ORGANIC LETTERS

2010
Vol. 12, No. 14
3152−3155

Syntheses of *trans*-SCH-A and *cis*-SCH-A via a Stereodivergent Cyclopropanation Protocol

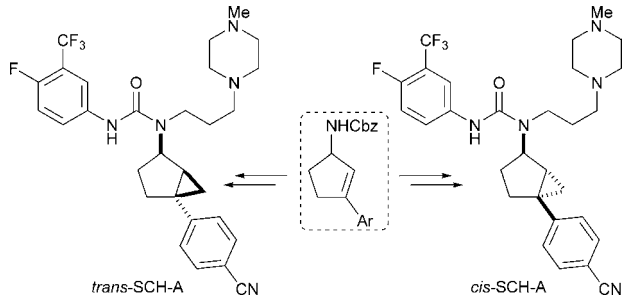
Kristína Csatayová, Stephen G. Davies,* James A. Lee, Kenneth B. Ling, Paul M. Roberts, Angela J. Russell, and James E. Thomson

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

steve.davies@chem.ox.ac.uk

Received May 5, 2010

ABSTRACT



A highly diastereoselective cyclopropanation protocol has been employed in the syntheses of *trans*-SCH-A and *cis*-SCH-A. This strategy encompasses a stereodivergent procedure for the preparation of *syn*- and *anti*-cyclopropane diastereoisomers in high dr from a common allylic carbamate precursor.

The cyclopropane motif is found in a wide range of natural products and biologically significant molecules,[1] with the conversion of an olefin into a cyclopropane using the Simmons−Smith reaction being one of the most widely used methods to access this structural unit.[2,3] Diastereoselective cyclopropanation relying upon delivery of the incoming methylene group by the binding of an allylic functional group to the zinc reagent[4] has been a common strategy for the stereoselective synthesis of cyclopropanes.[5] As part of an ongoing research program directed toward the chemo- and stereoselective functionalization of allylic amines at the olefin,[6] we became interested in the potential of allylic amines and their derivatives as substrates for cyclopropanation. Within this area, we have recently reported the stereodivergent cyclopropanation of allylic carbamate **1**, which gave either *syn*-**2** in >99:1 dr and 67% isolated yield

(1) For instance, see: (a) Patai, S.; Rappoport, Z. *The Chemistry of the Cyclopropyl Group*; Wiley & Sons: New York, 1987. (b) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589. (c) Faust, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251.

(2) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.

(3) New classes of highly reactive zinc carbenoids have been developed, and the substrate scope of the reaction has become immensely broad. See: (a) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621. (b) Charette, A. B.; Beauchemin, A.; Francoeur, S. *J. Am. Chem. Soc.* **2001**, *123*, 8139. (c) Lorenz, J. C.; Long, J.; Yang, Z.; Xue, S.; Xie, Y.; Shi, Y. *J. Org. Chem.* **2004**, *69*, 327. (d) Charette, A.; Beauchemin, A. *Org. React.* **2001**, *58*, 1. (e) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (f) Voituriez, A.; Zimmer, L. E.; Charette, A. B. *J. Org. Chem.* **2010**, *75*, 1244.

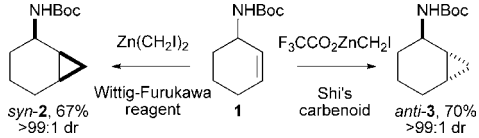
(4) (a) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254. (b) Kaye, P. T.; Molema, W. E. *Chem. Commun.* **1998**, 2479. (c) Marsh, E. A.; Hemperly, S. B.; Nelson, K. A.; Heidt, P. C.; Deusen, S. V. *J. Org. Chem.* **1990**, *55*, 2045. (d) Morikawa, T.; Sasaki, H.; Hanai, R.; Shibuya, A.; Taguchi, T. *J. Org. Chem.* **1994**, *59*, 97. (e) Evans, D. A.; Burch, J. D. *Org. Lett.* **2001**, *3*, 503. (f) Tanaka, K.; Uno, H.; Osuga, H.; Suzuki, H. *Tetrahedron: Asymmetry* **1994**, *5*, 1175. (g) Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986.

(5) Competing formation of a zinc-complexed ammonium ylide often thwarts cyclopropanation. For example, see: (a) Wittig, G.; Schwarzenbach, K. *Liebigs Ann. Chem.* **1961**, *650*, 1. (b) Aggarwal, V. K.; Fang, G. Y.; Charmant, J. P. H.; Meek, G. *Org. Lett.* **2003**, *5*, 1757.

10.1021/ol101295t © 2010 American Chemical Society
Published on Web 06/16/2010

upon treatment with $Zn(CH_2I)_2$ (the Wittig−Furukawa reagent, derived from Et_2Zn and CH_2I_2) or *anti*-**3** in >99:1 dr and 70% isolated yield upon treatment with $F_3CCO_2ZnCH_2I$ (Shi's carbenoid, derived from Et_2Zn, CH_2I_2, and TFA) (Scheme 1).[7]

Scheme 1. Stereodivergent Cyclopropanation of **1**



In this manuscript, we report the application of this methodology to the synthesis of the melanin-concentrating hormone receptor 1 (MCH-R1) antagonist *trans*-SCH-A **4**, which was developed by Schering−Plough,[8] and its epimer *cis*-SCH-A **5**. In their synthesis of *trans*-SCH-A **4**, Schering−Plough effected the Simmons−Smith cyclopropanation of an allylic alcohol, followed by oxidation of the alcohol to give the corresponding ketone. Subsequent diastereoselective reductive amination was then carried out to install the nitrogen atom.[8a] To date, there have not been any other syntheses of *trans*-SCH-A **4** reported, although an elegant synthesis of *cis*-SCH-A **5**, involving an intramolecular α-lithiated aziridine cyclopropanation process, has recently been reported by Hodgson et al. (Figure 1).[9]

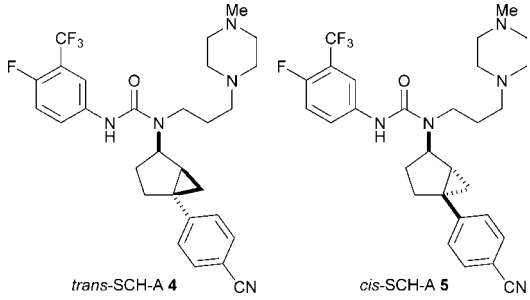


Figure 1. Structures of *trans*-SCH-A **4** and *cis*-SCH-A **5**.

Our strategy for the syntheses of *trans*-SCH-A **4** and *cis*-SCH-A **5** involved elaboration of the requisite diastereoisomers of cyclopropane **6**, which could in turn be accessed via the stereodivergent cyclopropanation of allylic carbamate **8**, followed by deprotection of the nitrogen atom. It was envisaged that if a *p*-silyloxymethyl group was incorporated in the C(3)-aryl substituent it would remain inert during the synthesis while allowing for the *p*-cyano group within **4** and **5** to be revealed (Figure 2).

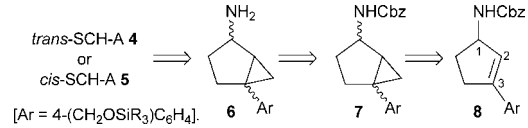
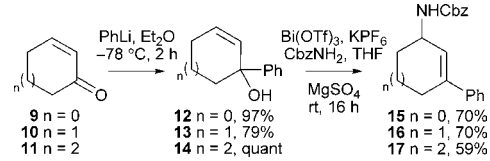


Figure 2. Retrosynthetic analyses of **4** and **5**.

A series of C(3)-phenyl-substituted allylic carbamates **15**−**17** were selected as model systems in which to screen both the effects of C(3)-aryl substitution and ring size on the stereochemical outcome of our stereodivergent cyclopropanation protocol. Allylic carbamates **15**−**17** were produced in two steps from the corresponding cyclic enones **9**−**11** via treatment with PhLi to give alcohols **12**−**14** followed by bismuth-catalyzed S_N' substitution of **12**−**14** with benzyl carbamate[10] to give **15**−**17** in 55−68% overall yield (Scheme 2).

Scheme 2. Synthesis of Allylic Carbamates **15**−**17**



In accordance with our previous studies concerning the stereodivergent cyclopropanation of allylic carbamate **1**, treatment of **16** with $Zn(CH_2I)_2$ gave *syn*-**19** in 84% yield and >99:1 dr. Similar treatment of **16** with $F_3CCO_2Zn(CH_2I)_2$ gave *anti*-**22** in 99% yield and >99:1 dr (Scheme 3). The relative configuration within *syn*-**19**

(6) (a) Aciro, C.; Claridge, T. D. W.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3751. (b) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3762. (c) Bond, C. W.; Cresswell, A. J.; Davies, S. G.; Fletcher, A. M.; Kurosawa, W.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *J. Org. Chem.* **2009**, *74*, 6735. (d) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thomson, J. E. *Org. Lett.* **2010**, *12*, 136.

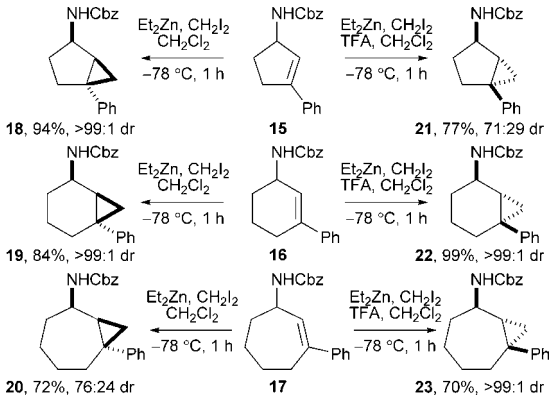
(7) Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Chem. Commun.* **2007**, 4029.

(8) (a) McBriar, M. D.; Guzik, H.; Xu, R.; Paruchova, J.; Li, S.; Palani, A.; Clader, J. W.; Greenlee, W. J.; Hawes, B. E.; Kowalski, T. J.; O'Neill, K.; Spar, B.; Weig, B. *J. Med. Chem.* **2005**, *48*, 2274. (b) McBriar, M. D.; Guzik, H.; Shapiro, S.; Xu, R.; Paruchova, J.; Clader, J. W.; O'Neill, K.; Hawes, B.; Sorota, S.; Margulis, M.; Tucker, K.; Weston, D. J.; Cox, K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4262. (c) Kowalski, T. J.; Spar, B. D.; Weig, B.; Farley, C.; Cook, J.; Ghibaudi, L.; Fried, S.; O'Neill, K.; Del Vecchio, R. A.; McBriar, M.; Guzik, H.; Clader, J.; Hawes, B. E.; Hwa, J. *Eur. J. Pharmacol.* **2006**, *535*, 182. (d) Kanuma, K.; Omodera, K.; Nishiguchi, M.; Funakoshi, T.; Chaki, S.; Nagase, Y.; Iida, I.; Yamaguchi, J.; Semple, G.; Tran, T.-A.; Sekiguchi, Y. *Bioorg. Med. Chem.* **2006**, *14*, 3307. (e) McBriar, M. D.; Guzik, H.; Shapiro, S.; Paruchova, J.; Xu, R.; Palani, A.; Clader, J. W.; Cox, K.; Greenlee, W. J.; Hawes, B. E.; Kowalski, T. J.; O'Neill, K.; Spar, B. D.; Weig, B.; Weston, D. J.; Farley, C.; Cook, J. *J. Med. Chem.* **2006**, *49*, 2294.

(9) Hodgson, D. M.; Humphreys, P. G.; Miles, S. M.; Brierley, C. A. J.; Ward, J. G. *J. Org. Chem.* **2007**, *72*, 10009.

(10) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.

Scheme 3. Stereodivergent Cyclopropanation of **15**−**17**



was unambiguously established via single-crystal X-ray analysis (Figure 3),[11] thus the relative configuration within *anti*-**22** could also be unambiguously assigned. These data indicate that the addition of a C(3)-aryl substituent does not adversely affect the sense of diastereoselectivity in this reaction manifold.

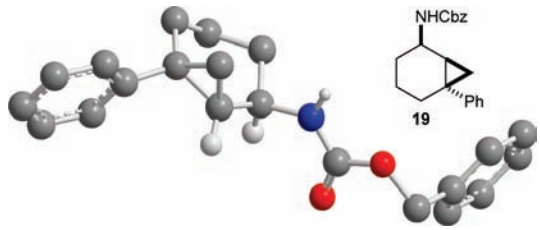
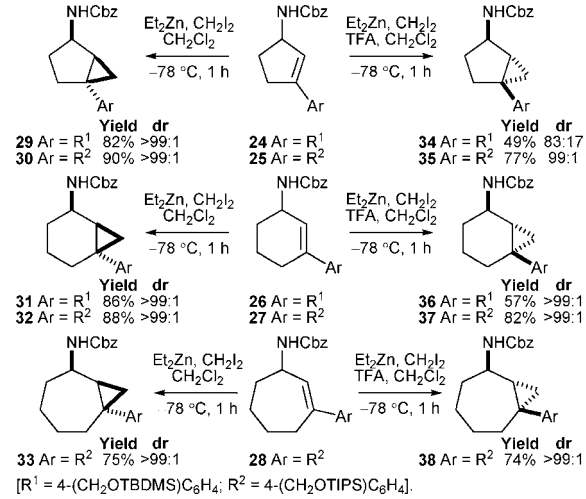


Figure 3. X-ray crystal structure of *syn*-**19** (some H-atoms have been omitted for clarity).

The stereodivergent cyclopropanation protocol was also found to be applicable to the corresponding five- and seven-membered ring analouges **15** and **17**, affording *syn*-cyclopropanes **18** and **20** as the major products upon treatment with $Zn(CH_2I)_2$ and *anti*-cyclopropanes **21** and **23** as the major products upon treatment with $F_3CCO_2Zn(CH_2I)_2$. With the exception of *syn*-**20** and *anti*-**21**, the cyclopropane products were isolated as single diastereoisomers (>99:1 dr) in each case (Scheme 3). The relative configurations within **18**, **20**, **21**, and **23** were assigned by analogy to those within *syn*-**19** and *anti*-**22**, and these assignments were further supported by ^{1}H NMR NOE analyses.

Subsequent studies focused upon the cyclopropanation of allylic carbamates **24**−**28**, incorporating C(3)-(*p*-silyloxymethyl)phenyl substituents, which were prepared in a directly analogous manner to the C(3)-phenyl model substrates **15**−**17**. In each case, treatment of **24**−**28** with $Zn(CH_2I)_2$ produced the corresponding *syn*-cyclopropanes **29**−**33** in >99:1 dr and good isolated yield. Similarly, treatment of **26**−**28** with $F_3CCO_2Zn(CH_2I)_2$ gave *anti*-cyclopropanes **36**−**38** as single diastereoisomers (>99:1 dr) in good isolated yield. Crucially, however, cyclopropanation of the five-membered ring substrates **24** and **25** with $F_3CCO_2ZnCH_2I$ showed improved levels of diastereoselectivity relative to the C(3)-phenyl-substituted model system (71:29 dr), with the *O*-TIPS protected derivative **35** being isolated in 77% yield and 99:1 dr (Scheme 4). The relative configurations

Scheme 4. Stereodivergent Cyclopropanation of **24**−**28**

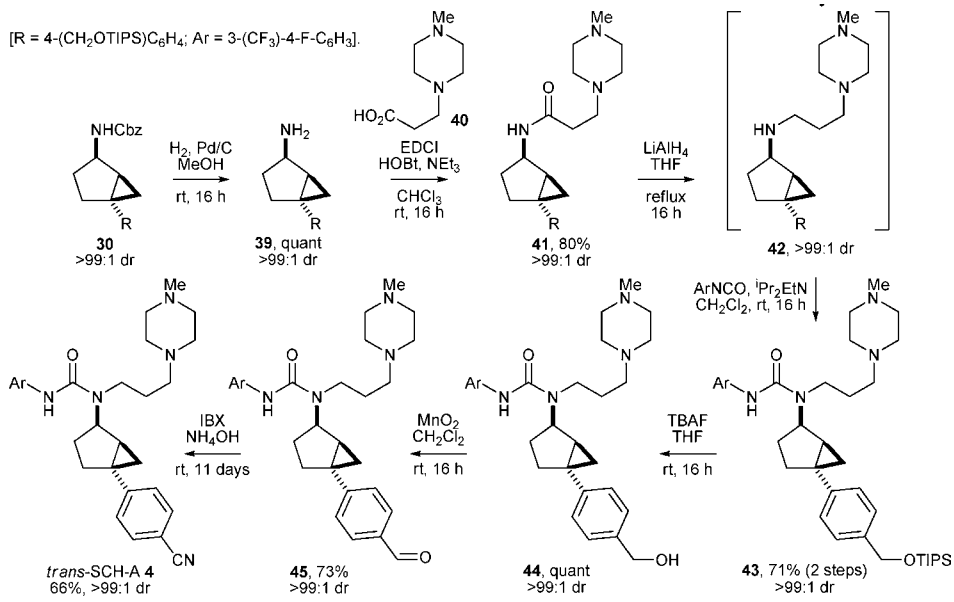


within cyclopropanes **29**−**38** were assigned by analogy to the model C(3)-phenyl-substituted systems; these assignments were also supported by ^{1}H NMR NOE analyses.

With diastereoisomerically pure (≥99:1 dr) samples of both *O*-TIPS protected cyclopropanes *syn*-**30** and *anti*-**35** in hand, their elaboration toward *trans*-SCH-A **4** and *cis*-SCH-A **5**, respectively, was undertaken. Hydrogenolysis of *syn*-**30** (>99:1 dr) gave primary amine **39** in quantitative yield, with no products arising from cleavage of the cyclopropane ring being observed. Coupling of **39** with carboxylic acid **40** (mediated by EDCI/HOBt) gave amide **41** in 80% yield and >99:1 dr after purification. Subsequent reduction of the amide functionality within **41** with $LiAlH_4$, followed by treatment with 4-fluoro-3-trifluoromethylphenyl isocyanate, gave urea **43** in 71% isolated yield (over 2 steps). *O*-TIPS deprotection of **43** was achieved upon treatment with 1.7 equiv of TBAF giving **44** in quantitative yield. Oxidation of the primary alcohol functionality within **44** with MnO_2 then gave aldehyde **45** in 73% isolated yield. Subsequent treatment of **45** with NH_4OH and 5.0 equiv of IBX for 11 days completed the synthesis of *trans*-SCH-A **4**, which was isolated as a single diastereoisomer (>99:1 dr) in 66% yield (Scheme 5). The ^{1}H NMR spectrum of our sample of *trans*-SCH-A **4** was found to be identical to that of an authentic sample provided by Schering−Plough (now Merck Research

(11) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 779449.

Scheme 5. Synthesis of *trans*-SCH-A **4**



Laboratories).[12,13] An analogous reaction sequence was also employed for the conversion of *anti*-**35** (99:1 dr) into *cis*-SCH-A **5** which was isolated in >99:1 dr and 14% overall yield (over 7 steps). The ^{1}H and ^{13}C NMR spectroscopic data for *cis*-SCH-A **5** were found to be in excellent agreement with those reported by Hodgson et al.[9] The assigned relative configurations within both *trans*-SCH-A **4** and *cis*-SCH-A **5** were also confirmed by ^{1}H NMR NOE analyses.

In conclusion, a highly chemo- and diastereoselective cyclopropanation protocol has been employed in the syntheses of *trans*-SCH-A (in 8 steps and 25% overall yield) and its epimer *cis*-SCH-A (in 8 steps and 11% overall yield) from a common allylic carbamate precursor. This strategy encompasses the stereodivergent preparation of both the *syn*- and *anti*-cyclopropane diastereoisomers in high dr from the corresponding cyclic allylic carbamate. Several further applications of this methodology are ongoing within our laboratory.

Acknowledgment. The authors would like to thank the Oxford Chemical Crystallography Service for the use of their X-ray diffractometers.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101295T

(12) Some major discrepancies exist between our ^{1}H NMR data for *trans*-SCH-A **4** and the ^{1}H NMR data for *trans*-SCH-A **4** which were originally reported by Schering−Plough (see ref 8a).

(13) We would like to thank Dr. J. W. Clader (Merck Research Laboratories) for providing a ^{1}H NMR spectrum of *trans*-SCH-A **4**.