Synthetic Studies toward the Total Synthesis of Tautomycetin

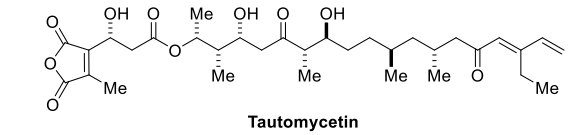
Danilo Pereira de Sant'ana, Celso de Oliveira Rezende Júnior, Jean-Marc Campagne, Luiz Carlos Dias, Renata Marcia de Figueiredo

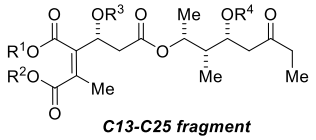
Synthetic Studies toward the Total Synthesis of Tautomycetin

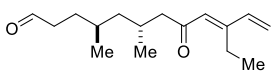
Danilo Pereira de Sant'Ana,[†§‡] Celso de Oliveira Rezende Júnior,[†‡] Jean-Marc Campagne,*[§] Luiz Carlos Dias,*[†] and Renata Marcia de Figueiredo*[§]

[†] Institute of Chemistry, University of Campinas, Campinas/São Paulo - 13083-970, Brazil.

[§] Institut Charles Gerhardt, UMR 5253, Univ Montpellier, CNRS, ENSCM, 240 Avenue du Professeur Emile Jeanbrau, 34296 Montpellier Cedex 5, France.







ABSTRACT: The studies culminating in the synthesis of two large subunits of tautomycetin are described. The first one, fragment C1-C12 that has an *anti*-1,3-dimethyl system and a terminal diene unit, was accomplished in 10 linear steps in 7.4% overall yield. The second one, fragment C13-C25 which bears the sensitive anhydride framework and the majority of the stereogenic centers, was prepared in 13 linear steps (longest sequence) in 8% overall yield. Among the key transformations used, a regioselective epoxide opening, a Pd-catalyzed addition of terminal alkyne to acceptor alkyne, a Mukaiyama aldol reaction, a Yamaguchi esterification and a homemade mild di-esterification can be cited. The chosen strategies allowed good yields, stereoselectivity, reproducibility and scalability for several important intermediates.

1. INTRODUCTION

Tautomycetin (TTN, **1**, Figure 1) is a natural linear polyketide isolated by Isono and co-workers in 1989 from extracts of *Streptomyces griseochromogenes* during a screening of soil microorganisms.[1-3] Initially recognized as an antifungal antibiotic able to induce morphological changes on human erythroid leukemia cell K562 in the late 1980s,[4] follow-up studies revealed its inhibitory activity toward protein phosphatases type 1 and 2 (PP1 and PP2). Compared to other natural products that share this biological activity [*i.e.* tautomycin (**2**), okadaic acid (**3**), forstriecin (**4**) and cantharidin (**5**), (Figure 1)],[5] TTN proved to be very specific toward PP1.[6] More recently, the potential of TTN against colorectal[7] and breast[8] cancer cells growth as well as its activity as immunosuppressor in organ transplantation,[9,10] have also been highlighted.[11]

Besides the impressive biological potential of TTN, this natural product has a unique and original chemical structure embedding eight stereogenic centers,[12] a terminal diene motif, an *anti*-1,3-dimethyl system and an anhydride moiety that exists as an equilibrium mixture with its open diacid form in a 4:6 ratio in methanol-buffer solution.[1,13]

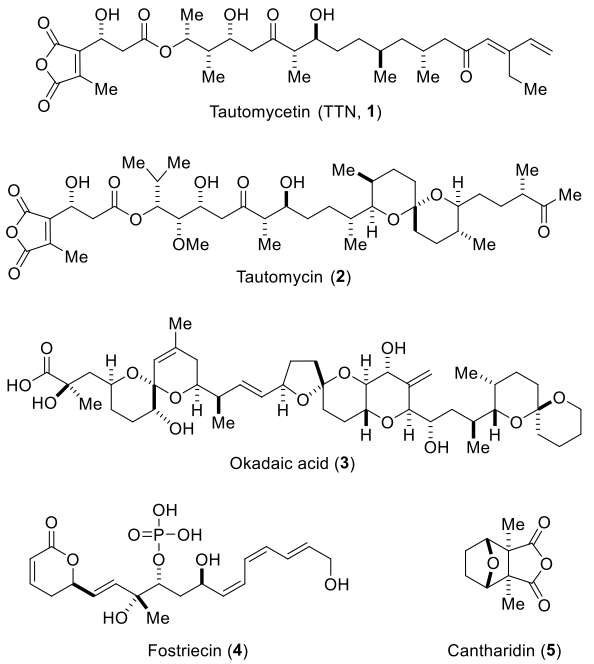
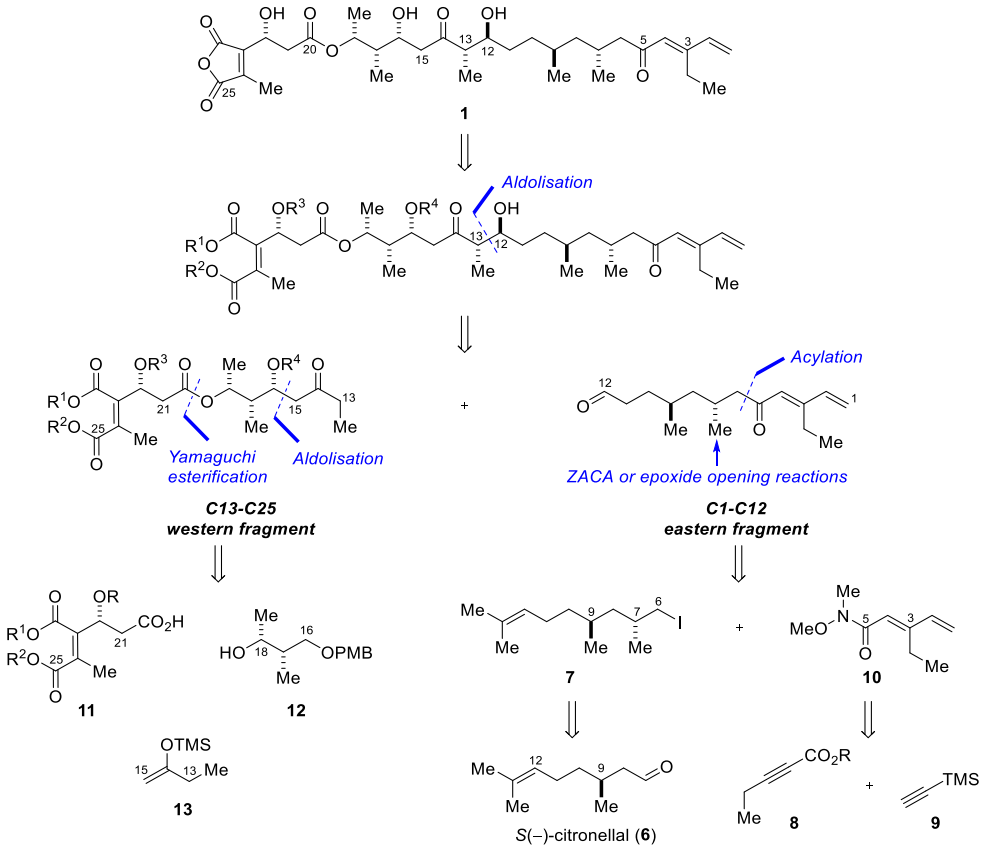


Figure 1. Tautomycetin (**1**) and selected examples of natural products that inhibit PP1 and PP2.



Scheme 1. Retrosynthesis of TTN. R^1, R^2, R^3, R^4 = protecting groups.

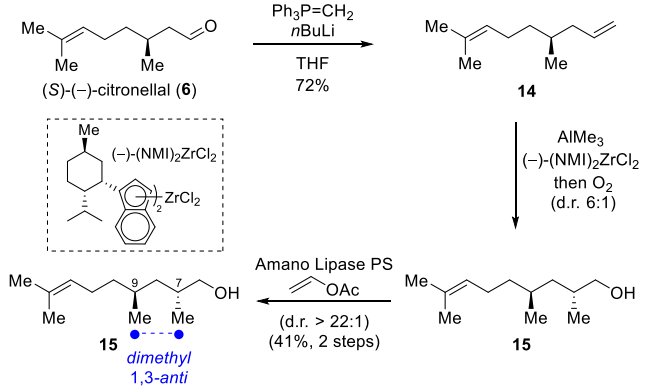
Due to the unique biological properties and structural complexity of TTN, we embarked into a program aimed at its total synthesis. Despite efforts devoted to this end by Oikawa and co-workers,[14,15] a total synthesis of TTN has not yet been achieved. Herein, we report the synthesis of two fragments (C1-C12 and C13-C25) and our synthetic efforts toward the assembly of the entire backbone of TTN.

The retrosynthetic strategy that we envisaged for accessing **1** is outlined in scheme 1. A disconnection on C12-C13 bond gives two fragments of more or less the same size. The linear backbone of TTN would be thus obtained through a boron mediated aldolisation. At last, a final general deprotection step would afford the synthetic TTN. We anticipated that C1-C12 moiety, which bears an *anti*-dimethyl system, would be formed *via* acylation of an organolithium derivative in order to form C5-C6 bond. The regio- and stereocontrolled introduction of the methyl group in C7 could derive either from a strategy based on the ZACA reaction or *via* a regioselective ring opening of an epoxide. The terminal diene system was to be formed by means of palladium-catalyzed addition of terminal alkyne to acceptor alkyne developed by Trost and co-workers.[16] Elaboration of C13-C25 challenging segment, that bears the anhydride moiety, would be achieved by a sequence of reactions including a Mukaiyama aldol addition (C15-C16 bond) and an esterification in the conditions of Yamaguchi (O19-C20 bond). The strategy pictured to reach the puzzling diester form of the dialkylmaleic anhydride moiety (segment **11**) was envisaged from an original step of di-esterification, under very mild conditions, previously developed in our laboratories.[17]

2. RESULTS AND DISCUSSION

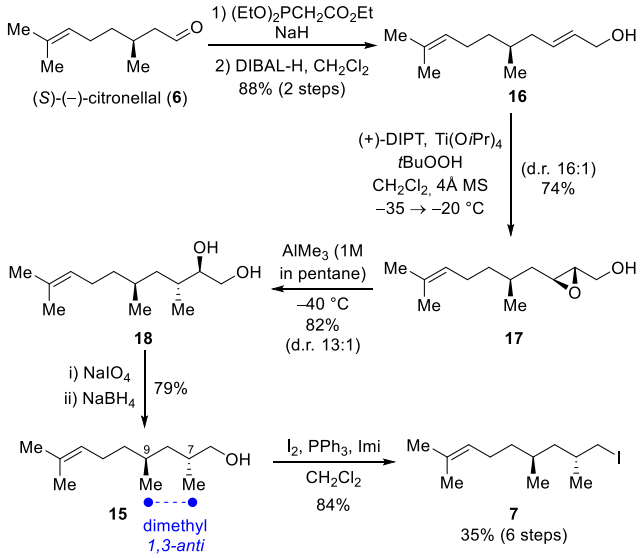
Synthesis of Fragment C1-C12

On the basis of Negishi's work,[18] known alcohol **15** was prepared in three steps from (S)-(–)-citronellal (**6**) in 30% overall yield (Scheme 2). Thanks to a Zr-catalyzed asymmetric carboalumination of alkene **14** (ZACA reaction), the *anti*-dimethyl system could be satisfactorily addressed. However, in our hands, this strategy appeared difficult to be reproduced on a multigram scale preserving the same outcomes in terms of both yield and selectivity. Therefore, a fallback method was envisaged.



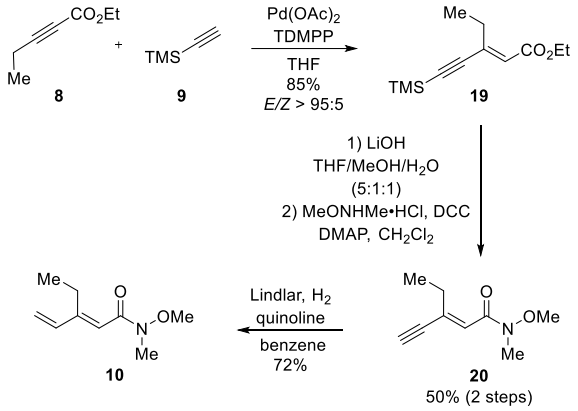
Scheme 2. Synthesis of the *anti*-1,3-dimethyl system *via* the ZACA reaction.[18a]

The intermediate **15** could also be synthesized following the strategy described in scheme 3. The Horner-Wadsworth-Emmons (HWE) reaction on **6** followed by the ester reduction to the corresponding alcohol (DIBAL-H at –78 °C), afforded the allylic alcohol **16** in 88% yield. Asymmetric epoxidation of **16** under Sharpless conditions[19] [(+)-DIPT, Ti(O*i*Pr)4, *t*BuOOH, 4Å MS, –35 to –20 °C] gave the epoxy alcohol **17** in 74% yield with a good diastereomeric ratio (d.r.) of 16:1. It might be mentioned that when the epoxidation was realized in the presence of less encumbered chiral ligand (+)-DEPT a better yield was observed (81%) however with lower diastereoselectivity (d.r 4.5:1). With epoxy alcohol **17** in hands, the regio- and diastereoselective ring opening studies were thus undertaken. The goal here was to favor the formation of the 1,2-diol **18**, that bears the 1,3-*anti* dimethyl system, instead of the 1,3 regioisomer. Within this purpose, this step was tried with trimethylaluminium in different solvents. Indeed, in our hands, this key step showed to be quite sensitive to the solvent used on the reaction. While the reaction fails when CH2Cl2 was used, which is a quite common solvent for this kind of transformation,[20] toluene gave moderate yield (55%) and d.r. (6:1). Interestingly, changing toluene by pentane allowed us to improve both yield and diastereoselectivity (82%, d.r. 13:1). Subsequent oxidative cleavage ($NaIO_4$) and reduction ($NaBH_4$) afforded the alcohol **15** in 79% yield. Following this strategy, **15** was obtained in five steps with improved overall yield (42% vs 30%)[21] and better scalability than the one described on scheme 2.[22] Finally, iodide **7** was prepared by using the conditions devised by Garegg-Samuelsson (PPh3, I2, and Imidazole) in 84% yield.[23]



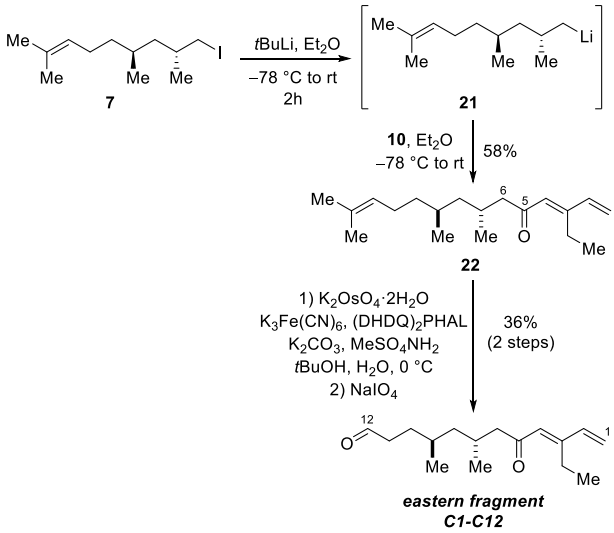
Scheme 3. Synthesis of the 1,3-dimethyl system *via* the epoxidation strategy.

Concerning the terminal diene moiety, a palladium-catalyzed addition of terminal alkyne **9** to the acceptor alkyne **8** [Pd(OAc)2, tris(2,6-dimethoxyphenyl)phosphine (TDMPP), THF] developed by Trost and co-workers[16] enabled the isolation of adduct **19** in good yield (85%) and excellent *E*/*Z* ratio (>95:5) (Scheme 4). The *E* geometry could be established by NOESY experiments after the reduction of the ester into the corresponding alcohol. Saponification of the ester function (LiOH, THF/MeOH/H2O 5:1:1) and Weinreb amide formation (MeONHOMe·HCl, DCC, DMAP, CH2Cl2) allowed the access to the ene-yne intermediate **20** that afforded the diene-amide **10** (31% overall yield for four steps) after reduction of the triple bond with the Lindlar catalyst.



Scheme 4. Synthesis of amide **10** bearing the terminal diene system.

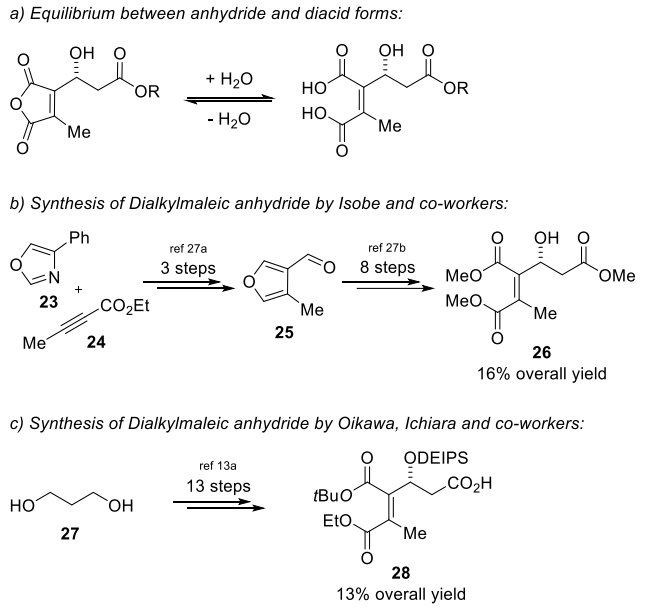
The stage was then set for the assembly of the backbone of the eastern fragment C1-C12 by the key acylation step *via* organolithium **21** (derived from *t*BuLi addition into iodide **7**) addition to the Weinreb amide **10**.[24] The transformation proceeded smoothly when conducted in Et2O at –78 °C and the required coupling adduct **22** was obtained in 58% yield (Scheme 5).[25] Next, the regio- and chemoselective oxidative cleavage of the more enriched double bond on the triene **22** afforded the fragment C1-12 in 36% yield for the two steps. The synthesis of subunit C1-C12, that embedded two among the eight stereocenters present in TTN and the dimethyl 1,3-*anti* system, was thus achieved in 10 linear steps from commercially available (S)-(–)-citronellal in 7.4% overall yield.[26]



Scheme 5. Accomplishment of the synthesis of fragment C1-C12.

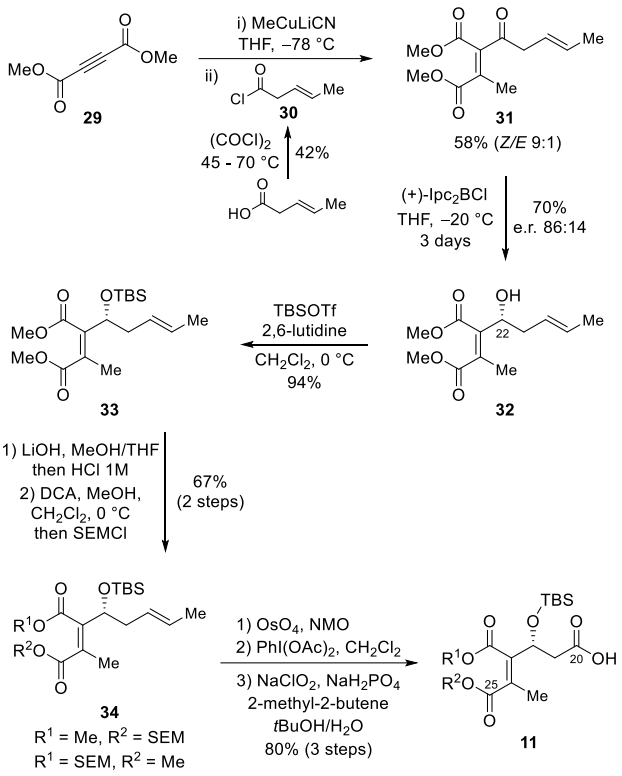
Synthesis of Fragment C13-C25

We have next initiated the studies toward the western fragment C13-C15 that bears the six other stereocenters and also the challenging anhydride moiety. Even though the preparation of the anhydride derivative seems to be straightforward, examples of syntheses reported in the literature showed that this is not the case due to the equilibrium between the anhydride and its opened diacid form (Scheme 6a). This point was indeed demonstrated during studies toward the total synthesis of tautomycin **2**, a structural analog of TTN (see figure 1), that bears the same tricky 2,3-disubstituted maleic anhydride segment. Isono and co-workers reported in 1993 the synthesis of the segment **26** (16% overall yield, 11 steps from **23** and **24**) (Scheme 6b),[27] and two years later, Oikawa, Ichiara and co-workers described the synthesis of compound **28** (13% overall yield, 13 steps from **27**) (Scheme 6c).[13a]



Scheme 6. a) Chemical behavior in aqueous media: equilibrium between anhydride and diacid forms. b) Synthesis of the dialkylmaleic anhydride **26** by Isono and co-workers. c) Synthesis of the dialkylmaleic anhydride **28** by Oikawa, Ichiara and co-workers. DEIPS = Diethylisopropylsilyl.

Considering this behavior, and keeping in mind the possible synthetic problems that this equilibrium can accommodate, we therefore envisaged a synthetic strategy where the anhydride was to be formed only in the last step of the synthesis [*i.e.* during the final deprotection of all protecting groups once the entire carbon backbone of the TTN has been built (see scheme 1)]. We envisioned the synthesis of the dialkylmaleic anhydride intermediate **11** starting from the commercially available dimethyl 2-butynedioate **29** (Scheme 7). By using the stereoselective addition of an organocopper reagent (MeCuLiCN),[28] followed by the trapping of the transiently formed β-disubstituted-α-carbethoxyvinyl)cuprate with **30**,[13b] the unsaturated ketone intermediate **31** was isolated in 58% yield in several grams scale. With **31** in hands, we undertook studies toward the enantioselective reduction of the ketone function. For this purpose, we first chose the Corey-Bakshi-Shibata (CBS) conditions which are broadly used in total syntheses.[29] Under these conditions (CBS catalyst, BH_3·BMS in THF at 0 °C) the expected alcohol could be isolated in a moderate yield of 40% and a disappointing enantiomeric ratio (e.r. 60:40). We were able to improve both yield and enantioselectivity by simply moving to (+)-Ipc2BCl at –20 °C for which alcohol **32** could be isolated in 70% yield with an e.r. of 86:14.[30] The configuration of the newly generated C22 stereogenic center was confirmed *via* Mosher ester analysis (see supporting information for details).[31] Silylation of **32** (TBSOTf, 2,6-lutidine, 0 °C) gave rise to the silylether **33** in 94% yield.

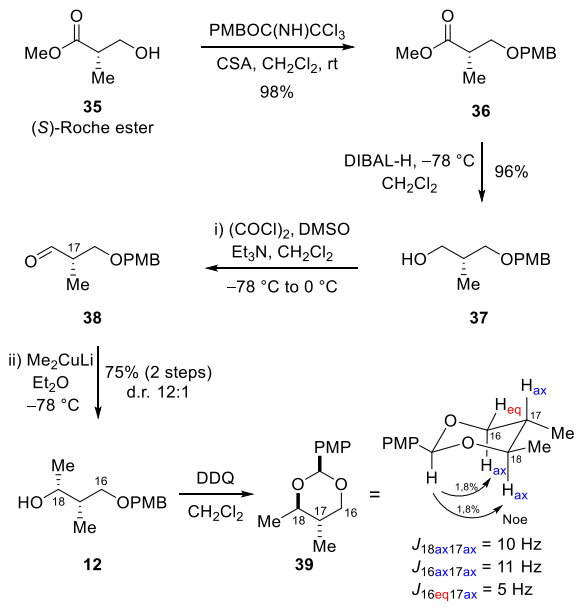


Scheme 7. Synthesis of C20-C25 moiety.

Aware of the difficulties encountered on precedent works toward the anhydride moiety synthesis,[13a,27] we have anticipated that the key for a robust strategy lies on an easy ester deprotection at the end of the synthesis. Therefore, a great deal of efforts and work were devoted to find a practical and mild methodology to form the strategic dialkylmaleic anhydride intermediate **34**. Indeed, among the weaknesses highlighted on previous strategies, the need for harsh conditions that are not always compatible with the polyfunctionalized structure of TTN or difficulties to find orthogonal protecting groups for the diester intermediate synthesis hamper the accomplishment of the total synthesis of **1**.[14,15] Thus, to overcome all this potential future complications, we relied on a mild and practical procedure for the esterification of free carboxylic acids with β-(trimethylsilyl)ethoxymethyl chloride developed in our laboratories.[17] Accordingly, an anhydride

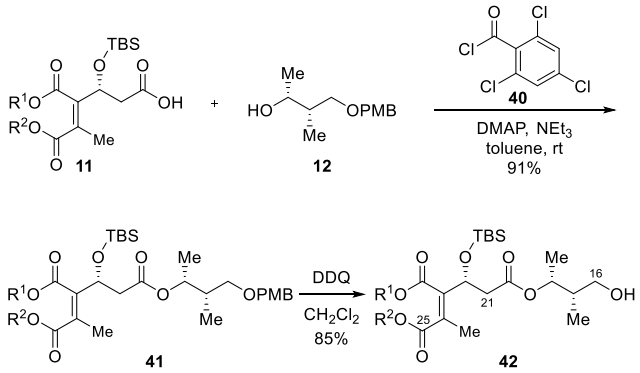
intermediate was formed through the saponification of **33** (LiOH, THF/H_2O, rt), then sequential bis-esterification (DCA, MeOH at 0 °C then SEMCl) led to di-ester **34** in 67% yield (2 steps). The use of such silyl/alkyl-ester derivative **34** has the advantage to allow a single late deprotection step of all silyl-protecting groups in the molecule under mild conditions avoiding strong basic conditions. Then, **34** was transformed into acid **11** by oxidative cleavage of the double bond [OsO_4, NMO, acetone/H_2O then $PhI(OAc)_2$ in CH_2Cl_2] followed by oxidation under Pinnick's conditions (80% over 3 steps).[32]

The synthesis of alcohol **12** commenced with the protection of (*S*)-Roche ester (**35**) in the presence of 4-methoxybenzyl trichloroacetimidate to form the *p*-methoxybenzyl (PMB) ether **36** (Scheme 8). DIBAL-H mediated reduction into alcohol **37** followed by Swern oxidation[33] provided aldehyde **38** in 71% yield for these three steps. In order to avoid both decomposition and C17 racemization, alcohol **37** was oxidized into aldehyde **38** prior to the step of methylation and directly used without further purification. Then, treatment of **38** with Gilman's reagent[34] (Me_2CuLi) in Et_2O at low temperature afforded the secondary alcohol **12** in good yield (75%) and diastereomeric ratio (12:1). The stereochemistry of the newly formed hydroxy group was established on the basis of NOE interactions between vicinal protons of the corresponding *p*-metoxybenzylidene acetal derivative **39**.[35] The sequence proposed to reach **12** works finely; it can be scaled up easily and all intermediates are very stable (with the exception of aldehyde **38**).



Scheme 8. Synthesis of secondary alcohol **12**.

Having synthesized the acid **11** and the secondary alcohol **12**, the coupling step was investigated (Scheme 9). Of the various esterification protocols that were examined, Yamaguchi's reagent (2,4,6-trichlorobenzoyl chloride **40**) proved the most fruitful, giving ester **41** in excellent 91% yield.[36] Removal of the PMB group from **41** using DDQ furnished the primary alcohol **42** in 85% yield.

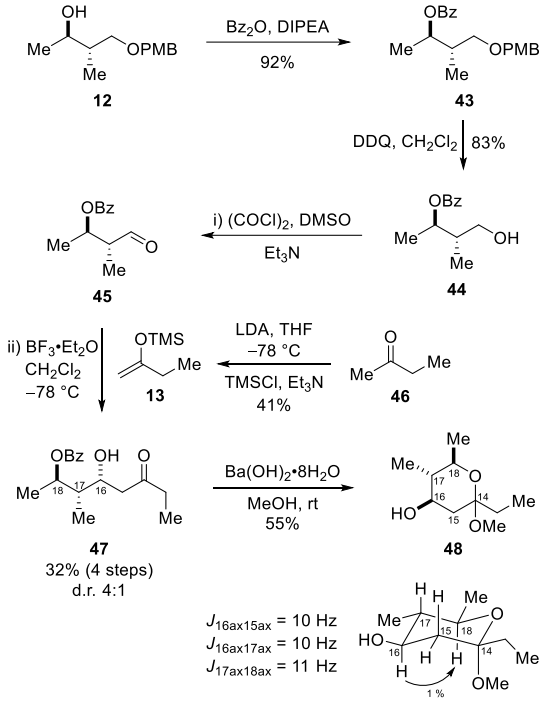


Scheme 9. Synthesis of primary alcohol **42**.

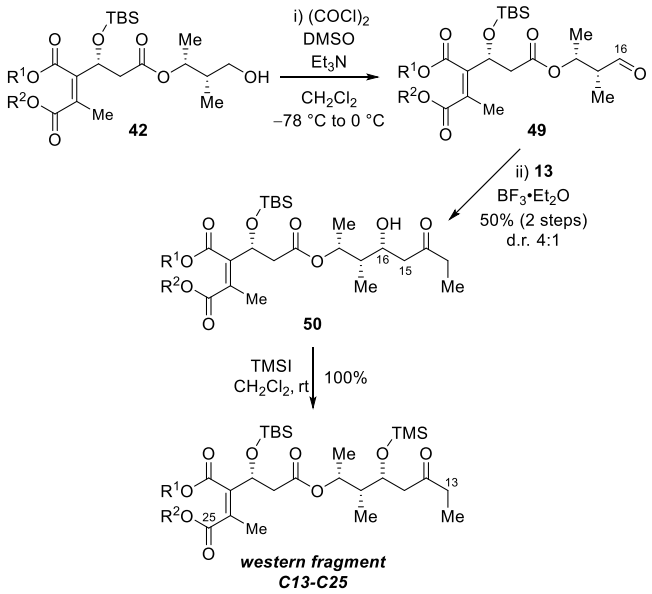
Prior to the oxidation of **42** into aldehyde and its use in the Mukaiyama aldol reaction with **13**, we studied this transformation on the model compound **45**. Starting from alcohol **12** (see scheme 8), model aldehyde **45** was synthesized in three steps *via* O-benzoylation (92%), PMB removal (83%) followed by Swern oxidation (Scheme 10). Exposure of **45** to 2-(trimethylsilyloxy)-1-butene **13** (easily prepared from butanone **46** in 41% yield) in the presence of $BF_3{\cdot}Et_2O$ in Et_2O at –78 °C furnished the aldol adduct **47** in 42% yield (two steps; oxidation/aldolisation) and a diastereomeric ratio of 4:1. The relative configuration of the newly formed stereocenter was established by conversion of **47** into ketal **48**, under $Ba(OH)_2$ treatment, and NOESY experiment. We could thus define a *trans* relative stereochemistry for C18, C17 and C16 for ketal **48**. Accordingly, the relative configuration of C17 and C16 on **47** is *syn*, and as the absolute stereochemistry of C17 is known (*S*), the one from the newly formed stereocenter is (*R*). Although we expected a better selectivity, this result is consistent with a Felkin/1,3-*anti* aldol adduct as an *anti*-relationship between the α- and β-substituents influences the facial bias of the carbonyl moiety under non-chelating conditions.[37]

On the basis of these encouraging model studies, the aldol condensation was thus investigated on our real substrate (Scheme 11). For this purpose, the oxidation of alcohol **42** (Scheme 7) furnished the required aldehyde **49**. Then, we were delighted to obtain the expected aldol adduct **50** in 50% yield (two steps; Swern oxidation and aldolisation) and a similar 4:1 diastereomeric ratio. Next, we proceeded with the TBS protection step of alcohol **50**. Although this transformation generally works well, in our case it proved to be more difficult than anticipated. Indeed, under the classical conditions (TBSOTf and 2,6-lutidine) the protection failed. By tuning the amounts of reagents (excess of TBSOTf) resulted extensive degradation of **50**. We believe that the reluctance of this substrate toward TBS protection might be due to the easy dehydration on C15-C16 under mild basic conditions as observed by Isono and co-workers.[2] Moving to milder conditions (TBSCl and imidazole in DMF) only provided the unchanged substrate **50**. To circumvent this problem, we decided to add a less encumbered TMS protecting group.

Gratefully, the TMS protection works finely in the presence of *N*-trimethylsilylimidazole in CH_2Cl_2 at room temperature (quantitative yield). This step concluded thus a sequence of 13 linear steps to provide the western C13-C25 fragment of TTN in 8% overall yield.



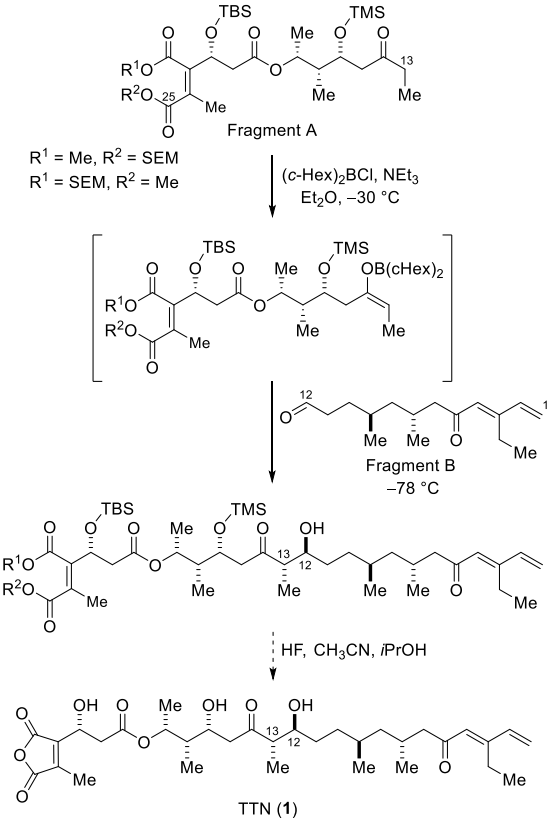
Scheme 10. Survey of the aldol reaction on the model aldehyde **45**.



Scheme 11. Assembly of the carbon backbone of the protected fragment C13-C25 *via* Mukaiyama's aldolisation. TMSI = *N*-Trimethylsilylimidazole.

Endgame strategy toward the TTN synthesis

With main fragments C1-C12 and C13-C25 of TTN synthetized, we were ready to proceed with their attachment in order to build the entire backbone of TTN. To remind, the endgame steps of our proposed strategy (see Scheme 1) relied on a key boron-mediated aldolisation to forge and control the relative stereochemistry of C12-C13 bond[38] followed by a final removal of all protecting groups. Knowing that 1,2-*anti* adducts are mostly like to be obtained *via E*-boron enolates,[39] we tried the condensation by pre-mixing fragment C13-C25 with (cHex)2BCl (which favors *E*-enolate formation) in the presence of Et3N in Et2O at –30 °C followed by the addition of aldehyde C1-C12 at –78 °C (Scheme 12). The usually recommended oxidative quench was avoided due to the presence of double bonds on both fragments which are prone to oxidation. Then, the crude material of the aldol reaction was engaged in the final deprotection step in the presence of HF in CH_3CN. Even though we got some evidence concerning the formation of TTN (a mass spectra of the crude material and an HPLC profile, see supporting information),[40] to our greatest regret, we were unable to purify and isolate the natural product. We probably encountered problems associated with the high instability of the natural product as described in the original papers (*i.e.* sites both prone to reduction and oxidation, the possible degradation *via* retro-aldol reactions and the quite unpredictable behavior of the anhydride moiety).



Scheme 12. Studies toward the completion of the TTN total synthesis.

3. CONCLUSION

We have described the synthesis of two advanced fragments of tautomycetin (TTN, **1**): the eastern one (C1-C12 segment, 10 linear steps; 7.4% yield) which bears both the terminal conjugated diene and the *anti*-1,3-dimethyl sys-

tem and the western one (C13-C25 segment, 13 linear steps; 8% overall yield) that includes four from the eight stereogenic centers present in the molecule and the tricky anhydride framework. Besides the remarkable and vast biological properties of this natural linear polyketide, its unique chemical structure displays a real challenge for chemical synthesis. Likewise, the very sensitive chemical nature of TTN in addition to its low natural availability were responsible for a late complete stereochemistry characterization.[12] Thus, to the best of our knowledge, no total synthesis of this natural product has been described so far. During our work on the endgame strategy to conclude the total synthesis, indications concerning the formation of TTN were obtained; regrettably, all attempts to purify and isolate the natural product failed in our hands. The difficulties faced might be related to the chemical instability previously observed for this compound.[12] Nonetheless, the synthesis of two large subunits of TTN was accomplished in good overall yields and stereocontrols. The strategies used allowed high reproducibility and easy scale-up of key intermediates and the challenging dialkylmaleic anhydride moiety could be efficiently prepared through a homemade method.

4. EXPERIMENTAL SECTION

4.1. General Method. Unless otherwise specified (see paragraph below), all commercial products and reagents were used as purchased, without further purification. Reactions were carried out in round-bottom flasks, and Schlenk tubes were equipped with a magnetic stirring bar under argon atmosphere. All reactions were carried out under an atmosphere of argon with dry solvents under anhydrous conditions unless otherwise stated. Analytical thin-layer chromatography (TLC) of all reactions was performed on silica gel 60 F254 TLC plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm), using *p*-anisaldehyde, $KMnO_4$, vanillin or phosphomolybdic acid stains. Flash chromatography was carried out on silica gel 60 Å (35–70 nm). FT-IR spectra were recorded with a PerkinElmer Spectrum 1000; absorptions are given in wave numbers (cm–1). ^1H (250, 400, 500 and 600 MHz) and ^{13}C (62.5, 100, 125 and 150 MHz) NMR spectra were recorded with a Bruker 250, 400, 500 and Ultra Shield 400 Plus. ^1H chemical shifts are reported in delta (δ) units in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d (residual $CHCl_3$). ^{13}C chemical shifts are reported in ppm relative to the central line of the triplet at 77.0 ppm for chloroform-d. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; l, large; and combinations thereof. All coupling constants (*J* values) are reported in hertz (Hz). Data are reported as follows: chemical shift (δ in ppm), multiplicity, coupling constants (Hz), integration, and attribution. Optical rotations were measured with a Bellingham + Stanley ADP 440 polarimeter or a PerkinElmer polarimeter with a sodium lamp at 589 nm. Low resolution mass spectra were recorded on a Waters QTof-I and LTQ FT (Thermo Scientific, Bremen, Germany), spectrometer using electrospray ionization and electron ionization. High-resolution mass spectra were obtained using the mass spectrometers operated by the "Laboratoire de Mesures Physiques of the University of Montpellier" and Unicamp. THF was dried by distillation over sodium metal and benzophenone under argon. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), 2,6-lutidine, toluene and diethyl ether (Et_2O) were dried by distillation over CaH_2 under argon. Methanol (MeOH) was distilled from $Mg(OMe)_2$.

4.1.1. **(*S*)-4,8-Dimethylnona-1,7-diene (14):**[18a] To a solution of methyltriphenylphosphine bromide (22.1 g, 64.3 mmol) in THF (81.0 mL) was added 1.6 M *n*BuLi (40.2 mL, 64.3 mmol) at 0° C. After 30 min at 0 °C, a solution of (*S*)-citronellal (5.00 g, 32.7 mmol) in THF (50.0 mL) was added. The reaction mixture was stirred for 3.5 h at 0° C and quenched by a saturated aqueous solution of NH_4Cl (50.0 mL). This mixture was extracted with Et_2O (3 x 25.0 mL). The combined organic extract were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography, eluting with 95:5 hexane:Et_2O to give 3.12 g of **14** (72% yield).

Rf = 0.88 (hexane:Et_2O 99:1). $[\alpha]_D^{25}$ = –2.0 (*c* 1.2, $CHCl_3$). **^1H NMR (250 MHz, $CDCl_3$)** δ 5.79 (m, 1H), 5.15 – 5.05 (m, 1H), 5.01 (dd, *J* 5.4, 1.2 Hz, 1H), 4.96 (s, 1H), 2.15 – 1.81 (m, 4H), 1.68 (s, 3H), 1.61 (s, 3H), 1.53 – 1.47 (m, 1H), 1.42 – 1.25 (m, 1H), 1.23 – 1.06 (m, 1H), 0.88 (d, *J* 6.6 Hz, 3H). **$^{13}C\{^1H\}$ NMR (62.5 MHz, CDCl3)** δ 137.7, 131.1, 124.9, 115.5, 41.4, 36.6, 32.4, 25.7, 25.6, 19.3, 17.6. **IR (Film)** 3076, 2966, 2914, 2874, 2854, 1641 cm^{-1}.

4.1.2. **(2*R*,4*S*)-2,4,8-Trimethylnon-7-en-1-ol (15)** *(method scheme 2)*:[18a] To a solution of $AlMe_3$ (1.80 mL, 18.6 mmol) and (–)-bis[(1-neomenthyl)indenyl]zirconium dichloride (250 mg, 0.37 mmol) in CH_2Cl_2 (18.0 mL) was added a solution of the olefin **14** (1.42 g, 9.30 mmol) in CH_2Cl_2 at room temperature. The reaction was stirred for 18 h at this temperature. Then, the mixture was cooled to 0° C and an intense flow of O_2 was bubbled into the solution for 1.5 h. The reaction was maintained under an O_2 atmosphere at room temperature for 5 h and quenched by the addition of a solution of HCl (0.5 M, 15.0 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10.0 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using 80:20 hexane:EtOAc as eluent to provide 1.13 g of **15** in 66% yield and 6:1 d.r.

1.10 g of this material (6.02 mmol) was solubilized in CH_2Cl_2 (20.0 mL). Then, Amano Lipase PS (180 mg, 30.0 mg/mmol) and vinyl acetate (2.80 mL, 30.1 mmol) were added. The reaction was stirred for 3 h. The mixture was filtered on Celite®, the solvent was evaporated and the crude was purified by flash chromatography on silica gel eluting with hexane:EtOAc 80:20 to give 684 mg of **15** in 44% yield from **14** and d.r. 22:1.

Rf = 0.57 (hexane:EtOAc 80:20). $[\alpha]_D^{25}$ = +23.0 (*c* 1.3, $CHCl_3$). **^1H NMR (500 MHz, $CDCl_3$)** δ 5.09 (t, *J* 7.0 Hz, 1H), 3.47 (dd, *J* 10.4, 5.8 Hz, 1H), 3.39 (dd, *J* 10.4, 6.6 Hz, 1H), 2.0 – 1.9 (m, 2H), 1.78 – 1.63 (m, 4H), 1.60 (s, 3H), 1.56 – 1.43 (m, 2H), 1.37 – 1.00 (m, 4H), 0.88 (d, *J* 6.7 Hz, 3H), 0.85 (d, *J* 6.5 Hz, 3H). **$^{13}C\{^1H\}$ NMR (125 MHz, CDCl3)** δ 131.1, 124.9, 69.1, 40.5, 38.0, 33.2, 29.6, 25.7, 25.5, 19.3, 17.7, 16.3. **IR (Film)** 3340 (broad), 2962, 2914, 2874, 2872, 2853, 1454, 1377 cm^{-1}.

4.1.3. **(*S,E*)-5,9-Dimethyldeca-2,8-dien-1-ol (16)**

4.1.3.a. To a suspension of NaH (60% mass/mass) (1.58 g, 39.6 mmol) in THF (112 mL) was added triethyl phosphonoacetate (8.00 mL, 39.6 mmol) dropwise at 0° C. The suspension was

stirred for 30 min at this temperature. A solution of (*S*)-citronellal (4.70 g, 30.5 mmol) in THF (51.0 mL) was added dropwise and the mixture was stirred at this temperature for 1 h. The temperature was allowed to reach room temperature and the reaction was stirred for an additional 18 h. A saturated aqueous solution of NH_4Cl was added (100 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50.0 mL). The organic extract was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 95:5 hexane:EtOAc to give 6.20 g of ethyl ester, 90% yield.

Rf = 0.50 (hexane:EtOAc 95:5). $[\alpha]_D^{25}$ = –2.0 (*c* 1.3; $CHCl_3$). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 6.93 (dt, *J* 15.4, 7.5 Hz, 1H), 5.8 (d, *J* 15.4 Hz, 1H), 5.07 (m, 1H), 4.17 (q, *J* 7.2 Hz, 2H), 2.21 (m, 1H), 2.00 (m, 3H), 1.67 (s, 3H), 1.60 (m, 1H), 1.59 (s, 3H), 1.37 (m, 1H), 1.29 (t, *J* 7.2 Hz, 3H), 1.17 (m, 1H), 0.89 (d, *J* 6.7 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, $CDCl_3$)** δ 166.6, 148.1, 131.4, 124.4, 122.4, 60.0, 39.6, 36.6, 32.0, 25.6, 25.4, 19.4, 17.6, 14.2. **IR (Film)** 2964, 2915, 2874, 2854, 1722 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{14}H_{25}O_2$ $[M+H]^+$ 225.1855, found 225.1964.

4.1.3.b.[41] To a solution of the ethyl ester intermediate (6.12 g, 27.3 mmol) in CH_2Cl_2 (270 mL) was added 1 M DIBAL-H (65.0 mL, 65.0 mmol) dropwise at –78° C (DIBAL-H solution was prepared immediately before use). After stirring at –78 °C for 2 h, MeOH (50.0 mL) and a solution of potassium tartrate (220 mL) were added and the mixture was stirred for 18 h. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 50.0 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using hexane:EtOAc 70:30 as eluent to provide 4.90 g of **16**, 98% yield.

Rf = 0.45 (hexane:EtOAc 80:20). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 5.71 – 5.61 (m, 2H), 5.09 (dd, *J* 7.7, 6.5 Hz, 1H), 4.09 (d, *J* 4.3 Hz, 2H), 2.14 – 1.80 (m, 4H), 1.68 (s, 3H), 1.60 (s, 3H), 1.54 – 1.44 (m, 1H), 1.41 – 1.24 (m, 2H), 1.23 – 1.05 (m, 1H), 0.88 (d, *J* 6.6 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, $CDCl_3$)** δ 131.9, 131.2, 130.1, 124.7, 63.8, 39.6, 36.6, 32.5, 25.7, 25.5, 19.3, 17.6. **IR (Film)** 3377 (broad), 3016, 2964, 2914, 2874, 2856, 1456, 1439, 1377, 1215 cm^{-1}.

4.1.4. **((2*S*,3*S*)-3-((*S*)-2,6-Dimethylep-5-enyl) oxiran-2-yl) methanol (17):** To a suspension of L-(+)-DIPT (3.90 mL, 19.0 mmol), MS 4Å (3.50 g) in CH_2Cl_2 (60.0 mL) was added $Ti(iOPr)_4$ (6.04 mL, 20.0 mmol) at –35° C and the mixture was stirred for 20 min. *t*BuOOH (8.40 mL, 41.8 mmol) was added and the suspension was stirred for another 40 min at –35 °C. A solution of alcohol **16** (3.47 g, 19.0 mmol) in CH_2Cl_2 (35.0 mL) was added dropwise. The suspension was left in the freezer at approximately –20° C for 18 h. Then, the mixture was filtered on Celite® and eluted with CH_2Cl_2. To this solution was added a solution of potassium sodium tartrate (100 mL) and the mixture was stirred for 18 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The organic extract was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with hexane:EtOAc (70:30) to provide 2.79 g of **17**, 74% yield.

Rf = 0.54 (hexane:EtOAc, 60:40). $[\alpha]_D^{25}$ = –19.0 (*c* 1.3, $CHCl_3$). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 5.14 – 4.97 (m, 1H), 3.90 (d, *J* 12.4 Hz, 1H), 3.70 – 3.50 (m, 1H), 3.01 – 2.92 (m, 1H), 2.89 – 2.85 (m, 1H), 2.06 – 1.92 (m, 3H), 1.67 (s, 4H), 1.59 (s, 3H), 1.56 – 1.30 (m, 3H), 1.26 – 1.15 (m, 1H), 0.97 (d, *J* 6.5 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, $CDCl_3$)** δ 131.4, 124.4, 61.6, 58.4, 54.8, 38.8, 36.8, 31.0, 25.7, 25.4, 19.9, 17.6. **IR (Film)** 3418 (broad), 2964, 2918, 2872, 2856, 1454, 1379 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{12}H_{23}O_2$ $[M+H]^+$ 199.1698, found 199.1699.

4.1.5. **(2*R*,3*R*,5*S*)-3,5,9-Trimethyldec-8-ene-1,2-diol (18):** To a solution of the epoxide **17** (3.90 g, 19.7 mmol) in hexane (100 mL) was added dropwise a freshly prepared solution of $AlMe_3$ (5.66 mL, 59.0 mmol) in hexane (30.0 mL) at –40° C. The reaction was stirred for 1 h at –40° C, then a saturated aqueous solution of NH_4Cl (10.0 mL) was added. The cold bath was removed, and a concentrated solution of sodium potassium tartrate was added (50.0 mL). The obtained mixture was stirred for 4 h. The layers were separated, and the organic extract was washed with a saturated aqueous NaCl solution (100 mL). The organic layer was thus extracted with EtOAc (3 x 50.0 mL). The organic extract was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography, eluting with hexane:EtOAc (70:30). After purification, 3.65 g of **18** was obtained, 86% yield.

Rf= 0.46 (hexane:EtOAc 60:40). $[\alpha]_D^{25}$ = +20 (*c* 0.86, $CHCl_3$). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 5.12-5.10 (m, 1H), 3.73 (dd, *J* 10.9, 2.2 Hz, 1H), 3.57 (dd, *J* 10.8, 8.4 Hz, 1H), 3.54 – 3.48 (m, 1H), 2.90 (s, 1H), 2.82 (s, 1H), 2.04-1.96 (m, 2H), 1.73 – 1.66 (m, 4H), 1.62 (s, 3H), 1.55 – 1.47 (m, 1H), 1.34 – 1.13 (m, 4H), 0.95 – 0.84 (m, 6H). **^{13}C{^{1}H} NMR (62.5 MHz, $CDCl_3$)** δ 131.1, 124.8, 76.8, 64.5, 39.6, 38.3, 33.6, 29.6, 25.7, 25.6, 18.9, 17.6, 15.1. **IR (ATR)** 3362 (broad), 2960, 2813, 2874, 1672, 1454, 1377, 1216 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{13}H_{27}O_2$ $[M+H]^+$ 215.2011, found 215.1998.

4.1.6. **(2*R*,4*S*)-2,4,8-Trimethylnon-7-en-1-ol (15)** *(method scheme 3)*: To a solution of the diol **18** (3.50 g, 16.4 mmol) in THF (131 mL) and water (32.8 mL) at room temperature was added $NaIO_4$ (21.0 g, 98.0 mmol) in a single portion. The reaction was stirred for 5 h and quenched by the addition of a saturated aqueous NaCl solution (150 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 60.0 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was used in the next step without further purification.

The material from the previous step was solubilized in methanol (164 mL) and cooled to 0° C. To this solution was added $NaBH_4$ (0.93 g, 24.5 mmol) in small portions over 5 minutes. The reaction was stirred for 15 min when a 0.5 M solution of citric acid (100 mL) and CH_2Cl_2 (50.0 mL) was added. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 50.0 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography using hexane:EtOAc (80:20) as eluent. After purification, 2.64 g of **15** was isolated in 87% yield for the two steps.

Rf = 0.57 (hexane:EtOAc 80:20). $[\alpha]_D^{25}$ = +23.0 (*c* 1.3, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.09 (t, *J* 7.0 Hz, 1H), 3.47 (dd, *J* 10.4, 5.8 Hz, 1H), 3.39 (dd, *J* 10.4, 6.6 Hz, 1H), 2.0 – 1.9 (m, 2H), 1.78 – 1.63 (m, 4H), 1.60 (s, 3H), 1.56 – 1.43 (m, 2H), 1.37 – 1.00 (m, 4H), 0.88 (d, *J* 6.7 Hz, 3H), 0.85 (d, *J* 6.5 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 131.1, 124.9, 69.1, 40.5, 38.0,

33.2, 29.6, 25.7, 25.5, 19.3, 17.7, 16.3. **IR (Film)** 3340 (broad), 2962, 2914, 2874, 2872, 2853, 1454, 1377 cm^{-1}.

4.1.7. **(6*S*,8*R*)-9-Iodo-2,6,8-trimethylnon-2-ene (7):** To a suspension of PPh_3 (2.70 g, 10.3 mmol) and imidazole (0.76 g, 11.2 mmol) in CH_2Cl_2 (10.0 mL) was added I_2 (2.62 g, 10.3 mmol) at 0° C. After 10 min stirring the suspension became dark red, then a solution of alcohol **15** (1.60 g, 8.60 mmol) in CH_2Cl_2 (7.00 mL) was added and the reaction was stirred for 18 h at the room temperature. The reaction was concentrated under reduced pressure and the residue purified by flash chromatography using 99:1 hexane:Et_2O as the eluent. After purification, 2.38 g of **7** was obtained, 94% yield.

$[\alpha]_D^{25}$ = +10.0 (*c* 0.8, $CHCl_3$). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 5.09 (t, *J* 7.0 Hz, 1H), 3.21 (dd, *J* 9.5, 4.9 Hz, 1H), 3.12 (dd, *J* 9.5, 6.2 Hz, 1H), 1.98 (dt, *J* 12.9, 6.3 Hz, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.56-1.42 (m, 2H), 1.36 – 1.10 (m, 4H), 0.95 (d, *J* 6.5 Hz, 3H), 0.87 (d, *J* 6.5 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, CDCl3)** δ 131.2, 124.7, 44.0, 37.5, 32.4, 29.8, 25.7, 25.4, 20.3, 19.5, 18.5, 17.7. **IR (Film)** 2960, 2913, 2869, 2850, 1455, 1377, 817 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{12}H_{24}I$ $[M+H]^+$ 295.0879, found 295.0908.

4.1.8. **(*E*)-Ethyl 3-ethyl-5-(trimethylsilyl)pent-2-en-4-ynoate (19):** A mixture of $Pd(AcO)_2$ (337 mg, 1.50 mmol) and tris-(2,6-dimethoxyphenyl)-phosphine (664 mg, 1.50 mmol) in THF (50.0 mL) was stirred for 30 min. Then, **8** (6.60 mL, 50.0 mmol) was added and the mixture was stirred for another 10 minutes. After this time, **9** (7.00 mL, 50.0 mmol) was added and the reaction was stirred for 18 h. Thus, the solvent was removed and the residue was purified by flash chromatography, eluting with pentane:EtOAc 90:10 to provide 9.36 g of **19**, 85% yield.

Rf = 0.72 (hexane:EtOAc 95:5). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 6.06 (t, *J* 1.0 Hz, 1H), 4.16 (q, *J* 7.1 Hz, 2H), 2.74 (qd, *J* 7.6, 1.0 Hz, 2H), 1.28 (t, *J* 7.1 Hz, 3H), 1.15 (t, *J* 7.6 Hz, 3H), 0.2 (s, 9H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 165.7, 143.9, 124.2, 105.2, 100.1, 60.0, 25.4, 14.2, 12.8, 0.3 (3C). **IR (Film)** 2996, 2932, 2878, 2147, 1718, 1612 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{12}H_{21}O_2Si$ $[M+H]^+$ 225.1311, found 225.1329.

4.1.9. **(*E*)-3-Ethyl-*N*-methoxy-*N*-methylpent-2-en-4-ynamide (20)**

4.1.9.a. To a solution of **19** (3.00 g, 13.4 mmol) in THF (111 mL) and MeOH /H_2O 1:1 (22.2 mL) was added LiOH (6.40 g, 267 mmol). The reaction was stirred at reflux for 18 h. Then the mixture was poured into an Et_2O/H_2O 1:1 mixture (100 mL) and acidified with 1N HCl (pH 1.0). The layers were separated and the aqueous layer was extracted with Et_2O (4 x 25.0 mL). The organic layer was washed with a saturated aqueous NaCl solution (25.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using hexane:EtOAc 60:40 as eluent to afford 1.38 g of the respective carboxylic acid intermediate, 83% yield.

Rf = 0.15 (hexane:EtOAc 80:20). **MP** 80-82 °C. **^{1}H NMR (250 MHz, $CDCl_3$)** δ 6.13 (s, 1H), 3.29 (s, 1H), 2.77 (q, *J* 7.0 Hz, 2H), 1.17 (t, *J* 7.0 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, $CDCl_3$)** δ 171.1, 145.9, 124.4, 83.7, 83.4, 25.8, 12.7. **IR (ATR)** 3295, 2969, 2936, 2878, 2095, 1686, 1606 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_7H_7O_2$ $[M-H]^-$ 123.0452, found 123.0456.

4.1.9.b. To a solution of this carboxylic acid (1.96 g, 15.8 mmol) and MeON(Me)H·HCl (3.08 g, 31.6 mmol) in CH_2Cl_2 (78.9 mL), were added DMAP (386 mg, 16.0 mmol) and DCC (6.52 g, 31.6 mmol). Then, Et_3N (4.40 mL, 31.6 mmol) was added dropwise. The reaction was stirred for 18 h at room temperature. The mixture was washed with H_2O (30.0 mL) and 1M HCl solution (2 x 15.0 mL). The organic layer was dried over $MgSO_4$, filtered and carefully concentrated (the product is volatile). The residue was purified by flash chromatography, eluting with hexane:EtOAc 80:20, to provide 1.60 g of the amide **20**, 60% yield. *Note: A high vacuum pump was not used to remove residual solvents; they were removed by co-evaporation with $CHCl_3$.*

Rf = 0.28 (hexane:EtOAc 80:20). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 6.57 (s, 1H), 3.68 (s, 3H), 3.21 (s, 3H), 3.11 (s, 1H), 2.70 (q, *J* 7.5 Hz, 2H), 1.16 (t, *J* 7.5 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, $CDCl_3$)** δ 166.2, 139.8, 123.9, 84.5, 80.3, 61.6, 32.1, 25.5, 12.8. **IR (ATR)** 3287, 3238, 2971, 2938, 2878, 2838, 2091, 1643, 1607 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_9H_{14}NO_2$ $[M+H]^+$ 168.1024, found 168.1054.

4.1.10. **(*E*)-3-Ethyl-*N*-methoxy-*N*-methylpent-2,4-dienamide (10):** To a solution of acetylene **20** (806 mg, 4.82 mmol) in benzene (24.1 mL), were added quinoline (0.14 mL, 0.96 mmol) and Lindlar's catalyst (718 mg, 0.24 mmol). The reaction was stirred under H_2 atmosphere for 30 min. The reaction mixture was filtered under Celite® and eluted with CH_2Cl_2. The solvent was carefully evaporated (the product is volatile). The residue was purified by flash chromatography using CH_2Cl_2:hexane 60:40 as eluent to provide 600 mg of the diene **10**, 72% yield. *Note: A high vacuum pump was not used to remove residual solvents; they were removed by co-evaporation with $CHCl_3$.*

Rf = 0.28 (hexane:EtOAc 80:20). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 6.29 (dd, *J* 17.5, 10.7 Hz, 1H), 6.15 (s, 1H), 5.4 (d, *J* 17.4 Hz, 1H), 5.27 (d, *J* 10.7 Hz, 1H), 3.62 (s, 3H), 3.17 (s, 3H), 2.71 (q, *J* 7.5 Hz, 2H), 1.7 (t, *J* 7.5 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, CDCl3)** δ 167.5, 155.5, 139.2, 117.8, 117.5, 61.4, 32.2, 20.4, 14.0. **IR (film)** 3093, 2970, 2937, 2877, 2819, 2091, 1651, 1619, 1599 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_9H_{16}NO_2$ $[M+H]^+$ 170.1181, found 170.1162.

4.1.11. **(7*R*,9*S*,*E*)-3-Ethyl-7,9,13-trimethyltetradeca-1,3,12-trien-5-one (22):**[25] To a solution of the iodide **7** (1.09 g, 3.72 mmol) in Et_2O (12.0 mL) at –78 °C was added dropwise a 1.7 M solution of *t*BuLi (4.37 mL, 7.44 mmol). The reaction was stirred at this temperature for 30 min. The temperature was thus allowed to reach room temperature for 2 h. After this time, the mixture was cooled again to –78 °C and a solution of the amide **10** (538 mg, 3.18 mmol) in Et_2O (3.90 mL) was added dropwise. The reaction was stirred for 1 h at this temperature. The cold bath was removed, and the temperature was allowed to reach room temperature. Then, NH_4Cl (15.0 mL) was added, the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10.0 mL). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ (10.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue obtained was purified by flash chromatography, eluting with 95:5 hexane:EtOAc to afford 510 mg of triene **22**, 58% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (dd, *J* 17.5, 10.8 Hz, 1H), 6.09 (s, 1H), 5.70 (d, *J* 17.4 Hz, 1H), 5.46 (d, *J* 10.7 Hz, 1H), 5.11 (t, *J* 7.1 Hz, 1H), 2.81 – 2.72 (m, 2H), 2.43 (dd, *J* 15.1, 5.8 Hz, 1H), 2.30 (dd, *J* 15.2, 7.9 Hz, 1H), 2.16-2.11 (m, 1H), 2.01-1.95 (m, 2H), 1.70 (s, 3H), 1.62 (s, 3H), 1.56 – 1.47 (m, 1H), 1.33 – 1.26 (m, 1H), 1.20 – 1.14 (m, 2H), 1.14 – 1.07 (m, 4H), 0.89 (d, *J* 4.0 Hz, 3H), 0.90 (d, *J* 4.0 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, CDCl3)** δ

201.3, 156.2, 139.2, 131.1, 126.3, 124.9, 120.0, 53.0, 44.5, 37.8, 29.7, 29.2, 27.3, 25.7, 25.5, 20.5, 19.3, 17.7, 13.9.

4.1.12. **(4*S*,6*R*,*E*)-10-Ethyl-4,6-dimethyl-8-oxododeca-9,11-dienal (Fragment C1-C12)**[26]

4.1.12.a. To a solution of polyene **22** (92.0 mg, 0.33 mmol) in *t*BuOH (1.70 mL) and H_2O (1.70 mL) were added $K_3Fe(CN)_6$ (329 mg, 1.00 mmol), K_2CO_3 (138 mg, 1.00 mmol), $MeSO_4NH_2$ (31.7 mg, 0.33 mmol), $(DHQ)_2PHAL$ (13.0 mg, 0.02 mmol) and $K_2OsO_4{\cdot}2H_2O$ (1.20 mg, 3.30 μmol). The reaction was stirred for 20 h at 0 °C. After this time, Na_2SO_3 (460 mg) and H_2O (10.0 mL) were added to the reaction mixture. The layers were separated and the aqueous layer extracted with EtOAc (5 x 10.0 mL). The organic extracts combined were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography using hexane:EtOAc 60:40 as eluent. After purification 41.0 mg of the diol intermediate was obtained.

4.1.12.b. To a solution of this diol (41.0 mg, 0.13 mmol) in H_2O (260 μL) and THF (1.06 mL) was added $NaIO_4$ (151 mg, 0.79 mmol) and the reaction was stirred for 2 h. After this time, the reaction was quenched by the addition of a saturated aqueous NaCl solution (0.50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 0.50 mL). The organic extracts combined were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography using hexane:EtOAc 90:10 as eluent. After purification, 30.0 mg of the fragment C1-C12 was obtained, 36% yield (2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (t, *J* 1.8 Hz, 1H), 6.27 (dd, *J* 17.4, 10.8 Hz, 1H), 6.07 (s, 1H), 5.69 (d, *J* 17.4 Hz, 1H), 5.45 (d, *J* 10.7 Hz, 1H), 2.73 (q, *J* 7.6, 2H), 2.42 (m, 3H), 2.30 (m, 1H), 2.13 (m, 1H), 1.63 (m, 1H), 1.48 (m, 2H), 1.13 (m, 2H), 1.09 (t, *J* 7.6 Hz, 3H), 0.89 (d, *J* 3.5 Hz, 3H), 0.87 (d, *J* 3.7 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 202.8, 201.0, 156.4, 139.2, 126.2, 120.2, 52.9, 44.2, 41.7, 29.8, 29.6, 27.1, 20.5, 19.6, 19.0, 14.0.

4.1.13. **(*E*)-Pent-3-enoyl chloride (30):**[13b] Freshly distilled oxalyl chloride (15.6 mL, 182 mmol) was slowly added to a solution of (*E*)-pent-3-enoic acid (9.24 mL, 91.0 mmol) at 45 °C. The reaction was stirred for 3 h, warmed up to 70 °C and stirred for 30 minutes. Excess of oxalyl chloride was removed under reduced pressure and the crude material was purified by distillation to provide 4.60 g of **30**, 42% yield.

^{1}H NMR (250 MHz, $CDCl_3$) δ 5.70 (m, 1H), 5.52 (m, 1H), 3.54 (dt, *J* 6.6, 1.1 Hz, 2H), 1.73 (dd, *J* 6.0, 1.2 Hz, 3H).

4.1.14. **Dimethyl 2-methyl-3-(*E*)-pent-3-enoylmaleate (31):** MeLi 1.6 M (20.1 mL, 32.2 mmol) was added dropwise to a mixture of CuCN (2.80 g, 32.2 mmol) in THF (117 mL) at −40 °C, after 30 minutes the mixture was cooled down to −78 °C and commercially available diester **29** (3.59 mL, 29.2 mmol) was added for 5 minutes. After 2.5 h, **30** (6.75 g, 43.9 mmol) was added at once and the reaction was stirred for 2 h. The reaction was warmed up to 0 °C and quenched by the addition of H_2O (14.0 mL). The mixture was filtered under Celite® and eluted with Et_2O. The mixture was washed with saturated aqueous solution of NaCl (70.0 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 50.0 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluted with hexane:AcOEt 85:15 to provide 4.10 g of **31**, 58% yield.

Rf = 0.36 (hexane:AcOEt 80:20). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 5.63 – 5.41 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.39 – 3.28 (m, 2H), 2.01 (s, 3H), 1.70 (d, *J* 4.9 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, $CDCl_3$)** δ 199.2, 168.3, 164.1, 142.3, 134.8, 130.6, 121.3, 52.4, 52.4, 46.3, 17.8, 17.0. **IR (film)** 2955, 1704, 1729 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{12}H_{16}O_5Na$ $[M+Na]^+$ 263.0895, found 263.0884.

4.1.15. **Dimethyl 2-((*R*,*E*)-1-hydroxypent-3-enyl)-3-methylmaleate (32):** (+)-DIPCl (11.0 mL, 19.8 mmol) was added to a solution of **31** (3.17 g, 13.2 mmol) in freshly distilled THF (66.0 mL) at −78 °C. The reaction was warmed up to −20 °C and stirred for 3 days at that temperature. Then, the reaction was warmed up to 0 °C. The reaction was quenched by the addition of a solution of H_2O_2 30% (1.70 mL), and MeOH (30.0 mL), and the mixture obtained was stirred for 2 h. Thus, the organic solvent was removed under reduced pressure and the aqueous layer was extracted with Et_2O (3 x 10.0 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluted with hexane:AcOEt 3:1 to provide 2.20 g of **32**, 70% yield.

Rf = 0.33 (hexane:AcOEt 3:2). $[\alpha]_D^{25}$ = −17.0 (*c* 1.1, $CHCl_3$). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 5.63-5.58 (m, 1H), 5.47 – 5.30 (m, 1H), 4.53 (s, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 2.71 (s, 1H), 2.55 – 2.37 (m, 1H), 2.37 – 2.22 (m, 1H), 1.91 (s, 3H), 1.64 (d, *J* 6.1 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, CDCl3)** δ 168.3, 168.0, 141.9, 130.5, 129.5, 125.8, 69.5, 52.3, 52.1, 39.1, 17.9, 14.6. **IR (Film)** 3477 (br), 3026, 3001, 2953, 2919, 2857 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{12}H_{18}O_5Na$ $[M+Na]^+$ 265.1052, found 265.1021. *e.r.* 86:14; ***S*-32** Retention Time 11 minutes and ***R*-32** Retention Time: 9 minutes (Chiralpak IC®, hexane:*i*PrOH 8:2, 1.0 mL/min, 254 nm).

4.1.16. **Dimethyl 2-((*R*,*E*)-1-((*tert*-butyldimethylsilyl)oxy) pent-3-en-1-il)-3-methylmaleate (33):** 2,6-lutidine (1.45 mL, 12.4 mmol) and TBSOTf (1.78 mL, 8.30 mmol) were added slowly to a solution of **32** (1.00 g, 4.15 mmol) in CH_2Cl_2 (41.5 mL) at 0 °C. The reaction was stirred for 1 h, after which the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (15.0 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 30.0 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluted with hexane:AcOEt 90:10 to provide 1.39 g of **33**, 94% yield.

Rf = 0.29 (hexane:AcOEt 90:10). $[\alpha]_D^{25}$ = −7.0 (*c* 1.1, $CHCl_3$). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 5.55-5.44 (m, 1H), 5.43 – 5.28 (m, 1H), 4.51 (dd, *J* 8.1, 5.7 Hz, 1H), 3.71 (d, *J* 3.8 Hz, 6H), 2.58 – 2.42 (m, 1H), 2.41 – 2.24 (m, 1H), 1.90 (s, 3H), 1.62 (d, *J* 6.2 Hz, 3H), 0.84 (s, 9H), 0.01 (d, *J* 6.5 Hz, 6H). **^{13}C{^{1}H} NMR (62.5 MHz, CDCl3)** δ 168.2, 167.9, 145.1, 128.5, 127.3, 126.8, 71.4, 52.2, 51.7, 40.0, 25.6 (3C), 18.1, 17.9, 14.4, −5.0, −5.2. **IR (film)** 3025, 2952, 2930, 2857, 1731 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{18}H_{33}O_5Si$ $[M+H]^+$ 357.2097, found 357.2094.

4.1.17. **Methyl 1-((2-(trimethylsilyl)ethoxy)methyl) 2-((*R*,*E*)-1-((*tert*-butyldimethylsilyl)oxy)pent-3-en-1-il)-3-metylmaleate and Methyl 4-((2-trimethylsilyl)ethoxy)methyl) 2-((*R*,*E*)-1-((*tert*-butyldimethylsilyl)oxy)pent-3-en-1-yl)-3-methylmaleate (34)**

4.1.17.a. LiOH (757 mg, 31.6 mmol) was added to a solution of **33** (751 mg, 2.11 mmol) in THF (15.8 mL) and H_2O (5.30 mL) at 0 °C. The reaction was warmed up to room temperature and stirred for 18 h, at which time HCl 1M (29.0 mL) was added (pH = 3.0). Then, the reaction was heated up to 60 °C

until the appearance of a spot on the TLC (Rf = 0.3, hexane:AcOEt 80:20) with concomitant disappearance of the spot observed on the baseline of the TLC (*i.e.* dicarboxylic acid intermediate). The THF was removed under reduced pressure and aqueous layer was extracted with AcOEt (5 x 20.0 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude compound was then engaged in the next step without further purification.

4.1.17.b. Dried MeOH (0.20 mL, 5.05 mmol) was added into a solution containing the residue of the previous step in CH_2Cl_2 (4.20 mL) dropwise at 0 °C. The, DIPA (0.83 mL, 5.79 mmol) was added dropwise. After 50 minutes, SEMCl (0.56 mL, 3.16 mmol) was added. The reaction was stirred for 1 h at 0 °C. After this time, the reaction was washed with H_2O (3 x 2.00 mL), and the organic layer was dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluted with hexane:AcOEt 80:20 to provide 642 mg of **34**, 67% yield (2 steps).

Rf = 0.43 (hexane:AcOEt 80:20). $[\alpha]_D^{25}$ = –6.0 (*c* 1.14, $CHCl_3$). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 5.62 – 5.22 (m, 4H), 4.62 – 4.47 (m, 1H), 3.83 – 3.63 (m, 5H), 2.60 – 2.45 (m, 1H), 2.43 – 2.25 (m, 1H), 1.93 (s, 3H), 1.64 (d, *J* 5.8 Hz, 3H), 1.01 – 0.91 (m, 2H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 9H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 168.1, 167.3, 144.4, 128.6, 126.9, 90.1, 71.5, 68.1, 52.2, 40.1, 32.0, 29.7, 25.7 (3C), 18.1, 18.0, 14.7, –1.4 (3C), –4.9, –5.1. **IR (film)** 2954, 2927, 1730 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{23}H_{44}NaO_6Si_2$ $[M+Na]^+$ 495.2574, found 495.2581.

4.1.18. **(*R,Z*)-3-((*tert*-Butyldimethylsilyloxy)-4-(methoxycarbonyl)-5-methyl-6-oxo-6-((2-(trimethylsilyl) ethoxy) methoxy)hex-4-enoic acid and (*R,Z*)-3-((*tert*-butyldimethylsilyloxy)-4-(methoxycarbonyl)-5-methyl-6-oxo-6-((2-(trimethylsilyl)ethoxy)methoxy)hex-4-enoic acid (11)**

4.1.18.a. NMO (219 mg, 1.87 mmol) and OsO_4 4% (0.24 mL, 0.04 mmol) were added to a solution of **34** in acetone (11.3 mL) and H_2O (1.13 mL). The reaction was stirred for 2 h and then quenched by the addition of a saturated aqueous solution of $Na_2S_2O_4$ (30.0 mL). The mixture was extracted with AcOEt (3 x 50.0 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was used in the next step without further purification.

4.1.18.b. PIDA (441 mg, 1.37 mmol) was added to a solution of the previously synthesized residue in CH_2Cl_2 (12.4 mL). The reaction was stirred for 2 h, and then filtered through a plug of silica gel and eluted with CH_2Cl_2. The solvent was removed under reduced pressure and engaged in the next step without further purification.

4.1.18.c. NaH_2PO_4 (383 mg, 3.19 mmol), 2-methyl-2-butene (0.51 mL, 4.79 mmol) and $NaClO_2$ (125 mg, 1.38 mmol) were added to a solution of the previously synthesized residue in *t*BuOH (12.1 mL) and H_2O (12.1 mL). The reaction was stirred for 18 h and then quenched by the addition of a saturated aqueous solution of NaCl (15.0 mL). The mixture was extracted with AcOEt (4 x 15.0 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluted with hexane:AcOEt:formic acid 75:24:1 to provide 474 mg of **11**, 80% yield.

Rf = 0.37 (hexane:AcOEt:formic acid 75:24:1). $[\alpha]_D^{25}$ = +2.0 (*c* 1.4, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.47-5.35 (m, 2H), 5.16 (dd, *J* 9.1, 3.9 Hz, 1H), 3.77 (s, 3H), 3.75 (m, 2H), 3.08-3.02 (m, 1H), 2.73-2.67 (m, 1H), 2.07 (d, *J* 2.9 Hz, 3H), 1.05 – 0.98 (m, 2H), 0.88 (m, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.05 (s, 9H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** δ 175.8, 168.1, 167.6, 167.0, 167.0, 142.8, 141.6, 130.8, 130.8, 90.3, 68.3, 67.4, 52.4, 52.1, 41.7, 29.7, 25.6 (3C), 18.1, 18.0, 14.9, 14.6, –1.44 (3C), –4.87, –5.44. **IR (film)** 3446, 2954, 2929, 2907, 2857, 1738, 1715 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{21}H_{40}O_8NaSi_2$ $[M+Na]^+$ 499.2159, found 499.2149.

4.1.19. **(2*S*)-Methyl 3-(4-methoxybenzyloxy)-2-methylpropionate (36):**[42] To a solution of the (*S*)-Roche ester (2.60 g, 22.1 mmol) in CH_2Cl_2 (50.0 mL) was added *p*-methoxybenzyl trichloroacetimidate (9.36 g, 33.2 mmol) and camphorsulfonic acid (0.50 g, 1.14 mmol). The reaction mixture was stirred at room temperature for 18 h. Thus, the mixture was diluted with Et_2O (200 mL) and washed with a saturated aqueous $NaHCO_3$ solution (2 x 45.0 mL) and NaCl (45.0 mL), followed by H_2O (2 x 45.0 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash chromatography, eluting with pentane:EtOAc 90:10 to provide 5.90 g of protected ester **36**, 98% yield.

$[\alpha]_D^{25}$ = +11.0 (*c* 1.1, $CHCl_3$). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 7.23 (d, *J* 8.5 Hz, 2H), 6.87 (d, *J* 8.6 Hz, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 3.69 – 3.57 (m, 1H), 3.46 (dd, *J* 9.1, 5.9 Hz, 1H), 2.85 – 2.69 (m, 1H), 1.17 (d, *J* 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, $CDCl_3$)** δ 175.3, 159.2, 130.2, 129.2 (2C), 113.7 (2C), 72.7, 71.6, 55.2, 51.7, 40.2, 14.0. **IR (film)** 3054, 2953, 2862, 1736 cm^{-1}.

4.1.20. **(2R)-3-(4-Methoxybenzyloxy)-2-methylpropan-1-ol (37):**[42] A solution of 1M DIBAL-H (61.0 mL, 61.0 mmol) was added into a solution of ester **36** (5.80 g, 24.4 mmol) in CH_2Cl_2 (190 mL) at –78 °C. The reaction was stirred for 1 h at this temperature. Then, MeOH (40.0 mL) was added followed by the addition of H_2O (24.0 mL) and an aqueous saturated solution of sodium and potassium tartrate (160 mL). The mixture was stirred until complete homogenization of the organic phase. Thus, the layers were separated, and the aqueous one was extracted with CH_2Cl_2 (2 x 50.0 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under educed pressure. The crude material was purified by flash chromatography, eluted with pentane:AcOEt 80:20 to provide 4.92 g of **37**, 96% yield.

$[\alpha]_D^{25}$ = +14.8 (*c* 1.15, $CHCl_3$). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 7.24 (d, *J* 8.7 Hz, 2H), 6.87 (d, *J* 8.7 Hz, 2H), 4.43 (s, 2H), 3.78 (s, 3H), 3.57 (d, *J* 6.3 Hz, 2H), 3.49-3.35 (m, 2H), 2.72 (sl, 1H), 2.13 – 1.91 (m, 1H), 0.87 (d, *J* 7.0 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, $CDCl_3$)** δ 159.2, 130.2, 129.2 (2C), 113.8 (2C), 74.8, 73.0, 67.4, 55.2, 35.6, 13.5. **IR (film)**. 3455 (br), 3016, 2960, 2864 cm^{-1}.

4.1.21. **(2*R*,3*S*)-4-(4-Methoxybenzyloxy)-3-methylbutan-2-ol (12)**[14]

4.1.21.a. A solution of oxalyl chloride (3.92 mL, 46.3 mmol) in CH_2Cl_2 (100 mL) was slowly added to a solution of DMSO (4.80 mL, 68.8 mmol) in CH_2Cl_2 (10.0 mL) at –78 °C. The mixture was stirred for 10 minutes. Thus, a solution of alcohol **37** (4.80 g, 22.8 mmol) in CH_2Cl_2 (48.0 mL) was slowly added to above mentioned mixture. After 1 h at –78 °C, Et_3N (15.8 mL, 114 mmol) was added dropwise. The reaction was quenched by addition of a saturated aqueous solution of

NH_4Cl (70.0 mL). Then, the mixture was allowed to warm up to room temperature. The layers were separated, and the aqueous one was extracted with Et_2O (3 x 50.0 mL). The combined organic extracts were washed with brine (50.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide the aldehyde intermediate **38** which was used for the next step without further purification.

4.1.21.b. MeLi 1.6 M (54.1 mL, 86.6 mmol) was added to a solution of CuI (8.24 g, 43.4 mmol) in Et_2O (24.0 mL) at −20 °C for 15 minutes. Thus, the solution was cooled to −78 °C, and a solution of the above-mentioned aldehyde **38** in Et_2O (32.0 mL) was added dropwise. The reaction was stirred for 12 h, and quenched by the addition of a saturated aqueous solution of NH_4Cl (30.0 mL) and warmed up to room temperature. The layers were separated, and the aqueous one was extracted with Et_2O (2 x 30.0 mL). The combined organic extracts were washed with brine (20.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluted with pentane:AcOEt 3:1 to provide 3.80 g of alcohol **12** (d.r. 12:1), 75% yield (2 steps).

Rf = 0.13 (hexane:AcOEt 80:20). $[\alpha]_D^{25}$ = +18.0 (c 0.9, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.25 (d, *J* 8.6 Hz, 2H), 6.89 (d, *J* 8.7 Hz, 2H), 4.47 (s, 2H), 3.81 (s, 3H), 3.67 (m, 1H), 3.57 (dd, *J* 9.2, 4.2 Hz, 1H), 3.42 (dd, *J* 9.3, 8.3 Hz, 1H), 2.93 (sl, 1H), 1.78 (m, 1H), 1.17 (d, *J* 6.1 Hz, 3H), 0.85 (d, *J* 7.1 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 159.1, 129.7, 129.2 (2C), 113.7 (2C), 75.1, 72.9, 72.4, 55.1, 39.9, 20.9, 13.5. **IR (film)** 3432 (br), 2966, 2932, 2902, 2876, 2837 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{13}H_{20}O_3Na$ $[M+Na]^+$ 247.1310; found 247.1303.

4.1.22. **(4*R*,5*S*)-2-(4-Methoxyphenyl)-4,5-dimethyl-1,3-dioxane (39):** DDQ (82.0 mg, 0.36 mmol) was added to a solution of alcohol **12** (54.0 mg, 0.24 mmol) in CH_2Cl_2 (2.00 mL) and phosphate buffer pH 7.0 (0.40 mL). The reaction was stirred for 1 h in an open flask, after which the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (2.00 mL). The mixture was filtered through a plug of Celite®, a plug of silica gel and eluted with CH_2Cl_2. The layers were separated, and the organic one was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluted with hexane:AcOEt 90:10 to provide 24.0 mg of **39**, 45% yield.

Rf = 0.39 (hexane:AcOEt 80:20). $[\alpha]_D^{25}$ = −10.0 (*c* 1.0, $CHCl_3$). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 (d, *J* 8.6 Hz, 2H), 6.92 (d, *J* 8.8 Hz, 2H), 5.49 (s, 1H), 4.12 (dd, *J* 11.3, 4.7 Hz, 1H), 3.83 (s, 3H), 3.57 (dd, *J* 9.7, 6.2 Hz, 1H), 3.51 (t, *J* 11.3 Hz, 1H), 1.89 – 1.76 (m, 1H), 1.35 (d, *J* 6.2 Hz, 3H), 0.83 (d, *J* 6.7 Hz, 3H). **^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)** δ 159.9, 131.3, 127.4 (2C), 113.6 (2C), 101.2, 79.5, 73.0, 55.3, 35.9, 19.1, 12.5. **IR (Film)** 2962, 2917, 2849, 1614, 1518, 1250 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{13}H_{19}O_3$ $[M+H]^+$ 223.1334, found 223.1364.

4.1.23. **1-((2*R*,3*S*)-4-((4-methoxybenzyl)oxy)-3-methylbutan-2-yl) 4-methyl 3-((2-(trimethylsilyl)ethoxy)methyl) (*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)pent-3-ene-1,3,4-tricarboxylate and 1-((2*R*,3*S*)-4-((4-methoxybenzyl)oxy)-3-methylbutan-2-yl) 3-methyl 4-((2-(trimethylsilyl)ethoxy)methyl) (*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)pent-3-ene-1,3,4-tricarboxylate (41):** Acid **11** (141 mg, 0.63 mmol) in toluene (9.00 mL), 2,4,6-trichlorobenzoyl chloride (0.11 mL, 0.69 mmol) and DMAP (230 mg, 1.88 mmol) were added to a solution of secondary alcohol **12** (329 mg, 0.69 mmol) in toluene (22.4 mL). Then, Et_3N (0.26 mL, 1.88 mmol) was added dropwise. The reaction was stirred for 4 h at room temperature. Thus, the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (28.0 mL) and extraction was performed with CH_2Cl_2 (3 x 20.0 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluted with hexane:AcOEt 80:20 to provide 390 mg of ester **41**, 91% yield.

Rf = 0.36 (hexane:AcOEt: 4:1). $[\alpha]_D^{25}$ = −2.0 (*c* 1.4, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.26 (d, *J* 8.0 Hz, 2H), 6.89 (d, *J* 8.5 Hz, 2H), 5.49 – 5.30 (m, 2H), 5.17 (ddd, *J* 9.8, 6.4, 3.8 Hz, 1H), 5.00 (quint, *J* 6.2 Hz, 1H), 4.42 (d, *J* 1.5 Hz, 2H), 3.82 (s, 3H), 3.80 – 3.72 (m, 5H), 3.41 (ddd, *J* 8.7, 5.9, 2.4 Hz, 1H), 3.35 – 3.23 (m, 1H), 2.94 (ddd, *J* 16.0, 8.8, 7.3 Hz, 1H), 2.57 (td, *J* 16.3, 3.7 Hz, 1H), 2.05 (s, 4H), 1.22 – 1.15 (m, 3H), 1.02-0.94 (m, 5H), 0.87 (d, *J* 3.8 Hz, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.05 (s, 9H). **^{13}C{^{1}H} NMR (125 MHz, CDCl3)** δ 170.4, 170.3, 168.0, 167.7, 167.0, 166.9, 159.1, 143.6, 142.5, 130.6, 129.2 (2C), 113.7 (2C), 90.1, 72.7, 72.5, 71.7, 68.2, 67.5, 67.4, 55.3, 52.3, 51.9, 42.1, 42.0, 37.9, 25.6 (3C), 18.0, 16.4, 14.8, 14.6, 12.8, −1.40 (3C), −4.9, −5.3. **IR (film)** 2953, 2942, 2898, 2857, 1738, 1732 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{34}H_{58}O_{10}NaSi_2$ $[M+Na]^+$ 705.3466, found 705.3466.

4.1.24. **1-((2*R*,3*S*)-4-hydroxy-3-methylbutan-2-yl) 4-methyl 3-((2-(trimethylsilyl)ethoxy)methyl) (*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)pent-3-ene-1,3,4-tricarboxylate and 1-((2*R*,3*S*)-4-hydroxy-3-methylbutan-2-yl) 3-methyl 4-((2-(trimethylsilyl)ethoxy)methyl) (*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)pent-3-ene-1,3,4-tricarboxylate (42):** DDQ (84.0 mg, 0.37 mmol) was added to a solution of **41** (126 mg, 0.18 mmol) in CH_2Cl_2 (1.60 mL) and phosphate buffer pH 7.0 (0.18 mL) at 0 °C. The reaction was stirred for 4 h, and then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (2.00 mL). The mixture was filtered through a plug of Celite® and eluted with CH_2Cl_2. The crude material obtained was purified by flash chromatography, eluted with hexane:AcOEt 3:1 to provide 88.0 mg of alcohol **42**, 85% yield.

Rf = 0.3 (hexane:AcOEt: 70:30). $[\alpha]_D^{25}$ = +2.0 (*c* 0.7, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 5.44-5.19 (m, 2H), 5.18 (dd, *J* 8.3, 5.0 Hz, 1H), 4.97-4.91 (m, 1H), 3.81 – 3.71 (m, 2H), 3.77 (s, 3H), 3.54 (qd, *J* 11.2, 4.6 Hz, 2H), 2.95 (dd, J = 15.6, 8.4 Hz, 1H), 2.73 (dd, *J* 15.7, 4.9 Hz, 1H), 2.06 (s, 3H), 1.82-1.77 (m, 1H), 1.25 (d, *J* 6.4 Hz, 3H), 1.02 – 0.97 (m, 5H), 0.87 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.05 (s, 9H). **^{13}C{^{1}H} NMR major regioisomer (125 MHz, CDCl3)** δ 170.9, 168.3, 166.9, 141.7, 130.8, 90.2, 72.6, 68.2, 67.3, 64.2, 52.0, 42.0, 40.6, 25.6 (3C), 18.0, 17.9, 17.6, 15.0, 13.2, −1.4 (3C), −5.0, −5.3. **IR (film)** 3486 (br), 3018, 2954, 2925, 2852, 1731, 1644 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{26}H_{50}O_9NaSi_2$ $[M+Na]^+$ 585.2891, found 585.2892.

4.1.25. **(2*R*,3*S*)-4-((4-Methoxylbenzyl)oxy)-3-methylbutan-2-yl benzoate (43):** Bz_2O (1.09 g, 4.81 mmol), DIPEA (1.12 mL, 6.42 mmol) and DMAP (39.2 mg, 0.32 mmol) were added to a solution of **12** (360 mg, 1.61 mmol) in CH_2Cl_2 (10.4 mL). The reaction was stirred for 18 h, after which ethylenediamine (1.80 mL) and H_2O (5.00 mL) were added. The layers were separated, and the aqueous one was extracted with CH_2Cl_2 (2 x 15.0 mL) and Et_2O (15.0 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concen-

trated under reduced pressure. The crude material was purified by flash chromatography, eluted with hexane:AcOEt 80:20 to provide 485 mg of **43**, 92% yield.

Rf = 0.53 (hexane:AcOEt 80:20). $[\alpha]_D$= −32.0 (*c* 1.4, $CHCl_3$). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 8.03 (d, *J* 7.3 Hz, 2H), 7.55 (t, *J* 7.3 Hz, 1H), 7.43 (t, *J* 7.5 Hz, 2H), 7.25 (d, *J* 8.5 Hz, 2H), 6.85 (d, *J* 8.5 Hz, 2H), 5.23 (quint, *J* 6.3 Hz, 1H), 4.44 (s, 2H), 3.78 (s, 3H), 3.52 (dd, *J* 9.2, 5.7 Hz, 1H), 3.40 (dd, *J* 9.2, 6.4 Hz, 1H), 2.20 (dt, *J* 12.9, 6.5 Hz, 1H), 1.33 (d, *J* 6.4 Hz, 3H), 1.06 (d, *J* 6.9 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, CDCl3)** δ 165.7, 158.9, 132.5 (2C), 130.6, 130.3, 129.3 (2C), 129.0, 128.1 (2C), 113.5 (2C), 72.5, 72.5, 71.5, 55.0, 38.1, 16.5, 12.9. **IR (ATR)** 3063, 3033, 2972, 2935, 2855, 1712, 1613 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{20}H_{24}O_4Na$ $[M+Na]^+$ 351.1572, found 351.1564.

4.1.26. **(2*R*,3*S*)-4-Hydroxy-3-methylbutan-2-yl benzoate (44):** DDQ (522 mg, 2.30 mmol) was added to a solution of **43** (464 mg, 1.41 mmol) in CH_2Cl_2 (13.8 mL) and phosphate buffer pH 7.0 (1.53 mL) at 0 °C. The reaction was stirred for 3.5 h, and then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (7.90 mL). The mixture was filtered through a plug of Celite® and eluted with CH_2Cl_2. The crude material was purified by flash chromatography, eluted with hexane:AcOEt 70:30 to provide 250 mg of **44**, 83% yield.

Rf = 0.32 (hexane:AcOEt 70:30). $[\alpha]_D^{25}$ = −22.0 (*c* 0.8, $CHCl_3$). **^{1}H NMR (250 MHz, $CDCl_3$)** δ 8.04 (d, *J* 7.1 Hz, 2H), 7.57 (t, *J* 7.4 Hz, 1H), 7.45 (t, *J* 7.4 Hz, 2H), 5.27 – 5.12 (m, 1H), 3.61 (d, *J* 4.7 Hz, 2H), 2.04-1.90 (m, 1H), 1.62 (sl, 1H), 1.37 (d, *J* 6.4 Hz, 3H), 1.07 (d, *J* 7.0 Hz, 3H). **^{13}C{^{1}H} NMR (62.5 MHz, CDCl3)** δ 166.6, 133.0, 130.4, 129.6 (2C), 128.4 (2C), 72.8, 64.3, 40.8, 17.5, 13.2. **IR (ATR)** 3437 (br), 2978, 2935, 2882, 1715, 1698, 1602, 1585 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{12}H_{16}O_3Na$ $[M+Na]^+$ 231.0997, found 231.0991.

4.1.27. **(2*R*,3*R*)-3-Methyl-4-oxobutan-2-yl benzoate (45):** Oxalyl chloride (68.0 µL, 0.78 mmol) was added dropwise to a solution of DMSO (74.0 µL, 1.04 mmol) in CH_2Cl_2 (4.00 mL) at −78 °C. The mixture was stirred for 15 minutes. Thus, a solution of **44** (108 mg, 0.52 mmol) in CH_2Cl_2 (2.00 mL) was slowly added. The reaction was stirred for 1 h and Et_3N (0.29 mL, 2.07 mmol) was added dropwise. The reaction was allowed to warm up to 0 °C. After reaching this temperature, quench by addition of a saturated aqueous solution of $NaHCO_3$ (10.0 mL) was performed. The mixture was extracted with CH_2Cl_2 (2 x 20.0 mL). The combined organic layers were filtered through silica gel and eluted with hexane:AcOEt 80:20. The crude aldehyde **45** obtained was used in the next step without further purification.

4.1.28. **(But-1-en-2-yloxy)trimethylsilane (13):**[43] *n*BuLi (72.1 mL, 180 mL mmol) was slowly added to a solution of DIPA (29.6 mL, 208 mmol) in THF (154 mL) at 0 °C. After which the mixture was cooled down to – 78 °C and TMSCl (35.5 mL, 277 mmol) was added. Thus, butanone (12.4 mL, 139 mmol) was added to the reaction and the mixture was stirred for 15 minutes. After, Et_3N (38.7 mL, 277 mmol) was added and the reaction was stirred for additional 30 minutes. The reaction was warmed up to room temperature and quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (20.0 mL). The layers were separated, and the aqueous one was extracted with pentane (3 x 60.0 mL). The combined organic layers were washed with a saturated aqueous solution of $CuSO_4$ (2 x 30.0 mL) and concentrated through vigreux column distillation (20.0 cm). The crude material was purified by distillation under reduced pressure to provide 8.30 g of **13**, 41% yield.

^{1}H NMR (250 MHz, $CDCl_3$) δ 4.04 (d, *J* 3.9 Hz, 2H), 2.01 (q, *J* 8.0 Hz, 2H), 1.03 (t, *J* 8.0 Hz, 3H), 0.2 (s, 9H).

4.1.29. **(2*R*,3*S*,4*R*)-4-Hydroxy-3-methyl-6-oxooctan-2-yl benzoate (47):** $BF_3{\cdot}OEt_2$ (72.0 µL, 0.57 mmol) was slowly added to a solution of the crude aldehyde **45** and enol silyl ether derivative **13** (0.14 mL, 0.78 mmol) in CH_2Cl_2 (6.50 mL) at −78 °C. The reaction was stirred for 1 h and then quenched by addition of a saturated aqueous solution of $NaHCO_3$ (8.00 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 8.00 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluted with hexane:AcOEt 70:30 to provide 60.0 mg of **47** (d.r. 4:1), 42% yield.

Rf = 0.37 (hexane:AcOEt 70:30). $[\alpha]_D^{25}$ = −15.0 (*c* 1.0, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$)** major diastereomer δ 8.06 (dd, *J* 7.2, 6.0 Hz, 2H), 7.59 (t, *J* 7.4 Hz, 1H), 7.47 (t, *J* 7.7 Hz, 2H), 5.22 (dq, *J* 13.0, 6.4 Hz, 1H), 4.28 (dt, *J* 9.4, 3.0 Hz, 1H), 3.06 (s, 1H), 2.74 (dd, *J* 16.9, 9.4 Hz, 1H), 2.51-2.47 (m, 3H), 1.84 – 1.76 (m, 1H), 1.40 (d, *J* 6.4 Hz, 3H), 1.07 (t, *J* 7.1 Hz, 3H), 1.03 (d, *J* 7.0 Hz, 3H). **^{13}C{^{1}H) NMR (125 MHz, $CDCl_3$)** major diastereomer δ 211.6, 166.5, 133.0, 130.6, 129.6 (2C), 128.3 (2C), 73.0, 66.5, 46.7, 42.9, 36.8, 17.8, 9.3, 7.5. **IR (film)** 3505, 2979, 2938, 1713, 1602, 1585 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{16}H_{22}O_4Na$ $[M+Na]^+$ 301.1416, found 301.1409.

4.1.30. **(2*S*,4*R*,5*S*,6*R*)-2-Ethyl-2-methoxy-5,6-dimethyltetrahydro-2*H*-pyran-4-ol (48)**: $Ba(OH)_2{\cdot}8H_2O$ (431 mg, 1.36 mmol) was added to a solution of **47** (38.0 mg, 0.14 mmol) in MeOH (19.5 mL) at room temperature. The reaction was stirred for 30 minutes. Thus, the mixture was filtered through silica gel and eluted with pure AcOEt to provide 14.0 mg of **48**, 55% yield.

Rf = 0.45 (hexane:AcOEt 70:30). $[\alpha]_D^{25}$ = −3.0 (*c* 0.3, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 3.68 (dq, *J* 10.1, 6.3 Hz, 1H), 3.37 (s, 3H), 3.28 – 3.20 (m, 1H), 2.23 (dd, *J* 12.5, 4.7 Hz, 1H), 1.82 (s, 1H), 1.66 (qd, *J* 7.5, 2.7 Hz, 2H), 1.27-1.22 (m, 2H), 1.18 (d, *J* 6.3 Hz, 3H), 0.97 (d, *J* 6.5 Hz, 3H), 0.99 (t, *J* 7.6 Hz, 3H). **^{13}C{^{1}H} NMR (125 MHz, CDCl3)** δ 98.4, 79.0, 70.5, 56.5, 43.7, 37.0, 36.1, 19.3, 13.0, 7.5. **IR (film)** 3590, 3412, 3012, 3005, 2971, 2929, 2851 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{10}H_{20}O_3Na$ $[M+Na]^+$ 211.1310, found 211.1305.

4.1.31. **1-((2*R*,3*S*,4*R*)-4-Hydroxy-3-methyl-6-oxooctan-2-yl) 3-methyl 4-((2-(trimethylsilyl)ethoxy)methyl) (*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)pent-3-ene-1,3,4-tricarboxylate and 1-((2*R*,3*S*,4*R*)-4-hydroxy-3-methyl-6-oxooctan-2-yl) 4-methyl 3-((2-(trimethylsilyl)ethoxy)methyl) (*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)pent-3-ene-1,3,4-tricarboxylate (50)**

4.1.31.a. Oxalyl chloride (84.0 µL, 0.97 mmol) was slowly added to a solution of DMSO (80.0 µL, 1.13 mmol) in CH_2Cl_2 (2.00 mL) at −78 °C. The mixture was stirred for 15 minutes and a solution of alcohol **42** (181 mg, 0.32 mmol) in CH_2Cl_2 (1.20 mL) was added dropwise. The reaction was stirred for 1 h and then Et_3N (0.27 mL, 1.93 mmol) was added dropwise. The reaction was allowed to warm up to 0 °C and thus quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (5.00 mL). The mixture was extracted with CH_2Cl_2 (2 x 10.0 mL). The combined organic layers were filtered through silica gel and eluted with hexane:AcOEt 80:20. The

crude aldehyde **49** obtained was used in the next step without further purification.

4.1.31.b. $BF_3{\cdot}OEt_2$ (30.0 µL, 0.25 mmol), was slowly added to a solution of the aldehyde previously synthesized and enol silyl ether derivative **13** (86.0 µL, 0.47 mmol) in CH_2Cl_2 (2.79 mL) at −78 °C. The reaction was stirred for 1 h and then it was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (8.00 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 8.00 mL). The combined organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluted with hexane:AcOEt 75:25 to provide 102 mg of intermediate **50**, 50% yield (2 steps).

Rf = 0.29 (hexane:AcOEt 70:30). $[\alpha]_D^{25}$ = +9.0 (*c* 0.8, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$)** major diastereomer δ 5.39 – 5.32 (m, 2H), 5.17 (dd, *J* 8.7, 4.3 Hz, 1H), 5.01 – 4.89 (m, 1H), 4.20 (dd, *J* 6.7, 2.7 Hz, 1H), 3.81 – 3.70 (m, 5H), 2.98 (dd, *J* 15.8, 8.7 Hz, 2H), 2.72 – 2.64 (m, 2H), 2.49 (q, *J* 7.2 Hz, 3H), 2.05 (s, 3H), 1.68 – 1.58 (m, 1H), 1.28 – 1.23 (m, 3H), 1.07 (t, *J* 7.3 Hz, 3H), 0.97 (dd, *J* 20.8, 12.6 Hz, 4H), 0.86 (d, *J* 6.6 Hz, 9H), 0.10 (s, 3H), 0.06 (s, 3H), 0.04 (s, 9H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** major diastereomer δ 211.7, 170.7, 168.2, 166.9, 141.8, 127.6, 90.2, 72.8, 68.1, 67.3, 66.2, 52.3, 46.8, 42.6, 42.0, 36.8, 25.6 (3C), 18.0, 18.0, 17.9, 14.9, 9.1, 7.5, −1.4 (3C), −4.9, −5.4. **IR (film)** 3528, 2954, 2930, 2858, 1732, 1644 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{30}H_{56}O_{10}NaSi_2$ $[M+Na]^+$ 655.3310, found 655.3310.

4.1.32. **4-Methyl 1-((2*R*,3*R*,4*R*)-3-methyl-6-oxo-4-((trimethylsilyl)oxy)octan-2-yl) 3-((2-(trimethylsilyl) ethoxy)methyl) (*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy) pent-3-ene-1,3,4-tricarboxylate and 3-methyl 1-((2*R*,3*R*,4*R*)-3-methyl-6-oxo-4-((trimethylsilyl)oxy)octan-2-yl) 4-((2-(trimethylsilyl)ethoxy)methyl) (*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)pent-3-ene-1,3,4-tricarboxylate (Fragment C13-C25):** TMS-imidazole (60.0 µL, 0.41 mmol) was added to a solution of **50** (26.0 mg, 0.04 mmol) in CH_2Cl_2 (0.40 mL) at room temperature. The reaction was stirred for 2 h and then filtered through silica gel and eluted with hexane:AcOEt 90:10 to provide 29.0 mg of the C13-C25 fragment, 100% yield.

Rf = 0.26 (hexane:AcOEt 90:10). $[\alpha]_D^{25}$ = +6.0 (*c* 0.5, $CHCl_3$). **^{1}H NMR (500 MHz, $CDCl_3$)** major diastereomer δ 5.40 – 5.33 (m, 2H), 5.19 (dd, *J* 9.2, 3.1 Hz, 1H), 4.82 – 4.75 (m, 1H), 4.39 – 4.33 (m, 1H), 3.81 – 3.72 (m, 5H), 3.02 (dd, *J* 16.3, 9.2 Hz, 1H), 2.70 (dd, *J* 16.1, 7.6 Hz, 1H), 2.58 (dd, *J* 16.2, 3.2 Hz, 1H), 2.51 – 2.41 (m, 3H), 2.05 (s, 3H), 1.22 (d, *J* 6.3 Hz, 3H), 1.08 (t, *J* 7.3 Hz, 3H), 1.02 – 0.97 (m, 2H), 0.91 – 0.85 (m, 12H), 0.14 – 0.03 (m, 25H). **^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)** major diastereomer δ 209.6, 170.5, 167.6, 167.0, 143.6, 128.9, 90.1, 72.6, 68.1, 68.0, 67.4, 51.9, 48.4, 43.3, 42.1, 37.3, 25.6 (3C), 18.0, 17.9, 17.5, 14.6, 9.5, 7.5, 0.2 (3C), −1,4 (3C), −5.0, −5.3. **IR (film)** 2954, 2930, 2858, 1731, 1644 cm^{-1}. **HRMS (ESI+)** *m/z* calculated for $C_{33}H_{64}O_{10}NaSi_3$ $[M+Na]^+$ 727.3705, found 727.3700.

AUTHOR INFORMATION

Corresponding Author

*E-mail: renata.marcia_de_figueiredo@enscm.fr
*E-mail: ldias@unicamp.br
*E-mail: jean-marc.campagne@enscm.fr

ORCID

Celso de Oliveira Rezende Júnior: 0000-0003-1402-2035
Jean-Marc Campagne: 0000-0002-4943-047X
Luiz Carlos Dias: 0000-0003-0628-9928
Renata Marcia de Figueiredo: 0000-0001-5336-6071

Present Addresses

‡ (D.P.S.) Eurofarma - 3.565, Presidente Castelo Branco Highway - Itaqui, Itapevi - São Paulo, 06696-000, Brazil. (C.O.R.J.) Institute of Chemistry, Federal University of Uberlândia, 38400-902, Uberlândia, Minas Gerais, Brazil.

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors are grateful to ENSCM, CNRS and UNICAMP-Campinas/SP. We also thank the CAPES-FAPESP (PhD grant of D.P.S., project FAPESP 2012/11220-9) and CNPq-FAPESP for post-doctoral fellowship of C.O.R.J. (projects: FAPESP 14/50249-8 and 15/08541-6, CNPq 303154/2015-2, 573.564/2008-6 and 158926/2014-5).

REFERENCES

(1) Kobayashi, Y.; Ko, K.; Yamaguchi, I.; Shen, Y.-C.; Isono, K. A New Antibiotic, Tautomycetin. *J. Antibiot*. **1989**, *42*, 141-144.

(2) Cheng, X.-C.; Ubukata, M.; Isono, K. The Structure of Tautomycetin, a Dialkylmaleic Anhydride Antibiotic. *J. Antibiot*. **1990**, *43*, 890-896.

(3) Choi, S.-S.; Nah, H.-J.; Pyeon, H.-r.; Kim, E.-S. Biosynthesis, Regulation, and Engineering of a Linear Polyketide Tautomycetin: A Novel Immunosuppressant in *Streptomyces sp*. CK4412. *J. Ind. Microbiol. Biotechnol*. **2017**, *44*, 555-561.

(4) Osada, H.; Magae, J.; Watanabe, C.; Isono, K. Rapid Screening Method for Inhibitors of Protein. *J. Antibiot*. **1988**, *41*, 925-931.

(5) Honkanen, R. E.; Golden, T. Regulators of Serine/Threonine Protein Phosphatases at the Dawn of a Clinical Era? *Curr. Med. Chem*. **2002**, *9*, 2055-2075.

(6) (a) Choy, M. S.; Swingle, M.; D'Arcy, B.; Abney, K.; Rusin, S. F.; Kettenbach, A. N.; Page, R.; Honkanen, R. E.; Peti, W. PP1: Tautomycetin Complex Reveals a Path toward the Developmentof PP1-Specific Inhibitors. *J. Am. Chem. Soc*. **2017**, *139*, 17703-17706. (b) Mitsuhashi, S.; Matsuura, N.; Ubukata, M.; Oikawa, H.; Shima, H.; Kikuchi, K. Tautomycetin is a Novel and Specific Inhibitor of Serine/Threonine Protein Phosphatase Type 1, PP1. *Biochem. Biophys. Res. Commun*. **2001**, *287*, 328-331.

(7) Lee, J.-H.; Lee, J.-S.; Kim, S.-E.; Moon, B.-S.; Kim, Y.-C.; Lee, S.-K.; Lee, S.-K.; Choi, K.-Y. Tautomycetin Inhibits Growth of Colorectal Cancer Cells through p21cip/WAF1 Induction *via* the Extracellular Signal-Regulated Kinase Pathway. *Mol. Cancer Ther*. **2006**, *5*, 3222-3231.

(8) Niu, M.; Sun, Y.; Liu, X.; Tang, L.; Qiu, R. Tautomycetin Induces Apoptosis by Inactivating Akt Through a PP1-Independent Signaling Pathway in Human Breast Cancer Cells. *J. Pharmacol. Sci*. **2013**, *121*, 17-24.

(9) Shim, J. H., Lee, H. K., Chang, E. J., Chae, W. J., Han, J. H., Han, D. J., Morio, T., Yang, J. J., Bothwell, A., Lee, S. K. Immunosuppressive Effects of Tautomycetin *in vivo* and *in vitro via* T

Cell-Specific Apoptosis Induction. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 10617-10622.
(10) Han, D.J.; Jeong, Y.L.; Wee, Y.M.; Lee, A.Y.; Lee, H.K.; Ha, J.C.; Lee, S.K.; Kim, S.C. Tautomycetin as a Novel Immunosuppressant in Transplantation. *Transplant. Proc*. **2003**, *35*, 547-547.
(11) Liu, S.; Yu, Z.; Yu, X.; Huang, S.-X.; Luo, Y.; Wu, L.; Shen, W.; Yang, Z.; Wang, L.; Gunawan, A. M.; Chan, R. J.; Shen, B.; Zhang, Z.-Y. SHP2 is a Target of the Immunosuppressant Tautomycetin. *Chem. Biol*. **2011**, 18, 101-110.
(12) Dai, J.-P.; Sodeoka, M.; Shibasaki, M. Determination of the C-7,9,12,13,17 and 18 Stereochemistries of Tautomycetin. Synthesis of the Tautomycetin Degradation Product. *Tetrahedron Lett*. **1996**, *37*, 491-494.
(13) A similar behavior can be also observed in the case of tautomycin (5, Figure 1), a natural product that share the same dialkylmaleic anhydride moiety. (a) Oikawa, M.; Ueno, T.; Oikawa, H.; Ichihara, A. Total Synthesis of Tautomycin. *J. Org. Chem*. **1995**, *60*, 5048-5068. (b) Sheppeck II, J. E.; Liu, W.; Chamberlin A. R. Total Synthesis of the Serine/Threonine-Specific Protein Phosphatase Inhibitor Tautomycin. *J. Org. Chem*. **1997**, *62*, 387-398.
(14) Oikawa, H.; Yoneta, Y.; Ueno, T.; Oikawa, M.; Wakayama, T.; Ichihara, A. Synthetic Study of Tautomycetin: Synthesis of Two Large Subunits. *Tetrahedron Lett*. **1997**, *38*, 7897-7900.
(15) Oikawa, H. Synthesis of Specific Protein Phosphatase Inhibitors, Tautomycin and Tautomycetin toward Structure-Activity Relationship Study. *Curr. Med. Chem*. **2002**, *9*, 2033-2054.
(16) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühter, G. Palladium-Catalyzed Additions of Terminal Alkynes to Acceptor Alkynes. *J. Am. Chem. Soc*. **1997**, *119*, 698-708.
(17) Suppo, J.-S.; de Sant'Ana, D. P.; Dias, L.-C.; de Figueiredo, R. M.; Campagne, J.-M. Efficient and Practical Procedure for the Esterification of the Free α-Carboxylic Acid of Amino Acid Residues with β-(Trimethylsilyl)ethoxymethyl Chloride and Triisopropylsilyl Chloride. *Synthesis* **2014**, *46*, 3075-3084.
(18) (a) Zhu, G.; Liang, B.; Negishi, E.-i. Efficient and Selective Synthesis of (*S,R,R,S,R,S*)-4,6,8,10,16,18-Hexamethyldocosane *via* Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA Reaction). *Org. Lett*. **2008**, *10*, 1099-1101. (b) Kondakov, D. Y.; Negishi, E.-i. Zirconium-Catalyzed Enantioselective Methylalumination of Monosubstituted Alkenes. *J. Am. Chem. Soc*. **1995**, *117*, 10771-10772. (c) Negishi, E.-i. Discovery of ZACA Reaction: Zr-Catalyzed Asymmetric Carboalumination of Alkenes. *ARKIVOC* **2011**, (viii), 34-53.
(19) Katsuki, T.; Sharpless, K. B. The First Practical Method for Asymmetric Epoxidation. *J. Am. Chem. Soc*. **1980**, *102*, 5974-5976.
(20) Roush, W. R.; Adam, M. A.; Peseckis, S. M. Regioselectivity of the Reactions of Trialkylaluminum Reagents with 2,3-Epoxyalcohols: Application to the Synthesis of α-Chiral Aldehydes. *Tetrahedron Lett*. **1983**, *24*, 1377-1380.
(21) The ^{13}C and ^{1}H NMR spectra are in agreement with the ones described by Negishi and co-workers, see ref. 18a.
(22) It should be noted that even though this route is slightly longer (two additional steps compared to the one devised by Negishi, see scheme 2), the reactions in this case are straightforward and scalable allowing us to make grams of this key intermediate.
(23) (a) Garegg, P.J. Some Apects of Regio-, Stereo- and Chemoselective Reactions in Carbohydrate Chemistry. *Pure and Appl. Chem*. **1984**, *56*, 845-858. (b) Garegg, P.J.; Samuelsson, B. Novel Reagent System for Converting a Hydroxy-Group into an Iodo-Group in Carbohydrates with Inversion of Configuration. Part 2. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866-2869.
(24) (a) Balasubramaniam, S.; Aidhen, I. S. The Growing Synthetic Utility of the Weinreb Amide. *Synthesis* **2008**, *23*, 3707-3738. (b) Nowak, M. Weinreb Amides. *Synthesis* **2015**, *26*, 561-562. (c) Kalepu, J.; Pilarski L. T. Weinreb Amides as Directing Groups for Transition Metal-Catalyzed C-H Functionalizations. *Molecules* **2019**, DOI:10.3390/molecules24050830.
(25) Triene **19** showed to be unstable and was used as soon as possible for the oxidative cleavage step.
(26) It might be mentioned, that segment C1-C12 supporting the aldehyde function could be synthesized in gram scale and also purified by flash chromatography. However, this key intermediate is not stable and might be used as soon as possible as extensive decomposition was observed under storage.
(27) (a) Ichikawa, Y.; Naganawan A.; Isobe, M. Synthesis of the 2,3-Disubstituted Maleic Anhydride Segment of Tautomycin. *Synlett* **1993**, 1993(10), 737-738. (b) Ichikawa, Y.; Tsuboi, K.; Naganawan A.; Isobe, M. Synthesis of the (+)-2,3-Disubstituted Maleic Anhydride Segment and (+)-Enone Segment with C-25 through C-19 of Tautomycin. *Synlett* **1993**, 1993(12), 907-908.
(28) (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K. Stereocontrolled *Cis* Addition of Organocopper Reagents RCu*BR'3 to α,β-Acetylenic Carbonyl Compounds. *J. Org. Chem*. **1979**, *44*, 1744-1746. (b) Marino, J. P.; Linderman, R. J. Chemistry of Substituted [α-(Carboethoxy)vinyl]cuprates and Their Synthetic Application to Cyclopentenone Annulations. *J. Org. Chem*. **1981**, *46*, 3696-3702. (c) Marino, J. P.; Linderman, R. J. Chemistry of Substituted (α-Carbethoxyvinyl)cuprates. 2. Stereospecific Olefin Synthesis. *J. Org. Chem*. **1983**, *48*, 4621-4628.
(29) Corey, E. J.; Bakshi, R. K.; Shibata, S. Highly Enantioselective Borane Reduction of Ketones Catalyzed by Chiral Oxazaborolidines. Mechanism and Synthetic Implications. *J. Am. Chem. Soc*. **1987**, *109*, 5551-5553.
(30) The same trend on this enantioselective reduction step, with either CBS or (+)-DIP-Chloride methods, has been previously observed by the group of Chamberlin, see ref 13b and Brown, H. C.; Ramachandran, V. Versatile α-Pinene-Based Borane Reagents for Asymmetric Syntheses. *J. Organomet. Chem*. **1995**, 500, 1-19.
(31) (a) Dale, J. A.; Mosher, H. S. Nuclear Magnetic Resonance Enantiomer Reagents. Configurational Correlations *via* Nuclear Magnetic Resonance Chemical Shifts of Diastereomeric Mandelate, O-Methylmandelate, and α-methoxy-α-trifluoromethylphenylacetate (MTPA) Esters. *J. Am. Chem. Soc*. **1973**, *95*, 512-519. (b) Seco, J. M.; Quiñoá, E.; Riguera, R. The Assignment of Absolute Configuration by NMR. *Chem. Rev*. **2004**, *104*, 17-118. (c) Hoye, T. R.; Jeffrey, C. S.; Shao, F. Mosher Ester Analysis for the Determination of Absolute Configuration of Stereogenic (Chiral) Carbinol Carbons. *Nature Protocols* **2007**, *2*, 2451-2458.
(32) Bal, B. S.; Childers, W. E.; Pinnick, H. W. Oxidation of α,β-unsaturated aldehydes. *Tetrahedron* **1981**, *37*, 2091-2096.
(33) Omura, K.; Swern, D. Oxidation of Alcohols by "Activated" Dimethyl Sulfoxide. A Preparative, Steric and Mechanistic Study. *Tetrahedron* **1978**, *34*, 1651-1660.
(34) (a) Gilman, H.; Jones, R. G.; Woods, L. A. The Preparation of Methylcopper and some Observations on the Decomposition of Organocopper Compounds. *J. Org. Chem*. **1952**, *17*, 1630-1634. (b) Normant, J. F. Organocopper(I) Compounds and Organocuprates in Synthesis. *Synthesis* **1972**, 1972(2), 63-80.
(35) Tsuda, M.; Hatakeyama, A.; Kobayashi, J. Synthesis of a Diastereoisomer of the C-15 ~ C-26 Segment of Amphidinolide L. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866-2869.
(36) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. A Rapid Esterification by Means of Mixed Anhydride and Its Application to Large-ring Lactonization. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989-1993. (b) Kawanami, Y.; Dainobu, Y.; Inanaga, J.; Katsuki, T.; Yamaguchi, M. Synthesis of Thiol Esters by Carboxylic Trichlorobenzoic Anhydrides. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 943-944. For a review, see: Yu, X.; Sun, D. Macrocyclic Drugs

and Synthetic Methodologies toward Macrocycles. *Molecules* **2013**, 6230-6268.
(37) (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. A Stereochemical Model for Merged 1,2- and 1,3-Asymmetric Induction in Diastereoselective Mukaiyama Aldol Addition Reactions and Related Processes. *J. Am. Chem. Soc*. **1996**, *118*, 4322-4343. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. Diastereoselective Aldol and Allylstannane Addition Reactions. The Merged Stereochemical Impact of α and β Aldehyde Substituents. *J. Am. Chem. Soc*. **1995**, *117*, 6619-6620. (c) Savall, B. M.; Blanchard, N.; Roush, W. R. Total Synthesis of the Formamicin Aglycon, Formamicinone. *Org. Lett*. **2003**, 5, 377-379.
(38) (a) Evans, D. A.; Vogel, E.; Nelson, J. V. Stereoselective Aldol Condensations *via* Boron Enolates. *J. Am. Chem. Soc*. **1979**, *101*, 6120-6123. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. Stereoselective Aldol Condensations *via* Boron Enolates. *J. Am. Chem. Soc*. **1981**, *103*, 3099-3111. (c) Brown, H. C.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. Major Effect of the Leaving Group in Dialkylboron Chlorides and Triflates in Controlling the Stereospecific Conversion of Ketones into either (*E*)- or (*Z*)-Enol Borinates. *J. Am. Chem. Soc*. **1989**, *111*, 3441-3442. (d) Brown, H. C.; Ganesan, K.; Dhar, R. K. Enolboration. 4. An Examination of the Effect of the Leaving Group (X) on the Stereoselective Enolboration of Ketones with Various R2BX/Triethylamine. New Reagents for the Selective Generation of either *Z* or *E* Enol Borinates from Representative Ketones. *J. Org. Chem*. **1993**, *58*, 147-153. (e) Cowden, C. J.; Paterson, I. Asymmetric Aldol Reactions Using Boron Enolates. In *Organic Reactions*; John Wiley & Sons, Inc., **1997**, Vol. *51*; p. 4.
(39) Dias, L. C.; Polo, E. C.; de Lucca Jr, E. C.; Ferreira, M. A. B. Asymmetric Induction in Aldol Additions. In *Modern Methods inStereoselective Aldol Reactions*; Mahrwald, R., Ed.; 1st ed.; Wiley-VCH: Weinheim, **2013**, p. 293.
(40) The mass spectrum and HPLC profile are furnished on the Supporting Information. HPLC profile was compared to the one published in 2012 by Shen and co-workers, see: Yang, D.; Li, W.; Huang, S.-X.; Shen, B. Functional Characterization of ttnI Completing the Tailoring Steps for Tautomycetin Biosynthesis in Streptomyces griseochromogenes. *Org. Lett*. **2012**, *14*, 1302-1305.
(41) Landa, A.; Puente, Á.; Santos, J. I.; Vera, S.; Oiarbide, M.; Palomo, C. Catalytic Conjugate Additions of Geminal Bis(sulfone)s: Expanding the Chemistry of Sulfones as Simple Alkyl Anion Equivalents. *Chem. Eur. J*. **2009**, *15*, 11954-11962.
(42) Dias, L. C.; Polo, E. C. Nhatrangin A: Total Syntheses of the Proposed Structure and Six of Its Diastereoisomers. *J. Org. Chem*. **2017**, *82*, 4072-4112.
(43) Muratake, H.; Watanabe, M.; Goto, K.; Natsume, M. Synthesis of (±)- and (−)-*cis*-Trikentrin A, (±)- and (−)-*trans*-Trinkentrin A, (±)-*cis*-Trikentrin B, (±)-*trans*-Trikentrin B, and (±)-*iso*-*trans*-Trikentrin B. *Tetrahedron* **1990**, *46*, 4179-4192.