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Tetrahedron 62 (2006) 5272–5279
Tetrahedron

Formal synthesis of Abyssomicin C

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Received 22 December 2005; revised 5 January 2006; accepted 8 January 2006
Available online 29 March 2006

Abstract—An alternative strategy towards Abyssomicin C (**1**) is described. The key ene-diene intermediate is synthesized via a Kishi type coupling of an *E*/*Z* mixture of triene-iodide **7** and a suitably functionalized derivative of 2,4-dimethylglutaric acid. A final in situ isomerization/intramolecular Diels–Alder cyclization resulted in the formation of the known intermediate **3** as a single isomer in high yield. Further heating of **3** using excess of iodine, afforded iodo-derivative **23**, having the entire carbon skeleton of Abyssomicin D.
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1. Introduction and retrosynthetic analysis

Antibiotics with high potency against pathogenic antibiotic-resistant bacterial strains will be of value in the clinic. Abyssomicin C (**1**, Fig. 1) recently discovered by Süssmuth et al.,[1] is a serious candidate since it possess an unprecedent complicated structure and an impressive biological profile. Abyssomicin C, inhibits the biosynthesis of *p*-amino-benzoic acid[2] (a pathway existing in bacteria but not in humans) and it is highly potent against resistant *Staphylococcus aureus* strains (methicillin-resistant MIC=4 μg mL^{-1}; vancomycin-resistant MIC=13 μg mL^{-1}).[2] Efficient chemical routes for the preparation of Abyssomicin C, as well as of related analogues, will have to be invented in order to facilitate possible pharmaceutical application of the new architecture. Not surprisingly many synthetic chemistry groups have already been alerted[3–5] and one year after its discovery an elegant total synthesis has been released by Sorensen et al.[6]

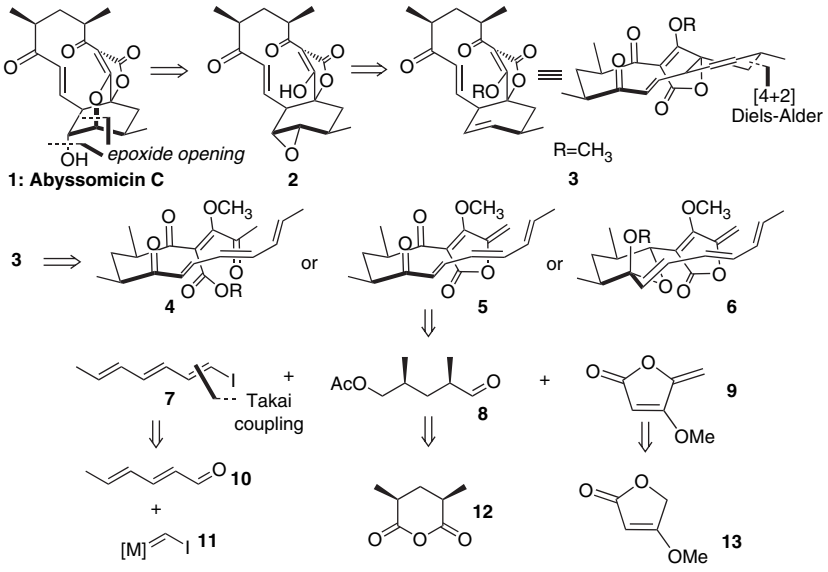

Figure 1. Retrosynthetic analysis towards a biomimetic route to Abyssomicin C.

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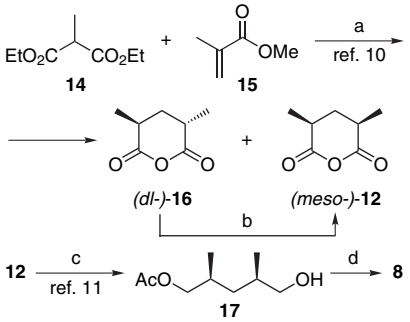
doi:10.1016/j.tet.2006.01.106

Aspiring to meet the challenge of constructing this impressive architecture, we focused our attention on synthetic strategies resembling a plausible biomimetic route as much as possible (Fig. 1). Thus, assuming that an intramolecular epoxide opening is possible, **1** can be disconnected to spirotetronate precursor **2**, which may be formed from **3** upon selective epoxidation and deprotection. The cyclohexenyl moiety of **3** called for an ene-diene precursor, is suitably designed to yield an intramolecular Diels–Alder cyclization. Although an in situ enolization of the terminal methyl ketone and concomitant stereoselective Diels–Alder seemed precarious, linear polyketidic triene **4**, was considered as a possible biomimetic retron of **3**. On the other hand, the alternative bicyclic precursor **6**, bearing an electron deficient exocyclic double bond and a hemiketalic connection between the adjacent α-methyl-carbonyls, is ideally preorganized for an efficient [4+2] cyclization. However, **6** features two new stereocenters and as a consequence, its synthesis can be anticipated to be lengthy. Thus, **5** was targeted as a more realistic compromise. Indeed, while our work was in progress, Sorensen et al.[6] and Snider and Zou[5] did prove independently that **5** may be transformed smoothly and in high yield to cyclized intermediate **3**. Moreover, the former succeeded in converting **3** to Abyssomicin C, following the depicted sequence. We report herein an alternative synthesis of key intermediate **3**.

Since the central core of **5** resembles reported *meso*-2,4-dimethylglutaric acid, the readily available aldehyde **8** was chosen to be the building block, as well as the chirality source. The tetronate moiety could be attached by a direct alkylation of **8** with anion of **9**.[7] Finally, the triene part was planned to be mounted after transformation of the terminal acetate to aldehyde, followed by a Kishi type coupling[8] with vinyl-iodide **7**, derived via a Takai olefination[9] of commercial hexadienal **10**.

2. Synthesis of key intermediate 3

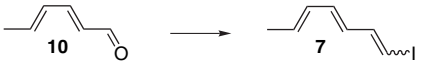
The key starting material, *meso*-2,4-dimethylglutaric anhydride **12**, was prepared on a multi-gram scale from diethylmethyl malonate and methyl methacrylate within three steps adopting two related syntheses[10] (Scheme 1). *meso*-Isomer **12**, selectively crystallizes out of the derived mixture of *dl*- and *meso*-forms. We were pleased to observe that the isomeric ratio of the crystallization mother liquor (which was enriched in the *dl*-form) could be reversed upon equilibration by heating with a mild base, thus raising the reported yield from 30 to 65%. The optically pure alcohol **17** was then prepared within two steps[11] and Swern oxidation[12] of the latter furnished aldehyde **8**, which was taken forward to the next step without further purification.



Scheme 1. Reagents and conditions: (a) i. Na, EtOH, rt, ii. HCl, AcOH, 105 °C, iii. Ac_2O, reflux, and iv. recrystallization (30% of **12**, three steps); (b) i. Et_3N, THF, reflux and ii. recrystallization, 52%; (c) i. LAH, THF, 0 °C and ii. AcOCH=CH_2, Amano lipase AK, THF, 0 °C (58%, two steps); (d) $(COCl)_2$, DMSO, DCM, Et_3N, 95%.

The remaining coupling partner, vinyl-iodide **7** was prepared from commercially available sorbaldehyde **10**,[†] in good yield (Table 1). However, under all conditions tried (Takai[9] or Evans[13,14] conditions for *E* selectivity or Stork's[15] conditions for *Z* selectivity), the obtained stereoselectivity was very poor. Moreover, all efforts to isomerize[16,17] resulted in 1:1 *E*/*Z* mixtures, indicating the presence of an equilibrium.[18] Nonetheless, since possible double bond in situ isomerization during the IMDA reaction would result in a very short scheme, we opted to continue our efforts employing vinyl-iodide **7** as a mixture of isomers (approximately 2:1 *E*/*Z* ratio).

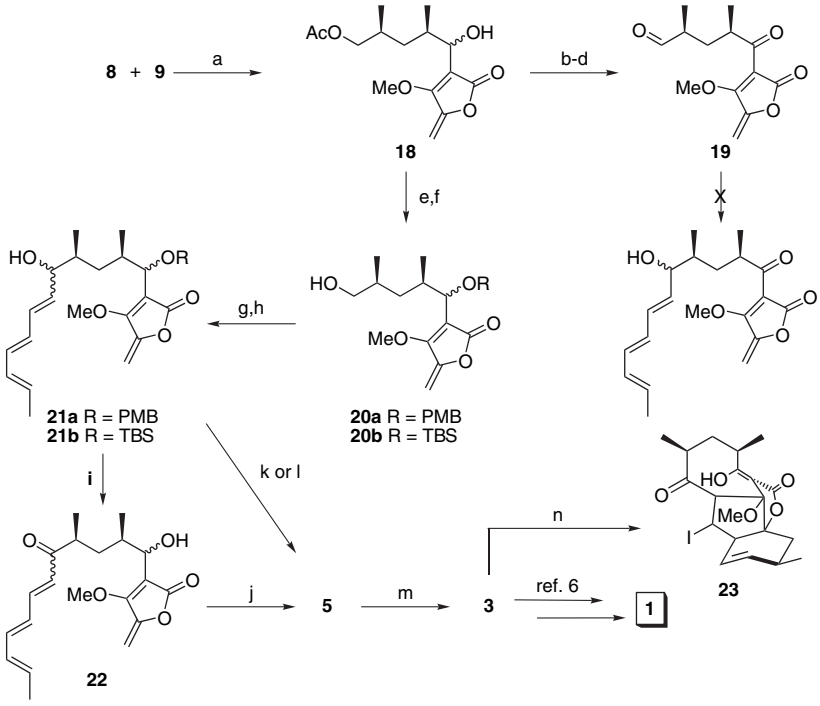
Table 1. Synthesis of vinyl-iodide **7**



Entry	Reagents/conditions	Solvents	*E*/*Z*	Yield (%)
1	$CrCl_2$, CHI_3, 0 °C	THF	2/1	85
2	$CrCl_2$, CHI_3, 0 °C	THF/dioxane 6/1	2/1	75
3	$Ph_3P^+(I^-)CH_2I$, NaHMDS, −78 °C	THF	1.2/1	87

The assembly of intermediate **5** commenced with coupling between aldehyde **8** and tetronate **9** (Scheme 2). After some experimentation, alcohol **18** was synthesized in relatively high yield along with partial recover of the starting materials. Alcohol **18** was formed as a diastereomeric mixture in 1:1 ratio, however oxidation of this stereocenter at a subsequent step would alleviate this problem. Thus, oxidation of the allylic alcohol with IBX,[19] enzymatic cleavage[20] of the acetate and subsequent oxidation of the resulting primary alcohol furnished keto-aldehyde **19**. Deacylation of all tetronate derivatives under alkaline conditions resulted usually in very low yields. We found that Novozyme 435 was quite efficient in this case. Though the chemical yields of these sequence were good, the stability of all intermediates upon chromatographic manipulations and storage was low. In addition, any further attempt to introduce the triene moiety (using $CrCl_2$ or the lithium anion of the respective triene) led only to immediate polymerization of aldehyde **19**. Thus, alcohol **18** was protected as the corresponding *p*-methoxy benzyl ether, anticipating that upon treatment with DDQ the allylic alcohol would be concomitantly transformed to the required ketone. Since Novozyme 435 reacted very slowly on this substrate, alcohol **20a** was prepared using Amano Lipase AK. It should be noted that all PMB-protected intermediates were by far more stable than the respective keto derivatives. In addition, Swern oxidation of **20a** and subsequent coupling

[†] Commercial sorbaldehyde contains up to 10% of the Z isomer. As it has been already reported by Snider[5] the wrong isomer remains unreacted in the final cyclization step. For clarity reasons this isomer is not depicted in the schemes or mentioned in the text.



Scheme 2. Reagents and conditions: (a) **9** (3 equiv), LDA, THF, −100 °C, then **8**, 45–58%, (20% recover of **8**, 50% recover of **9**); (b) IBX, DMSO, 78%; (c) Novozyme 435, toluene/phosphate buffer, 52% (16% recover); (d) IBX, DMSO, 70%; (e) PMBO(C=NH)CCl_3, cyclohexane/DCM, cat. CSA, 98% or TBS-Cl, imid., DMF, 85%; (f) Lipase AK, acetonitrile/phosphate buffer, 81% for R=PMB, 15% for R=TBS (recover 70%) or guanidine hydrochloride, EtOH/4 N NaOH, 78% for R=TBS; (g) IBX, DMSO, 88%; (h) **7**, $CrCl_2$, $NiCl_2$, THF/DMSO, 40% (recover 47%) for R=PMB, 50% (recover 30%) for R=TBS; (i) DDQ, DCM/H_2O, 20% for R=PMB; (j) Dess–Martin, DCM, 95%; (k) for R=PMB: i. MnO_2, Et_2O, 90%. ii. DDQ, DCM/$NaHCO_{3aq}$, 35%. iii. Dess–Martin, DCM, 95%; (l) for R=TBS: i. TBAF, THF, 83%. ii. IBX, DMSO, 85%; (m) toluene, cat. I_2, 100 °C, 3 h, 75%, (*n*) toluene, excess I_2, 100 °C, 3 h, 87%.

of the resulted aldehyde with vinyl-iodide **7**, under Kishi conditions, successfully lead to the targeted linear analogue of Abyssomicins **21a**. At this point we attempted an one pot, direct transformation of alcohol **21a** to di-keto-ene-diene **5** by a PMB deprotection and subsequent double oxidation of both allylic alcohols using DDQ.[21] Unfortunately, this reaction was messy and only keto-alcohol **22** could be isolated in low yield (5–30%). The latter was oxidized to diketone **5**.[5] Alternatively, **5** could be derived from **21a** following a three steps protocol (MnO_2 oxidation, DDQ deprotection and Dess–Martin periodinate oxidation),[22] yet in low overall yield (20%).

In order to improve the total yield towards **6**, the previous sequence was repeated using *t*-$BuMe_2Si$ instead of PMB for the protection of the hydroxyl group. This time, saponification of the acetate moiety was performed by employing guanidine under buffered conditions, since both of the previously used enzymes reacted very slowly. Alcohol **21b**, upon desilylation with TBAF and subsequent double oxidation of the resulting diol using IBX, afforded the targeted precursor **5** in very good yield. It should be pointed out that the aforementioned diol is a mixture of two diasteromeric centers and possesses the *E*/*Z* double bond stereochemistry originating from the used vinyl-iodide (total eight isomers). However, the derived diketone **5** was only a mixture of the *E*/*Z* isomers and, to our delight, this mixture upon heating at 100 °C in toluene with a catalytic amount of I_2, was smoothly converted in high yield to the cyclized advanced intermediate of Abyssomicin C, **3**, as a single isomer. Interestingly, by adding excess of I_2 and heating for additional 3 h, iodo-derivative **23** was isolated as the only product, giving rise to the Abyssomicin D carbon skeleton in a similar manner that Snider observed for a sulfide analogue.[5]

3. Conclusion

In conclusion we have presented herein an efficient and straightforward synthesis of a key advanced intermediate towards **1**. We are currently working towards a scaled up synthesis of Abyssomicin C as well as of related derivatives in order to explore their antibacterial activities.

4. Experimental

4.1. General techniques

All reactions were carried out under anhydrous conditions and an argon atmosphere using dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, dichloromethane (DCM) from CaH_2, and toluene from sodium. Yields refer to chromatographically and spetroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All reagents were purchased at highest commercial quality and used without further purification, unless otherwise stated. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F254) using UV light as visualizing agent and ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra

were recorded on Bruker Avance DRX-500 or AC-250 instruments. The following abbreviations were used to explain NMR signal multiplicities: br s = broad singlet, br d = broad doublet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR or Nicolet Magna system 550 FTIR instruments. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions and matrix-assisted (MALDI-FTMS) mass spectra were recorded on a PerSeptive Biosystems Voyager IonSpect mass spectrometer.

4.1.1. *meso*-2,4-Dimethylglutaric anhydride 12. To a solution of *dl*-2,4-dimethylglutaric anhydride (52.0 g, 0.366 mol) in THF (270 mL) was added triethylamine (255 mL, 1.83 mol) under argon. The reaction mixture was heated under reflux for 60 h and the solvents were removed under reduced pressure. The residue was distilled under high vacuum using air-cooled condenser to afford a colorless solid. This material was dissolved in AcOEt (50 mL) and the solution was allowed to stand at room temperature for 12 h, in the freezer for 6 h and at −20 °C for 2 h. The colorless solid was recrystallized from AcOEt (25 mL), to give *meso*-2,4-dimethylglutaric anhydride (27 g, 52%) as a colorless solid. Mp 90.5–91.9 °C (lit.[23] 91.4–92.8 °C).

4.1.2. Aldehyde 8. To a stirred solution of oxalyl chloride (1.53 mL, 0.018 mol) in dry DCM (20 mL) at −78 °C, DMSO (2.90 mL, 0.038 mol) was added drop-wise under an argon atmosphere. After 30 min, a solution of alcohol **17** (2.0 g, 0.014 mol) in dry DCM (20 mL) was added to the reaction mixture. After 30 min of stirring at −78 °C, Et_3N (13.8 mL, 0.10 mol) was added and the reaction was stirred for 1 h at ambient temperature. The reaction mixture was quenched with saturated NH_4Cl_{aq} solution (30 mL) and extracted with DCM (30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude aldehyde, **8**, was used in the next step without further purification.

4.1.3. Alcohol 18. To a stirred solution of 4-methoxy-5-methylene-2(5*H*)-furanone, **9**, (2.07 g, 16.4 mmol) in THF (235 mL), at (−100 °C) under an argon atmosphere was added, via cannula, a cooled (−100 °C) LDA solution [prepared from *i*-Pr_2NH (2.7 mL, 19.05 mmol) and *n*-BuLi (1.6 M in Hexane; 10.3 mL, 16.53 mmol) in THF (83 mL) after stirring for 1 h at 0 °C] over a period of 2 min. After stirring for 6 min, a solution of the crude aldehyde **8** (943 mg, 5.48 mmol) in THF (46 mL) was added, over a period of 2 min via cannula. After being stirred at −100 °C −90 °C for 15 min, the reaction was quenched with saturated NH_4Cl_{aq} (50 mL) and then allowed to warm at room temperature. The mixture was extracted with ethyl acetate (2×40 mL) and the combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was subjected to flash chromatography (SiO_2, Hexane/AcOEt 8:2 to 7:3) to afford alcohol **18** (mixture of two diastereoisomers, ratio 1:1; 948 mg, 3.18 mmol; 58%) as a yellow oil, and recovered starting materials: aldehyde **8** (188 mg, 1.09 mmol; 20%) and 4-methoxy-5-methylene-2(5*H*)-furanone, **9** (1.0 g, 7.93 mmol). R_f=0.22 (Hexane/AcOEt 8:2); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 5.07 (s, 4H, =CH_2), 4.46 (d, ^3J(H,H)=7.5 Hz, 1H, C*H*OH), 4.40 (d, ^3J(H,H)=8.6 Hz, 1H, C*H*OH), 4.12 (s, 6H, OCH_3), 3.96 (dd, ^3J(H,H)=4.6, 10.3 Hz, 1H, AcOCH_2), 3.92–3.79 (m, 3H, AcOCH_2), 3.41–3.09 (br s, 2H, *OH*), 2.03 (s, 3H, *Ac*O), 1.99 (s, 3H, *Ac*O), 1.99–1.90 (m, 2H, CH_3C*H*CHOH), 1.89–1.79 (m, 2H, AcOCH_2C*H*CH_3), 1.42–1.13 (m, 4H, CHCH_2CH), 1.05 (d, ^3J(H,H)=6.3 Hz, 3H, *CH_3*), 0.97 (d, ^3J(H,H)= 6.9 Hz, 3H, *CH_3*), 0.93 (d, ^3J(H,H)=6.3 Hz, 3H, *CH_3*), 0.85 (d, ^3J(H,H)=6.9 Hz, 3H, *CH_3*) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ 171.7, 171.6, 169.9, 162.1, 149.7, 107.4, 107.3, 93.9, 71.6, 70.9, 69.6, 69.1, 68.5, 68.3, 60.9, 37.9, 37.7, 37.6, 37.5, 33.4, 31.8, 30.6, 30.5, 30.4, 30.0, 21.3, 21.1, 19.1, 18.8, 17.6, 16.3 ppm; FTIR (neat): $\overline{\nu}_{max}$ 3492, 2964, 2933, 2877, 1767, 1736, 1669, 1624, 1460, 1392, 1281, 1245, 1156, 1036, 979, 878, 784 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{22}O_6$ ([M+Na]$^+$): *m*/*z* 321.1308, found 321.1309.

4.1.4. Aldehyde 19. To a solution of alcohol **18** (247 mg, 0.828 mmol) in DMSO (1.6 mL) was added IBX (463 mg, 1.654 mmol) at room temperature under an argon atmosphere. After stirring for 2 h the reaction was quenched with water (5 mL) and AcOEt (5 mL). The iodosocarboxylic acid, which precipitated as a white amorphous solid, was removed by filtration through Celite. The filtrate was extracted with AcOEt (2×10 mL) and the combined organic layers were washed with saturated $NaHCO_{3aq}$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was subjected to flash chromatography (silica gel, Hexane/AcOEt 8:2) to afford the respective ketone (191 mg, 0.646 mmol; 78%) as yellow oil. R_f=0.44 (Hexane/AcOEt 8:2); $[\alpha]_D^{2.5}$ −5° (*c* 7.2 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 5.27 (d, ^2J(H,H)=2.9 Hz, 1H, =CH_2), 5.22 (d, ^2J(H,H)=2.9 Hz, 1H, =CH_2), 4.11 (s, 3H, OCH_3), 3.95 (dd, ^3J(H,H)=5.7, 10.9 Hz, 1H, AcOCH_2), 3.89 (dd, ^3J(H,H)=6.3, 10.9 Hz, 1H, AcOCH_2), 3.72 (dd, ^3J(H,H)=6.9, 13.8 Hz, 1H, C*H*CO), 2.06 (s, 3H, *Ac*O), 1.95–1.77 (m, 1H, CH_2C*H*CH_2), 1.32–1.22 (m, 2H, CHCH_2CH), 1.15 (d, ^3J(H,H)=7.5 Hz, 3H, CH_3), 0.97 (d, ^3J(H,H)=6.9 Hz, 3H, CH_3) ppm; ^{13}C NMR (62.8 MHz, $CDCl_3$, 25 °C): δ 200.5, 171.2, 168.8, 166.2, 148.9, 104.7, 95.8, 69.0, 62.8, 41.8, 36.5, 30.5, 29.7, 17.5, 17.4 ppm; FTIR (neat): $\overline{\nu}_{max}$ 2964, 2934, 2876, 2855, 1772, 1738, 1684, 1666, 1592, 1456, 1390, 1366, 1287, 1241, 1155, 1040, 994, 882, 793, 738 cm^{-1}; HRMS (ESI) calculated for $C_{15}H_{20}O_6$ ([M+Na]$^+$): *m*/*z* 319.1152, found 319.1152.

Novozyme 435 (Candida Antarctica lipase immobilized on a macroporous acrylic resin, Novo Nordisk; 441 mg) was added in a well-stirred solution of the previous ketone (245 mg, 0.827 mmol), in toluene (6 mL) and sodium phosphate buffer (pH 6.2; 6 mL, 0.1 M), at room temperature. After 48 h (TLC indicated no further conversion) the reaction mixture was filtered and the retained enzyme was washed with AcOEt (20 mL) and water (20 mL). The organic layer was separated and the aqueous layer of the filtrate was extracted with AcOEt (2×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and

concentrated under reduced pressure. The residue was subjected to column chromatography (SiO_2, Hexane/AcOEt 8:2–7:3) to afford the respective alcohol (110 mg, 0.433 mmol; 52%) as yellow oil, along with recovered starting material (40 mg, 0.157 mmol; 16%). R_f=0.28 (Hexane/AcOEt 7:3); ^{1}H NMR (500 MHz, Acetone-d_6, 25 °C): δ 5.30 (d, ^2J(H,H)=2.9 Hz, 1H, =CH_2), 5.27 (d, ^2J(H,H)=2.9 Hz, 1H, =CH_2), 4.14 (s, 3H, OCH_3), 3.70–3.60 (m, 1H, C*H*CO), 3.46–3.40 (m, 1H, CH_2OH), 3.35–3.29 (m, 1H, CH_2OH), 1.97–1.88 (m, 1H, HOCH$_2$C*H*), 1.71–1.61 (m, 1H, CHCH_2CH), 1.19–1.04 (m, 1H, CHCH_2CH), 1.14 (d, ^3J(H,H)=6.9 Hz, 3H, CH_3), 0.94 (d, ^3J(H,H)=6.9 Hz, 3H, CH_3) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ 202.2, 170.1, 167.9, 150.9, 130.1, 96.7, 68.4, 64.3, 43.6, 38.4, 35.5, 18.8, 18.5 ppm.

To a solution of the previous alcohol (37 mg, 0.146 mmol) in DMSO (1 mL) was added IBX (160 mg, 0.571 mmol) at room temperature under an argon atmosphere. After stirring for 2 h the reaction was quenched with water (3 mL) and AcOEt (3 mL). The iodosocarboxylic acid, which precipitated as a white amorphous solid, was removed by filtration through Celite. The filtrate was extracted with AcOEt (2×5 mL) and the combined organic layers were washed with saturated $NaHCO_{3aq}$ (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was subjected to flash chromatography (SiO_2, Hexane/AcOEt 8:2) to afford the aldehyde **19** (26 mg, 0.102 mmol; 70%) as colorless oil. R_f=0.37 (Hexane/AcOEt 7:3); $[\alpha]_D^{25}$ +31° (*c* 0.15 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 9.62 (s, 1H, C*H*O), 5.30 (d, ^2J(H,H)=2.9 Hz, 1H, =CH_2), 5.24 (d, ^2J(H,H)=2.9 Hz, 1H, =CH_2), 4.13 (s, 3H, OCH_3), 3.77–3.65 (m, 1H, CH$_2$C*H*CO), 2.48–2.37 (m, 1H, C*H*CHO), 2.34–2.24 (m, 1H, CHCH_2CH), 1.35–1.25 (m, 1H, CHCH_2CH), 1.18 (d, ^3J(H,H)=7.5 Hz, 3H, CH_3), 1.15 (d, ^3J(H,H)=6.9 Hz, 3H, CH_3) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ 204.4, 199.9, 148.8, 141.8, 133.3, 127.9, 96.1, 62.9, 44.4, 41.9, 32.9, 17.9, 13.9 ppm; FTIR (neat): $\overline{\nu}_{max}$ 2962, 2924, 2875, 2852, 1769, 1726, 1686, 1667, 1585, 1455, 1390, 1286, 996, 738 cm^{-1}.

4.1.5. Alcohol 20a. A solution of *p*-methoxy benzyl trichloroacetimidate (2.06 g, 7.29 mmol) in cyclohexane (3.9 mL) was added to a solution of alcohol **18** (726 mg, 2.43 mmol) in DCM (1.9 mL) under an argon atmosphere. The resulting mixture was cooled to 0 °C and treated with (±)-camphorsulfonic acid (120 mg, 0.504 mmol). The reaction mixture was warmed to room temperature and stirred for 7 h, slowly developing a white precipitate. The suspension was filtered and washed with CCl_4 (2×15 mL). The filtrate was washed with saturated $NaHCO_{3aq}$ (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hexane/AcOEt 9:1) to afford the PMB-ether (mixture of two diastereoisomers, ratio 1:1; 1.0 g, 2.39 mmol; 98%) as colorless oil. R_f=0.40 (Hexanes/AcOEt 8:2); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.25–7.17 (m, 4H, Ar*H*), 6.86 (d, ^3J(H,H)=8.5 Hz, 4H, Ar*H*), 5.10–5.03 (m, 4H, =CH_2), 4.48 (d, ^2J(H,H)=11.3 Hz, 1H, OC*H*HAr), 4.45 (d, ^2J(H,H)=11.3 Hz, 1H, OCH*H*Ar), 4.28 (d, ^2J(H,H)=11.3 Hz, 2H, OCH_2Ar), 4.14 (s, 6H, OCH_3), 4.11–4.05 (m, 2H, C*H*OPMB), 3.96 (dd, ^3J(H,H)=4.9, 10.8 Hz, 1H, C*H*HOAc), 3.90–3.81 (m, 2H, CH_2OAc), 3.79 (s, 6H, Ar-OCH$_3$), 3.76–3.71 (m, 1H, CH*H*OAc), 2.03–1.95 (m, 8H, C*H*CHOPMB, OA*c*), 1.90–1.75 (m, 2H, C*H*CH$_2$OAc), 1.33–1.22 (m, 2H, CHCH_2CH), 1.08 (d, ^3J(H,H)=6.6 Hz, 3H, CH_3), 1.04–0.99 (m, 2H, CHCH_2CH), 0.97 (d, J=6.6 Hz, 3H, CH_3), 0.92 (d, J=6.8 Hz, 3H, CH_3), 0.83 (d, J=6.8 Hz, 3H, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ 171.1, 169.6, 169.5, 163.6, 159.3, 149.8, 129.7, 129.5, 129.4, 128.2, 113.8, 110.3, 104.8, 92.6, 92.5, 77.5, 76.8, 71.2, 71.15, 68.7, 68.0, 61.7, 55.4, 55.2, 38.4, 37.3, 36.9, 36.6, 34.9, 30.4, 29.9, 20.8, 20.7, 18.6, 18.3, 17.2, 16.6; HRMS (ESI) calculated for $C_{23}H_{30}O_7$ ([M+Na]$^+$): *m*/*z* 441.1882, found 441.1883.

Amano Lipase AK (*Pseudomonas fluorescens*, Aldrich; 1.05 g) was added in a well-stirred solution of the previous PMB–ether (950 mg, 2.27 mmol) in acetonitrile (12.6 mL) and sodium phosphate buffer (pH 6.2; 50.5 mL; 0.1 M), at room temperature. The reaction was completed after 12 h (TLC), was filtered through Celite and the retained enzyme was washed with AcOEt (50 mL) and water (30 mL). The aqueous layer of the filtrates was extracted with AcOEt (2×30 mL) and the combined organic layers were washed with saturated $NaHCO_{3aq}$ (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was filtered through a silica pad (SiO_2, Hexane/AcOEt 7:3) to afford alcohol **20a** (mixture of two diastereoisomers, ratio 1:1; 692 mg, 1.838 mmol; 81%) as yellow oil. R_f=0.25 (Hexane/AcOEt 7:3); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.29–7.18 (m, 4H, Ar*H*), 6.86 (d, ^3J(H,H)=8.0 Hz, 4H, Ar*H*), 5.10–5.04 (m, 4H, =CH_2), 4.54–4.44 (m, 2H, OCH_2Ar), 4.33–4.26 (m, 2H, OCH_2Ar), 4.14 (s, 6H, OCH_3), 4.14–4.10 (m, 1H, C*H*OPMB), 3.80–3.86 (m, 1H, C*H*OPMB), 3.80 (s, 6H, Ar-OCH$_3$), 3.50–3.43 (m, 2H, CH_2OH), 3.42–3.36 (m, 2H, CH_2OH), 2.16–1.97 (m, 2H, C*H*CHOPMB), 1.87–1.72 (m, 2H, C*H*CH$_2$OH), 1.71–1.49 (m, 2H, CHCH_2CH), 1.36–1.19 (m, 2H, CHCH_2CH), 1.09 (d, ^3J(H,H)=6.6 Hz, 3H, CH_3), 0.96 (d, ^3J(H,H)=6.5 Hz, 3H, CH_3), 0.93 (d, ^3J(H,H)=6.7 Hz, 3H, CH_3), 0.85 (d, ^3J(H,H)=6.9 Hz, 3H, CH_3) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ 169.6, 163.9, 159.3, 149.8, 146.2, 139.1, 129.7, 129.6, 113.9, 113.8, 92.7, 92.6, 71.3, 71.1, 67.6, 66.9, 61.7, 59.6, 55.3, 38.4, 37.5, 36.6, 36.4, 32.8, 31.2, 29.7, 18.4, 18.1, 17.3, 17.2 ppm; HRMS (ESI) calculated for $C_{21}H_{28}O_6$ ([M+Na]$^+$): *m*/*z* 399.1778, found 399.1779.

4.1.6. Alcohol 20b. To a solution of alcohol **18** (200 mg, 0.670 mmol) in DMF (0.1 mL) was added imidazole (91 mg, 1.34 mmol), TBDMS-Cl (152 mg, 1.00 mmol) and DMAP (8.18 mmol, 0.067 mmol) at room temperature under argon an atmosphere. After being stirred for 12 h the reaction was quenched with MeOH (0.5 mL) and saturated NH_4Cl_{aq} (10 mL). The mixture was extracted with AcOEt (15 mL) and organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hexane/AcOEt 95:5) to afford the corresponding silyl ether (mixture of two diastereoisomers, ratio 1:1; 235 mg, 0.569 mmol; 85%) as colorless oil. R_f=0.65 (Hexanes/AcOEt 9:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 5.08–5.02 (m, 4H, =CH_2), 4.31–4.26 (m, 2H, C*H*OTBS), 4.26 (s, 3H, OCH_3), 4.25 (s, 3H, OCH_3), 3.98 (dd,

^2J(H,H)=3.9 Hz, ^3J(H,H)=10.8 Hz, 1H, CH*H*OAc), 3.91 (m, 3H, CH_2OAc), 2.03 (s, 3H, *Ac*), 1.99 (s, 3H, *Ac*), 1.96–1.78 (m, 4H, C*H*CH$_3$), 1.28–1.17 (m, 2H, CHCH_2CH), 1.06 (d, ^3J(H,H)=6.5 Hz, 3H, CH_3), 0.99 (d, ^3J(H,H)=6.4 Hz, 3H, CH_3), 0.98–0.90 (m, 2H, CHCH_2CH), 0.93 (d, ^3J(H,H)=6.8 Hz, 3H, CH_3), 0.88 (s, 18H, *TBS*), 0.81 (d, ^3J(H,H)=6.8 Hz, 3H, CH_3), 0.09 (s, 6H, *TBS*), −0.04 (s, 6H, *TBS*) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ 202.9, 171.3, 169.7, 162.9, 149.9, 107.4, 92.6, 92.6, 71.2, 70.9, 68.3, 67.6, 61.8, 39.4, 39.3, 38.0, 36.1, 30.1, 29.7, 25.8, 20.9, 20.8, 18.9, 18.6, 17.9, 17.4, 15.9, 3.6, 3.1 ppm.

To a solution of the previous acetyl ester (155 mg, 0.375 mmol) in EtOH (1.5 mL) was added guanidine (1 M in EtOH; 0.48 mmol) [prepared from guanidine hydrochoride (525 mg, 5.50 mmol) and NaOH (4 N; 1.3 mL) in EtOH (3.93 mL)] at 0 °C and stirred for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl_{aq} (10 mL) and extracted with AcOEt (2×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hexane/AcOEt 8:2) to afford alcohol **20b** (mixture of two diastereoisomers, ratio 1:1; 109 mg, 0.293 mmol; 78%) as yellow oil. R_f=0.45 (Hexane/AcOEt 7:3); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 5.08–5.02 (m, 4H, =CH_2), 4.39–4.23 (m, 2H, C*H*OTBS), 4.27 (s, 3H, OCH_3), 4.26 (s, 3H, OCH_3), 3.59–3.51 (m, 1H, CH_2OH), 3.51–3.44 (m, 1H, CH_2OH), 3.44–3.28 (m, 2H, CH_2OH), 2.06–1.86 (m, 2H, C*H*CH$_3$), 1.88–1.66 (m, 2H, C*H*CH$_3$), 1.25–1.16 (m, 2H, CHCH_2CH), 1.06 (d, ^3J(H,H)=6.5 Hz, 3H, *CH*$_3$), 1.05–0.95 (m, 2H, CHCH_2CH), 0.98 (d, ^3J(H,H)=6.4 Hz, 3H, *CH*$_3$), 0.92 (d, ^3J(H,H)=6.7 Hz, 3H, CH_3), 0.83 (d, ^3J(H,H)=6.8 Hz, 3H, *CH*$_3$), 0.1 (s, 3H, *TBS*), 0.09 (s, 3H, *TBS*), −0.04 (s, 6H, *TBS*) ppm.

4.1.7. Triene-iodide 7. Anhydrous $CrCl_2$ (1.9 g, 0.015 mol) was suspended in THF (25 mL) under an argon atmosphere. A solution of 2,4-hexadienal, **10** (0.3 mL, 2.72 mmol) and iodoform (1.5 g, 3.81 mmol) in THF (13.6 mL) was added drop-wise to the suspension at 0 °C via cannula. After stirring at 0 °C for 1 h the reaction was completed (TLC), the mixture was filtered through Celite and washed with Et_2O (50 mL). The combined filtrates were washed with water (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography (Al_2O_3, Hexane) to afford the iodide, **7** (510 mg, 2.31 mmol; 85%, mixture of isomers *E*/*Z* 2:1) as a yellow solid. R_f=0.82 (Hexane); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.51–7.41 (m, 1H), 7.18–7.06 (m, 1H), 7.02 (dd, ^3J(H,H)=14.3, 14.3 Hz, 1H), 6.83–6.74 (m, 1H), 6.71 (dd, ^3J(H,H)=10.0, 10.0 Hz, 1H), 6.57–6.48 (m, 1H), 6.44 (dd, ^3J(H,H)=14.9, 14.9 Hz, 1H), 6.38–6.08 (m, 7H), 6.08–5.95 (m, 4H), 5.93–5.76 (m, 3H), 5.75–5.60 (m, 3H), 1.79 (d, ^3J(H,H)=6.8 Hz, 3H, *CH*$_3$), 1.76 (d, ^3J(H,H)=7.0 Hz, 3H, *CH*$_3$), 1.83–1.75 (m, 6H, *CH*$_3$) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ 145.4, 138.4, 137.3, 133.8, 132.8, 132.3, 132.0, 131.7, 131.5, 130.9, 129.8, 129.6, 129.5, 129.2, 128.7, 128.6, 128.3, 127.5, 81.9, 81.2, 78.4, 77.5, 29.7, 18.5 ppm.

4.1.8. Alcohol 21a. To a solution of alcohol **20a** (380 mg, 1.011 mmol) in DMSO (7.2 mL) was added IBX (1.38 g, 3.225 mmol) at room temperature under argon an atmosphere. After stirring for 2 h the reaction was quenched with water (5 mL) and AcOEt (5 mL). The iodosocarboxylic acid, which precipitated as a white amorphous solid, was removed by filtration through Celite. The filtrate was extracted with AcOEt (2×10 mL) and the combined organic layers were washed with saturated $NaHCO_{3aq}$ (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was subjected to flash chromatography (SiO_2, Hexane/AcOEt 8:2) to afford the corresponding aldehyde (mixture of two diastereoisomers, ratio 1:1; 334 mg, 0.892 mmol; 88%) as yellow oil. R_f=0.40 (Hexane/AcOEt 7:3); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 9.53 (d, ^3J(H,H)=2.3 Hz, 1H, C*H*O), 9.52 (d, ^3J(H,H)=2.3 Hz, 1H, C*H*O), 7.22 (d, ^3J(H,H)=8.6 Hz, 2H, Ar*H*), 7.21 (d, ^3J(H,H)=8.6 Hz, 2H, Ar*H*), 6.87 (d, ^3J(H,H)=8.6 Hz, 2H, Ar*H*), 6.86 (d, ^3J(H,H)=8.6 Hz, 2H, Ar*H*), 5.12 (d, ^2J(H,H)=2.4 Hz, 1H, =CH_2), 5.09 (d, ^2J(H,H)=2.4 Hz, 1H, =CH_2), 5.08–5.05 (m, 2H, =CH_2), 4.48 (d, ^3J(H,H)=11.5 Hz, 1H, OCH_2Ar), 4.47 (d, ^3J(H,H)=11.5 Hz, 1H, OCH_2Ar), 4.28 (d, ^3J(H,H)=11.5 Hz, 2H, OCH_2Ar), 4.19 (s, 3H, OCH_3), 4.15 (s, 3H, OCH_3), 4.12 (d, ^3J(H,H)=6.9 Hz, 1H, C*H*OPMB), 4.10 (d, ^3J(H,H)=6.9 Hz, 1H, C*H*OPMB), 3.81 (s, 3H, Ar-OCH_3), 3.80 (s, 3H, Ar-OCH_3), 2.56–2.57 (m, 1H, C*H*CHO), 2.47–2.38 (m, 1H, C*H*CHO), 2.31–2.24 (m, 1H, CHCH_2CH), 2.04–1.93 (m, 2H, C*H*CHOPMB), 1.70–1.61 (m, 1H, CHCH_2CH), 1.20–1.09 (m, 2H, CHCH_2CH), 1.11 (d, ^3J(H,H)=6.9 Hz, 3H, *CH*$_3$), 1.07 (d, ^3J(H,H)=7.5 Hz, 3H, *CH*$_3$), 1.05 (d, ^3J(H,H)=6.9 Hz, 3H, *CH*$_3$), 0.82 (d, ^3J(H,H)=6.9 Hz, 3H, *CH*$_3$) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ 205.6, 205.0, 170.4, 170.1, 164.2, 159.8, 150.3, 150.2, 130.1, 130.0, 128.7, 114.3, 114.2, 93.3, 93.2, 77.1, 71.7, 71.5, 62.3, 62.2, 55.7, 44.7, 44.1, 38.0, 37.8, 35.9, 34.2, 30.1, 17.2, 16.9, 15.3, 15.1 ppm.

A solution of the previous aldehyde (230 mg, 0.614 mmol) and freshly prepared vinyl-iodide **7** (338 mg, 1.53 mmol) in THF/DMSO (5.4 mL/2.4 mL) was treated under an argon atmosphere with $CrCl_2$ (798 mg, 6.148 mmol) and $NiCl_2$ (11.5 mg, 0.082 mmol) (thoroughly premixed and flame-dried in vacuo). After stirring for 12 h at room temperature, the reaction mixture was diluted with water (20 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, Hexanes/AcOEt/Et_3N 8:2:0.1) to afford alcohol **21a** (mixture of four diastereoisomers; 115 mg, 0.246 mmol; 40%) as colorless oil, along with recovered aldehyde (108 mg, 0.288 mmol; 47%). R_f=0.55 (Hexanes/AcOEt 7:3); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.25–7.18 (m, 32H, Ar*H*), 6.90–6.83 (m, 32H, Ar*H*), 6.59–6.41 (m, 3H), 6.41–5.89 (m, 60H), 5.89–5.44 (m, 30H), 5.44–5.26 (m, 3H), 5.16–4.97 (m, 32H, C=CH_2), 4.57–4.40 (m, 18H), 4.39–4.24 (m, 18H), 4.24–3.92 (m, 75H), 3.92–3.70 (m, 49H), 2.18–1.97 (m, 16H), 1.97–1.81 (m, 10H), 1.81–1.74 (m, 36H), 1.74–1.53 (m, 10H), 1.52–1.17 (m, 32H), 1.17–1.04 (m, 24H), 1.04–0.73 (m, 80H); FTIR (neat): $\bar{\nu}_{max}$ 3514, 3058, 3018, 2964, 2928, 2873, 2853, 1769, 1669, 1622, 1513, 1462, 1383, 1282, 1251, 1175, 1078, 1035, 1002, 977, 824, 740, 707 cm^{-1}.

4.1.9. Alcohol 21b. To a solution of alcohol **20b** (86 mg, 0.231 mmol) in DMSO (1.8 mL) was added IBX (130 mg,

0.462 mmol) at room temperature under an argon atmosphere. After stirring for 1.5 h the reaction was quenched with water (5 mL) and AcOEt (5 mL). The iodosocarboxylic acid, which precipitated as a white amorphous solid, was removed by filtration through Celite. The filtrate was extracted with AcOEt (2×10 mL) and the combined organic layers were washed with saturated $NaHCO_{3aq}$ (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was filtered through a small pad of SiO_2 (Hexane/AcOEt 8:2) to afford the corresponding aldehyde (73 mg) as yellow oil, which was subjected to the next step without further purification.

A solution of the aldehyde (73 mg, 0.197 mmol) and freshly prepared vinyl-iodide **7** (107 mg, 0.486 mmol) in THF/DMSO (1.73 mL/0.72 mL) was treated under an argon atmosphere with $CrCl_2$ (264 mg, 2.034 mmol) and $NiCl_2$ (11 mg, 0.0071 mmol) (thoroughly premixed and flame-dried in vacuo). After stirring for 12 h at room temperature, the reaction mixture was diluted with water (15 mL) and extracted with Et_2O (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (SiO_2, Hexanes/AcOEt/Et_3N 85:15:0.1) to afford **21b** (mixture of four diastereoisomers; 45 mg, 0.098 mmol; 50%) as colorless oil, along with recovered aldehyde (22 mg, 0.059 mmol; 30%). R_f=0.55 (Hexanes/AcOEt 7:3).

4.1.10. Alcohol 22. To a solution of alcohol **21a** (95 mg, 0.203 mmol) in Et_2O (8.6 mL) was added activated MnO_2 (1.51 g) and the mixture was stirred at room temperature for 3 h (TLC indicated the end of the reaction). The solution was filtrated through Celite, to remove MnO_2 and concentrated under reduced pressure to provide the corresponding trienone (82 mg, 0.180 mmol; 90%) as yellow oil, which was subjected to the next step without further purification. R_f=0.40 (Hexane/AcOEt 8:2); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.78–7.68 (m, 8H), 7.57–7.49 (m, 8H), 7.44–7.31 (m, 6H), 7.27–7.13 (m, 22H), 6.86 (dd, ^3J(H,H)=8.9, 9.9 Hz, 16H), 6.60–6.49 (m, 6H), 6.25–6.07 (m, 8H), 6.01–5.89 (m, 4H), 5.81–5.73 (m, 2H), 5.09 (d, ^2J(H,H)=2.5 Hz, 4H), 5.07 (d, ^2J(H,H)=2.2 Hz, 4H), 5.05–5.02 (m, 8H), 4.46 (d, ^3J(H,H)=10.9 Hz, 4H), 4.44 (d, ^3J(H,H)=11.2 Hz, 4H), 4.33–4.29 (m, 1H), 4.28 (d, ^3J(H,H)=10.5 Hz, 4H), 4.26 (d, ^3J(H,H)=11.4 Hz, 4H), 4.21–4.16 (m, 1H), 4.16 (s, 6H), 4.16 (s, 6H), 4.12 (s, 6H), 4.12 (s, 6H), 4.10–4.03 (m, 6H), 3.80 (s, 12H), 3.79 (s, 12H), 2.94–2.79 (m, 6H), 2.35–2.25 (m, 2H), 1.93–1.77 (m, 4H), 1.84 (d, ^3J(H,H)=6.9 Hz, 24H), 1.77–1.57 (m, 10H), 1.50–1.32 (m, 6H), 1.21–1.10 (m, 2H), 1.11 (d, ^3J(H,H)=6.9 Hz, 9H), 1.05 (d, ^3J(H,H)=6.9 Hz, 9H), 1.02 (d, ^3J(H,H)=6.4 Hz, 3H), 0.99–0.82 (m, 14H), 0.79 (d, ^3J(H,H)=6.9 Hz, 9H) ppm; ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ 143.5, 143.2, 142.7, 142.5, 136.0, 135.9, 131.8, 131.7, 131.3, 130.0, 129.9, 129.4, 129.3, 128.8, 128.6, 128.5, 127.5, 127.2, 114.2, 93.1, 92.9, 71.7, 71.5, 67.9, 66.0, 62.3, 62.2, 55.7, 42.9, 42.1, 40.3, 38.5, 38.3, 38.1, 36.4, 31.0, 30.9, 30.1, 19.6, 19.1, 19.0, 18.8, 17.6, 16.9, 14.1 ppm; HRMS (ESI) calculated for $C_{28}H_{34}O_6$ ([M+Na]$^+$): *m*/*z* 489.2245, found 489.2244.

A solution of the previous *p*-methoxy benzyl ether (82 mg, 0.180 mmol) in DCM/0.5% $NaHCO_{3aq}$ (9:1; 5.8 mL) was treated with DDQ (120 mg, 0.528 mmol) at 0 °C for 2.5 h. The reaction mixture was filtered through a short pad of silica gel and washed with Hexanes/AcOEt/Et_3N (7:3:0.1; 20 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (SiO_2, Hexane/AcOEt/Et_3N 8:2:0.1) to afford **22** (mixture of two diastereoisomers; 23 mg, 35%) as colorless oil. R_f=0.35 (Hexanes/AcOEt 7:3); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.40–7.27 (m, 3H), 7.00–6.89 (m, 5H), 6.89–6.80 (m, 2H), 6.73–6.64 (m, 2H), 6.64–6.52 (m, 4H), 6.39–6.25 (m, 8H), 6.25–6.09 (m, 16H), 6.05–5.90 (m, 4H), 5.86–5.72 (m, 4H), 5.08 (br s, 16H), 4.32–4.03 (m, 4H), 4.14 (br s, 24H), 3.82–3.76 (m, 1H), 3.68–3.60 (m, 1H), 3.47–3.37 (m, 2H), 2.97–2.80 (m, 8H), 1.92–1.80 (m, 24H), 1.80–1.71 (m, 8H), 1.45–1.38 (m, 8H), 1.29–1.23 (m, 8H), 1.17–1.08 (m, 24H), 1.04–0.95 (m, 24H); HRMS (ESI) calculated for $C_{20}H_{26}O_5$ ([M+Na]$^+$): *m*/*z* 369.1672, found 369.1673.

4.1.11. Alcohol 22. (One pot oxidation-deprotection of **21a**.) A solution of the crude trienone (90 mg, 0.193 mmol) in DCM/0.5% $NaHCO_{3aq}$ (9:1; 6.4 mL) was treated with DDQ (131.4 mg, 0.579 mmol) at 0 °C for 2.5 h. The reaction mixture was filtered through a short pad of silica gel and washed with Hexanes/AcOEt/Et_3N (7:3:0.1; 20 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (SiO_2, Hexane/AcOEt/Et_3N 8:2:0.1) to afford alcohol **22** (16 mg, 25%) as colorless oil.

4.1.12. Diketone 5 from 22. A solution of alcohol **22** (20 mg, 0.058 mmol) in DCM (1.3 mL) was treated with Dess–Martin periodinate (30 mg, 0.071 mmol) at ambient temperature for 1 h. The reaction was quenched with saturated $Na_2S_2O_3$ and stirred for 30 min. The mixture was separated and the aqueous layer was extracted with DCM (2×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hexanes/AcOEt/Et_3N 8:2:0.1) to afford **5** as colorless oil (mixture of *E*/*Z* isomers; 19 mg, 95%). R_f=0.32 (Hexanes/AcOEt 7:3); $[\alpha]_D^{2.5}$ −20.1° (*c* 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.26 (dd, ^3J(H,H)=10.7, 15.0 Hz, 1H), 6.59 (dd, ^3J(H,H)=10.8, 14.8 Hz, 1H), 6.28–6.09 (m, 3H), 6.01–5.89 (m, 1H), 5.27 (br d, ^2J(H,H)=2.7 Hz, 1H), 5.21 (br d, ^2J(H,H)=2.7 Hz, 1H), 4.12 (s, 3H), 3.71–3.59 (m, 1H), 2.81 (ddq, ^3J(H,H)=6.9, 6.9, 6.9 Hz, 1H), 2.27–2.16 (m, 1H), 1.84 (br d, *J*=6.0 Hz, 3H), 1.37–1.25 (m, 1H), 1.15 (d, ^3J(H,H)=7.1 Hz, 3H), 1.13 (d, ^3J(H,H)=7.0 Hz, 3H); (ZEE, partial) 7.32 (dd, ^3J(H,H)=11.4, 15.0 Hz, 1H), 6.94 (dd, ^3J(H,H)=12.3, 15.1 Hz, 1H), 6.38–6.28 (m, 1H), 5.81–5.73 (m, 1H), 1.87 (br d, ^3J(H,H)=7.2 Hz, 3H); HRMS (ESI) calculated for $C_{20}H_{24}O_5$ ([M+H]$^+$): *m*/*z* 337.1515, found 337.1518.

4.1.13. Diketone 5 from 21b. To a solution of silyl ether **21b** (32 mg, 0.069 mmol) in THF (0.23 mL) was added TBAF (0.21 mL of 1 M solution in THF, 0.207 mmol) at 0 °C. After 5 min the ice bath was removed, the reaction mixture was stirred for additional 1 h at ambient temperature (TLC indicated the end of the reaction). The reaction mixture was extracted with AcOEt (2×5 mL). The combined organic layers were washed with saturated NH_4Cl_{aq} (5 mL) and brine (3 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was subjected to flash

chromatography (SiO_2, Hexane/AcOEt 1:1) to afford the corresponding diol (mixture of diastereoisomers; 20 mg, 0.057 mmol; 83%) as colorless oil. R_f=0.45 (Hexanes/AcOEt 1:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.60–6.46 (m, 1H), 6.38–5.95 (m, 31H), 5.83–5.50 (m, 15H), 5.49–5.28 (m, 1H), 5.18–4.98 (m, 16H), 4.62–4.28 (m, 10H), 4.20–3.92 (m, 30H), 3.65–3.48 (m, 2H), 3.45–3.26 (m, 4H), 2.22–1.84 (m, 12H), 1.84–1.64 (m, 26H), 1.58–1.47 (m, 2H), 1.45–1.35 (m, 2H), 1.33–1.14 (m, 8H), 1.12–0.76 (m, 48H).

To a solution of the previous diol (18 mg, 0.052 mmol) in DMSO (0.4 mL) was added IBX (44 mg, 0.156 mmol) at room temperature under an argon atmosphere. After stirring for 1.5 h the reaction was quenched with water (1 mL) and AcOEt (1 mL). The iodosocarboxylic acid, which precipitated as a white amorphous solid, was removed by filtration through Celite. The filtrate was extracted with AcOEt (2×5 mL) and the combined organic layers were washed with saturated $NaHCO_{3aq}$ (4 mL) and brine (3 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was subjected to flash chromatography (SiO_2, Hexanes/AcOEt/Et_3N 8:2:0.1) to afford **5** as colorless oil (mixture of *E*/*Z* isomers; 15 mg, 0.044 mmol 85%).

4.1.14. Diels–Alder product 3. A solution of trienone **5** (5 mg, 0.015 mmol) in degassed toluene (2.5 mL; 0.006 M) was stirred at 100 °C in the presence of catalytic iodine under an argon atmosphere. After 3 h (TLC indicated no further conversion) the solvent was removed under reduced pressure and the residue was subjected to flash chromatography (SiO_2, Hexanes/AcOEt 8:2) to afford **3** (4 mg, 0.011 mmol, 75%). as colorless oil. R_f=0.45 (Hexanes/AcOEt 8:2); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.48 (dd, ^3J(H,H)=6.8, 16.8 Hz, 1H, C*H*═), 6.25 (dd, ^4J(H,H)=1.2 Hz, ^3J(H,H)=16.8 Hz, 1H, C*H*═), 5.86 (dt, ^3J(H,H)=3.1, 9.9 Hz, 1H, C*H*═), 5.67 (dt, ^3J(H,H)=2.4, 9.9 Hz, 1H, C*H*═), 3.91 (s, 3H, OCH_3), 3.48–3.42 (m, 1H, ═CHC*H*CH═), 3.16–3.08 (m, 1H, C*H*CH_3), 3.00–2.90 (m, 1H, COC*H*CH_3), 2.69–2.59 (m, 1H, C*H*CH_3), 2.40 (dd, ^2J(H,H)=14.4 Hz, ^3J(H,H)=7.9 Hz, 1H, CH*H*CHCH_3), 1.88 (ddd, ^3J(H,H)=4.2, 5.9 Hz, ^2J(H,H)=15.2 Hz, 1H, CHC*H*HCH), 1.82 (dd, ^3J(H,H)=4.6 Hz, ^2J(H,H)=14.4 Hz, 1H, C*H*HCHCH_3), 1.24–1.12 (m, 1H, CHCH*H*CH), 1.21 (d, ^3J(H,H)=6.8 Hz, 3H, CH_3), 1.19 (d, ^3J(H,H)=6.8 Hz, 3H, CH_3), 1.15 (d, ^3J(H,H)=7.3 Hz, 3H, CH_3).

Acknowledgments

Financial support co-funded by the General Secretariat for Research and Technology of the Hellenic Ministry of Development and the European Community is acknowledged along with the scholarship provided to A.D. Magos by the Institute of Physical Chemistry of N.C.S.R. “Demokritos”. We would also like to thank Dr. E. Pitsinos and Dr. A. Strongilos for their valuable discussions and comments as well as Professor A. Giannis for kindly offering his MS facilities.

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