Alkaloid Synthesis

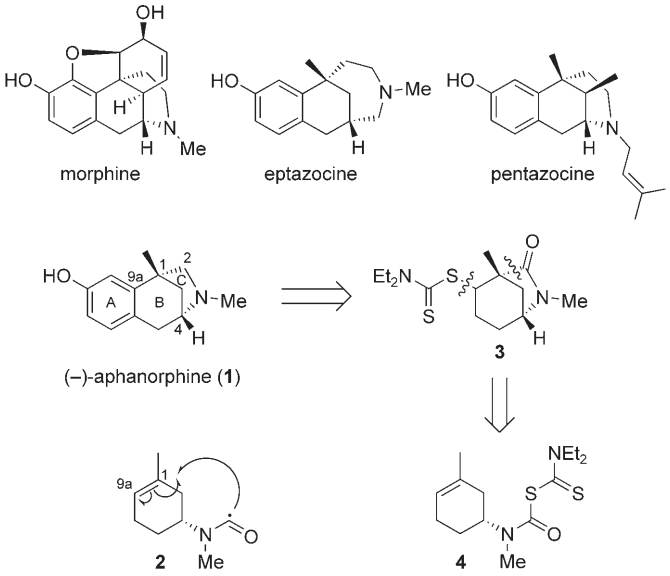
DOI: 10.1002/anie.200701055

Formal Synthesis of (−)-Aphanorphine Using Sequential Photomediated Radical Reactions of Dithiocarbamates**

Richard S. Grainger and Emma J. Welsh*

Aphanorphine (**1**), an alkaloid isolated from the freshwater blue-green alga *Aphanizomenon flos-aquae*,[1] has attracted considerable attention from the synthetic community owing to its structural similarity to natural and non-natural analgesics such as morphine, eptazocine, and pentazocine (Scheme 1).[2] Approaches to aphanorphine developed to date have all relied on the formation of the B or C ring to complete the *C*-norbenzomorphan skeleton, typically exploiting the rigidity of the bridged tricyclic 3-benzazepine structure to set the second stereocenter from a preexisting quaternary benzylic stereocenter at C1,[2a–d,i,k] or from an α-branched amine at C4.[2n,o,r,t–v,x,y] In this communication we present a complementary strategy for the synthesis of aphanorphine which is characterized by the late-stage incorporation of the aromatic A ring, and formation of the pyrrolidine C ring through a novel carbon–carbon bond-forming reaction.

We have recently reported a new method for the generation of carbamoyl (aminoacyl) radicals from dithiocarbamate precursors, and their subsequent intramolecular addition—dithiocarbamate group-transfer reactions with alkenes.[3] Application of this methodology to the synthesis of the core 6-azabicyclo[3.2.1]octane ring system of aphanorphine was envisaged based upon a regioselective 5-*exo*-trig cyclization of carbamoyl radical **2** followed by dithiocarbamate group transfer to give the functionalized bicyclic lactam **3** (Scheme 1). It was further envisaged that the dithiocarbamate group in **3** would provide a handle for phenol annulation. Critical to the success of such an approach is the ability of carbamoyl radicals generated from dithiocarbamate precursors to undergo potentially difficult cyclizations onto unactivated alkenes.[3,4] Previous work by Quirante, Bonjoch, et al. had shown that α-amino radicals undergo analogous cyclizations onto alkenes carrying electron-withdrawing groups at C9a (aphanorphine numbering);[5] however, unactivated alkenes did not undergo cyclization. The effect of a further alkene substituent at C1, which may also disfavor 5-*exo*-trig cyclization, was not evaluated.[6]



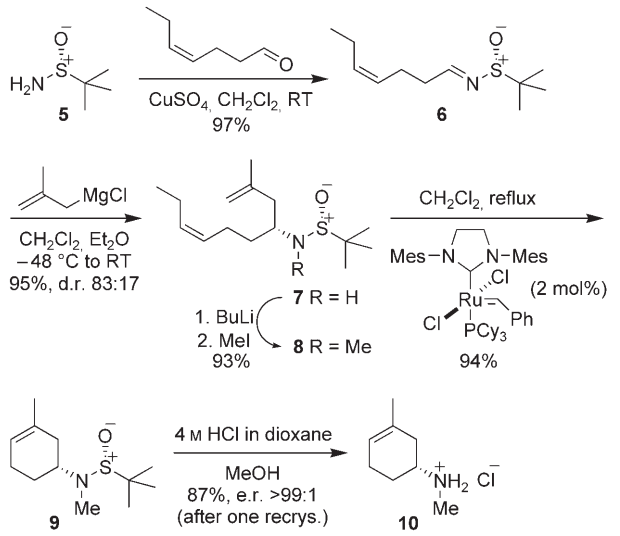
Scheme 1. Analgesics structurally related to aphanorphine and a retrosynthesis of (−)-aphanorphine (**1**).

An asymmetric synthesis of the requisite secondary cyclohexenylamine is outlined in Scheme 2 and relies on Ellman's sulfinamide auxiliary to set the amino-substituted stereocenter destined to be C4 of aphanorphine.[7,8] Condensation of enantiomerically pure (*R*)-*tert*-butanesulfinamide (**5**) with commercially available *cis*-4-heptenal gave the expected (*E*)-sulfinimine **6** (Scheme 2).[9,10] Addition of 2-methylallylmagnesium chloride gave rise to sulfinamide **7** in excellent yield as a 83:17 mixture of diastereoisomers.[11] The configuration of the major stereoisomer **7** was predicted to be *R* on the basis of the Ellman model[7] and was ultimately proven through a formal synthesis of (−)-aphanorphine. Separation of the two diastereomers could not be achieved at this stage, and so the mixture was carried through the following steps. Following N-methylation of **7**,[12] 1,7-diene **8** was subjected to ring-closing metathesis using the Grubbs second-generation catalyst,[13] which furnished the trisubstituted alkene **9** in excellent yield.[14] Finally removal of the sulfinyl auxiliary under acidic conditions gave the hydrochloride salt **10**.[7] At this stage, a single recrystallization of **10** gave enantiomerically pure material.[15]

[*] Dr. R. S. Grainger, E. J. Welsh
School of Chemistry
University of Birmingham
Edgbaston, Birmingham B15 2TT (UK)
Fax: (+44) 121-414-4403
E-mail: r.s.grainger@bham.ac.uk
Homepage: http://www.chem.bham.ac.uk/staff/grainger.shtml

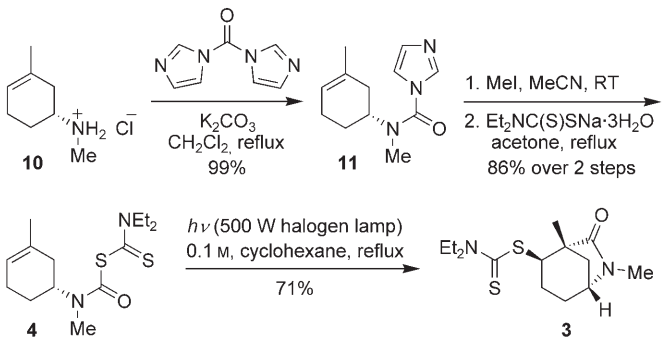
[**] We thank EPSRC, King's College London, and University of Birmingham for funding (DTA studentship to E.J.W.). R.S.G. thanks EPSRC for the award of an Advanced Research Fellowship (2005–2010). We additionally thank Dr. Andreas E. Goeta (Durham University) for X-ray crystallography, Dr. Neil Spencer (University of Birmingham) for NMR experiments, and Graham Burns (University of Birmingham) for HPLC analysis.

Supporting information for this article (experimental procedures, analytical data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds, and structure of **3** from X-ray coordinates) is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Asymmetric synthesis of secondary amine. Cy = cyclohexyl, Mes = mesityl.

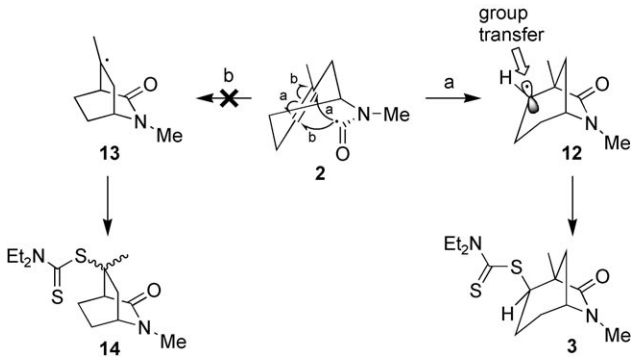
We have previously developed a two-step synthesis of carbamoyl dithiocarbamates from secondary amines by first treatment with triphosgene and pyridine to give the carbamoyl chloride, followed by chloride displacement with sodium diethyldithiocarbamate at room temperature in acetone.[3] Although such a procedure could in principle be used in the case of the free base derived from **10**, we were wary of volatility issues associated with such a low-molecular-weight amine and instead sought to develop a method that avoided the isolation of the free amine. Batey et al. have recently reported carbamoylimidazolium salts as synthetic alternatives to carbamoyl chorides in displacement reactions with amines, alcohols, and thiols.[16] Treatment of ammonium salt **10** with carbonyldiimidazole in the presence of potassium carbonate gave the carbamoylimidazole **11** in essentially quantitative yield (Scheme 3). Activation of **11** through N-methylation gave a carbamoyl imidazolium salt.[16] Using sodium diethyldithiocarbamate as a nucleophile, displacement was best achieved in refluxing acetone to give the radical-cyclization precursor **4** in 86% yield over two steps. Gratifyingly, **4** underwent clean photoinitiated group-transfer radical cyclization under our standard conditions[3] to give a single



Scheme 3. Formation of carbamoyl dithiocarbamate and group-transfer radical cyclization.

product **3**, isolated in 71% yield. The structure of **3** was ultimately confirmed by X-ray crystallography.[17]

The formation of **3** is consistent with a 5-*exo*-trig cyclization of carbamoyl radical **2** to form a bridged azabicyclo-[3.2.1]octane ring system (path a, Scheme 4), followed by a

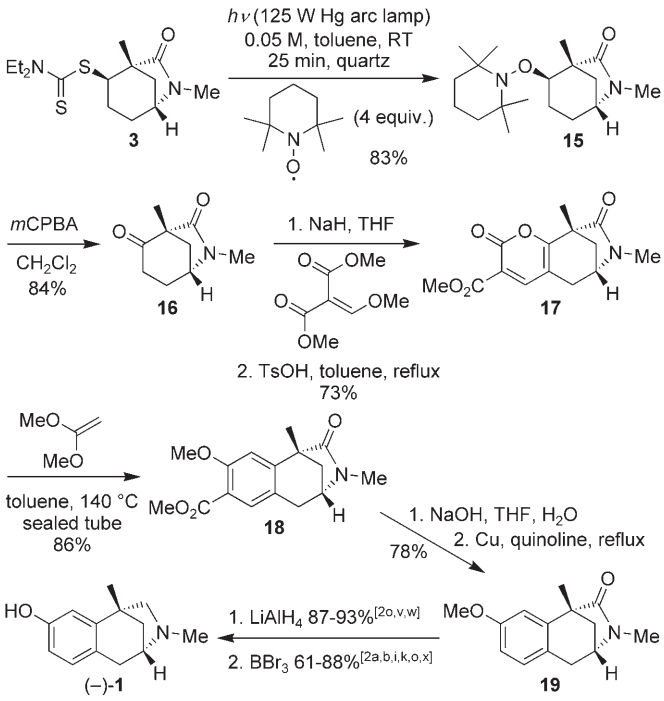


Scheme 4. Regio- and stereoselectivity in dithiocarbamate group-transfer radical cyclization.

stereoselective group-transfer to the secondary radical **12** to give the axial dithiocarbamate **3**. We did not observe formation of any products **14** containing the azabicyclo-[2.2.2]octane ring system derived from a 6-*endo*-trig cyclization onto the less-substituted end of the double bond (path b). The presence of a methyl group at the site of attack on the double bond is clearly not sufficient to unduly influence this particular radical cyclization.[6]

With formation of the bridged 6-azabicyclo[3.2.1]octane ring system in hand, our attention turned to using the dithiocarbamate group as a means to introduce the phenol ring of the natural product. We were particularly attracted by the idea of having a carbonyl group in place of the dithiocarbamate in **3** (see below). Although a number of sequences can be envisaged for such a transformation,[18] we were intrigued by the possibility of initiating a new radical process from dithiocarbamate **3**. Although the trapping of free radicals with both the 2,2,6,6-tetramethyl-1-piperidinoxyl radical (TEMPO) and oxygen to form new carbon–oxygen single bonds is well precedented,[19] use of dithiocarbamates as precursors to alkyl radicals is relatively rare,[20] and we are aware of only one example of a radical-chain process using Bu_3SnH having been reported.[21] Keen to avoid the use of Bu_3SnH due to toxicology and potential separation issues,[22] we instead elected to further our investigations into the use of light to initiate radical processes from dithiocarbamates. To our delight, irradiation of a solution of dithiocarbamate **3** with a medium-pressure mercury arc lamp in a quartz reaction vessel in the presence of TEMPO resulted in the formal replacement of a carbon–sulfur bond with a carbon–oxygen bond and the clean formation of a single adduct **15** (Scheme 5). We believe this result is consistent with radical **12** being regenerated and stereoselectively trapped with TEMPO[23] and represents a new reaction manifold for dithiocarbamates.[24]

The TEMPO adduct **15** was directly oxidized to ketone **16** using *m*CPBA (Scheme 5).[25] Initial attempts to use ketone **16**



Scheme 5. Photomediated dithiocarbamate–TEMPO exchange and phenol annulation.

for phenol formation using modified Robinson annulation conditions met with failure.[26] However, use of an alternative procedure developed by Boger and Mullican proved more successful.[27] Hence, reaction of **16** with dimethoxymethylene malonate under basic conditions followed by acid-catalyzed dehydration gave the electron-deficient pyrone **17** in 73% overall yield. Inverse-electron-demand Diels–Alder reaction with dimethoxyethylene ketal followed by in situ loss of CO_2 and MeOH gave the tetrasubstituted aromatic compound **18**. Removal of the ester group was accomplished by first hydrolysis to the corresponding carboxylic acid, followed by copper-mediated decarboxylation.[27] The resulting lactam **19** had an optical rotation consistent with that reported in the literature,[2v] and its preparation constitutes a formal total synthesis of (−)-aphanorphine (**1**). Conversion of **19** to the natural product has previously been accomplished in two steps—reduction of the amide to the amine using $LiAlH_4$ in 87–93% yield,[2o,v,w] followed by O-demethylation using BBr_3 in yields ranging from 61–88%.[2a,b,i,k,o,x]

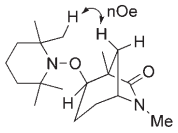
In conclusion, a formal total synthesis of (−)-aphanorphine has been achieved using a carbamoyl radical cyclization to prepare the 6-azabicyclo[3.2.1]octane ring system of the natural product, followed by a novel photomediated dithiocarbamate–TEMPO exchange reaction to introduce oxygen functionality and facilitate formation of the aromatic ring. Lactam **19**, a known intermediate in aphanorphine synthesis, was prepared in 13 steps and 14% overall yield starting from commercially available materials. In the course of this work a new method for the synthesis of carbamoyl dithiocarbamates has also been developed.

Received: March 9, 2007
Published online: June 6, 2007

Keywords: cyclization · metathesis · oxidation · radical reactions · sulfinamides

[1] N. Gulavita, A. Hori, Y. Shimizu, P. Laszlo, J. Clardy, *Tetrahedron Lett.* **1988**, *29*, 4381–4384.
[2] Total and formal syntheses: a) S. Takano, K. Inomata, T. Sato, K. Ogasawara, *J. Chem. Soc. Chem. Commun.* **1989**, 1591–1592; b) S. Takano, K. Inomata, T. Sato, M. Takahashi, K. Ogasawara, *J. Chem. Soc. Chem. Commun.* **1990**, 290–292; c) T. Honda, A. Yamamoto, Y. Cui, M. Tsubuki, *J. Chem. Soc. Perkin Trans. 1* **1992**, 531–532; d) A. I. Meyers, W. Schmidt, B. Santiago, *Heterocycles* **1995**, *40*, 525–529; e) A. N. Hulme, S. S. Henry, A. I. Meyers, *J. Org. Chem.* **1995**, *60*, 1265–1270; f) A. Fadel, P. Arzel, *Tetrahedron: Asymmetry* **1995**, *6*, 893–900; g) K. O. Hallinan, T. Honda, *Tetrahedron* **1995**, *51*, 12211–12216; h) M. Node, H. Imazato, R. Kurosaki, Y. Kawano, T. Inoue, K. Nishide, K. Fuji, *Heterocycles* **1996**, *42*, 811–819; i) S. Shiotani, H. Okada, K. Nakamata, T. Yamamoto, F. Sekino, *Heterocycles* **1996**, *43*, 1031–1047; j) A. Fadel, P. Arzel, *Tetrahedron: Asymmetry* **1997**, *8*, 283–291; k) M. Shimizu, T. Kamikubo, K. Ogasawara, *Heterocycles* **1997**, *46*, 21–26; l) A. Fadel, P. Arzel, *Tetrahedron: Asymmetry* **1997**, *8*, 371–374; m) K. Tanaka, T. Taniguchi, K. Ogasawara, *Tetrahedron Lett.* **2001**, *42*, 1049–1052; n) O. Tamura, T. Yanagimachi, T. Kobayashi, H. Ishibashi, *Org. Lett.* **2001**, *3*, 2427–2429; o) J. R. Fuchs, R. L. Funk, *Org. Lett.* **2001**, *3*, 3923–3925; p) A. S. ElAzab, T. Taniguchi, K. Ogasawara, *Heterocycles* **2002**, *56*, 39–43; q) S. K. Taylor, M. Ivanovic, L. J. Simons, M. M. Davis, *Tetrahedron: Asymmetry* **2003**, *14*, 743–747; r) O. Tamura, T. Yanagimachi, H. Ishibashi, *Tetrahedron: Asymmetry* **2003**, *14*, 3033–3041; s) Y. Kita, J. Futamura, Y. Ohba, Y. Sawama, J. K. Ganesh, H. Fujioka, *J. Org. Chem.* **2003**, *68*, 5917–5924; t) H. Zhai, S. Luo, C. Ye, Y. Ma, *J. Org. Chem.* **2003**, *68*, 8268–8271; u) H. Hu, H. Zhai, *Synlett* **2003**, 2129–2130; v) J. F. Bower, P. Szeto, T. Gallagher, *Chem. Commun.* **2005**, 5793–5795; w) M. Katoh, H. Inoue, A. Suzuki, T. Honda, *Synlett* **2005**, 2820–2822; x) M. Li, P. Zhou, H. F. Roth, *Synthesis* **2007**, 55–60; y) Z. Ma, H. Zhai, *Synlett* **2007**, 161–163; z) J. F. Bower, P. Szeto, T. Gallagher, *Org. Biomol. Chem.* **2007**, *5*, 143–150.
[3] R. S. Grainger, P. Innocenti, *Angew. Chem.* **2004**, *116*, 3527–3530; *Angew. Chem. Int. Ed.* **2004**, *43*, 3445–3448.
[4] This principle has been extensively developed by Zard for the generation and reaction of a number of radicals using xanthate precursors. For a recent review see: B. Quiclet-Sire, S. Z. Zard, *Chem. Eur. J.* **2006**, *12*, 6002–6016.
[5] J. Quirante, X. Vila, C. Escolano, J. Bonjoch, *J. Org. Chem.* **2002**, *67*, 2323–2328.
[6] For competitive formation of [3.2.1] vs. [2.2.2] bicyclic ring systems through radical cyclization see: a) W. F. Berkowitz, P. J. Wilson, *J. Org. Chem.* **1991**, *56*, 3097–3102; b) A. Srikrishna, P. Hemamalini, *Tetrahedron* **1992**, *48*, 9337–9354; c) M. Toyota, M. Yokota, M. Ihara, *Tetrahedron Lett.* **1999**, *40*, 1551–1554; d) M. Toyota, M. Yokota, M. Ihara, *J. Am. Chem. Soc.* **2001**, *123*, 1856–1861; e) E. W. Della, P. A. Smith, *J. Chem. Soc. Perkin Trans. 1* **2001**, 445–451.
[7] D. A. Cogan, G. Liu, J. Ellman, *Tetrahedron* **1999**, *55*, 8883–8904.
[8] For a recent review on the use of sulfinimines in asymmetric synthesis see: D. Morton, R. A. Stockman, *Tetrahedron* **2006**, *62*, 8869–8905.
[9] G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 1278–1284.
[10] (*R*)-*tert*-Butanesulfinamide (**5**) is commercially available but can be readily prepared on large scale: D. J. Weix, J. A. Ellman, *Org. Synth.* **2005**, *82*, 157–165.

[11] The d.r. value was determined by integration of the ^{1}H NMR spectrum of the crude reaction mixture and confirmed by HPLC analysis.
[12] S. Colonna, G. Germinario, A. Manfredi, C. J. M. Stirling, *J. Chem. Soc. Perkin Trans. 1* **1988**, 1695 – 1698.
[13] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953 – 956.
[14] For a further example of ring-closing metathesis in the presence of the sulfinamide group see: F. A. Davis, Y. Wu, *Org. Lett.* **2004**, *6*, 1269 – 1272. For a recent review on metathesis reactions in total synthesis, see: K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564 – 4601; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490 – 4527.
[15] The e.r. value was determined by chiral HPLC analysis of corresponding carbamoylimidazole **11**.
[16] J. A. Grzyb, M. Shen, C. Yoshina-Ishii, W. Chi, R. S. Brown, R. A. Batey, *Tetrahedron* **2005**, *61*, 7153 – 7175. For earlier precedent see: D. G. Oakenfull, K. Salvesen, W. P. Jenks, *J. Am. Chem. Soc.* **1971**, *93*, 188 – 194.
[17] CCDC-639680 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The structure of **3** from X-ray coordinates is also shown in the Supporting Information.
[18] This formal transformation has been achieved on allylic dithiocarbamates by deprotonation with lithium diisopropylamide, trapping with MeSSMe, and hydrolysis of the resulting mixed thioacetal to an α,β-unsaturated aldehyde: T. Nakai, H. Shiono, M. Okawara, *Tetrahedron Lett.* **1974**, *15*, 3625 – 3628. Attempts to deprotonate adjacent to the dithiocarbamate group in **3** followed by trapping with electrophiles have so far proved unsuccessful.
[19] C. Ollivier, P. Renaud in *Radicals in Organic Synthesis*, *Vol. 2* (Eds: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, **2001**, pp. 93 – 112.
[20] Dithiocarbamates have been used as mediators in free-radical polymerization by the RAFT method. For a review see: a) G. Moad, E. Rizzardo, S. H. Thang, *Aust. J. Chem.* **2005**, *58*, 379 – 410; For trapping of alkyl radicals with dithiocarbamates see: b) G. Bouhadir, N. Legrand, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1999**, *40*, 277 – 280; c) S. H. Thang, Y. K. Chong, R. T. A. Mayadunne, G. Moad, E. Rizzardo, *Tetrahedron Lett.* **1999**, *40*, 2435 – 2438; d) D. Harakat, J. Pesch, S. Marinkovic, N. Hoffmann, *Org. Biomol. Chem.* **2006**, *4*, 1202 – 1205.
[21] M. Yanagawa, O. Moriya, Y. Watanabe, Y. Ueno, T. Endo, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2203 – 2204.
[22] a) P. A. Baguley, J. C. Walton, *Angew. Chem.* **1998**, *110*, 3272 – 3283; *Angew. Chem. Int. Ed.* **1998**, *37*, 3072 – 3082; b) A. Studer, S. Amrein, *Synthesis* **2002**, 835 – 849.
[23] The relative stereochemistry in **15** has been assigned as shown on the basis of nOe spectroscopy and the expectation that the trapping of cyclohexenyl radical **12** by TEMPO will occur with the same facial selectivity as that observed in the dithiocarbamate group-transfer reaction (Scheme 4).



[24] If the cyclization of **4** to **3** is run in the presence of TEMPO, dithiocarbamate **3** is not obtained. Instead the initial carbamoyl radical **2** is trapped with the TEMPO prior to cyclization.
[25] T. Inokuchi, H. Kawafuchi, *Tetrahedron* **2004**, *60*, 11 969 – 11 975.
[26] a) D. L. Boger, M. D. Mullican, *J. Org. Chem.* **1980**, *45*, 5002 – 5004. b) O. Barun, S. Nandi, K. Panda, H. Ila, H. Junjappa, *J. Org. Chem.* **2002**, *67*, 5398 – 5401.
[27] D. L. Boger, M. D. Mullican, *J. Org. Chem.* **1984**, *49*, 4033 – 4044.

