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Total Synthesis of Manzamine A and Related Alkaloids

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Supporting Information

ABSTRACT: Total syntheses of three structurally complex marine natural products, manzamine A, ircinol A, and ircinal A, are reported. The route pivoted on the construction of a late-stage protecting-group-free pentacyclic enol triflate coupling partner, from which all three family members were accessed divergently via palladium-catalyzed reactions. The rapid synthesis of this key pentacyclic enol triflate was achieved by a highly convergent union of five fragments through a stereoselective Michael addition, a three-component nitro-Mannich lactamization cascade, an unprecedented and highly stereoselective reductive nitro-Mannich cyclization cascade, a stereoselective organometallic addition, and a *Z*-selective alkene ring-closing metathesis. Altogether this chemistry has allowed the shortest synthetic route to date for manzamine A (18-step longest linear sequence) via a late-stage diversification point that is ideal for future manzamine A analogue synthesis.

Manzamine A (**1**) is a marine alkaloid first isolated by Higa et al. in 1986 from a sponge in the Okinawa Sea. It exhibits a range of potent biological properties, including insecticidal, anti-bacterial, anti-inflammatory, anti-cancer, and anti-malarial activity.[1] Manzamine A (**1**) has a pentacyclic (ABCDE) core comprising 6-, 6-, 5-, 13-, and 8-membered rings, two *Z*-olefins, two tertiary amines, and five stereocenters including four contiguous and two quaternary centers. Attached to the B ring is a β-carboline heteroaromatic ring system. The unique biological profile of manzamine A (**1**) and its complex structure make it a highly desirable target for synthesis.

To date, there have been many papers describing synthetic efforts toward the core[2] and three published total syntheses by Winkler,[3] Martin,[4] and Fukuyama.[5] The shortest route, that of Martin, was completed in 23 steps from commercial material, but the average step count still remains high at ~28. All three of these elegant routes converged on ircinal A as the precursor to manzamine A, and demonstrably this is a successful strategy. However, our analysis identified enol triflate **2** (Figure 1) as a synthetically valuable late-stage intermediate. From the outset our aim was to synthesize enol triflate **2** on scale, via the shortest route possible, and then diversify from this point using metal-catalyzed coupling reactions, thus providing access to manzamine A and other family members such as ircinol A and ircinal A. Herein we report our findings.

To access enol triflate **2**, our aim was to develop a short route founded on a key stereoselective Michael addition of 8,5-pronucleophile **7** to a nitro olefin coupling partner **6**, possessing protected enone functionality. The nitro ester Michael adduct **5**

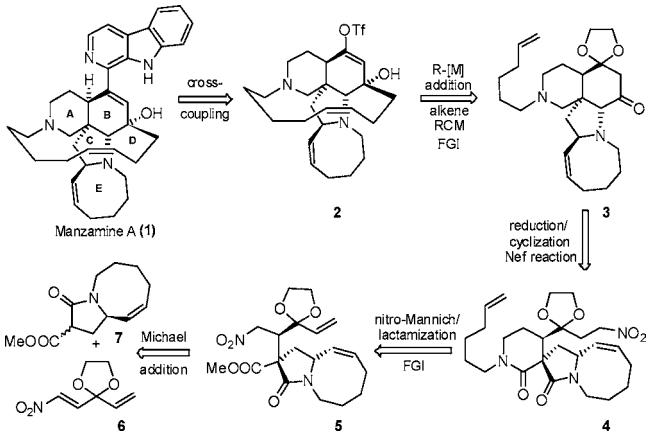

Figure 1. Retrosynthetic analysis of manzamine A.

would be primed for annulation via a nitro-Mannich/lactamization cascade (to provide the A ring) and suitably equipped for further elaboration into the B ring, provided a new annulation method to unite the terminal carbon of Michael acceptor **6** with the carbonyl carbon of the pyrrolidinone ring could be developed. For this we planned to employ nitroalkane **4** as an intermediate. The nitro group would play dual roles in allowing an intramolecular Mannich type reaction to occur on an in situ-generated iminium ion (following full reduction of the piperidinone carbonyl group and partial reduction of the pyrrolidinone carbonyl group) and a subsequent oxidation via a Nef reaction to cyclohexanone **3**. A stereoselective addition of a 3-butenyl anion equivalent to the resulting carbonyl group, followed by enol triflate formation and a *Z*-selective ring-closing metathesis (RCM), would provide the key late-stage intermediate **2**.

Key to the multigram preparation of the nitro olefin coupling partner **6** (Scheme 1) was the synthesis of homoallylic alcohol **10** from commercial starting materials using scalable synthetic procedures.

Nucleophilic substitution of the hindered neopentylic bromide **8** by acetate was nontrivial but was achieved using neat Aliquat 336 and potassium acetate at 120 °C.[6] Methanolysis of the resulting ester **9** occurred smoothly using potassium carbonate in methanol at room temperature. Alcohol **10** was obtained in 49% yield (84% based on recovered starting material). Oxidation of alcohol **10** using the Swern protocol occurred without incident, and the crude aldehyde **11** reacted with nitromethane under basic conditions to give Henry

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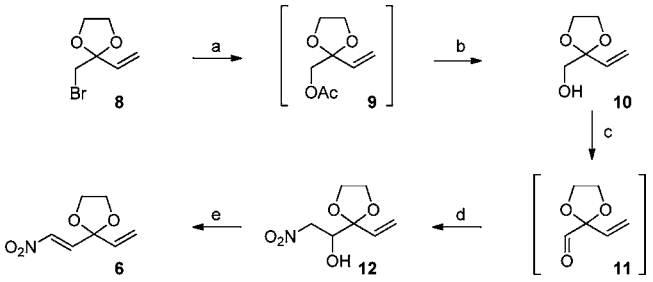
Scheme 1. Synthesis of Electrophile 6[a]

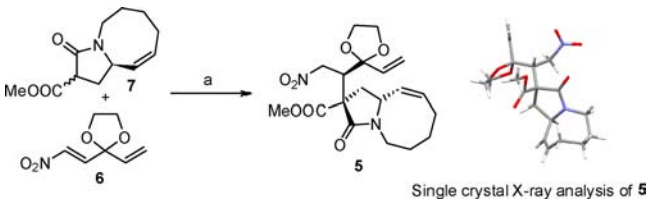


[a]Reagents and conditions: (a) KOAc, Aliquat 336, 120 °C, 16 h; (b) K_2CO_3, MeOH, RT, 1 h, 49% (84% brs) (over two steps); (c) $COCl_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to RT, 0.5 h; (d) CH_3NO_2, EtOH, 0 °C, 2 h, 90% (over two steps); (e) MsCl, Et_3N, CH_2Cl_2, −15 °C to RT, 15 min, 90%.

product **12** in 90% over two steps. Dehydration with methanesulfonyl chloride and triethylamine gave the desired nitro olefin **6** in 90% yield. All of the five steps of this route were reproducible, and multigram quantities of **6** were obtained.

With Michael acceptor **6** in hand, its diastereoselective union with known 8,5-pronucleophile **7**[7] was investigated. Dissimilar to our previous study, the organocatalyzed Michael addition[7−9] was not viable, presumably owing to the steric hindrance of the adjacent acetal and vinyl group in **6**. Nonetheless, desirable reactivity was witnessed when stoichiometric potassium hexamethyldisilazide was used as the base in conjunction with a mole equivalent of 18-crown-6. The naked enolate imparted moderate diastereoselectivity toward the desired diastereoisomer **5** (dr ∼73:27:0:0 in the crude mixture). Fortunately, the diastereomers were readily separated via flash column chromatography, and the isolated 65% yield of the pure major diasteromer was respectable for such a key chemical union. The stereochemistry of **5** was unambiguously determined by single-crystal X-ray diffraction (Scheme 2) and is consistent with our previous findings.[7,9]

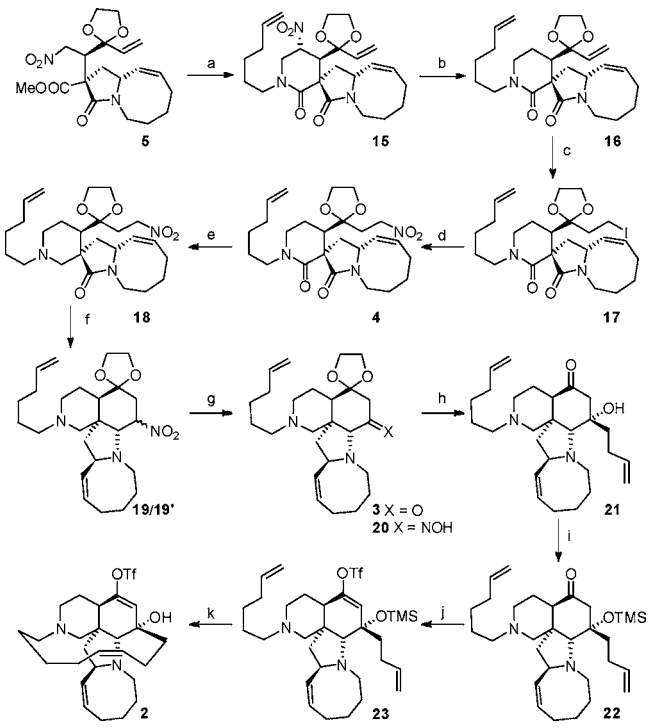
Scheme 2. Stereoselective Michael Addition of Key Building Blocks[a]



[a]Reagents and conditions: (a) KHMDS, 18-crown-6, −94 °C, THF, 1 h, 65% of **5**, 21% of minor isomer **5′**.

Following the development of a nitro-Mannich/lactamization cascade[10] nitro ester Michael adduct **5** was reacted with formaldehyde (**13**) and hex-5-en-1-amine (**14**) in refluxing methanol to afford 4-nitro-piperidin-2-one **15** as a single diastereoisomer in high yield (Scheme 3). Nitro group removal under modified Ono's conditions[11] gave the functionalized tricyclic core **16** ready for further elaboration. Conversion of alkene **16** to nitroalkane **4** was made possible by the intermediacy of iodide **17** generated by anti-Markovnikov addition of HI to the double bond.[12] Reaction of iodide **17** with silver nitrite gave the substitution product, nitro alkane **4**, in

Scheme 3. Synthesis of the Pentacyclic Core of Manzamine Alkaloids[a]



[a]Reagents and conditions: (a) CH_2O (**13**), hex-5-en-1-amine (**14**), MeOH, reflux, 10 h, 88%; (b) AIBN, Bu_3SnH, toluene, reflux, 30 min, 77%; (c) TMSCl, KI, 4 Å MS, MeCN, RT, 50 min, 81%; (d) $AgNO_2$, Et_2O, RT, 48 h, 63%; (e) DIBAL, toluene, −78 to −20 °C, 1 h, 74% of **18** and 7% of **19** (dr 83:17); (f) $Ti(OiPr)_4$, Ph_2SiH_2, hexane, 0 °C, 2 h, 81% (dr 83:17); (g) $TiCl_3$, THF, water, RT, 5 h, 56% of **3**, 21% of **20**; (h) 3-butenylmagnesium bromide (**24**), THF, $CeCl_3$, 0 °C, 0.5 h then HCl, 40 h, RT, 91%; (i) TMSOTf, Et_3N, Et_2O, RT, 30 min, 72%; (j) Commins' reagent (**25**), KHMDS, THF, −78 °C, 20 min, 90%; (k) Grubbs' first-generation catalyst (20 mol %), CH_2Cl_2, reflux, 3 h, 73%, 70:30 *Z*/*E*.

63% yield. Conversion of **4** to nitro amine **19** was without precedent and required a series of precise and controlled chemoselective reductions, followed by an intramolecular Mannich reaction. Our initial concerns about the tolerance of the nitro group to fairly harsh reducing conditions were unfounded; the piperidinone carbonyl could be selectively reduced with DIBAL, and the piperidine **18** was isolated in 74% yield. Importantly, alongside piperidine **18**, tetracyclic product **19** was isolated in 7% yield, thus validating the concept of our reductive nitro-Mannich cyclization cascade.[13] Following this chemoselective reduction, a range of reducing agents with the potential to deliver hydride to the pyrrolidinone carbonyl of **18**, but without causing over-reduction to the pyrrolidine or reduction of either double bond, the acetal, or the nitro group, were systematically explored. Pleasingly, the titanium tetraisopropoxide/diphenylsilane reducing agent system introduced by Buchwald[14] provided the necessary chemoselectivity and reactivity profile. Reaction with pyrrolidinone **18** halted after the first hydride addition and gave, after a silica gel workup, the desired intramolecular nitro-Mannich product **19** as two of the possible four diastereomers, epimeric at the carbon atom bearing the nitro group, in a 83:17 ratio, in 81% yield. Presumably, the high diastereofacial selectivity arises from preferred attack of the tethered nitronate nucleophile to the

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proximal *Si* face of the spirocyclic iminium ion intermediate. With the suitably configured nitro-Mannich product **19**/**19′** in hand, our attention turned to its transformation into ketone **3**.

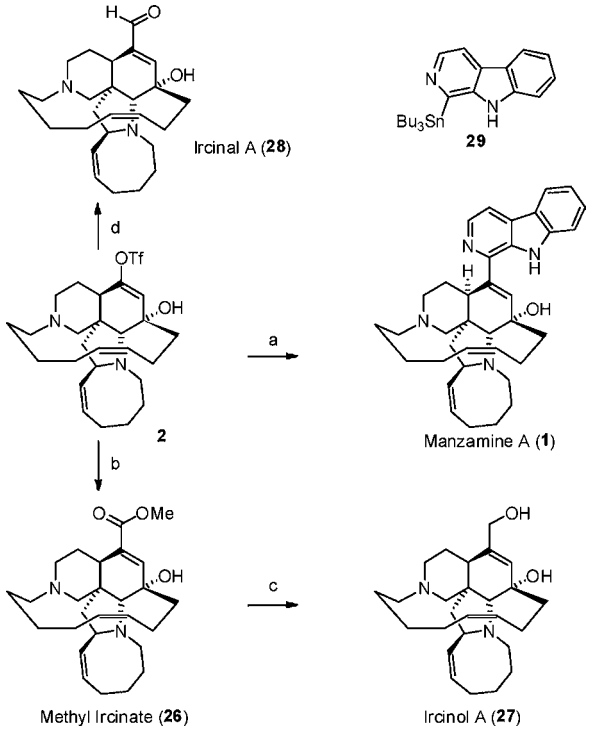
Although the Nef reaction has been well-studied and a plethora of reagents is available,[15] such transformations are rarely attempted on complex tertiary amine-containing substrates.[16] The presence of the acid-labile acetal functionality, the retro-Mannich-prone skeleton, and the oxidizable tertiary amine moieties of **19** complicated our study. However, after considerable screening, the use of the McMurry modification of a reductive Nef reaction[15] employing titanium trichloride in THF/water at low pH gave the key tetracyclic ketone **3** in 56% isolated yield (together with 21% yield of intermediate oxime **20**). Transformation of ketone **3** into TMS-protected enol triflate **23** required three steps and was relatively straightforward. Thus, a highly stereoselective addition of a 3-butenylcerium-derived organometallic followed by acetal hydrolysis on workup gave hydroxy ketone **21** in nearly quantitative yield. TMS ether protection under standard conditions efficiently gave **22** which on treatment with Commins' reagent (**25**) then KHMDS gave the TMS-protected enol triflate **23** in 90% yield. To complete the synthesis of the key late-stage coupling intermediate **2**, a *Z*-selective RCM was required. From our screening of commonly employed, commercially available Ru-based catalysts for alkene RCM, only the Grubbs' first-generation catalyst tolerated the labile TMS protecting group on **23** during the reaction. Acidic workup and silica gel chromatography gave the separable pentacyclic deprotected products **2** and **2′** in 73% yield as a 70:30 *Z*:*E* mixture of diastereomers.

With access to the key late-stage intermediate **2** established, the cross-coupling of the *β*-carboline moiety was investigated. Pleasingly, the synthesis of tributylstannylated *β*-carboline **29** was possible (see Supporting Information) and its coupling under palladium(0) catalysis successful, and manzamine A (**1**) was afforded in 52% yield (Scheme 4). The spectroscopic data (^{1}H NMR, ^{13}C NMR), high-resolution mass spectrometric data, and specific rotation of our synthetic material were in excellent agreement with published data.

Having demonstrated the utility of **2** for the preparation of manzamine A (**1**), we then explored its utility for the preparation of other family members. Thus, an alkoxycarbonylation reaction[17] with methanol and carbon monoxide under palladium catalysis gave methyl ircinate (**26**) in 78% yield (Scheme 4). This compound was readily reduced to ircinol A[18] (**27**) using excess DIBAL at low temperature. Finally a reductive carbonylation[19] with carbon monoxide and tributyltin hydride under palladium(0) catalysis gave ircinal A[20] (**28**) in 58% yield. The spectroscopic data of synthetic **27** and **28** were in excellent agreement with the published values.

In conclusion, we have developed a short and stereoselective synthesis (18-step longest linear sequence) of manzamine A (**1**). Not only is this the shortest to date, but it is distinguished from other synthetic routes by the adoption of a cross-coupling strategy to attach the *β*-carboline, important for its biological activity,[21] to key late-stage intermediate enol triflate **2**. This approach allowed us to synthesize ircinal A (**28**) and methyl ircinate (**26**) via alternative coupling reactions and is ideally suited for future manzamine A analogue synthesis. Investigations to this end are ongoing, and the results will be disclosed in due course.

Scheme 4. Completion of the Total Syntheses of Manzamine A, Ircinol A, and Ircinal A[a]



[a]Reagents and conditions: (a) $Pd(PPh_3)_4$ (12 mol %), **29**, DMF, 60 °C, 1 h, 52%; (b) $Pd(OAc)_2$ (18 mol %), PPh_3 (40 mol %), CO, Et_3N, MeOH, DMF, 60 °C, 1 h, 78%; (c) DIBAL, toluene, −78 °C, 2 h, 82%; (d) $Pd(PPh_3)_4$ (10 mol %), CO, LiCl, Bu_3SnH, toluene, 50 °C, 30 min, 58%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures; spectroscopic and analytical data for all new compounds including ^{1}H and ^{13}C NMR spectra; X-ray crystallographic data (CIF) for **5** and **20**. 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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■ REFERENCES

(1) (a) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404. (b) Zhang, B.; Higuchi, R.; Miyamoto, T.; Soest, R. W. M. V. *Chem. Pharm. Bull.* **2008**, *56*, 866. For the proposed biosynthesis of manzamine alkaloids, see: (c) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D.

R.; Whitehead, R. C. *Chem.—Eur. J.* **1999**, *5*, 3154. (d) Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059.
(2) (a) Brands, K. M. J.; Meekel, A. A. P.; Pandit, U. K. *Tetrahedron* **1991**, *47*, 2005. (b) Winkler, J. D.; Axten, J.; Hammach, A. H.; Kwak, Y.-S.; Lengweiler, U.; Lucero, M. J.; Houk, K. N. *Tetrahedron* **1998**, *54*, 7045. (c) Coldham, I.; Crapnell, K. M.; Fernàndez, J.-C.; Moseley, J. D.; Rabot, R. *J. Org. Chem.* **2002**, *67*, 6181. (d) Herdemann, M.; Al-Mourabit, A.; Martin, M.-T.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 1890. (e) Magnus, P.; Fielding, M. R.; Wells, C.; Lynch, V. *Tetrahedron Lett.* **2002**, *43*, 947. (f) Solberghe, G. F.; Markó, I. E. *Tetrahedron Lett.* **2002**, *43*, 5061. (g) Giral, A. L.; Mahuteau-Betzer, F.; Gateau-Olesker, A.; Marazano, C. *Eur. J. Org. Chem.* **2003**, 1859. (h) Sanchez-Salvatori, M. d. R.; Marazano, C. *J. Org. Chem.* **2003**, *68*, 8883. (i) Coldham, I.; Pih, S. M.; Rabot, R. *Synlett* **2005**, 1743. (j) Hourcade, S.; Ferdenzi, A.; Retailleau, P.; Mons, S.; Marazano, C. *Eur. J. Org. Chem.* **2005**, 1302. (k) Tokumaru, K.; Arai, S.; Nishida, A. *Org. Lett.* **2005**, *8*, 27. (l) Kita, Y.; Toma, T.; Kan, T.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 3251. (m) Mihara, Y.; Matsumura, T.; Terauchi, Y.; Akiba, M.; Arai, S.; Nishida, A. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1520. (n) Stockman, R. A.; McDermott, P. J.; Newton, A. F.; Magnus, P. *Synlett* **2010**, 559.
(3) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425.
(4) (a) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. (b) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584.
(5) Toma, T.; Kita, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 10233.
(6) Valentin, M.-L.; Bolte, J. *Bull. Soc. Chim. Fr.* **1995**, *132*, 1167.
(7) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632.
(8) Rigby, C. L.; Dixon, D. J. *Chem. Commun.* **2008**, 3798.
(9) Jakubec, P.; Kyle, A. F.; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011**, *52*, 6094.
(10) (a) Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 4267. (b) Kyle, A. F.; Jakubec, P.; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. *Chem. Commun.* **2011**, *47*, 10037. (c) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88. (d) Jakubec, P.; Cockfield, D. M.; Helliwell, M.; Raftery, J.; Dixon, D. J. *Beilstein J. Org. Chem.* **2012**, *8*, 567.
(11) Ono, N.; Kaji, A. *Synthesis* **1986**, 693.
(12) Feringa, B. L. *Synth. Commun.* **1985**, *15*, 87.
(13) Further attempts to improve the yield of **19** directly from **4** were unsuccessful. Accordingly, the reductive nitro-Mannich cyclization cascade was further optimized on substrate **18**.
(14) Bower, S.; Kreutzer, K. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1996**, *35*, 1515.
(15) (a) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017. (b) McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367.
(16) For example, see: Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4556.
(17) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
(18) Tsuda, M.; Kawasaki, N.; Kobayashi, J. *Tetrahedron* **1994**, *50*, 7957.
(19) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7175.
(20) Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480.
(21) Winkler, J. D.; Londregan, A. T.; Ragains, J. R.; Hamann, M. T. *Org. Lett.* **2006**, *8*, 3407.