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A Chemoenzymatic Total Synthesis of the Structure Assigned to the Alkaloid (+)-Montabuphine

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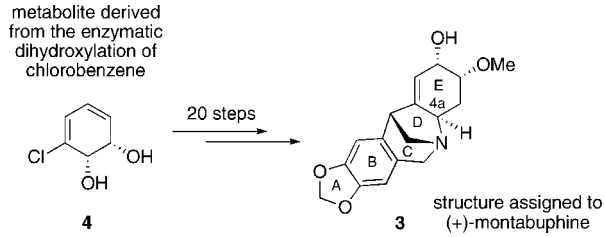
ABSTRACT



An enantioselective synthesis of the structure, 3, assigned to the alkaloid (+)-montabuphine has been achieved using the readily available metabolite 4 as starting material. A comparison of the physical and spectral data recorded on compound 3 with those reported for (+)-montabuphine suggests that they are different compounds.

The montanine alkaloids are a small group of natural products isolated from various *Amaryllidaceae* species and characterized by the presence of a 5,11-methanomorphanthridine framework incorporating, in varying configurations, hydroxy and/or methoxy groups at C2 and C3 or at C3 and C4.[1] A modest number of biological properties have been attributed to these alkaloids including anticonvulsive, antidepressive, anxiolytic and weak hypertensive activities.[2] Representative members of the class, which include (−)-brunsvigine (**1**, Figure 1) and (−)-nangustine (**2**), have been the subject of various synthetic studies that have served to confirm their structures.[3] The isolation of (+)-montabuphine, which was assigned structure **3**, from *Boophane flava*, an *Amaryllidaceae* species endemic to winter rainfall areas in southern Africa, has attracted considerable attention because this suggests that both enantiomeric forms of the montanine alkaloid framework occur in nature.[4,5] Given the unique position (+)-montabuphine appears to hold within the class it is surprising that no efforts to synthesize it have been reported thus far. Accordingly, we now describe the total synthesis of compound **3** in the illustrated enantiomeric form and report that the physical and spectral data derived from this material do not match those recorded for the natural product.

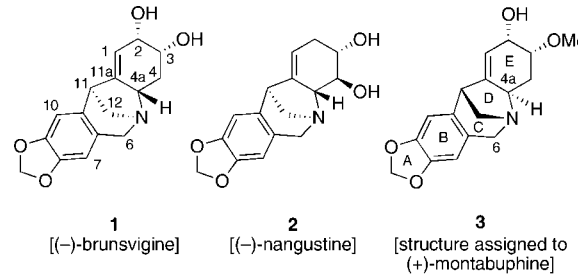


Figure 1. Structures assigned to the montanine alkaloids (−)-brunsvigine, (−)-nangustine, and (+)-montabuphine.

Our synthetic approach to compound **3** was based on related ones that we have used recently to prepare the non-natural enantiomeric forms of (−)-brunsvigine (**1**) and (−)-nangustine

(1) For reviews dealing with this class of alkaloid see: (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 30, p 251. (b) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 51, p 323. (c) Lewis, J. R. *Nat. Prod. Rep.* 2000*17*57, and previous reviews in the series.

(2) See, for example: (a) Labraña, J.; Machocho, A. K.; Kricsfalusy, V.; Brun, R.; Codina, C.; Viladomat, F.; Bastida, J. *Phytochemistry* **2002**, *60*, 847. (b) Schurman da Silav, A. F.; de Andrade, J. P.; Bevilaqua, L. R. M.; da Souza, M. M.; Izquierdo, I.; Henriques, A. T.; Zuanazzi, J. A. S. *Pharmacol., Biochem. Behav.* **2006**, *85*, 148.

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(**2**), namely, *ent*-**1**[3k] and *ent*-**2**.[3l] The starting material employed in these cases, and in the present work, was the enantiopure *cis*-1,2-dihydrocatechol **4** (Figure 2) which can be obtained in large quantity via the whole-cell mediated biotransformation of chlorobenzene.[6] The synthetic sequence involves three critical transformations, an Overman rearrangement[7] to introduce the nitrogen, a novel radical addition/elimination reaction[3k,l,8] to establish the D-ring of target **3** and a late-stage Pictet−Spengler reaction[9] to introduce the C6-methylene unit and thereby form the C-ring.

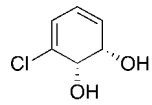

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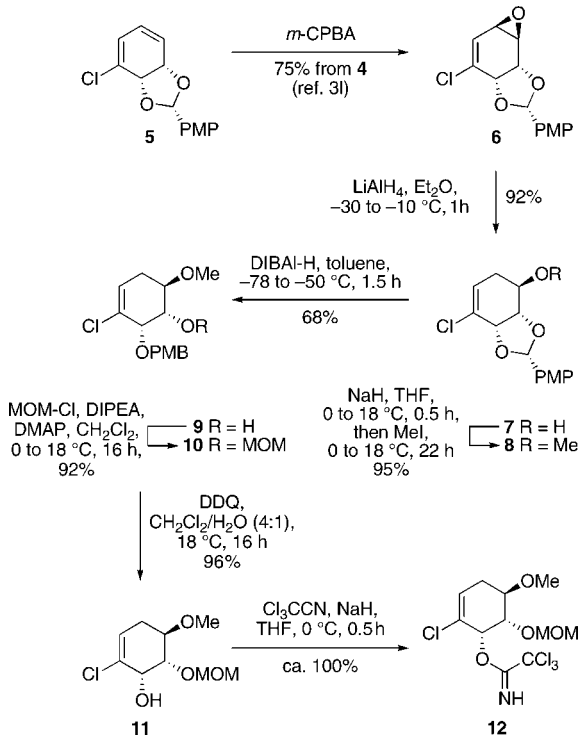
Figure 2. Starting material used in the synthesis of compound **3**.

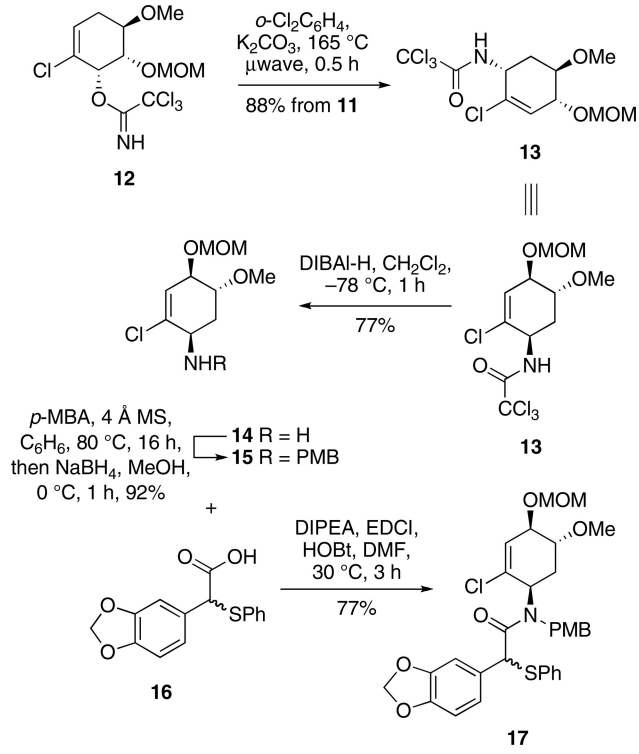
The route used in preparing the substrate required for the Overman rearrangement is shown in Scheme 1 and started with the known[3l] and readily generated PMP-acetal derivative, **5**, of *cis*-1,2-dihydrocatechol **4**. Epoxidation of acetal **5** with *m*-chloroperbenzoic acid (*m*-CPBA) proceeded in a regio- and stereo-selective fashion to give the previously reported[3l] oxirane **6** (75% yield from **4**) and this underwent selective reductive cleavage on exposure to lithium aluminum hydride to give alcohol **7** in 92% yield. *O*-Methylation of the last compound with methyl iodide in the presence of sodium hydride afforded acetal/ether **8** (95%) that, on exposure to di-isobutyl aluminum hydride (DIBAl-H), engaged in smooth reductive cleavage to the bis-ether **9** (68%).[10] The free hydroxy group within this last compound was protected, under standard conditions, as the corresponding MOM-ether **10** and this was then treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) so as to cleave the PMB ether moiety and thus giving the allylic alcohol **11** (91% from **9**). In anticipation of the foreshadowed Overman rearrangement reaction, compound **11** was treated with trichloroacetonitrile in the presence of sodium hydride and so affording the pivotal but rather unstable trichloroacetimidate **12**.

Exposure of an *o*-dichlorobenzene solution of compound **12** containing potassium carbonate to microwave irradiation (Scheme 2) afforded the anticipated rearrangement product **13** (88% from **11**), the acetamide residue of which was immediately subjected to reductive cleavage using DIBAl-H and thus giving the corresponding primary amine **14** in 77% yield. Reductive amination of this last compound with *p*-methoxybenzaldehyde (*p*-MBA) in the presence of sodium borohydride then afforded the expected secondary amine **15** (92%) which could be coupled

Scheme 1. Substrate Synthesis for the Overman Rearrangement



Scheme 2. Synthesis of the Substrate for the Radical Addition/Elimination Reaction

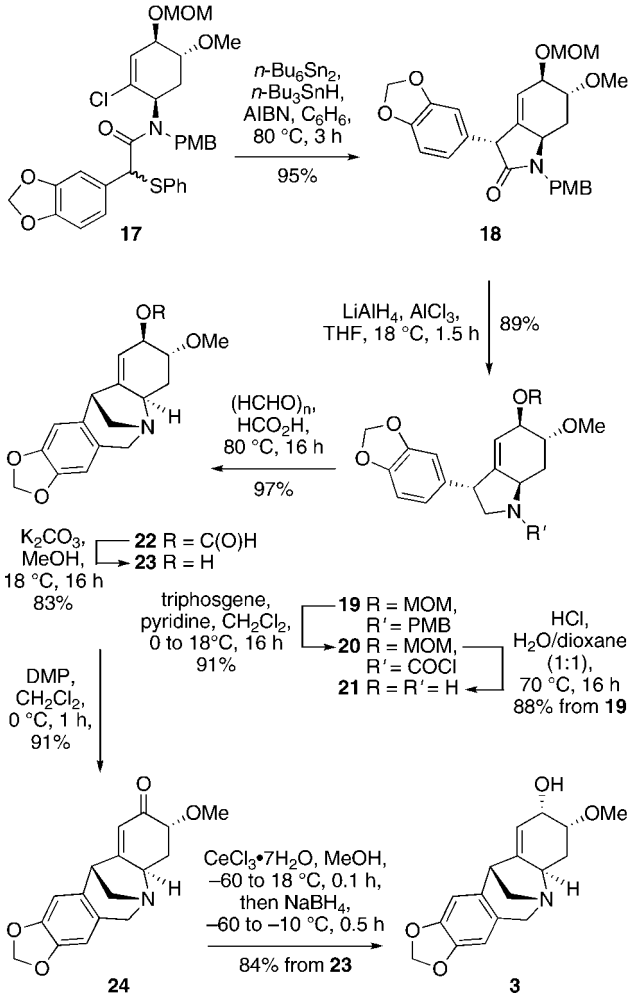


(3) (a) Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005. (b) Ishizaki, M.; Hoshino, O.; Iitaka, Y. *J. Org. Chem.* **1992**, *57*, 7285. (c) Ishizaki, M.; Kurihara, K.-I.; Tanazawa, E.; Hoshino, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 101. (d) Overman, L. E.; Shim, J. *J. Org. Chem.* **1993**, *58*, 4662. (e) Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 5773. (f) Pearson, W. H.; Lian, B. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1724. (g) Ikeda, M.; Hamada, M.; Yamashita, T.; Matsui, K.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1949. (h) Sha, C.-K.; Hong, A.-W.; Huang, C.-M. *Org. Lett.* **2001**, *3*, 2177. (i) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Kemmler, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1345. (j) Pandey, G.; Banerjee, P.; Kumar, R.; Puranik, V. G. *Org. Lett.* **2005**, *7*, 3713. (k) Banwell, M. G.; Kokas, O. J.; Willis, A. C. *Org. Lett.* **2007**, *9*, 3503. (l) Kokas, O. J.; Banwell, M. G.; Willis, A. C. *Tetrahedron* **2008**, *64*, 6444.

with the racemic modification of the previously reported[3g] acid **16** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI)/1-hydroxybenzotriazole (HOBt). In this manner the substrate required for the foreshadowed radical addition/elimination reaction,[8] namely amide **17**, was obtained in 77% yield and as a ca. 1:1 mixture of diastereoisomers.

The final stages of the synthesis of target compound **3** are shown in Scheme 3 and involve the subjection of compound

Scheme 3. Completion of the Synthesis of Compound **3**



17 to reaction with a combination of hexa-*n*-butylditin and tri-*n*-butyltin hydride. Under such conditions the pivotal radical addition/elimination process takes place and such that lactam **18** is obtained, as a single diastereoisomer, in 95% yield. This reaction is presumed to involve initial homolytic cleavage of the thiophenyl residue then cyclization, via a highly diastereoselective 5-*exo*-*trig* process, of the resulting benzylic radical onto the proximate terminus of the chloroalkene. The α-chlorinated cyclohexyl radical so-formed then collapses with ejection

(4) Viladomat, F.; Bastida, J.; Codina, C.; Campbell, W. E.; Mathee, S. *Phytochemistry* **1995**, *40*, 307.

(5) In assigning structure **3** to (+)-montabuphine, Codina et al.[4] did not explicitly define the stereochemistry at C4a but their commentary and the subsequent interpretations of others means that the illustrated *R*-configuration at this center is now widely assumed.

Table 1. Comparison of the ^{13}C NMR Data for Naturally-Occurring (+)-Montabuphine, Synthetically-Derived **3**, and Other Montanine Alkaloid-Type Structures

montabuphine (δ_C)[a]	**3** (δ_C)[b]	**23** (δ_C)[b]	**25** (δ_C)[c]	**26** (δ_C)[c]	**27** (δ_C)[d]
150.8	153.6	154.4	156.1	154.3	154.0
146.9	146.7	146.7	146.8	146.7	146.7
146.3	145.9	145.9	145.9	145.9	145.9
130.9	132.1	132.2	132.1	132.5	131.5
122.6	124.5	124.6	125.0	124.8	124.3
117.6	116.8	114.7	111.9	112.9	116.2
107.6	107.7	107.4	107.8	107.3	107.5
106.7	106.7	106.8	106.9	106.8	106.7
100.8	100.7	100.7	100.8	100.7	100.7
77.0	77.6	81.3	77.7	79.8	75.2
67.8	68.2	67.3	65.6	69.2	74.6
60.0	61.2	61.0	61.2	60.9	63.0
58.7	58.2	58.6	58.1	58.7	61.0
57.4	57.4	57.0	56.7	57.6	–
55.1	55.7	55.6	55.7	55.4	55.5
44.8	45.5	45.6	46.0	45.6	45.1
31.6	32.8	28.8	36.0	32.7	37.8

[a] Data from ref 4 and recorded in $CDCl_3$ at 50 MHz. [b] Data arising from work reported in this paper and recorded in $CDCl_3$ at 75 MHz. [c] Data from ref 3e and recorded in $CDCl_3$ at 125 MHz. [d] Data from ref 3d and recorded in $CDCl_3$ at 125 MHz.

of a chlorine radical to reinstate, in a completely regioselective fashion, the cyclohexenyl double-bond and so deliver the observed product **18**. The origins of the pleasing diastereoselectivity observed in the cyclization process remain unclear at the present time. As a prelude to carrying out the Pictet−Spengler reaction, the lactam carbonyl within compound **18** was removed using aluminum hydride generated in situ from $AlCl_3$ and $LiAlH_4$. The PMB residue associated with the resulting pyrrolidine **19** (89%) was cleaved using triphosgene[11] and the carbamoyl chloride **20** so-formed was subjected to acid-catalyzed hydrolysis and thus providing the amino-alcohol **21** in 88% yield from precursor **19**. Treatment of compound **21** with a mixture of paraformaldehyde and formic acid at 80 °C for 16 h effected the desired Pictet−Spengler reaction but this was accompanied by formylation of the free hydroxyl group within the substrate and such that the formate ester **22** was obtained in 97% yield. Hydrolysis of the latter compound was readily achieved with potassium carbonate in methanol and thus delivering the epimer, **23**, of target compound **3** in 83% yield. The structure of compound **23** was secured through a single-

(6) Compound **4** can be obtained from the Aldrich Chemical Co. (Catalogue Number 489492) or from Questor, Queen's University of Belfast, Northern Ireland (http://questor.qub.ac.uk/newsite/contact.htm). For reviews on methods for generating *cis*-1,2-dihydrocatechols by microbial dihydroxylation of the corresponding aromatics, as well as the synthetic applications of these metabolites, see: (a) Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichim. Acta* **1999**, *32*, 35. (b) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Vögtle, M. *Pure Appl. Chem.* **2003**, *75*, 223. (c) Johnson, R. A. *Org. React.* **2004**, *63*, 117.

(7) (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (b) Overman, L. E.; Carpenter, N. E. *Org. React.* **2005***66*1, and references cited therein.

(8) For related examples of this type of radical reaction, see: (a) Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2006**, *8*, 2143. (b) Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Chem. Asian J.* **2007**, *2*, 1127.

(9) For a very useful review of the Pictet−Spengler reaction, see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.

(10) The regioselectivity observed in the conversion **8** → **9** has been rationlized elsewhere, see: Matveenko, M.; Banwell, M. G.; Willis, A. C. *Tetrahedron* **2008**, *64*, 4817.

(11) Banwell, M. G.; Coster, M. J.; Harvey, M. J.; Moraes, J. *J. Org. Chem.* **2003**, *68*, 613.

Table 2. Comparison of the ^{1}H NMR Data for Naturally-Occurring Montabuphine and Synthetically-Derived **3** and **23**

montabuphine (δ_H)[a]	**3** (δ_H)[b]	**23** (δ_H)[b]
6.54 (s, 1H)	6.54 (s, 1H)	6.54 (s, 1H)
6.46 (s, 1H)	6.45 (s, 1H)	6.45 (s, 1H)
5.88 (d, J = 1.5 Hz, 1H)	5.88 (d, J = 1.0 Hz, 1H)	5.89 (d, J = 1.5 Hz, 1H)
5.86 (d, J = 1.5 Hz, 1H)	5.85 (d, J = 1.0 Hz, 1H)	5.86 (d, J = 1.5 Hz, 1H)
5.53 (dd, J = 2.5 and 2.0 Hz, 1H)	5.50 (m, 1H)	5.53 (broad s, 1H)
4.38 (d, J = 16.5 Hz, 1H)	4.30 (d, J = 16.5 Hz, 1H)	4.34 (d, J = 16.5 Hz, 1H)
4.18 (ddd, J = 5.0, 3.5 and 2.5 Hz, 1H)	4.20 (broad s, 1H)	4.07 (broad s, 1H)
3.87 (d, J = 16.5 Hz, 1H)	3.79 (d, J = 16.5 Hz, 1H)	3.81 (d, J = 16.5 Hz, 1H)
3.70 (ddd, J = 5.0, 4.5 and 1.5 Hz, 1H)	3.72 (m, 1H)	3.54 (m, 1H)
3.54 (broad, J = 13.0 Hz, 1H)	3.43 (broad m, 1H)	3.38 (s, 3H)
3.39 (s, 3H)	3.41 (s, 3H)	3.34 (m, 1H)
3.30 (d, J = 2.0 Hz, 1H)	3.20 (broad d, J = 1.5 Hz, 1H)	3.27 (broad s, 1H)
3.11 (dd, J = 11.0 and 2.0 Hz, 1H)	3.02 (d, J = 11.0 Hz, 1H)	3.07 (m, 1H)
3.07 (d, J = 11.0 Hz, 1H)	3.00 (dd, J = 11.0 and 2.0 Hz, 1H)	3.04 (d, J = 11.5 Hz, 1H)
2.70 (ddd, J = 13.0, 4.5 and 4.5 Hz, 1H)	2.57 (td, J = 13.0 and 4.5 Hz, 1H)	2.28 (m, 1H)
—	—	1.72 (broad s, 1H, OH)
1.58 (ddd, J = 13.0, 13.0 and 1.5 Hz, 1H)	1.48 (td, J = 13.0 and 1.5 Hz, 1H)	1.49 (td, J = 13.0 and 3.5 Hz, 1H)

[a] Data from ref 4 and recorded in $CDCl_3$ at 500 MHz. [b] Data arising from work reported in this paper and recorded in $CDCl_3$ at 500 MHz.

crystal X-ray analysis. Initial attempts to effect the conversion of allylic alcohol **23** into its epimer involved subjecting the former compound to a Mitsunobu reaction with α-chloroacetic acid as nucleophile.[12] However, no useful outcomes were obtained under such conditions. Accordingly, compound **23** was oxidized to the corresponding enone **24** (91%) using the Dess−Martin periodinane (DMP)[13] and this was then reduced to target **3** (84% from **23**) using the Luche reagent.[14]

The physical and spectral data derived from compound **3** were in full accord with the assigned structure[15] but did not match those reported[4] for (+)-montabuphine. Thus, the specific rotation of the synthetically-derived material is +120 (*c* 0.10, ethanol) whereas that recorded for the title alkaloid is +157 (*c* 0.106, ethanol). Furthermore, compound **3** was obtained as a microcrystalline solid melting between 62 and 66 °C while (+)-montabuphine is reported[4] to have a melting range of 162 to 164 °C. While the EI mass spectra and the infrared spectra of the two compounds compare reasonably well, the corresponding ^{13}C NMR spectra (Table 1) do not. Most obviously, the lowest field of the signals observed in the spectrum of the natural product appears at δ 150.8 while in the spectrum of synthetically-derived **3** the equivalent signal appears at δ 153.6, in keeping with the chemical shifts observed for the analogous carbon in the related compounds **23**, **25** [(−)-coccinine], **26** [(−)-montanine], and **27** (Figure 3).

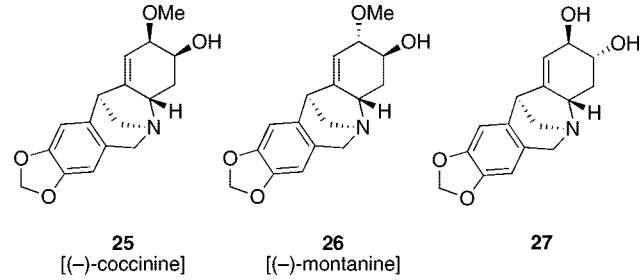


Figure 3. Structures of compounds **25**−**27**.

A comparison of the ^{1}H NMR spectral data recorded on compounds **3** and **23** with those reported[4] for (+)-montabuphine is presented in Table 2. Once again, there are discrepancies between the data sets for the natural product and the synthetically-derived material. On this basis, and given the variations noted above, we conclude that structure **3** has been incorrectly assigned to the alkaloid (+)-montabuphine. Work is now underway in our laboratories to try and establish the true structure of this natural product.

Acknowledgment. We thank the Institute of Advanced Studies and the Australian Research Council for generous financial support. Robert J. Dancer (H. Lundbeck A/S, Denmark) is thanked for helpful discussions.

Supporting Information Available: Full experimental procedures; ^{1}H and/or ^{13}C NMR spectra of compounds **3**, **7**−**15**, and **18**−**24**; single-crystal X-ray data and atomic displacement ellipsoid plots for compound **23** and the oxalate salt of **3** (CCDC numbers 697100 and 699621, respectively). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Saïah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317.

(13) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. A very well-defined method for preparing this useful reagent has been reported: (c) Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **1999**, *77*, 141.

(14) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Luche, J.-L.; Rodriguez-Hahn, L.; Crabbé, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601. For a useful review of lanthanide reagents in organic synthesis, see: (c) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

(15) The structure of synthetically-derived **3** was confirmed by a single crystal X-ray analysis of its oxalate salt.