ORGANIC LETTERS

2003
Vol. 5, No. 11
1899−1902

Directed *ortho* Metalation Approach to C-7-Substituted Indoles. Suzuki–Miyaura Cross Coupling and the Synthesis of Pyrrolophenanthridone Alkaloids

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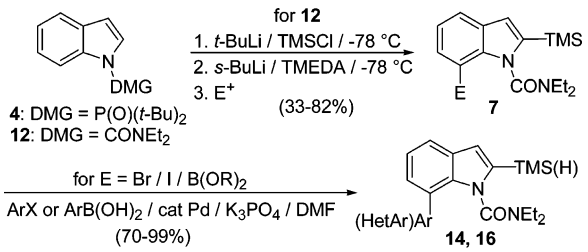
Received March 19, 2003

ABSTRACT



Although the indole *N*-phosphinoyl derivative 4 undergoes *n*-BuLi deprotonation/electrophile quench to afford C-7-substituted products, its deprotection requires harsh conditions. On the other hand, the *N*-amide 12, upon sequential or one-pot C-2 metalation, silylation, C-7 metalation, and electrophile treatment, furnishes indoles 7 in good overall yields. In combination with the Suzuki–Miyaura protocol, C-7 aryl (heteroaryl)-substituted indoles 14 and 16 are obtained, including hippadine and pratosine, members of the pyrrolophenanthridone alkaloid family.

We wish to report a new, general, and efficient method for the preparation of C-7 functionalized indoles, **5**, **7**, **13**, **14**, and **16**, by directed *ortho* metalation (D*o*M) and combined D*o*M/Suzuki−Miyaura cross-coupling strategies.[1] These findings provide an entry into a difficult indole substitution and bear general consequences on the synthesis of alkaloids[2] and bioactive molecules, which incorporate the key indole moiety.

In addition to traditional methodologies that rely on incorporation of functionality prior to indole ring construction,[2b,3] recent routes to substituted indoles have been dominated by D*o*M protocols. Although C-2 and C-3 functional group introduction may be thereby readily achieved (**A**, Scheme 1),[4,5] relatively minor effort has been dedicated to benzenoid ring functionalization via metalation tactics.[6]

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(1) For recent reviews, see: (a) Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. (b) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, Germany, 2002; p 330.

(2) (a) Lounasmaa, M.; Hanhihen, P. *The Alkaloids* **2001**, *55*, 1−89. (b) Sundberg, R. J. *Indoles*, 2nd ed.; Academic Press: San Diego, CA, 1996.

(3) For a selection of de novo methods of indole ring construction, see: (a) Batcho, A. D.; Leimgruber, W. *Org. Synth.* **1985**, *63*, 214. (b) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Palmieri, G.; Marcantoni, E. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2757. (c) Soederberg, B. C.; Shriver, J. A. *J. Org. Chem.* **1997**, *62*, 5838, and refs cited therein. (d) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045 and refs cited therein. (e) Beller, M.; Breindl, C.; Riermeier, T. H.; Tillack, A. *J. Org. Chem.* **2001**, *66*, 1403. (f) Lindsay, D. M.; Dohle, W.; Jensen, A. E.; Kopp, F.; Knochel, P. *Org. Lett.* **2002**, *4*, 1819.

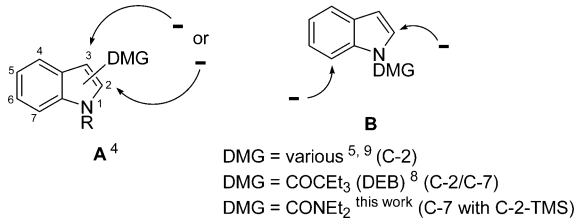
(4) (a) Gribble, G. W. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; Jai Press: Greenwich, CT, 1990; Vol. 1, p 43. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Turck, A.; Ple, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489. For relevant selected indole metalation chemistry, see: (d) Comins, D. L. *Synlett* **1992**, 615. (e) Matsuzono, M.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* **2001**, *42*, 7621. (f) Vasquez, E.; Davies, I. W.; Payack, J. F. *J. Org. Chem.* **2002**, *67*, 7551.

(5) (a) Rewcastle, G. W.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1993**, *56*, 172. (b) Ishikura, M.; Matsuzaki, Y.; Agata, I. *Heterocycles* **1997**, *45*, 2309.

(6) (a) Greenhill, J. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, p 497. (b) Chauder, B.; Larkin, A.; Snieckus, V. *Org. Lett.* **2002**, *4*, 815. For C-4/C-6 D*o*M chemistry on C-5 *O*-carbamates, see: (c) Griffen, E. J.; Roe, D. G.; Snieckus, V. *J. Org. Chem.* **1995**, *60*, 1484.

10.1021/ol0344772 CCC: $25.00
Published on Web 05/01/2003

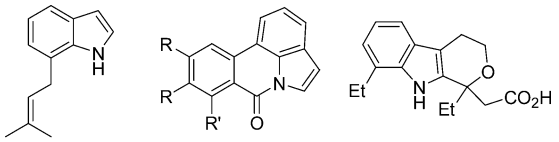
Scheme 1. Indole Functionalization by DoM



Iwao has provided two DoM approaches for C-7-substituted indoles: via *N*-Boc indolines followed by oxidation[7] and, recently, via *N*-(diethylbutanoyl)(DEB)indoles.[8,9] In the excellent latter study, while good yields of C-7 products were achieved, the value of the method was compromised by C-7/C-2 regioselectivity (**B**, Scheme 1).[10]

The method described herein uses the silicon protection tactic[11] at C-2 for clean C-7 deprotonation leading to indoles **7**, which may be readily N-deprotected and, by cross coupling, converted into compounds **14** and **16**, including pyrrolophenanthridone alkaloids **2a**,**b**. The significance of the new methodology relates to the existence of natural products (e.g., 7-prenylindole **1** as a prototype[12] and pyrrolophenanthridone alkaloids **2a**−**c**,[13] Scheme 2) and to the demand, in today's drug discovery programs, for interesting indole scaffolds (e.g., Etodolac **3**[14]).

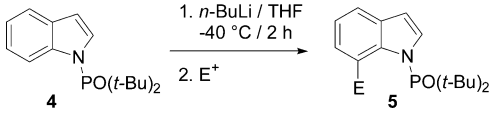
Scheme 2. 7-Substituted Indole Alkaloids and Drugs



2a: R = OMe, R′ = H: Pratosine
2b: R = OCH_2O, R′ = H: Hippadine
2c: R = OCH_2O, R′ = OH: Kalbretorine

In an early test, the powerful P(O)(*t*-Bu)$_2$ Directed Metalation Group (DMG)[15] was appended to indole ((1) *n*-BuLi/THF/0 °C and then ClP(*t*-Bu)$_2$; (2) H_2O_2/MeOH) to give **4** in 78% overall yield. Highly regioselective C-2 or C-7 deprotonation of **4** was achieved by choice of conditions. Thus, using 2 equiv of LDA at 0 °C for 15 min provided, after TMSCl quench, *N*-di-*tert*-butylphosphinoyl-2-trimethylsilylindole in 82% yield. In complete regioselective contrast, use of 2.2 equiv of *n*-BuLi at −40 °C for 2 h and TMSCl quench afforded **5a** exclusively (Table 1). Other

Table 1. Metalation and Electrophile Quench of *N*-(Di-*tert*-butylphosphinoyl)indole **4**



E^+	product (E)	yield (%)
Me_3SiCl	**5a** ($SiMe_3$)	72
MeI	**5b** (Me)	93
$BrCH_2CH{=}CMe_2$	**5c** ($CH_2CH{=}CMe_2$)	87
DMF	**5d** (CHO)	53
$ClPPh_2$	**5e** (PPh_2)	44
I_2	**5f** (I)	78

representative electrophiles gave the identical regioselectivity result providing indoles **5b**−**f** in modest to very good yields.[16] In consonance with the proposal by Iwao for the corresponding DEB-indole (**B**, DMG = $COCEt_3$, Scheme 1),[8] the high steric demand of the *tert*-butyl groups may lead to a complex in which the P═O bond orientation favors C-7 hydrogen abstraction rather than the normal higher thermodynamically acidic C-2 site.[17] The proposed phosphinoyl group orientation is evident in the single-crystal X-ray analysis of **5c** (Supporting Information, CCDC 207794). Deprotection of **5c** and other C-7-substituted indoles in this series was unsuccessful using basic or acidic conditions but was achieved by reduction ($LiAlH_4$/toluene/reflux). For example, the natural product **1** (Scheme 2) was thereby obtained in 44% yield from **5c**.[16]

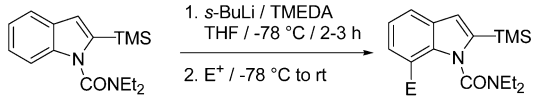
The harsh conditions for cleavage of **5** prompted a search for alternative *N*-DMGs that would promote this direct C-7 deprotonation and yet be cleaved under mild conditions. Considerable experimentation of numerous conditions using *N*-DMG = Boc, SO_2Ph, $CONR_2$ (R = Et, *i*-Pr, Ph, pyrrolidinyl) showed that only C-2 deprotonation was achievable. Furthermore, adapting the silicon protection mode to the above substrates[11] afforded clean results of C-7 lithiation with only the *N*-$CONEt_2$ derivative **6** (preparation from indole: (1) NaH/$ClCONEt_2$/THF/0 °C to room temperature, >98% yield (Kugelrohr distillation); (2) TMSCl/*t*-BuLi/THF/−78 °C, 97%).

Using the optimized metalation conditions (1.5−2.5 equiv of *s*-BuLi/TMEDA/THF/−78 °C/2−3 h)[18] on **6** followed by electrophile quench gave products **7a**−**k** and **8** in moderate

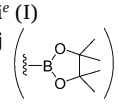
(7) Iwao, M.; Kuraishi, T. *Heterocycles* **1992**, *34*, 1031.
(8) Fukuda, T.; Maeda, R.; Iwao, M. *Tetrahedron* **1999**, *55*, 9151.
(9) For C-7 functionalization via $Cr(CO)_3$ derivatives, see: (a) Masters, N. F.; Mathews, N.; Nechvatal, G.; Widdowson, D. A. *Tetrahedron* **1989**, *45*, 5955. Via C−H activation, see: (b) Chatani, N.; Yorimitsu, S.; Asaumi, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2002**, *67*, 7557.
(10) For use of DEB−indole for C-2 and C-3 functionalization by metalation reactions, see: Fukuda, T.; Mine, Y.; Iwao, M. *Tetrahedron* **2001**, *57*, 975.
(11) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372.
(12) Achenbach, H.; Renner, C. *Heterocycles* **1985**, *23*, 2075.
(13) Grundon, M. F. *Nat. Prod. Rep.* **1989**, *6*, 79.
(14) Jones, R. A. *Inflammopharmacology* **2001**, *9*, 63.
(15) Gray, M.; Chapell, B. J.; Felding, J.; Taylor, N. J.; Snieckus, V. *Synlett* **1998**, 422.
(16) For the complete study, see: Chapell, B. J., Ph.D. Thesis, University of Waterloo, Waterloo, ON, Canada, 2001.
(17) This may be reasonably rationalized by a complex induced proximity effect (CIPE): Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.
(18) Success of this reaction is highly dependent on the quality and quantity of the *s*-BuLi; see also footnote 23 in ref 8.

to high yields (Table 2). Although deuteration is not quantitative (entry 1), a variety of carbon (entries 2−6),

Table 2. Metalation and Electrophile Quench of 1-(*N*,*N*-Diethylcarbamoyl)-2-trimethylsilylindole **6**[a]



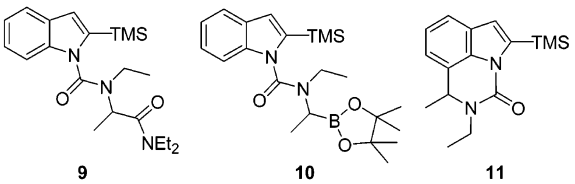
6 **7a-k**

entry	E^+	product (E)	yield (%)
1	MeOD	**7a** (D)	>99[b]
2	MeI	**7b** (Me)	81
3	EtI	**7c** (Et)	70
4[c]	$BrCH_2CH{=}CMe_2$	**7d** ($CH_2CH{=}CMe_2$)	66
5	DMF	**8**[d] (CHO)	40
6[c]	$ClCONEt_2$	**7e**[e] ($CONEt_2$)	72
7	Me_3SiCl	**7f**[e] ($SiMe_3$)	82
8	Bu_3SnCl	**7g** ($SnBu_3$)	33
9[c]	$BrCH_2CH_2Br$	**7h** (Br)	69
10[c]	I_2	**7i**[e] (I)	75
11[c]	(1) $B(O^iPr)_3$, (2) pinacol	**7j** 	60
12[c]	(1) $B(O^iPr)_3$, (2) H_2O_2	**7k**[e] (OH)	58

[a] Typical procedure: (1) 2.5 equiv of *s*-BuLi/TMEDA/THF/−78 °C/2−3 h/0.5 M; (2) E^+/−78 °C to room temperature/8−12 h. [b] D:H = 5:1. [c] *s*-BuLi (1.5 equiv)/TMEDA. [d] Product: 7-formyl-indole-1-carboxylic acid diethylamide. [e] **7e**, **7f**, **7i**, and **7k** can be obtained without chromatography by direct recrystallization of the crude product.

silicon (entry 7), tin (entry 8), halogen (entries 9 and 10), boron (entry 11), and oxygen (entry 12) electrophiles are introduced.[19] To improve operational efficacy, on the basis of the observation that C-2 TMS introduction proceeds in quantitative yield (GC analysis), a one-pot procedure was developed (Scheme 3) that provided the 7-functionalized indole derivatives in yields within experimental error to those obtained by stepwise reactions. Further walk-around-the-ring metalation was demonstrated by the conversion of **7e** into the 6-TMS derivative **13** in high yield. *N*-$CONEt_2$ (and simultaneous 2-TMS) cleavage was effected using (i) 25% KOH or 25% aqueous NaOH (EtOH/reflux/1−16 h),[20] (ii) 5 equiv of KO*t*Bu (THF/rt/1.5−12 h), or (iii) 1 equiv of TBAF (THF, 1 h) and then 2.2 equiv of KO*t*Bu (THF/rt/2

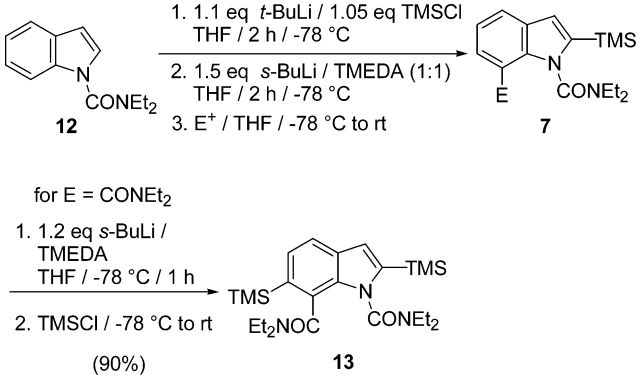
(19) For entries 6 and 11, products **9** (10%) and **10** (16%) were isolated; for entries 9 and 10, **11** (10−20%) was obtained. Product **11**, presumably the result of benzyne formation of the normal product (**7h**, **7i**) followed by carbamoyl α-deprotonation−cyclization, is formed in 50% yield under the following conditions: (1) 3 equiv of *s*-BuLi/TMEDA/THF/−78 °C/2 h; (2) 3 equiv of Br_2 or I_2/−78 °C → rt (Supporting Information).



9 **10** **11**

(20) Comins, D. L.; Stroud, E. D. *Tetrahedron Lett.* **1986**, *27*, 1869. (b) Castells, J.; Troin, Y.; Diez, A.; Rubiralta, M.; Grierson, D. S.; Husson, H. P. *Tetrahedron* **1991**, *47*, 7911.

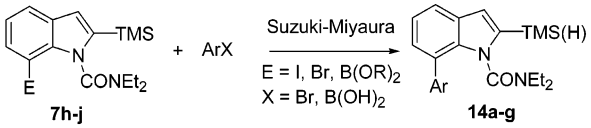
Scheme 3. One-Pot Conversion of **12** into 2,7-Substituted Indole Derivatives **7** and Further C-6 Functionalization to **13**



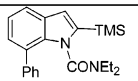
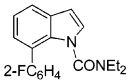
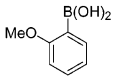
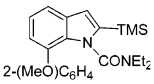
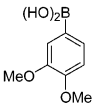
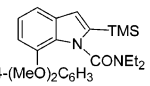
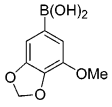
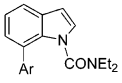
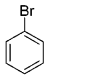
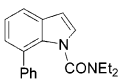
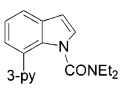
12 **7** **13**

h). Corresponding C-7-substituted indoles were thus obtained: indole from **6** (i, 85%; ii, 94%; iii, 92%), 7-methyl indole from **7b** (i, 75%), 7-TMS indole from **7f** (i, 94%), 7-bromo indole from **7h** (ii, 88%), 7-diethylcarboxamide indole from **7e** (ii, 82%), and 7-phenylindole from **14f** (ii but reflux, 15 h, 71%).

Table 3. Suzuki−Miyaura Cross-Coupling Reactions of the 7-Iodo, 7-Bromo, and 7-Pinacolboronate Indole Derivatives[a]



7h-j **14a-g**

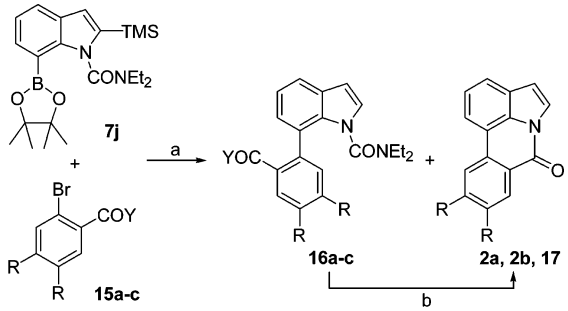
entry	E	ArX	product		yield (%)
1[b]	I (**7i**)			**14a**	90
2	I (**7i**)			**14b**	82
3	I (**7i**)			**14c**	70
4	I (**7i**)			**14d**	99
5[c]	I (**7i**)			**14e**	91
6	Br (**7h**)				83
7	$B(OR)_2$ (**7j**)			**14f**	94
8	$B(OR)_2$ (**7j**)			**14g**	89

[a] Typical procedure: 1.2 equiv of ArX/5 mol % $Pd(PPh_3)_4$/DMF/3 equiv of K_3PO_4/80 °C/15−20 h. [b] $Pd(PPh_3)_4$(2 mol %)/DME/H_2O/1.5 equiv of Na_2CO_3/80 °C/16 h. [c] After 20 h: addition of 1.1 equiv TBAF in THF/2 h/rt.

To explore combined D*o*M/Suzuki−Miyaura cross-coupling methodology, a general theme pursued in our laboratories,[1a] the haloindoles **7h** and **7i** along with indole boronate **7j** were tested with representative aryl boronic acids and halides (Table 3), respectively.[21] Thus, coupling of iodide **7i** and bromide **7h** with phenyl boronic acid (entry 1) and substituted phenylboronic acids (entries 2−6) afforded products **14a**−**e** in generally high yields even in *ortho*-substituted cases. Inversion of the coupling partners (entries 7 and 8) also efficiently furnished products **14f** and **14g**. In some cases of the Suzuki−Miyaura processes, concurrent C-2 desilylation was observed (entries 2 and 5−8).

As an application of the overall method, the synthesis of representative members of the pyrrolophenanthridone alkaloids (*Amaryllidaceae*), exhibiting antitumor and other biological activities,[13] was targeted.[22] Thus, Suzuki−Miyaura reaction of the boron pinacolate **7j** with aryl bromides **15a**−**c** provided products **16a**−**c** (Scheme 4) accompanied by **2a**

Scheme 4. Synthesis of Pyrrolophenanthridone Alkaloids[a]



[a] Key: (a) 1.2 equiv of ArX **15**/ 5−7.5 mol % $Pd(PPh_3)_4$/DMF/3 equiv of K_3PO_4/80 °C/20−24 h. **a**: R = OMe, Y = NEt_2, **16a** 40%, **2a** 18% (Pratosine). **b**: R = $-OCH_2O-$, Y = OEt, **16b** 90%, **2b** 7% (Hippadine). **c**: R = H, Y = OEt, **16c** 76%, **17** 13%. (b) LiOH (2.5 M) in MeOH/THF or 25% aqueous NaOH in EtOH/reflux/6−60 h/66−88%.

(pratosine) (18%), **2b** (hippadine) (7%), and **17** (13%) as side products. Prolonged cross-coupling reaction times or hydrolysis of the isolated compounds **16a**−**c** (LiOH/MeOH/THF/reflux or aqueous NaOH/EtOH/reflux) afforded **2a**, **2b**, and **17** in good yields (up to 80% for the hydrolysis of **16a**−**c** with LiOH or NaOH).

In summary, while the indole *N*-P(O)(*t*-Bu)$_2$ is a powerful DMG for selective C-2 or C-7 indole deprotonation (Table 1), its synthetic value is compromised by severe cleavage conditions. On the other hand, the *N*-CONEt$_2$ derivative **12** with prior C-2 TMS protection is very effective for the synthesis of C-7-substituted indoles (**7a**−**k**) and, via subsequent Suzuki−Miyaura cross-coupling reactions, for 7-aryl indoles (**14a**−**g** and **16a**−**c**), including pyrrolophenanthridone alkaloids (**2a**, **2b**, and **17**). The dependence on indole as a starting point (rather than de novo construction[3] from intermediate anilines or nitrobenzenes), the formulation of a one-pot procedure by metalation of **12**, and the demonstration of further D*o*M chemistry (**13**) allow anticipation of further application of this methodology for the construction of natural products and bioactive molecules.

Acknowledgment. We are grateful to NSERC Canada for support of our synthetic programs. We thank Sheldon Lyn and Yen Dang for their diligent work on this project and Nicholas J. Taylor for measuring and solving the X-ray structure. C.G.H. and A.F. thank the Alexander von Humboldt Foundation and the DAAD for postdoctoral fellowships, respectively.

Supporting Information Available: Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Considering the explosion of cross-coupling chemistry, it is fair to say that indole C-7 derivatives have been infrequently described: see, e.g.: (a) Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1523. (b) Sakamoto, T.; Yasukura, A.; Kondo, Y.; Yakamaka, H. *Heterocycles* **1993**, *36*, 2597. (c) Black, D. S. C.; Keller, P. A.; Kumar, N. *Tetrahedron* **1993**, *49*, 151. (d) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockeless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2551. (e) Hutchings, R. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 1004. (f) Carbonnelle, A.-C.; Zamora, E. G.; Beugelmans, R.; Rossi, G. *Tetrahedron Lett.* **1998**, *39*, 4467 and refs cited therein. (g) Tsuge, O.; Hatta, T.; Tsuchiyama, H. *Chem. Lett.* **1998**, 155.

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