Catalytic Asymmetric Synthesis

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Catalytic Asymmetric Aldol Equivalents in the Enantioselective Synthesis of the Apoptolidin C Aglycone**

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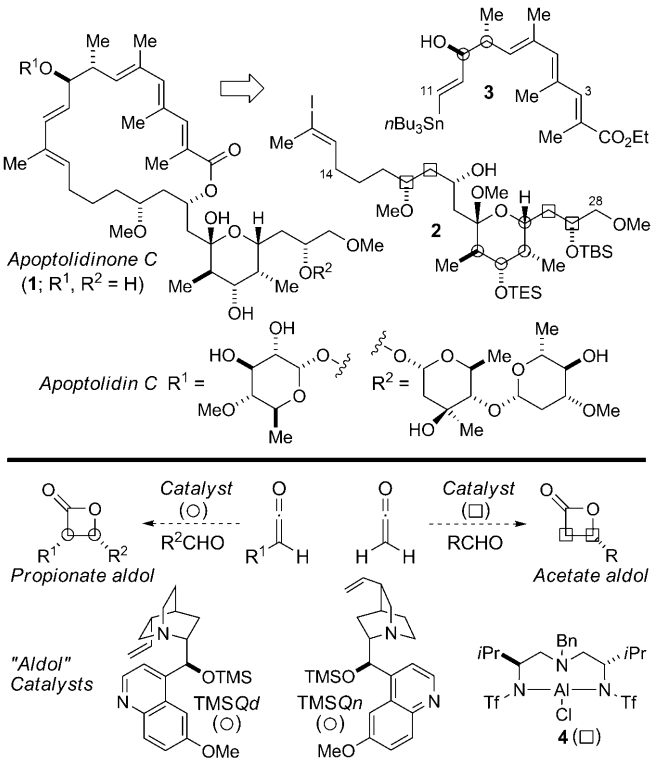
Apoptolidins A–E are a family of macrolide natural products that have attracted considerable attention as highly selective apoptosis regulators.[1] The critical need for achieving greater selectivity in cancer chemotherapeutics has stimulated efforts to elucidate the mechanistic and structural basis for the apoptolidin's unique pharmacological profile. These efforts include several total syntheses of apoptolidin A, each of which has provided invaluable insights into strategies for chemically modifying the natural product for expanded pharmacological profiling.[2] Similar considerations inspired our interest in developing an enantioselective synthesis of the apoptolidins exploring the capacity of catalytic asymmetric aldol reaction surrogates to facilitate the synthesis of these natural products. Toward this goal, we describe herein an enantioselective synthesis of apoptolidinone C (**1**), the apoptolidin C aglycone, wherein catalytic asymmetric C–C bond constructions provide the conduit to all ten of the requisite stereogenic centers.

Their utility in assembling acetate- or propionate-derived polyketide architecture is among the defining characteristics of modern aldol-based reaction technologies. There exists an array of aldol or aldol equivalents utilizing stoichiometric chiral controllers that provide exceptionally reliable and predictable methods for constructing complex polyacetate and polypropionate arrays.[3] For our purposes, the apoptolidin C aglycone provided a platform for evaluating whether similar levels of operational efficiency and expediency could be achieved in similar synthesis endeavors wherein stereocontrol would derive exclusively from catalyst-based substoichiometric chiral controllers. Specifically, catalytic asymmetric acyl halide–aldehyde cyclocondensation (AAC) reactions provide highly stereoselective acetate or propionate aldol equivalents using Al^{III}-based Lewis acid or cinchona alkaloid Lewis base catalysts, respectively.[4] Complex polyketide assemblage predicated on the AAC methodology follows a reiterative pattern of catalyst controlled C–C bond construction followed by β-lactone refunctionalization to the β-alkoxy aldehyde required for continued chain homologation in a sequence reminiscent of the iterative homologation–refunctionalization sequence observed in biosynthetic polyketide assembly.

A synthesis of apoptolidinone C (**1**) emerges from the preceding analysis by disconnecting **1** across the C1–O and C11–C12 bonds to reveal the mixed acetate/propionate-derived C12–C28 fragment **2** and the extensively dehydrated polypropionate C1–C11 fragment **3** (Scheme 1). The synthesis of lower fragment **2** highlights the iterative assembly of stereodefined polyketide units enabled by the AAC methodology. Thus, Al^{III}-triamine (**4**)-catalyzed cyclocondensation of acetyl bromide with methoxyacetaldehyde provided β-lactone **5** as an acetate aldol equivalent (91%, ≥95% *ee*) (Scheme 2).[4] Converting lactone **5** to aldehyde **6** required for continued chain elongation involved amine-mediated ring opening (MeO(Me)NH, Me_2AlCl), protection of the incipient alcohol (TBSOTf, 2,6-lutidine), and amide reduction (iBu_2AlH, THF) (94% over three steps).[5] Further homologation of **6** proceeded by *O*-trimethylsilylquinidine (TMS*Qd*)-catalyzed cyclocondensation with propionyl chloride to establish the C24,C25 *syn* propionate aldol relation-



Scheme 1. Catalytic asymmetric synthesis of apoptolidinone C (**1**).

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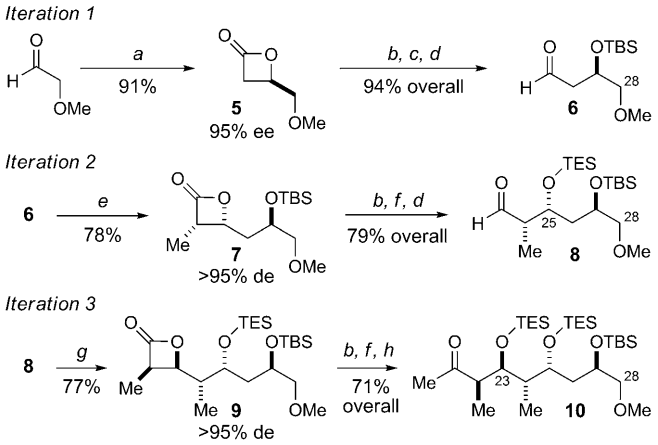
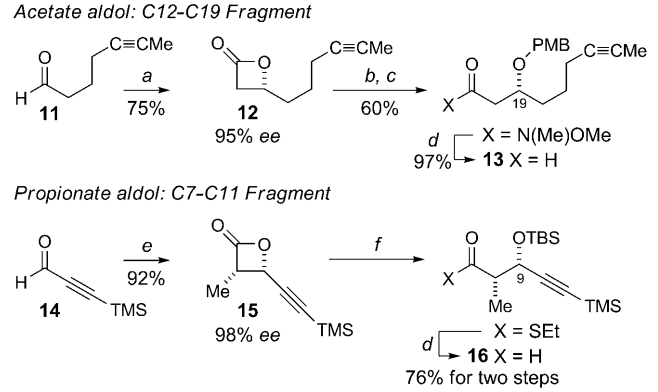


Scheme 2. Iterative catalyzed aldol additions: a) 10 mol% **4**, MeCOBr, iPr$_2$NEt, −60 °C. b) Me$_2$AlCl, (MeO)MeNH$_2$Cl. c) TBSOTf, 2,6-lutidine, −60 °C. d) iBu$_2$AlH, THF, −78 °C. e) 10 mol% TMS*Qd*, EtCOCl, LiClO$_4$, iPr$_2$NEt, −78 °C. f) Et$_3$SiOTf, 2,6-lutidine, −60 °C. g) 10 mol% TMS*Qn*, EtCOCl, LiI, iPr$_2$NEt, −78 °C. h) MeMgBr, THF, 0 °C. TBS = *tert*-butyl dimethylsilyl, TMS*Qd* = *O*-trimethylsilylquinidine, TMS*Qn* = *O*-trimethylsilylquinine.

ship in providing β-lactone **7** (78%, >95% *de*). The last aldol iteration was accomplished by Weinreb amide-mediated refunctionalization of **7** to aldehyde **8** (79% for three steps) and ensuing propionyl chloride AAC homologation, this time using *O*-trimethylsilyquinine (TMS*Qn*) as catalyst, to provide the *syn*,*anti*,*syn* β-lactone **9** as a single stereoisomer (77%, >95% *de*). The C20–C28 fragment was completed by converting β-lactone **9** to the methyl ketone **10** using the same amine-mediated β-lactone refunctionaliztion procedure, substituting MeMgBr addition to the intervening amide for the typical terminal reduction step (71% over three steps).[5]

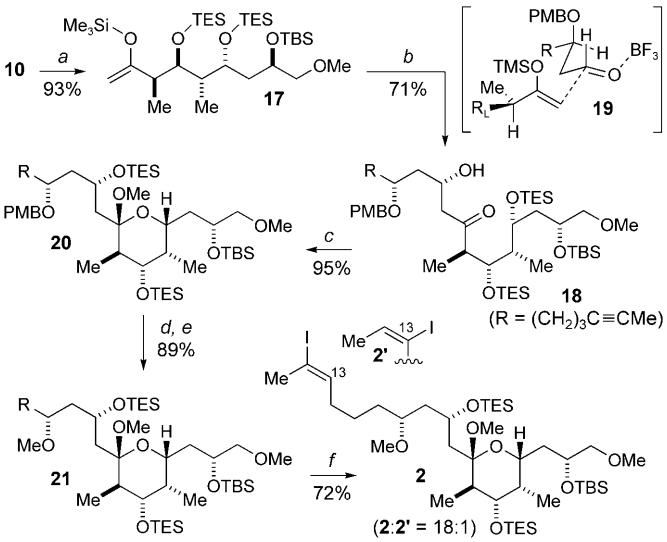
Catalytic asymmetric AAC reactions similarly served as aldol surrogates in establishing the isolated C17–C19 acetate and C7–C9 propionte aldol relationships embedded in the aglycone (Scheme 3). The Al^{III}-catalyzed cyclocondensation



Scheme 3. Catalytic asymmetric acetate and propionate aldols: a) 10 mol% *ent*-**4**, MeCOBr, iPr$_2$NEt, −60 °C. b) Me$_2$AlCl, (MeO)MeNH$_2$Cl. c) PMBOC(NH)CCl$_3$, 15 mol% BF$_3$·Et$_2$O, CH$_2$Cl$_2$. d) iBu$_2$AlH, THF, −78 °C. e) 10 mol% TMS*Qd*, EtCOCl, MgCl$_2$, iPr$_2$NEt, −78 °C. f) 10 mol% KHMDS, EtSH, THF then TBSOTf, 2,6-lutidine. PMB = *p*-methoxybenzyl, KHMDS = potassium hexamethyldisilazide.

of 5-heptynal (**11**)[6] with acetyl bromide provided the enantioenriched β-lactone **12** incorporating C17 carbinol stereocenter (75%, ≥95% *ee*). Amine-mediated lactone ring opening was followed by installation of the C17 *p*-methoxybenzyl ether; ensuing amide reduction provided β-alkoxy aldehyde **13** representing C12–C17 of the algycone (58% over three steps). Alkaloid catalysis provided the conduit to the C7–C9 propionate relationship through TMS*Qn*-catalyzed cyclocondensation of 3-trimethylsilylpropynal (**14**) with propionyl chloride to generate β-lactone **15** with near perfect absolute and relative stereocontrol. In this instance, two-step thiolate-mediated conversion of lactone **15** to the corresponding β-silyloxy aldehyde **16** (10 mol% KHMDS, EtSH; TBSOTf then iBu$_2$AlH) (76% for two steps) revealed the AAC-derived β-lactone as the requisite *syn* propionate aldol equivalent.

Assembling the lower C12–C28 fragment **2** was predicated on the aldol coupling of ketone **10** and aldehyde **13** proceeding to correctly establish the, as yet, unaddressed C17 stereocenter (Scheme 4). To this end, the kinetic enol silane



Scheme 4. Synthesis of lower fragment **2**: a) NaHMDS, THF; TMSCl, 2,6-lutidine. b) **13**, BF$_3$·OEt$_2$ (1 equiv), CH$_2$Cl$_2$, −78 °C. c) 1. TFA, 1:1 MeOH:CH$_2$Cl$_2$; 2. TESOTf, 2,6-lutidine, −55 °C. d) DDQ, 2:1 CH$_2$Cl$_2$:pH 7 phosphate buffer. e) Me$_3$OBF$_4$, proton sponge, CH$_2$Cl$_2$. f) [Cp$_2$ZrHCl], 2,6-lutidine, THF then I$_2$. Cp = cyclopentadienyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TFA = trifluoroacetic acid.

17 derived from ketone **10** participated in highly 1,3-*anti* selective Mukaiyama aldol addition to aldehyde **13** (BF$_3$·OEt$_2$, CH$_2$Cl$_2$, −78 °C) affording β-hydroxy ketone **18** as a single diastereomer (71%);[7] diastereoselection in this aldol coupling is consistent with a matched pairing of aldehyde and enolate facial biases according to the transition-state model **19**.[8] Reacting **18** with acidic methanol cleaved the C23 and C25 triethylsilyl ethers and elicited concomitant hemiketal formation to generate pyran **20** as a single β-anomer. Appropriately configuring both the temporary and permanent ether functionalities required for advanc-

ing the synthesis was accomplished by installing the C19 and C23 triethylsilyl ethers (TESOTf, 2,6-lutidine), removing the C17 *p*-methoxybenzyl ether and methylating the resulting alcohol (DDQ; Me_3OBF_4, proton sponge) to afford **21** (85% from **18**). Regioselective alkyne hydrozirconation and iodination of the resulting Zr–C bond ([Cp_2ZrHCl], 2,6-lutidine; I_2) constituted the final steps in completing the lower major fragment **2** (72%, C12–I (**2**):C13–I (**2′**) = 18:1).[9]

Synthesis of the C1–C11 fragment **1** representing the dehydrated polypropionate region of apoptolidinone C employed aldehyde **16** as a platform for constructing the conjugated trienone array. Thus, aldehyde **16** was reacted with CBr_4/PPh_3 to provide alkylidene dibromide **22** (80%) (Scheme 5). Engaging (*E*,*E*)-5-iodo-2,4-dimethylpenta-2,4-dienoate (**23**)[10] in Pd^0-catalyzed metathesis of the C–I bond with bis(pinacolborane) provided the alkenyl boronic ester **24** required for union with **22**.[11] In the event, dibromide **22** and boronic ester **24** were engaged in chemoselective Suzuki cross coupling (10 mol% [$Pd(PPh_3)_4$], TlOEt) to afford the all *E* trienoate **25** as a single olefin isomer (66%).[12] The less reactive C–Br σ-bond remaining from the Suzuki reaction was next exploited in the Negishi cross coupling with Me_2Zn (7 mol% [$Pd(PtBu_3)_2$], THF) to complete construction of the three conjugated trisubstituted olefins in providing **26** (90%, $E_{C6\text{-}C7}$:$Z_{C6\text{-}C7}$ = 6.6:1).[13] Finally, removing the terminal trimethylsilyl group (83%) and Pd^0-catalyzed hydrostannylation of the resulting terminal alkyne provided the alkenyl stannane **3** (68%) along with the regioisomeric 1,1-disubstituted alkenyl stannane (20%).[14]

The final fragment coupling leading to apoptolidinone C (**1**) involved the union of the major lower and upper subsections, **2** and **3**, respectively, through construction of the conjugated C10–C13 diene (Scheme 5). For this purpose, the Pd^0-catalyzed Stille coupling of vinyl iodide **2** and alkenyl stannane **3** provided the desired *E*,*E*-diene **27** as the major constituent of a 12:1 mixture of C10–C11 olefin isomers (10 mol% [$PdCl_2(MeCN)_2$], $Ph_2PO_2NnBu_4$, DMF) (75%). Success in this fragment coupling was critically dependent on including tetrabutylammonium diphenylphosphinate (**28**) as a scavenger for tin-derived by-products;[15] attempted Stille couplings excluding **28** yielded extensive olefin isomerization.[16] Saponification of the C1 carboxylate ester (LiOH, aq THF/MeOH) was accompanied by partial, non-selective TES ether cleavage, that produced a mixture of the expected carboxylic acid, the regioisomeric mono TES ethers **29a/b** as well as the carboxylic acid triol **30** (78% of mixture). Reacting this mixture with TFA completed removal of the TES ethers to afford the carboxylic acid triol **30** (61% yield). Ensuing chemoselective macrolactonization of triol **30** was accomplished using modified Yamaguchi conditions to afford the protected aglycone **31** (57%) along with minor quantities (≈8%) of the regioisomeric macrolactone.[17] Utilizing Koert's conditions for simultaneous ketal hydrolysis and silyl ether removal (H_2SiF_6, aq CH_3CN) successfully converted **31** to apoptolidinone C (**1**).[2d]

The apoptolidinone C synthesis highlights the utility of catalytic asymmetric aldol equivalents in the synthesis of stereochemically complex polyketide architecture. In this context, the catalytic asymmetric AAC-based aldol equivalents complement highly successful auxiliary-based methods for accessing polyacetate- and polypropionate-derived natural products.

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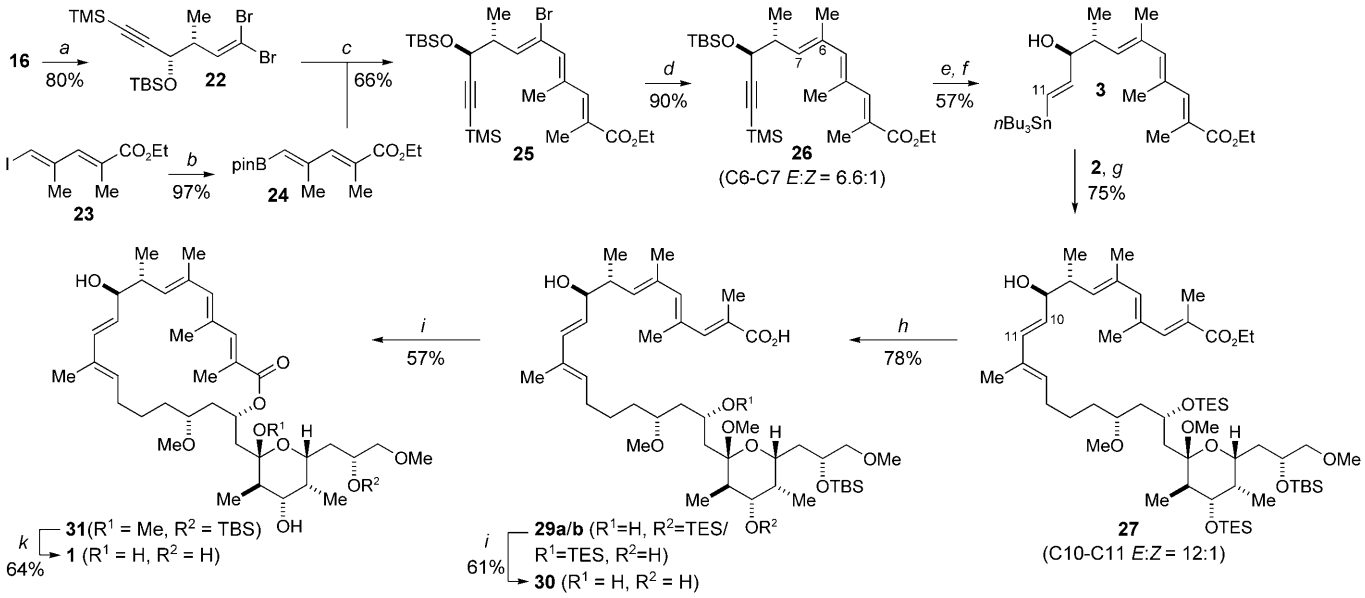

Scheme 5. Major fragment assembly and synthesis of apoptolidinone C (**1**): a) CBr_4, PPh_3, CH_2Cl_2. b) $(pinB)_2$, 3 mol% [$Pd(dppf)Cl_2$], KOAC, DMSO, 85 °C. c) **24**, 10 mol% [$Pd(PPh_3)_4$], TlOEt, aq THF. d) $ZnMe_2$, 7 mol% [$Pd(PtBu_3)_2$], THF. e) nBu_4NF, THF. f) nBu_3SnH, 3 mol% [$PdCl_2(PPh_3)_2$], THF. g) 10 mol% [$PdCl_2(MeCN)_2$], $Ph_2PO_2N(nBu)_4$, DMF. h) LiOH, 6:2:1 THF:MeOH:H_2O. i) TFA. j) 2,4,6-$(Cl_3C_6H_2)COCl$, DMAP, Et_3N, THF. k) H_2SiF_6, aq CH_3CN. DMAP = 4-dimethylaminopyridine, dppf = 1,1′-bis(diphenylphosphino)ferrocenyl, pin = pinacol ($C_6H_4O_2$).

[1] P. T. Daniel, U. Koert, J. Schuppan, *Angew. Chem.* **2006**, *118*, 886 – 908; *Angew. Chem. Int. Ed.* **2006**, *45*, 872 – 893.

[2] a) K. C. Nicolaou, Y. Li, K. C. Fylaktakidou, H. J. Mitchell, K. Sugita, *Angew. Chem.* **2001**, *113*, 3972 – 3976; *Angew. Chem. Int. Ed.* **2001**, *40*, 3854 – 3857; b) K. C. Nicolaou, Y. Li, K. Sugita, H. Monenschein, P. Guntupalli, H. J. Mitchell, K. C. Fylaktakidou, D. Vourloumis, P. Giannakakou, A. O'Brate, *J. Am. Chem. Soc.* **2003**, *125*, 15443 – 15454; c) H. Wehlan, M. Dauber, M.-T. M. Fernaud, J. Schuppan, R. Mahrwald, B. Ziemer, M.-E. J. Garcia, U. Koert, *Angew. Chem.* **2004**, *116*, 4698 – 4702; *Angew. Chem. Int. Ed.* **2004**, *43*, 4597 – 4601; d) J. Schuppan, H. Wehlan, S. Keiper, U. Koert, *Angew. Chem.* **2001**, *113*, 2125 – 2128; *Angew. Chem. Int. Ed.* **2001**, *40*, 2063 – 2066; e) B. Wu, Q. Liu, G. A. Sulikowski, *Angew. Chem.* **2004**, *116*, 6841 – 6843; *Angew. Chem. Int. Ed.* **2004**, *43*, 6673 – 6675; f) M. T. Crimmins, H. S. Christie, K. Chaudhary, A. Long, *J. Am. Chem. Soc.* **2005**, *127*, 13810 – 13812; g) B. Wu, Q. Liu, B. Jin, T. Qu, G. A. Sulikowski, *Eur. J. Org. Chem.* **2006**, 277 – 284; h) J. Schuppan, H. Wehlan, S. Keiper, U. Koert, *Chem. Eur. J.* **2006**, *12*, 7364 – 7377; i) H. Wehlan, M. Dauber, M. T. M. Fernaud, J. Schuppan, S. Keiper, R. Mahrwald, M. E. J. Garcia, U. Koert, *Chem. Eur. J.* **2006**, *12*, 7378 – 7397; j) M. T. Crimmins, H. S. Christie, A. Long, K. Chaudhary, *Org. Lett.* **2009**, *11*, 831 – 834.

[3] a) L. M. Geary, P. G. Hultin, *Tetrahedron: Asymmetry* **2009**, *20*, 131 – 173; b) L. Jun, D. Menche, *Synthesis* **2009**, 2293 – 2315.

[4] a) S. G. Nelson, T. J. Peelen, Z. Wan, *J. Am. Chem. Soc.* **1999**, *121*, 9742 – 9743; b) S. G. Nelson, C. Zhu, X. Shen, *J. Am. Chem. Soc.* **2004**, *126*, 14 – 15; c) X. Shen, A. S. Wasmuth, J. Zhao, C. Zhu, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 7438 – 7439.

[5] A. Basha, M. Lipton, S. M. Weinreb, *Tetrahedron Lett.* **1977**, *18*, 4171 – 4172.

[6] H. Gu, W. M. Xu, T. H. Kinstle, *Tetrahedron Lett.* **2005**, *46*, 6449 – 6451.

[7] T. Mukaiyama, K. Banno, K. Naraska, *J. Am. Chem. Soc.* **1974**, *96*, 7503 – 7509.

[8] D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322 – 4343.

[9] a) D. W. Hart, T. F. Blackburn, J. Schwartz, *J. Am. Chem. Soc.* **1975**, *97*, 679 – 680; b) for an application in the total synthesis of apoptolidin A, see Ref. [2a,b].

[10] Alkenyl iodide **23** was prepared using the procedure reported for the corresponding bromide, see: M. Handa, K. A. Scheidt, M. Bossart, N. Zheng, W. R. Roush, *J. Org. Chem.* **2008**, *73*, 1031 – 1035.

[11] J. Takagi, K. Takahashi, T. Ishiyama, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 8001 – 8006.

[12] S. A. Frank, H. Chen, R. K. Kunz, M. J. Schnaderbeck, W. R. Roush, *Org. Lett.* **2000**, *2*, 2691 – 2694.

[13] a) X. Zeng, M. Qian, Q. Hu, E. Negishi, *J. Am. Chem. Soc.* **2003**, *125*, 13636 – 13637; b) X. Zeng, M. Qian, Q. Hu, E. Negishi, *Angew. Chem.* **2004**, *116*, 2309 – 2313; *Angew. Chem. Int. Ed.* **2004**, *43*, 2259 – 2263.

[14] a) H. X. Zhang, F. Guibé, G. Balavoine, *J. Org. Chem.* **1990**, *55*, 1857 – 1867; b) for an application in the total synthesis of apoptolidin A, see Ref. [2a,b].

[15] J. Srogl, G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1997**, *119*, 12376 – 12377.

[16] A. B. Smith III, S. Dong, *Org. Lett.* **2009**, *11*, 1099 – 1102.

[17] a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989 – 1993; b) M. Hikota, H. Tone, K. Horita, O. Yonemitsu, *Tetrahedron* **1990**, *46*, 4613 – 4628.

