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SYNTHESIS OF BOTH THE ENANTIOMERS OF METHYL EPIJASMONATE

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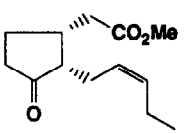
Abstract ---- Both the pure enantiomers of methyl epijasmonate **1** with potato-tuber inducing activity were synthesized stereoselectively starting from 2-oxabicyclo[3 3 0]-oct-6-en-3-one **6** in 20% yield through 11steps

INTRODUCTION

As described in our previous paper,[1] methyl epijasmonate **1**[2] and its analogs, methyl tuberonate **2**[3], β-D-glucopyranosyltuberonic acid **3**[3] and its methyl ester **4**[3] have remarkable bioactivities, such as strong jasmine note[2a,b,c], pheromone synergest[2b,c] and/or potato-tuber induction[3].

As for the potato-tuber inducing activity, there have been several interesting reports on structure-activity relationship[4] and also on the correlation between disappearance of microtubules and tuberization by the addition of (±)-methyl epijasmonate (±)-**1** [5] Yoshihara and co-workers reported that both (+)- and (–)-methyl jasmonate **5** showed nearly the same activity on tuberization, although optical purities of those materials were not rigorously determined [4] On the other hand, Tazaki and co-workers reported that (±)-methyl epijasmonate (±)-**1** were active both on tuberization and disappearance of microtubles [5] None of these workers, however, examined to use both enantiomers of optically pure methyl epijasmonate **1** and/or methyl tuberonate **2**

In order to make clear the critical point on remarkable bioactivities, we started the synthetic study Although only a report on the synthesis of (±)-methyl epijasmonate (±)-**1** was appeared in 1975, overall yield was not very high and chemical purity of (±)-**1** was hitherto unknown Furthermore, the final oxidation step taking rather long



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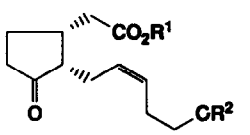
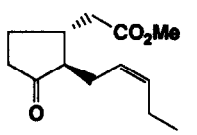


2 R^1=Me, R^2=H
3 R^1=H, R^2=β-D-Glu
4 R^1=Me, R^2=β-D-Glu



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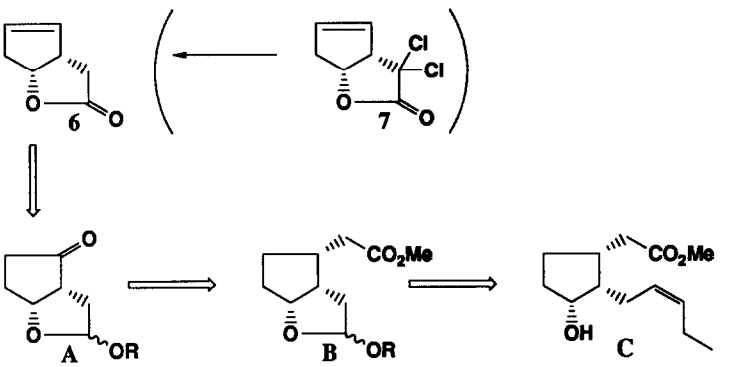
time might cause epimerization of (±)-**1** to (±)-**5** We already reported the selective synthesis of (±)-**1** via *cis*-oxahydrindanone system [1] As its starting material, (±)-3-oxacyclopentanecarboxylic acid is known to be resolved giving the optically active acid,[7] the scheme could be applicable for the chiral synthesis of **1** and **2** However, we wish to describe herein more efficient synthesis of optically pure **1** from 2-oxabicyclo[3 3 0]oct-6-en-3-one **6** During the course of the preparation of our manuscript, Helmchen and co-workers reported the synthesis of (+)-**1** *via* asymmetric Diels-Alder route [8]

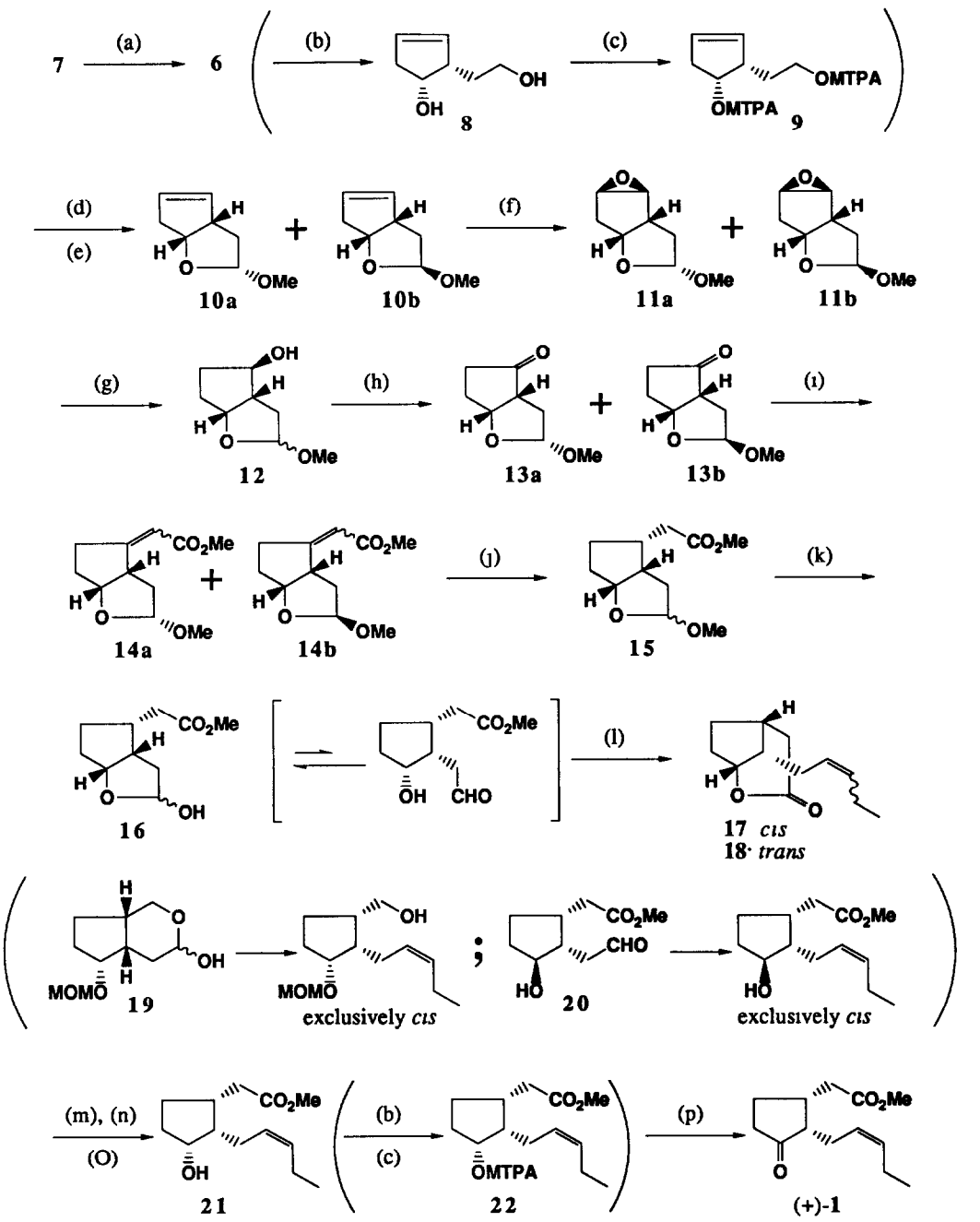
RESULTS AND DISCUSSION

It is well known that the bicyclic lactone **6** is a useful building block for the synthesis of prostaglandins.[9] Recently, both the enantiomers of **6** became available *via* practical procedure for optical resolution of the precursor, dichlorolactone **7** [10] Thus, we decided to use this chiral building block for our synthesis The key intermediate was a keto acetal **A**, derivable from **6** Extension of C_2-unit and stereoselective hydrogenation from convex site should give **B** Formation of *cis*-pentenyl side chain by the Wittig reaction should be the final stage to afford all *cis*-alcohol **C**



Both enantiomers of **6** were recrystallized from diethyl ether and portions of them were converted to diols **8**, which were esterified with (*R*)- and (*S*)-MTPACl[11] to give bis-MTPA esters **9**. HPLC analysis showed (–)-(*1S,5R*)-**6** and (+)-(*1R,5S*)-**6** to be 99 2% and 99 6% *e e* respectively. DIBAL reduction of (–)-**6** followed by the treatment with TsOH in MeOH gave a mixture of volatile acetals **10a,b** Epoxidation of **10a,b** with MCPBA gave epoxides **11a,b** (79 4% from **6**) ^{1}H-NMR data suggested only exo-epoxy group was produced from the corresponding olefin, although stereochemistry of epoxides was not important as they were convertible to the same ketone In fact, reduction of **11a,b** with $LiAlH_4$ gave an unseparable mixture of alcohols **12** and successive PDC oxidation yielded a mixture of ketones **13a,b** (=**A**) as single regioisomers (75 5% from **11**) Horner-Wittig reaction of **13a,b** with trimethyl phosphonoacetate and NaH gave olefins **14a,b** (73 1%) Hydrogenation of **14a,b** over platinum catalyst proceeded exclusively from convex face to give endo-products **15** (93 2%)

Hydrolysis of cyclic acetals with warm 75% aqueous AcOH gave the hemiacetal **16**, which directly was treated with salt-free propylidenetriphenylphosphorane in DME[1,12] to give a *cis-trans* mixture of bicyclic lactones **17** and **18** (80 0%) Formation of bridged lactone due to the attack of the resulting alkoxide ion to ester carbonyl group was unambiguous proof for the stereoselective hydrogenation of **14a,b** from less-hindered face



(a) Zn, NH_4Cl / MeOH, (b) $LiAlH_4$ / Et_2O, (c) (*R*)-, (*S*)-MTPACl / py., (d) DIBAL / tol , –70°C, (e) MeOH TsOH, (f) MCPBA / CH_2Cl_2, (g) $LiAlH_4$ / Et_2O, (h) PDC / CH_2Cl_2; (i) $(MeO)_2P(O)CH_2CO_2Me$, NaH / THF -DMF(1 1), (j) H_2, PtO_2 / EtOAc; (k) 75%AcOHaq , 60°C; (l) $Ph_3P(Br)CH_2CH_2CH_3$, n-BuLi / DME, (m) $AgNO_3$-SiO_2 chromatog , (n) 2N KOHaq -MeOH(4 1), (o) CH_2N_2 / Et_2O, (p) H_2CrO_4 / Et_2O-H_2O

Stereoselectivity on the formation of olefin in the side chain, however, was not extremely high and *cis-/trans*-ratio was ca 89/11 This result was much different from those obtained by reaction of the δ-lactol **19**[1] or free aldehyde **20**[13], giving *cis*-olefin almost exclusively A plausible explanation might be as follows *cis*-γ-lactol in **16** tends to present mostly as a cyclic form (not aldehyde form), so the Wittig reaction should be much slower than those with **19** and **20** in which aldehyde form is predominant or exclusive A similar lower selectivity was reported for γ-lactol [14] Thus, it was presumed that slow reaction caused contamination of *trans*-olefin Chromatography using silica gel impregnated with $AgNO_3$ gave pure **17** with 100% purity by GLC analysis Mild alkaline hydrolysis of lactone bridge, followed by diazomethane treatment afforded *cis*-cyclopentanol (–)-**21** MTPA ester **22** was prepared from (–)-**21** by the standard manner [11] Optical purity of (–)-**21** was shown to be ~100% *e e* by HPLC analysis Finally, two-phase oxidation with chromic acid under Brown's procedure[15] at 0° for 7min gave unnatural (–)-methyl epijasmonate (–)-**1** (20% from (–)-**6**) $[\alpha]_D^{22}$ –53 2° (c=0 98, MeOH), Lit [2d], $[\alpha]_D^{25}$ –58° (c=0 2, MeOH), GLC analysis showed (–)-**1** to be 97% pure with 3% of *trans*-epimer **5** In the same manner, natural enantiomer (+)-**1** was synthesized (20% from (+)-**6**) $[\alpha]_D^{22}$ +53 3° (c=0 95, MeOH), Lit [2d], $[\alpha]_D^{25}$ +50° (c=0 14, MeOH), GLC, 97% pure

Biological study using our synthetic samples is now in progress and preliminary result shows that natural (+)-**1** clearly has higher activity than (–)-**1** in several cases including potato-tuberization Detailed result and discussion will be reported in due course [16]

In conclusion, both the enantiomers of methyl epijasmonate **1** were efficiently synthesized in stereoselective manner Syntheses were accomplished in 20% overall yield for natural (+)-**1** and unnatural (–)-**1** through 11 steps from both enantiomers of 2-oxabicyclo[3 3 0]oct-6-en-3-one **6** Chiral syntheses of (+)- and (–)-methyl tuberonate and analogs are in progress and will be reported in due course

EXPERIMENTAL

All m p s and b p.s are uncorrected IR spectra were measured on a Jasco IRA-102 spectrometer ^{1}H-NMR spectra were recorded with TMS as an internal standard at 100MHz on a JEOL JNM FX-100 spectrometer Optical rotations were measured on a Jasco DIP-140 polarimeter

(1S, 5R)-2-Oxabicyclo[3.3.0]-oct-6-en-3-one ent-**6**. To a stirred solution of ent-**7** (4 95g) in MeOH(70ml) was added NH_4Cl powder (7 88g) and Zinc dust (9.50g) over 10min at 0°C The reaction mixture was heated under reflux with stirring for 2hr The remaining Zinc dust and $ZnCl_2$ were filtered off through florisil and the filter cake was washed with CH_2Cl_2 The filtrate was evaporated under reduced pressure to give the crystalline ent-**6** (3 19g, quant) Recrystallization from Et_2O gave colorless needles

Similarly, 19 9g of **7** gave crystalline **6** (12.8g, quant)

Ent-**6** m p 44 5~45 5°C, $[\alpha]_D^{22}$ –105° (c=1.00, MeOH), Lit.[6b] m.p. 45~46°C, $[\alpha]_D^{20}$ –105° (c=1 0, MeOH) IR ν_{max} (KBr disk) 3050(w), 1760(s), 1610(w) cm^{-1}, ^{1}H-NMR δ(100MHz, $CDCl_3$) 2 30~2.95(4H,m), 3 42~3 62(1H,m), 5 08~5 20(1H,m), 5.52~5.85(2H,m), Found: C, 67 59, H, 6.61. Calc for $C_7H_8O_2$: C, 67 73, H, 6 50 **6**: m p 44 5~45 5°C, $[\alpha]_D^{21}$ +106° (c=1.03, MeOH), Lit [6b] m p. 44.5~46°C; $[\alpha]_D^{20}$ +104° (c= 1.0, MeOH), Found· C, 67 56, H, 6 45. Calc for $C_7H_8O_2$: C, 67.73, H, 6.50.; IR and ^{1}H-NMR spectra were identical with those of ent-**6**

Determination of the enantiomeric purity of ent-6. To a stirred slurry of $LiAlH_4$ (100mg) in dry Et_2O (2 0ml) was added dropwise a solution of ent-**6** (127mg) in dry Et_2O (1.0ml) at 0°C. The mixture was stirred at room temp for 1hr, and was then worked up as usual to give the diol ent-**8** (118mg, 90 0%). Ent-**8** was converted into corresponding (*R*)- and (*S*)-MTPA esters ent-**9** in the usual manner. Both the diastereomers were analyzed by HPLC to give the result that the enantiomeric purity of ent-**6** was 99.2% *e e* Operating conditions. Column, Silica-2251-N, 25cmx6mmϕ, Solvent, n-hexane-THF (30:1), Flow rate, 1ml/min const ; Detected at 254nm. Retention time(min) (*R*)-**9** 24.49, (*S*)-**9** 27.86.

Similarly, the enantiomeric purity of **6** was turned out to be 99.6% *e e*

(1S, 3RS, 5R)-3-Methoxy-2-oxabicyclo[3.3.0]oct-6-ene ent-**10**. To a stirred solution of ent-**6** (3.09g) in dry toluene (50ml) was added dropwise a solution of diisobutylaluminum hydride in toluene (1.0mol/l, 26.0ml) over 60min at –70°C under Ar. The reaction mixture was stirred for further 1hr at –70°C. To this was added 1N HClaq. (52 0ml) over 10min below –50°C. The mixture was stirred for 1hr at room temp. and extracted with Et_2O. The extract was washed with satd $NaHCO_3$aq. and brine, dried over $MgSO_4$, and concentrated to give subliming crystal (3.01g, crude).

The crystal was immediately dissolved in MeOH (20ml). To this was added catalytic amount of p-toluenesulfonic acid at 0°C. After stirring for 2hr at room temp., powdered K_2CO_3 was added to this for neutralization, and the mixture was stirred for further 30 min Insoluble salts were filtered off, MeOH was evaporated under atmospheric pressure and the residue was extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated to give the mixture of volatile acetal ent-**10** (3.07g, crude), which was used for the next reaction without further purification.

Similarly, 12.5g of **6** gave the diastereomeric mixture of **10** (12.4g, crude).

A part of both ent-**10** and **10** were chromatographed to separate two diastereomers giving the less polar and the more polar one.

Less polar ent-**10a**: $[\alpha]_D^{27}$ –195° (c=1.07, MeOH), IR ν_{max} (film) 3060(m), 1610(w), 1039(s); ^{1}H-NMR δ (100MHz, $CDCl_3$) 1.83(1H,dt,J=4.9,13.7Hz), 2.18(1H,ddd,J=1.2,9.5,13.7Hz), 2.42~2 62(2H,m,H-8), 3.22 ~3 62(1H,m), 3.37(3H,s), 4.73(1H,td,J=2 1,5 9Hz), 5.02(1H,dd,J=1.2,4.9Hz), 5.50~5.70(2H,m). More polar ent-**10b**· $[\alpha]_D^{28}$ +65 0° (c=0 30, MeOH), IR ν_{max} (film) 3060(w), 1610(w), 1041(s); ^{1}H-NMR δ(100MHz, $CDCl_3$) 1 79~2.30(2H,m), 2.45~2 70(2H,m), 3 18~3.54(1H,m), 3.30(3H,s), 4.87(1H,td,J=2 9, 6.5Hz), 5.00(1H,dd,J=1.8,5.3Hz), 5.55~5 80(2H,m). Less polar **10a**: $[\alpha]_D^{21}$ +199° (c=1.21, MeOH). More polar **10b** $[\alpha]_D^{25}$ –62 9° (c=0.92, MeOH), IR and ^{1}H-NMR spectra were identical with those of ent-**10**.

(1S, 3RS, 5S, 6R, 7S)-6, 7-Epoxy-3-methoxy-2-oxabicyclo[3.3.0]octane ent-**11**. To a stirred solution of an epimeric mixture of ent-**10** (2.87g, crude) in dry CH_2Cl_2 was added m-chloroperbenzoic acid (7.32g, 80%pure) and $NaHCO_3$ (2.89g) below 0°C. The reaction mixture was stirred for 12hr at 0°C, then poured into ice-cooled 20%Na_2SO_3aq. (30ml) and extracted with Et_2O The extract was washed with satd $NaHCO_3$aq and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel to give the epoxide ent-**11** (2.80g, 79 4% from ent-**6**).

Similarly, 12.2g of an epimeric mixture of **10** gave the diastereomeric mixture of **11** (12 2g, 78 0% from **6**)

A part of both ent-**11** and **11** were chromatographed to separate two diastereomers giving the less polar and the more polar one

Less polar ent-**11a**· $[\alpha]_D^{22}$ –75 9° (c=1.50, MeOH), IR ν_{max} (film) 3030(m), 1041(s); ^{1}H-NMR δ(100MHz, $CDCl_3$) 1 63~2.21(4H,m), 2.80~2.98(1H,m), 3 33(3H,s), 3.43~3.51(1H,m), 3 49~3 63(1H,m), 4 55(1H,td,J =2 3,7 7Hz), 5 02(1H,d,J=5 1Hz), Found C, 61 62, H, 7 65 Calc for $C_8H_{12}O_3$: C, 61.52, H, 7.75 More polar ent-**11b** $[\alpha]_D^{22}$ –158° (c=0.98, MeOH), IR ν_{max} (film) 3030 (m), 1060(s); ^{1}H-NMR δ(100MHz, $CDCl_3$) 1 97~2 27(4H,m), 2 75~2 96(1H,m), 3.29(3H,s), 3 40~3.53(1H,m), 3 54~3.65(1H,m), 4.67(1H,t,J=7 4Hz), 5 10(1H,dd,J=0.8,5.2Hz); Found. C, 61 64, H, 7.68. Calc for $C_8H_{12}O_3$· C, 61.52; H, 7.75. Less polar **11a**: $[\alpha]_D^{22}$ +76.0° (c=1.50, MeOH), Found. C, 61 67, H, 7.71 Calc for $C_8H_{12}O_3$· C, 61 52; H, 7.75. More polar **11b**. $[\alpha]_D^{22}$ +166° (c=0 99, MeOH), Found. C, 61 47, H, 7.68 Calc for $C_8H_{12}O_3$: C, 61 52; H, 7 75 ; IR and ^{1}H-NMR spectra were identical with those of ent-**11**.

(1S, 3RS, 5R, 6R)-3-Methoxy-2-oxabicyclo[3.3.0]octan-6-ol ent-**12**. To a stirred slurry of $LiAlH_4$ (1 32g) in dry Et_2O (20ml) was added dropwise a solution of an epimeric mixture of ent-**11** (2 54g) in dry Et_2O (5ml) at 0°C The reaction mixture was stirred for 2hr at room temp., and worked up as usual to give the unseparable mixture of the alcohol ent-**12** (2 59g, quant).

Similarly, 12.0g of an epimeric mixture of **11** gave the mixture of **12** (12.1g, 99.1%)

The mixture of ent-**12**: $[\alpha]_D^{22}$ –59 9° (c=1 14, MeOH); IR ν_{max} (film) 3420(s), 1034(s); ^{1}H-NMR δ(100MHz, $CDCl_3$) 1 22~2 45(7H,m), 2 50~2 96(1H,m), 3 30 and 3 32(3H,s), 3.99~4.37(1H,m), 4.45~4.87(1H,m), 4 90~5.15(1H,m), Found C, 60.48; H, 8 84 Calc for $C_8H_{14}O_3$: C, 60 74, H, 8.92 The mixture of **12**· $[\alpha]_D^{22}$ +98 2° (c=0 99, MeOH); Found· C, 60 58, H, 8 81 Calc for $C_8H_{14}O_3$ C, 60 74, H, 8 92 , IR and ^{1}H-NMR spectra were similar to those of ent-**12**

(1S, 3RS, 5S)-3-Methoxy-2-oxabicyclo[3.3.0]octan-6-one ent-**13** To a stirred solution of an epimeric mixture of ent-**12** (6 55g) in dry CH_2Cl_2 (100ml) was added powdered molecular sieves 3A (32.0g) and pyridinium dichromate (31.8g) at 0C° The reaction mixture was stirred for 3hr at room temp , filtered through sufficient amount of florisil and washed with Et_2O The filtrate was washed with satd $CuSO_4$aq , satd $NaHCO_3$aq and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed over silica gel to give the ketoacetal ent-**13** (4 88g, 75 5%).

Similarly, 9 33g of an epimeric mixture of **12** gave the mixture of **13** (7.03g, 76 3%).

A part of both ent-**13** and **13** were chromatographed to separate two diastereomers giving the less polar and the more polar one.

Less polar ent-**13a**: $[\alpha]_D^{17}$ +52.8° (c=1.49, MeOH), IR ν_{max} (film) 1740(s), 1034(s); ^{1}H-NMR δ(100MHz, $CDCl_3$) 1 97~2 52(6H,m), 2 67~2.85(1H,m), 3 35(3H,s), 4 74~4 84(1H,m), 4.99~5.07(1H,m); Found: C, 61 24, H, 7 71. Calc for $C_8H_{12}O_3$· C, 61.52; H, 7.75. More polar ent-**13b**: $[\alpha]_D^{22}$ +252° (c=0.80, MeOH); IR ν_{max} (film) 1740 (s), 1034(s), ^{1}H-NMR δ(100MHz, $CDCl_3$) 1.98~2.74(7H,m), 3 26(3H,s), 4 83~4.99(2H,m); Found. C, 61 24; H, 7.78. Calc for $C_8H_{12}O_3$: C, 61.52, H, 7.75. Less polar **13a**: $[\alpha]_D^{21}$ –53.0° (c=1.00, MeOH); Found. C, 61 80; H, 7 90. Calc for $C_8H_{12}O_3$ C, 61 52; H, 7 75 More polar **13b**: $[\alpha]_D^{21}$ –258° (c=0 99, MeOH); Found C, 61 42; H, 7.95 Calc for $C_8H_{12}O_3$. C, 61 52, H, 7.75., IR and ^{1}H-NMR spectra were identical with those of ent-**13**

(1S, 3RS, 5R)-3-Methoxy-6-methoxycarbonylmethylidene-2-oxabicyclo[3.3.0]octane ent-**14**. To a stirred slurry of NaH (1.29g, mineral oil had been washed off with n-hexane.) in THF-DMF (20ml, 1:1, anhydrous) was added a solution of trimethyl phosphonoacetate (11.1g, 98%) in THF-DMF (30ml) at 0°. The reaction mixture was stirred for 40min at room temp To this was added dropwise a solution of an epimeric mixture of ent-**13** (4 67g) in THF-DMF (20ml) at 0°C and the mixture was stirred for 12hr at room temp. This was poured into ice-cooled satd NH_4Claq. (50ml) and extracted with Et_2O The extract was washed with water and brine, dried over $MgSO_4$ and concentrated The residue was chromatographed over silica gel to give the oily compound ent-**14** (4 64g, 73 1%)

Similarly, 6.00g of an epimeric mixture of **13** gave the mixture of **14** (5.54g, 67.9%).

A part of both ent-**14** and **14** were chromatographed to separate two diastereomers giving the less polar and the more polar one.

Less polar ent-**14a**· $[\alpha]_D^{22}$ +92 0° (c=1.11, MeOH), IR ν_{max} (film) 3000(m), 1720(s), 1655(m), 1048(s); ^{1}H-NMR δ(100MHz, $CDCl_3$) 1.64~3.29(7H,m), 3.36(3H,s), 3 71(3H,s), 4.56~4.68(1H,m), 5.00~5.06(1H,m), 5 70~5 82(1H,m), Found: C, 62 00; H, 7.63 Calc for $C_{11}H_{16}O_4$: C, 62.25; H, 7 60. More polar ent-**14b**: $[\alpha]_D^{22}$ +228° (c=0 20, MeOH), IR ν_{max} (film) 3000(m), 1715(s), 1655(m), 1040(s), ^{1}H-NMR δ(100MHz, $CDCl_3$) 1 75~3.24(7H,m), 3 29(3H,s), 3 71(3H,s), 4.66~4 78(1H,m), 4.95~5.01(1H,m), 5.75~5.83(1H,m); Found C, 62 55, H, 7.64 Calc for $C_{11}H_{16}O_4$· C, 62 25, H, 7.60. Less polar **14a**: $[\alpha]_D^{22}$ –93.1° (c=1 09, MeOH), Found C, 62 43; H, 7 64. Calc for $C_{11}H_{16}O_4$ C, 62.25; H, 7.60 More polar **14b**: $[\alpha]_D^{22}$ –227° (c= 0 24, MeOH); Found: C, 62.54; H, 7 64 Calc for $C_{11}H_{16}O_4$ C, 62 25; H, 7.60 ; IR and ^{1}H-NMR spectra were identical with those of ent-**14**

(1S, 3RS, 5R, 6S)-3-Methoxy-6-methoxycarbonylmethyl-2-oxabicyclo[3.3.0]octane ent-**15**. To a stirred suspension of PtO_2 (0 22g) in EtOAc (50ml) under H_2 was added a dropwise a solution of an epimeric mixture of ent-**14** (4 45g) in EtOAc (30ml) at 0°C. The reaction mixture was stirred for 12hr at room temp. and then filtered. The filtrate was concentrated and the residue was chromatographed over silica gel to give the unseparable mixture of ent-**15** (4 19g, 93 2%).

Similarly, 5.45g of an epimeric mixture of **14** gave the mixture of **15** (5 50g, quant.).

The mixture of ent-**15** $[\alpha]_D^{15}$ –77.2° (c=1 05, MeOH); IR ν_{max} (film) 1738(s), 1044(s); ^{1}H-NMR δ(100MHz, $CDCl_3$) 1 10~3 08(10H,m), 3.30(3H,s), 3 68(3H,s), 4 51~4.75(1H,m), 4.88~5.12(1H,m), Found· C, 61.38; H, 8.48 Calc for $C_{11}H_{18}O_4$ C, 61 66, H, 8 47. The mixture of **15**: $[\alpha]_D^{22}$ +84.8° (c=1.05, MeOH); Found C, 61 80, H, 8 50 Calc for $C_{11}H_{18}O_4$ C, 61 66, H, 8 47 , IR and ^{1}H-NMR spectra identical with those of ent-**15**.

(1S, 5R, 6S)-6-Methoxycarbonylmethyl-2-oxabicyclo[3.3.0]octan-3-ol ent-**16** An epimeric mixture of Ent-**15** (116mg) was dissolved in 75%AcOHaq. (2.5ml) and the mixture was stirred for 5hr at 60°C and then poured over powdered $NaHCO_3$ (4 00g) To this was added proper amount of water and the mixture was stirred until bubbling ceased and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel to give the hemiacetal ent-**16** (103mg, 95.0%)

Similarly, 113mg of an epimeric mixture of **15** gave **16** (102mg, 96.6%)

Ent-**16**: $[\alpha]_D^{22}$ –12 0° (c=1 00, MeOH), IR ν_{max} (film) 3440(s), 1740(s), ^{1}H-NMR δ(100MHz, $CDCl_3$) 1 12~3 17(11H,m), 3 68(3H,s), 4.69~4 81(1H,m), 5 53~5.57(1H,m), Found C, 59.96; H, 7.99. Calc for $C_{10}H_{16}O_4$ C, 59 98, H, 8 05 **16**. $[\alpha]_D^{23}$ +12 5° (c=1.01, MeOH), (Found: C, 60 20, H, 8.24. Calc for $C_{10}H_{16}O_4$ C, 59 98, H, 8 05 , IR and ^{1}H-NMR spectra were identical with those of ent-**16**.

(1S, 2R, 8R)-8-(2-cis-Penteryl)-2-oxabicyclo[3.2.1]octan-3-one ent-**17**. To a stirred solution of ent-**16** (93mg) in dry DME (0 5ml) was added a salt-free DME solution of n-propylidenetriphenylphosphorane prepared from n-propyltriphenylphosphonium bromide (1.79g) and n-butyllithium (2.6ml, 1 58mol/l in n-hexane) at 0°C under Ar and the reaction mixture was stirred for 2hr at room temp. To this was added water (2.0ml), and the mixture was extracted with Et_2O The extract was washed with satd NH_4Claq and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed over silica gel to give the mixture of ent-**17** and ent-**18** (76mg, 84.2%), which

were separated by chromatography using silica gel impregnated with 16.7% of $AgNO_3$ to give pure ent-**17** (65mg, 85 5%)

Similarly, 91mg of **16** gave pure **17** (63mg, 71 4%)

Ent-**17** $[\alpha]_D^{23}$ +65 7° (c=1 05, MeOH), IR ν_{max} (film) 3000(m), 1738(s), 1650(w); ^{1}H-NMR δ(100MHz, $CDCl_3$) 0 97(3H,t,J=7 6Hz), 1.54~2 95(12H,m), 4 54~4.66(1H,m), 5 24~5 62(2H,m); Found C, 74 10, H, 9 41 Calc for $C_{12}H_{18}O_2$ C, 74 19; H, 9 34 **17** $[\alpha]_D^{23}$ –64 8° (c=1 01, MeOH); Found C, 74 10, H, 9 35 Calc for $C_{12}H_{18}O_2$ C, 74 19; H, 9 34 , IR and ^{1}H NMR spectra were identical with those of ent-**17**

(1S, 2R, 3S)-3-Methoxycarbonylmehtyl-2-(cis-2-pentenyl)- 1-cyclopentanol ent-**21** A solution of ent-**17** (49 mg) in 2N KOHaq -MeOH (1 0ml, 4·1) was stirred for 5hr at room temp The solution was neutralized with 1N HClaq (1 6ml), roughly concentrated and extracted with Et_2O The extract was washed with water and brine, dried over $MgSO_4$ and concentrated. The residue was immediately treated with diazomethane in the usual manner and then chromatographed over silica gel to give the hydroxyester ent-**21** (53mg, 92 8%)

Similarly, 46mg of **17** gave **21**(50mg, 93 3%)

Ent-**21** $[\alpha]_D^{15}$ +2 51° (c=1 08, MeOH); IR ν_{max} (film) 3500(s), 3000(m), 1738(s), 1654(w), ^{1}H-NMR δ(100MHz, $CDCl_3$) 0 97(3H,t,J=7.7Hz), 1.53~2 51(13H,m), 3 67 (3H,s), 4 13~4 29(1H,m), 5.32~5 48(2H, m), Found C, 68 84, H, 9 86 Calc for $C_{13}H_{22}O_3$ C, 68 99, H, 9 80 **21** $[\alpha]_D^{21}$ –2 40° (c=1 24, MeOH), Found C, 68 87, H, 9 85 Calc for $C_{13}H_{22}O_3$ C, 68 99, H, 9 80 ; IR and ^{1}H-NMR spectra were identical with those of ent-**21**

Determination of the enantiomeric purity of ent-21 Ent-**21** was converted into corresponding (*R*)- and (*S*)-MTPA esters ent-**22** in the usual manner Both the diastereomers were analyzed by HPLC to give the result that the enantiomeric purity of ent-**21** was ~100% *e e* Operating conditions: Column, Silica-2251-N, 25cmx6mmφ, Solvent, n-hexane-THF (60 1), Flow rate, 1ml/min const , Detected at 254nm Retention time(min) (*R*)-ent-**22** 48 11, (*S*)-ent-**22** 45 52

Similarly, the enantiomeric purity of **21** was turned out to be ~100% *e e*

(2R, 3S)-3-Methoxycarbonylmethyl-2-(cis-2-pentenyl)-1-cyclopentanone (ent-Methyl epijasmonate) ent-**1** To a stirred solution of chromic acid (0 25ml, $H_2Cr_2O_7$ 0 67mol/l) was added dropwise a solution of ent-**21** (38mg) in Et_2O (1 25ml) at 0C°. The two-phase reaction mixture was stirred for 7min at 0°. To this was added excess 2-propanol and then $NaHCO_3$ The mixture was filtered and extracted with Et_2O and the extract was washed with water and brine, dried over $MgSO_4$, concentrated and chromatographed over silica gel to give unnatural (–)-methyl epijasmonate ent-**1** (28mg, 74.3%).

Similarly, 31mg of **21** gave natural (+)-methyl epijasmonate **1** (24mg, 78 1%)

Ent-**1** $[\alpha]_D^{22}$ –53.2° (c=0 98, MeOH), IR ν_{max} (film) 3000(m), 1740(s), 1654(w); ^{1}H-NMR δ(100MHz, $CDCl_3$) 0.97(3H,t,J=7 4Hz), 1 63~2 99(12H,m), 3 64(3H,s), 5.20~5 56(2H,m), GLC (*2R*) (*2S*)=97 3 Operating conditions Column, OV-101, 50mx0 25mmφ, Carrier, N_2, 0 8kg/cm^2, Temp, 170°C const , Detected by F I D Retention time(min) (*2R*) 14 5, (*2S*) 13 5, Found. C, 69.43, H, 9 07. Calc for $C_{13}H_{20}O_3$ C, 69 61; H, 8 99. **1** $[\alpha]_D^{22}$ +53 3° (c=0 95, MeOH), GLC (*2S*) (*2R*)=97 3; Found C, 69 81, H, 9 09 Calc for $C_{13}H_{20}O_3$ C, 69 61, H, 8 99., IR and ^{1}H-NMR spectra were identical with those of ent-**1**.

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