Natural Products

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Total Synthesis of Tulearin C**

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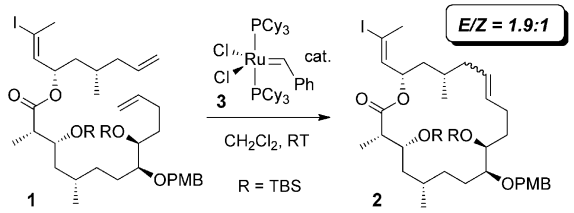
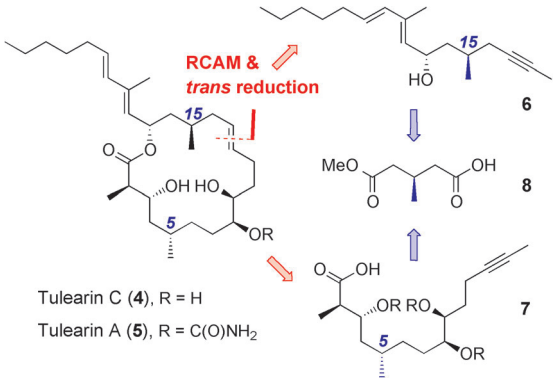
Ring-closing olefin metathesis (RCM) provides efficient access to carbo- and heterocycles of virtually all ring sizes, but usually affords mixtures of the corresponding *E*- and *Z*-configured cycloalkenes when applied to medium-sized or macrocyclic systems.[1,2] Although the product ratios are difficult to predict, the reversible nature of metathesis favors the thermodynamically more stable isomer, which is often the *E* alkene, in particular when "second generation" catalysts are used. However, inherently *E*-selective catalysts capable of overriding an insufficient or even unfavorable thermodynamic bias, are currently unknown.[3]

The critical implications of this lack of *E*-selective metathesis catalysts surface, for example, in an approach to tulearin A reported in the literature (Scheme 1).[4] The required 18-membered core structure **2** was formed from substrate **1** in an *E*/*Z* ratio of only 1.9:1, which could neither be improved by the use of more active catalysts nor by changing the peripheral protecting groups.[5]



Scheme 1. Stereo-unselective approach to a non-natural isomer of tulearin A based on RCM.[4] Cy = cyclohexyl, PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.

Challenged by this outcome, we sought to develop an alternative solution based on ring-closing alkyne metathesis (RCAM).[6,7] This transformation greatly benefits from the recent generation of highly active, exceedingly tolerant, and user-friendly catalysts.[8] They might allow tulearin C (**4**) to be assembled from two fragments, **6** and **7**, of similar size and complexity, both of which can be traced back to (*R*)-3-methyl glutarate monoester **8** (Scheme 2). Compound **4** is the least abundant member of a small family of macrolides isolated from a Madagascan *Fascaplysinopsis* sponge.[9] Although the limited supply prevented a detailed biological assessment, preliminary data showed that the sister compound tulearin A (**5**), endowed with a carbamate at the C8-OH group, exhibits strong and differential antiproliferative effects against human leukemia cell lines.[9]



Scheme 2. Structures of tulearin A and C, and retrosynthetic analysis of **4**.

Desymmetrization of the cheap dimethyl 3-methylglutarate (**9**) with the aid of pig liver esterase, followed by recrystallization of the cinchonidine salt furnished acid **8** in optically pure form (≥98% *ee*, 20 g single largest batch; Scheme 3).[10] This compound was then converted into lactone **10**, which served as a convenient building block for the northern and the southern sectors of tulearin C (**4**) alike.

The further elaboration of **10** into the alcohol segment **6** hinged upon a reductive elimination of the derived *gem*-dichloro olefin **11**.[11] Rather than employing lithium sand in THF as commonly practiced to generate terminal alkynes from substrates of this type,[12] we reasoned that the use of MeLi would allow us to prepare the required nonterminal alkyne **13** in a single operation.[13] It can be envisaged that the methyl chloride, generated by an initial metal–halogen exchange, might C-alkylate the lithium acetylide, derived from the vinylidene intermediate **12** primarily formed, provided that premature loss of this low-boiling compound (b.p. = −24 °C) can be avoided. Alternatively and more likely, MeLi could attack the carbenoid intermediate **12** directly.[14] Irrespective of the actual mechanism, which is currently under investigation, the desired nonterminal alkyne **13** was obtained in up to 90% yield upon exposure of compound **11** to excess MeLi in Et_2O or THF (Scheme 3 and Table 1).

Although the scope of this new method still needs to be explored in full detail, the examples compiled in Table 1 suggest that this alkylative elimination provides ready access to a variety of nonterminal alkynes. As expected, *n*-alkyllithium reagents other than MeLi can also be employed (entry 6). All dichloroalkenes derived from lactones with six

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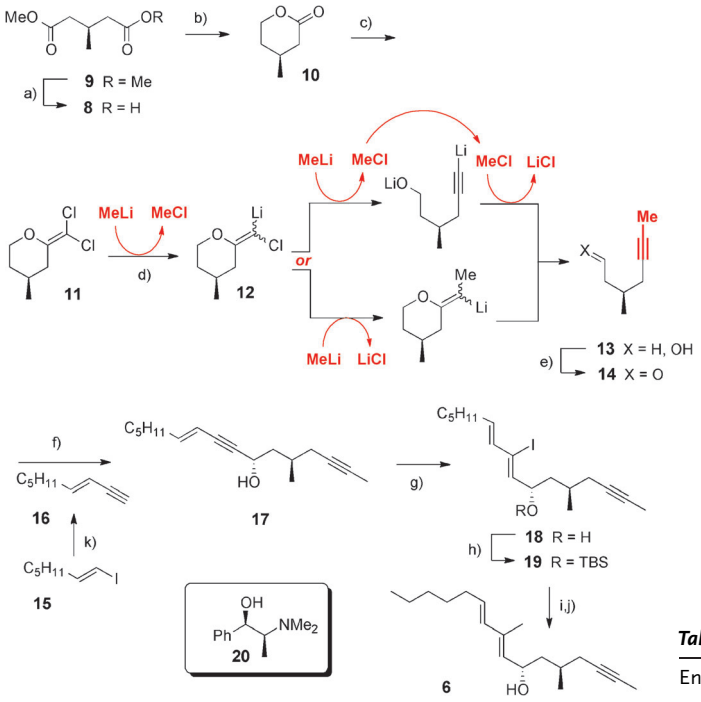


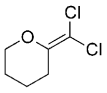
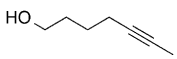
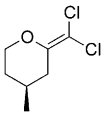
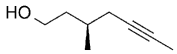
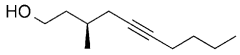
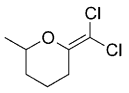
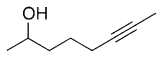
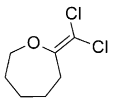
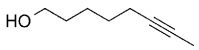
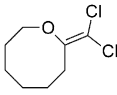
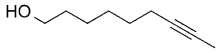
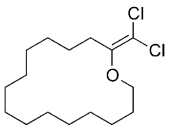
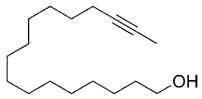
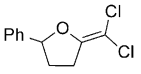
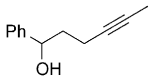
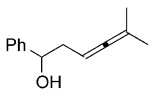
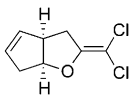
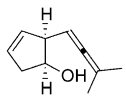
Scheme 3. a) i) Pig liver esterase, NaOH (1 M), MeOH, pH 7 buffer, 78%; ii) (−)-cinchonidine, aq. acetone, then aq. HCl (≥98% *ee*); b) i) aq. LiOH; ii) $LiBH_4$, THF; iii) aq. HCl, 92%; c) CCl_4, PPh_3, THF, reflux, 92%; d) MeLi, Et_2O, RT, 90%; e) Dess–Martin periodinane, CH_2Cl_2; f) **16**, $Zn(OTf)_2$, (−)-*N*-methyl ephedrine (**20**), $(iPr)_2NEt$, toluene, M.S. (3 Å), 57% (over both steps), d.r. = 98:2; g) i) Red-Al, Et_2O, M.S. (3 Å), 0 °C → RT; ii) I_2, −20 °C, 99%; h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 94%; i) Me_2Zn, $[(dppf)PdCl_2]\cdot CH_2Cl_2$ (5 mol%), THF, Et_3N, 65 °C, 90%; j) TBAF, THF, 96%; k) HC≡CMgBr, $[Pd(PPh_3)_4]$ (3 mol%), THF, 72%. dppf = 1,1′-bis(diphenylphosphino)ferrocene, M.S. = molecular sieves, Red-Al = sodium bis(2-methoxyethoxy)aluminium hydride, TBAF = tetra-*n*-butylammonium fluoride, TfO = trifluoromethanesulfonyloxy, THF = tetrahydrofuran.

or more ring atoms behaved uniformly well, even though the reaction times are long when the somewhat higher yielding diethyl ether is used as the solvent (compare entries 2 and 3, and 4 and 5). Interestingly however, a striking dependence on the solvent was observed for substrates derived from five-membered lactones: in Et_2O, the expected alkyne was formed as the major product (entry 11), whereas the use of THF led to a trisubstituted allene instead (entry 12). The additional example shown in entry 13 suggests that this competing pathway also holds preparative potential. It is assumed that allene formation occurs if the metal–halogen exchange leading to the alkyne is outperformed by allylic deprotonation; the necessary orbital overlap may be reached more easily by conformationally flexible furanoid substrates (Scheme 4).[15] This and other aspects are subject to ongoing studies.

Oxidation of alcohol **13** to the corresponding aldehyde **14** followed by asymmetric addition of enyne **16** under the aegis of (−)-*N*-methyl-ephedrine (**20**)[16] gave propargyl alcohol **17** in a diastereomeric ratio of 98:2 (Scheme 3). Treatment of this product with Red-Al in Et_2O[17] followed by an iodine quench[18] afforded the sensitive dienyl iodide **18**, which could be cross-coupled with Me_2Zn in the presence of $[PdCl_2(dppf)]$ as the catalyst after temporary protection of the OH group.[19,20] It was imperative though to use fresh Me_2Zn to avoid partial isomerization and/or protodeiodination during the Negishi reaction of **19**. Under this condition, the required alcohol segment **6** was obtained in good yield and excellent purity.

Lactone **10** also served as a convenient starting material for the preparation of the acid sector of tulearin C (Scheme 5). Specifically, a Claisen condensation with EtOAc followed by asymmetric reduction of the resulting β-ketoester **21** (in equilibrium with the hemiketal form) paved a scalable route to product **22**; the best result (d.r. = 99:1) was obtained with (*R*)-SYNPHOS (**31**) as the ligand in the hydrogenation step.[21] Since all attempts to C-methylate the trianion derived from **22** were unsatisfactory, the primary hydroxy group was protected and the resulting TBDPS ether **23** subjected

Table 1: Alkylative elimination of lactone-derived dichoroalkenes.[a]

Entry	Dichloroalkene[b]	Solvent	*t* [h]	Alkyne	Yield [%]
1		THF	8		60[c]
2		THF	2		80
3		Et_2O	48		93
4		THF	2[d]		75[c]
5		Et_2O	48		90
6		Et_2O	5		74[e]
7		THF	4		88
8		THF	1		88
9		THF	4		84
10		THF	4		80
11		Et_2O	72		60[f]
12		THF	2		58[g]
13		THF	1		84

[a] All reactions were performed using 5 equivalents of MeLi (1.8 M in Et_2O) at ambient temperature, unless stated otherwise. [b] Prepared according to Ref. [11]. [c] Using only 2.1 equivalents of MeLi. [d] The mixture was warmed from −78 °C to ambient temperature over the course of 30 min and then stirred at RT for 1.5 h. [e] Using *n*BuLi (1.6 M in hexane). [f] Together with 10% of the corresponding allene. [g] Together with 25% of the corresponding alkyne.

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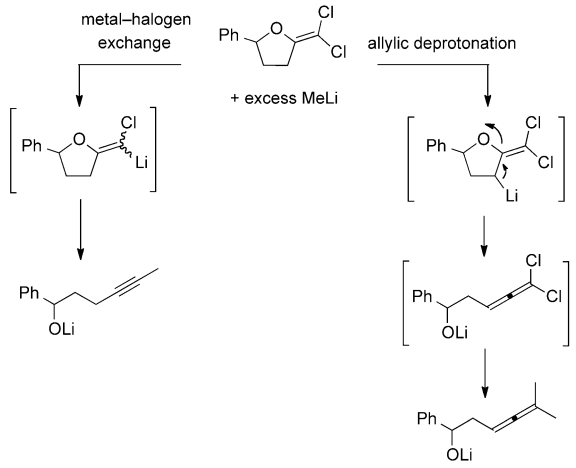
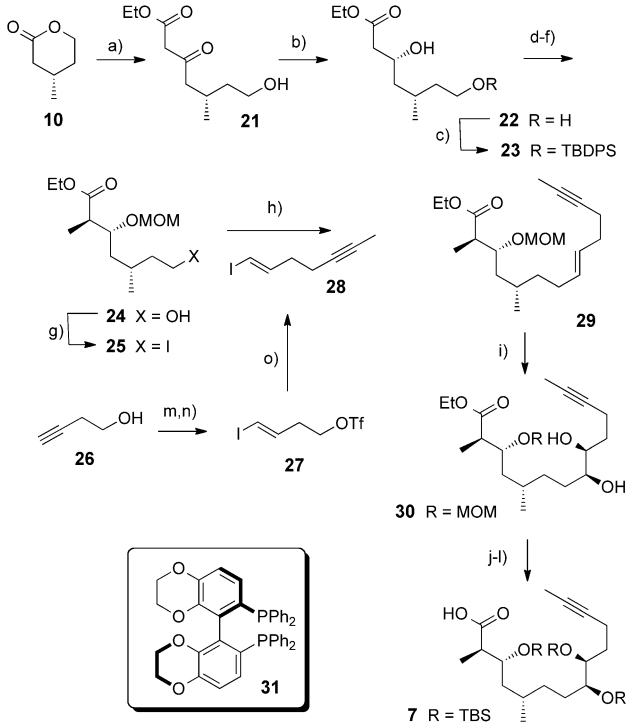


Scheme 4. Possible mechanistic explanation for the dichotomy in the behavior of dichloroolefin substrates derived from five-membered lactones.



Scheme 5. a) EtOAc, LDA, THF, −78 °C, 90%; b) H_2 (10 atm), $RuCl_3$ (1 mol%), (*R*)-SYNPHOS (**31**; 1 mol%), EtOH, 80 °C, 89% (d.r. = 99:1); c) TBDPSCl, Et_3N, DMAP cat., CH_2Cl_2, 95%; d) LDA, THF/DMPU, −78 °C→−40 °C, then MeI, −78 °C→0 °C, 79% (d.r. = 85:15); e) MOMCl, $(iPr)_2NEt$, CH_2Cl_2, reflux, 97%; f) TBAF, THF, 83%; g) I_2, PPh_3, imidazole, CH_2Cl_2, 90%; h) i) Zn/Cu, toluene/dimethylacetamide (19:1), 70 °C; ii) $[Pd(PPh_3)_4]$ (5 mol%), **28**, 60 °C, 72%; i) AD-mix-α, $MeSO_2NH_2$, *t*BuOH, H_2O, 0 °C, 83%; j) HCl, MeOH, 99%; k) TBSOTf, 2,6-lutidine, CH_2Cl_2, 90%; l) aq. LiOH, MeOH/THF (1:1), 99%; m) DIBAL-H, Cp_2ZrCl_2, THF, RT, then I_2, −78 °C, 80%; n) Tf_2O, CH_2Cl_2, pyridine, −20 °C→RT; o) propynyllithium, THF, −20 °C→0 °C, 76% (over both steps). Cp = cyclopentadienyl, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMPU = 1,3-dimethyltetrahydro-2-pyrimidinone, LDA = lithium diisopropylamide, MOM = methoxymethyl, TBDPS = *tert*-butyldiphenylsilyl, SYNPHOS = [(5,6),-(5′,6′)-bis(ethylenedioxy)biphenyl-2,2′-diyl]bis(diphenylphosphine).

to a standard Fráter–Seebach alkylation.[22] Although the diastereoselectivity was moderate (d.r. = 85:15), isomerically pure product could be secured by routine flash chromatography at the stage of compound **24**. Conversion into the corresponding iodide preceded an advanced Negishi coupling of the derived organozinc reagent with alkenyl iodide **28**.[23] This coupling partner was best prepared by a zirconocene-catalyzed hydroalumination/iodination of butynol **26**[24] followed by alkylation of the rather unstable triflate **27** with excess propynyllithium. A Sharpless dihydroxylation[25] of the alkene site in **29** followed by routine protecting group management led to the required acid **7** in good yield.

Esterification of **6** and **7** set the stage for the crucial ring closure by RCAM, which proceeded smoothly and with a remarkable rate when catalyzed by the alkylidyne complex **35** (Scheme 6).[8,26] However, a reaction temperature of 50 °C was necessary to override the ring strain of the incipient cycloalkyne **33**. This outcome attests to the excellent performance of the latest generation of alkyne metathesis catalysts, which owe their activity and selectivity to the well-balanced Lewis acidic character imposed on the high valent Mo center by the triarylsilanolate ligands.[27] Moreover, these complexes can be rendered air stable by complexation with phenanthroline, which greatly facilitates their handling.[8]

The subsequent conversion of compound **33** into the corresponding *E* alkene required some optimization. Despite our good experiences with $BnMe_2SiH$ as a reagent in ruthenium-catalyzed *trans*-hydrosilylation reactions,[28–30] applications to the current target met with limited success. The addition step was surprisingly inefficient and the protodesilylation troublesome, requiring the use of excess TBAF at ≥ 50 °C, which endangered the integrity of the aldol substructure of this delicate product; attempted desilylations under acidic conditions caused complex transannular rearrangements.[31] Gratifyingly though, the use of $(EtO)_3SiH$ allowed both problems to be solved. The *trans* addition catalyzed by $[Cp^*Ru(MeCN)_3]PF_6$ progressed smoothly, provided the reaction was performed neat. The resulting regioisomeric alkenylsiloxanes **34** were immediately protodesilylated with AgF as a carbophilic fluoride source,[29] followed by cleavage of the peripheral TBS ethers with TBAF. Careful inspection by NMR spectroscopy and HPLC showed that no other isomer integrating to more than 3% was present in the crude product, from which analytically pure tulearin C (**4**) was isolated in up to 60% yield over three steps.[31b] The spectral data matched well, and the impeccable purity of the synthetic samples favorably compared to the authentic natural product (see the Supporting Information).

Although the major application of alkyne metathesis in the past was the stereoselective preparation of *Z*-alkenes by a Lindlar-type semireduction of the cycloalkynes primarily formed,[7,32] it now becomes increasingly clear that this method also excels in the *E*-alkene series.[30] This notion is showcased by the stereoselective tulearin synthesis outlined above, which surpasses the approach based on conventional RCM[4] as long as no inherently *E*-selective alkene metathesis

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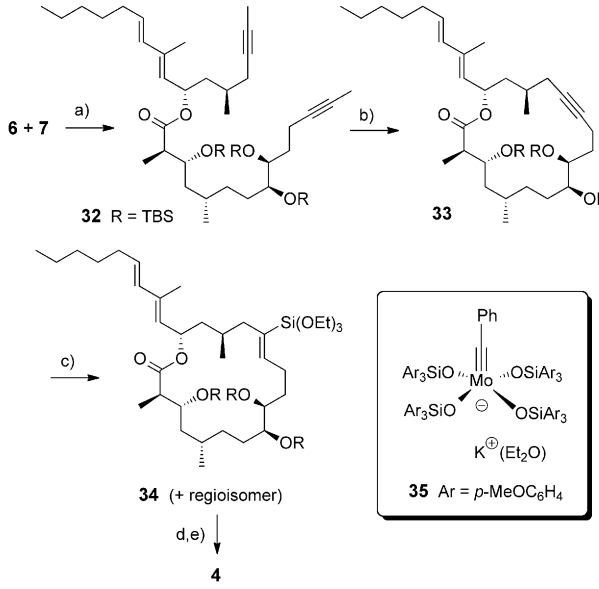

Scheme 6. a) EDC·HCl, DMAP, CH_2Cl_2, 98%; b) **35** (4 mol%), toluene (2 mM), M.S. (5 Å), 50°C, 96%; c) $(EtO)_3SiH$, $[Cp^*Ru(MeCN)_3]PF_6$ (10 mol%), 0°C; d) AgF, THF/MeOH/H_2O (10:9:1); e) TBAF, THF, 43–60% (over three steps). Cp* = pentamethylcyclopentadienyl, EDC = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide.

catalysts are available. Since (cyclo)alkynes also provide ample opportunity for functionalization by post-metathesis transformations other than semireductions,[33] the outreach of this method is significant.

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Keywords: alkyne metathesis · alkynes · hydrosilylation · natural products · total synthesis

[1] a) *Handbook of Metathesis, Vol. 1–3* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564–4601; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490–4527; c) A. H. Hoveyda, A. R. Zhugralin, *Nature* **2007**, *450*, 243–251; d) A. Fürstner, *Chem. Commun.* **2011**, *47*, 6505–6511; e) J. Prunet, *Angew. Chem.* **2003**, *115*, 2932–2936; *Angew. Chem. Int. Ed.* **2003**, *42*, 2826–2830.

[2] a) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; b) A. Fürstner, K. Langemann, *Synthesis* **1997**, 792–803; c) A. Fürstner, K. Langemann, *J. Org. Chem.* **1996**, *61*, 3942–3943.

[3] In contrast, progress has been made in the design of *Z*-selective catalysts, see: a) S. J. Meek, R. V. O'Brien, J. Llaveria, R. R. Schrock, A. H. Hoveyda, *Nature* **2011**, *471*, 461–466; b) A. J. Jiang, Y. Zhao, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 16630–16631; c) K. Endo, R. H. Grubbs, *J. Am. Chem. Soc.* **2011**, *133*, 8525–8527, and references therein.

[4] A non-natural isomer had been targeted in this study because the correct stereostructure of tulearin A was disclosed only after the synthesis had been completed, see: A. L. Mandel, V. Bellosta, D. P. Curran, J. Cossy, *Org. Lett.* **2009**, *11*, 3282–3285.

[5] Seemingly remote protecting groups can exert considerable influence on the outcome of RCM macrocyclizations, see: a) D. Meng, D.-S. Su, A. Balog, P. Bertinato, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zeng, T.-C. Chou, L. He, S. B. Horwitz, *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734; b) A. Fürstner, T. Dierkes, O. R. Thiel, G. Blanda, *Chem. Eur. J.* **2001**, *7*, 5286–5298.

[6] a) A. Fürstner, G. Seidel, *Angew. Chem.* **1998**, *110*, 1758–1760; *Angew. Chem. Int. Ed.* **1998**, *37*, 1734–1736; b) A. Fürstner, O. Guth, A. Rumbo, G. Seidel, *J. Am. Chem. Soc.* **1999**, *121*, 11108–11113.

[7] a) A. Fürstner, P. W. Davies, *Chem. Commun.* **2005**, 2307–2320; b) W. Zhang, J. S. Moore, *Adv. Synth. Catal.* **2007**, *349*, 93–120; c) R. R. Schrock, C. Czekelius, *Adv. Synth. Catal.* **2007**, *349*, 55–77.

[8] a) J. Heppekausen, R. Stade, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 11045–11057; b) M. Bindl, R. Stade, E. K. Heilmann, A. Picot, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2009**, *131*, 9468–9470.

[9] a) A. Bishara, A. Rudi, I. Goldberg, M. Aknin, Y. Kashman, *Tetrahedron Lett.* **2009**, *50*, 3820–3822; b) A. Bishara, A. Rudi, M. Aknin, D. Neumann, N. Ben-Califa, Y. Kashman, *Org. Lett.* **2008**, *10*, 153–156.

[10] a) L. K. P. Lam, R. A. H. F. Hui, J. B. Jones, *J. Org. Chem.* **1986**, *51*, 2047–2050; b) L. Poppe, L. Novák, P. Kolonits, Á. Bata, C. Szántay, *Tetrahedron* **1988**, *44*, 1477–1487.

[11] M. Lakhrissi, Y. Chapleur, *J. Org. Chem.* **1994**, *59*, 5752–5757.

[12] a) J. S. Yadav, V. Prahlad, M. C. Chander, *J. Chem. Soc. Chem. Commun.* **1993**, 137–138; b) J. S. Yadav, C. Venugopal, *Synlett* **2007**, 2262–2266.

[13] We are aware of only one example in which a *gem*-diiodoalkenyl ether was directly transformed into a nonterminal alkyne, see: R. M. Black, G. B. Gill, *J. Chem. Soc. Perkin Trans. 1* **1980**, 410–418.

[14] Alkali metal vinylidene-type carbenoids react with nucleophiles by a metal-assisted ionization mechanism: a) G. Köbrich, F. Ansari, *Chem. Ber.* **1967**, *100*, 2011–2020; b) M. Duraisamy, H. M. Walborsky, *J. Am. Chem. Soc.* **1984**, *106*, 5035–5037; c) M. Topolski, M. Duraisamy, J. Rachon, J. Gawronski, K. Gawronska, V. Goedken, H. M. Walborsky, *J. Org. Chem.* **1993**, *58*, 546–555.

[15] For deprotonations of carbohydrate-derived dichloroolefins, see: A. Bandzouzi, Y. Chapleur, *Carbohydr. Res.* **1987**, *171*, 13–24.

[16] a) D. Boyall, D. E. Frantz, E. M. Carreira, *Org. Lett.* **2002**, *4*, 2605–2606; b) D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.

[17] S. E. Denmark, T. K. Jones, *J. Org. Chem.* **1982**, *47*, 4595–4597.

[18] Attempts to trap the organoaluminum intermediate directly with MeI were unsuccessful.

[19] E. Negishi, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 233–257.

[20] a) X. Zeng, M. Qian, Q. Hu, E. Negishi, *Angew. Chem.* **2004**, *116*, 2309–2313; *Angew. Chem. Int. Ed.* **2004**, *43*, 2259–2263; b) K. C. Nicolaou, A. L. Nold, R. R. Milburn, C. S. Schindler, *Angew. Chem.* **2006**, *118*, 6677–6682; *Angew. Chem. Int. Ed.* **2006**, *45*, 6527–6532.

[21] a) J. Madec, X. Pfister, P. Phansavath, V. Ratovelomanana-Vidal, J.-P. Genêt, *Tetrahedron* **2001**, *57*, 2563–2568; b) C. Roche, N. Desroy, M. Haddad, P. Phansavath, J.-P. Genêt, *Org. Lett.* **2008**, *10*, 3911–3914.

[22] a) G. Fráter, U. Müller, W. Günther, *Tetrahedron* **1984**, *40*, 1269–1277; b) D. Seebach, J. Aebi, D. Wasmuth, *Org. Synth.* **1985**, *63*, 109–119.

[23] a) Y. Tamaru, H. Ochiai, T. Nakamura, K. Tsubaki, Z. Yoshida, *Tetrahedron Lett.* **1985**, *26*, 5559–5562; b) Y. Tamaru, H. Ochiai, T. Nakamura, Z. Yoshida, *Tetrahedron Lett.* **1986**, *27*, 955–958; c) C. Aïssa, R. Riveiros, J. Ragot, A. Fürstner, *J. Am. Chem. Soc.* **2003**, *125*, 15512–15520.

[24] Z. Huang, E. Negishi, *Org. Lett.* **2006**, *8*, 3675–3678.

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[25] R. A. Johnson, K. B. Sharpless in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, pp. 357 – 398.

[26] Complex **35** bearing *p*-methoxyphenyl rather than unsubstituted phenyl groups allowed for easier separation of the silanoles from the product during workup. The activity of the catalyst remains largely unchanged by this peripheral modification.

[27] For other applications in total synthesis, see Ref. [30,33c] and the following: a) V. Hickmann, M. Alcarazo, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 11042 – 11044; b) V. Hickmann, A. Kondoh, B. Gabor, M. Alcarazo, A. Fürstner, *J. Am. Chem. Soc.* **2011**, *133*, 13471 – 13480.

[28] For the development of the *trans*-hydrosilylation method, see: a) B. M. Trost, Z. T. Ball, T. Jöge, *J. Am. Chem. Soc.* **2002**, *124*, 7922 – 7923; b) B. M. Trost, Z. T. Ball, *J. Am. Chem. Soc.* **2001**, *123*, 12726 – 12727; c) B. M. Trost, Z. T. Ball, *Synthesis* **2005**, 853 – 887.

[29] For the first application to the formation of macrocyclic *E*-alkenes, see: a) A. Fürstner, K. Radkowski, *Chem. Commun.* **2002**, 2182 – 2183; b) F. Lacombe, K. Radkowski, G. Seidel, A. Fürstner, *Tetrahedron* **2004**, *60*, 7315 – 7324; c) A. Fürstner, M. Bonnekessel, J. T. Blank, K. Radkowski, G. Seidel, F. Lacombe, B. Gabor, R. Mynott, *Chem. Eur. J.* **2007**, *13*, 8762 – 8783.

[30] K. Micoine, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 14064 – 14066.

[31] a) Details will be reported in a future full paper; b) in this context it is noteworthy that the synthesis of the non-natural isomer of tulearin A reported in Ref. [4] faced significant problems in the final deprotection, which was accomplished with TBAF in THF in only 19%.

[32] For representative cases, see: a) A. Fürstner, K. Grela, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **2000**, *122*, 11799 – 11805; b) A. Fürstner, K. Radkowski, J. Grabowski, C. Wirtz, R. Mynott, *J. Org. Chem.* **2000**, *65*, 8758 – 8762; c) A. Fürstner, C. Mathes, K. Grela, *Chem. Commun.* **2001**, 1057 – 1059; d) A. Fürstner, L. Turet, *Angew. Chem.* **2005**, *117*, 3528 – 3532; *Angew. Chem. Int. Ed.* **2005**, *44*, 3462 – 3466; e) A. Fürstner, M. Bindl, L. Jean, *Angew. Chem.* **2007**, *119*, 9435 – 9438; *Angew. Chem. Int. Ed.* **2007**, *46*, 9275 – 9278; f) A. Fürstner, D. De Souza, L. Turet, M. D. B. Fenster, L. Parra-Rapado, C. Wirtz, R. Mynott, C. W. Lehmann, *Chem. Eur. J.* **2007**, *13*, 115 – 134; g) V. V. Vintonyak, M. E. Maier, *Angew. Chem.* **2007**, *119*, 5301 – 5303; *Angew. Chem. Int. Ed.* **2007**, *46*, 5209 – 5211; h) B. J. Smith, G. A. Sulikowski, *Angew. Chem.* **2010**, *122*, 1643 – 1646; *Angew. Chem. Int. Ed.* **2010**, *49*, 1599 – 1602; i) M. G. Nilson, R. L. Funk, *Org. Lett.* **2010**, *12*, 4912 – 4915; j) A. F. Kyle, P. Jakubec, D. M. Cockfield, E. Cleator, J. Skidmore, D. J. Dixon, *Chem. Commun.* **2011**, *47*, 10037 – 10039.

[33] For the conversion of cycloalkynes formed by RCAM into products other than stereodefined alkenes, see: a) A. Fürstner, A.-S. Castanet, K. Radkowski, C. W. Lehmann, *J. Org. Chem.* **2003**, *68*, 1521 – 1528; b) A. Fürstner, O. Larionov, S. Flügge, *Angew. Chem.* **2007**, *119*, 5641 – 5644; *Angew. Chem. Int. Ed.* **2007**, *46*, 5545 – 5548; c) S. Benson, M.-P. Collin, A. Arlt, B. Gabor, R. Goddard, A. Fürstner, *Angew. Chem.* **2011**, *123*, 8898 – 8903; *Angew. Chem. Int. Ed.* **2011**, *50*, 8739 – 8744.

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