Studies towards the Synthesis of Ionomycin

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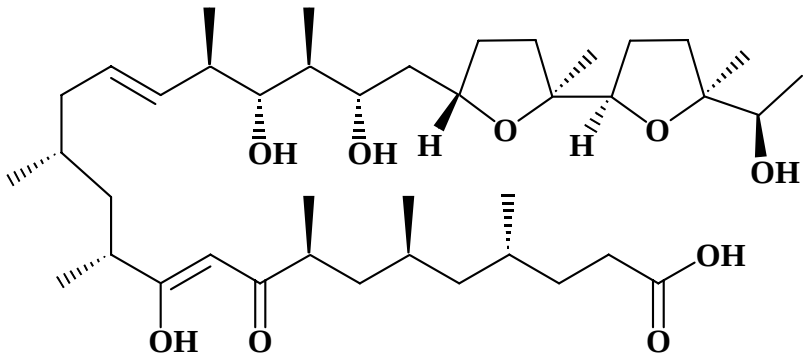
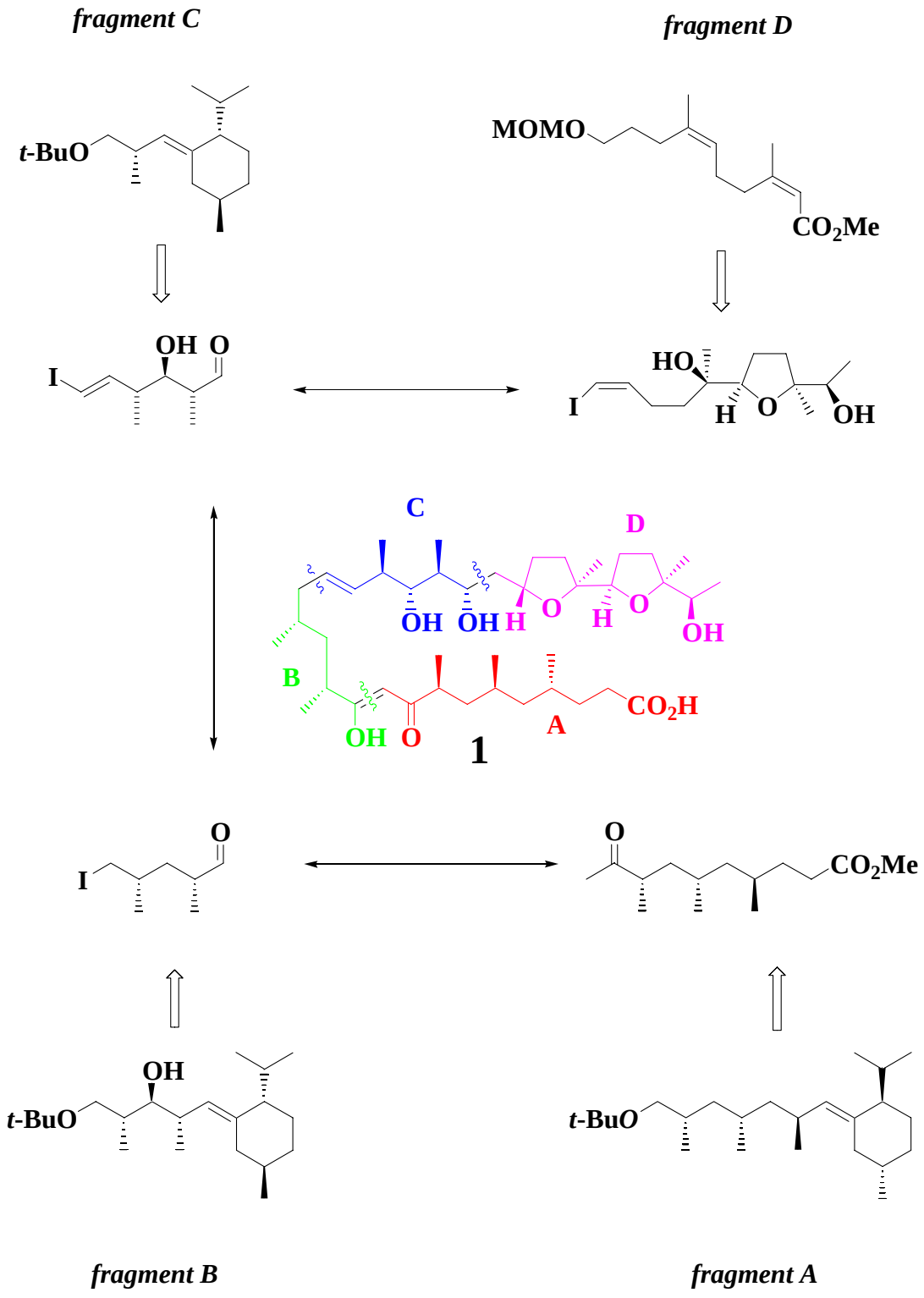
Introduction:

Ionomycin (**1**), a polyether antibiotic was isolated as its hexane-soluble calcium complex from the organism Streptomyces conglobatus[1]. In 1979 the X ray structure and absolute stereochemistry of both the calcium and cadmium complexes of ionomycin were reported by Gorgoutas and co-workers[2]. There are three previous total syntheses have been published by the Evans, Hanessian and Lautens[3]. Our retrosynthetic analysis of ionomycin is similar to that of the reported earlier[3]. The three points of disconnection are at the β-diketone, the trans olefin, and the first tetrahydrofuran ring (Scheme 1). The synthesis of ionomycin fragments A, B and C has been published recently using an iterative approach by Spino et al[4].



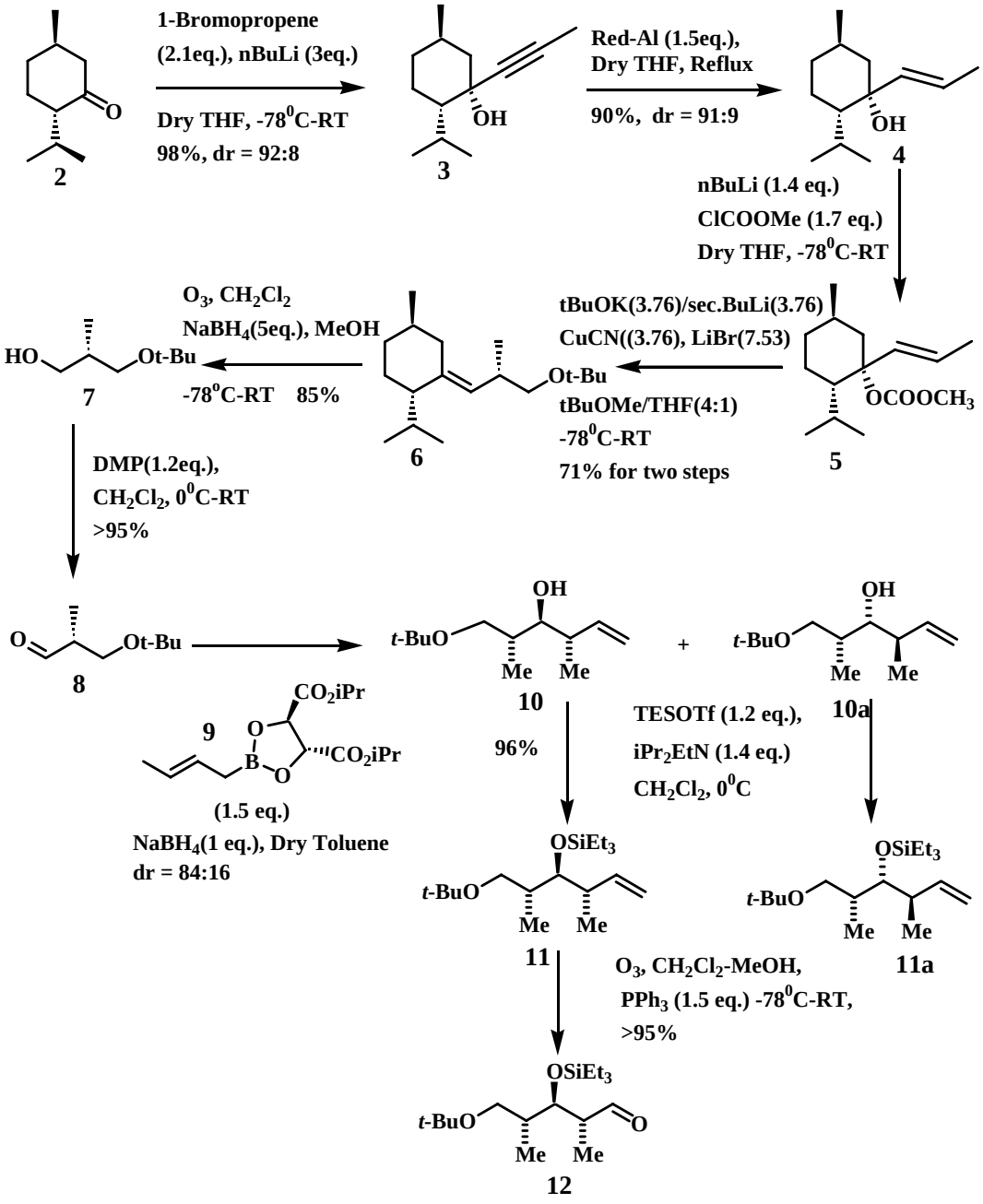
Ionomycin (1)


fragment C
fragment D
t-BuO
MOMO
CO2Me
OH
O
I
HO
H
O
OH
C
D
OH
OH
H
O
H
O
OH
B
CO2H
OH
O
A
1
O
I
O
CO2Me
OH
t-BuO
t-BuO
fragment B
fragment A

Scheme 1

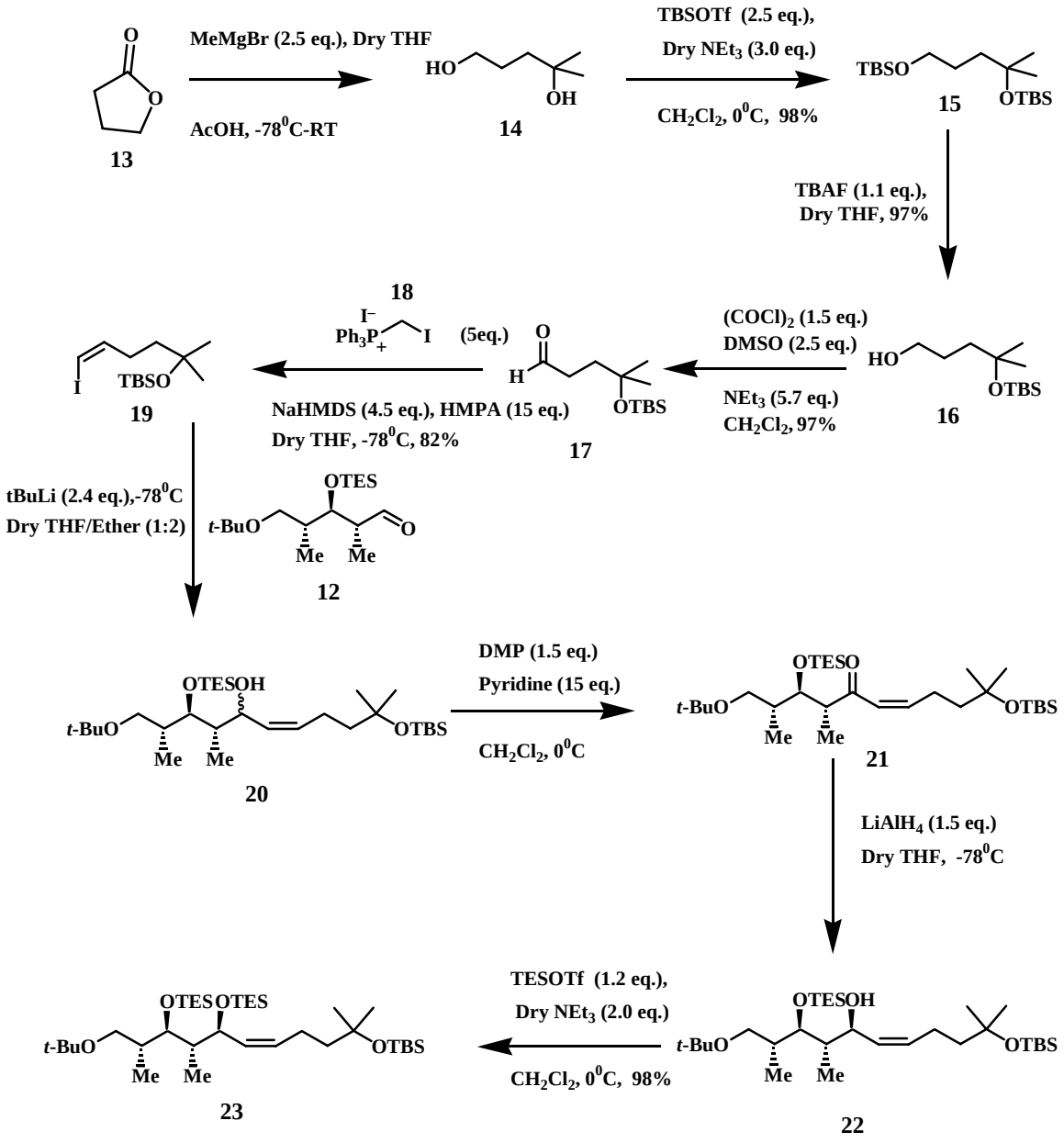
Model studies towards the synthesis of Fragment C & D:

Precursor to the fragment C (**12**) was synthesized using the recently published method[4], except the intermediate allylic alcohol **4** was prepared by treatment of E/Z-bromopropene/nBuLi with menthone (**2**), followed by selective reduction of corresponding alkyne with Red-Al. The selectivity in addition of lithiated propyne as well as reduction step was good and provided allylic alcohols **4** in 91:1 ratio (Scheme 2). Model fragment D (**19)** was synthesized in five steps starting from χ-butyrolactone (**13**) (Scheme 3). χ-Butyrolactone was subjected to addition of excess MeMgBr to yield open chain diol **14**. The diol was protected with TBS using 2.5 equivalent of TBSOTf and triethylamine in dichloromethane to obtain **15**. Selective deprotection of primary alcohol with 1.1 equiv. of TBAF gave alcohol **16**. Swern oxidation of the same, followed by Wittig reaction with **18** gave model fragment D (**19**). Coupling of aldehyde **12** with **19** gave Z-alkene **20**. The secondary alcohol of **20** was subjected to Dess-Martin oxidation to obtain ketone **21**. Various reducing agents to obtain cis-1,3 diol (**22**) were attempted (Mr. Martin Allan's M.Sc. Thesis) and found that $LiAlH_4$ in THF gives complete selectivity i.e. >99% only β-isomer (**22)**. The secondary alcohol was protected with triethylsilyl group using TESOTf/NEt_3 to obtain **23**. Having synthesized model fragment C & D (**23**), it needs to under go the following transformations: (a) removal of TBS group of tertiary alcohol for cyclization step which would provide the tetrafuranfuran ring; (b) removal of the t.Bu protecting group from **23** to carry out further transformations. Selective deprotection of TBS group from **23** with various deprotecting agents does not gave required product, instead gave mixture of products. (TES and TBS deprotection).



Scheme 2

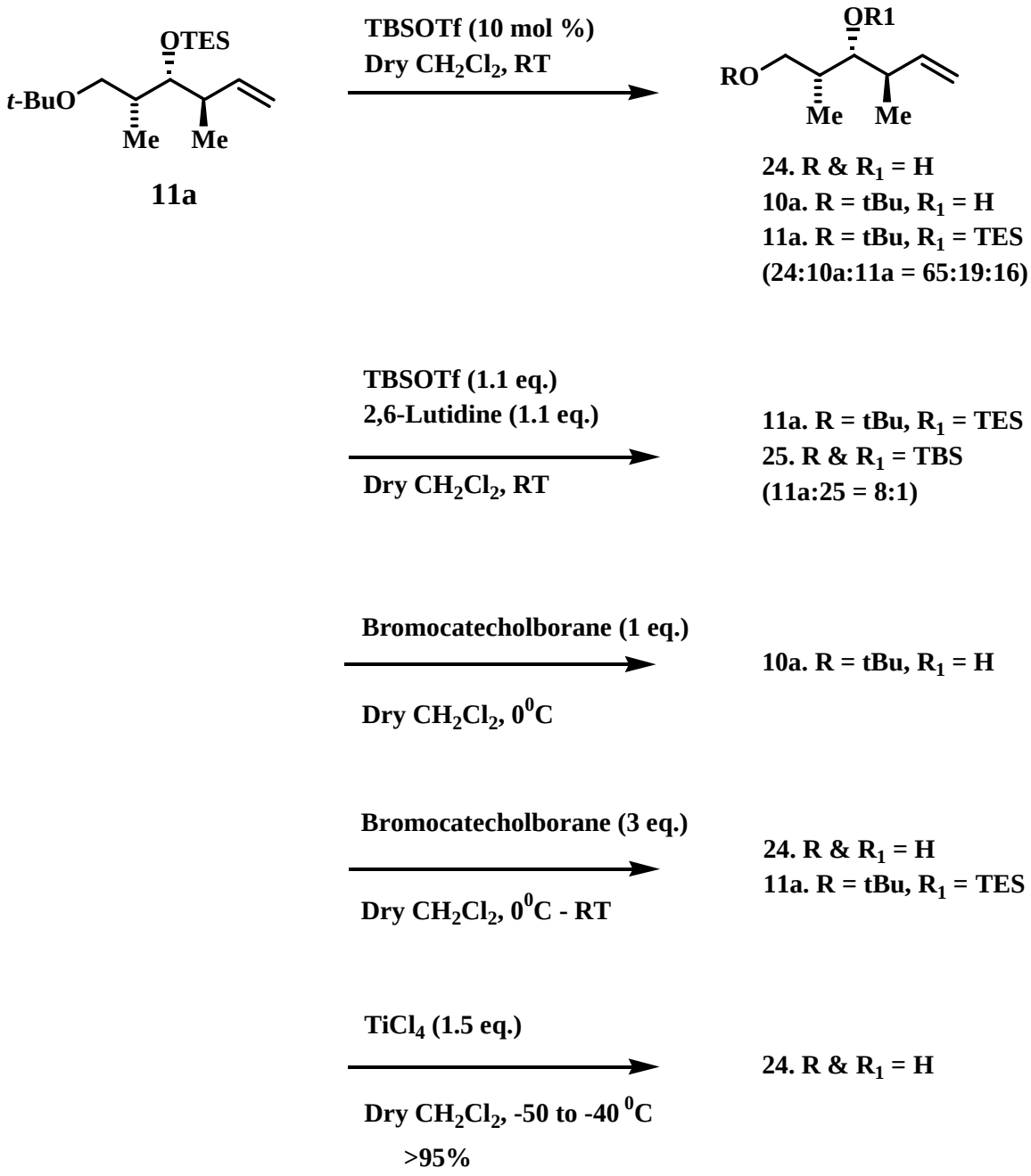
At this stage we decided to remove the t.Bu group from **11/11a** and protect the primary alcohol with benzyl or some other protecting groups so that it will be easier to remove selectively after construction of tetrahydrofuran ring. Compound **11a** (minor isomer is used for these studies) was treated with various deprotecting agents as shown in Scheme 4. All the effort to selectively remove t.Bu in presence of TES group failed and we were able to isolate corresponding diol **24** in good yield by treatment with $TiCl_4$.



Scheme 3

The primary alcohol of compound **24** can be selectively protected with benzyl group using recently published method by Sirkecioglu et al[5] and then secondary alcohol can be protected with appropriate group. Thus **24** was subjected to selective protection of primary alcohol in presence of secondary alcohol by using $PhCH_2Cl$ and catalytic amount $Cu(acac)_2$ at reflux temperature of benzyl chloride (Ref). Unfortunately this method of selective protection of primary alcohol does not work with our substrate. We were able to

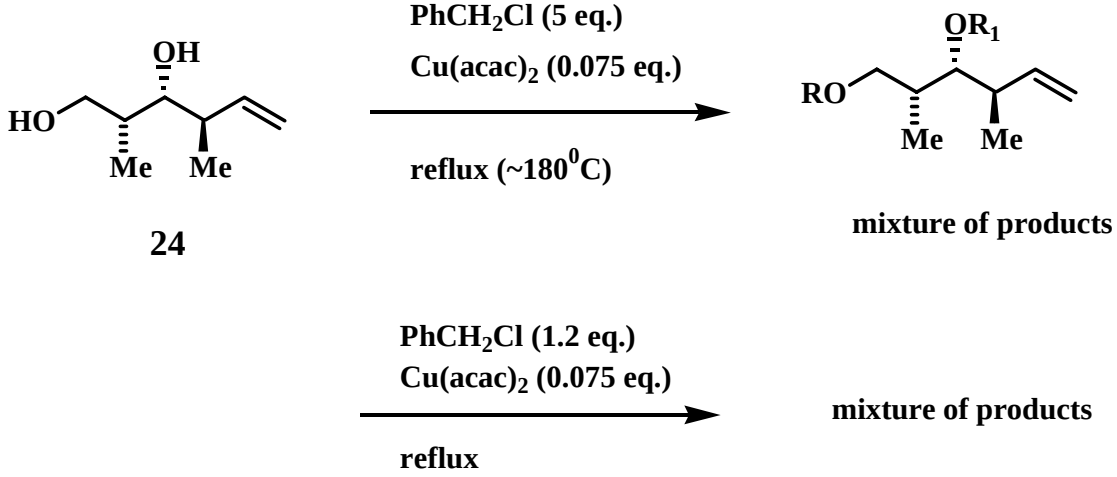
identify trace amount of required product and >90% of degraded products by proton NMR and GCMS of crude reaction mixture (Scheme 5).



Scheme 4

With these results in hand, it would be appropriate to remove the t.Bu group at earlier stages of synthesis. Initial trials of **6** with $TiCl_4$ (1.5 equiv.), TBSOTf (10mol%)

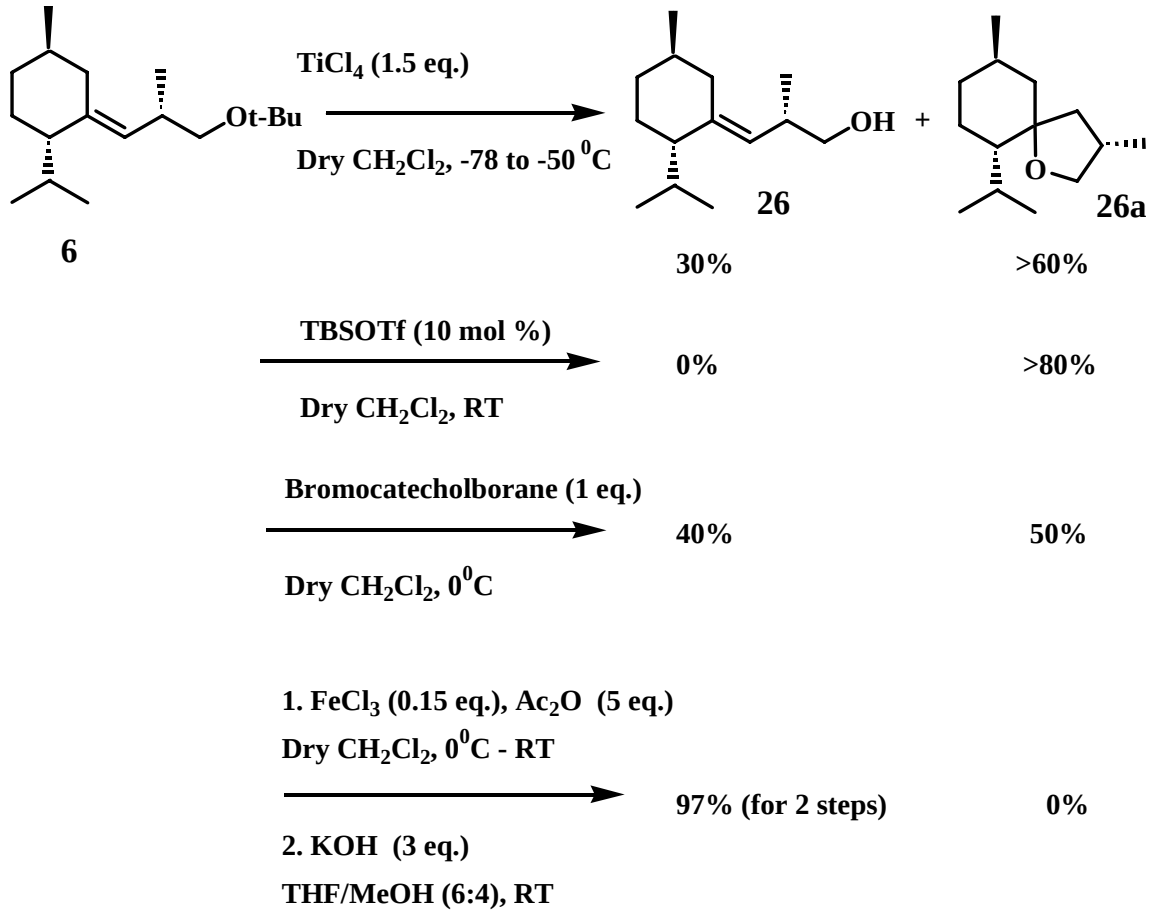
and bromocatecholborane (1 equiv.) in CH_2Cl_2 to remove t.Bu group gave required compound **26** and cyclized compound **26a** in the ratio of 30:60, 0:80 and 40:50 respectively, as a isolated yield (%) (Scheme 6). Treatment of **6** with catalytic amount of $FeCl_3$ and excess acetic anhydride in CH_2Cl_2 gave quantitative yield of corresponding acetate intermediate. Hydrolysis of the same with KOH in THF-MeOH mixture gave required compound **26** in 97% isolated yield for two steps.



24

Scheme 5

Alcohol **26** was then subjected to treatment with benzyl bromide and sodium hydride in THF and obtained alkene **27** in 95 % yield (Scheme 7). Which was further subjected to the similar sequence of reactions (ref. Scheme 2) to obtain precursor to the fragment C (**32**). Crotonylation of aldehyde **29** with Rosh's borane **9** gave 84:16 ratio of alcohols **30** and **30a**. Protection of sec.alcohol of compound **30** with TESOTf/iPr_2EtN gave **31** in 96% yield. Ozonolysis of terminal alkene of **31** and treatment with PPh_3 in CH_2Cl_2-MeOH gave aldehyde **32**. Compound **32,** has now protecting group, which is easy to remove after constructing tetrahydrofuran ring of fragment D. Compound **32** was coupled with model fragment D **19** to obtain **33**. Which was subjected to Dess-Martin oxidation to obtain Z-α,β-unsaturated ketone **34**. Selective reduction of ketone **34** to β-alcohol (cis-1,3 diol) **35** was achieved by treatment of $LiAlH_4$ in THF (Scheme 8).

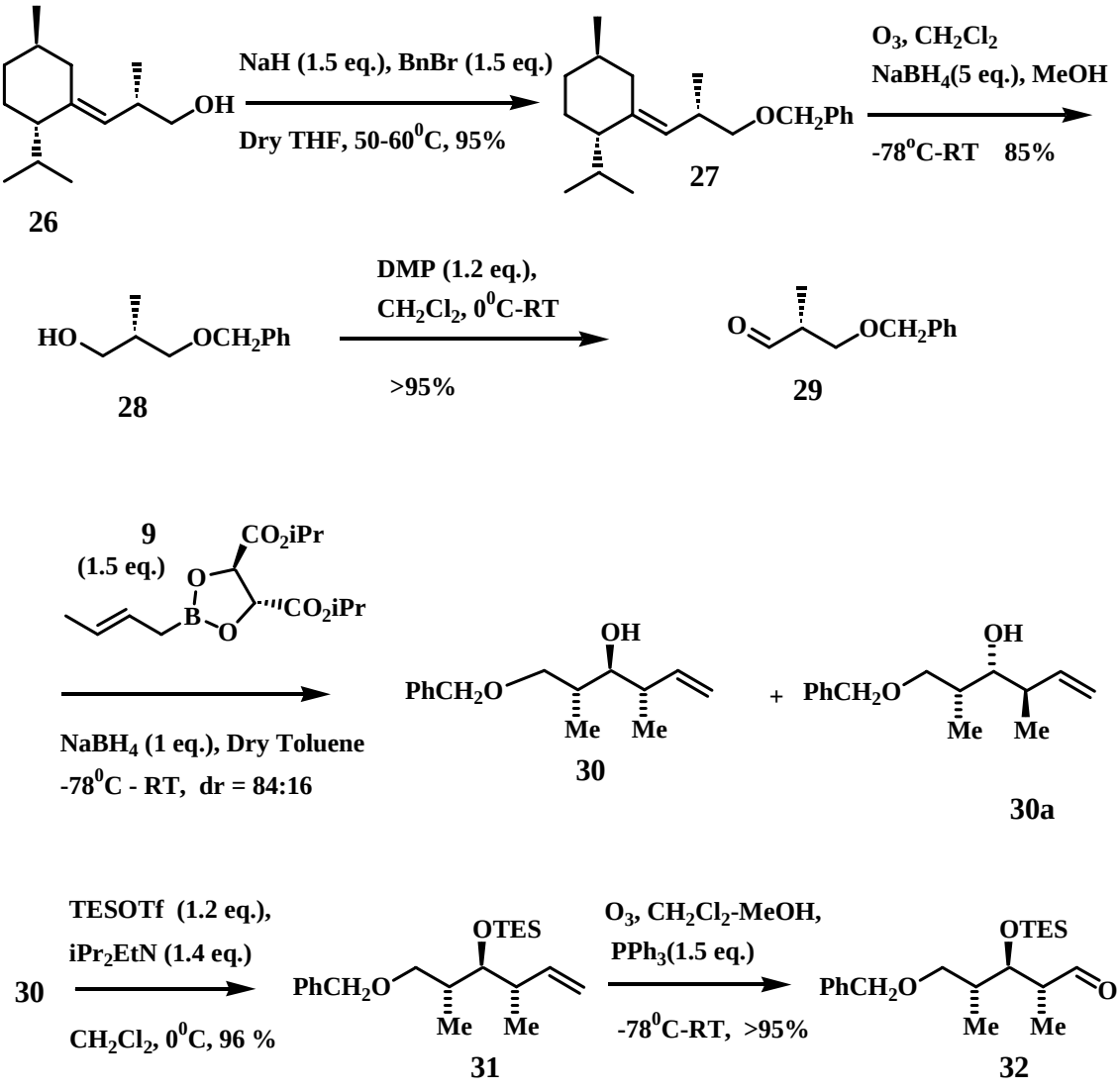


Scheme 6

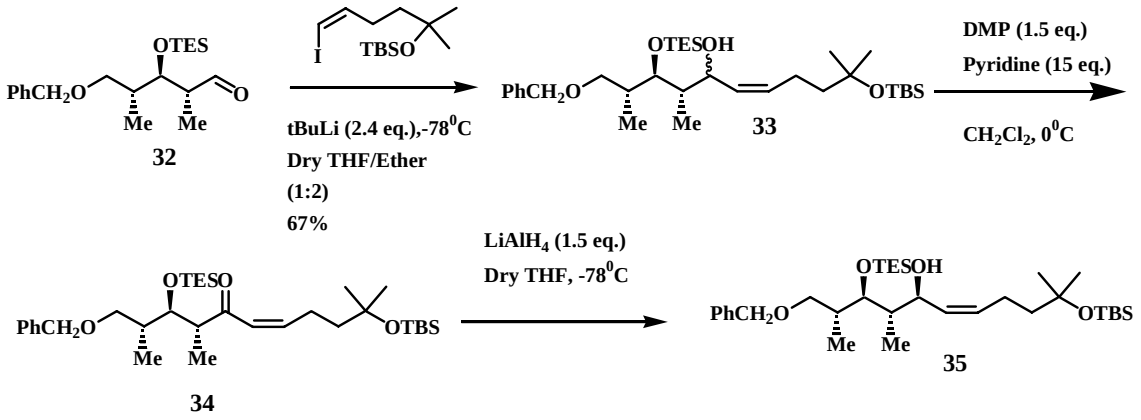
Synthesis of tetrahydrofuran ring with model fragment:

Compound **22** and **35** was converted to corresponding diols **36** and **37** in quantitative yield (95 and 98% respectively) by treatment of TBAF in THF. Protection of cis-1,3 diols of **36** and **37** with 1,1-dimethoxymethane and catalytic amount of camphorsulphonic acid in acetone gave 89 and 95 % isolated yield of **38** and **39,** respectively (Scheme 9). Initial trials of selective removal of TBS group from **38** and **39** with 1-2 equivalent of TBAF in THF did not gave any required compound, treatment with HF.pyridine in acetonitrile gave deprotection of TBS as well as acetonide. Finally we were able to remove selectively TBS group of **38** and **39** by treatment of excess TBAF at reflux temperature and furnished **41** and **42,** in respectively 93 and 98% isolated yield. Cyclization of tertiary alcohol of **41** and **42** with mercury (II) acetate and $NaBH_4$ in CH_2Cl_2 gave required tetrahydrofuran ring compound **43** and **44,** in respectively 79 and 45 % isolated yield (Refer Prof. Claude Spino's PhD Thesis). At this stage we were sure

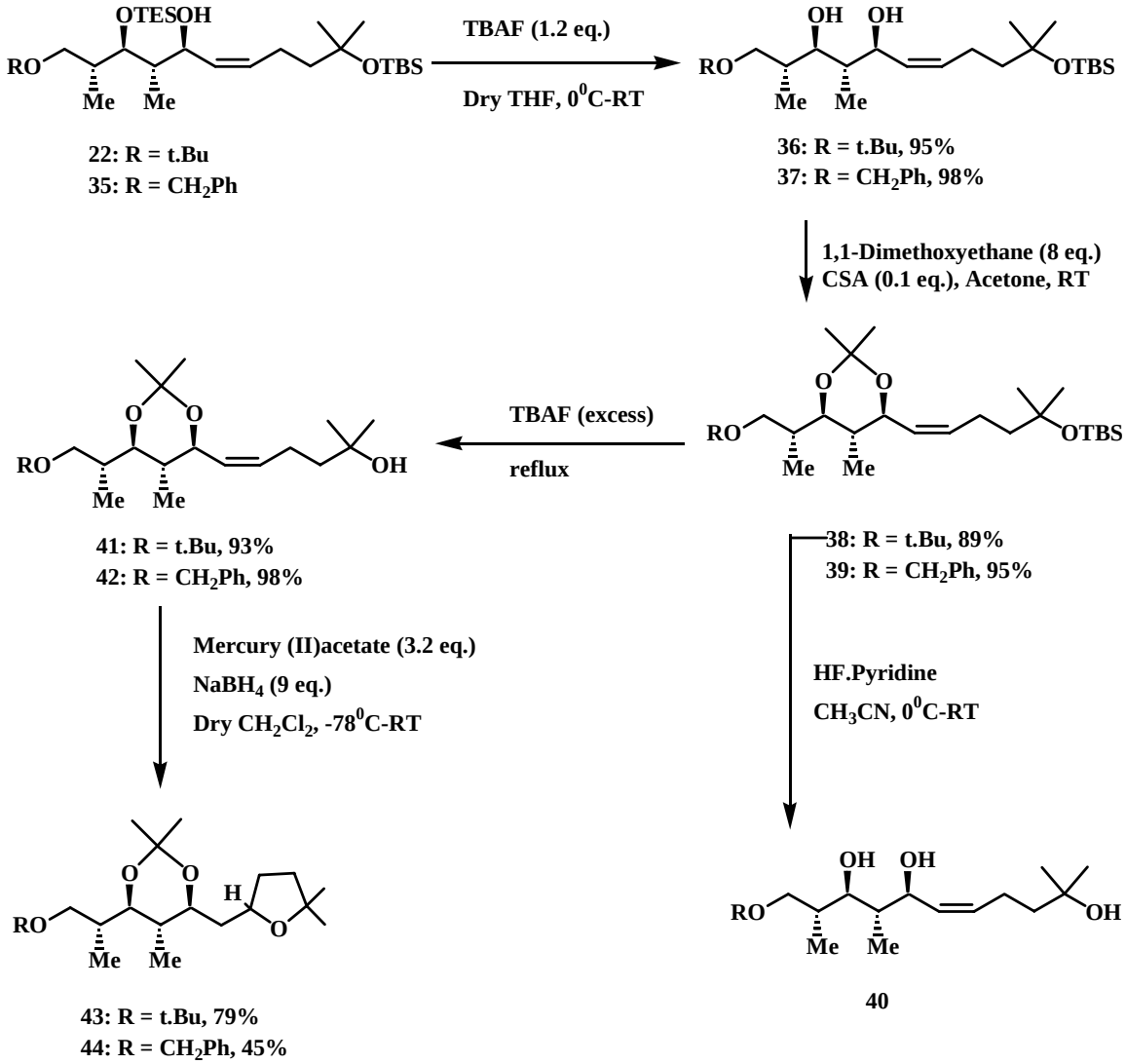
that treatment of **44** with Pd-C would provide us the primary alcohol, which can be converted to appropriate function for coupling with fragment B. With this result of successful construction of tetrahydrofuran ring with **41** and **42,** we were in interested in making real fragment D.



Scheme 7



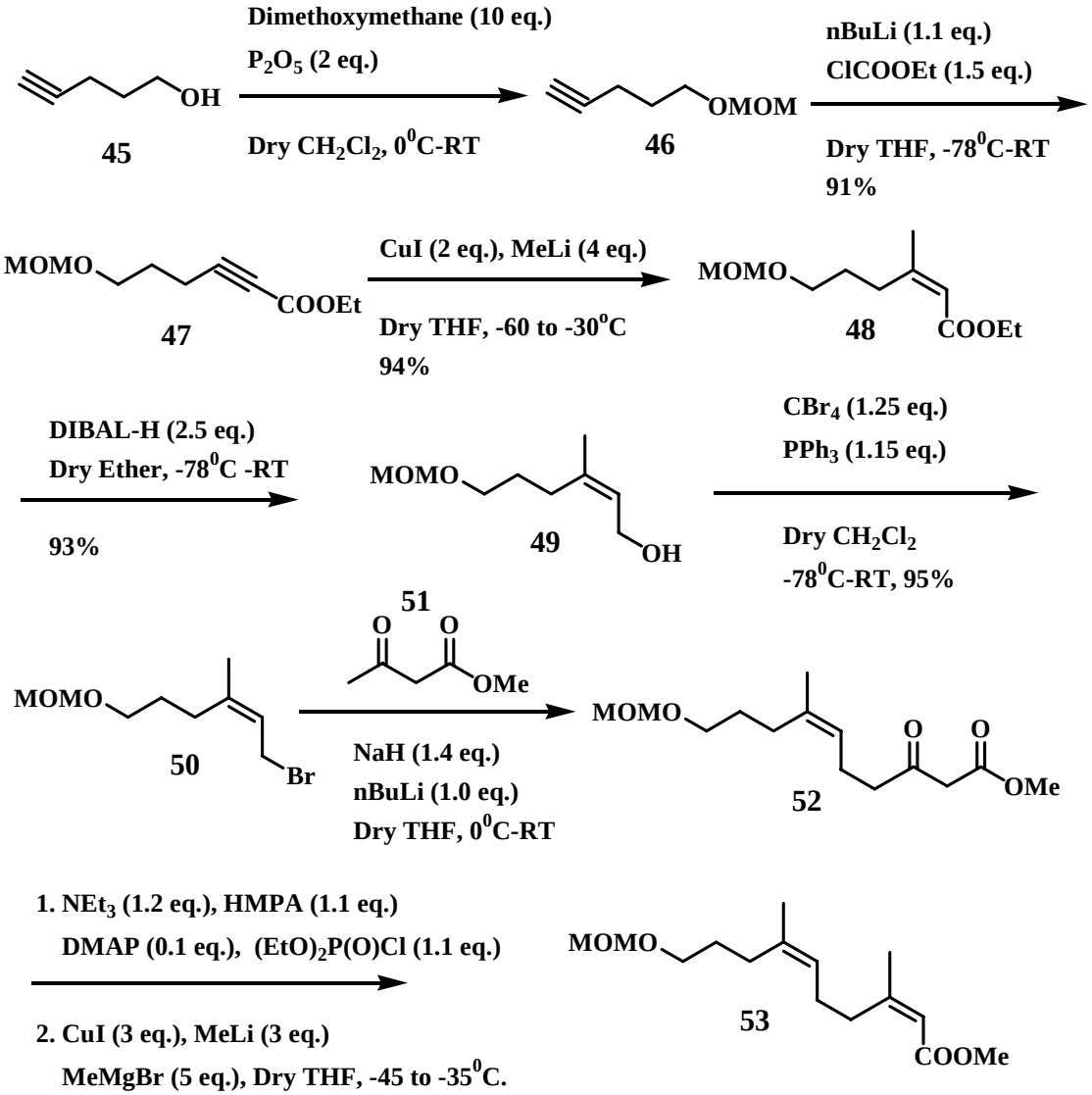
Scheme 8



Scheme 9

Synthesis of Fragment D:

The synthesis of fragment D was started with simple starting material, 1-pentyne-5-ol (**45**) (Refer Prof. Claude Spino's PhD Thesis). Protection of primary alcohol with MOM afforded **46** in –yield. Treatment of **46** with nBuLi/ClCOOEt in THF gave **47** in 91 % yield (Scheme 10). Dimethyl cuprate addition on alkyne gave selectively only cis alkene **48** in 94% yield. Reduction of ester group of **48** with DIBAL-H gave primary alcohol in 93% yield. Alcohol **49** was converted to corresponding bromide **50** by treatment of carbon tetrabromide and triphenyl phosphine in CH_2Cl_2. Treatment of dianion of **51** with bromide **50** gave compound **52** in 60% isolated yield which was then converted to **53** (precursor of fragment D).



Scheme 10

References:

1. Liu, W.-C.; Smith-Slusarchyk, D.; Astle, G.; Trejo, W. H.; Brown, W. E.; Meyers, E. *J. Antibiot.* **1978**, 31, 815-819.
2. Toeplitz, B. K.; Cohen, A. I.; Funke, P.T.; Parker, W. L.; Gougoutas J. Z. *J. Am. Chem. Soc*. **1979**, 101, 3344-3353.).
3. (a). Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, 112, 5290-5313. (b). Hanessian S.; Cooke N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, 112, 5276-5290. (c). Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith N. D.; Bouchain, G. *Org. Lett.* **2002**, 4, 1879-1882.
4. Spino, C. and Allan, M. *Can. J. Chem.* **2004**, 82, 177-184.
5. Sirkecioglu, O; Karliga, B.; Talinli, N.; *Tetrahedron Lett.* **2003**, 44, 8483-8485.

Experimental Section

Experiments involving organometallics were carried out under positive pressure of argon. All glassware's were assembled under a stream of argon. Dry ice and liquid nitrogen were used as cryoscopic fluids. Ether and THF were distilled from sodium-benzophenone ketyl. Dichloromethane, triethylamine and HMPA were distilled from calcium hydride. Organolithium and organomagnesium reagents were titrated with salicylaldehyde phenylhydrazone. Thin Layer Chromatography (TLC) were performed on silica gel and visualized by using a 10% phosphomolibdic acid solution in ethanol followed by heating. IR spectra were recorded on a Perkin-Elmer 420. NMR spectra have been recorded on a BRUKER ARX 300, in $CDCl_3$ as solvent. Chemical shifts are reported in ppm relative to TMS.

Compound 3

To the stirred solution of 1-bromoprpene (41.17 g = 29.14 mL, 0.3403 mol) (cis and trans mixture) in dry THF (300 mL) was added solution of nBuLi (2.5 M solution in hexane, 194.48 mL, 0.4862 mol) at –78 ^{0}C over a period of 0.5 h. The reaction mixture then stirred at same temperature for 2 h. Menthone (25.0 g = 22.32 mL, 0.1620 mol) in dry THF (50 mL) was added slowly. Reaction was allowed to warm gradually to room temperature and stirred for 18 h. The reaction was quenched by adding aq. NH_4Cl (700 mL) and extracted with diethyl ether (3 x 200 mL). Combined organic layers washed with brine (300 mL) dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The crude compound was purified by flash chromatography over silica gel (hexane to 10 % ethyl acetate/hexane gradient eluent) to give the desired alcohol **3** (25.2, 80%) as a colorless thick liquid. (GCMS of the crude reaction mixture showed 92:8 ratios of alcohols.)

Compound 4

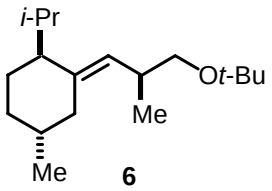
To the stirred solution of alkyne **3** (22.0 g, 0.1132 mol) in dry THF (300 mL) was slowly added Red-Al (65 wt % solution in toluene, 34.33 g = 50.97 mL, 0.1698 mol) at room temperature. The mixture was heated to reflux temperature for 20 h. After that it was cooled to ambient temperature, poured into ice-cold 10% aq. H_2SO_4 (800 mL) and

extracted with diethyl ether (3 x 200 mL). Combined organic layers washed with water (300 mL), brine (300 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield crude compound. Which was purified by flash chromatography over silica gel (hexane to 10 % ethyl acetate/hexane gradient eluent) to give the desired alcohol **4** (20.1, 90.42 %) as a colorless thick liquid. (GCMS of the crude reaction mixture showed 91:9 ratios of alcohols).

Compound 5

To the stirred solution of alcohol **4** (12.0 g, 0.06112 mol) in dry THF (160 mL) was slowly added *n*BuLi (2.0 M solution in hexane, 42.78 mL, 0.0855 mol) at –78 ^{0}C. The mixture was continued stirring for 2 h at the same temperature. After which time methyl chlorformate (9.81 g = 8.02 mL, 0.1039 mol) was added. Reaction was allowed to warm gradually to room temperature and stirred for 18 h. After which time it was poured into aq. NH_4Cl (700 mL) and extracted with diethyl ether (3 x 200 mL). Combined organic layers washed with water (300 mL), brine (300 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield crude carbonate **5** (15.52 g, 100 % crude). Which was used for the next step without purification.

Compound 6:

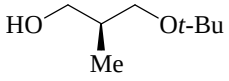


6

A solution of tert-butyl ether (840 mL) and potassium ter-butoxide (25.78 g, 0.2297 mol) was cooled to –78 ^{0}C, and then s-BuLi (164.1 mL, 0.2297 mol, 1.4 M solution in cyclohexane) was added dropwise. The resulting mixture was stirred at –78 ^{0}C for 1 h and at –50 ^{0}C for 1.5 h. In another flask, a solution of CuCN (20.58 g, 0.0.2297 mol) and LiBr (39.95 g, 0.4601 mol) in dry THF (180 mL) was added dropwise to the first one by cannula and the stirring continued at –78 ^{0}C for 1 more hour. The carbonate compound 5

(15.52 g, 0.0611 mol) was dissolved in 25 mL of dry THF, then added to the mixture dropwise. The mixture was allowed to warm gradually to room temperature while stirring for 18 h. The reaction was quenched by adding a 500 mL saturated aq. NH_4Cl and NH_4OH (9:1) solution. Aqueous portion was extracted with diethyl ether (3 x 200 mL). Combined organic layers washed with water (300 mL), brine (300 mL), dried over anhydrous $MgSO_4$, filtered, concentrated to dryness. Purification by flash chromatography over silica gel (hexane to 10 % ethyl acetate/hexane gradient eluent) afforded the desired cuprate adduct **6** (15.2 g, 71.26 %) as a colorless thick liquid. ^1H NMR in $CDCl_3$: δ 4.85 (d, 1H, *J* = 9.4 Hz), 3.23 (dd, 1H, *J* = 8.3 & 5.5 Hz), 3.03 (t, 1H, *J* = 8.5 Hz), 2.65-2.31 (m, 1H), 2.35 (dm, 1H, *J* = 16.5 Hz), 1.90 (sx, 1H, *J* = 6.8 Hz), 1.81-1.65 (m, 4H), 1.58-1.51 (m, 1H), 1.33-1.04 (m, 2H), 1.17 (s, 9H), 0.94 (d, 3H, *J* = 6.6 Hz), 0.91 (d, 3H, *J* = 6.6 Hz), 0.87 (d, 3H, *J* = 7.2 Hz), 0.84 (d, 3H, *J* = 7.2 Hz). ^{13}C NMR in $CDCl_3$: δ 139.8 (s), 125.0 (d), 72.3 (s), 67.0 (t), 51.1 (d), 35.6 (t), 32.8 (d), 32.4 (d), 31.9 (t), 27.6 (q), 26.9 (t), 26.5 (d), 22.1 (q), 20.6 (q), 19.8 (q), 18.6 (q). IR (cm^{-1}): 2970, 2869, 1461. LR-MS (m/z (relative intensity)): 266 (M^+, 5), 210 (35), 109 (100). HR-MS calcd. for $C_{18}H_{34}O$: 266.2610; found: 266.2614. [ ]$_D$ = -2.82º ($CHCl_3$, c = 1.44).

Alcohol 7:

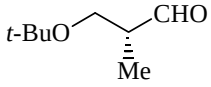


7

The alkene **6** (6.0 g, 0.02253 mol) was dissolved in CH_2Cl_2 / MeOH (4:1) (225 mL) and the solution was cooled to –78 ^0C. Ozone was bubbled through till the solution remained blue, indicating excess ozone. The flow was stopped and excess ozone was removed by bubbling N_2. Sodium borohydride (4.26 g, 0.1126 mol) was added and resulting slurry was allowed to warm to room temperature and stirred for 20 h. After which time solvent was evaporated and the residue was poured into water (150 mL) and extracted with diethyl ether (3 x 50 mL). Crude compound was purified by flash chromatography over silica gel (20-40 % ethyl acetate/hexane gradient eluent) to give the

desired alcohol **7** (2.7 g, 82 %) as a colorless thick liquid. ^{1}H NMR in $CDCl_3$: δ 3.66-3.50 (m, 3H), 3.28 (t, 1H, *J* = 8.8 Hz), 2.00 (m, 1H), 1.21 (s, 9H), 0.85 (d, 3H, *J* = 7.15 Hz). IR (cm^{-1}): 3384. LR-MS (m/z (relative intensity)): 131 (M^+-Me, 80), 89 (100), 87 (10). HR-MS calcd. for $C_7H_{14}O_2$: 131.1072; found: 131.1076. $[\alpha]_D$ = -16.8º ($CHCl_3$, c = 1.84).

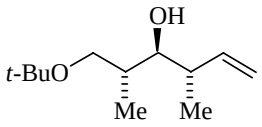
Aldehyde 8:



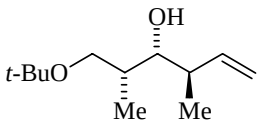
8

To the stirred solution of alcohol **7** (4.0 g, 0.0273 mol) in wet CH_2Cl_2 (200 mL) was slowly added Dess-Martin periodinane (13.94 g, 0.0328 mol) at 0 ^{0}C. The mixture was allowed to warm gradually to room temperature while stirring for 4 h. After which it was poured into 50 mL saturated solution of aq. $NaHCO_3$ and $Na_2S_2O_3$ (2:1) and extracted with CH_2Cl_2 (3 x 50 mL). Combined organic layers washed with water (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield crude aldehyde **8**. Which was used without further purification in the next step.

Compound 10 & 10a:



10

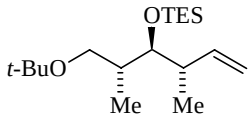


10a

To a solution of Roush's crotyl borane **9** (40.11 mL, 0.02808 mol, 0.7 M solution in toluene) was added 4 A^o molecular sieves (0.35 g). This mixture was stirred for 10 min, and then chilled to –78 ^{0}C. Crude aldehyde **8** (2.7 g, 0.01872 mol) in dry toluene (20 mL) was added dropwise and reaction stirred for 4 h at the same temperature. $NaBH_4$ (0.708 g, 0.01872 mol) in abs. EtOH (5 mL) was added dropwise and the resulting mixture was warmed to 0 ^{0}C. NaOH (13.5 mL, 2N aqueous solution) was added and stirred at room temperature for 1.5 h. The reaction was poured into water (50 mL). The aqueous layer

was extracted with diethyl ether (3 x 50 mL). Combined organic layers washed with water (25 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification by flash chromatography over silica gel (hexane to 10 % ethyl acetate/hexane gradient eluent) afforded the alcohol **10** (1.39 g, 37.06 % for 2 steps) and its diastereomer **10a** (0.564 g, 15.04 % for 2 steps) as colorless thick liquid. (GCMS of the crude reaction mixture showed 86:14 ratios of alcohols). **10:** ^{1}H NMR in $CDCl_3$: δ 6.01-5.89 (m, 1H), 5.07-5.02 (m, 2H), 4.37 (s, 1H), 3.49 (dd, 1H, *J* = 8.8 & 3.9 Hz), 3.37-3.31 (m, 2H), 2.37-2.31 (m, 1H), 1.89-1.77 (m, 1H), 1.20 (s, 9H), 1.10 (d, 3H, *J* = 6.6. Hz), 0.82 (d, 6H, *J* = 7.2 Hz). ^{13}C NMR in $CDCl_3$: δ 139.9 (d), 114.7 (t), 80.8 (d), 76.5 (s), 67.7 (t), 41.1 (d), 36.2 (d), 27.2 (q), 17.8 (q), 13.5 (q). IR (cm^{-1}): 3415, 3078, 2970, 1458. LR-MS (m/z (relative intensity)): 185 (M^+-Me, 5), 145 (30), 84 (100). HR-MS calcd. for $C_{11}H_{21}O_2$ (M-CH_3): 185.1541; found: 185.1535. $[\alpha]_D$ = -29.3º ($CHCl_3$, c = 2.09). **10a:** ^{1}H NMR in $CDCl_3$: δ 5.89-5.77 (m, 1H), 5.13-5.05 (m, 2H), 3.52-3.44 (m, 3H), 3.21 (d, 1H, *J* = 1.7 Hz), 2.26 (sx, 1H, *J* = 6.6 Hz), 1.90-1.80 (m, 1H), 1.18 (s, 9H), 0.97 (d, 3H, *J* = 7.2. Hz), 0.94 (d, 3H, *J* = 6.6 Hz). IR (cm^{-1}): 3466, 3079, 2976, 1455. LR-MS (m/z (relative intensity)): 218 ($MNH4^+$, 100), 201 (MH^+, 40). HR-MS calcd. for $C_{12}H_{25}O_2$ (MH^+): 201.1852; found: 201.1850. $[\alpha]_D$ = +6.6 º ($CHCl_3$, c = 3.72).

Compound 11:

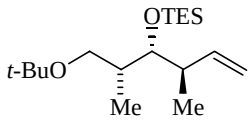


11

To a solution of alcohol **10** (1.2 g, 0.00599 mol) in CH_2Cl_2 (40 mL) at 0 ^{0}C was added i-Pr_2EtN (1.08 g = 1.459 mL, 0.008386 mol), followed by TESOTf (1.9 g = 1.63 mL, 0.007186 mol). The resulting mixture was stirred at 0 ^{0}C for 2 h. The reaction was quenched by adding a saturated aq. $NaHCO_3$ (50 mL) solution. The aqueous layer was extracted with diethyl ether (3 x 25 mL). Combined organic layers washed with water (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification by flash chromatography over silica gel (hexane to 5 % ethyl acetate/hexane

gradient eluent) afforded the desired silyl ether **11** (1.8 g, 95.74 %) as colorless thick liquid. ^{1}H NMR in $CDCl_3$: δ 5.88 (ddd, 1H, *J* = 17.6, 10.4, & 8.2 Hz), 5.00-4.94 (m, 2H), 3.49-3.44 (m, 2H), 3.09 (t, 1H, *J* = 8.3. Hz), 2.43-2.31 (m, 1H), 1.84-1.71 (m, 1H), 1.16 (s, 9H), 1.02 (d, 3H, *J* = 7.2 Hz), 0.97 (t, 9H, *J* = 8.3 Hz), 0.89 (d, 3H, *J* = 6.6 Hz), 0.62 (q, 6H, *J* = 8.3 Hz). IR (cm^{-1}): 3072, 2968, 2879, 1455. LR-MS (m/z (relative intensity)): 259 (M^+-C_4H_7, 40), 229 (45), 173 (100). HR-MS calcd. for $C_{14}H_{31}O_2Si$ (M-C_4H_7): 259.2093; found: 259.2090. $[\alpha]_D$ = +16.8º ($CHCl_3$, c = 1.98).

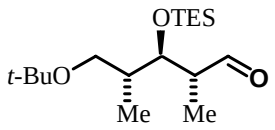
Compound 11a:



11a

To a solution of alcohol **10a** (0.36 g, 0.001797 mol) in CH_2Cl_2 (20 mL) at 0 ^{0}C was added i-Pr_2EtN (0.325 g = 0.438 mL, 0.00281 mol), followed by TESOTf (0.57 g = 0.48 mL, 0.002156 mol). The resulting mixture was stirred at 0 ^{0}C for 2 h. The reaction was quenched by adding a saturated aq. $NaHCO_3$ (25 mL) solution. The aqueous layer was extracted with diethyl ether (3 x 25 mL). Combined organic layers washed with water (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification by flash chromatography over silica gel (hexane to 5 % ethyl acetate/hexane gradient eluent) afforded the desired silyl ether **11a** (0.537 g, 95 %) as colorless thick liquid. ^{1}H NMR in $CDCl_3$: δ 5.9-5.78 (m, 1H), 5.02-4.95 (m, 2H), 3.58-3.55 (m, 1H), 3.3 (m, 1H), 3.10 (t, 1H, *J* = 8.3. Hz), 2.42-2.25 (m, 1H), 1.8 (m, 1H), 1.16 (s, 9H), 0.97-0.85 (m, 15H), 0.62 (q, 6H, *J* = 8.3 Hz). IR (cm^{-1}): 3072, 2968, 2879, 1455. LR-MS (m/z (relative intensity)): 315 (MH^+, 100), 259 (M^+-C_4H_7, 85), 229 (35), 173 (60). HR-MS calcd. for $C_{18}H_{39}O_2Si$ (MH^+): 315.2719; found: 315.2726. $[\alpha]_D$ = +16.8º ($CHCl_3$, c = 1.98).

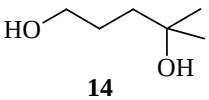
Aldehyde 12:



12

The alkene **11** (0.8 g, 0.002543 mol) was dissolved in CH_2Cl_2 / MeOH (4:1) (25 mL) and the solution was cooled to –78 ^{0}C. Ozone was bubbled through till the solution remained blue, indicating excess ozone. The flow was stopped and N_2 was bubbled to remove excess of ozone. Triphenyl phosphine (0.99 g, 0.00381 mol) was added and resulting solution was allowed to warm to room temperature and stirred for 16 hrs. After which time solvent was evaporated and the residue was triturated with hexane (3 x 25 mL). The combined hexane layers evaporated to dryness to give desired crude aldehyde. Which was used for the next step without purification.

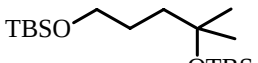
Compound 14:



14

To a solution of χ-butyrolactone **13** (28.0 g, 0.3255 mol) in dry THF (500 mL) at -78 ^{0}C was slowly added a solution of MeMgBr (271.31 g, 0.8139 mol, 3.0 M solution in diethyl ether) and continued stirring at the same temperature for 1.5 h. Reaction mixture was then gradually warmed to 0 ^{0}C over a period of 1 h. Glacial acetic acid (48.87 g = 50 mL, 0.8139 mol) was added slowly (exothermic reaction) and stirred at room temperature for 3 h. The reaction was quenched by adding a 20 % aq. solution of citric acid (500 mL). The aqueous layer was extracted with diethyl ether (3 x 250 mL). Combined organic layers washed with water (250 mL), brine (250 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to afford >90 % pure diol **14** (29.0g, 75.5%) as colorless thick liquid. ^{1}H NMR in $CDCl_3$: δ 3.68 (t, 2H, *J* = 6.1 Hz), 1.71-1.64 (m, 2H), 1.61-1.55 (m, 2H), 1.25 (s, 6H). IR (cm^{-1}): 3253, 2970, 2871, 1468. LR-MS (m/z (relative intensity)): 136 (MNH_4^+, 10), 119 (MH^+, 60), 101 (100). HR-MS calcd. for $C_6H_{15}O_2$ (MH^+): 119.1072; found: 119.1070.

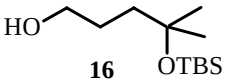
Compound 15:



15

To a solution of diol **14** (5.7 g, 0.0483 mol) in CH_2Cl_2 (60 mL) at 0 ^{0}C was added dry Me_3N (19.55 g = 27.15 mL, 0.1932 mol), followed by TBSOTf (38.3 g = 33.3 mL, 0.1449 mol). The resulting mixture was stirred at 0-5 ^{0}C for 3 h. The reaction was quenched by adding a saturated aq. $NaHCO_3$ (100 mL) solution. The aqueous layer was extracted with dichloromethane (3 x 50 mL). Combined organic layers washed with water (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification by flash chromatography over silica gel (hexane to 5 % ethyl acetate/hexane gradient eluent) afforded the desired compound **15** (15.0 g, 89.6 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 3.59 (t, 2H, *J* = 6.0 Hz), 1.63-1.54 (m, 2H), 1.44-1.39 (m, 2H), 1.19 (s, 6H), 0.89 (s, 9H), 0.84 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H). IR (cm^{-1}): 2953, 2856, 1468. LR-MS (m/z (relative intensity)): 331 (M^+-CH_3, 5), 289 (M^+-C_4H_9, 10), 247 (80), 147 (100). HR-MS calcd. for $C_{17}H_{39}O_2Si_2$ (M-CH_3): 331.2488; found: 331.2483.

Compound 16:

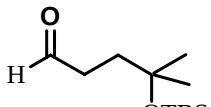


16

To a solution of **15** (12.5 g, 0.03605 mol) in dry THF (300 mL) at 0 ^{0}C was slowly added 1.0 M solution of TBAF (36.05 mL, 0.03605 mol). The resulting mixture was stirred at 0 ^{0}C to room temperature for 3 h. The reaction was quenched by adding a saturated aq. NH_4Cl (250 mL). The aqueous layer was extracted with diethyl ether (3 x 100 mL). Combined organic layers washed with water (100 mL), brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification by flash

chromatography over silica gel (hexane to 20 % ethyl acetate/hexane gradient eluent) afforded the desired alcohol **16** (8.1 g, 96.65 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 3.64 (q, 2H, *J* = 6.1 Hz), 1.71-1.63 (m, 2H), 1.50-1.40 (m, 2H), 1.21 (s, 6H), 0.85 (s, 9H), 0.07 (s, 6H). IR (cm^{-1}): 3326, 2952, 2856, 1462. LR-MS (m/z (relative intensity)): 217 (M^+-CH_3, 5), 175 (M^+-C_4H_9, 10), 173 (35), 133 (100). HR-MS calcd. for $C_{11}H_{25}O_2Si$(M-CH_3): 217.1624; found: 217.1631.

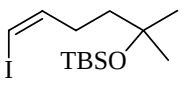
Aldehyde 17:



17

To the stirred solution of alcohol **16** (5.0 g, 0.02151 mol) in CH_2Cl_2 (70 mL) and H_2O (0.58 mL, 0.03226 mol) was slowly added Dess-Martin periodinane (13.68 g, 0.0322 mol) at 0 ^{0}C. The mixture was allowed to warm gradually to room temperature while stirring for 2 h. After which it was poured into saturated solution of aq. $NaHCO_3$ and $Na_2S_2O_3$ (2:1)(100 mL) and extracted with CH_2Cl_2 (3 x 75 mL). Combined organic layers washed with water (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield crude aldehyde. Purification by flash chromatography over silica gel (hexane to 5 % ethyl acetate/hexane gradient eluent) afforded the desired aldehyde **17** (3.65 g, 92.4 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 9.79 (t, 1H, *J* = 1.7 Hz), 2.54 (td, 2H, *J* = 7.7 & 1.7 Hz), 1.75 (t, 2H, *J* = 7.7 Hz), 1.22 (s, 6H), 0.85 (s, 9H), 0.07 (s, 6H). IR (cm^{-1}): 2973, 2935, 2888, 1726, 1463. LR-MS (m/z (relative intensity)): 215 (M^+-CH_3, 10), 197 (5), 173 (M^+-C_4H_9, 90), 75 (100). HR-MS calcd. for $C_{11}H_{23}O_2Si$ (M-CH_3): 215.1467; found: 215.1464.

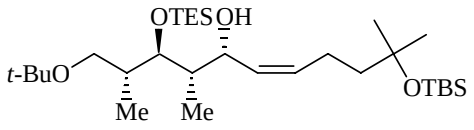
Compound 19:



19

To the stirred solution of iodomethyltriphenylphosphonium iodide **18** (11.5 g, 0.02169 mol) in dry THF (50 mL) was slowly added sodium bis(trimethylsilyl)amide (19.52 mL, 0.0195 mol, 1.0 M solution in THF) at room temperature and stirred for 2 min. After which time it was cooled to –78 ^{0}C and was added hexamethylphosphoramide (11.66 g = 11.32 mL, 0.0650 mol) and stirred for 5 min. Aldehyde **17** (1.0 g, 0.00433 mol) in dry THF (5 mL) was added slowly and continued stirring at the same temperature for 1 h. After which time cooling bath was removed and allowed stir at room temperature for 0.5 h. After which it was poured into saturated solution of aq. NH_4Cl (250 mL) and extracted with ether (3 x 75 mL). Combined organic layers washed with water (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification of hexane soluble part of crude by flash chromatography over silica gel (hexane eluent) afforded the desired cis vinyl iodide **19** (1.25 g, 81.69 %) as light pink liquid. ^{1}H NMR in $CDCl_3$: δ 6.21-6.13 (m, 2H), 2.28-2.13 (m, 2H), 1.53-1.47 (m, 2H), 1.23 (s, 6H), 0.87 (s, 9H), 0.08 (s, 6H). IR (cm^{-1}): 3073, 2974, 2931, 2856, 1610, 1468. LR-MS (m/z (relative intensity)): 339 (M^+-CH_3, 10), 297 (30), 173 (20), 75 (100). HR-MS calcd. for $C_9H_{18}IOSi$ (M-C_4H_9): 297.0172; found: 297.0180.

Compound 20:

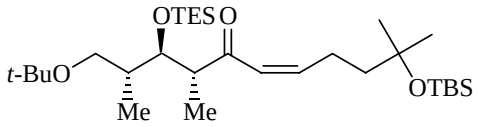


20

To the stirred solution of vinyliodo compound **19** (1.074 g, 0.003032 mol) in dry diethyl ether (20 mL) was slowly added t-BuLi (3.56 mL, 0.00606 mol, 1.7 M solution in pentane) and continued stirring at –78 ^{0}C for 1.5 h and at 0 ^{0}C for 1.5 h. After 3 h it was cooled to –78 ^{0}C and aldehyde **12** (0.8 g, 0.002527 mol) in dry THF (10 mL) was added dropwise. Reaction mixture was gradually warmed to room temperature and stirred for 20 h. After which it was poured into saturated aq. NH_4Cl (100 mL) solution and extracted with ether (3 x 50 mL). Combined organic layers washed with water (50 mL), brine (50

mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification by flash chromatography over silica gel (hexane to 5 % ethyl acetate/hexane gradient eluent) afforded the desired compound **20** (1.068 g, 71.0 %) as a colorless liquid. **20.** ^{1}H NMR in $CDCl_3$: δ 5.50-5.35 (m, 2H), 4.90 (d, 1H, *J* = 7.7 Hz), 3.72 (dd, 1H, *J* = 7.2 & 2.8 Hz), 3.56 (s, 1H), 3.40 (dd, 1H, *J* = 8.8 & 5.0 Hz), 3.19 (dd, 1H, *J* = 8.8 & 7.1 Hz), 2.29-1.99 (m, 3H), 1.73-1.65 (m, 1H), 1.53-1.40 (m, 2H), 1.19 (s, 6H), 1.17 (s, 9H), 1.05 (d, 3H, *J* = 7.2 Hz), 0.99 (t, 9H, *J* = 7.7 Hz), 0.96 (d, 3H, *J* = 7.2 Hz), 0.86 (s, 9H), 0.69 (q, 6H, *J* = 7.7 Hz), 0.06 (s, 6H). IR (cm^{-1}): 3505, 2961, 2879, 1459. LR-MS (m/z (relative intensity)): 545 (MH^+, 5), 413 (20), 395 (35), 263 (80), 173 (84), 73 (100). HR-MS calcd. for $C_{30}H_{65}O_4Si_2$ (MH^+): 545.4421; found: 545.4402. $[\alpha]_D$ = +5.12º ($CHCl_3$, c = 1.25).

Ketone 21:

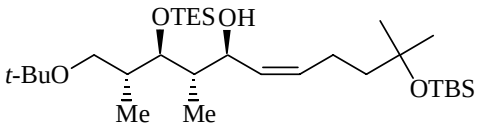


21

To the stirred solution of alcohol **20** (0.75 g, 0.001376 mol) in CH_2Cl_2 (20 mL) and H_2O (0.037 mL, 0.00206 mol) was slowly added pyridine (1.63 g = 1.68 mL, 0.0206 mol), followed by Dess-Martin periodinane (0.875 g, 0.02064 mol) at 0 ^{0}C. The mixture was allowed stir at the same temperature for 3 h. After which it was poured into saturated solution of aq. $NaHCO_3$ and $Na_2S_2O_3$ (2:1)(50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). Combined organic layers washed with water (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield crude compound. Purification by flash chromatography over silica gel (hexane to 3 % ethyl acetate/hexane gradient eluent) afforded the desired ketone **21** (0.65 g, 87 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 6.19 (d, 1H, *J* = 11.0 Hz), 6.08 (dt, 1H, *J* = 11.6 & 7.2 Hz), 3.97 (dd, 1H, *J* = 7.7 & 3.9 Hz), 3.48 (dd, 1H, *J* = 8.8 & 5.5 Hz), 3.10 (t, 1H, *J* = 7.7 Hz), 2.85 (qi, 1H, *J* = 7.2 Hz), 2.73-2.65 (m, 2H), 1.88-1.80 (m, 1H), 1.52 (t, 2H, *J* = 8.8 Hz), 1.21 (s, 6H), 1.17 (s, 9H),

1.02 (d, 3H, *J* = 7.2 Hz), 0.93 (t, 9H, *J* = 7.7 Hz), 0.90 (d, 3H, *J* = 7.2 Hz), 0.85 (s, 9H), 0.58 (q, 6H, *J* = 7.7 Hz), 0.06 (s, 6H). IR (cm^{-1}): 2972, 2882, 1688, 1455. LR-MS (m/z (relative intensity)): 543 (MH^+, 10), 243 (100). HR-MS calcd. for $C_{30}H_{62}O_4Si_2$: 543.4265; found: 543.4258. $[\alpha]_D$ = -27.4º ($CHCl_3$, c =1.36).

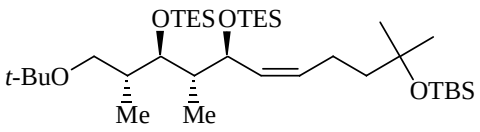
Compound 22:



22

To the stirred solution of **21** (0.65 g, 0.001197 mol) in dry ether (25 mL) was slowly added $LiAlH_4$ (5.98 mL, 0.005983 mol, 1.0 M solution in diethyl ether) at –78 ^{0}C and stirred for 1 h. After which it was poured into saturated aq. NH_4Cl (50 mL) solution and extracted with ether (3 x 25 mL). Combined organic layers washed with water (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield crude compound. Purification by flash chromatography over silica gel (hexane to 25 % ethyl acetate/hexane gradient eluent) afforded the **22** (0.210 g, 32.2 %) and **36** (0.175 g, 33.98%) as colorless liquid. **22.** ^{1}H NMR in $CDCl_3$: δ 5.51 (dt, 1H, *J* = 11.0 & 7.2 Hz), 5.30 (t, 1H, *J* = 8.8 Hz), 4.36 (t, 1H, *J* = 9.4 Hz), 3.80-3.76 (m, 2H), 3.40 (dd, 1H, *J* = 9.4 & 6.1 Hz), 3.12 (dd, 1H, *J* = 8.8 & 7.7 Hz), 2.27-2.06 (m, 2H), 1.98-1.87 (m, 1H), 1.82-1.70 (m, 1H), 1.59-1.37 (m, 2H), 1.19 (s, 6H), 1.16 (s, 9H), 1.00 (t, 9H, *J* = 7.7 Hz), 0.97 (d, 3H, *J* = 7.2 Hz), 0.85 (s, 9H), 0.79 (d, 3H, *J* = 7.2 Hz), 0.68 (q, 6H, *J* = 7.7 Hz), 0.06 (s, 6H). IR (cm^{-1}): 3480, 2968, 2879, 1459. LR-MS (m/z (relative intensity)): 545 (MH^+, 40), 471 (5), 395 (28), 263 (100). HR-MS calcd. for $C_{30}H_{65}O_4Si_2(MH^+)$: 545.4421; found: 545.4429. $[\alpha]_D$ = -2.04º ($CHCl_3$, c = 1.58).

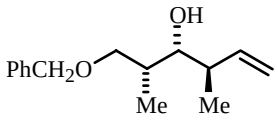
Compound 23:



23

To a solution of alcohol **22** (0.37 g, 0.00678 mol) in CH_2Cl_2 (20 mL) at 0 ^{0}C was added i-Pr_2EtN (0.421 g = 0.567 mL, 0.003258 mol), followed by TESOTf (0.43 g = 0.368 mL, 0.001629 mol). The resulting mixture was stirred at 0 ^{0}C for 2 h. The reaction was quenched by adding a saturated aq. $NaHCO_3$ (50 mL) solution. The aqueous layer was extracted with diethyl ether (3 x 25 mL). Combined organic layers washed with water (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification by flash chromatography over silica gel (hexane to 3 % ethyl acetate/hexane gradient eluent) afforded the desired di-silyl ether **23** (0.417 g, 94.77 %) as colorless thick liquid. ^{1}H NMR in $CDCl_3$: δ 5.36-5.3 (m, 1H), 5.24-5.17 (t, 1H, *J* = 8.8 Hz), 4.36 (t, 1H, *J* = 9.4 Hz), 3.95 (m, 1H), 3.58 (dd, 1H, *J* = 9.4 & 6.1 Hz), 3.1 (t, 1H, *J* = 7.7 Hz), 2.12 (m, 2H), 1.91 (m, 1H), 1.75 (m, 1H), 1.5-1.4 (m, 2H), 1.21 (s, 6H), 1.2 (d, 3H merged), 1.16 (s, 9H), 1.05-0.9 (m, 18H), 0.85 (s, 9H), 0.79 (d, 3H, *J* = 7.15 Hz), 0.68-0.5 (m, 12H), 0.06 (s, 6H). IR (cm^{-1}): 3480, 2968, 2879, 1459. LR-MS (m/z (relative intensity)): 658 (M^+, 2), 526 (10), 469 (20), 279 (45), 260 (80), 189 (100). HR-MS calcd. for $C_{36}H_{79}O_4Si_3$ (MH^+): 659.5286; found: 659.5272.

Compound 24:



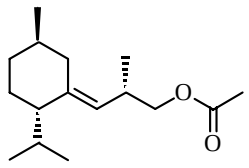
24

To a solution of **11a** (1.44 g, 0.007188 mol) in dry CH_2Cl_2 (10 mL) at -50 ^{0}C was slowly added $TiCl_4$ (2.045 g, 0.01078 mol) and stirred at the same temperature for 10 min. The reaction was quenched by adding a saturated aq. NH_4Cl (50 mL) solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layers washed with water (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to yield >95 % pure diol **23** (1.03 g, 100 % = crude) as colorless thick liquid. ^{1}H NMR in $CDCl_3$: δ 5.72-5.63 (m, 1H), 5.18-5.13 (m, 2H), 3.76 (m, 2H), 3.5 (dd, 1H, *J* = 8.8 & 1.3 Hz), 2.29-2.21 (m, 1H), 1.85 (m, 1H), 0.97 (d, 6H, *J* = 7.15 Hz).

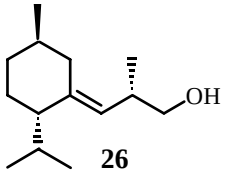
Compound 26:

To a solution of **6** (3.0 g, 0.01126 mol) in dry ether (150 mL) was added acetic anhydride (5.75 g = 5.32 mL, 0.0563 mol), followed by Fe(III)Cl_3 (0.274 g, 0.001689 mol) in dry ether (5 mL). The resulting mixture was stirred at room temperature for 20 h. The reaction was quenched by adding a saturated aq. Na_2HPO_4 (28.16 mL) solution and stirred for 3 h. It was then diluted with water (50 mL). The aqueous layer was extracted with diethyl ether (3 x 25 mL). Combined organic layers washed with water (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to yield >95 % pure acetate (3.0 g, crude) as colorless liquid.

To a solution of acetate ((3.0 g crude) 2.84 g, 0.01125 mol) in THF (60 mL) was added KOH (1.89 g, 0.03376 mol) in MeOH (40 mL). The resulting mixture was stirred at room temperature for 20 h. Reaction solvent was removed under reduced pressure and the residue was poured into saturated aq. NH_4Cl (75 mL) solution and extracted with ether (3 x 50 mL). Combined organic layers washed with water (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification of crude by flash chromatography over silica gel (hexane to 15 % ethyl acetate/hexane gradient eluent) afforded the desired alcohol **26** (2.3 g, 97.45 % for 2 steps) as colorless thick liquid.



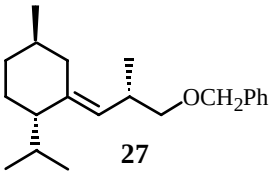
^{1}H NMR in $CDCl_3$: δ 4.86 (d, 1H, *J* = 9.35 Hz), 3.94-3.81 (m, 2H), 2.8 (m, 1H), 2.35 (m, 1H), 2.1 (s, 3H), 1.95-1.88 (m, 1H), 1.8-1.62 (m, 4H), 1.55 (m, 1H), 1.3 (m, 1H), 1.12 (m, 1H), 0.96-0.81 (m, 12H). LR-MS (m/z (relative intensity)): 252 (M^+, 5), 237 (2), 177 (35), 149 (100). HR-MS calcd. for $C_{16}H_{28}O_2$: 252.2089; found: 252.2091.



26

26. ^{1}H NMR in $CDCl_3$: δ 4.84 (d, 1H, *J* = 9.35 Hz), 3.47 (dd, 1H, *J* = 10.45 & 6.05 Hz), 3.34 (dd, 1H, *J* = 10.45 & 7.7 Hz), 2.68 (m, 1H), 2.4 (m, 1H), 1.95 (m, 1H), 1.81-1.6 (m, 5H), 1.34-1.24 (m, 1H), 1.18-1.1 (m, 1H), 0.93-0.84 (m, 13H). ^{13}C NMR in $CDCl_3$: δ 142.28 (s), 124.10 (d), 68.0 (t), 50.99 (d), 35.85 (t), 34.55 (d), 32.55 (d), 31.9 (t), 26.72 (t), 26.4 (d), 22.0 (q), 20.71 (q), 19.61 (q), 17.6 (q). LR-MS (m/z (relative intensity)): 210 (M^+, 30), 179 (20), 149 (100). HR-MS calcd. for $C_{14}H_{26}O$: 210.1984; found: 210.1990.

Compound 27:

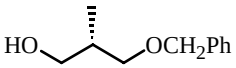


27

To a washed NaH (0.385 g, 0.016043 mol) in THF (50 mL) was added alcohol **26** (2.25 g, 0.01069 mol) in dry THF (25 mL) at 0 ^{0}C. The resulting mixture was stirred at the same temperature for 0.5 h. Benzyl bromide (2.74 g = 1.9 mL, 0.01604 mol), followed by catalytic amount of Bu_4NI (0.09 g) was added and reaction stirred for 24 h at 50-60 ^{0}C. Reaction was poured into saturated aq. NH_4Cl (100 mL) solution and extracted with ether (3 x 50 mL). Combined organic layers washed with water (50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification of crude by flash chromatography over silica gel (hexane to 15 % ethyl acetate/hexane gradient eluent) afforded compound **27** (2.9 g, 90.34 %) as colorless thick liquid. ^{1}H NMR in $CDCl_3$: δ 7.34-7.27 (m, 5H), 4.88 (d, 1H, *J* = 9.35 Hz), 4.51 (s, 2H), 3.35 (dd, 1H, *J* = 10.45 & 6.05 Hz), 3.22 (dd, 1H, *J* = 10.45 & 7.7 Hz), 2.76 (m, 1H), 2.34 (m, 1H), 1.92 (m, 1H), 1.8-1.61 (m, 4H), 1.55 (m, 1H), 1.33 (m, 1H), 1.12 (m, 1H), 0.98 (d, 3H, *J* =

7.25 Hz), 0.90-0.83 (m, 9H). LR-MS (m/z (relative intensity)): 300 (M^+, 10), 209 (25), 191 (15), 91 (100). HR-MS calcd. for $C_{21}H_{32}O$: 300.2453; found: 300.2443.

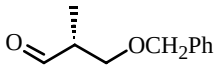
Alcohol 28:



28

The alkene **27** (1.73 g, 0.005757 mol) was dissolved in CH_2Cl_2 / MeOH (4:1) (50 mL) and the solution was cooled to –78 ^{0}C. Ozone was bubbled through till the solution remained blue, indicating excess ozone. The flow was stopped and excess ozone was removed by bubbling N_2. Sodium borohydride (1.089 g, 0.02878 mol) was added and resulting slurry was allowed to warm to room temperature and stirred for 15 h. After which time solvent was evaporated and the residue was poured into water (100 mL) and extracted with diethyl ether (3 x 50 mL). Crude compound was purified by flash chromatography on silica gel (50-100 % ethyl acetate/hexane gradient eluent) to give the desired alcohol **28** (0.85 g, 82.52 %) as a colorless thick liquid. ^{1}H NMR in $CDCl_3$: δ 7.38-7.28 (m, 5H), 4.52 (s, 2H), 3.65-3.53 (m, 3H), 3.42 (t, 1H, *J* = 9.3 Hz), 2.08 (m, 1H), 0.88 (d, 3H, *J* = 7.15 Hz). ^{13}C NMR in $CDCl_3$: δ 137.81 (s), 127.78 (d), 127.01 (d), 73.37 (t), 72.53 (t), 65.35 (t), 35.39 (d), 13.27(q). LR-MS (m/z (relative intensity)): 180 (M^+, 10), 161 (15), 107 (70), 91 (100). HR-MS calcd. for $C_{11}H_{16}O_2$: 180.1150; found: 180.1145.

Aldehyde 29:



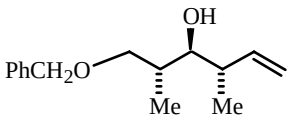
29

To the stirred solution of alcohol **28** (0.8 g, 0.004438 mol) in wet CH_2Cl_2 (25 mL) was slowly added Dess-Martin periodinane (2.259 g, 0.005326 mol) at 0 ^{0}C. The mixture was

allowed to warm gradually to room temperature while stirring for 1.5 h. After which it was poured into saturated solution of aq. $NaHCO_3$ and $Na_2S_2O_3$ (2:1, 50 mL) and extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layers washed with water (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield crude aldehyde (0.755 g). Which was used without further purification in the next step. ^{1}H NMR in $CDCl_3$: δ 9.73 (s, 1H), 7.35-7.28 (m, 5H), 4.52 (s, 2H), 3.66 (m, 2H), 2.66 (m, 1H), 1.13 (d, 3H, *J* = 7.15 Hz). LR-MS (m/z (relative intensity)): 196 (MNH_4^+, 30), 179 (MH^+, 30), 107 (55), 91 (100).

Compound 30 & 30a:

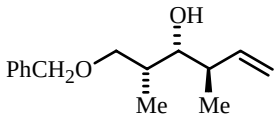
To a solution of Roush's crotyl borane **9** (12.62 mL, 0.06312 mol, 0.5 M solution in toluene) was added 4 A^o molecular sieves (0.1 g). This mixture was stirred for 10 min, and then chilled to –78 ^{0}C. Crude aldehyde **29** (0.75 g, 0.004208 mol) in dry toluene (5 mL) was added dropwise and reaction stirred for 4 h at the same temperature. $NaBH_4$ (0.159 g, 0.004208 mol) in abs. EtOH (3 mL) was added dropwise and the resulting mixture was warmed to 0 ^{0}C over a period of 1 h. NaOH (3.75 mL, 2N aqueous solution) was added and stirred at room temperature for 1 h. The reaction was poured into water (50 mL). The aqueous layer was extracted with diethyl ether (3 x 50 mL). Combined organic layers washed with water (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification by flash chromatography over silica gel (hexane to 5 % ethyl acetate/hexane gradient eluent) afforded the alcohol **30** (0.49 g, 46.66 % for 2 steps) and its diastereomer **30a** (0.12 g, 11.42 % for 2 steps) as colorless thick liquid. (GCMS of the crude reaction mixture showed 84:16 ratios of alcohols).



30

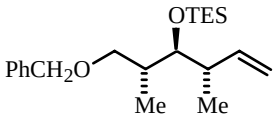
30: ^{1}H NMR in $CDCl_3$: δ 7.34-7.28 (m, 5H), 5.96-5.84 (m, 1H), 5.08-5.03 (m, 2H), 4.51 (s, 2H), 3.6-3.48 (m, 2H), 3.38-3.35 (m, 1H), 2.35 (m, 1H), 1.93 (m, 1H), 1.10 (d,

3H, *J* = 7.15 Hz), 0.88 (d, 3H, *J* = 7.15 Hz). LR-MS (m/z (relative intensity)): 235 (MH^+, 38), 179 (25), 91 (100). HR-MS calcd. for $C_{15}H_{23}O_2$ (MH^+): 235.1698; found: 235.1702.



30a

30a: ^{1}H NMR in $CDCl_3$: δ 7.34-7.28 (m, 5H), 5.86-5.73 (m, 1H), 5.14-5.10 (m, 2H), 4.51 (s, 2H), 3.65-3.8 (m, 3H), 2.3 (m, 1H), 2.0 (m, 1H), 0.98-0.85 (d, 6H, *J* = 7.15 Hz). LR-MS (m/z (relative intensity)): 235 (MH^+, 18), 179 (10), 91 (100). HR-MS calcd. for $C_{15}H_{23}O_2$ (MH^+): 235.1698; found: 235.1702.



31

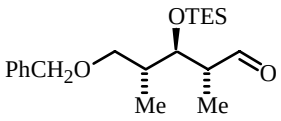
31: ^{1}H NMR in $CDCl_3$: δ 7.34-7.27 (m, 5H), 5.92-5.8 (m, 1H), 4.98 (d, 2H, *J* = 5.5 Hz), 4.48 (d, 2H, *J* = 5.5 Hz), 3.56-3.49 (m, 2H), 3.33 (dd, 1H, *J* = 8.8 & 7.15 Hz), 2.34 (m, 1H), 1.90 (m, 1H), 1.01 (d, 3H, *J* = 7.15 Hz), 0.96-0.91 (m, 12H), 0.6 (q, 6H, *J* = 7.7 Hz). LR-MS (m/z (relative intensity)): 319 ($M\text{-}C_2H_5^+$, 5), 293 (15), 187 (30), 91 (100). HR-MS calcd. for $C_{19}H_{31}O_2Si$ ($M\text{-}C_2H_5^+$) : 319.2093; found: 319.2096.

Compound 31:

To a solution of alcohol **30** (0.49 g, 0.002091 mol) in CH_2Cl_2 (20 mL) at 0 ^{0}C was added i-Pr_2EtN (0.378 g = 0.509 mL, 0.002927 mol), followed by TESOTf (0.66 g = 0.567 mL, 0.002509 mol). The resulting mixture was stirred at 0 ^{0}C for 3 h. The reaction was quenched by adding a saturated aq. $NaHCO_3$ (50 mL) solution. The aqueous layer was extracted with diethyl ether (3 x 25 mL). Combined organic layers washed with water (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification by flash chromatography over silica gel (hexane to 3 % ethyl acetate/hexane

gradient eluent) afforded the desired silyl ether **31** (0.708 g, 96.72 %) as colorless thick liquid.

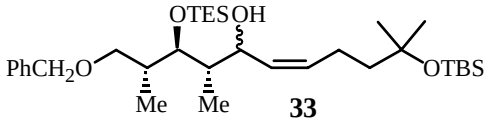
Aldehyde 32:



32

The alkene **31** (0.315 g, 0.0009039 mol) was dissolved in CH_2Cl_2 / MeOH (4:1) (20 mL) and the solution was cooled to –78 ^{0}C. Ozone was bubbled through till the solution remained blue, indicating excess ozone. The flow was stopped and N_2 was bubbled to remove excess of ozone. Triphenyl phosphine (0.358 g, 0.001355 mol) was added and resulting solution was allowed to warm to room temperature and stirred for 15 hrs. After which time solvent was evaporated and the residue was triturated with hexane (3 x 20 mL). The combined hexane layers evaporated to dryness to give desired crude aldehyde. Which was used for the next step without purification. ^{1}H NMR in $CDCl_3$: δ 9.77 (d, 1H, *J* = 1.2 Hz), 7.34-7.27 (m, 5H), 4.48 (d, 2H, *J* = 5.5 Hz), 4.0 (m, 1H), 3.48 (dd, 1H, *J* = 8.8 & 7.15 Hz), 3.36 (dd, 1H, *J* = 8.8 & 7.15 Hz), 2.56 (m, 1H), 2.05 (m, 1H), 1.10 (d, 3H, *J* = 7.15 Hz), 0.96-0.9 (m, 12H), 0.6 (q, 6H, *J* = 7.7 Hz). LR-MS (m/z (relative intensity)): CI; 366 (MNH_4^+, 5), 351 (MH^+, 13), 279 (55), 91 (100).

Compound 33:

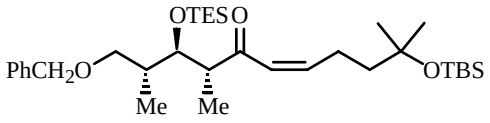


33

To the stirred solution of vinyl iodo compound **19** (0.5 g, 0.001411 mol) in dry diethyl ether (15 mL) was slowly added t-BuLi (1.66 mL, 0.002822 mol, 1.7 M solution in pentane) and continued stirring at –78 ^{0}C for 1.5 h and at 0 ^{0}C for 1.5 h. After 3 hrs it was

cooled to –78 ^{0}C and aldehyde **32** (0.315 g, 0.000899 mol) in dry THF (5 mL) was added dropwise. Reaction mixture was gradually warmed to room temperature and stirred for 18 h. After which it was poured into saturated aq. NH_4Cl (50 mL) solution and extracted with ether (3 x 25 mL). Combined organic layers washed with water (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Purification by flash chromatography over silica gel (hexane to 5 % ethyl acetate/hexane gradient eluent) afforded the desired compound **33** (0.353 g, 66.88 % for 2 steps) as a colorless liquid. ^{1}H NMR in $CDCl_3$: δ 7.37-7.25 (m, 5H), 5.45-5.31 (m, 2H), 4.50 (s, 2H), 4.12 (m, 1H), 3.65 (dd, 1H, *J* = 7.7 & 3.5 Hz), 3.48-3.33 (m, 2H), 2.2-2.02 (m, 4H), 1.75 (m, 1H), 1.48 (m, 2H), 1.2 (m, 4H), 1.12 (d, 3H, *J* = 7.2 Hz), 0.98 (t, 6H, *J* = 8.8 Hz), 0.9-0.75 (m, 16H), 0.6 (q, 6H, *J* = 7.7 Hz), 0.05 (s, 6H). LR-MS (m/z (relative intensity)): 596 (MNH_4^+, 5), 579 (MH^+, 10), 297 (100). HR-MS calcd. for $C_{33}H_{63}O_4Si_2$ (MH^+): 579.4265; found: 579.4250.

Ketone 34:

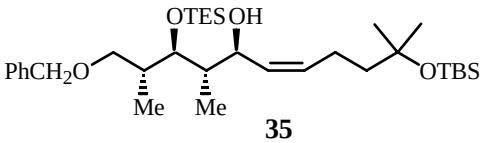


34

To the stirred solution of alcohol **33** (0.345 g, 0.0005958 mol) in CH_2Cl_2 (10 mL) and H_2O (0.1 mL) was slowly added pyridine (0.7068 g = 0.728 mL, 0.00893 mol), followed by Dess-Martin periodinane (0.379 g, 0.000893 mol) at 0 ^{0}C. The mixture was allowed stir at the same temperature for 3 h. After which it was poured into saturated solution of aq. $NaHCO_3$ and $Na_2S_2O_3$ (2:1)(50 mL) and extracted with CH_2Cl_2 (3 x 20 mL). Combined organic layers washed with water (25 mL), brine (25 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield crude compound. Purification by flash chromatography over silica gel (hexane to 3 % ethyl acetate/hexane gradient eluent) afforded the desired ketone **34** (0.2 g, 58.47 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 7.34-7.27 (m, 5H), 6.2-6.02 (m, 2H), 4.48 (s, 2H), 3.98 (dd, 1H, *J* = 7.7 & 3.9 Hz), 3.6 (dd, 1H, *J* = 8.8 & 5.5 Hz), 3.3 (t, 1H, *J* = 7.7 Hz), 2.78 (qi, 1H, *J* = 7.2 Hz), 2.67 (m,

1H), 2.0 (m, 1H), 1.52 (t, 2H, *J* = 8.8 Hz), 1.2 (s, 6H), 1.16 (m, 1H), 1.02 (d, 3H, *J* = 7.2 Hz), 0.95-0.8 (m, 21H), 0.55 (q, 6H, *J* = 7.7 Hz), 0.05 (s, 6H). LR-MS (m/z (relative intensity)): 547 ($M-C_2H_5^+$, 10), 415 (30), 359 (5), 187 (50), 91 (100). HR-MS calcd. for $C_{31}H_{55}O_4Si_2$ (M- C_2H_5) : 547.3639; found: 547.3629.

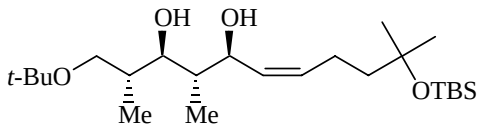
Compound 35:



35

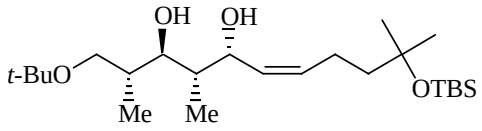
To the stirred solution of ketone **34** (0.115 g, 0.0001993 mol) in dry ether (6 mL) was slowly added $LiAlH_4$ (0.996 mL, 0.000996 mol, 1.0 M solution in diethyl ether) at –78 ^{0}C and stirred for 1 h. After which it was poured into saturated aq. NH_4Cl (25 mL) solution and extracted with ether (3 x 15 mL). Combined organic layers washed with water (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield crude compound. Purification by flash chromatography over silica gel (hexane to 20 % ethyl acetate/hexane gradient eluent) afforded the **35** (0.065 g, 56.52 %) and **37** (0.012 g, 12.95 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 7.34-7.27 (m, 5H), 5.51 (m, 1H), 5.3 (t, 1H, *J* = 9.35 Hz), 4.48 (s, 2H), 4.36 (t, 1H, *J* = 9.35 Hz), 3.81 (t, 1H, *J* = 4.95 Hz), 3.64 (d, 1H, *J* = 1.1 Hz), 3.51 (dd, 1H, *J* = 9.35 & 6.05 Hz), 3.31 (dd, 1H, *J* = 9.34 & 7.14 Hz), 2.16 (m, 3H), 1.78 (m, 1H), 1.5 (m, 2H), 1.2 (s, 6H), 0.95 (t and d, merged, 12H), 0.85 (s, 9H), 0.77 (d, 3H, *J* = 6.6 Hz), 0.65 (q, 6H, *J* = 7.7 Hz), 0.06 (s, 6H). ^{13}C NMR in $CDCl_3$: δ 138.52 (s), 132.90 (d), 130.70 (d), 128.24 (d), 127.46 (d), 79.65 (d), 73.18 (s), 72.98 (t), 72.40 (t), 70.33 (d), 44.77 (t), 40.83 (d), 39.66 (d), 29.70 (q), 29.57 (q), 25.82 (q), 23.16 (t), 18.05 (s), 16.11 (q), 13.72 (q), 6.93 (q), 5.05 (t), -2.12 (q). LR-MS (m/z (relative intensity)): 579 (MH^+, 5), 549 (3), 297 (100), 173 (70), 91 (60). HR-MS calcd. for $C_{33}H_{63}O_4Si_2$ (MH^+) : 579.4265; found: 579.4250.

Compound 36:



36

To the stirred solution of **22** (0.450 g, 0.0006825 mol) in dry THF (10 mL) was slowly added TBAF (1.365 mL, 0.001365 mol, 1.0 M solution in THF) at 0 ^{0}C and stirred for 1 h at room temperature. After which it was poured into saturated aq. NH_4Cl (50 mL) solution and extracted with ether (3 x 20 mL). Combined organic layers washed with water (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield crude compound. Purification by flash chromatography over silica gel (hexane to 20 % ethyl acetate/hexane gradient eluent) afforded the **36** (0.290 g, 98.63 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 5.52 (dt, 1H, *J* = 11.0 & 7.7 Hz), 5.37 (dd, 1H, *J* = 11.0 & 9.3 Hz), 5.07 (s, 1H), 4.58-4.55 (m, 1H), 4.46 (t, 1H, *J* = 8.8 Hz), 3.73 (dd, 1H, *J* = 8.8 & 2.8 Hz), 3.55-3.44 (m, 2H), 3.36 (dd, 1H, *J* = 8.8 & 3.3 Hz), 2.18 (oc, 2H, *J* = 5.5 Hz), 1.97 (oc, 1H, *J* =3.9 Hz), 1.71 (sx, 1H, *J* = 7.2 Hz), 1.55-1.37 (m, 2H), 1.20 (s, 9H), 1.19 (s, 6H), 1.14 (d, 3H, 6.6 Hz), 0.85 (s, 9H), 0.75 (d, 3H, *J* = 7.2 Hz), 0.06 (s, 6H). IR (cm^{-1}): 3376, 2972, 2854, 1459. LR-MS (m/z (relative intensity)): 431 (MH^+, 5), 299 (30), 263 (100), 207 (70), 145 (92). HR-MS calcd. for $C_{24}H_{51}O_4Si$ (MH^+): 431.3556; found: 431.3543. $[\alpha]_D$ = +8.32^o ($CHCl_3$, c =1.63).

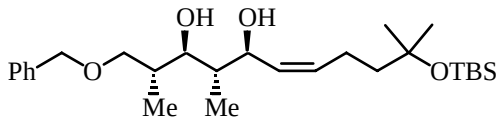


(36a, minor alcohol)

36a. ^{1}H NMR in $CDCl_3$: δ 5.56-5.39 (m, 2H), 5.07-5.06 (m, 1H), 4.82 (d, 1H, *J* = 8.3 Hz), 4.27-4.26 (m, 1H), 3.64 (dd, 1H, *J* = 8.8 & 3.3 Hz), 3.59-3.54 (m, 1H), 3.34 (t, 1H, *J* = 8.8 Hz), 2.29-2.02 (m, 3H), 1.82-1.74 (m, 1H), 1.53-1.37 (m, 2H), 1.22 (s, 9H), 1.19 (s, 6H), 1.03 (d, 3H, *J* = 7.2 Hz), 0.90 (d, 3H, *J* = 7.2 Hz), 0.85 (s, 9H), 0.06 (s, 6H). IR (cm^{-1}): 3390, 2968, 2936, 1559, 1459. LR-MS (m/z (relative intensity)): 431 (MH^+, 5), 263

(100). HR-MS calcd. for $C_{24}H_{51}O_4Si$: 431.3556; found: 431.3547. $[\alpha]_D$ = -9.47º ($CHCl_3$, c =1.39).

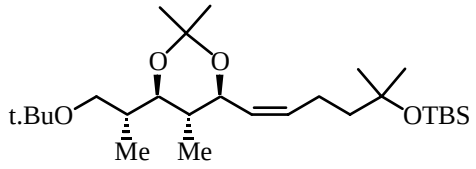
Compound 37:



37

To the stirred solution of **35** (0.060 g, 0.0001036 mol) in dry THF (5 mL) was slowly added TBAF (0.103 mL, 0.0001036 mol, 1.0 M solution in THF) at 0 ^{0}C and stirred for 1 h at room temperature. After which it was poured into saturated aq. NH_4Cl (25 mL) solution and extracted with ether (3 x 15 mL). Combined organic layers washed with water (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield crude compound. Purification by flash chromatography over silica gel (hexane to 15 % ethyl acetate/hexane gradient eluent) afforded the **37** (0.047 g, 96.7 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 7.38-7.29 (m, 5H), 5.53 (m, 1H), 5.34 (d, 1H, *J* = 10.99 & 9.34 Hz), 4.56-4.43 (m, 3H), 3.72 (dd, 1H, *J* = 9.34 & 3.85 Hz), 3.52 (m, 2H), 2.2 (m, 2H), 2.02 (m, 1H), 1.7 (m, 1H), 1.45 (m, 2H), 1.19 (s, 6H), 1.16 (d, 3H, *J* = 7.15 Hz), 0.85 (s, 9H), 0.74 (d, 3H, *J* = 7.15 Hz), 0.06 (s, 6H). ^{13}C NMR in $CDCl_3$: δ 137.55 (s), 132.90 (d), 131.15 (d), 128.5 (d), 127.85 (d), 127.66 (d), 82.24 (d), 73.7 (t), 73.18 (s), 72.92 (d), 72.47 (t), 44.84 (t), 41.60 (d), 35.00 (d), 29.83 (q), 29.57 (q), 25.82 (q), 22.91 (t), 18.05 (s), 15.72 (q), 13.72 (q), -2.06 (q). LR-MS (m/z (relative intensity)): 465 (MH^+, 8), 369 (2), 315 (80), 297 (100), 191 (72), 173 (65), 91 (55). HR-MS calcd. for $C_{27}H_{49}O_4Si$ (MH^+) : 465.3400; found: 465.3390.

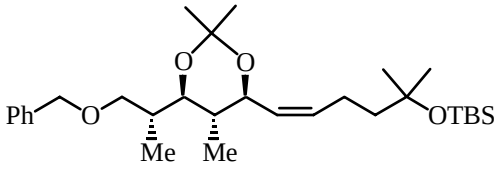
Compound 38:



38

To the stirred solution of **36** (0.165 g, 0.0003828 mol) in acetone (5 mL) was added 10-camphorsulfonic acid (0.00887 g, 0.0000382 mol), followed by 2,2-dimethoxypropane (0.318 g = 0.376 mL, 0.003062 mol) and stirred for 18 h at room temperature. The reaction was quenched by adding a 0.3 mL of NEt_3. Solvent was removed and residue was poured into saturated aq. NH_4Cl (20 mL) solution and extracted with ether (3 x 15 mL). Combined organic layers washed with water (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness. Purification by flash chromatography over silica gel (hexane to 5 % ethyl acetate/hexane gradient eluent) afforded the ketal **38** (0.155 g, 86.11 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 5.62 (dt, 1H, *J* = 11.0 & 7.7 Hz), 5.27 (dd, 1H, *J* = 10.5 & 8.8 Hz), 4.24 (t, 1H, *J* = 9.9 Hz), 3.55 (dd, 1H, *J* = 8.8 & 5.5 Hz), 3.47 (dd, 1H, *J* = 10.4 & 1.7 Hz), 3.11 (t, 1H, *J* = 8.3 Hz), 2.27-2.11 (m, 2H), 2.01-1.90 (m, 1H), 1.71-1.60 (m, 1H), 1.54-1.40 (m, 2H), 1.44 (s, 3H), 1.37 (s, 3H), 1.20 (s, 6H), 1.18 (s, 9H), 0.98 (d, 3H, *J* = 7.2 Hz), 0.86 (s, 9H), 0.74 (d, 3H, *J* = 6.6 Hz), 0.07 (s, 6H). ^{13}C NMR in $CDCl_3$: δ 134.8 (d), 129.0 (d), 98.0 (s), 77.6 (d), 73.1 (s), 72.5 (s), 70.9 (d), 62.1 (t), 44.7 (t), 35.9 (d), 34.6 (d), 30.2 (q), 29.8 (q), 29.6 (q), 27.6 (q), 25.8 (q), 23.2 (t), 19.4 (q), 18.1 (s), 16.0 (q), 12.1 (q), -2.1 (q). IR (cm^{-1}): 2972, 2933, 1559, 1455. LR-MS (m/z (relative intensity)): 488 (MNH_4^+, 45), 471 (MH^+, 25), 413 (80), 395 (100). HR-MS calcd. for $C_{27}H_{55}O_4Si$ (MH^+): 471.3869; found: 471.3862. $[\alpha]_D$ = +21.4º ($CHCl_3$, c =1.09).

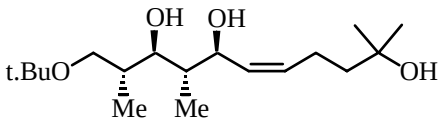
Compound 39:



39

To the stirred solution of **37** (0.035 g, 0.0000753 mol) in acetone (2 mL) was added 10-camphorsulfonic acid (0.00174 g, 0.0000075 mol), followed by 2,2-dimethoxypropane (0.0627 g = 0.074 mL, 0.0006024 mol) and stirred for 24 h at room temperature. The reaction was quenched by adding a 0.1 mL of NEt_3. Solvent removed and residue was poured into saturated aq. NH_4Cl (10 mL) solution and extracted with ether (3 x 15 mL). Combined organic layers washed with water (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield >95 % pure ketal **39** (0.36 g, 94.73 %) as colorless liquid. ^1H NMR in $CDCl_3$: δ 7.35-7.29 (m, 5H), 5.65 (m, 1H), 5.35 (dd, 1H, *J* = 10.45 & 8.8 Hz), 4.5 (s, 2H), 4.24 (t, 1H, *J* = 9.35 Hz), 3.7 (dd, 1H, *J* = 9.35 & 5.5 Hz), 3.48 (dd, 1H, *J* = 10.45 & 1.65 Hz), 2.25-2.1 (m, 3H), 1.6 (m, 1H), 1.55-1.45 (m, 1H), 1.45 (s, 3H), 1.36 (s, 3H), 1.20 (s, 6H), 1.04 (d, 3H, *J* = 6.6 Hz), 0.87 (s, 9H), 0.75 (d, 3H, *J* = 6.6 Hz), 0.07 (s, 6H). LR-MS (m/z (relative intensity)): 522 (MNH_4^+, 100), 505 (MH^+, 10), 447 (45), 297 (70). HR-MS calcd. for $C_{30}H_{53}O_4Si$ (MH^+): 505.3713; found: 505.3701.

Compound 40:

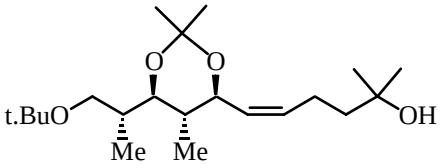


40

To the stirred solution of **38** (0.09 g) in acetonitrile (10 mL) was added HF-pyridine (1 mL) and stirred for 1 h at room temperature. After which time a phosphate buffer (2 mL) was added and poured into saturated aq. NH_4Cl (20 mL) solution and extracted with ether (3 x 15 mL). Combined organic layers washed with water (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness to yield >95 % pure **40** (0.03 g) as colorless liquid. ^1H NMR in $CDCl_3$: δ 5.78 (m, 1H), 5.48 (m, 1H), 4.38 (m, 1H), 3.5 (m, 1H), 3.3 (m, 2H), 2.35 (m, 1H), 2.05 (m, 1H), 1.7-1.6 (m, 4H), 1.26 (s, 6H), 1.2 (s, 9H), 1.12 (d, 3H, *J* = 6.6 Hz), 0.78 (d, 3H, *J* = 7.25 Hz). LR-MS (m/z (relative intensity)): 316

(MNH_4^+-H_2O, 10), 299 (30), 243 (60), 225 (100), 207 (85), 136 (75). HR-MS calcd. for $C_{18}H_{38}NO_3$ (MNH_4^+-H_2O) : 316.2852; found: 316.2848.

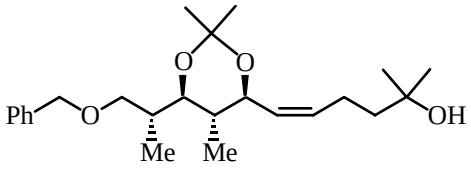
Compound 41:



41

Compound **38** (0.1 g) in 1.0 M solution of TBAF (3.0 mL) was stirred for 15 h at reflux temperature (80-90 ^{0}C). The reaction was poured in water (15 mL). The aqueous layer was extracted with diethyl ether (3 x 15 mL). Combined organic layers washed with water (10 mL), brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness. Purification by flash chromatography over silica gel (hexane to 20 % ethyl acetate/hexane gradient eluent) afforded the desired alcohol **41** (0.07 g, 92.4 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 5.62 (m, 1H), 5.28 (dd, 1H, *J* = 8.8 & 5.5 Hz), 4.23 (t, 1H, *J* = 9.34 Hz), 3.53 (dd, 1H, *J* = 8.79 & 5.49 Hz), 3.47 (dd, 1H, *J* = 10.45 & 1.65 Hz), 3.11 (t, 1H, *J* = 7.7 Hz), 2.3-2.1 (m, 2H), 1.95 (m, 1H), 1.65 (m, 1H), 1.55 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H), 1.21 (s, 6H), 1.18 (s, 9H), 0.97 (d, 3H, *J* = 6.8 Hz), 0.74 (d, 3H, *J* = 7.15 Hz). ^{13}C NMR in $CDCl_3$: δ 134.64 (d), 129.27 (d), 98.09 (s), 77.64 (d), 76.54 (s), 72.47 (s), 70.78 (d), 62.05 (t), 43.16 (t), 35.98 (d), 34.55 (d), 30.15 (q), 29.55 (q), 27.56 (q), 23.16 (t), 19.41 (q), 15.98 (q), 12.10 (q). LR-MS (m/z (relative intensity)): 374 (MNH_4^+, 20), 357 (MH^+, 10), 316 (100), 300 (55). HR-MS calcd. for $C_{21}H_{41}O_4$ (MH^+) : 357.3005; found: 357.3012.

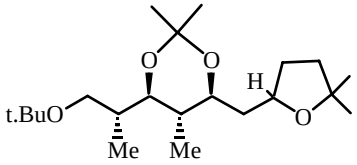
Compound 42:



42

Compound **39** (0.025 g) in 1.0 M solution of TBAF (2.0 mL) was stirred for 18 h at reflux temperature (80-90 ^{0}C). The reaction was poured in water (15 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL). Combined organic layers washed with water (10 mL), brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to dryness to yield >95 % pure alcohol **42** (0.019 g, 98.23 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 7.35-7.29 (m, 5H), 5.65 (m, 1H), 5.3 (dd, 1H, *J* = 10.45 & 8.8 Hz), 4.5 (s, 2H), 4.24 (t, 1H, *J* = 9.35 Hz), 3.68 (dd, 1H, *J* = 9.35 & 5.5 Hz), 3.48 (dd, 1H, *J* = 10.45 & 1.65 Hz), 3.3 (dd, 1H, *J* = 9.35 & 7.7 Hz), 2.3-2.1 (m, 3H), 1.7-1.52 (m, 4H), 1.45 (s, 3H), 1.35 (s, 3H), 1.23 (s, 6H), 1.02 (d, 3H, *J* = 6.6 Hz), 0.76 (d, 3H, *J* = 6.6 Hz). LR-MS (m/z (relative intensity)): 408 (MNH_4^+, 10), 350 (75), 333 (100), 315 (60), 91 (45). HR-MS calcd. for $C_{24}H_{42}NO_4$ (MNH_4^+) : 408.3114; found: 408.3118.

Compound 43:

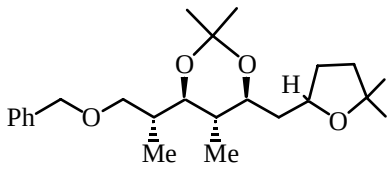


43

To the stirred solution of **41** (0.028 g, 0.0000785 mol) in dry CH_2Cl_2 (2 mL) at –78 ^{0}C was added mercuric acetate (0.08005 g, 0.0002512 mol) and the resulting mixture was stirred for 1 h. Then the solution was allowed to warm gradually to room temperature over a period of 4 h and it was stirred for additional 2 h. Then the solution was cooled to –78 ^{0}C and $NaBH_4$ (0.0267 g, 0.000706 mol) in a mixture of 5 mL of MeOH, 1 mL of H_2O, 0.5 mL of aqueous 15 % NaOH at –78 ^{0}C were added in one portion. The resulting mixture was stirred at –78 ^{0}C for 15 min and room temperature for 1 h. The solution was diluted with water (20 mL) and extracted with ether (3 x 15 mL). Combined organic

layers washed with water (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness. Purification by flash chromatography over silica gel (hexane to 10 % ethyl acetate/hexane gradient eluent) afforded **43** (0.022 g, 78.57 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 4.1 (m, 1H), 3.55 (dd, 1H, *J* = 9.3 & 5.4 Hz), 3.48-3.3 (m, 2H), 3.09 (dd, 1H, *J* = 9.3 & 7.6 Hz), 2.0 (m, 2H), 1.85 (m, 1H), 1.73-1.52 (m, 5H), 1.46 (m, 1H), 1.32 (s, 3H), 1.3 (s, 3H), 1.24 (s, 6H), 1.18 (s, 9H), 0.98 (d, 3H, *J* = 6.6 Hz), 0.78 (d, 3H, *J* = 6.8 Hz). LR-MS (m/z (relative intensity)): 357 (MH^+, 25), 341 (35), 299 (60), 243 (60), 225 (90), 99 (100). HR-MS calcd. for $C_{21}H_{41}O_4$ (MH^+) : 357.3005; found: 357.3008.

Compound 44:

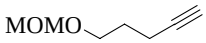


44

To the stirred solution of **42** (0.018 g, 0.000046 mol) in dry CH_2Cl_2 (2 mL) at –78 ^{0}C was added mercuric acetate (0.046 g, 0.0001472 mol) and the resulting mixture was stirred for 1 h. Then the solution was allowed to warm gradually to room temperature over a period of 4 h and it was stirred for additional 2 h. Then the solution was cooled to –78 ^{0}C and $NaBH_4$ (0.0156 g, 0.00044 mol) in a mixture of 5 mL of MeOH, 1 mL of H_2O, 0.5 mL of aqueous 15 % NaOH at –78 ^{0}C were added in one portion. The resulting mixture was stirred at –78 ^{0}C for 15 min and room temperature for 1 h. The solution was diluted with water (20 mL) and extracted with ether (3 x 15 mL). Combined organic layers washed with water (20 mL), brine (20 mL), dried over anhydrous $MgSO_4$ and evaporated to dryness. Purification by flash chromatography over silica gel (hexane to 10 % ethyl acetate/hexane gradient eluent) afforded **44** (0.008 g, 44.44 %) as colorless liquid. ^{1}H NMR in $CDCl_3$: δ 7.33-7.28 (m, 5H), 4.48 (d, 2H, *J* = 2.2 Hz), 4.12 (m, 1H), 3.68 (dd, 1H, *J* = 9.35 & 5.5 Hz), 3.44 (m, 2H), 3.27 (dd, 1H, *J* = 9.35 & 7.7 Hz), 2.13 (m, 1H), 2.0 (m, 1H), 1.85 (m, 1H), 1.8-1.55 (m, 5H), 1.35 (s, 3H), 1.3 (s, 3H), 1.23 (s, 3H), 1.22 (s,

3H), 1.01 (d, 3H, *J* = 6.6 Hz), 0.78 (d, 3H, *J* = 6.8 Hz). LR-MS (m/z (relative intensity)): 408 (MNH_4^+, 20), 391 (MH^+, 50), 333 (25), 301 (10), 99 (100). HR-MS calcd. for $C_{24}H_{39}O_4$: 391.2848; found: 391.2856.

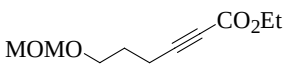
Compound 46:



46

46. To a 1 liter three-neck RB flask under argon was equipped with a mechanical stirrer was taken dimethoxymethane (135.68 g = 157.76 mL, 1.783 mol) and 4-pentyn-1-ol (15.0 g = 0.1783 mol) in dichloromethane (250mL). The resulting solution was cooled to 0 °C and phosphorus pentoxide (50.62 g, 0.3566 mol) was added in lots (1-2 g each time) under vigorous stirring. The mixture was then stirred for 2 h at room temperature. The resulting suspension was hydrolysed with a saturated solution of $NaHCO_3$. The organic layer was separated and aqueous layer was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4 and filtered. The solvents were distilled off under reduced pressure to yield MOM-protected alkyne **46** (15.0g, 65.64%). ^{1}H NMR in $CDCl_3$: δ 1.85 (quin, 2H, J = 6.6 Hz), 1.95 (t, 1H, J = 3.3 Hz), 2.32 (d.t., 2H, J = 3.3 Hz, J = 7.7 Hz), 3.37 (s, 3H), 3.63 (t, 2H, J = 6.6 Hz), 4.63 (s, 2H). ^{13}C NMR in $CDCl_3$: δ 15.1, 28.5, 54.9, 65.7, 68.5, 83.5, 96.3. LR-MS (m/z (relative intensity)): 127 ($M\text{-}H^+$, 25), 113 (5), 97 (80), 85 (30), 45 (100). HR-MS calcd. for $C_7H_{11}O_2$ (M-H): 127.0759; found: 127.0756.

Compound 47:

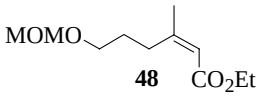


47

To a stirred solution of **46** (8.8 g, 0.06865 mol) in anhydrous THF (150 mL) was slowly added *n*-butyllithium (2.5 M solution in pentane, 30.20mL, 0.07552 mol) at -78°C under

argon atmosphere. After 30 minutes stirring at -78°C ethyl chloroformate (11.17 g = 9.81 mL, 0.1029 mol) was added. The reaction was stirred at -78° for 30 min, after which the cooling bath was removed and the reaction mixture was stirred for 2.5 h at room temperature. Reaction progress was monitored by TLC (15 % ethylacetate/hexane). The solution was hydrolysed with 0.5 N aq. HCl. The organic layer was separated and aqueous layer was extracted with diethyl ether (3 x 100mL). The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography using hexane to 10% ethyl acetate/hexane as a gradient eluent. Evaporation of the appropriate fractions gave **47** as a colorless liquid (12.5g, 90.97%). ^{1}H NMR in $CDCl_3$: δ 1.26 (t, 3H, J = 6.6 Hz), 1.82 (quin, 2H, J = 6.6 Hz), 2.43 (t, 2H, J = 7.7 Hz), 3.32 (s, 1H), 3.57 (t, 2H, J = 6.6 Hz), 4.16 (q, 2H, J = 7.7 Hz), 4.57 (s, 2H). ^{13}C NMR in $CDCl_3$: δ 13.9, 15.5, 27.6, 55.1, 61.7, 65.6, 73.3, 88.3, 96.3, 153.6. IR (cm^{-1}): 2935, 2880, 2233, 1713, 1369, 1253, 1072, 1036, 915. LR-MS (m/z (relative intensity)): 199 ($M-H^+$, 5), 185 (2), 169 ($M-OMe^+$, 10), 155 ($M-OEt^+$, 10), 139 (50), 111 (100). HR-MS calcd. for $C_{10}H_{15}O_4$ (M-H): 199.0970; found: 199.0975.

Compound 48:

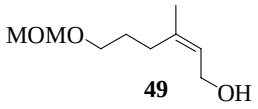


48

To a stirred solution of cuprous iodide (19.02 g, 0.09986 mol) in anhydrous THF (400 mL) was slowly added 1.4 M solution of MeLi (142.69 mL, 0.1997 mol) over a period of 50 min. at -60 to -50 ^{0}C. The mixture was stirred at –30 °C for 1 h. (until the solution is clear). The solution was then cooled to -78°C and **47** (10.0g, 0.04994 mol) in THF (50 mL) was added. The mixture was stirred for 2.5 h at the same temperature. The resulting yellow solution was hydrolysed with absolute ethanol (25 mL) at -78°C and left to stir for 10 min. The 9:1 mixture of saturated aqueous NH_4Cl/NH_4OH (500mL) was added to the solution at room temperature and the mixture was stirred for 2 h. The aqueous layer was extracted with diethyl ether (3 x 200mL). The combined organic layers were washed with a saturated solution of aqueous NaCl, dried over Na_2SO_4, filtered and evaporated to

dryness to yield crude compound. Purification of the crude using flash chromatography over silica column and hexane to 10 % ethyl acetate/hexane gradient eluent gave cuprate adduct **48** (10.58g, 98%) as a colorless liquid. ^{1}H NMR in $CDCl_3$: δ 1.26 (t, 3H, J = 7.7 Hz), 1.77 (m, 2H), 1.9 (s, 3H), 2.69 (m, 2H), 3.36 (s, 3H), 3.56 (t, 2H, J = 6.6 Hz), 4.14 (q, 2H, J = 7.7 Hz), 4.62 (s, 2H), 5.67 (s, 1H). ^{13}C NMR in $CDCl_3$: δ 14.2, 25.1, 28.2, 30.1, 55.1, 59.4, 67.6, 96.3, 116.4, 159.8, 166.2. LR-MS (m/z (relative intensity)): 185 ($M\text{-}OMe^+$, 25), 171 ($M\text{-}OEt^+$, 30), 154 (50), 141 (95), 111 (100). HR-MS calcd. for $C_{10}H_{17}O_3$ (M-OMe): 185.1178; found: 185.1170.

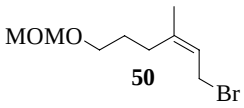
Compound 49:



49

To the stirred solution of ester compound **48** (12.3 g, 0.056873 mol) in dry diethyl ether (300 mL) at -78°C was slowly added a 1.0 M solution of diisobutylaluminium hydride in dichloromethane (142.18 mL, 0.1421 mol) over a period of 20 minutes. Reaction mixture continued stirring at the same temperature for 4 h and at room temperature for 2 h. After which time reaction mixture again chilled to -78 ^{0}C and was slowly poured in to the ice cold 400 mL of 1N aq. HCl solution. This was extracted with diethyl ether (3 x 200 mL). The combined organic layers were washed with aq. $NaHCO_3$, brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by flash chromatography over silica column using 10-20% ethyl acetate/ hexane as gradient eluent. Evaporation of the required fractions gave allylic alcohol **49** (9.1 g, 92.72 %) as a colorless liquid. ^{1}H NMR in $CDCl_3$: δ 1.69 (m, 2H), 1.73 (s, 3H), 1.8 (t, 1H, J = 6.6 Hz), 2.19 (t, 2H, J = 7.7 Hz), 3.36 (s, 3H), 3.51 (t, 2H, J = 6.6 Hz), 4.1 (t, 1H, J = 6.6 Hz), 4.61 (s, 2H), 5.49 (t, 1H, J = 6.6 Hz). ^{13}C NMR in $CDCl_3$: δ 23, 27.6, 28, 55.1, 58.4, 66.9, 96.2, 125.1, 138.3. IR (cm^{-1}): 3406, 2936, 2878, 1667, 1446, 1384, 1109, 1034, 914. LR-MS (m/z (relative intensity)): 157 ($M\text{-}OH^+$, 3), 142 ($M\text{-}CH_3OH^+$, 10), 129 (15), 111 (20), 97 (100). HR-MS calcd. for $C_9H_{17}O_2$ (M-OH): 157.1228; found: 157.1237.

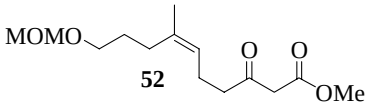
Compound 50:



50

To a stirred solution of alcohol **49** (5.0 g, 0.02869 mol) in dichloromethane (150 mL) was slowly added CBr_4 (11.89 g, 0.03587 mol) in lots followed by PPh_3 (8.655g, 0.0330 mol) in lots over a time of 15 min. at –78 ^{0}C and the mixture stirred for 2 h at the same temperature under argon atmosphere. After which time cooling bath was removed and reaction stirred at room temperature for 1 h. Dichloromethane was evaporated and the residue was triturated/stirred with petroleum ether (3 x 300 mL). Pet. ether layers were filtered and evaporated to dryness to yield light yellowish liquid. Crude compound was passed through short bed of silica and washed with pet ether. Combined pet ether layers evaporated to obtain pure bromo compound **50** (6.0g, 88.23%) as a colorless liquid. ^{1}H NMR in $CDCl_3$: δ 1.72 (m, 2H), 1.77 (s, 3H), 2.22 (t, 2H, J = 7.7 Hz), 3.36 (s, 3H), 3.55 (m, 2H), 4.02 (d, 2H, J = 7.7 Hz), 4.62 (s, 2H), 5.54 (t, 1H, J = 7.7 Hz). LR-MS (m/z (relative intensity)): 254,256 (MNH_4^+, 85), 205,207 (40), 157 (50), 125 (100), 95 (55). HR-MS calcd. for $C_9H_{21}NBrO_2$ (M+NH_4): 254.0756; found: 254.0750.

Compound 52:

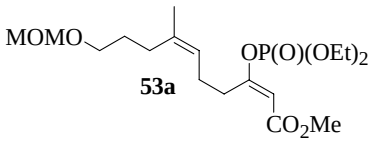


52

To the washed sodium hydride (1.44 g, (60% dispersion in mineral oil = 2.4 g), 0.06028 mol) in dry THF (70 mL) under argon at 0°C were added distilled/dry methylacetoacetate (5.0 g = 4.64 mL, 0.04305 mol) and, after 10 min, *n*-butyllithium (2.5 M solution in hexane, 17.22mL, 0.04305 mol). The resulting orange solution was allowed to stir at 0°C for 30 min. Then compound **50** (6.8 g, 0.02870 mol) in THF (25 mL) was added slowly and the solution was stirred at 0°C for 15 min and at r.t. for 2 h. Citric acid solution

(20%) was added and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and evaporated. This product was used directly in the next step without further purification (4.5g, 45%). ^{1}H NMR in $CDCl_3$: δ 1.61 (m, 2H), 1.67 (s, 3H), 2.09 (t, 2H, J = 6.6 Hz), 2.29 (q, 2H, J = 7.7 Hz), 2.55 (t, 2H, J = 7.7 Hz), 3.36 (s, 3H), 3.44 (s, 2H), 3.49 (t, 2H, J = 6.6 Hz), 3.73 (s, 3H), 4.61 (s, 2H), 5.07 (t, 1H, J = 7.7 Hz). ^{13}C NMR in $CDCl_3$: δ 21.8, 23.2, 28, 28.2, 43.2, 49, 52.3, 55.1, 67.4, 96.4, 123.2, 136.3, 167.6, 202.3. IR (cm^{-1}): 1110, 1154, 1251, 1441, 1690, 1746, 2915.

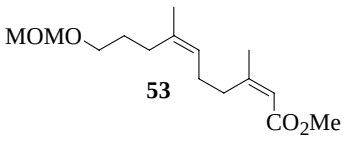
Compound 53a:



53a

To a mixture of DMAP (0.1 eq: 21.3 mg), triethylamine (1.1 eq: 290 μL) and HMPA (1.1 eq :364 μL) at 0°C under argon was added **52** (1.9 mmol) in HMPA (2 mL). The reaction mixture was stirred at 0°C for 0.5 h. Then it was cooled at -20°C with a bath of brine and liquid nitrogen and diethyl chlorophosphate (1.1 eq: 302 μL) was added dropwise. The resulting thick beige slurry was stirred for 6 h at room temperature. The mixture was hydrolysed at 0 °C with 1N HCl (5 mL). The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with a saturated solution of $CuSO_4$, brine, dried over Na_2SO_4, filtered and evaporated. This product was used directly in the next step without further purification.

Compound 53:



53

A three-neck flask under argon equipped with a low temperature thermometer and a mechanic stirrer was charged with copper iodide (3 eq: 914 mg) in dry THF (25 mL). The resulting suspension was cooled to -10°C with a bath of brine and liquid nitrogen then methyllithium (3 eq: 3.6 mL) was added dropwise. The solution was then cooled to -35°C with a cryostat and methylmagnesium bromide (5 eq: 2.7 mL) was added dropwise. This mixture was cooled to -45°C and stirred for 1 h 30. Then **53a** (1.6 mmol) was added slowly and the suspension was stirred at -45°C overnight. The resulting solution was hydrolysed at 0°C with saturated solution of aqueous NH_4Cl and NH_4OH. The aqueous layer was extracted with diethyl ether, washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash chromatography using hexane/ether: 70/30. Yield: 200 mg (46%). ^1H NMR in $CDCl_3$: δ 1.68 (s, 3H), 1.68 (m, 2H), 1.88 (s, 3H), 2.07-2.17 (m, 4H), 2.62 (t, 2H, J = 7.7 Hz), 3.36 (s, 3H), 3.5 (t, 2H, J = 6.6 Hz), 3.67 (s, 3H), 4.61 (s, 2H), 5.17 (t, 1H, J = 7.7 Hz), 5.65 (s, 1H).