

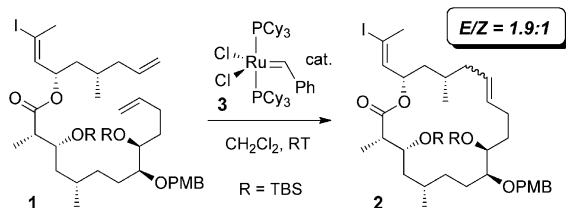
## Natural Products

## Total Synthesis of Tulearin C\*\*

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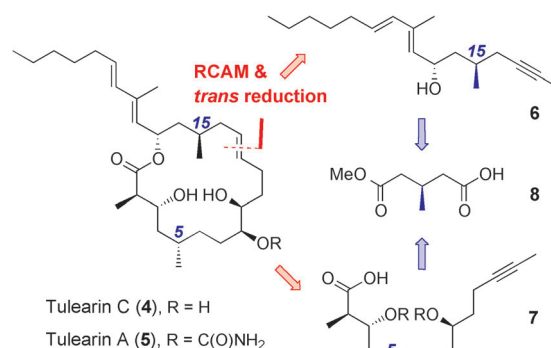
Ring-closing olefin metathesis (RCM) provides efficient access to carbo- and heterocycles of virtually all ring sizes, but usually affords mixtures of the corresponding *E*- and *Z*-configured cycloalkenes when applied to medium-sized or macrocyclic systems.<sup>[1,2]</sup> Although the product ratios 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.<sup>[3]</sup>

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).<sup>[4]</sup> 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.<sup>[5]</sup>



**Scheme 1.** Stereo-unselective approach to a non-natural isomer of tulearin A based on RCM.<sup>[4]</sup> 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).<sup>[6,7]</sup> This transformation greatly benefits from the recent generation of highly active, exceedingly tolerant, and user-friendly catalysts.<sup>[8]</sup> 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.<sup>[9]</sup> Although the



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

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.<sup>[9]</sup>

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 ( $\geq 98\%$  ee, 20 g single largest batch; Scheme 3).<sup>[10]</sup> 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.

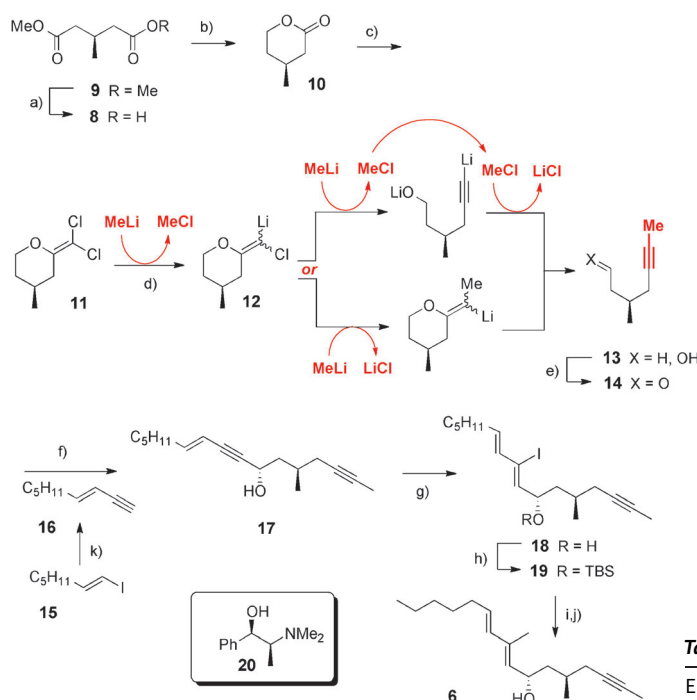
The further elaboration of **10** into the alcohol segment **6** hinged upon a reductive elimination of the derived *gem*-dichloro olefin **11**.<sup>[11]</sup> Rather than employing lithium sand in THF as commonly practiced to generate terminal alkynes from substrates of this type,<sup>[12]</sup> we reasoned that the use of MeLi would allow us to prepare the required nonterminal alkyne **13** in a single operation.<sup>[13]</sup> 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. =  $-24^\circ\text{C}$ ) can be avoided. Alternatively and more likely, MeLi could attack the carbenoid intermediate **12** directly.<sup>[14]</sup> 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<sub>2</sub>O 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*-alkyl-lithium 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 ( $\geq 98\%$  ee); b) i) aq. LiOH; ii) LiBH<sub>4</sub>, THF; iii) aq. HCl, 92%; c) CCl<sub>4</sub>, PPh<sub>3</sub>, THF, reflux, 92%; d) MeLi, Et<sub>2</sub>O, RT, 90%; e) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>; f) **16**, Zn(OTf)<sub>2</sub>, (–)-*N*-methyl ephedrine (**20**), (iPr)<sub>2</sub>NH, toluene, M.S. (3 Å), 57% (over both steps), d.r. = 98:2; g) i) Red-Al, Et<sub>2</sub>O, M.S. (3 Å), 0°C → RT; ii) I<sub>2</sub>, –20°C, 99%; h) TBSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 94%; i) Me<sub>2</sub>Zn, [(dppf)PdCl<sub>2</sub>].CH<sub>2</sub>Cl<sub>2</sub> (5 mol%), THF, Et<sub>3</sub>N, 65°C, 90%; j) TBAF, THF, 96%; k) HC≡CMgBr, [Pd(PPh<sub>3</sub>)<sub>4</sub>] (3 mol%), THF, 72%. dppf = 1,1'-bis(diphenylphosphino)ferrocene, M.S. = molecular sieves, Red-Al = sodium bis(2-methoxyethoxy)aluminum 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<sub>2</sub>O, 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).<sup>[15]</sup> 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**)<sup>[16]</sup> gave propargyl alcohol **17** in a diastereomeric ratio of 98:2 (Scheme 3). Treatment of this product with Red-Al in Et<sub>2</sub>O<sup>[17]</sup> followed by an iodine quench<sup>[18]</sup> afforded the sensitive dienyl iodide **18**, which

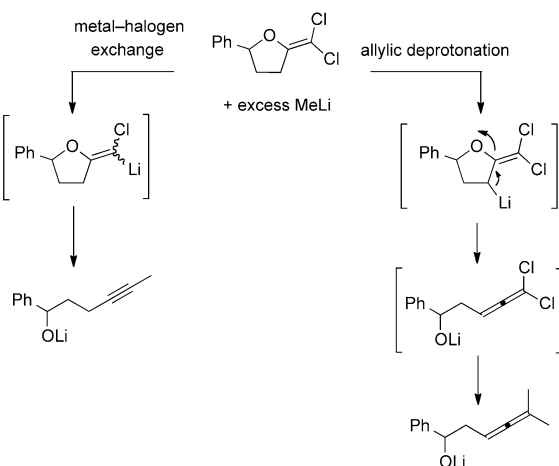
could be cross-coupled with Me<sub>2</sub>Zn in the presence of [PdCl<sub>2</sub>(dppf)] as the catalyst after temporary protection of the OH group.<sup>[19,20]</sup> It was imperative though to use fresh Me<sub>2</sub>Zn to avoid partial isomerization and/or proto-deiodination during the Negishi reaction 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 tularin 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.<sup>[21]</sup> 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.<sup>[a]</sup>

| Entry | Dichloroalkene <sup>[b]</sup> | Solvent           | t [h]            | Alkyne                                 | Yield [%]         |
|-------|-------------------------------|-------------------|------------------|----------------------------------------|-------------------|
| 1     |                               | THF               | 8                | HO(CH <sub>2</sub> ) <sub>4</sub> C≡CH | 60 <sup>[c]</sup> |
| 2     |                               | THF               | 2                | HO(CH <sub>2</sub> ) <sub>4</sub> C≡CH | 80                |
| 3     |                               | Et <sub>2</sub> O | 48               | HO(CH <sub>2</sub> ) <sub>4</sub> C≡CH | 93                |
| 4     |                               | THF               | 2 <sup>[d]</sup> | HO(CH <sub>2</sub> ) <sub>4</sub> C≡CH | 75 <sup>[c]</sup> |
| 5     |                               | Et <sub>2</sub> O | 48               | HO(CH <sub>2</sub> ) <sub>4</sub> C≡CH | 90                |
| 6     |                               | Et <sub>2</sub> O | 5                | HO(CH <sub>2</sub> ) <sub>4</sub> C≡CH | 74 <sup>[e]</sup> |
| 7     |                               | THF               | 4                | HO(CH <sub>2</sub> ) <sub>4</sub> C≡CH | 88                |
| 8     |                               | THF               | 1                | HO(CH <sub>2</sub> ) <sub>4</sub> C≡CH | 88                |
| 9     |                               | THF               | 4                | HO(CH <sub>2</sub> ) <sub>4</sub> C≡CH | 84                |
| 10    |                               | THF               | 4                | HO(CH <sub>2</sub> ) <sub>4</sub> C≡CH | 80                |
| 11    |                               | Et <sub>2</sub> O | 72               | PhCH(OH)CH <sub>2</sub> C≡CH           | 60 <sup>[f]</sup> |
| 12    |                               | THF               | 2                | PhCH(OH)CH <sub>2</sub> C≡CH           | 58 <sup>[g]</sup> |
| 13    |                               | THF               | 1                | PhCH(OH)CH <sub>2</sub> C≡CH           | 84                |

[a] All reactions were performed using 5 equivalents of MeLi (1.8 M in Et<sub>2</sub>O) 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.

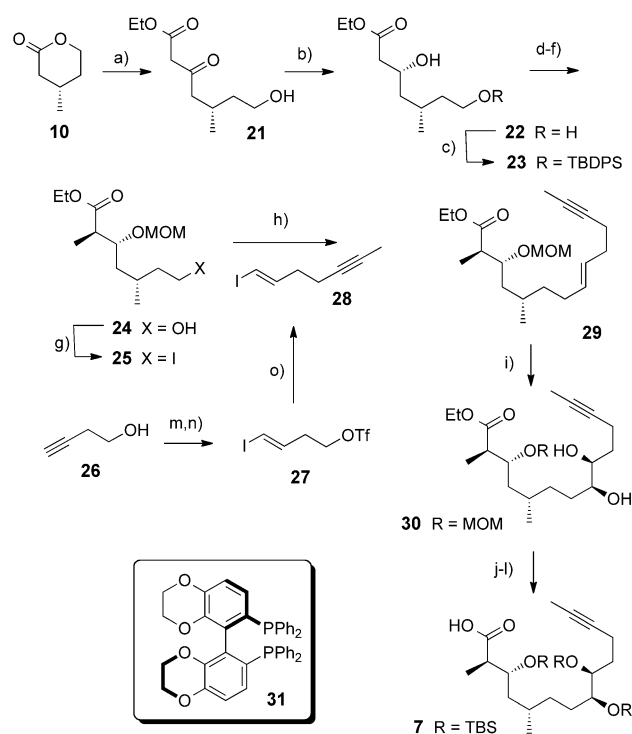


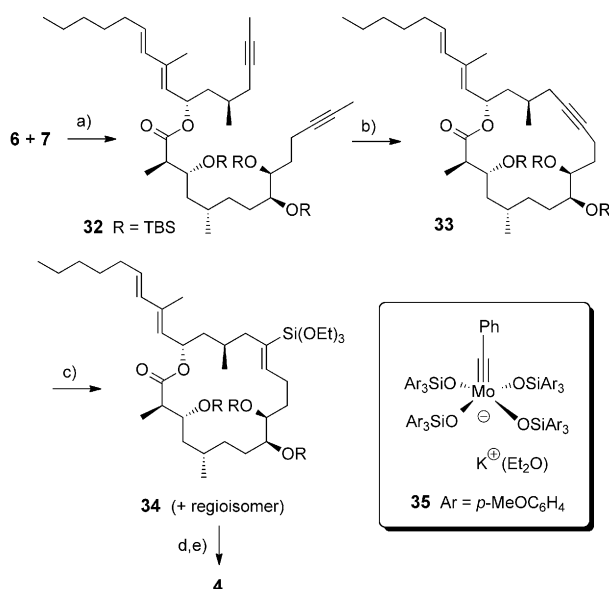
**Scheme 4.** Possible mechanistic explanation for the dichotomy in the behavior of dichloroolefin substrates derived from five-membered lactones.

to a standard Fráter–Seebach alkylation.<sup>[22]</sup> 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**.<sup>[23]</sup> This coupling partner was best prepared by a zirconocene-catalyzed hydroalumination/iodination of butynol **26**<sup>[24]</sup> followed by alkylation of the rather unstable triflate **27** with excess propynyllithium. A Sharpless dihydroxylation<sup>[25]</sup> 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).<sup>[8,26]</sup> 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.<sup>[27]</sup> Moreover, these complexes can be rendered air stable by complexation with phenanthroline, which greatly facilitates their handling.<sup>[8]</sup>

The subsequent conversion of compound **33** into the corresponding *E* alkene required some optimization. Despite our good experiences with  $\text{BnMe}_2\text{SiH}$  as a reagent in ruthenium-catalyzed *trans*-hydrosilylation reactions,<sup>[28–30]</sup> 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  $\geq 50^\circ\text{C}$ , which endangered the integrity of the aldol substructure of this delicate product; attempted desilylations under acidic conditions caused complex transannular rearrangements.<sup>[31]</sup> Gratifyingly though, the use of  $(\text{EtO})_3\text{SiH}$  allowed both problems to be solved. The *trans* addition catalyzed by  $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$  progressed smoothly, provided the reaction was performed neat. The resulting





**Scheme 6.** a) EDC-HCl, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 98%; b) **35** (4 mol %), toluene (2 mM), M.S. (5 Å), 50°C, 96%; c) (EtO)<sub>3</sub>SiH, [Cp\*Ru(MeCN)<sub>3</sub>]PF<sub>6</sub> (10 mol %), 0°C; d) AgF, THF/MeOH/H<sub>2</sub>O (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,<sup>[33]</sup> the outreach of this method is significant.

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- [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.