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Improved Biomimetic Total Synthesis of D,L-Stephacidin A

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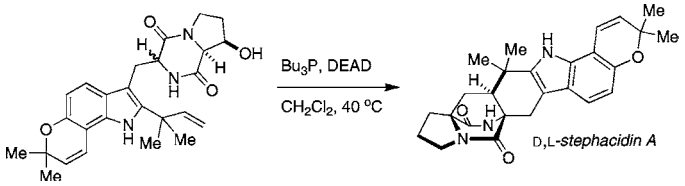
ABSTRACT



The direct conversion of *β*-hydroxyproline derivatives into 5-hydroxypyrazin-2(1*H*)-ones under Mitsunobu conditions has been discovered to be a general biomimetic protocol generating IMDA intermediates and has been applied to the concise, biomimetic total syntheses of D,L-stephacidin A and D,L-brevianamide B.

Marine organisms, particularly fungi, are seemingly inexhaustible sources of biologically active natural products that possess complex and diverse ring systems. Prenylated indole alkaloids such as the paraherquamides,[1] brevianamides,[2] stephacidins,[3] and notoamides[4] (Figure 1) are fungal metabolites whose synthesis and biogenetic origin have been extensively investigated in our laboratory.[5] These fungal metabolites are all believed to arise biogenetically from tryptophan, isoprene, and proline or derivatives of proline.[5] Previous disclosures from our laboratory,[5] as well as the pioneering work of Sammes[6a] and Birch[6b] have suggested that the core bicyclo[2.2.2]diazaoctane ring system that is characteristic of this family of alkaloids likely arises in nature via a biosynthetic intramolecular Diels−Alder construction

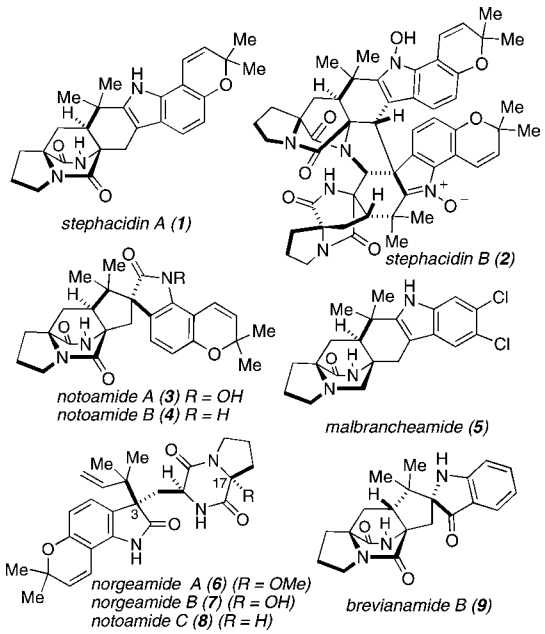


Figure 1. Structures of several prenylated indole alkaloids.

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(1) (a) Yamazaki, M.; Okuyama, E. *Tetrahedron Lett.* **1981**, *22*, 135. (b) Ondeyka, J. G.; Goegelman, R. T.; Schaeffer, J. M.; Kelemen, L.; Zitano, L. *J. Antibiot.* **1990**, *43*, 1375. (c) Liesch, J. M.; Wichmann, C. F. *J. Antibiot.* **1990**, *43*, 1380. (d) Banks, R. M.; Blanchflower, S. E.; Everett, J. R.; Manfer, B. R.; Reading, C. J. *J. Antibiot.* **1997**, *50*, 840.

(2) (a) Birch, A. J.; Wright, J. J. *J. Chem. Soc. Chem. Commun.* **1969**, 644. (b) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329. (c) Birch, A. J.; Russell, R. A. *Tetrahedron* **1972**, *28*, 2999.

(3) (a) Qian-Cutrone, J.; Huang, S.; Shu, Y.-Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klohr, S. E.; Gao, Q. *J. Am. Chem. Soc.* **2002**, *124*, 14556. (b) Qian-Cutrone, J.; Krampitz, K.; Shu, Y.-Z.; Chang, L. P. U.S. Patent 6,291,461, 2001.

(4) Kato, H.; Yoshida, T.; Tokue, T.; Nojiri, Y.; Hirota, H.; Ohta, T.; Williams, R. M.; Tsukamoto, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 2254.

(5) (a) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (b) Williams, R. M. *Chem. Pharm. Bull.* **2002**, *50*, 711. (c) Williams, R. M.; Stocking, E. M.; Sanz-Cevera, J. F. *Topics Curr. Chem.* **2000**, *209*, 98.

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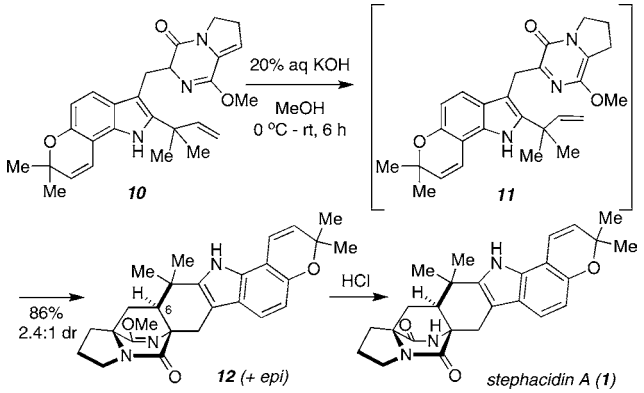
Scheme 1. Generation and Cycloaddition of a Protected Azadiene Intermediate En Route to the Bicyclo[2.2.2]diazaoctane Ring System



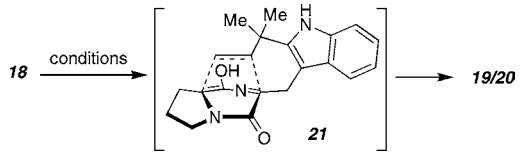
of a 5-hydroxypyrazin-2(1*H*)-one (Scheme 1). While [4+2] cycloadditions are perhaps the most powerful tool for the rapid construction of highly functionalized six-membered rings in synthetic organic chemistry,[8] there are relatively few documented examples of natural products that have been rigorously proven to arise via a biosynthetic Diels−Alder construction, despite a multitude of proposed biogeneses.[9] We have recently proposed some provocative biogenetic relationships between between the stephacidins and notoamides in which an intramolecular [4+2] hetero-Diels−Alder cycloaddition of a 5-hydroxypyrazin-2(1*H*)-one was postulated as the key biosynthetic transformation linking natural products such as notoamide C (**8**) and the norgeamides A (**6**) and B (**7**) to the core bicyclo[2.2.2]-diazaoctane ring system embodied in notoamides A (**3**) and B (**4**), as well as stephacidin A (**1**).[10]

Recently, we have successfully deployed this basic biomimetic Diels−Alder cycloaddition strategy[7] to the total synthesis of several prenylated indole alkaloids containing the common bicyclo[2.2.2]diazaoctane ring system, including VM55599,[11] brevianamide B (**9**),[7] stephacidin A (**1**),[10b] marcfortine C,[12] and the recently discovered natural products notoamide B (**4**) and malbrancheamide (**5**)[13] (Figure 1). To date, the most efficient and reliable biomimetic approach to the bicyclo[2.2.2]diazaoctane ring system of these substances has involved formation of a lactim ether version of the key azadiene intermediate that participates in the intramolecular Diels−Alder cycloaddition reaction, which requires subsequent deprotection of the lactim ether. For example, treatment of lactim ether **10** with 20% aqueous KOH in MeOH effected tautomerization to the intermediate 5-methoxypyrazin-2(1*H*)-one (**11**), which spontaneously suffered IMDA cycloaddition to produce the cycloadduct **12** along with its C-6 epimer (2.4:1, respectively) in 86% yield (Scheme 1).[10b]

Interestingly, the intermediate methoxy-protected azadiene **11** is a metastable substance that could be observed by both TLC and ^{1}H NMR analysis. Upon completion of the cycloaddition, cleavage of the lactim ether protecting group (0.1 M HCl, THF) was required to complete the total synthesis of D,L-stephacidin A (**1**).[10b]

Although the cycloaddition reactions of methoxy-protected azadienes such as **11** have proven to be successful substrates for constructing bicyclo[2.2.2]- diazaoctane ring systems,[7] we have long sought to develop a more concise method that lacked the need for amide protecting group manipulations both before and after the cycloaddition reaction. A truly biomimetic approach would involve generation and IMDA cyclization of the key unprotected 5-hydroxypyrazin-2(1*H*)-one (see **21** for example, Table 1). This approach was recently realized in our biomimetic total synthesis of D,L-marcfortine C.[12]

Table 1. Mitsunobu Conditions



entry	conditions	results
1	5 equiv PBu_3, 5 equiv DEAD CH_2Cl_2, 40 °C, 20 h[a]	**19** and **20** (2.1:1) 70% combined yield
2	CH_2Cl_2, 40 °C, 20 h	recovered SM
3	5 equiv PBu_3 CH_2Cl_2, 40 °C, 20 h	recovered SM
4	5 equiv DEAD CH_2Cl_2, 40 °C, 20 h	recovered SM
5	5 equiv $EtO_2CNHNHCO_2Et$ CH_2Cl_2, 40 °C, 20 h	recovered SM

[a] Cycloaddition proceeded cleanly regardless of the order of addition of the reagents.

On the basis of our recent successful generation and IMDA cycloaddition reaction of the first known 5-hydroxypyrazin-2(1*H*)-one intermediate en route to the bicyclo[2.2.2]-diazaoctane ring system embodied in marcfortine C, we were

(6) (a) Porter, A. E. A.; Sammes, P. G. *J. Chem. Soc. Chem. Commun.* **1970**, 1103. (b) Baldas, J.; Birch, A. J.; Russell, R. A. *J. Chem. Soc. Perkin Trans I* **1974**, 50.

(7) (a) Williams, R. M.; Sanz-Cervera, J. F.; Sancenon, F., Marco, J. A.; Halligan, K. *J. Am. Chem. Soc.* **1998**, *120*, 1090. (b) Williams, R. M.; Sanz-Cervera, J. F.; Sancenón, F.; Marco, J. A.; Halligan, K. *Bioorg. Med. Chem.* **1998**, *6*, 1233. (c) Sanz-Cervera, J. F.; Williams, R. M.; Marco, J. A.; López-Sánchez, J. M.; González, F.; Martínez, M. E.; Sancenón, F. *Tetrahedron* **2000**, *56*, 6345. (d) Adams, L. A.; Valente, M. W. N.; Williams, R. M. *Tetrahedron* **2006**, *62*, 5195.

(8) For recent reviews on the Diels−Alder reaction, see (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Corey, E. J.; *Angew. Chem., Int. Ed.* **2002**, *41*, 1650. (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668.

(9) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078.

(10) (a) Grubbs, A. W.; Artman, G. D., III; Tsukamoto, S.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2257. (b) Greshock, T. J.; Grubbs, A. W.; Tsukamoto, S.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2262.

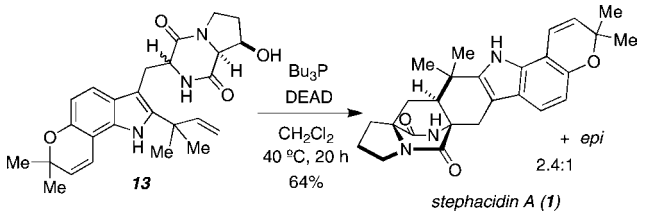
(11) (a) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 1675. (b) Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 2556.

(12) Greshock, T. J.; Grubbs, A. W.; Williams, R. M. *Tetrahedron* **2007**, *63*, 6124.

(13) (a) Martinez-Luis, S.; Rodriguez, R.; Acevedo, L.; Gonzalez, M. C.; Lira-Rocha, A.; Mata, R. *Tetrahedron*, **2006**, *62*, 1817. (b) Valente, M. W. N.; Williams, R. M. *Heterocycles* **2006**, *70*, 249.

compelled to determine the generality of these conditions on additional substrates. Indeed, we were pleased to find that subjecting the intermediate alcohol from our recent stephacidin A synthesis,[10b] (compound **13**, Scheme 2), to the

Scheme 2. Improved Total Synthesis of D,L-Stephacidin A

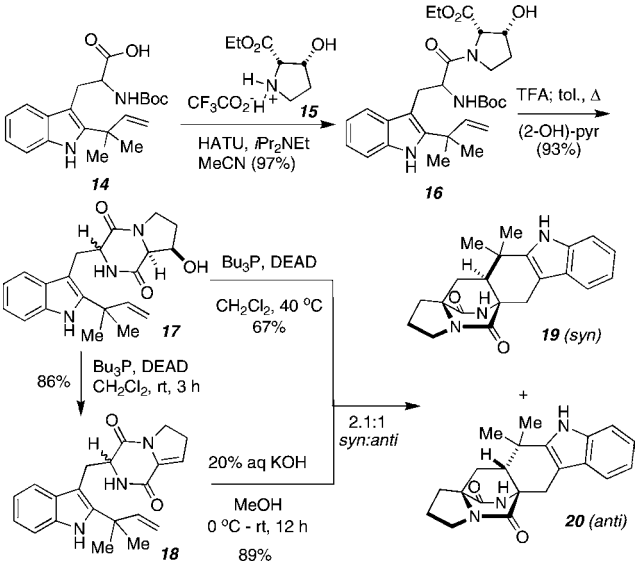


identical conditions employed in the marcfortine C synthesis (PBu_3, DEAD, 40 °C, 20 h) directly afforded stephacidin A (**1**) along with 6-*epi*-stephacidin A (2.4:1, respectively) in 64% combined yield. Separation of stephacidin A (**1**) from 6-*epi*-stephacidin A via chromatography proved extremely difficult. Fortuitously, these two diastereomeric compounds were found to have some extraordarily distinct physical properties. Upon concentration of the reaction mixture and chromatographic separation from the PBu_3 and DEAD byproducts, the diastereomeric mixture could be diluted with methanol, which completely dissolved the 6-*epi*-stephacidin A, while stephacidin A, which has limited solubility in virtually every organic solvent, precipitated out of solution as a clean white powder. The conversion of alcohol **13** directly to stephacidin A (**1**) improved our previous synthetic route from 17 steps to 14 steps. In addition, we have made improvements in the overall yield (from 5.4% in the previous synthesis to 11.1% overall yield from commercially available materials).[14]

We next directed our attention toward the total synthesis of D,L-brevianamide B (**9**), another member of the prenylated indole alkaloid family (Figure 1) which could be rapidly accessed via this newly developed cycloaddition methodology. Brevianamide B (**9**) was isolated, along with brevianamide A, by Birch and co-workers from *Pennicillium brevicompactum* in 1969[2] and marked the birth of this unique family of prenylated indole alkaloids containing the characteristic, but hitherto unknown, bicyclo[2.2.2]-diazaoctane core. With respect to the relative stereochemistry within the core bicyclo[2.2.2]diazaoctane ring system, all of the known members of the paraherquamides, stephacidins (**1**, **2**), asperparalines, notoamides (**3**, **4**), and marcfortines have been shown to possess the syn stereochemstry (C-20, paraherquamide numbering), while only the brevianamides have been shown to possess the anti relative configuration (Figure 1).[15]

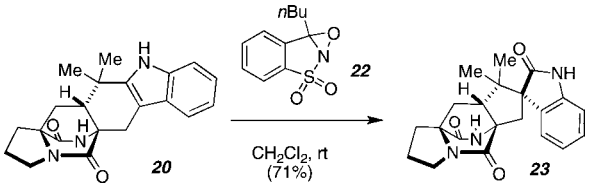
We have previously reported both an asymmetric total synthesis of (+)-brevianamide B[16] and biomimetic IMDA-based syntheses of D,L-brevianamide B.[7] Following a similar protocol to that above, coupling of *cis*-3-hydroxyproline ethyl ester (as the TFA salt) **15**[17] with the readily prepared D,L-tryptophan derivative **14**[11a] in the presence of HATU afforded amide **16** in 97% yield as an inseparable mixture of diastereomers (Scheme 3). Peptide **16** was treated with TFA

Scheme 3. Construction of the Bicyclo[2.2.2]diazaoctane Core **20** En Route to Brevianamide B (**9**)



to afford an intermediate primary amine, which was immediately cyclized to the corresponding diketopiperazine **17** (93%) by heating with 2-hydroxypyridine. Warming a solution of **17** with excess PBu_3 and DEAD to 40 °C smoothly produced the desired cycloadducts **19**[18] and **20** as a 2.1:1 mixture of diasteromers, once again favoring the syn stereochemistry.

Scheme 4. Synthesis of Oxindole **23**



During the course of our studies we also discovered that the enamide intermediate **18**, derived from subjecting **17** to the Mitsunobu conditions at room temperature, was also a

(14) The yields of other steps, in addition to those described here, were also improved along the synthetic route (see Supporting Information).

(15) The syn/anti relationship refers to the relative stereochemistry between the C-20 stereogenic center (paraherquamide numbering) and the cyclic amino acid residue (proline, β-methylproline, or pipecolic acid).

(16) (a) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 808. (b) Williams, R. M.; Glinka, T.; Kwast, E. *J. Am. Chem. Soc.* **1988**, *110*, 5927.

(17) Prepared via $NaBH_4$ reduction of the corresponding *N*-Boc-3-ketoproline ethyl ester, see: Williams, R. M.; Cao, J.; Tsujishima, H.; Cox, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 12172. See the Supporting Information for a modified preparation of the *N*-Boc-3-ketoproline ethyl ester.

useful substrate for the [4+2] IMDA cycloaddition reaction. Treatment of enamide **18** with 20% aqueous KOH in MeOH also effected enolization and tautomerization to the intermediate hydroxy-azadiene which spontaneously suffered IMDA cycloaddition to produce the cycloadducts **19** and **20** as a 2.1:1 mixture of diastereomers (89%).

In order to gain some mechanistic insight into these intriguing transformations, a series of experiments was conducted to determine what role, if any, each of the reagents (PBu_3 and DEAD) played in effecting formation of the proposed biosynthetic 5-hydroxypyrazin-2(1*H*)-one intermediate from the β-hydroxyproline-containing substrates. On the basis of the results discussed above (**18** → **19** + **20**), basic conditions (KOH, MeOH) readily mediated the formation of the key azadiene intermediate from enamide **18**. Thus, in the case of converting alcohol **17** directly to cycloadducts **19** and **20** via the Mitsunobu conditions at 40 °C, it appears reasonable to assume that enamide **18** is formed along this pathway as well. Indeed, we found that enamide **18** when subjected to the "standard conditions" (PBu_3, DEAD, CH_2Cl_2, 40 °C) cleanly furnished cycloadducts **19** and **20** in good yield (entry 1, Table 1).

Several control experiments were conducted to help determine what reagents and/or intermediate(s) could be responsible for the proposed enolization/tautomerization reaction (Table 1). Interestingly, we found that the cycloaddition reaction only proceeded when the combination of PBu_3 and DEAD were used in equal amounts in excess (entry 1). When individually subjected to the reaction conditions (CH_2Cl_2, 40 °C, 20 h), neither PBu_3 (entry 3) nor DEAD (entry 4) alone were successful in converting enamide **18** into cycloadducts **19** and **20**. In addition, subjecting compound **18** to diethyl 1,2-hydrazine-dicarboxylate (the reduced byproduct of DEAD from the Mitsunobu reaction) resulted in recovery of the starting material as well (entry 5). These results suggest that the obligate combination of PBu_3 and DEAD is uniquely responsible for converting the incipient enamide **18** into the putative the 5-hydroxypyrazin-2(1*H*)-one intermediate **21**, which subsequently undergoes IMDA cylization to produce the desired cycloadducts **19** and **20**. It is conceivable that a zwitterionic complex formed from the nucleophilic attack of PBu_3 onto DEAD is acting as a proton chaperone en route to azadiene **21**. A possible species and a mechanism for the tautomerization mediated by a putative PBu_3−DEAD complex coordinated to the substrate is shown in Figure 2.

With anti cycloadduct **20**[19] in hand, this substance was subjected to the well-precedented oxidation and pinacol rearrangement to brevianamide B (**9**, 45% overall from **20**).

Interestingly, we found that the corresponding spiro-oxindole product **23** could be obtained exclusively upon

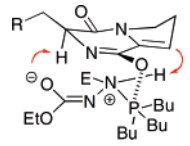


Figure 2. Possible mechanism for the tautomerization of enamide **18** into azadiene **21**.

treatment of indole **20** with excess oxaziridine **22**.[10,20] The regiochemistry of this transformation can be rationalized via ring-opening of the incipient indole 2,3-epoxide to the alternative 2-alkoxyindole intermediate, which subsequently undergoes an α-face ring contraction by a [1,5] sigmatropic shift to produce the spiro-oxindole **23**.[10,21]

It is further noteworthy that the major cycloadduct **19** is a plausible biosynthetic precursor to malbrancheamide and perhaps the stephacidins. The rapid access to this substrate by the route described herein and the ease of incorporation of either stable or radioisotopes into the amino acid precursors **14** and **15** are currently being harnessed to interrogate these biosynthetic speculations.

In conclusion, we have significantly improved the efficiency of our biomimetic total synthesis of D,L-stephacidin A (**1**) from 17 to 14 steps by employing the Mitsunobu-based IMDA cycloaddition and we have completed a concise biomimetic total synthesis of D,L-brevianamide B (**9**) in 11 linear steps and 3.5% overall yield from indole. The unique complex of Bu_3P and DEAD effectively mediates the enolization/tautomerization of enamide **18** to azadiene **21**. To our knowledge, these are the very first examples of such cycloadditions wherein the putative biosynthetic azadiene species is generated with a free hydroxyl residue. The facility with which the putative 5-hydroxypyrazin-2(1*H*)-one intermediates are generated under these conditions was striking and provides provocative support for the possible intermediacy of such a species in the biological construction of this ring system within this family of secondary metabolites. Further studies to experimentally corroborate the validity of putative 5-hydroxypyrazin-2(1*H*)-one intermediates in the biosynthesis of this family of fungal metabolites are under investigation and will be reported in due course.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Compound **19** has been previously described, see: (a) Williams, R. M.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 451. (b) Jin, S.; Wessig, P.; Liebscher, J. *J. Org. Chem.* **2001**, *66*, 3984. (c) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. *J. Am. Chem. Soc.* **2006**, *128*, 8678.

(19) Anti cycloadduct **20** has been previously prepared in our laboratories; see ref 18a.

(20) (a) Davis, F. A.; Townson, J. C.; Vashi, D. B.; Thimma, Ready, R.; McCauley, J. P.; Harakal, M. E.; Gosciniak, D. J. *J. Org. Chem.* **1990**, *55*, 1254. (b) Snider, B. B.; Zeng, H. *J. Org. Chem.* **2003**, *68*, 545.

(21) Williams, R.M.; Glinka, T.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 5575.