JOC The Journal of Organic Chemistry

Article

Intramolecular Diels-Alder approaches to the decalin core of verongidolide. The origin of the exo-selectivity: a DFT analysis.

Baba Maiga-Wandiam, Andrei Corbu, Georges Massiot, Francois Sautel, Peiyuan Yu, Bernice Wan-Yi Lin, Kendall N. Houk, and Janine Cossy

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00566 • Publication Date (Web): 01 May 2018

Just Accepted

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Intramolecular Diels-Alder approaches to the decalin core of verongidolide. The origin of the *exo*-selectivity: a DFT analysis.

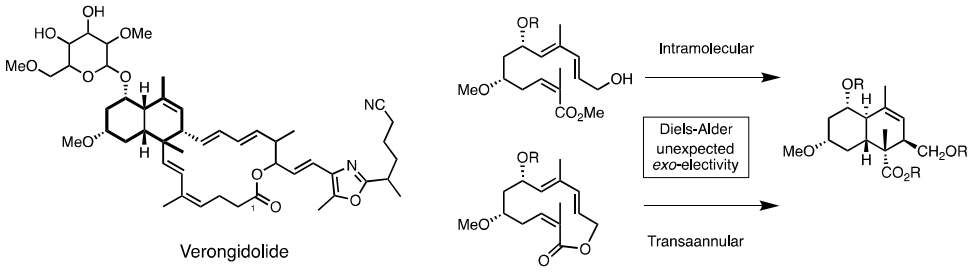
Baba Maiga-Wandiam,[†] Andrei Corbu,[†] Georges Massiot,[‡] François Sautel,[§] Peiyuan Yu,[⊥] Bernice Wan-Yi Lin,[⊥] K. N. Houk,[⊥] Janine Cossy[†*]

[†]Laboratoire de Chimie Organique, Institute of Chemistry, Biology and Innovation (CBI), ESPCI Paris, PSL Research University, CNRS, 10 rue Vauquelin, 75231 Paris, France.

[‡] Université de Reims Champagne-Ardenne, Institut de Chimie Moléculaire de Reims, CNRS, UFR des Sciences Exactes et Naturelles, Campus Sciences, Moulin de la Housse, 51687 Reims Cedex 2, France.

[§] CNRS/Pierre Fabre USR 3388, Centre de Recherche et Développement Pierre Fabre, 3 avenue Hubert Curien, 31035 Toulouse Cedex 01, France

[⊥]Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90065, United States



Abstract

Verongidolide, is a natural macrolactone recently isolated from a New Caledonia sponge, *Verongidolae*. The structure of this natural product is similar to the structure of superstolides, also isolated from a New Caledonian sponge, *Neosiphonia superstes*. From a biological point of view, verongidolide and superstolides A and B present potent cytotoxicity against human oral carcinoma KB (0.3 nM). By comparing the ^{1}H-NMR chemical shifts as well as the coupling constants, we conclude that verongidolide possesses a *cis*-decalin core and we hypothesize that the relative configuration of the *cis*-decalin core is similar to the one of superstolide A. To verify this hypothesis, an intramolecular and a transannular Diels-Alder were attempted to construct the decalin core. Unexpectedly, the selectivity of the Diels-Alder reactions was *exo* and an in-depth DFT calculation of the key reaction mechanism was achieved in order to understand the factors controlling this unexpected selectivity.

Introduction

Macrolactone **1**, is a natural product recently isolated from a New Caledonia sponge, *Verongidolae*, to which we gave the name verongidolide.[1] The structure of this natural product is similar to the structure of superstolides, also isolated from a New Caledonian sponge, *Neosiphonia superstes* (Figure 1).[2] From a biological point of view, verongidolide and superstolides A and B present a potent cytotoxicity against human oral carcinoma KB (0.3 nM).

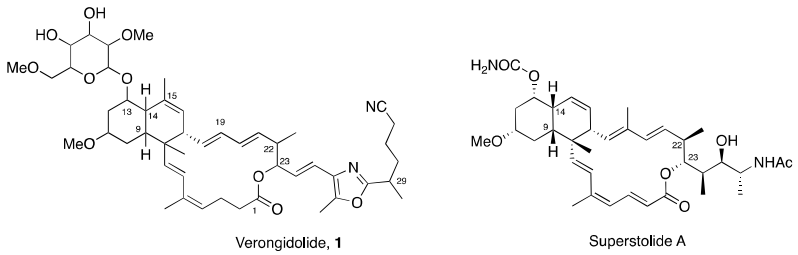
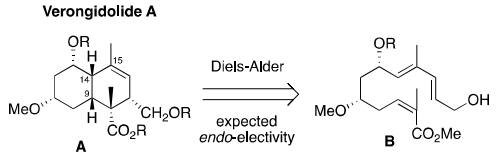


Figure 1. Natural macrolactones: verongidolide and superstolide A

If the planar structure of verongidolide was established, no reliable information about the relative and absolute configuration of the stereogenic centers was reported. By comparing the structure of the decalin core of verongidolide to the structure of superstolide A, one can notice that verongidolide possesses a glycosidic substituent at C13 and a methyl at C15 *versus* a carbamate group at C13 and a hydrogen at C15 for superstolide A. Structural differences can also be noticed in the macrolactone region. The macrolactone of verongidolide is not substituted by a methyl at C19 as in superstolide A and a conjugated diene is present instead of a triene in superstolide A. A major difference between verongidolide and superstolide A is the side chain at C23. In verongidolide, the side chain possesses a trisubstituted oxazole ring and a terminal nitrile group and in the case of superstolide A the side chain is constituted by a *N*-acetyl 1,2-amino alcohol. By comparing the ^{1}H-NMR spectra of both natural products, we conclude that verongidolide has a *cis*-decalin core and we hypothesize that the relative configurations of the substituents on the *cis*-decalin are similar to the ones of superstolide A.[3]

Results and Discussion

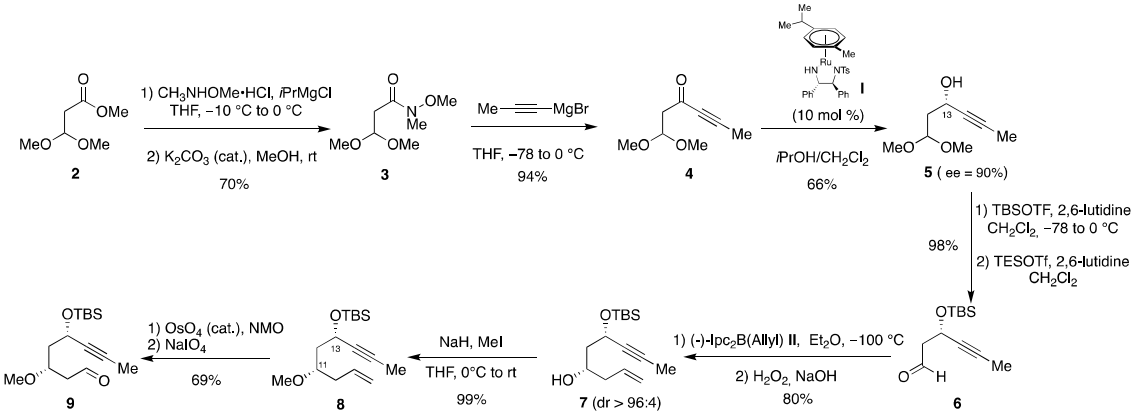
Based on precedents, two Diels-Alder type of reactions[4] can be used to access a *cis*-decalin system present in macrocyclic compounds, either an intramolecular Diels-Alder reaction (IMDA) or a transannular Diels-Alder reaction (TADA).[5] At first, we chose to study an IMDA reaction to produce the *cis*-decalin system present in verongidolide.[6] To access the *cis*-decalin **A**, according to an *endo*-selective IMDA process, the required triene **B** possessing a (*Z*)-α,β-unsaturated ester and a (*Z,E*)-diene has to be synthesized (Scheme 1).



Scheme 1. Retrosynthetic analysis: access to the verongidolide decalin core by IMDA

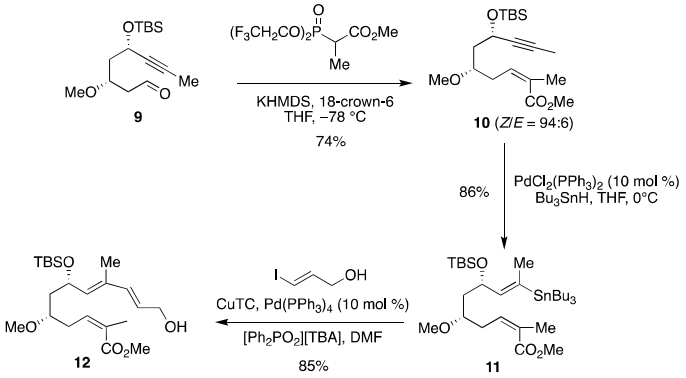
The synthesis of triene **B** started from methyl 3,3-dimethoxy propionate **2**. After treatement of **2** with the Weinreb amine hydrochloride under basic conditions (*i*PrMgCl, THF, −10 °C to 0 °C) followed by the addition of methanol, in the presence of K_2CO_3 (cat.), **3** was isolated in 70% yield (over the 2 steps). The transformation of **3** to (*R*)-hydroxyaldehyde **6** was achieved in 4 steps. After converting acetal **3** into ketone **4** by addition of propynylmagnesium bromide (THF, −78 °C to 0 °C, 94%),[7] the ketone was enantioselectively reduced by applying a Noyori asymmetric hydrogen transfer using Ts-DPEN-RuCl(*p*-cymene) **I** (10 mol %, *i*PrOH-CH_2Cl_2) to produce **5** in 66% yield with an excellent ee (ee = 90%).[8] The reaction needed a high loading in Noyori's catalyst (10 mol%), to increase the reaction rate, as at lower loading (5 mol%), a competitive reduction of the triple bond was eroding the yields in the desired propargylic alcohol **5**. After an alcohol protection/acetal hydrolysis sequence (TBSOTf, 2,6-

lutidine then TESOTf, 2,6-lutidine), aldehyde **6** was isolated in 98% yield. The control of the stereogenic center at C13 was achieved by applying an enantioselective Brown allylboration to aldehyde **6**. Thus, treatment of **6** with (−)$Ipc_2BAllyl$ **II** led to homoallylic alcohol **7** with an excellent diastereoselectivity (dr>96:4).[9] The resulting hydroxyl group in **7** was methylated (NaH, MeI, 0 °C to rt, 99%) and, after a selective oxidative cleavage of the double bond (OsO_4, NMO then $NaIO_4$), aldehyde **9** was isolated in 69% yield. By using two face selective agents (**I** and **II**), the control of the stereogenic centers at C11 and C13 was achieved with an excellent diastereo- and enantioselectivity (Scheme 2).



Scheme 2. Synthesis of aldehyde **9**

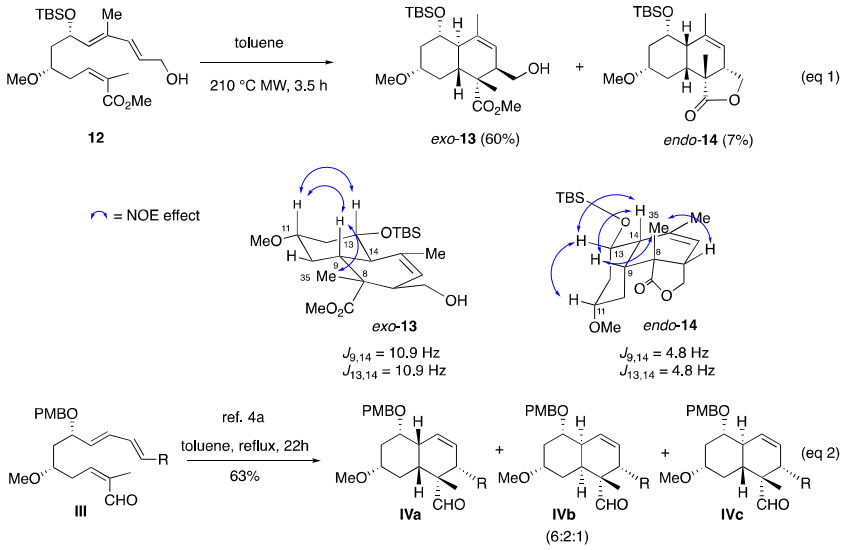
With aldehyde **9** in hand, this compound was transformed to the precursor of the Diels-Alder adduct in three steps. The first step, to install the required (*Z*)-α,β-unsaturated ester, was a Still-Gennari olefination [KHMDS, 18-crown-6, $(CF_3CH_2CO)_2PO$-CH(Me)CO_2Me] which afforded **10** in 74% yield with a *Z*/*E* ratio of 94:6.[10] The (*Z*,*E*)-diene counterpart was introduced by using a palladium-catalyzed stereoselective hydrostannlyation of the alkyne group [$PdCl_2(PPh_3)_2$, *n*Bu_3SnH, THF, 0 °C, 86%] followed by a Stille coupling reaction of the ensued vinylstannane **11** with (*E*)-3-iodopropenol. The required Diels-Alder precursor **12** was isolated in 85% yield and with an excellent (*Z*,*E*) selectivity (Scheme 3).[11]



Scheme 3. Synthesis of the Diels-Alder precursor **12**

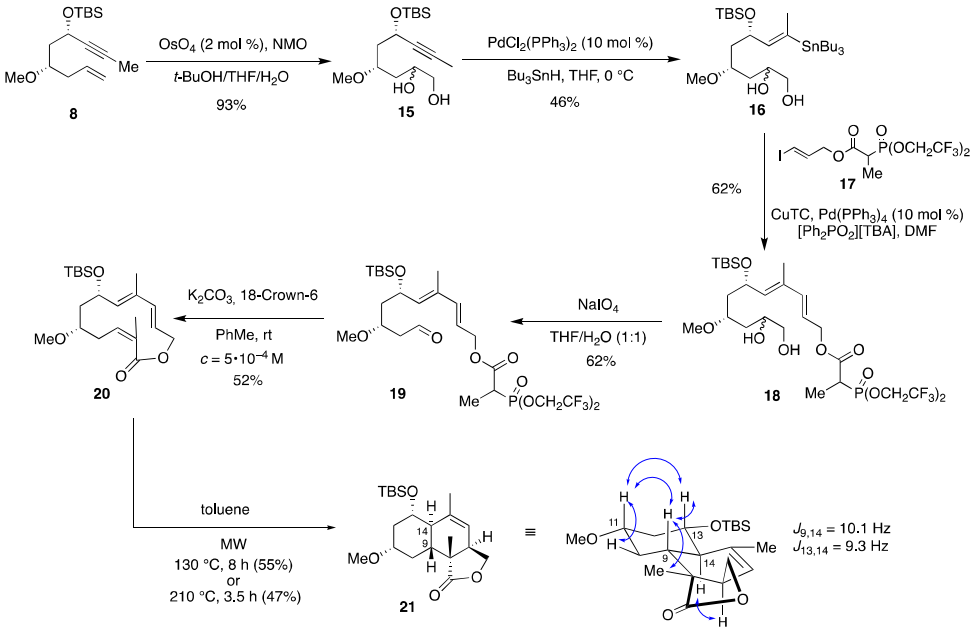
Intermediate **12** was heated at 210 °C in toluene under microwave irradiation. Unfortunately, the *trans*-decalin **13** was obtained as the major product in 60% yield, which corresponds to the *exo*-adduct ($J_{H9\text{-}H14}$ = 10.9 Hz) accompanied by the tricyclic lactone **14** possessing a *cis*-decalin ring system (7%) ($J_{H9\text{-}H14}$ = 4.8 Hz), which corresponds to the *endo*-adduct (Scheme 4, eq 1).[12] It is worth mentioning that, during the total synthesis of superstolide A, compound **III** was transformed to a mixture of decalins **IV** by using an IMDA process, **IVa** being the major product (63%, 6:2:1) (Scheme 4, eq 2).[4a] The major difference between precursors **12** and **III**,

being the methyl group on the diene at C15 thus, we suspected this methyl group to be at the origin of the favored *exo*-transition state during the transformation of **12** to the Diels-Alder adducts (Figure 3).[13]



Scheme 4. Intramolecular Diels-Alder reaction

As the *endo*-IMDA did not produce the *cis*-decalin system, we have envisaged the addition of an extra strain in the *exo*-transition state by switching to a transannular Diels-Alder (TADA) reaction by targeting directly lactone **14**.[14] This lactone may be synthesized from macrolactone **20** available from the already prepared enyne **8** (5 steps) (Scheme 5).[15] At first, a selective dihydroxylation was performed (OsO_4, *t*-BuOH, THF, H_2O, 93%) followed by a stereoselective hydrostannylation to produce **16** [*n*-Bu_3SnH, $PdCl_2(PPh_3)_2$, THF, 0 °C, 46%]. A Stille coupling was realized, under Fürstner *et al.*[16] conditions between vinylstannane **16** and vinyl iodide **17** (CuTC, $Pd(PPh_3)_4$, $[Ph_2PO_2][TBA]$, DMF). Diene **18** was isolated in 62% yield and, after oxidative cleavage of the diol ($NaIO_4$, 62%), the resulting aldehyde **19** was engaged in an intramolecular Still-Gennari olefination to produce the desired macrocyclic lactone **20**. This lactone was heated under microwave irradiation at 130 °C and also at 210 °C but, again, the *trans*-decalin **21** was obtained in 55% and 47% yield respectively (Scheme 3). The *trans*-junction of the 5-membered ring lactone was not sufficient to counterbalance the presence of the methyl group at C15, as even the TADA reaction proceeded according to an *exo*-process.



Scheme 5. Trans-annular Diels-Alder approach

To verify whether the methyl group at C15 is the main contributor to the *exo*-Diels-Alder pathway or if other reasons were responsible of the *exo*-transition state, DFT calculations of the transition states were undertaken. In previous studies, we have shown that the computation of transition states energies can be performed reliably for complex and difficult Diels-Alder reactions.[17] Simplified models, where a TBS protecting group was replaced by a methyl group, e.g. trienes **III'**, **12'** and **20'** were studied (Figures 2-4). In the case of **III'**, a triene without a C15 methyl group (as in superstolide A), the *endo*-transition state (*endo*-**TS1**) is favored compared to the *exo*-transition state (*exo*-**TS1**) by 2.2 kcal/mol. In the case of **12'**, in which a methyl group is present at C15, the *exo*-**TS2** transition state is more stable than the *endo*-**TS1** transition state by 1.3 kcal/mol (Figure 2). The *endo* transition structure has unfavorable steric interactions between the methyl group and the axial hydrogens on the tether. Thus, the presence of a methyl group is reversing the *endo/exo* selectivity of the IMDA reaction.

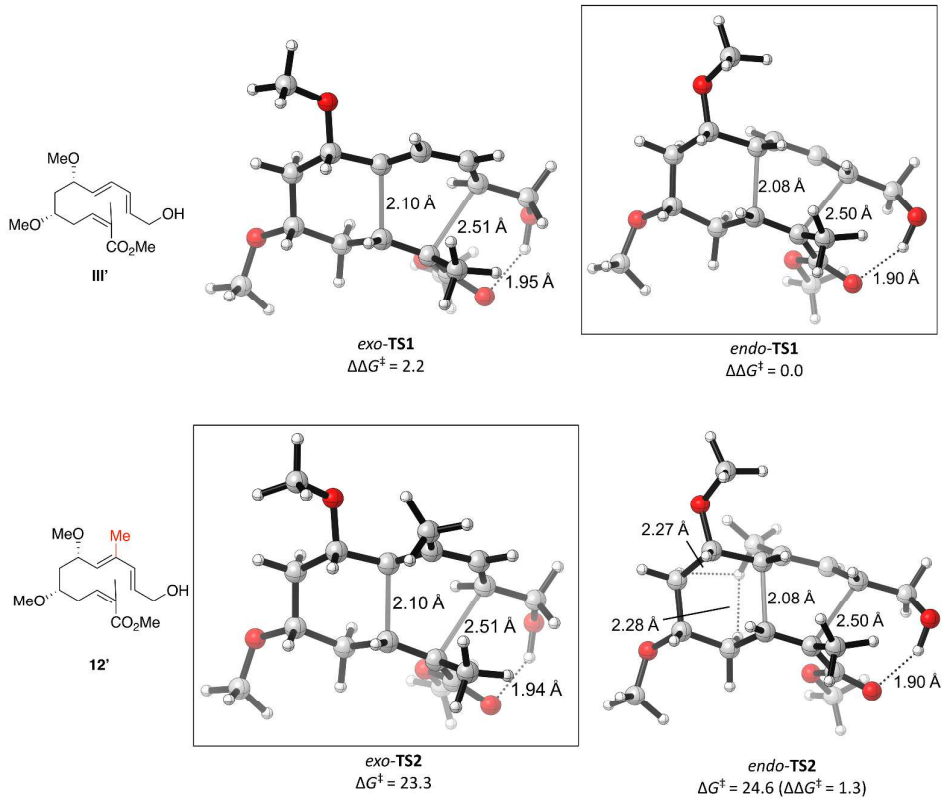


Figure 2. Transition structures for the IMDA reactions of substrates with and without the methyl group on the 3-position of the diene. Free energies are in kcal/mol.

For the relevant model **12'**, both the *endo* and *exo* pathways were fully modeled, and the relative stabilities of the resulting *exo*-**13'** and *endo*-**14'** decalins were calculated. There is no significant difference between them (0.3 kcal/mol). These theoretical results suggest that the Diels-Alder reaction, in the case of **12'**, is under kinetic control (Figure 3). Two additional *endo*- and *exo*- transition structures were also computed (Figure S1). Their energies are higher than that of *exo*-**TS1** by 2.6 and 5.3 kcal/mol, respectively. The corresponding products were not observed experimentally, in agreement with the computed barriers.

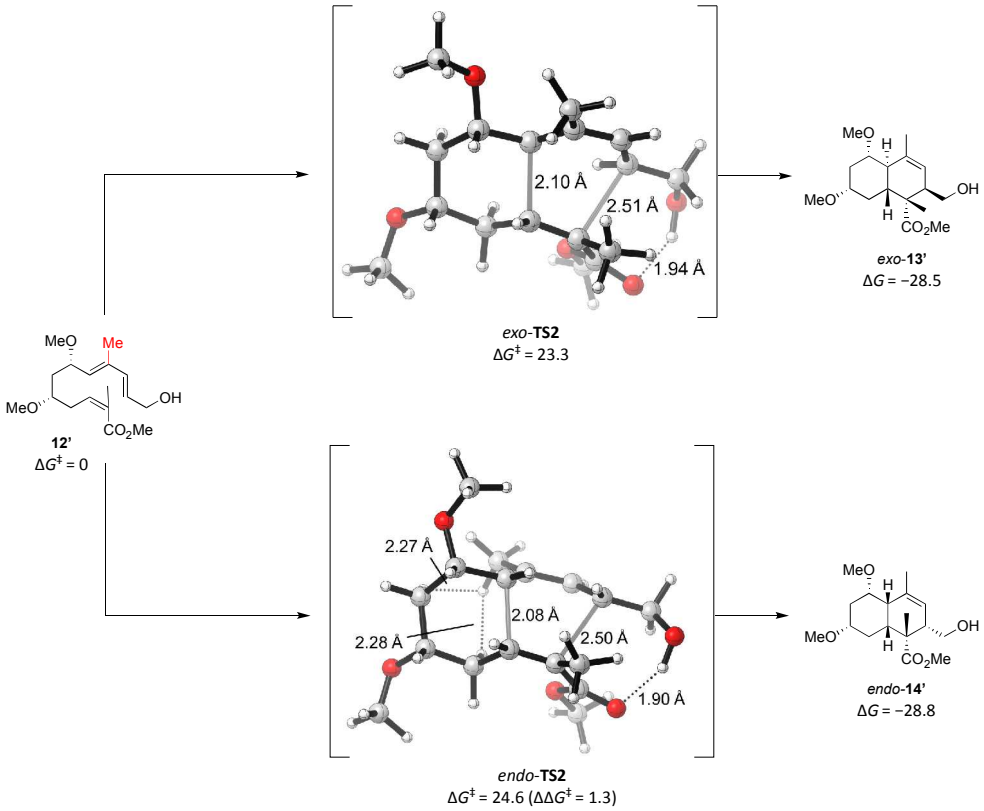


Figure 3. Full pathway for the IMDA reaction of **12'** that leads to the corresponding *exo*- and *endo*-products, respectively. Free energies are in kcal/mol.

We next explored the TADA reaction pathway on the model macrolactone **20'** (Figure 4). As predicted, the *exo* product that has a *trans*-fused [5,6]-bicyclic structure is much less stable than the *endo* product by 10.8 kcal/mol (Figure 4). The transition structures are more synchronous in the TADA reaction. The activation energies are ~3 kcal/mol higher than the corresponding IMDA reactions. However, the *exo*-transition state *exo*-**TS3** is still favored over the *endo*-**TS3** by 1.2 kcal/mol. The experimentally observed selectivity could be explained by the irreversibility of the reaction (still under kinetic control).

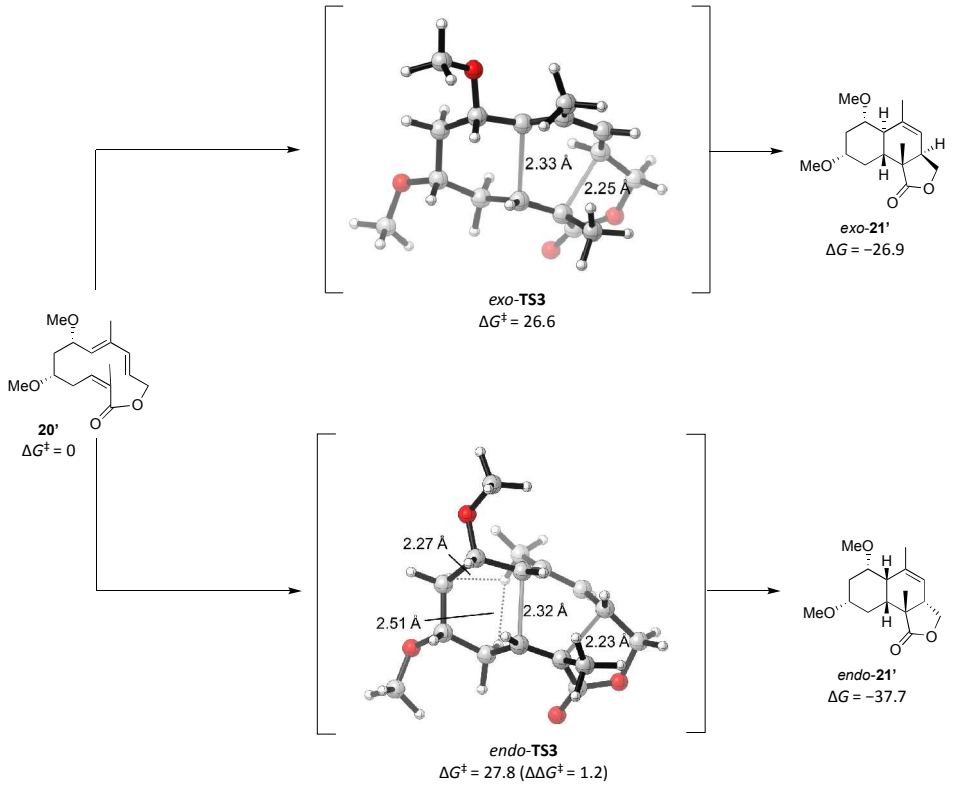


Figure 4. Full pathway for the TADA reaction of **20'** that leads to the corresponding *exo* and *endo* products, respectively. Free energies are in kcal/mol.

Based on the experimental results and on the calculations, the access to the *cis*-decalin core of verongidolide will be difficult through an IMDA or a TADA process applied to diverse trienes having a methyl group at C15. In consequence, another approach to synthesize the *cis*-decalin core of verongidolide is under investigation in our laboratory and will be reported in due course.

Experimental Section

Computational details

All density functional theory (DFT) calculations were performed using *Gaussian 09*.[18] Geometry optimizations and frequency calculations were performed at the M06-2X/6-31G(d) level of theory.[19] Normal vibrational mode analysis confirmed that optimized structures are minima or transition structures. Truhlar's quasiharmonic correction was used to compute molecular entropies to reduce error caused by the breakdown of the harmonic oscillator approximation.[20] More accurate M06-2X/6-311+G(d,p) single-point energies with the SMD solvation model were computed.[21] All reported energies are Gibbs free energies determined by summing these higher level single-point electronic energies and ZPE and thermal corrections determined at the lower level.

Experimental section

General Experimental Methods. All moisture and oxygen sensitive reactions were carried out in oven-dried glassware under an argon atmosphere. THF, Et_2O, and CH_2Cl_2 were dried

using a purificator. Acetone, petroleum ether (PE), pentane, and ethyl acetate (EtOAc) were used as received. Commercially available reagents were used as received. Reactions run at room temperature were performed between 20 and 25 °C. Reactions run under microwave heating were performed in a microwave reactor, the temperature being controlled by an IR sensor that was calibrated by an internal probe. Solvent evaporations were conducted under reduced pressure at temperatures less than 45 °C. TLC was performed on silica gel plates visualized either with a UV lamp (254 nm) or using a staining solution (p-anisaldehyde or $KMnO_4$) followed by heating. Column chromatography was carried out under positive pressure using silica gel (Merck-Kieselgel 60, 230−400) and the indicated solvents [v/v; used without purification, including petroleum ether (boiling range 40−60 °C)]. ^{1}H NMR spectra of samples were run at 400 MHz, and chemical shifts are given in ppm (δ) comparatively to the residual solvent signal, which was used as an internal reference (benzene-d_6: δ = 2.16 ppm; $CDCl_3$: δ = 7.26 ppm). Coupling constants (*J*) are given in Hertz (Hz), and the following abbreviations are used to describe the signal multiplicity: s (singlet), br (broad), d (doublet), t (triplet), q (quadruplet), quint (quintuplet), and m (multiplet, massif). ^{13}C NMR spectra of the samples were run at 100 MHz. Chemical shifts are given in ppm (δ) comparatively to the residual solvent signal, which was used as an internal reference (benzene-d_6: δ = 128.06 ppm; $CDCl_3$: δ = 77.0 ppm). Infrared (IR) spectra were recorded neat (IRFT), and wavenumbers are indicated in cm^{-1}. High-resolution mass spectra (HRMS) were performed using ESI and a TOF mass analyzer.

N,3,3-Trimethoxy-N-methylpropanamide (**3**).[7] To a solution of *N,O*-dimethylhydroxylamine hydrochloride (8.32 g, 85.34 mmol, 1.1 equiv) in THF (155 mL), cooled to −10 °C, was added dropwise *i*PrMgCl (2M in THF, 89.2 mL, 178.43 mmol, 2.3 equiv). The mixture was stirred for 10 min at the same temperature, then methyl 3,3-dimethoxypropionate (11 mL, 77.58 mmol, 1 equiv) was added dropwise and the reaction was allowed to warm to room temperature and stirred for 24 h. A second portion of *i*PrMgCl (2M in THF, 30 mL, 60 mmol, 0.7 equiv) was added and the reaction was stirred for 3 h. After confirming completion by GC monitoring, the reaction mixture was poured into a mixture of ice and a saturated aqueous solution of NH_4Cl. The phases were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product obtained was contaminated with 35% of MeOH elimination byproduct. A solution of the crude product obtained above in MeOH (85 mL) was treated with potassium carbonate (1.98 g, 14.33 mmol, 18.5 mol %) and the mixture was stirred at room temperature for 4.5 h with concomitant GC monitoring. After complete conversion of MeOH elimination byproduct, the solvent was evaporated *in vacuo*. The residue obtained was diluted with CH_2Cl_2 and washed with water and brine. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE/EtOAc = 5:5 to 3:7) to afford the Weinreb amide **3** as a colorless oil (9.67 g, 70%). IR (neat) 1656, 1609, 1442, 1388, 1235, 1182, 1118, 1063, 995, 921, 836, cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 4.84 (t, *J* = 5.7 Hz, 1H), 3.67 (s, 3H), 3.37 (s, 6H), 3.16 (s, 3H), 2.75 (d, *J* = 5.7 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 170.4, 102.2, 61.3, 54.1 (2C), 36.3, 31.8; MS (EI) *m/z* (%) 177 ($M^{+\bullet}$, <1), 146 ($[M\text{-}OMe]^+$, 10), 117(19), 104(15), 85 (39), 75 (100), 60 (9).

1,1-Dimethoxyhex-4-yn-3-one (**4**). To a solution of Weinreb amide **3** (9.28 g, 52.74 mmol, 1 equiv) in THF (300 mL), cooled to −78 °C, was added dropwise 1-propynylmagnesium bromide (0.5 M solution in THF, 115 mL, 57.61 mmol, 1.1 equiv) over 30 min. The mixture was stirred for 10 min at −78 °C, then it was warmed to 0 °C and stirred for 14 h. The reaction mixture was poured into a cold saturated aqueous solution of ammonium chloride and diluted with EtOAc. The phases were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography (PE/EtOAc = 9:1 to 4:1) to afford ketone **4** as an orange oil (7.74 g, 94%). IR (neat) 1671, 1444, 1364, 1252, 1165, 1116, 1072, 1052, 1000, 974 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 4.91 (t, *J* = 5.8 Hz, 1H), 3.33 (s, 6H), 2.83 (d, *J* = 5.8 Hz, 2H), 2.00 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 183.5, 100.6, 91.0, 80.2, 53.4 (, 2C), 48.7, 4.0; HRMS (ESI) *m*/*z* $[M+Na]^+$ calculated for $(C_8H_{12}O_3)Na^+$: 179.0679, found: 179.0679.

(S)-1,1-Dimethoxyhex-4-yn-3-ol (**5**). To a solution of propargylic ketone **3** (6.36 g, 40.75 mmol, 1 equiv) in *i*PrOH (764 mL) and CH_2Cl_2 (30 mL) at room temperature was added Noyori catalyst **I** [(*S*,*S*)-Ru] (2.44 g, 4.07 mmol, 10 mol %) in CH_2Cl_2 (11 mL). The reaction mixture was stirred for 2.5 h and then concentrated under vacuum. The crude mixture was purified by silica gel column chromatography (PE/EtOAc = 4:1) to afford the propargylic alcohol **5** as a light yellow oil (4.25 g, 66%) along with the an over reduction byproduct as a yellow oil (1.96 g, 30%, see SI for details). $[\alpha]_D^{20}$ – 11.0 (*c* = 1.0, $CHCl_3$); IR (neat) 1385, 1190, 1190, 1123, 1052, 912, 831, 755 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 4.68 (t, *J* = 5.8 Hz, 1H), 4.48 (tq, *J* = 5.7, 2.2 Hz, 1H), 3.36 (s, 3H), 3.34 (s, 3H), 1.98 (t, *J* = 5.8 Hz, 2H), 1.83 (d, *J* = 2.0 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 102.8, 81.0, 79.5, 59.3, 53.4, 53.1, 39.8, 3.5; HRMS (ESI) *m*/*z* $[M+Na]^+$ calculated for $(C_8H_{14}O_3)Na^+$: 181.0835, found: 181.0836. The OH group was not detected in the ^{1}H-NMR.

(S)-(S)-1,1-dimethoxyhex-4-yn-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate, Mosher ester of **5**. To a solution of propargylic alcohol **5** (10.1 mg, 64 μmol, 1 equiv) in dry CH_2Cl_2 (1.1 mL) at room temperature was added pyridine (16 μL, 198 μmol, 3.1 equiv), followed by *S*-(−)-MTPACl (23 μL, 122 μmol, 1.9 equiv). The mixture was stirred at room temperature for 19 h and then quenched with water. After dilution with Et_2O, the phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. After proton NMR analysis, the crude product was purified by preparative-TLC plate to afford the Mosher ester as a colorless oil (13 mg, 54.2%, dr = 95:5). $[\alpha]_D^{20}$ + 2.0 (*c* = 1.0, $CHCl_3$); IR (neat) ν 2948, 1750, 1451, 1390, 1270, 1248, 1167, 1123, 990, 963, 754, 648 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.42-7.38 (m, 3H), 5.53 (ddq, *J* = 8.1, 6.3, 2.1, 1H), 4.50 (t, *J* = 5.9 Hz, 1H), 3.55 (d, *J* = 1.0 Hz, 3H), 3.33 (s, 3H), 3.31 (s, 3H), 2.21-2.15 (m, 1H), 2.09 (td, *J* = 14.0, 6.2 Hz, 1H), 1.83 (d, *J* = 2.0 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.5, 132.0, 129.6 (2C), 128.3, 127.5 (2C), 101.0, 83.4, 74.9, 63.9, 55.5, 53.1, 53.0, 37.9, 3.5; HRMS (ESI) *m*/*z* $[M+Na]^+$ calculated for $(C_{18}H_{21}F_3O_5)Na^+$: 397.1233, found: 397.1230.

(S)-tert-butyl((1,1-dimethoxyhex-4-yn-3-yl)oxy)dimethylsilane, TBS protected ether of **5**. To a solution of propargylic alcohol **5** (5.09 g, 32.14 mmol) in CH_2Cl_2 (184 mL) at −78 °C was added 2,6-lutidine (8.2 mL, 70.71 mmol, 2.2 equiv), followed by TBSOTf (11.08 mL, 48.21

mmol, 1.5 equiv). The mixture was stirred at −78 °C for 0.5 h and at 0 °C for 2 h. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ and the phases were separated. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration and concentration under vacuum, the crude product was obtained and purified by silica gel column chromatography (PE/EtOAc = 10:0.2 to 10:0.3) to afford quantitatively the protected alcohol as an orange oil (8.76 g). $[\alpha]_D^{20}$ – 48.8 (*c* = 1.0, $CHCl_3$); IR (neat) 2955, 1472, 1386, 1362, 1251, 1190, 1148, 972, 833, 776, 666 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 4.53 (dd, *J* = 6.7, 5.0 Hz, 1H), 4.40 (ddq, *J* = 8.1, 5.6, 2.2 Hz, 1H), 3.32 (s, 3H), 3.31 (s, 3H), 1.99-1.86 (m, 2H), 1.81 (d, *J* = 2.2 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 101.7, 80.4, 80.3, 59.8, 53.10, 52.6, 41.8, 25.8 (3C), 18.1, 3.5, −4.5, −5.1; HRMS (ESI) *m*/*z* calculated for $(C_{14}H_{28}O_3Si)Na^+$: 295.1700, found: 295.1704.

(S)-3-[(tert-Butyldimethylsilyl)oxy]hex-4-ynal (**6**). To a solution of TBS-protected alcohol **5** (7.53 g, 27.63 mmol, 1 equiv) in CH_2Cl_2 (270 mL), cooled to −78 °C, was added 2,6-lutidine (9.64 mL, 82.91 mmol, 3 equiv), followed by TESOTf (12.5 mL, 55.27 mmol, 2 equiv). The mixture was warmed to 0 °C and stirred for 2 h at the same temperature. After confirming the disappearance of the starting material by TLC or GC analysis, the reaction mixture was quenched by addition of water and stirred for 1 h at 0 °C. The phases were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography (PE/EtOAc = 95:5) to afford the aldehyde **6** as an orange oil (6.25 g, quant.). $[\alpha]_D^{20}$ – 58.9 (*c* = 1.0, $CHCl_3$); IR (neat) 1727, 1472, 1342, 1252, 1087, 1005, cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.81 (t, *J* = 2.3 Hz, 1H), 4.81 (ddq, *J* = 6.7, 5.1, 2.1 Hz, 1H), 2.71 (ddd, *J* = 16.1, 6.6, 2.5 Hz, 1H), 2.63 (ddd, *J* = 16.1, 5.0, 2.2 Hz, 1H), 1.82 (d, *J* = 2.1, 3H), 0.87 (s, 9H), 0.14 (s, 3H), 0.10 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 200.1, 81.9, 79.2, 58.5, 51.7, 25.7 (3C), 18.1, 3.5, −4.5, −5.2; HRMS (ESI) *m*/*z* calculated for $(C_{12}H_{22}O_2Si)Na^+$: 249.1281, found: 249.1283.

(4S,6S)-6-[(tert-Butyldimethylsilyl)oxy]non-1-en-7-yn-4-ol (**7**). A (−)-Ipc_2B(allyl)borane solution (1M in pentane, 25 mL, 25 mmol, 1 equiv) was added to a round bottom flask containing anhydrous Et_2O (50 mL) and cooled to −100 °C (MeOH, liq N_2). To this solution, was slowly added along the side of the flask, via cannula, a solution of aldehyde **6** (5.66 g, 25 mmol, 1 equiv) in Et_2O (25 mL). The mixture was stirred for 2 h at −100 °C, then methanol (1 mL) was added to quench the reaction. The reaction mixture was allowed to warm to room temperature, and then NaOH (3N, 10 mL) was added, followed by H_2O_2 (20 mL). After stirring for 8 h at room temperature, the reaction mixture was diluted with Et_2O and water. The phases were separated and the aqueous layer was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography (PE/EtOAc = 10:0.3 to 95:5) to afford the alcohol **7** as a colorless oil (5.37 g, 80%, dr = 96:4). $[\alpha]_D^{20}$ –41.9 (*c* = 1.0, $CHCl_3$); IR (neat) 1471, 1361, 1251, 1146, 1071, 1003, 913, 834 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ •(ppm) 5.83 (ddd, *J* = 17.1, 10.3, 7.2 Hz, 1H), 5.13-5.07 (m, 2H), 4.55 (tq, *J* = 6.8, 2.2 Hz, 1H), 3.89 (m, *J* = 6.0 Hz, 1H), 2.25-2.21 (m, 2H), 1.82-1.78 (m, 2H), 1.81 (d, *J* = 2.1 Hz, 3H), 0.90 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ •(ppm) 134.6, 117.6, 81.3, 80.2, 69.8, 63.1, 44.6, 41.9, 25.7 (3C), 18.0, 3.5, −4.3, −5.0; HRMS (ESI) *m*/*z* calculated for $(C_{15}H_{28}O_2Si)Na^+$: 291.1751, found: 291.1749. The OH group was not detected in the ^{1}H-NMR.

tert-Butyl[((4S,6S)-6-methoxynon-8-en-2-yn-4-yl)oxy]dimethylsilane (**8**). To a solution of alcohol **7** (4.71 g, 17.55 mmol, 1 equiv) in THF (180 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 2.81 g, 70.21 mmol, 4 equiv). The reaction mixture was stirred at 0 °C for 10 min, then MeI (7.65 mL, 122.86 mmol, 7 equiv) was added. The resulting mixture was stirred at room temperature for 19 h, and then the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl. The phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (PE/EtOAc = 98:2 to 95:5) to afford enyne **8** as a colorless oil (4.96 g, quant.). $[\alpha]_D^{20}$ – 17.8 (*c* = 1.0, $CHCl_3$); IR (neat) 1641, 1471, 1462, 1360, 1250, 1149, 1076 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 5.82 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.11-5.04 (m, 2H), 4.48 (ddq, *J* = 8.2, 6.1, 2.1 Hz, 1H), 3.45 (dtd, *J* = 8.1, 5.7, 4.6 Hz, 1H), 3.33 (s, 3H), 2.29 (dddt, *J* = 7.1, 5.8, 2.6, 1.5 Hz, 2H) 1.90-1.79 (m, 1H), 1.83 (d, *J* = 2.1 Hz, 3H), 1.71 (ddd, *J* = 13.7, 8.2, 4.6, 1H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 134.5, 117.1, 80.6, 80.5, 77.5, 60.9, 56.7, 43.1, 37.9, 25.8 (3C), 18.2, 3.5, −4.5, −5.0; HRMS (ESI) *m*/*z* calculated for $(C_{16}H_{30}O_2Si)Na^+$: 305.1907, found 305.1904.

(3R,5S)-5-[(tert-Butyldimethylsilyl)oxy]-3-methoxyoct-6-ynal (**9**). To a solution of enyne **8** (2.0 g, 7.09 mmol, 1 equiv) in *t*-BuOH/THF/H_2O (64:12.8:6.4 mL) at room temperature was added 4-methylmorpholine *N*-oxide (NMO) (1.41 g, 12.05 mmol, 1.7 equiv), followed by OsO_4 (2.5% wt in *t*BuOH, 4.6 mL, 0.35 mmol, 0.05 equiv). The reaction mixture was stirred for 2 h at room temperature and then quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$. After dilution with EtOAc, the phases were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography (PE/EtOAc = 1:1 to 2:3) to afford the corresponding diol as a yellow oil (2.09 g, 93%, dr = 60:40). To a solution of the diol intermediate (2.82 g, 8.29 mmol, 1 equiv) in THF (30 mL) and H_2O (30 mL) at room temperature was added $NaIO_4$ (5.32 g, 24.88 mmol, 3 equiv). The mixture was stirred for 2 h at room temperature, and then quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$. The phases were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude material was purified by silica gel column chromatography (PE/EtOAc = 9:1) to yield aldehyde **9** as a colorless oil (1.77 g, 75%). $[\alpha]_D^{20}$ – 29.1 ($CHCl_3$, *c* = 1.0); IR (neat) 1713, 1463, 1362, 1252, 1147, 1084, 1005, 939, 911 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.79 (t, *J* = 2.2 Hz, 1H), 4.49 (ddq, *J* = 6.8, 6.2, 2.0 Hz, 1H), 3.96 (qd, *J* = 6.6, 5.0 Hz, 1H), 3.34 (s, 3H), 2.69-2.57 (m, 2H), 2.03 (dt, *J* = 13.8, 6.4 Hz, 1H), 1.83 (d, *J* = 2.2 Hz, 3H), 1.82-1.72 (m, 1H), 0.88 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 201.4, 81.1, 80.0, 73.7, 60.5, 56.9, 48.3, 42.9, 25.8 (3C), 18.1, 3.5, −4.5, −5.1; HRMS (ESI) *m*/*z* $[M+Na]^+$ calculated for $(C_{15}H_{28}O_3Si)Na^+$: 307.1700, found: 307.1701.

(5S,7S,Z)-Methyl 7-[(tert-butyldimethylsilyl)oxy]-5-methoxy-2-methyldec-2-en-8-ynoate (**10**). To a solution of methyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)propanoate (1.70 g, purity = 90%, 4.61 mmol, 1.2 equiv) and 18-crown-6 ether (5.07 g, 19.2 mmol, 5 equiv) in anhydrous THF (62 mL), cooled to − 78 °C, was added dropwise a solution of KHMDS (0.5 M in toluene, 9.2 mL, 4.61 mmol, 1.2 equiv). The mixture was stirred for 30 min at the same temperature, and then a solution of aldehyde **9** (1.09 g, 3.84 mmol, 1 equiv) in THF (14 mL) was added dropwise. After stirring for 1 h, the reaction was quenched with a saturated

aqueous solution of NH_4Cl. The mixture was diluted with Et_2O and extracted three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude material was purified by silica gel column chromatography (PE/EtOAc = 10:0.5) to yield the α,β-unsaturated ester **10** as a colorless oil (1.0 g, 74%). $[\alpha]_D^{20}$ – 13.3 (*c* = 1.0, $CHCl_3$); IR (neat) 1717, 1460, 1435, 1361, 1249, 1222, 1131, 1085, cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 6.02 (td, *J* = 7.2, 1.5 Hz, 1H), 4.47 (ddq, *J* = 7.8, 6.3, 2.0 Hz, 1H), 3.73 (s, 3H), 3.52-3.48 (m, 1H), 3.33 (s, 3H), 2.73 (ddt, *J* = 7.3, 5.6, 1.8 Hz, 2H), 1.91 (q, *J* = 1.9 Hz, 4H), 1.83 (d, *J* = 2.2 Hz, 3H), 1.68 (ddd, *J* = 13.7, 7.9, 4.8 Hz, 1H), 0.88 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 168.2, 138.8, 128.5, 80.6, 80.5, 77.4, 60.9, 56.6, 51.2, 43.2, 33.1, 25.8 (3C), 20.80, 18.2, 3.53, −4.5, −5.0; HRMS (ESI) *m/z* calculated for $(C_{19}H_{34}O_4Si)Na^+$: 377.2118, found: 377.2118.

(2Z,5S,7S,8E)-Methyl 7-[(tert-butyldimethylsilyl)oxy]-5-methoxy-2-methyl-9-(tributylstannyl) deca-2,8-dienoate (**11**). To a solution of alkyne **10** (819 mg, 2.31 mmol) in dry THF (26 mL), cooled to 0 °C, was added $PdCl_2(PPh_3)_2$ (162 mg, 0,231 mmol, 10 mol %), followed by a slow syringe pump addition of Bu_3SnH (870 μL, 3.23 mmol, 1.4 equiv) over 1 h. The reaction mixture was stirred at 0 °C for 1 h, then concentrated under vacuum. The crude mixture was purified by silica gel column chromatography (PE/EtOAc = 98:2 to 97:3) to afford the vinyl stannane **11** as a colorless oil (1.28 g, 86%).**Error! Bookmark not defined.** $[\alpha]_D^{20}$ – 2.7 (*c* = 1.0, $CHCl_3$); IR (neat) 1720, 1460, 1435, 1376, 1250, 1220, 1136, 1073, 1004, 963, 939 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 6.01 (td, *J* = 7.1, 1.6 Hz, 1H), 5.44 (dq, *J* = 8.3, 1.9 Hz, 1H), 4.66 (dt, *J* = 8.2, 6.7 Hz, 1H), 3.72 (s, 3H), 3.28 (s, 4H), 2.76 (m, 2H), 1.91 (d, *J* = 1.5 Hz, 3H), 1.85 (d, *J* = 1.7 Hz, 4H), 1.54-1.38 (m, 7H), 1.35-1.25 (m, 6H), 0.90-0.86 (m, 24H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 168.2, 144.3, 139.1, 138.1, 128.3, 77.3, 65.6, 56.0, 51.2, 42.1, 32.7, 29.2 (3C), 27.4 (3C), 25.9 (3C), 20.8, 19.4, 18.2, 13.7 (3C), 9.1 (3C), −4.2, −4.9; HRMS (ESI) *m/z* calculated for $(C_{31}H_{62}O_4SiSn)Na^+$: 669.3332, found: 669.3332.

(E)-3-iodoprop-2-en-1-ol. To a suspension of Cp_2ZrCl_2 (7.0 g, 24 mmol, 1.2 equiv) in THF (90 mL) at 0 °C was added DIBAL-H (1M in THF, 22 mL, 22 mmol, 1.1 equiv). The reaction mixture was stirred for 0.5 h in the dark to obtain a white suspension of Schwartz reagent (Cp_2ZrHCl). Meanwhile, in another flask, propargyl alcohol (1.2 mL, 20 mmol, 1 equiv) was added dropwise in a solution of DIBAL-H (1M in THF, 24 mL, 24 mmol, 1.2 equiv) at −78 °C. After stirring at 0 °C for 0.5 h, the deprotonated solution of propargyl alcohol was added via cannula to the white suspension of Schwartz reagent at 0 °C and stirring was continued for 2 h at the same temperature. The reaction was then cooled down to −78 °C and a solution of iodine (7.61 g, 30 mmol, 1.5 equiv) in THF (20 mL) was added dropwise via cannula. The resulting mixture was stirred at −78 °C for 0.5 h, and then quenched by addition of a saturated aqueous solution of ammonium chloride. The mixture was diluted with Et_2O and extracted three times. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography (PE/EtOAc = 8:2) to afford the vinyl iodide as a yellow oil (2.45, 67%). IR (neat) 3300 (br), 2917, 1606, 1414, 1359, 1280, , 962, 927, 751, 662 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 6.69 (dt, *J* = 14.6, 5.5 Hz, 1H), 6.39 (dt, *J* = 14.5, 1.6 Hz, 1H), 4.09 (dd, *J* = 5.4, 1.6 Hz, 2H), 1.86 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) • δ (ppm) 144.6, 77.8, 65.1; MS (EI) *m/z* (%) 184 ($M^{+\bullet}$, 12), 183 (1), 167 (2), 153 (2), 127 (19), 57 (100), 55 (12), 53 (2). Analytical data are in agreement with those reported in the literature.[22]

(2Z,5S,7S,8E,10E)-Methyl 7-[(tert-butyldimethylsilyl)oxy]-12-hydroxy-5-methoxy-2,9-dimethyldodeca-2,8,10-trienoate (**12**). A solution of vinyl stannane **11** (929 mg, 1.44 mmol, 1 equiv) and (*E*)-3-iodoprop-2-en-1-ol (794 mg, 4.32 mmol, 3 equiv) in freshly distilled DMF was degassed for 45 min. The degassed solution was then added to a round bottom flask containing flame dried $[Ph_2PO_2][NBu_4]$ (1.32 g, 2.88 mmol, 2 equiv). Copper-thiophene carboxylate (CuTC) (549 mg, 2.88 mmol, 2 equiv) was then added, followed by $Pd(PPh_3)_4$ (166.3 mg, 0.144 mmol, 10 mol %) and the mixture was stirred at room temperature for 2 h. The reaction was quenched with water and diluted with Et_2O. The phases were separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by silica gel column chromatography to yield the triene **12** as a yellow oil (502 mg, 85%).[Error! Bookmark not defined.] $[\alpha]_D^{20}$ + 2.8 (*c* = 1.0, $CHCl_3$); IR (neat) 1716, 1459, 1435, 1362, 1249, 1217, 1137, 1083, 1064 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 6.25 (dt, *J* = 15.7, 1.5 Hz, 1H), 6.0 (ddd, *J* = 7.6, 6.4, 1.7 Hz, 1H), 5.79 (dt, *J* = 15.6, 6.0 Hz, 1H), 5.37 (d, *J* = 9.5 Hz, 1H), 4.62 (ddd, *J* = 9.0, 7.3, 6.3 Hz, 1H), 4.22 (dd, *J* = 6.0, 1.5 Hz, 2H), 3.72 (s, 3H), 3.27 (s, 3H), 3.27-3.22 (m, 1H), 2.82-2.65 (m, 2H), 1.91 (q, *J* =1.6 Hz, 3H), 1.85 (dd, *J* = 13.8, 7.1 Hz, 1H), 1.76 (d, *J* = 1.2 Hz, 3H) 1.45 (ddd, *J* = 13.8, 7.3, 5.1 Hz, 1H), 0.85 (s, 9H), 0.02 (s, 3H), -0.02 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 168.2, 138.8, 136.0 (2C), 132.2, 128.5, 127.1, 77.0, 66.7, 63.8, 56.0, 51.3, 42.4, 32.6, 25.8 (3C), 20.8, 18.1, 12.8, −4.2, −4.8; HRMS (ESI) *m*/*z* calculated for $(C_{22}H_{40}O_5Si)Na^+$: 435.2537, found: 435.2539. The OH group was not detected in the ^{1}H-NMR.

(1R,2R,4aR,5S,7S,8aR)-Methyl 5-[(tert-butyldimethylsilyl)oxy]-2-(hydroxymethyl)-7-methoxy-1,4-dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carboxylate (*exo*-**13**) and *(3aS,5aS,6S,8S,9aR,9bR)-6-[(tert-butyldimethylsilyl)oxy]-8-methoxy-5,9b-dimethyl-3,3a,5a,6,7,8,9,9a-octahydronaphtho[1,2-c]furan-1(9bH)-one* (*endo*-**14**). In a microwave vial was added triene **12** (74.5 mg, 0.18 mmol, 1 equiv), followed by toluene (16 mL), argon was then bubbled into the solution for 0.5 h. The vial was then fitted with a cap and heated at 210 °C in a microwave reactor for 3.5 h. The reaction was then concentrated under vacuum and purified by silica gel column chromatography (PE/EtOAc = 8:2 to 7:3) to afford the *exo*-decalin **13** as a colorless oil (45 mg, 60%) along with a minor product, the *endo*-decalin **14** (yellow oil, 6 mg, 8%). Major Product (*exo*-**13**): $[\alpha]_D^{20}$ – 9.7 (*c* = 1.0, $CHCl_3$); IR (neat) 1726, 1462, 1377, 1255, 1209, 1146, 1118, 1078, 1006, 774, 736, 702, 669, 595 cm^{-1}; ^{1}H-NMR (400 MHz, benzene-d_6) δ (ppm) 5.40 (dt, *J* = 5.8, 1.8, 1H), 3.57 (ddd, *J* =10.8, 9.5, 4.3 Hz, 1H), 3.48 (dd, *J* = 11.2, 4.6, 1H), 3.40 (dd, *J* = 11.2, 5.5 Hz, 1H), 3.24 (s, 3H), 3.19 (s, 3H), 2.98 (tt, *J* = 11.0, 4.4 Hz, 1H), 2.84-2.77 (m, 1H), 2.50-2.44 (m, 1H), 2.41 (t, *J* = 10.8 Hz, 1H), 2.26 (ddt, *J* = 12.2, 4.5, 2.2 Hz, 1H), 2.04 (s, 3H), 1.78 (q, *J* =12.1 Hz, 1H), 1.65 (q, *J* = 11.5 Hz, 1H), 1.48 (ddd, *J* = 12.7, 10.2, 2.3, 1H), 1.19 (s, 3H), 0.94 (s, 9H), 0.07 (s, 6H); ^{13}C-NMR (100 MHz, benzene-d_6) δ (ppm) 176.4, 140.2, 124.9, 77.5, 74.7, 62.6, 55.6, 51.2, 49.7, 47.2, 45.4, 44.1, 40.2, 32.4, 26.4 (3C), 25.1, 22.2, 18.3, –3.1, –3.7; HRMS (ESI) *m*/*z* calculated for $(C_{22}H_{40}O_5Si)Na^+$: 435.2537, found: 435.2536. The OH group was not detected in the ^{1}H-NMR.

Minor product (lactone *endo*-**14**) $[\alpha]_D^{20}$ – 32.0 (*c* = 0.8, $CHCl_3$); IR (neat) 1767, 1725, 1453, 1381, 1255, 1223, 1108, 1086, 1003 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 5.35 (br s, 1H), 4.38 (dd, *J* = 10.0, 8.8 Hz, 1H), 3.81 (dd, *J* = 10.4, 8.9 Hz, 1H), 3.72-3.67 (m, 1H), 3.30 (s, 3H), 3.11 (tt, *J* = 11.0, 4.5 Hz, 1H), 2.77-2.72 (m, 1H), 2.55 (br s, 1H), 2.08-2.03 (m, 1H), 1.91 (s, 3H), 1.77-1.73 (m, 1H), 1.63 (ddd, *J* = 13.1, 3.7, 3.1 Hz, 1H), 1.47-1.37 (m, 1H), 1.31 (s, 3H), 1.28-1.22 (m, 1H), 0.90 (s, 9H), 0.08 (2s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm)

181.6, 135.7, 120.0, 76.9, 72.4, 70.2, 56.1, 43.8, 41.6, 40.4, 39.0, 37.8, 30.0, 25.8 (3C), 24.4, 23.4, 17.9, –4.8 (2C); HRMS (ESI) *m*/*z* calculated for $(C_{21}H_{36}O_4Si)Na^+$: 403.2275, found: 403.2277.

(E)-3-iodoallyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)propanoate (**17**). To a stirred solution of methyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)propanoate[23] (415.2 mg, 1.25 mmol, 1 equiv) in 0.1M phosphate buffer (pH = 7.4) (31.5 mL) and acetone (3.5 mL) was added PLE (Sigma, E-2884, 28.1 mg/mL, 163 µL, 1000 UN) and the mixture was stirred at room temperature for 23 h. The reaction was quenched by addition of 10% aqueous solution of hydrochloric acid and diluted with EtOAc. The phases were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography ($CHCl_3$/MeOH = 9:1) to afford the corresponding 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)propanoic acid as a white solid (337 mg, 85%). ^{1}H-NMR (400 MHz, methanol-d_4) δ (ppm) 4.65-4.53 (m, 4H), 3.16 (dq, *J* = 22.3, 7.4 Hz, 1H), 1.43 (dd, *J* = 20, 7.4 Hz, 3H). Analytical data are in agreement with those reported in the literature.[24]

To a solution of 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)propanoic acid (535 mg, 1.68 mmol, 1 equiv) in CH_2Cl_2 (4 mL) was added a catalytic amount of DMF (2 drops) and the mixture was cooled down to 0 °C. Oxalyl chloride (213 µL, 2.523 mmol, 1.5 equiv) was added dropwise and the reaction mixture was stirred for 20 min at 0 °C. The reaction was then warm to room temperature and stirred for 2 h. The volatiles were removed under reduced pressure and the crude acyl chloride was used as such in the next step. To a solution of (*E*)-3-iodoprop-2-en-1-ol (619 mg, 3.36 mmol, 2 equiv) in CH_2Cl_2 (6.3 mL), cooled to 0 °C, was added pyridine (204 µL, 2.52 mmol, 1.5 equiv) and DMAP (10.27 mg, 84 µmol, 0.05 equiv). To the obtained solution was added at 0 °C a solution of the crude acyl chloride obtained above in CH_2Cl_2 (2.5 mL). The reaction was then warmed to room temperature and stirred overnight. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography (PE/EtOAc = 8:2) to afford the phosphonate **17** as a colorless oil (501 mg, 62%). IR (neat) 2969, 1740, 1613, 1293, 1260, 1164, 961, 863, 841, 658 cm^{-1}; ^{1}H-NMR (400 MHz, C_6D_6) δ (ppm) 6.18 (dt, *J* = 14.7, 5.9 Hz, 1H), 6.07 (dt, *J* = 14.6, 1.4 Hz, 1H), 4.03-3.89 (m, 6H), 2.65 (dq, *J* = 23.4, 7.4 Hz, 1H), 1.15 (dd, *J* = 19.0, 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, C_6D_6) δ (ppm) 167.7, 138.8, 81.9, 66.6, 62.4 (2C), 39.5 (d, J_d = 139.2 Hz), 11.32 (d, J_d = 6.45 Hz); HRMS (ESI) *m*/*z* $[M+Na]^+$ calculated for $(C_{10}H_{12}F_6IO_5P)Na^+$: 506.9263, found: 506.9252.

(2E,4E,6S,8R)-6-[(tert-Butyldimethylsilyl)oxy]-8-methoxy-4-methyl-10-oxodeca-2,4-dien-1-yl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]propanoate (**19**). To a stirred solution of the intermediate diol, precursor to aldehyde **9**, obtained as a mixture of diastereoisomers (400 mg, 1.26 mmol) in dry THF (15 mL), cooled to 0 °C, was added $PdCl_2(PPh_3)_2$ (88.7 mg, 0,126 mmol, 10 mol %), followed by a slow addition using a syringe pump of Bu_3SnH (476 µL, 1.77 mmol, 1.4 equiv) over 1 h. The mixture was stirred at 0 °C for 1 h and then concentrated under vacuum. The crude product was filtered over a silica gel pad (PE/EtOAc = 6:4 to 5:5) to afford the vinyl stannane **16** as a mixture of diastereoisomers (386 mg, 50%) which was directly involved in the Stille coupling. A solution of vinyl stannane **16** (227 mg, 374 µmol, 1 equiv) and vinyl iodide **17** (235 mg, 486 µmol, 1.3 equiv) in distilled DMF (10 mL) was degassed for 45 min. This solution was added to a round bottom flask containing flame dried

$[Ph_2PO_2][NBu_4]$ (344 mg, 0.75 mmol, 2 equiv). Copper-thiophene carboxylate (CuTC) (143 mg, 748 μmol, 2 equiv) was then added, followed by $Pd(PPh_3)_4$ (43.2 mg, 37.4 μmol, 10 mol %) and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched by addition of water and diluted with Et_2O. The phases were separated and the aqueous layer was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel column chromatography (PE/EtOAc = 6:4 to 7:3) to yield diol **18** as a mixture of diastereoisomers (148 mg, 62%). To a solution of the product obtained above (148 mg, 219 μmol, 1 equiv) in THF (2 mL) and H_2O (2 mL) at room temperature was added $NaIO_4$ (141 mg, 658 μmol, 3 equiv). The mixture was stirred for 2 h at room temperature and then quenched by addition of a saturated aqueous solution of sodium thiosulfate. The phases were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The crude mixture was purified by silica gel column chromatography (PE/EtOAc = 7:3 to 6:4) to yield aldehyde **19** as a yellow oil (87 mg, 62%). $[\alpha]_D^{20}$ – 7.2 (*c* = 1.0, $CHCl_3$); IR (neat) 1729, 1460, 1420, 1385, 1297, 1420, 1073, 963 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 9.79 (t, *J* = 2.3 Hz, 1H), 6.31 (dd, *J* = 15.6, 0.7 Hz, 1H), 5.70 (dt, *J* = 16.0, 6.7, Hz, 1H), 5.45 (d, *J* = 8.9 Hz, 1H), 4.73-4.68 (m, 2H), 4.63 (dt, *J* = 8.9, 6.6 Hz, 1H), 4.48-4.35 (m, 4H), 3.70 (dq, *J* = 7.1, 5.8 Hz, 1H), 3.28 (s, 3H), 3.30-3.17 (m, 1H), 2.63-2.60 (m, 2H), 1.96 (dt, *J* = 13.8, 6.9, Hz, 1H), 1.76 (d, *J* = 1.2 Hz, 3H), 1.57-1.49 (m, 4H), 0.86 (s, 9H), 0.02 (s, 3H), -0.02 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 201.3, 168.2, 139.7, 137.1, 131.9, 120.8, 73.3, 66.8, 66.4, 62.8-62.3 (2C), 56.3, 47.7, 42.3, 39.5 (dd, J_d = 140.0 Hz), 25.8 (3C), 18.0, 12.6, 11.6 (qd, J_d = 6.4 Hz), –4.3, –4.9; HRMS (ESI) *m*/*z* $[M+Na]^+$ calculated for $(C_{25}H_{41}F_6O_8PSi)Na^+$: 665.2105, found: 665,2106. The carbons of the CF_3 groups were not detected in the ^{13}C-NMR.

(3Z,6S,8S,9E,11E)-8-[(tert-Butyldimethylsilyl)oxy]-6-methoxy-3,10-dimethyloxacyclotrideca-3,9,11-trien-2-one (**20**). To a solution of 18-crown-6 ether (518 mg, 1.96 mmol, 12 equiv) in toluene (167 mL) was added potassium carbonate (135.5 mg, 0.980 mmol, 6 equiv) and the mixture was stirred for 3 h at room temperature. A solution of aldehyde **19** (105 mg, 163.4 μmol, 1 equiv) in toluene (167 mL) was then added via cannula to the reaction mixture. The reaction was then allowed to stir at room temperature for two days. After dilution with Et_2O, the mixture was washed with water and brine. The combined aqueous layers were extracted twice with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (PE/EtOAc = 9:1) to afford lactone **20** as a colorless oil (32.6 mg, 52.4%). $[\alpha]_D^{20}$ – 49.5 (*c* = 1.0, $CHCl_3$); IR (neat) 1710, 1459, 1385, 1361, 1250, 1207, 1136, 1084, 966 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 6.27 (d, *J* = 15.7 Hz, 1H), 6.06 (ddd, *J* = 9.1, 6.2, 1.7 Hz, 1H), 5.71 (ddd, *J* = 15.8, 7.2, 5.5 Hz, 1H), 5.38 (d, *J* = 8.8 Hz, 1H), 4.83 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.63-4.53 (m, 2H), 3.26 (s, 3H), 3.36-3.20 (m, 1H), 2.99 (ddd, *J* = 14.8, 9.1, 4.4 Hz, 1H), 2.53 (ddd, *J* = 15.2, 6.4, 5.7, Hz, 1H), 1.94 (s, 3H), 1.87 (td, *J* = 14.1, 7.1 Hz, 1H), 1.66 (s, 3H), 1.42 (dt, *J* = 13.9, 6.2 Hz, 1H), 0.87 (s, 9H), 0.03 (s, 3H), -0.02 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 167.8, 138.2, 137.5, 137.0, 131.7, 129.2, 122.0, 76.9, 66.8, 64.9, 56.1, 42.4, 32.6, 25.8 (3C), 21.0, 18.1, 12.7, –4.2, –4.9; HRMS (ESI) *m*/*z* $[M+Na]^+$ calculated for $(C_{21}H_{36}O_4Si)Na^+$: 403, 2275, found: 403.2276.

(3aR,5aR,6S,8S,9aR,9bR)-6-[(tert-Butyldimethylsilyl)oxy]-8-methoxy-5,9b-dimethyl-3,3a,5a,6,7,8,9,9a-octahydronaphtho[1,2-c]furan-1(9bH)-one (**21**). A microwave vial was charged with lactone **20** (14.6 mg, 38 μmol, 1 equiv) in toluene (4.2 mL), then it was

degassed by purging with Ar for 0.5 h. The vial was then fitted with a cap and heated at 130 °C in a microwave reactor for 8 h. The reaction mixture was then concentrated under reduced pressure and purified by silica gel column chromatography (PE/EtOAc = 9:1) to afford lactone **21** as a light yellow oil (8 mg, 55%). $[\alpha]_D^{20}$ + 59.7 (*c* = 1.0, $CHCl_3$); IR (neat) 1727, 1462, 1376, 1362, 1252, 1104, 1083, 1007, 969 cm^{-1}; ^{1}H-NMR (400 MHz, benzene-d_6) δ (ppm) 4.86 (d quint, *J* = 3.9, 2.1 Hz, 1H), 4.39 (t, *J* = 11.8 Hz, 1H), 4.10-3.99 (m, 1H), 3.68 (ddd, *J* = 11.2, 9.9, 4.6 Hz, 1H), 3.43-3.32 (m, 1H), 3.14 (s, 3H), 2.75 (tdd, *J* = 10.9, 4.0, 3.2 Hz, 1H), 2.43 (d sext, *J* = 11.5, 2.8, Hz, 1H), 2.28 (br t, *J* = 10.4 Hz, 1H), 2.14 (dt, *J* = 12.3, 3.5 Hz, 1H), 1.92 (s, 3H), 1.58-1.40 (m, 2H), 1.16 (s, 3H), 0.95 (s, 9H), 0.70 (br td, *J* = 12.6, 3.6 Hz, 1H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C-NMR (100 MHz, benzene-d_6) δ (ppm) 175.8, 141.9, 121.6, 76.9, 70.9, 62.7, 55.6, 49.7, 48.0, 47.1, 42.4, 41.2, 32.8, 26.3 (3C), 21.4, 19.6, 18.3, –2.4, –3.6; HRMS (ESI) *m*/*z* $[M+Na]^+$ calculated for $(C_{21}H_{36}O_4Si)Na^+$: 403.2275, found: 403.2276.

Supporting Information Available:
NMR data for compounds **3**-**21** and computational data.

References

[1] Carletti, I.; Massiot, G. Macrolides Utiles Comme Agents Anticancereux. **2014**, EP2951189 B1.

[2] a) D'Auria, M. V.; Debitus, C.; Paloma, L. G.; Minale, L.; Zampella, A. Superstolide A: a Potent Cytotoxic Macrolide of a New Type From the New Caledonian Deep Water Marine Sponge Neosiphonia Superstes. *J. Am. Chem. Soc.* **1994**, *116*, 6658; b) D'Auria, M. V.; Paloma, L. G.; Minale, L.; Zampella, A.; Debitus, C. A Novel Cytotoxic Macrolide, Superstolide B, Related to Superstolide a, From the New Caledonian Marine Sponge Neosiphonia Superstes. *J. Nat. Prod.* **1994**, *57*, 1595.

[3] Natural products coupling constants $J_{H9\text{-}14} = 8$ Hz ; M. Badertscher, P. Bühlmann, E. Pretsch, *Structure Determination of Organic Compounds*, Springer Berlin Heidelberg, Berlin, Heidelberg, **2009**, 162-173.

[4] a) Roush, W. R.; Champoux, J. A.; Peterson, B. C. Diastereoselective Synthesis of the Cis-Octahydronaphthalene Nucleus of Superstolides a and B. *Tetrahedron Lett.* **1996**, *37*, 8989; b) Tortosa, M.; Yakelis, N. A.; Roush, W. R. Total Synthesis of (+)-Superstolide A. *J. Am. Chem. Soc.* **2008**, *130*, 2722; c) Tortosa, M.; Yakelis, N. A.; Roush, W. R. Total Synthesis of (+)-Superstolide A. *J. Org. Chem.* **2008**, *73*, 9657.

[5] Reviews of Diels-Alder and applications in similar cases: Takao, K.-I.; Munakata, R.; Tadano, K.-I. Recent Advances in Natural Product Synthesis by Using Intramolecular Diels−Alder Reactions. *Chem. Rev.* **2005**, *105*, 4779; Juhl, M.; Tanner, D. Recent Applications of Intramolecular Diels–Alder Reactions to Natural Product Synthesis. *Chem. Soc. Rev.* **2009**, *38*, 2983; Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. The Transannular Diels–Alder Strategy: Applications to Total Synthesis. *Tetrahedron* **2001**, *57*, 4243; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. Transannular Reactions in Asymmetric Total Synthesis. *Tetrahedron* **2014**, *70*, 9461; Heravi, M. M.; Vavsari, V. F. Recent Applications of Intramolecular Diels–Alder Reaction in Total Synthesis of Natural Products. *RSC Adv.* **2015**, *5*, 50890; Dhambri, S.; Mohammad, S.; Van Buu, O. N.; Galvani, G.; Meyer, Y.; Lannou, M. I.; Sorin, G.; Ardisson, J. Recent Advances in the Synthesis of Natural Multifunctionalized Decalins. *Nat. Prod. Rep.* **2015**, *32*, 841.

[6] a) Miyaoka, H.; Shida, H.; Yamada, N.; Mitome, H.; Yamada, Y. Total Synthesis of Marine Diterpenoid Kalihinene X. *Tetrahedron Lett.* **2002**, *43*, 2227; b) Coe, J. W.; Roush, W. R. Studies of an Intramolecular Diels-Alder Approach to the Nargenicins: Involvement of Boatlike Transition States in the Cyclizations of Substituted 1,7,9-Decatrien-3-Ones. *J. Org. Chem.* **1989**, *54*, 915; c) Dineen, T. A.; Roush, W. R. Stereoselective Synthesis of the Octahydronaphthalene Unit of Integramycin via an Intramolecular Diels−Alder Reaction. *Org. Lett.* **2005**, *7*, 1355.

[7] Greshock, T. J.; Johns, D. M.; Noguchi, Y.; Williams, R. M. Improved Total Synthesis of the Potent HDAC Inhibitor FK228 (FR-901228). *Org. Lett.* **2008**, *10*, 613.

[8] a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. Asymmetric Transfer Hydrogenation of A, B-Acetylenic Ketones. *J. Am. Chem. Soc.* **1997**, *119*, 8738; b) Barbazanges, M.; Meyer, C.; Cossy, J. Total Synthesis of Amphidinolide J. *Org. Lett.* **2008**, *10*, 4489.

[9] Brown, H.; Jadhav, P. Asymmetric Carbon-Carbon Bond Formation via B-Allyldiisopinocampheylborane. Simple Synthesis of Secondary Homoallylic Alcohols with Excellent Enantiomeric Purities. *J. Am. Chem. Soc.* **1983**, *105*, 2092.

[10] Still, W. C.; Gennari, C. Direct Synthesis of Z-Unsaturated Esters. A Useful Modification of the Horner-Emmons Olefination. *Tetrahedron Lett.* **1983**, *24*, 4405.

[11] Fürstner, A.; Funel, J.-A.; Tremblay, M.; Bouchez, L. C.; Nevado, C.; Waser, M.; Ackerstaff, J.; Stimson, C. C. A Versatile Protocol for Stille–Migita Cross Coupling Reactions. *Chem. Commun.* **2008**, 2873.
[12] NOESY experiments also confirmed the required vicinities.
[13] The C15-methylated analog of aldehyde **III** used by Roush et al. was prepared but the same *exo*-adduct was obtained upon heating.
[14] Hayashi, N.; Suzuki, T.; Usui, K.; Nakada, M. Alternative Synthetic Approach for (+)-Phomopsidin via the Highly Stereoselective TADA Reaction. *Tetrahedron* **2009**, *65*, 888; Tadano, K.-I. Natural Product Synthesis Featuring Intramolecular Diels–Alder Approaches – Total Syntheses of Tubelactomicins and Spiculoic Acid A. *Eur. J. Org. Chem.* **2009**, 4381.
[15] Parenty, A.; Moreau, X.; Niel, G.; Campagne, J.-M. Update 1 of: Macrolactonizations in the Total Synthesis of Natural Products. *Chem. Rev.* **2013**, *113*, PR1.
[16] Fürstner, A.; Nevado, C.; Waser, M.; Tremblay, M.; Chevrier, C.; Teplý, F.; Aïssa, C.; Moulin, E.; Müller, O. Total Synthesis of Iejimalide a−D and Assessment of the Remarkable Actin-Depolymerizing Capacity of These Polyene Macrolides. *J. Am. Chem. Soc.* **2007**, *129*, 9150.
[17] See, for example: a) Hayden, A. E.; DeChancie, J.; George, A. H.; Dai, M.; Yu, M.; Danishefsky, S. J.; Houk, K. N. Origins of the Regioselectivities in the Diels-Alder Reactions of Vinylindenes with 1,4-Quinone Monoketal and Acrolein Dienophiles. *J. Org. Chem.* **2009**, *74*, 6770; b) Paton, R. S.; Mackey, J. L.; Kim, W. H.; Lee, J. H.; Danishefsky, S. J.; Houk, K. N. Origins of Stereoselectivity in the Trans Diels-Alder Paradigm. *J. Am. Chem. Soc.* **2010**, *132*, 9335; c) Jones, G. A.; Paddon-Row, M. N.; Sherburn, M. S.; Turner, C. I. On the Endo/Exo Stereoselectivity of Intramolecular Diels−Alder Reactions of Hexadienylacrylates: An Interesting Failure of Density Functional Theory. *Org. Lett.* **2002**, *4*, 3789; d) Pham, H. V.; Paton, R. S.; Ross, A. G.; Danishefsky, S. J.; Houk, K. N. Intramolecular Diels–Alder Reactions of Cycloalkenones: Stereoselectivity, Lewis Acid Acceleration, and Halogen Substituent Effects. *J. Am. Chem. Soc.* **2014**, *136*, 2397.
[18] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, revision D.01; Gaussian, Inc.: Wallingford, CT, **2013**.
[19] a) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. *Theor. Chem. Account* **2007**, *120*, 215; b) Zhao, Y.; Truhlar, D. G. Density Functionals with Broad Applicability in Chemistry. *Acc. Chem. Res.* **2008**, *41*, 157.
[20] Zhao, Y.; Truhlar, D. G. Computational Characterization and Modeling of Buckyball Tweezers: Density Functional Study of Concave–Convex Π···Π Interactions. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2813.

[21] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378.
[22] Yin, N.; Wang, G.; Qian, M.; Negishi, E. Stereoselective Synthesis of the Side Chains of Mycolactones a and B Featuring Stepwise Double Substitutions of 1,1-Dibromo-1-Alkenes. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 2916.
[23] Messik, F.; Oberthür, M. An Expedient Access to Still–Gennari Phosphonates. *Synthesis* **2012**, *45*, 167.
[24] Sano, S.; Abe, S.; Azetsu, T.; Nakao, M.; Nagao, M. S. A. Y. Diastereoselective Horner-Wadsworth-Emmons Reaction for the Synthesis of Tetrasubstituted Alkenes with an Axis of Chirality. *Letters in Organic Chemistry* **2006**, *3*, 798.