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Synthetic Studies toward the Total Synthesis of Tautomycetin

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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 Strepotmyces 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), forstrieicin (4) and cantharidin (5), (Figure 1)],5 TTN proved to be very specific toward PP1.6 More recently, the potential of TTN against colorectal7 and breast8 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.13

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

2. RESULTS AND DISCUSSION

Synthesis of Fragment C1-C12

On the basis of Negishi's work, 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 1. Retrosynthesis of TTN. R1, R2, R3, R4 = protecting groups.

Scheme 2. Synthesis of the anti-1,3-dimethyl system via the ZACA reaction.
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 \((+)-\text{DIPT, Ti(OiPr)}_4, \text{BuOOH, 4Å MS, } -35 \text{ to } -20 \degree\text{C}\) 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 \((+)-\text{DEPT}\) 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 regiosomer. 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 (NaO4) and reduction (NaBH4) 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-workers24 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/MethOH/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 tBuLi 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 \((S)-(\cdot)-(\cdot)-\text{citronellal in 7.4% overall yield.}\)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), and two years later, Oikawa, Ichiara and co-workers described the synthesis of compound 28 (13% overall yield, 13 steps from 27) (Scheme 6c). 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)].

Aware of the difficulties encountered on precedent works toward the anhydride moiety synthesis, 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. 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. Accordingly, an anhydride...
intermediate was formed through the saponification of 33 (LiOH, THF/H2O, rt), then sequential bis-esterification (DCA, MeOH at 0 °C then SEMCI) 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 [OsO4, NMO, acetone/H2O then Phl(OAc)2 in CH2Cl2] followed by oxidation under Pinck’s conditions (80% over 3 steps).12

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 oxidation31 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 reagent29 (Me2CuLi) in Et2O at low temperature afforded the secondary alcohol 12 in good yield (75%) and a diastereomeric ratio (1:2). The stereochemistry of the newly formed hydroxy group was established on the basis of NOE interactions between vicinal protons of the corresponding p-methoxybenzylidene acetal derivative 39.30 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.](image)

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. Removal of the PMB group from 41 using DDQ furnished the primary alcohol 42 in 85% yield.

![Scheme 9. Synthesis of primary alcohol 42.](image)

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-benzylation (92%), PMB removal (83%) followed by Swern oxidation (Scheme 10). Exposure of 45 to 2-(trimethylsilyl)oxy)-1-butene (easily prepared from butanone 46 in 41% yield) in the presence of BF3·Et2O in Et2O 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 (TBSCl and 2,6-lutidine) the protection failed. By tuning the amounts of reagents (excess of TBSCl) 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.3 Moving to milder conditions (TBSCI 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 CH₂Cl₂ 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 synthesized, 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 followed by a final removal of all protecting groups. Knowing that 1,2-anti adducts are mostly likely to be obtained via E-boron enolates, 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 CH₃CN. 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), 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 sy-
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. 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. 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, KMnO4, 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 13C chemical shifts are reported in ppm relative to the singlet at 7.26 ppm for chloroform (δ). 2D- and 3D-NMR spectra were recorded with a Bruker 250, 400, 500 and Ultra Shield 400 Plus. 1H 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 (CH2Cl2), triethylamine (Et3N), 2,6-lutidine, toluene and diethyl ether (Et2O) were dried by distillation over CaH2 under argon. Methanol (MeOH) was distilled from Mg(OEt)2.

4.1.1. (S)-4,8-Dimethylnona-1,7-diene (14): To a solution of methyltriphenylphosphorane (22.1 g, 64.3 mmol) in THF (81.0 mL) was added 1.6 M nBuLi (40.2 mL, 64.3 mmol) at 0° C. After 30 min at 0° C, a solution of (S)-citronellol (5.0 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 NH4Cl (50.0 mL). This mixture was extracted with Et2O (3 x 25.0 mL). The combined organic extract were dried over MgSO4 filtered and concentrated under reduced pressure. The crude was purified by flash chromatography, eluting with 95:5 hexane:EtOAc to give 3.12 g of 14 (72% yield).

RF = 0.88 (hexane:EtOAc 99:1). [α]25°D = -2.0 (c 1.2, CHCl3) 1H NMR (250 MHz, CDCl3) δ 5.79 (m, 1H), 5.15 – 5.05 (m, 1H), 5.00 (dd, J 5.4, 1.2 Hz, 1H), 4.96 (s, 1H), 2.31 – 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). 9C[H] NMR (62.5 MHz, CDC13) δ 177.7, 171.1, 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. (2R,4S)-2,4,8-Trimethylnon-7-en-1-ol (15) (method scheme 2): To a solution of AlMe3 (1.80 mL, 18.6 mmol) and (-)-bis(1-neomenthol)lindenylidenezirconium dichloride (250 mg, 0.37 mmol) in CH2Cl2 (18.0 mL) was added a solution of the olefin 14 (1.42 g, 9.30 mmol) in CH2Cl2 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 O2 was bubbled into the solution for 1.5 h. The reaction was maintained under an O2 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 CH2Cl2 (2 x 10.0 mL). The organic extract was dried over MgSO4, 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 61:1 d.r.

1.10 g of this material (6.02 mmol) was solubilized in CH2Cl2 (20.0 mL). Then, Amano Lipase PS (180 mg, 30 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). [α]25°D = +23.0 (c 1.3, CHCl3). 1H NMR (500 MHz, CDCl3) δ 5.09 (t, J 7.0 Hz, 1H), 3.47 (dd, J 10.4, 5.8 Hz, 1H), 3.49 (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). 9C[H] NMR (125 MHz, CDC13) δ 141.1, 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, 1545, 1377 cm⁻¹.

4.1.3. (S,E)-5,9-Dimethyldec-2,8-dien-1-ol (16) To a suspension of NaNH (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 satu-
rated aqueous solution of NH₄Cl was added (100 mL), the layers
were separated, and the aqueous layer was extracted with
CH₂Cl₂ (2 x 50.0 mL). The organic extract was dried with
Na₂SO₄, 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). [α]D²⁵ = 2.0 (c 1.3; CHCl₃).

**¹H NMR (250 MHz, CDCl₃)** 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).

**¹³C[¹H] NMR (62.5 MHz, CDCl₃)** δ 166.8, 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 C₂₅H₄₅O₂ [M+H]⁺: 375.3232, found 375.3228.

For a solution of the ethyl ester intermediate (6.12 g,
27.3 mmol) in CH₂Cl₂ (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 Na₂SO₄, 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 8:20). [α]D²⁵ = 2.0 (c 1.86, CHCl₃).

**¹H NMR (600 MHz, CDCl₃)** 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). **¹³C[¹H] NMR (62.5 MHz, CDCl₃)** δ 131.1, 124.8,
76.8, 64.5, 38.3, 32.6, 29.7, 25.6, 18.9, 17.6, 15.1. IR
(ATR) 3362 (broad), 2960, 2813, 2874, 1762, 1454, 1377, 1216
cm⁻¹. HRMS (ESI+) m/z calculated for C₂₃H₂₃O₂ [M+H]⁺:
321.1501, found 321.1502.

For a solution of the diol 18 (3.50 g, 16.4 mmol) in THF
(31 mL) and water (32.8 mL) at room temperature was
added NaIO₄ (21.0 g, 98.0 mmol) in one 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 CH₂Cl₂
(3 x 60.0 mL). The organic layer was dried with Na₂SO₄,
filtered and concentrated under reduced pressure. The
residue was purified by flash chromatography using hexane:
EtOAc (70:30) 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). [α]D²⁵ = 23.0 (c 1.3, CHCl₃).

**¹H NMR (500 MHz, CDCl₃)** 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).

**¹³C[¹H] NMR (125 MHz, CDCl₃)** δ 131.1, 124.9, 69.1, 40.5, 38.0,
indlar’s catalyst (718 mg, 0.24 mmol) and MeON(Me)H (6.52 g, 31.6 mmol). Then, Et4N(I) and imidazole (0.76 g, 11.75 mmol) were added dropwise. The reaction was stirred for 18 h at room temperature. The residue was mixed and filtered with flash chromatography using 99:1 hexane:EtOAc as the eluent. After purification, 2.38 g of the product was obtained, 94% yield.

[1] 25 \(1^1{H} NMR (250 MHz, CDCl_3) \quad \delta \quad \text{[M+H]+}\). The residue was purified by flash chromatography using 99:1 hexane:EtOAc to provide 2.00 g of the product, 80% yield.

8. (E)-3-Ethyl-5-(trimethylsilyl)pent-2-en-4-ynoate (19): A mixture of Pd(AcO) (337 mg, 1.50 mmol) and triis(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:hexane (1:10) to provide 9.36 g of 19, 85% yield.

9. (E)-3-Ethyl-5-\(\text{N-methoxy-N-methylpent-2-en-4-ynoate}\) (20): To a solution of 19 (3.00 g, 13.4 mmol) in MeOH/H2O (11:22.2 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 EtOH/H2O mixture (100 mL) and acidified with HCl (pH 1.0). The layers were separated and the aqueous layer was extracted with EtO (4 x 25.0 mL). The organic layer was washed with a saturated aqueous NaCl solution (25.0 mL), dried over MgSO4, and filtered under reduced pressure. The residue was purified by flash chromatography using hexane:EtOAc:hexane:EtOAc (60:40:10) to afford 1.38 g of the respective carboxylic acid intermediate, 83% yield.

10. (E)-3-Ethyl-7,9,13-trimethyleneadamantane-1,3,12-trien-5-one (22): To a solution of the iodoide (7.09 mg, 3.72 mmol) in EtO (12.0 mL) at -78 °C was added dropwise a 1.7 M solution of 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 (538 mg, 31.8 mmol) in EtO (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, NH2Cl (15.0 mL) was added, the layers were separated, and the aqueous layer was extracted with EtO (3.00 mL). The organic extracts were combined, washed with saturated aqueous NaHCO3 (10.0 mL), dried over MgSO4, and filtered under reduced pressure. The residue was purified by flash chromatography, eluting with hexane:EtOAc to afford 1.38 g of the respective carboxylic acid intermediate, 83% yield.

11. (E)-3-Ethyl-7,9,13-trimethyleneadamantane-1,3,12-trien-5-one (22): To a solution of the iodoide (7.09 mg, 3.72 mmol) in EtO (12.0 mL) at -78 °C was added dropwise a 1.7 M solution of BuLi (4.37 mL, 7.44 mmol). 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, NH2Cl (15.0 mL) was added, the layers were separated, and the aqueous layer was extracted with EtO (3.00 mL). The organic extracts were combined, washed with saturated aqueous NaHCO3 (10.0 mL), dried over MgSO4, and filtered under reduced pressure. The residue was purified by flash chromatography, eluting with hexane:EtOAc to afford 1.38 g of the respective carboxylic acid intermediate, 83% yield.

12. (E)-3-Ethyl-N-methoxy-N-methylpent-2-en-4-ynoate (19): A mixture of Pd(AcO) (337 mg, 1.50 mmol) and triis(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:hexane (1:10) to provide 9.36 g of 19, 85% yield.

13. (E)-3-Ethyl-N-methoxy-N-methylpent-2-en-4-ynoate (19): A mixture of Pd(AcO) (337 mg, 1.50 mmol) and triis(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:hexane (1:10) to provide 9.36 g of 19, 85% yield.

14. (E)-3-Ethyl-N-methoxy-N-methylpent-2-en-4-ynoate (19): A mixture of Pd(AcO) (337 mg, 1.50 mmol) and triis(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:hexane (1:10) to provide 9.36 g of 19, 85% yield.

15. (E)-3-Ethyl-N-methoxy-N-methylpent-2-en-4-ynoate (19): A mixture of Pd(AcO) (337 mg, 1.50 mmol) and triis(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:hexane (1:10) to provide 9.36 g of 19, 85% yield.

16. (E)-3-Ethyl-N-methoxy-N-methylpent-2-en-4-ynoate (19): A mixture of Pd(AcO) (337 mg, 1.50 mmol) and triis(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:hexane (1:10) to provide 9.36 g of 19, 85% yield.
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.

A solution of polyene 22 (92.0 mg, 0.33 mmol) in tBuOH (1.70 mL) and H2O (1.70 mL) were added K3Fe(CN)6 (359 mg, 1.00 mmol), K2CO3 (158 mg, 1.00 mmol), MeSO4·NH2 (31.7 mg, 0.33 mmol), (DHQ)2PHAL (13.0 mg, 0.02 mmol) and K3OsO4·2H2O (1.20 mg, 3.30 mmol). The reaction was stirred for 20 h at 0 °C. After this time, Na2SO4 (460 mg) and H2O (10.0 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (5 x 10.0 mL). The organic extracts combined were dried over MgSO4, filtered and concentrated under reduced pressure.

1. To a solution of this diol (41.0 mg, 0.13 mmol) in H2O (260 mL) and THF (1.06 mL) was added NaI (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 CH2Cl2 (3 x 0.50 mL). The organic extracts combined were dried over MgSO4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography using hexane:EtOAc 90:10 as eluent. The best purification (30.0 mg of the fragment C1-C2 was obtained, 36% yield (2 steps).

2. To a solution of this diol (41.0 mg, 0.13 mmol) in H2O (260 mL) and THF (1.06 mL) was added NaI (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 CH2Cl2 (3 x 0.50 mL). The organic extracts combined were dried over MgSO4, 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-C2 was obtained, 36% yield (2 steps).

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). 1H NMR (500 MHz, CDCl3) δ 7.97 (t, J = 1.8 Hz, H1), 6.27 (dd, J = 17.4, 8.0 Hz, H2), 6.07 (s, H3), 5.69 (dd, J = 17.4, 4.8 Hz, H4), 5.45 (d, J = 10.7 Hz, H5), 2.73 (q, J = 7.6 Hz, H6), 2.42 (m, H7), 2.30 (m, H8), 1.21 (m, H9), 1.63 (m, H10), 1.48 (m, H11), 1.33 (m, H12), 1.09 (d, J = 7.6 Hz, H13), 0.89 (d, J = 3.5 Hz, H14), 0.87 (d, J = 3.7 Hz, H15). 13C NMR (125 MHz, CDCl3) 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.

3. A solution of this diol (41.0 mg, 0.13 mmol) in H2O (260 mL) and THF (1.06 mL) was added NaI (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 CH2Cl2 (3 x 0.50 mL). The organic extracts combined were dried over MgSO4, 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-C2 was obtained, 36% yield (2 steps).

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). 1H NMR (500 MHz, CDCl3) δ 7.97 (t, J = 1.8 Hz, H1), 6.27 (dd, J = 17.4, 8.0 Hz, H2), 6.07 (s, H3), 5.69 (dd, J = 17.4, 4.8 Hz, H4), 5.45 (d, J = 10.7 Hz, H5), 2.73 (q, J = 7.6 Hz, H6), 2.42 (m, H7), 2.30 (m, H8), 1.21 (m, H9), 1.63 (m, H10), 1.48 (m, H11), 1.33 (m, H12), 1.09 (d, J = 7.6 Hz, H13), 0.89 (d, J = 3.5 Hz, H14), 0.87 (d, J = 3.7 Hz, H15). 13C NMR (125 MHz, CDCl3) 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.
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 aqeous layer was extracted with AcOEt (5 x 20.0 mL). The combined organic layers were dried over MgSO₄, 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 CH₂Cl₂ (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 H₂O (3 x 2.00 mL), and the organic layer was dried over MgSO₄, 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). [α]D²⁵ + = -6.0 (c 1.14, CHCl₃).

1H NMR (250 MHz, CDCl₃) δ 6.52 - 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), 0.66 (s, 3H), 0.04 (s, 3H), 0.03 (s, 9H).

13C{1H} NMR (125 MHz, CDCl₃) 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) 3097, 2970, 1730 cm⁻¹. HRMS (ESI+) m/z calculated for C₇₃H₆₄NaO₉Si [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-en-4-ol.

4.1.18.a. NMO (219 mg, 1.87 mmol) and OsO₄ 4% (0.24 mL, 0.04 mmol) were added to a solution of 34 in acetone (11.3 mL) and H₂O (1.13 mL). The reaction was stirred for 2 h and then quenched by the addition of a saturated aqueous solution of Na₂SO₄ (30.0 mL). The mixture was extracted with AcOEt (3 x 50.0 mL). The combined organic layers were dried over MgSO₄, filtrated and concentrated under reduced pressure. The residue was used in the next step without further purification.

4.1.18.b. PIDA (4.41 mg, 1.37 mmol) was added to a solution of the previously synthesized residue in CH₂Cl₂ (12.4 mL). The reaction was stirred for 2 h, and then filtered through a plug of silica gel and eluted with CH₂Cl₂. The solvent was removed under reduced pressure and engaged in the next step without further purification.

4.1.18.c. NaH₂PO₄ (383 mg, 3.19 mmol), 2-methyl-2-buten (0.51 mL, 4.79 mmol) and NaClO₂ (125 mg, 1.38 mmol) were added to a solution of the previously synthesized residue in tBuOH (12.1 mL) and H₂O (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 MgSO₄, filtrated and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluted with hexane:AcOEt:formic acid 75:2:4:1 to provide 474 mg of 11, 80% yield.
NH₂Cl (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 Et₂O (3 x 50.0 mL). The combined organic extracts were washed with brine (50.0 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to provide the aldehyde intermediate 38 which was used for the next step without further purification.

Rf = 0.13 (hexane:AcOEt 80:20). [α]D²⁵ = +8.0 (c 0.9, CHCl₃).

1H NMR (400 MHz, CDCl₃) δ 7.26 (d, J 8.6 Hz, 2H), 6.89 (d, J 8.7 Hz, 2H), 4.47 (s, 2H), 3.85 (s, 2H), 3.67 (m, 1H), 3.57 (d, J 9.2, 4.2 Hz, 1H), 3.42 (dd, J 9.3, 8.3 Hz, 1H), 2.93 (s, 1H), 1.78 (m, 1H), 1.17 (d, J 6.1 Hz, 3H), 0.85 (d, J 7.1 Hz, 3H).

13C NMR (100 MHz, CDCl₃) δ 159.3, 129.7, 129.2 (2C), 113.7 (2C), 75.1, 72.9, 74.4, 55.4, 39.9, 20.9, 13.5.

IR (Film) 3342, 2966, 2898, 2857 cm⁻¹. HRMS (ESI⁻) m/z calculated for C₃₂H₆₆O₇Na [M+Na⁺] = 574.4101, found 574.4090.

Fourier transform infrared spectroscopy (FT-IR) and nuclear magnetic resonance (NMR) studies revealed the presence of the desired compound in the crude mixture.

Rf = 0.3 (hexane:AcOEt 70:30). [α]D²⁵ = +2.0 (c 0.7, CHCl₃).

1H NMR (500 MHz, CDCl₃) δ 5.44-5.10 (m, 2H), 4.97-4.91 (m, 1H), 3.81-3.71 (m, 2H), 3.77 (s, 3H), 3.54 (d, 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, 1H), 1.82-1.77 (m, 1H), 1.25 (d, J 6.4 Hz, 3H), 1.02 - 0.97 (m, 3H), 0.87 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.05 (s, 9H).

13C NMR (150 MHz, CDCl₃) δ 170.9, 168.3, 166.9, 141.7, 130.9, 129.2, 117.0, 76.2, 68.2, 57.3, 54.2, 42.0, 40.6, 25.6 (3C), 18.0, 17.9, 17.6, 15.0, 13.2, -1.4 (3C), -5.0, -5.3.

Rf = 0.25 (2R,3S)-4-(4-Methoxybenzyl)oxy)-3-methylbutan-2-yl benzolate (43): Bz₂O (1.09 g, 4.81 mmol), DIPPEA (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 CH₂Cl₂ (10.4 mL). The reaction was stirred for 18 h, after which the reaction mixture was filtered through a plug of Celite and eluted with CH₂Cl₂. The crude material was purified by flash chromatography, eluted with hexane:AcOEt 31:3 and 39:45 yield.
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). [α]D = −32.0 (c 14, CHCl3).

1H NMR (250 MHz, CDCl3) δ 8.03 (d, J 7.3 Hz, 2H), 7.35 (t, J 7.3 Hz, 2H), 7.43 (t, J 7.5 Hz, 2H), 2.75 (d, J 8.5 Hz, 2H), 6.85 (d, J 8.5 Hz, 2H), 5.23 (quint, J 6.3 Hz, 2H), 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).

13C{1H} 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, 53.0, 31.6, 12.9. IR (ATR) 3063, 3033, 2972, 2935, 2855, 1712, 1613 cm−1. HRMS (ESI+) m/z calculated for C11H15O4Na [M+Na]+ 351.1572, found 351.1564.

4.1.26. (2R,3S)-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 CHCl3 (13.8 mL) and phosphate buffer pH 7.0 ± 0.15 mL at 0 °C. The reaction was stirred for 3.5 h and then quenched by the addition of a saturated aqueous solution of NaHCO3 (7.90 mL). The mixture was ﬁltered through a plug of Celite® and eluted with CHCl3. The crude material was puriﬁed by flash chromatography, eluted with hexane:AcOEt 70:30 to provide 250 mg of 44, 87% yield.

RF = 0.32 (hexane:AcOEt 70:30). [α]D = −22.0 (c 0.8, CHCl3).

1H NMR (250 MHz, CDCl3) δ 8.04 (d, J 7.1 Hz, 2H), 7.57 (t, J 7.4 Hz, 2H), 7.45 (t, J 7.4 Hz, 2H), 5.27 ~ 5.12 (m, 3H), 5.06 (d, J 4.7 Hz, 2H), 2.04 ~ 1.90 (m, 1H), 1.62 (s, 1H), 1.37 (d, J 6.4 Hz, 3H), 1.07 (d, J 7.0 Hz, 3H).

13C{1H} 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.

IR (ATR) 3437 (br), 2978, 2935, 2882, 1715, 1608, 1602, 1585 cm−1. HRMS (ESI+) m/z calculated for C11H15O4Na [M+Na]+ 231.0997, found 231.0997.

4.1.27. (2R,3R)-3-Methyl-4-oxobutan-2-yl benzoate (45): Oxaly chloride (68.0 µL, 0.78 mmol) was added dropwise to a solution of DMSO (7.40 µL, 1.04 mmol) in CH2Cl2 (4.00 mL) at −78 °C. The mixture was stirred for 15 minutes. Thus, the mixture was treated under reduced pressure. The crude material was puriﬁed by distillation under reduced pressure to provide 8.30 g of 13, 41% yield.

RF = 0.52 (hexane:AcOEt 70:30). [α]D = −15.0 (c 1.0, CHCl3).

1H NMR (500 MHz, CDCl3) 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 (dq, 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).

13C{1H} NMR (125 MHz, CDCl3) major diastereomer δ 211.6, 166.5, 133.0, 130.6, 129.6 (2C), 128.3 (2C), 73.0, 66.5, 47.6, 42.0, 36.8, 17.8, 9.3, 7.5. IR (film) 3505, 2979, 2938, 1736, 1602, 1585 cm−1. HRMS (ESI+) m/z calculated for C12H15O5Na [M+Na]+ 301.1416, found 301.1409.

4.1.30. (2S,3R,5S,6R)-2-Ethyl-1-methoxy-5,6-dimethyltetrahydro-2H-pyran-4-ol (48): Ba(OH)2, H2O (43 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 0.75 mL of 48, 55% yield.

RF = 0.45 (hexane:AcOEt 70:30). [α]D = −3.0 (c 0.3, CHCl3).

1H NMR (500 MHz, CDCl3) δ 3.68 (dq, J 10.1, 6.3 Hz, 1H), 3.37 (s, 3H), 3.28 ~ 3.20 (m, 2H), 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 6.7 Hz, 3H).

13C{1H} NMR (125 MHz, CDCl3) δ 98.4, 79.0, 70.5, 55.6, 43.7, 37.0, 36.1, 19.3, 13.0, 7.5. IR (film) 3590, 3412, 3012, 2905, 2971, 2929, 2851 cm−1. HRMS (ESI+) m/z calculated for C51H81O5Na+ [M+NaH]+ 211.1310, found 211.1290.

4.1.31. 1-((2R,3S,4R)-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 (50).

4.1.31.a. Oxaly chloride (84.0 µL, 0.97 mmol) was slowly added to a solution of DMSO (80.0 µL, 1.13 mmol) in CH2Cl2 (2.00 mL) at −78 °C. The mixture was stirred for 15 minutes and a solution of alcohol 42 (81 mg, 0.32 mmol) in CH2Cl2 (1.20 mL) was added dropwise. The reaction was stirred for 1 h and then Et3N (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 NaHCO3 (5.00 mL). The mixture was extracted with CH2Cl2 (2 x 10.0 mL). The combined organic layers were washed through silica gel and eluted with hexane:AcOEt 80:20. The
crude aldehyde 49 obtained was in the next step without further purification.

4.3.1 b. BF₃·OEt₂ (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 CH₂Cl₂ (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 NaHCO₃ (8.00 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 8.00 mL). The combined organic layers were dried over MgSO₄, filtered 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). [α]ᵢ²⁵ = +9.0 (c 0.8, CHCl₃).

^1H NMR (500 MHz, CDCl₃) 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). ^13C{H} NMR (125 MHz, CDCl₃) major diastereomer δ 171.7, 170.7, 168.2, 166.9, 141.8, 127.6, 90.2, 72.8, 68.1, 67.3, 66.2, 52.3, 48.6, 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 C₁₅H₁₆O₅NaSi [M+Na]⁺ 655.330, found 655.3310.

**4.3.2** 4-Methyl 1-((2R,3R,4R)-3-methyl-6-o xo-4-((trimethylsilyl)oxy)octan-2-yl) 3-((2-(trimethylsilyl)ethoxy)methyl) (R,Z)-2-((tert-butyldimethylsilyloxy)pent-3-ene-1,3,4-tricarboxylate and 3-methyl 1-((2R,3R,4R)-3-methyl-6-o xo-4-((trimethylsilyl)oxy)octan-2-yl) 4-((2-(trimethylsilyl)ethoxy)methyl) (R,Z)-2-((tert-butyldimethylsilyloxy)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 CH₂Cl₂ (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). [α]ᵢ²⁵ = +6.0 (c 0.5, CHCl₃).

^1H NMR (500 MHz, CDCl₃) 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 (dd, 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).

^13C{H} NMR (125 MHz, CDCl₃) 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 C₁₅H₁₆O₅NaSi [M+Na]⁺ 727.3705, found 727.3700.

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(23) 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.


(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 ttnl Completing the Tailoring Steps for Tautomycetin Biosynthesis in Streptomyces griseochromogenes. *Org. Lett.* 2012, **14**, 1302-1305.

