

# Asymmetric Synthesis of Unsaturated Monocyclic and Bicyclic Nitrogen Heterocycles

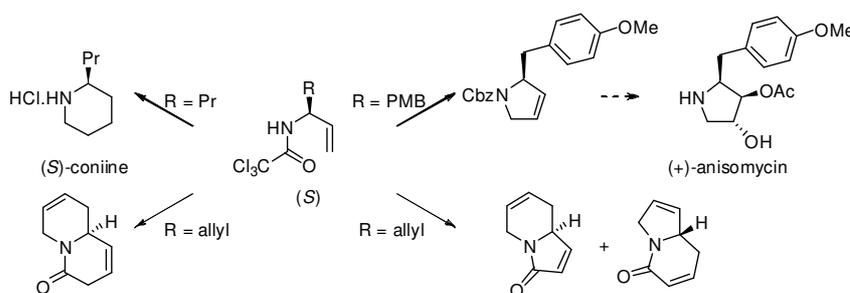
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## ABSTRACT



Hydrolysis of scalemic trichloroacetamides  $\text{Cl}_3\text{CCONHCH(R)CHCH}_2$  and allylation, or acylation with but-3-enoic acid, followed by ring-closing metathesis resulted in the formation of unsaturated pyrrolidine and piperidine building blocks. These were employed in the synthesis (*S*)-coniine ( $\text{R} = \text{Pr}$ ) and a formal synthesis of (+)-anisomycin ( $\text{R} = p\text{-MeOC}_6\text{H}_4$ ). Extension of this methodology with  $\text{R} = \text{CH}_2\text{CHCH}_2$  employing two ring-closing metatheses resulted in the synthesis of unsaturated quinolizidinone and indolizidinone frameworks.

The advent of active and accessible ruthenium based ring-closing metathesis (RCM) catalysts has transformed the synthesis of cyclic organic compounds.<sup>1</sup> Not least amongst the categories of compounds synthesised in this way are alkaloids, especially examples where RCM is employed as a key step in the synthesis of pyrrolidines, piperidine, and other nitrogen heterocycles.<sup>2</sup> Although desymmetrising RCM reactions are now well established for the synthesis of non-racemic compounds,<sup>3</sup> the asymmetric syntheses of chiral 5- and 6-membered ring

alkaloids generally employ scalemic amino dienes derived from a variety of chiral pool and asymmetric catalysis sources.<sup>4</sup> Within the latter category, transition-metal catalysed allylic amination reactions have been extensively investigated.<sup>5</sup> An alternative and highly enantioselective method for the synthesis of chiral allylic amines is the allylic imidate (or Overman) rearrangement of trifluoroacetimidates<sup>6</sup> and trichloroacetimidates **1**,<sup>7</sup>

(1) (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, 28, 446-452. (b) Grubbs, R. H.; Chang S. *Tetrahedron* **1998**, 54, 4413-4450.

(2) (a) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693-3712. (b) Brenneman, J. B.; Martin, S. F. *Curr. Org. Chem.* **2005**, 9, 1535-1549. (c) Compain, P. *Adv. Synth. Cat.* **2007**, 349, 1829-1846.

(3) For application to the asymmetric synthesis of nitrogen heterocycles see: (a) Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, 124, 6991-6997. (b) Dolman, S. J.; Schrock, R. R.; Hoveyda, A. H. *Org. Lett.* **2003**, 5, 4899-4902.

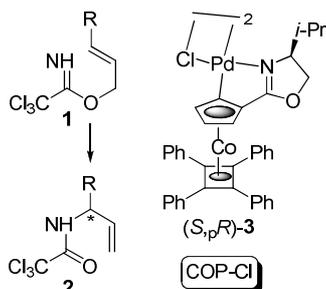
(4) (a) Liu, S.; Fan, Y.; Peng, X.; Wang, W.; Hua, W.; Akber, H.; Liao, L. *Tetrahedron Lett.* **2006**, 47, 7681-7684. (b) Angle, S. R.; Bensa, D.; Belanger, D. S. *J. Org. Chem.* **2007**, 72, 5592-5597. (c) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudeon, P. *Org. Lett.* **2007**, 9, 2473-2476. (d) Pearson, M. S. M.; Evain, M.; Mathé-Allainmat, M.; Lebreton, J. *Eur. J. Org. Chem.* **2007**, 4888-4894. (e) Murruzzu, C.; Riera, A. *Tetrahedron: Asymmetry* **2007**, 18, 149-154.

(5) (a) Welter, C.; Moreno, R. M.; Streiff, S.; Helmchen, G. *Org. Biomol. Chem.* **2005**, 3266-3268. (b) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675-691. (c) Singh, O. V.; Han, H. *J. Am. Chem. Soc.* **2007**, 129, 774-775.

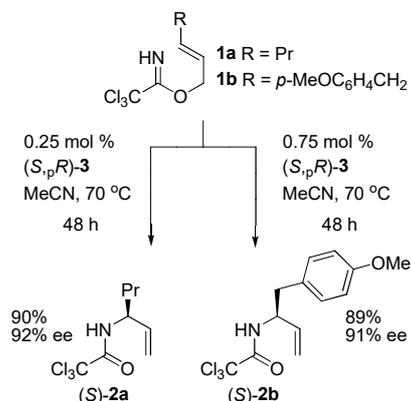
(6) Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org. Lett.* **2003**, 5, 1809-1812.

catalysed by the chloride-bridged cobalt oxazoline palladacycle **3** (Scheme 1).<sup>8</sup> In this Letter we illustrate the use of the products of this reaction for the generation of unsaturated mono- and bicyclic nitrogen heterocycles, scalemic building blocks with the potential to be applied to the synthesis of a variety of alkaloids and related structures.<sup>9,10</sup>

**Scheme 1.** The allylic imidate rearrangement and catalyst **3**.



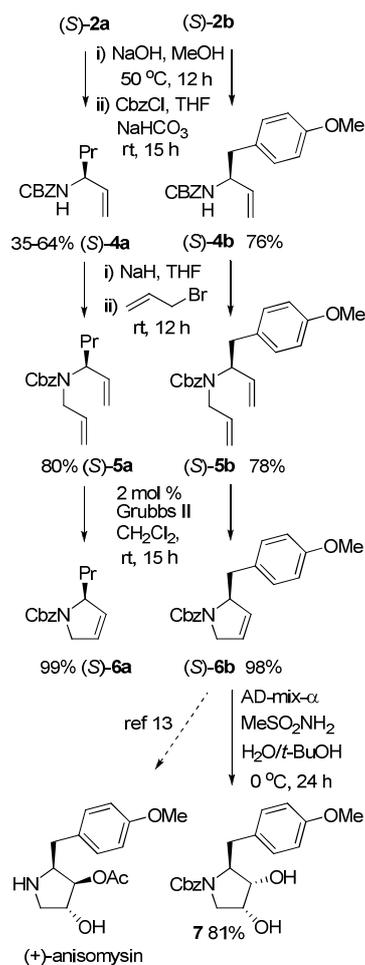
**Scheme 2.** COP-Cl catalysed allylic imidate rearrangements.



We have previously reported that the rearrangement of trichloroacetimidate **1a** catalysed by just 0.25 mol % of (*S<sub>p</sub>R*)-**3** in acetonitrile at 70 °C resulted in the isolation of (*S*)-**2a** in 90% yield and 92% ee (Scheme 2).<sup>7d</sup> Due to the stability of the conjugate base of **2a**, the direct allylation

of this compound proved to be low yielding.<sup>11</sup> Instead, following facile hydrolysis of the trichloroacetamide and subsequent Cbz-protection to give (*S*)-**4a** (Scheme 3), allylation proceeded satisfactorily to give amino diene (*S*)-**5a**. Application of 2 mol % of Grubbs' 2<sup>nd</sup> generation catalyst resulted in an essentially quantitative conversion into unsaturated pyrrolidine (*S*)-**6a**.

**Scheme 3.** The synthesis of 3,4-dehydropyrrolidines and application to the synthesis of protected azasugar **7**.



This methodology was extended to the formal synthesis of (+)-anisomysin starting from the (*E*)-4-(4'-methoxyphenyl)but-2-enol<sup>12</sup> derived trichloroacetimidate **1b**. The use of *S<sub>p</sub>R*-**3** at a catalyst loading of 0.75 mol % gave (*S*)-**2b** in high yield and with an ee of 91% (Scheme 2). Subsequent transformations as before resulted in the isolation of (*S*)-**6b** with an overall yield of 58% (Scheme 3). This compound, previously synthesised by the use of a valine-based chiral formamidine as a chiral auxiliary, was reported as an intermediate in the synthesis of (+)-

(7) (a) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412-12413. (b) Kirsch, S. F.; Overman, L. E.; Watson, M. P. *J. Org. Chem.* **2004**, *69*, 8101-8104. (c) Watson, M. P.; Overman, L. E.; Bergman, R. G. *J. Am. Chem. Soc.* **2007**, *129*, 5031-5044. (d) Nomura, H.; Richards, C. J. *Chem. Eur. J.* **2007**, *13*, 10216-10224.

(8) (a) Stevens, A. M.; Richards, C. J. *Organometallics*, **1999**, *18*, 1346-1348. (b) Anderson, C. E.; Kirsch, S. F.; Overman, L. E.; Richards, C. J.; Watson, M. P. *Org. Synth.* **2007**, *84*, 148-155.

(9) First reported at the 236<sup>th</sup> ACS National Meeting, Philadelphia, PA, ORGN 460.

(10) The application of sequential (*S*)-COP-Cl catalysed allylic imidate rearrangement and RCM was recently reported for the synthesis of 1-trichloroacetamidocyclohex-2-ene: Swift, M. D.; Sutherland, A. *Org. Lett.* **2007**, *9*, 5239-5242.

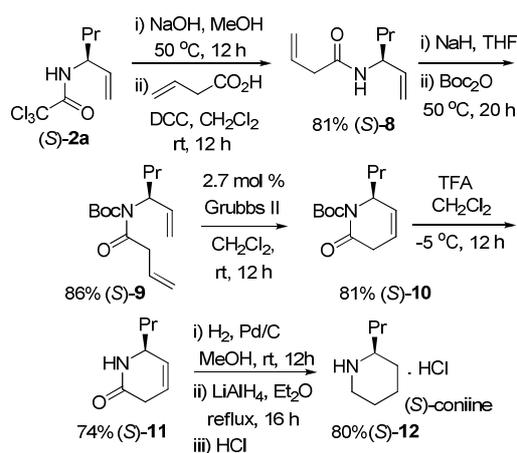
(11) The highest yield obtained was 47% using sodium hydride, allyl bromide and 18-crown-6.

(12) Taber, D. F.; Sikkander, M. I.; Berry, J. F.; Frankowski, K. J. *J. Org. Chem.* **2008**, *73*, 1605-1607.

anisomycin.<sup>13</sup> Dihydroxylation of (*S*)-**6b** with AD-mix- $\alpha$  gave (*2S,3S,4R*)-**7** as a single diastereoisomer after purification by chromatography.<sup>14,15</sup> Enantiomeric (*2R,3R,4S*)-2-epidesacetylanisomycin has previously been identified as a nanomolar  $\alpha$ -galactosidase inhibitor.<sup>16</sup>

With the objective of synthesising a piperidine analogue of the unsaturated pyrrolidine (*S*)-**6a**, it was found that the homoallylation of (*S*)-**4a** with 3-butenylbromide was unsuccessful. Instead hydrolysis of trichloroacetamide (*S*)-**2a** was followed by DCC mediated acylation with but-3-enoic acid to give (*S*)-**8** (Scheme 4). Combination with 7 mol % of Grubbs' 2<sup>nd</sup> generation catalyst resulted in the direct formation of (*S*)-**11** (70% yield), but reducing the catalyst loading led to a significant deterioration in yield. This problem was partly circumvented by NH to NBoc conversion to give (*S*)-**9**, RCM with 2.7 mol % catalyst, and subsequent TFA mediated deprotection to give (*S*)-**11** in 52% overall yield. Alkene hydrogenation gave a known intermediate in the synthesis of (*S*)-coniine **12**,<sup>17</sup> and this alkaloid was isolated in 80% yield as a hydrochloride salt following subsequent amide reduction.

**Scheme 4.** Synthesis of the 4,5-dehydropiperidinone framework and (*S*)-coniine.



The extension of this methodology to the synthesis of bicyclic indolizidine and quinolizidine frameworks required the replacement of the propyl group of allylic

(13) (a) Meyers, A. I.; Dupre, B. *Heterocycles* **1987**, *25*, 113-116. (b) Schumacher, D. P.; Hall, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 6076-6080.

(14) AD-mix- $\alpha$  was used for convenience as this reaction is primarily under substrate control. AD-mix- $\beta$  also resulted in the formation of **7**, but in a lower yield, 45%. AD-mix- $\alpha$  or  $\beta$  gave the same diastereoisomer and in higher diastereoselectivity than OsO<sub>4</sub>/NMO for a related dihydroxylation yielding a 1,2-dihydroxyindolizidine derivative: Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774-7780.

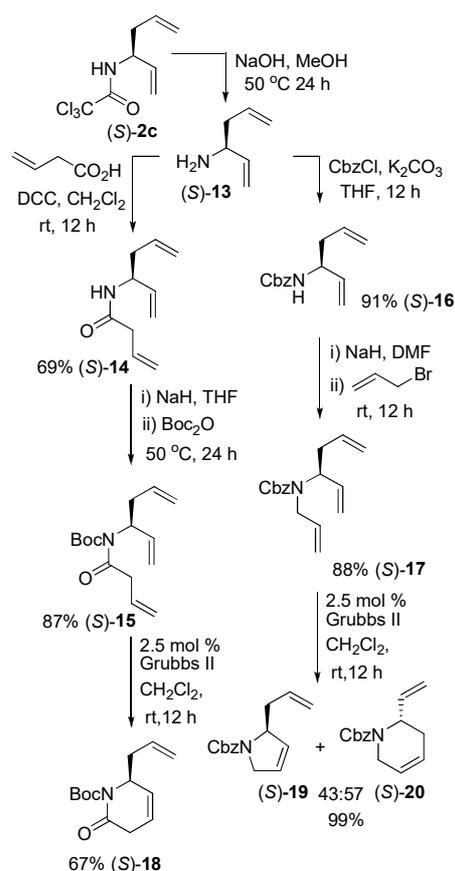
(15) Dihydroxylation facial stereoselectivity was assigned by analogy to related reactions with 2-substituted-2,5-dihydropyrroles. See reference 14 and: Martín, R.; Alcón, M.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2002**, *67*, 6896-6901.

(16) Chapman, T. M.; Courtney, S.; Hay, P.; Davis, B. G. *Chem. Eur. J.* **2003**, *9*, 3397-3414.

(17) Burke, A. J.; Davies, S. G.; Garner, A. C.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Vickers, R. *J. Org. Biomol. Chem.* **2004**, *2*, 1387-1394.

amide **2a** with a propenyl substituent, which can then be used in a RCM reaction for the generation of a second five or six-membered ring. To this end we have demonstrated previously the application of the COP-Cl catalysed allylic imidate rearrangement to the synthesis of (*S*)-**2c** (68% yield, 84% ee).<sup>7d</sup> Following hydrolysis to (*S*)-**13**, a protecting group and a third alkene containing moiety was introduced using the methodologies already described in Schemes 4 and 3 to give (*S*)-**15** and (*S*)-**17** respectively (Scheme 5).

**Scheme 5.** Synthesis and ring-closing metathesis of trienes **17** and **19**.



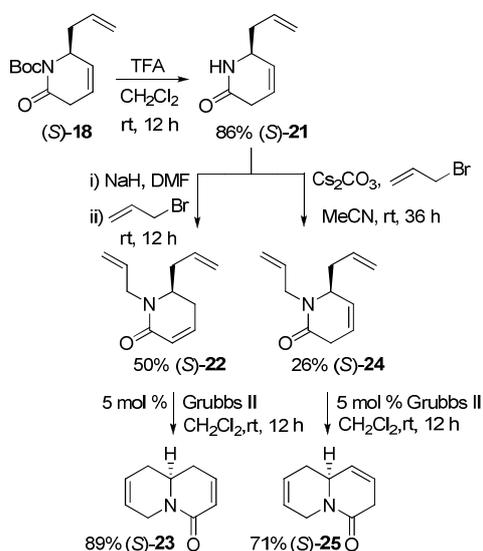
On addition of Grubbs' 2<sup>nd</sup> generation catalyst (*S*)-**15** cyclised to give only the six-membered derivative (*S*)-**18** and none of the four and seven-membered alternatives. In contrast the RCM reaction of (*S*)-**17** resulted in the generation of both the five and six-membered products (*S*)-**19** and (*S*)-**20** in a 3:4 ratio.<sup>18</sup> This ratio of products remained the same during the course of the reaction. However, after standing at room temperature in the presence of the catalyst for approximately two months the ratio of (*S*)-**19** and (*S*)-**20** was 1:2. The latter observation points to the initial 3:4 product ratio being a consequence

(18) These were identified by the characteristic ddd pattern for CHCH=CH<sub>2</sub> in the <sup>1</sup>H NMR spectrum of (*S*)-**20**.

of kinetic control;<sup>19</sup> a combination of any difference in the reactivity of the three mono-substituted alkenes, and five versus six membered ring formation for the one alkene where these two options are available.

The synthesis of an unsaturated quinolizidinone framework was completed as outlined in Scheme 6. Removal of the Boc group from (*S*)-**18** was followed by allylation of (*S*)-**21** employing sodium hydride as the base. This resulted in the isolation of the conjugated enamide (*S*)-**22** which underwent RCM to give (*S*)-**23**.<sup>20</sup> Double bond isomerisation was avoided by the use of caesium carbonate as the base which resulted in a low yield of (*S*)-**24**, which in turn led to the isolation of (*S*)-**25** following RCM.<sup>21</sup>

**Scheme 6.** Synthesis of the quinolizidinone framework.



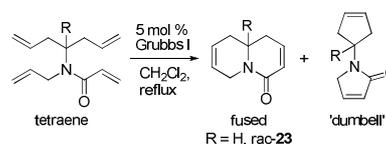
Although an analogous methodology with intermediates (*S*)-**19** and (*S*)-**20** could have been used for the synthesis of the indolizidine framework, we chose instead a related strategy based on the double cyclisation of a tetraene. This approach has been applied to the synthesis of racemic quinolizidinones and a challenge is achieving selectivity between the desired fused and undesired 'dumbbell' bicyclic products (Scheme 7).<sup>20</sup> With chiral tetraene (*S*)-**26**, generated from (*S*)-**17** by deprotection and coupling with acrylic acid (Scheme 8), we reasoned 'dumbbell' cyclisation would be avoided due to the reduced reactivity of the conjugated alkene, the initial cyclisation mirroring that of (*S*)-**17** (Scheme 5).

(19) Kinetic control with Grubbs' second generation catalyst has been observed in a number of macrocyclisation reactions: (a) Fürstner, A.; Müller, C. *Chem. Commun.* **2005**, 5583-5585. (b) Matsuya, Y.; Takayanagi, S.; Nemoto, H. *Chem. Eur. J.* **2008**, *14*, 5275-5281.

(20) Compounds **22** and **23** have previously been reported as racemates: (a) Ma, S.; Ni, B. *Org. Lett.* **2002**, *4*, 639-641. (b) Ma, S.; Ni, B. *Chem. Eur. J.* **2004**, *10*, 3286-3300.

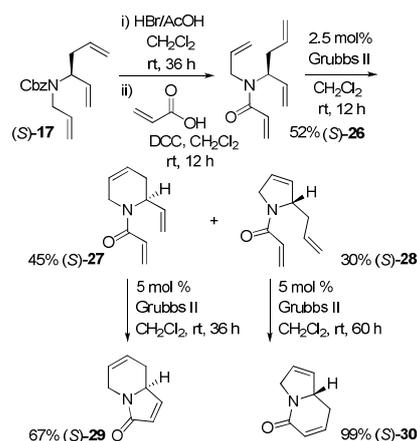
(21) Compounds **24** and **25** have previously been reported as racemates: Sośnicki, J. G. *Tetrahedron Lett.* **2006**, *47*, 6809-6812.

**Scheme 7.** A double RCM strategy for the synthesis of racemic quinolizidinones (reference 20).



Accordingly, exposure to 2.5 mol % of Grubbs' 2<sup>nd</sup> generation catalyst resulted in a 1.5:1 ratio of (*S*)-**27** and (*S*)-**28**. Following separation and an increase in the catalyst loading, the new indolizidinone (*S*)-**29** and the known indolizidinone (*S*)-**30**<sup>22</sup> were generated without any cross-contamination, further evidence that the initial cyclisation proceeds under kinetic control.

**Scheme 8.** A double RCM strategy for the synthesis of scalemic indolizidinones.



In summary, the combination of a catalytic asymmetric allylic imidate rearrangement with a catalytic ring-closing metathesis provides rapid access to a range of unsaturated nitrogen heterocycles, versatile building blocks for the synthesis of natural products and related compounds.

**Acknowledgment** We thank the EPSRC National Mass Spectrometry Centre (University of Wales, Swansea), and Prof. Sośnicki (Technical University of Szczecin, Poland) for <sup>13</sup>C NMR spectral data for **24** and **25**.

**Supporting Information Available:** Synthesis and characterisation data for all the compounds reported, and the method of ee determination for compound **2b**. This

(22) Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371-382.

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<http://pubs.acs.org>.