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An Enantiospecific Synthesis of (+)-Methyl Epijasmonate and (−)-Methyl Cucurbate from L-Glutamic acid

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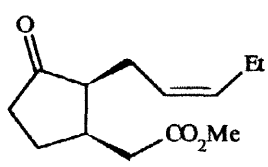
Abstract : An enantiospecific route to jasmonoid natural products, (+) - methyl epijasmonate and (-) -methyl cucurbate from L-glutamic acid is reported. The key step is a 5-(3,4) ene cyclization of a functionalized 1,6-diene as chiron, which sets up three chiral centres with a high degree of diastereoselectivity.

Introduction

Recently, we have reported an intramolecular ene-based methodology for the stereocontrolled construction of 1,2-disubstituted and 1,2,3-trisubstituted cyclopentanes.[1] This synthesis allows introduction of a versatile allylsilane side chain which can be exploited for further elaboration of the ring systems. Herein, we wish to report the first 'chiral pool' synthesis of (+)-methyl epijasmonate **(1)** and (-)-methyl cucurbate **(2)** using this ene cyclization as the key step.[2] Methyl epijasmonate **1**[3] and its analogs, methyl tuberonate **3**,[4] β-D-glucopyranosyltuberonic acid **4**[4] and its methyl ester **5**[4] as well as cucurbic acid **6**[5] have remarkable bioactivities, such as strong jasmine note,[3a,b,c] pheromone synergest,[3b,c] potato-tuber induction[4] and plant growth regulation.[5] In view of their numerous biological activities, jasmonoids including **1** and **2** have been the targets of many synthetic efforts, and recently various enantioselective synthesis of these molecules have appeared in the literature.[6]



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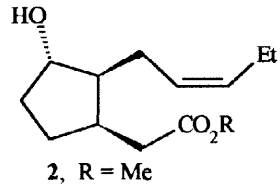
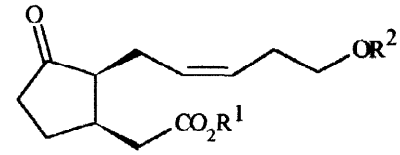


2, R = Me
6, R = H



3 ; R^1 = Me, R^2 = H
4 ; R^1 = H, R^2 = β-D-Glu
5 ; R^1 = Me, R^2 = β-D-Glu

Results and Discussion

As shown in Scheme 1, our retrosynthetic analysis involves the 5-(3,4) ene cyclization of chiron **8** to the 1,2,3-trisubstituted cyclopentane derivative **7** containing an allylorganometallic side chain. Chiron **8** should be available from L-glutamic acid **10** *via* the α-alkoxy aldehyde **9** by usual synthetic methodology.

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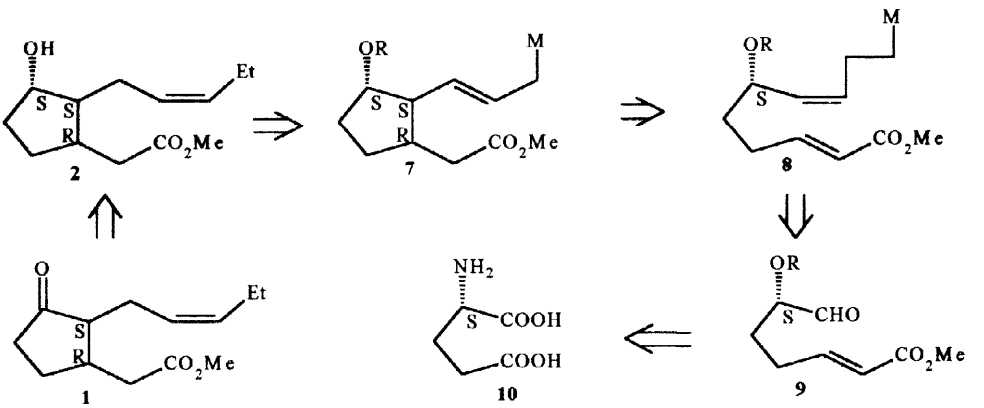
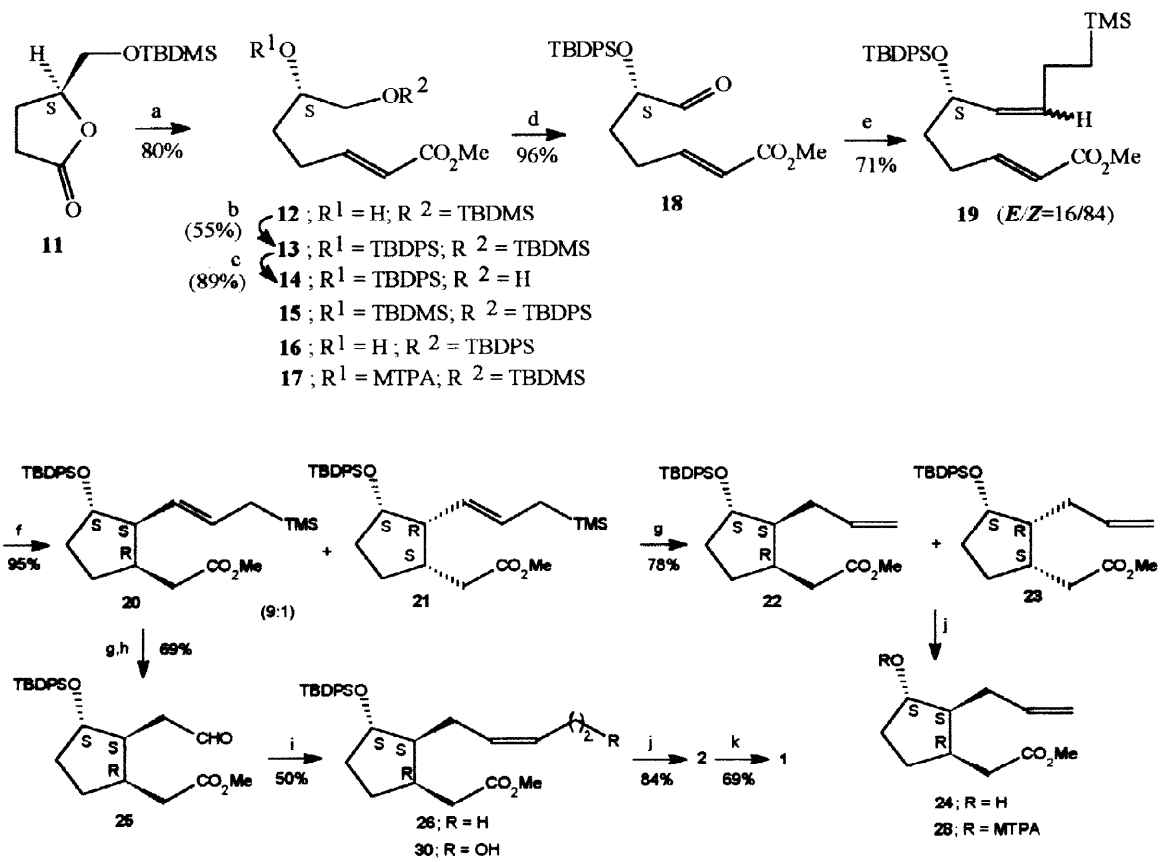
Scheme 1



Scheme 2



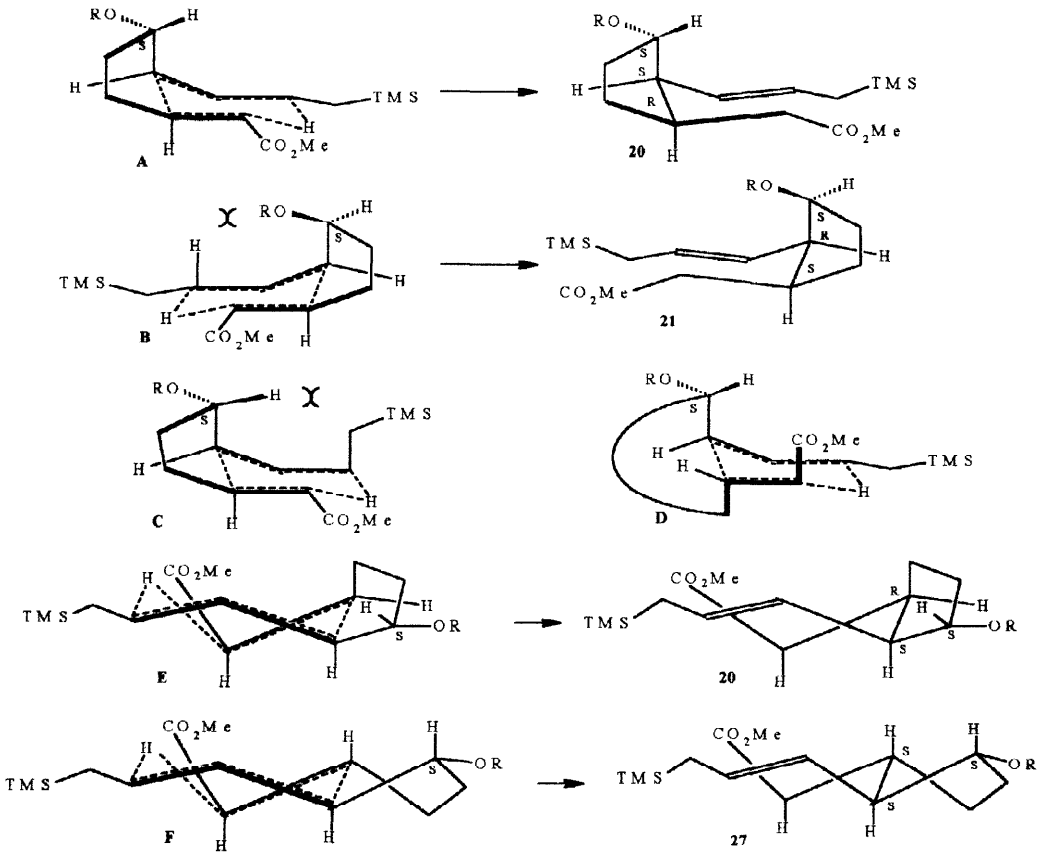
a) DIBAL-H,THF,-78°C,1h, $Ph_3P{=}CHCO_2Me$, -78°C →r.t., 5h,80%. b) *t* -$BuPh_2SiCl$, Im, DMF, r.t., 12h, 55%. c) PPTS, EtOH, r.t., 89%. d) DMSO, $(COCl)_2$, Et_3N, - 60°C→ r.t., 96%. e) $Ph_3(CH_2CH_2CH_2TMS)PBr$, $NaN(TMS)_2$, THF, - 78°C → r.t., 71%. f) 235°C, 18h, 95%. g) HI, bz, r.t., 78%. h) O_3, - 78°C, 1h, then Me_2S, 88%. i) $Ph_3(Pr)PBr$, $NaN(TMS)_2$, THF, - 78°C →r.t., 1h, 50%. j) n-Bu_4NF, THF, r.t., 84%. k) H_2CrO_4, ether, 0°C, 20min, 69%.

Putting this plan to action, the known lactone **11**,[7] readily made from L-glutamic acid, was transformed to **12** in one-pot[8] by reduction with DIBAL-H followed by the addition of the necessary phosphorane (Ph_3PCHCO_2Me) in 80% yield and 95% *ee* (Scheme 2). The enantiomeric excess was determined by preparing Mosher esters[9] with both (R)-(+)-MTPA and (S)-(-)-MTPA and ^{19}F-NMR analysis of the diastereomers. With **12** in hand, attempts were made to transform it to the silylether **13** by exposure to TBDPS-Cl / Im at ambient temperature. However, under the usual conditions, an exchange product, e.g., **15** (20-30%) always accompanied the desired product **13**. This type of migration is not, however, uncommon in the literature.[10] Modified conditions were soon worked out by mixing the reagents at a low temperature (-30^{0}C) and then slowly warming up to room temperature and this minimized the by-product **15** (~5%) so as to increase the yield of **13** to a respectable 55%. Selective mono-desilylation[11] using PPTS in MeOH was uneventful and **14** was obtained in very high yield (89%). It may be mentioned here that formation of **15** during the conversion **12**→**13** was actually confirmed by selective monodesilylation of **15** to **16** and analysis of its ^{1}H-NMR. For example, while the olefinic and allylic protons in **16** appear at lower fields, C_6 -H actually resonates at a higher field when compared to similar protons of **14**.

Swern oxidation of **14** afforded the α-silyloxy aldehyde **18** in 96% yield which without further purification was immediately subjected to Bestmann-Wittig[12] olefination (using $Ph_3(TMSCH_2CH_2CH_2)PBr/NaN(TMS)_2$) in THF to ultimately deliver the chiron **19** (***E/Z***=16/84) in 71% yield. Nonetheless, these last two steps warrant some in-depth discussion. α-Alkoxy aldehydes are generally labile and there are several cases reported in the literature[13] where oxidation of carbinols leading to α-alkoxy aldehydes were complicated by facile epimerization at the α-centre and consequent racemization. This is the reason why crude aldehyde **18** was promptly subjected to Wittig-olefination (**18**→**19**) under salt-free conditions. Considerable experimental efforts were expended to find a suitable condition for the olefination step (**18**→**19**), though, which proved very frustrating in the beginning as the yield was very poor (10-20%) and *E/Z* ratio also varied from batch to batch. That an α-alkoxy substituent on aldehydes and ketones can result in abnormal Wittig reaction stereochemistry, depending on experimental conditions, is well-documented and this area has recently been reviewed by Maryanoff.[14] In some runs, formation of 7*E*-**19** and 7*Z*-**19** in even 1:1 ratio was also observed, especially when the phosphonium salt ($Ph_3(TMSCH_2CH_2CH_2)PBr$) and $NaN(TMS)_2$ were allowed to stir at room temperature in THF for about an hour for completion of ylide formation. It may be mentioned here that the above experimental condition work very well with ordinary aldehydes for high-yield synthesis of *Z*-olefins as reported earlier from this laboratory.[1c] Later it was found that the ylide, $Ph_3PCHCH_2CH_2TMS$, has to be added within 10 mins of its preperation to the aldehyde **18** whereby the yield (71%) as well as stereoselectivity (*E/Z*=16/84) improved dramatically. The reason for this improvement is not clear to us at present.

The remaining steps of the synthesis are as described previously for the racemic series.[2] Thus, heating a 5% solution of **19** in toluene in a sealed tube under argon at 235°C for 18h smoothly effected carbocyclization to a mixture of allylsilanes **20** and **21** in a ratio of 90:10 in 95% yield.

In order to rationalize the high stereoselectivities observed in the present ene cyclization, the Oppolzer model[15] of transition states is invoked as the Houk model[16] is inadequate in the case of activated enophiles. The exclusive formation of *E*-allylsilanes **20** and **21** from *Z*-**19** is accountable in terms of relevant transition states, namely **A** which is favoured over **C** due to 1,3- diaxial interaction. The transition state **A** is more stable than **B** as the alkoxy group in **B** is endo and this explains the formation of the minor diastereomer **21**. The other transition state e.g., D leading to the 1,2-*trans* disubstituted product is discarded due to obvious angle strain reasons.



In the case of cyclization of *E*-**19**, the steric interactions are relatively subtle and, therefore, diastereoselection and diastereofacial selection are expected to be only low to moderate on the basis of Nakai's pinoneering work.[17] The two transition states **E** and **F** are, respectively, equally likely from (*E*)-**19** leading to **20** and **27**. However, based on our experimental results it seems that contribution from TS-**F** is minimal at best.

To determine the extent of internal asymmetric induction in the ene cyclization step, **20** and **21** were protodesilylated (with HI) and the products **22**, **23** subjected to desilylation (with n-Bu_4NF) to give **24** which has an *ee* of 87% as determined by Mosher ester analysis.[9] Unfortunately, the conversion of **12** to **20** and **21** was unavoidably accompanied with some racemization. Probably, partial racemization occurs at the aldehyde **18** stage during Swern oxidation. Oxidative cleavage (with O_3) of the protodesilylated products **22, 23** gave the jasmonoid building block **25** (88%) (only one diastereomer is shown henceforth for convenience). Wittig olefination (50%) under salt-free condition,[12] followed by exposure of the product to n-Bu_4NF gave (-)-methyl cucurbate (**2**) in 84% yield and *ca.* 87% *ee*. During the later step, the minor C_3 -β isomer (~ 10%) carried over from **20** / **21** was eliminated presumably *via* a lactone.[2] The optical rotation $[\alpha]_D$= -2.03 (C=1.12 in MeOH) of **2** agreed with literature [6c] value ($[\alpha]_D$ = -2.20 , C = 0.22 in MeOH). Incidentally, saponification of **2** with KOH in aqueous MeOH at 50^{0}C gave (+) - cucurbic acid **6** in 98% yield (~ 87% *ee*). The optical rotation of **6**, $[\alpha]_D$ = +20.29 (C= 0.32 in MeOH) also agreed with those reported in the literature[5] for natural cucurbic acid ($[\alpha]_D$ = +25, C= 0.36 in MeOH). Finally oxidation with chromic acid under Brown's condition[18] yielded (+)-methyl epijasmonate (**1**) (87% *ee*) in 69% yield (5% overall yield from **11**). The synthetic (+)-methyl epijasmonate **1** has a very intense, typical "jasmonte fragrance". Furthermore, since modified working conditions were used in Brown oxidation step, our synthetic (+)-**1** seems to be free from its C-2 epimer (methyl jasmonate). The optical rotation $[\alpha]_D$ = +50.4 (C= 0.96 in MeOH) of **1** agreed with the literature[6c] value ($[\alpha]_D$= +53.3, C = 0.98 in MeOH).

Having developed a new synthetic route to the chiral jasmonoid building block **25**, it was of interest to channelize the same to methyl tuberonate (**3**) and congeners **4, 5**. Unfortunately, in our hands, exposure of **25** to the ylide $Ph_3PCH(CH_2)_2OTMS$ (**29**)[19] has thus far failed to give even traces of **30**, precursor for tuberonates.

In summary, we have developed a new enantio- and diastereoselective synthesis of jasmonoids using 5-(3,4) ene cyclization as the key step and our synthesis now joins four other[6c,f,g,h] enantioselective syntheses of **1** and/or **2**.

EXPERIMENTAL

(S)-Methyl (2*E*)-6-hydroxy-7-(*tert*-butyldimethylsilyloxy)-2-heptenoate (12): To a well stirred solution of **11**(2 g, 8.7 mmol) in 25 mL THF was added a 1.5(M) solution of DIBAL-H in hexane (6.37 mL, 9.56 mmol) over 1.5 h. During the addition the temperature was kept below -68^{0}C. After an additional 30 min, the solution of carbomethoxymethylenetriphenylphosphorane (3.48 g, 10.4 mmol) in 25 mL of dichloromethane was added to the stirred solution at -78^{0}C. The mixture was stirred for 1 h at -78^{0}C and then slowly brought to room temperature. The mixture was quenched with water and extracted with dichloromethane. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Column chromatography of the crude product on silica gel and elution with ethyl acetate-petroleum ether (60-80^{0}C) (1:9) gave **12** (2 g, 80%)

as a colourless oil. $[\alpha]_D$ = -7.3 (C= 1.00 in MeOH); IR (film)ν_{max}: 3471, 2943, 2861, 1720, 1654, 1442, 1168, 841, 777 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.97 (dt, 1H, 15.6 & 6.8Hz), 5.84 (dt, 1H, 15.6 & 1.5Hz), 3.68 (s, 3H), 3.69-3.57 (m, 2H), 3.44-3.35 (m, 1H), 2.43-2.45 (m, 2H), 2.06 (bs, 1H), 1.61-1.48 (m, 2H), 0.89 (s, 9H); ^{13}C-NMR(50 MHz, $CDCl_3$): δ 167.0 (s), 148.9 (d), 121.0 (d), 70.9 (d), 67.0 (t), 51.3 (q), 31.1 (t), 28.3 (t), 25.8 (q), 18.2 (s), -5.38 (q), -5.43 (q). Anal.Calcd. for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78; Found: C, 58.33; H, 9.81.

***Determination of the enantiomaric purity of* 12.** **12** was converted into corresponding (R)- and (S)-MTPA esters **17** in the usual manner. Both the diastereomers were analysed by ^{19} F-NMR (400 MHz). The CF_3 signals of the two diastereomers appear at δ 60.9 and 61.0 and from their relative integral values, the *ee* of **12** was readily determined to be about 95%.

(S)-Methyl(2*E*)-6-(*tert*-butyldiphenylsilyloxy)-7-(*tert*-butyldimethylsilyloxy)-2-heptenoate (13) : To a solution of **12** (5 g, 17.3 mmol) and imidazole (4.81 g, 70 mmol) in dimethylformamide (37mL) was added *tert*-butyldiphenylchlorosilane (5.2 g, 19mmol) under argon at -30^{0}C.The mixture was slowly warmed to room temperature and stirred for 10h. The mixture was poured into water (130mL) and extracted with ether (5 x 40mL). The combined ether extracts were washed with water, brine, dried ($MgSO_4$) and concentrated. Column chromatography of the residue on silica gel and elution with ethyl acetate petroleum ether (60 -80^{0}C) (3:97) gave a colourless thick oil **13** (5.5 g, 55%). $[\alpha]_D$ = +1.06 (C=1.03 in CH_2Cl_2). IR (film)ν_{max}: 2938, 2860 1726, 1656, 1452, 1106, 703 cm^{-1}; ^{1}H-NMR (200 MHz ,$CDCl_3$): δ 7.69 - 7.63 (m, 4H), 7.43- 7.31 (m, 6H), 6.88 (dt, 1H, J = 15.6 & 6.8Hz), 5.79 (dt, 1H, J = 15.6 & 1.6Hz), 3.75-3.71 (m, 1H), 3.71 (s, 3H), 3.51-3.35 (m, 2H), 2.24-2.17 (m, 2H), 1.71-1.58 (m, 2H), 1.05 (s, 9H), 0.80 (s, 9H), -0.08 (s, 3H), -0.11 (s, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 166.7 (s), 149.4 (d), 135.8 (d), 135.6 (d) , 134.2 (s), 134.0 (s), 129.7 (d), 129.6 (d), 127.7 (d), 127.6 (d), 120.9 (d), 72.8 (d), 65.9 (t), 51.2 (q), 32.1 (t), 27.3 (t) 27.0 (q), 25.95 (q), 19.43 (s), -5.4 (q).

(S) -Methyl (2*E*) -7-hydroxy-6- (*tert*-butyldiphenylsilyloxy)-2- heptenoate(14): To a solution of **13** (5.59 g, 11 mmol) in methanol (150ml) was added pyridinium p-toluene-4-sulphonate (461 mg) and the mixture was stirred for 24h. Removal of the solvent in vacuo followed by chromatography of the residue on silica gel and elution with 20% ethyl acetate - petroleum ether (60-80^{0}C) gave **14** as a colourless thick oil (3.9 g, 89%). IR (film)ν_{max}: 3423, 2931, 1720, 1650, 1428, 1056, 822, 738 cm^{-1}; ^{1}H -NMR (200 MHz, $CDCl_3$): δ 7.70 -7.63 (m, 4H), 7.44-7.34 (m, 6H), 6.76 (dt, 1H, J= 15.6 & 6.83Hz), 5.66 (dt, 1H, J= 15.6, 1.45Hz), 3.70 (s, 3H), 3.78 -3.72 (m, 1H), 3.6 -3.49 (m, 2H), 2.13-2.06 (m, 2H) , 1.69-1.56 (m, 2H), 1.07 (s, 9H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 166.7 (s), 148.6 (d), 135.8 (d) 135.6 (d), 133.7 (s), 133.4 (s), 129.9 (d), 127.7 (d), 127.7 (d), 121.0 (d), 73.2 (d), 65.7 (t), 51.2 (q), 31.8 (t), 27.7 (t), 27.0 (q), 19.2 (s).

(S)-Methyl (*2E*) -6- hydroxy -7- (*tert*-butyldiphenylsilyloxy -2- heptenoate (16):

a) To a solution of **12** (500 mg, 1.7 mmol) and imidazole (0.4 g, 5.8 mmol) in dimethylformamide (5mL) was added *tert*-butyldiphenylchlorosilane (0.5 g, 2 mmol) under argon at room temperature and stirred for 10h. The mixture was poured into water (10mL) and extracted with ether (5 x 4mL). The combined ether extracts were washed with water, brine, dried ($MgSO_4$) and concentrated. Column chromatography of the residue on silica gel and elution with ethyl acetate-petroleum ether (60 - 80^{0}C) (3:97) gave a mixture of **13** and **15** as a colourless oil (200mg).

b) The oil as obtained above was selectively deproctected following the procedure as described for **14** to give **14** (110mg) as major product and **16** (80 mg) as minor product. IR (film)ν_{max}: 3426, 3070, 2928, 2860, 1720, 1450, 1060, 738 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$): δ 7.65 - 7.61 (m, 4H), 7.43 - 7.33 (m, 6H), 6.93 (dt, 1H, J= 15.6 & 6.88Hz), 5.79 (dt, 1H, J = 15.6 & 1.4Hz), 3.71 (s, 3H), 3.68 -3.60 (m, 2H), 3.51-3.42 (m, 1H), 2.41 -2.22 (m, 2H), 1.63 -1.5 (m, 2H), 1.06 (s, 9H).

(S)-Methyl (2*E*)-7-oxo-6-(*tert*- butyldiphenylsilyloxy) -2- heptenoate(18): To a solution of oxalyl chloride (0.73 mL, 7.5 mmol) in dichloromethane (20 mL) at - 60^{0}C was added dropwise with stirring a solution of dimethyl sulfoxide (1 mL) in dichloromethane (25 mL) under an atmosphere of argon over a period of 20 min. To this, after stirring for 15min, **14** (2.7 g, 6.3 mmol) was added in dichloromethane (10 mL) over a period of 15 min. Stirring was continued for an additional 30 min and triethylamine (4.7mL) was added at the same temperature. After 10 min the reaction mixture was allowed to attain room temperature, diluted with water (25 mL) and the aqueous phase extracted with dichloromethane (3 x 15 mL). The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. The residue was passed through a short bed of silica gel and elution with ethyl acetate - petroleum ether (60 - 80°C) (1:9) gave **18** (2.5g, 93%) as an oil. IR (film)ν_{max}: 3063, 2929, 2858, 1726, 1653, 1553, 1475, 1334, 1178, 1098, 711 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 9.59 (s, 1H), 7.64-7.59 (m, 4H), 7.41-7.38 (m, 6H), 6.81(dt, 1H, J = 15.6 & 6.8Hz), 5.6 (dt, 1H, J = 15.6 & 1.5Hz), 4.2-4 (m, 1H), 3.70 (s, 3H), 2.2-2.3 (m, 2H), 1.88-1.7 (m, 2H), 1.11 (s, 9H).

(S) -Methyl (2*E*,7*Z*) -10- (trimethylsilyl)-6-(*tert*-butyldiphenylsilyloxy) -2, 7 - decadienoate (19): To a mixture of 3- (trimethylsilyl)-propyltriphenylphosphonium bromide[1c] (12.5 g, 27.4 mmol) and sodium hexamethyldisilazide (4.8 g, 26.2 mmol) was added dry THF (50mL) using a hypodermic syringe under an atmosphere of argon. The reaction mixture was stirred for 10 min, during this period the reaction mixture developed a bright orange colour indicating the formation of the ylide. This was added to a solution of **18** (2.5 g, 6.0 mmol) at -78^{0}C, the resulting mixture stirred for 1h and then slowly brought to room temperature. This was diluted with petroleum ether (60-80^{0}C) and the precipitated triphenylphosphine oxide separated by filtration. The filtrate was concentrated and the residue passed through a bed of silica gel. The crude oil, thereby, obtained was chromatographed over silica gel and eluted with ethyl acetate-petroleum ether (60 - 80^{0}C) (3 : 97) to give **19** (*E*/*Z* = 16:84) as a colourless thick oil (2.2 g , 71%). $[\alpha]_D$ = +20.9 (C = 0.876 in MeOH);

IR (film)ν_{max}: 2942, 1724, 1654, 1442, 1266, 1182, 1080, 842, 705 cm^{-1}; ^1H -NMR (200 MHz, $CDCl_3$): δ 7.75 -7.63 (m, 4H), 7.5-7.3 (m, 6H), 6.88 (dt, 1H, J= 15 & 8Hz), 5.68 (d, 1H, J= 15Hz), 5.4 -5.20 (m, 2H), 4.44 - 4.34 (m, 1H), 3.70 (s, 3H), 2.2 -2.07 (m, 2H), 1.7 - 1.46 (m, 4H), 1.03 (s, 9H), 0.35 -0.23 (m, 2H), -0.037 (s, 9H, from 7 *E* isomer), - 0.133 (s, 9H); ^{13}C-NMR (200 MHz, $CDCl_3$): δ 166.98 (s), 149.35 (d), 135.99 (d), 135.84 (d), 134.26 (s), 134.14 (s), 133. 52 (d), 130.60 (d), 129.60 (d), 129.45 (d), 127.55 (d), 127.35 (d), 120.81 (d), 68.68 (d), 51.28 (q), 36.64 (t), 27.68 (t), 27.00 (q), 21.85 (t), 19.27 (s), 16.72 (t), -1.85 (q); ^{13}C-NMR (partial) for 7*E* -**19** - isomer: δ 149.54 (d), 73.83 (d), 36.24 (t), 26.29 (t), 15.92 (t), -1.70 (q); Anal. Calcd. for $C_{30}H_{44}O_3Si_2$: C, 70.82; H, 8.71; Found: C, 70.95; H, 8.74.

Methyl (1R, 2S, 3S) - 2 - [2 - [(*E*) - 3 - (trimethylsilyl)-1- propenyl] -3- (*tert*-butyldiphenylsilyloxy) cyclopentyl] acetate (20) and Methyl (1S,2R, 3S) - 2 - [2 - [(*E*) - 3 - (trimethylsilyl) - 1 - propenyl] -3 - (*tert*-butyldiphenylsilyloxy) - cyclopentyl]acetate (21): A solution of **19** (1.4 g, 2.9 mmol) in dry toluene (30mL) was taken in 7 corning tubes (30 cm long, 2cm diameter), purged with argon and sealed. These sample tubes were heated at 235°C (± 2°C) for 18h in a constant temperature oven. After cooling to room temperature, the solvent was removed in vacuo and preparative layer chromatography [silica gel, 2.5% ethyl acetate- petroleum ether (60 - 80°C) as developing solvent] of the residue gave **20** and **21** (1.33 g, 95%) as a colourless thick oil. $[\alpha]_D$ = -17.108 (C=1.66 in MeOH); IR (film)ν_{max}: 3050, 2942, 1738, 1624, 1440, 1258, 1168, 1092, 842, 704 cm^{-1}; ^1H-NMR for major isomer **20** (200 MHz, $CDCl_3$): δ 7.65 - 7.61 (m, 4H), 7.41 - 7.32 (m, 6H), 5.13 (dd, 1H, J=15 & 8Hz), 4.73 (dd, 1H, J = 15 & 10Hz), 4.00 -3.99 (m, 1H), 3.65 (s, 3H), 2.79 - 2.69 (m, 1H), 2.52 (t, 1H, J = 8Hz), 2.29 (dd, 1H, J= 15.5 & 6.7Hz), 2.14 (dd, 1H, J= 15.5 and 8.7Hz), 1.99 -1.92 (m, 1H), 1 .86 -1.78 (m, 1H), 1.66 -1.59 (m, 1H), 1.29 (d, 2H, J = 8Hz), 1.25 -1.17 (m, 1H), 1.07 (s, 9H), -0.07 (s, 9H). ^1H-NMR for other minor diastereomer **21** (partial): δ 5.36 -5.34 (m, 2H), 4.21 - 4.15 (m, 1H), 3.63 (s, 3H), 2.4 - 2.22 (m, 2H), 1.03 (s, 9H), 0.02 (s, 9H); ^{13}C-NMR for major isomer **20** (50 MHz, $CDCl_3$): δ 173. 48 (s), 135.94 (d), 135.82 (d), 134.69 (s), 134.50 (s), 129.48 (d), 129.17 (d), 127.54 (d), 125. 64 (d), 80.39 (d) 55.54 (d), 51.21 (q), 37.07 (d), 36.36 (t), 33.43 (t), 28.58 (t), 27.19 (q), 23. 23 (t) 19.28 (s), -1.77 (q); ^{13}C-NMR for other minor diastereomer **21**: δ 124.86 (d), 77.18 (d), 50.11, 35.40, 32.62 (t), 29. 79, 28.32; Anal. Calcd. for $C_{30}H_{44}O_3Si_2$: C, 70.82; H, 8.71; Found: C 70.91; H, 8.75.

Methyl (1R,2S, 3S) - 2-[2-(2-propenyl) -3-(*tert* -butyldiphenylsilyloxy)cyclopentyl acetate (22) Methyl (1S,2R, 3S) - 2-[2-(2-propenyl) -3-(*tert* -butyldiphenylsilyloxy)cyclopentyl acetate (23): To a stirred solution of **20** and **21** (450 mg, 0.8 mmol) in dry benzene (12 mL) was added 57% aqueous hydrogen iodide (0.1 μL) and stirred for 12h at room temperature. The organic layer was washed with water (2 x 15 mL), brine, dried (Na_2SO_4) and concentrated. Preparative layer chromatography [silia gel, 2% ethyl acetate - petroleum ether (60 - 80°C) as developing solvent] of the residue gave **22, 23** (300 mg, 78%) as a colourless thick oil. $[\alpha]_D$ = + 5.15 (C = 0.35 in MeOH); IR (film) ν_{max}: 3056, 2942, 1736, 1642, 1444, 1362, 1268, 1174, 1090, 914, 826, 706 cm^{-1}; ^1H -NMR (200 MHz, $CDCl_3$): δ 7.75-7.62 (m, 4H). 7.48-7.32 (m, 6H), 5.53 - 5.27

(m, 1H), 4.90-4.75 (m, 2H), 4.08-3.98 (m, 1H), 3.65 (s, 3H), 2.92-2.7 (m, 1H), 2.24 (dd, 1H, J=15.09 & 6.4 Hz), 1.98 (dd, 1H, J= 15.09 & 9.4Hz), 2.1-1.55 (m, 6H), 1.33-1.14 (m, 1H), 1.05 (s, 9H); ^{1}H NMR for other minor diastereomer **23**: δ 4.28-4.18 (m, 1H), 3.66 (s, 3H), 2.62 -2.52 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.78 (s), 137.08 (d), 135. 85 (d), 134.62 (s), 134.38 (s), 129.45 (d), 127.47 (d), 115.48 (t), 78.18 (d), 51.42 (q), 50.05 (d), 36.15 (d), 35.42 (t), 32.51 (t), 31.470 (t), 28.18 (t), 27.01 (3q), 19.13 (s); Anal. Calcd. for $C_{27}H_{36}O_3Si$: C, 74.27; H, 8. 31; Found: C, 74.77; H, 8.35.

Methyl (1R, 2S, 3S) -2-[2-[2-propenyl] -3- hydroxycyclopentyl]acetate (24): To a solution of **22** and **23** (67 mg, 0.15 mmol) in tetrahydrofuran (5mL) was added tetrabutylammonuim fluoride trihydrate (96 mg, 0.307 mmol) under an argon atmosphere. After being stirred for 24h at room temperature, the mixture was partitioned between ether and saturated aqueous sodium chloride, and the aqueous layer was extracted with ether (4 x 5 mL). The combined ether extracts were dried ($MgSO_4$) and concentrated in vacuo. Preparative layer chromatography [silica gel, 15% ethyl acetate- petroleum ether (60 - 80^0 C) as developing solvent] of the residue afforded **24** (25 mg, 83 %) as a colourless oil. $[\alpha]_D$ = + 4.43 (C= 0.29 in MeOH); IR (film)ν_{max}: 3430, 2970, 1735, 1643, 1444, 1310, 1250, 810, 600 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.88-5.75 (m, 1H), 5.10-5.01 (m, 2H), 4.05 - 3.98 (m, 1H), 3.66 (s, 3H), 2.69-2.62 (m, 1H), 2.41 (dd, 1H, J= 15.09 & 6.2 Hz), 2.17 (dd, 1H, J= 15. 09 & 9.4Hz), 2.09 -1.6 (m, 6H), 1.35 -1.00 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 173. 6 (s), 137.2 (d), 116.1 (t), 77.31 (d), 51 5 (q), 49.7 (d), 36.42 (d), 35.16 (t), 32.45 (t), 29.59 (t), 28.3 (t).

***Determination of the enantiomaric purity of* 24.** **24** was converted into corresponding (R)- and (S)-MTPA esters **28** in the usual manner. Both the diastereomers were analysed by ^{19} F-NMR (400 MHz). The CF_3 signals of the two diastereomers appear at δ60.9 and 60.78 and from their relative integral values, the *ee* of **24** was readily determined to be about 87%.

Methyl-(1R, 2S ,3S) -2-[2-(2-oxo -Methyl)-3- (*tert*-butyldiphenylsilyloxy)cyclopentyl]- acetate (25): Ozone was bubbled through a solution of **22** and **23** (265 mg, 0.6 mmol) in methanol (20 mL) at -78^0 C till the blue colour persisted for more than 10min. The excess ozone was removed by allowing nitrogen gas to bubble through the solution at - 78^0 C. Dimethyl sulfide (3 mL) was added dropwise at the same temperature. The mixture was allowed to attain room temperature and stirred for 2h. Excess dimethyl sulfide was removed in vacuo. Preparative layer chromatography [silica gel, 5% ethyl acetate petroleum ether (60-80^0 C) as developing solvent] of the residue gave **25** (237 mg, 88%). IR (film)ν_{max}: 2932, 2720(w), 1728, 1444, 1268, 1178, 1098, 824, 708 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 9.28 (unresolvable triplet), 7.7-7.6 (m, 4H), 7.48 7.33 (m, 6H), 3.98-3.88 (m, 1H), 3.65 (s, 3H), 2.95-2.72 (m, 1H), 2.58-1.55 (m, 8H), 1.27-1.12 (m, 1H), 1.058 (s, 9H).

Methyl -2-2-[2-[(*Z*)-2-penteny1] -3-(*tert*- butyldiphenylsilyloxy) cyclopenty1] - acetate (26): To a mixture of triphenylpropylphosphonium bromide (554 mg, 1.43 mmol) and sodium hexamethyldisilazide (234 mg, 1.3 mmol) was added tetrahydrofuran (10mL) under an argon atmosphere. The mixture was stirred for 10

min at room temperature. During this period the mixture developed a bright orange colour indicating the formation of the ylide. To a solution of **25** (76 mg, 0.18 mmol) in tetrahydrofuran (4 mL) was added the solution of the ylide at -78^0 C during 30 min. The mixture was stirred for 1.5h at -78^0 C, 1h at -50^0 C, 1h at -30^{0}C, 1.5h at 0^0 C and then the mixture allowed to attain room temperature and stirred overnight whereby the orange colour disappeared and a whitish suspension formed. This was diluted with petroleum ether (60- 80^0 C) and the precipitated triphenylphosphine oxide separated by filtration. The filtrate was concentrated and the residue passed through a bed of silica gel. The crude oil thereby obtained was chromatographed over silica gel and eluted with ethyl acetate - petroleum ether (60- 80^0 C) (3:97) to give **26** as a colourless thick oil (40 mg, 50%). IR (film)ν_{max}: 2924, 2856, 1744, 1611, 1248, 1158, 1098, 1053, 841, 698, 611 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.77-7.58 (m, 4H), 7.48-7.3 (m, 6H), 5.35- 5.12 (m, 1H), 5.0 - 4.85 (m, 1H), 4.05-3.96 (m, 1H), 3.67 (s, 3H), 2.91-2.75 (m, 1H), 2.38 (dd, 1H, J=15 & 6.4Hz), 2.18 (dd, 1H, J=15 & 9.4Hz), 2.1-1.55 (m, 8H), 1.38-1.15 (m, 1H), 1.05 (s, 9H), 0.85 (t, 3H, J=7.5Hz).^{1}H-NMR for other minor diastereomer (partial): δ 4.25-4.15 (m, 1H), 2.6-2.45 (m, 1H), 0.95 (t, 3H, J=7.5Hz).^{13}C-NMR (50 MHz, $CDCl_3$): δ 173.76 (s), 135.77 (d), 134.52 (s), 134.45 (s), 132.26 (d), 129.39 (d), 127.35 (d), 127.01 (d), 78.29 (d), 51.33 (q), 50.77 (d), 36.19 (d), 35.42 (t), 32.57 (t), 28.11 (t), 26.94 (q), 24.39 (t), 20.40 (t), 19.05 (s), 14.01 (q); ^{13}C-NMR for other minor diastereomer (partial): δ 128.21 (d), 48.45, 33.14, 28.74, 22.88.

(-)-Methyl (1R, 2S, 3S)-2[2-(Z)-2-pentenyl]-3-hydroxycyclopentyl]acetate[*(-)methyl cucurbate*] (2): To a solution of **26** (120 mg, 0.25 mmol) in tetrahydrofuran (5 mL) was added tetrabutylammonium fluoride trihydrate (198 mg, 0.63 mmol) under an argon atmosphere. After being stirred for 24h at room temperature, the mixture was partitioned between ether and saturated aqueous sodium chloride, and the aqueous layer was extracted with ether (3 x 15 mL). The combined ether exracts were dried ($MgSO_4$) and concentrated in vacuo. Preparative layer chromatography [silica gel, 15% ethyl acetate - petroleum ether (60-80^0 C) as developing solvent] of the residue afforded **2** (50 mg, 84%) as a colourless oil. $[\alpha]_D$ = - 2.03(C=1.12 in MeOH). (Lit.[6c] $[\alpha]_D$ = -2.20, C = 0.22 in MeOH); IR (film)ν_{max}: 3420, 2924, 2857, 1730, 1631, 1454, 1250, 1162, 1054, 689, 615 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.5-5.2 (m, 2H), 4.06-3.83 (m, 1H), 3.67 (s, 3H), 2.8-2.45 (m, 1H), 2.40 (dd, 1H, J=15.1 & 6.3Hz), 2.14 (dd, 1H, J=15.1 & 9.3Hz), 2.11-1.85 (m, 7H), 1.62-1.52 (m, 2H), 1.4-1.2 (m, 1H), 0.98 (t, 3H, J=7.5Hz). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 173. 70 (s), 133.13 (d), 127.09 (d), 77.54 (d), 51.50 (q), 50.64 (d), 36.75 (d), 35.30 (t), 32.55 (t), 28.33 (t), 25.32 (t), 20.64 (t), 14.14 (q).

(+)-(1S, 2S, 3R) -2 -[2-[(*Z*) -2 -pententyl]-3- hydroxycyclopentyl]acetic acid [(+)-*cucurbic acid*] (6): A solution of **2** (45 mg, 0.2 mmol) in 1mL 10% aqueous methanolic potassium hydroxide was stirred overnight under an argon atmosphere at 50^{0}C. Solvent was removed under vacuum. To the residue, 2 to 3 drops of water was added and it was acidified with 2(N) HCl. Aqueous phase was extracted with ether (3 x 10mL). The combined ether extracts were washed with brine (2mL), dried ($MgSO_4$) and concentrated.

Column chromatography of the residue on silica gel and elution with ethyl acetate gave a colourless thick oil **6** (40 mg, 94%). $[\alpha]_D$ = +20.23 (C= 0.34 in MeOH). (Lit.[5] $[\alpha]_D$ = +25, C = 0.56 in MeOH); IR (film)ν_{max}: 3600, 2850, 2400, 1712, 1655, 890 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.37 (bs), 5.52 -5.31 (m, 2H), 4.02-4.01 (m, 1H), 2.80-1.25 (m,12 H), 0.96 (t, 3H, J= 7.5Hz); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 178.7 (s), 133.2 (d), 126.94 (d), 77.5 (d), 50.4 (d), 36.5 (d), 35.2 (t), 32.4 (t), 28.3 (t), 25.2 (t), 20.6 (t), 14.1 (q).

(+)-Methyl(1R,2S)-2-[2-[(Z)-2-pentenyl]-3-oxo-cyclopentyl]acetate[(-)-*methyl epijasmonate*] (1): A chromic acid solution was prepared from sodium dichromate (5.0 g, 16.8 mmol) and 95% sulfuric acid (6.93 g, 54.2 mmol) and diluted with water to make up 25 mL of total volume. To a solution of **2** (35 mg, 0.1 mmol) in ether (2.5 mL) was added chromic acid solution (0.29 mL of the stock solution) with ice-cooling. The mixture was stirred for 20 min and the top ether layer was separated and to this was added excess 2-propanol and then sodium bicarbonate at the same temperature. The mixture was filtered and washed with ether. The ether extract was washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over silica gel and eluted with ethyl acetate - petroleum ether (60-80^0 C) (1:9) to give **1** (24 mg, 69%). $[\alpha]_D$ = +50.4 (C = 0.96 in MeOH). (Lit.[6c] $[\alpha]_D$ = +53.3, C = +0.98 in MeOH); IR (film)ν_{max}: 2960, 1737, 1642, 1442, 1311, 1259, 1168, 1021, 807, 696, 616 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.5-5.2 (m, 2H), 3.64 (s, 3H), 2.95-2.7 (m, 1H), 2.43-1.62 (m, 11H), 0.90 (t, 3H, J=7.5Hz); ^{13}C-NMR (50 MHz, $CDCl_3$): δ 218.83 (s), 172.87 (s), 133.49 (d), 125.44 (d), 52.68 (d), 51.70 (q), 35.57 (d), 35.25 (t), 33.72 (t), 25.65 (t), 22.94 (t), 20.64 (t), 14.03 (q).

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