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Total Synthesis of Callyspongiolide, Part 2: The Ynoate Metathesis / *cis*-Reduction Strategy

Bernhard Wölfl, Guillaume Mata, and Alois Fürstner*

Abstract: The macrocyclic core of the cytotoxic marine natural product callyspongiolide (**1**) was forged by ring closing alkyne metathesis (RCAM) of an ynoate precursor using a molybdenum alkylidyne complex endowed with triarylsilanolate ligands as the catalyst. This result is remarkable in view of the failed attempts documented in the literature at converting electron deficient alkynes with the aid of more classical catalysts. The subsequent *Z*-selective semi-reduction of the resulting cycloalkyne by hydrogenation over nickel boride required careful optimization in order to minimize overreduction and competing dehalogenation of the compound's alkenyl iodide terminus as needed for final attachment of the side chain of **1** by Sonogashira coupling. The required cyclization precursor itself was prepared via Kocienski olefination.

Introduction

The marine macrolide callyspongiolide (**1**) encodes promising biological activity in a rather unique molecular framework.[1] Most notably, the compound's high cytotoxicity against different human cancer cell lines seems to be the result of a caspase-independent and hence probably non-apoptotic mode of action. Three independent total syntheses of this target were reported to date,[2,3,4,5] which corrected the absolute configuration originally attributed to the macrolide core of **1** by the isolation team and firmly established the configuration of the C21 chiral center in the side chain, which had defied unambiguous assignment before.[1]

For our longstanding interest in bioactive marine natural products,[6] we wished to develop an independent access route to this promising lead compound. As reported in the accompanying paper,[7] our approach had originally predicated on the formation of the macrocyclic ring by ring closing alkyne metathesis (RCAM)[8,9] at the C10-C11 bond followed by *trans*-reduction of the cycloalkyne primarily formed (**D** $\rightarrow$ **C** $\rightarrow$ **A**) (Scheme 1). Whereas the metathesis step worked nicely, the projected *trans*-addition of R_3EH (E = Sn, Si) was unsatisfactory,[10,11] most likely because the methyl branches adjacent to the triple bond in **C** prevent reactive encounter of the sterically hindered substrate with the required bulky [Cp*Ru]-based catalyst (Cp* = pentamethylcyclopentadienyl).[12]

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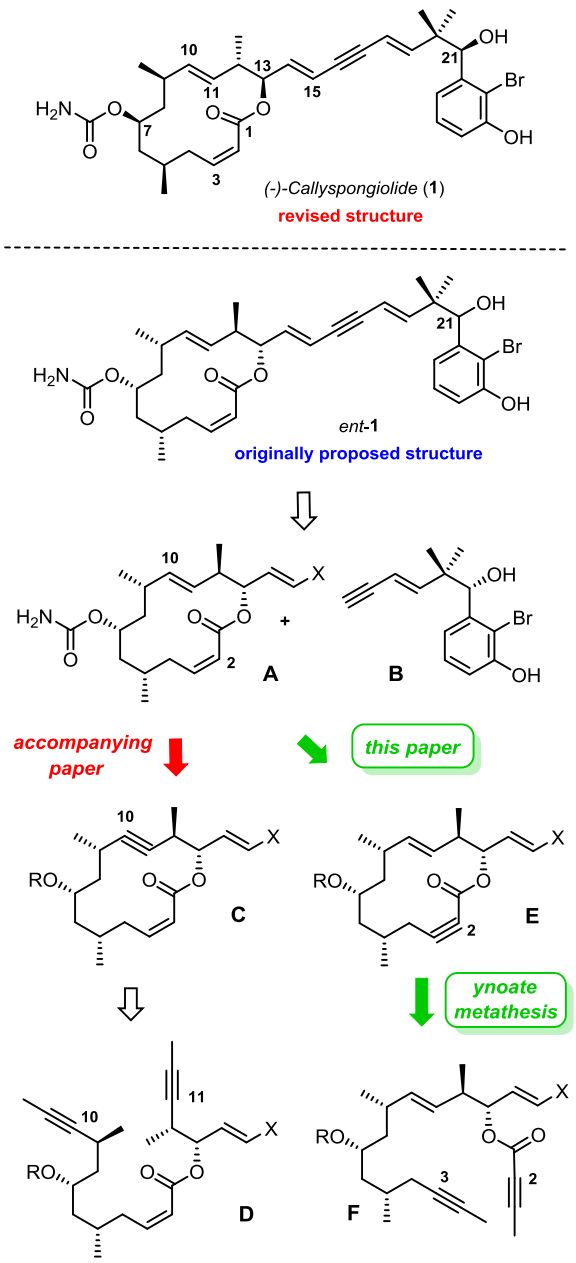

Scheme 1. Two approaches to callyspongiolide based on RCAM followed by semi-reduction; R = generic protecting group; X = halide; the bent drawing of the alkyne units throughout this paper is for convenience only and has no physical meaning

Confronted with this impasse, the synthesis blueprint was adjusted such that the *Z*-configured enoate became the strategic site of disconnection (Scheme 1). This structural motif might be formed by RCAM of an alkynoate precursor followed by ordinary Lindlar-type reduction (**F** → **E** → **A**). While the second step of this approach was deemed fairly safe in view of the plethora of canonical *Z*-selective semi-hydrogenation reactions (and synthetic equivalents thereof) known in the literature,[13,14] the projected ring closure of an ynoate derivative actually bore considerable risk. The very few attempted metathesis reactions to substrates of this type using the classical Schrock catalyst [(*t*BuO)$_3$W≡CC(Me$_3$)] had invariably failed.[15,16] Only after the advent of molybdenum

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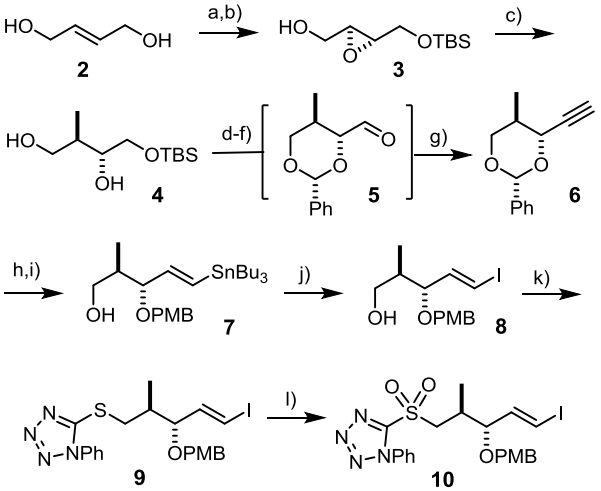
alkylidynes endowed with triarylsilanolate ligands as a new generation of catalysts with a largely improved application profile[17,18] became ynoate ring closure possible. The few recorded examples, however, are hardly more than proof-of-concept as they led to entirely unstrained and basically unfunctionalized macrocycles;[19,20] despite the lack of any serious molecular constraints in these model studies, cyclodimerization infringed with the formation of a 14-membered ring.[19] Yet, the risk associated with the plan to forge the equally 14-membered core of callyspongiolide by ynoate ring closure/semi-reduction was offset by the opportunity to explore a frontier of alkyne metathesis while trying to establish a productive route to this important lead compound. Since this study had been initiated before the absolute stereochemistry of callyspongiolide was corrected, we targeted *ent*-**1** as the structure originally proposed by the isolation team.[1] Adaptation to the natural series, however, would meet no difficulty.

Results and Discussion

Preparation of the Building Blocks. Based on ample experience with the Kocienski variant of the Julia olefination as late-stage maneuver in total synthesis,[21,22,23] we resorted to this reaction for the formation of the C10–C11 double bond; moreover, this step has precedent in the total syntheses of **1** reported by the Ye and the Gosh groups.[2,3] The preparation of the required sulfone **10** commenced with the mono-silylation of but-2-en-1,4-diol (**2**), which gave good results on scale when carried out at low temperature (Scheme 2). Sharpless epoxidation of the resulting product furnished compound **3** (93% ee),[24,25] which underwent a highly selective hydroxy-directed ring opening with MeMgBr/CuI to give multigram quantities of diol **4** in excellent yield.[25]



Scheme 2. a) TBSCl, NaH, THF, 69%; b) Ti(O*i*Pr)$_4$ (24 mol%), L-(+)-diethyl tartrate (30 mol%), *t*BuOOH, CH_2Cl_2, −20°C, 88% (93% ee); c) MeMgBr, CuI (30 mol%), Et_2O/THF, −20°C, 91%; d) $MeOC_6H_4CH(OMe)_2$, PPTS (10 mol%), CH_2Cl_2, 85%; e) TBAF, THF, 88%; f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C; g) $H_3CC(=O)C(=N_2)P(=O)(OMe)_2$, NaOMe, THF, −78°C → −50°C, 74% (over both steps); h) Bu_3SnH, AIBN, benzene, reflux, 84% (*E*:*Z* = 8:1); i) Dibal-H, CH_2Cl_2, 0°C, 68%; j) I_2, CH_2Cl_2, 0°C → RT, 94%; k) 1-phenyl-1*H*-tetrazole-5-thiol, DEAD, PPh_3, quant.; l) aq. H_2O_2,

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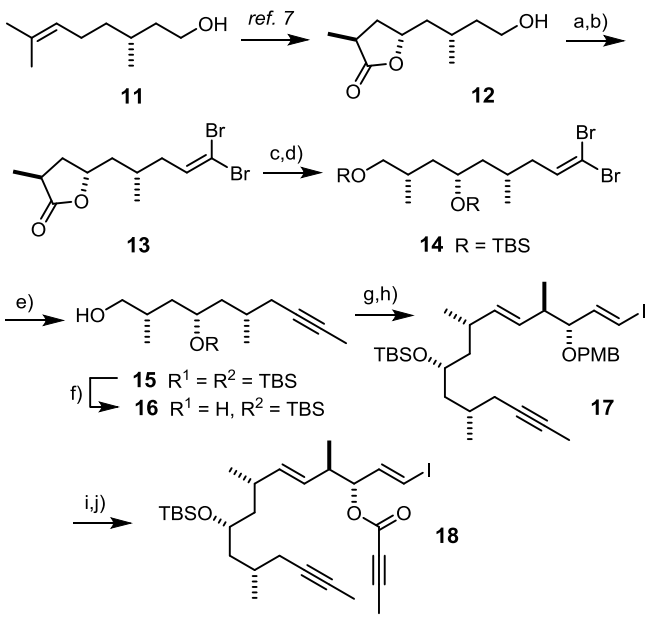
$(NH_4)_6Mo_7O_{24}$ (50 mol%), EtOH, 72%; DEAD = diethyl azodicarboxylate; PPTS = pyridinium *p*-toluenesulfonate; TBAF = tetra-*n*-butylammonium fluoride; TBS = *tert*-butyldimethylsilyl

The derived *p*-methoxybenzylidene acetal was readily transformed into aldehyde **5**, which proved rather sensitive and epimerization-prone.[26] Although **5** could be elaborated via Takai olefination[27,28] into an adequate alkenyl iodide, as necessary for the later attachment of the side chain of callyspongiolide, this reaction required a large excess of $CrCl_2$; moreover, the subsequent reductive acetal opening with Dibal-H to give the targeted compound **8** also proved surprisingly troublesome. Therefore we pursued an alternative route to this compound, in which aldehyde **5** was first transformed into the corresponding terminal alkyne **6** on treatment with Bestmann-Ohira reagent[29] which had to be preactivated with NaOMe prior to addition of the aldehyde to avoid epimerization.[30,31] The alkenylstannane formed by hydrostannation of alkyne **6** under free radical conditions underwent reductive opening of the *p*-methoxybenzylidene acetal ring to give the desired regioisomer **7** as the major product in appreciable yield.[32] Since the subsequent tin/iodine exchange also worked well, this detour was clearly the more practical and scalable route to compound **8**. Two routine steps then sufficed to complete the synthesis of sulfone **10** as necessary for fragment coupling.



Scheme 3. a) O_2, $[Cu(MeCN)_4]BF_4$ (5 mol%), 2,2'-bipyridine (5 mol%), TEMPO, NMI, MeCN, 97%; b) CBr_4, PPh_3, CH_2Cl_2, 92%; c) $LiBH_4$, MeOH, Et_2O, 97%; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 98%; e) *n*BuLi, MeI, THF, −78°C → RT, 96%; f) HF·pyridine, pyridine, THF, 63% (77% brsm); g) $(COCl)_2$, DMSO, *i*Pr_2NEt, CH_2Cl_2, −78°C; h) **10**, LiHMDS, DMF, −78°C, 57% (*E/Z* = 15:1); i) DDQ, CH_2Cl_2, phosphate buffer (pH 7.4), 63%; j) 2-butynoic acid, DIC, DMAP, CH_2Cl_2, 87%; DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone; DIC = N.N'-diisopropylcarbodiimide; DMAP = 4-(dimethylamino)pryridine; LiHMDS = lithium hexamethyldisilazide; TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl radical; Tf = trifluoromethanesulfonyl

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The required aldehyde partner was attained by adaptation of a fragment synthesis described in the accompanying paper.[7] To this end, the readily available butyrolactone derivative **12** was subjected to Stahl oxidation[33] and the resulting aldehyde transformed into dibromoolefin **13** by standard means (Scheme 3).[34] Reduction of the lactone moiety, persilylation of the resulting diol, and treatment of compound **14** thus formed with *n*BuLi/MeI afforded alkyne **15** in good yield. Not unexpectedly, however, the selective cleavage of the primary TBS-ether in **15** proved delicate and was best accomplished with HF·pyridine in THF/pyridine by stopping the reaction prior to full conversion in order to minimize global desilylation (although the resulting diol can be recycled, if necessary). The crude aldehyde derived from **16** by Swern oxidation[35] was subjected to the Kocienski olefination without delay.[21,22] Careful optimization of the reaction conditions showed the use of LiHMDS as the base and DMF as the solvent to be optimal; for the sake of robustness and yield, a slight excess of the lithiated sulfone **10** (1.45-1.5 equiv.) was used, which could be largely recovered after work-up. Under these conditions, the olefination was clean and well reproducible, furnishing alkene **17** with high selectivity for the required *E*-isomer (57%, *E/Z* = 15:1). Oxidative cleavage of the PMB-group[36] under buffered conditions followed by DIC-mediated esterification of the resulting secondary alcohol with 2-butynoic acid furnished diyne **18** in readiness for macrocyclization.

Ynoate Metathesis and Completion of the Total Synthesis. Despite the largely missing precedent for alkyne metathesis reactions of ynoates in general (vide supra), treatment of compound **18** with the molybdenum alkylidyne complex **22** resulted in fast, clean and essentially quantitative ring closure at ambient temperature when carried out in the presence of molecular sieves (5 Å) to scavenge the released 2-butyne;[17] the desired cycloalkyne **19** was isolated in analytically pure form in 96% yield (Scheme 4). This remarkable outcome further attests to the maturity that alkyne metathesis has reached in recent years as well as to the excellent application profile of this class of alkyne metathesis catalysts previously developed in our laboratory.[17,18] Moreover, the ease of formation of **19** shows that metathesis of ynoates and related electron deficient substrates certainly warrants more detailed investigation.

The remarkable chemoselectivity of catalyst **22**, which activates triple bonds under mild conditions but leaves alkenes of all sorts untouched, is best appreciated when compared with the application profile of the standard reagents or catalysts used for the semi-reduction of alkynes.[14] Compound **19** is a particularly stringent test because of possible overreduction at three different sites and the daunting cleavage of the C–I bond at the alkenyl iodide terminus.[37] In fact, an initial survey quickly showed that standard Lindlar hydrogenation,[38] the use of activated zinc dust,[39,40] and even reduction over nickel boride[41] all furnished product mixtures comprising appreciable amounts of the corresponding dehalogenated product (up to 18% by HPLC/MS).[42] Focusing on the use of nickel boride (generated from $Ni(OAc)_2 \cdot 4H_2O$, $NaBH_4$ and ethylenediamine),[41] as the arguably most promising starting point,[37,43] the evolution of the product distribution was monitored with time. These control experiments showed that overreduction and deiodination rapidly increased once the alkyne was

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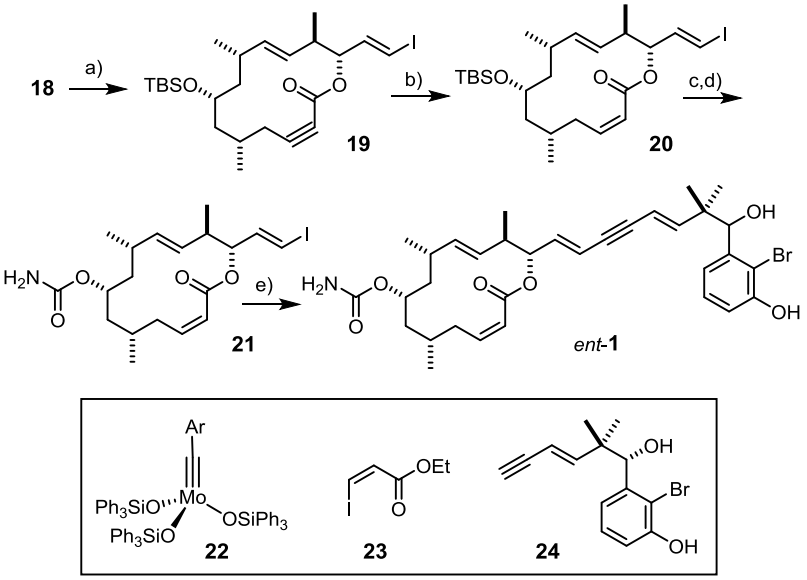
consumed; the amount of added ethylenediamine, in contrast, had little effect on the outcome. This differential reactivity suggested that addition of an adequate sacrificial alkene to the mixture might allow the problem to be remedied. While the use of excess cyclohexene failed to give a better product ratio, iodoacrylate **23** as a proper mimic of the actual substrate proved effective: in its presence (3 equiv.), dehalogenation as well as overreduction of the precious cycloalkyne **19** were reliably reduced to as little as ≤ 4% and ≤ 12% (NMR), respectively; importantly, no increase in deiodination of the desired product **20** was noticed on prolonged stirring (HPLC/MS). Since **20** was easily separated from all other organic components, this protocol was deemed a practical solution for an otherwise hardly manageable selectivity problem.



Scheme 4. a) **22** (15 mol%), toluene, MS 5Å, RT, 96%; b) $Ni(OAc)_2{\cdot}4H_2O$, $NaBH_4$, ethylenediamine, H_2, **23**, EtOH, 0°C → RT; c) camphorsulfonic acid, CH_2Cl_2/MeOH; d) chlorosulfonyl isocyanate, CH_2Cl_2, then aq. THF, 76% (over three steps); e) **24**, $Pd(PPh_3)_4$ (10 mol%), CuI, *i*Pr_2NEt, THF, 80%; Ar = *p*-methoxyphenyl

With a robust access to **20** secured, the total synthesis of callyspongiolide was completed by cleavage of the remaining TBS-ether and installation of the conspicuous carbamate functionality.[44,45] In the final step the side chain was attached via Sonogashira coupling[46,47] of **21** with alkyne **24**, for which an efficient asymmetric synthesis is outlined in the accompanying paper.[7] The analytical and spectral data of our synthetic samples of callyspongiolide were in excellent accord with those reported in the literature,[1-4] except that we had been misled at the outset of our project by the mis-assigned absolute configuration in the original report to pursue the non-natural enantiomer *ent*-**1**.[1]

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Conclusions

A project that had originally intended to merely establish an efficient entry into the cytotoxic marine macrolide callyspongiolide gradually turned into a much broader investigation into scope and limitations of contemporary alkyne metathesis and relevant downstream chemistry. Overall, the status of RCAM was found highly satisfactory in that this transformation allowed the macrocyclic ring of the target to be closed with similar efficiency at either the C2-C3 or the C10–C11 site. In this context it is of note that this study provides the first convincing illustration that even complex ynoates succumb to productive alkyne metathesis, a transformation that had previously met with failure using the classical alkyne metathesis catalysts.[15,16] This favorable outcome nicely illustrates the excellent performance of the latest generation of molybdenum alkylidyne complexes endowed with triarylsilanolate ligands.[17,18]

The maturity of alkyne metathesis manifest in these examples stands in certain contrast to the difficulties encountered during the subsequent semi-reduction of the cycloalkyne products thus formed. The emerging field of ruthenium catalyzed *trans*-addition chemistry as a gateway to *E*-alkenes, though successfully used in the context of natural product synthesis on many occasions,[11,48] obviously finds an important limitation when it comes to applications to sterically hindered triple bonds. Even the stereo-complementary formation of *Z*-alkenes by canonical Lindlar-type reduction, however, still faces considerable and in part unsolved problems when polyfunctional substrates need to be addressed.[14] Although these challenges were ultimately mastered and a robust entry into callyspongiolide was established, this total synthesis project revealed significant gaps in methodological coverage and inspires investigations into better catalysts for stereoselective alkyne semi-reduction.[49] Work along these lines is underway in our laboratory.

Experimental Section

All experimental details can be found in the Supporting Information. The material includes compound characterization data and copies of spectra of new compounds.

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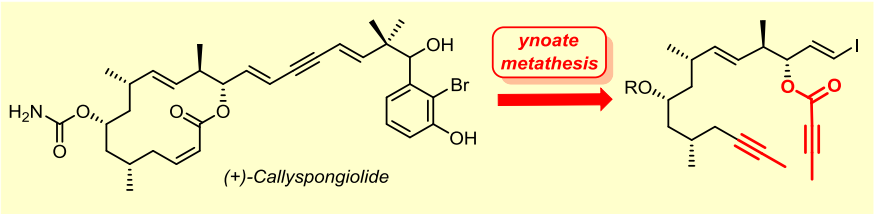
For the Table of Contents



First of its kind: Alkynes as electron deficient as ynoates had basically defied productive metathesis for decades; the latest generation of molybdenum alkylidynes, however, now allowed ynoate metathesis to be used as the corner stone of a productive entry into the marine macrolide callyspongiolide, which shows promising cytotoxic properties.

Keywords: alkyne metathesis · macrolides · molybdenum alkylidynes · natural products · total synthesis

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