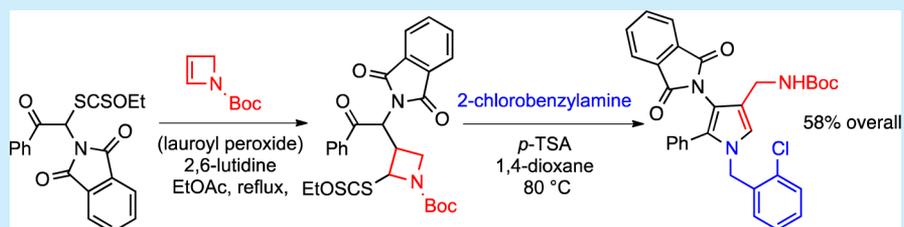


## Modular Approach to Substituted Boc-Protected 4-(Aminomethyl)pyrroles

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**S** Supporting Information



**ABSTRACT:** The radical addition of various  $\alpha$ -xanthy ketones to Boc-protected azetidine gives adducts which, when treated with ammonia or primary amines, furnish 2,4-disubstituted, 2,3,4-trisubstituted, and polycyclic pyrroles having a protected aminomethyl group at position 4. An unusual ring-opening was observed in the case of a cyclobutanone precursor.

The pyrrole ring is one of the basic heteroaromatic motifs found as a structural element in numerous biologically active alkaloids, pharmaceutical products, or even in such materials as conducting polymers.<sup>1</sup> For instance, Lipitor, a pyrrole-based statin, was for many years the largest selling drug, with yearly sales in excess of 10 billion U.S. dollars.<sup>2</sup> 2,4-Disubstituted pyrroles are especially interesting since they are useful intermediates for the synthesis of more highly substituted derivatives and are present in a few pharmacologically significant products.<sup>3</sup> Three examples of 2,4-disubstituted pyrrole natural products are displayed in Figure 1: Hymenidin is an antagonist of serotonergic receptors,<sup>3b,c</sup> pyrrolostatin is a potent inhibitor of lipid peroxidation,<sup>3d</sup> and heronapyrroles A and B display antibiotic activity against Gram-positive bacteria such as *Staphylococcus aureus* and *Bacillus subtilis*.<sup>3e</sup>

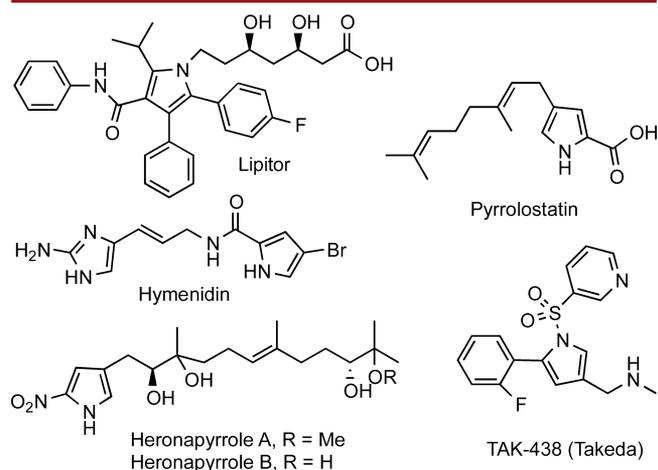


Figure 1. Examples of biologically active pyrroles.

We were, however, intrigued by TAK-438, an unusual pyrrole developed by Takeda, where the introduction of a methylaminomethyl group at the 4-position of the ring greatly improved its potential as a gastric antisecretory agent.<sup>4</sup> Indeed, this compound was selected as a drug candidate for the treatment of gastroesophageal reflux disease (GERD), peptic ulcer, and other gastric acid-related diseases.

There are a plethora of methods for the synthesis of pyrroles, such as the classical Hantzsch, Knorr, and Paal–Knorr reactions, and metal-based or 1,3-dipolar cycloadditions strategies;<sup>5,6</sup> however, only a limited number of examples dealing with metal-free, modular, and direct construction of the more unusual 2,4-disubstituted pyrroles have been reported (the Hantzsch reaction being most prominent).<sup>7</sup> In particular, the current methods to obtain 4-(aminomethyl)-substituted pyrroles are mainly based on reductive amination of the corresponding pyrrole 4-carboxaldehydes.<sup>4,8</sup> Recently, Huestis et al. reported a rhodium-catalyzed approach to unsymmetrical 2,3-aliphatic-substituted indoles and pyrroles, but only one example had a *tert*-butyl carbamate-protected aminomethyl group on position 3 of the pyrrole ring.<sup>9</sup>

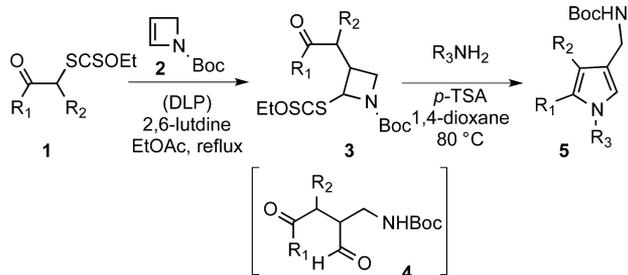
The need for modular and direct synthetic protocols encouraged us to examine the applicability of xanthate chemistry to design flexible routes to pyrroles related to TAK-438. Xanthates allow many otherwise difficult inter- or intramolecular additions to olefins to occur,<sup>10</sup> and the ability to add to various strained alkanes such as cyclopropenes, cyclobutenes, and azetines opens numerous possibilities to access unusual structures.<sup>11</sup> In the present context, the addition of an  $\alpha$ -ketonyl xanthates **1** to Boc-protected azetidine **2** would give adducts **3**. These compounds represent in principle

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compact synthetic equivalents of 1,4-ketoaldehydes **4**, which would be extremely difficult to access. The reaction of adducts **3** with ammonia or a primary amine in the presence of acid should therefore lead to the desired pyrroles **5** (Scheme 1). We

### Scheme 1. Route to Aminomethyl-Substituted Pyrroles

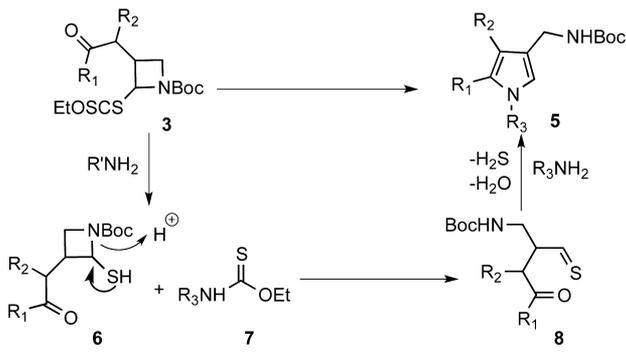


had in the past tested successfully a conceptually related approach involving addition to vinyl pivalate.<sup>12</sup> By this route, 2-substituted or 2,3-disubstituted pyrroles are readily available, but not 2,4-di- or 2,3,4-trisubstituted derivatives **5**.

*N*-Protected azetidine **2** is easily prepared from cheap commercially available *N*-Boc-3-hydroxyazetidine by sulfonylation and elimination (Scheme 1).<sup>13</sup> In the event, the lauroyl peroxide (DLP) mediated radical addition of various xanthates to azetidine **2** proceeded in generally good yield, and exposure of the resulting adducts **3** to the action of a range of primary amines or ammonia and *p*-TsOH (0.5 equiv with respect to the adduct **3**) in hot dioxane (80 °C) indeed furnished the corresponding pyrroles **5** very efficiently within a short reaction time (ca. 1 h).

A plausible mechanism for the pyrrole formation is outlined in Scheme 2. Aminolysis of the xanthate group results in the

### Scheme 2. Mechanism for the Formation of Pyrroles



formation of thiol **6**, which must readily undergo ring-opening to thioaldehyde **8** to relieve the strain of the azetidine ring. Finally, condensation of the amine with both the reactive thioaldehyde and the ketone provides the pyrrole. The last step is analogous to the chemical condensation of primary amines or ammonia with 1,4-diketones or 1,4-ketoaldehydes (Paal–Knorr reaction).

Our results are compiled in Tables 1 and 2. The two steps could be performed without purification of the intermediate adducts and with the same overall efficiency. This is illustrated by the synthesis of pyrroles **5m** and **5n** in Table 1 and by all the pyrroles compiled in Table 2. While the pyrroles in Table 1 are 2,4-disubstituted, those in Table 2 are 2,3,4-trisubstituted derivatives.

Table 1. Formation of 2,4-Disubstituted Pyrroles

xanthate <b>1</b>	adduct <b>3</b> <sup>a</sup>	amine	pyrrole <b>5</b> (yield %)
		benzylamine	 <b>5a</b> (87%)
		cyclopropylamine	 <b>5b</b> (93%)
		ammonia	 <b>5c</b> (95%)
		3,4-dichloro-benzylamine	 <b>5d</b> (91%)
		ammonia	 <b>5e</b> (91%)
		2-methoxyethylamine	 <b>5f</b> (94%)
		ammonia	 <b>5g</b> (82%)
		furfurylamine	 <b>5h</b> (92%)
		2-methylallylamine	 <b>5i</b> (88%)
		2-chlorobenzylamine	 <b>5j</b> (83%)
		2-chlorobenzylamine	 <b>5k</b> (64%)
		2-chlorobenzylamine	 <b>5k'</b> (18%)
		ammonia	 <b>5l</b> (92%)
		benzylamine	 <b>5m</b> (63%) <sup>b</sup>
		allylamine	 <b>5n</b> (68%) <sup>b</sup>

<sup>a</sup>The dr was measured by NMR spectroscopy after purification by column chromatography. <sup>b</sup>Overall yield for the two steps.

The radical addition to azetidine **2** to give the intermediate adducts **3** is regioselective in part because of polar effects: the ketonyl radicals derived from xanthates **1** are electrophilic in nature and prefer to add to the most nucleophilic terminus of the alkene. Steric hindrance by the Boc- group also favors the

Table 2. Synthesis of 2,3,4-Trisubstituted Pyrroles

xanthate <b>1</b>	adduct <b>3<sup>d</sup></b>	amine	pyrrole <b>5</b> (yield %) <sup>b</sup>
		ammonia	
		propargylamine	
		allylamine	
		allylamine	
		2-chlorobenzylamine	
		2-chlorobenzylamine	
		benzylamine	

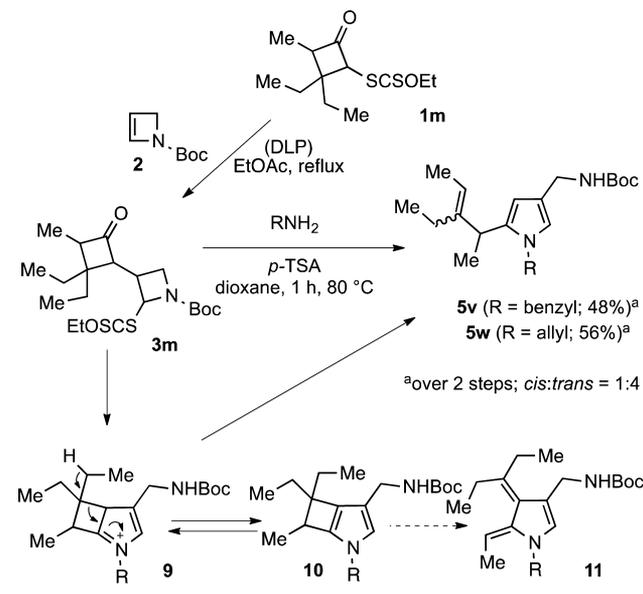
<sup>a</sup>The crude adduct was used directly in the second step after a quick purification on silica gel. <sup>b</sup>Overall yield for the two steps.

observed regiochemistry. Furthermore, it is clear from the transformations in both tables that numerous functional groups may be introduced, either through the xanthate partner or through the amine moiety. Thus, functionality in the xanthate allows the incorporation of an aryl, a cyclopropyl, or a trifluoromethyl group (examples **5a–f,m,n,t**), an ethoxycarbonylmethyl, or a phosphonomethyl group as in pyrroles **5k** and **5l**. In the former case, it was necessary to use a full equivalent of *p*-TsOH to avoid aminolysis of the ester group. This, however, came at a small cost since some acid-catalyzed de-ethoxycarboxylation leading to **5k'** was also observed.

Perhaps more interesting is the synthesis of pyrroles containing differentially protected aminomethyl motifs such as **5o–q** and **5j** (Tables 1 and 2). In the former, the second aminomethyl moiety is embedded in a fused six-membered ring. The ease of access to polycyclic pyrroles by this approach is also worthy of note. The acetal in intermediate **3l** did not withstand the acidic conditions and directly furnished pyrrolecarboxaldehyde **5u**. This compound could in principle be subjected to reductive amination reactions leading to more elaborate 3,4-bis-(aminomethyl)pyrroles. Finally, pyrrole **5t** is in fact a masked 3-aminopyrrole, since the phthalimido group is directly linked to the pyrrole nucleus. Routes to amino pyrroles are very scarce, and rely essentially on reduction of the corresponding nitropyrroles.<sup>5</sup> Furthermore, free amino-pyrroles are labile entities that are highly sensitive to air oxidation and the presence of the electron-withdrawing phthalimide is essential in stabilizing the structure.

We made an unexpected observation in the case of cyclobutanone adduct **3m** derived by addition of xanthate **1m** to azetidine **2** (Scheme 3).<sup>14</sup> Upon treatment with benzylamine

Scheme 3. Ring-Opening of a Cyclobutane Intermediate



or allylamine and toluenesulfonic acid, a pyrrole was indeed obtained but the 4-membered ring ruptured under the reaction conditions to afford derivatives **5v** and **5w** in moderate yield. Presumably, the strain inherent in a pyrrolocyclobutanone **10** forces the reaction to proceed by ring-opening of the cyclobutanone in the final aromatization steps, as shown in intermediate **9**. No products arising from a thermal electrocyclic ring-opening to diene **11** were observed.<sup>15</sup>

In summary, we have accomplished a flexible synthesis of diversely substituted pyrroles related to TAK-438. Most of the compounds described herein would be exceedingly tedious to prepare by traditional routes based on ionic or organometallic pathways. The possibility of placing almost any side chain on the nitrogen atom of the pyrrole ring by simply modifying the amine partner is another valuable feature for building libraries. Normally, such side chains are introduced by alkylation, after pyrrole formation, and this often constitutes a serious limitation. Our approach will hopefully allow a better exploration of the pharmacological profile of this class of pyrroles. An ancillary benefit may further be derived from intermediates **3**, since reductive removal of the xanthate group would deliver variously functionalized azetidines scaffolds.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, full spectroscopic data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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## ■ DEDICATION

This paper is dedicated with respect to the memory of Prof. Alan R. Katritzky (University of Florida).

## ■ REFERENCES

- (1) (a) Young, I. S.; Thornton, P. D.; Thompson, A. *Nat. Prod. Rep.* **2010**, *27*, 1801. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264. (c) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517. (d) Gale, P. A. *Acc. Chem. Res.* **2006**, *39*, 465. (e) Baraldi, P. G.; Nunez, M. C.; Tabrizi, M. A.; De Clercq, E.; Balzarini, J.; Bermejo, J.; Esterez, F.; Romagnoli, R. *J. Med. Chem.* **2004**, *47*, 2877. (f) Srivastava, S. K.; Shefali, C. N. M.; Aceto, M. D.; Traynor, J. R.; Lewis, J. W.; Husbands, S. M. *J. Med. Chem.* **2004**, *47*, 6645.
- (2) Thompson, R. B. *FASEB J.* **2001**, *15*, 1671.
- (3) (a) Bergauer, M.; Hubner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1937. (b) Kobayashi, J.; Ohizumi, Y.; Nakamura, H.; Hirata, Y. *Experientia* **1986**, *42*, 1176. (c) Han, S.; Siegel, D. S.; Morrison, K. C.; Hergenrother, P. J.; Movassaghi, M. *J. Org. Chem.* **2013**, *78*, 11970. (d) Kato, S.; Shindo, K.; Kawai, H.; Odagawa, A.; Matsuoka, M.; Mochizuki, J. *J. Antibiot.* **1993**, *46*, 892. (e) Raju, R.; Piggott, A. M.; Barrientos Diaz, L. X.; Khalil, Z.; Capon, R. J. *Org. Lett.* **2010**, *12*, 5158.
- (4) (a) Arikawa, Y.; Nishida, H.; Kurasawa, O.; Hasuoka, A.; Hirase, K.; Inatomi, N.; Hori, Y.; Matsukawa, J.; Imanishi, A.; Kondo, M.; Tarui, N.; Hamada, T.; Takagi, T.; Takeuchi, T.; Kajino, M. *J. Med. Chem.* **2012**, *55*, 4446. (b) Nishida, H.; Hasuoka, A.; Arikawa, Y.; Kurasawa, O.; Hirase, K.; Inatomi, N.; Hori, Y.; Sato, F.; Tarui, N.; Imanishi, A.; Kondo, M.; Takagi, T.; Kajino, M. *Bioorg. Med. Chem.* **2012**, *20*, 3925.
- (5) For general reviews, see: (a) *Pyrrroles, Part II*; Jones, R. A., Ed.; Wiley: New York, 1992. (b) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, U.K., 1996; Vol. 2, p 119ff.
- (6) For selected recent examples of pyrrole syntheses, see: (a) Yan, R.; Kang, X.; Zhou, X.; Li, X.; Liu, X.; Xiang, L.; Li, Y.; Huang, G. *J. Org. Chem.* **2014**, *79*, 465. (b) Yeh, M.-C. P.; Lin, M.-N.; Hsu, C.-H.; Liang, C. J. *J. Org. Chem.* **2013**, *78*, 12381. (c) Zhou, Y.; Yan, X.; Chen, C.; Xi, C. *Organometallics* **2013**, *32*, 6182. (d) Shi, Y.; Gevorgyan, V. *Org. Lett.* **2013**, *15*, 5394. (e) Chaudhuri, R.; Uli Kazmaier, U. *Organometallics* **2013**, *32*, 5546. (f) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384. (g) Alford, J. S.; Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 11712. (h) Wang, X.; Xu, X.-P.; Wang, S.-Y.; Zhou, W.; Ji, S.-J. *Org. Lett.* **2013**, *15*, 4246. (i) Miura, T.; Hiraga, K.; Biyajima, T.; Nakamuro, T.; Murakami, M. *Org. Lett.* **2013**, *15*, 3298. (j) Hu, Y.; Wang, C.; Wang, D.; Wu, F.; Wan, B. *Org. Lett.* **2013**, *15*, 3146. (k) Feng, X.; Wang, Q.; Lin, W.; Dou, G.-L.; Huang, Z.-B.; Shi, D.-Q. *Org. Lett.* **2013**, *15*, 2542. (l) Gabriele, B.; Veltri, L.; Plastina, P.; Mancuso, R.; Vetere, M. V.; Maltese, V. *J. Org. Chem.* **2013**, *78*, 4919. (m) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N. *Org. Lett.* **2013**, *15*, 1966. (n) Parr, B. T.; Green, S. A.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 4716. (o) Iida, K.; Miura, T.; Ando, J.; Saito, S. *Org. Lett.* **2013**, *15*, 1436. (p) Ngwerume, S.; Lewis, W.; Camp, J. E. *J. Org. Chem.* **2013**, *78*, 920. (q) Meng, L.; Wu, K.; Liu, C.; Lei, A. *Chem. Commun.* **2013**, *49*, 5853. (r) Cheng, G.; Wang, X.; Bao, H.; Cheng, C.; Liu, N.; Hu, Y. *Org. Lett.* **2012**, *13*, 1062. (s) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11088. (t) Xin, X.; Wang, D.; Li, X.; Wang, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 1693. (u) Jiang, Y.; Chan, W. C.; Park, C. M. *J. Am. Chem. Soc.* **2012**, *134*, 4104. (v) Herath, A.; Cosford, N. D. P. *Org. Lett.* **2010**, *12*, 5182. (w) Bonnamour, J.; Bolm, C. *Org. Lett.* **2011**, *13*, 2012. (x) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (y) Liu, W.; Jiang, H.; Huang, L. *Org. Lett.* **2010**, *12*, 312.
- (7) See, for example: (a) Zhao, M.-N.; Ren, Z. H.; Wang, Y. Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 608. (b) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Commun.* **2013**, *49*, 591. (c) Chen, F.; Shen, T.; Cui, Y.; Jiao, N. *Org. Lett.* **2012**, *14*, 4926.
- (8) Direct aminoalkylation of pyrroles usually takes place on position 2; see: (a) Korakas, D.; Varvounis, G. *Synthesis* **1994**, *2*, 164. (b) Katritzky, A. R.; Wang, J.; Yang, B. *Synth. Commun.* **1995**, *17*, 2631.
- (9) (a) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338. The synthesis of cyclic 3-aminoalkyl pyrroles has been recently disclosed: (b) Zhuo, C. K.; Wu, Q.-F.; Zhao, Q.; Xu, Q. L.; You, S.-L. *J. Am. Chem. Soc.* **2013**, *135*, 8169. Note that position 3 can become position 4 because the presence of other substituents can modify the numbering around the pyrrole ring.
- (10) For reviews on the xanthate radical addition-transfer process, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (c) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663. (d) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205. (e) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519. For a review on its application to the synthesis of heteroaromatics, see: (f) El Qacemi, M.; Petit, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2012**, *10*, 5707.
- (11) (a) Ferjančić, Z.; Ceković, Z.; Saičić, R. N. *Tetrahedron Lett.* **2000**, *41*, 2979. (b) Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000**, *41*, 9815.
- (12) Quiclet-Sire, B.; Quintero, L.; Sanchez-Jimenez, G.; Zard, S. Z. *Synlett* **2003**, 75.
- (13) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027 3-Hydroxyazetidide (25 g, 32€) and N-Boc-3-hydroxyazetidide (25 g, 78€) are commercially available from Fluorochem.
- (14) This xanthate is prepared by a nontrivial substitution reaction: Heng, R.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2009**, *50*, 3613.
- (15) Only two pyrrolocyclobutanes have been reported; see: (a) Buhr, G. *Chem. Ber.* **1973**, *106*, 3544. (b) Yamasaki, K.; Saito, I.; Matsuura, T. *Tetrahedron Lett.* **1975**, *16*, 313. One diene of type **11** has been generated and captured via a Diels–Alder cycloaddition: (c) Janicki, S. Z.; Petillo, P. A.; Vessels, J. T. *Org. Lett.* **2000**, *2*, 73.