A Concise Cross-Metathesis Route to Enantiopure 1-Azaspirocycles

Zhen James Wang, Nicolas Daniel Spiccia, Christopher James Gartshore, Jayamini Illingshe, William Roy Jackson, Andrea Jane Robinson*

School of Chemistry, Monash University, Clayton 3800, Australia
Fax +61(3)99054597; E-mail: andrea.robinson@monash.edu
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-proline derivatives via the CM of allylglycine derivatives employed a catalytic two-step synthesis of 5,5-dimethylalkene cycloaddition of acyclic diene intermediates, generated via olefin cross-metathesis (CM), 12 has also been developed into chiral spirocyclic piperidines. Ring expansion of the spiroproline system, via an aziridinium intermediate, grants access to the homologous spiropiperidine ring system with excellent stereo-retention.

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 histrionicothxin (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 rearrangement10 and acid-catalysed diene–iminium cyclisation.11 Nitrene–alkene cycloaddition of acyclic diene intermediates, generated via olefin cross-metathesis (CM),12 has also been used to generate the spiropiperidine core of histrionicothxin (7).13 To the best of our knowledge, with the exception of this single communication, the use of CM chemistry to efficiently construct 1-azaspiroyclic 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 methylene cycloalkanes 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 methylene cyclohexane (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
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 and necessary to achieve quantitative 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 pendant amide functionality (general structure of 13–15) via traditional olefination chemistry has been reported. In comparison, these other methods 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, nucleophilic substitution of prefunctionalised alkenyl halides, quenching of a zirconocene complex with ketenes, and aldol condensation or nickel(0)-catalysed addition of isocyanates to vinylcyclohexane. We believe that CM represents a facile and synthetically viable approach to trisubstituted alkenes such as 13–15.

Next, the key acid-catalysed cationic cyclisation was investigated. Trifluoromethanesulfonic acid induced cyclisation of olefin intermediates 13–15 gave the corresponding spiroyrrolidines 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 spiroyrrolidines 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 alkenyl 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; 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 spiroyrrolidine 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.

---

Table 1 Optimisation of the CM Reaction between 9 and 11

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GII</td>
<td>heat, 48 h</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>GII</td>
<td>MW (100 W), 100 °C, 2 h</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>HGII</td>
<td>MW (100 W), 100 °C, 2 h</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>HGII</td>
<td>MW (100 W), 100 °C, 4 h</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>HGII</td>
<td>MW (100 W), 100 °C, 4 h</td>
<td>96</td>
</tr>
</tbody>
</table>

* Determined by 'H NMR spectroscopy.
* Volatiles purged after 2 h.

Table 2 Preparation of Enantiopure 1-Azaspirocycles 16–18

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cross partner</th>
<th>Yield (%) of 13–15</th>
<th>Yield (%) of 16–18</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 (m = 0)</td>
<td>13, 95</td>
<td>16, 85 (87)</td>
</tr>
<tr>
<td>2</td>
<td>11 (m = 1)</td>
<td>14, 96</td>
<td>17, 79 (80)</td>
</tr>
<tr>
<td>3</td>
<td>12 (m = 2)</td>
<td>15, 79</td>
<td>18, 80 (67)</td>
</tr>
</tbody>
</table>

* Volatiles purged at 2 h.
* Yield in parentheses obtained via the telescopic method.
Interestingly, when 25 was subjected to Appel conditions using carbon tetrabromide, a 1:1 mixture of regioisomers 26 and 27 (X = Br) 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 (S). Chiral HPLC analysis of the thiocyanate analogue 29 showed high retention of enantiomeric excess.

In conclusion, a facile and generic route to enantiopure spiropyrrrolidine 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 spiropyrrrolidine analogues. These spiropyrrrolidines 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 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. 1H and 13C NMR spectra were recorded on a Bruker DPX 300 spectrometer (300 MHz for 1H NMR, 75 MHz for 13C NMR) or a Bruker DRX 400 spectrometer (400 MHz for 1H NMR, 100 MHz for 13C 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 [α]D 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 HP1-1 (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 Daicel Chiralcel OD column using a flow rate of 1.0 mL/min at 254 nm with a solvent mixture of n-PrOH–hexane (1:9). Microwave reactions were carried out using a CEM Discover® system fitted with a benchmate.
option. CH₂Cl₂ was supplied by Merck and distilled over CaH₂ prior to use. CHCl₃, EtOAc, hexane and MeOH were used as supplied by Merck. Et₂O and THF were stored over Na wire and distilled prior to use. [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolylidenedi]dichloro(α-isopropanoxymethylene) ruthenium (HGII) and benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolyliden]-dichloro(tricyclohexyliophosphine)ruthenium (GII) were used as supplied by Aldrich.

(5)-Methyl 2-Benzamidopent-4-enoate (9)

(5)-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 H₂O (10 mL) and sat. aq NaHCO₃ (10 mL), and the MeOH was removed under reduced pressure. The aqueous phase was then extracted with CH₂Cl₂ (3 × 25 mL), and the combined organic extract was washed with H₂O (25 mL) and brine (25 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure to give 9 as a colourless solid; yield: 1.05 g (99%); mp 44–47 °C.

Conventional Cross-Metathesis; General Procedure

In a nitrogen-filled drybox, a microwave reactor vessel was loaded with substrate (50 mg), deoxygenated solvent, reacting olefin and catalyst (5 mol%). The system was sealed, removed from the drybox, stirred at r.t. for 18 h, the reaction mixture was cooled to r.t. and exposed to air. The solvent was then removed under reduced pressure. The resulting reduced pressure. The crude product was purified via 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 (1 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.

(5)-Methyl 2-Benzamido-4-cyclopentylidenedibutanoate (13)

(5)-Methyl 2-benzamidopent-4-enoate (9) was subjected to the microwave cross-metathesis procedure with methylencyclopropanone (10) under the following conditions: (5)-9 (50 mg, 0.22 mmol), CH₂Cl₂ (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 (5)-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): tR = 24.9 min (>99% ee).

IR (KBr): 3323 (s), 2944 (s), 1744 (s), 1644 (s), 1603 (w), 1580 (w), 1538 (m), 1489 (m), 1438 (w), 1360 (m), 1218 (m), 1175 (m), 1097 (w) cm⁻¹.


H NMR analysis showed 60% conversion into compound (S)-9. The crude product was purified via chiral GC (run isothermally at 200 °C for 40 min): tR = 24.9 min (>99% ee).

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

IR: 3323 (s), 2944 (s), 1744 (s), 1644 (s), 1603 (w), 1580 (w), 1538 (m), 1489 (m), 1438 (w), 1360 (m), 1218 (m), 1175 (m), 1097 (w) cm⁻¹.


(5)-Methyl 2-Benzamido-4-cyclohexyldibutanoate (14)

Table 1, Entry 1

The cross-metathesis of (5)-methyl 2-benzamidopent-4-enoate (9) and methylene cyclohexane (11) was carried out according to the conventional cross-metathesis procedure under the following conditions: (5)-9 (50 mg, 0.21 mmol), GII (9.0 mg, 5 mol%), 11 (240 µL, 2.14 mmol), CH₂Cl₂ (2.0 mL), 50 °C, 48 h. ¹H NMR analysis showed 40% conversion into compound 14.

Table 1, Entry 2

The cross-metathesis of (5)-methyl 2-benzamidopent-4-enoate (9) and methylene cyclohexane (11) was carried out according to the microwave cross-metathesis procedure under the following conditions: (5)-9 (50 mg, 0.21 mmol), HGII (7.0 mg, 5 mol%), 11 (240 µL, 2.14 mmol), CH₂Cl₂ (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 (5)-methyl 2-benzamidopent-4-enoate (9) and methylene cyclohexane (11) was carried out according to the microwave cross-metathesis procedure under the following conditions: (5)-9 (50 mg, 0.21 mmol), HGII (7.0 mg, 5 mol%), 11 (240 µL, 2.14 mmol), CH₂Cl₂ (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 (5)-methyl 2-benzamidopent-4-enoate (9) and methylene cyclohexane (11) was carried out according to the microwave cross-metathesis procedure under the following conditions: (5)-9 (50 mg, 0.21 mmol), HGII (7.0 mg, 5 mol%), 11 (240 µL, 2.14 mmol), CH₂Cl₂ (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 (5)-methyl 2-benzamidopent-4-enoate (9) and methylene cyclohexane (11) was carried out according to the microwave cross-metathesis procedure under the following conditions: (5)-9 (50 mg, 0.21 mmol), HGII (7.0 mg, 5 mol%), 11 (240 µL, 2.14 mmol), CH₂Cl₂ (2.0 mL), 100 °C, 100 W, 4 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.
(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), CH2Cl2 (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-ÅtOAc, 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 (s). HRMS (ESI +, MeOH): [M + Na]+ calcd for C19H25NNaO3: 312.1414; found: 312.1409.

Yield from telescopic method: 87%.

HRMS (ESI, MeOH): m/z [M + Na]+ calcd for C19H23NNaO3; 310.1414; found: 310.1409.

(S)-Methyl 1-Benzoyl-1-azaspiro[4.4]nonane-2-carboxylate (16)
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 CHCl3 (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 NaHCO3 (10 mL). The phases were separated and the aqueous phase was extracted with Et2O (2 × 15 mL). The combined organic extract was washed with H2O (20 mL) and brine (20 mL), dried (MgSO4), filtered and concentrated in vacuo to give a pale yellow oil. Purification via silica gel column chromatography (hexane-ÅtOAc, 4:1) gave 16 as a colourless oil; yield: 40 mg (80%).

Yield from telescopic method: 67%.

IR (neat): 2920 (s), 2867 (s), 1744 (s), 1577 (w), 1444 (m), 1394 (s), 1272 (m), 1200 (s), 1177 (s), 1106 (w), 1017 (w) cm⁻¹.

1H NMR (400 MHz, CDCl3, 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).

13C NMR (100 MHz, CDCl3, 100 °C): δ = 172.2, 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(06).

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

HRMS (ESI, MeOH): m/z [M + Na]+ calcd for C19H23NNaO3; 310.1414; found: 310.1409.

Z. J. Wang et al.

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

The 1H and 13C NMR spectroscopy showed a mixture of compounds 23 and 24.

([S]-1-Benzyl-1-azaspiro[5.5]decane-2-yl)methanol (25) Freshly distilled THF (3.0 mL) was added to LiAlH4 (0.8 mL). Vigorous gas formation was observed and further stirring resulted in a white suspension. The reaction mixture was dried (MgSO4) 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%).

HRMS (ESI+, MeOH); m/z [M + Na]+ calcd for C17H25ClN: 280.1646; found: 280.1641.

([S]-1-benzyl-1-azaspiro[4.5]decane (26) and ([S]-1-benzyl-1-azaspiro[5.5]decane (27) Carbon tetrachloride (48.0 μL, 0.49 mmol) was added to a stirred solution of ([S]-1-benzyl-1-azaspiro[4.5]decane-2-yl)methanol (25; 115 mg, 0.44 mmol) in CHCl3 (4.0 mL). The reaction mixture was cooled to 0 °C before a solution of Ph3P (128 mg, 0.49 mmol) in CHCl3 (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, 1:1) gave compound 26, and the isomeric piperidine isomer 27, as an inseparable 1:1 mixture; yield: 79 mg (64%).

HRMS (ESI+, MeOH); m/z [M + Na]+ calcd for C19H26NO3: 316.1907; found: 316.1912.

Downloaded by: Monash University. Copyrighted material.
HRMS (ESI, MeOH): m/z [M + H]^+ calc'd for C_{18}H_{25}N_{2}S: 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

This article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References


