ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Asymmetric Synthesis of the Tropane Alkaloid (+)-Pseudococaine via Ring-Closing Iodoamination

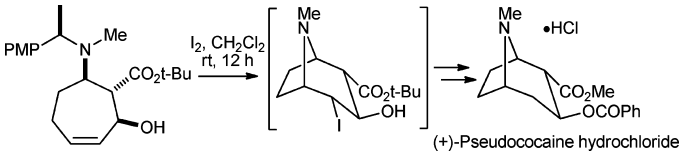
E. Anne Brock, Stephen G. Davies,* James A. Lee, Paul M. Roberts, and James E. Thomson

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

steve.davies@chem.ox.ac.uk

Received July 25, 2012

ABSTRACT



Ring-closing iodoamination of *tert*-butyl 2-hydroxy-7-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]cyclohept-3-ene-1-carboxylates proceeds with concomitant loss of the *N*-α-methyl-*p*-methoxybenzyl group to give the corresponding 8-azabicyclo[3.2.1]octane scaffolds in >99:1 dr. Subsequent elaboration of one of these templates provided access to (+)-pseudococaine hydrochloride, in seven steps and 31% overall yield from commercially available starting materials.

Albert Niemann first reported the isolation of the tropane alkaloid (−)-cocaine **1** in 1860 from the leaves of the Peruvian *Erythroxylon coca* plant.[1] The medicinal significance[2] of this compound combined with its privileged molecular architecture has stimulated research into the synthesis of cocaine **1** and other tropane alkaloids, such as (+)-pseudococaine **2**, although to date there have been relatively few asymmetric syntheses of these compounds reported that do not rely on resolution protocols (Figure 1).

We have previously reported a novel iodine mediated ring-closing iodoamination reaction to generate pyrrolidine scaffolds[3,4] and also recently extended this methodology

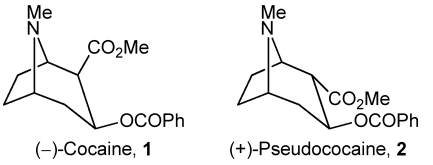


Figure 1. Cocaine, **1**, and its C(2)-epimer, **2**.

to encompass transannular processes for the synthesis of pyrrolizidines.[5] For example, treatment of hexahydroazocine **3** with I_2 and $NaHCO_3$ induced transannular iodoamination with concomitant *N*-debenzylation to give the corresponding pyrrolizidine hydroiodide salt **4**·HI in 79% yield. Subsequent functional group manipulations then enabled the preparation of (−)-7a-*epi*-hyacinthacine A1 **5** in 64% overall yield from **4** (Scheme 1). Herein we report an alternative application of this protocol for the synthesis of substituted 8-azabicyclo[3.2.1]octanes from enantiopure cyclohept-4-enamine scaffolds.[6] These substrates can be prepared readily using our lithium amide

(1) Niemann, A. *Arch. Pharm.* **1860**, *153*, 129.

(2) (a) Lounasmaa, M. *The Alkaloids* **1988**, *33*, 1. (b) Koob, G. F.; Bloom, F. E. *Science* **1988**, *242*, 715. (c) Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 969.

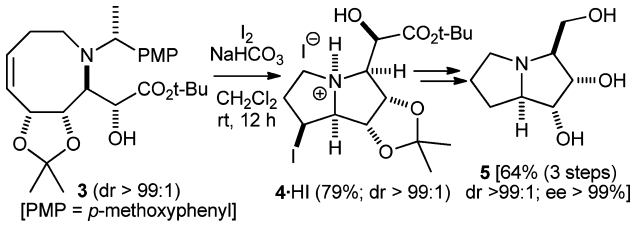
(3) (a) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Smith, A. D. *Synlett* **2004**, 901. (b) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758. (c) Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; West, C. J. *Tetrahedron Lett.* **2011**, *52*, 6477. (d) Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E.; West, C. J. *Tetrahedron* **2012**, *68*, 4302.

(4) For a related appoach towards the asymmetric synthesis of piperidines, see: (a) Davies, S. G.; Hughes, D. G.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Synlett* **2010**, 567. (b) Davies, S. G.; Fletcher, A. M.; Hughes, D. G.; Lee, J. A.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Tetrahedron* **2011**, *67*, 9975.

(5) Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 1594.

10.1021/ol3020607

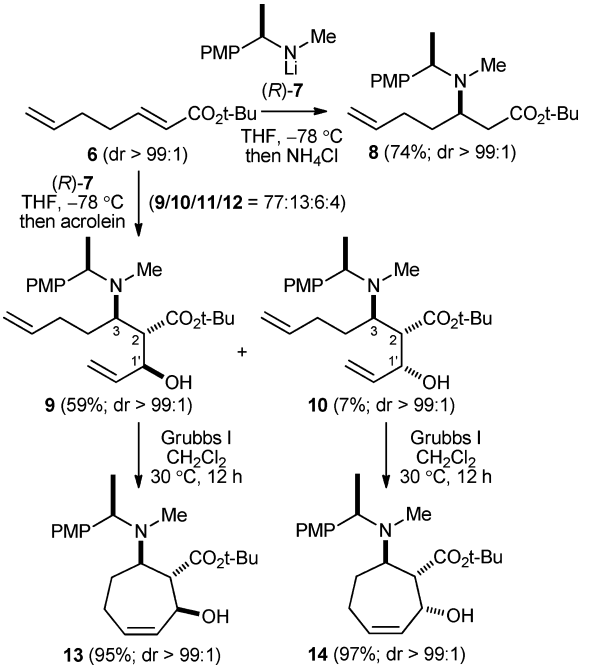
Scheme 1



conjugate addition methodology[7] with in situ enolate alkylation, followed by ring-closing metathesis of the resultant β-amino ester. This methodology enabled the rapid and efficient asymmetric synthesis of the tropane alkaloid (+)-pseudococaine hydrochloride **2**·HCl.

Sequential treatment of $\alpha,\beta,\varepsilon,\zeta$-diunsaturated ester **6**[8,9] with lithium (*R*)-*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)-amide **7** and then saturated aq NH_4Cl produced β-amino ester **8** in 74% yield and >99:1 dr.[10,11] Conjugate addition of (*R*)-**7** to **6** followed by in situ aldol reaction of the intermediate lithium (*Z*)-β-amino enolate[12] with acrolein, however, gave a 77:13:6:4 [**9/10/11/12**] mixture of diastereoisomeric products. Following chromatographic purification, the major product **9** was isolated in 59% yield and >99:1 dr, in addition to **10** which was isolated in 7% yield and >99:1 dr (Scheme 2). The relative configuration within **9** was unambiguously established by single crystal X-ray diffraction analysis,[13] with the absolute (2*S*,3*R*,1′*S*,αS)-configuration within **9** following from the known (*R*)-configuration of the *N*-α-methyl-*p*-methoxybenzyl stereocenter (Figure 2). This analysis also confirmed the assigned absolute configuration within **8**, and given the high diastereoselectivity observed upon formation of **8** it was reasoned that the configurations of the minor diastereoisomers **10**–**12** differed from that of **9** at the C(2) and/or C(1′) positions, rather than at the C(3) position; the configuration within **10** was subsequently confirmed by single crystal X-ray diffraction analysis of a derivative. Treatment of **9** and **10** with Grubbs I catalyst effected ring-closing metathesis to give 7-aminocyclohept-3-ene-1-carboxylates **13** and **14** in 95 and 97% isolated yield, respectively. It was found that for **13** the overall yield and scalability of this process could be improved by omitting the purification of intermediate **9**: in this case the crude reaction mixture from the tandem conjugate addition/alkylation reaction was immediately treated with Grubbs I catalyst which gave **13** in >99:1 dr and 66% overall yield from **6** (Scheme 2). The (1*S*,2*S*,7*R*,αR)-configuration within **13** was also confirmed by single crystal X-ray diffraction analysis (Figure 3).[13]

Scheme 2



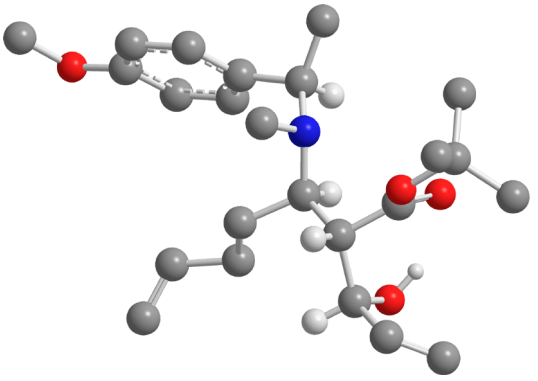


Figure 2. X-ray crystal structure of (2*S*,3*R*,1′*S*,αS)-**9** (selected H-atoms are omitted for clarity).

(6) For a related approach towards a tropane scaffold from a cyclohept-3-enamine precursor, see: Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2001**, *42*, 4633.

(7) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833.

(8) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192.

(9) Compound **6** was produced from commercially available 4-pentenal in 91% yield and >99:1 dr using our highly (*E*)-selective MeMgBr mediated Wadsworth–Emmons procedure; see: Claridge, T. D.W.; Davies, S. G.; Lee, J. A.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Toms, S. M. *Org. Lett.* **2008**, *10*, 5437.

(10) The stereochemical outcome of this reaction was initially assigned by reference to our transition state mnemonic which rationalizes the diastereoselectivity observed upon conjugate addition of lithium amides derived from α-methylbenzylamine; see: Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *10*, 1999.

(11) Reaction of the corresponding methyl ester produced a mixture of products including those resulting from direct 1,2-addition of the lithium amide reagent to the methyl ester functionality.

(12) (a) Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Chem. Commun.* **1993**, 1153. (b) Davies, S. G.; Dixon, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2635.

(13) Crystallographic data (excluding structure factors) for the structures of **9**, **13**, **17**, **20**·HI, and **22** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 883481–883485, respectively.

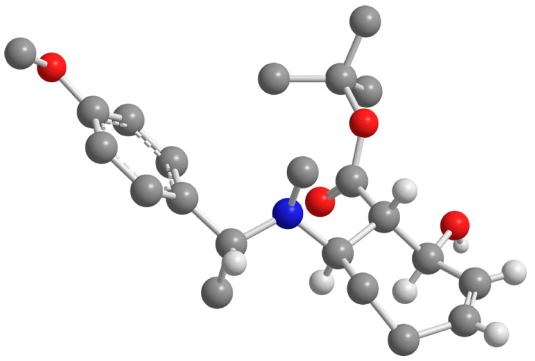


Figure 3. X-ray crystal structure of (1*S*,2*S*,7*R*,α*R*)-**13** (selected H-atoms are omitted for clarity).

Following our optimized procedure for transannular iodoamination,[5] treatment of **14** with I_2 in CH_2Cl_2 (EtOH stabilized)[14] produced a complex mixture of products containing α-methyl-*p*-methoxybenzyl ethyl ether **18**[5] and *p*-acetanisole **19**. Upon basification of the crude reaction mixture with K_2CO_3 in THF, and subsequent chromatographic purification, C(4)-iodo substituted 8-azabicyclo[3.2.1]octane **17** was isolated in 11% yield and >99:1 dr (Scheme 3).[15] Recrystallization of this mixture from CH_2Cl_2/Et_2O enabled the relative configuration within **17** to be unambiguously assigned via single crystal X-ray diffraction analysis[13] (Figure 4), and the determination of a Flack *x* parameter[16] of −0.04(3) for the crystal structure of **17** allowed the absolute (1*R*,2*S*,3*S*,4*R*,5*S*)-configuration within **17** (and therefore the absolute configurations within **10** and **14**) to be unambiguously assigned. This stereochemical outcome is entirely consistent with our previous observations concerning this class of ring-closing iodoamination reaction[5] and a mechanism in which reversible formation of iodonium ion **15** is followed by cyclization of the amino group onto the C(4) carbon atom [i.e., distal to the C(2)-hydroxyl group][17,18] to give ammonium ion **16**. Subsequent loss of the α-methyl-*p*-methoxybenzyl cation then gives 8-azabicyclo[3.2.1]octane **17**, and the α-methyl-*p*-methoxybenzyl cation is trapped by EtOH giving **18**;[14,19] presumably the formation of **19** occurs via a similar *N*-oxidation pathway.

(14) The presence of EtOH is not required, but it does make the procedure more practical as the *p*-methoxybenzyl residues are efficiently scavenged by the EtOH enabling their separation from the desired reaction product.

(15) Attempted optimization did not improve the yield of **17**, which was also found to be susceptible to decomposition.

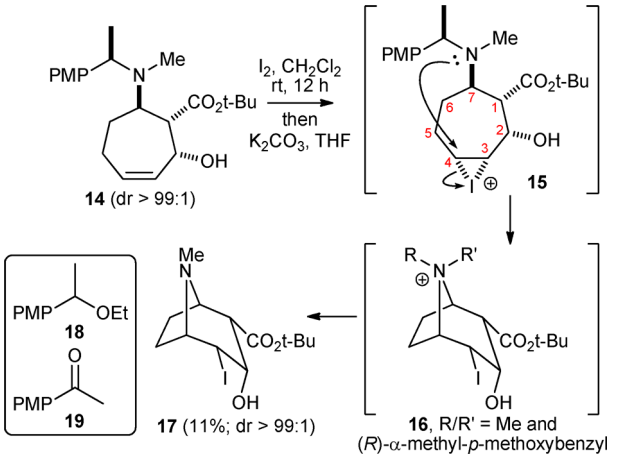
(16) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876.

(17) (a) Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737. (b) Addy, J. K.; Parker, R. E. *J. Chem. Soc.* **1963**, 915.

(18) We have also observed this phenomenon during our investigations into the chemo- and diastereoselective oxidation of allylic and homoallylic amines; see: (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) Davies, S. G.; Fletcher, A. M.; Kurosawa, W.; Lee, J. A.; Poce, G.; Roberts, P. M.; Thomson, J. E.; Williamson, D. M. *J. Org. Chem.* **2010**, *75*, 7745.

(19) See also: Srihari, P.; Bhunia, D. C.; Sreedhar, P; Yadav, J. S. *Synlett* **2008**, 1045.

Scheme 3



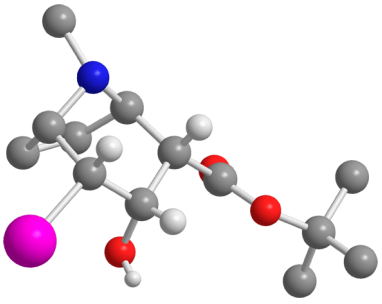
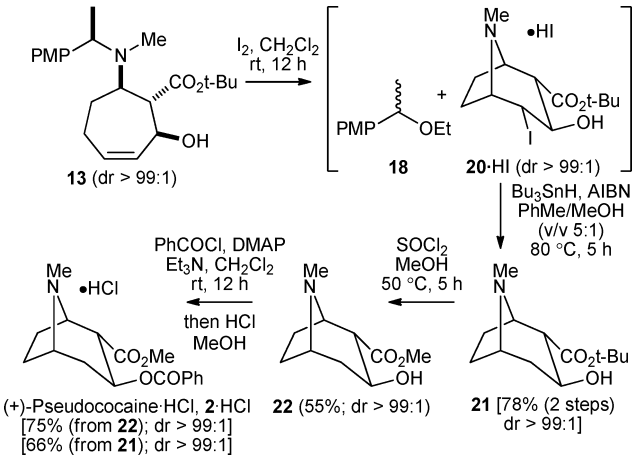


Figure 4. X-ray crystal structure of (1*R*,2*S*,3*S*,4*R*,5*S*)-**17** (selected H-atoms are omitted for clarity).

Treatment of **13**, however, with I_2 in CH_2Cl_2 (EtOH stabilized)[14] proceeded very cleanly to give a mixture of only **18**[5] and C(4)-iodo substituted 8-azabicyclo-[3.2.1]octane **20** as the corresponding hydroiodide salt. Recrystallization of this mixture from CH_2Cl_2/Et_2O gave **20**·HI in 72% yield and >99:1 dr and also enabled the relative configuration within **20**·HI to be unambiguously assigned via single crystal X-ray diffraction analysis (Figure 5).[13] Furthermore, the determination of a Flack *x* parameter[16] of −0.01(7) for the crystal structure of **20**·HI allowed the absolute (1*R*,2*S*,3*R*,4*R*,5*S*)-configuration within **20** to be assigned unambiguously. In an effort to isolate **20** as the free base, a mixture of **18** and **20**·HI was partitioned between 1.0 M aq KOH and $CHCl_3$ which gave **20** in 46% yield after chromatographic purification. However, it was found that the yield of **20** could be improved further upon stirring the crude reaction mixture from the ring-closing iodoamination reaction with K_2CO_3 in THF, prior to chromatographic purification, which gave **20** in 92% isolated yield. Reduction of the C−I bond within **20** with

Scheme 4



Bu_3SnH gave **21** in 66% yield and >99:1 dr, after flash column chromatography on silica doped with 10% KF.[20] However, when the crude reaction mixture of **18** and **20**·HI was immediately subjected to reduction with Bu_3SnH, **21** was isolated in 78% yield (from **13**), also after chromatographic purification on silica doped with 10% KF.[20] Transesterification of **21** upon treatment with $SOCl_2$ in MeOH (followed by basification) gave (+)-pseudoecgonine methyl ester **22** in 55% isolated yield and >99:1 dr. The spectroscopic data for this sample of **22** {mp 111−113 °C; $[\alpha]_D^{20}$ +17.5 (*c* 0.4 in H_2O)} were found to be in close agreement with those reported previously {lit.[21] mp 114−116 °C; $[\alpha]_D^{20}$ +22.8 (*c* 1.7 in H_2O); lit.[22] mp 113−114 °C; $[\alpha]_D^{23}$ +23.1 (*c* 1 in H_2O)}; lit.[23] for *ent*-**22**: mp 114−115 °C; $[\alpha]_D^{20}$ −22.5 (*c* 1 in H_2O)}. Furthermore, the relative configuration within **22** was unambiguously confirmed by single crystal X-ray diffraction analysis (Figure 6).[13] Finally, *O*-benzoylation of the hydroxyl functionality within **22** followed by treatment of **2**[24] with HCl in MeOH gave (+)-pseudococaine hydrochloride **2**·HCl in 75% yield and >99:1 dr. The overall yield of **2**·HCl was improved further by isolating **22**·HCl directly from the transesterification reaction and immediately subjecting this compound to the benzoylation reaction conditions, which gave **2**·HCl in 66% overall yield from **21** (Scheme 4). The spectroscopic data for these samples of **2**·HCl {mp 209−211 °C; $[\alpha]_D^{20}$ +43.7 (*c* 0.2 in H_2O)} were in excellent agreement with those reported previously {lit.[25] $[\alpha]_D^{20}$ +42 (*c* 1.5 in H_2O); lit.[23] for *ent*-**2**·HCl: mp 210−212 °C; $[\alpha]_D^{24}$ −42.3 (*c* 1 in H_2O)}.

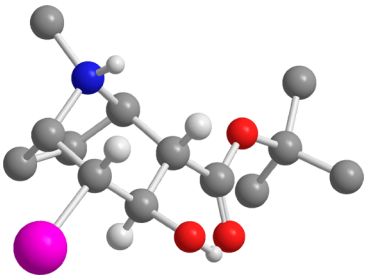


Figure 5. X-ray crystal structure of (1*R*,2*S*,3*R*,4*R*,5*S*)-**20**·HI (selected H-atoms and the I^- counterion are omitted for clarity).

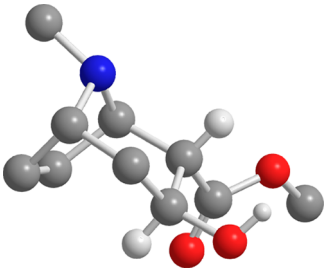


Figure 6. X-ray crystal structure (1*R*,2*S*,3*R*,5*S*)-**22** (selected H-atoms are omitted for clarity).

In conclusion, the conjugate addition of lithium (*R*)-*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to *tert*-butyl (*E*)-hept-2,6-dienoate and in situ aldol reaction of the resultant lithium (*Z*)-*β*-amino enolate with acrolein was followed by ring-closing metathesis of the *β*-amino ester products to give two diastereoisomeric *tert*-butyl 2-hydroxy-7-[*N*-methyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]cyclohept-3-ene-1-carboxylates. Ring-closing iodoamination of these substrates proceeded in each case with concomitant loss of the *N*-α-methyl-*p*-methoxybenzyl group to give the corresponding 8-azabicyclo[3.2.1]octane scaffolds as single diastereoisomers. Subsequent elaboration of one of these templates provided access to (+)-pseudococaine hydrochloride, in seven steps and 31% overall yield from commercially available starting materials. Further applications of this methodology are under investigation within our laboratory.

Supporting Information Available. Experimental procedures, characterization data, copies of ^1H and ^{13}C NMR spectra, and crystallographic data (for structures CCDC 883481−883485). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(20) Harrowven, D. C.; Guy, I. L. *Chem. Commun.* **2004**, 1968.
(21) Findlay, S. P. *J. Am. Chem. Soc.* **1954**, *76*, 2855.
(22) Carroll, F. I.; Lewin, A. H.; Abraham, P.; Parham, K.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1991**, *34*, 883.
(23) Lewin, A. H.; Naseree, T.; Carrol, F. I. *J. Heterocycl. Chem.* **1987**, *24*, 19.
(24) Carroll, F. I.; Coleman, M. L.; Lewin, A. H. *J. Org. Chem.* **1982**, *47*, 13.
(25) Kozikowski, A. P.; Simoni, D.; Baraldi, P. G.; Lampronti, I.; Manfredini, S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 441.