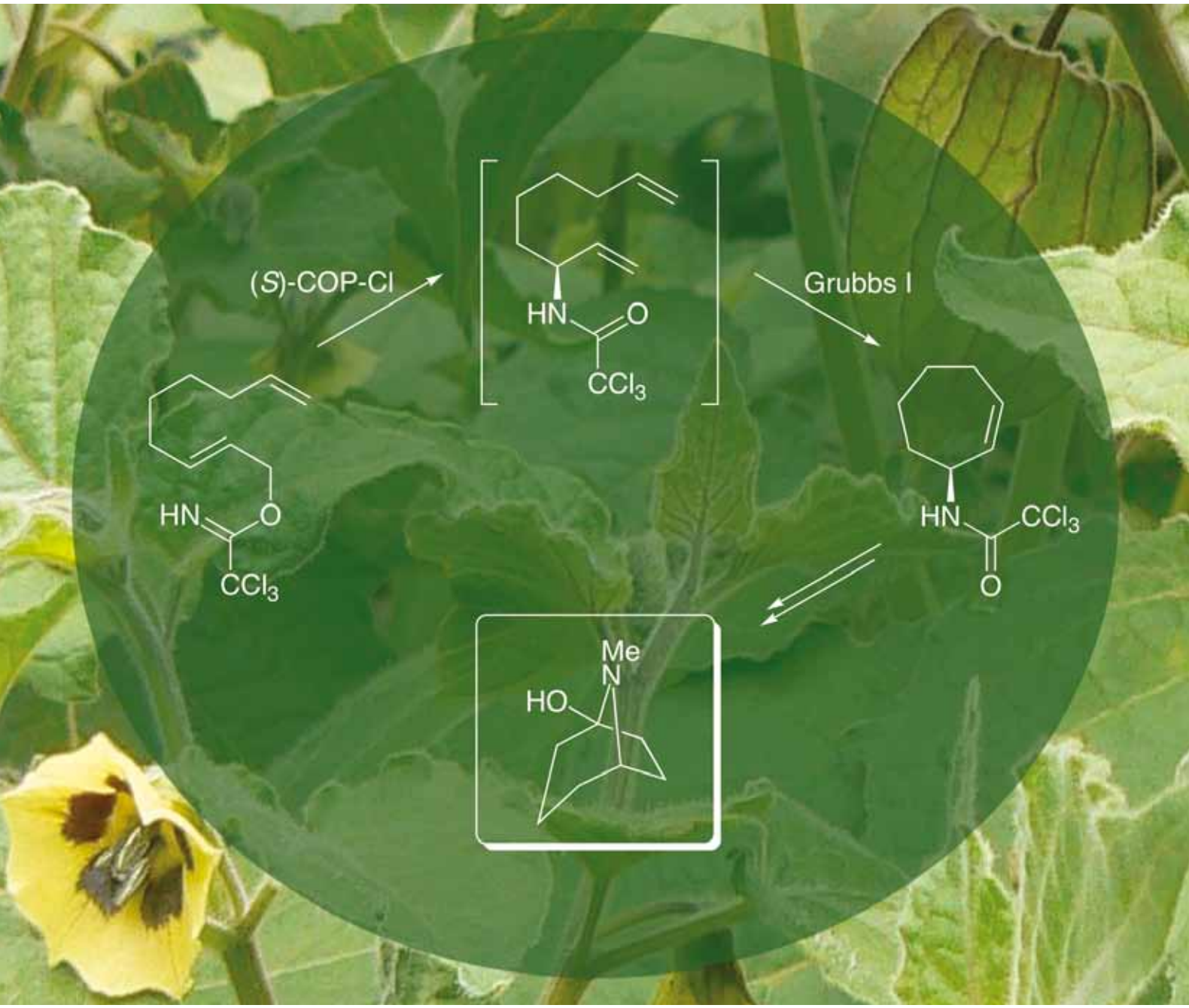
Organic & Biomolecular Chemistry

www.rsc.org/obc

Volume 7 | Number 13 | 7 July 2009 | Pages 2657–2820



ISSN 1477-0520

COMMUNICATION

Ahmed M. Zaed *et al.*

A stereoselective synthesis of (+)-physoperuvine using a tandem aza-Claisen rearrangement and ring closing metathesis reaction

Chemical Biology

In this issue...

1477-0520(2009)7:13;1-E

RSC Publishing

A stereoselective synthesis of (+)-physoperuvine using a tandem aza-Claisen rearrangement and ring closing metathesis reaction†

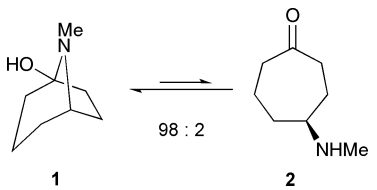
Ahmed M. Zaed, Michael D. Swift and Andrew Sutherland*

Received 14th April 2009, Accepted 6th May 2009
First published as an Advance Article on the web 13th May 2009
DOI: 10.1039/b907341h

A stereoselective synthesis of (+)-physoperuvine, a tropane alkaloid from *Physalis peruviana* Linne has been developed using a one-pot tandem aza-Claisen rearrangement and ring closing metathesis reaction to form the key amino-substituted cycloheptene ring.

Introduction

(+)-Physoperuvine **1** is a tropane alkaloid found in the leaves and roots of the Indian plant *Physalis peruviana* Linne.[1] Based on chemical and spectroscopic studies, the structure of (+)-physoperuvine was originally assigned as 3-methylaminocycloheptanone.[1] A re-investigation using primarily, X-ray crystallography allowed determination of the absolute configuration and showed that the structure is (*S*)-4-methylaminocycloheptanone **2**, which is in equilibrium with the bicyclic tautomer **1** (Scheme 1).[2,3] Analysis of the equilibrium using both CD and NMR spectroscopy revealed that (+)-physoperuvine exists almost entirely in the bicyclic form.[2,4]

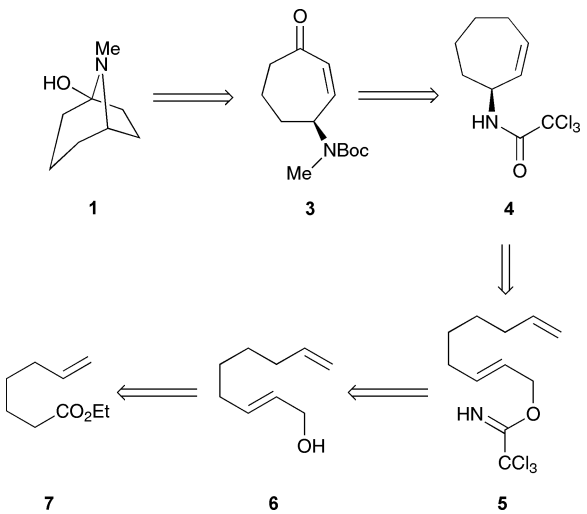


Scheme 1

Elucidation of the bicyclic hemiaminal structure of **1** has resulted in a number of stereoselective syntheses of (+)-physoperuvine and its enantiomer.[5] The groups of Ogasawara[5a] and Majewski[5b,c] synthesised (+)-physoperuvine by desymmetrisation of *meso*-intermediates while Wightman and co-workers synthesised (−)-physoperuvine by cycloaddition of cyclohepta-1,3-diene with an α-chloronitroso derived carbohydrate.[5d,e] Recently, we reported the highly efficient synthesis of 5-, 6-, 7- and 8-membered carbocyclic amides from allylic trichloroacetimidates using a one-pot tandem Overman rearrangement and ring-closing metathesis (RCM) reaction.[6] A stereoselective version of this process was also achieved for the preparation of *N*-(cyclohexenyl)-trichloroacetamides using chiral palladium(II)-catalysts.[6] In this paper, we report the first use of the asymmetric version of this one-pot tandem process for the highly efficient synthesis of an *N*-(cycloheptenyl)-trichloroacetamide and the elaboration of this carbocyclic amide to complete a novel total synthesis of (+)-physoperuvine.

Results and discussion

As outlined in Scheme 2, our strategy for synthesising **1** required the asymmetric synthesis of (*S*)-*N*-(cycloheptenyl)-trichloroacetamide **4**. It was proposed that this could be achieved using an asymmetric one-pot tandem Overman rearrangement and RCM reaction of allylic trichloroacetimidate **5**, which in turn could be easily prepared from commercially available ethyl 6-heptenoate **7** using standard procedures. After the one-pot process, the final stage would then involve an allylic oxidation of the cycloheptene ring leading to ketone **3**. Hydrogenation and deprotection of **3** would then give aminoketone **2**, which would cyclise to form (+)-physoperuvine **1**.

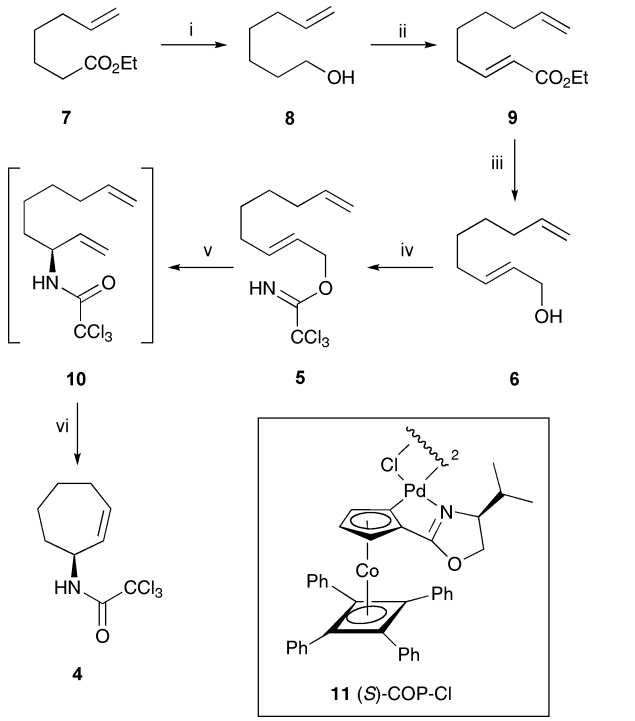


Scheme 2 Retrosynthesis of (+)-physoperuvine **1**.

Synthesis of key allylic trichloroacetimidate **5** started from commercially available ethyl 6-heptenoate **7** which was reduced to 6-hepten-1-ol **8** in 94% yield using DIBAL-H (Scheme 3). 6-Hepten-1-ol **8** was then subjected to a one-pot Swern oxidation and Horner–Wadsworth–Emmons reaction[7] which gave (*E*)-α,β-unsaturated ester **9** in 85% yield over the two steps. Allylic alcohol **6** was then formed by DIBAL-H reduction of **9** and this was converted to allylic trichloroacetimidate **5** using trichloroacetonitrile and catalytic amounts of DBU. With allylic trichloroacetimidate **5** in hand, this was then subjected to a one-pot Overman rearrangement and RCM reaction using commercially available

WestChem, Department of Chemistry, The Joseph Black Building, University of Glasgow, Glasgow, UK G12 8QQ. E-mail: andrews@chem.gla.ac.uk; Fax: +44 (0)141 330 4888; Tel: +44 (0)141 330 5936

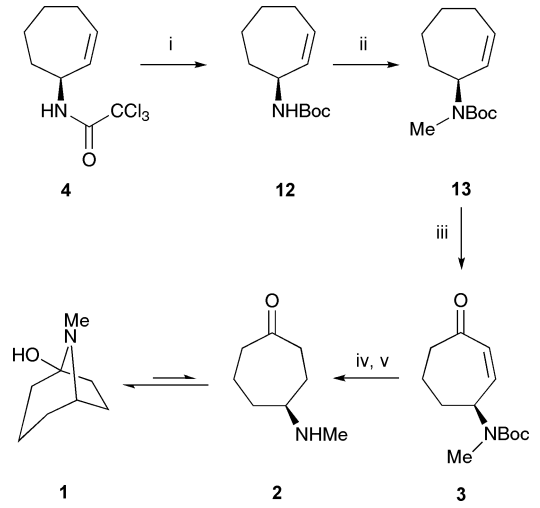
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all compounds. See DOI: 10.1039/b907341h



Scheme 3 *Reagents and conditions*: i. DIBAL-H (2.2 eq.), Et_2O, −78 °C to RT, 94%; ii. $(COCl)_2$, Et_3N, DMSO, CH_2Cl_2, −78 °C to RT, then triethyl phosphonoacetate, LiCl, DBU, MeCN, 85%; iii. DIBAL-H (2.2 eq.), Et_2O, −78 °C to RT, 100%; iv. DBU, Cl_3CCN, CH_2Cl_2; v. (*S*)-COP-Cl **11** (10 mol%), CH_2Cl_2, 45 °C; vi. Grubbs' 1st generation catalyst (10 mol%), Δ, 82% from **6**.

(*S*)-COP-Cl[8] **11** to catalyse the rearrangement and Grubbs' first generation catalyst to effect the RCM reaction. This gave (*S*)-*N*-(cycloheptenyl)-trichloroacetamide **4** in an excellent 82% yield from allylic alcohol **6** and in 84% ee.[9] The enantiomeric excess of **4** was improved to >99% on recrystallisation from a mixture of ethyl acetate and petroleum ether. It should be noted that the facile synthesis of dienol substrates such as **6** in combination with this one-pot tandem process allows the highly efficient and rapid synthesis of allylic carbocyclic amides (e.g. 66% overall yield of **4** from **7**).

The next stage of the synthesis of (+)-physoperuvine required introduction of the *N*-methyl group and this was initially attempted by methylating the amide of trichloroacetamide **4** using the standard conditions of sodium hydride and iodomethane.[10] However, treatment of **4** with sodium hydride led to hydrolysis of the trichloroacetamide functional group and recovery of the corresponding amine. This problem was easily overcome by the one-pot conversion of **4** to Boc-analogue **12** in quantitative yield (Scheme 4).[11] Subsequent methylation then proceeded smoothly to give **13** in 84% yield. The last key transformation in the synthesis of (+)-physoperuvine involved the allylic oxidation of the cycloheptene ring. While a number of general procedures do exist for the mild and efficient allylic and benzylic oxidation of organic compounds,[12] relatively few have been utilized for the oxidation of cycloheptenes.[13] Initial attempts of allylic oxidation of **13** utilised a manganese(III) acetate catalysed procedure with *t*-BuOOH as the oxidant under an atmosphere of oxygen.[12c] Despite investigating various conditions and increasing amounts of oxidant, this gave



Scheme 4 *Reagents and conditions*: i. 2 M NaOH then Boc_2O, 100%; ii. NaH, MeI, THF, 84%; iii. 10% Pd/C, *t*-BuOOH, K_2CO_3, CH_2Cl_2, 45%; iv. 10% Pd/C, H_2, MeOH, 66%; v. TFA, CH_2Cl_2, 60%.

α,β-unsaturated ketone **3** in only 22% yield. A second attempt at the allylic oxidation of **13** used a protocol reported by Yu and Corey which involved a palladium mediated oxidation with *t*-BuOOH as the oxidant under basic conditions.[12b] This gave α,β-unsaturated ketone **3** in an improved yield of 45%. Hydrogenation of **3** under standard conditions then gave the saturated ketone in 66% yield and TFA deprotection of the amine completed the eleven-step synthesis of (+)-physoperuvine **1**. The optical rotation and spectroscopic data of our synthetic material was in complete agreement with those reported for the naturally derived (+)-physoperuvine.[2–5]

Conclusions

In summary, we have developed a novel approach for the synthesis of the tropane alkaloid, (+)-physoperuvine using for the first time a highly efficient one-pot tandem Overman rearrangement and RCM reaction for the asymmetric preparation of a *N*-(cycloheptenyl)-trichloroacetamide.

Acknowledgements

The authors gratefully acknowledge financial support from the Libyan People's Bureau, London (studentship to A.M.Z.), EPSRC (studentship to M.D.S.) and the University of Glasgow.

References

1 (*a*) A. B. Ray, M. Sahai and P. D. Sethi, *Chem. Ind.*, 1976, 454; (*b*) M. Sahai and A. B. Ray, *J. Org. Chem.*, 1980, **45**, 3265.
2 A. B. Ray, Y. Oshima, H. Hikino and C. Kabuto, *Heterocycles*, 1982, **19**, 1233.
3 (*a*) A. R. Pinder, *J. Org. Chem.*, 1982, **47**, 3607; (*b*) A. T. McPhail and A. R. Pinder, *Tetrahedron*, 1984, **40**, 1661.
4 D. E. Justice and J. R. Malpass, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2559.
5 (*a*) K. Hiroya and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1995, 2205; (*b*) M. Majewski and R. Lazny, *Synlett*, 1996, 785; (*c*) M. Majewski, R. Lazny and A. Ulaczyk, *Can. J. Chem.*, 1997, **75**, 754; (*d*) A. Hall, P. D. Bailey, D. C. Rees and R. H. Wightman, *Chem.*

Commun., 1998, 2251; (*e*) A. Hall, P. D. Bailey, D. C. Rees, G. M. Rosair and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 2000, 329.
6 M. D. Swift and A. Sutherland, *Org. Lett.*, 2007, **9**, 5239.
7 (*a*) R. E. Ireland and D. W. Norbeck, *J. Org. Chem.*, 1985, **50**, 2198; (*b*) M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masumune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183.
8 (*a*) L. E. Overman, C. E. Owen, M. M. Pavan and C. J. Richards, *Org. Lett.*, 2003, **5**, 1809; (*b*) C. E. Anderson and L. E. Overman, *J. Am. Chem. Soc.*, 2003, **125**, 12412; (*c*) C. E. Anderson, L. E. Overman and M. P. Watson, *Org. Synth.*, 2005, **82**, 134; (*d*) M. P. Watson, L. E. Overman and R. G. Bergman, *J. Am. Chem. Soc.*, 2007, **129**, 5031.
9 The enantiomeric excess of compound **4** was determined by chiral HPLC. See, supplementary information for full details.
10 R. Bischoff, N. McDonald and A. Sutherland, *Tetrahedron Lett.*, 2005, **46**, 7147.
11 A. G. Jamieson and A. Sutherland, *Org. Lett.*, 2007, **9**, 1609.
12 For example, see: (*a*) T. Nagai, K. Ogawa, M. Morita, M. Koyama, A. Ando, T. Miki and I. Kumadaki, *Chem. Pharm. Bull.*, 1989, **37**, 1751; (*b*) J.-Q. Yu and E. J. Corey, *Org. Lett.*, 2002, **4**, 2727; (*c*) T. K. M. Shing, Y.-Y. Yeung and P. L. Su, *Org. Lett.*, 2006, **8**, 3149; (*d*) G. Pandey, K. N. Tiwari and V. G. Puranik, *Org. Lett.*, 2008, **10**, 3611; (*e*) E. C. McLaughlin, H. Choi, K. Wang, G. Chiou and M. P. Doyle, *J. Org. Chem.*, 2009, **74**, 730; (*f*) R. Martin, A. W. Schmidt, G. Theumer, T. Krause, E. V. Entchev, T. V. Kurzchalia and H.-J. Knölker, *Org. Biomol. Chem.*, 2009, **7**, 909.
13 (*a*) N. Chidambaram and S. Chandrasekaran, *J. Org. Chem.*, 1987, **52**, 5048; (*b*) J.-Q. Yu and E. J. Corey, *J. Am. Chem. Soc.*, 2003, **125**, 3232; (*c*) J.-Q. Yu, H.-C. Wu and E. J. Corey, *Org. Lett.*, 2005, **7**, 1415.

