Synthetic Studies towards Leiodermatolide: Rapid Stereoselective Syntheses of Key Fragments

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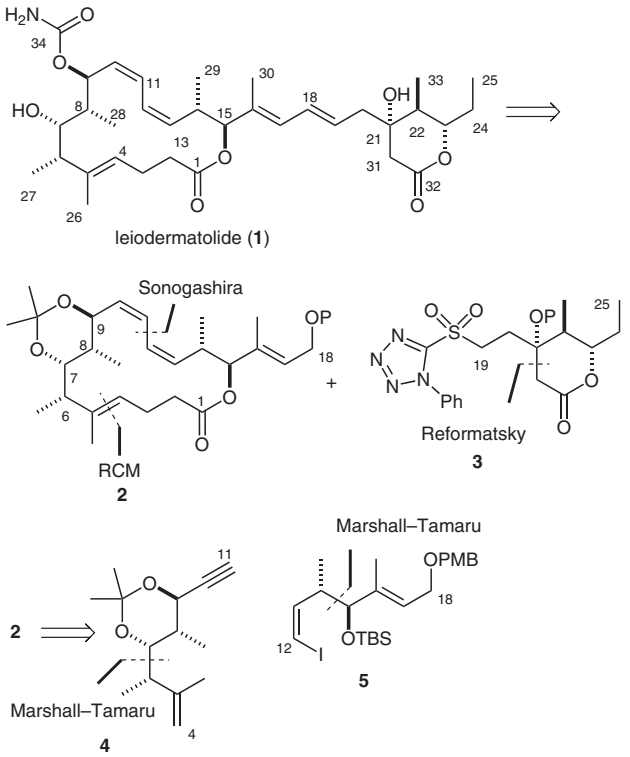
Abstract: The synthesis of three key fragments of the novel 16-membered macrolide leiodermatolide is described. The stereotetrad-containing building block was prepared via a Marshall–Tamaru reaction on an aldehyde obtained by organocatalysis. For a second building block, a Marshall–Tamaru reaction was used as well. The side-chain fragment containing a hydroxy δ-lactone could be obtained by intramolecular Reformatsky reaction.

Key words: leiodermatolide, macrolide, Marshall–Tamaru reaction, intramolecular Reformatsky reaction, Fráter–Seebach alkylation

Leiodermatolide (**1**) is a potent antimitotic agent, recently isolated by the group of Amy Wright from the sponge *Leiodermatium*, which belongs to the order Lithistida (Scheme 1).[1] It displays cytotoxicity at nanomolar level against a variety of human tumor cell lines[2] while showing reduced toxicity to normal cell lines. Leiodermatolide does not show much similarity to other cytotoxic polyketides, however, it shares a carbamate function, for example with palmerolide[3] and discodermolide.[4] This novel polyketides features a 16-membered macrolide, with a six-membered lactone ring on the side chain and has nine stereocenters together with a *Z*,*Z*- and *E*,*E*-diene system. Although, the initial report of Wright et al.[1] just contained a flat structure of this macrolide, more recently additional data with stereochemical information as shown in Scheme 1 appeared on the web.[5]

Taking into account the remarkable potent antiproliferative activity and the unique structural features which are calling for proof, leiodermatolide (**1**) deserves attention for total synthesis. As outlined in the retrosynthetic plan in Scheme 1, we decided to remove part of the side chain by cutting the C18–C19 *trans* double bond (Julia–Kocienski olefination).[6] For macrolactone formation a ring-closing metathesis approach was considered.[7,8] Alternatively, other C–C bond-forming reactions or lactonization reactions (Yamaguchi/Mitsunobu) might be options. The internal *Z*,*Z*-diene would come from an enyne precursor. This way, a Sonogashira cross-coupling followed by *Z*-selective reduction is obvious. This leads to two building blocks **4** and **5**, both having roughly equal size. For these, we decided to apply a Marshall–Tamaru



Scheme 1 Proposed structure of leiodermatolide (**1**) together with key retrosynthetic cuts; P = protecting group

reaction[9,10] that would secure the *anti* stereochemistry at C6/C7 and C14/C15 carbons.

The synthesis of alkyne **4** started from known aldehyde (+)-**6**, which was obtained via L-proline-catalyzed cross-aldol reaction of α-silyloxyacetaldehyde using a known literature procedure (Scheme 2).[11,12] With this aldehyde in hand, which was used as a mixture of diastereomers, we tested the Marshall–Tamaru conditions hoping for separable diastereomeric diols. To our surprise, when (*R*)-mesylate[13] **7** (2.0 equiv) was added into the reaction mixture containing $Pd(OAc)_2$ (0.05 equiv), Ph_3P (0.05 equiv) and aldehyde **6** followed by slow addition of diethyl zinc (3.0 equiv) and stirred for 48 hours, diol **8** was isolated as a single isomer in 61% yield after chromatographic purification. This reaction outcome can be understood based on Felkin–Anh-like transition state ***A*** which is akin to attack of an *E*-enolate to an α-substituted aldehyde (Scheme 2). Due to an angle of 120° between the C=O and the OH-dipole this transition state also minimizes dipole interactions.[14] We assume that the major *anti* diastereo-

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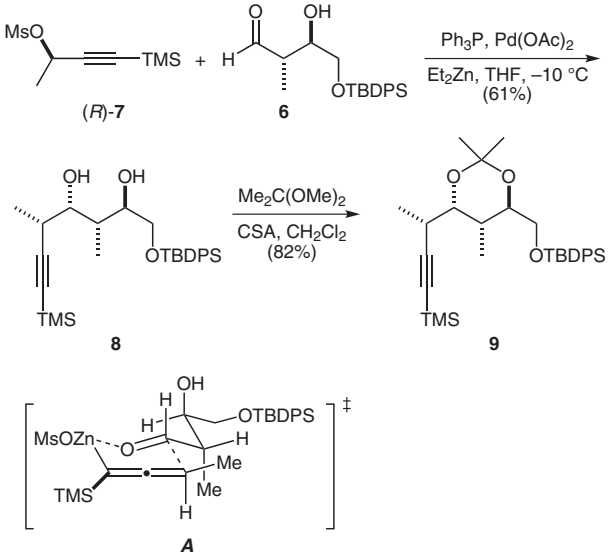
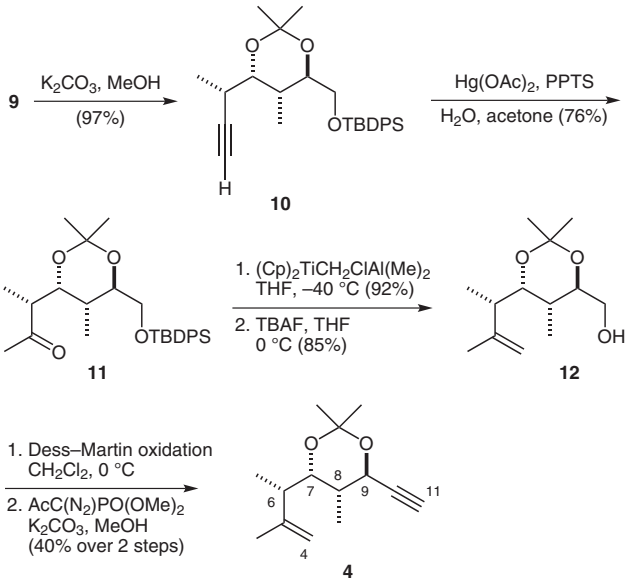
mer **6** reacts faster than the corresponding *syn* isomer.[15] Subsequent diol protection as acetal **9** additionally proved the 1,3-*anti* relationship. In particular, the two methyl groups of the acetal appear at similar chemical shifts in the ^{13}C NMR spectrum (δ = 23.7 and 24.9 ppm, respectively).[16]



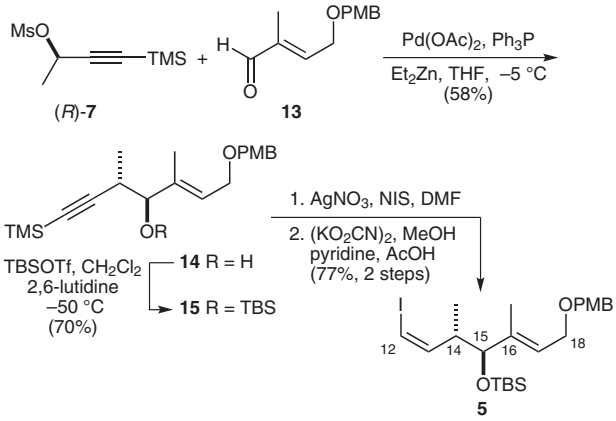
Scheme 2 Synthesis of heptyne **9** via Marshall–Tamaru reaction between aldehyde **6** and mesylate (*R*)-**7**

For further functionalization of the triple bond we found the Kutcheroff alkyne hydration[17,18] and Tebbe olefination[19] to be optimal, since classical carbometalation reactions on alkyne **10** were not successful. Accordingly, the TMS group of **9** was removed using K_2CO_3 in MeOH followed by reaction of alkyne **10** with mercury(II) acetate in wet acetone to give the corresponding methyl ketone **11** which was then transformed to alkenol **12** via Tebbe olefination and cleavage of the silyl ether (Scheme 3). This two-step sequence was achieved in 70% overall yield. Alcohol **12** was then oxidized with Dess–Martin reagent to the corresponding aldehyde followed by reaction with dimethyl-1-diazo-2-oxopropylphosphonate[20] (Bestmann–Ohira protocol)[21] in the presence of K_2CO_3 to give the desired alkyne **4** in 40% yield over two steps. One should mention that no epimerization was detected during alkyne formation.

For the synthesis of *Z*-iodoalkene **5** the same Marshall–Tamaru reagent (*R*)-**7** served as a perfect synthetic tool to establish the desired C14/C15 *anti* stereochemistry (Scheme 4). Starting from known aldehyde[23] **13** and applying the same conditions as for the synthesis of homopropargyl alcohol **8**, alcohol **14** could be isolated in 58% as a single isomer. Subsequent alcohol protection with TBSOTf in the presence of 2,6-lutidine furnished silyl ether **15** in 70% yield. Further functionalization of the triple bond called for terminal iodination and *Z*-selective reduction. Thus, treatment of trimethylsilyl alkyne **15** with *N*-iodosuccinimide in the presence of silver nitrate[24] resulted in almost quantitative conversion to the corresponding iodoalkyne, which was directly subjected to *Z*-specific diimide reduction.[25] Thus, slow addition (6 h) of acetic acid to a solution of the iodoalkyne, potassium azodicarboxylate and pyridine gave *Z*-iodoalkene **5** in 77% yield over two steps.



Scheme 3 Synthesis of the C4–C11 fragment **4** featuring the stereotetrad[22] of leiodermatolide



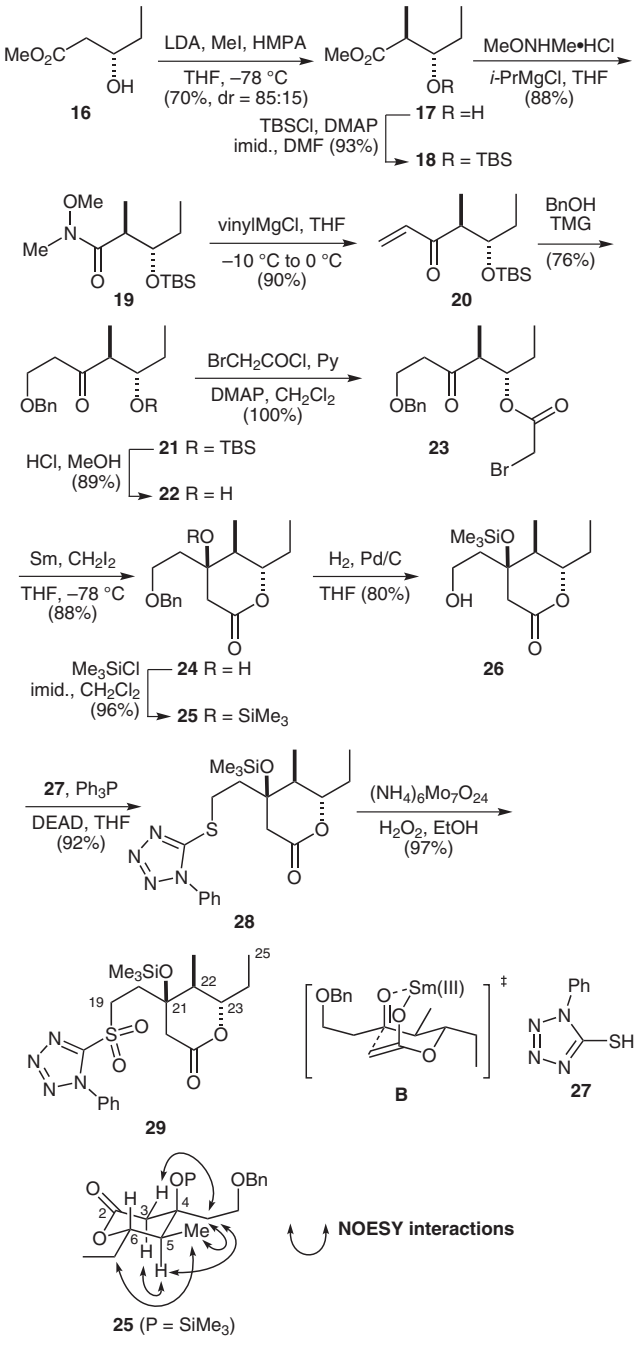
Scheme 4 Synthesis of *Z*-iodoalkene **5** (C12–C18 fragment)

After successful synthesis of Sonogashira coupling partners **4** and **5** we then concentrated on the construction of the side chain lactone **3**. Here we started the synthesis from known methyl (3*S*)-3-hydroxypentanoate[26] (**16**), which underwent a Fráter–Seebach alkylation[27] with MeI to give ester[28] **17** (Scheme 5). The diastereoselectivity of this reaction could be determined from the ^1H NMR to be 85:15. Subsequent protection of the free hydroxy function as TBS ether followed by Weinreb amide formation[29] allowed us to prepare amide **19** in 82% yield and on a gram-scale. Initial Grignard reaction to give enone **20** was followed by Michael addition of benzyl alcohol induced by 1,1,3,3-tetramethylguanidine (1.0 equiv)[30] resulting in ketone **21** in 76% yield. After removal of the TBS group

(HCl, MeOH) resulting in hydroxyketone **22**, esterification of the obtained alcohol function with bromoacetyl chloride delivered Reformatsky precursor **23** in high yield.

A smooth intramolecular Reformatsky reaction[31,32] took place when ester **23** was introduced to a SmI_2 solution[33] at –78 °C giving alcohol **24** as a single isomer (Scheme 5). The formation of hydroxylactone **24** is in accordance with a chair-like transition state ***B*** with the keto group adopting a pseudoaxial orientation to allow for intramolecular chelation with the Sm(III) center. Thereafter, the tertiary alcohol function was protected as trimethylsilyl ether **25** (96% yield). At this stage the stereochemistry of the tertiary alcohol function was deduced from the ^{1}H NMR NOESY spectrum ($CDCl_3$). In particular the H-5–4-CH_2 (weak) correlation is only possible with the C-4 side chain in equatorial position. The absence of a H-6–4-CH_2 cross peak also supports this assignment. Surprisingly, the ^{13}C chemical shifts of C-4 (δ = 71.97 ppm) and C-6 (δ = 84.53 ppm) of hydroxy lactone **24** in CD_3OD are comparable to the corresponding shifts in the natural product (δ = 72.73, 85.56 ppm). This could mean that the assigned stereochemistry at C-21 requires revision. Next, the benzyl ether was cleaved via catalytic hydrogenation to provide primary alcohol **26**. A subsequent two-step protocol involving Mitsunobu reaction of alcohol **26** with tetrazole **27** gave thio ether **28** which upon oxidation with hydrogen peroxide in the presence molybdate furnished the desired sulfone **29** in 89% yield over two steps.

In summary, the stereoselective synthesis of all three key fragments of leiodermatolide (**1**) has been accomplished utilizing a Marshall–Tamaru reaction as a key transformation for two units and an internal Reformatsky aldol reaction for the side chain. Further work is currently underway to achieve the total synthesis of **1**.



Scheme 5 Synthesis of bromoacetate **23** and its intramolecular Reformatsky reaction; TMG = 1,1,3,3-tetramethylguanidine

Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

(1) Wright, A. E.; Reed, J. K.; Roberts, J.; Longley, R. E. U.S. Patent Appl., US2008033035, **2008**; *Chem. Abstr.* **2008**, *148*: 230104.

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

(3) Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. *J. Am. Chem. Soc.* **2006**, *128*, 5630.

(4) (a) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912; correction: *J. Org. Chem.* **1991**, *56*, 1346. (b) Kalesse, M. *ChemBioChem* **2000**, *1*, 171. (c) Florence, G. J.; Gardner, N. M.; Paterson, I. *Nat. Prod. Rep.* **2008**, *25*, 342.

(5) (a) See: http://www.fau.edu/hboi/MarineDrugDiscovery/MDDleiodermatium.php. (b) See: http://www.rsmas.miami.edu/groups/ohh/courses/23nov12wrightmarinenaturalproductsdrugdiscovery.pdf. Both accessed on October 26, 2010.

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

(7) For some reviews, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490; *Angew. Chem.* **2005**, *117*, 4564. (c) Gradillas, A.; Castells, J. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086; *Angew. Chem.* **2006**, *118*, 6232. (d) Samojlowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708.
(8) For examples of relay metathesis, see: (a) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210. (b) Wallace, D. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 1912; *Angew. Chem.* **2005**, *117*, 1946. (c) Yun, S. Y.; Hansen, E. C.; Volchkov, I.; Cho, E. J.; Lo, W. Y.; Lee, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 4261; *Angew. Chem.* **2010**, *122*, 4353.
(9) (a) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812. (b) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201. (c) Marshall, J. A.; Eidam, P.; Eidam, H. S. *J. Org. Chem.* **2006**, *71*, 4840.
(10) See also: Jägel, J.; Maier, M. E. *Synlett* **2006**, 693.
(11) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 2152; *Angew. Chem.* **2004**, *116*, 2204.
(12) For a large-scale synthesis of aldehyde **6**, see: Smith, A. B.; Tomioka, T.; Risatti, C. A.; Sperry, J. B.; Sfouggatakis, C. *Org. Lett.* **2008**, *10*, 4359.
(13) (a) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 3369. (b) Marshall, J. A.; Chobanian, H. *Org. Synth.* **2005**, *82*, 43. (c) Marshall, J. A.; Chobanian, H. *Org. Synth., Coll. Vol. XI*; Wiley: New York, **2009**, 1056–1067.
(14) (a) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.* **2001**, *66*, 7825. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.
(15) It is assumed that the minor *syn* isomer in organocatalytic aldol reactions has the OH inverted. The configuration of the methyl-bearing stereocenter would remain the same: (a) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. (b) Storer, R. I.; MacMillan, D. W. C. *Tetrahedron* **2004**, *60*, 7705.
(16) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9.
(17) Kutscheroff, M. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 13.
(18) For a review, see: Hintermann, L.; Labonne, A. *Synthesis* **2007**, 1121.
(19) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2386. (c) Pine, S. H.; Kim, G.; Lee, V. *Org. Synth.* **1990**, *69*, 72. (d) Pine, S. H.; Kim, G.; Lee, V. *Org. Synth., Coll. Vol. VIII*; Wiley: New York, **1993**, 512–516.
(20) Pietruszka, J.; Witt, A. *Synthesis* **2006**, 4266.
(21) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521. (c) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59.
(22) Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677.
(23) Kanada, R. M.; Itoh, D.; Nagai, M.; Niijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotake, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 4350; *Angew. Chem.* **2007**, *119*, 4428.
(24) Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485.
(25) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2004**, *126*, 12432; and references therein.
(26) (a) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1992**, *71*, 1. (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth., Coll. Vol. IX*; Wiley: New York, **1998**, 589–597.
(27) (a) Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825. (b) Züger, M.; Weller, T.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 2005. (c) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269. (d) Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth.* **1985**, *63*, 109. (e) Seebach, D.; Aebi, J.; Wasmuth, D. *Org. Synth., Coll. Vol. VII*; Wiley: New York, **1990**, 153–162.
(28) (a) Mori, K.; Ebata, T. *Tetrahedron* **1986**, *42*, 4685. (b) Guan, Y.; Wu, J.; Sun, L.; Dai, W.-M. *J. Org. Chem.* **2007**, *72*, 4953. (c) Dunetz, J. R.; Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, *130*, 16407.
(29) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Procedure according to: Grant, S. W.; Zhu, K.; Zhang, Y.; Castle, S. L. *Org. Lett.* **2006**, *8*, 1867. (c) Review article: Singh, J.; Satyamurthi, N.; Aidhen, I. S. *J. Prakt. Chem.* **2000**, *342*, 340.
(30) (a) Fehr, C.; Guntern, O. *Helv. Chim. Acta* **1992**, *75*, 1023. (b) Fehr, C.; Galindo, J. *Helv. Chim. Acta* **2005**, *88*, 3128.
(31) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P. J. *J. Am. Chem. Soc.* **1991**, *113*, 8036.
(32) For a review, see: Fürstner, A. *Synthesis* **1989**, 571.
(33) For a review, see: Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371.