ORGANIC LETTERS

2011
Vol. 13, No. 5
1234–1237

Synthesis of (±)-7-Hydroxylycopodine

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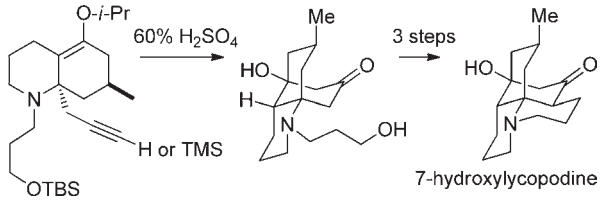
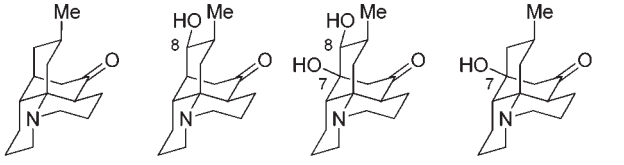
Received January 14, 2011

ABSTRACT



A six step synthesis of (±)-7-hydroxylycopodine has been achieved in 5% overall yield. In the key step, a Prins cyclization of a bicyclic keto alkyne in 60% H_2SO_4 forms a tricyclic dihydroxy amino ketone.

Sauroine (**3**, 7,8-dihydroxylycopodine), from *Huperzia saururus*,[1a] was reported in 2004 and shown in 2009 to improve memory retention in the step-down test in male Wistar rats, significantly increasing hippocampal plasticity (see Scheme 1).[1b] The lycopodium alkaloids are a large and extensively studied alkaloid family.[2] Huperzine A, the medicinally most significant lycopodine alkaloid as a potential treatment for Alzheimer's disease, functions as an acetylcholinesterase inhibitor but may have other roles as has been addressed in several recent reviews.[3]



1 (lycopodine) **2** (clavolonine) **3** (sauroine) **4** (7-hydroxylycopodine)

Lycopodine (**1**) has been synthesized many times over the past 40 years[4] but is still a significant target with the first synthesis in optically pure form reported by Carter in 2008.[4j] 8-Hydroxylycopodine (**2**, clavolonine) has been known for many years and has been synthesized by Wenkert in racemic form and recently by Evans and Breit in optically pure form.[5] 7-Hydroxylycopodine (**4**) was

(1) (a) Ortega, M. G.; Agnese, A M.; Cabrera, J. L. *Tetrahedron Lett.* **2004**, *45*, 7003–7005. (b) Vallejo, M. G.; Ortega, M. G.; Cabrera, J. L.; Carlini, V. P.; Rubiales de Barioglio, S.; Almiron, R. S.; Ramirez, O. A.; Agnese, A. M. *J. Nat. Prod.* **2009**, *72*, 156–158; note that the methyl group of sauroine is attached to the wrong carbon.

(2) For recent reviews on lycopodium alkaloids, see: (a) Kobayashi, J.; Morita, H. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier: San Diego, CA, 2005; Vol. 61, pp 1−57. (b) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772. (c) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679–729.

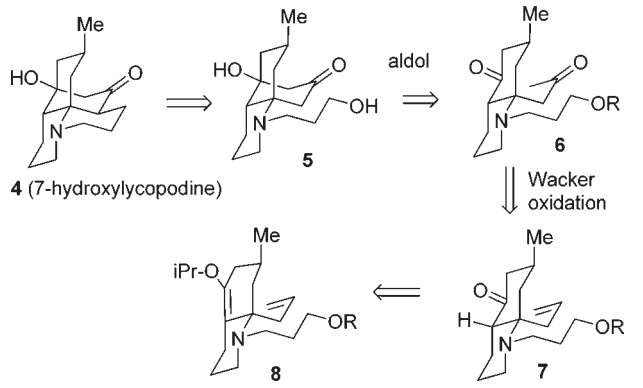
(3) For recent reviews on huperzine A for treatment of Alzheimer's disease, see: (a) Hostettmann, K.; Borloz, A.; Urbain, A.; Marston, A. *Curr. Org. Chem.* **2006**, *10*, 825–847. (b) Zhu, D.-Y.; Tan, C.-H.; Li, Y.-M. In *Medicinal Chemistry of Bioactive Natural Products*; Liang, X.-T., Fang, W.-S., Eds.; WILEY-VCH: New York, 2006; pp 143−182. (c) Bai, D. *Pure Appl. Chem.* **2007**, *79*, 469–479. (d) Little, J. T.; Walsh, S.; Aisen, P. S. *Exp. Opin. Invest. Drugs* **2008**, *17*, 209–215. (e) Desilets, A. R.; Gickas, J. J.; Dunican, K. C. *Ann. Pharmacother.* **2009**, *43*, 514–518.

(4) (a) Stork, G.; Kretchmer, R. A.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 1647–1648. (b) Ayer, W. A.; Bowman, W. R.; Joseph, T. C.; Smith, P. *J. Am. Chem. Soc.* **1968**, *90*, 1648–1650. (c) Kim, S.; Bando, Y.; Horii, Z. *Tetrahedron Lett.* **1978**, 2293–2294. (d) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. *J. Am. Chem. Soc.* **1982**, *104*, 1054–1068. (e) Schumann, D.; Müller, H.-J.; Naumann, A. *Liebigs Ann. Chem.* **1982**, 1700–1705. (f) Kraus, G. A.; Hon, Y. S. *J. Am. Chem. Soc.* **1985**, *107*, 4341–4342. *Heterocycles* **1987**, *25*, 377–386. (g) Padwa, A.; Brodney, M. A.; Marino, J. P.; Sheehan, S. M. *J. Org. Chem.* **1997**, *62*, 78–87. (h) Greico, P. A.; Dai, Y. J. *J. Am. Chem. Soc.* **1998**, *120*, 5128–5129. (i) Mori, M.; Hori, K.; Akashi, M.; Hori, M.; Sato, Y.; Nishida, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 636–637. (j) Yang, H.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238–9239. (k) Yang, H.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 4929–4938. (l) For a review of lycopodine syntheses, see: Hudlický, T.; Reed, J. W. *The Way of Synthesis*; Wiley-VCH: Weinheim, 2007; pp 573−602.

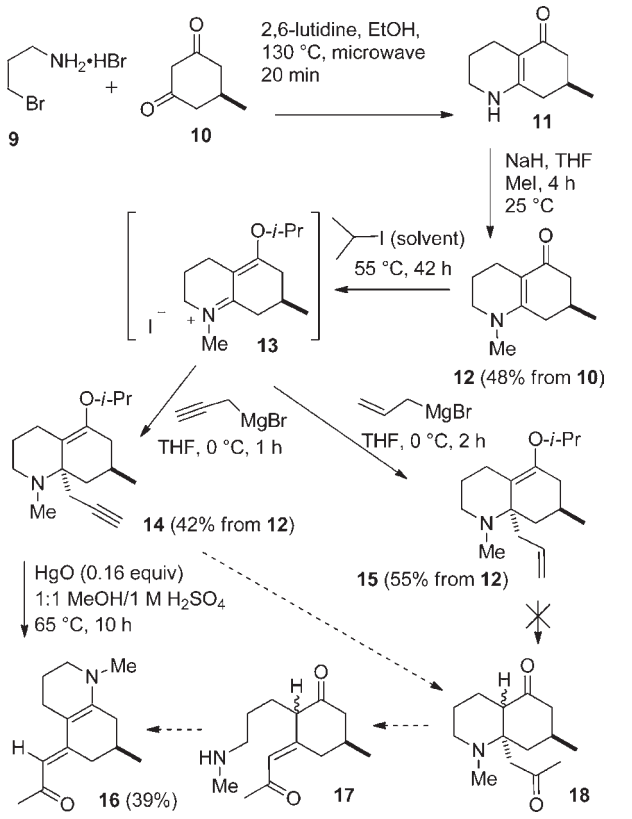
(5) (a) Wenkert, E.; Broka, C. A. *J. Chem. Soc., Chem. Commun.* **1984**, 714–715. (b) Evans, D. A.; Scheerer, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 6038–6042. (c) Laemmerhold, K. M.; Breit, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 2367–2370.

10.1021/ol200119h
Published on Web 01/27/2011

Scheme 1. Retrosynthesis of 7-Hydroxylycopodine



Scheme 2. Unsuccessful Approach to Diketone



reported in 2004.[6] The bridgehead hydroxy group of sauroine (**3**) and 7-hydroxylycopodine (**4**) precludes the use of most of the methods that have been developed for lycopodine and clavolonine synthesis, but they also make aldol and Prins approaches more attractive. We decided to synthesize 7-hydroxylocopodine (**4**) first and then modify that route to prepare sauroine (**3**) with the additional 8-hydroxy group so that these molecules will be available for further biological evaluation.

We planned to construct the final ring of **4** from dihydroxy ketone **5** by a modified Oppenauer oxidation−aldol reaction sequence as developed by Heathcock in his lycopodine synthesis[4d] (see Scheme 1) and later used by Kraus and Carter.[4f,j,k] We planned to prepare the β-hydroxycyclohexanone of **5** from diketone **6** by an intramolecular aldol reaction. The 2-oxopropyl side chain of **6** should be available by Wacker oxidation of the allyl side chain of **7**, which will be prepared by hydrolysis of enol ether **8**. This route is appealing because Wiesner reported an efficient synthesis of **15**, the analogue of **8** with an *N*-methyl substituent.[7b] We were concerned about the stereochemistry of the ring fusion that will be introduced by protonation of the enol ether of **8** because related work from Wiesner's laboratory led to the synthesis of 12-epilycopodine.[7c,d] Nevertheless, the brevity of this approach was very appealing.

Before addressing the synthesis of **5**, we chose to carry out a model study for the preparation of the tricylic framework with an *N*-methyl rather than a protected *N*-hydroxypropyl group. Reaction of 3-bromopropylamine hydrobromide (**9**), 5-methyl-1,3-cyclohexanedione (**10**), and 2,6-lutidine in ethanol at 130 °C afforded the enamide which underwent an intramolecular alkylation to give racemic **11** (see Scheme 2).[7b,8,9] Alkylation of **11** with iodomethane using NaH in THF gave **12** in 48% yield from **10**. Following Wiesner's procedure, vinylogous amide **12** was heated in isopropyl iodide at 55 °C for 42 h to provide cation **13**, which was treated with allylmagnesium bromide to give **15** in 55% yield from **12**. Hydrolysis of the enol ether of **15** with 1 M hydrochloric acid afforded a 1.7:1 mixture of stereoisomeric ketones in 77% yield. Unfortunately, we were unable to prepare **18** by a Wacker oxidation of keto amino alkene **15**, although amino alkenes have been successfully oxidized to amino methyl ketones.[10]

We then attempted to prepare methyl ketone **18** by hydrolysis of alkyne **14**. Addition of propargylmagnesium bromide to cation **13** gave ketone **14** in 42% yield from **12**. Hydration of the triple bond of **14** with HgO in 1:1 MeOH/1 M aqueous H_2SO_4 at 65 °C also failed to give the desired methyl ketone **18**. Instead we obtained dienone **16** in 39% yield. A plausible mechanism for the formation of **16** involves the desired hydration of the alkyne to give **18**, which under the acidic conditions undergoes a retro conjugate addition to give amino diketone **17**. Condensation

(6) (a) Tan, C.-H. Ph. D. Thesis, Shanghai Institute of Materia Medica, 2001. (b) Tan, C.-H.; Zhu, D.-Y. *Helv. Chim. Acta* **2004**, *87*, 1963–1967.

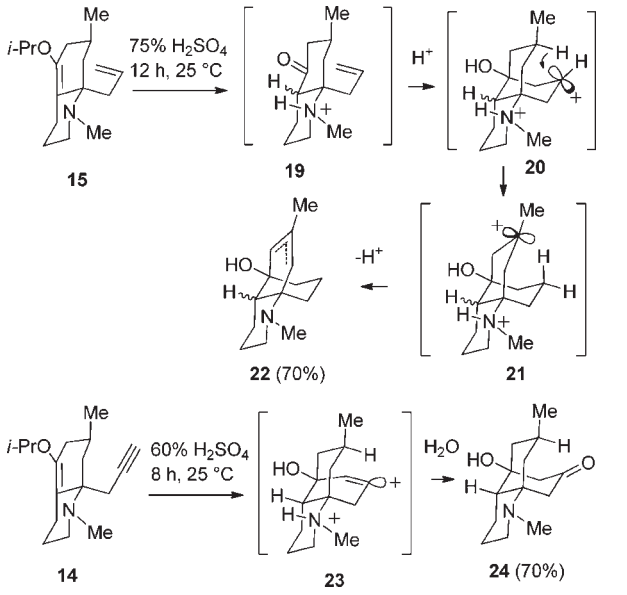
(7) (a) Valenta, Z.; Deslongchamps, P.; Ellison, R. A.; Wiesner, K. J. *J. Am. Chem. Soc.* **1964**, *86*, 2533–2534. (b) Dugas, H.; Ellison, R. A.; Valenta, Z.; Wiesner, K.; Wong, C. M. *Tetrahedron Lett.* **1965**, 1279–1286. (c) Dugas, H.; Hazenberg, M. E.; Valenta, Z.; Wiesner, K. *Tetrahedron Lett.* **1967**, 4931–4936. (d) Wiesner, K.; Musil, V.; Wiesner, K. J. *Tetrahedron Lett.* **1968**, 5643–5646.

(8) Reinshagen, H. *Angew. Chem.* **1964**, *76*, 994.

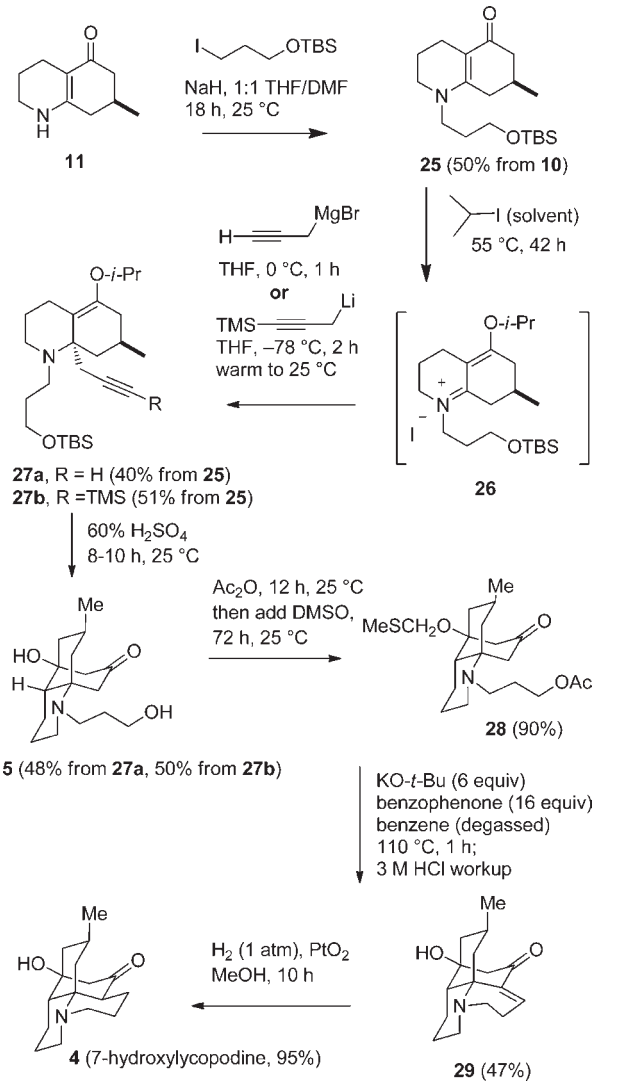
(9) For the preparation of related vinylogous amides by this method, see: (a) Rohloff, J. C.; Dyson, N. H.; Gardner, J. O.; Alfredson, T. V.; Sparacino, M. L.; Robinson, J., III. *J. Org. Chem.* **1993**, *58*, 1935–1938. (b) Zhao, Y.; Zhao, J.; Zhou, Y.; Lei, Z.; Li, L.; Zhang, H. *New J. Chem.* **2005**, *29*, 769–772.

(10) For examples of Wacker oxidations in the presence of an amine, see: (a) Li, W.-D.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931–2934. (b) Berry, M. B.; Craig, D.; Jones, P. S.; Rowlands, G. J. *Beilstein J. Org. Chem.* **2007**, *3*, no. 39.

Scheme 3. Synthesis of Model Tricyclic Hydroxy Ketone **24**



Scheme 4. Synthesis of 7-Hydroxylycopodine (**4**)



of the amine with the cyclohexanone will then give the fully conjugated δ-amino dienone **16**. This suggests that decomposition of **18** might be responsible for the failure of the Wacker oxidation of **15**.

Fortunately, the alkyne of **14** provided us with another method to form the desired tricyclic hydroxy ketone **5**. Wiesner reported that reaction of **15** in 75% H_2SO_4 for 12 h afforded **22** in 70% yield as a single isomer with unknown regio- and stereochemistry. Hydrolysis of enol ether **15** afforded ketone **19**, which underwent a Prins cyclization to give secondary cation **20** (see Scheme 3). A 1,5-hydride shift afforded tertiary cation **21**, which lost a proton to give **22**. The desired stereochemistry with a β-hydrogen, which would result from formation of trans-fused bicylic ketone **19**, was suggested on the basis of kinetic and thermodynamic conformational arguments. However, later work from this group leading to two syntheses of the undesired 12-*epi*-lycopodine[7c,d] raises questions about this stereochemical suggestion. Amino alkene **22** is not useful for lycopodine synthesis because the functionality is now in the wrong ring.

We decided to subject alkyne **14** to these acidic conditions with the hope that hydrolysis of the enol ether and cyclization would give vinyl cation **23** analogously to the formation of secondary cation **20**. A 1,5-hydride shift cannot occur in **23** because the hydrogen is too far from the vacant sp^2 orbital. Cation **23** should react with water to give an enol that will tautomerize to the desired tricylic ketone **24**. We were delighted to find that reaction of **14** in 60% aqueous H_2SO_4 for 8 h afforded tricylic amino hydroxy ketone **24** in 70% yield. Prins reactions with alkynes are uncommon but known.[11] The isolation of β-hydroxy ketones from Prins reactions of keto alkynes is not usually observed but occurs here because ring strain prevents dehydration to form the enone with a bridgehead double bond. The stereochemistry of **24** was assigned from NOE studies as described in detail in the Supporting Information. The stereoisomer derived from the cis-fused bicyclic ketone was not formed, possibly because the trans-fused bicyclic ketone is 1.4 kcal/mol more stable than the cis isomer as determined by molecular mechanics calculations.

For the synthesis of 7-hydroxylycopodine precursor **5** we simply needed to replace the methyl group of **14** with a 3-hydroxypropyl group. Crude enaminoketone **11** was alkylated with I(CH$_2$)$_3$OTBS[12] using NaH in 1:1 THF/DMF for 18 h at 25 °C to give **25** in 50% yield from

(11) For examples of Prins additions of ketones and aldehydes to alkynes, see: (a) Rodini, D. J.; Snider, B. B. *Tetrahedron Lett.* **1980**, *21*, 3857–3860. (b) Keirs, D.; Overton, K.; Thakker, K. *J. Chem. Soc., Chem. Commun.* **1990**, 310–311. (c) Harding, C. E.; King, S. L. *J. Org. Chem.* **1992**, *57*, 883–886. (d) Wempe, M. F.; Grunwell, J. R. *J. Org. Chem.* **1995**, *60*, 2714–2720. (e) Balog, A.; Geib, S. J.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345–352. (f) Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, *7*, 2493–2495. (g) Jin, T.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259–5262. (h) Miranda, P. O.; Ramírez, M. A.; Martín, V. S.; Padrón, J. I. *Chem.—Eur. J.* **2008**, *14*, 6260–6268. (i) Chavre, S. N.; Choo, H.; Lee, J. K.; Pae, A. N.; Kim, Y.; Cho, Y. S. *J. Org. Chem.* **2008**, *73*, 7647–7471.

cyclohexanedione **10** (see Scheme 4). A solution of **25** in 2-iodopropane was heated at 55 °C for 42 h to give the intermediate cation **26**, which was treated with propargylmagnesium bromide to give **27a** in 40% yield from **25**. Stirring **27a** in 60% aqueous H_2SO_4 for 8 h at 25 °C afforded the desired tricylic dihydroxy ketone **5** in 48% yield. The sequence was improved by adding trimethylsilylpropargyllithium, prepared by deprotonation of 1-trimethylsilylpropyne with *n*-BuLi, to cation **26** to give **27b** in 51% yield. Stirring **27b** in 60% sulfuric acid for 10 h at 25 °C afforded **5** in 50% yield. The stereochemistry of **5** was established by NOE studies as detailed in the Supporting Information. During the conversion of **27b** to **5**, the enol ether is hydrolyzed, the TBS ether and TMS alkyne are deprotected, and the keto alkyne undergoes the Prins reaction to form the third ring.

The modified Oppenauer oxidation−aldol reaction of **5** with benzophenone and KO-*t*-Bu using conditions developed by Heathcock in his lycopodine synthesis for the oxidation of the analogue of **5** lacking the tertiary hydroxy group gave a complex mixture containing ~5% of the desired enone **29**.[4d,13] We suspect that a retro aldol reaction of the β-hydroxy ketone occurred under the strongly basic conditions. We eventually found that the primary alcohol could be selectively oxidized to the aldehyde with *t*-BuOMgCl and azodicarbonyldipiperidine in THF,[14] but all attempts to carry out the aldol reaction resulted in a retro conjugate addition with loss of acrolein to form the tricyclic secondary amine.

We therefore decided to protect the tertiary alcohol and re-examine the modified Oppenauer oxidation−aldol reaction sequence. Both alcohol groups of **5** were differently protected in a single reaction to give **28** in 90% yield by stirring **5** for 12 h in Ac_2O to form the primary acetate and adding DMSO and continuing stirring for 72 h to form the methylthiomethyl ether of the tertiary alcohol.[15] Keto acetate **28** was treated with KO-*t*-Bu (6 equiv) and benzophenone (16 equiv) in carefully degassed benzene at 110 °C for 1 h. Under these conditions, the acetate is cleaved, the resulting primary alcohol is oxidized to the aldehyde, and the aldol reaction occurs to form the enone. The methylthiomethyl protecting group is cleaved with 3 M hydrochloric acid during the workup to give **29** in 47% yield. Hydrogenation of enone **29** over PtO_2 with 1 atm of H_2 for 10 h afforded 7-hydroxylycopodine (**4**) in 95% yield. The spectral data for the hydrochloride salt of **4** in CD_3OD are identical to those reported for the natural product.[6]

In conclusion, we have developed a practical six step synthesis of (±)-7-hydroxylycopodine (**4**) that proceeds in a 5% overall yield making it readily available for further biological evaluation. The key step is the Prins reaction of **27a** or **27b** that proceeds in 60% H_2SO_4 to give tricyclic dihydroxy amino ketone **5**. We are currently investigating methods to prepare the starting vinylogous amide **11** in optically pure form and to introduce a hydroxy group adjacent to the carbonyl group of **25** to give an intermediate that will be elaborated analogously to sauroine (**3**, 7,8-dihydroxylycopodine).

Acknowledgment. We are grateful to the National Institutes of Health (GM-50151) for generous financial support. We thank Dr. C.-H. Tan, Shanghai Institute of Materia Medica, for a copy of his Ph.D. thesis containing an HMQC spectrum of **4**.

Supporting Information Available. Complete experimental procedures and copies of ^1H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Warnhoff, E. W.; Reynolds-Warnhoff, R. *J. Org. Chem.* **1963**, *28*, 1431–1433. (b) Koenig, J.-J.; de Rostolan, J.; Bourbier, J.-C.; Jarreau, F.-X. *Tetrahedron Lett.* **1978**, 2779–2782.

(14) Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773–2776.

(15) (a) Yamada, K.; Kato, K.; Nagase, H.; Hirata, Y. *Tetrahedron Lett.* **1976**, 65–66. (b) Pojer, P. M.; Angyal, S. J. *Aust. J. Chem.* **1978**, *31*, 1031–1040.