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An approach to triquinane synthesis using the Pauson–Khand reaction

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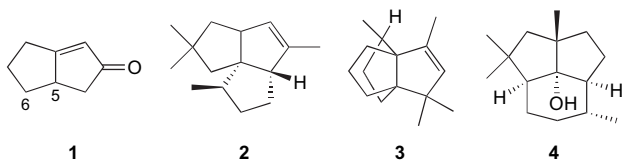
Abstract—Tricyclic skeletons have been generated from acyclic enyne precursors by using an intramolecular Pauson–Khand reaction in combination with aldol, Michael and alkylation reactions.

1. Introduction

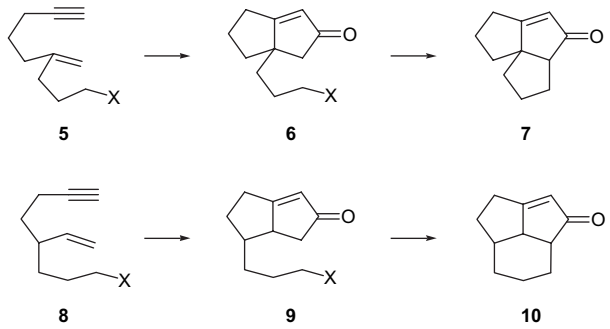
The Pauson–Khand reaction (PKR) is widely regarded as one of the most efficient and versatile methods for cyclopentenone synthesis.[1] The reaction is a cobalt mediated [2+2+1] cycloaddition and has been shown to be a powerful method for the generation of the bicyclo[3.3.0]oct-1-ene-3-one system **1** (Fig. 1).[2] It has been used as a key step in the synthesis of a number of natural products including hirsutene,[3] kainic acid,[4] pentalenene,[5] brefeldin-A,[6] asteriscanolide,[7] and epoxydictymene.[8] Pauson–Khand reactions have been used in tandem[9] with other processes to make tricycles, for example, Clive's synthesis of angularly fused triquinanes via the PKR, leaving a chain in the allylic position, followed by a radical cyclization.[10] Triquinanes continue to be a focus of interest, in part due to their inherently interesting structures but also since some possess biological activity.[11,12]

The goal of this study was a one-pot synthesis of tricycles using Pauson–Khand reactions followed by aldol or alkylation processes.[9] Unexpectedly, the enone moiety of the bicyclooctenones formed in the PKR was quite reactive and became the unanticipated focal point of subsequent cyclizations. Incorporation of a side chain bearing reactive functionality at either C-5 or C-6 of bicyclooctenone **1** was found to be useful in key transformations providing access to the ring systems found in tricyclic natural products such as pentalenene (**2**),[5,13] modhephene (**3**),[14,15,16] and presilphiperfolanol (**4**).[17] Intramolecular Pauson–Khand reactions with enynes such as **5** and **8** (Scheme 1) should provide bicyclooctenones **6** and **9**, which after a second appropriate carbon–carbon bond forming reaction, would be expected to generate tricycles **7** and **10**, respectively.



1 2 3 4

Figure 1.



Scheme 1.

2. Results and discussion

Our first goal was synthesis of the tricyclo[6.3.0.0]undecane ring system. Toward this end, bromide **11**[18] was transformed into the corresponding Grignard reagent and then treated with aldehyde **18**[19] generating alcohol **12** in 58% yield

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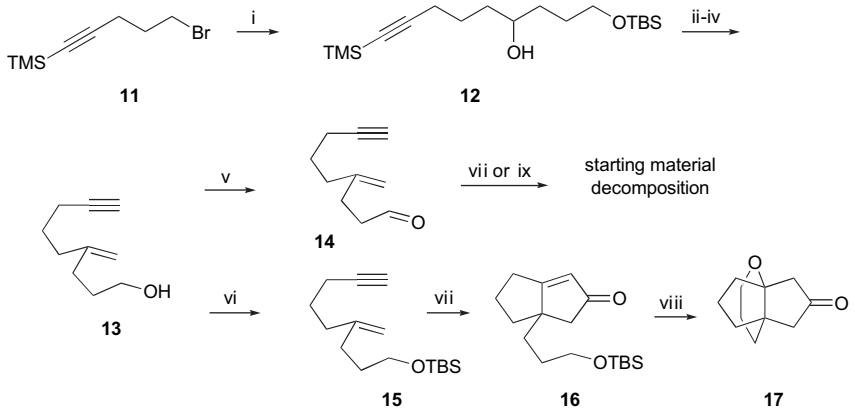
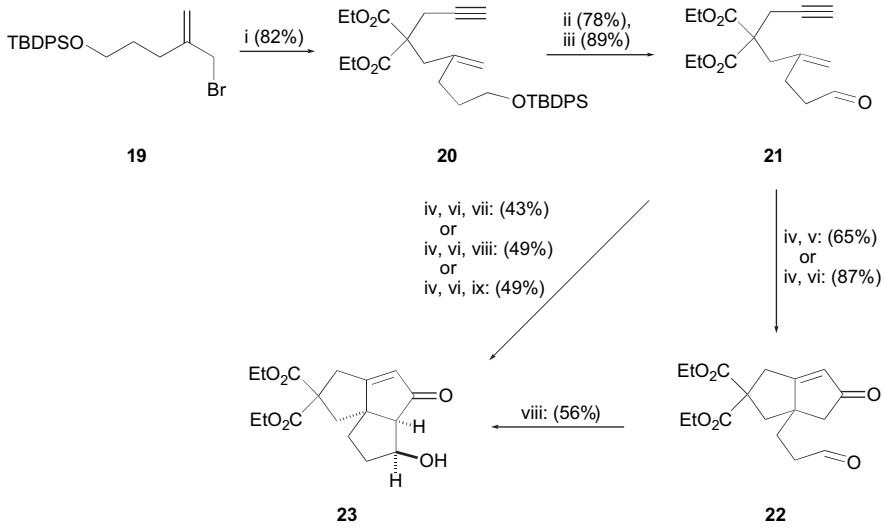


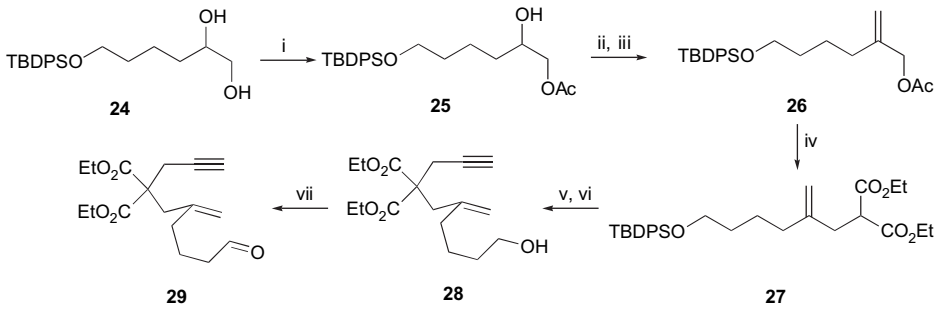
Scheme 2. Reagents and conditions: (i) a, Mg, Et_2O, rt; b, $TBSOCH_2CH_2CH_2CHO$ **18**[19] Et_2O, rt 58%; (ii) $(COCl)_2$, DMSO, NEt_3, THF, −78 °C, 94%; (iii) Tebbe reagent, THF, −40 °C, 78%; (iv) TBAF, THF, rt, 49%; (v) PCC, CH_2Cl_2, rt, 73%; (vi) TBSCI, imidazole, CH_2Cl_2, rt, 88%; (vii) $CO_2(CO)_8$, toluene, 110 °C, 32%; (viii) TBAF, THF, rt, 44%; and (ix) a, $Co_2(CO)_8$, CH_2Cl_2, rt; b, $NMO{\cdot}H_2O$, CH_2Cl_2, rt.

(Scheme 2). Swern oxidation of alcohol **12**, followed by Tebbe olefination and deprotection (TBAF) of both the silyl ether and acetylene moieties gave enyne **13** in 36% overall yield. PCC oxidation of alcohol **13** gave aldehyde **14**, which when subjected to either thermal or trialkylamine *N*-oxide promoted Pauson–Khand reaction conditions, resulted in only decomposition of the starting material. Alcohol **13** was subsequently protected as the TBS ether **15**. Subjection of enyne **15** to *N*-methylmorpholine *N*-oxide (NMO)-promoted Pauson–Khand reaction conditions led only to alkyne decomplexation, whereas, thermal conditions gave a modest yield of bicyclooctenone **16**. No other identifiable compounds were isolable. Interestingly and unexpectedly, attempted desilylation of enone **16** under a variety of conditions gave [4.3.3]propellane **17** resulting from conjugate addition of the alcohol to the cyclopentenone moiety.

Due to the low yield in the Pauson–Khand reaction of enyne **16**, a diester moiety was incorporated into the enyne to provide Thorpe–Ingold assistance[20] in the Pauson–Khand reaction. Thus, our attention was next turned to the synthesis and reactions of enynal **21** (Scheme 3). The synthesis of **21** was achieved via palladium-catalyzed alkylation[21] of allylic bromide **19**[22] using the sodium salt of propargyl diethyl malonate, which gave enyne **20** in 82% yield. Deprotection of the silyl protected alcohol using TBAF followed by Swern oxidation gave aldehyde **21** in 69% overall yield. Pauson–Khand reaction of enynal **21**, under thermal conditions, led to decomposition of the starting material. In contrast, the NMO-promoted Pauson–Khand reaction gave bicyclooctenone **22** in 65% yield, however, when anhydrous Me_3NO (TMANO) was used,[23] bicyclooctenone **22** was obtained in 85% yield. Aldol cyclization of **22** was investigated next. Use of potassium carbonate, cesium carbonate, zirconium(IV)*tert*-butoxide, and potassium methoxide all led to decomposition of the starting material. However, when DBU was used in the aldol cyclization of **22**, tricyclo[6.3.0.0]-undecane **23** was obtained in 56% yield. Having established that the stepwise Pauson–Khand sequence from enynal **21** to triquinane **23**, was successful, we then considered the possibility of performing a one-pot transformation. Use of the optimal Me_3NO-promoted conditions for the Pauson–Khand



Scheme 3. Reagents and conditions: (i) Na-propargyl diethyl malonate, $Pd(OAc)_2$, PPh_3, THF, Δ; (ii) TBAF, THF, rt; (iii) $(COCl)_2$, DMSO, NEt_3, THF, -78 °C; (iv) $Co_2(CO)_8$, CH_2Cl_2, rt; (v) $NMO{\cdot}H_2O$, CH_2Cl_2, rt; (vi) Me_3NO, CH_2Cl_2, rt; (vii) DBU, CH_2Cl_2, rt; (viii) DBN, CH_2Cl_2, rt; and (ix) 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine, CH_2Cl_2, rt.



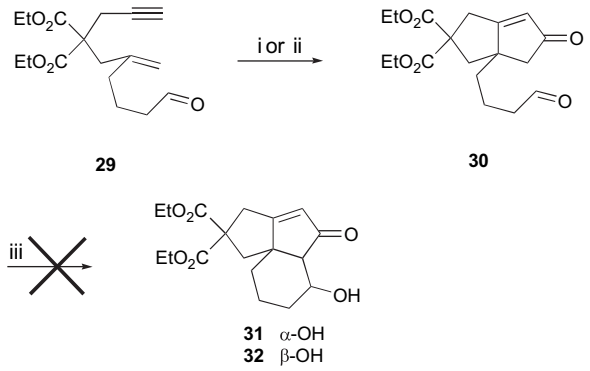
Scheme 4. Reagents and conditions: (i) AcCl, 2,4,6-collidine, CH_2Cl_2, −78 °C, 100%; (ii) Jones reagent, benzene, rt, 80%; (iii) Ph_3PCH_2, THF, −78 °C, 65%; (iv) Na-diethyl malonate, PdCl(allyl)PPh_3, THF, Δ, 68%; (v) a, NaH, THF, 0 °C; b, propargyl bromide, rt, 82%; (vi) TBAF, THF, rt, 88%; and (vii) PCC, CH_2Cl_2, rt, 90%.

reaction with DBU as base gave triquinane **23** in 43% yield as a single diastereomer. Changing the base to DBN or 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine resulted in the formation of triquinane **23** in 49% yield for both of the one-pot processes. It was therefore possible to prepare tricycle **23** in four synthetic operations from allylic bromide **19**. As anticipated, geminal substitution on the tether between the alkene and alkyne greatly facilitated the PKR with the substituted alkene.

Having gained access to the tricyclo[6.3.0.0]undecane ring system found in pentalenene **2**, the length of the side chain at the ring fusion of PK bicyclooctenone **22** was increased by one carbon in an attempt to prepare a homolog of **23**. The synthesis of enynal **29** started from the known diol **24**[24] (Scheme 4), which was selectively acetylated[25] to give alcohol **25**. Jones oxidation to the corresponding ketone followed by Wittig olefination using methyltriphenylphosphonium bromide gave allylic acetate **26** in 55% overall yield. Palladium-catalyzed alkylation[21] using the sodium salt of diethyl malonate provided malonate **27** in 68% yield. Alkylation of malonate **27** using propargyl bromide followed by deprotection of the silyl ether gave alcohol **28** in 72% overall yield. Oxidation of alcohol **28** using PCC provided enyne aldehyde **29** in 90% yield.

Pauson–Khand reaction of enynal **29** under thermal conditions again led to decomposition of the starting material. However, the NMO-promoted Pauson–Khand reaction gave enone **30** in 63% yield and the Me_3NO-promoted[23] reaction cleanly provided enone **30** in 82% yield (Scheme 5). Unfortunately, treatment of enone **30** with DBU or piperidine did not generate the desired tricyclic alcohols **31** or **32**.

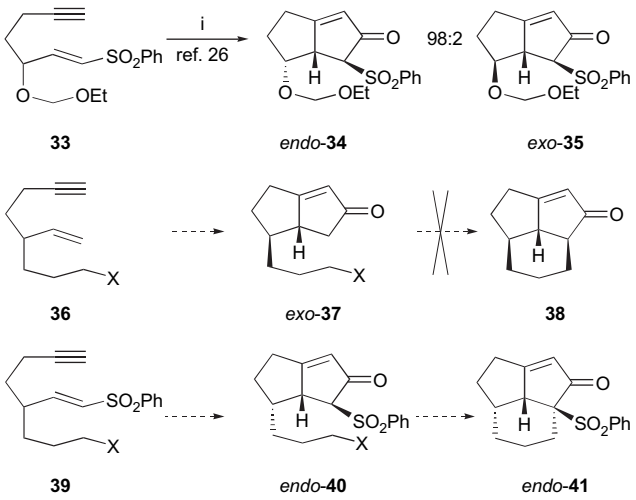
Another ring system examined was the tricyclo[6.2.1.$0^{4,11}$]-undecane motif found in presilphiperfolanol **4**. In order to follow a PKR with an enolate alkylation to generate the bridging ring (Scheme 1), *endo* selectivity in the PKR is required. Carretero has reported that incorporation of an α,β-unsaturated phenylsulfone moiety as the alkene component in intramolecular Pauson–Khand reactions results in high levels of *endo* selectivity with certain enynes.[26] When enyne **33** was subjected to Me_3NO-promoted Pauson–Khand[23] reaction conditions bicyclooctenones **34** and **35** were obtained in 76% yields (>98:<2, *endo*:*exo*, Scheme 6).[26] Pauson–Khand reaction of enyne **36** might be expected to give *exo*-bicyclooctenone **37**, which would place the side chain bearing reactive functionality at C-6 of the bicyclooctenone



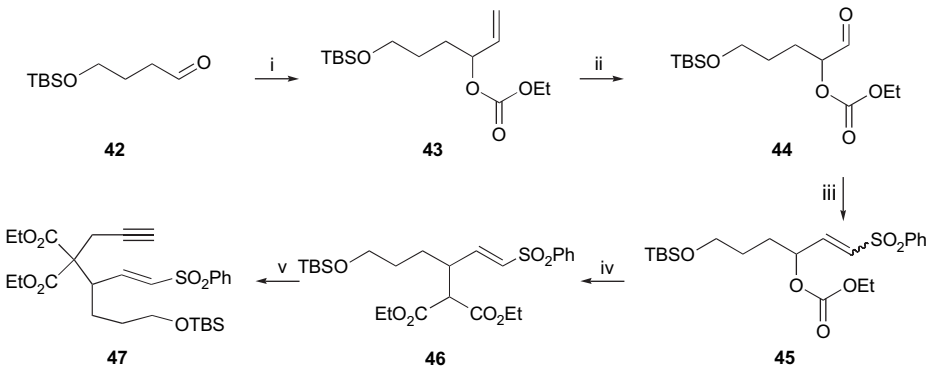
Scheme 5. Reagents and conditions: (i) a, $Co_2(CO)_8$, hexane, rt; b, $NMO\cdot H_2O$, CH_2Cl_2, rt, 63%; (ii) a, $Co_2(CO)_8$, hexane; b, Me_3NO, CH_2Cl_2, O_2(g), rt, 82%; and (iii) DBU, CH_2Cl_2, rt, or piperidine, rt, CH_2Cl_2.

ring on the *exo* face. The subsequent base promoted cyclization to triquinane **38** would therefore not occur due to steric constraints. In contrast, based on Carretero's results, incorporation of an α,β-unsaturated phenylsulfone moiety into enyne **39** should give *endo*-bicyclooctenone **40**, allowing for a facile six-membered ring closure to tricyclo-[6.2.1.$0^{4,11}$]undecane **41**.

Enyne **47** was identified as a potential target to test the PKR/alkylation sequence. Treatment of aldehyde **42**[27] with



Scheme 6. Reagents and conditions: (i) a, $Co_2(CO)_8$, CH_2Cl_2, rt; b, $Me_3NO\cdot 2H_2O$, rt, 76%, *endo* **34**:*exo* **35**, 98:2.

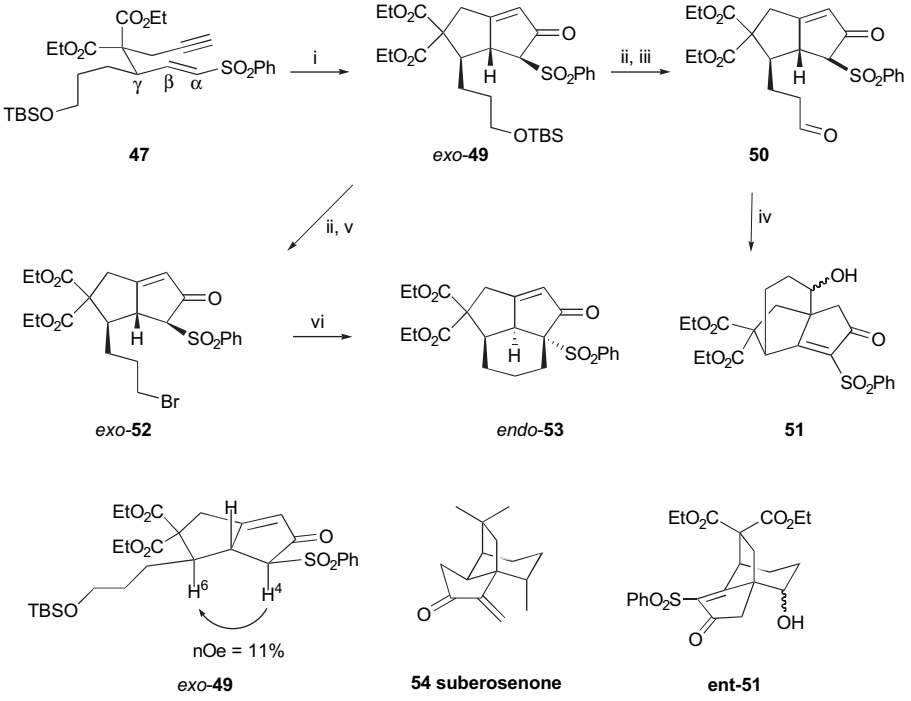


Scheme 7. Reagents and conditions: (i) a, vinylmagnesium bromide, THF, rt; b, $ClCO_2Et$, NEt_3, THF, rt, 66%; (ii) a, O_3, CH_2Cl_2, −78 °C; b, NEt_3, CH_2Cl_2, −78 °C, 86%; (iii) $(EtO)_2P(O)CHLiSO_2Ph$ **48**,[28] THF, −78 °C to rt, 73%; (iv) diethyl malonate, Pd_2dba_3, dppe, 4 Å MS, THF, Δ, 81%; and (v) a, NaH, THF, rt; (b) propargyl bromide, THF, rt, 99%.

vinylmagnesium bromide followed by quenching of the resultant alkoxide with ethyl chloroformate gave allylic carbonate **43** in 66% yield (Scheme 7). Ozonolysis of **43** gave aldehyde **44** in 86% yield, which upon treatment with $(EtO)_2P(O)CHLiSO_2Ph$ **48**,[28] provided α,β-unsaturated sulfone **45** in 73% yield (*E*/*Z*, 2.5:1). Palladium-catalyzed alkylation[29] of carbonate **45** using the sodium salt of diethyl malonate gave exclusively the thermodynamically preferred (*E*)-α,β-unsaturated sulfone **46** in 81% yield, presumably via a π–σ–π isomerization with a corresponding bond rotation.[30] Alkylation of **46** using sodium hydride followed by propargyl bromide gave enyne **47** in 99% yield.

When enyne **47** was subjected to Me_3NO-promoted Pauson–Khand reaction conditions *exo*-bicyclooctenone **49** was formed exclusively in 82% yield (Scheme 8). The stereoselectivity was confirmed by the presence of a NOE enhancement between H_4 and H_6 and X-ray crystallography (Fig. 2). The observed *exo* selectivity can be explained by considering the precyclization conformation of enyne **47** (Scheme 8). Carretero's study showed that there was a qualitative correlation between the value of $J_{\beta,\gamma}$ and the *endo*/*exo* ratios of the bicyclooctenone products. Enynes with the lowest $J_{\beta,\gamma}$ values gave rise to predominantly *endo* selective Pauson–Khand reactions, whereas higher $J_{\beta,\gamma}$ values gave *exo* selectivity. For enyne **47**, $J_{\beta,\gamma}$=10.3 Hz, which was higher than any of the $J_{\beta,\gamma}$ values found in substrates was examined in Carretero's study. A high $J_{\beta,\gamma}$ value places H_β and H_γ in an *anti* configuration, with the substituent at C_γ in a sterically more favored pseudoequatorial position in the precyclization conformation.

Despite the fact that the side chain bearing reactive functionality of bicyclooctenone **49** was on the *exo* face, it seemed



Scheme 8. Reagents and conditions: (i) a, $Co_2(CO)_8$, hexane, rt; (b) Me_3NO, CH_2Cl_2, rt, 82%; (ii) $B_{10}H_{14}$, MeOH, 94%; (iii) PCC, CH_2Cl_2, 81%; (iv) DBU, CH_2Cl_2, 47%; (v) Br_2, PPh_3, imidazole, CH_2Cl_2, 0 °C, 86%; and (vi) DBU, CH_2Cl_2, Δ, 70%.

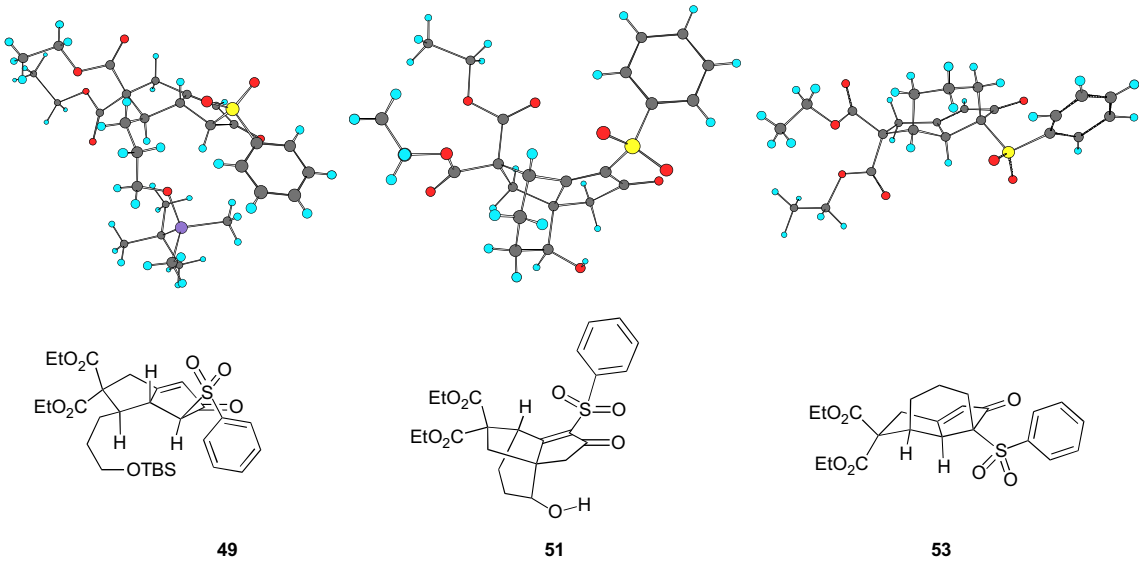


Figure 2. X-ray crystal structures of **49**, **51**, and **53**.

likely that a set of conditions for the formation of the tricyclo[6.2.1.0^{4,11}]undecane ring system could be found. The acidic H-5 proton might be expected to epimerize with the correct choice of base. Deprotection of silyl ether **49** using decaborane[31] followed by PCC oxidation gave aldehyde **50** in 76% overall yield. Surprisingly, reaction of aldehyde **50** with DBU gave rise to the unexpected tricyclo[4.3.2.0^{1,5}]undecane **51** in 47% yield as a 3:2 mixture of carbinol isomers via an isomerization and aldol cyclization (X-ray structure of one isomer, Fig. 2). The tricyclo[4.3.2.0^{1,5}]undecane motif is present in the cytotoxic sesquiterpene suberosenone **54**.[32] This result is particularly surprising in light of the failure of a related Michael addition to generate an analogous tricyclic ring system.[33] Our attention next turned to bromide **52**, which was prepared by silyl ether deprotection followed by bromination using bromine and triphenylphosphine. Treatment of bromide **52** with DBU in CH_2Cl_2 gave no reaction at rt however, after refluxing it overnight *endo*-tricyclo[6.2.1.0^{4,11}]undecane **53** was obtained in 70% yield. The structure was again confirmed by X-ray crystallography (Fig. 2). Formation of the six-membered ring in *endo*-**53** was presumably made possible by epimerization of the ring fusion proton of *exo*-**52** to *endo*-**52**, via the dienolate, under the basic reaction conditions.

In conclusion, we have used an intramolecular Pauson–Khand reaction in combination with, aldol, Michael, and alkylation reactions to gain rapid access to tricyclo[6.3.0.0]undecane, tricyclo[6.2.1.0^{4,11}]undecane, and tricyclo[4.3.2.0^{1,5}]undecane ring systems. We are currently using the methodology developed herein in the total synthesis of tricyclic natural products.

3. Experimental

3.1. General

Solvents for reactions were reagent grade and distilled from the indicated drying agents: tetrahydrofuran (THF) was distilled from lithium aluminum hydride and diethyl ether (Et_2O) was distilled from potassium. Methylene chloride (CH_2Cl_2), triethylamine (NEt_3), and pyridine were distilled from calcium hydride. Hexane, chloroform, methanol, and ethyl acetate (EtOAc) were distilled prior to use. All reactions were performed under an atmosphere of nitrogen unless otherwise specified. Melting points were obtained in an open capillary and are uncorrected. ^{1}H NMR spectra were obtained at 500 MHz on a Varian Gemini spectrometer and ^{13}C NMR spectra were obtained at 75 MHz on a Bruker AC 300 spectrometer in $CDCl_3$ solutions unless otherwise stated. Infrared spectra (IR) were obtained on a Perkin–Elmer Paragon 1000 FT-IR neat as thin films. Low-resolution mass spectra were obtained on a Finnigan 4510 GC/MS instrument and high-resolution mass spectra were obtained on a AEI MS 902 instrument. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Flash column chromatography was performed with silica gel 60 particle size 40–63 μm.

3.1.1. Malonate (20). Propargyl diethyl malonate (1.23 g, 5.80 mmol) in THF (10 mL) was added dropwise to an ice cold suspension of hexane washed 60% sodium hydride (0.28 g, 6.96 mmol) in THF (20 mL). After stirring for 15 min the mixture was allowed to warm to rt. This solution was added to a mixture of bromide **19**[22] (2.42 g, 5.80 mmol) in THF (20 mL) followed by $Pd(OAc)_2$ (26 mg, 0.12 mmol) and triphenylphosphine (122 mg, 0.46 mmol) and the resulting mixture was refluxed overnight. After allowing the solution to cool to rt the reaction mixture was washed with water, and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was passed through a plug of silica (EtOAc). After evaporation of solvent the resultant yellow oil was further purified by flash column chromatography (hexane/EtOAc, 9:1) to give malonate **20** (2.53 g, 82%) as a clear oil: IR 2932, 2360, 1729, 1428 cm^{-1}; ^{1}H NMR δ 7.65 (4H, dd, J=7.5, 1.5 Hz, Ar*H*), 7.43–7.36 (6H, m, Ar*H*), 4.90 (1H, d, J=1.5 Hz, $(CH_2)_2CCHH$), 4.87 (1H, br s, CCH_2CCH_2CCH, CCH_2CCH), 4.21 (2H, ABq, J_{AB}=10.8,

J=7.3 Hz, CH_3CH_2), 4.14 (2H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 3.64 (2H, t, J=6.4 Hz, TBDPSOCH_2), 2.83 (4H, br s, $(CH_2)_2CCH_2$), 2.03 (2H, t, J=7.8 Hz, TBSPSOCH$_2$CH$_2$CH_2), 2.00 (1H, t, J=2.4 Hz, CH_2CCH), 1.72–1.67 (2H, m, TBDPSOCH$_2$CH_2), 1.24 (6H, t, J=7.3 Hz, CH_2CH_3), 1.04 (9H, s, $C(CH_3)_3$); ^{13}C NMR δ 170.1, 143.6, 135.5, 133.9, 129.5, 127.6, 114.9, 79.3, 71.7, 63.3, 61.6, 56.5, 37.2, 32.8, 30.8, 26.8, 22.5, 19.2, 14.0; Anal. Calcd for $C_{32}H_{42}O_5Si$: C, 71.87; H, 7.92. Found: C, 72.01; H 7.99.

3.1.2. 2-[2-(3-Oxo-propyl)-allyl]-2-prop-2-ynyl-malonic acid diethylester (21). Tetrabutylammonium fluoride 1.0 M (7.1 mL, 7.1 mmol) was added to silyl ether **20** (2.53 g, 4.73 mmol) in THF (15 mL). After stirring for 3 h, water (200 mL) was added and the mixture extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 4:1) to give the corresponding alcohol (1.09 g, 78%) as a colorless oil: IR 3282, 2942, 2360, 1716 cm^{-1}; ^{1}H NMR δ 4.95 (1H, d, J=1.5 Hz, $(CH_2)_2CCHH$), 4.92 (1H, br s, $(CH_2)_2CCHH$), 4.23 (2H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 4.18 (2H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 3.63 (2H, dt, J=6.0, 6.0 Hz, $HOCH_2$), 2.85 (2H, br s, $(CO_2Et)_2CCH_2CCH_2$), 2.84 (2H, d, J=2.9 Hz, $HCCCH_2$), 2.03 (1H, t, J=2.4 Hz, CH_2CCH), 2.02 (2H, t, J=7.8 Hz, $HOCH_2CH_2CH_2$), 1.71 (2H, tt, J=6.9, 6.9 Hz, $HOCH_2CH_2$), 1.29 (1H, t, J=5.8 Hz, OH), 1.26 (6H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR δ 170.1, 143.3, 115.2, 79.1, 71.7, 62.1, 61.7, 56.4, 37.0, 32.5, 30.7, 22.5, 13.9; HRESIMS calcd for $C_{16}H_{24}O_5Na$ ([M+Na]$^+$): 319.1521; found: 319.1517.

Pyridinium chlorochromate (457 mg, 2.12 mmol) was added to the alcohol (315 mg, 1.06 mmol) in CH_2Cl_2 (10 mL). After stirring for 2 h the mixture was filtered through a plug of silica gel and the solvent was evaporated. The resultant oil was purified by flash column chromatography (hexane/EtOAc, 9:1) to give aldehyde **21** (254 mg, 81%) as a colorless oil: IR 2285, 2984, 2726, 2360, 1758 cm^{-1}; ^{1}H NMR δ 9.75 (1H, t, J=1.5 Hz, CHO), 4.95 (1H, br s, $(EtO_2C)_2CCH_2CCHH$), 4.92 (1H, d, J=1.0 Hz, $(EtO_2C)_2CCH_2CCHH$), 4.23 (2H, ABq, J_{AB}=10.8, J=7.2 Hz, CH_3CH_2), 4.18 (2H, ABq, J_{AB}=10.8, J=7.2 Hz, CH_3CH_2), 2.86 (2H, br s, $(EtO_2C)_2CCH_2CCHH$), 2.84 (2H, d, J=2.7 Hz, $(EtO_2C)_2CCH_2CCH$), 2.58 (2H, td, J=7.3, 1.5 Hz, $CHOCH_2$), 2.27 (2H, t, J=7.3 Hz, $CHOCH_2CH_2$), 2.04 (1H, t, J=2.9 Hz, CH_2CCH), 1.26 (6H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR δ 201.5, 169.8, 142.1, 115.6, 79.0, 71.9, 61.7, 56.3, 41.9, 37.4, 28.5, 22.5, 13.9; HRESIMS calcd for $C_{16}H_{22}O_5Na$ ([M+Na]$^+$): 317.1365; found: 317.1376.

3.1.3. Enone (22). Dicobaltoctacarbonyl (309 mg, 0.93 mmol) was added to aldehyde **21** (254 mg, 0.86 mmol) in hexane (3 mL). After the enyne was consumed according to TLC, the solvent was evaporated and CH_2Cl_2 (17 mL) was added. Anhydrous trimethylamine *N*-oxide (59 mg, 0.86 mmol) was added every 30 min (four times) and the mixture was stirred for an additional 1 h under an oxygen atmosphere. The mixture was passed through a plug of silica gel (hexane/EtOAc, 1:1). After evaporation of solvent the resultant oil was further purified by flash column chromatography (hexane/EtOAc, 3:1) to give bicyclooctenone **22** (236 mg, 85%) as a colorless oil: IR 3460, 2982, 2728, 1724, 1636 cm^{-1}; ^{1}H NMR δ 9.73 (1H, br s, CHO), 5.93 (1H, d, J=1.5 Hz, $(CH_2)_2CCH$), 4.27 (2H, q, J=7.3 Hz, CH_3CH_2), 4.19 (2H, q, J=7.3 Hz, CH_3CH_2), 3.39 (1H, dd, J=17.6, 1.5 Hz, $CHOCH_2CH_2CCH_2CCHH$), 3.28 (1H, d, J=17.6 Hz, $CHOCH_2CH_2CCH_2CCHH$), 2.71 (1H, d, J=13.9 Hz, $(EtO_2C)_2CCHHCCH_2$), 2.44 (1H, ddd, J=15.1, 10.3, 5.9 Hz, $CHOCHH$), 2.38 (1H, d, J=17.6 Hz, $HCCOCHHC$), 2.32 (1H, dddd, J=15.1, 10.3, 5.9, 1.0 Hz, $CHOCHH$), 2.29 (1H, d, J=17.6 Hz, $HCCOCHHC$), 2.15 (1H, d, J=13.9 Hz, $(EtO_2C)_2CCHHCCH_2$), 1.82 (1H, ddd, J=14.7, 9.8, 5.4 Hz, $CHOCH_2CHH$), 1.68 (1H, ddd, J=14.7, 9.8, 5.4 Hz, $CHOCH_2CHH$), 1.29 (3H, t, J=7.3 Hz, CH_2CH_3), 1.24 (3H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR (C_6D_6) δ 207.3, 200.2, 186.0, 171.9, 171.5, 126.2, 62.5, 62.3, 53.1, 49.2, 43.2, 39.8, 34.7, 29.7, 14.3, 14.2; HRESIMS calcd for $C_{17}H_{23}O_6$ ([M+H]$^+$): 323.1495; found: 323.1492.

3.1.4. Tricyclic enone (23). 1,3,4,6,7,8-Hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine (96 μL, 0.67 mmol) was added to aldehyde **22** (216 mg, 0.67 mmol) in CH_2Cl_2 (6.7 mL) containing 4 Å powdered molecular sieves (5 g) and the reaction mixture was stirred overnight. The solution was filtered then washed with saturated aqueous ammonium chloride. The organic layer was dried over $MgSO_4$, filtered, and evaporated, and the resultant oil filtered through a plug of silica gel (EtOAc). After evaporation of the solvent the resultant oil was purified by flash column chromatography (hexane/EtOAc, 3:2) to give tricycle **23** (106 mg, 49%) as a colorless oil (stereochemistry determined by ^{1}H NOE NMR spectroscopy): ^{1}H NMR δ 5.98 (1H, s, $(EtO_2C)_2CCH_2CCH$), 4.29 (1H, partly obscured ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 4.24 (1H, partly obscured ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 4.17 (1H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 4.10 (1H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 4.24 (1H, obscured m, HOCH), 3.87 (1H, d, J=3.9 Hz, CH_2CCHCO), 2.95 (1H, d, J=14.7 Hz, $HOCHCH_2CH_2CCHH$), 2.35 (1H, AB, J_{AB}=18.1 Hz, $HOCHCHCOCHCCHH$), 2.30 (1H, AB, J_{AB}=18.1 Hz, $HOCHCHCOCHCCHH$), 1.98 (1H, dd, J=5.8, 5.8 Hz, $HOCHCH_2CHHC$), 1.92 (1H, dd, J=14.7, 1.0 Hz, $HOCHCH_2CH_2CCHH$), 1.87 (1H, m, $HOCHCHHCH_2C$), 1.71 (1H, ddd, J=12.7, 12.7, 5.4 Hz, $HOCHCH_2CHHC$), 1.62 (1H, dd, J=12.7, 5.4 Hz, $HOCHCHHCH_2C$), 1.29 (3H, t, J=7.3 Hz, CH_2CH_3), 1.20 (3H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR (C_6D_6) δ 208.5, 187.4, 171.1, 169.3, 124.6, 70.4, 62.2, 51.8, 49.4, 49.2, 39.8, 37.4, 27.1, 14.3, 14.1; HRESIMS calcd for $C_{17}H_{22}O_6Na$ ([M+Na]$^+$): 345.1303; found: 345.1314.

3.1.4.1. Procedure for the one-pot synthesis of tricyclic enone (23). Dicobaltoctacarbonyl (60 mg, 0.18 mmol) was added to a solution of aldehyde **21** (47 mg, 0.16 mmol) in CH_2Cl_2 (7 mL). After the enyne was consumed according to TLC, trimethylamine *N*-oxide (60 mg, 0.80 mmol) was added to the solution. The mixture was stirred for 12 h at rt then 4 Å powdered molecular sieves (1 g) were added. After 1 h, DBN (20 μL, 0.16 mmol) was added and the reaction mixture was stirred overnight. The solution was filtered then washed with saturated aqueous ammonium chloride. The

organic layer was dried over $MgSO_4$, filtered, and evaporated, and the resultant oil filtered through a plug of silica gel (EtOAc). After evaporation of the solvent the resultant oil was purified by flash column chromatography (hexane/EtOAc, 3:2) to give tricycle **23** (27 mg, 49%) as a colorless oil.

3.1.5. Acetic acid 6-(*tert*-butyldiphenylsilanyloxy)-2-hydroxy-hexylester (25). 2,4,6-Collidine (10.6 mL, 80.5 mmol) was added dropwise to a solution of diol **24**[24] (10.0 mL, 40.3 mmol) in CH_2Cl_2 (200 mL) at −78 °C. After stirring for 30 min acetyl chloride (3.43 mL, 48.3 mmol) in CH_2Cl_2 (25 mL) was added dropwise and the mixture was stirred for an additional 3 h. The reaction mixture was allowed to warm to rt and the organic layer was washed with 2 M HCl (200 mL), water (200 mL), dried over $MgSO_4$, filtered, and evaporated, and the resultant oil purified by flash column chromatography (hexane/EtOAc, 9:1) to give alcohol **25** (11.3 g, 100%) as a colorless oil: IR 3458, 2930, 1736, 1589 cm^{-1}; ^1H NMR δ 7.66 (4H, d, J=6.8 Hz, Ar*H*), 7.44–7.36 (6H, m, Ar*H*), 4.12 (1H, dd, J=11.2, 3.0 Hz, AcOC*H*HCH), 3.92 (1H, dd, J=11.2, 7.3 Hz, AcOCH*H*CH), 3.79–3.84 (1H, m, C*H*OH), 3.66 (2H, t, J=5.9 Hz, CH_2OTBDPS), 2.10 (3H, s, $COCH_3$), 1.97 (1H, d, J=4.4 Hz, O*H*), 1.61–1.42 (6H, m, TBDPSOCH$_2$CH_2CH_2CH_2), 1.04 (9H, s, C(CH_3)$_3$); ^{13}C NMR δ 171.2, 135.5, 134.0, 129.5, 127.6, 69.8, 68.7, 63.6, 33.0, 32.3, 26.8, 21.7, 20.9, 19.2; MS (ESI^+) *m*/*z* 437 (M+Na); Anal. Calcd for $C_{24}H_{34}O_4Si$: C, 69.53; H, 8.27. Found: C, 69.24; H, 8.24.

3.1.6. Acetic acid 2-[4-(*tert*-butyldiphenylsilanyloxy)-butyl]-allylester (26). Jones reagent (2.67 M) was added to a solution of alcohol **25** (44.0 g, 0.106 mol) in benzene (200 mL) until there was a persistent orange color. The excess Jones reagent was quenched by addition of isopropyl alcohol and the solution was washed with water. The organic layer was dried over $MgSO_4$, filtered, and evaporated, and the resultant oil purified by flash column chromatography (hexane/EtOAc, 99:1) to give the requisite ketone (35.0 g, 80%) as a colorless oil: IR 3070, 2931, 2858, 1753, 1736, 1589 cm^{-1}; ^1H NMR δ 7.65 (4H, dd, J=7.8, 1.5 Hz, Ar*H*), 7.43–7.36 (6H, m, Ar*H*), 4.61 (2H, s, AcOCH_2), 3.66 (2H, t, J=5.9 Hz, TBDPSOCH_2), 2.40 (2H, t, J=7.3 Hz, CH_2COCH$_2$OAc), 2.16 (3H, s, $COCH_3$), 1.71 (2H, tt, J=7.3, 7.3 Hz, CH_2CH$_2$COCH$_2$OAc), 1.59–1.54 (2H, m, TBDPSOCH$_2$CH_2), 1.05 (9H, s, C(CH_3)$_3$); ^{13}C NMR δ 203.7, 170.2, 135.5, 133.8, 129.6, 127.6, 67.9, 63.3, 38.4, 31.7, 26.8, 20.5, 19.7, 19.2; MS (ESI^+) *m*/*z* 435 (M+Na); Anal. Calcd for $C_{24}H_{32}O_4Si$: C, 69.86; H, 7.82. Found: C, 69.88; H, 7.86.

Butyllithium (9.6 mL, 1.44 M, 13.8 mmol) was added dropwise to a solution of methyltriphenylphosphonium bromide (5.28 g, 14.8 mmol) in THF (100 mL) at −78 °C. After stirring for 30 min the reaction mixture was warmed to 0 °C and above ketone (4.07 g, 9.9 mmol) in THF (20 mL) was added dropwise. The reaction mixture was allowed to warm to rt and was stirred for 1 h. Water (100 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 98:2) to give alkene **26** (2.65 g, 65%) as a colorless oil: IR 3071, 3050, 2932, 2858, 1744, 1654, 1589 cm^{-1}; ^1H NMR δ 7.66 (4H, m, Ar*H*), 7.43–7.36 (6H, m, Ar*H*), 5.02 (1H, br s, (CH$_2$)$_2$CC*H*H), 4.92 (1H, br s, (CH$_2$)$_2$CCH*H*), 4.50 (2H, s, AcOCH_2), 3.67 (2H, t, J=5.9 Hz, TBDPSOCH_2), 2.08 (3H, s, $COCH_3$), 2.05 (2H, t, J=7.8 Hz, $CH_2CH_2CCH_2OAc$), 1.59–1.51 (4H, m, TBDPSOCH$_2$CH_2CH_2), 1.05 (9H, s, C(CH_3)$_3$); ^{13}C NMR δ 170.7, 143.8, 135.6, 134.0, 129.5, 127.6, 112.2, 66.9, 63.6, 33.9, 32.1, 26.9, 23.7, 20.9, 19.2; Anal. Calcd for $C_{24}H_{34}O_3Si$: C, 73.13; H, 8.35. Found: C, 73.08; H, 8.28.

3.1.7. Malonate (27). Diethyl malonate (3.3 mL, 21.9 mmol) was added dropwise to an ice cold suspension of hexane washed 60% sodium hydride (0.90 g, 22.5 mmol) in THF (30 mL). After stirring for 15 min the mixture was allowed to warm to rt. This solution was added to a mixture of allyl acetate **26** (5.00 g, 12.2 mmol) in THF (60 mL) followed by Pd(allyl)PPh_3Cl (0.55 g, 1.22 mmol) and the resulting mixture was refluxed for 48 h. After cooling to rt the reaction mixture was washed with water, and then extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was passed through a plug of silica (EtOAc). After evaporation of solvent the resultant yellow oil was further purified by flash column chromatography (hexane/EtOAc, 99:1) to give malonate **27** (4.20 g, 68%) as a colorless oil: IR 3071, 2933, 2858, 1735, 1648, 1589 cm^{-1}; ^1H NMR δ 7.66 (4H, dd, J=7.8, 1.5 Hz, Ar*H*), 7.43–7.36 (6H, m, Ar*H*), 4.77 (1H, s, (CH$_2$)$_2$CC*H*H), 4.75 (1H, s, (CH$_2$)$_2$CCH*H*), 4.18 (4H, q, J=7.2 Hz, CH_3CH_2), 3.66 (2H, t, J=5.9 Hz, TBDPSOCH_2), 3.56 (1H, t, J=7.8 Hz, (EtO$_2$C)$_2$C*H*), 2.60 (2H, d, J=7.8 Hz, (EtO$_2$C)$_2$CHCH_2), 2.01 (2H, t, J=7.3 Hz, TBDPSO(CH$_2$)$_3$CH_2), 1.58–1.48 (4H, m, TBDPSOCH$_2$CH_2CH_2), 1.25 (6H, t, J=7.3 Hz, CH_2CH_3), 1.04 (9H, s, C(CH_3)$_3$); ^{13}C NMR δ 169.1, 145.5, 135.5, 134.0, 129.5, 127.6, 111.0, 63.7, 61.4, 50.6, 35.6, 34.7, 32.1, 26.8, 23.7, 19.2, 14.1; Anal. Calcd for $C_{30}H_{42}O_5Si$: C, 70.55; H, 8.29. Found: C, 70.68; H, 8.24.

3.1.8. 2-[2-(4-Hydroxy-butyl)-allyl]-2-prop-2-ynyl-malonic acid diethylester (28). Malonate **27** (9.15 g, 17.9 mmol) in THF (70 mL) was added to a suspension of hexane washed 60% sodium hydride (1.43 g, 35.8 mmol) in THF (70 mL) at 0 °C. After stirring for 15 min the mixture was allowed to warm to rt and was stirred for 30 min. A solution of 80% propargyl bromide in toluene (39.9 mL, 0.358 mol) was added and the mixture was stirred overnight. Water (100 mL) was added and the mixture extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 98:2) to give the enyne (8.10 g, 82%) as a colorless oil: IR 3290, 3071, 2934, 2859, 1736, 1641, 1589 cm^{-1}; ^1H NMR δ 7.65 (4H, dd, J=7.8, 1.5 Hz, Ar*H*), 7.43–7.36 (6H, m, Ar*H*), 4.88 (1H, s, (CH$_2$)$_2$CC*H*H), 4.87 (1H, s, (CH$_2$)$_2$CCH*H*), 4.21 (2H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 4.14 (2H, ABq, J_{AB}=10.8, J=7.3 Hz, CH_3CH_2), 3.63 (2H, t, J=6.4 Hz, TBDPSOCH_2), 2.81 (4H, br s, CCH_2CCHH, CCH_2CCH), 2.00 (1H, t, J=2.4 Hz, CH_2CCH), 1.89 (2H, t, J=7.8 Hz, TBDPSO(CH$_2$)$_3$CH_2), 1.53–1.46 (4H, m, TBDPSOCH$_2$CH_2CH_2), 1.24 (6H, t, J=6.8 Hz, CH_2CH_3), 1.04 (9H, s, C(CH_3)$_3$); ^{13}C NMR δ 170.0, 143.7, 135.4, 133.9, 129.4, 127.5, 114.9, 79.2,

71.6, 63.6, 61.5, 56.4, 36.9, 36.1, 32.0, 23.9, 22.4, 19.1, 13.9; MS (ESI$^+$) *m/z* 571 (M+Na); Anal. Calcd for $C_{33}H_{44}O_5Si$: C, 72.22; H, 8.08. Found: C, 72.02; H, 8.07.

Tetrabutylammonium fluoride (120 mL, 1.0 M, 120 mmol) was added to the silyl ether enyne (6.70 g, 12.2 mmol) in THF (20 mL). After stirring for 3 h, water (200 mL) was added and the mixture was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 4:1) to give alcohol **28** (3.32 g, 88%) as a colorless oil: IR 3289, 2938, 2122, 1732, 1642 cm^{-1}; ^{1}H NMR δ 4.92 (1H, d, J=1.5 Hz, $(EtO_2C)_2CCH_2CHH$), 4.89 (1H, br s, $(EtO_2C)_2CCH_2CHH$), 4.23 (2H, ABq, J_{AB}=11.0, J=7.3 Hz, CH_3CH_2), 4.17 (2H, ABq, J_{AB}=11.0, J=7.3 Hz, CH_3CH_2), 3.64 (2H, t, J=5.9 Hz, $HOCH_2$), 2.84 (2H, s, $(EtO_2C)_2CCH_2CCHH$), 2.83 (2H, d, J=2.9 Hz, $(EtO_2C)_2CCH_2CCH$), 2.03 (1H, t, J=2.9 Hz, CH_2CCH), 1.95 (2H, t, J=7.3 Hz, $HO(CH_2)_3CH_2$), 1.57–1.47 (4H, m, $HOCH_2CH_2CH_2$), 1.26 (6H, t, J=6.8 Hz, CH_2CH_3); ^{13}C NMR δ 170.0, 143.6, 115.0, 79.2, 71.7, 62.5, 61.6, 56.4, 36.9, 36.1, 32.1, 23.9, 22.5, 13.9; HRESIMS calcd for $C_{17}H_{26}O_5Na$ ([M+Na]$^+$): 333.1678; found: 333.1677.

3.1.9. Aldehyde (29). Pyridinium chlorochromate (420 mg, 1.94 mmol) was added to alcohol **28** (300 mg, 0.97 mmol) in CH_2Cl_2 (10 mL). After stirring for 2 h the mixture was filtered through a plug of silica gel and the solvent was evaporated. The resultant oil was purified by flash column chromatography (hexane/EtOAc, 9:1) to give aldehyde **29** (270 mg, 90%) as a colorless oil: IR 3279, 2982, 2939, 2723, 1733, 1642 cm^{-1}; ^{1}H NMR δ 9.76 (1H, t, J=1.5 Hz, CHO), 4.93 (2H, s, $(EtO_2C)_2CCH_2CCH_2$), 4.23 (2H, ABq, J_{AB}=10.6, J=7.2 Hz, CH_3CH_2), 4.17 (2H, ABq, J_{AB}=10.6, J=7.2 Hz, CH_3CH_2), 2.83 (4H, br s, $(EtO_2C)_2CCH_2CCH$ and $(EtO_2C)_2CCH_2CCH_2$), 2.41 (2H, td, J=7.3, 1.5 Hz, $CHOCH_2$), 2.03 (1H, t, J=2.4 Hz, CH_2CCH), 1.98 (2H, t, J=7.3 Hz, $(EtO_2C)_2CCH_2CCH_2(CH_2)_2$), 1.78 (2H, tt, J=7.3, 7.3 Hz, $CHOCH_2CH_2$), 1.25 (6H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR (C_6D_6) δ 201.1, 170.3, 144.1, 116.0, 79.9, 72.8, 62.0, 57.1, 43.4, 37.8, 36.3, 23.4, 20.7, 14.3; HRESIMS calcd for $C_{17}H_{24}O_5Na$ ([M+Na]$^+$): 331.1521; found: 331.1533.

3.1.10. Bicyclooctenone (30). Dicobaltoctacarbonyl (200 mg, 0.58 mmol) was added to aldehyde **29** (180 mg, 0.58 mmol) in hexane (12 mL). After the enyne was consumed according to TLC, the solvent was evaporated and CH_2Cl_2 (12 mL) was added. Anhydrous trimethylamine *N*-oxide (40 mg, 0.58 mmol) was added every 30 min (four times) and the mixture was stirred for an additional 1 h under an oxygen atmosphere. The mixture was passed through a plug of silica gel (hexane/EtOAc, 1:1). After evaporation of solvent the resultant oil was further purified by flash column chromatography (hexane/EtOAc, 3:1) to give bicyclooctenone **30** (160 mg, 82%) as a colorless oil: IR 3459, 2982, 1728, 1636 cm^{-1}; ^{1}H NMR δ 9.72 (1H, br s, CHO), 5.90 (1H, d, J=1.5 Hz, $(EtO_2C)_2CCH_2CCH$), 4.26 (2H, q, J=7.3 Hz, CH_3CH_2), 4.18 (2H, q, J=7.3 Hz, CH_3CH_2), 3.37 (1H, dd, J=17.6, 2.4 Hz, $CHO(CH_2)_3CCCHH$), 3.24 (1H, d, J=17.6 Hz, $CHO(CH_2)_3CCCHH$), 2.71 (1H, d, J=14.0 Hz, $CHO(CH_2)_3CCHHC(CO_2Et)_2$), 2.49 (1H, d, J=17.6 Hz, $CCHHCO$), 2.41 (2H, t, J=6.8 Hz, $CHOCH_2$), 2.27 (1H, d, J=17.6 Hz, $CCHHCO$), 2.13 (1H, d, J=14.0 Hz, $CHO(CH_2)_3CCHHC(CO_2Et)_2$), 1.64–1.40 (4H, m, $CHOCH_2(CH_2)_2$), 1.28 (3H, t, J=7.3 Hz, CH_2CH_3), 1.24 (3H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR (C_6D_6) δ 208.0, 207.8, 200.7, 186.3, 186.1, 172.0, 171.6, 125.9, 62.4, 62.3, 60.4, 53.9, 49.4, 43.7, 42.9, 37.3, 34.7, 18.9, 18.0, 14.3, 14.2; HRESIMS calcd for $C_{18}H_{24}O_6Na$ ([M+Na]$^+$): 359.1471; found: 359.1472.

3.1.11. Carbonate (43). Vinylmagnesium bromide (28.6 mL, 28.6 mmol) was added to a solution of 4-(*tert*-butyl-dimethylsilanyloxy)-butyraldehyde **42**[27] (5.73 g, 28.3 mmol) in THF (280 mL) and the mixture was stirred for 10 min. Ethyl chloroformate (5.4 mL, 56.6 mmol) followed by triethylamine (11.8 mL, 84.9 mmol) were added and the mixture was stirred for 30 min. Ether (200 mL) was added and the reaction mixture was washed with 2 M HCl (300 mL) then brine (200 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 97:3) to give carbonate **43** (5.7 g, 66%) as a colorless oil: IR 2955, 2858, 1747, 1648 cm^{-1}; ^{1}H NMR δ 5.79 (1H, ddd, J=17.1, 10.3, 6.8 Hz, $CH(OCO_2Et)CHCH_2$), 5.30 (1H, d, J=17.1 Hz, $CH(OCO_2Et)CHCHH$), 5.21 (1H, d, J=10.3 Hz, $CH(OCO_2Et)CHCHH$), 5.07 (1H, td, J=6.8, 6.8 Hz, $CH_2CH(OCO_2Et)$), 4.18 (2H, q, J=7.3 Hz, CH_3CH_2), 3.63 (1H, ABt, J_{AB}=10.1, J=6.8 Hz, $TBSOCHH$), 3.61 (1H, ABt, J_{AB}=10.1, J=6.8 Hz, $TBSOCHH$), 1.76–1.66 (2H, m, $TBSOCH_2CH_2CH_2$), 1.63–1.51 (2H, m, $TBSOCH_2CH_2$), 1.30 (3H, t, J=7.3 Hz, CH_2CH_3), 0.88 (9H, s, $C(CH_3)_3$), 0.04 (6H, s, $(H_3C)_3CSi(CH_3)_2$); ^{13}C NMR δ 154.6, 136.0, 117.4, 78.6, 63.8, 62.6, 30.6, 28.2, 25.9, 18.3, 14.2, −5.4; Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.77; H, 9.96.

3.1.12. Aldehyde (44). Ozone was bubbled through a solution of alkene **43** (7.34 g, 24.3 mmol) at −78 °C in CH_2Cl_2 (240 mL) until there was a persistent blue color. The excess ozone was removed by bubbling nitrogen through the reaction mixture until the solution was clear. Triethylamine (3.4 mL, 24.3 mmol) was added dropwise at −78 °C and a stream of nitrogen was bubbled through the reaction mixture for 30 min. After warming to rt the solvent was evaporated and the resultant oily residue was purified by passing through a plug of silica gel (hexane/EtOAc, 85:15) to give aldehyde **44** (6.34 g, 86%) as a colorless oil: IR 3479, 2929, 1746, 1470 cm^{-1}; ^{1}H NMR δ 9.58 (1H, d, J=1.0 Hz, CHO), 4.92 (1H, dd, J=8.3, 4.9 Hz, $CHOCH$), 4.26 (1H, ABq, J=10.3, 7.3 Hz, $CHHCH_3$), 4.24 (1H, ABq, J=10.3, 7.3 Hz, $CHHCH_3$), 3.65 (1H, ABt, J_{AB}=10.2, J=5.7 Hz, $TBSOCH_2$), 3.63 (1H, ABt, J_{AB}=10.2, J=5.7 Hz, $TBSOCH_2$), 1.98 (1H, ABddd, J_{AB}=14.3, J=8.8, 7.3, 4.8 Hz, $CHOCHCHH$), 1.82 (1H, ABtd, J_{AB}=14.3, J=8.2, 5.9 Hz, $CHOCHCHH$), 1.69–1.63 (2H, m, $TBSOCH_2CH_2$), 1.35 (3H, t, J=7.3 Hz, CH_3CH_2), 0.89 (9H, s, $C(CH_3)_3$), 0.04 (6H, s, $(H_3C)_3CSi(CH_3)_2$); ^{13}C NMR δ 198.0, 154.7, 80.9, 64.7, 62.1, 27.8, 25.9, 25.5, 18.3, 14.1, −5.4; HRESIMS calcd for $C_{14}H_{28}O_5SiNa$ ([M+Na]$^+$): 327.1604; found: 327.1606.

3.1.13. Vinyl sulfone (45). Butyllithium (32.3 mL, 1.42 M, 45.8 mmol) was added dropwise to methylphenylsulfone (3.60 g, 22.9 mmol) in THF (150 mL) at 0 °C and the solution was stirred for 30 min. Diethylchlorophosphate (3.6 mL, 22.9 mmol) in THF (30 mL) was added dropwise and the mixture was stirred for 30 min. After cooling to −78 °C, aldehyde **44** (6.34 g, 20.8 mmol) in THF (30 mL) was added and the mixture was stirred for 3 h. Upon warming to rt the mixture was stirred for an additional 2 h. Brine (200 mL) was added and the mixture extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated, and the resultant oil passed through a plug of silica gel (hexane/EtOAc, 1:1). After evaporation of the solvent the resultant oil was further purified by flash column chromatography (hexane/EtOAc, 95:5) to give vinylsulfone **45** as a 2.5:1 mixture of *E*/*Z* isomers (6.76 g, 73%) as a colorless oil: IR 3063, 2953, 1748, 1634, 1585 cm^{-1}; MS (ESI^+) *m*/*z* 465 (M+Na); Anal. Calcd for $C_{21}H_{34}O_6SSi$: C, 56.98; H, 7.74. Found: C, 57.07; H, 7.80.

3.1.14. Malonate (46). A solution of diethyl malonate (1.6 mL, 10.6 mmol) and allylcarbonate **45** (1.18 g, 2.66 mmol) in degassed THF (26 mL) was added to a suspension of tris(dibenzylideneacetone)dipalladium(0)-chloroform (140 mg, 0.13 mmol), 1,2-bis(diphenylphosphino)ethane (210 mg, 0.53 mmol), and 4 Å powdered molecular sieves (0.6 g, half by weight of allylcarbonate (**45**) in degassed THF (10 mL). After heating to reflux for 12 h the mixture was cooled to rt, passed through Celite and the solvent was evaporated. The resultant oil was purified by flash column chromatography (hexane/EtOAc, 95:5) to give malonate **46** (1.1 g, 81%) as a white solid, mp 62–64 °C: IR 3059, 2931, 2857, 1733, 1625 cm^{-1}; ^1H NMR δ 7.87–7.85 (2H, m Ar*H*), 7.60 (1H, tt, *J*=7.3, 1.0 Hz, Ar*H*), 7.52 (2H, t, *J*=7.3 Hz, Ar*H*), 6.88 (1H, dd, *J*=15.1, 9.3 Hz, PhO_2SCHCH), 6.39 (1H, d, *J*=15.1 Hz, PhO_2SCHCH), 4.12 (2H, q, *J*=6.8 Hz, CH_3CH_2), 4.06 (1H, ABq, J_{AB}=10.0, *J*=6.8 Hz, CH_3CH*H*), 4.03 (1H, ABq, J_{AB}=10.0, *J*=6.8 Hz, CH_3CH*H*), 3.55 (2H, t, *J*=5.9 Hz, $TBSOCH_2$), 3.43 (1H, d, *J*=8.3 Hz, $(EtO_2C)_2CH$), 2.99 (1H, ddt, *J*=9.3, 8.3, 5.0 Hz, $(EtO_2C)_2CHCH$), 1.65 (1H, m, $TBSOCH_2CH_2CH$H), 1.55–1.37 (3H, m, $TBSOCH_2CH_2CH$H), 1.21 (3H, t, *J*=6.8 Hz, CH_2CH_3), 1.18 (3H, t, *J*=6.8 Hz, CH_2CH_3), 0.86 (9H, s, $C(CH_3)_3$), 0.01 (6H, s, $(H_3C)_3CSi(CH_3)_2$); ^{13}C NMR δ 167.3, 167.1, 145.7, 140.3, 133.3, 132.7, 129.1, 127.5, 62.3, 61.6, 61.5, 55.7, 41.2, 30.0, 28.3, 25.8, 18.2, 13.9, −5.5; Anal. Calcd for $C_{25}H_{40}O_7SSi$: C, 58.56; H, 7.86. Found: C, 58.87; H, 7.87.

3.1.15. Enyne (47). Malonate **46** (0.81 g, 1.57 mmol) was added to an ice cold suspension of hexane washed 60% sodium hydride (69 mg, 1.73 mmol) in THF (16 mL) and the mixture was stirred for 3 h. Propargyl bromide (3.5 mL, 31.4 mmol) was added and the mixture was stirred overnight. Water (30 mL) was added and the mixture was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated and the resultant oil purified by flash column chromatography (hexane/EtOAc, 9:1) to give enyne **47** (0.86 g, 99%) as a colorless oil: IR 3276, 2930, 2857, 1732 cm^{-1}; ^1H NMR δ 7.89–7.87 (2H, m, Ar*H*), 7.60 (1H, tt, *J*=7.8, 1.5 Hz, Ar*H*), 7.53 (2H, br t, *J*=7.8 Hz, Ar*H*), 6.87 (1H, dd, *J*=15.1, 10.3 Hz, $PhSO_2CHCH$), 6.47 (1H, d, *J*=15.1 Hz, $PhSO_2CH$), 4.22–4.11 (4H, m, CH_3CH_2), 3.55 (2H, t, *J*=5.9 Hz, $TBSOCH_2$), 3.09 (1H, ddd, *J*=10.3, 10.3, 2.4 Hz, $PhSO_2CHCHCH$), 2.84 (1H, dd, *J*=17.1, 2.4 Hz, HCCCHH), 2.70 (1H, dd, *J*=17.1, 2.4 Hz, HCCCHH), 1.98 (1H, t, *J*=2.4 Hz, CH_2CCH), 1.87–1.81 (1H, m, $TBSOCH_2CH_2CH$H), 1.49–1.40 (1H, m, $TBSOCH_2CH$H), 1.4–1.3 (2H, m, $TBSOCH_2CH$HCHH), 1.24 (3H, t, *J*=7.3 Hz, CH_2CH_3), 1.22 (3H, t, *J*=7.3 Hz, CH_2CH_3), 0.87 (9H, s, $C(CH_3)_3$), 0.01 (6H, s, $(H_3C)_3CSi(CH_3)_2$); ^{13}C NMR δ 168.6, 168.5, 145.0, 140.6, 133.6, 133.3, 129.2, 127.5, 78.4, 72.2, 62.4, 61.9, 59.7, 44.3, 30.9, 25.9, 23.6, 18.2, 13.9, −5.4; HRESIMS calcd for $C_{28}H_{42}O_7SiSNa$ ($[M+Na]^+$): 573.2318; found: 573.2320.

3.1.16. Bicyclooctenone (49). Dicobaltoctacarbonyl (1.31 g, 3.83 mmol) was added to enyne **47** (2.01 g, 3.65 mmol) in hexane (18 mL). After the enyne was consumed according to TLC the solvent was evaporated and CH_2Cl_2 (73 mL) was added. Anhydrous trimethylamine *N*-oxide (250 mg, 3.65 mmol) was added every 30 min four times under an oxygen atmosphere and the mixture was stirred until the alkyne cobalt complex was consumed according to TLC. The mixture was passed through a plug of silica gel (EtOAc). After evaporation of solvent the resultant oil was further purified by flash column chromatography (hexane/EtOAc, 4:1) to give bicyclooctenone **49** (1.73 g, 82%) as a white solid: mp 109–111 °C; IR 3066, 2929, 1713, 1644, 1586 cm^{-1}; ^1H NMR δ 7.94–7.92 (2H, m, Ar*H*), 7.67 (1H, t, *J*=7.3 Hz, Ar*H*), 7.57 (2 H, br t, *J*=7.3 Hz, Ar*H*), 5.86 (1H, d, *J*=1.0 Hz, $(EtO_2C)_2CCH_2CCH$), 4.32 (1H, ABq, J_{AB}=10.5, *J*=7.3 Hz, CH_3CH*H*), 4.26 (1H, ABq, J_{AB}=10.5, *J*=7.3 Hz, CH_3CH*H*), 4.22 (1H, ABq, J_{AB}=10.5, *J*=7.3 Hz, CH_3CH*H*), 4.19 (1H, ABq, J_{AB}=10.5, *J*=7.3 Hz, CH_3CH*H*), 3.97 (1H, d, *J*=2.9 Hz, PhO_2SCH), 3.73–3.61 (3H, m, $TBSOCH_2$ and $PhSO_2CHCH$), 3.60 (1H, partly obscured d, *J*=18.4 Hz, $(EtO_2C)_2CCH$H), 3.03 (1H, d, *J*=18.4 Hz, $(EtO_2C)_2CCH$H), 2.40 (1H, ddd, *J*=12.2, 7.3, 6.3 Hz, $TBSO(CH_2)_3CH$), 1.88–1.68 (4H, m, $TBSOCH_2CH_2CH_2$), 1.32 (3H, t, *J*=7.3 Hz, CH_2CH_3), 1.27 (3H, t, *J*=7.3 Hz, CH_2CH_3), 0.88 (9H, s, $C(CH_3)_3$), 0.05 (3H, s, $(H_3C)_3CSi(CH_3)_2$), 0.04 (3H, s, $(H_3C)_3CSi(CH_3)_2$); ^{13}C NMR δ 196.8, 183.3, 170.5, 138.1, 134.1, 129.3, 128.9, 124.9, 72.5, 63.2, 63.0, 62.1, 61.8, 50.8, 49.1, 36.6, 31.1, 27.3, 25.9, 18.2, 14.0, 13.9, −5.4; Anal. Calcd for $C_{29}H_{42}O_8SSi$: C, 60.18; H, 7.31. Found: C, 59.93; H, 7.40.

3.1.17. Aldehyde (50). Decaborane (15 mg, 0.12 μmol) was added to a solution of enone **49** (1.34 g, 2.32 mmol) in methanol (18 mL) and THF (5 mL). After stirring at rt for 2 h the solvent was evaporated. The resultant oily residue was purified by flash column chromatography (hexane/EtOAc, 3.2) to give alcohol (1.01 g, 94%) as a colorless oil: IR 3548, 2937, 1720, 1639 cm^{-1}; ^1H NMR δ 7.93 (2H, d, *J*=7.3 Hz, Ar*H*), 7.68 (1H, t, *J*=7.3 Hz, Ar*H*), 7.58 (2H, t, *J*=7.3 Hz, Ar*H*), 5.87 (1H, s, $(EtO_2C)_2CCH_2CCH$), 4.33 (1H, ABq, J_{AB}=10.8, *J*=6.9 Hz, CH_3CH*H*), 4.28 (1H, ABq, J_{AB}=11.2, *J*=7.3 Hz, CH_3CH*H*), 4.27 (1H, ABq, J_{AB}=11.2, *J*=7.3 Hz, CH_3CH*H*), 4.18 (1H, ABq, J_{AB}=10.8, *J*=7.3 Hz, CH_3CH*H*), 3.92 (1H, d, *J*=3.4 Hz, PhO_2SCH), 3.73–3.64 (3H, m, $HOCH_2$ and $PhSO_2CHCH$), 3.59 (1H, d, *J*=18.6 Hz, $(EtO_2C)_2CCH$H), 3.01 (1H, d, *J*=18.6 Hz, $(EtO_2C)_2CCH$H), 2.40 (1H, ddd, *J*=12.2, 7.3, 4.9 Hz, $HO(CH_2)_3CH$), 1.92–1.73 (4H, m, $HOCH_2CH_2CH_2$), 1.33

(3H, t, J=7.3 Hz, CH_2CH_3), 1.27 (3H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR δ 196.6, 183.1, 170.6, 170.3, 137.7, 134.1, 129.3, 128.9, 124.8, 72.5, 62.8, 62.2, 62.1, 61.9, 51.0, 48.5, 36.4, 30.7, 26.5, 14.0, 13.8; HRESIMS calcd for $C_{23}H_{28}O_8SNa$ ([M+Na]$^+$): 487.1402; found: 487.1406. PCC (370 mg, 1.71 mmol) was added to a solution of alcohol (400 mg, 0.86 mmol) in CH_2Cl_2 (9 mL) and the mixture was stirred for 1 h at rt. The reaction mixture was then passed through a plug of silica gel (hexane/EtOAc, 1:1). After evaporation of the solvent the resultant oil was further purified by flash column chromatography (hexane/EtOAc, 3:2) to give aldehyde **50** (320 mg, 81%) as a colorless oil: IR 2982, 1721, 1641 cm^{-1}; ^{1}H NMR δ 9.81 (1H, s, C*H*O), 7.96–7.94 (2H, m, Ar*H*), 7.69 (1H, t, J=7.3 Hz, Ar*H*), 7.59 (2H, br t, J=7.3 Hz, Ar*H*), 5.87 (1H, d, J=1.0 Hz, $(EtO_2C)_2CCH_2CCH$), 4.34 (1H, ABq, J_{AB}=10.7, J=6.8 Hz, CH_3CHH), 4.30 (1H, ABq, J_{AB}=10.7, J=6.8 Hz, CH_3CHH), 4.25 (1H, ABq, J_{AB}=10.7, J=6.8 Hz, CH_3CHH), 4.18 (1H, ABq, J_{AB}=10.7, J=6.8 Hz, CH_3CHH), 3.97 (1H, d, J=3.4 Hz, $PhSO_2CH$), 3.66 (1H, br d, J=19.0, $(EtO_2C)_2$-CC*H*H), 3.64 (1H, partly obscured dm, J=12.0 Hz, $PhSO_2CHCH$), 3.01 (1H, d, J=19.0 Hz, $(EtO_2C)_2CCH$*H*), 2.92 (1H, br dt, J=18.1, 7.3 Hz, CHOC*H*H), 2.61 (1H, ddt, J=18.1, 1.0, 7.3 Hz, CHOCH*H*), 2.42 (1H, ddd, J=12.7, 6.8, 6.8 Hz, $CHO(CH_2)_2CH$), 2.28 (1H, ABdt, J_{AB}=14.8, J=7.2, 6.8 Hz, $CHOCH_2CHH$), 1.80 (1H, ABdt, J_{AB}=14.8, J=6.8, 6.8 Hz, $CHOCH_2CHH$), 1.34 (3H, t, J=7.3 Hz, CH_2CH_3), 1.27 (3H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR (C_6D_6) δ 201.1, 196.5, 181.6, 170.9, 170.6, 139.4, 133.9, 130.0, 129.1, 125.5, 73.3, 63.6, 62.4, 62.0, 51.3, 48.5, 42.2, 36.6, 23.3, 14.4, 14.1; HRESIMS calcd for $C_{23}H_{26}O_8SNa$ ([M+Na]$^+$): 485.1246; found: 485.1236.

3.1.18. Tricycle (51). Diazabicycloundecane (54 μL, 0.60 mmol) was added to aldehyde **50** (280 mg, 0.60 mmol) in CH_2Cl_2 (12 mmol) and the mixture was stirred for 4 h at rt. The reaction mixture was washed with 1 M HCl (10 mL) and water (10 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, and the resultant oil purified by flash column chromatography (hexane/EtOAc, 3:2) to give tricycle **51** as a 3:2 mixture of carbinol isomers (130 mg, 47%, white solid: mp 134–138 °C); HRESIMS calcd for $C_{23}H_{26}O_8SNa$ ([M+Na]$^+$): 485.1246; found: 485.1250; Anal. Calcd for $C_{23}H_{26}O_8SSi$: C, 59.73; H, 5.67. Found: C, 59.84; H, 5.60.

3.1.19. Keto-bromide (52). Triphenylphosphine (120 mg, 0.46 mmol) was added to a solution of bromine (23 μL, 0.46 mmol) in CH_2Cl_2 (4 mL) followed by imidazole (31 mg, 0.46 mmol) then alcohol (190 mg, 0.42 mmol). After stirring at rt for 15 min, 1 M HCl (5 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with water (5 mL), dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 4:1) to give bromide **52** (190 mg, 86%) as a colorless oil: IR 3036, 2982, 2937, 1714, 1644, 1585 cm^{-1}; ^{1}H NMR δ 7.96–7.94 (2H, m, Ar*H*), 7.69 (1H, t, J=7.3 Hz, Ar*H*), 7.59 (2H, t, J=7.3 Hz, Ar*H*), 5.89 (1H, d, J=1.0 Hz, $(EtO_2C)_2CCH_2CCH$), 4.37–4.16 (4H, m, CH_3CH_2), 3.83 (1H, d, J=2.9 Hz, PhO_2SCH), 3.64 (1H, br dd, J=19.0, 1.9 Hz, $(EtO_2C)_2$-CC*H*H), 3.63 (1H, obscured m, $PhSO_2CHCH$), 3.51 (1H, ABt, J_{AB}=10.0, J=5.8 Hz, $BrCH_2$), 3.44 (1H, ABdd, J_{AB}=10.0, J=8.3, 6.3 Hz, $BrCH_2$), 3.02 (1H, d, J=19.0 Hz, $(EtO_2C)_2CCH$*H*), 2.34 (1H, dt, J=12.7, 6.8 Hz, $Br(CH_2)_3CH$), 2.24–2.16 (1H, m, $BrCH_2CHH$), 2.03 (1H, m, $BrCH_2CH$*H*), 1.90–1.79 (2H, m, $BrCH_2CH_2CH_2$), 1.34 (3H, t, J=7.3 Hz, CH_2CH_3), 1.28 (3H, t, J=7.3 Hz, CH_2CH_3); ^{13}C NMR δ 196.3, 182.6, 170.4, 170.2, 137.8, 134.1, 129.2, 129.0, 124.9, 72.5, 62.8, 62.2, 61.9, 50.9, 48.2, 36.6, 33.5, 30.8, 28.8, 14.0, 13.8; HRESIMS calcd for $C_{23}H_{27}O_7BrSNa$ ([M+Na]$^+$): 549.0558; found: 549.0558.

3.1.20. Tricycle (53). Diazabicycloundecane (37 μL, 0.25 mmol) was added to bromide **52** (132 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) and the mixture was refluxed overnight. Cooling to rt the reaction mixture was washed with 1 M HCl (5 mL) and water (5 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated, and the resultant oil was purified by flash column chromatography (hexane/EtOAc, 3:1) to give tricycle **53** (78 mg, 70%) as a white solid: mp 163–165 °C; IR 2940, 2360, 1729, 1638, 1584 cm^{-1}; ^{1}H NMR δ 8.00–7.99 (2H, m, Ar*H*), 7.66 (1H, t, J=7.3 Hz, Ar*H*), 7.57 (2H, t, J=7.3 Hz, Ar*H*), 5.83 (1H, d, J=2.0 Hz, $(EtO_2C)_2CCH_2CCH$), 4.32–4.13 (4H, m, CH_3CH_2), 4.03 (1H, d, J=6.8 Hz, $PhSO_2CCHCH$), 3.59 (1H, d, J=21.0 Hz, $(EtO_2C)_2CCH$*H*), 3.11 (1H, d, J=21.0 Hz, $(EtO_2C)_2CCH$*H*), 3.03 (1H, td, J=6.8, 6.8 Hz, $PhSO_2CCHCH$), 2.59 (1H, br d, J=15.6 Hz, $PhSO_2CCHHCH_2$), 1.60–1.59 (1H, m, $PhSO_2CCHHCH_2$), 1.53–1.36 (3H, m, $PhSO_2CCH_2CH_2$ and $PhSO_2CCH_2CH_2CHH$), 1.29 (3H, t, J=6.8 Hz, CH_2CH_3), 1.26 (3H, t, J=6.8 Hz, CH_2CH_3), 0.68 (1H, dtd, J=13.2, 13.2, 2.5 Hz, $PhSO_2CCH_2CH_2CH$*H*); ^{13}C NMR, δ 182.3, 170.6, 168.4, 159.1, 136.4, 134.1, 130.6, 128.9, 122.4, 73.1, 65.0, 62.1, 61.9, 60.3, 50.8, 40.5, 33.7, 26.3, 22.0, 21.0, 14.0; MS (ESI$^+$) m/z 469.2 (M+Na); Anal. Calcd for $C_{23}H_{26}O_7S$: C, 61.87; H, 5.87. Found: C, 61.92; H, 5.90.

3.2. Crystallographic information

X-ray crystal data tables for compounds **49**, **51**, and **53**. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 229389–229391. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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