A Concise Cross-Metathesis Route to Enantiopure 1-Azaspirocycles

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Received: 06.07.2013; Accepted after revision: 20.08.2013

We dedicate this manuscript to Adrian Blackman (University of Tasmania) and wish him well in his retirement.

Abstract: A concise synthesis of spiropyrrolidines and spiropiperidines has been developed. The approach employs a ruthenium–alkylidene-catalysed cross-metathesis reaction of enantiopure N-protected allylglycine with methylenecycloalkanes. The resultant alkene intermediates can then undergo a tandem acid-catalysed cyclisation to form spiropyrrolidines. Ring expansion of the spiropyrrolidine system, via an aziridinium intermediate, grants access to the homologous spiropiperidine ring system with excellent stereoretention.

Key words: spiro compounds, metathesis, ring expansion, catalysis, piperidines, pyrrolidines

The 1-azaspirocyclic ring system **1** (Figure 1) can be found in a number of bioactive natural product families.[1] Lepadiformine (**2**),[2] cephalotaxine (**3**)[3] and cylindricine A (**4**)[4] all share a common spirocyclic pyrrolidine core (n = 1), and fasicularin (**5**),[2e,5] halichlorine (**6**),[6] histrionicotoxin (**7**)[7] and cylindricine B (**8**)[8] possess a homologous spirocyclic piperidine centre (n = 2). Many different strategies have been developed to construct the azaspirocyclic motif within these alkaloids and these include the use of Diels–Alder cycloaddition,[9] semipinacol rearrangement[10] and acid-catalysed diene–iminium cyclisation.[11] Nitrone–alkene cycloaddition of acyclic diene intermediates, generated via olefin cross-metathesis (CM),[12] has also been used to generate the spiropiperidine core of histrionicotoxin (**7**).[13] To the best of our knowledge, with the exception of this single communication, the use of CM chemistry to efficiently construct 1-azaspirocyclic structures **1** has not yet been explored. Herein, we report the development of a generic, catalysis-driven approach to 1-azaspiranes exploiting an alkene CM reaction and subsequent Brønsted acid induced cyclisation (Scheme 1). Advantages of this strategy include high functional group tolerance, modular design and telescopic processing to form the target spirocyclic pyrrolidine architecture. In addition, a commercially available α-amino acid is used to provide requisite alkaloid stereochemistry and ring expansion into chiral spirocyclic piperidines.

Our synthetic approach is based on previous work which employed a catalytic two-step synthesis of 5,5-dimethylproline derivatives via the CM of allylglycine derivatives with isobutylene.[14] In this study, we extended this strategy to the CM of the *N*-benzoylallylglycine **9** with the methylenecycloalkanes **10**–**12** to rapidly generate alkene intermediates **13**–**15** for subsequent cationic cyclisation.[15] Unfortunately, this ruthenium–alkylidene-catalysed transformation was initially found to be capricious and optimum conditions were therefore firstly developed for the CM of **9** with methylenecyclohexane (**11**) (Table 1). Under conventional heating in a Fischer–Porter tube, the reaction suffered from poor conversion despite a long reaction time (Table 1, entry 1). When conventional heating was replaced by microwave (MW) irradiation, an enhancement in conversion was achieved in a shorter reaction time (Table 1, entry 2).

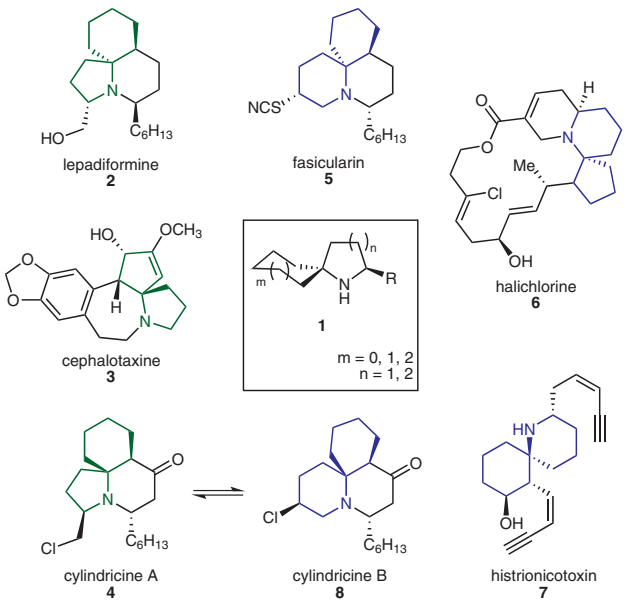
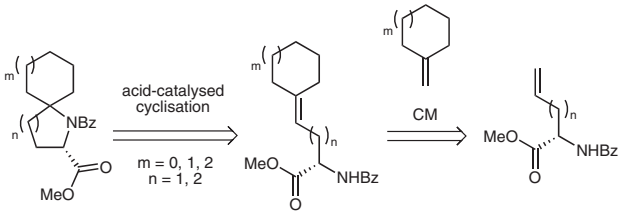


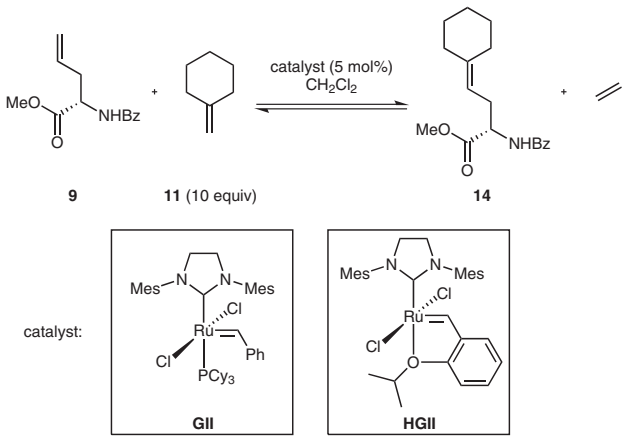
Figure 1 Marine alkaloids bearing the 1-azaspirocyclic core



Scheme 1 Tandem CM/acid-catalysed cyclisation route to 1-azaspirocycles

SYNTHESIS 2013, 45, 3118–3124
Advanced online publication: 27.09.2013
DOI: 10.1055/s-0033-1338527; Art ID: SS-2013-N0463-OP

Table 1 Optimisation of the CM Reaction between **9** and **11**



Entry	Catalyst	Conditions	Conversion[a] (%)
1	**GII**	heat, 48 h	40
2	**GII**	MW (100 W), 100 °C, 2 h	60
3	**HGII**	MW (100 W), 100 °C, 2 h	76
4	**HGII**	MW (100 W), 100 °C, 4 h	79
5	**HGII**	MW (100 W), 100 °C, 4 h[b]	96

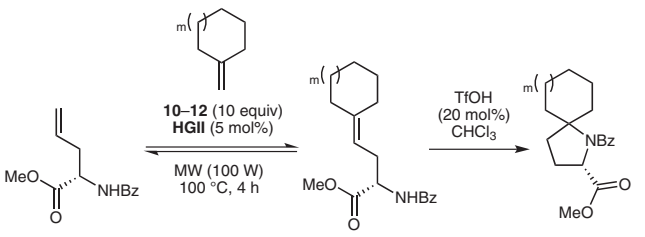
[a] Determined by ^{1}H NMR spectroscopy.
[b] Volatiles purged after 2 h.

Further improvement in conversion was achieved when second-generation Grubbs catalyst (**GII**) was replaced with second-generation Hoveyda–Grubbs catalyst (**HGII**) (Table 1, entries 3 and 4). Optimal CM conditions were obtained when the reaction was microwave-irradiated (100 W) at 100 °C for four hours with a purge of the volatile ethylene byproduct after two hours (Table 1, entry 5). Attempts were made to lower the equivalents of alkene **11**, however this resulted in reduced conversion into **14** in all cases; the given stoichiometry (10 equiv) was deemed necessary to achieve quantitative conversion into **14**. Nevertheless, excess, unreacted **11** could be readily recovered by distillation and recycled in subsequent reactions.

With the optimised reaction conditions in hand, CM of **9** with homologous methylenecycloalkanes **10** and **12** were explored. Gratifyingly, the corresponding alkenes **13** and **15** were also obtained in good to excellent yields from **10** and **12**, respectively (Table 2).

It should be noted that access to trisubstituted alkenes bearing pendent amide functionality (general structure of **13**–**15**) via traditional olefination chemistry has been reported. In comparison, these other methods[16] require a higher number of synthetic steps and/or do not yield an enantiopure product. More specifically, access to the general trisubstituted alkenyl amide structure has been achieved via Wittig olefination of cyclohexanone followed by functional group interconversion,[16a,b] nucleophilic substitution of prefunctionalised alkenyl halides,[16c,d] quenching of a zirconocene complex with ketenes,[16e] and aldol condensation[16f] or nickel(0)-catalysed addition of isocyanates to vinylcyclohexane.[16g] We believe that CM represents a facile and synthetically viable approach to trisubstituted alkenes such as **13**–**15**.

Table 2 Preparation of Enantiopure 1-Azaspirocycles **16**–**18**

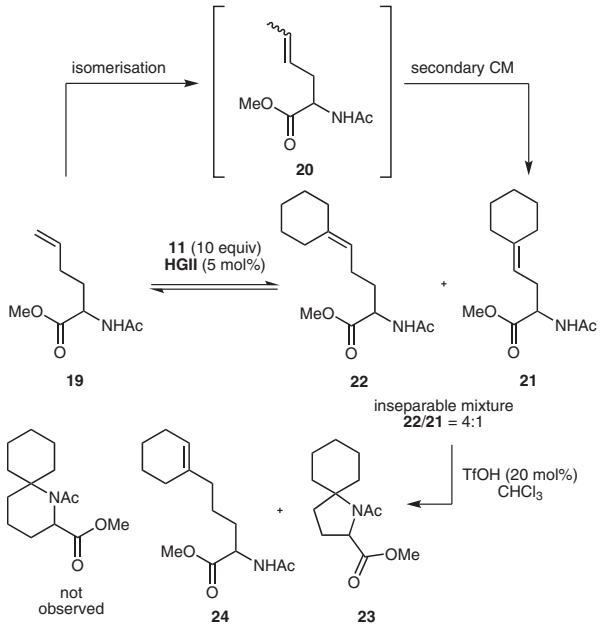


Entry	Cross partner[a]	Yield (%) of **13**–**15**	Yield[b] (%) of **16**–**18**
1	**10** (m = 0)	**13**, 95	**16**, 85 (87)
2	**11** (m = 1)	**14**, 96	**17**, 79 (80)
3	**12** (m = 2)	**15**, 79	**18**, 80 (67)

[a] Volatiles purged at 2 h.
[b] Yield in parentheses obtained via the telescopic method.

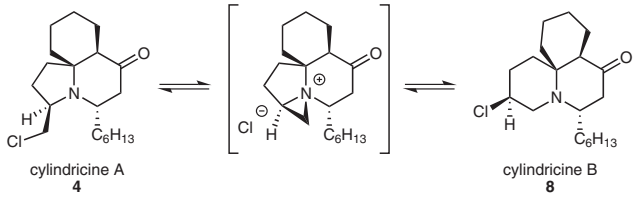
Next, the key acid-catalysed cationic cyclisation was investigated. Trifluoromethanesulfonic acid induced (20 mol%) cyclisation of olefin intermediates **13**–**15** gave the corresponding spiropyrrolidines **16**–**18** in 85%, 79% and 80% yield, respectively. Chiral HPLC analysis showed no loss of enantiopurity over the two catalytic steps. Furthermore, comparable yields were obtained when telescopic processing was employed to generate the target spiropyrrolidines **16**–**18** (Table 2, yields in parentheses). This conveniently eliminates the need for intermediate isolation and purification.

Unfortunately, extension of this chemistry towards the construction of homologous spiropiperidines was unsuccessful. Cross-metathesis of the N-protected homoallylglycine **19** with methylenecyclohexane (**11**) under the previously optimised reaction conditions led to partial isomerisation of **19** to the crotylglycine derivative **20** which upon sequential CM reaction with **11** gave the truncated alkene byproduct **21** (Scheme 2). This byproduct was chromatographically inseparable from the desired cross product **22**. Additives such as benzoquinone and acetic acid have been used previously to suppress such isomerisation;[17] however, the addition of benzoquinone to these CM reactions merely suppressed the overall yields without eliminating the isomerisation process. In addition, attempts to cyclise the mixture of **21** and **22** only resulted in the spiropyrrolidine analogue **23** (generated from **21**) and endo-isomerised alkene **24** (generated from **22**). Our attempts to prepare spiropiperidine compounds via acid-catalysed cyclisation were unsuccessful, as per the observations made by Haskins and Knight.[15]



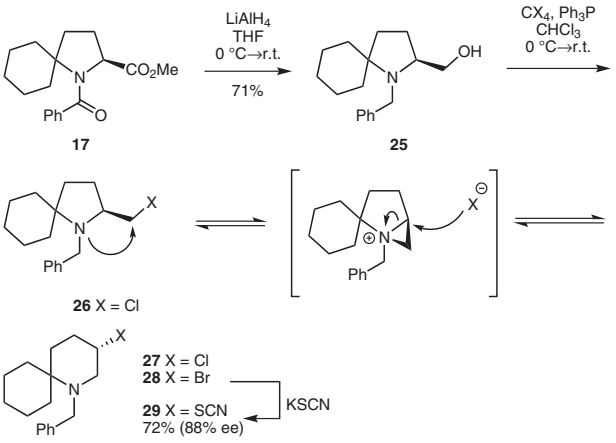
Scheme 2 Attempted preparation of spiropiperidines

Fortunately, nature provides the key to a viable synthesis of the elusive spiropiperidine framework. Interconversion between the spirocyclic marine alkaloids cylindricine A and B is postulated to involve a stereospecific ring expansion of the pyrrolidine via an aziridinium intermediate (Scheme 3).[4a–c,18] Hence, we postulated that access to spiropyrrolidine and spiropiperidine systems could be realised through a common and readily prepared CM-generated precursor.



Scheme 3 Interconversion between cylindricine A and B

Towards this end, the previously prepared spiropyrrolidine **17** was globally reduced with lithium aluminum hydride to give amino alcohol **25** in good yield (Scheme 4). Interestingly, when **25** was subjected to Appel conditions using carbon tetrachloride, a 1:1 mixture of regioisomers **26** and **27** (X = Cl) was obtained. The equilibrium that exists between chlorides **26** and **27** mirrors that found in the cylindricine family, notably cylindricine A and B. In contrast, when carbon tetrabromide was used in the Appel reaction, only the spiropiperidine analogue **28** was observed. Due to its instability on silica gel during chromatography, isolation of **28** proved to be difficult; however, it was conveniently converted in situ into the thiocyanate analogue **29** (Scheme 4), a motif found in the ascidian alkaloids cylindricine J and fasicularin (**5**). Chiral



Scheme 4 Ring expansion of a spiropyrrolidine to access spiropiperidines

HPLC analysis of the thiocyanate analogue **29** showed high retention of enantiomeric excess.

In conclusion, a facile and generic route to enantiopure spiropyrrolidine and spiropiperidine frameworks has been achieved through a common trisubstituted alkene. Ruthenium-catalysed CM of commercially available allylglycine and methylenecycloalkanes followed by acid-catalysed cyclisation facilitates expedient access to synthetically useful, chiral spiropyrrolidine analogues. These spiropyrrolidines can then be ring expanded to generate spiropiperidine analogues. In order to complete the synthesis of tricyclic marine alkaloids (Figure 1) via this strategy, the methylenecycloalkane CM partner needs to bear reactive functionality in the α-position. We have recently described chemistry for the cross-metathesis of this olefin subtype[19] which should provide facile entry into 1-azaspirocyclic alkaloid natural products in the future.

Melting points were determined using a Reichert hot-stage melting point apparatus. IR spectra were recorded on a Perkin-Elmer 1600 series Fourier transform infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX300 spectrometer (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR) or a Bruker DRX400 spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR). Low-resolution electrospray ionisation (ESI) mass spectra were recorded on a Micromass Platform Electrospray mass spectrometer (quadrupole mass electrometry) as solutions in the specified solvents. High-resolution electrospray mass spectra (HRMS) were recorded on a Bruker BioApex 47e Fourier transform mass spectrometer (4.7 tesla magnet). Optical rotations $[\alpha]_D^{25}$ were measured on a Perkin-Elmer model 141 polarimeter. Gas chromatograms were recorded on an Agilent 6850 GC system equipped with an SGE capillary column HP1-(PN190912-413) (30 m × 0.32 mm × 0.25 μm). The capillary column was operated with standard parameters, which involved holding the system at a constant 80 °C for 1 min, a ramp of 10 °C/min until 280 °C was reached, and a second hold period at this temperature for 9 min. Chiral GC was performed on a [50CP2/XE60.SVALSAPEA] column (50 cm × 0.25 mm), using helium as the carrier gas (5 mL/min). Chiral HPLC was performed on an Agilent 1200 LC binary system with an Agilent variable UV–vis detector. Analysis was performed on a Daicel Chiralcel OD column using a flow rate of 1.0 mL/min at 254 nm with a solvent mixture of *i*-PrOH–hexane (1:9). Microwave reactions were carried out using a CEM Discover® system fitted with a benchmate

option. CH_2Cl_2 was supplied by Merck and distilled over CaH_2 prior to use. $CHCl_3$, EtOAc, hexane and MeOH were used as supplied by Merck. Et_2O and THF were stored over Na wire and distilled prior to use. [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(*o*-isopropoxyphenylmethylene)ruthenium (**HGII**) and benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (**GII**) were used as supplied by Aldrich.

(*S*)-Methyl 2-Benzamidopent-4-enoate (9)

(*S*)-2-Benzamidopent-4-enoic acid (1.00 g, 4.57 mmol) was dissolved in a solution of methanolic HCl (50 mL, pH 2). After being stirred at r.t. for 18 h, the reaction mixture was diluted with H_2O (10 mL) and sat. aq $NaHCO_3$ (10 mL), and the MeOH was removed under reduced pressure. The aqueous phase was then extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extract was washed with H_2O (25 mL) and brine (25 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **9** as a colourless solid; yield: 1.05 g (99%); mp 44–47 °C.

Chiral GC (run isothermally at 200 °C for 40 min): t_R = 16.8 min (>99% ee).

$[\alpha]_D^{25}$ +50.7 (*c* 1.09, $CHCl_3$).

IR (KBr): 3325 (br, w), 3062 (w), 2955 (w), 2360 (w), 1743 (s), 1644 (s), 1603 (w), 1580 (w), 1538 (m), 1489 (m), 1438 (w), 1360 (w), 1268 (w), 1225 (w), 1159 (w), 1075 (w), 1028 (w), 925 (m), 802 (w), 714 (w), 668 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.76 (m, 2 H), 7.52–7.39 (m, 3 H), 6.71 (br d, *J* = 6.5 Hz, 1 H), 5.81–5.67 (m, 1 H), 5.18–5.12 (m, 2 H), 4.91–4.85 (m, 1 H), 3.76 (s, 3 H), 2.74–2.56 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 167.3, 134.1, 132.7, 131.9, 128.7, 127.3, 119.2, 52.5, 52.3, 36.6.

MS (ESI^+, MeOH): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{15}NNaO_3$: 256.1; found: 256.2.

Conventional Cross-Metathesis; General Procedure

In a nitrogen-filled drybox, a Fischer–Porter tube was loaded with substrate (50 mg), deoxygenated solvent, reacting olefin and catalyst (5 mol%). The system was sealed, removed from the drybox, immersed in a water bath and heated at a specified temperature for a specified period of time. The reaction mixture was then exposed to air and the solvent was removed under reduced pressure. Metathesis experiments are described using the following format: substrate (mg), catalyst (mg), reacting olefin (10 equiv), solvent (mL), reaction temperature (°C), reaction time (h). Reaction conversion into the desired cross product was determined by ^1H NMR spectroscopy. The crude product was purified by column chromatography. Chromatographic purification conditions and isolated yields (%) are listed where applicable.

Microwave Cross-Metathesis; General Procedure

In a nitrogen-filled drybox, a microwave reactor vessel was loaded with substrate (50–100 mg), deoxygenated solvent, reacting olefin and catalyst (5 mol%). The system was sealed, removed from the drybox, and microwave-irradiated and stirred at 100 °C. After 2–4 h, the reaction mixture was cooled to r.t. and exposed to air. The solvent was then removed under reduced pressure. Metathesis experiments are described using the following format: substrate (mg), catalyst (mg), reacting olefin (10 equiv), solvent (mL), reaction temperature (°C), microwave power (W), reaction time (h). Reaction conversion into the desired cross product was determined by ^1H NMR analysis. The crude product was purified by column chromatography. Chromatographic purification conditions and isolated yields (%) are listed where applicable.

(*S*)-Methyl 2-Benzamido-4-cyclopentylidenebutanoate (13)

(*S*)-Methyl 2-benzamidopent-4-enoate (**9**) was subjected to the microwave cross-metathesis procedure with methylenecyclopentane (**10**) under the following conditions: (*S*)-**9** (50 mg, 0.22 mmol), **HGII** (6.27 mg, 5 mol%), **10** (227 μL, 2.15 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 4 h (evacuate and purge with argon at time = 2 h). Purification by silica gel column chromatography (hexane–EtOAc, 3:1) gave (*S*)-**13** as a colourless crystalline solid; yield: 58.7 mg (95%); mp 74.0–76.2 °C.

Chiral GC (run isothermally at 200 °C for 40 min): t_R = 24.9 min (>99% ee).

IR (KBr): 3323 (s), 2944 (s), 1744 (s), 1641 (s), 1580 (w), 1533 (s), 1487 (s), 1435 (m), 1354 (w), 1277 (w), 1221 (m), 1200 (m), 1097 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.75 (m, 2 H), 7.52–7.39 (m, 3 H), 6.70 (br d, *J* = 7.5 Hz, 1 H), 5.23–5.16 (m, 1 H), 4.83 (dt, *J* = 7.5, 5.5 Hz, 1 H), 3.76 (s, 3 H), 2.67–2.54 (m, 2 H), 2.28–2.12 (m, 4 H), 1.64–1.55 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 167.0, 148.6, 134.3, 131.8, 128.8, 127.1, 113.1, 52.5(3), 52.5(0), 33.9, 32.6, 29.1, 26.3(7), 26.3(6).

HRMS (ESI^+, MeOH): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{21}NNaO_3$: 310.1414; found: 310.1399.

(*S*)-Methyl 2-Benzamido-4-cyclohexylidenebutanoate (14)

Table 1, Entry 1

The cross-metathesis of (*S*)-methyl 2-benzamidopent-4-enoate (**9**) and methylenecyclohexane (**11**) was carried out according to the conventional cross-metathesis procedure under the following conditions: (*S*)-**9** (50 mg, 0.21 mmol), **GII** (9.0 mg, 5 mol%), **11** (240 μL, 2.14 mmol), CH_2Cl_2 (2.0 mL), 50 °C, 48 h. ^1H NMR analysis showed 40% conversion into compound **14**.

Table 1, Entry 2

The cross-metathesis of (*S*)-methyl 2-benzamidopent-4-enoate (**9**) and methylenecyclohexane (**11**) was carried out according to the microwave cross-metathesis procedure under the following conditions: (*S*)-**9** (50 mg, 0.21 mmol), **GII** (9.0 mg, 5 mol%), **11** (240 μL, 2.14 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 2 h. ^1H NMR analysis showed 60% conversion into compound **14**.

Table 1, Entry 3

The cross-metathesis of (*S*)-methyl 2-benzamidopent-4-enoate (**9**) and methylenecyclohexane (**11**) was carried out according to the microwave cross-metathesis procedure under the following conditions: (*S*)-**9** (50 mg, 0.21 mmol), **HGII** (7.0 mg, 5 mol%), **11** (240 μL, 2.14 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 2 h. ^1H NMR analysis showed 76% conversion into compound **14**.

Table 1, Entry 4

The cross-metathesis of (*S*)-methyl 2-benzamidopent-4-enoate (**9**) and methylenecyclohexane (**11**) was carried out according to the microwave cross-metathesis procedure under the following conditions: (*S*)-**9** (50 mg, 0.21 mmol), **HGII** (7.0 mg, 5 mol%), **11** (240 μL, 2.14 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 4 h. ^1H NMR analysis showed 79% conversion into compound **14**.

Table 1, Entry 5

The cross-metathesis of (*S*)-methyl 2-benzamidopent-4-enoate (**9**) and methylenecyclohexane (**11**) was carried out according to the microwave cross-metathesis procedure under the following conditions: (*S*)-**9** (50 mg, 0.21 mmol), **HGII** (7.0 mg, 5 mol%), **11** (240 μL, 2.14 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 4 h (evacuate and purge with argon at time = 2 h). ^1H NMR analysis showed 99% conversion into compound **14**. The crude product was purified via silica gel column chromatography (hexane–EtOAc, 1:4) to give (*S*)-**14** as a colourless solid; yield: 60.5 mg (96%); mp 72.6–73.5 °C.

IR (KBr): 3344 (br, s), 3060 (w), 3026 (w), 2926 (s), 2852 (s), 1751 (s), 1641 (s), 1527 (s), 1489 (m), 1432 (m), 1218 (m), 1175 (m), 1101 (w), 818 (w), 721 (w), 693 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.68 (m, 2 H), 7.48–7.32 (m, 3 H), 6.62 (br d, *J* = 5.5 Hz, 1 H), 4.95 (t, *J* = 7.5 Hz, 1 H), 4.77 (dt, *J* = 7.5, 5.5 Hz, 1 H), 3.71 (s, 3 H), 2.75–2.43 (m, 2 H), 2.05–1.95 (m, 4 H), 1.50–1.25 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 167.2, 145.1, 134.3, 131.9, 128.8, 127.3, 114.2, 52.8, 52.6, 37.5, 30.0, 29.0, 28.9, 28.1, 26.9.

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{24}NO_3$: 302.1756; found: 302.1751.

(*S*)-Methyl 2-Benzamido-4-cycloheptylidenebutanoate (15)

The cross-metathesis of (*S*)-methyl 2-benzamidopent-4-enoate (**9**) and methylenecycloheptane (**12**) was carried out according to the microwave cross-metathesis procedure under the following conditions: (*S*)-**9** (50 mg, 0.21 mmol), **HGII** (7.0 mg, 5 mol%), **12** (236 mg, 2.14 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 4 h (evacuate and purge with argon at time = 2 h). Purification by silica gel column chromatography (hexane–EtOAc, 4:1) gave (*S*)-**15** as a colourless solid; yield: 53.3 mg (79%); mp 71.8–72.4 °C.

IR (KBr): 3317 (m), 2921 (s), 2850 (m), 1743 (m), 1643 (m), 1603 (w), 1580 (w), 1532 (m), 1489 (w), 1439 (w), 1213 (w), 695 (w), 632 (w), 579 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.76 (m, 2 H), 7.51–7.46 (m, 1 H), 7.43–7.39 (m, 2 H), 6.71 (br d, *J* = 7.5 Hz, 1 H), 5.08 (t, *J* = 7.5 Hz, 1 H), 4.84 (dt, *J* = 7.5, 5.5 Hz, 1 H), 3.76 (s, 3 H), 2.73–2.51 (m, 2 H), 2.23–2.18 (m, 4 H), 1.53–1.45 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 167.0, 146.2, 134.1, 131.7, 128.7, 127.1, 117.8, 52.4(9), 52.4(7), 38.0, 30.5, 30.1, 29.8, 29.3, 29.1, 27.0.

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{25}NNaO_3$: 338.1727; found: 338.1728.

1-Azaspirocycles 16–18 by the Telescopic Method; General Procedure

A microwave vessel was charged with (*S*)-methyl 2-benzamidopent-4-enoate (**9**; 50 mg, 0.21 mmol), **HGII** (7.0 mg, 5 mol%), methylenecycloalkane **10**, **11** or **12** (2.14 mmol, 10 equiv) and CH_2Cl_2 (2.0 mL). The reaction vessel was sealed and microwave-irradiated (100 W) whilst being stirred at 100 °C for 4 h (evacuate and purge with argon at time = 2 h). Then, the reaction mixture was cooled to r.t. and the solvent was removed in vacuo to afford the crude cross product as a brown oil. To the crude reaction mixture was then added a solution of TfOH (3.8 μL, 0.04 mmol) in $CHCl_3$ (4.0 mL). The system was sealed and microwave-irradiated (40 W) whilst being stirred at 50 °C. After 60 min, the reaction mixture was cooled to r.t. and quenched with sat. aq $NaHCO_3$ (10 mL). The phases were then separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic extract was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale yellow oil. Purification via column chromatography yielded the desired spirocyclic product **16**–**18**.

(*S*)-Methyl 1-Benzoyl-1-azaspiro[4.4]nonane-2-carboxylate (16)

In a microwave vessel under argon atmosphere, TfOH (7.4 μL, 0.083 mmol) was added to a stirred solution of (*S*)-methyl 2-benzamido-4-cyclopentylidenebutanoate (**13**; 120 mg, 0.42 mmol) in $CHCl_3$ (5.0 mL). The system was sealed and microwave-irradiated (40 W) whilst being stirred at 50 °C for 30 min. The reaction mixture was then cooled to r.t. and quenched with sat. aq $NaHCO_3$ (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic extract was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale yellow oil. Purification via silica gel column chromatography (hexane–EtOAc, 4:1) gave **16** as a colourless oil; yield: 102 mg (85%).

Yield from telescopic method: 87%.

Chiral GC: t_R = 19.8 min (>99% ee).

$[\alpha]_D^{25}$ –101.2 (*c* 1.00, $CHCl_3$).

IR (neat): 2944 (s), 2867 (s), 1744 (s), 1644 (s), 1577 (w), 1444 (m), 1394 (s), 1272 (m), 1200 (s), 1177 (s), 1106 (w), 1017 (w) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, 55 °C): δ = 7.34–7.31 (m, 3 H), 7.30–7.27 (m, 2 H), 4.34 (dd, *J* = 8.0, 2.0 Hz, 1 H), 3.53 (s, 3 H), 2.79–2.57 (m, 2 H), 2.21–2.11 (m, 1 H), 2.03–1.88 (m, 5 H), 1.63–1.46 (m, 4 H).

^{13}C NMR (100 MHz, $C_2D_2Cl_4$, 100 °C): δ = 172.6, 169.7, 138.6, 128.8, 128.0, 126.1, 73.0, 63.0, 51.6, 40.7, 36.6, 36.4, 28.3, 25.0(7), 25.0(6).

The ^{1}H and ^{13}C NMR spectra were recorded at elevated temperatures, due to the presence of rotamers.

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{21}NNaO_3$: 310.1414; found: 310.1409.

(*S*)-Methyl 1-Benzoyl-1-azaspiro[4.5]decane-2-carboxylate (17)

In a microwave vessel under argon atmosphere, TfOH (2.9 μL, 0.033 mmol) was added to a stirred solution of (*S*)-methyl 2-benzamido-4-cyclohexylidenebutanoate (**14**; 50 mg, 0.17 mmol) in $CHCl_3$ (5.0 mL). The system was sealed and microwave-irradiated (40 W) whilst being stirred at 50 °C for 1 h. The reaction mixture was then cooled to r.t. and quenched with sat. aq $NaHCO_3$ (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic extract was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale yellow oil. Purification via silica gel column chromatography (hexane–EtOAc, 4:1) gave **17** as a colourless solid; yield: 40.5 mg (79%); mp 116–118 °C.

Yield from telescopic method: 80%.

IR (KBr): 2935 (s), 2857 (s), 1741 (s), 1715 (w), 1642 (s), 1396 (s), 1364 (s), 1235 (w), 1212 (s), 1103 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, 55 °C): δ = 7.32–7.30 (m, 3 H), 7.25–7.23 (m, 2 H), 4.33 (m, 1 H), 3.54 (s, 3 H), 2.95–2.65 (m, 2 H), 2.16–2.06 (m, 2 H), 1.94–1.86 (m, 2 H), 1.81–1.74 (m, 3 H), 1.61–1.56 (m, 1 H), 1.45–1.27 (m, 4 H).

^{13}C NMR (100 MHz, $C_2D_2Cl_4$, 100 °C): δ = 172.7, 170.3, 139.0, 128.6, 127.7, 125.9, 67.9, 63.1, 51.6, 34.5, 34.3, 32.7, 27.4, 25.0, 24.5, 24.0.

The ^{1}H and ^{13}C NMR spectra were recorded at elevated temperatures, due to the presence of rotamers.

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{24}NO_3$: 302.1756; found: 302.1752.

(*S*)-Methyl 1-Benzoyl-1-azaspiro[4.6]undecane-2-carboxylate (18)

In a microwave vessel under argon atmosphere, TfOH (2.8 μL, 0.032 mmol) was added to a stirred solution of (*S*)-methyl 2-benzamido-4-cycloheptylidenebutanoate (**15**; 50 mg, 0.16 mmol) in $CHCl_3$ (5.0 mL). The system was sealed and microwave-irradiated (40 W) whilst being stirred at 50 °C for 1 h. The reaction mixture was then cooled to r.t. and quenched with sat. aq $NaHCO_3$ (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic extract was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a pale yellow oil. Purification via silica gel column chromatography (hexane–EtOAc, 4:1) gave **18** as a colourless oil; yield: 40 mg (80%).

Yield from telescopic method: 67%.

IR (neat): 2920 (m), 2857 (m), 1748 (s), 1639 (s), 1447 (m), 1391 (s), 1356 (m), 1195 (m), 1173 (s), 1028 (m) cm^{-1}.

^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 100 °C): δ = 7.34–7.33 (m, 3 H), 7.28–7.26 (m, 2 H), 4.35 (dd, *J* = 8.0, 3.0 Hz, 1 H), 3.54 (s, 3 H), 2.83–2.61 (m, 2 H), 2.23–2.14 (m, 1 H), 2.03–1.99 (m, 2 H), 1.96–1.80 (m, 4 H), 1.75–1.52 (m, 5 H), 1.47–1.40 (m, 2 H).

^{13}C NMR (100 MHz, $C_2D_2Cl_4$, 100 °C): δ = 172.7, 169.9, 139.0, 128.6, 127.9, 126.0, 70.9, 63.0, 51.5, 37.9, 37.7, 37.1, 28.5, 28.2, 27.3, 24.2, 23.6.

The ^{1}H and ^{13}C NMR spectra were recorded at elevated temperatures, due to the presence of rotamers.

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{26}NO_3$: 316.1907; found: 316.1912.

(±)-Methyl 2-Acetamidohex-5-enoate (19)

(±)-2-Acetamidohex-5-enoic acid (2.00 g, 11.7 mmol) was added to a stirred solution of methanolic HCl (50 mL, pH 2). After being stirred at r.t. for 18 h, the reaction mixture was diluted with sat. aq $NaHCO_3$ (50 mL), and the MeOH was removed under reduced pressure. The aqueous phase was then extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic extract was washed with H_2O (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give **19** as a colourless solid; yield: 2.16 g (99%); mp 57.0–58.5 °C.

IR (KBr): 3362 (br, s), 3080 (m), 2979 (s), 2929 (m), 1740 (s), 1663 (s), 1506 (s), 1466 (m), 1450 (m), 1390 (w), 1370 (w), 1313 (m), 1270 (m), 1202 (m), 1143 (m), 1097 (m), 1079 (m), 1032 (w), 915 (m), 858 (m), 813 (w), 785 (w), 759 (w), 684 (w), 640 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.07 (br s, 1 H), 5.81–5.72 (m, 1 H), 5.06–4.96 (m, 2 H), 4.66–4.58 (m, 1 H), 3.73 (s, 3 H), 2.09–2.06 (m, 2 H), 1.99 (s, 3 H), 2.01–1.73 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 170.1, 136.9, 115.6, 53.4, 51.8, 31.5, 29.5, 22.3.

MS (ESI$^+$, MeOH): *m*/*z* $[M + Na]^+$ calcd for $C_9H_{15}NNaO_3$: 208.1; found: 208.0.

Attempted Synthesis of Methyl 2-Acetamido-5-cyclohexylidenepentanoate (22)

The cross-metathesis of (±)-methyl 2-acetamidohex-5-enoate (**19**) and methylenecyclohexane (**11**) was carried out according to the microwave cross-metathesis procedure under the following conditions: (±)-**19** (38.9 mg, 0.21 mmol), **HGII** (7.0 mg, 5 mol%), **11** (240 μL, 2.14 mmol), CH_2Cl_2 (2.0 mL), 100 °C, 100 W, 4 h (evacuate and purge with argon at time = 2 h). The reaction mixture was concentrated in vacuo and gave a chromatographically inseparable mixture of alkenes **21** and **22** in ca. 1:4 ratio. Further attempts to isolate compound **22** were unsuccessful.

Attempted Synthesis of Methyl 1-Acetyl-1-azaspiro[5.5]undecane-2-carboxylate

In a microwave vessel under argon atmosphere, TfOH (2.9 μL, 0.033 mmol) was added to a stirred solution of a mixture of alkenes **21** and **22** (1:4) in $CHCl_3$ (5.0 mL). The system was sealed and microwave-irradiated (40 W) whilst being stirred at 50 °C for 1 h. The reaction mixture was then cooled to r.t. and quenched with sat. aq $NaHCO_3$ (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic extract was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Analysis of the residue by ^{1}H NMR spectroscopy showed a mixture of compounds **23** and **24**.

[(*S*)-1-Benzyl-1-azaspiro[4.5]decan-2-yl]methanol (25)

Freshly distilled THF (3.0 mL) was added to $LiAlH_4$ (65.0 mg, 1.71 mmol) under an inert atmosphere. The resultant grey suspension was cooled to 0 °C before a solution of (*S*)-methyl 1-benzoyl-1-azaspiro[4.5]decane-2-carboxylate (**17**; 172 mg, 0.571 mmol) in THF (2.0 mL) was added dropwise via syringe. The reaction mixture was stirred for a further 16 h at r.t. Upon complete conversion of the starting material **17**, the reaction mixture was quenched by sequential addition of H_2O (0.4 mL), 20% NaOH solution (0.4 mL) and H_2O (0.8 mL). Vigorous gas formation was observed and further stirring resulted in a white suspension. The reaction mixture was dried ($MgSO_4$), filtered and concentrated in vacuo to give a clear oil. Purification by silica gel flash chromatography (EtOAc–hexane, 1:3) gave **25** as a colourless oil; yield: 105 mg (71%).

IR (neat): 3441 (br, s), 3085 (m), 3062 (m), 3028 (s), 2921 (s), 1603 (w), 1493 (s), 1453 (s), 1394 (m), 1356 (m), 1322 (m), 1255 (m), 1209 (m), 1184 (m), 1132 (m), 1078 (m), 1029 (m), 963 (w), 942 (w), 904 (m), 880 (w), 847 (w), 825 (w), 737 (m), 700 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.11 (m, 5 H), 4.02 (d, *J* = 14.5 Hz, 1 H), 3.22 (d, *J* = 14.5 Hz, 1 H), 3.02 (dd, *J* = 11.0, 1.5 Hz, 1 H), 2.94–2.90 (m, 1 H), 2.83 (dd, *J* = 11.0, 3.0 Hz, 1 H), 2.00 (br s, 1 H), 1.94–0.98 (m, 14 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5, 128.5, 127.8, 126.9, 66.0, 65.5, 63.5, 52.2, 38.6, 33.8, 28.3, 26.5, 26.2, 24.8, 24.1.

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{26}NO$: 260.2009; found: 260.2012.

(*S*)-1-Benzyl-2-(chloromethyl)-1-azaspiro[4.5]decane (26) and (*S*)-1-Benzyl-3-chloro-1-azaspiro[5.5]undecane (27)

Carbon tetrachloride (48.0 μL, 0.49 mmol) was added to a stirred solution of [(*S*)-1-benzyl-1-azaspiro[4.5]decan-2-yl]methanol (**25**; 115 mg, 0.44 mmol) in $CHCl_3$ (4.0 mL). The reaction mixture was cooled to 0 °C before a solution of Ph_3P (128 mg, 0.49 mmol) in $CHCl_3$ (2 mL) was added dropwise via syringe. The reaction mixture was stirred at r.t. for 72 h and then concentrated in vacuo to give a yellow oil. Purification by silica gel flash chromatography (EtOAc–hexane, 1:10) gave compound **26**, and the isomeric piperidine isomer **27**, as an inseparable 1:1 mixture; yield: 79 mg (64%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (compound **26**) = 7.38–7.19 (m, 5 H), 4.11 (d, *J* = 15.0 Hz, 1 H), 3.45 (d, *J* = 15.0 Hz, 1 H), 3.18–3.10 (m, 1 H), 2.96 (dd, *J* = 12.0, 3.0 Hz, 1 H), 2.87 (dd, *J* = 12.0, 1.0 Hz, 1 H), 2.09–1.28 (m, 14 H); δ (compound **27**) = 7.38–7.19 (m, 5 H), 4.03–3.93 (m, 1 H), 3.96 (d, *J* = 15 Hz, 1 H), 3.43 (d, *J* = 15.0 Hz, 1 H), 2.85–2.81 (m, 1 H), 2.73 (dd, *J* = 12.0, 9.0 Hz, 1 H), 2.09–1.28 (m, 14 H).

HRMS (ESI$^+$, MeOH): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{25}{}^{35}ClN$: 278.1676; found: 278.1669; *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{25}{}^{37}ClN$: 280.1646; found: 280.1641.

(*R*)-1-Benzyl-1-azaspiro[5.5]undecan-3-yl Thiocyanate (29)

Carbon tetrabromide (194 mg, 0.586 mmol) was added to a stirred solution of [(*S*)-1-benzyl-1-azaspiro[4.5]decan-2-yl]methanol (**25**; 75.9 mg, 0.293 mmol) in $CHCl_3$ (2.0 mL). The reaction mixture was cooled to 0 °C before a solution of Ph_3P (84.5 mg, 0.322 mmol) in $CHCl_3$ (2.0 mL) was added dropwise via syringe. The reaction mixture was stirred at r.t. for 24 h and then concentrated in vacuo to give a yellow oil. The residue, containing crude bromide **28**, was dissolved in acetone (5.0 mL) and potassium thiocyanate (287 mg, 2.93 mmol) was added. The reaction mixture was stirred for a further 12 h and then concentrated in vacuo to give a white solid. Purification by silica gel flash chromatography (EtOAc–hexane, 1:10) gave **29** as an off-white solid; yield: 63.0 mg (72%); mp 89.4–90.2 °C.

Chiral HPLC: t_R = 11.0 min (minor enantiomer) and 13.0 min (major enantiomer), 88% ee.

$[\alpha]_D^{25}$ –49.2 (*c* 1.00, CH_2Cl_2).

IR (KBr): 3021 (w), 2929 (s), 2853 (s), 2150 (s), 1493 (w), 1455 (s), 1447 (s), 1419 (w), 1368 (w), 1316 (w), 1224 (m), 1208 (m), 1194 (m), 1127 (m), 1074 (m), 1009 (w), 888 (w), 754 (m), 728 (s), 698 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.15 (m, 5 H), 4.00 (d, *J* = 14.0 Hz, 1 H), 3.26 (d, *J* = 14.0 Hz, 1 H), 3.24–3.19 (m, 1 H), 2.56 (dd, *J* = 12.5, 2.0 Hz, 1 H), 2.43 (dd, *J* = 12.5, 5.0 Hz, 1 H), 2.11–0.92 (m, 14 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 128.4, 128.3, 127.1, 114.2, 66.4, 63.2, 52.2, 41.7, 38.1, 33.1, 28.8, 27.9, 26.1, 24.8, 24.1.

HRMS (ESI$^+$, MeOH): *m/z* $[M + H]^+$ calcd for $C_{18}H_{25}N_2S$: 301.1733; found: 301.1735.

Acknowledgment

Financial support from the Australian Research Council (for Z.J.W. and N.D.S.) is gratefully acknowledged.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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