Communication

Total Synthesis of (-)-Sinulariadiolide. A Transannular Approach

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# Total Synthesis of (−)-Sinulariadiolide. A Transannular Approach

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ABSTRACT: The constrained tricyclic skeleton of the *nor*-cembranoid sinulariadiolide (**1**) with a nine-membered nexus was obtained by a cascade of transannular Michael reaction, carbonate elimination, butenolide formation and spontaneous oxa-Michael addition of MeOH. The required macrocyclic precursor was prepared by ring closing alkyne metathesis followed by *trans*-hydrostannation/carbonylation.

Soft corals of the *Sinularia* genus have evolved a prodigiously rich secondary metabolome for their chemical defense. Macrocyclic *nor*-cembranoids are the most conspicuous constituents, which often co-occur with even more complex polycyclic congeners.[1] Sinulariadiolide (**1**) and 5-episinuleptolide (**2**) are representative (Scheme 1):[2] both were isolated from the same Okinawan *Sinularia* specimen and seem to be biosynthetically linked by transannular bond formation/oxidative bond cleavage.[2]

Scheme 1. Proposed Biosynthetic Pathway[2]

5-episinuleptolide (**2**)   **sinulariadiolide** ((+)-**1**)
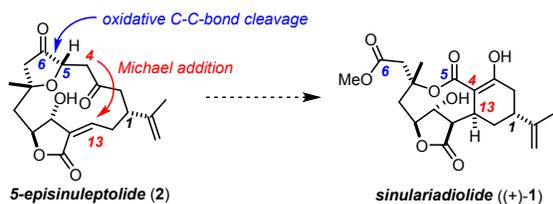
Although the tricyclic scaffold comprising a nine-membered lactone is unique, sinulariadiolide (**1**) failed to draw attention from the synthetic community for more than two decades, perhaps because the isolation team did not investigate its biological activity.[3] Moreover, the absolute stereochemistry is uncertain: although the 1*R*-configuration prevalent in the furanocembranoid series seems likely,[1] exceptions are known that make a rigorous proof mandatory.

Though small in size, **1** is a formidable target. For the strain entailed by the medium-sized nexus,[4] it was by no means intuitive whether a bio-inspired transannular approach is feasible. Even if the reaction proceeds, macrocyclic stereocontrol over transannular reactivity has to be carefully considered,[5] as it can either strongly enhance or completely outweigh reagent/catalyst control: matching cases often lead to exquisite levels of selectivity, but unfavorable settings are usually difficult − if not even impossible − to correct.[6,7]

With these caveats in mind, we refrained from emulating the putative biosynthetic route from **2** to **1**: conformational arguments,[8] the necessary merger of enolate chemistry with oxidative bond cleavage, and the prospect of sacrificing a pre-

exisiting ring spoke against this plan. Rather, a substrate of type **A** was deemed more appropriate (Scheme 2): several conformers seem accessible in which the enolate π-bond and the π*-system of the acceptor unit reside in transannular proximity, aligned for orbital overlap. Provided that this setting allows the nine-membered ring to be formed, a (*Z*)-configured enoate should lead to the proper ring junction at C13. This analysis explicitly acknowledges our uncertainty as to whether the β-ketoester entity reacts in a chelated *Z*-enolate (e. g. **C**) or dipole-minimized *E*-enolate form (e. g. **D**).[9] Since the β-dicarbonyl region of sinulariadiolide is enolized and the stereochemical features of the incoming nucleophile hence get erased,[2] this ambiguity was initially of minor concern.

Scheme 2. Retrosynthetic and Conformational Considerations
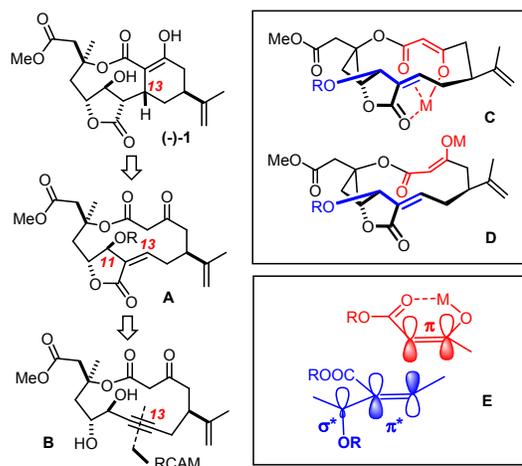
Moreover, **C** as well as **D** might benefit from the disposition of the incipient C-C-bond *anti* to the σ*-orbital of the allylic −OR substituent (cf. **E**). Although this stereoelectronic argument relates to a Michael reaction, it mirrors the rationale behind the Felkin-Ahn model for additions to carbonyl groups carrying a non-chelating O-substituent at the α-position.[10] However, the presence of an allylic leaving group gives the resulting enolate the chance to eliminate before protonation might occur. This scenario is least likely if R = H, but even for a protected variant (R ≠ H) could it be possible to avoid elimination under protic conditions.

Substrate **A** seemed accessible by *trans*-hydro-metalation/carbonylation of cycloalkyne **B**,[11-13] which in turn lends itself to formation by ring closing alkyne metathesis (RCAM).[14] Given the success of RCAM in numerous complex settings, we were convinced that the "macrocycle challenge", which had seriously impeded systematic exploration of

transannular reactivity in the past,[6] would not obstruct the projected case.

Scheme 3.[a]
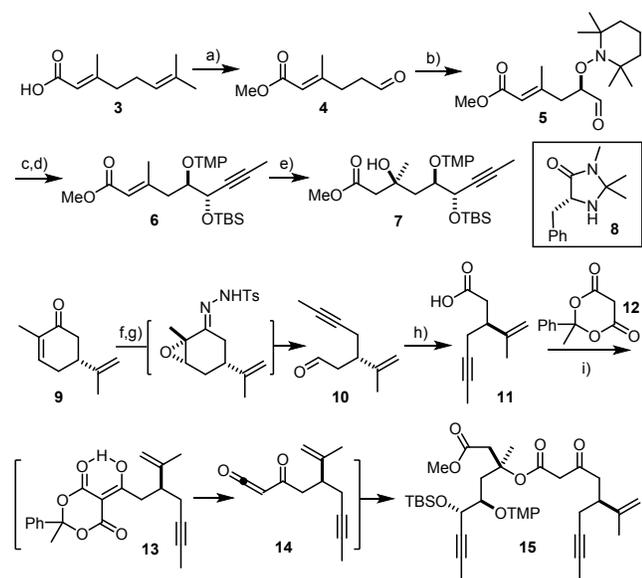
[a] Reagents and Conditions: (a) Me$_2$SO$_4$, iPr$_2$NEt, MeCN, 0°C; then O$_3$, CH$_2$Cl$_2$, −78°C, 58%; (b) **8**·HBF$_4$ (25 mol%), CuCl$_2$ (12 mol%), TEMPO, DMF, MS 4Å, −10°C, 81% (ee 65%); (c) propyn-1-ylmagnesium bromide, pentane, −20°C; (d) TBSCl, imidazole, DMF, 67% (over two steps); (e) (i) B$_2$(pin)$_2$, tBuONa (15 mol%), CuCl (6 mol%), (*S,S*)-methyl-DUPHOS (6 mol%), MeOH, THF, 0°C; (ii) NaBO$_3$·6H$_2$O, aq. THF, 90°C, 64%; (f) aq. H$_2$O$_2$, NaOH, MeOH, 0°C, quant.; (g) TsNHNH$_2$, HOAc, CH$_2$Cl$_2$, 0°C → 10°C, 52%; (h) NaClO$_2$, NaH$_2$PO$_4$, 2-methylbut-2-ene, tBuOH/H$_2$O, 0°C, 94%; (i) **12**, DCC, DMAP, Et$_3$N, CH$_2$Cl$_2$, then **7**, toluene, 60°C, quant.

Geranic acid (**3**) served as point of departure, even though commercial samples are not isomerically pure (*E:Z* ≈ 85:15) (Scheme 3). Esterification followed by ozonolysis afforded aldehyde **4**, which underwent an organocatalytic oxyamination to give compound **5** in good yield but modest enantioselectivity (65% ee).[15] As this flaw could be corrected downstream at the borylation/oxidation stage and the material throughput up to this point proved easy, no effort was made to find a better α-oxyaldehyde surrogate. The addition of propynylmagnesium bromide to **5** was *anti*-selective,[16] furnishing **6** after silylation of the crude material. Truly instrumental for the fragment synthesis, however, was the subsequent highly catalyst-controlled conjugate borylation/oxidation:[17] in the presence of a catalyst formed from CuCl and (*S,S*)-methyl-DUPHOS, a −B(pin) unit was transferred with remarkable efficiency and selectivity to the enoate entity of **6**, despite the β,β-disubstitution. The quarternary borylated center in the resulting product was oxidized with NaBO$_3$·6H$_2$O.[18] All isomers could be separated at this stage by flash chromatography, thus giving access to multigram quantities of fragment **7** in diastereomerically and enantiomerically pure form.

Since the absolute configuration of sinulariadiolide had been unknown at the outset of our investigation, we simply chose the cheaper antipode of carvone for the preparation of the second building block. Specifically, (*R*)-(−)-**9** was subjected to epoxidation[19] and formation of the corresponding tosylhydrazone, which upon Eschenmoser fragmentation gave aldehyde **10**.[20] Chain extension of the derived acid (*S*)-**11** to the corresponding β-keto acid was merged with the *a priori* non-trivial esterification with the elimination-prone tertiary alcohol **7**. To this end, it

sufficed to treat **11** with excess **12** in the presence of DCC/DMAP; addition of **7** to the resulting product **13** and heating of the mixture to 60°C released acyl-ketene **14**, which is sufficiently reactive to intercept the sterically hindered −OH group.[21] In this way, the potentially difficult fragment coupling became operationally simple and scalable.

Scheme 4.[a]
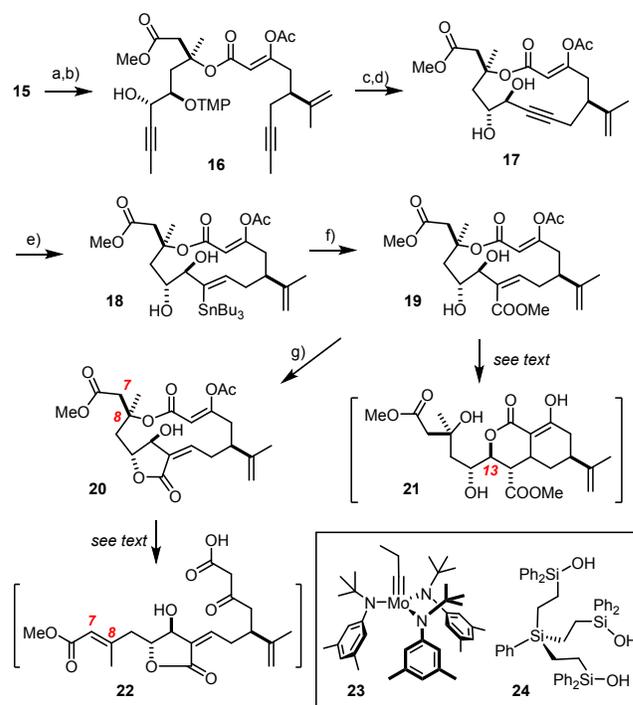
[a] Reagents and Conditions: (a) Ac$_2$O, DMAP (20 mol%), Et$_3$N, CH$_2$Cl$_2$, −40°C; b) aq. HF, THF, 73% (over both steps); c) **23** (30 mol%), **24** (30 mol%), toluene, 120°C; d) Zn, HOAc, THF/H$_2$O, 76% (over both steps); (e) Bu$_3$SnH, [Cp*RuCl]$_4$ (11 mol%), CH$_2$Cl$_2$, 66%; f) CO (1 atm), Pd(OAc)$_2$ (20 mol%), AsPh$_3$ (40 mol%), 1,4-benzoquinone, F$_3$CCOOH (40 mol%), MeOH, 57%; (g) F$_3$CCOOH, CH$_2$Cl$_2$, 71%.

We were apprehensive that diyne **15** thus formed might not be the best substrate for RCAM: unprotected 1,3-dicarbonyl compounds are amongst the few functionalities that are not well tolerated by molybdenum alkylidynes endowed with silanolate ligands.[22,23] Moreover, for the bulk of their ligands, such catalysts find limitations when it comes to metathesize sterically hindered triple bonds.[24] Therefore, **15** was elaborated into **16** in which the β-ketoester is capped but the propargylic −OH group is freed from the bulky O-TBS substituent (Scheme 4). Treatment of this compound with a catalyst generated from **23** and the chelating silanol **24**[25] resulted in clean macrocyclization; the strain of the incipient 13-membered ring, however, mandated that the reaction be carried out at elevated temperature under high dilution conditions. It is paradoxical from the organometallic viewpoint that an alkyne carrying an *unprotected* −OH group is the substrate of choice if one considers that Schrock alkylidyne complexes are inherently nucleophilic and basic.[26] The silanolate-bearing variants define new standards in terms of functional group compatibility.[14,22-25]

The crude cycloalkyne was treated with Zn/HOAc to cleave the O−N bond.[27] The resulting diol **17** underwent *trans*-hydrostannation on treatment with Bu$_3$SnH and [Cp*RuCl]$_4$ as the catalyst.[28] In addition to the unorthodox stereochemical course,

this reaction is distinguished by high regioselectivity, in that the tin residue is delivered to the proximal end of a propargylic site. This outcome reflects cooperativity between the polarized [Ru−Cl] unit of the catalyst and the −OH group of the substrate, which engage in hydrogen bonding and thereby impose directionality on the ensuing hydrometalation reaction.[11,12] The resulting alkenylstannane **18** underwent palladium catalyzed methoxycarbonylation[13] to furnish enoate **19** and the derived butanolide **20** as possible substrates for the projected transannular Michael addition.

However, numerous attempts to trigger ring contraction upon cleavage of the enol acetate in **19** or **20** met with failure; activation of the enoate under Lewis-acidic conditions was equally unrewarding. Although an unambiguous analysis of the resulting mixtures proved impossible, compounds such as **21** and **22** seemed to be present; though tentative, these assignments suggested that opening of the medium-sized ring by elimination of the aldol terminus or translactonization by an unprotected −OH group thwarted success.

Scheme 5.[a]
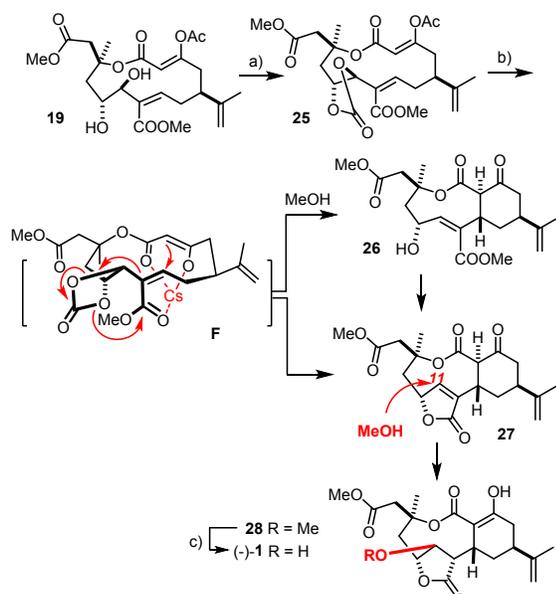
[a] Reagents and Conditions: (a) triphosgene, CH$_2$Cl$_2$, pyridine, 0°C, 97%; (b) Cs$_2$CO$_3$, CH$_2$Cl$_2$, MeOH/H$_2$O, 86% (**28**) + 11% (**26**); (c) BBr$_3$, 2-methyl-2-butene, CH$_2$Cl$_2$, −15°C, 72%

Therefore we turned our attention to substrates bearing protected −OR groups despite the risk for elimination. Ironically, it was this very property that ultimately proved enabling (Scheme 5). The decisive observations were made when the cyclic carbonate **25** was treated with Cs$_2$CO$_3$ in aq. MeOH/CH$_2$Cl$_2$: the resulting mixtures comprised the expected elimination product **26**, the derived butenolide **27** and *sinulariadiolide methyl ether* **28**; after optimization, **28** was isolated in well reproducible 86% yield. Since this compound is obviously formed by 1,4-addition of MeOH to **26** or **27**,[29] attempts were made to engage water as the nucleophile which would lead directly to **1**. Yet, the reaction failed in the absence of MeOH or when *i*PrOH was chosen instead; with aq. Cl$_3$CCH$_2$OH the cascade stopped at the butenolide stage (87%). Interestingly, the unsaturated compound **27** exists in the β-ketoester form, whereas the derived adduct **28** and sinularidiolide (**1**)[2] are fully enolized (NMR).

The total synthesis of sinulariadiolide was completed by cleavage of the methyl ether in **28** with BBr$_3$/2-methyl-2-butene, which proceeded cleanly ≤ −15°C. The spectroscopic data of synthetic **1** were in excellent accord with the literature.[2] Our sample, derived from (−)-carvone (**9**), was levorotatory, whereas the natural product is dextrorotatory. Natural sinulariadiolide (+)-(**1**) is hence (1*R*)-configured as the majority of *nor*-cembranoids known to date.[1]

Some comments on the cascade that transforms **25** into **28** are warranted:[30] deacetylation of the enol acetate occurs prior to cleavage of the carbonate and prompts an efficient transannular event with formation of the challenging nine-membered lactone. Despite the protic medium, quenching of the enolate primarily formed is too slow under the basic conditions such that β-elimination and cleavage of the cyclic carbonate can proceed. The released alkoxide either gets protonated to give **26** or cyclizes to butenolide **27**, which intercepts MeOH from the medium in an oxa-Michael reaction.[29] That the elimination/addition sequence occurs with formal retention at C11 is unsurprising, but the spontaneous addition of MeOH is striking if one considers that this nucleophile is a poor Michael donor.[31] We assume that the bridgehead position of the double bond in **27** largely accounts for the driving force, as sp^2 → sp^3 rehybridization alleviates the product from additional strain. In any case, an integral yield of 86% for a cascade comprising five steps is deemed remarkable, particularly if one considers the level of stereocontrol and increase in molecular complexity manifest in the formation of a single tricyclic scaffold comprising a nine-membered core.

The role of the cyclic carbonate is presumably manifold: while enhancing reactivity by rigidifying the macrocyclic perimeter of **25**, it springs open once the new C-C-bond is formed; this fragmentation relieves the primary product of strain energy and, in so doing, preserves the integrity of the emerging nine-membered ring. This notion is corroborated by comparison with the corresponding isopropylidene derivative **29** (Scheme 6): while C−C-bond formation also takes place, the poorer leaving group property of the acetal prevents elimination from occurring; the extra annulated ring renders the lactone susceptible to transesterification with formation of the ring-opened product **30**.

Scheme 6.[a]
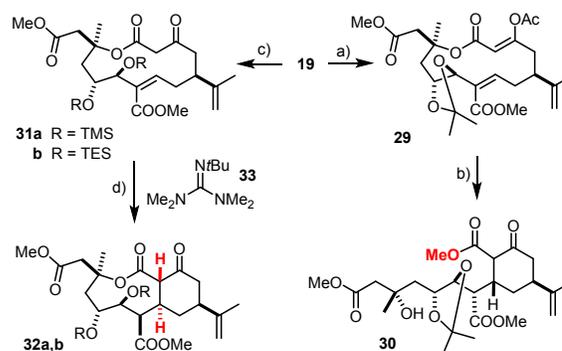
[a] Reagents and Conditions: (a) 2,2-dimethoxypropane, PPTS, DMF; (b) Cs$_2$CO$_3$, MeOH, 0°C, ≤55% (NMR, over both steps); (c) TMSCl, imidazole, DMF; (d) **33**, MeCN, 56% (R = TMS, over both steps)

Finally, we like to refine our view concerning the actual Michael reaction. Our initial planning had been predicated on the notion that either a *Z*-enolate (**C**) or an *E*-enolate (**D**) might afford the desired product, provided that the acceptor unit is oriented as drawn. We implicitly thought to meet this condition by choosing metal carbonate bases as promoter, since the cation might chelate

the oxygen atoms and hence counterbalance possible dipole repulsion. Indeed, Cs_2CO_3 proved uniquely effective and selective in transforming **25** into **28**.[32] Control experiments, however, had to be carried out with ketoester **31** devoid of the cyclic carbonate since attempted activation of **25** with organic bases met with failure.[33] Thus, treatment of **31** with guanidine **33** gave product **32** featuring the opposite non-natural stereochemistry at the ring junction (dr ≥ 20:1), whereas Cs_2CO_3 resulted in a dr ≈ 1.2:1. This notable difference highlights the critical role of the metal cation; it suggests that a chelated enolate entertaining an extra transannular contact, as tentatively drawn in **F,** accounts for the formation of **1**.

The concise synthesis of the enticing *nor*-cembranoid sinulariadiolide (**1**) outlined above capitalizes on a remarkable transannular Michael addition/elimination/cyclization/oxa-Michael cascade. While this transformation showcases the power and intricacy of macrocyclic stereocontrol, the route to the required precursor attests to the maturity of RCAM and catalytic alkyne-*trans*-addition[34] as the enabling downstream chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at ##############
Experimental section including characterization data, HPLC traces and NMR spectra of new compounds
Control experiments

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Notes
The authors declare no competing financial interests

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(27) This order of events is crucial: cleavage of the O−N bond prior to metathesis resulted in attack of the released −OH group onto the methyl ester.

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(29) Treatment of **27** with Cs_2CO_3 in CH_2Cl_2/aq. MeOH afforded **28** as a single diastereomer in 94% yield. Under the same conditions, enoate **26** was less efficient (69%); actually, close monitoring indicated that **26** first transforms into **27**, which seems to be the acceptor in this oxa-Michael reaction.

(30) (a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Cascade Reactions in Total Synthesis. *Angew. Chem. Int. Ed.* **2007**, *45*, 7134-7186. (b) Tietze, L. F.; Brasche, G.; Gericke, K. Domino Reactions in Organic Synthesis, Wiely-VCH, Weinheim, 2006.

(31) Harrison-Marchand, A.; Chataigner, I.; Maddaluno, J., Hetero-Michael Additions: Addition of Alcohols. *Science of Synthesis* **2005**, *26*, 1240.

(32) K_2CO_3 or Li_2CO_3 in CH_2Cl_2/aq. MeOH lead to the same stereochemical outcome as Cs_2CO_3, but were less efficient in the original screening; no optimization was attempted.

(33) Guanidine **33** in CH_2Cl_2 does not cleave the acetate in substrate **25**, whereas Me_2NH entailed rapid decomposition.

(34) Fürstner, A. *trans*-Hydrogenation, *gem*-Hydrogenation, and *trans*-Hydrometalation of Alkynes: An Interim Report on an Unorthodox Reactivity Paradigm. *J. Am. Chem. Soc.* **2018** (doi: 10.1021/jacs.8b09782).

cascade comprising

acetate cleavage
transannular Michael addition
elimination & carbonate cleavage
lactonization
oxa-Michael addition of MeOH

RCAM