines substitués. Différents énynes polysubstitués ont été métallés en position propargylique. Après transmétallation en organozincique, une rapide réaction de cyclisation anionique a lieu pour conduire à des tétrahydrofurannes et des pyrrolidines de géométrie définie selon un état de transition de type zinca-ène-allène.

carbocyclisation / organozincique allènique / tétrahydrofuranne / pyrrolidine / zinca-ène-allène

We have already disclosed an internal carbozincation of δ-ethylenic organozinc compounds which gives access to cyclopentyl methyl organozinc derivatives. The use of zinc, instead of lithium, proved to be very efficient in several cases [1]: (i) if the organometallic is located on a secondary carbon; (ii) if the substrate bears functions (such as an ester) which do not tolerate an organolithium reagent; (iii) if the C=C double bond is 1,2-disubstituted. These situations are displayed in figure 1.

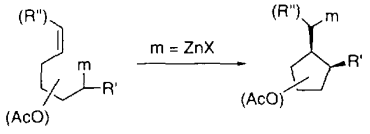

Fig 1

We found in particular that when R′ is an alkynyl moiety the corresponding propargylic zinc reagent (which is in fact present as an allenic metallotrope) [2] cyclises very rapidly (5–10 min at 0 °C) to form a pure *cis*-disubstituted cyclopentane [3].

By analogy with the magnesium-ene cyclisation [4] we have proposed a zinca-ene-allene process (fig 2) which accounts for the high stereoselection in favor of the *cis*-product. This process should be amenable to the synthesis of five membered heterocycles. We report here on the cases where an oxygen [5] or nitrogen atom is incorporated on the propargylic position of the linear substrate, in order to get to the important class of stereospecifically substituted tetrahydrofurans [6] and pyrrolidines [7].

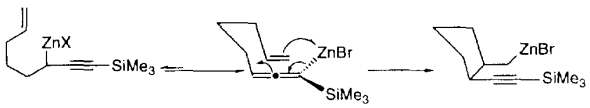

Fig 2

For a straightforward access to propargyl-homoallyl ethers, we adapted the method of Markò [8] to propargylic alcohols. Thus, a mixture of an aldehyde (or ketone), a bis-silylated propargylic alcohol and allyl trimethylsilane are treated by a catalytic amount of trimethylsilyl triflate to give directly the expected product (fig 3). This procedure is convenient for cyclohexanone or benzaldehyde, but for aliphatic aldehydes, it is preferable to prepare the symmetrical acetal first [9].

1 is easily metalated with *sec*-BuLi in ether at −70 °C and subsequent slow addition of $ZnBr_2$ (in ether) induces the formation of the allenyl zinc bromide **4** which cyclizes readily in less than 5 min at

† Dedicated to Henri Kagan, in appreciation for his fundamental contributions to organic and organometallic chemistry for the last forty years.

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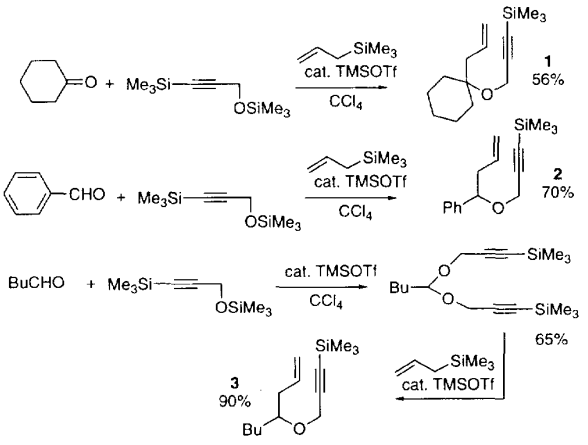

Fig 3

−40 °C. This acceleration is attributed to a *gem-dialkyl effect* [10]. The metalated tetrahydrofuran **5** [11] thus formed can be iodinated to **6** (67%) or vinylated under Pd catalysis [12] to give **7** (50%) or transmetalated to a copper reagent [13] via CuCN, in order to react with methallyl bromide, leading to **8** (74%). All these compounds (fig 4) display an exclusive *cis* relationship between the two substituents on positions 2 and 3 [14].

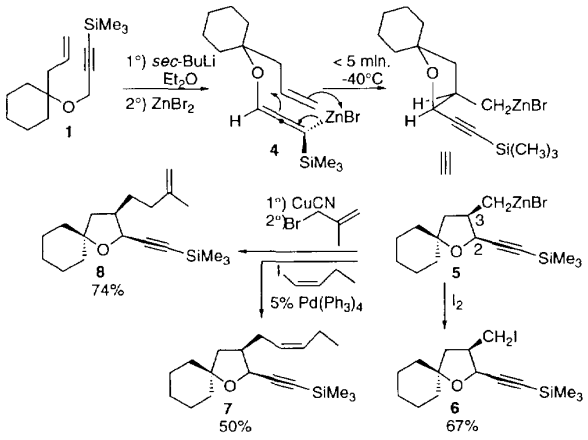

Fig 4

In the case of substituted propargylic ethers **2** and **3**, a new stereogenic center is introduced, and we anticipated that it should be governed by the intermediate transition state since the R group (Ph or Bu) would adopt a pseudo-equatorial rather than a pseudo-axial position (fig 5).

Thus **2** and **3** were metalated with *sec*-BuLi in ether, then transmetalated with $ZnBr_2$. Cyclization occured within 10 min at −10 °C to give, after protonation, respectively **9** and **10**. In both, the methyl and silyl ethynyl groups are exclusively *cis* to each other, the phenyl group in **9** being also *cis* in a 80:20 ratio whereas for **10** the butyl group adopts the *cis* position in a 92:8 ratio. In both cases, the *cis/trans* isomers are separated by chromatography on silica gel and ^{1}H- and ^{13}C-NMR

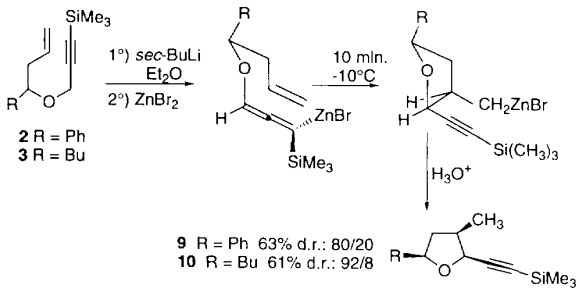

Fig 5

chemical shifts are established by COSY techniques. The all *cis* configuration of the major isomer of **9** as well as the relative configuration of the minor isomer were determined by differential nuclear Overhauser effects. A substituent can be located on the propargylic position (for example **11** in fig 6). This starting material is prepared like **1** (fig 1), using a bis-silylated but-3-yn-2-ol (yield 42%). When subjected to our conditions (*sec*-BuLi in THF followed by $ZnBr_2$, warming from −40 to +20 °C and protonolysis) **11** gave the pentasubstituted tetrahydrofuran **13** in 71% yield as a single isomer, which entails coupling between a quaternary and ternary carbon atom.

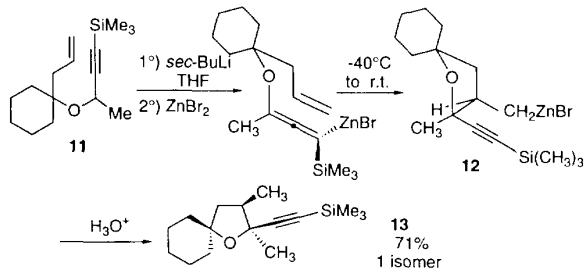

Fig 6

Since the creation of two vicinal quaternary carbons by carbometalation is a difficult task [15], we attempted to reach this in the oxygenated series starting from **8** (fig 4). The latter was deprotonated by *sec*-BuLi on the propargylic position, transmetalated with $ZnBr_2$, and the mixture was warmed from −40 to +20 °C. Iodinolysis led to a single isomer of **14** in 60% yield, showing that such cyclization is possible, and is also diastereoselective (fig 7).

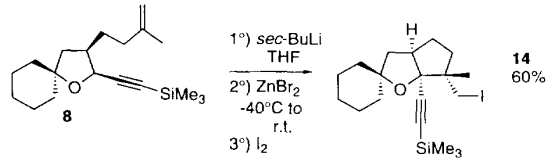

Fig 7

The *cis* relationship of the alkynyl and the iodomethylene moieties was established after semi-hydrogenation of the triple bond to form a *Z* vinyl

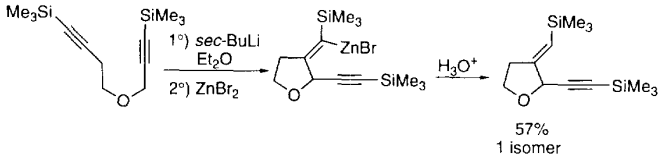

Fig 8

silane and a study of the differential nuclear Overhauser effect between the vinylic protons and those of the $-CH_2I$ unit. This methodology can be extended to the intramolecular carbometalation of ω-acetylenic metalated propargylic ethers (fig 8). The stereochemistry of the exocyclic vinyl silane was deduced from our previously reported carbocyclization of δ-acetylenic propargylic zinc reagents [16].

During this study on ethereal substrates, we observed that the *gem-dialkyl effect* not only boosted the cyclization of the organozinc reagent, but also made possible a double carbolithiation reaction: the organolithium reagent, precursor of **4** (fig 4) is able, for the first time in the absence of added zinc salts, to cyclize [17]. However, as already shown by Bailey in the linear series [18], the formed primary organolithium derivative **5Li**, is able to re-cyclize in a 4-*exo* mode to yield, after protonolysis, a tricyclic compound **15** in 61% yield, as a single isomer (fig 9). Indeed, vinyllithium compounds with α-silyl substitution are known to undergo facile *cis–trans* isomerization at room temperature and then the 4-*exo*-dig cyclization might be expected as a *syn* addition of the C–Li unit to the triple bond followed by a rapid isomerization. The unique stereochemistry of the vinyl silane was determined by a differential nuclear Overhauser effect between the vinylic and the allylic protons.

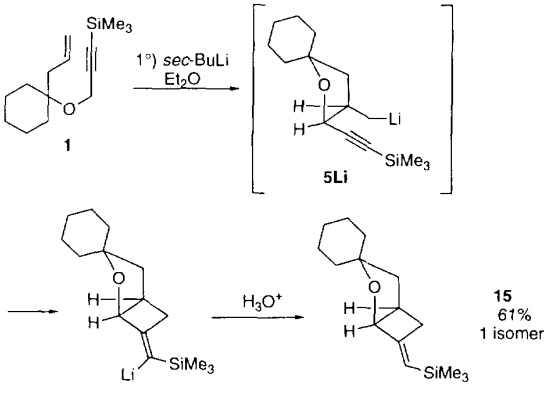

Fig 9

The case of amino en-ynes was also investigated. The tertiary amine **17** was prepared from benzyl amine according to figure 10.

The introduction of the homoallyl residue was made according to [19] followed by the addition of propargyl bromide. Treatment of **17** by *tert*-BuLi in ether, followed by the lithium to zinc exchange with $ZnBr_2$ and

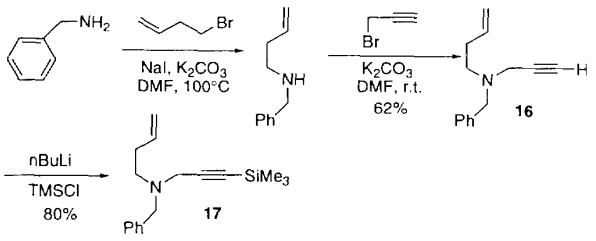

Fig 10

warming up to room temperature gave the corresponding 2,3-disubstituted metalated pyrrolidine **18**, which was quenched by protonolysis to **19** in 60% yield or by iodinolysis to **20** in 70% yield. Both **19** and **20** were obtained, (as in the oxygenated series) as single isomers (fig 11).

We also checked what in this case was the steric outcome of a substituent ending up on position 5 of the formed pyrrolidine and thus a cyclohexyl residue was introduced on the homoallylic carbon of **17** according to figure 12. **21** was submitted to the cyclization protocol described above (fig 12) and led by protolysis of the intermediate zinc derivative **22**, to the trisubstituted 1-methylpyrrolidine **23**, whereas zinc/copper exchange of **22** allowed a reaction with allyl bromide, to give **24**. In both **23** and **24**, the cyclohexyl moiety was predominantly positioned *cis* to the other two substituents in a ratio of 85:15, determined by ^1H and ^{13}C NMR on the crude reaction mixture, reminiscent of the values obtained in the oxygenated series (fig 5) where ratios of 80:20 to 92:8 were established [20]. Here again, in the absence of added zinc salts, the propargyl-allenyl lithium **21Li** undergoes a 5-*exo*-trig carbolithiation reaction, followed by a 4-*exo*-dig cyclization to give the corresponding bicyclo derivative, as a single isomer, determined by a differential nuclear Overhauser effect, in 61% yield as described in figure 13. In this case, the double carbolithiation reaction is probably due to the presence of the nitrogen atom in the heterocycle [21].

In conclusion, the creation of cyclopentyl methyl zinc derivatives from linear δ-ethylenic organozinc reagents can be extended to the heterocyclic series. Propargylic organozinc reagents bearing an ether or amino function are amenable to such cyclizations leading to tetrahydrofurans or pyrrolidines. A *gem-dialkyl effect* is beneficial but not necessary. In this study we have shown that 2,3,5-trisubstituted tetrahydrofurans of definite geometry can be constructed, as well as 2,3,5-trisubstituted pyrrolidines.

Work is underway to extend this methodology to more functionalized substrates.

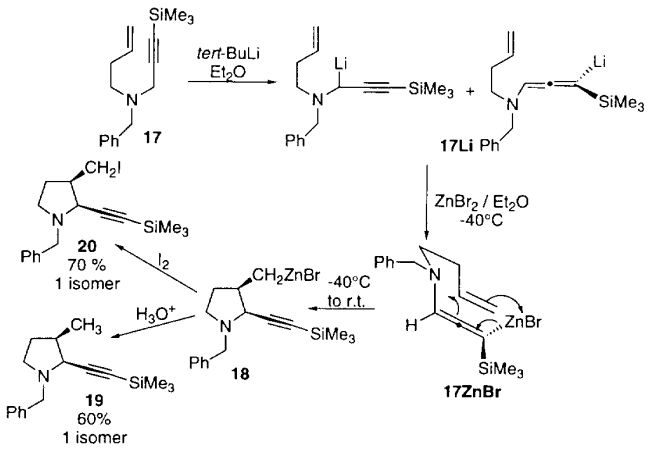

Fig 11

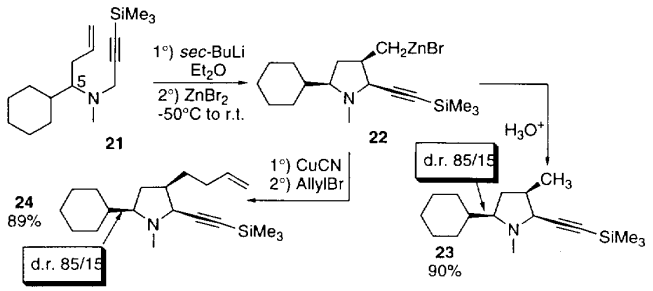

Fig 12

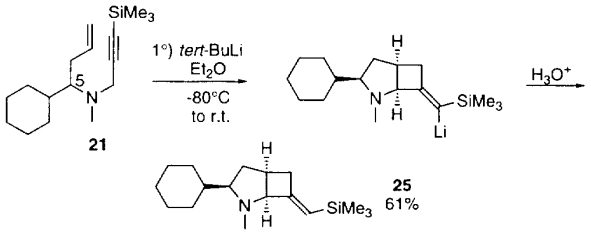

Fig 13

Experimental section

1-(Prop-2-enyl)-1-[3-(trimethylsilyl)-prop-2-ynyloxy] cyclohexane **1**

To a solution of cyclohexanone (30 mmol, 2.94 g) in CCl_4 (80 mL) was added allyltrimethylsilane (36 mmol, 4.1 g) and 1-[(trimethylsilyl)oxy]-3-trimethylsilylprop-2-yne (30 mmol, 6 g) at −20 °C. To the resulting mixture trimethylsilyl triflate (3.6 mmol, 0.67 mL) was added. After stirring for 2 h at 0 °C, the reaction mixture was poured into saturated $NaHCO_3$ (50 ml). The layers were separated, and the aqueous one was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 95:5) to give 4.16 g (56%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddt, 1H, J = 17.3, 10.1 Hz), 5.03 (m, 2H), 4.07 (s, 2H), 2.23 (d, 2H, J = 7.15 Hz), 1.73–1.23 (m, 10H), 0.15 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 117.5, 103.6, 89.6, 76.85, 50.1, 41.8, 34.4 (2C), 25.9, 22.0 (2C), 0.0.

5-Phenyl-1-trimethylsilyl-4-oxaoct-7-en-1-yne **2**

To a solution of benzaldehyde (27 mmol, 2.77 g) in CCl_4 (80 mL) was added allyltrimethylsilane (33 mmol, 3.73 g) and 1-[(trimethylsilyl)oxy]-3-trimethylsilylprop-2-yne (27 mmol, 5.45 g) at −20 °C. To the resulting mixture trimethylsilyl triflate (2.7 mmol, 0.49 mL) was added. After stirring for 2 h at 0 °C, the reaction mixture was poured into saturated $NaHCO_3$ (50 mL). The layers were separated, and the aqueous one was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether 80:20) to give 4.87 g (70%) of the title compound.

IR (neat film) 3 060, 2 950–2 930, 2 160, 1 640, 1 490, 1 450, 1 345, 1 245, 1 080, 990, 840, 755, 695.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.78 (tdd, 1H, J = 17.1, 10.2, 6.8 Hz), 5.01 (m, 2H), 4.53 (dd, 1H, J = 7.5, 6.07 Hz), 4.11 (d, 1H, J = 15.9 Hz), 3.87 (d, 1H, J = 16Hz), 2.71–2.55 (m, 1H), 2.51–2.36 (m, 1H), 0.16 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 141.0, 134.8, 128.5 (2C), 128.0, 127.2 (2C), 117.8, 101.7, 90.9, 80.6, 56.7, 42.2, 0.0.

1,1-Bis{[3-(trimethylsilyl)prop-2-ynyl]oxy}pentane

To a solution of valeraldehyde (10 mmol, 0.86 g) in CCl_4 (30 mL) was added 1-[(trimethylsilyl)oxy]-3-(trimethylsilyl)prop-2-yne (20 mmol, 4 g) at 0 °C. To the resulting mixture trimethylsilyl triflate (1 mmol, 0.18 mL) was added. After stirring for 2 h at 0 °C, the reaction mixture was poured into saturated $NaHCO_3$ (30 mL). The layers were separated, and the aqueous one was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 95:5) to give 1.93 g (60%) of the title compound.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.77 (t, 1H, J = 5.7 Hz), 4.2 (s, 4H), 1.66–1.58 (m, 2H), 1.37–1.30 (m, 4H), 0.9–0.84 (m, 3H), 0.12 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 102.05, 102.0, 90.5, 54.2, 33.2, 26.9, 22.6, 14.2.

5-Butyl-1-trimethylsilyl-4-oxaoct-7-en-1-yne **3**

To a solution of 1,1-bis{3-[(trimethylsilyl)prop-2-ynyl]oxy}-pentane (5.55 mmol, 1.8 g) in CCl_4 (20 mL) was added allyltrimethylsilane (5.55 mmoL, 0.63 g) at room temperature. To the resulting mixture trimethylsilyl triflate (0.55 mmol, 0.1 mL) was added dropwise. After stirring for 15 min at room temperature, the reaction mixture was poured into saturated $NaHCO_3$ (20 mL). The layers were separated, and the aqueous one was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 98:2) to give (1.18 g) 90% of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77–5.87 (m, 1H), 5.08 (dd, 1H, J = 17.0, 2.0 Hz), 5.04 (dd, 1H, J = 9.4, 2.0 Hz), 4.19 (d, 1H, J = 16.5 Hz), 4.15 (d, 1H, J = 16.5 Hz), 3.55–3.49 (m, 1H), 2.25 (dd, 2H, J = 6.6, 5.5 Hz), 1.54–1.29 (m, 6H), 0.9 (t, 3H, J = 7.1 Hz), 0.17 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 117.1, 102.7, 90.65, 78.3, 57.2, 38.25, 33.6, 27.7, 22.95, 0.2.

Typical procedure for the cyclized product **5**

A solution of **1** (2 mmol, 0.5 g) in dry ether (15 mL) was cooled to −90 °C as *sec*-butyllithium (1.3 M in cyclohexane/hexane 98:2, 4 mmol, 3 mL) was added dropwise. After stirring for 5 min at −80 °C, zinc bromide (1 M in ether, 4 mmol, 4 mL) was added dropwise. The reaction mixture was then allowed to warm to room temperature. The cyclized organozinc species is ready for further conversions.

(2S,3R*)-3-Iodomethyl-2-[(trimethylsilyl)ethynyl]-1-oxaspiro[4.5]decane* **6**

The cyclized product was cooled to −40 °C as an excess of solid iodine (4 mmol, 1 g) in THF (5 mL) was added. After stirring for 10 min. at room temperature, 1 M hydrochloric acid (10 mL) and ether (10 mL) were added. The layers were separated, the aqueous one being extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ (20 mL), and diluted with saturated $Na_2S_2O_3$. They were stirred for at least 3 h with a few Na_2S–$9H_2O$ crystals. These were then removed by filtration, and the organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 95:5) to give 0.70 g (67%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (d, 1H, J = 7.15 Hz), 3.29 (dd, 1H, J = 9.90, 7.96 Hz), 3.21 (dd, 1H, J = 9.90, 7.70 Hz), 2.72–2.78 (m, 1H), 2.08 (dd, 1H, J = 12.1, 7.15 Hz), 1.32–1.68 (m, 11H), 0.15 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 102.8, 92.3, 84.3, 71.3, 46.0, 42.9, 39.6, 37.8, 34.2, 25.3, 23.7, 4.7, −0,17.

Anal calc for $C_{15}H_{25}IOSi$: C, 47.87; H, 6.70. Found: C, 47.85; H, 6.98.

(2S,3R*)-3-(Pent-2(Z)-enyl)-2-[(trimethylsilyl)-ethynyl]-1-oxaspiro[4.5]decane* **7**

The cyclized product **5** was cooled to 0 °C as a solution of (*Z*) 1-iodobut-1-ene (4 mmol, 0.73 g) and $Pd(PPh_3)_4$ (0.6 mmol, 0.7 g) in THF (10 mL) was added. The reaction mixture was then heated to 30–40 °C. After stirring for 2 h 1 M hydrochloric acid (10 mL) and ether (10 mL) were added. The combined extracts were washed with saturated $NaHCO_3$ (30 mL) and stirred for at least 3 h with a few Na_2S–$9H_2O$ crystals. These were then removed by filtration, and the organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 98:2) to give 0.294 g (50%) of the title compound.

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.30 (m, 2H), 4.54 (d, 1H, J = 6.16 Hz), 2.22 (m, 3H), 2.09–1.82 (m, 3H), 1.64–1.13 (m, 11H), 0.98 (t, 3H, J = 7.55 Hz), 0.13 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 132.8, 127.1, 104.8, 91.5, 84.0, 71.4, 43.5, 41.5, 40.0, 38.1, 28.3, 27.0, 25.6, 24.1, 20.8, 14.3, 0.0.

(2S,3R*)-3-(3-Methylbut-3-enyl)-2-[(trimethylsilyl)-ethynyl]-1-oxaspiro[4.5]decane* **8**

The cyclized product **5** was cooled to −20 °C as copper cyanide (0.35 g, 4 mmol) in THF (10 mL) was added. The resultant mixture was slowly allowed to warm to −5 °C and stirred for 15 min. It was then cooled to −40 °C as methallylbromide (0.54 g, 4 mmol) was injected into the flask. The reaction mixture was slowly allowed to warm to room temperature overnight and was subsequently quenched with NH_4Cl/NH_4OH (2:1). The layers were separated and the aqueous one was extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 95:5) to give 0.45 g (74%) of the title compound.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.64 (d, 2H, J = 0.86 Hz), 4.60 (d, 1H, J = 7.0 Hz), 2.30–2.18 (m, 1H), 2.03–1.85 (m, 4H), 1.73–1.54 (m, 10H), 1.49–1.29 (m, 5H), 0.1 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 145.8, 110.2, 104.8, 91.4, 84.1, 71.4, 42.7, 41.9, 40.1, 38.3, 36.7, 29.0, 25.7, 24.3, 24.1, 22.5, 0.5.

(2S,3R*,5R*)-3-Methyl-5-phenyl-2-[(trimethylsilyl)-ethynyl]tetrahydrofuran* **9**

A solution of **2** (2 mmol, 0.52 g) in dry ether was cooled to −90 °C as *sec*-butyllithium (1.3 M in cyclohexane/hexane, 98:2, 4 mmol, 3 mL) was added dropwise. After stirring for 5 min at −80 °C zinc bromide (1 M in ether, 4 mmol, 4 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature. It was then cooled to −5 °C as 1 M hydrochloric acid (10 mL) was added slowly. Ether was added and the layers were separated, the aqueous one being extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ (20 mL) and stirred

for at least 3 h with a few Na_2S–$9H_2O$ crystals. These were then removed by filtration, and the organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 90:10) to give 0.325 g (63%) of the title compound as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 2H, J = 7.69 Hz), 7.32 (t, 2H, J = 7.4 Hz), 7.25 (t, 1H, J = 3.6 Hz), 4.96 (dd, 1H, J = 9.9, 6.05 Hz), 4.76 (d, 1H, J = 7.15 Hz), 2.55 (m, 1H), 2.37 (m, 1H), 1.73 (m, 1H), 1.17 (d, 3H, J = 6.6 Hz), 0.20 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 128.3 (2C), 127.4, 126.5 (2C), 104.1, 92.6, 82.5, 74.0, 43.1, 38.7, 14.8, 0.0.

Anal calc for $C_{16}H_{29}OSi$: C, 74.36; H, 8.58. Found: C, 74.30; H, 8.68.

(2S,3R*,5S*)-5-Butyl-3-methyl-2-[(trimethylsilyl)-ethynyl]tetrahydrofuran* **10**

A solution of **3** (0.88 mmol, 0.21 g) in dry ether was cooled to −90 °C as *sec*-butyllithium (1.3 M in cyclohexane/hexane 98:2, 1.76 mmol, 1.35 mL) was added dropwise. After stirring for 5 min at −80 °C zinc bromide (1 M in ether, 1.76 mmol, 1.76 mL) was added dropwise. The reaction mixture was then allowed to warm to room temperature. After 15 min stirring, it was cooled to −5 °C as 1 M hydrochloric acid (10 mL) was added slowly. Ether was added and the layers were separated, the aqueous one being extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ (20 mL) and stirred for at least 3 h with a few Na_2S–$9H_2O$ crystals. These were removed by filtration, and the organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 95:5) to give 0.128 g (61%) of the title compound as an oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 4.52 (d, 1H, J = 7.2 Hz), 3.90 (m, 1H), 2.34 (m, 1H), 2.10 (ddd, 1H, J = 12.1, 6.21, 6.21 Hz), 1.70 (m, 1H), 1.55 (m, 1H), 1.43–1.27 (m, 5H), 1.10 (d, 3H, J = 6.8Hz), 0.89 (t, 3H, J = 6.74 Hz), 0.14 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 104.2, 91.6, 80.4, 72.9, 39.6, 37.9, 36.5, 28.5, 23.0, 15.8, 14.2, −0.1.

Anal calc for $C_{14}H_{26}OSi$: C, 70.52; H, 10.99. found: C, 70.44; H, 10.98.

1-(Prop-2-enyl)-1-[(3-trimethylsilyl-1-methylprop-2-ynyl)oxy]cyclohexane **11**

To a solution of cyclohexanone (20 mmol, 1.96 g) in CCl_4 (80 mL) was added allyltrimethylsilane (24 mmol, 2.73 g) and 2-[(trimethylsilyl)oxy]-4-trimethylsilyl-but-3-yne (20 mmol, 4.28 g) at −20 °C. To the resulting mixture trimethylsilyl triflate (0.2 mmol, 0.45 mL) was added dropwise. After stirring for 2 h at 0 °C, the reaction mixture was poured into saturated $NaHCO_3$ (50 mL). The layers were separated, and the aqueous one was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 95:5) to give 2.21 g (42%) of the title compound.

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.01–5.80 (m, 1H), 5.00 (m, 1H), 4.98 (m, 1H), 4.27 (q, 1H, J = 6.7 Hz), 2.40 (ddt, 1H, J = 14.6, 6.2, 1.4 Hz), 2.20 (ddt, 1H, J = 15.0, 8.5, 0.9 Hz), 1.74–1.16 (m, 10H), 1.41 (d, 3H, J = 6.7 Hz), 0.15 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 116.95, 109.3, 87.8, 77.5, 57.15, 42.7, 35.4, 34.5, 26.05, 24.25, 22.35, 22.3, 0.0.

(2S,3R*)-2,3-Dimethyl-2-[(trimethylsilyl)ethynyl]-1-oxaspiro[4.5]decane* **13**

A solution of **11** (2.65 mmol, 0.7 g) in dry THF (10 mL) was cooled to −90 °C as *sec*-butyllithium (1.3 M in cyclohexane/hexane 98:2, 5.3 mmol, 4 mL) was added dropwise. After stirring for 20 min at −40 °C zinc bromide (1 M in ether, 5.3 mmol, 5.3 mL) was added dropwise at −80 °C. The reaction mixture was allowed to warm to room temperature. After 15 min stirring, it was cooled to −5 °C as 1 M hydrochloric acid (10 mL) was added slowly. Ether was then added and the layers were separated, the aqueous one being extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ (20 mL) and stirred for at least 3 h with a few Na_2S–$9H_2O$ crystals. These were then removed by filtration, and the organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 98:2) to give 0.497 g (71%) of the title compound.

^{1}H NMR (200 MHz, $CDCl_3$) δ 1.94 (m, 2H), 1.72–1.55 (m, 5H), 1.39 (s, 3H), 1.48–1.17 (m, 6H), 1.03 (d, 3H, J = 6.1 Hz), 0.1 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 108.35, 89.4, 82.6, 79.3, 44.3, 39.9, 39.0, 27.05, 25.7, 24.6, 24.1, 14.6.

(1R,5R*,8S*)-8'-Iodomethyl-8'-methyl-1'-[2-(trimethylsilyl)ethynyl]spiro[cyclohexane-1,3'-2'-oxabicyclo[3.3.0]octane]* **14**

A solution of **8** (1.96 mmol, 0.59 g) in dry THF (15 mL) was cooled to −90 °C as *sec*-butyllithium (1.3 M in cyclohexane/hexane 98:2, 3.9 mmol, 3 mL) was added dropwise. After stirring for 15 min at −60 °C zinc bromide (1 M in ether, 3.9 mmol, 3.9 mL) was added dropwise at −80 °C. The reaction mixture was then allowed to warm to room temperature and stirred overnight. The reaction mixture was cooled to −5 °C as 1 M hydrochloric acid (10 mL) was added slowly. Ether was then added and the layers were separated, the aqueous one being extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ (20 mL) and stirred for at least 3 h with a few Na_2S–$9H_2O$ crystals. These were then removed by filtration, and the organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 95:5) to give 0.52 g (60%) of the title compound as an oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.4 (dd, 1H, J = 10.2, 1.7 Hz), 3.18 (dd, 1H, J = 10.25, 0.7 Hz), 2.9 (m, 1H), 2.24 (dd, 1H, J = 12.7, 8.9 Hz), 1.9 (m, 1H), 1.85–1.14 (m, 14H), 1.53 (dd, 1H, J = 12.7, 4.3 Hz), 1.13 (s, 3H), 0.12 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 102.05, 101.9, 90.5, 54.2, 33.2, 26.9, 22.6, 14.2.

2-[(Trimethylsilyl)ethynyl]-3(E)-[(trimethylsilyl)-methylidene]tetrahydrofuran

A solution of 1,8-bis(trimethylsilyl)-4-oxaocta-1,7-diyne (2 mmol, 0.5 g) in dry ether (15 mL) was cooled to −90 °C as *sec*-butyllithium (1.3 M in cyclohexane/hexane 98:2, 4 mmol, 3 mL) was added dropwise. After stirring for 5 min at −80 °C zinc bromide (1 M in ether, 4 mmol, 4 mL) was added dropwise. The reaction mixture was then allowed to warm to room temperature. After 15 min stirring, it was cooled to −5 °C as 1 M hydrochloric acid (10 mL) was added slowly. Ether was added and the layers were separated, the aqueous one being extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ (20 mL) and stirred for at least 3 h with a few Na_2S–$9H_2O$ crystals.

These were removed by filtration, and the organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 85:15) to give 0.29 g (57%) of the title compound.

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.63 (q, 1H, J = 2.17 Hz), 4.81 (m, 1H), 4.07–4.02 (m, 1H), 3.89–3.78 (m, 1H), 2.61–2.49 (m, 2H), 0.11 (s, 9H), 0.10 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 155.6, 120.7, 103.8, 90.7, 73.6, 67.8, 31.6, −0.1, −0.6.

(1'S,5'S*)-7'(E)-[(Trimethylsilyl)methylidene]-spiro[cyclohexane-1,3'-2'-oxabicyclo[3.2.0]heptane]* **15**

A solution of **1** (5.6 mmol, 1.4 g) in dry ether (25 mL) was cooled to −80 °C as *sec*-butyllithium (1.3 M in cyclohexane/hexane 98:2, 11.3 mmol, 8.7 mL) was added dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. It was then cooled to −5 °C as 1 M hydrochloric acid (10 mL) was added slowly. Ether was then added and the layers were separated, the aqueous one being extracted with ether. The combined organic extracts were washed with saturated $NaHCO_3$ (20 mL), and the organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 90:10) to give 0.85 g (61%) of the title compound.

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.65 (m, 1H), 4.74 (m, 1H), 2.84 (m, 2H), 2.33 (m, 1H), 1.93 (dd, 1H, J = 12.9, 9.3 Hz), 1.73 (m, 5H), 1.47 (m, 6H), 0.13 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 124.9, 88.2, 84.2, 40.0, 38.9, 38.4, 36.6, 36.4, 25.8, 24.1, 24.0, −0.6.

Anal calc for $C_{15}H_{26}OSi$: C, 71.93; H, 10.46. Found: C, 71.88; H, 10.64.

N-Benzyl-N-but-3-enyl-prop-2-ynylamine **16**

A solution of *N*-benzylbut-3-enylamine (9.9 mmol, 1.45 g), K_2CO_3 (9.9 mmol, 1.84 g) and propargyl bromide (11.9 mmol, 1.41 g) in dry DMF (25 ml) was stirred at room temperature during 60 h. The reaction mixture was then treated with H_2O (20 mL) and extracted with ether (2 × 25 mL). The organic layer was washed with saturated NaCl (3 × 50 mL), dried over $MgSO_4$ and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 60:40) to give 1.15 g (62%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.28 (m, 5H), 5.95–5.85 (m, 1H), 5.15 (d, 1H, J = 17.16 Hz), 5.08 (dd, 1H, J = 10.16, 0.68 Hz), 3.70 (s, 2H), 3.39 (d, 2H, J = 2.05 Hz), 2.71 (t, 2H, J = 7.24 Hz), 2.35 (m, 2H), 2.29 (t, 1H, J = 2.05 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 136.8, 129.2, 128.4, 127.3, 115.8, 78.6, 73.3, 57.8, 52.9, 41.45, 32.25.

N-Benzyl-N-but-3-enyl-3-(trimethylsilyl)prop-2-ynylamine **17**

A solution of *N*-benzyl-*N*-but-3-enyl-prop-2-ynylamine (1.4 g, 6.2 mmol) in dry THF (20 mL) was cooled to −50 °C as *n*-butyllithium (1.6 M in hexanes, 7.43 mmol, 4.65 mL) was added slowly. After stirring for 10 min at room temperature, trimethylchlorosilane (1.2 mL, 9.3 mmol) was added at 0 °C. The resultant mixture was warmed to room temperature, and stirred for 20 min. It was then cooled to −20 °C, and poured into a solution of NH_4Cl/NH_4OH 2:1 (20 mL). The layers were separated and the aqueous one was extracted with ether (2 × 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 80:20) to give 1.26 g (80%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 5.87 (tdd, 1H, J = 17.1, 10.25, 6.68 Hz), 5.12 (m, 1H), 5.05 (m, 1H), 3.69 (s, 2H), 3.37 (s, 2H), 2.67 (t, 2H, J = 7.12 Hz), 2.35–2.30 (m, 2H), 0.23 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 136.9, 129.3, 128.5, 127.3, 115.7, 101.1, 90.3, 57.8, 53.0, 42.55, 32.2, 0.3.

Typical procedure for cyclized product **18**

A solution of **17** (0.78 mmol, 0.2 g) in dry ether (15 mL) was cooled to −80 °C as *tert*-butyllithium (1.5 M in pentane, 0.78 mL, 1.5 mmol) was added dropwise. After stirring for 5 min at −50 °C zinc bromide (1 M in ether, 1.5 mmol, 1.5 mL) was added dropwise at −80 °C. The reaction mixture was then allowed to warm to room temperature. The cyclized organozinc species is ready for further conversions.

(2S,3R*)-1-Benzyl-3-methyl-2-[(trimethylsilyl)-ethynyl]pyrrolidine* **19**

The cyclized product **18** was cooled to 0 °C as NH_4Cl/NH_4OH 2:1 was added slowly. Ether was added and the layers were separated, the aqueous one being extracted with ether. The combined organic extracts were washed with brine and stirred for at least 3 h with a few Na_2S–$9H_2O$ crystals. These were then removed by filtration. The organic layers were dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 60:40) to give 0.12 g (60%) of the title compound.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.22 (m, 5H), 3.80 (d, 1H, J = 12.79 Hz), 3.63 (d, 1H, J = 12.79 Hz), 3.47 (d, 1H, J = 6.65 Hz), 2.76–2.54 (m, 2H), 2.34–2.22 (m, 1H), 2.04–1.87 (m, 1H), 1.51–1.35 (m, 1H), 1.08 (d, 3H, J = 6.84 Hz), 0.20 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 139.2, 129.4, 128.3, 127.05, 102.5, 92.5, 59.6, 56.9, 51.1, 36.2, 31.1, 0.5.

Anal calc for $C_{17}H_{25}NSi$: C, 75.21; H, 9.28; N, 5.16. Found: C, 75.27; H, 9.29; N, 5.07.

(2S,3R*)-1-Benzyl-3-iodomethyl-2-[(trimethylsilyl)-ethynyl]pyrrolidine* **20**

The cyclized product **18** was cooled to 0 °C as an excess of solid iodine (1.56 mmol, 0.4 g) was added. After stirring for 10 min at room temperature, a solution of NH_4Cl/NH_4OH 2:1 was added slowly. Ether was added and the layers were separated, the aqueous one being extracted with ether. The combined organic extracts were diluted with saturated $Na_2S_2O_3$, washed with brine and stirred for at least 3 h with a few Na_2S–$9H_2O$ crystals. These were then removed by filtration and the organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 70:30) to give 0.21 g (70%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 3.79 (d, 1H, J = 12.8 Hz), 3.73 (d, 1H, J = 6.52 Hz), 3.69 (d, 1H, J = 12.8 Hz), 3.39 (dd, 1H, J = 9.4, 8.0 Hz), 3.25 (dd, 1H, J = 9.4, 8.0 Hz), 2.89–2.84 (m, 1H), 2.73–2.65 (m, 2H), 2.14–2.09 (m, 1H), 1.55–1.50 (m, 1H), 0.22 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 129.2, 128.4, 127.3, 99.6, 94.1, 59.2, 56.6, 51.1, 44.9, 30.2, 27.0, 7.5, 0.3.

Typical procedure for cyclized product **22**

A solution of **21** (1.5 mmol, 0.417 g) in dry ether (15 mL) was cooled to −50 °C as *sec*-butyllithium (1.3 M in cyclohexane/hexane 98:2, 6 mmol, 4.6 mL) was added dropwise. After stirring for 20 min at −50 °C zinc bromide (1 M in ether, 6 mmol, 6 mL) was added dropwise. The reaction mixture was then allowed to warm to room temperature. The cyclized organozinc species is ready for further conversions.

(2S,3R*,5S*)-5-Cyclohexyl-1,3-dimethyl-2-[(trimethylsilyl)ethynyl]pyrrolidine* **23**

The cyclized product **22** was cooled to 0 °C as a solution of NH_4Cl/NH_4OH 2:1 was added slowly. Ether was added and the layers were separated, the aqueous one being extracted with ether. The combined organic extracts were washed with brine, stirred for at least 3 h with a few Na_2S–$9H_2O$ crystals. These were then removed by filtration. The organic layers were dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 80:20) to give 0.375 g (90%) of the title compound.

• *Major*

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (d, 1H, J = 7.08 Hz), 2.32 (s, 3H), 1.99–1.95 (m, 1H), 1.84–1.81 (m, 1H), 1.74–1.70 (m, 1H), 1.60–1.56 (m, 5H), 1.41–1.35 (m, 1H), 1.28–0.96 (m, 6H), 1.09 (d, 3H, J = 6.8 Hz), 0.0 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 105.6, 89.2, 70.95, 64.0, 40.0, 39.0, 33.1, 31.2, 29.6, 26.9 (2C), 26.2, 26.0, 18.55, 0.0.

• *Minor*

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (d, 1H, J = 6.04 Hz), 2.43–2.19 (m, 3H), 2.35 (s, 3H), 1.77–1.67 (m, 5H), 1.26–0.94 (m, 6H), 1.46–1.44 (m, 1H), 1.07 (d, 3H, J = 6.68 Hz), 0.19 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 105.6, 89.2, 67.4, 63.4, 39.8, 37.4, 35.5, 33.4, 31.1, 26.4 (2C), 26.3, 15.9, 0.3.

(2S,3R*,5S*)-3-(But-3-enyl)-5-cyclohexyl-1-methyl-2-[(trimethylsilyl)ethynyl]pyrrolidine* **24**

The cyclized product **22** was cooled to −20 °C as copper cyanide (0.54 g, 6 mmol) in THF (10 mL) was added. The resultant mixture was slowly allowed to warm to −5 °C and stirred for 15 min. It was then cooled to −40 °C as allyl bromide (0.73 g, 6 mmol) was injected into the flask. The reaction mixture was slowly allowed to warm to room temperature overnight and was subsequently quenched with a solution of NH_4Cl/NH_4OH (2:1). The layers were separated and the aqueous one was extracted with ether. The combined extracts were washed with brine, stirred for at least 3 h with a few Na_2S–$9H_2O$ crystals. These were then removed by filtration, the organic layers were dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 60:40) to give 0,425 g (89%) of the title compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87–5.81 (m, 1H), 5.03 (m, 1H), 4.96 (m, 1H), 3.08 (d, J = 7.06 Hz), 2.32 (s, 3H), 2.2–1.9 (m, 3H), 1.8–1.0 (m, 16H), 0.19 (s, 9H).

(1S,3S*,5S*)-3-Cyclohexyl-2-methyl-7-[(trimethylsilyl)methylidene]-2-azabicyclo[3.2.0]heptane* **25**

A solution of **21** (2 mmol, 0.556 g) in dry ether (25 mL) was cooled to −50 °C as *sec*-butyllithium (1.3 M in cyclohexane/hexane 98:2, 4 mmol, 3 mL) was added dropwise. The reaction mixture was then allowed to warm to +5 °C. It was stirred for 15 min and treated with a solution of NH_4Cl/NH_4OH (2:1). The layers were separated and the aqueous one was extracted with ether. The combined organic extracts were washed with brine, the organic layers were dried over $MgSO_4$, and concentrated. The crude material was purified by chromatography on silica gel (eluent: cyclohexane/ether, 70:30) to give 0,335 g (61%) of the title compound.

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.42 (m, 1H), 3.33 (m, 1H), 2.81–2.77 (m, 1H), 2.65–2.61 (m, 1H), 2.49–2.31 (m, 2H), 2.30 (s, 3H), 1.95–1.91 (m, 1H), 1.81–1.75 (m, 5H), 1.58–1.55 (m, 1H), 1.47–1.43 (m, 1H), 1.27–1.17 (m, 3H), 1.0–0.95 (m, 2H), 0.09 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 159.9, 120.4, 76.7, 75.7, 40.9, 39.2, 33.9, 32.8, 31.7, 26.95, 26.6, 26.4, −0.5.

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