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Formal Total Synthesis of the Algal Toxin (−)-Polycavernoside A

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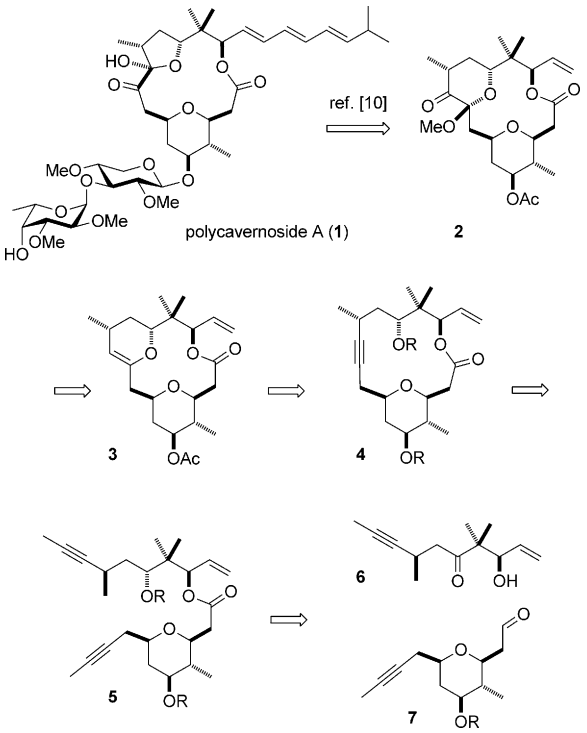
Abstract: A concise and largely catalysis-based approach to the potent algal toxin polycavernoside A (**1**) is described that intercepts a late-stage intermediate of a previous total synthesis; from there on, this challenging target can be reached in a small number of steps. Key to success was a sequence of a molybdenum-catalyzed ring-closing alkyne metathesis (RCAM) reaction to forge the macrocyclic frame, followed by a gold-catalyzed and strictly regioselective transannular hydroalkoxylation of the resulting cycloalkyne that allows the intricate oxygenation pattern of the macrolactone ring of **1** to be properly set. The required cyclization precursor **5** was assembled by the arguably most advanced fragment coupling process based on an Evans–Tishchenko redox esterification known to date, which was optimized to the extent that the precious coupling partners could be used in an almost equimolar ratio (**6**/**7** 1:1.3). The preparation of these building blocks features, *inter alia*, the power of the $Sc(OTf)_3$-catalyzed Leighton crotylation as well as the superb selectivities of alkene cross metathesis, asymmetric keto-ester hydrogenation, and the Jacobsen epoxidation/epoxide resolution technologies.

Keywords: alkynes · gold · metathesis · molybdenum · natural products · samarium

Introduction

Cases of deadly foodborne intoxication reported in Guam in the Spring of 1991 were traced back to the red alga *Gracilaria edulis* (*Polycavernosa tsudai*), even though this widely consumed seaweed had never before caused any harm.[1] This sudden outburst seemed to be a tragic episode until similarly fatal incidents occurred in the Philippines about a decade later.[2,3] A masterful investigation allowed Yasumoto and co-workers to identify the glycosylated macrolides of the polycavernoside series as the causative toxins contained in the poisonous algal crops.[4–6] For their potent bioactivity and intricate structures, these targets spurred considerable synthetic efforts worldwide. The interest does not seem to cease even many years after the first conquest of polycavernoside A (**1**), by which the absolute configuration of this parent family member had been formally established.[7–13]

We now present a concise alternative entry and formal total synthesis of this challenging marine natural product, which intercepts a key intermediate of the successful approach reported by Woo and Lee.[10] Specifically, compound **3** had been converted by these authors into **1** by a short and productive sequence based on the oxidation of the endocyclic enol ether to the masked α-dicarbonyl derivative **2**; this particular product cleanly rearranged to the conspicuous five-membered hemiketal contained within the macrocyclic frame of **1** while elaborating the lateral chain of the target (Scheme 1). Compound **3** derives from cycloalkyne **4** by a transannular hydroalkoxylation with the aid of a carbophilic catalyst.[14] We surmised that product **4**, in turn, provides an excellent opportunity to scrutinize ring-closing alkyne metathesis (RCAM)[15—17] in a challenging synthetic context.



Scheme 1. Retrosynthetic analysis of polycavernoside A (**1**).

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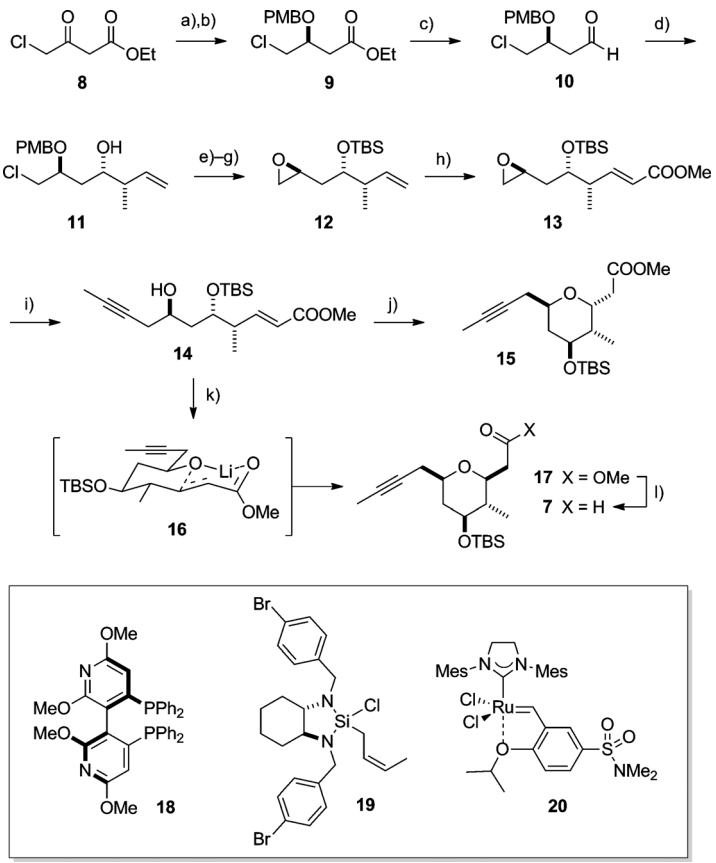
Moreover, the 1,3-*anti*-diol monoester motif present in the prospective cyclization precursor **5** invites the use of an Evans–Tishchenko coupling reaction.[18,19] It is of note, however, that this redox-esterification typically mandates the use of a (large) excess of the aldehyde component relative to the hydroxy-ketone partner. This unfavorable stoichiometry may well explain why Evans–Tishchenko reactions—despite an excellent track record—have hardly ever been applied to advanced fragment coupling processes.[20] In any case, the use of this transformation in the projected synthesis of **1** is only warranted if the rather advanced building blocks **6** and **7** can be used in roughly equimolar ratio; this challenge has yet to be met. Furthermore, we wished to strictly base the material supply on asymmetric synthesis and catalysis but avoid any recourse to the "chiral pool", which had served as the dominating source of chirality in the reported total syntheses of **1** (pantolactone, citronellal, malic acid).[7—11]

Results and Discussion

The preparation of the tetrahydropyran segment **7** commenced with an asymmetric hydrogenation of the commercial β-ketoester **8** using P-Phos (**18**) as the chiral ligand, which delivered multigram quantities of the corresponding chlorohydrin in excellent optical purity (94%, 96% *ee*) (Scheme 2).[21] A copper-catalyzed PMB protection allowed any premature epoxide ring formation to be avoided and set the basis for a DIBAl-H reduction of the ester group in **9** to the corresponding aldehyde **10**. Exposure of this compound to the *Z*-crotylsilane reagent **19** in the presence of catalytic amounts of $Sc(OTf)_3$ furnished the desired homoallyl alcohol **11** in good yield and excellent *syn*-selectivity (d.r. $\geq$28:1),[22] which clearly surpassed the results obtained by a classical Brown crotylation (d.r. 9:1);[23] the ready separation and recovery of the chiral diamine ligand to silicon is an additional bonus of this method. Protection of the newly formed secondary alcohol as a TBS-ether followed by cleavage of the PMB-group and treatment of the resulting material with KOH in EtOH gave epoxide **12** without incident. This compound underwent a clean cross metathesis with methyl acrylate to give product **13**, without the reactive oxirane interfering, which was best effected by ruthenium carbene complex **20** (Zhan catalyst 1B).[24–27]

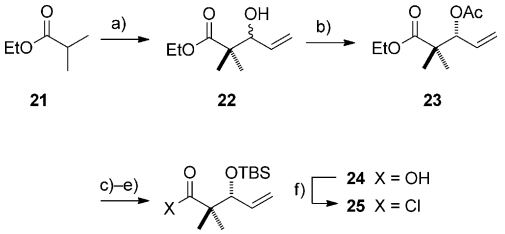
Originally, it was hoped that the opening of the oxirane in **13** with 1-propynyllithium might result in a spontaneous closure of the pyran ring by an oxy-Michael reaction of the intermediate lithium alkoxide; in practice, however, this overall transformation would proceed only when carried out in two separate operations. Best results were obtained when the epoxide opening was carried out in the presence of $BF_3{\cdot}Et_2O$. As expected, the subsequent 1,4-addition of the resulting alcohol to the *E*-configured enoate function in **14** furnished the undesired 2,6-*trans*-disubstituted pyran **15** as the major product,[28] when performed with catalytic amounts of KO*t*Bu in THF.[29] Gratifyingly though, the use



Scheme 2. Preparation of the aldehyde building block: a) $[RuCl_2((R)\text{-P-Phos})](DMF)_n$ (0.12 mol%), H_2 (35 bar), EtOH/CH_2Cl_2 9:1, 95°C, 94% (96% *ee*); b) $PMBOC(NH)CCl_3$, $Cu(OTf)_2$ (2.8 mol%), toluene, −10 → 0°C, 82%; c) DIBAl-H, toluene, −78°C, 88%; d) **19**, $Sc(OTf)_3$ (4.5 mol%), CH_2Cl_2, 0°C, 78% (d.r. $\geq$28:1); e) TBSCl, imidazole, DMAP cat., CH_2Cl_2, 85%; f) DDQ, CH_2Cl_2, pH 7 buffer, 99%; g) KOH, EtOH, 0°C → RT, 94%; h) methyl acrylate, **20** (3.5 mol%), toluene, 70°C, 75%; i) *n*BuLi, propyne, $BF_3{\cdot}Et_2O$, THF, −78°C, 89%; j) KO*t*Bu (10 mol%), THF, −10°C, 58% (**15**) + 9% (**17**); k) DBU, LiCl, MeCN, 100°C (sealed tube), 84% (**17**/**15** $\geq$20:1); l) DIBAl-H, toluene, −78°C, 86%; PMB = *p*-methoxybenzyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DIBAl-H = diisobutylaluminum hydride; DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; TBS = *tert*-butyldimethylsilyl; OTf = trifluoromethanesulfonate.

of DBU/LiCl in MeCN at elevated temperature (100°C, sealed tube) allowed the outcome to be rectified.[30] Under these conditions, compound **17** was obtained in high yield, virtually as a single isomer (*cis*/*trans* $\geq$20:1). We assume that the equilibration of the minor isomer **15** in combination with a favorable chelate transition state **16** for the forward process accounts for this favorable outcome. DIBAl-H reduction of **17** then completed the synthesis of the required aldehyde building block **7** in readiness for the envisaged Evans–Tishchenko reaction.

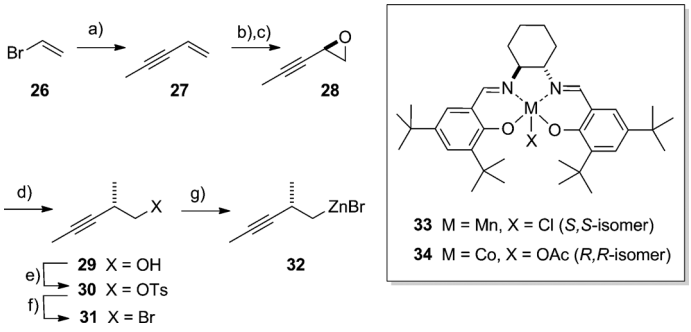
Access to the Northern hemisphere was secured by an aldol addition of ethyl isobutyrate **21** to acrolein[31] followed by a lipase-catalyzed kinetic resolution of the resulting product **22** (Scheme 3).[32] Acetate (+)-**23** thus available in large quantities and optically pure form ($\geq$98% *ee*)[33] was readily converted into acid **24** by routine protecting-group manipu-



Scheme 3. a) LDA, acrolein, THF, −78 °C, 94 %; b) Novozyme 435, vinyl acetate, toluene, 70 °C, 33 % (≥98 % *ee*); c) NaOH, MeOH, 0 °C → RT; d) TBSCl, imidazole, DMF; e) K_2CO_3, THF/H_2O/MeOH 2:1:1, 67 % (over three steps); f) $(COCl)_2$, CH_2Cl_2, quant.

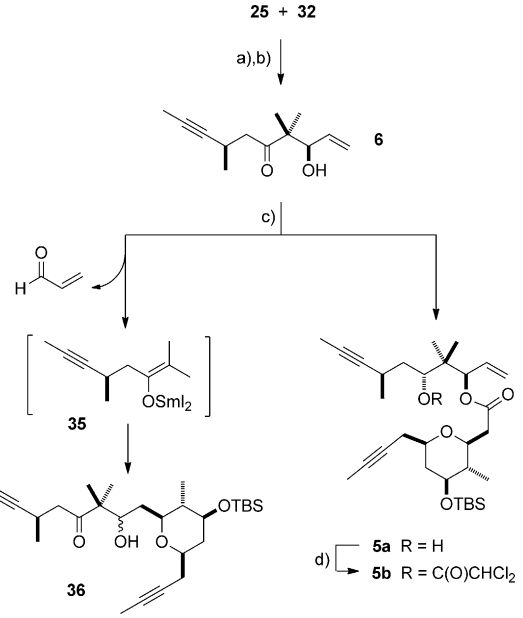
lations. It was planned to couple an activated derivative thereof (acid chloride, Weinreb amide etc.) with a suitable homo-propargyl donor derived from bromide **31**. The development of a scalable route to the latter building block, though small in size, was actually non-trivial and required careful optimization.

A satisfactory solution was found by Sonogashira coupling[34] of propyne with vinyl bromide (**26**) to give enyne **27** in good yield (Scheme 4). The corresponding epoxide **28** was obtained in almost perfect optical purity (*ee* ≥99 %) by a sequence of Mn–salen catalyzed epoxidation followed by a



Scheme 4. a) Propyne, $[(PPh_3)_2PdCl_2]$ (1.5 mol %), CuI (3 mol %), Et_3N, −78 °C → RT (sealed tube), 81 %; b) **33** (5 mol %), NaOCl, CH_2Cl_2, 0 °C; c) **34** (0.5 mol %), H_2O, Et_2O, 73 % (over both steps) (≥99 % *ee*); d) MeLi, $BF_3{\cdot}Et_2O$, −78 °C; e) TsCl, Et_3N, DMAP cat., CH_2Cl_2, 70 % (over both steps); f) LiBr, DMF, 60 °C, 86 % (≥99 % *ee*); g) Zn, dimethylacetamide, 75 °C; LDA = lithium diisopropylamide; Ts = tosyl; DMAP = 4-dimethylaminopyridine.

Co–salen catalyzed hydrolytic kinetic resolution, as previously described for the other enantiomer.[35] The subsequent ring opening with a methyl donor turned out to be surprisingly capricious: after some experimentation, it was found that the use of MeLi in combination with $BF_3{\cdot}Et_2O$ ensured a reliable and clean S_N2 pathway.[36] In contrast, MeMgX (X = Cl, Br) or Me_2Mg, under a variety of experimental conditions, led to a noticeable and—in part—even very significant erosion of the optical purity of the resulting α-branched alcohol **29** (36–97 % *ee*) and/or to the formation of product mixtures. The conversion of this volatile material into the equally volatile bromide **31** was best achieved via the easy-to-handle tosylate **30**. Gratifyingly, product **31** formed by this route had an impeccable *ee* of ≥99 %. Exposure to activated zinc dust in dimethylacetamide at 75 °C followed by acylation of the resulting organozinc reagent by freshly prepared acid chloride **25** in the presence of CuCN·2 LiCl[37] at −30 °C furnished the sterically hindered hydroxy ketone **6** in appreciable overall yield after cleavage of the silyl protecting group with trifluoroacetic acid (Scheme 5).



Scheme 5. Fragment coupling by an Evans–Tishchenko reaction: a) CuCN·2 LiCl, THF, −30 °C; b) TFA, CH_2Cl_2, 67 % (over both steps); c) **7**, SmI_2 (50 mol %), THF, −50 °C, 68 % (**5a**), see text; d) dichloroacetic acid anhydride, pyridine, CH_2Cl_2, 0 °C, 94 %; TFA = trifluoroacetic acid.

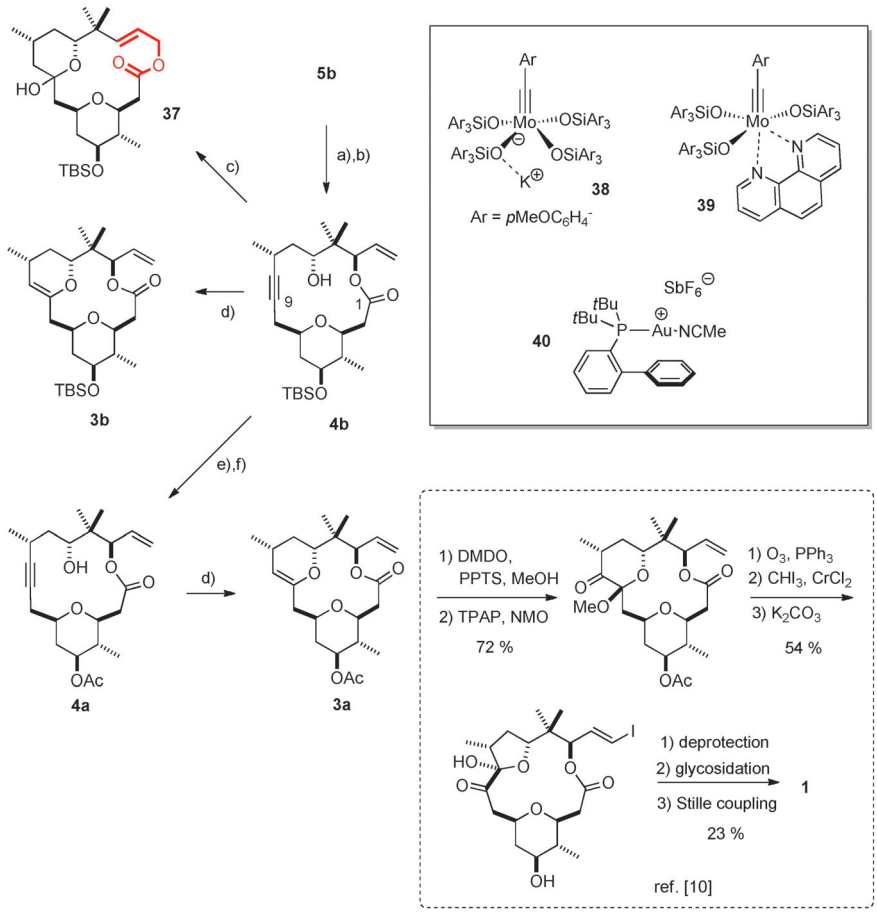
With aldol **6** and aldehyde **7** in hand, the stage was set for the key fragment coupling via an Evans–Tishchenko reaction (Scheme 5). Although the formation of the desired 1,3-*anti*-diol monoester **5a** could be observed under the standard reaction conditions (35 mol % of SmI_2 in THF at −10 °C),[18] a by-product was formed in almost equal quantity to which structure **36** was assigned based on spectroscopic evidence. Its formation is best explained by a retro-aldol/aldol sequence via a transient samarium enolate of type **35** as shown in Scheme 5.[38] Although this parasitic process could be largely suppressed by lowering the temperature to −50 °C, an increase of the catalyst loading was then mandatory to ensure complete conversion. The use of 50 mol % of SmI_2 was the best compromise, while a larger amount negatively impacted on the mass balance. Under these conditions, the two reaction partners **6** and **7** could be used in a 1:1.3 ratio to give the *anti*-configured product **5a** with a diastereoselectivity of ≥10:1 (HPLC); no more than 2 % of the byproduct **36** were detected in the crude material. Even though the minor *syn*-isomer could only be separated by preparative HPLC, the desired compound **5a** was still obtained in respectable 68 % yield.[39] We believe that this fa-

vorable outcome should encourage a wider use of the Evans–Tishchenko redox-esterification reaction as a means for the coupling of elaborate fragments in advanced organic synthesis.

Compound **5a** undergoes a surprisingly facile intramolecular transesterification, leading to an equilibrium mixture with the corresponding 1,3-transposed ester derivative. Therefore the secondary hydroxyl group of **5a** was temporarily protected as an orthogonal dichloroacetate and the resulting diyne **5b** subjected to macrocyclization by ring-closing alkyne metathesis (RCAM). In line with our expectations, the reaction proceeded smoothly when catalyzed by the molybdenum alkylidyne ate-complex **38** endowed with triarylsilanolate ligands (Scheme 6).[40] This example is another important entry in the rapidly growing list of success stories of this new type of catalysts,[41] which are well accessible, highly active and remarkably selective at the same time. It is emphasized that the neutral alkylidyne species $[(Ar_3SiO)_3Mo{\equiv}CC_6H_4OMe]$ (Ar = *p*-$MeOC_6H_4$-), which is formed in situ as the active principle from the ate-complex **38** by loss of Ar_3SiOK, can also be generated from the indefinitely bench-stable phenanthroline adduct **39** on treatment with either $MnCl_2$ or $ZnCl_2$, as previously reported by our group; this procedure is particularly user friendly.[40]

Next, cycloalkyne **4b** thus formed was subjected to a transannular hydroalkoxylation with formation of enol ether **3b**. Although Woo and Lee had previously effected a closely related transformation with the aid of $PtCl_2/CO$,[10,42] we observed a secondary process when **4b** was exposed to catalytic amounts of $[PtCl_2(C_2H_4)]_2$ as a more soluble platinum source. Although the alkyne was selectively attacked at the C9 position by the secondary OH group, the intermediate enol ether was hydrolyzed to the corresponding hemiketal[43,44] and the allylic ester concomitantly rearranged. It is the relieve of strain caused by the congested neopentylic environment about the C–O bond in **4b** that provides the driving force for the formation of the primary allylic ester **37** by this platinum-catalyzed Overman-type [3,3]-sigmatropic rearrangement.[45]

Gratifyingly though, both secondary processes could be completely suppressed and the desired enol ether formation accomplished in good yield with the aid of the cationic gold complex **40** bearing a bulky phosphine ligand.[46] Although we have no reason to believe that compound **3b** could not be elaborated into polycavernoside A (**1**) according to the published literature route,[10] it should be noticed that this particular product differs from the key intermediate used by Woo and Lee in that it carries a TBS-ether rather than an acetyl group on the pyran moiety. To exclude any doubts and ensure full identity, we bothered to swap this protecting group after the macrocyclization (**4b** → **4a**). As expected, the transannular functionalization by the alkynophilic gold catalyst was not affected by this peripheral modification; actually, the isolated yield of the resulting enol ether **3a** was even better. In any case, compound **3a** is identical in all regards with the key intermediate that had previously been elaborated into polycavernoside A (**1**) in eight straightforward operations with an average yield of 74% per step.[10]



Scheme 6. Completion of the (formal) total synthesis of polycavernoside A: a) **38** (5 mol%), toluene, MS 5 Å, 80°C, 91%; b) K_2CO_3, MeOH, 40°C, 80%; c) $[PtCl_2(C_2H_4)]_2$ (10 mol%), Et_2O, 77%; d) **40** (10 mol%), MS 4 Å, CH_2Cl_2, 67% (**3b**), 84% (**3a**); e) TFA, CH_2Cl_2, 40°C, 76%; f) Ac_2O, pyridine, CH_2Cl_2, 40°C, 97%; for the completion of the total synthesis from **3a** onward, see ref. [10]; DMDO = dimethyldioxirane; PPTS = pyridinium *p*-toluenesulfonate; TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine-*N*-oxide.

Conclusion

A formal total synthesis of the challenging algal toxin polycavernoside A (**1**) is presented, which is concise, productive and largely catalysis-based. Our entry features the arguably most advanced case of an Evans–Tishchenko reaction for the coupling of two elaborate building blocks and showcases the maturity of the latest generation of catalysts for alkyne metathesis. This result highlights the notion that RCAM provides ample opportunity for advanced organic synthesis, in particular when combined with the power of noble metal catalysis for the selective activation of the resulting acetylenic products. Although the use of carbophilic Lewis acids in general has seen an explosive growth during the last decade, late-stage applications to the targeted pursuit of complex natural products are still scarce.[47] It is hoped that the polycavernoside case study will encourage further investigations along these lines, although it also illustrates the subtle differences in the behavior of platinum- and gold catalysts. Ongoing projects in this laboratory intend to contribute to a better understanding of the underpinning reactivity patterns and try to find new applications of carbophilic activation in concert with alkyne metathesis.

Experimental Section

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

Acknowledgements

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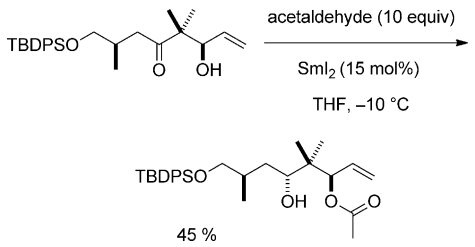

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