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Stereoselective approaches to 2,3,6-trisubstituted piperidines. An enantiospecific synthesis of quinolizidine (−)-217A†

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The enantiospecific and diastereocontrolled total synthesis of alkaloid (−)-217A is described that employs a stepwise [3 + 3] annelation strategy and a piperidine 2,3-cyclopropanation–ring opening reaction as the key steps.

Quinolizidine alkaloid (−)-217A was isolated from the Madagascan frog *Mantellabaroni* in 1993 by Daly and co-workers,[1] and is a member of a wider class of alkaloids possessing a broad range of biological activities.[2] As amphibian sources generally provide only small quantities of such compounds, there has been widespread interest in the development of efficient synthetic routes to this family of alkaloid natural products. With specific regard to quinolizidine 217A, Pearson reported the first total synthesis of this compound in 1998.[3] Although a racemic synthesis, this study provided confirmation of the relative stereochemistry of this natural product. Since that time, three approaches to (−)-217A have been reported by the groups of Panek[4] and Danheiser,[5] with the most recent disclosure in 2010 by Lhommet *et al.*[6]

Recent studies in our laboratory have focused on the use of aziridines as three-atom components in a series of [3 + 3] annelation processes[7] for the stereoselective synthesis of piperidines.[8] During our methodology development, we have had the opportunity to test these strategies in the synthesis of alkaloid natural products,[9] and this has provided much impetus to develop new and more general variants of this unusual ring forming approach.[10] With regard to the present study, investigations into the synthesis of alkaloid (−)-217A have provided a further platform for investigating stereoselective functionalisation of olefin containing piperidines. We report herein the realisation of an enamide cyclopropanation—ring opening strategy for the diastereoselective synthesis of 2,3,6-trisubstituted piperidines and the application of this method in the synthesis of (−)-217A.

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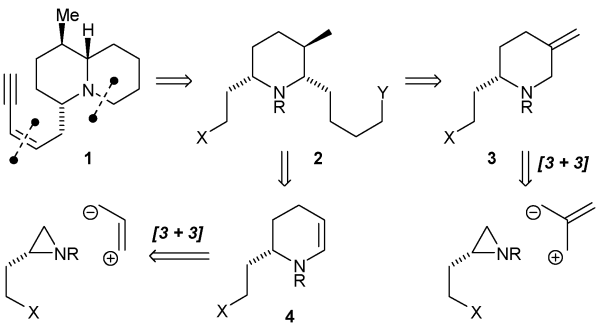
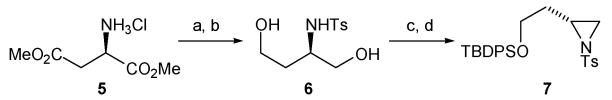
Our underlying strategy was to develop a stereoselective synthesis of the 2,3,6-trisubstituted core of (−)-217A **1** thereby ensuring relatively simple closing steps towards the natural product. As outlined in Scheme 1, the synthesis of key piperidine **2** relied on the successful diastereoselective functionalisation of *exo*-olefin containing **3**, or tetrahydropyridine **4**. We envisaged that heterocyclic intermediates **3** and **4** would each be accessible by [3 + 3] annelations developed in our labs.[7]

Our first goal was to devise an efficient route to the key aziridine required for both [3 + 3] annelation approaches. We chose to employ an enantiospecific synthesis starting from commercially available dimethyl aspartate **5**, and our route is shown in Scheme 2. Amine tosylation followed by $LiBH_4$ reduction proceeded smoothly to furnish diol **6** in high yield. Cyclisation of the diol to the corresponding aziridine took place selectively under Mitsunobu conditions and the remaining hydroxyl-group was protected as a TBDPS-ether to furnish **7**. This four step sequence took place in 53% overall yield and provided multigram quantities of the key aziridine **7** for the [3 + 3] annelation studies.

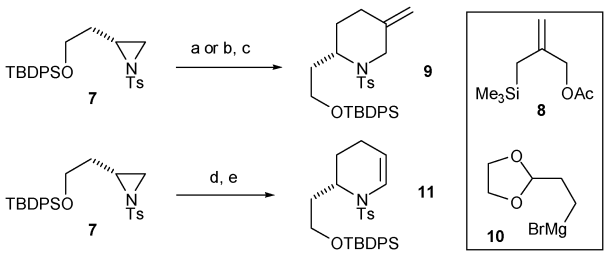
We have shown that functionalised enantiopure piperidines can be prepared by the addition of Pd-trimethylenemethane (Pd-TMM)[7a,b] or functionalised organomagnesium reagents[7c,d] to aziridines. We therefore decided to examine each of these methods for the transformation of **7** into an enantiopure functionalised piperidine, our results are highlighted in Scheme 3. Use of Trost's conjunctive reagent **8**[11] in the presence of a Pd-catalyst resulted in formation of piperidine **9** in good yield. Unfortunately however, this reaction was found to be highly capricious and efficient cycloaddition



Scheme 1 Retrosynthetic analysis of quinolizidine (−)-217A



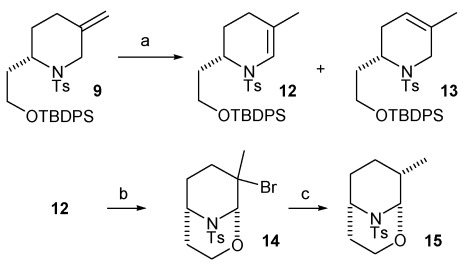
Scheme 2 *Reagents and conditions*: (a) TsCl, Et_3N, THF, 84%. (b) $LiBH_4$, THF, 87%. (c) PBu_3, ADDP, toluene, 81%. (d) TBDPSCl, imidazole, THF, 90%. ADDP: 1,1′-(azodicarbonyl)dipiperidine.



Scheme 3 *Reagents and conditions*: (a) **8**, 10% $Pd(OAc)_2$, 60% $P(OPr^i)_3$, 20% BuLi, THF, reflux, 16 h, 65%. (b) (i) $CH_2{=}C(Me)CH_2OH$, BuLi (2.1 eq.), TMEDA (2.1 eq.), Et_2O, 16 h; (ii) $MgBr_2$ (2.1 eq.), THF, r.t., 85%. (c) 10% $Pd(OAc)_2$, 40% PPh_3, 4 Å M.S., tol., reflux, 16 h, 84%. (d) **10**, 25% CuBr·DMS, THF, r.t., 16 h, 80%. (e) TFA, acetone, r.t., 20 h, 88%.

proved to be irreproducible. We therefore turned our attention to a stepwise annelation process (conditions b, Scheme 3) which provided **9** reproducibly in 72% yield over two steps. Finally, we prepared piperidine **11** through an alternative stepwise sequence involving addition of Büchi Grignard **10** to **7** followed by acid catalysed cyclisation.

We anticipated that piperidine **9** would be most appropriate for elaboration to (−)-217A as the *exo*methylene moiety appeared to be well placed to install the Me-group at C-1 of the natural product. Accordingly, we carried out the Rh-catalysed isomerisation of **9** towards enamide **12** (Scheme 4). Whilst this process was poorly selective, isomers **12** and **13** could be separated allowing desired enamide **12** to be isolated in 66% yield. Treatment of **12** with NaOMe, bromine resulted in the formation of bicycle **14** in high yield.[12] Subjection of bromide **14** to efficient Sn-mediated debromination provided compound **15** as a single diastereoisomer, that provided suitable crystals for X-ray analysis. Disappointingly however, these showed that the undesired *endo*-Me stereochemistry had been produced. Whilst compound **15** represents a useful intermediate for the synthesis of all-*cis* 2,3,6-trisubstituted piperidines, this particular stereochemical outcome coupled with the inefficient olefin isomerisation step prompted us to explore an alternative synthesis of (−)-217A from **11**.

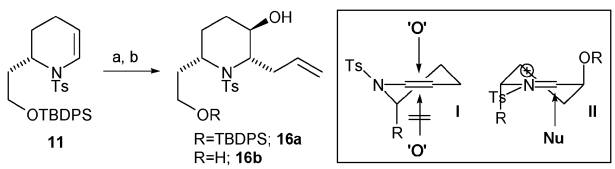


Scheme 4 *Reagents and conditions*: (a) 10% $RhCl(PPh_3)_3$, DBU, 4 Å M.S., EtOH, 100%, **12**:**13** 2:1; (b) NaOMe, Br_2, 95%; (c) Bu_3SnH, AIBN, C_6H_6, reflux, 16 h, 90%.

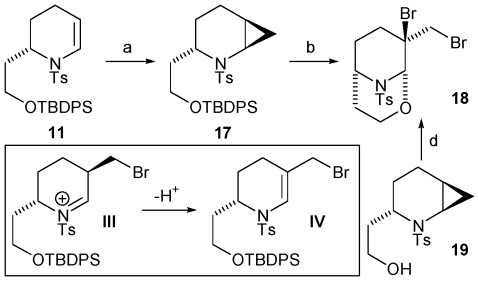
The successful elaboration of **11** to an appropriate piperidine precursor for the synthesis of (−)-217A hinged upon a diastereoselective functionalisation of the enamide that provided efficient installation of the C-1 Me-group and the hydrocarbon chain for assembly of the quinolizidine moiety. We began our studies towards this end by investigating a sequence involving enamide epoxidation followed by Lewis acid catalysed allylation. As outlined in Scheme 5, treatment of **11** with DMDO followed by $BF_3{\cdot}OEt_2$ mediated allylation of the crude epoxide provided 2,3,6-trisubstituted piperidine in high yield as a single diastereoisomer. The product was accompanied by a small amount of silyl ether hydrolysis product **16b**, which showed identical relative stereochemistry as evidenced by TBAF desilylation of **16a**. The high levels of stereocontrol exhibited in this sequence was intriguing and a rationale is put forward in models **I**, **II** in Scheme 5. The propensity for 6-alkyltetrahydropyridines to adopt an axial orientation[13] may encourage reagent addition onto the olefin face opposite to the alkyl group (**I**). Lewis acid catalysed opening then forms an iminium (**II**) that will undergo stereoelectronically controlled addition *syn*-to the 6-alkyl group. Indeed, Rutjes and Blaauw have highlighted a similar diastereoselective functionalisation sequence in the synthesis of 5-hydroxypipecolic acid derivatives.[14]

The studies outlined in Scheme 5 demonstrated that piperidine **11** could be elaborated to an appropriately substituted intermediate with correct stereochemistry for the synthesis of (−)-217A **1**. However further modification of compound **16a** to install the C-1 Me-group raised the prospect of engineering further diastereocontrol within any given synthetic sequence. Much more attractive, was the notion of using a similar paradigm but exploiting a cyclopropane linchpin rather than an epoxide. This strategy would require the analogous ring opening of a piperidine 2,3-cyclopropane. Such processes are relatively rare and generally require the use of an activated cyclopropyl ester,[15] although non-activated systems have also been exploited.[16] With specific regard to heteroatom promoted cyclopropane ring opening—nucleophile addition, significantly more precedent is available in the pyran series. In this regard, cyclopropane haloetherification seemed potentially very attractive.[17]

In the event, cyclopropanation of enamide **11** proceeded in excellent yield to provide **17** as a single diastereoisomer. Upon treatment with NBS however, we were disappointed to find that *vicinal*-dibromide **18** was formed, albeit in good yield. Apparently, the iminium intermediate **III** undergoes loss of a proton and a second bromination reaction. We repeated the reaction with alcohol **19** in the hope that the alcohol would cyclise onto the iminium and preclude the formation of enamide **IV**, unfortunately this approach failed to obviate the formation of **18** (Scheme 6).



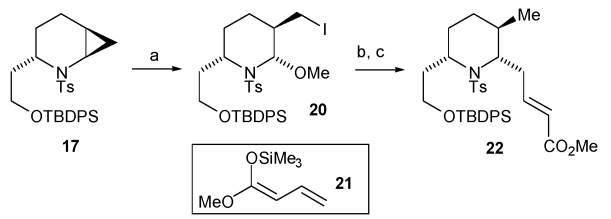
Scheme 5 *Reagents and conditions*: (a) DMDO, CH_2Cl_2; (b) $BF_3{\cdot}OEt_2$, $CH_2{=}CHCH_2SiMe_3$, 80% over two steps, **16a**:**16b**: 7:1.



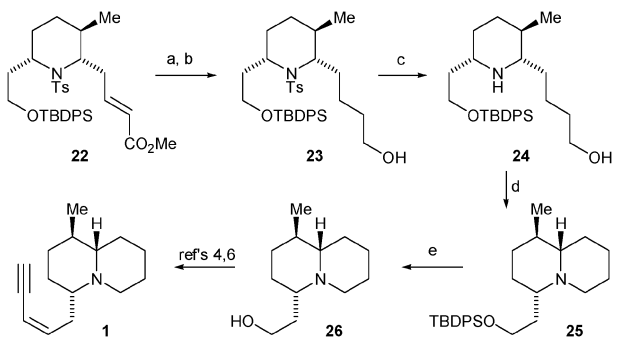
Scheme 6 *Reagents and conditions*: (a) CH_2I_2, Et_2Zn, toluene, 85% (>95 : 5 d.r.); (b) NBS (7 equiv), MeOH, 91%; (c) TBAF, THF, 99%; (d) NBS (1 equiv), MeOH, 40% (50% borsm).

NIS has also been employed in heteroatom promoted cyclopropane cleavage reactions. We proposed that the larger iodonium ion may reduce the rate of the second halogenation step and therefore set about exploring the haloetherification under these conditions. To our delight, cyclopropane **17** underwent smooth ring opening to provide aminal **20**. Compound **20** proved to be extremely sensitive to decomposition on silica gel, or by warming above ambient temperature so we decided to explore the subsequent steps on the crude material. In the event, reduction of the iodide followed by allylation with ketene acetal **21** provided the desired piperidine intermediate **22** as a single diastereoisomer in good yield over three steps (Scheme 7).

With a stereoselective route to the key 2,3,6-trisubstituted piperidine **22** in hand, we turned our attention to the elaboration of this advanced intermediate towards the target compound. Firstly, we successfully assembled the remaining ring of the quinolizidine core by a two-step reduction of the



Scheme 7 *Reagents and conditions*: (a) NIS, MeOH; (b) Bu_3SnH, AIBN, toluene; (c) **21**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 59% over three steps.



Scheme 8 *Reagents and conditions*: (a) 10% Pd/C, H-Cube™, EtOAc, 93%; (b) LAH, THF, 100%; (c) Na, $C_{10}H_{10}$, DME, 79%; (d) PPh_3, I_2, imidazole, CH_2Cl_2, 79%; (e) TBAF, THF, 100%.

enoate moiety to provide **23**, followed by removal of the Ts-group and cyclization. Hydrolysis of the silyl ether **25** proceeded without incident to provide alcohol **26**, that was elaborated to the natural product according to previously described methods[4,6] to provide **1**. Our sample exhibited identical spectroscopic data to that reported in previous structural and synthetic studies in (−)-217 A (Scheme 8).

In conclusion, [3 + 3] annelation strategies offer a convenient and stereoselective method for the synthesis of piperidines. This method has successfully delivered alkaloid (−)-217 A.

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Notes and references

1 P. Jain, H. M. Garraffo, H. Yeh, T. F. Spande, J. W. Daly, N. R. Andriamaharavo and M. Andriantsiferana, *J. Nat. Prod.*, 1996, **59**, 1174.
2 J. P. Michael, *Nat. Prod. Rep.*, 2004, **21**, 625.
3 W. H. Pearson and H. Suga, *J. Org. Chem.*, 1998, **63**, 9910.
4 H. Huang, T. F. Spande and J. S. Panek, *J. Am. Chem. Soc.*, 2003, **125**, 626.
5 K. M. Maloney and R. L. Danheiser, *Org. Lett.*, 2005, **7**, 3115.
6 M. Fellah, M. Santarem, G. Lhommet and V. Mouriès-Mansuy, *J. Org. Chem.*, 2010, **75**, 7803.
7 (*a*) S. J. Hedley, W. J. Moran, A. H. G. P. Prenzel, D. A. Price and J. P. A. Harrity, *Synlett*, 2001, 1596; (*b*) S. J. Hedley, W. J. Moran, D. A. Price and J. P. A. Harrity, *J. Org. Chem.*, 2003, **68**, 4286; (*c*) K. M. Goodenough, P. Raubo and J. P. A. Harrity, *Org. Lett.*, 2005, **7**, 2993; (*d*) L. C. Pattenden, R. A. J. Wybrow, S. A. Smith and J. P. A. Harrity, *Org. Lett.*, 2006, **8**, 3089.
8 For recent reviews of synthetic routes to piperidines see: (*a*) P. R. Girling, T. Kiyoi and A. Whiting, *Org. Biomol. Chem.*, 2011, **9**, 3105; (*b*) J. P. A. Harrity and O. Provoost, *Org. Biomol. Chem.*, 2005, **3**, 1349; (*c*) M. G. P. Buffat, *Tetrahedron*, 2004, **60**, 1701; (*d*) F.-X. Felpin and J. Lebreton, *Eur. J. Org. Chem.*, 2003, 3693; (*e*) P. M. Weintraub, J. S. Sabol, J. M. Kane and D. R. Borcherding, *Tetrahedron*, 2003, **59**, 2953; (*f*) S. Laschat and T. Dickner, *Synthesis*, 2000, 1781.
9 (*a*) W. J. Moran, K. M. Goodenough, P. Raubo and J. P. A. Harrity, *Org. Lett.*, 2003, **5**, 3427; (*b*) K. M. Goodenough, W. J. Moran, P. Raubo and J. P. A. Harrity, *J. Org. Chem.*, 2005, **70**, 207; (*c*) O. Y. Provoost, S. J. Hedley, A. J. Hazelwood and J. P. A. Harrity, *Tetrahedron Lett.*, 2006, **47**, 331; (*d*) O. Y. Provoost, A. J. Hazelwood and J. P. A. Harrity, *Beilstein J. Org. Chem.*, 2007, **3**, 8.
10 For an overview of alternative [3 + 3] annelations see: (*a*) R. P. Hsung, A. V. Kurdyumov and N. Sydorenko, *Eur. J. Org. Chem.*, 2005, 23; (*b*) G. S. Buchanan, J. B. Feltenberger and R. P. Hsung, *Curr. Org. Synth.*, 2010, **7**, 363.
11 B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1.
12 The stereochemistry of compound **14** was not determined.
13 (*a*) L. C. Pattenden, H. Adams, S. A. Smith and J. P. A. Harrity, *Tetrahedron*, 2008, **64**, 2951; (*b*) D. Craig, R. McCague, G. A. Potter and M. R. V. Williams, *Synlett*, 1998, 55.
14 P. N. M. Botman, F. J. Dommerholt, R. de Gelder, Q. B. Broxterman, H. E. Schoemaker, F. P. J. T. Rutjes and R. Blaauw, *Org. Lett.*, 2004, **6**, 4941.
15 (*a*) E. Wenkert and T. Hudlický, *J. Org. Chem.*, 1988, **53**, 1953; (*b*) M. D. Kaufman and P. A. Grieco, *J. Org. Chem.*, 1994, **59**, 7197; (*c*) A. Padwa, P. Rashatasakhan, A. D. Ozdemir and J. Willis, *J. Org. Chem.*, 2005, **70**, 519.
16 L. Larquetoux, N. Ouhamou, A. Chiaroni and Y. Six, *Eur. J. Org. Chem.*, 2005, 4654.
17 (*a*) P. Bertinato, E. J. Sorensen, D. Meng and S. J. Danishefsky, *J. Org. Chem.*, 1996, **61**, 8000; (*b*) C. V. Ramana, R. Murali and M. Nagarajan, *J. Org. Chem.*, 1997, **62**, 7694; (*c*) E. Megia-Fernandez, N. Gourlaouen, S. V. Ley and G. J. Rowlands, *Synlett*, 1998, 991.