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Asymmetric Synthesis of Unsaturated Monocyclic and Bicyclic Nitrogen Heterocycles

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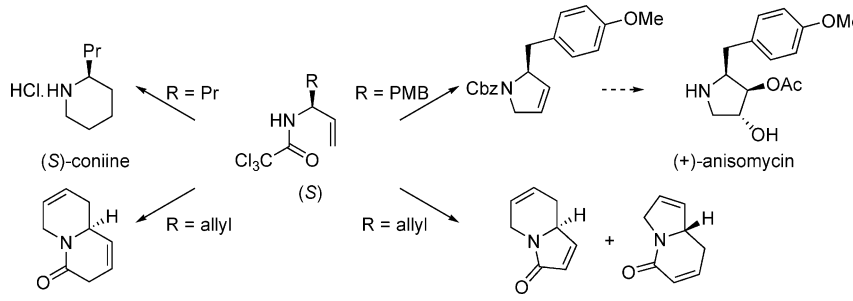
ABSTRACT



Hydrolysis of scalemic trichloroacetamides $Cl_3CCONHCH(R)CHCH_2$ 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 of (*S*)-coniine (R = Pr) and a formal synthesis of (+)-anisomycin (R = *p*-$MeOC_6H_4$). Extension of this methodology with R = CH_2CHCH_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.[1] Not least among the categories of compounds synthesized 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.[2] Although desymmetrizing RCM reactions are now well established for the synthesis of nonracemic compounds,[3] the asymmetric syntheses of chiral five- and six-membered-ring alkaloids generally employ scalemic amino dienes derived from a variety of chiral pool and asymmetric catalysis sources.[4] Within the latter category, transition-metal-catalyzed allylic amination reactions have been extensively investigated.[5] An alternative and highly enantioselective method for the synthesis of chiral allylic amines is the allylic imidate (or Overman) rearrangement

(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. Catal.* **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.; Grandclaudon, 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.

(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.

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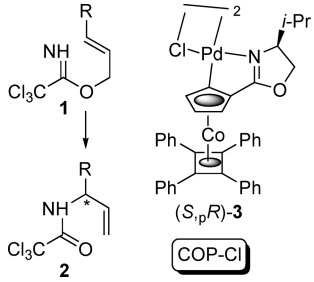
of trifluoroacetimidates[6] and trichloroacetimidates **1**,[7] catalyzed by the chloride-bridged cobalt oxazoline palladacycle **3** (Scheme 1).[8] In this paper, we illustrate the use of the

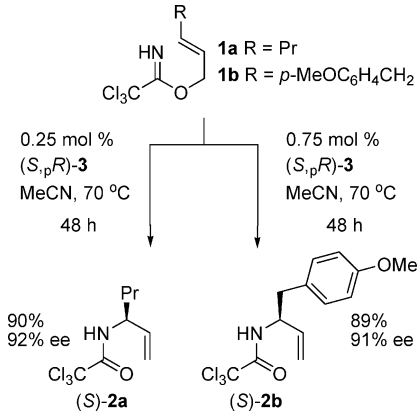
Scheme 1. Allylic Imidate Rearrangement and Catalyst **3**



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.[9,10]

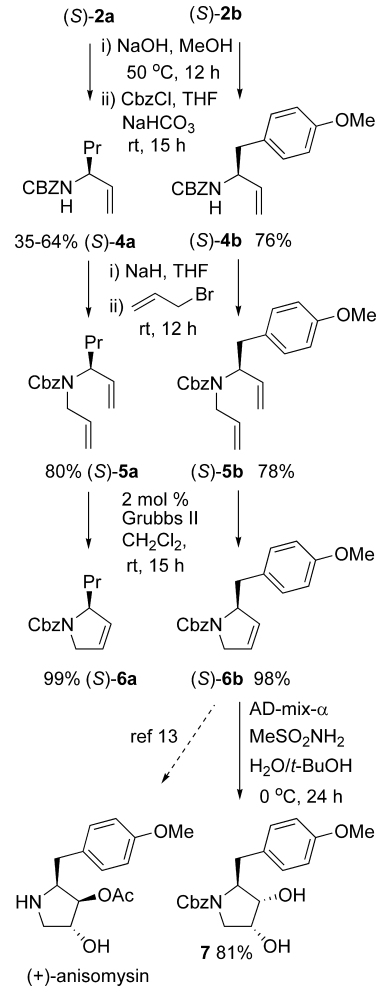
We have previously reported that the rearrangement of trichloroacetimidate **1a** catalyzed by just 0.25 mol % of (*S*,p*R*)-**3** in acetonitrile at 70 °C resulted in the isolation of (*S*)-**2a** in 90% yield and 92% ee (Scheme 2).[7d] Due to the

Scheme 2. COP-Cl-Catalyzed Allylic Imidate Rearrangements



stability of the conjugate base of **2a**, the direct allylation of this compound proved to be low yielding.[11] Instead, following facile hydrolysis of the trichloroacetamide and subsequent Cbz-protection to give (*S*)-**4a** (Scheme 3), allylation pro-

Scheme 3. Synthesis of 3,4-Dehydropyrrolidines and Application to the Synthesis of Protected Azasugar **7**



ceeded satisfactorally to give amino diene (*S*)-**5a**. Application of 2 mol % of Grubbs' second-generation catalyst resulted in an essentially quantitative conversion into unsaturated pyrrolidine (*S*)-**6a**.

This methodolgy was extended to the formal synthesis of (+)-anisomysin starting from the (*E*)-4-(4′-methoxyphenyl)-but-2-enol[12]-derived trichloroacetimiate **1b**. The use of (*S*,p*R*)-**3** at a catalyst loading of 0.75 mol % gave (*S*)-**2b** in high yield 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 synthesized by the use of a valine-based chiral formamidine as a chial auxiliary, was reported as an intermediate in the synthesis of (+)-anisomysin.[13] Dihydroxylation of (*S*)-**6b** with AD-mix-α gave (2*S*,3*S*,4*R*)-**7** as a single diastereoisomer after purification by chromatography.[14,15] Enantiomeric (2*R*,3*R*,4*S*)-2-epidesacetylanisomycin has previously been identified as a nanomolar α-galactosidase inhibitor.[16]

(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 236th ACS National Meeting, Philadelphia, PA, ORGN 460.

(10) The application of sequential (*S*)-COP-Cl-catalyzed 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.

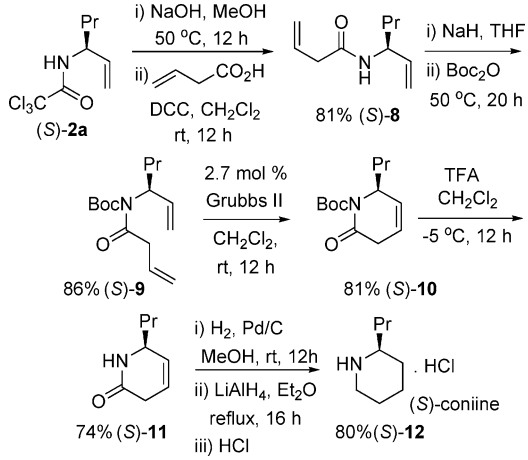
(11) The highest yield obtained was 47% using sodium hydride, allyl bromide, and 18-crown-6.

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

(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.

With the objective of synthesizing a piperidine analogue of the unsaturated pyrrolidine (*S*)-**6a**, it was found that the homoallylation of (*S*)-**4a** with 3-butenyl bromide 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

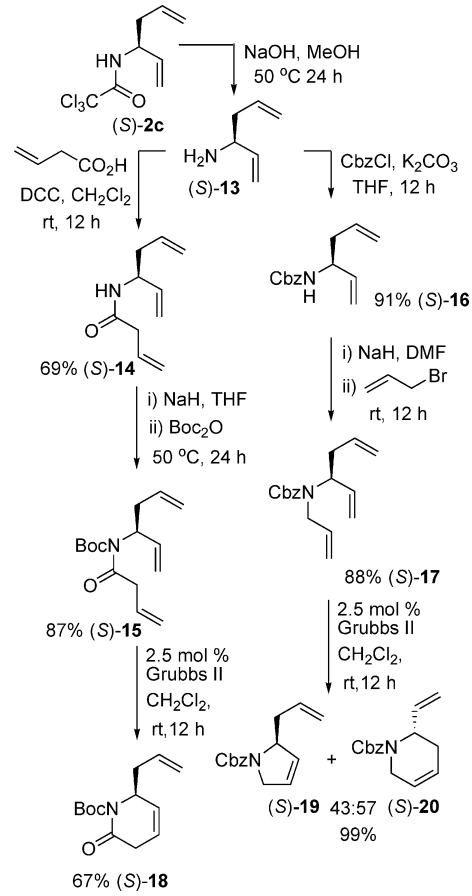
Scheme 4. Synthesis of the 4,5-Dehydropiperidinone Framework and (*S*)-Coniine



Grubbs' second-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**,[17] and this alkaloid was isolated in 80% yield as a hydrochloride salt following subsequent amide reduction.

The extension of this methodology to the synthesis of bicyclic indolizidine and quinolizidine frameworks required the replacement of the propyl group of allylic 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-catalyzed allylic imidate rearrangement to the synthesis of (*S*)-**2c** (68% yield, 84% ee).[7d] Following hydrolysis to (*S*)-**13**, a protecting group and a third alkene-containing moiety were 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' second-generation catalyst, (*S*)-**15** cyclized 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.[18] 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 2 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 of kinetic control;[19] a combination of any difference in the reactivity of the three monosubstituted alkenes and five- versus six-membered ring formation for the one alkene where these two options are available.

(14) AD-mix-α was used for convenience as this reaction is primarily under substrate control. AD-mix-β also resulted in the formation of **7**, but in a lower yield, 45%. AD-mix-α or β gave the same diastereoisomer and in higher diastereoselectivity than OsO_4/NMO for a related dihyroxylation 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 ref 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.

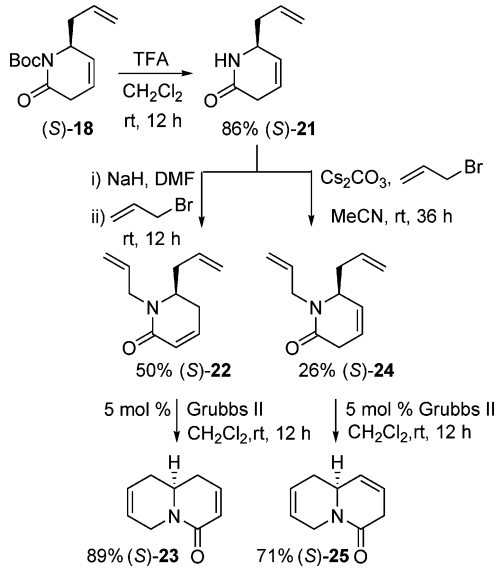
(17) Burke, A. J.; Davies, S. G.; Garner, A. C.; McCarthy, T. D.; Roberts, P. M.; Smith, A. D.; Rodriguez-Solla, H.; Vickers, R. J. *Org. Biomol. Chem.* **2004**, *2*, 1387–1394.

(18) These were identified by the characteristic ddd pattern for CHC*H*=CH_2 in the ^{1}H NMR spectrum of (*S*)-**20**.

(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.

The synthesis of an unsaturated quinolizidinone framework was completed as outlined in Scheme 6. Removal of the Boc

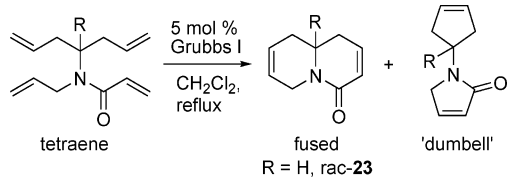
Scheme 6. Synthesis of the Quiniolizidinone Framework



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**.[20] Double-bond isomerization was avoided by the use of cesium 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.[21]

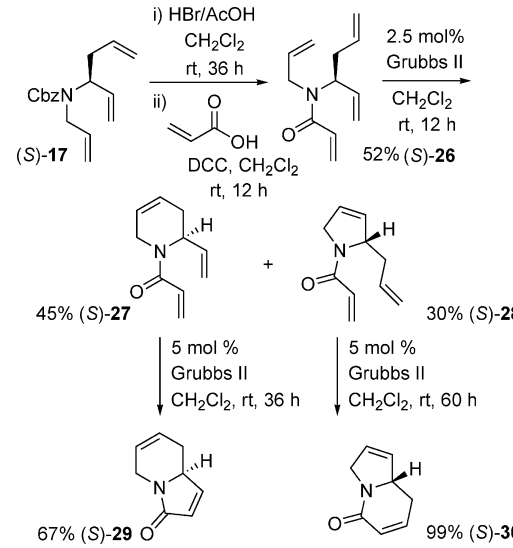
Although an analogous methodology with intermediates (*S*)-**19** and (*S*)-**20** could have been used for the synthesis of the indolizidine framework, we chose instead a related strategy based on the double cyclization of a tetraene. This approach has been applied to the synthesis of racemic quinolizidinones, and a challenge is achieving selectivity between the desired fused and undesired "dumbell" bicyclic products (Scheme 7).[20] With chiral tetraene (*S*)-**26**, generated

Scheme 7. Double-RCM Strategy for the Synthesis of Racemic Quinolizidinones[20]



from (*S*)-**17** by deprotection and coupling with acrylic acid (Scheme 8), we reasoned "dumbell" cyclization would be

Scheme 8. Double-RCM Strategy for the Synthesis of Scalemic Indolizidinones



avoided due to the reduced reactivity of the conjugated alkene, the initial cyclization mirroring that of (*S*)-**17** (Scheme 5).

Accordingly, exposure to 2.5 mol % of Grubbs' second-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 indolzidinone (*S*)-**29** and the known indolzidinone (*S*)-**30**[22] were generated without any cross-contamination, further evidence that the initial cyclization proceeds under kinetic control.

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, versitile 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 ^{13}C NMR spectral data for **24** and **25**.

Supporting Information Available: Synthesis and characterization data for all compounds reported and the method of ee determination for compound **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(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.

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