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Synthesis of the core ring system of awajanomycin from *N*-Boc-3-methoxycarbonyl-2-pyridinone

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ABSTRACT

Awajanomycin, which was isolated from marine-derived fungus, possesses unique structural features and cytotoxic activity against A549 cells. Due to its unique structure, no total synthesis has yet been reported, and neither the relative stereochemistry nor the absolute configuration has been determined. We report the synthesis of the core ring system of awajanomycin, which includes: (i) regioselective addition of the acetate unit onto C4-position of *N*-Boc-3-methoxycarbonyl-2-pyridinone; (ii) stereoselective installation of a hydroxyl group on C3-position; and (iii) stereo- and regioselective epoxide-opening reaction by Me_3Al.

Because nitrogen-containing six-membered compounds are frequently found in natural products and many are known to possess valuable biological activities, they have long been of interest to organic and bio-organic chemists.[1] Utilization of nitrogen-containing six-membered heteroaromatic compounds seems to be a useful method to achieve stereoselective construction of functionalized piperidine ring systems because they are readily available. Reactions of pyridinium salts or dihydropyridine derivatives have been thoroughly investigated recently,[2] and the syntheses of many biologically active compounds have also been reported.[3] On the other hand, the utilization of the 2-pyridinone derivatives has been mainly carried out for the Diels–Alder reaction.[4] To the best of our knowledge, a few examples for the introduction of the allyl group to 2-pyridinone derivatives[5] and some literatures about the reactions of the related compounds and their applications to the organic synthesis also could be found.[6]

During our ongoing research to develop novel methods for the introduction of functional groups in heterocyclic compounds, we reported the regioselective addition of the acetate unit into 2-pyridinone derivatives in the presence of catalytic amounts of Lewis acid.[7] In particular, we successively carried out both the C4-selective functionalization of N-substituted-3-methoxycarbonyl-2-pyridinone derivatives **2a** and **2b** (Scheme 1A) and the introduction of an acetate unit into the C6-position of N-substituted-5-methoxycarbonyl-2-pyridinone derivative **5** (Scheme 1B).[8] In this Letter, we describe an application of this methodology to the synthesis of the core ring system of awajanomycin (**1**), which has anti-cancer activity.

Awajanomycin (**1**) was isolated in 2006 from extracts of the marine-derived fungus *Acremonium* sp. AWA16-1 by Jang et al., and reported to possess cytotoxic activity against A549 cells (IC_{50} = 27.5 μg/mL).[9] The structural features of awajanomycin (**1**) are: (i) a bicyclo[3.2.1]-ring system including a γ-lactone and a δ-lactam; (ii) four adjacent asymmetric centers (C1, C8, C5, and C4); (iii) a tertiary alcohol at the α-position of γ-lactone and δ-lactam (C1–OH); and (iv) an axially oriented C4-methyl group (Fig. 1).[10]

Due to its unique structure and difficulties in the stereo-controlled introduction of stereogenic centers, total synthesis of **1** is yet to be reported; in addition the absolute configuration and relative stereochemistry of the allylic alcohol of **1** have, so far, also not been determined.

The retrosynthetic analysis of **1** is shown in Scheme 2. In this convergent strategy, **1** could be synthesized from 1-decen-3-ol (**8**) and the core ring system **9** by a cross-metathesis reaction. The vinyl group of **9** could be prepared from the ethoxycarbonyl group of **10**, by sequential reduction of the ester and dehydration of the resultant alcohol. We designed two synthetic strategies to synthesize **10**. In first route, acetal **11a,** sulfide **11b,** or the sulfone **11c** was postulated as precursors to introduce the C6-methyl group. Epoxide **12** was envisioned as precursor to **10** in the second strategy. All these precursors **11a–c** and **12** could be obtained from the enamine **13**, which was projected to arise

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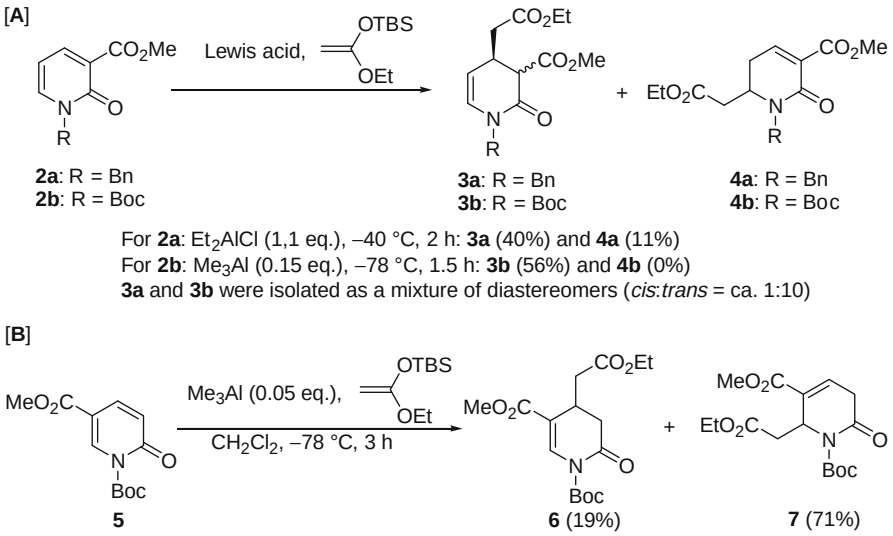


Scheme 1.

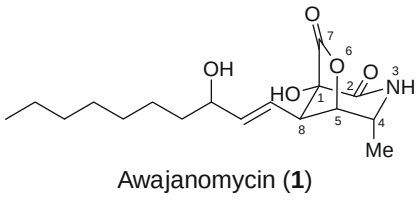
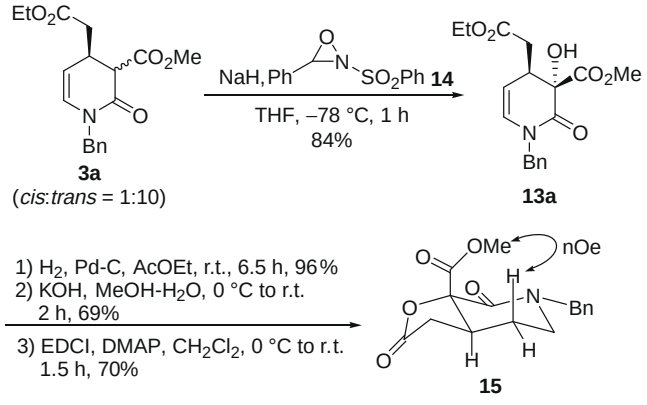


Figure 1.

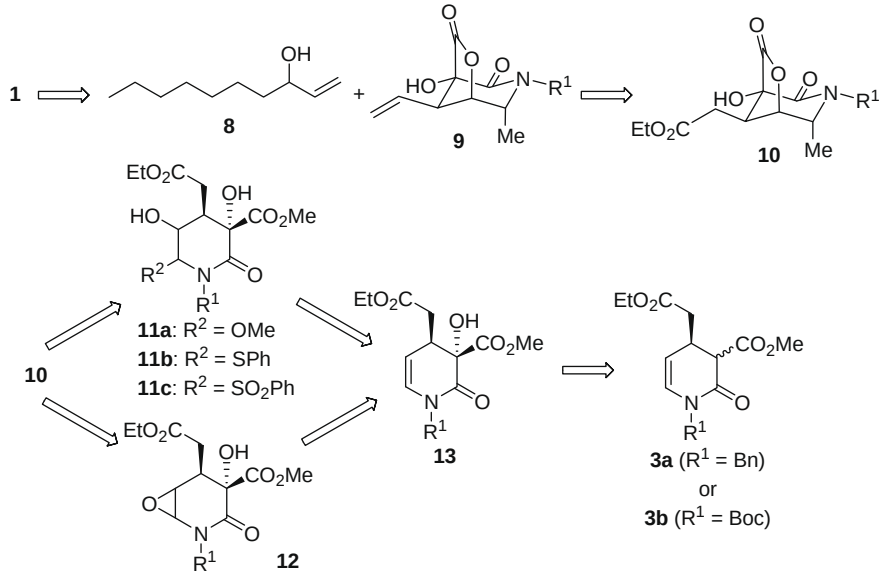
from the stereoselective hydroxylation reaction of either α-methoxycarbonyl-δ-lactam **3a** or **3b**.

We selected **3a**[7b,8] as the starting material for the first synthetic trial. Installation of the hydroxyl group was carried out using *N*-sulfonyloxaziridine **14**[11] in the presence of NaH, and afforded **13a** as a sole product in 84% yield. The stereochemistry of the hydroxyl group in **13a** was determined by nOe experiment on **15**, which was converted from **13a** by reduction of the double bond, selective hydrolysis of the ethyl ester, and lactone ring formation (Scheme 3).

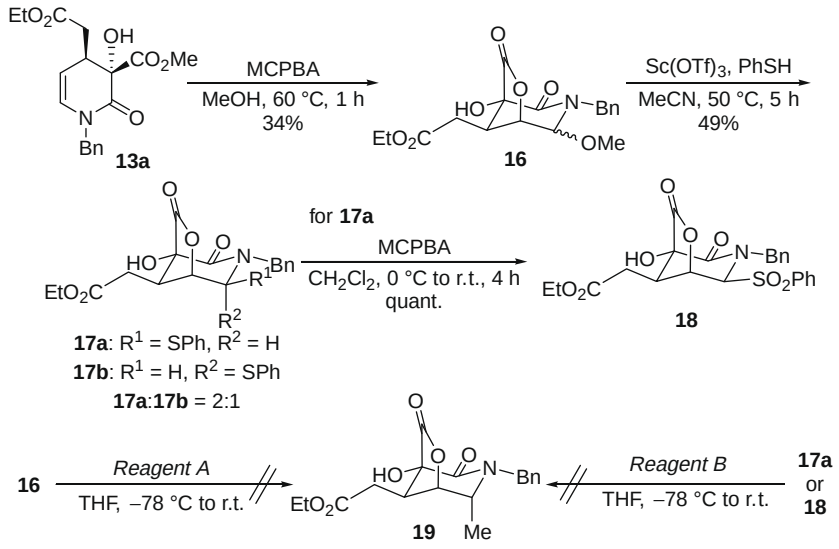


Scheme 3.

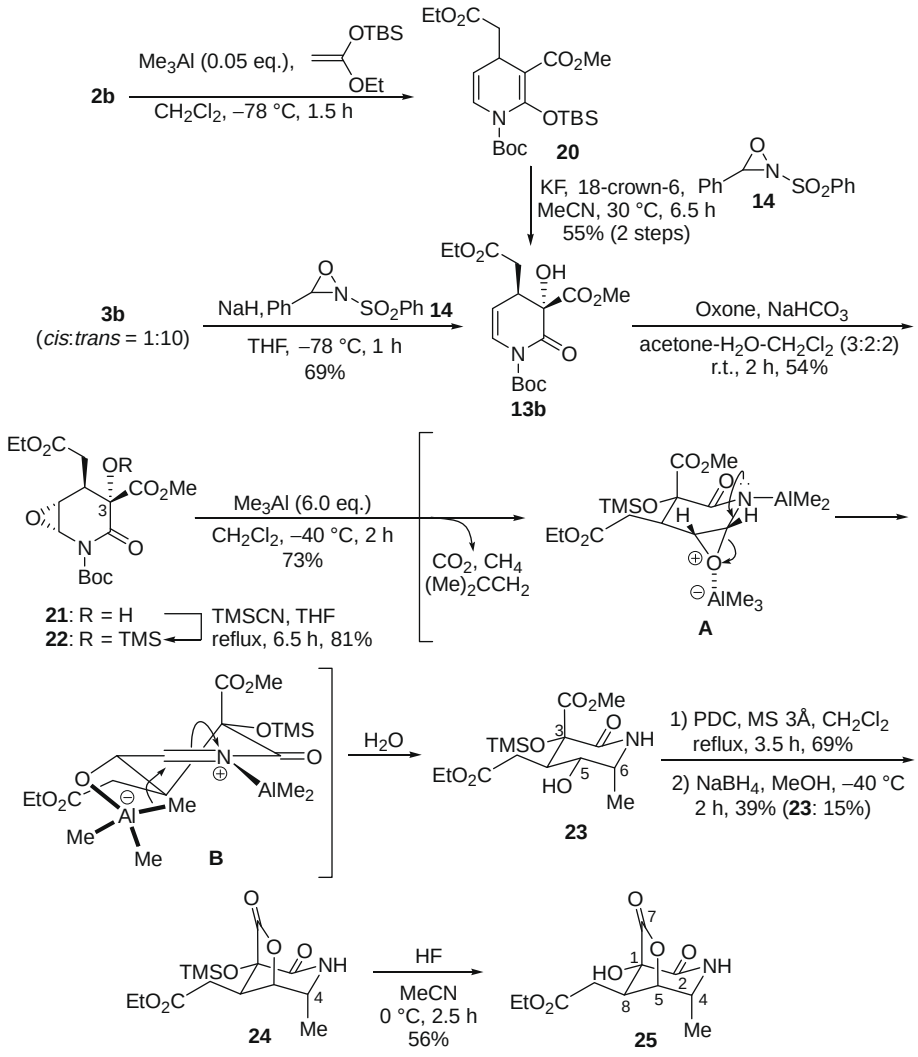
With the desired **13a** in hand, the next task was functionalization of the enamine moiety. Fortunately, bicyclic acetal **16**[12] was



Scheme 2.



Scheme 4.



Scheme 5.

obtained from the reaction of **13a** with MCPBA in methanol. This product **16** was then converted to the corresponding sulfides **17a** and **17b** (2:1) by reaction with $Sc(OTf)_3$ and thiophenol.[13] Sulfide **17a** was finally oxidized by MCPBA to afford sulfone **18** in quantitative yield (Scheme 4).

Installation of the methyl group at the C6-position proved more challenging. Neither methyl cuprate ($Me_2CuLi–BF_3$) nor the higher-order cuprate [$Me_2Cu(CN)Li_2–BF_3$] did produce the desired product **19** from compound **16**.[14] Reaction of either sulfide **17a** or sulfone **18** with the methyl anion equivalents [$Me_2Zn–Zn(OTf)_2$,[15] $Me_2Zn–AgOTf$, $Me_2Cu(CN)Li_2–BF_3$,[14] or $MeMgBr–ZnCl_2$[16]] did not provide satisfactory results, and only recovery or decomposition of the starting material was observed (Scheme 4).

These disappointing results let us to focus on our second strategy; Boc-carbamate **3b** was selected as starting material. The hydroxylation reaction of **3b** was carried out under the above-described conditions, and **13b** was obtained as the sole product in 69% yield (Scheme 5). Alternatively, **13b** could be prepared from **20**, obtained by the reaction of **2b** with TBS-ketene acetal catalyzed by Me_3Al without acidic workup,[8] by reaction with **14** in the presence of KF and 18-crown-6[17] (overall yield of 55%). The stereoselective epoxidation of **13b** was conducted by DMDO prepared in situ[18] and epoxide **21** was isolated as a single isomer in 54% yield. The epoxide-opening reaction in **21** failed with either Me_3Al or methyl cuprate, even in the presence of an additive (e.g., $BF_3{\cdot}OEt_2$,[19a] TMSOTf,[19b] H_2O[19c] for the former reagent, or $BF_3{\cdot}OEt_2$[14] for the latter reagent) and the decomposition of **21** was observed in these cases. This difficulty could be overcome by protection of the C3-hydroxyl group. When TMS-ether **22** (prepared from **21** and TMSCN[20]) was reacted with excess Me_3Al, the methyl group could be installed in a regioselective and stereoselective manner, and the desired alcohol **23** was obtained in 73% yield as a sole product. The methyl group at C6 in **23** was assumed to be axial, as unambiguous stereochemical assessment could not be obtained at this point (see below). In this reaction, three steps may be involved: (i) removal of Boc group with the action of Me_3Al to produce **A**; (ii) Me_3Al-coordinated epoxide opening by the lone pair on the nitrogen atom to give iminium cation **B**; and (iii) incorporation of the methyl group in an intramolecular manner to **B** from an axial direction (Scheme 5).

The hydroxyl group on C5 was inverted by an oxidation/reduction sequence to afford lactone **24** and recovered **23** in 39% and 15% yields, respectively. The axial configuration of the methyl group on C4 in **24** was determined by a NOESY spectrum. The ^1H NMR and ^{13}C NMR spectra of **25** (obtained by treatment of **24** with HF in acetonitrile at 0 °C) were identified primarily from the reported values.[9] We thereby furnished the synthesis of a core ring system of awajanomycin (Table 1).

Table 1
^1H NMR and ^{13}C NMR spectral data for **1** and **25** in DMSO-d_6

Carbon number	^1H NMR δ (multiplicity, J)		^{13}C NMR δ	
	1[a]	**25**[b]	**1**[a]	**25**[b,c]
1	—	—	77.1	75.8
2	—	—	165.9	165.1
3-NH	8.20 (s)	8.21 (br s)	—	—
4	3.68 (d, 6.7)	3.68 (m)	51.6	50.9
5	4.64 (s)	4.62 (t, 1.8)	79.6	78.6
7	—	—	172.5	171.9
8	3.30 (d, 6.4)	2.93 (dd, 9.9 and 4.5)	43.7	38.4
C4-**Me**	1.22 (d, 6.7)	1.19 (d, 6.9)	18.1	17.6
C1-OH	5.92 (d, 4.1)	6.26 (s)	—	—

[a] Values were reproduced from Ref.[9] (750 MHz for ^1H NMR and 250 MHz for ^{13}C NMR).
[b] 600 MHz for ^1H NMR and 150 MHz for ^{13}C NMR.
[c] Assignment of ^{13}C-signals was carried out using HMQC and HMBC spectra.

In conclusion, we successfully synthesized the core ring system of awajanomycin in seven steps from **2b**. Synthesis of **25** in an optically active form and total synthesis of awajanomycin are underway in our laboratory.

References and notes

1. (a) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159–2191; (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729; (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989.
2. Recent examples of the reaction of pyridinium salts, see: (a) Rudler, H.; Parlier, A.; Sandoval-Chavez, C.; Herson, P.; Daran, J.-C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6843–6846; (b) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300–9301; (c) Minato, D.; Imai, M.; Kanda, Y.; Onomura, O.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 5485–5488; (d) Kiselyov, A. S. *Chem. Soc. Rev.* **2005**, *34*, 1031–1037; (e) Yamada, S.; Morita, C. *J. Am. Chem. Soc.* **2002**, *124*, 8184–8185; (f) Rudler, H.; Denise, B.; Parlier, A.; Daran, J.-C. *Chem. Commun.* **2002**, 940–941; (g) Charette, A.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829–11830; Selected examples for the reaction of dihydropyridine derivatives, see: (h) Krow, G. R.; Huang, Q.; Szczepanski, S. W.; Hausheer, F. H.; Carroll, P. J. *J. Org. Chem.* **2007**, *72*, 3458–3466; (i) Davis, F. A.; Xu, H.; Zhang, J. *J. Org. Chem.* **2007**, *72*, 2046–2052; (j) Sales, M.; Charette, A. *Org. Lett.* **2005**, *7*, 5773–5776; (k) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. *Org. Lett.* **2004**, *6*, 3517–3520.
3. (a) McCall, W. S.; Grillo, T. A.; Comins, D. L. *Org. Lett.* **2008**, *10*, 3255–3257. and references cited therein; (b) Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 11808–11809; (c) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 5219–5231; (d) Comins, D. L.; Flup, A. B. *Tetrahedron Lett.* **2001**, *42*, 6839–6841; (e) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719–4728.
4. (a) Chou, S.-S. P.; Wang, H.-C.; Chen, P.-W.; Yang, C.-H. *Tetrahedron* **2008**, *64*, 5291–6297; (b) Kipassa, N. T.; Okamura, H.; Kina, K.; Hamada, T.; Iwagawa, T. *Org. Lett.* **2008**, *10*, 815–816; (c) Teysott, M.-L.; Lormier, A.-T.; Chataigner, I.; Piettre, S. R. *J. Org. Chem.* **2007**, *72*, 2364–2373; (d) Okamura, H.; Nagaike, H.; Kipassa, N. T.; Iwagawa, T.; Nakatani, M. *Heterocycles* **2006**, *68*, 2587–2594; (e) Fujita, R.; Watanabe, K.; Ikeura, W.; Ohtaka, Y.; Hongo, H.; Harigaya, Y.; Matsuzaki, H. *Tetrahedron* **2001**, *57*, 8841–8850; (f) Okamura, H.; Nagaike, H.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **2000**, *41*, 8317–8321; (g) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111–9171. and references cited therein.
5. (a) Sośnicki, J. G. *Tetrahedron Lett.* **2006**, *47*, 6809–6812; (b) Sośnicki, J. G. *Tetrahedron Lett.* **2005**, *46*, 4295–4298.
6. (a) Sasaki, Y.; Niida, A.; Tsuji, T.; Shigenaga, A.; Fujii, N.; Otaka, A. *J. Org. Chem.* **2006**, *71*, 4969–4979; (b) Niida, A.; Mizumoto, M.; Narumi, T.; Inokuchi, E.; Oishi, S.; Ohno, H.; Otaka, A.; Kitaura, K.; Fujii, N. *J. Org. Chem.* **2006**, *71*, 4118–4129; (c) Niida, A.; Tanigaki, H.; Inokuchi, E.; Sasaki, Y.; Oishi, S.; Ohno, H.; Tamamura, H.; Wang, Z.; Peiper, S. C.; Kitaura, K.; Otaka, A.; Fujii, N. *J. Org. Chem.* **2006**, *71*, 3942–3951; (d) Amat, M.; Llor, N.; Huguet, M.; Molins, E.; Espinosa, E.; Bosch, J. *Org. Lett.* **2001**, *3*, 3257–3260; (e) Brewster, A. G.; Broady, S.; Hughes, M.; Moloney, M. G.; Woods, G. *Org. Biomol. Chem.* **2004**, *2*, 1800–1810.
7. (a) Hiroya, K.; Jouka, R.; Katoh, O.; Sakuma, T.; Anzai, M.; Sakamoto, T. *Arkivoc* **2003**, *viii*, 232–246; (b) Hiroya, K.; Kawamoto, K.; Sakamoto, T. *Synlett* **2006**, 2636–2640.
8. Hiroya, K.; Kawamoto, K.; Inamoto, K.; Sakamoto, T.; Doi, T., in preparation.
9. Jang, J.-H.; Kanoh, K.; Adachi, K.; Shizuri, Y. *J. Nat. Prod.* **2006**, *69*, 1358–1360.
10. In this Letter, the numbering of the atoms of awajanomycin (**1**) was done following the IUPAC rules, which is different from the numbering written in Ref. 9. IUPAC name for awajanomycin (**1**) is (*E*)-1-hydroxy-8-(3-hydroxyundec-1-enyl)-4-methyl-6-oxa-3-azabicyclo[3.2.1]octane- 2,7-dione.
11. Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth. Coll.* **1993**, *8*, 546–550 (**1988**, *66*, 203−207).
12. The stereochemistry of methoxy group in **16** could not be determined by either ^1H NMR or NOESY spectrum.
13. Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809–823.
14. (a) Ibuka, T.; Yamamoto, Y. In *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; pp 143–158; (b) Ishibuchi, S.; Ikematsu, Y.; Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1991**, *32*, 3523–3526; (c) Wistrand, L.-G.; Skrinjar, M. *Tetrahedron* **1991**, *47*, 573–582; (d) Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J. *J. Am. Chem. Soc.* **1988**, *110*, 4834–4835; (e) Alexakis, A.; Jachiet, D.; Normant, J. F. *Tetrahedron* **1986**, *42*, 5607–5619; (f) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959–5962.
15. (a) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834–6839; (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *Org. Lett.* **2000**, *2*, 1971–1973.
16. (a) Takasu, K.; Ohsato, H.; Ihara, M. *Org. Lett.* **2003**, *5*, 3017–3020; (b) Huang, P. Q.; Tang, X.; Chen, A. Q. *Synth. Commun.* **2000**, *30*, 2259–2268.
17. Artamkina, G. A.; Kovalenko, S. V.; Beletskaya, I. V.; Reutov, O. A. *J. Organomet. Chem.* **1987**, *329*, 139–150.
18. Murray, R. W.; Singh, M. *Org. Synth. Coll.* **1997**, *9*, 288–293 (**1997**, *74*, 91−96).
19. (a) Fotsch, C. H.; Chamberlin, A. R. *J. Org. Chem.* **1991**, *56*, 4141–4147; (b) Crawley, G. C.; Briggs, M. T. *J. Org. Chem.* **1995**, *60*, 4264–4267; (c) Miyazawa, M.; Ishibashi, N.; Ohnuma, S.; Miyashita, M. *Tetrahedron Lett.* **1997**, *38*, 3419–3422.
20. Mai, K.; Patil, G. *J. Org. Chem.* **1986**, *51*, 3545–3548.