Organic LETTERS

Letter

pubs.acs.org/OrgLett

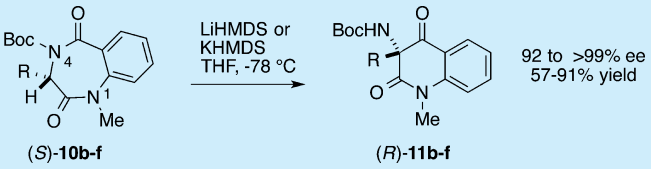
Enantioselective Deprotonative Ring Contraction of *N*1-Methyl-*N*4-Boc-benzo[*e*][1,4]diazepine-2,5-diones

Stephanie A. Antolak, Zhong-Ke Yao, Gary M. Richoux, Carla Slebodnick, and Paul R. Carlier*

Department of Chemistry, Virginia Tech, Blacksburg, Virginia 24061, United States

Supporting Information

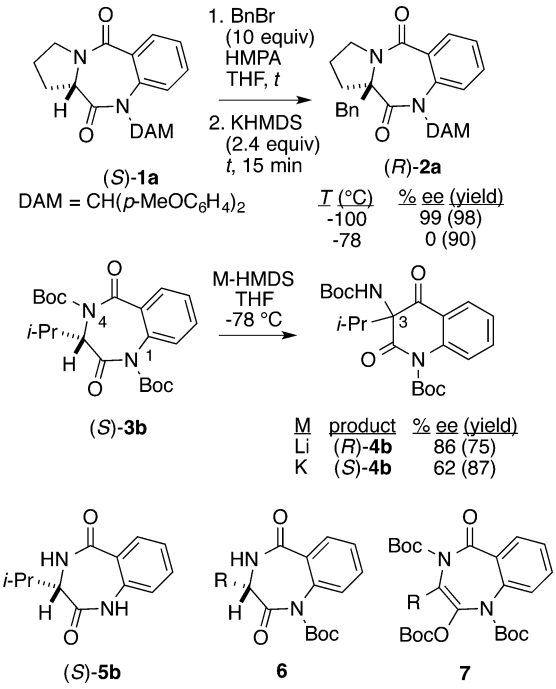
ABSTRACT: *N*1-Methyl-*N*4-Boc-benzo[*e*][1,4]diazepine-2,5-diones were prepared in good yield and high stereochemical purity from five amino acids. Upon deprotonation, these compounds undergo ring contraction to the corresponding quinolone-2,4-diones with high enantioselectivity, providing efficient entry to a potentially useful drug scaffold. Mechanistic commentary and comparisons to related reactions are provided.



(*S*)-**10b-f** (*R*)-**11b-f**

Benzo[*e*][1,4]diazepin-2,5-diones feature prominently in medicinal chemistry,[1] and we have previously reported enantioselective synthetic methods to increase available diversity within this scaffold.[2] Deprotonation of Pro-derived (*S*)-**1a** at −100 °C in the presence of carbon electrophiles gives quaternary benzodiazepine-2,5-diones such as (*R*)-**2a** in high yield and enantiomeric excess (Scheme 1). If this reaction is performed at a warmer temperature (−78 °C), racemic **2a** is obtained, suggesting the intermediacy of a quickly racemizing, axially chiral enolate. Recently Dewynter reported that deprotonation of a Val-derived (*S*)-**3b** in the absence of an electrophile resulted in enantioselective ring contraction to **4b**.[3] Interestingly, LiHMDS and KHMDS were found to give enantiomeric products, in 86% and 62% ee, respectively. This ring contraction constitutes an example of the acyl-amino variant of the Chan reaction,[4] and a related transformation of a benzodiazepine-2,5-dione affording achiral products has been recently disclosed.[5] We were intrigued by the enantiodivergent paths taken by the Li and K enolates derived from (*S*)-**3b**, as well as the potential usefulness of 3,3-disubstituted quinoline-2,4-diones such as **4b** as drug scaffolds.[6] Unfortunately, (*S*)-**3b** was the only substrate investigated in this reaction. Whereas Val-derived (*S*)-**5b** was easily transformed to the *N*1, *N*4-di-Boc derivative (*S*)-**3b**, the same transformation was not possible with substrates derived from L-Ala, Ile, Phe, and phenylglycine; in these reactions only mono- and tri-Boc derivatives **6** and **7** were obtained.[3]

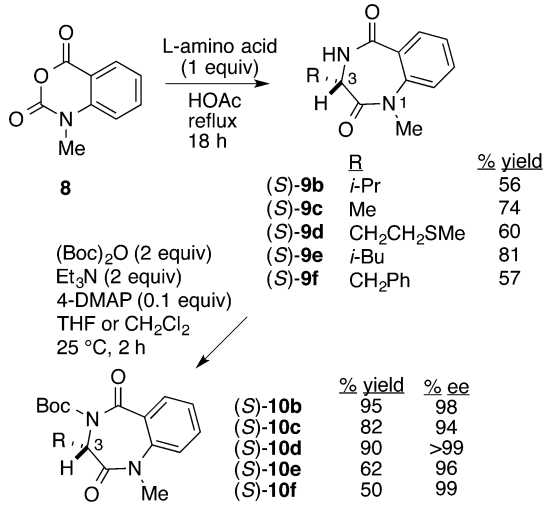
Scheme 1. Enantioselective Deprotonation/Alkylation[2] and Deprotonative Ring-Contraction[3] Reactions of Benzo[*e*][1,4]diazepin-2,5-diones



Received: September 3, 2014
Published: September 23, 2014

   dx.doi.org/10.1021/ol502586n | *Org. Lett.* 2014, 16, 5204−5207

Scheme 2. Preparation of Ring-Contraction Reaction Substrates (*S*)-10b–f



Interestingly, in the case of Met-derived **9d**, the racemate crystallized out of solution, and the enantiomerically pure material remained in solution. Installation of a single Boc group on (*S*)-**9b–f** was not problematic, and derivatives (*S*)-**10b–f** were prepared in moderate to excellent yields and in 94 to >99% ee.

The NMR spectra of (*S*)-**9b–f** are easily interpreted and are consistent with one predominant conformation. Based on our previous studies of 3-substituted benzodiazepine-2-ones,[7] we expected the C3-substituent to adopt a pseudoequatorial orientation, and X-ray crystallography demonstrates this conformation for (±)-**9d** (Figure 1). In contrast, with the exception of (*S*)-**10b**, the room temperature NMR spectra of the *N*4-Boc derivatives (*S*)-**10** are broad and often difficult to interpret. We speculated that these compounds exist as slowly interconverting mixtures of pseudoaxial and -equatorial conformers (Figure 2). We have previously demonstrated such conformational isomerism in 3,3-disubstituted ("quaternary") benzodiazepin-2-ones,[2b,7] and this conformation mobility was invoked to explain the stereochemical course of ring contractions of related substrate (*S*)-**3b**.[3]

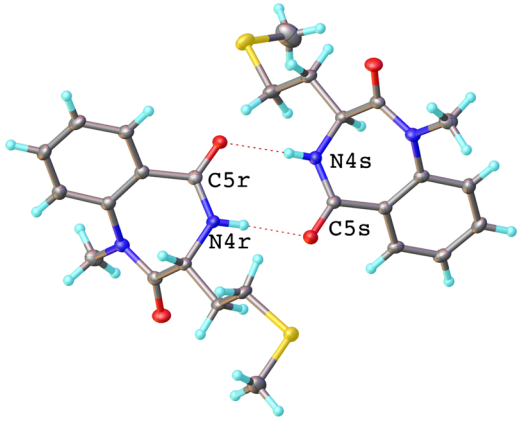


Figure 1. Anisotropic ellipsoid drawing (50%) of (±)-**9d**. The left and right molecules are (*R*)- and (*S*)-configured, respectively. Figure generated using OLEX2.[8]

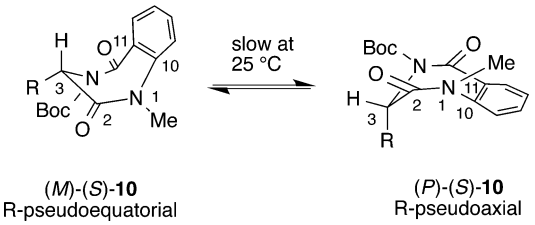


Figure 2. Conformational isomerism in **10**. Axial chirality descriptors (*M*)- and (*P*)- are determined by the sign of the C2–N1–C10–C11 dihedral.[7c]

Consistent with this proposal, NMR spectroscopy of (*S*)-**10c–f** at 0 °C accomplished decoalescence, demonstrating doubling of most nuclei in each compound. In addition, X-ray crystallographic analysis of (*S*)-**10e** remarkably shows both conformers in the unit cell: the R-pseudoequatorial (*M*)-conformer is well-resolved, but the R-pseudoaxial (*P*)-isomer is partly disordered (Figure 3).

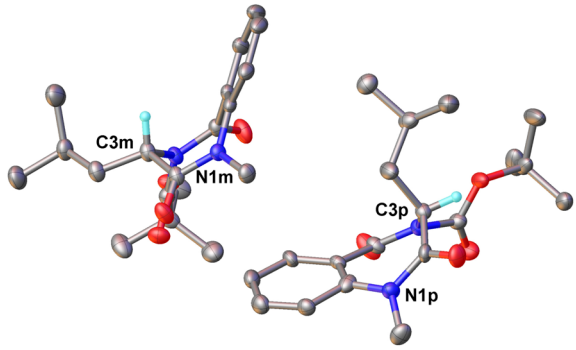
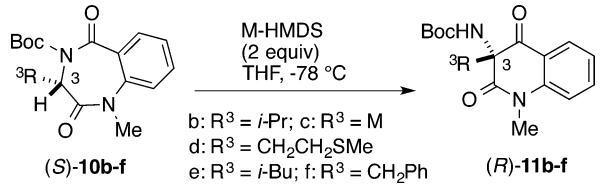


Figure 3. Anisotropic ellipsoid drawing (50%) of (*S*)-**10e**. Both (*M*)- and (*P*)-conformations are present in the unit cell, with the *i*-Bu substituents in the pseudoequatorial and pseudoaxial positions, respectively. Except at C3, hydrogens are omitted for clarity. The (*P*)-conformer (right) is partly disordered: the major (66%) orientation is shown here, and the minor orientation (34%) is shown in the Supporting Information.

With the desired substrates (*S*)-**10b–f** in hand we carried out deprotonations with LiHMDS and KHMDS in THF (Table 1). As can be seen, reaction of (*S*)-**10b** with both bases gave the desired ring-contracted product (−)-**11b** in good yield and excellent enantioselectivity (98% ee). Furthermore, chiral stationary phase HPLC indicated that both bases gave the same major enantiomer, contrary to the published observations of (*S*)-**3b** (Scheme 1).[3] This levorotatory product was crystallized, and anomalous dispersion indicated (*R*)-configuration (Supporting Information). Reactions of (*S*)-**10c–f** proceeded similarly in moderate to good yields and good to excellent enantioselectivities. Again, in each case, reactions with LiHMDS and KHMDS gave the same major enantiomer. In the case of **10c** and **10e**, KHMDS gave superior enantioselectivity; for **10f**, LiHMDS proved optimum. Only in the case of (*S*)-**10e** (KHMDS, 92% ee) was greater than 95% ee not attained. The absolute configurations of the products **11c–f** derived from (*S*)-**10c–f** are all deduced to be (*R*)- by analogy, supported by two additional observations. First, the major enantiomers of **11b–f** derived from (*S*)-**10b–f** are uniformly first-eluting on Chiralcel OD HPLC. Second, in each case the sign of optical rotation of the products conforms to that of the starting materials.

dx.doi.org/10.1021/ol502586n | *Org. Lett.* 2014, 16, 5204–5207

Table 1. Deprotonative Ring-Contraction Reactions

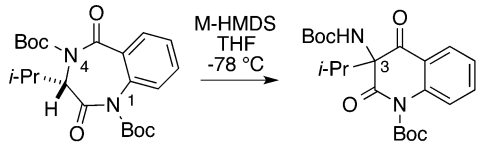


entry	substrate	M	product	yield	% ee (config)
1	(*S*)-(−)-**10b**	Li	(−)-**11b**	84	98 (*R*)[a]
2		K	(−)-**11b**	84	98 (*R*)[a]
3	(*S*)-(+)-**10c**	Li	(+)-**11c**	69	92 (*R*)[b]
4		K	(+)-**11c**	57	97 (*R*)[b]
5	(*S*)-(−)-**10d**	Li	(−)-**11d**	91	>99 (*R*)[b]
6		K	(−)-**11d**	63	>99 (*R*)[b]
7	(*S*)-(−)-**10e**	Li	(−)-**11e**	56	84 (*R*)[b]
8		K	(−)-**11e**	58	92 (*R*)[b]
9	(*S*)-(−)-**10f**	Li	(−)-**11f**	85	98 (*R*)[b]
10		K	(−)-**11f**	82	92 (*R*)[b]

[a]The absolute configuration of (−)-**11b** was established as (*R*)- by X-ray crystallography (Supporting Information). [b]The products of rearrangement of (*S*)-**10c−f** (**11c−f**) are assigned an (*R*)-configuration based on HPLC elution order and conformity of optical rotation (in every case the sign of rotation is preserved from (*S*)-**10b−f** to products **11b−f**).

Since the *N*1-Me, *N*4-Boc substrates (*S*)-**10b−f** gave (*R*)-configured ring-contraction products **11b−f** regardless of whether LiHMDS or KHMDS was used, we thought it prudent to independently confirm the literature reactions of (*S*)-**3b**. Following a slight modification of the original procedure, we prepared (*S*)-**3b** and subjected it to both bases (Scheme 3).

Scheme 3. Confirmation of Enantiodivergent Outcomes in Reactions of (*S*)-3b (97% ee) with LiHMDS and KHMDS

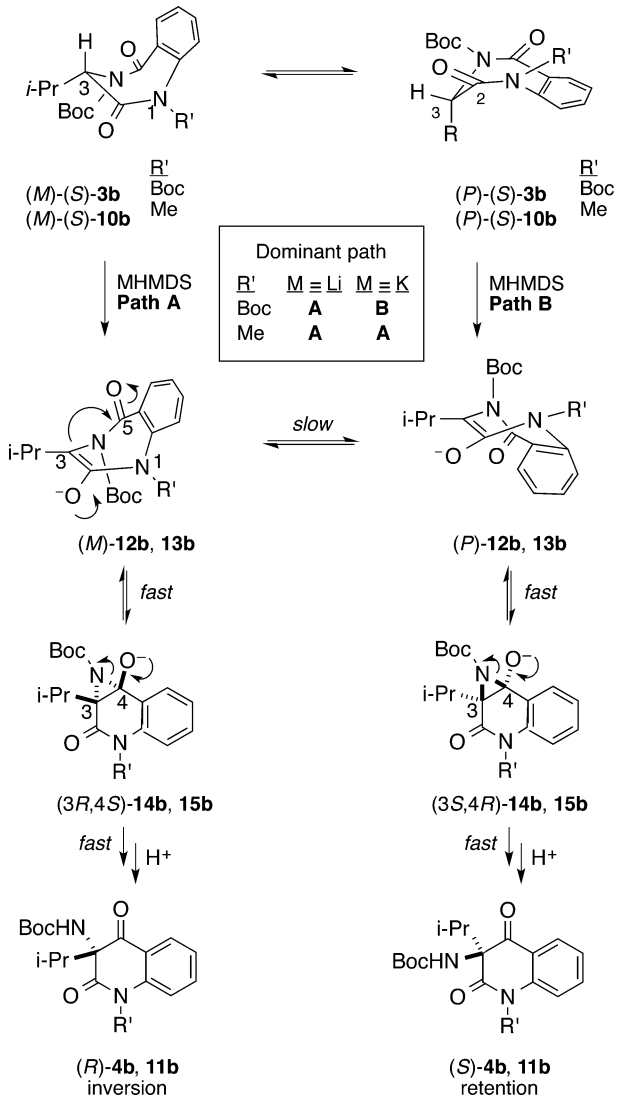


M	product	% ee (yield)
Li	(*R*)-**4b**	68 (39)
K	(*S*)-**4b**	74 (95)

As reported by Dewynter and co-workers,[3] we found that deprotonation of (*S*)-**3b** with LiHMDS gave (*R*)-(−)-**4b**, and deprotonation with KHMDS gave (*S*)-(+)-**4b**. Comparing the different outcomes of related substrates (*S*)-**3b** and (*S*)-**10b** with KHMDS, it is clear the identity of the N1 substituent plays a major role in the stereochemical course of these reactions.

How can the enantiodivergent outcomes of (*S*)-**3b** with LiHMDS and KHMDS be reconciled with the uniform (*R*)-selectivity seen in reactions of (*S*)-**10b−f**? In the case of (*S*)-**3b**, Dewynter and co-workers proposed that deprotonation of both (*M*)- and (*P*)-conformers could occur, with LiHMDS favoring the former, and KHMDS the latter[3] (Scheme 4). As can be seen, the C3 protons of (*M*)-(*S*)-**3b** and (*M*)-(*S*)-**10b** are pseudoaxial and appear stereoelectronically well-disposed for deprotonation, as we have established in studies of related benzodiazepin-2-ones.[2b,7a,c,9] In contrast the C3 protons of (*P*)-(*S*)-**3b** and (*P*)-(*S*)-**10b** are pseudoequatorial and deprotonation appears difficult because of poor overlap between the C3−H σ and the C2−O π^*.

Scheme 4. Possible Stereochemical Pathways for Deprotonation of (*S*)-3b and 10b (Adapted from Dewynter[3])



Thus, for any given base we would normally expect that pseudoaxial deprotonation (Path A) to dominate, leading to the observed invertive course of reaction seen for (*S*)-**3b** with LiHMDS and that for (*S*)-**10b−f** with both bases.

To account for pseudoequatorial deprotonation of (*S*)-**3b** by KHMDS (Path B) would require detailed computational studies of possible transition structures. Nevertheless, comparison of the solid-state structures of the substrates involved might provide a clue as to how a Path B deprotonation of (*S*)-**3b** might be more favorable than that of (*S*)-**10b−f**. To that end an X-ray quality crystal of (*S*)-**3b** was obtained, which demonstrated that the C3-substituent adopts a pseudoaxial conformation (Figure 4). So the (*P*)-conformation of (*S*)-**3b** required for Path B deprotonation is readily accessible or even preferred, as suggested by previous calculations.[3] The structures of (*M*)-(*S*)-**10e**, (*P*)-(*S*)-**10e**, and (*P*)-(*S*)-**3b** were then compared. In all three structures sp^2-hydridization at N was indicated by the sum of angles at N1 and N4 ($\theta \geq 357.9°$, Supporting Information). However, these structures differ in the extent of amide resonance within, and external to, the benzodiazepine ring. We assessed the extent of resonance by

dx.doi.org/10.1021/ol502586n | *Org. Lett.* 2014, 16, 5204−5207

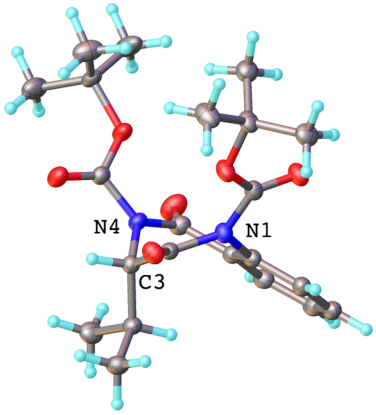
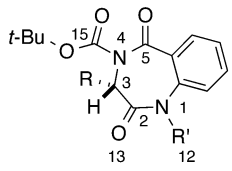
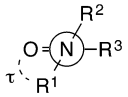


Figure 4. Anisotropic ellipsoid drawing (50%) of (*S*)-**3b**.

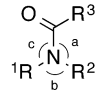
examining amide twist torsion angles τ[10] along the N1−C2, N4−C5, N4−C15, and N1−C12 bonds (where applicable, see Table 2). For (*S*)-**10e** (both conformers), values of τ_{1-2} and

Table 2. Select Torsion Angles for (*S*)-10e and (*S*)-3b[a]





$\tau = (\omega_1+\omega_2)/2$
ω_1 = O-C-N-R^1
ω_2 = R^3-C-N-R^2



θ = a + b + c

	(*M*)-(*S*)-**10e**	(*P*)-(*S*)-**10e**[b]	(*P*)-(*S*)-**3b**
R′	Me	Me	Boc
R	*i*-Bu	*i*-Bu	*i*-Pr
τ_{1-2}	4.7 ± 0.4°	−13.5 ± 1.8°	−36.4 ± 0.3°
τ_{4-5}	3.4 ± 0.4°	−16.7 ± 0.9°	−31.9 ± 0.4°
τ_{4-15}	−45.6 ± 0.4°	−39.6 ± 0.7°	−19.4 ± 0.3°
τ_{1-12}	na	na	3.3 ± 0.3°
HC3C2O13	132.8 ± 0.2°	15.2 ± 1.3°	21.6 ± 0.2°

[a]Error in torsion angles calculated from ESDs (Supporting Information). [b]The (*P*)-conformer of (*S*)-**10e** is disordered; torsion angles are listed for the major orientation (see Figure 3).

τ_{4-5} are much closer to zero than are the values of τ_{4-15}, indicating endocyclic amide resonance (N1−C2, N4−C5) is more important than exocyclic (N4−C15) amide resonance (Table 2). However, in (*P*)-(*S*)-**3b** the situation is reversed: the exocyclic amide resonance of N1 and N4 with their attached Boc groups is stronger than that within the ring (cf. τ_{1-12} and τ_{1-2}, τ_{4-15} and τ_{4-5}, Table 2).

Reduced endocyclic amide resonance for **3b** compared to **10b−f** suggests greater flexibility of **3b** along the N1−C2 and N4−C5 axes. Thus, stereoelectronically acceptable HC3C2O13 torsion angles might be more easily obtained in the KHMDS deprotonation of (*P*)-(*S*)-**3b** than that of (*P*)-(*S*)-**10b−f**. In the solid state the HC3C2O13 torsion angle for (*P*)-(*S*)-**3b** is indeed larger than that of (*P*)-(*S*)-**10e** (21.6° vs 15.2°).

In conclusion we have repeated the findings of Dewynter and co-workers[3] on deprotonation of (*S*)-**3b** and found that, by replacing the *N*1-Boc group by an alkyl group (Me), a wider variety of ring-contraction substrates may be prepared. Unlike (*S*)-**3b**, deprotonations of (*S*)-**10b−f** are (*R*)-selective with both LiHMDS and KHMDS. Enantioselective ring contractions of (*S*)-**10b−f** occur in higher enantiomeric excess than that of (*S*)-**3b**, potentially opening a route to diversely functionalized enantioenriched 3-amino-3-alkylquinolone-2,4-diones **11**. Work is in progress to further expand the scope of this reaction as well as to better understand the enantiodivergent outcomes of (*S*)-**3b**.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, analytical data, chromatograms, NMR spectra, X-ray structure of (*R*)-**11b**, and .cif files for (*S*)-**3b**, (±)-**9d**, (*S*)-**10e**, and (*R*)-**11b**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pcarlier@vt.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the NSF (CHE-0750006) and the Department of Chemistry, Virginia Tech.

■ REFERENCES

(1) (a) Loudni, L.; Roche, J.; Potiron, V.; Clarhaut, J.; Bachmann, C.; Gesson, J.-P.; Tranoy-Opalinski, I. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4819. (b) Joseph, C. G.; Wilson, K. R.; Wood, M. S.; Sorenson, N. B.; Phan, D. V.; Xiang, Z.; Witek, R. M.; Haskell-Luevano, C. *J. Med. Chem.* **2008**, *51*, 1423. (c) Cheng, M.-F.; Yu, H.-M.; Ko, B.-W.; Chang, Y.; Chen, M.-Y.; Ho, T.-I.; Tsai, Y.-M.; Fang, J.-M. *Org. Biomol. Chem.* **2006**, *4*, 510.

(2) (a) MacQuarrie-Hunter, S.; Carlier, P. R. *Org. Lett.* **2005**, *7*, 5305. (b) Carlier, P. R.; Zhao, H.; MacQuarrie-Hunter, S. L.; DeGuzman, J. C.; Hsu, D. C. *J. Am. Chem. Soc.* **2006**, *128*, 15215.

(3) Farran, D.; Archirel, P.; Toupet, L.; Martinez, J.; Dewynter, G. *Eur. J. Org. Chem.* **2011**, 2043.

(4) (a) Lee, S. D.; Chan, T. H.; Kwon, K. S. *Tetrahedron Lett.* **1984**, *25*, 3399. (b) Hara, O.; Ito, M.; Hamada, Y. *Tetrahedron Lett.* **1998**, *39*, 5537. (c) Wipf, P.; Methot, J.-L. *Org. Lett.* **2001**, *3*, 1261.

(5) Vrijdag, J. L.; Van den Bogaert, A. M.; De Borggraeve, W. M. *Org. Lett.* **2013**, *15*, 1052.

(6) (a) McCormick, J. L.; McKee, T. C.; Cardellina, J. H.; Boyd, M. R. *J. Nat. Prod.* **1996**, *59*, 469. (b) Ahmed, N.; Brahmbhatt, K. G.; Sabde, S.; Mitra, D.; Singh, I. P.; Bhutani, K. K. *Bioorg. Med. Chem.* **2010**, *18*, 2872. (c) Seong, C. M.; Park, W. K.; Park, C. M.; Kong, J. Y.; Park, N. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 738.

(7) (a) Carlier, P. R.; Zhao, H.; DeGuzman, J.; Lam, P. C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 11482. (b) Lam, P. C.-H.; Carlier, P. R. *J. Org. Chem.* **2005**, *70*, 1530. (c) Hsu, D. C.; Lam, P. C.-H.; Slebodnick, C.; Carlier, P. R. *J. Am. Chem. Soc.* **2009**, *131*, 18168.

(8) Dolomanov, O. V.; Bouris, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339.

(9) Carlier, P. R.; Sun, Y.-S.; Hsu, D. C.; Chen, Q.-h. *J. Org. Chem.* **2010**, *75*, 6588.

(10) (a) Otani, Y.; Nagae, O.; Naruse, Y.; Inagaki, S.; Ohno, M.; Yamaguchi, K.; Yamamoto, G.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 15191. (b) Dunitz, J. D.; Winkler, F. K. *Acta Crystallogr.* **1975**, *B31*, 251.