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Ti(II) and Rh(I) Complexes as Reagents towards Thapsigargin Core

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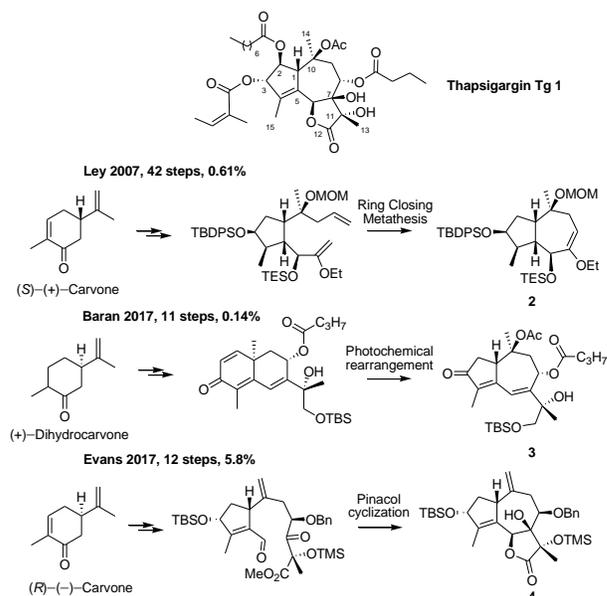
Natural products • Multi-step synthesis • Thapsigargin • Titanium(II) complexes • Rhodium(I) complexes.

ABSTRACT: A novel approach towards the [5–7] fused bicyclic core of thapsigargin, a potent inhibitor of the endo/sarcoplasmic calcium ATPase (SERCA), is presented. The synthetic route includes an original low valent titanium-mediated hydroxy-directed reductive coupling of an enantiomerically enriched propargylic alcohol and an intramolecular Rh(I)-catalyzed cyclocarbonylation reaction as key steps. Interestingly, through first experiments of titanocene-mediated reductive cyclization of a 1,8-enyne, a seven-membered cycle was isolated as a unique product with a total diastereoselectivity. The structure of key compounds was confirmed by X-ray crystallography.

Sesquiterpene lactones of the guaianolide type are widespread in natural products and have recently attracted much interest from the synthetic community.¹ Among them, the guaianolide thapsigargin (Tg) **1**, isolated from the Mediterranean plant species *Thapsia (Apiaceae)*,² is a very potent inhibitor of the endo/sarcoplasmic calcium ATPase (SERCA), related to a subnanomolar affinity for this enzyme.³ Consequently, Tg is a major tool for investigation of the Ca²⁺ homeostasis in cells, and, in addition, conjugating thapsigargin to peptides has recently provided several prodrugs as efficient treatments of various cancer types such as prostate cancers.⁴ Structurally, Tg **1** presents a challenging complex chemical structure, including a polyoxygenated [5–7–5] fused tricyclic core possessing eight stereogenic centres and functionalized with five different ester groups.⁵

The promising therapeutic potential associated to the unique structure of Tg have attracted many efforts aimed at the achievement of its total synthesis. Remarkably, Ley *et al.* succeeded in the first total synthesis of Tg **1** from (*S*)-carvone by means of a key ring-closing diene metathesis step (**2**).^{6a-c} Very recently, two elegant, scalable and concise total syntheses were reported by Baran and Evans groups through, respectively, a photochemical rearrangement (**3**) and a pinacol cyclization (**4**) also from carvone derivatives (Scheme 1).^{6d,e} A few other efforts have led to alternative interesting approaches,⁷ through either ring-closing metathesis,^{7d,k} photochemical rearrangement,^{7a,e,i} cycloaddition [2+2] / ring expansion sequence^{7b,f,g} or allenic Pauson-Khand type annelation.^{7h,j}

Scheme 1: Ley's, Baran's and Evans' total synthesis of Tg 1.



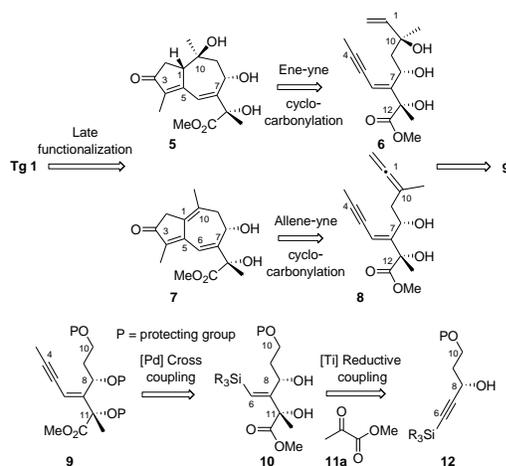
In our laboratories, a combined program towards the synthesis of Tg **1** and analogues aimed at developing two synthetic approaches. In this context, a diastereoselective route from commercial 2-methyl-cyclopentane-1,3-dione and involving a ring-closing enyne metathesis for the construction of the bicyclic core has been very recently reported.^{7j} We envisioned an alternative approach towards Tg **1** framework comprising two

main stages, installation of the chains on either side of the quaternary center at C7 starting from a central enantiopure epoxide and formation of the bicyclic system through subsequent allene–yne Rh(I)–catalyzed Pauson–Khand annelation (APKR).^{7h} More recently, we have successfully performed intramolecular Rh(I)–catalyzed Pauson–Khand cyclocarbonylation reactions of alkoxyallene–ynes with the alkoxy group at the proximal position, to access [5–7] fused ring systems bearing an enol ether moiety.⁸

Herein, we report a new route towards the bicyclic core of Tg **1** including a diastereoselective titanium–mediated reductive coupling of a propargylic alcohol and an intramolecular cyclocarbonylation reaction as key steps.

To address the challenges in forming the bicyclic system of Tg **1** and ensuring the installation of the range of functional groups throughout the cyclic system, we planned to develop a new sequence involving the stereoselective construction of the key C4–C10 (*E*)–enyne subunit **9**. Indeed, this segment could be considered as a critical precursor for the elaboration of the bicyclic dienone **5** or trienone **7** from respectively 1,8–enyne **6** or allene–yne **8** by intramolecular carbocyclisation (Scheme 2).

Scheme 2. Retrosynthetic analysis.



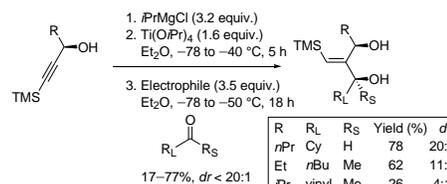
The major milestone of our strategy was to efficiently synthesize the C4–C10 fragment **9**. The latter comprises a tertiary and a secondary alcohol at respectively C11 and C8 in a *syn* relationship linked to a (*E*) double bond at C6–C7. Such fragment is frequently encountered in the skeleton of natural products **9** or synthetic intermediates **6d** and a general method for its elaboration could be very useful.

Enyne **9** would derive from (*E*)–vinylic silane **10** by palladium–catalyzed cross–coupling reaction. The diastereoselective construction of the *syn*–1,3–diol moiety at C8–C11 in the segment **9** was designed to be implemented using a Ti(II) mediated hydroxy–directed reductive coupling of propargylic alcohol **12** with methyl pyruvate **11a** (Scheme 2).

This reaction was related to that performed by Yang *et al.*^{10a} in 2010. It is interesting to note that, in 1995, pioneering works were achieved by Sato *et al.* who established that low–valent titanium alkoxide Ti(O*i*Pr)₂, obtained by a combination of Ti(O*i*Pr)₄ / 2 *i*PrMgCl, regioselectively incorporates silylacetylenes to provide titanacyclopropene complexes which act as versatile vicinal vinylic dianions.^{10b–e} Sequential reactions with two different electrophiles were validated with high regio– and (*E*)/(*Z*) stereoselectivity. More particularly, Sato described the

reductive coupling of silylalkyne with a ketone to provide an allylic alcohol in high yield and regioselectivity. Later, Yang reported that, when this reaction involved a propargylic alcohol and an aldehyde as starting materials, an hydroxy–directed reductive coupling could occur providing *syn*–1,3–diols with good to high yields and diastereoselectivities. However, only a limited range of ketones was tested and reactions revealed sometimes less effective, with moderate yields and 1,3–diol diastereoselectivities, although no rationalization was provided (Scheme 3).

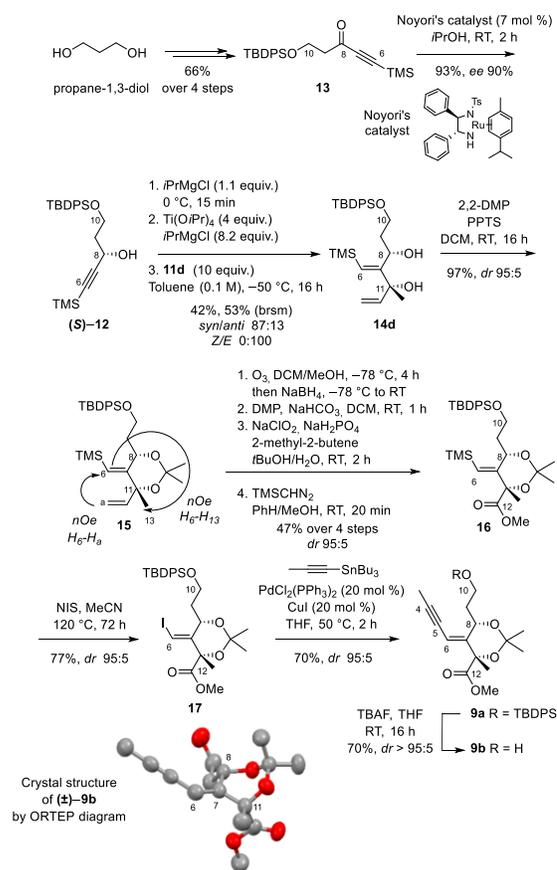
Scheme 3. Yang's reductive coupling reactions.



Therefore, inspired by these works,¹⁰ we have envisioned the synthesis of (*E*)–enyne **9** by diastereoselective titanium reductive coupling reaction between propargylic alcohol (*S*)–**12** and methyl pyruvate **11a**, as this sequence would represent a highly concise route to the key C4–C10 segment (Scheme 2).

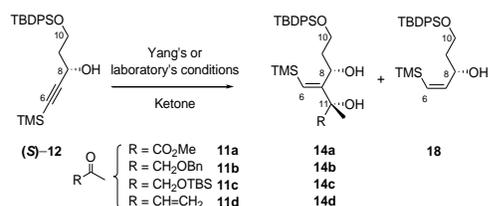
The synthesis of (*E*)–enyne **9b** began with the preparation of enantiomerically enriched propargylic alcohol (*S*)–**12**, which was readily achieved in 93% yield and 90% *ee* by means of Noyori reduction¹¹ of known ynone **13** (derived from propane–diol in 66% yield over four steps) (Scheme 4).^{12,13,14}

Scheme 4. Synthesis of enyne **9b**.



Subsequent reductive coupling reaction of propargylic alcohol (*S*)-**12** turned out to be more challenging than expected. The results are summarized in Scheme 5. Despite several attempts, the coupling reaction between (*S*)-**12** and methyl pyruvate **11a** under Yang's conditions failed to give **14a** (Entry 1). A methodologic survey of the coupling reaction between (*S*)-**12** and several ketones (**11b–d**) was thus realized. The reactivity of α -oxygenated methylketones **11b** and **11c** was examined under Yang's conditions; however, starting material was systematically recovered in both cases (Entry 1). Methyl vinyl ketone **11d** was next considered, since resulting diol (**14d**) would be a relevant intermediate in the elaboration of key enyne **9**. For the purpose of improving Yang's results (Scheme 3), the reaction was performed after initial formation of the corresponding alkoxide with one equivalent of *i*PrMgCl and generation of the titanium(II) / acetylene complex [produced *in situ* in the presence of *i*PrMgCl (8 equivalents) and Ti(O*i*Pr)₄ (4 equivalents), for 2 h at -35°C]. In diethyl ether as solvent, the formation of diol **14d** appeared rather sluggish, since 65% conversion was observed along with a 45:55 ratio **14d** / (*Z*)-alkene **18** (Entry 2, ¹H NMR estimation). Finally, toluene was found to be the most suitable solvent for this transformation; when extending the reaction time to 16 h at -50°C , propargylic alcohol (*S*)-**12** displayed a conversion of 62% (*ratio* diol **14d** / **18**: 82:18) and, after purification, 1,3-diol **14d** was isolated in 42% yield (53% brsm), with *syn/anti* *dr* 87:13 and (*E*)/(*Z*) *dr* > 95:5 (entry 3, ¹H NMR estimation). Remarkably, no regioisomer was detected in the crude NMR spectra. Finally, through optimized conditions, this reaction could be carried out on a 33 mmol scale of propargylic alcohol (*S*)-**12** in a reproducible manner.¹⁵ Unfortunately, when implementing optimized conditions to ketones **11a–c**, no significant improvement was observed.

Scheme 5. Optimization of the titanium reductive coupling reaction.



- ^a Yang's conditions: 1. *i*PrMgCl (3.2 equiv.), Ti(O*i*Pr)₄ (1.6 equiv.), Et₂O, -78 to -40°C , 5 h;
² Ketone **11a–d** (3.5 equiv.), Et₂O, -78 to -50°C , 18 h
^b Laboratory's conditions: 1. *i*PrMgCl (1.1 equiv.), 0 $^\circ\text{C}$, 15 min;
² Ti(O*i*Pr)₄ (4 equiv.), *i*PrMgCl 1.35 M in Et₂O (8.2 equiv.) 2 h, -35°C , solvent (0.1 M);
³ Ketone **11a–d** (10 equiv.).

| Entry | Ketone | Conditions | Conv. % Ratio 14 / 18 | 14 <i>dr</i> <i>syn/anti</i> | Isolated Yield % |
|-------|--------------|--|--|--|------------------------------|
| 1 | 11a–c | ^a | 0 | - | - |
| 2 | 11d | ^b 11d , Et ₂ O 2h, -50°C | 65 45:55 | (14d) 87:13 | - |
| 3 | 11d | ^b 11d , Tol. 16h, -50°C | 62 82:18 | (14d) 87:13 | (14d) 42 53 brsm |

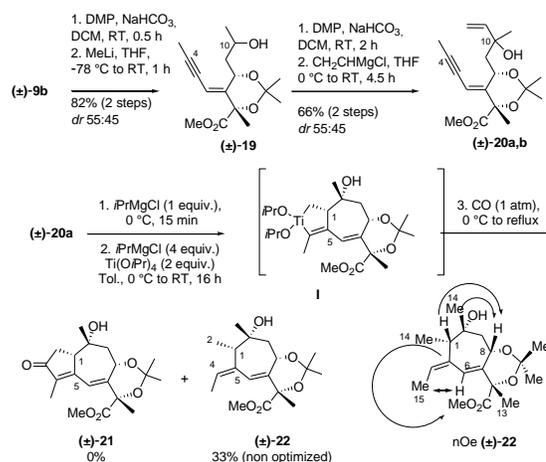
At this stage, protection of the 1,3-diol **14d** as cyclic ketal **15** (97% yield, *dr* 95:5), followed by classical transformation of the terminal double bond into an ester function in four steps (reductive ozonolysis, Dess–Martin periodinane oxidation, Pinnick oxidation¹⁶ and esterification), delivered **16** in 47% yield (*dr* 95:5).¹⁷ The relative configuration of cyclic ketal **15** was established by nOe NMR experiments. Finally, a three step sequence involving iododesilylation (**17**) followed by Stille coupling (**9a**)¹⁸ and cleavage of silyl ether at C10 afforded alcohol

9b (*dr* > 95:5). The structure of **9b** was unambiguously confirmed by X-ray crystallography (Scheme 4).¹⁹

With enyne **9b** in hands, we focused on the intramolecular cyclocarbonylation step for the elaboration of bicycles **5** and **7** (Scheme 2). At this stage, the sequence was studied in racemic series from easy accessible (\pm)-**9b**.^{15,20}

Towards bicyclic (\pm)-dienone **5** comprising the tertiary alcohol at C10 of Tg **1**, 1,8-enyne (\pm)-**20** was prepared in a classical four step sequence, *via* alcohol (\pm)-**19**, as a separable mixture of diastereomers [(\pm)-**20a,b** *dr* 55:45]. To our knowledge, elaboration of [5–7] fused bicyclic pentenones by Pauson–Khand reactions from 1,8-enynes is scarcely reported.²¹ First attempts in the presence of Co(CO)₈ and CO were not conclusive despite the use of different additives. Therefore, we turned our attention towards a similar reaction mediated by low-valent titanium alkoxide reagent (η^2 -propene)-Ti(O*i*Pr)₂, mainly reported by Buchwald and Sato.^{22,23} Notably, the elaboration of [5–5] and [5–6] fused cores was described through the formation of a titanabicyclic intermediate, which could be intercepted with CO.

Scheme 6. First attempts towards the preparation of bicyclic dienone (\pm)-21.

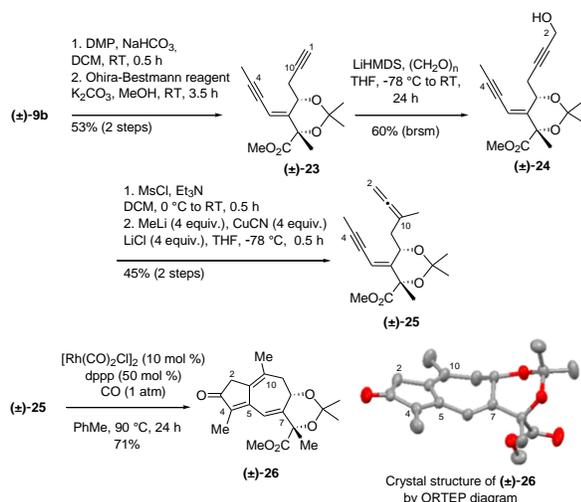


In our case, the reaction was performed after initial formation of the corresponding alkoxide with one equivalent of *i*PrMgCl, generation of the titanabicyclic complex **I** in the presence of *i*PrMgCl (4 equivalents) and Ti(O*i*Pr)₄ (2 equivalents), in toluene for 16 h at 0 $^\circ\text{C}$ to RT and final CO trapping under atmospheric pressure. Under these conditions, a unique product was isolated corresponding to the seven-membered cycle (\pm)-**22**, in a non-optimized 33% yield and a total diastereoselectivity [the relative configuration of (\pm)-**22** was established by nOe NMR experiments, thus also evidencing the configuration of (\pm)-**20a** at C10]. The formation of this seven-membered cycle through titanocene-mediated reductive cyclization of 1,8-enyne (\pm)-**20** is very promising but demonstrates that the insertion of CO to afford the bicyclic system (\pm)-**21** is more challenging than expected and should deserve further studies (Scheme 6).²⁴

An alternative sequence was also investigated involving an intramolecular Rh(I)-catalyzed Pauson–Khand reaction of allene–yne **8** to access the bicyclic core **7** of Tg **1**, in accordance with our previous studies.^{7h} Methyl–allene (\pm)-**25** was easily prepared in five steps from alcohol (\pm)-**9b**. Dess–Martin oxidation followed by Ohira–Bestmann reaction²⁵ afforded the alkyne (\pm)-**23**. Further homologation in the presence of freshly prepared LiHMDS and paraformaldehyde furnished primary alcohol (\pm)-**24** in 60% yield (brsm). Finally, mesylation and S_N2' reaction completed the synthesis of expected methyl–allene

(±)-**25** in 45% yield over two steps.^{7h,26a} We next addressed the formation of the [5–7] bicyclic trienone (±)-**26** by intramolecular allene–yne PKR from allene–yne (±)-**25**. Hence, Mukai,²⁶ Brummond²⁷ and our group^{7h,8} reported that Rh(I)–catalyzed intramolecular APKR was an efficient method for the construction of bicyclo[5.3.0] ring systems.²⁸ Exposure of (±)-**25** to 10 mol % of [Rh(CO)₂Cl]₂ in the presence of 1,3–bis(diphenylphosphino)propane (dppp) (50 mol %) in toluene at 90 °C, under 1 atm of CO, cleanly afforded the desired bicyclic trienone (±)-**26** in 71% yield. Finally, the structure of trienone (±)-**26**, comporting the bicyclic core of Tg **1** was readily confirmed by X–ray crystallography (Scheme 7).²⁹

Scheme 7. Synthesis of bicyclic trienone (±)-**26**.



In summary, an advanced [5–7] fused bicyclic intermediate of Tg **1**, has been synthesized in a 15 step sequence starting from known propargylic alcohol **12**. The synthetic route relies upon the elaboration of key (*E*)–enyne **9b**, through a low–valent titanium–mediated diastereoselective reductive coupling involving enantioenriched propargylic alcohol (*S*)–**12** and methyl vinyl ketone **11d**. This transformation allows the control of the stereochemistry of tertiary alcohol at C11 and of the alkene at C6–C7 using inexpensive and eco–friendly titanium isopropoxide and can be conducted on a 33 mmol scale (and even on a 65.7 mmol scale in cheaper racemic series). Interestingly, by first experiments of titanocene–mediated reductive cyclization of the 1,8–enynes (±)-**20**, a seven–membered cycle (±)-**22** is isolated as a unique product with a total diastereoselectivity. Further studies would permit the insertion of CO towards the formation of bicyclic pentenone (±)-**21**. Finally, a Rh(I)–catalyzed intramolecular allene–yne Pauson–Khand reaction, conducted in racemic series, enables the elaboration of the [5–7] fused bicyclic trienone (±)-**26** in 71% yield, from allene–yne (±)-**25**. The structure of key compounds was confirmed by X–ray crystallography. The present study demonstrates the possibility of elaborating a highly functionalized scaffold necessary for the further synthesis of complex guaianolides such as thapsigargin by using the previously described APKR strategy. The enantioselective synthesis of intermediate **26** as well as its further transformation into Tg **1** is currently under investigation in our laboratories.

Experimental section

General Remarks: All reactions sensitive to moisture and/or air were carried out under argon atmosphere in dry, freshly distilled solvents under anhydrous conditions using oven–dried

glassware, unless otherwise noted. THF and toluene were distilled over sodium/benzophenone system, DCM, DMSO and DMF were distilled over calcium hydride, MeOH and EtOH were distilled over magnesium turnings. Reactions were monitored by TLC (silica gel 60 F254 plates) and visualization was accomplished with UV light (254 nm & 366 nm) and subsequent use of phosphomolybdic acid solution in EtOH (5%), KMnO₄ solution or vanillin/sulphuric acid solution in EtOH, followed by heating at 100–110 °C. Flash chromatography was performed with silica gel 60 (particle size 0.040–0.063 μm). Yield refers to chromatographically and spectroscopically pure compounds, unless otherwise noted. ¹H NMR spectra were recorded at 300 and 400 MHz. Chemical shifts are expressed in ppm, relative to the residual ¹H solvent signal (CDCl₃; δ = 7.26 ppm) as the internal reference. Coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to designate the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; quint. = quintet, sext. = sextet, sept. = septet, m = multiplet; br = broad. ¹H NMR assignments were confirmed by 2D COSY spectra. The given multiplicities reflect apparent signal patterns. Diastereomer ratio (*dr*) was estimated by ¹H NMR spectroscopic analysis (300 or 400 MHz), unless otherwise noted. ¹³C{¹H} NMR spectra were recorded at 75 MHz and 100 MHz. Chemical shifts are given in ppm relative to the residual ¹³C solvent signal (CDCl₃; δ = 77.16 ppm, CD₃OD; δ = 49.00 ppm). ¹³C NMR assignments were confirmed by 2D HSQC and HMBC spectra. IR spectra were recorded with a FT–IR spectrometer. High–resolution mass spectra (HRMS) were measured on a mass spectrometer equipped with a TOF system and an electrospray ionization (ESI) ion source.

(*S*)-5–((*tert*-butyldiphenylsilyloxy)-1–(trimethylsilyl)pent-1-yn-3-ol **12.** To a solution of dichloro(*p*-cymene)ruthenium(II) dimer (0.042 g, 0.069 mmol, 0.056 equiv.) in dry DCM (0.034 M, 2 mL) was added (1*S*, 2*S*)-(+)-*N*-para-toluenesulfonyl-1,2-diphenylethylenediamine (0.050 g, 0.137 mmol, 0.11 equiv.) and KOH (0.055 g, 0.991 mmol, 0.82 equiv.) at RT. The purple mixture was stirred for 20 min before being quenched by water. After 10 min of vigorous stirring, the mixture was extracted with DCM (3x). The combined organic extracts were dried over CaH₂, filtered and concentrated under reduced pressure to give a purple solid. To the freshly prepared catalyst dissolved in *i*PrOH (0.013 M, 5 mL) was added a solution of ketone **13**¹² (0.500 g, 1.22 mmol, 1 equiv.) in *i*PrOH (0.493 M, 5 mL) at RT.¹³ After 30 min stirring, the solvent was evaporated and the crude product was purified by flash chromatography over silica gel (cyclohexane/EtOAc, 90:10) to afford alcohol (*S*)–**12** (0.465 g, 1.13 mmol, 93%, ee = 90%) as a yellow oil. Analytical data were in agreement with those reported in the literature.¹² RN: 225114-87-4.

(*S*)-5–((*tert*-butyldiphenylsilyloxy)-1–(trimethylsilyl)pent-1-yn-3-yl (*R*)-2-methoxy-2-phenylacetate. Propargylic alcohol **12** (70 mg, 0.17 mmol, 1.0 equiv.) was dissolved in anhydrous dichloromethane (0.05 M, 3 mL) and (*R*)-methoxyphenylacetic acid (72 mg, 0.43 mmol, 2.5 equiv.), DMAP (21 mg, 0.17 mmol, 1.0 equiv.) and DCC (43 mg, 0.43 mmol, 2.5 equiv.) were successively added. The mixture was stirred at room temperature for 30 min before addition of diethyl ether (10 mL). The crude mixture was filtered through a pad of Celite[®], which was rinsed with diethyl ether. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc, 90:10) to furnish corresponding (*R*)-MPA ester (87 mg, 0.156 mmol, 92% yield) as a colourless oil. **FTIR** (*neat*) 2956, 2876, 1462,

1428, 1372, 1251, 1087, 1096, 1006, 953, 821, 737, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.63-7.52 (m, 4H), 7.44-7.27 (m, 11H), 5.71 (t, *J* = 6.4 Hz, 1H), 4.78 (s, 1H), 3.66-3.57 (m, 1H), 3.49-3.40 (m, 1H), 3.40 (s, 3H), 1.99-1.84 (m, 2H), 1.00 (s, 9H), 0.14 (s, 9H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 169.6, 136.2, 135.6(4C), 133.7 (2C), 129.7 (2C), 128.8 (2C), 128.7 (2C), 127.8 (4C), 127.4, 102.1, 91.1, 82.6, 62.4, 59.4, 57.5, 37.7, 26.9 (3C), 19.3, -0.1 (3C).

(*S*)-5-((*tert*-butyldiphenylsilyloxy)-1-(trimethylsilyl)pent-1-yn-3-yl (*S*)-2-methoxy-2-phenylacetate. Propargylic alcohol **12** (70 mg, 0.17 mmol, 1.0 equiv.) was dissolved in anhydrous dichloromethane (0.05 M, 3 mL) and (*S*)-methoxyphenylacetic acid (72 mg, 0.43 mmol, 2.5 equiv.), DMAP (21 mg, 0.17 mmol, 1.0 equiv.) and DCC (43 mg, 0.43 mmol, 2.5 equiv.) were successively added. The mixture was stirred at room temperature for 30 min before addition of diethyl ether (10 mL). The crude mixture was filtered through a pad of Celite[®], which was rinsed with diethyl ether. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc, 90:10) to furnish corresponding (*S*)-MPA ester (90 mg, 0.16 mmol, 95% yield) as a colourless oil. RN: 1477482-31-7. ¹H NMR (300 MHz, CDCl₃) δ 7.77-7.58 (m, 4H), 7.51-7.29 (m, 11H), 5.73 (t, *J* = 6.9 Hz, 1H), 4.77 (s, 1H), 3.82-3.64 (m, 2H), 3.44 (s, 3H), 2.14-1.95 (m, 2H), 1.05 (s, 9H), 0.09 (s, 9H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 169.6, 135.9, 135.6 (4C), 133.6 (2C), 129.6 (2C), 128.8 (2C), 128.6 (2C), 127.8 (4C), 127.4, 101.7, 91.0, 82.6, 62.6, 59.7, 57.4, 37.6, 27.0 (3C), 19.3, -0.2 (3C). Analytical data are in agreement with those reported in the literature.¹²

(*3*R*,5*S*,*E*)-7-((*tert*-butyldiphenylsilyloxy)-3-methyl-4-((trimethylsilyl)methylene)hept-1-ene-3,5-diol 14d.* To a solution of propargylic alcohol (*S*)-**12** (13.68 g, 33.30 mmol, 1 equiv.) in dry toluene (0.11 M, 300 mL) was added *i*PrMgCl (1.35 M in Et₂O, 27 mL, 36.64 mmol, 1.1 equiv.) at 0 °C. After 15 min, freshly distilled Ti(O*i*Pr)₄ (39.4 mL, 133.2 mmol, 4 equiv.) was added. The mixture was cooled to -35 °C and *i*PrMgCl (1.35 M in Et₂O, 200 mL, 273.1 mmol, 8.2 equiv.) was added dropwise by means of dropping funnel. The black mixture was stirred for 2 h at -35 °C and 3-buten-2-one (27 mL, 333 mmol, 10 equiv.) was added dropwise. The mixture was stirred for 16 h at -50 °C before being quenched with HCl 4 M and warmed to RT. The mixture was vigorously stirred then extracted with Et₂O (3x). The combined organic extracts were washed with brine and dried over MgSO₄. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography over silica gel (cyclohexane/Et₂O, 90:10 to 85:15) to afford diol **14d** (6.75 g, 14.0 mmol, 42%, 53% brsm, *Z/E* = 0:100) as an inseparable mixture of diastereomers at C11 (*dr* 87:13).¹⁵ **Major diastereomer:** FTIR (neat) (mixture of diastereomers) 3315, 2957, 2930, 2856, 1472, 1427, 1389, 1318, 1248, 1105, 1080, 852, 841, 736, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.76-7.63 (m, 4H), 7.50-7.35 (m, 6H), 5.97 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.50 (s, 1H), 5.30 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.04 (dd, *J* = 10.6, 1.2 Hz, 1H), 4.89 (dd, *J* = 10.4, 1.8 Hz, 1H), 4.29 (br s, 2H), 3.81 (m, 2H), 2.53-2.40 (m, 1H), 1.67-1.57 (m, 1H), 1.48 (s, 3H), 1.06 (s, 9H), 0.13 (s, 9H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 161.9, 145.8, 135.7 (4C), 132.9 (2C), 130.0 (2C), 128.0 (4C), 126.3, 111.4, 78.5, 77.4, 64.3, 38.8, 31.1, 26.9 (3C), 19.1, 0.8 (3C); HRMS (ESI) calcd for C₂₈H₄₂O₃Si₂Na⁺ [(M+Na)⁺] 505.2570, found (mixture of diastereomers) 505.2583. **Minor diastereomer:** ¹H NMR (400 MHz, CDCl₃) δ 7.76-7.63 (m, 4H), 7.50-7.35 (m, 6H), 6.06 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.47 (s, 1H), 5.22 (dd, *J* = 17.2,

1.0 Hz, 1H), 5.04 (dd, *J* = 10.6, 1.0 Hz, 1H), 4.89 (dd, *J* = 10.4, 1.8 Hz, 1H), 4.18 (br s, 2H), 3.94-3.81 (m, 2H), 2.59-2.51 (m, 1H), 1.77-1.69 (m, 1H), 1.46 (s, 3H), 1.06 (s, 9H), 0.13 (s, 9H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 162.6, 147.3, 135.7 (4C), 132.8 (2C), 130.0 (2C), 128.0 (4C), 126.2, 110.8, 78.5, 77.4, 64.0, 39.1, 29.8, 26.9 (3C), 19.1, 0.8 (3C).

(*S,Z*)-5-((*tert*-butyldiphenylsilyloxy)-1-(trimethylsilyl)pent-1-en-3-ol (±)-18. FTIR (neat) 3435, 3072, 3050, 2931, 2895, 2858, 1428, 1248, 1106, 1079, 836, 765 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.74-7.67 (m, 4H), 7.48-7.38 (m, 6H), 6.32 (dd, *J* = 8.3, 14.5 Hz, 1H), 5.65 (d, *J* = 14.5 Hz, 1H), 4.57 (td, *J* = 8.3, 3.6 Hz, 1H), 3.95-3.80 (m, 2H), 2.92 (br.s, 1H), 1.90-1.68 (m, 2H), 1.08 (s, 9H), 0.15 (s, 9H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 150.0, 135.7 (4C), 133.3, 133.2, 131.1, 129.9 (2C), 127.9 (4C), 71.6, 62.6, 39.1, 27.0 (3C), 19.2, 0.6 (3C). HRMS (ESI) calcd for Na⁺ [(M+Na)⁺], found .

***tert*-butyldiphenyl(2-((4*S*,6*R*,*E*)-2,2,6-trimethyl-5-((trimethylsilyl)methylene)-6-vinyl-1,3-dioxan-4-yl)ethoxy)silane 15.** 2,2-dimethoxypropane (7.5 mL, 60.8 mmol, 10 equiv.) and PPTS (0.152 g, 0.61 mmol, 0.1 equiv.) were successively added to a solution of diol **14d** (2.93 g, 6.08 mmol, 1 equiv.) in DCM (0.62 M, 10 mL) and the reaction was stirred for 16 h. A saturated solution of NaHCO₃ was added and the mixture was extracted with DCM (3x). The combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc, 95:5) to afford acetone **15** (3.08 g, 5.89 mmol, 97%, *dr* 95:5) as a colorless oil. FTIR (neat) 2956, 2933, 2858, 1472, 1428, 1368, 1250, 1202, 1074, 951, 863, 843, 736, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.80-7.63 (m, 4H), 7.47-7.32 (m, 6H), 5.95 (dd, *J* = 17.1, 10.5 Hz, 1H), 5.60 (s, 1H), 5.24 (d, *J* = 17.1 Hz, 1H), 5.00-4.87 (m, 2H), 3.88 (td, *J* = 9.9, 4.2 Hz, 1H), 3.72-3.63 (m, 1H), 2.05 (tt, *J* = 14.1, 4.2 Hz, 1H), 1.96-1.83 (m, 1H), 1.45 (s, 6H), 1.37 (s, 3H), 1.05 (s, 9H), 0.21 (s, 9H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 159.4, 145.9, 135.8 (4C), 134.0 (2C), 129.6 (2C), 127.6 (4C), 122.1, 112.0, 98.5, 78.8, 69.8, 60.5, 41.1, 30.5, 28.8, 26.9 (3C), 26.1, 19.4, 0.4 (3C); HRMS (ESI) *m/z* calcd for C₃₁H₄₆O₃Si₂Na⁺ [(M+Na)⁺] 545.2883, found 545.2872.

Methyl (4*S*,6*S*,*E*)-6-(2-((*tert*-butyldiphenylsilyloxy)ethyl)-2,2,4-trimethyl-5-((trimethylsilyl)methylene)-1,3-dioxane-4-carboxylate 16. To a solution of acetone **15** (3.13 g, 6.00 mmol, 1 equiv.) in a 1:1 DCM/ MeOH mixture (0.1 M, 60 mL) was bubbled O₃ at -78 °C until completion of the reaction (monitored by TLC) then NaBH₄ (1.59 g, 42 mmol, 7 equiv.) was added. The mixture was warmed to RT, stirred for 30 min and subsequently quenched with a saturated solution of NH₄Cl. The aqueous layer was extracted with DCM (3x) then the combined organic extracts were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (cyclohexane/EtOAc, 85:15) to afford alcohol (2.15 g, 4.08 mmol, 68%, *dr* 95:5) as a white solid. FTIR (neat) 3475, 3071, 2956, 2933, 2858, 1473, 1428, 1379, 1250, 1204, 1112, 1075, 864, 846, 739, 702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.77-7.65 (m, 4H), 7.46-7.33 (m, 6H), 5.61 (d, *J* = 2.0 Hz, 1H), 4.93 (dt, *J* = 10.4, 2.0 Hz, 1H), 3.98-3.86 (td, *J* = 10.0, 4.8 Hz, 1H), 3.76-3.71 (ddd, *J* = 10.0, 6.4, 3.2 Hz 1H), 3.68-3.64 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.48-3.35 (dd, *J* = 10.4, 7.2 Hz, 1H), 2.00-1.87 (m, 2H), 1.46 (s, 3H), 1.38 (s, 6H), 1.06 (s, 9H), 0.22 (s, 9H); ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 157.6, 135.7 (4C),

133.7 (2C), 129.6 (2C), 127.6 (4C), 125.4, 98.3, 79.4, 70.3, 69.2, 60.2, 40.8, 30.5, 26.9 (3C), 25.5, 25.4, 19.3, 0.4 (3C); **HRMS (ESI)** m/z calcd for $C_{30}H_{46}O_4Si_2Na^+$ [(M+Na)⁺] 549.2832, found 549.2820.

To a cooled solution of previous alcohol (3.90 g, 7.40 mmol, 1 equiv.) in DCM (0.093 M, 80 mL) was successively added $NaHCO_3$ (1.86 g, 22.20 mmol, 3 equiv.) and Dess-Martin Periodinane (3.76 g, 8.88 mmol, 1.2 equiv.) at RT. After 30 min, the mixture was quenched by a saturated aqueous $Na_2S_2O_3$ solution and extracted with DCM (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure.

The crude aldehyde was dissolved in a mixture of *t*BuOH (0.016 M, 445 mL) and 2-methyl-2-butene (0.073 M, 100 mL). To this mixture was added a solution of $NaClO_2$ (1.0 g, 11.1 mmol, 1.5 equiv.) and NaH_2PO_4 (1.33 g, 11.1 mmol, 1.5 equiv.) in water (38 mL) at RT. After 1 h, an additional solution of $NaClO_2$ (1.0 g, 11.1 mmol, 1.5 equiv.) and NaH_2PO_4 (1.33 g, 11.1 mmol, 1.5 equiv.) in water (38 mL) was added. The reaction was quenched after 1 h with a 0.1 M HCl solution and extracted with DCM (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure.

To the carboxylic acid dissolved in a mixture of dry benzene (0.025 M, 296 mL) and MeOH (0.09 M, 82 mL) was added dropwise a solution of trimethylsilyldiazomethane (2.0 M in hexane, 4.07 mL, 8.14 mmol, 1.1 equiv.) at RT. After 30 min, the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc, 88:12) to afford ester **16** (3.14 g, 5.65 mmol, 69% over 3 steps,¹⁷ *dr* 95:5) as a white solid. **FTIR (neat)** 2952, 2858, 1757, 1732, 1462, 1428, 1379, 1250, 1111, 1074, 847, 701 cm^{-1} ; **¹H NMR (400 MHz, $CDCl_3$)** δ 7.43-7.41 (m, 4H), 7.14-7.10 (m, 6H), 5.49 (d, $J = 2.0$ Hz, 1H), 4.73 (dt, $J = 11.2, 2.0$ Hz, 1H), 3.60 (td, $J = 10.4, 3.6$ Hz, 1H), 3.42 (m, 4H), 1.76-1.68 (m, 1H), 1.58-1.50 (m, 1H), 1.27 (s, 3H), 1.22 (s, 3H), 1.16 (s, 3H), 0.79 (s, 9H), -0.01 (s, 9H); **¹³C{¹H} NMR (100 MHz, $CDCl_3$)** δ 175.6, 156.2, 135.8 (4C), 133.9 (2C), 129.8 (2C), 127.8 (4C), 123.8, 100.4, 77.8, 69.5, 60.2, 52.0, 39.6, 29.2, 26.9 (3C), 25.7, 24.0, 19.3, 0.3 (3C); **HRMS (ESI)** m/z calcd for $C_{31}H_{46}O_5Si_2Na^+$ [(M+Na)⁺] 577.2782, found 577.2773.

Methyl (4S,6S,E)-6-(2-((tert-butyl)diphenylsilyloxy)ethyl)-5-(iodomethylene)-2,2,4-trimethyl-1,3-dioxane-4-carboxylate 17. A flame dried Schlenk was charged with **16** (4.63 g, 8.35 mmol, 1 equiv.), *N*-iodosuccinimide (5.64 g, 25.07 mmol, 3 equiv.) and freeze-pump-thaw degassed CH_3CN (0.5 M, 15 mL), and the mixture was stirred at 120 °C in the dark for 72 h. It was then poured on a saturated aqueous $NaHCO_3/Na_2S_2O_3$ (1:1) solution and subsequently extracted with Et_2O (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (cyclohexane/ Et_2O , 85:15) to afford vinyl iodide **17** (3.90 g, 6.42 mmol, 77%, *dr* 95:5) as a colorless oil. **FTIR (neat)** 2988, 2938, 2857, 1757, 1733, 1462, 1428, 1372, 1227, 1109, 1080, 738, 702 cm^{-1} ; **¹H NMR (400 MHz, $CDCl_3$)** δ 7.74-7.68 (m, 4H), 7.45-7.34 (m, 6H), 6.56 (d, $J = 1.8$ Hz, 1H), 4.83 (dt, $J = 8.8, 1.8$ Hz, 1H), 3.91 (td, $J = 10.4, 4.4$ Hz, 1H), 3.77-3.71 (m, 1H), 3.70 (s, 3H), 2.44-2.35 (m, 1H), 1.68-1.59 (m, 1H), 1.52 (s, 3H), 1.51 (s, 3H), 1.35 (s, 3H), 1.07 (s, 9H); **¹³C{¹H} NMR (100 MHz, $CDCl_3$)** δ 174.1, 149.4, 135.8 (4C), 134.0 (2C), 130.0 (2C), 127.8 (4C), 101.1, 77.0, 76.8, 72.8,

60.0, 52.3, 35.4, 29.0, 27.0 (3C), 25.1, 23.5, 19.4; **HRMS (ESI)** m/z calcd for $C_{28}H_{37}IO_5SiNa^+$ [(M+Na)⁺] 631.1353, found 631.1348.

Methyl (4S,6S,E)-5-(but-2-yn-1-ylidene)-6-(2-((tert-butyl)diphenylsilyloxy)ethyl)-2,2,4-trimethyl-1,3-dioxane-4-carboxylate 9a. A flame-dried round-bottomed flask was charged with **17** (4.12 g, 6.76 mmol, 1 equiv.), $PdCl_2(PPh_3)_2$ (0.474 g, 0.67 mmol, 0.10 equiv.), CuI (0.257 g, 1.35 mmol, 0.20 equiv.), THF (0.13 M, 52 mL) and tributyl(1-propynyl)tin.¹⁸ Argon was bubbled until the yellow mixture turned black and the reaction was stirred at 60 °C for 1 h. The solvent was removed under pressure and the crude product was purified by flash chromatography over silica gel (cyclohexane/ Et_2O , 85:15) to afford enyne **9a** (2.46 g, 4.73 mmol, 70%, *dr* 95:5) as a yellow oil. **FTIR (neat)** 3072, 2991, 2933, 2857, 1756, 1734, 1473, 1458, 1258, 1209, 1111, 1082, 738, 703 cm^{-1} ; **¹H NMR (400 MHz, $CDCl_3$)** δ 7.72-7.63 (m, 4H), 7.44-7.33 (m, 6H), 5.64 (quint, $J = 2.0$ Hz, 1H), 5.16-5.10 (dt, $J = 10.8, 2.0$ Hz, 1H), 3.89 (td, $J = 10.0, 4.0$ Hz, 1H), 3.76-3.68 (m, 1H), 3.69 (s, 3H), 2.48-2.37 (m, 1H), 1.92 (d, $J = 2.0$ Hz, 3H), 1.71-1.62 (m, 1H), 1.50 (s, 3H), 1.47 (s, 3H), 1.38 (s, 3H), 1.06 (s, 9H); **¹³C{¹H} NMR (100 MHz, $CDCl_3$)** δ 174.9, 151.6, 135.7 (4C), 134.2 (2C), 129.6 (2C), 127.7 (4C), 105.5, 100.8, 95.4, 75.9, 75.4, 68.9, 60.1, 52.2, 36.6, 29.2, 26.9 (3C), 25.4, 23.3, 19.4, 4.7; **HRMS (ESI)** m/z calcd for $C_{31}H_{40}O_5SiNa^+$ [(M+Na)⁺] 543.2543, found 543.2547.

Methyl (4S,6S,E)-5-(but-2-yn-1-ylidene)-6-(2-hydroxyethyl)-2,2,4-trimethyl-1,3-dioxane-4-carboxylate 9b. Tetraabutylammonium fluoride (1 M in THF, 3 mL, 2.98 mmol, 2 equiv.) was added dropwise to a solution of **9a** (780 mg, 1.49 mmol, 1 equiv.) in dry THF (0.2 M, 8 mL) at 0 °C. After stirring for 12 h at RT, the mixture was quenched with water and extracted with $EtOAc$ (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (cyclohexane/ $EtOAc$, 60:40) to afford alcohol **9b** (0.292 g, 1.03 mmol, 70%, *dr* > 95:5) as a brown solid. $[\alpha]_D^{20} +23.4$ (c 1.02, $CHCl_3$); **FTIR (neat)** 3399, 2952, 2858, 1771, 1171, 1126, 1046, 971 cm^{-1} ; **¹H NMR (400 MHz, $CDCl_3$)** δ 5.63 (quint, $J = 2.4$ Hz, 1H), 4.91 (dt, $J = 10.1, 2.4$ Hz, 1H), 3.81-3.75 (m, 2H), 3.73 (s, 3H), 2.22 (dddd, $J = 14.4, 6.3, 4.3, 2.4$ Hz, 1H), 2.14 (dd, $J = 7.5, 3.4$ Hz, 1H), 2.00 (d, $J = 2.4$ Hz, 3H), 1.85 (dddd, $J = 14.4, 10.1, 7.5, 4.3$ Hz, 1H), 1.50 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H); **¹³C{¹H} NMR (75 MHz, $CDCl_3$)** δ 174.6, 150.5, 106.1, 100.8, 95.9, 75.9, 75.3, 72.7, 61.6, 52.4, 36.4, 29.1, 25.5, 23.3, 4.7; **HRMS (ESI)** m/z calcd for $C_{15}H_{22}O_5Na^+$ [(M+Na)⁺] 305.1365, found 305.1375.

Methyl (4S,6S,E)-5-(but-2-yn-1-ylidene)-6-(2-hydroxypropyl)-2,2,4-trimethyl-1,3-dioxane-4-carboxylate (±)-19. $NaHCO_3$ (261 mg, 3.11 mmol, 3 equiv.) and Dess-Martin Periodinane (528 mg, 1.24 mmol, 1.2 equiv.) were successively added to alcohol (±)-**9b** (292 mg, 1.04 mmol, 1 equiv.) dissolved in DCM (0.093 M, 11 mL). The mixture was stirred for 30 min at RT then quenched with a saturated aqueous $NaHCO_3/Na_2S_2O_3$ (1:1) solution and extracted with DCM (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude aldehyde was directly used in the next step without further purification. **FTIR (neat)** 2952, 2857, 1733, 1378, 1252, 1112, 1126, 1046, 971 cm^{-1} ; **¹H NMR (400 MHz, $CDCl_3$)** δ 9.78 (dd, $J = 2.4, 1.2$ Hz, 1H), 5.64 (app. quint, $J = 2.4$ Hz, 1H), 5.31 (dt, $J = 10.0, 2.4$ Hz, 1H), 3.73 (s, 3H), 3.05-2.97

(ddd, $J = 17.2, 2.4, 1.2$ Hz 1H), 2.74 (ddd, $J = 17.2, 10.0, 2.4$ Hz, 1H), 2.00 (d, $J = 2.4$ Hz, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.41 (s, 3H); $^{13}\text{C}\{1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 200.3, 174.6, 150.0, 106.2, 101.1, 96.9, 75.8, 75.0, 67.6, 52.4, 47.8, 28.9, 25.3, 22.9, 4.6.

The crude aldehyde (1.04 mmol, 1 equiv.) was dissolved in dry THF (0.11 M, 9 mL) and methyllithium (1.6 M in Et_2O , 0.7 mL, 1.14 mmol, 1.1 equiv.) was added dropwise at -78°C . The mixture was slowly warmed up to RT then stirred for 1 h. A solution of saturated aqueous NH_4Cl was added and the aqueous layer was extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (cyclohexane/ EtOAc , 75:25 to 60:40) to afford alcohol (\pm)-**19** (253 mg, 0.85 mmol, 82% over 2 steps) as a mixture of two unseparable diastereomers (dr 55:45). ^1H NMR (300 MHz, CDCl_3) δ 5.56 (m, 1H), 5.00 and 4.85 (dt, $J = 9.9, 2.4$ Hz, 1H), 3.96 (m, 1H), 3.68 and 3.70 (s, 3H), 2.11-2.00 (m, 1H), 1.96 (m, 3H), 1.78-1.55 (m, 1H), 1.45-1.34 (m, 9H), 1.20-1.13 (m, 3H); $^{13}\text{C}\{1\text{H}\}$ NMR (75 MHz, CDCl_3) δ 174.4 and 174.6, 151.1 and 150.2, 106.0 and 105.6, 100.7, 95.9 and 95.9, 75.9 and 75.8, 75.3 and 75.2, 73.6 and 69.9, 67.9 and 65.4, 52.3 and 52.2, 42.4 and 42.1, 29.0, 25.4, 23.4, 23.2 and 23.1, 4.6 and 4.5; HRMS (ESI) m/z calcd for $\text{C}_{17}\text{H}_{22}\text{O}_5\text{Na}^+$ [(M+Na) $^+$] 329.1365, found 329.1355.

Methyl (4S,6S,E)-5-(but-2-yn-1-ylidene)-6-(2-hydroxy-2-methylbut-3-en-1-yl)-2,2,4-trimethyl-1,3-dioxane-4-carboxylate (\pm)-**20**. NaHCO_3 (930 mg, 11.09 mmol, 3 equiv.) and Dess-Martin Periodinane (1.9 g, 4.43 mmol, 1.2 equiv.) were successively added to alcohol (\pm)-**19** (mixture of two diastereoisomers, dr 55:45) (1.1 g, 3.70 mmol, 1 equiv.) dissolved in DCM (0.093 M, 39 mL). The mixture was stirred for 2 h at RT then quenched with a saturated aqueous $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$ (1:1) solution. The aqueous layer is extracted with DCM (3x) and the combined organic extracts were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The crude ketone was engaged in the next step without further purification. FTIR (neat) 2991, 2945, 1753, 1725, 1435, 1374, 1256, 1127, 1112, 1074, 908, 730 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.64 (quint, $J = 2.4$ Hz, 1H), 5.26 (td, $J = 9.4, 2.4$ Hz, 1H), 3.77 (s, 3H), 2.99 (dd, $J = 16.8, 2.4$ Hz, 1H), 2.75 (dd, $J = 16.8, 9.4$ Hz, 1H), 2.17 (s, 3H), 1.98 (d, $J = 2.4$ Hz, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.40 (s, 3H). $^{13}\text{C}\{1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 206.1, 174.9, 151.0, 105.9, 101.1, 96.6, 75.8, 75.1, 68.8, 52.4, 47.8, 30.6, 28.9, 25.4, 22.9, 4.7.

The crude ketone (3.70 mmol, 1 equiv.) was dissolved in dry THF (0.11 M, 33 mL) and vinylmagnesium chloride (1.6 M in Et_2O , 4.6 mL, 7.39 mmol, 2 equiv.) was added dropwise at 0°C . The mixture was stirred for 4.5 h at RT then a solution of saturated aqueous NH_4Cl was added. The aqueous phase was extracted with EtOAc (3x), the combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (cyclohexane/ EtOAc , 75:25 to 60:40) to afford alcohol (\pm)-**20a** and (\pm)-**20b** (0.52 g, 0.80 mmol, 66% over 2 steps) as a separable mixture of two diastereoisomers (dr 55:45). Major diastereoisomer (\pm)-**20a**: FTIR (neat) 3542, 2989, 2941, 1755, 1733, 1455, 1373, 1248, 1208, 1110, 995, 730 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.91 (dd, $J = 17.2, 10.8$ Hz, 1H), 5.61 (qd, $J = 2.8, 1.2$ Hz, 1H), 5.26 (dt, $J = 10.8, 1.2$ Hz, 1H), 5.24 (dd, $J = 17.2, 1.6$ Hz, 1H), 5.00

(dd, $J = 10.4, 1.6$ Hz, 1H), 3.74 (s, 3H), 2.20 (dd, $J = 14.8, 2.0$ Hz, 1H), 2.00 (d, $J = 2.8$ Hz, 3H), 1.81 (dd, $J = 14.8, 10.8$ Hz, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H); $^{13}\text{C}\{1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 174.0, 150.7, 145.5, 111.3, 105.9, 100.9, 96.2, 76.0, 75.4, 72.7, 70.8, 52.4, 44.4, 29.1, 26.5, 25.4, 23.2, 4.7; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{26}\text{O}_5\text{Na}^+$ [(M+Na) $^+$] 345.1678, found 345.1682. Minor diastereoisomer (\pm)-**20b**: FTIR (neat) 3537, 2988, 2940, 1755, 1732, 1453, 1374, 1249, 1208, 1110, 995, 730 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.92 (dd, $J = 17.2, 10.8$ Hz, 1H), 5.59 (qd, $J = 2.4, 1.8$ Hz, 1H), 5.37 (dd, $J = 17.2, 1.6$ Hz, 1H), 5.15 (dd, $J = 10.8, 1.6$ Hz, 1H), 4.98 (dt, $J = 10.8, 1.8$ Hz, 1H), 3.78 (s, 3H), 2.22 (dd, $J = 14.8, 1.8$ Hz, 1H), 2.03 (d, $J = 2.4$ Hz, 3H), 1.87 (dd, $J = 14.8, 10.8$ Hz, 1H), 1.50 (s, 3H), 1.46 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H); $^{13}\text{C}\{1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 174.4, 150.7, 144.2, 112.6, 105.8, 100.9, 95.9, 76.0, 75.4, 73.8, 71.9, 52.5, 43.7, 29.6, 29.1, 25.4, 23.1, 4.7; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{26}\text{O}_5\text{Na}^+$ [(M+Na) $^+$] 345.1678, found 345.1682.

Methyl (4S,6S,E)-5-(but-2-yn-1-ylidene)-6-(2-hydroxy-2-methylbut-3-en-1-yl)-2,2,4-trimethyl-1,3-dioxane-4-carboxylate (\pm)-**22**. A solution of $i\text{PrMgCl}$ (1.35 M in Et_2O , 0.06 mL, 0.08 mmol, 1.1 equiv.) was added dropwise to a solution of allylic alcohol (\pm)-**20a** (22 mg, 0.07 mmol, 1 equiv.) in dry toluene (0.1 M, 0.7 mL) at 0°C in a flame dried Schlenk. After 15 min, $\text{Ti}(\text{O}i\text{Pr})_4$ (0.04 mL, 0.14 mmol, 2 equiv.) and $i\text{PrMgCl}$ (1.35 M in Et_2O , 0.21 mL, 0.28 mmol, 4 equiv.), were successively added dropwise over 5 min. The mixture was warmed up to RT and stirred for 6 h. A CO atmosphere was then installed at 0°C , the mixture was warmed up from 0°C to reflux over 16 h and subsequently quenched with a 0.1 M HCl solution. The aqueous layer was extracted with Et_2O (3x), the combined organic extracts were washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel (cyclohexane/ EtOAc , 75:25 to 60:40) to afford cycloheptene (\pm)-**22** (8.5 mg, 0.026 mmol, 33%, $dr > 98:2$): FTIR (neat) 3470, 2987, 1751, 1736, 1456, 1372, 1252, 1210, 1134, 1106, 1051, 997 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.16 (s, 1H), 5.52 (qd, $J = 6.8, 1.8$ Hz, 1H), 4.24 (dt, $J = 11.8, 1.8$ Hz, 1H), 3.75 (s, 3H), 2.35 (q, $J = 6.8$ Hz, 1H), 2.06 (t, $J = 11.8$ Hz, 1H), 1.67-1.60 (m, 4H), 1.56 (s, 3H), 1.48 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 1.10 (dd, $J = 6.8$ Hz, 3H). $^{13}\text{C}\{1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 175.1, 141.3, 138.1, 125.8, 122.3, 100.9, 76.5, 72.7, 68.1, 52.3, 51.3, 41.8, 28.8, 27.7, 25.2, 24.1, 14.3, 13.9; HRMS (ESI) m/z calcd for $\text{C}_{18}\text{H}_{28}\text{O}_5\text{Na}^+$ [(M+Na) $^+$] 347.1834, found 347.1822.

Methyl (4S,6S,E)-5-(but-2-yn-1-ylidene)-2,2,4-trimethyl-6-(prop-2-yn-1-yl)-1,3-dioxane-4-carboxylate (\pm)-**23**.

Alcohol (\pm)-**9b** (107 mg, 0.38 mmol, 1 equiv.) was oxidized in corresponding aldehyde as previously described for the synthesis of (\pm)-**19**. The crude aldehyde was directly used in the next step without further purification.

Ohira-Bestmann reagent ²⁵ (0.087 g, 0.453 mmol, 1.2 equiv.) in dry MeOH (0.46 M, 1 mL) and K_2CO_3 (0.104 g, 0.756 mmol, 2 equiv.) were successively added to the crude aldehyde (0.38 mmol, 1 equiv.) dissolved in dry MeOH (0.156 M, 2.4 mL). The mixture was stirred for 3.5 h at RT then a solution of saturated aqueous NaHCO_3 was added. The aqueous phase was extracted with Et_2O (3x), the combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by flash chro-

matography over silica gel (cyclohexane/EtOAc, 60:40) to afford alkyne (\pm)-**23** (0.055 g, 0.198 mmol, 53% over 2 steps) as a colorless oil. **FTIR (neat)** 3289, 2991, 2942, 1756, 1732, 1451, 1373, 1258, 1209, 1112, 999, 714 cm^{-1} ; **^1H NMR (400 MHz, CDCl_3)** δ 5.64 (quint, $J = 2.4$ Hz, 1H), 4.87 (dt, $J = 10.2$, 2.4 Hz, 1H), 3.73 (s, 3H), 2.93 (dt, $J = 17.2$, 2.4 Hz, 1H), 2.45 (ddd, $J = 17.2$, 10.2, 2.4 Hz, 1H), 2.04 (d, $J = 2.4$ Hz, 3H), 1.99 (t, $J = 2.4$ Hz, 1H), 1.52 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H); **$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3)** δ 174.5, 149.8, 107.0, 101.2, 96.7, 82.1, 75.7, 75.0, 72.0, 69.0, 52.4, 29.0, 25.4, 24.2, 23.0, 4.7; **HRMS (ESI)** m/z calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4\text{Na}^+$ [(M+Na) $^+$] 299.1259, found 299.1256.

Methyl (4S,6S,E)-5-(but-2-yn-1-ylidene)-6-(4-hydroxybut-2-yn-1-yl)-2,2,4-trimethyl-1,3-dioxane-4-carboxylate (\pm)-**24**. Freshly prepared LiHMDS (1 M, 1.62 mL, 1.62 mmol, 3 equiv.) was added dropwise to a solution of alkyne (\pm)-**23** (150 mg, 0.54 mmol, 1 equiv.) in THF (0.05 M, 10 mL) at -78 $^\circ\text{C}$. The reaction mixture was stirred for 1 h at -78 $^\circ\text{C}$ then paraformaldehyde (100 mg, 3.33 mmol, 6 equiv.) was added in one portion. The mixture was allowed to warm up to RT, stirring was maintained 3 h and the reaction was quenched by addition of a solution of saturated aqueous NH_4Cl . The aqueous phase was extracted with Et_2O (3x), the combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc, 80:20) to afford propargylic alcohol (\pm)-**24** (64 mg, 0.209 mmol, 60% brsm) as a colorless oil. **FTIR (neat)** 3411, 2989, 2919, 2219, 1785, 1756, 1434, 1373, 1258, 1210, 1113, 1019, 954 cm^{-1} ; **^1H NMR (400 MHz, CDCl_3)** δ 5.65 (quint, $J = 2.4$ Hz, 1H), 4.85-4.83 (dt, $J = 9.8$, 2.4 Hz, 1H), 4.26 (t, $J = 2.4$ Hz, 2H), 3.73 (s, 3H), 2.96-2.90 (dq, $J = 17.2$, 2.4 Hz, 1H), 2.54-2.46 (ddt, $J = 17.2$, 9.8, 2.4 Hz, 1H), 2.04 (d, $J = 2.4$ Hz, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H); **$^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3)** δ 174.7, 149.5, 107.2, 101.2, 96.7, 83.7, 79.3, 75.8, 75.0, 72.0, 52.5, 51.6, 29.0, 25.4, 24.5, 23.1, 4.8; **HRMS (ESI)** m/z calcd for $\text{C}_{17}\text{H}_{22}\text{O}_5\text{Na}^+$ [(M+Na) $^+$] 329.1365, found 329.1372.

Methyl (4S,6S,E)-5-(but-2-yn-1-ylidene)-2,2,4-trimethyl-6-(2-methylbuta-2,3-dien-1-yl)-1,3-dioxane-4-carboxylate (\pm)-**25**. To a solution of primary alcohol (\pm)-**24** (0.029 g, 0.094 mmol, 1 equiv.) in dry DCM (0.15 M, 0.6 mL) at 0 $^\circ\text{C}$, were added Et_3N (14 μL , 0.103 mmol, 1.1 equiv.) and MsCl (8 μL , 0.103 mmol, 1.1 equiv.). The mixture was stirred for 0.5 h at RT then a solution of saturated aqueous NH_4Cl was added. The aqueous phase was extracted with DCM (3x), the combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was filtered through a short pad of silica gel to furnish crude intermediate mesylate.

CuCN (34 mg g, 0.378 mmol, 4 equiv.) and LiCl (32 mg, 0.759 mmol, 8 equiv.) were heated under vacuum at 130 $^\circ\text{C}$ for 2 h. After cooling to RT, THF (0.37 mL) was added. To the resulting solution at -78 $^\circ\text{C}$, was added dropwise MeLi (1.6 M, 0.24 mL, 0.378 mmol, 4 equiv.), the mixture was warmed up to -20 $^\circ\text{C}$. After cooling again to -78 $^\circ\text{C}$, the crude mesylate (0.094 mmol) in THF (0.6 mL) was added. The reaction was stirred for 0.5 h at the same temperature and quenched by addition of a solution of saturated aqueous NH_4Cl . The aqueous phase was extracted with Et_2O (3x), the combined organic extracts were washed with brine, dried over MgSO_4 , filtered and

concentrated under reduced pressure. The crude residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc, 80:20) to afford allene (\pm)-**25** (13 mg, 0.042 mmol, 45% over 2 steps) as a colorless oil. **FTIR (neat)** 2988, 2941, 2918, 1960, 1757, 1732, 1435, 1371, 1257, 1242, 1210, 1112, 997 cm^{-1} ; **^1H NMR (400 MHz, CDCl_3)** δ 5.60 (quint, $J = 2.4$ Hz, 1H), 4.86-4.83 (dt, $J = 10.0$, 2.4 Hz, 1H), 4.63-4.61 (sext, $J = 3.1$ Hz, 2H), 3.73 (s, 3H), 2.68-2.62 (dtd, $J = 17.2$, 3.1, 2.4 Hz, 1H), 2.10 (ddt, $J = 17.2$, 10.0, 3.1 Hz, 1H), 2.00 (d, $J = 2.4$ Hz, 3H), 1.73 (t, $J = 3.1$ Hz, 3H), 1.48 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H); **$^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3)** δ 206.8, 174.9, 152.0, 105.6, 100.9, 96.6, 95.9, 75.8, 75.4, 74.3, 72.1, 52.3, 38.2, 29.1, 25.4, 23.0, 19.1, 4.7; **HRMS (ESI)** m/z calcd for $\text{C}_{18}\text{H}_{24}\text{O}_4\text{Na}^+$ [(M+Na) $^+$] 327.1572, found 327.1563.

Methyl (4S,10aS)-2,2,4,6,9-pentamethyl-7-oxo-7,8,10,10a-tetrahydro-4H-azulenol[6,5-d][1,3]dioxine-4-carboxylate (\pm)-**26**. Allene (\pm)-**25** (13 mg, 0.042 mmol, 1 equiv.) was dissolved in freshly distilled toluene (0.1 M, 0.42 mL). The reaction mixture was degassed by bubbling with argon for 5 min then a CO atmosphere was installed. Dppp (8.6 mg, 0.021 mmol, 0.5 equiv.) and $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (1.5 mg, 0.004 mmol, 0.1 equiv.) were successively added and CO was bubbled again for 2 min. The mixture was then heated at 90 $^\circ\text{C}$ for 24 h, then the mixture was cooled to RT and the solvent was removed. The crude residue was purified by flash chromatography over silica gel (cyclohexane/EtOAc, 80:20) to afford cyclopentenone (\pm)-**26** (9.6 mg, 0.029 mmol, 71%) as a white solid. **FTIR (neat)** 2989, 2925, 2854, 1753, 1690, 1380, 1252, 1213, 1110, 998, 864 cm^{-1} ; **^1H NMR (400 MHz, CDCl_3)** δ 6.43 (d, $J = 2.4$ Hz, 1H), 4.78-4.74 (dt, $J = 11.6$, 2.4 Hz, 1H), 3.77 (s, 3H), 3.06-3.01 (d, AB syst $J = 11.3$ Hz, 1H), 3.01-2.95 (d, AB syst $J = 11.3$ Hz, 1H), 2.93-2.86 (dd, $J = 16.8$, 11.6, 1H), 2.39-2.34 (dd, $J = 16.8$, 2.4 Hz, 1H), 1.91 (s, 3H), 1.88 (s, 3H), 1.63 (s, 3H), 1.52 (s, 3H), 1.42 (s, 3H); **$^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3)** δ 204.5, 174.3, 157.2, 150.0, 140.8, 131.7, 129.7, 116.2, 101.4, 76.5, 69.4, 52.6, 40.4, 40.2, 28.7, 25.1, 24.3, 23.3, 8.7; **HRMS (ESI)** m/z calcd for $\text{C}_{19}\text{H}_{24}\text{O}_5\text{Na}^+$ [(M+Na) $^+$] 345.1624, found 345.1700.

ASSOCIATED CONTENT

Supporting Information.

This material is available free of charge via the Internet at <http://pubs.acs.org>.

Experimental details as well as compound characterization data and copies of ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra are available in the Supporting Information.

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SYNOPSIS TOC.

