DOI: 10.1002/adsc.200700589

Total Synthesis of (−)-Basiliskamide B

Luiz C. Dias[a,*] and Caroline da Costa S. Gonçalves[a]

[a] Instituto de Química, Universidade Estadual de Campinas, UNICAMP, C.P. 6154, 13084-971, Campinas, SP, Brazil
Phone: (+55)-19-3521-3097; fax: (+55)-019-3521-3023; e-mail: ldias@iqm.unicamp.br

Received: December 14, 2007; Published online: March 17, 2008

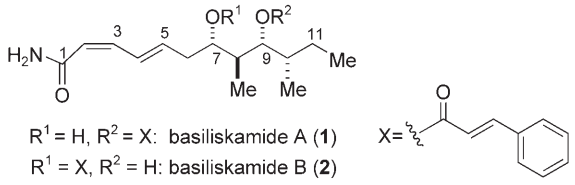
Dedicated to Professor Andreas Pfaltz on the occasion of his 60th anniversary.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: The total synthesis of the polyketide antibiotic (−)-basiliskamide B is described. The convergent asymmetric synthesis relies on the use of a diastereoselective ethyl ketone aldol reaction followed by a *syn* selective reduction of a β-hydroxy ketone and a Stille cross-coupling between a *Z*-vinylstannane and an *E*-vinyl iodide to establish the *(Z,E)*-dienamide moiety.

Keywords: aldol reaction; antitumor compounds; Stille cross-coupling; total synthesis

The basiliskamides A (**1**) and B (**2**) are two antifugal polyketides isolated from the marine bacterium PNG-276 from the coast of Papua New Guinea (Scheme 1).[1,2] Both **1** and **2** show potent *in vitro* activity against *Candida albicans* and *Aspergillus fumigatus* with MIC values of 1.0 and 2.5 μg mL^{-1}, respectively, for basiliskamide A and MIC values of 3.1 and 5.0 μg mL^{-1} for basiliskamide B.[1] The only difference between basiliskamides A and B is the relative position of the cinnamate ester (C-9 in basiliskamide A and C-7 in basiliskamide B). The *in vitro* activities of basiliskamide A (**1**) and B (**2**) are similar to that of amphotericin B. Basiliskamides A and B also showed at least 4-fold less cytotoxixity for normal human fibroblast cells when compared to amphotericin B. Basiliskamide A shows toxicity against human diploid fibroblast cells *in vitro* at 100 μg mL^{-1} and amphotericin B shows toxic effects at 12 mg mL^{-1}, destroying the cells at 100 μg mL^{-1}.[1] The relative configurations of basiliskamides A (**1**) and B (**2**) were proposed by Andersen and co-workers and further supported by means of NMR experiments.[1,3] The relative and absolute configurations for basiliskamides A (**1**) and B (**2**) have been recently confirmed by their first total synthesis, completed by the Panek group, as being 7*S*,8*S*,9*R*,10*S*.[4]

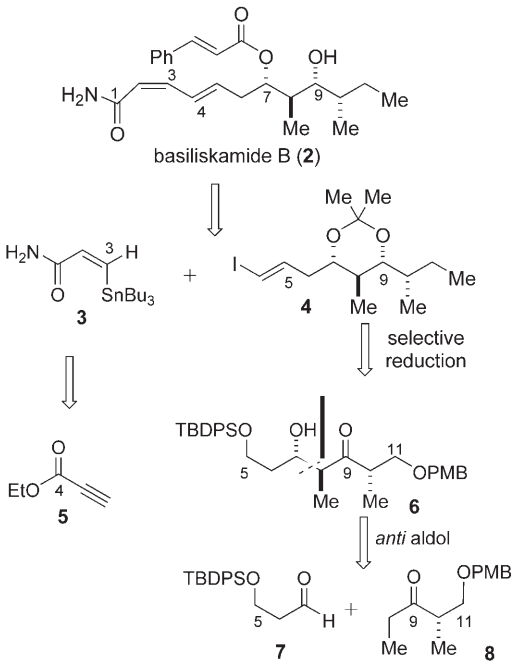


Scheme 1. Basiliskamides A and B.

To provide material for more extensive biological evaluation, along with access to novel analogues, we have undertaken the total synthesis of the polyketide antibiotic basiliskamide B. Basiliskamide B is a primary amide containing four contiguous stereogenic centers, a *Z,E*-diene system and a cinnamoyl ester at the less hindered oxygen.

Not surprisingly, our first disconnection, summarized in Scheme 2, involved cleavage of the *Z,E*-diene portion (C-3–C–4 bond) to give *Z*-vinylstannane **3** (C-1–C-3 fragment) and *E*-vinyl iodide **4** (C-4–C-12 fragment) bearing the 4 stereogenic centers of the basiliskamides.[4,5] Of the available options, we speculated that the C-9 stereocenter could be constructed by a selective hydroxy ketone reduction in **6**, which may be further dissected in a straightforward manner to give aldehyde **7** and ethyl ketone **8**. The C-1–C-3 fragment **3** is viewed as arising from α,β-acetylenic ester **5**, providing control for the *Z* geometry of the double bond.

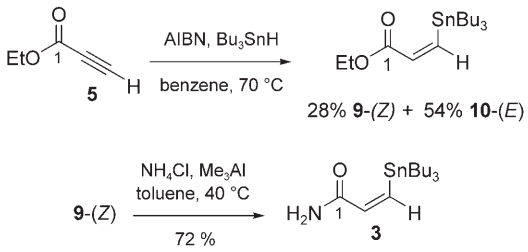
The *Z*-vinylstannane **3** corresponding to the C-1–C-3 fragment was easily prepared using a two-step protocol from commercially available α,β-acetylenic ester **5** (Scheme 3). Tributylstannylation of **5** under reflux in benzene gave a mixture of **9-**(*Z*) and **10-**(*E*) vinylstannanes, which were separated by column chromatography.[6] Ester-amide exchange, was accomplished by treatment of vinylstannane (*Z*)-**9** with Me_3Al and NH_4Cl in toluene at 40 °C, giving *Z*-vinylstannane **3**



Scheme 2. Retrosynthetic analysis.

after purification by column chromatography (72% yield).[7]

Our approach for the preparation of ethyl ketone **8** was initiated with Roche ester **11** following the strategy developed by Paterson and co-workers

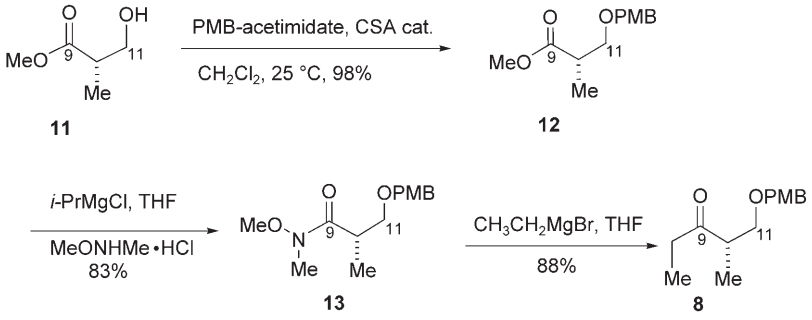


Scheme 3. Preparation of vinylstannane **3**.

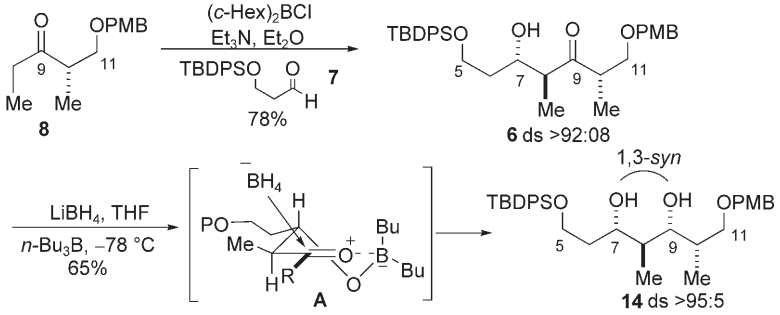
(Scheme 4).[8] Treatment of ester **11** with PMB-acetimidate and catalytic amounts of CSA in CH_2Cl_2 gave ester **12** in 98% yield.[9] Ester **12** was then converted to *N*-methoxy-*N*-methylamide **13** (83% yield), which was reacted with ethyl magnesium bromide to provide the desired chiral ethyl ketone **8** in 88% yield.[7,8]

It was with some gratification that enolization of ketone **8** with $(c\text{-Hex})_2BCl$ and Et_3N in Et_2O followed by addition of aldehyde **7**, provided the *anti*-aldol **6** in 78% isolated yield and 92:8 diastereomeric purity (Scheme 5).[8,10] Stereoselective reduction of the *anti*-aldol **6** under modified Narasaka's conditions gave the requisite 1,3-*syn* diol **14** in 65% yield (*ds* > 95:5).[11]

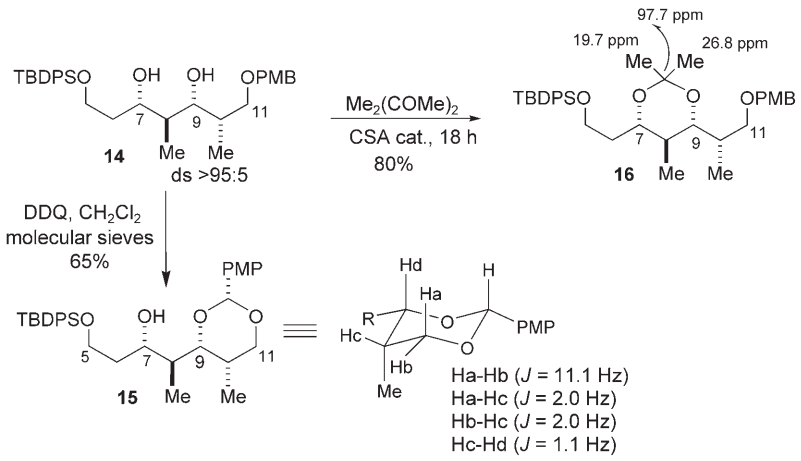
In order to determine the relative stereochemistry of the aldol bond construction and β-hydroxy ketone reduction steps, diol **14** was transformed to the corresponding cyclic acetal (Scheme 6). Treatment of 1,3-diol **14** with DDQ gave benzylidene acetal **15** in 65%



Scheme 4. Preparation of ethyl ketone **8**.



Scheme 5. Aldol coupling of ethyl ketone **8**.



Scheme 6. Determination of the relative stereochemistry for diol **14**.

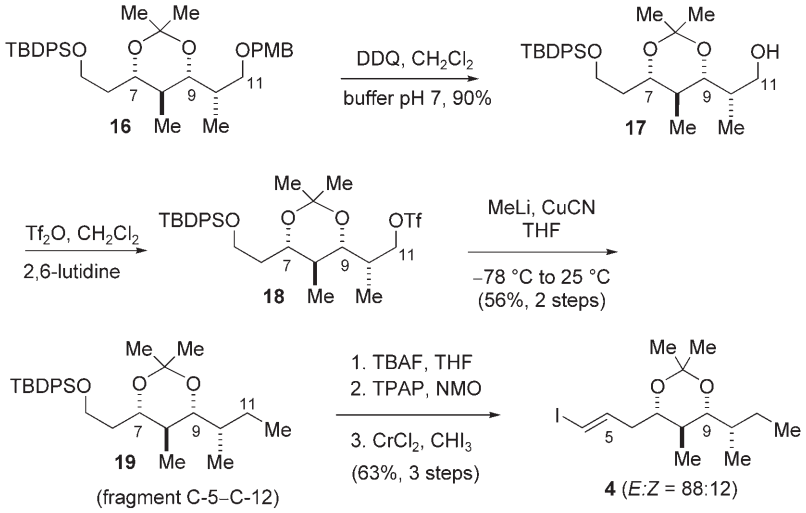
yield.[12] The relative stereochemistry of C-9 and C-10 stereocenters was determined by analysis of the ^{1}H NMR spectra of the acetal **15**. The small coupling constants between Ha-Hc (2.0 Hz) and Hc-Hd (1.1 Hz), together with the small observed value between Hb-Hc (2.0 Hz), unambiguously established the proposed relative stereochemistry for C-9–C-10 bond in **15**.

The stereochemistry of the secondary alcohols at C-7 and C-9 was determined on the basis of the ^{13}C NMR analysis of the corresponding 1,3-diol acetonide **16**, prepared in 80% yield from diol **14** (Scheme 4). ^{13}C NMR resonances at 19.7, 26.8, and 97.7 ppm are characteristic of a *syn* acetonide.[13]

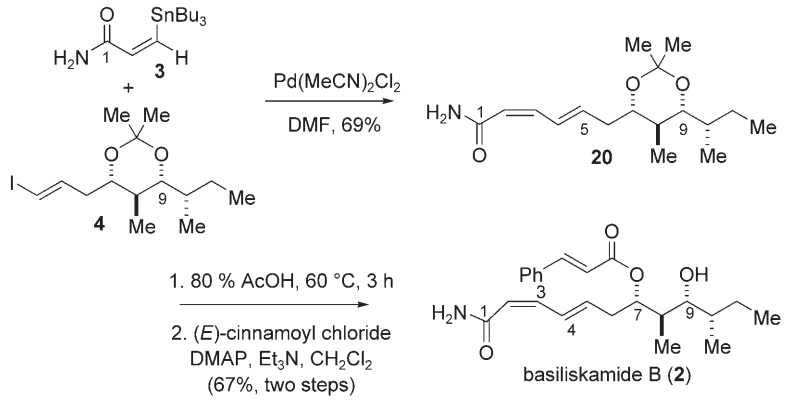
A sequence of PMB removal from **16** with DDQ (90% yield), followed by protection of the primary OH function in **17** with Tf_2O in the presence of 2,6-lutidine provided triflate **18** (Scheme 7).[14] The next step involved coupling of triflate **18** with MeLi/CuCN to give compound **19** in 56% overall yield for the two-step sequence.[14]

With compound **19** in hand, only three synthetic operations remained to arrive at an intermediate suitable for coupling with *Z*-vinylstannane **3** (Scheme 7). Removal of the TBDPS protecting group at C-5 in **19** gave a primary alcohol, which was followed by TPAP oxidation to give the intermediate aldehyde.[15] All that remained was to carry out the necessary Takai olefination reaction.[15] Treatment of the unpurified aldehyde with $CrCl_2$ and CHI_3 proceeded smoothly to produce *E*-vinyl iodide **4** (*E,Z* = 88:12), corresponding to the C-4–C-12 segment of basiliskamide B in 63% overall yield for the two-step sequence.[16]

With synthesis of the requisite C-1–C-3 and C-4–C-11 fragments in hand, their coupling was undertaken. This was done by using Stille cross-coupling conditions (Scheme 8).[17,18] Treatment of a solution of *E*-vinylstannane **3** and *E*-vinyl iodide **4** in DMF with a



Scheme 7. Synthesis of (*E*)-vinyl iodide **4**.



Scheme 8. Total synthesis of basiliskamide B.

catalytic amount of $Pd(MeCN)_2Cl_2$ at 25 °C afforded **20** in 69% yield after purification by silica gel column chromatography.[17,18]

Removal of the isopropylidene acetal with 80% AcOH followed by selective acylation of the less hindered oxygen with *E*-cinnamoyl chloride gave basiliskamide B (**2**) in 67% overall yield (Scheme 8). The spectroscopic and physical data [^{1}H and ^{13}C NMR, IR, $[\alpha]_D$, R_f] were identical in all respects with the published data.[1,4] The 12-step sequence starting from **8** proceeded in 6% overall yield and is amenable to a multigram scale-up.

The total synthesis of basiliskamide B has been completed. Notable features of this approach include convergence, a boron enolate-mediated aldol reaction to set up the desired C-8 and C-9 stereocenters and a Stille cross-coupling between a Z-vinylstannane and a vinyl iodide. The synthesis required 12 steps (longest linear sequence) from ethyl ketone **8** and produced the desired product in 6% overall yield. This approach compares very well with a previously published route. As a result, the route to (−)-basiliskamide B presented here is, in principle, readily applicable for the preparation of additional novel structural analogues. Further optimization of the synthesis as well as application of this strategy to the synthesis of basiliskamide A and analogues is underway and the results will be described in a full accout of this work.

Experimental Section

(2*S*,4*S*,5*S*)-1-(4-Methoxybenzyloxy)-7-(*tert*-butyldiphenylsilyloxy)-5-hydroxy-2,4-dimethylheptan-3-one (6)

To a stirred solution of dicyclohexylboron chloride (1.9 mL, 8.6 mmol) in Et_2O (8.2 mL) at 0 °C was added Et_3N (1.3 mL, 9.15 mmol). Ketone (*S*)-**8** (1.4 g, 5.7 mmol) in Et_2O (4 mL) was added *via* cannula and the reaction mixture was stirred for 1 h at 0 °C before cooling to −78 °C. A solution of aldehyde **7** (11.4 mmol) in Et_2O (2 mL) was added *via* cannula and stirring continued for 15 min before aging in the freezer (−20 °C, 18 h). The reaction mixture was then partioned between Et_2O (3×10 mL) and pH 7 buffer solution (20 mL), the organic extracts were concentrated under vacuum to give an oil, which was taken up in methanol (29 mL) and pH 7 buffer solution (29 mL) and stirred at 0 °C. Hydrogen peroxide (30% aqueous, 8,6 mL) was added dropwise. After stirring for 2 h at 0 °C the mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification by flash chromatography (10% EtOAc/hexanes) afforded **6**; yield: 2.5 g (4.5 mmol, 78%; *ds* = 92:08).

tert-Butyl-(2-{(4*S*,5*S*,6*R*)-6-[(*S*)-*sec*-butyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}ethoxy)diphenylsilane (19)

A solution of alcohol **17** (56 mg, 0.13 mmol) in CH_2Cl_2 (2.6 mL) was treated with 2.6-lutidine (0.045 mL, 0.39 mmol) and cooled to −78 °C. The solution was treated with triflic anhydride (0.032 mL, 0.195 mmol) and stirred at −78 °C for 30 min. The reaction was then quenched with saturated aqueous $NaHCO_3$ (2.7 mL). The aqueous phase was extracted with CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under vacuum, to provide triflate **18**. Methyllithium (1.3 mmol, 1.0 mL of a 1 M solution in ether) and CuCN (0.06 g, 0.67 mmol) were stirred in dry THF (1 mL) at −78 °C for 30 min. A solution of the crude triflate **18** (0.13 mmol) in dry THF (0.5 mL) was added, the mixture stirred at −78 °C for 1.5 h, and at room temperature for 1 h. After cooling to 0 °C, aqueous saturated NH_4Cl solution was added, the layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (5% EtOAc/hexanes) to give compound **19**; yield: 34 mg (0.073 mmol).

(2*Z*,4*E*)-6-{(4*S*,5*S*,6*R*)-6-[(*S*)-*sec*-Butyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}hexa-2,4-dienamide (20)

Vinyl iodide **4** (0.17 g, 0.48 mmol) was treated with a solution of vinylstannane **3** (0.243 g, 0.672 mmol) in DMF (8.2 mL). Dichloro(bis)acetonitrilepalladium(II) (6.2 mg, 0.024 mmol) in DMF (1.7 mL) was then added. The reaction was protected from light and stirred at ambient temperature

for 18 h. The mixture was diluted with EtOAc (5 mL) and washed with water. The combined aqueous layers were extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (50% EtOAc/hexanes) afforded diene **20**; yield: 0.097 g (0.33 mmol, 69%).

Basiliskamide B (2)

The diene **20** was dissolved in 80% acetic acid. The reaction was protected from light and warmed to 60 °C for 3 h. The reaction was then allowed to reach ambient temperature and adjusted to pH 7.0 with NH_4OH. The aqueous phase was extracted with EtOAc (2×10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. A solution of the corresponding crude diol (0.14 mmol) in CH_2Cl_2 (3 mL) was treated with Et_3N (0.08 mL, 0.6 mmol) and DMAP (1.7 mg, 0.014 mmol) and cooled to 0 °C. The solution was treated with of (*E*)-cinnamoyl chloride (46 mg, 0.28 mmol). The reaction was protected from light and allowed to reach ambient temperature for 48 h. The reaction was then quenched with water. The aqueous phase was extracted with CH_2Cl_2. Purification by flash column chromatography (80% EtOAc/CH_2Cl_2) afforded basiliskamide **2**; yield: 36 mg (0.094 mmol, 67%).

Acknowledgements

We are grateful to FAEP-UNICAMP, FAPESP and CNPq (Brazil) for financial support. We also thank Prof. Carol H. Collins, from IQ-UNICAMP, for helpful suggestions about English grammar and style and Leonardo José Steil for helpful comments and suggestions.

References

[1] T. Barsby, M. T. Kelly, R. Andersen, *J. Nat. Prod.* **2002**, *65*, 1447–1451.
[2] A. M. S. Mayer, M. T. Hamann, *Comp. Biochem. Physiol.* **2005**, ##*140C*, 265–286.
[3] For a stereochemcial assignment of basiliskamides through NMR, see: J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote, M. R. Prinsep, *Nat. Prod. Rep.* **2004**, *21*, 1–49.
[4] D. J. Lipomi, N. F. Langille, J. S. Panek, *Org. Lett.* **2004**, *6*, 3533–3536.
[5] The numbering of **2** follows that suggested in ref.[1]
[6] M. S. Ermolenko, *Tetrahedron Lett.* **1996**, *37*, 6711–6712.
[7] a) A. Basha, M. Lipton, S. M. Weinreb, *Tetrahedron Lett.* **1977**, 4171–4174; b) J. I. Levin, E. Turos, S. M. Weinreb, *Synth. Commun.* **1982**, *12*, 989–993; c) L. C. Dias, L. G. de Oliveira, J. D. Vilcachagua, F. Nigsch, *J. Org. Chem.* **2005**, *70*, 2225–2234; d) L. C. Dias, L. G. de Oliveira, *Org. Lett.* **2001**, *3*, 3951–3954.
[8] a) I. Paterson, G. J. Florence, K. G. Gerlach, J. P. Scott, N. Sereinig, *J. Am. Chem. Soc.* **2001**, *123*, 9535–9544; b) I. Paterson, J. M. Goodman, M. Isaka, *Tetrahedron Lett.* **1989**, *30*, 7121–7124; c) I. Paterson, M. V. Perkins, *Tetrahedron* **1996**, *52*, 1811–1834; d) J. M. Goodman, I. Paterson *Tetrahedron Lett.* **1992**, *33*, 7223–7226; e) A. Vulpetti, A. Bernardi, C. Gennari, J. M. Goodman, I. Paterson, *Tetrahedron* **1993**, *49*, 685–696; f) W. R. Roush, L. Banfi, *J. Am. Chem. Soc.* **1988**, *110*, 3979–3982.
[9] K. C. Nicolaou, A. P. Patron, K. Ajito, P. K. Richter, H. Khatuya, P. Bertinato, R. A. Miller, M. J. Tomaszewshi, *Chem. Eur. J.* **1996**, *2*, 847–868.
[10] Aldehyde **7** is easily prepared from 1,3-propanediol after selective protection with NaH and TBDPSCl in THF (79% yield) and oxidation under standard Swern conditions.
[11] a) K. Narasaka, F. C. Pai, *Tetrahedron* **1984**, *40*, 2233–2238; b) S. Bode, M. Wolberg, M. Müller, *Synthesis* **2006**, 557–588; c) I. Paterson, R. D. Norcross, R. A. Ward, P. Romea, M. A. Lister, *J. Am. Chem. Soc.* **1994**, *116*, 11287–11314.
[12] a) A. B. Smith III, T. J. Beauchamp, M. J. LaMarche, M. D. Kaufman, Y. P. Qiu, H. Arimoto, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 8654–8664; b) L. C. Dias, R. Z. Baú, M. A. Sousa, J. Z. Schpector, *Org. Lett.* **2002**, *4*, 4325–4327.
[13] a) S. D. Rychnovsky, D. J. Skalitzky, *Tetrahedron Lett.* **1990**, *31*, 945–948; b) D. A. Evans, D. L. Rieger, J. R. Gage, *Tetrahedron Lett.* **1990**, *31*, 7099–7100; c) S. D. Rychnovsky, B. N. Rogers, T. I. Richardson, *Acc. Chem. Res.* **1998**, *31*, 9–17; d) C. F. Tormena, L. C. Dias, R. Rittner, *J. Phys. Chem. A* **2005**, *109*, 6077–6082.
[14] a) S. C. Archibald, D. J. Barden, J. F. Y. Bazin, I. Fleming, C. F. Foster, A. K. Mandal, A. K. Mandal, D. Parker, K. Takaki, A. C. Ware, A. R. B. Willians, A. B. Zwicky, *Org. Biomol. Chem.* **2004**, *2*, 1051–1064; b) H. Tanaka, K. Kawai, K. Fujiwara, A. Murai, *Tetrahedron* **2002**, *58*, 10017–10031.
[15] a) S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639–666; b) R. Bloch, C. Brillet, *Synlett* **1991**, 829–830.
[16] a) K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410; b) I. Paterson, H. G. Lombart, C. Allerton, *Org. Lett.* **1999**, *1*, 19–22.
[17] Recent review: P. Espinet, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 4808–4839; *Angew. Chem. Int. Ed.* **2004**, *43*, 4704–4734.
[18] a) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504–519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524; b) M. A. J. Duncton, G. Pattenden, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1235–1246; c) J. K. Stille, B. L. Groh, *J. Am. Chem. Soc.* **1987**, *109*, 813–817.

