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An Approach to the Core Structure of Leiodermatolide

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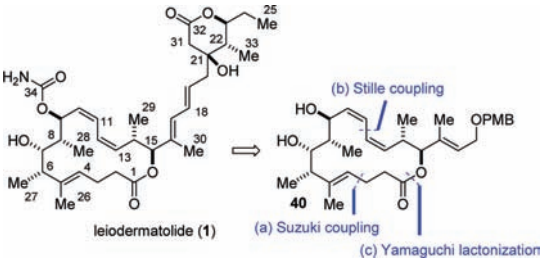
ABSTRACT



The synthesis of the 16-membered core structure of leiodermatolide 40 has been achieved in 26 linear steps starting from (*R*)-Roche ester. The key steps in the synthesis of 40 are a Stille cross-coupling between two main fragments 11 and 33 having roughly equal size. For the trisubstituted C4/C5 double bond a carbometalation reaction followed by a Suzuki coupling was used. A Yamaguchi macrolactonization furnished macrolactone 39.

Leiodermatolide (**1**) was isolated by the Wright group from the Harbor Branch Oceanographic Institution at Florida University.[1] The source is the sponge *Leiodermatium*, which grows in depths of 200−500 m. This novel macrolide shows cytotoxicity at a nanomolar level against a variety of human tumor cell lines.[2] It features nine stereocenters, a conjugated *Z*,*Z*-diene, and a conjugated *E*,*E*-diene system, terminating in a 6-membered lactone as part of the side chain. Initially, only the constitution of leiodermatolide was published,[1] but more recently additional data with stereochemical information was released on the Internet (Figure 1).[3] Because of its potent antiproliferative activity and its unique structural features, leiodermatolide appeared as an interesting target for a synthesis program. Even though structure **1** was possibly not 100% correct, we chose it as a starting point. Because of the 14-H/15-H coupling constant of 10.3 Hz, the *anti*-configuration seemed highly likely. Some doubts remained, however, regarding the stereocenters C6−C9 since force field calculations (MacroModel 7.0) on all stereoisomers of the simpler model compound **2** (C14, C15 D,D configuration) showed isomer **2a** to have the highest energy (241.9 vs 230.3 kJ mol^{-1} for isomer **2b**) (Figure 1) (for details, see the Supporting Information). Application of the Kishi method[4,5] to the ^{13}C shifts of leiodermatolide for this region in CD_3OD also did not favor stereoisomer **1** as a likely candidate. Most recently, a detailed NMR and calculation study by the Paterson and

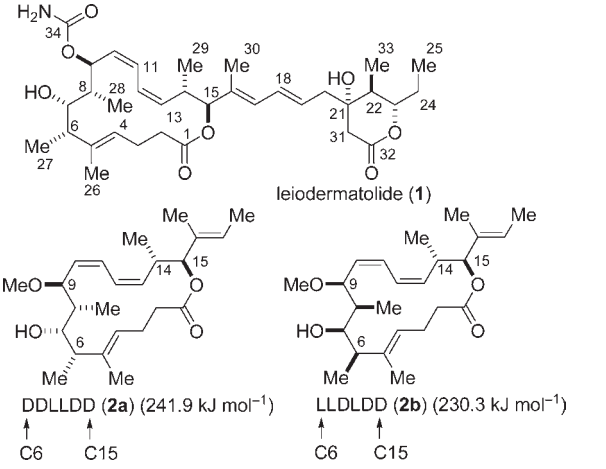


Figure 1. Proposed structure of leiodermatolide **1** and simplified model **2** used for force field calculations.

(1) Wright, A. E.; Reed, J. K.; Roberts, J.; Longley, R. E. U.S. Pat. Appl. Publ. (USA), US2008033035, 14 pp; *Chem. Abstr.* **2008**, *148*, 230104.

(2) The following IC_{50} values were reported in the patent: A549, P399 = 3.3 nM, PANC-1 = 5.0 nM, DLD-1 = 8.3 nM, NCI-ADR-Res = 233 nM.

(3) http://www.rsmas.miami.edu/groups/ohh/courses/23nov12wright marinenaturalproductsdrugdiscovery.pdf. Accessed on March 25, 2011.

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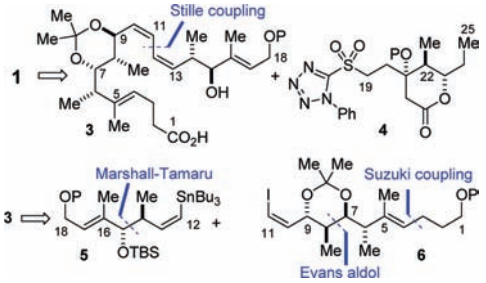
Wright groups found that the 6,8-*epi*-isomer of **1** (both methyl-bearing stereocenters inverted) was the correct one.[6] Even though we might not reach the correct stereostructure with isomer **1**, the developed route was envisioned to pave the way for accessing natural leiodermatolide.

Our retrosynthetic plan for the synthesis of the stereoisomer **1** of leiodermatolide is illustrated in Scheme 1. We

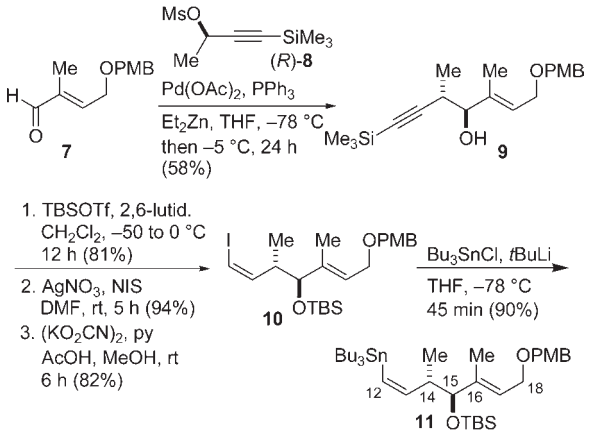
Scheme 1. Retrosynthetic Plan for Leiodermatolide (**1**) (P = Protecting Group)



decided to remove part of the side chain by cutting the C18−C19 *trans* double bond, which would be installed, for example, by Julia−Kocienski olefination.[7] For macrolactone formation, a macrolactonization reaction was planned.[8] The internal *Z*,*Z*-diene would come from a Stille cross coupling. This led to two building blocks, stannane **5** and vinyl iodide **6**, both of roughly equal size.[9] A precursor for stannane **5** was already published during our synthesis of key fragments of leiodermatolide,[10] as well as a δ-lactone fragment **4** (P = $SiMe_3$). For vinyl iodide **6** we decided to use an Evans aldol reaction to establish the *syn*-stereochemistry at C7/C8 and a hydride-based stereoselective reduction in order to guarantee the C7/C9 *anti*-stereochemistry. For the highly substituted double bond at C4/C5 a carbometalation appeared expedient, followed by a Suzuki coupling to attach the C1−C3 section.

Preparation of stannane **11** started from the known aldehyde[11] **7** and (*R*)-mesylate[12] **8** with a Marshall−Tamaru reaction[13] followed by protection of the free hydroxyl function as a TBS ether (Scheme 2).[10] Homopropargylic alcohol was obtained as a single diastereomer with an ee of 94% (determined by Mosher analysis).[8,10] The triple bond was then functionalized by terminal iodination with *N*-iodosuccinimide and silver nitrate[14] and *Z*-selective reduction to the vinyl iodide[10] **10** by diimide reduction.[15] In the following step, a *Z*-selective replacement of the iodide with tributylstannane using tributyltin chloride in THF and addition of *t*-BuLi delivered stannane **11**. One should mention that the order of addition (tin chloride before *t*-BuLi) turned out to be crucial. Using the chloride and the base, the other way around, in this case, only induced elimination leading to the corresponding alkyne as a byproduct.

Scheme 2. Preparation of Vinylstannane **11** (C12−C18 Fragment)



The synthesis of vinyl iodide **18** proceeded via alkyne **17**, which was obtained from (*R*)-Roche ester (**12**) using a known literature sequence[16] (Scheme 3). Methyl (*R*)-(+)-hydroxyisobutyrate was protected as a TBS ether. This was followed by reduction of the ester and oxidation of the alcohol **14** to the corresponding aldehyde **15**. Thereafter, a Corey−Fuchs reaction via dibromide **16** led to alkyne **17**. This five-step sequence was achieved in 78% overall yield. Alkyne **17** was introduced in a carbometalation using bis(cyclopentadienyl)zirconium-(IV) dichloride (1.5 equiv) and Me_3Al (2.2 equiv) followed by quenching with iodine to provide vinyl iodide **18** in 66% yield. One should note that comparable carbometalation reactions on larger fragments were not successful. Vinyl iodide **18** was then elongated by Suzuki coupling with PMB-protected allylic alcohol[17] using $Pd(PPh_3)_4$ (0.05 equiv) and K_2CO_3 (4.0 equiv) in DMF/water, leading to the corresponding product **19** as a single diastereomer in 81% yield. The TBS group of ether **19** was removed (TBAF, THF) prior to Swern oxidation of the

(4) (a) Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2177–2180. (b) Lee, J.; Kobayashi, Y.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2181–2184.

(5) For reviews, see: Bifulco, G.; Dambruoso, P.; Gomez-Paloma, L.; Riccio, R. *Chem. Rev.* **2007**, *107*, 3744–3779. (b) Menche, D. *Nat. Prod. Rep.* **2008**, *25*, 905–918.

(6) Paterson, I.; Dalby, S. M.; Roberts, J. C.; Naylor, G. J.; Guzmán, E. A.; Isbrucker, R.; Pitts, T. P.; Linley, P.; Divlianska, D.; Reed, J. K.; Wright, A. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 3219–3223.

(7) (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28. (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

(8) A ring-closing metathesis strategy (formation of the C4−C5 double bond) did not work in our hands. Vaidotas, N. Ph.D. Thesis, University of Tübingen, 2011.

(9) Coupling of a C1−C11 vinylstannane with a C12−C18 vinyl iodide (1-OTBS) did not give the corresponding conjugated diene.

(10) Navickas, V.; Rink, C.; Maier, M. E. *Synlett* **2011**, 191–194.

(11) Kanada, R. M.; Itoh, D.; Nagai, M.; Niijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotake, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4350–4355.

(12) (a) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 3369–3372. (b) Marshall, J. A.; Chobanian, H. *Org. Synth.* **2005**, *82*, 43–54. *Organic Synthesis*; Wiley: New York, 2009; Collect. Vol. XI, pp10561067

(13) (a) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812–3813. (b) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201–5204. (c) Marshall, J. A.; Eidam, P.; Eidam, H. S. *J. Org. Chem.* **2006**, *71*, 4840–4844.

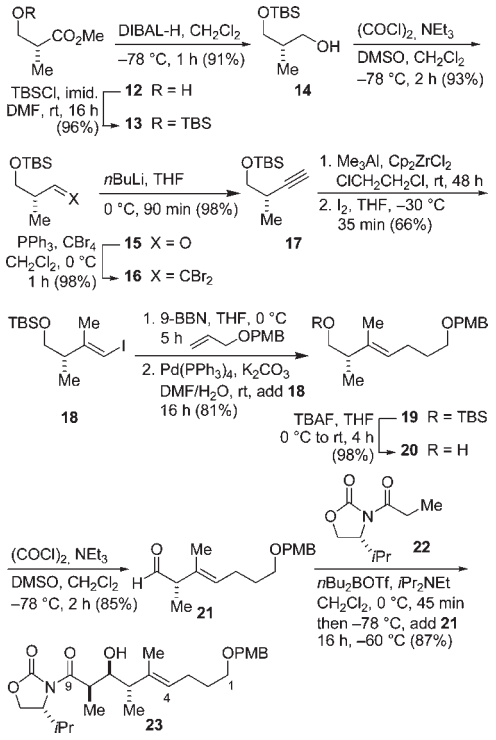
(14) Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485–486.

(15) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2004**, *126*, 12432–12440.

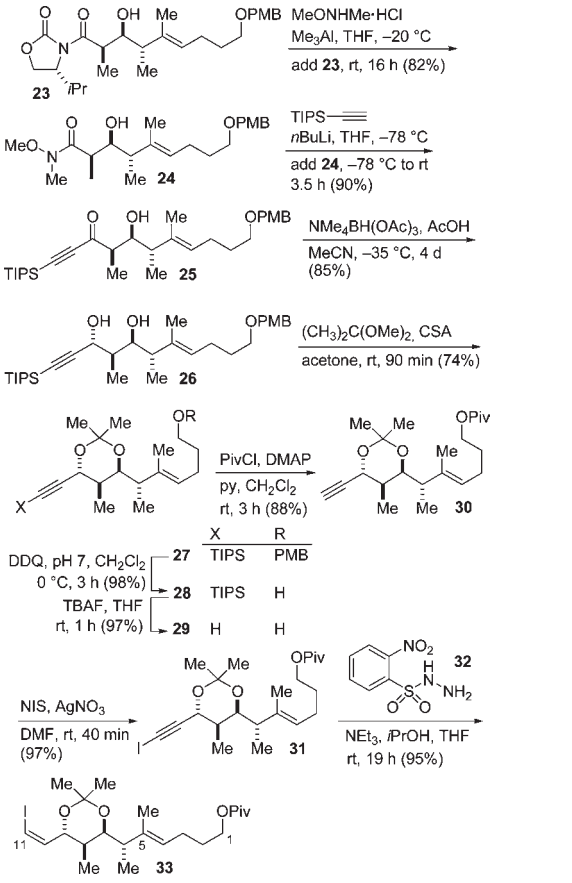
(16) Zeng, F.; Negishi, E.-i. *Org. Lett.* **2002**, *4*, 703–706.

(17) Chenevert, R.; Dasser, M. *J. Org. Chem.* **2000**, *65*, 4529–4531.

Scheme 3. Preparation of Aldol Product **23** (C1−C9 Fragment)



Scheme 4. Preparation of Vinyl Iodide **33** (C1−C11 Fragment)



primary alcohol **20**. The resulting aldehyde **21** was subjected to an Evans−aldol[18] reaction, which was carried out using oxazolidinone[19] **22** (1.4 equiv), *n*-Bu_2BOTf[19] (1.4 equiv), and *i*-Pr_2NEt (1.6 equiv) in CH_2Cl_2 at −78 to −60 °C, which gave rise to aldol product **23**. The diastereoselectivity of this reaction was determined from ^1H NMR to be 92:8.

In the next step, we converted aldol product **23** into the Weinreb amide **24** using *N*,*O*-dimethylhydroxylamine hydrochloride (3.0 equiv) and Me_3Al (2.9 equiv).[20] This was followed by addition of TIPS-acetylide (4.0 equiv) to obtain alkynone **25** in 69% yield over two steps (Scheme 4). Protection of the free hydroxyl function was not necessary in this case. Because diastereoselective reduction by the typical Noyori protocol failed, a directed reduction with tetramethylammonium triacetoxyborohydride was used.[21] A solution of the hydride (5.0 equiv) in acetonitrile and glacial acetic acid was treated with alkynone **25** at −35 °C leading to diol **26** in high yield. The diastereoselectivity of this reaction was determined by ^1H NMR to be 88:12. Separation of the isomers was possible at the stage of the acetal **27**. After protection of the diol **26** (2,2-dimethoxypropane, CSA) as acetal **27**, the PMB-protecting group (DDQ, pH 7 buffer) and the TIPS-function (TBAF) was cleaved and the primary hydroxy was protected as a pivaloyl ester (PivCl, DMAP, pyridine) to obtain alkyne **30**. This four-step sequence was achieved in 63% yield. The 1,3-*anti* relationship of the two acetal-protected hydroxyl functions in **30** was evident from the chemical shift of the acetal C-atom in its ^{13}C NMR spectrum [measured ^{13}C shift of $C(CH_3)_2$: desired diastereomer 100.4 ppm; undesired diastereomer 99.2 ppm].[22]

For further functionalization of the terminal triple bond iodination and *Z*-selective reduction was evaluated. Thus, treatment of alkyne **30** with *N*-iodosuccinimide in the presence of silver nitrate resulted in iodoalkyne **31** in 97% yield, which was then subjected to a *Z*-specific reduction using *o*-nitrobenzenesulfonyl hydrazide[23] (**32**) (1.6 equiv) and triethylamine in THF/*i*-PrOH leading to vinyl iodide **33** in 95% yield. However, this key fragment contained 12% of a byproduct, resulting from over-reduction of the C10/C11 double to single bond. All other common approaches [$(KO_2CN)_2$, Cy_2BH] for *Z*-selective reduction resulted in higher concentrations of this byproduct. Fortunately, this impurity was not participating in the subsequent coupling reaction.

(18) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 83–91. *Organic Synthesis*; Wiley: New York, 1993; Collect. Vol. VIII, pp 339343

(19) (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111. (b) Vo, L.; Ciula, J.; Gooding, O. W. *Org. Process Res. Dev.* **2003**, *7*, 514–520. (c) Guerlavais, V.; Carroll, P. J.; Joullie, M. M. *Tetrahedron: Asymmetry* **2002**, *13*, 675–680. (d) Lu, C.-D.; Zakarian, A. *Org. Synth.* **2008**, *85*, 158–171.

(20) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818. (b) Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340–347.

(21) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

(22) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9–17.

(23) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

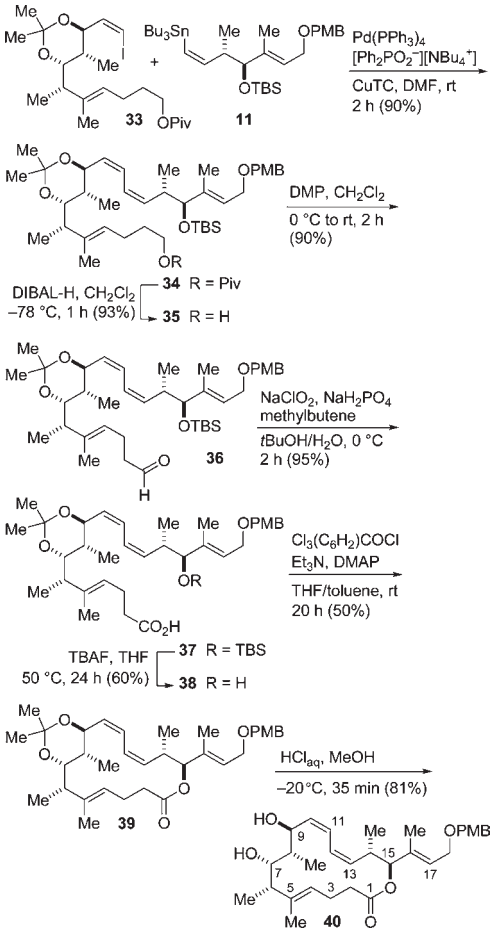
(24) Substrate **33** with a TBS protecting group at 1-OH instead of the pivaloyl group did not react in the Stille cross-coupling.

After successful synthesis of the two building blocks **11** and **33**, we now concentrated on their cross coupling (Scheme 5). Accordingly, we investigated a range of conditions for the Stille coupling trying different catalysts ($Pd(PPh_3)_4$, $Pd(MeCN)Cl_2$, $Pd(dba)_3$) and additives ($[Ph_2PO_2^-][NBu_4^+]$, $(2\text{-furyl})_3P$, $i\text{-}Pr_2NEt$, Ph_3As, Cu(I)Cl, CuTC).[24] The only variation[25] that was effective involved $Pd(PPh_3)_4$ (0.1 equiv), $[Ph_2PO_2^-][NBu_4^+]$[26] (1.1 equiv), and CuTC[27] (1.5 equiv) in DMF at room temperature, leading to pivaloyl-protected conjugated diene **34** in 85% yield as a single *Z*,*Z*-stereoisomer.

After removal of the pivaloyl group (DIBAL-H), alcohol **35** was converted to acid **37** by Swern oxidation and further Pinnick oxidation[28] of the intermediate aldehyde. This three-step sequence proceeded in 75% yield. Next, the TBS group was cleaved (TBAF) to give *seco* acid **38** in reasonable yield (60%) but represented the best result for deprotection in comparison to other methods (HCl, MeOH; HF·pyridine; aqueous HF). With *seco*-acid **38** in hand, we tested different lactonization methods (Trost–Kita,[29] Shiina[30]), but Yamaguchi conditions[31,32] offered the best results. Thus, 2,4,6-trichlorobenzoyl chloride (5.0 equiv), triethylamine (6.0 equiv), and DMAP (25.0 equiv) were used to obtain macrolactone **39** in 50% yield. Cleavage of the acetal-group protecting group was realized under acidic conditions (HCl, MeOH) resulting in diol **40**. Unfortunately, the following selective carbamate formation at C9 was not successful. Instead, we observed reaction of diol **40** with $Cl_3C(CO)NCO$[33] at the more hindered 7-OH group. This was evident from the downfield shift of 7-H (4.89 ppm). This is surprising, since electrophilic attack on related precursors always took place selectively on 9-OH and not on 7-OH. Also, selective protection of the diol **40** was not possible because moderate amounts of base always resulted in substantial elimination with formation of a C8–C9 double bond.

The core structure **40** allowed us to compare its NMR data with that from the natural product. Excellent agreement was seen in the ^1H and ^{13}C NMR spectra for the chemical shifts of the stereocenters at C15 and C14. Also, for the conjugated *Z*,*Z*-diene system the shifts and the coupling constants are fitting quite well. From this we assume that this stereochemical information suggested by the Wright group[3,6] is probably correct (see the table of chemical shifts of the natural product and the synthesized core structure **40** in the Supporting Information).

Scheme 5. Stille Cross-Coupling to Tetraene **34** and Macrolactonization to the Core Structure **40** of Leiodermatolide



In summary, the synthesis of the core structure **40** of leiodermatolide was achieved in a convergent way in 26 steps (longest linear sequence) starting from (*R*)-Roche ester. While structure **40** most likely does not represent the correct stereochemistry, slight modifications of this route should allow for preparation of the correct isomer. Further work is currently underway to achieve the total synthesis of leiodermatolide (**1**).

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Supporting Information Available. Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

(25) Fürstner, A.; Funel, J.-A.; Tremblay, M.; Bouchez, L. C.; Nevado, C.; Waser, M.; Ackerstaff, J.; Stimson, C. C. *Chem. Commun.* **2008**, 2873–2875.

(26) Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 12376–12377.

(27) See also :Gallagher, W. P.; Maleczka, R. E. *J. Org. Chem.* **2003**, *68*, 6775–6779.

(28) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.

(29) (a) Kita, Y.; Maeda, H.; Omori, K.; Okuno, T.; Tamura, Y. *Synlett* **1993**, 273–274. (b) Trost, B. M.; Chisholm, J. D. *Org. Lett.* **2002**, *4*, 3743–3745.

(30) (a) Shiina, I. *Tetrahedron* **2004**, *60*, 1587–1599. (b) Shiina, I.; Hashizume, M.; Yamai, Y.-s.; Oshiumi, H.; Shimazaki, T.; Takasuna, Y.-j.; Ibuka, R. *Chem.—Eur. J.* **2005**, *11*, 6601–6608.

(31) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(32) For a review, see: Parenty, A.; Moreau, X.; Campagne, J. M. *Chem. Rev.* **2006**, *106*, 911–939.

(33) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521–5524.