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Evaluation of possible intramolecular [4+2] cycloaddition routes for assembling the central tetracyclic core of the potent marine antiinflammatory agent mangicol A

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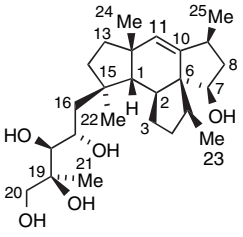
Abstract—A plan for enantioselective construction of the mangicol A framework by means of intramolecular Diels–Alder cycloaddition is outlined. First to be assembled is the enantiopure cyclopentenecarboxylic acid **16**. Of the several approaches targeting the 1,3-diene component **56**, only that involving palladium-catalyzed enyne cyclization proved successful. Following the coupling of **16** to **56**, we were unable to bring about any detectable level of ($4\pi+2\pi$) cycloaddition. Activation of the diene by incorporation of an $OSiEt_3$ substituent on a terminal sp^2-hybridized center likewise proved unsuccessful. Further facilitation was sought in the form of cyclopentenonecarboxylate **66**. However, thermal activation, Lewis acid catalysis, and high-pressure conditions proved ineffective and did not lead to C–C bond formation. These studies serve to underscore the extent to which steric complications can complicate matters and the extent to which they must be skirted to arrive at the title compound.

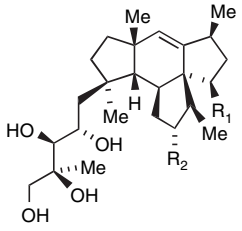
1. Introduction

Two reports emanating from the Fenical group in 1998[1] and 2000[2] described the isolation, structural elucidation, biological properties, and biosynthesis of a new class of spirotetracyclic sesterterpenoids named mangicols **A**–**G** (**1**–**7**). The highly complex carbon framework of these fascinating metabolites is generated by a marine fungus believed to be *Fusarium heterosporum*, which was collected from driftwood discovered in a mangrove habitat at Sweetings Cay in the Bahamas. Also identified were the neomangicols **8**–**10** whose potent cytotoxic and antibiotic activity profiles differentiate them from **1**–**7**. Mangicol A (**1**) has shown very significant antiinflammatory activity in the phorbol myristate acetate (PMA) mouse ear edema assay.[3] On the basis of its medicinal potential, **1** has come to be regarded as an attractive target for total synthesis.[4]

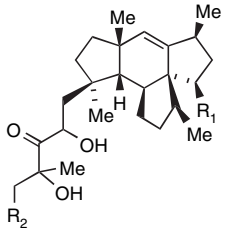
Any plan for the de novo elaboration of **1** must take into account its intertwined rings and 11 stereogenic centers, several of which are quaternary in nature. The biogenetic proposal that has been advanced[2] is of little value in suggesting an avenue by which to attack this challenging problem. To us, the presence of a central six-membered ring suggested the possible utilization of a protocol based upon an intramolecular (4+2) reaction.



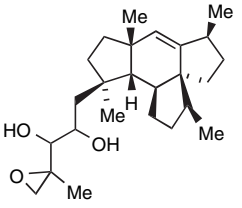
1, Mangicol A



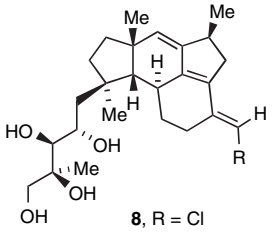
2, Mangicol B: R_1 = H, R_2 = OH
3, Mangicol C: R_1 = H, R_2 = H



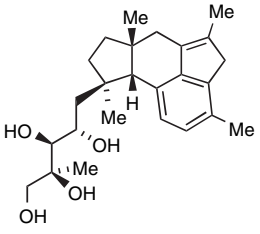
4, Mangicol D: R_1 = OH, R_2 = H
5, Mangicol E: R_1 = H, R_2 = OH
6, Mangicol F: R_1 = H, R_2 = H



7, Mangicol G



8, R = Cl
9, R = Br



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Keywords: Mangicols; Pd-catalyzed enyne cyclization; Intramolecular aldol cyclizations; Chiral nonracemic substituted cyclopentadienones; Enantioselective diene synthesis.
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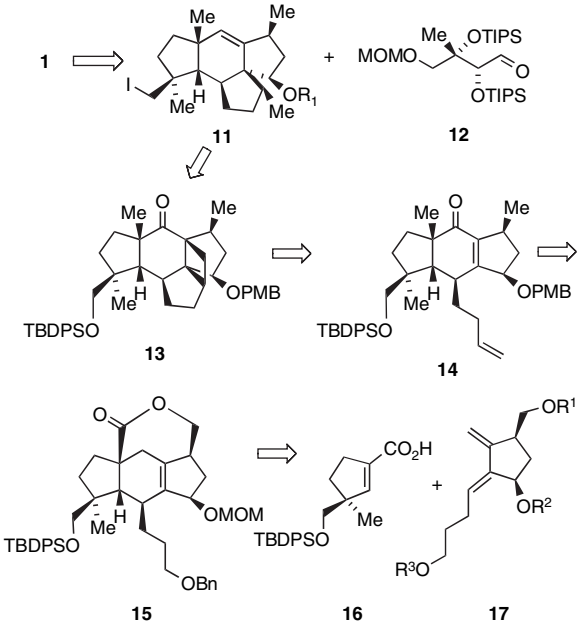
This type of cycloaddition is recognized to be amenable to catalysis by enzymes known collectively as Diels–Alderases,[5] and to play a useful role in select biosynthetic applications.[6] In this light, the source of our inspiration converges nicely with the general theme of this Symposium-in-Print.

2. Synthetic analysis

From the outset, it was envisioned that the final diastereoselective addition of an organometallic intermediate generated from iodide **11** to aldehyde **12**[7] would result in eventual arrival at the target molecule (Scheme 1).

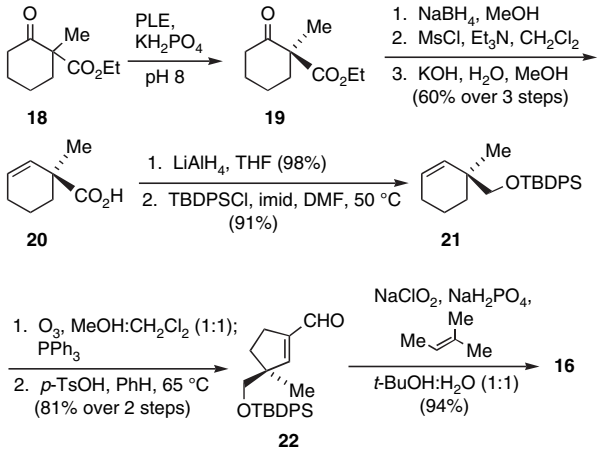


Scheme 1.

The framework of **11** was to be made available by samarium diiodide-promoted cleavage of the cyclobutane ring in **13**[8] followed by a Shapiro reaction.[9] A key feature of this reductive step is its capability for unveiling the C(23) methyl group in its proper configuration. Cyclobutane **13** was to stem from an intramolecular photochemical (2+2) cycloaddition involving the terminal alkene and α,β-unsaturated ketone subunits resident in **14**.[10,11] It was further conjectured that **14** would be accessible by suitable chemical modification of **15**, the construction of which was to be realized by thermally induced or Lewis acid-catalyzed cycloaddition involving the ester to be formed from **16** and **17** or activated forms thereof. As will be seen, provision was made for the anticipated need that modest structural variations might be necessary at this stage. Should the cyclization proceed as required, the lactone bridge was to serve the role of progenitor to the two cis-related angular methyl groups positioned at C(9) and C(12).

2.1. Construction of (+)-cyclopentenecarboxylic acid 16

Pig liver esterase-mediated kinetic resolution of the racemic keto ester **18** made available the desired *S*-enantiomeric **19** at the 91% ee level as determined by chiral HPLC[12] (Scheme 2). The action of sodium borohydride on **19** gave rise to two diastereomeric alcohols, which converged to the identical cyclohexenecarboxylic acid **20** by mesylate-mediated elimination with subsequent saponification.[13] Treatment of **20** with lithium aluminum hydride furnished the primary carbinol that was protected as the *tert*-butyldiphenylsilyl ether **21**. At this point, the stage was set for a ring cleavage-reclosure sequence[14] involving ozonolysis to the dialdehyde and *p*-toluenesulfonic acid-promoted intramolecular aldolization. As a result of the substitution plan, only that reaction channel leading to **22** is operative (81% for the two steps). Oxidation of **22** to **16** was readily and efficiently accomplished with sodium chlorite.[15]



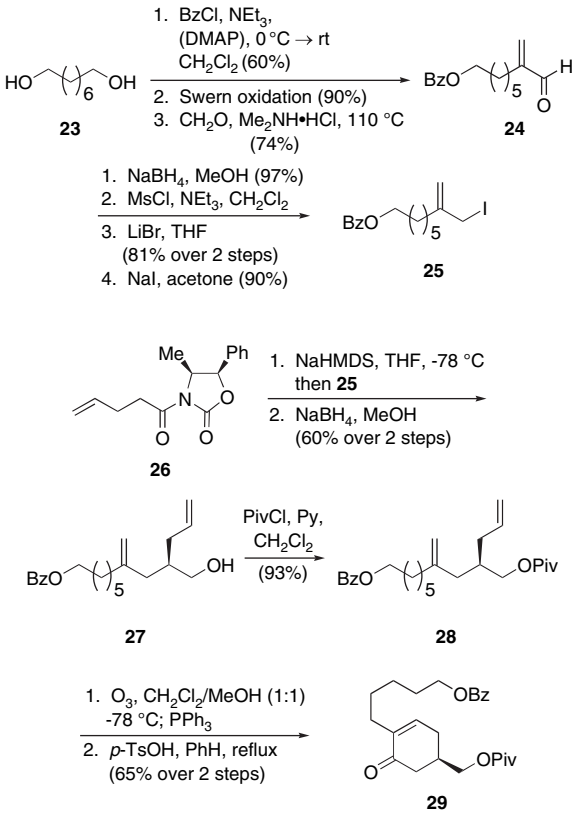
Scheme 2.

2.2. Exploration of a possible enantioselective route to a diene of type 17

This phase of our investigation began with the generation from commercially available 1,8-octanediol (**23**) of its monobenzoylated derivative. The latter was subjected to Swern oxidation and homologated to produce α,β-unsaturated aldehyde **24** via an improved Mannich reaction[16] (Scheme 3). The reduction of **24** with sodium borohydride gave rise to the primary carbinol, which was sequentially transformed via the mesylate and bromide into allylic iodide **25**. The Finkelstein displacement step[17] was performed immediately prior to the utilization of **25** in subsequent chemical maneuvers.

Next to be explored was the enantioselective alkylation of the sodium enolate derived from **26**[18] with **25**. In this instance, C–C bond formation proceeded very smoothly, thus allowing direct reductive cleavage of the chiral oxazolidinone with sodium borohydride in methanol. The configuration depicted for alcohol **27** formed in this two-step sequence (de>95%) is founded on extensive prior precedent.[19] Esterification of the unmasked hydroxyl group in **27** with pivaloyl chloride afforded **28** (93%). With this intermediate in hand, its ozonolytic conversion to a keto aldehyde and ensuing acid-promoted aldol cyclization to generate cyclohexenone **29** were accomplished without event.

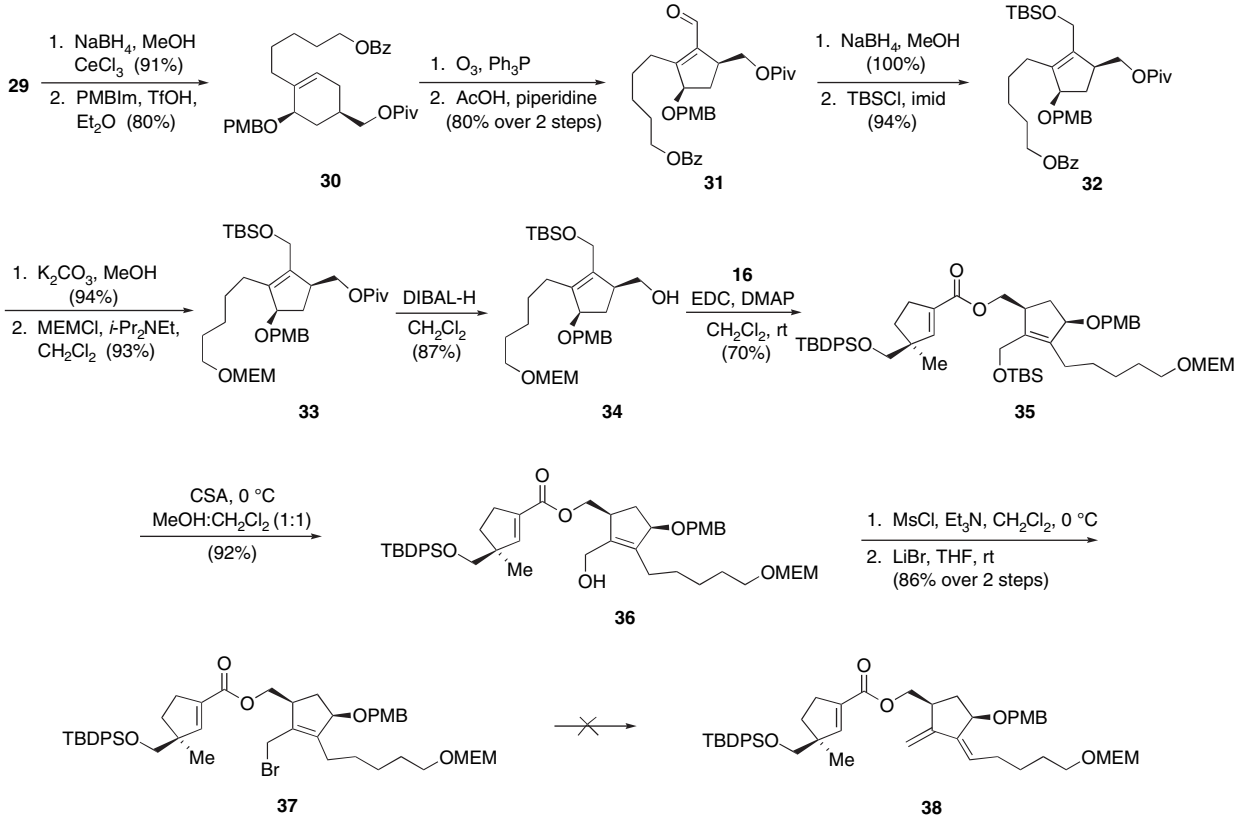
Reduction of enone **29** under Luche conditions[20] gave rise to the equatorial alcohol[21] as the only detectable product (Scheme 4), where protection as the PMB ether was affected



Scheme 3.

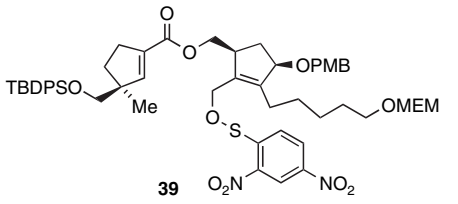
by way of trichloroacetimidate technology.[22] Aldehyde **31** was in turn produced by careful ozonolysis followed directly by aldol ring closure in the presence of piperidine and acetic acid.[14] The primary alcohol obtained from **31** by borohydride reduction reacted smoothly with *tert*-butyldimethylsilyl chloride and imidazole to furnish the quadruply functionalized (−)-cyclopentene **32**. When stirred with potassium carbonate in methanol at rt, this intermediate was efficiently debenzoylated, thus allowing replacement with an MEM protecting group at that site as in **33**. Subsequent removal of the pivaloyl ester with DIBAL-H resulted in formation of the key building block **34** whose role was to be coupled to **16**. The utilization of EDC[23] was quickly found to be well suited to the generation of ester **35**. In line with expectation, the OTBS group in **35** could subsequently be cleaved selectively without incurring unwanted side reactions.[24] This step lent itself to the uncomplicated generation of alcohol **36** (92%), whose hydroxyl group proved quite amenable to activation as the bromide **37** as well as other derivatives.

Quite unexpectedly, all attempts to accomplish the conversion of **37** into diene **38** were to no avail. Recovery of unchanged starting material or complete decomposition[25] was the alternative encountered. In an effort to bypass this complication, **36** was treated with 2,4-dinitrobenzenesulfenyl chloride in the expectation that **39** so formed would undergo [1,3] sigmatropic shift to generate the sulfoxide that would, in turn, experience elimination.[26] However, the



Scheme 4.

intended sequential transformation did not occur and no allylic alcohol was detected.[27]



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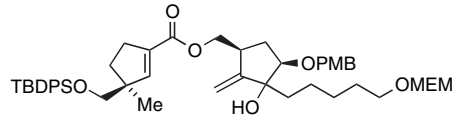
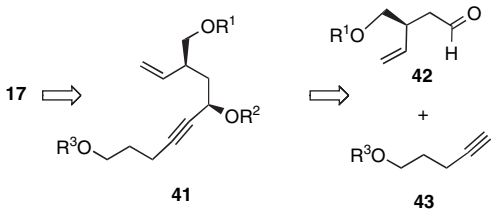


40

We also undertook exploration of the conversion of **36** to the rearranged allylic alcohol **40** via a three-step sequence involving Sharpless epoxidation,[28] treatment of the resulting epoxy alcohol with triphenylphosphine, imidazole, and iodine,[29] and finally warming to 40 °C in water. While this conversion proceeded satisfactorily, **40** resisted xanthate formation at every turn,[27] thereby thwarting its eliminative transformation into **38**. At this point, the decision was made to undertake an alternate approach to subunit **17**.

2.3. Implementation of alternative palladium-mediated diene construction

The observations detailed above led us to entertain a series of retrosynthetic disconnections within **17** that would involve somewhat less complex intermediates (Scheme 5). More specifically, the applicability of an appropriate transition metal-mediated cycloisomerization as a direct route from **41** to **17** could constitute a more straightforward route to its generation. Success here would open up the possibility that precursor compounds such as **42** and **43**[30] might also contribute to greater expediency. To this end, lactone **44**, readily available in two steps from ascorbic acid,[31] was used to define the absolute configuration of **45** via an established one-pot procedure[32] (Scheme 6). The ester was reduced with DIBAL-H and the carbinol so formed was protected as the *tert*-butyldiphenylsilyl ether. Although attempts to hydrolyze the acetonide in **46** chemoselectively with methanolic HCl caused concomitant desilylation, diol **47** could be secured in 90% yield following treatment with 80% acetic acid at rt. Continued success was realized with site-specific introduction of a second OTBDPS group as long as coupling to the silyl chloride was performed in THF at −10 °C.[33] Subsequent acetylation delivered **48** in excellent overall yield.



Scheme 5.

Application of Ireland–Claisen conditions[34] to **48** resulted in smooth conversion to the silyl ether, direct hydrolysis of which with 8 N lithium hydroxide in THF and ensuing exposure to methyl iodide and potassium carbonate gave rise to **49** in 73% yield over the three steps. Advantage was next taken of the ease of conversion of **49** to aldehyde **50**. The subsequent hurdle was the enantioselective 1,2-addition of 5-benzyloxy-1-pentyne[30] to **50**. Unfortunately, the standard conditions reported by Carreira et al.[35] proved inapplicable to our system. Attempts to bring about effective scale-up of the reaction (to a maximum of 1.8 g) furnished only a 1:1 mixture of diastereomers.

To overcome this problem, the mixture of alcohols was oxidized to **51** by means of activated manganese dioxide. At this juncture, recourse was made to the *R*-CBS reagent,[36] whose reactivity potential could be commandeered to deliver the *R* alcohol quantitatively with a de=88%.

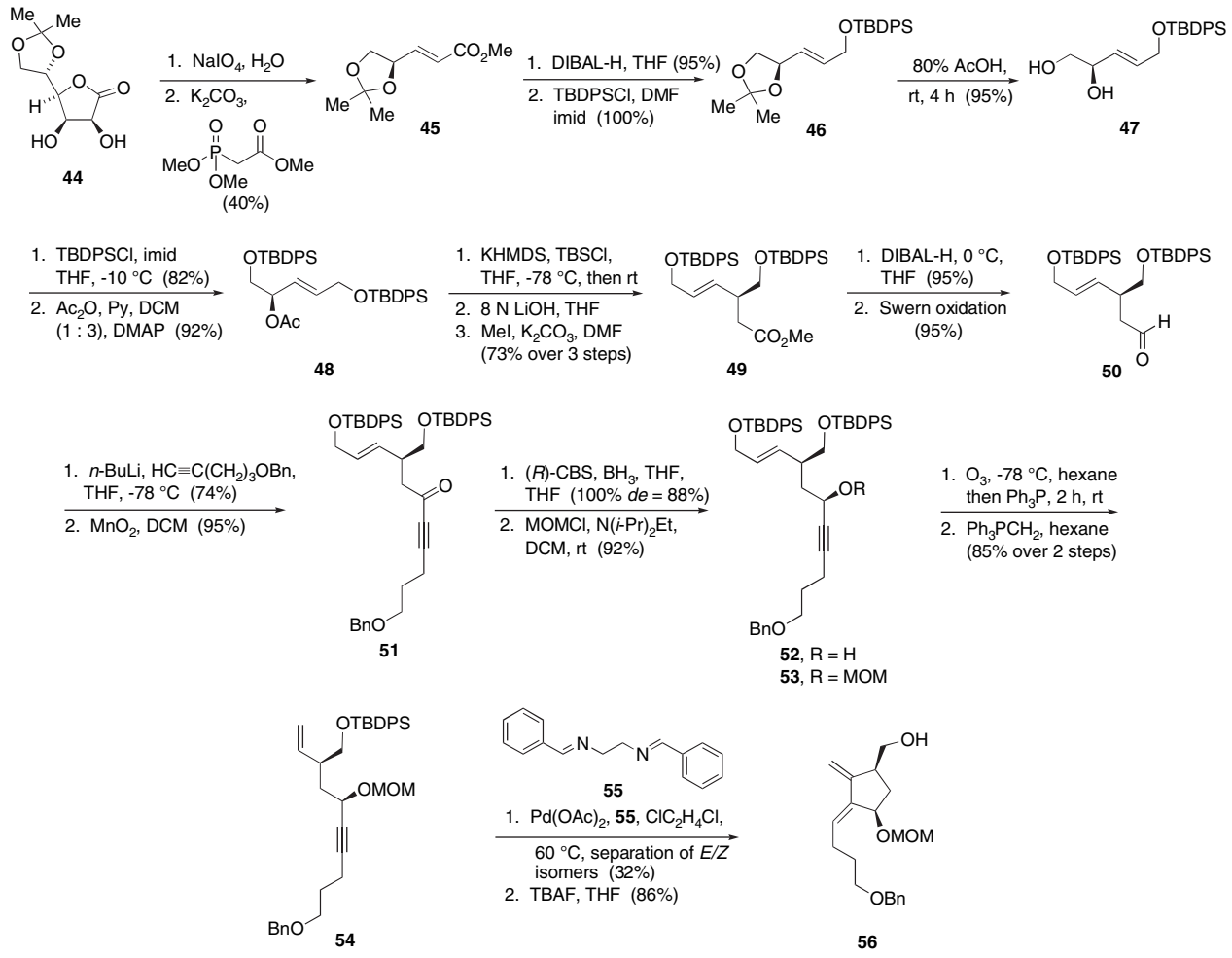
Formation of the MOM ether **53** allowed ozonolytic cleavage of the olefinic bond to be performed. Since the resulting aldehyde is prone to β-elimination, the Wittig olefination with methylenetriphenylphosphorane must be performed under controlled conditions. A particularly attractive option is to conduct the ozonolysis in hexane at −78 °C, to stir with triphenylphosphine at rt for 2 h, and to introduce the $Ph_3P{=}CH_2$ reagent in ether without further delay.

The availability of **54** led us to explore the possibility for palladium-catalyzed cycloisomerization.[37] Under conditions recommended for comparable applications[38,39] (Table 1), three catalysts were examined in a move to achieve optimization. Unsatisfactory conversion was observed in the first three runs. Recourse instead of palladium(II) acetate in combination with *N,N*-bis(benzylidene)ethylenedimine (**55**) as the ligand in 1,2-dichloroethane solution did prove effective (*E*:*Z*=4:1). The minimum temperature to realize complete conversion was 60 °C. Subsequent treatment with TBAF generated **56** without incident.

This result made possible the opportunity to esterify **56** with **16**, thereby generating **57**, the substrate desired for validation of its Type II Diels–Alder reactivity[40] (Scheme 7). We next sought to transform **57** into **58** by purely thermal means (e.g., toluene, 220 °C, 7 h) or under milder Lewis acid-catalyzed conditions such as with Et_2AlCl in CH_2Cl_2 at rt. Under no circumstance was conversion into **58** seen. This body of experiments provided convincing evidence that conditions for intramolecular cycloaddition within **57** as in **57'** were not likely to be found. Our attention was consequently directed instead to the incorporation of activated components.

2.4. Development of routes to a diene and a dienophile with intent to enhance reactivity

We hoped to solve the total synthesis problem via the intermediacy of either a substituted cyclopentenone or a 1-silyloxybutadiene derivative. It is widely recognized that rendering dienophiles more electron-deficient and dienes more electron-rich contributes in utilitarian fashion because of decreases in HOMO–LUMO gaps. With the availability of alcohol **36**, it proved an easy matter to achieve oxidation to the aldehyde level with manganese dioxide as a prelude to



Scheme 6.

O-silylation as in **60** (Scheme 8). At this point, it quickly became apparent that the hurdle of engaging **60** in intermolecular cycloaddition was not to be surmounted. All attempts to achieve cyclization under basic, acidic, purely thermal, or high-pressure conditions failed to come to fruition.[41] Simply stated, **60** proved to be too sensitive for our purposes. When intermolecular variants designed to avoid the incorporation of a lactone bridge were also found to lead to decomposition,[42] dienophile activation was pursued.

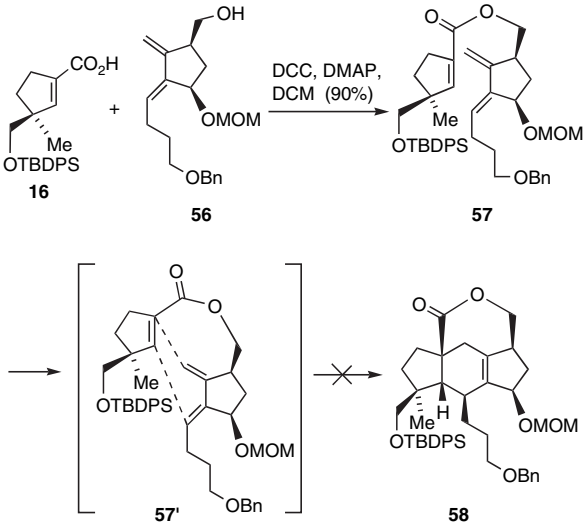
To arrive at the levorotatory keto ester **62**, the racemic cyclopentanonecarboxylate **61** was kinetically resolved by application of Brown's (−)-DIPCl methodology[43] (Scheme 9). Cyclopentene **63** was subsequently generated by mesylate-mediated dehydration.

After adjustment of the substitution plan about the quaternary carbon as in **64**, sequential allylic oxidation[44] and α-iodination[45] followed to provide **65**. Finally, the carbomethoxy group was incorporated in palladium-catalyzed carbonylation.[46] The diactivated dienophile **66** was isolated in 61% yield.

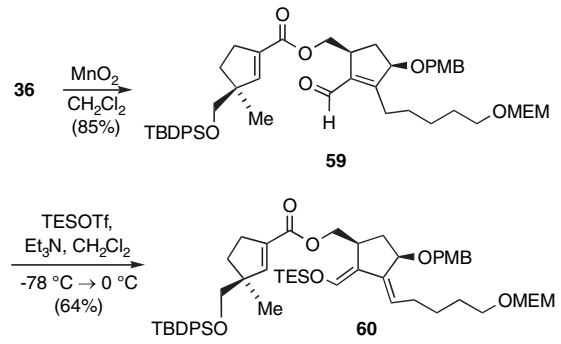
The recalcitrance of **66** to function as a dienophile in intermolecular Diels–Alder reactions involving **67** soon became apparent. Decomposition and/or polymerization were clearly operative under conditions involving either purely thermal conditions (e.g., toluene, sealed tube, 160 °C),[47] catalysis by select Lewis acids (e.g., $AlBr_3$/$AlMe_3$, −10 to 0 °C),[48] or high-pressure conditions (e.g., CH_2Cl_2, rt).[49]

Table 1. Conditions employed for the Pd(II)-catalyzed cycloisomerization of **54**

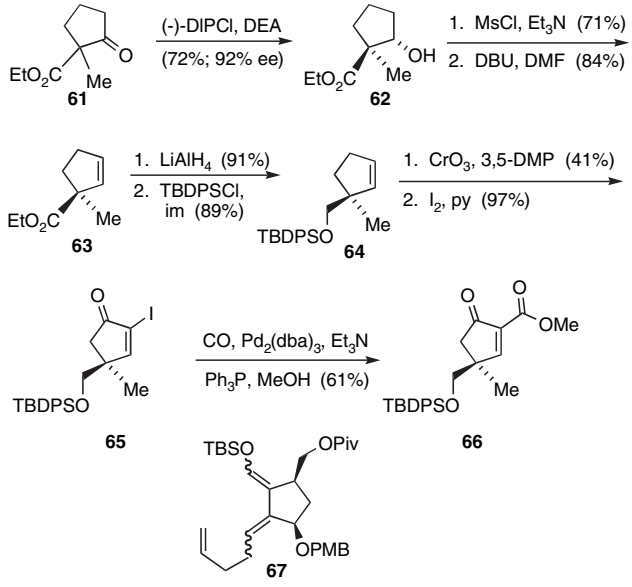
Run	Catalyst	Ligand	Additive	Solvent	Time, h	Temperature, °C	% Conversion	*E/Z* ratio
1	$Pd_2(dba)_3 \cdot CHCl_3$	Ph_3P	HOAc	Benzene	48	60	30	—
2	$Pd_2(dba)_3 \cdot CHCl_3$	Ph_3P	HOAc	Benzene	24	90	40	—
3	$Pd[P(o\text{-tol})_3]_2(OAc)_2$	—	—	$ClCH_2CH_2Cl$	48	60	0	—
4	$Pd(OAc)_2$	**55**	—	Benzene	22	63	100	2:1
5	$Pd(OAc)_2$	**55**	—	$ClCH_2CH_2Cl$	22	63	100	3–4:1



Scheme 7.



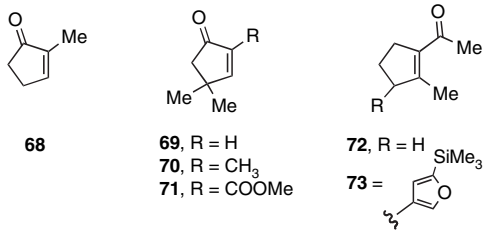
Scheme 8.



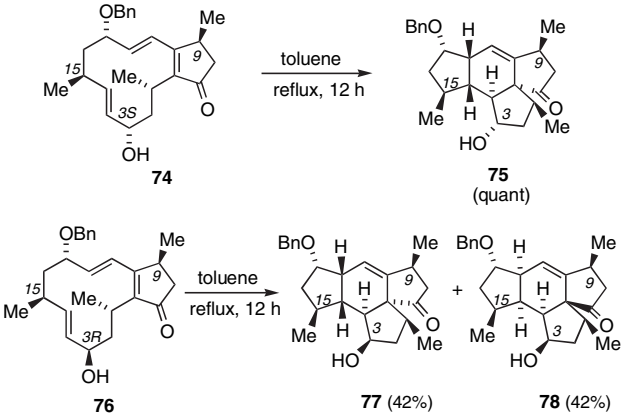
Scheme 9.

3. Overview

The history dealing with the participation of substituted 2-cyclopentenones and other electron-deficient cyclopentenes in intermolecular (4+2) cycloadditions is a checkered one. In general, this compound class performs poorly and as a result has not been made recourse to with a great deal of frequency. The presence of a 2-methyl group as in **68** has no apparent deleterious consequences[50] relative to the parent system.[51] In contrast, exceptionally low reactivity has been noted for **69**[52] and **70**.[53] Their complete failure to react has been attributed to the effective shielding brought on by the quaternary nature of C-4. The significant transition state destabilizing effect operative in these substrates can be offset to some degree by the proper positioning of a carbomethoxy group as in **71**.[47,53] Seemingly more advantageous yet is the acetylcyclopentene motif present in **72** and **73**,[48] and esters of similar type.[54]



Although intramolecular Diels–Alder cycloadditions have long been recognized to offer heightened reactivity advantages stemming from favorable entropic contributions,[55] these effects were not apparent in transition states typified by **57′**. In contrast, Uemura and co-workers found **74** and **76** to cyclize efficiently in refluxing toluene with formation of the mangicol core (Scheme 10).[4] An added bonus was the co-discovery of a remarkable interrelationship between stereoselectivity and the configuration of the secondary hydroxyl group. Both possible *endo* avenues of approach are clearly subject to subtle nonbonded steric interactions. Not withstanding, the kinetic advantages associated with the preformation of a 12-membered cyclic trienone framework are notable and promising.



Scheme 10.

The studies that have been detailed above serve to underscore the sorts of steric complications that may beset intramolecular cycloaddition reactions. These complexities obviously need to be avoided, and we hope to report on one or more alternative synthetic routes to mangicol A in the near future.

4. Experimental

4.1. (*S*)-1-Methyl-2-oxo-cyclohexanecarboxylic acid ethyl ester (19)

To a rapidly stirred solution of racemic **18** (10.4 g, 0.06 mol) in KH_2PO_4 buffer (250 mL, 0.1 M) was added pig liver esterase (0.17 g, 20,000 Units) at pH 8.0 and rt. The mixture was stirred for 24 h while the pH was maintained at 8.0 by pH stat-controlled addition of 1.0 N aqueous NaOH solution, and extracted with CH_2Cl_2 (2×800 mL). The combined organic phases were dried and evaporated to give a residue that was purified by column chromatography on silica gel (elution with 10:1 hexane–ethyl acetate) to give 3.16 g (61%) of **19** as a colorless liquid; IR (neat, cm^{-1}) 1714, 1260, 1158; ^1H NMR (300 MHz, $CDCl_3$) δ 4.24–4.15 (m, 2H), 2.55–2.45 (m, 3H), 2.04–2.02 (m, 1H), 1.75–1.64 (m, 3H), 1.51–1.44 (1H), 1.29 (s, 3H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 172.2, 60.4, 56.3, 39.9, 37.5, 26.9, 22.0, 20.5, 13.4; HRMS ES *m/z* $(M+Na)^+$ calcd 207.0992, obsd 207.1000; $[\alpha]_D^{25}$ +109.0 (*c* 1.0, $CHCl_3$).

4.2. (*S*)-1-Methylcyclohex-2-enecarboxylic acid ethyl ester (20)

To a cold (−78 °C) suspension of $NaBH_4$ (1.23 g, 32.6 mmol) in anhydrous MeOH (30 mL) was added dropwise a solution of **19** (5.0 g, 27.2 mmol) in the same solvent (50 mL). The mixture was stirred at −78 °C for 2 h, quenched with 10% aqueous HCl solution (50 mL), warmed to rt, and stirred for 15 min. This solution was extracted with CH_2Cl_2 (3×100 mL), and the combined organic phases were dried and evaporated to give a mixture of diastereomeric hydroxy esters.

To a cold (0 °C) solution of the above material in dry CH_2Cl_2 (100 mL) was added Et_3N (5.49 g, 54.3 mmol) and MsCl (6.22 g, 54.3 mmol) in sequence. The cloudy solution was stirred at 0 °C for 1.5 h before being quenched with 10% aqueous HCl (50 mL) and diluted with H_2O (100 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried and concentrated to give a mixture of mesylates as yellow oil.

To a solution of the mesylate mixture from above in MeOH (200 mL) and H_2O (25 mL) was added KOH (10.67 g, 190.19 mmol). The mixture was heated to 60 °C for 16 h, cooled to rt, evaporated under vacuum, and acidified to pH 1 by careful addition of 1 N HCl solution. The aqueous layer was extracted with CH_2Cl_2 (4×100 mL). The combined organic phases were dried and evaporated to leave a residue that was purified by column chromatography on silica gel (elution with 5:1 hexane–ethyl acetate) to give 2.28 g (60% over three steps) of **20** as a colorless liquid; IR (neat, cm^{-1}) 1697, 1296, 1188; ^1H NMR (250 MHz, $CDCl_3$) δ 5.85–5.67 (m, 2H), 2.20–2.14 (m, 1H), 2.05–1.98 (m, 2H), 1.70–1.66 (m, 2H), 1.53–1.48 (m, 1H), 1.32–1.24 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.7, 130.0, 128.3, 42.8, 32.6, 26.1, 24.6, 19.4; HRMS ES *m/z* $(M+Na)^+$ calcd 140.0832, obsd 140.0824; $[\alpha]_D^{25}$ −100.9 (*c* 1.2, $CHCl_3$).

4.3. *tert*-Butyl-((*S*)-1-methylcyclohex-2-enylmethoxy) diphenylsilane (21)

To a cold (0 °C) suspension of $LiAlH_4$ (1.25 g, 32.86 mmol) in dry THF (40 mL) was added a solution of **20** (2.0 g, 14.29 mmol) in dry THF (40 mL) via an addition funnel. After the addition was complete, the cold bath was removed and the reaction mixture was stirred at rt for 14 h, cooled to 0 °C, carefully quenched with 1 N NaOH solution (1.25 mL) followed by H_2O (3.75 mL), and stirred at 0 °C for 1 h during which time a white precipitate formed. The precipitate was filtered off and washed with Et_2O (100 mL). The filtrate was concentrated under vacuum to leave a light yellow residue that was purified by column chromatography on silica gel (elution with 5:1 hexane–ethyl acetate) to give 1.77 g (98%) of the primary alcohol as a colorless oil; IR (neat, cm^{-1}) 3355; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90–5.78 (m, 1H), 5.41–5.37 (m, 1H), 3.43–3.30 (m, 2H), 2.00–1.95 (m, 2H), 1.71–1.60 (m, 2H), 1.40–1.27 (m, 2H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.0, 128.1, 70.8, 36.7, 31.5, 25.0, 24.1, 18.8; $[\alpha]_D^{25}$ +8.5 (*c* 1.0, $CHCl_3$).

To a solution of the above alcohol (1.77 g, 14.05 mmol) in dry DMF (7 mL) were added TBDPSCl (4.63 g, 16.86 mmol) and imidazole (2.87 g, 42.15 mmol). The mixture was heated to 50 °C for 2 h before being cooled to rt and diluted with H_2O (100 mL). The aqueous layer was extracted with Et_2O (5×100 mL), and the organic layers were combined, dried, and evaporated to leave a residue that was purified by column chromatography on silica gel (elution with 40:1 hexane–ethyl acetate) to obtain 4.65 g (91%) of **21** as a colorless oil; IR (neat, cm^{-1}) 1470, 1361; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70–7.66 (m, 4H), 7.46–7.27 (m, 6H), 5.71–5.64 (m, 1H), 5.46–5.31 (m, 1H), 3.44–3.33 (m, 2H), 1.97–1.70 (m, 2H), 1.70–1.53 (m, 3H), 1.41–1.33 (m, 1H), 1.08–1.05 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7 (4C), 134.0 (2C), 133.8, 129.5 (2C), 127.6 (4C), 127.1, 71.5, 37.2, 31.9, 26.9 (3C), 25.4, 24.8, 19.5, 19.0; HRMS ES *m/z* $(M+Na)^+$ calcd 387.2115, obsd 387.2092; $[\alpha]_D^{25}$ −28.2 (*c* 1.4, $CHCl_3$).

4.4. (*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-3-methyl-cyclopent-1-enecarbaldehyde (22)

Ozone was passed through a cold (−78 °C) solution of **21** (4.0 g, 10.98 mmol) in a 1:1 mixture of CH_2Cl_2 and MeOH (130 mL each). After the reaction was over, PPh_3 (3.17 g, 12.09 mmol) was added and the mixture was stirred at rt for 4 h. The solvent was evaporated under vacuum; the residue was further evaporated with benzene (250 mL), and redissolved in benzene (250 mL). To this solution was added *p*-TsOH (0.63 g, 3.29 mmol) and the mixture was heated to 65 °C for 20 h. The solvent was removed and the residue was purified by column chromatography on silica gel (elution with 5:1 hexane–ethyl acetate) to give 3.36 g (81% over two steps) of **22** as a colorless oil; IR (neat, cm^{-1}) 1681, 1105; ^1H NMR (250 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.71–7.63 (m, 4H), 7.48–7.36 (m, 6H), 6.90–6.61 (m, 1H), 3.55 (s, 2H), 2.58–2.52 (m, 2H), 2.02–1.94 (m, 1H), 1.73–1.59 (m, 1H), 1.17 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 158.5, 146.3, 135.7 (4C), 133.5

(2C), 129.7 (2C), 127.7 (4C), 70.4, 52.6, 33.4, 27.6, 26.8 (3C), 22.7, 19.3; HRMS ES *m/z* $(M+Na)^+$ calcd 401.1907, obsd 401.1900; $[\alpha]_D^{25}$ −40.4 (*c* 0.6, $CHCl_3$).

4.5. (*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-3-methyl-cyclopent-1-enecarboxylic acid (16)

To a stirred mixture of **22** (3.0 g, 7.94 mmol) and 2-methyl-2-butene (5.57 g, 79.4 mmol) in *t*-BuOH (20 mL) was added an aqueous solution of $NaClO_2$ (2.87 g, 31.8 mmol) and NaH_2PO_4 (3.29 g, 23.8 mmol) in H_2O (20 mL). The resulting solution was stirred at rt overnight before it was quenched with 10% HCl solution to reach pH 5.0. The aqueous layer was extracted with EtOAc (5×50 mL), and the combined organic phases were dried and evaporated to leave a residue that was purified by column chromatography on silica gel (elution with 5:1 hexane–ethyl acetate) to afford 2.94 g (94%) of **16** as a colorless liquid; IR (neat, cm^{-1}) 2858, 1684, 1280; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67–7.63 (m, 4H), 7.46–7.35 (m, 6H), 6.73–6.71 (m, 1H), 3.53–3.46 (m, 2H), 2.64–2.58 (m, 2H), 2.05–1.96 (m, 1H), 1.71–1.61 (m, 1H), 1.15 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 152.1, 135.6 (4C), 135.1, 133.5 (2C), 129.6 (2C), 127.6 (4C), 70.4, 52.5, 33.7, 30.3, 26.8 (3C), 22.7, 19.3; HRMS ES *m/z* $(M+Na)^+$ calcd 417.1856, obsd 417.1876; $[\alpha]_D^{25}$ +18.3 (*c* 1.3, $CHCl_3$).

4.6. Benzoic acid 7-formyl-oct-7-enyl ester (24)

To a cold (−78 °C), stirred solution of oxalyl chloride (48.2 g, 0.38 mol) in dry CH_2Cl_2 (400 mL) was added a solution of DMSO (44.5 g, 0.57 mol) in dry CH_2Cl_2 (300 mL) under N_2. After 30 min of stirring, a solution of the monobenzoate of 1,8-octanediol (48.0 g, 0.19 mol) in dry CH_2Cl_2 (300 mL) was added over 30 min at −78 °C. The resulting cloudy solution was stirred at −78 °C for 1 h before Et_3N (96.0 g, 0.95 mol) was introduced. The cold bath was removed and the mixture was allowed to warm to 0 °C before being quenched with a saturated solution of NH_4Cl (500 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3×500 mL). The organic layers were combined, dried, and evaporated to leave a yellow residue that was purified by column chromatography on silica gel (elution with 5:1 petroleum ether–ethyl acetate) to afford 42.4 g (90%) of the saturated aldehyde as a colorless oil.

A mixture of above aldehyde (13.0 g, 52.4 mmol), $Et_2NH\cdot HCl$ (5.6 g, 68.2 mmol), and CH_2O (5.53 mL of 37% aqueous solution, 68.2 mmol) was heated to 110 °C for 16 h, cooled to rt, diluted with H_2O (200 mL), and extracted with CH_2Cl_2 (4×200 mL). The organic layers were combined, dried, and evaporated to leave a yellow residue that was purified by column chromatography on silica gel (elution with 10:1 petroleum ether–ethyl acetate) to yield 10.6 g (74%) of **24** as colorless oil; IR (neat, cm^{-1}) 1718, 1692, 1117; ^1H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.05–8.02 (m, 2H), 7.58–7.53 (m, 1H), 7.46–7.41 (m, 2H), 6.25 (s, 1H), 5.99 (s, 1H), 4.33–4.29 (m, 2H), 2.28–2.23 (m, 2H), 1.79–1.72 (m, 2H), 1.51–1.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 166.3, 149.9, 133.8, 132.6, 130.2, 129.3 (2C), 128.1 (2C), 64.7, 28.7, 28.4, 27.5, 27.4, 25.6; HRMS ES *m/z* $(M+Na)^+$ calcd 283.1305, obsd 283.1306.

4.7. Benzoic acid 7-iodomethyloct-7-enyl ester (25)

To a cold (−20 °C), stirred solution of **24** (31.7 g, 115.8 mmol) in anhydrous MeOH (250 mL) was added $NaBH_4$ (4.4 g, 115.8 mmol) in portions. The resulting mixture was stirred at −20 °C for 30 min before being quenched with 10% HCl solution (200 mL). The mixture was extracted with CH_2Cl_2 (4×300 mL). The combined organic layers were dried and evaporated to leave a residue that was purified by column chromatography (elution with 4:1 petroleum ether–ethyl acetate) to afford 31.0 g (91%) of the alcohol as a colorless oil; IR (neat, cm^{-1}) 3422, 1720, 1118; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07–8.03 (m, 2H), 7.57–7.54 (m, 1H), 7.48–7.42 (m, 2H), 5.02 (s, 1H), 4.88 (s, 1H), 4.33 (t, *J*=6.6 Hz, 2H), 4.08 (d, *J*=5.8 Hz, 2H), 2.12–2.06 (m, 2H), 1.81–1.76 (m, 2H), 1.54–1.40 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 148.7, 132.5, 130.0, 129.2 (2C), 128.0 (2C), 108.5, 65.1, 64.7, 32.5, 28.7, 28.3, 27.2, 25.5; HRMS ES *m/z* $(M+Na)^+$ calcd 285.1461, obsd 285.1473.

To a cold (−78 °C), stirred solution of the above alcohol (14.7 g, 53.15 mmol) in dry CH_2Cl_2 (150 mL) was added Et_3N (10.8 g, 106.3 mmol) followed by MsCl (12.2 g, 106.3 mmol) under N_2. The resulting solution was slowly warmed to 0 °C and stirred at 0 °C for 1.5 h before being quenched with 10% HCl (100 mL). The separated aqueous layer was extracted with CH_2Cl_2 (4×100 mL). The combined organic layers were dried and evaporated to leave a residue that was dissolved in dry THF (100 mL) and treated with anhydrous LiBr (9.2 g, 106.2 mmol) at 0 °C. The mixture was stirred at rt for 2 h before it was filtered through a pad of silica gel. The solid residue was washed with Et_2O (4×100 mL) and the combined filtrates were evaporated under vacuum to afford a yellow residue, which was purified by column chromatography on silica gel (elution with 40:1 hexane–ethyl acetate) to furnish 14.60 g (81% over two steps) of the allylic bromide as a light yellow oil; IR (neat, cm^{-1}) 1721, 1451, 1275; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07–8.03 (m, 2H), 7.59–7.53 (m, 1H), 7.47–7.41 (m, 2H), 5.16 (s, 1H), 4.96 (s, 1H), 4.32 (t, *J*=6.64 Hz, 2H), 3.97 (s, 2H), 2.25–2.20 (m, 2H), 1.83–1.74 (m, 2H), 1.56–1.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 145.3, 132.6 (2C), 130.3, 129.4, 128.2 (2C), 114.8, 64.8, 36.7, 33.0, 28.7, 28.5, 27.0, 25.7.

To a stirred solution of the above product (10.0 g, 30.8 mmol) in acetone (50 mL) was added NaI (6.92 g, 46.15 mmol) at rt. The resulting cloudy solution was stirred in the dark for 24 h before being quenched with H_2O (50 mL). The resulting solution was extracted with Et_2O (3×100 mL). The combined organic layers were evaporated under vacuum to give 11.0 g of crude **25** as an orange oil; IR (neat, cm^{-1}) 1716, 1451, 1271; ^1H NMR (250 MHz, $CDCl_3$) δ 8.08–8.04 (m, 2H), 7.57–7.54 (m, 1H), 7.48–7.42 (m, 2H), 5.24 (s, 1H), 4.92 (s, 1H), 4.34 (t, *J*=6.61 Hz, 2H), 3.94 (s, 2H), 2.27–2.24 (m, 2H), 1.80–1.78 (m, 2H), 1.55–1.43 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 145.9, 132.4 (2C), 130.1, 129.1, 128.0 (2C), 113.1, 64.6, 33.5, 28.5, 28.3, 26.8, 25.5; HRMS ES *m/z* $(M+Na)^+$ calcd 395.0478, obsd 395.0475.

4.8. Benzoic acid (*R*)-9-hydroxymethyl-7-methylenedodec-11-enyl ester (27)

To a cold (−78 °C), stirred solution of **26** (1.8 g, 6.95 mmol) in dry THF (24 mL) was added NaHMDS (7.3 mL of 1.0 M solution in THF, 7.3 mmol) slowly over 5 min under N_2. After 45 min of stirring at this temperature, a solution of **25** (1.27 g, 3.42 mmol) in THF (12 mL) was introduced. The resulting mixture was stirred for 5 h at −78 °C before being quenched with saturated NH_4Cl solution (30 mL). The mixture was allowed to warm to rt, stirred for an additional 10 min, and diluted with H_2O (50 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried and evaporated to leave a residue that was dissolved in anhydrous MeOH (90 mL). To a cold (0 °C) flask of this solution was added $NaBH_4$ (1.3 g, 34.4 mmol) in portions and the resulting solution was allowed to stir at 0 °C overnight prior to quenching with saturated NH_4Cl solution (100 mL) followed by H_2O (100 mL). The mixture was extracted with CH_2Cl_2 (4×200 mL) and the combined organic layers were dried and evaporated to yield a residue that was purified by column chromatography on silica gel (elution with 5:1 hexane–ethyl acetate) to afford 0.68 g (60% over two steps) of **27** as a colorless oil; IR (neat, cm^{-1}) 3424, 1721, 1641, 1176; ^1H NMR (250 MHz, $CDCl_3$) δ 8.07–8.03 (m, 2H), 7.56–7.52 (m, 1H), 7.47–7.27 (m, 2H), 5.84–5.77 (m, 1H), 5.10–5.01 (m, 2H), 4.80–4.77 (m, 2H), 4.32 (t, J=6.6 Hz, 2H), 3.55 (d, J=5.3 Hz, 2H), 2.13–2.00 (m, 6H), 1.84–1.75 (m, 3H), 1.50–1.37 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 148.1, 136.8, 132.8, 130.4, 129.5 (2C), 128.3 (2C), 116.4, 110.9, 65.5, 65.0, 38.14, 38.10, 35.7, 35.4, 28.9, 28.6, 27.4, 25.9; HRMS ES *m/z* $(M+Na)^+$ calcd 353.2087, obsd 353.2061; $[\alpha]_D^{20}$ +0.3 (*c* 1.0, $CHCl_3$).

4.9. Benzoic acid (*R*)-9-(2,2-dimethylpropionyloxymethyl)-7-methylenedodec-11-enyl ester (28)

To a cold (0 °C), stirred solution of **27** (1.7 g, 5.15 mmol) in dry CH_2Cl_2 (30 mL) was added pyridine (1.2 g, 15.5 mmol) followed by PivCl (1.24 g, 10.3 mmol). The mixture was stirred at rt overnight prior to quenching with 10% HCl (30 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried and evaporated to obtain a residue that was purified by column chromatography on silica gel (elution with 20:1 hexane–ethyl acetate) to provide 1.98 g (93%) of **28** as a colorless oil; IR (neat, cm^{-1}) 1724, 1641, 1160; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06–8.03 (m, 2H), 7.58–7.53 (m, 1H), 7.46–7.41 (m, 2H), 5.82–5.70 (m, 1H), 5.06–4.99 (m, 2H), 4.77 (d, J=15.5 Hz, 2H), 4.32 (t, J=6.62 Hz, 2H), 3.99–3.91 (m, 2H), 2.13–1.94 (m, 7H), 1.80–1.73 (m, 2H), 1.55–1.33 (m, 6H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 166.4, 146.8, 135.8, 132.6 (2C), 131.3, 129.4 (2C), 128.2, 116.7, 111.3, 65.8, 64.8, 38.9, 37.6, 35.4, 35.3, 35.2, 28.8, 28.6, 27.4, 27.1 (3C), 25.8; HRMS ES *m/z* $(M+Na)^+$ calcd 437.2662, obsd 437.2681; $[\alpha]_D^{20}$ −3.0 (*c* 1.2, $CHCl_3$).

4.10. Benzoic acid 5-[(*R*)-4-(2,2-dimethylpropionyloxy methyl)-6-oxocyclohex-1-enyl]-pentyl ester (29)

Ozone was passed through a cold (−78 °C) solution of **28** (0.82 g, 1.99 mmol) in a 1:1 mixture of CH_2Cl_2/MeOH (20 mL each). After the reaction was complete, PPh_3 (3.17 g, 12.09 mmol) was added and the mixture was stirred at rt for 6 h. The solvent was evaporated under vacuum, the residue was further evaporated with benzene (60 mL), and redissolved in benzene (60 mL). To this solution was added *p*-TsOH (0.20 g, 1.04 mmol) and the mixture was heated to 65 °C for 15 h. The solvent was removed and the residue was purified by column chromatography on silica gel (elution with 5:1 hexane–Et_2O) to afford 0.52 g (65% over two steps) of **29** as a colorless oil; IR (neat, cm^{-1}) 1720, 1674, 1480; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06–8.03 (m, 2H), 7.59–7.53 (m, 1H), 7.47–7.42 (m, 2H), 6.70–6.68 (m, 1H), 4.32 (t, J=6.6 Hz, 2H), 4.03–4.00 (m, 2H), 2.60–2.53 (m, 1H), 2.46–2.39 (m, 2H), 2.28–2.18 (m, 4H), 1.81–1.77 (m, 2H), 1.48–1.43 (m, 4H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 178.2, 166.6, 143.2, 139.7, 132.8 (2C), 130.5, 129.5 (2C), 128.3, 66.9, 64.9, 41.2, 38.8, 34.9, 29.2, 28.8, 28.5, 28.2, 27.2 (3C), 25.7; HRMS ES *m/z* $(M+Na)^+$ calcd 423.2142, obsd 423.2112; $[\alpha]_D^{20}$ −3.0 (*c* 1.2, $CHCl_3$).

4.11. Benzoic acid 5-[(4*R*,6*R*)-4-(2,2-dimethylpropionyloxy methyl)-6-(5-methoxybenzyloxy) cyclohex-1-enyl]-pentyl ester (30)

To a mixture of **29** (1.0 g, 2.5 mmol) and $CeCl_3 \cdot 7H_2O$ (1.4 g, 3.8 mmol) in anhydrous MeOH (20 mL) was added $NaBH_4$ (0.12 g, 3.0 mmol) in portions at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was quenched with saturated NH_4Cl solution (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were dried and evaporated to leave a residue that was purified by column chromatography on silica gel (elution with 5:1 petroleum ether–ethyl acetate) to afford 0.93 g (92%) of the allylic alcohol as a colorless oil; IR (neat, cm^{-1}) 3503, 1721, 1480; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07−8.03 (m, 2H), 7.59–7.53 (m, 1H), 7.48–7.42 (m, 2H), 5.49–5.46 (m, 1H), 4.36–4.28 (m, 3H), 3.97 (d, J=6.0 Hz, 2H), 2.30–2.28 (m, 1H), 2.16–2.00 (m, 5H), 1.82–1.78 (m, 3H), 1.49–1.31 (m, 4H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 165.8, 139.5, 131.9 (2C), 130.2, 128.6 (2C), 127.4, 121.5, 67.5, 67.2, 64.1, 38.0, 35.4, 32.1, 31.5, 27.8, 27.7, 26.5, 26.3 (3C), 24.9; HRMS ES *m/z* $(M+Na)^+$ calcd 425.2298, obsd 425.2285; $[\alpha]_D^{20}$ −24.1 (*c* 1.1, $CHCl_3$).

To a cold (0 °C), stirred mixture of the above alcohol (2.15 g, 5.35 mmol) and *p*-methoxybenzyl trichloroacetimidate (2.27 g, 8.02 mmol) in dry Et_2O (72 mL) was added TfOH (0.16 mL, 0.16 mmol). The resulting mixture was stirred at rt for 5 h prior to quenching with a saturated $NaHCO_3$ solution (20 mL) followed by H_2O (100 mL). The separated aqueous layer was extracted with Et_2O (3×50 mL), the combined organic layers were dried and evaporated, and the residue was purified by column chromatography on silica gel (elution with 10:1 petroleum ether–ethyl acetate) to afford 2.23 g (80%) of **30** as a colorless oil; IR (neat, cm^{-1}) 1721, 1612, 1160; ^1H NMR (250 MHz, $CDCl_3$) δ 8.07–8.03 (m, 2H), 7.57–7.53 (m, 1H), 7.47–7.41 (m, 2H), 7.29–7.25 (m, 2H), 6.89–6.85 (m, 2H), 5.52–5.49 (m, 1H), 4.59 (d, J=11.3 Hz, 1H), 4.40 (d, J=11.3 Hz, 1H), 4.38–4.29 (m, 2H), 4.03–3.98 (m, 3H), 3.79 (s, 3H), 2.30–1.76 (m, 8H), 1.49–1.36 (m, 5H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 166.6, 159.0,

139.2, 132.8, 130.7, 130.4, 129.5 (2C), 129.2 (2C), 128.3 (2C), 123.0, 113.7, (2C), 74.4, 70.1, 68.2, 65.0, 55.2, 38.8, 32.73, 32.70, 31.5, 28.6, 28.5, 27.4, 27.2 (3C), 25.8; HRMS ES *m/z* $(M+Na)^+$ calcd 545.2874, obsd 545.2842; $[\alpha]_D^{20}$ −34.8 (*c* 0.8, $CHCl_3$).

4.12. Benzoic acid 5-[(3*S*,5*R*)-3-(2,2-dimethylpropionyloxy methyl)-2-formyl-5-(4-methoxybenzyloxy)cyclopent-1-enyl]pentyl ester (31)

To a stirred solution of **30** (1.3 g, 2.49 mmol) in a 1:1 mixture of CH_2Cl_2/MeOH (30 mL each) was passed O_3 at −78 °C. After reaction was complete, PPh_3 (0.72 g, 2.74 mmol) was added and the resulting mixture was stirred at rt for 4 h. Solvent was evaporated under vacuum, the residue was further evaporated with Et_2O (75 mL), and redissolved in Et_2O (75 mL). To this solution was added piperidine (78 mg, 0.92 mmol) and the resulting mixture was stirred at rt before HOAc (97 mg, 1.62 mmol) was added. The mixture was heated to reflux for 20 h, the solvent was removed under vacuum, and the residue was purified by column chromatography on silica gel (elution with 5:1 petroleum ether–ether) to afford 1.06 g (80%) of **31** as a colorless liquid; IR (neat, cm^{-1}) 1719, 1671, 1611; ^1H NMR (250 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.06–8.02 (m, 2H), 7.57–7.54 (m, 1H), 7.48–7.42 (m, 2H), 7.28–7.24 (m, 2H), 6.90–6.86 (m, 2H), 4.60 (d, *J*=11.5 Hz, 1H), 4.51–4.48 (m, 1H), 4.42–4.29 (m, 4 H), 4.20–4.13 (m, 1H), 3.79 (s, 3H), 3.20–3.12 (m, 1H), 2.79–2.54 (m, 2H), 2.35–2.21 (m, 1H), 1.76–1.45 (m, 7H), 1.18 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.7, 178.3, 166.5, 165.1, 137.7, 132.9, 130.3, 129.9, 129.54 (2C), 129.50 (2C), 128.3 (2C), 113.8 (2C), 82.7, 71.4, 65.5, 64.5, 55.2, 41.4, 38.8, 32.2, 28.4, 28.1, 27.1 (3C), 26.0, 25.8; HRMS ES *m/z* $(M+Na)^+$ calcd 559.2666, obsd 559.2646; $[\alpha]_D^{20}$ +7.1 (*c* 0.7, $CHCl_3$).

4.13. Benzoic acid 5-[(3*S*,5*R*)-2-(*tert*-butyldimethylsilanyloxy methyl)-3-(2,2-dimethylpropionyloxymethyl)-5-(4-methoxybenzyloxy)cyclopent-1-enyl]pentyl ester (32)

To a cold (0 °C), stirred solution of **31** (0.49 g, 0.91 mmol) in anhydrous MeOH (25 mL) was added $NaBH_4$ (70 mg, 1.85 mmol) in portions. The resulting mixture was stirred at 0 °C for 20 min prior to quenching with saturated NH_4Cl solution (30 mL), and extracted with CH_2Cl_2 (4×50 mL). The organic layers were combined, dried, and evaporated to leave a residue that was purified by column chromatography on silica gel (elution with 4:1 petroleum ether–ethyl acetate) to afford 0.49 g (100%) of the allylic alcohol as a colorless oil; IR (neat, cm^{-1}) 3475, 1722, 1612; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06–8.03 (m, 2H), 7.59–7.54 (m, 1H), 7.47–7.42 (m, 2H), 7.27–7.23 (m, 2H), 6.89–6.84 (m, 2H), 4.54 (d, *J*=11.4 Hz, 1H), 4.44–4.11 (m, 8H), 3.79 (s, 3H), 3.00–2.95 (m, 1H), 2.33–2.18 (m, 3H), 1.77–1.72 (m, 3 H), 1.47–1.42 (m, 4H), 1.21 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 166.3, 158.8, 141.8, 138.0, 132.5 (2C), 130.5, 130.1, 129.2 (2C), 128.9 (2C), 128.0 (2C), 113.4, 83.3, 70.4, 66.7, 64.5, 57.0, 54.8, 43.2, 38.5, 32.5, 28.2, 27.5, 26.8 (3C), 25.6; HRMS ES *m/z* $(M+Na)^+$ calcd 561.2823, obsd 561.2800; $[\alpha]_D^{20}$ −20.0 (*c* 0.1, $CHCl_3$).

To a stirred solution of above alcohol (0.88 g, 1.63 mmol) in dry CH_2Cl_2 (15 mL) was added imidazole (0.33 g, 4.89 mmol) followed by TBSCl (0.37 g, 2.44 mmol). The mixture was stirred at rt for 1 h before it was quenched with H_2O (20 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The organic layers were combined, dried, and evaporated to leave a residue that was purified by column chromatography on silica gel (elution with 15:1 petroleum ether–ethyl acetate) to afford 1.0 g (94%) of **32** as a colorless oil; IR (neat, cm^{-1}) 1713, 1613, 1169; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09–8.03 (m, 2H), 7.57–7.53 (m, 1H), 7.47–7.41 (m, 2H), 7.27–7.24 (m, 2H), 6.88–6.85 (m, 2H), 4.53 (d, *J*=11.6 Hz, 1H), 4.38–4.27 (m, 6 H), 4.16 (d, *J*=12.5 Hz, 1H), 4.08–3.91 (m, 1H), 3.79 (s, 3 H), 3.02–3.95 (m, 1H), 2.29–2.12 (m, 3 H), 1.78–1.70 (m, 2H), 1.64–1.55 (m, 1H), 1.48–1.39 (m, 4H), 1.19 (s, 9H), 0.88 (s, 9 H), 0.07–0.03 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 166.5, 159.0, 140.5, 138.2, 132.7 (2C), 130.9, 130.4, 129.4, 129.2 (2C), 128.2 (2C), 113.6 (2C), 83.8, 70.4, 66.6, 64.6, 58.1, 54.9, 43.5, 38.6, 32.6, 28.4, 27.6, 27.0 (3C), 25.9, 25.7 (3C), 25.6, 18.0, −5.6 (2C); HRMS ES *m/z* $(M+Na)^+$ calcd 675.3688, obsd 675.3660; $[\alpha]_D^{20}$ −17.4 (*c* 0.06, $CHCl_3$).

4.14. 2,2-Dimethylpropionic acid (1*S*,4*R*)-2-(*tert*-butyldimethylsilanyloxymethyl)-4-(4-methoxybenzyloxy)-3-[5-(2-methoxyethoxymethoxy) pentyl]cyclopent-2-enylmethyl ester (33)

To a stirred solution of **32** (1.0 g, 1.53 mmol) in anhydrous MeOH (60 mL) was added K_2CO_3 (1.06 g, 7.65 mmol). The mixture was stirred at rt overnight before it was quenched with saturated NH_4Cl solution (30 mL). The mixture was extracted with EtOAc (4×40 mL). The combined organic layers were dried and evaporated to leave a residue that was purified by column chromatography on silica gel (elution with 2:1 petroleum ether–ethyl acetate) to afford 0.78 g (94%) of the primary alcohol as a colorless oil; IR (neat, cm^{-1}) 3443, 1731, 1613; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28–7.23 (m, 2H), 6.89–6.84 (m, 2H), 4.53 (d, *J*=11.5 Hz, 1H), 4.43–4.26 (m, 4H), 4.15 (d, *J*=12.4 Hz, 1H), 4.05–3.80 (m, 1H), 3.80 (s, 3 H), 3.62–3.57 (m, 2H), 2.99–2.95 (m, 1H), 2.30–2.20 (m, 1H), 2.15–2.11 (m, 2H), 1.64–1.50 (m, 3H), 1.37–1.18 (m, 13H), 0.88 (s, 9H), 0.06–0.03 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 159.0, 140.6, 138.1, 130.9, 129.2 (2C), 113.6 (2C), 83.8, 70.5, 66.7, 62.6, 58.2, 55.1, 43.5, 38.7, 32.7, 32.5, 27.8, 27.1 (3C), 26.0, 25.76 (3C), 25.70, 18.1, −5.5 (2C); HRMS ES *m/z* $(M+Na)^+$ calcd 571.3425, obsd 571.3434; $[\alpha]_D^{20}$ −21.3 (*c* 0.08, $CHCl_3$).

To a stirred solution of the above alcohol (1.29 g, 2.35 mmol) in dry CH_2Cl_2 (7 mL) was added *i*-Pr_2NEt (0.91 g, 7.05 mmol) followed by MEMCl (0.59 g, 4.70 mmol) at 0 °C under N_2. The resultant solution was stirred at rt for 18 h before it was quenched with 10% HCl (10 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried and evaporated to provide a residue, which was purified by column chromatography on silica gel (elution with 5:1 petroleum ether–ether) to afford 1.39 g (93%) of **33** as a colorless oil; IR (neat, cm^{-1}) 1726, 1612, 1251; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.27 (m, 2H), 6.94–6.90 (m, 2H), 4.76 (s, 2H), 4.60–4.56 (m, 1H), 4.49–4.31 (m, 4H), 4.23–4.19 (m, 1H), 4.10–4.04 (m, 1H), 3.86 (s, 3H),

3.79–3.73 (m, 2H), 3.64–3.45 (m, 4H), 3.45 (s, 3H), 3.11–2.94 (m, 1H), 2.35–2.25 (m, 1H), 2.20–2.16 (m, 2H), 1.70–1.60 (m, 3H), 1.49–1.27 (m, 4H), 1.24 (s, 9H), 0.93 (s, 9 H), 0.12–0.08 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 159.0, 140.6, 138.1, 131.0, 129.1 (2C), 113.6 (2C), 95.4, 83.9, 71.7, 70.5, 67.8, 66.8, 66.6, 58.9, 58.2, 55.2, 43.6, 38.7, 32.8, 29.5, 28.1, 27.2 (3C), 26.3, 26.1, 25.8 (3C), 18.2, −5.4, −5.5; HRMS ES *m/z* $(M+Na)^+$ calcd 659.3949, obsd 659.3914; $[\alpha]_D^{20}$ −15.1 (*c* 1.7, $CHCl_3$).

4.15. (*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-3-methylcyclopent-1-enecarboxylic acid (1*S*,4*R*)-2-(*tert*-dimethylsilanyloxymethyl)-4-(4-methoxybenzyloxy)-3-[5-(2-methoxyethoxymethoxy)pentyl]cyclopent-2-enylmethyl ester (34)

To a stirred solution of **33** (0.62 g, 0.97 mmol) in dry CH_2Cl_2 (10 mL) was added DIBAL-H (2.43 mL of 1.0 M solution in hexane, 2.43 mmol) at −78 °C under N_2. The resultant solution was stirred at −78 °C for 0.5 h and at 0 °C for 1 h before it was quenched with a saturated solution of potassium sodium tartrate (10 mL). The resultant cloudy solution was stirred at rt overnight, diluted with water (20 mL), and extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried, and evaporated to provide a residue that was purified by column chromatography on silica gel (elution with 2:1 petroleum ether–ethyl acetate) to furnish 0.42 g (78%) of **34** as a colorless oil; IR (neat, cm^{-1}) 3457, 1612, 1514, 1249; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.23 (m, 2H), 6.91–6.84 (m, 2H), 4.71 (s, 2H), 4.58–4.53 (m, 1H), 4.39–4.29 (m, 3H), 4.15–4.11 (m, 1H), 3.80 (s, 3H), 3.74–3.66 (m, 2H), 3.57–3.48 (m, 6H), 3.40 (s, 3H), 2.82–2.68 (m, 1H), 2.27–2.09 (m, 3H), 1.61–1.50 (m, 3H), 1.43–1.29 (m, 4H), 0.88 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 141.7, 138.7, 130.5, 129.3 (2C), 113.6 (2C), 95.4, 82.9, 71.7, 70.6, 67.7, 66.6, 64.5, 58.9, 58.5, 55.2, 47.6, 32.5, 29.5, 28.0, 26.3, 26.0, 25.8 (3C), 18.2, −5.4, −5.5; HRMS ES *m/z* $(M+Na)^+$ calcd 575.3375, obsd 575.3362; $[\alpha]_D^{20}$ −31.5 (*c* 0.72, $CHCl_3$).

4.16. (*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-3-methylcyclopent-1-ene carboxylic acid (1*S*,4*R*)-2-(*tert*-butyldimethylsilanyloxymethyl)-4-(4-methoxybenzyloxy)-3-[5-(2-methoxyethoxymethoxy)pentyl]cyclopent-2-enyl methyl ester (35)

To a mixture of alcohol **34** (0.25 g, 0.46 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.26 g, 1.38 mmol), and DMAP (0.06 g, 0.46 mmol) in dry CH_2Cl_2 (5 mL) was added a solution of **34** (0.18 g, 0.46 mmol) in dry CH_2Cl_2 (3 mL) via cannula. The resulting mixture was stirred at rt for 24 h, freed of solvent, and subjected to column chromatography on silica gel (elution with 5:1 petroleum ether–ethyl acetate) to give 0.30 g (70%) of **35** as a colorless oil; IR (neat, cm^{-1}) 1714, 1613, 1514, 1251; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.63 (m, 4H), 7.44–7.34 (m, 6H), 7.26–7.22 (m, 2H), 6.89–6.84 (m, 2H), 6.57 (s, 1H), 4.71 (s, 2H), 4.55–4.16 (m, 6H), 4.08–4.02 (m, 1H), 3.80 (s, 3H), 3.71–3.68 (m, 2H), 3.58–3.47 (m, 6H), 3.40 (s, 3H), 3.09–2.98 (m, 1H), 2.61–2.56 (m, 2H), 2.28–2.23 (m, 1H), 2.14–2.11 (m, 2H), 1.99–1.95 (m, 1H), 1.69–1.54 (m, 4H), 1.34–1.26 (m, 4H), 1.12 (s, 3H), 1.05 (s, 9H), 0.88 (s, 9H), 0.05–0.04 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 158.9, 148.9, 140.7, 138.3, 135.7, 135.6 (4C), 133.5, 133.4, 130.8, 129.52, 129.49, 129.1 (2C), 127.5 (4C), 113.6 (2C), 95.3, 83.7, 71.7, 70.4, 67.7, 67.1, 66.5, 58.9, 58.2, 55.1, 52.1, 43.6, 33.7, 32.8, 30.6, 30.2, 29.5, 27.9, 26.7 (3C), 26.3, 26.1, 25.8 (3C), 22.7, 19.2, 18.1, −5.5 (2C); HRMS ES *m/z* $(M+Na)^+$ calcd 951.5233, obsd 951.5210.

4.17. (*S*)-3-(*tert*-Butyldiphenylsilanyloxy)-3-methylcyclopent-1-enecarboxylic acid (1*S*,4*R*)-2-hydroxymethyl-4-(4-methoxybenzyloxy)-3-[5-(2-methoxyethoxymethoxy)pentyl]cyclopent-2-enylmethyl ester (36)

To a stirred solution of **35** (0.57 g, 0.61 mmol) in a 1:1 mixture of CH_2Cl_2/MeOH (10 mL each) at 0 °C was added CSA (0.14 g, 0.61 mmol). The mixture was stirred at 0 °C for 1 h, quenched with saturated $NaHCO_3$ solution (20 mL), and extracted with CH_2Cl_2 (3×20 mL). The organic layers were combined, dried, and evaporated to leave a residue, purification of which by chromatography on silica gel (elution with 1:1 petroleum ether–ether) afforded 0.46 g (92%) of **36** as a colorless oil; IR (neat, cm^{-1}) 3482, 1714, 1613; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.61 (m, 4H), 7.44–7.34 (m, 6H), 7.26–7.23 (m, 2H), 6.91–6.83 (m, 2H), 6.60–6.59 (m, 1H), 4.70 (s, 2H), 4.55–4.51 (m, 1H), 4.41–4.16 (m, 6H), 3.79 (s, 3H), 3.70–3.66 (m, 2H), 3.57–3.48 (m, 6H), 3.39 (s, 3H), 3.08–2.92 (m, 1H), 2.61–2.56 (m, 2H), 2.27–2.26 (m, 1H), 2.20–2.15 (m, 2H), 2.00–1.96 (m, 1H), 1.66–1.55 (m, 4H), 1.44–1.26 (m, 3H), 1.26 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 159.1, 149.5, 142.3, 138.6 (2C), 135.5 (2C), 133.5, 130.8, 129.5 (4C), 129.2 (4C), 127.6 (2C), 113.7 (2C), 95.4, 83.4, 71.8, 70.6, 70.4, 67.7, 67.3, 66.7, 58.9, 57.7, 55.2, 52.2, 43.5, 33.7, 32.8, 30.6, 29.6, 27.7, 26.8 (3C), 26.0, 25.7, 22.7, 19.3 (2C); HRMS ES *m/z* $(M+Na)^+$ calcd 837.4368, obsd 837.4348; $[\alpha]_D^{20}$ −24.5 (*c* 1.08, $CHCl_3$).

4.18. (*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-3-methylcyclopent-1-ene carboxylic acid (1*S*,4*R*)-2-bromomethyl-4-(4-methoxybenzyloxy)-3-[5-(2-methoxyethoxymethoxy)pentyl]cyclopent-2-enyl methyl ester (37)

To a solution of **36** (30 mg, 0.036 mmol) in dry CH_2Cl_2 (1 mL) was added freshly distilled Et_3N (0.01 mL, 0.074 mmol) followed by MsCl (6 μL, 0.074 mmol) at 0 °C under N_2. The mixture was stirred at 0 °C for 30 min and quenched with 1 N HCl (2 mL) followed by H_2O (1 mL). The separated aqueous phase was washed with CH_2Cl_2 (2×5 mL). The combined CH_2Cl_2 layers were dried and concentrated under vacuum to provide the allyl mesylate as yellowish oil.

The above material was dissolved in dry THF (2 mL) and anhydrous LiBr (5 mg, 0.06 mmol) was added at rt. The mixture was stirred at rt for 1.5 h and filtered through a pad of silica gel, where the pad was further washed with ether (50 mL). The filtrate was concentrated under vacuum to afford a yellowish oil, which was purified by chromatography on silica gel (elution with 3:1 petroleum ether–ethyl acetate) to furnish 27 mg (86%) of **37** as a colorless liquid; IR (neat, cm^{-1}) 1711, 1658, 1513, 1249; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.61 (m, 4H), 7.45–7.34 (m, 6H), 7.27–7.23 (m, 2H), 6.89–6.84 (m, 2H), 6.63–6.62 (m, 1H), 4.71

(s, 2H), 4.55–4.51 (m, 1H), 4.43–4.34 (m, 2H), 4.27–4.14 (m, 3 H), 4.05–4.02 (m, 1H), 3.80 (s, 3H), 3.71–3.68 (m, 2H), 3.58–3.48 (m, 6H), 3.39 (s, 3H), 3.15–3.08 (m, 1H), 2.63–2.57 (m, 2H), 2.37–2.33 (m, 1H), 2.21–2.18 (m, 2H), 2.04–1.95 (m, 1H), 1.68–1.54 (m, 4H), 1.40–1.32 (m, 4H), 1.12 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 159.2, 149.8, 146.1, 135.7 (2C), 135.6, 133.6 (2C), 130.6, 129.6 (4C), 129.3 (4C), 127.6 (2C), 113.8 (2C), 95.5, 82.9, 71.8, 70.8, 70.5, 67.8, 66.7, 66.6, 59.0, 55.3, 52.3, 42.7, 38.9, 33.7, 32.5, 30.7, 29.7, 27.7, 26.9 (3C), 26.8, 26.4, 26.2, 22.8, 19.4; HRMS ES *m/z* $(M+Na)^+$ calcd 899.3524, obsd 899.3547; $[\alpha]_D^{20}$ −47.0 (*c* 0.83, $CHCl_3$).

4.19. (*E*)-(*R*)-5-(*tert*-Butyldiphenylsilanyloxy)pent-3-ene-1,2-diol (47)

A solution of **46** (3.86 g, 1.8 mmol) in 170 mL of 80% HOAc at 0 °C was allowed to warm to rt, stirred for 12 h, poured into a slurry of 200 g of $NaHCO_3$ suspended in 1 L of water, and extracted with ether (4×150 mL). The combined organic phases were dried and evaporated to leave a residue that was purified by chromatography on silica gel (hexane–ethyl acetate 2:1) to give **47** as a colorless oil (2.78 g, 84%); IR (neat, cm^{-1}) 3416, 1472, 1427; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.13 (m, 4H), 7.50–7.32 (m, 6H), 5.57 (dt, *J*=10.2, 2.2 Hz, 1H), 5.23 (dd, *J*=10.2, 6.3 Hz, 1H), 4.32–4.20 (m, 3H), 3.63 (dd, *J*=9.4, 1.8 Hz, 1H), 3.47 (dd, *J*=8.1, 10.3 Hz, 1H), 2.95–2.15 (bm, 1H), 1.07 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 132.3, 131.8, 129.7, 128.2, 127.7, 72.6, 67.1, 63.7, 26.8, 18.5; HRMS ES *m/z* $(M+Na)^+$ calcd 379.1700, obsd 379.1713; $[\alpha]_D^{20}$ −7.0 (*c* 3.46, $CHCl_3$).

4.20. Acetic acid (*E*)-(*R*)-4-(*tert*-butyldiphenylsilanyloxy)-1-(*tert*-butyldiphenylsilanyloxymethyl)-but-2-enyl ester (48)

Diol **47** (10.7 g, 41.2 mmol) was dissolved in dry THF (80 mL) containing imidazole (3.65 g, 53.6 mmol), cooled to −15 °C, and treated with a solution of TBDPSCl (9.51 mL, 37.1 mmol) in 10 mL of dry THF via syringe pump over 2.5 h. Stirring was continued at −15 °C for another 2 h and a second portion of TBDPSCl (0.76 mL, 2.96 mmol) was added slowly at the same temperature within 30 min. The reaction mixture was stirred for another hour and a third portion of TBDPSCl (0.76 mL, 2.96 mmol) was introduced at −15 °C, quenched an hour later with saturated ammonium chloride solution (50 mL), and extracted with ether (4×80 mL). The combined organic layers were dried and evaporated to dryness to give a colorless oil, which was purified by chromatography on silica gel (gradient elution with hexane–ethyl acetate 25:1 to 7:1) to give 20.02 g (82%) of pure alcohol in the form of a colorless oil; IR (neat, cm^{-1}) 3420, 1472, 1427; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77–7.60 (m, 8H), 7.50–7.28 (m, 12H), 5.83 (dt, *J*=18.1, 2.5 Hz, 1H), 5.70 (dd, *J*=18.1, 8.4 Hz, 1H), 4.30–4.10 (m, 1H), 4.18 (d, *J*=5.8 Hz, 2H), 3.66 (dd, *J*=8.2, 5.6 Hz, 1H), 3.53 (dd, *J*=8.2, 5.9 Hz, 1H), 2.65–2.54 (m, 1H), 1.08 (s, 9 H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.54, 135.48, 134.8, 133.5, 133.1, 133.0, 131.4, 129.8, 129.6, 129.5, 127.79, 127.78, 127.63, 127.60, 72.3 (d), 67.8, 63.7, 26.83, 26.79, 19.2, 18.9 (s); HRMS ES *m/z* $(M+Na)^+$ calcd 617.2878, obsd 617.2861; $[\alpha]_D^{20}$ +0.6 (*c* 1.33, $CHCl_3$).

The alcohol from above (20.02 g, 33.7 mmol) was dissolved in a mixture of pyridine–CH_2Cl_2=1:4 (375 mL) and cooled to 0 °C. DMAP (411 mg, 3.37 mmol) was introduced followed by acetic anhydride (31.6 mL, 0.34 mmol) in dropwise fashion. The mixture was allowed to warm to rt, stirred overnight, and freed of solvent. The residue was purified by column chromatography on silica gel (gradient elution with hexane–ethyl acetate 50:1 to 25:1) to give 19.7 g (92%) of **48** as a colorless oil; IR (neat, cm^{-1}) 1738, 1472, 1369; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.63 (m, 8H), 7.50–7.32 (m, 12H), 5.87–5.81 (m, 2H), 5.52 (dd, *J*=4.2 Hz, 1H), 4.23 (s, 2H), 3.82–3.68 (m, 2H), 2.09 (s, 3H), 1.08 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 135.7, 135.6, 135.5, 135.3, 133.5, 127.74, 127.71, 124.6, 74.6, 65.6, 63.5, 26.94, 26.87, 21.2, 19.3, 19.1; HRMS ES *m/z* $(M+Na)^+$ calcd 659.2983, obsd 659.2948; $[\alpha]_D^{20}$ −8.3 (*c* 1.34, $CHCl_3$).

4.21. (*E*)-(*S*)-6-(*tert*-Butyldiphenylsilanyloxy)-3-(*tert*-diphenylsilanyloxymethyl)hex-4-enoic acid methyl ester (49)

The above acetate (4.00 g, 6.28 mmol) dissolved in 80 mL of dry THF was treated with TBDMSCl (3.92 g, 25.1 mmol) and cooled to −78 °C. KHMDS (28.5 mL, 18.8 mmol) was introduced and the mixture was kept for 3 h at −78 °C, allowed to warm to rt overnight prior to quenching with a mixture of saturated NaCl solution (200 mL) and 1 N HCl (40 mL). The aqueous phase was extracted with ether (3× 60 mL), and the combined organic phases were filtered and freed of solvent to give a mixture of ester and the corresponding carboxylic acid. To obtain pure acid, the crude product was dissolved in 80 mL of THF and 4 N LiOH (20 mL) was added at 0 °C. After 1 h or stirring at 0 °C, the TBS ester was cleaved quantitatively to the carboxylic acid and the reaction was stopped by acidification with 1 N HCl (160 mL) and extraction with ether (3×60 mL) and CH_2Cl_2 (3× 60 mL). The combined organic phases were dried, filtered, and distilled to give almost pure carboxylic acid. The acid was further purified by column chromatography on silica gel (gradient elution with ethyl acetate–hexane 1:10 to 1:7) to give 3.98 g (100%) of colorless oil; IR (neat, cm^{-1}) 2856, 1710, 1471; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77–7.58 (m, 8H), 7.47–7.28 (m, 12H), 5.62–5.58 (m, 2H), 4.12 (s, 2H), 3.65 (dd, *J*=9.7, 4.6 Hz, 1H), 3.51 (dd, *J*=9.7, 6.9 Hz, 1H), 2.86–2.73 (m, 1H), 2.72 (dd, *J*=15.4, 5.9 Hz, 1H), 2.37 (dd, *J*=15.5, 7.6 Hz, 1H), 1.04 (s, 9 H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 135.6, 135.5, 133.7, 133.5, 130.8, 129.7, 129.6, 129.4, 127.7, 127.6, 66.5, 64.2, 40.9, 36.2, 26.8, 19.8, 19.3, 19.2; HRMS ES *m/z* $(M+Na)^+$ calcd 659.2984, obsd 659.3016; $[\alpha]_D^{20}$ +5.3 (*c* 0.87, $CHCl_3$).

The carboxylic acid (4.49 g, 7.06 mL) was dissolved in 44 mL of dry DMF and methyl iodide (5.27 mL, 84.7 mmol) was added. The reaction was started by the addition of dry K_2CO_3 (5.85 g, 42.3 mmol). The mixture was stirred at rt for 1.5 h and stopped by the addition of hexane (100 mL) and water (300 mL). The aqueous phase was extracted with hexane (4×100 mL), dried, and evaporated to afford a crude oil that was purified by chromatography on silica gel (hexane–ethyl acetate 25:1) to afford 3.33 g (73%) of **49** as a colorless oil; IR (neat, cm^{-1}) 1730, 1428, 1112; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.60 (m, 8H), 7.49–7.29 (m, 12H), 5.62 (s, 1H), 5.61 (d, *J*=0.5 Hz, 1H),

4.13 (s, 2H), 3.63 (s, 3H), 3.68–3.53 (m, 1H), 3.53 (dd, J=9.5, 6.6 Hz, 1H), 2.69 (dd, J=9.5, 5.8 Hz, 1H), 2.27 (dd, J=15.2, 8.4 Hz, 1H), 1.08 (s, 9 H), 1.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 135.6, 135.5, 133.8, 133.6, 130.7, 129.7, 129.6, 127.7, 127.6, 66.5, 643, 51.5, 41.3, 36.4, 26.9, 26.8, 19.3, 19.2; HRMS ES m/z $(M+Na)^+$ calcd 673.3140, obsd 673.3101; $[\alpha]_D^{20}$ +4.8 (c 3.38, $CHCl_3$).

4.22. (*E*)-(*S*)-6-(*tert*-Butyldiphenylsilanyloxy)-3-(*tert*-butyldiphenylsilanyloxymethyl)hex-4-enal (50)

A solution of **49** (2.09 g, 3.21 mmol) in dry THF was cooled to −78 °C and treated with DIBAL-H (9.64 mL, 9.64 mmol, 1 M in hexane). The reaction mixture was stirred at −78 °C for 10 min, warmed to 0 °C, and stirred for an additional 40 min in ice and 30 min at rt. Then 2 mL of methanol was added to quench and the resulting mixture was stirred for 10 min at rt prior to the introduction of saturated KNa-tartrate solution (60 mL) and ether (60 mL). Stirring was continued until the mixture was clear (2–4 h). The mixture was extracted with ether (4×50 mL), dried, and freed of solvents. The crude product was purified by chromatography on silica gel (hexane–ethyl acetate 7:1) to furnish the alcohol as a colorless oil (1.91 g, 95%); IR (neat, cm^{-1}) 3440, 1644, 1471; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76–7.60 (m, 8H), 7.50–7.29 (m, 12H), 5.62–5.53 (m, 2H), 4.20–4.12 (m, 2H), 3.75–3.52 (m, 4H), 2.47–2.33 (m, 1H), 2.10–1.88 (dt, J=19.8, 6.8 Hz, 1H), 1.61 (dt, J=22.0, 6.0 Hz, 1H), 1.08 (s, 9H), 1.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 135.5, 133.8, 133.6, 131.4, 130.4, 129.7, 129.6, 127.7, 127.6, 67.6, 64.4, 61.2, 42.4, 34.8, 26.99, 26.86, 19.3, 19.2; HRMS ES m/z $(M+Na)^+$ calcd 645.3191, obsd 645.3161; $[\alpha]_D^{20}$ +2.9 (c 1.13, $CHCl_3$).

Oxalyl chloride (70.1 μL, 0.83 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and cooled to −78 °C. Dry DMSO (117.5 μL, 1.66 mmol) was slowly added and after 1 h the above alcohol (258 mg, 0.41 mmol) dissolved in dry CH_2Cl_2 (5 mL) was introduced. The reaction mixture was stirred for 15 min at −78 °C, triethylamine (349 μL, 2.49 mmol) was added, and the reaction mixture was warmed to 0 °C, stirred for 30 min, and quenched with saturated NH_4Cl solution (10 mL). The product was extracted into ether (3×15 mL) and the combined organic phases were dried, evaporated to dryness, and quickly filtered through silica (hexane–ethyl acetate 7:1) to give pure **50** (259 mg, 100%); IR (neat, cm^{-1}) 1727, 1427, 1112; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (t, J=2.25 Hz, 1H), 7.69–7.56 (m, 8H), 7.47–7.28 (m, 12H), 5.58 (d, J=3.9 Hz, 2H), 4.13 (s, 2H), 3.64 (dd, J=5.02, 7.5 Hz, 1H), 3.49 (dd, J=7.5, 9.9 Hz, 1H), 2.33–2.96 (m, 1H), 2.66 (ddd, J=16.5, 6.1, 2.2 Hz, 1H), 2.43 (ddd, J=16.5, 7.7, 2.2 Hz, 1H), 1.04 (s, 9H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 135.6, 135.5, 133.7, 131.1, 129.7, 129.6, 129.2, 127.7, 127.6, 66.8, 64.1, 45.7, 39.6, 26.8, 19.22, 19.19; HRMS ES m/z $(M+Na)^+$ calcd 643.3034, obsd 643.3030; $[\alpha]_D^{20}$ +1.6 (c 0.57, $CHCl_3$).

4.23. (*E*)-(*S*)-11-Benzyloxy-1-(*tert*-butyldiphenylsilanyloxy)-4-(*tert*-butyldiphenylsilanyloxymethyl)undec-2-en-7-yn-6-one (51)

Benzyloxy-1-pentyne (7.88 g, 45.2 mmol) was dissolved in 200 mL of dry THF (200 mL) and n-BuLi (28.3 mL, 45.2 mmol, 1.6 N in hexane) was added at −65 °C. The mixture was warmed to −40 °C and stirred at that temperature for 1 h and returned to −78 °C. At this point, **50** (12.48 g, 20.1 mmol) was added via cannula as a solution in dry THF (50 mL), the temperature was raised slowly to −40 °C within 1 h, saturated NH_4Cl solution was added and the product was extracted into ether (3×150 mL). The combined organic layers were dried and evaporated to leave a residue that was purified by flash chromatography on silica gel (gradient elution with hexane–ethyl acetate 25:1 to 10:1) to yield 14.15 g (87%) of the alcohol as a 1:1 mixture of diastereomers.

The above alcohol mixture (94.3 mg, 0.119 mmol) was dissolved in CH_2Cl_2 (2.2 mL) and activated MnO_2 (104 mg, 1.19 mmol) was added. The reaction mixture was stirred for 15 h, treated with fresh MnO_2 (208 mg, 2.38 mmol), stirred for an additional 4 h, filtered through Celite, and purified by chromatography on silica gel (gradient elution with hexane–ethyl acetate 25:1 to 10:1) to afford 89.6 mg (95%) of pure **51**; IR (neat, cm^{-1}) 1673, 1472, 1428; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77–7.60 (m, 10H), 7.52–7.25 (m, 14H), 5.67–5.57 (m, 2H), 4.53 (s, 2H), 4.18 (d, J=1.5 Hz, 2H), 3.67 (dd, J=10.1, 5.3 Hz, 1H), 3.59 (t, J=5.8 Hz, 2H), 3.52–3.50 (m, 1H), 3.10–2.97 (m, 1H), 2.90 (dd, J=15.9, 5.8 Hz, 1H), 2.57 (dd, J=15.9, 7.8 Hz, 1H), 2.53 (t, J=7.0 Hz, 2H), 1.90 (q, J=7.0 Hz, 2H), 1.10 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 135.7, 135.6, 133.74, 133.71, 133.5, 130.9, 129.7, 129.6, 129.4, 128.4, 127.74, 127.71, 127.67, 93.6, 81.4, 73.1, 68.4, 66.5, 64.3, 46.4, 40.7, 28.1, 26.9, 19.32, 19.26, 16.0; HRMS ES m/z $(M+Na)^+$ calcd 815.3922, obsd 815.3908; $[\alpha]_D^{20}$ +5.0 (c 4.21, $CHCl_3$).

4.24. [(*E*)-(4*S*,6*S*)-11-Benzyloxy-4-(*tert*-butyldiphenylsiloxy)-6-methoxymethoxyundec-2-en-7-ynyloxy-*tert*-butyldiphenylsilane (53)

Ketone **51** (112 mg, 0.14 mmol) was dissolved in dry THF (2.7 mL) and the CBS reagent (0.4 mL, 0.4 M solution in THF, 0.16 mmol) was added. The reaction mixture was cooled to −78 °C, treated with borane (0.71 mL, 0.71 mmol, 1 M in THF), warmed to −40 °C within 15 min and kept at that temperature for an hour. When reaction was found to be complete (TLC analysis), MeOH (0.7 mL) was added and stirring was continued for another 10 min. After the addition of saturated NH_4Cl solution, the mixture was extracted with ether (3×5 mL), and the combined organic layers were dried and evaporated to dryness. The residue was purified by flash chromatography on silica gel (hexane–ethyl acetate 10:1) to give 112 mg (100%) of **52** as a colorless oil; IR (neat, cm^{-1}) 3433, 1472, 1428; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.54 (m, 10H), 7.46–7.21 (m, 14H), 5.67–5.46 (m, 2H), 4.50 (s, 2H), 4.38–4.28 (m, 1H), 4.14 (d, J=4.0 Hz, 2H), 3.48–3.10 (m, 4 H), 2.62–2.47 (m, 1H), 2.35 (dt, J=1.6, 7.0 Hz, 2H), 2.12–1.98 (m, 1H), 1.96–1.80 (m, 1H), 1.81 (q, J=6.8 Hz, 2H), 1.75–1.63 (m, 1H), 1.05 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 135.7, 135.6, 133.7, 133.6, 131.1, 131.0, 129.7, 128.4, 127.72, 127.69, 127.6, 84.5, 82.0, 68.8, 67.6, 64.4, 60.8, 41.8, 40.6, 28.9, 26.93, 26.91, 19.3, 15.7; HRMS ES m/z $(M+Na)^+$ calcd 817.4079, obsd 817.4060; $[\alpha]_D^{20}$ +2.5 (c 6.51, $CHCl_3$).

This enantiomerically enriched alcohol (2.45 g, 3.09 mmol) was dissolved in CH_2Cl_2 (50 mL) and Hünig's base (2.64 mL, 15.4 mmol) was added. The mixture was cooled to 0 °C, treated with MOMCl (1.16 mL, 15.4 mmol), stirred for 8.5 h, and quenched with saturated NH_4Cl solution (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3×30 mL), the combined organic layers were dried, and evaporated to give a crude product that was purified by chromatography on silica gel (gradient elution with hexane–ethyl acetate 25:1 to 10:1) to afford 2.48 g (96%) of **53**; IR (neat, cm^{-1}) 1472, 1428, 1112; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83–7.67 (m, 10H), 7.50–7.26 (m, 14H), 5.73–5.62 (m, 2H), 5.00 (d, J=6.7 Hz, 1H), 4.62 (d, J=6.7 Hz, 1H), 4.54 (s, 2H), 4.50–4.38 (m, 1H), 4.25 (s, 2H), 3.72–3.58 (m, 4 H), 3.38 (s, 3H), 2.54–2.58 (m, 1H), 2.5–2.37 (m, 2H), 2.18–2.04 (m, 1H), 1.87 (q, J=6.7 Hz, 2H), 1.78–1.55 (m, 1H), 1.14 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 135.7, 133.8, 131.1, 129.6, 128.4, 127.68, 127.65, 127.58, 94.0, 85.4, 79.4, 73.0, 68.9, 65.4, 64.5, 63.9, 55.8, 41.4, 35.6, 28.9, 26.9, 19.4, 19.3, 15.8; HRMS ES m/z $(M+Na)^+$ calcd 861.4341, obsd 861.4389; $[\alpha]_D^{20}$ +36.9 (c 4.39, $CHCl_3$).

4.25. ((2*S*,4*R*)-9-Benzyloxy-4-methoxymethoxy-2-vinylnon-5-ynyloxy)-*tert*-butyldiphenylsilane (54)

Enyne **53** (500 mg, 0.596 mmol) was dissolved in hexane (34 mL) and ozone was bubbled through the solution at −78 °C for 15 min. The solution was purged with oxygen for 15 more minutes, treated with a solution of PPh_3 (469 mg, 1.79 mmol) in ether (1 mL), and stirred at 0 °C for 3.5 h at rt. Simultaneously, methylenetriphenylphosphorane was prepared in a separate flask by adding n-BuLi (2.98 mL, 4.17 mol, 1.4 N solution in hexane) to a suspension of $PPh_3CH_3^{\ddagger}Br^-$ (2.34 g, 6.56 mmol) in ether (9.8 mL). The suspension was stirred at 0 °C for 4 h and then added to the phosphorane over a period of 10 min at 0 °C. Stirring was continued overnight and the reaction mixture was allowed to warm to rt, quenched with saturated NH_4Cl solution (30 mL), and extracted with ether (4×20 mL) and CH_2Cl_2 (1×20 mL). The combined organic layers were dried and freed of solvent prior to chromatography on silica gel (gradient elution with pure hexane to hexane–ethyl acetate 3:1) to afford 291 mg (85%) of **54**; IR (neat, cm^{-1}) 1468, 1527, 1112; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80–7.67 (m, 5H), 7.50–7.25 (m, 10H), 5.84–5.78 (m, 1H), 5.64 (s, 1H), 5.00 (d, J=9.7 Hz, 1H), 4.90 (d, J=6.8 Hz, 1H), 4.58 (d, J=6.8 Hz, 1H), 4.52 (s, 2H), 4.44–4.34 (m, 1H), 3.13 (d, J=5.6 Hz, 2H), 3.57 (t, J=6.2 Hz, 2H), 3.38 (s, 3H), 2.64–2.50 (m, 1H), 2.36 (t, J=7.0 Hz, 2H), 2.05 (ddd, J=9.3, 4.6, 4.6 Hz, 1H), 1.82 (q, J=6.5 Hz, 2H), 1.72 (ddd, J=9.3, 4.6, 4.6 Hz, 1H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 138.5, 135.70, 135.67, 135.5, 134.8, 133.8, 129.7, 129.6, 128.4, 127.7, 127.63, 127.58, 116.5, 94.0, 85.4, 79.3, 73.0, 68.8, 67.3, 63.9, 55.8, 42.8, 37.9, 28.9, 26.9, 19.3, 15.6; HRMS ES m/z $(M+Na)^+$ calcd 593.3058, obsd 593.3070; $[\alpha]_D^{20}$ +53.4 (c 0.99, $CHCl_3$).

4.26. {(1*S*,4*R*)-3-[4-Benzyloxybut-(*Z*)-ylidene]-4-methoxymethoxy-2-methylenecyclopentyl}methanol (56)

A solution of **54** (221 mg, 0.39 mmol) in deoxygenated dichloroethane was treated with $Pd(OAc)_2$ (17.4 mg, 0.08 mmol) and *N,N*-bis-(benzylidene)ethylenediamine (**55**) (18.3 mg, 0.08 mmol) and stirred at 60 °C for three days until all starting material was consumed. The solvent was removed to leave a residue (*E:Z*=3.5:1) from which it was possible to separate the major part of the desired *E*-isomer **56** (72.5 mg, 31%) from the *E:Z* mixture (63.7 mg, 32%) (silica gel, gradient elution from 25:5 hexane–ethyl acetate; IR (neat, cm^{-1}) 1468, 1427, 1112; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80–7.60 (m, 5H), 7.51–7.26 (m, 10H), 6.04 (t, J=7.5 Hz, 1H), 5.45 (s, 1H), 4.81 (s, 2H), 4.72 (d, J=6.9 Hz, 1H), 4.56 (d, J=6.9 Hz, 1H), 4.52 (s, 2H), 3.85–3.68 (m, 2H), 3.51 (t, J=6.3 Hz, 2H), 3.36 (s, 3H), 2.90–2.74 (m, 1H), 2.52–2.24 (m, 2H), 2.14–2.00 (m, 1H), 1.99–1.58 (m, 3 H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 140.9, 135.6, 134.1, 129.5, 128.4, 127.64, 127.61, 127.55, 127.48, 104.0, 94.4, 75.6, 72.9, 69.8, 68.1, 55.6, 45.7, 32.9, 29.7, 26.9, 26.0, 19.3; HRMS ES m/z $(M+Na)^+$ calcd 593.3058, obsd 593.3080; $[\alpha]_D^{20}$ −32.0 (c 3.63, $CHCl_3$).

The above material (66.9 mg, 0.12 mmol) was dissolved in dry THF (3.9 mL) and TBAF (123 μL, 1 M in THF, 0.12 mmol) was added. The reaction mixture was stirred at rt for 4 h and diluted with water (5 mL) and ether (2 mL). The mixture was extracted with ether (3×4 mL) and the combined organic layers were dried and evaporated. The residue was purified by chromatography on silica gel (gradient elution with hexane–ethyl acetate 10:1 to 2:1) to give 34 mg (88%) of pure **56**; IR (neat, cm^{-1}) 3428, 1453, 1147; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.18 (m, 5 H), 6.07 (dt, J=7.2, 1.0 Hz, 1H), 5.41 (d, J=1.8 Hz, 1H), 4.91 (d, J=1.3 Hz, 1H), 4.72 (d, J=5.4 Hz, 1H), 4.63 (dd, J=18.2, 6.9 Hz, 2H), 4.50 (s, 3H), 3.70 (d, J=6.3 Hz, 2H), 3.37 (s, 3H), 2.76–2.88 (m, 1H), 2.53–2.22 (m, 2H), 2.01 (ddd, J=18.9, 14.4, 5.3 Hz, 1H), 1.94–1.63 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 140.3, 138.5, 128.4, 128.2, 127.6, 127.5, 127.4, 104.3, 94.3, 75.1, 72.9, 69.7, 66.3, 55.8, 45.3, 33.9, 29.6, 26.1; HRMS ES m/z $(M+Na)^+$ calcd 355.1880, obsd 355.1861; $[\alpha]_D^{20}$ −20.6 (c 1.81, $CHCl_3$).

4.27. (*S*)-3-(*tert*-Butyldiphenylsilanyloxymethyl)-3-methylcyclopent-1-enecarboxylic acid (1*S*,4*R*)-3-[4-benzyloxybut-(*Z*)-ylidene]-4-methoxymethoxy-2-methylenecyclopentyl methyl ester (57)

Diene **56** (7.3 mg, 0.014 mmol) was dissolved in dry CH_2Cl_2 (1.8 mL) and carboxylic acid **16** (28.3 mg, 0.072 mmol) and DMAP (20.5 mg, 0.168 mmol) were added. Finally DCC (34.7 mg, 0.168 mmol) was added and the reaction mixture was stirred for three days. The reaction was arrested by the addition of water (5 mL) and extraction with CH_2Cl_2 (3×5 mL). The combined organic layers were dried and evaporated to leave a residue that was purified by flash chromatography on silica gel (gradient elution with hexane–ethyl acetate 25:1 to 10:1) to give 9.2 mg (90%) of **57** as a colorless oil; IR (neat, cm^{-1}) 1715, 1646, 1456; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.61 (m, 4H), 7.47–7.25 (m, 11H), 6.62 (t, J=2.0 Hz, 1H), 6.08 (t, J=7.6 Hz, 1H), 5.91 (d, J=1.6 Hz, 1H), 5.40 (d, J=1.6 Hz, 1H), 4.75–4.69 (m, 1H), 4.65 (s, 2H), 4.52 (s, 2H), 4.31 (dd, J=10.4, 7.2 Hz, 1H), 4.36 (dd, J=10.2, 8.4 Hz, 1H), 3.53–3.47 (m, 4H), 3.37 (s, 3H), 3.00–2.90 (m, 1H), 2.68–2.58 (m, 4H), 2.97–2.25 (m, 2H),

2.24–1.60 (m, 6H), 1.16 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 165.4, 154.0, 149.3, 148.0, 140.2, 139.4, 139.0, 135.6, 133.6 (2C), 129.6, 128.4, 127.6, 127.1, 105.0, 100.0, 99.9, 94.5, 75.5, 72.9, 70.5, 70.2, 69.7, 68.0, 58.8, 55.7, 33.7, 33.0, 31.0, 29.7, 26.9, 26.8, 26.6, 24.6, 22.8, 22.7, 14.1; HRMS ES *m/z* $(M+Na)^+$ calcd 731.3738, obsd 731.3740; $[\alpha]_D^{20}$ −8.9 (*c* 0.46, $CHCl_3$).

4.28. (*S*)-3-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-cyclopent-1-enecarboxylic acid (1*S*,4*R*)-2-formyl-4-(4-methoxybenzyloxy)-3-[5-(2-methoxyethoxymethoxy) pentyl]cyclopent-2-enylmethyl ester (59)

To a solution of **36** (179 mg, 0.19 mmol) in dry CH_2Cl_2 (17 mL) was added MnO_2 (334 mg, 3.84 mmol). After 15 h of stirring at rt, the MnO_2 was removed by filtration over a pad of Celite. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (hexane–ethyl acetate 4:1) to give 122 mg (85%) of pure **59** as a colorless oil; IR (neat, cm^{-1}) 1714, 1672, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.68–7.59 (m, 4H), 7.47–7.34 (m, 6H), 7.24 (d, *J*=11.6 Hz, 2H), 6.86 (d, *J*=11.6 Hz, 2H), 6.55 (s, 1H), 4.70 (s, 2H), 4.58 (d, *J*=11.5 Hz, 1H), 4.48 (dd, *J*=10.7, 4.3 Hz, 1H), 4.36 (d, *J*=11.5 H, 1H), 4.17 (dd, *J*=10.7, 7.7 Hz, 1H), 3.79 (s, 3H), 3.70–3.64 (m, 2H), 3.58–3.47 (m, 4H), 3.45 (s, 3H), 3.39 (s, 3H), 3.26–3.14 (m, 1H), 2.74–2.41 (m, 4H), 2.35–2.22 (m, 1H), 2.01–1.87 (m, 1H), 1.78–1.16 (m, 8H), 1.12 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.8, 165.3, 159.4, 149.3, 137.9, 135.7, 135.6, 133.6, 133., 130.0, 129.6, 129.5, 127.6, 113.8, 95.5, 82.8, 71.8, 71.4, 70.5, 67.6, 66.7, 65.8, 59.0, 55.2, 41.5, 33.8, 32.3, 31.9, 30.7, 29.4 (2C), 29.2, 28.4, 26.9, 26.3, 26.0, 22.7 (2C), 19.4, 14.1; HRMS ES *m/z* $(M+Na)^+$ calcd 835.4212, obsd 835.4236; $[\alpha]_D^{20}$ −0.77 (*c* 4.81, $CHCl_3$).

4.28.1. (*S*)-3-(*tert*-Butyldiphenylsilanyloxy)-3-methyl-cyclopent-1-enecarboxylic Acid (1*S*,4*R*)-2-[1-(*tert*-butyl-dimethylsilanyloxy)-meth-(*E*)-ylidene]-4-(4-methoxy-benzyloxy)-3-[5-(2-methoxyethoxymethoxy)pent-(*Z*)-ylidene]cyclopentylmethyl ester (60).

A solution of **59** (21.2 mg, 0.026 mmol) and triethylamine (40 μL, 0.29 mmol) in dry CH_2Cl_2 (1 mL) was cooled to −78 °C and triethylsilyl triflate (22 μL, 0.098 mmol) was added. The reaction mixture was warmed to 0 °C and kept at that temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 (2 mL) and evaporated, and the residue was purified by flash chromatography (hexane–ethyl acetate 10:1) to give 15.5 mg (64%) of **60** as a colorless oil; IR (neat, cm^{-1}) 1716, 1652, 1457; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.62 (m, 4H), 7.48–7.34 (m, 6H), 7.26 (d, *J*=8.4 Hz, 2H), 6.86 (d, *J*=8.4 Hz, 2H), 6.82 (s, 1H), 6.60 (s, 1H), 5.67 (t, *J*=7.6 Hz, 1H), 4.73 (s, 2H), 4.64 (dd, *J*=10.4, 4.8 Hz, 1H), 4.50 (d, *J*=10.8 Hz, 1H), 4.43–4.51 (m, 1H), 4.11 (t, *J*=10.4 Hz, 1H), 3.80 (s, 3 H), 3.72–3.67 (m, 2H), 3.61–3.47 (m, 4H), 3.42 (s, 3H), 3.32–3.11 (m, 1H), 2.68–2.49 (m, 2H), 2.31 (d, *J*=20.8 Hz, 1H), 2.23–2.07 (m, 2H), 2.03–1.93 (q, *J*=7.6 Hz, 1H), 1.75–1.20 (m, 9H), 1.17 (s, 3H), 1.07 (s, 9H), 1.00 (t, *J*=6.5 Hz, 6H), 0.70 (q, *J*=6.5 Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 159.0, 139.5, 136.1, 135.7, 135.6, 134.2, 133.7, 133.6, 130.8, 129.6, 129.5, 129.1, 127.7, 127.6, 126.0, 125.8, 123.8, 121.4, 120.2, 113.7, 95.5, 78.6, 71.8, 70.6, 69.7, 67.8, 66.7, 65.9, 60.4, 59.0, 55.2, 52.2, 39.4, 37.1, 33.8, 29.7, 29.4, 29.3, 26.5, 22.9, 22.7, 22.6, 19.4, 14.2, 14.1, 11.4, 6.5, 4.5; HRMS ES *m/z* $(M+Na)^+$ calcd 949.5077, obsd 949.5119; $[\alpha]_D^{20}$ −15.7 (*c* 0.78, $CHCl_3$).

4.29. (*S*)-1-Methylcyclopent-2-enecarboxylic acid ethyl ester (63)

Dry triethylamine (237 mL, 1.70 mol) and methanesulphonyl chloride (57 mL, 0.74 mol) were added to a stirred solution (2*S*)-hydroxy-(1*S*)-methylcyclopentanecarboxylic acid ethyl ester (97.45 g, 0.567 mol) in dry CH_2Cl_2 (1.15 L) at 0 °C under N_2. The mixture was stirred at 0 °C for 3 h, diluted with CH_2Cl_2 (800 mL), and washed with brine (1 L). The aqueous phase was extracted with CH_2Cl_2 (500 mL), the combined organic layers were dried and freed of solvent to leave a residue that was purified by chromatography on silica gel (gradient elution with pure hexane to hexane–ethyl acetate 3:1) to afford the mesylate (101.1 g, 71%) as a yellow oil; IR (neat, cm^{-1}) 3548, 1725, 1466; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.32–5.23 (m, 1H), 3.80 (q, *J*=7.1Hz, 2H), 3.03 (s, 3 H), 2.32–1.58 (m, 6H), 1.31 (s, 3H), 1.27 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 89.3, 60.6, 52.1, 37.5, 34.7, 30.7, 19.8, 17.8, 13.6; HRMS ES *m/z* $(M+Na)^+$ calcd 273.0767, obsd 273.0771; $[\alpha]_D^{20}$ +46.7 (*c* 1.4, $CHCl_3$).

1,8-Diazabicyclo[5.4.0]undec-7-ene (91 mL, 0.61 mol) was added to a solution of the above mesylate (101.1 g, 0.404 mol) in dry DMF (300 mL) at rt under N_2. The reaction mixture was heated at 160 °C for 12 h, diluted with ether (800 mL), and washed with water (2×800 mL). The combined organic layers were dried and evaporated to leave a brown oil, which was purified by chromatography on silica gel (hexane–ethyl acetate 99:1) to afford **63** (35.05 g, 84%) as a pale yellowish oil; IR (neat, cm^{-1}) 1731, 1464, 1372; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (dt, *J*=5.5, 2.1 Hz, 1H), 5.69 (dt, *J*=5.5, 2.0 Hz, 1H), 4.13 (q, *J*=7.1 Hz, 2H), 2.51–2.35 (m, 4H), 1.31 (s, 3H), 1.25 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 134.8, 131.0, 89.3, 59.9, 55.1, 34.6, 31.3, 24.2, 13.7; HRMS ES *m/z* $(M+Na)^+$ calcd 177.0886, obsd 177.0885; $[\alpha]_D^{20}$ −78.5 (*c* 1.1, $CHCl_3$).

4.30. *tert*-Butylmethyl-((*S*)-1-methylcyclopent-2-enyl-methoxy) phenylsilane (64)

Lithium aluminum hydride (11.2 g, 0.295 mol) was added portion wise over a period of 2 h to a stirred solution of **63** (35.05 g, 0.227 mol) in dry ether (450 mL) at rt. The mixture was stirred for 30 min, cooled to 0 °C, treated with 1.0 N NaOH solution until the mixture turned white, and extracted with CH_2Cl_2 (3×1 L). The combined organic phases were dried and freed of solvent. The residue was chromatographed on silica gel (hexane–ethyl acetate 5:1) to give the primary carbinol (23.25 g, 91%) as a pale yellow oil; IR (neat, cm^{-1}) 3370, 1457, 1379; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.81 (dt, *J*=5.6, 2.3 Hz, 1H), 5.46 (dt, *J*=5.6, 2.2 Hz, 1H), 3.50–3.31 (m, 2H), 2.45–2.33 (m, 2H), 2.00–1.87 (m, 1H), 1.65–1.49 (m, 1H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.6, 131.0 69.9, 50.8, 33.3, 31.7, 23.0; HRMS ES molecular ion too fleeting for accurate mass measurement; $[\alpha]_D^{20}$ −32.0 (*c* 1.3, $CHCl_3$).

Imidazole (28.3 g, 0.416 mmol) was added to a solution of the above alcohol (23.2 g, 0.208 mol) in DMF (100 mL) at 0 °C. After 20 min, *tert*-butyldiphenylsilyl chloride (60 mL, 0.23 mol) was added, and the resulting solution was stirred for 15 h at rt, diluted with ether (600 mL), and washed with water (2×500 mL). The organic layer was dried and the solvent was removed to leave a residue that was purified by chromatography on silica gel (hexane) to give **64** as a colorless foam (64.33 g, 89%); IR (neat, cm^{-1}) 1656, 1589, 1486; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.63 (m, 4H), 7.47–7.32 (m, 6H), 5.70 (dt, J=5.6, 2.2 Hz, 1H), 5.57 (dt, J=5.6, 2.1 Hz, 1H), 3.48 (d, J=9.4 Hz, 1H), 3.44 (d, J=9.4 Hz, 1H), 2.40–2.31 (m, 2H), 1.93–1.82 (m, 1H), 1.54–1.48 (m, 1H), 1.12 (s, 3 H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 135.7, 134.0, 130.2, 129.5, 127.6, 71.3, 51.4, 33.9, 31.8, 26.9, 23.8, 19.4; HRMS ES *m/z* $(M+Na)^+$ calcd 373.1958, obsd 373.1967; $[\alpha]_D^{20}$ −31.9 (*c* 1.6, $CHCl_3$).

4.31. (*S*)-4-(*tert*-Butylmethylphenylsilanyloxymethyl)-2-iodo-4-methylcyclopent-2-enone (65)

3,5-Dimethylpyrazole (179 g, 1.87 mol) was added to a suspension of chromium(VI) oxide (189.9 g, 1.899 mol) in dry CH_2Cl_2 (1 L) at −15 °C and stirred at this temperature for 20 min prior to the introduction of a solution of **64** (43.67 g, 0.125 mol) in dry CH_2Cl_2 (200 mL). The mixture was stirred for 1 h at −15 °C, filtered through a pad of SiO_2 (ethyl acetate 1:hexane 3), and freed of solvent. The residue was purified by chromatography on silica gel (hexane–ethyl acetate 5:1) to afford the enone as a pale orange oil (18.74 g, 41%); IR (neat, cm^{-1}) 1717, 1589, 1472; ^1H NMR (250 MHz, $CDCl_3$) δ 7.65–7.58 (m, 4H), 7.49–7.32 (m, 7H), 6.12 (d, J=5.6 Hz, 1H), 3.56 (s, 2H), 2.46 (d, J=18.4 Hz, 1H), 2.08 (d, J=18.4 Hz, 1H), 1.21 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 169.9, 135.4, 133.0, 132.8, 129.6, 127.5, 69.4, 47.2, 45.0, 26.6, 22.3, 19.0; HRMS ES *m/z* $(M+Na)^+$ calcd 387.1751, obsd 387.1752; $[\alpha]_D^{20}$ −55.4 (*c* 0.8, $CHCl_3$).

To a solution of iodine (41.2 g, 0.162 mol) in dry CH_2Cl_2 (100 mL) and dry pyridine (80 mL) at 0 °C was added via cannula to a solution of the above ketone (27.54 g, 0.076 mol) in a l:l mixture of dry CH_2Cl_2 and pyridine (300 mL). The resulting mixture was stirred for 5 min at 0 °C and at rt for 22 h prior to dilution with H_2O (500 mL) and cooling to 0 °C. 2 M HCl was slowly added until pH 4 was reached, at which point the separated aqueous layer was extracted with CH_2Cl_2 (600 mL). The combined organic phases were washed with saturated sodium thiosulphate solution (1 L) and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried and the solvent evaporated to leave a brown oil, which was purified by chromatography on silica gel (hexane–ethyl acetate 1:1) to give **65** as a pale yellow oil (35.9 g, 97%); IR (neat, cm^{-1}) 1721, 1578, 1472; ^1H NMR (250 MHz, $CDCl_3$) δ 7.68–7.58 (m, 4H), 7.50–7.32 (m, 6H), 7.37 (s, 1H), 3.55 (s, 2H), 2.62 (d, J=18.3 Hz, 1H), 2.19 (d, J=18.3 Hz, 1H), 1.19 (s, 3H), 1.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 174.6, 135.4, 132.6, 129.7, 127.6, 101.7, 68.9, 49.6, 42.1, 26.6, 21.9, 14.0; HRMS ES *m/z* $(M+Na)^+$ calcd 513.0717, obsd 513.0727; $[\alpha]_D^{20}$ 55.4 (*c* 2.6, $CHCl_3$).

4.32. (*S*)-3-(*tert*-Butylmethylphenylsilanyloxymethyl)-3-methyl-5-oxocyclopent-1-enecarboxylic acid methyl ester (66)

Triethylamine (31 mL, 0.22 mol) and anhydrous MeOH (6.0 mL, 0.15 mol) were added to a stirred solution of **65** (35.92 g, 73.3 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (2.62 g, 2.86 mmol), and Ph_3P (3.0 g, 0.01 mol) in dry DMF (260 mL) at rt under a carbon monoxide atmosphere. The resulting mixture was heated at 70 °C for 20 h, cooled to rt, diluted with ether (1.2 L), and washed with water (2×1 L). The organic phase was dried and the solvent was removed to give a black residue that was purified by chromatography on silica gel (hexane–ethyl acetate 5:1) to afford **66** as a yellow oil (18.98 g, 61%); IR (neat, cm^{-1}) 1755, 1727, 1624; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.67–7.54 (m, 4H), 7.49–7.34 (m, 6H), 3.86 (s, 3H), 3.59 (s, 2H), 2.66 (d, J=18.5 Hz, 1H), 2.27 (d, J=18.5 Hz, 1H), 1.23 (s, 3 H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 176.7, 162.0, 135.7, 135.4, 132.5, 129.7, 127.6, 69.0, 49.6, 51.7, 46.4, 44.8, 26.5, 21.7, 19.0; HRMS ES *m/z* $(M+Na)^+$ calcd 445.1806, obsd 445.1784; $[\alpha]_D^{20}$ −38.4 (*c* 1.0, $CHCl_3$).

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