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An Efficient and Stereocontrolled Syntheses of (±)-Methyl Epijasmonate and (±)-Cucurbic Acid

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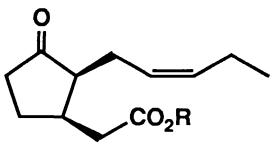
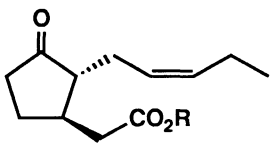
The total synthesis of epijasmonoids, (±)-methyl epijasmonate and (±)-cucurbic acid, starting from norbornene was described, where a key intermediate, 5β-hydroxy-2β-methoxycarbonylmethylcyclopentane 1β-acetic acid γ-lactone was efficiently prepared *via* a highly regioselective Baeyer-Villiger oxidation of 7-*syn*-substituted norbornanone based on remote substituent control.

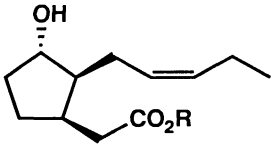
Epijasmonoid species, new members of jasmonoid family possessing *cis* configuration of the side chains with respect to the cyclopentane ring, are of current importance on jasmonoid chemistry. It has been recently known that the characteristic odor of jasmin flavor was caused by methyl epijasmonate (**1b**) rather than the popularly known methyl jasmonate (**2b**),[1] and a real metabolite in jasmonoid biosynthesis was epijasmonic acid (**1a**) rather than jasmonic acid (**2a**).[2] Although two approaches to the synthesis of biologically active epijasmonoids have been reported so far,[3] these suffered from low chemo- and stereocontrol in the crucial steps on the construction of the thermodynamically unstable vicinally *cis*-disubstituted cyclopentane system.



1a; R=H
1b; R=Me



2a; R=H
2b;R=Me

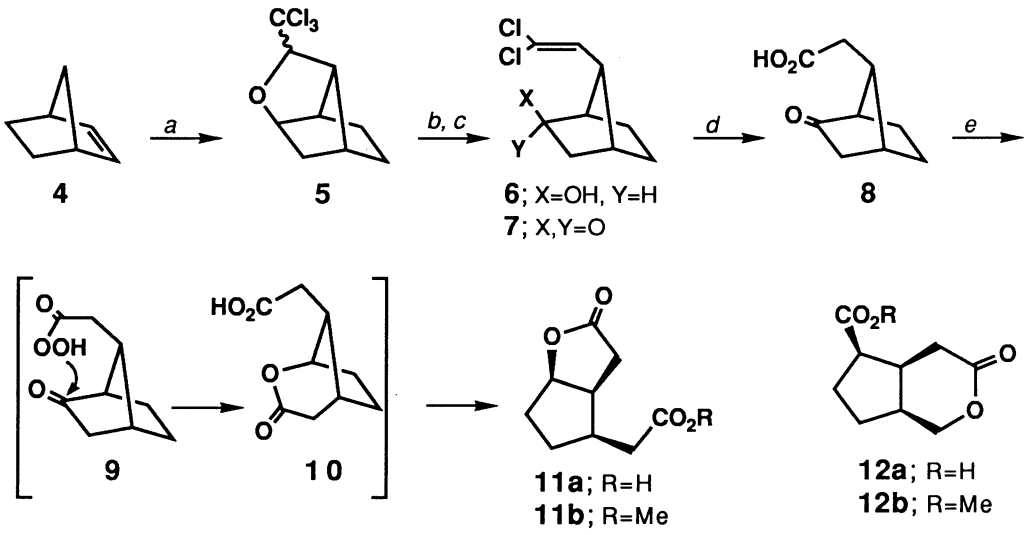


3a; R=H
3b;R=Me

We now report a novel and stereoselective total synthesis of (±)-methyl epijasmonate (**1b**) and a new type of plant growth regulator, (±)-cucurbic acid (**3a**),[4] where a suitable intermediate for epijasmonoid synthesis, 5β-hydroxy-2β-methoxycarbonylmethylcyclopentane 1β-acetic acid γ-lactone (**11b**), was efficiently prepared in 5 steps from norbornene (**4**) *via* a highly regio- and chemoselective Baeyer-Villiger oxidation of **8** assisted by its C_7-acetic acid moiety.

Scheme 1 outlines a degradative pathway up to the key intermediate **11b**, comprising the A and C ring openings of the tricyclic compound **5** which was readily available in 89% yield by the reaction of norbornene (**4**) and chloral in the presence of a catalytic amount of aluminum chloride according to Fritz's procedure.[5]

On treatment of **5** with large excess of zinc powder and acetic acid in ether at room temperature for 5 h, the reductive cleavage of β,β,β-trichloroethyl ether moiety occurred cleanly to



a; CCl_3CHO (1 equiv.), $AlCl_3$ (0.07 equiv.), CH_2Cl_2, r.t., 5 h. *b;* Zn (8.4 equiv.), AcOH (13.9 equiv.), Et_2O, r.t., 5 h. *c;* PCC (2.4 equiv.), 3 Å-molecular sieve (1.2 g per gram of PCC), CH_2Cl_2, 0 °C, 2.5 h. *d;* 95% H_2SO_4 (2 ml per mmol of **7**), r.t., 2 days. *e;* 30% H_2O_2 (2.5 equiv.), 95% H_2SO_4 (0.5 equiv.), MeOH, r.t.,1 day.

Scheme 1.

give hydroxynorbornane **6**[13] [mp 77.5-78.5 °C] quantatively, which on oxidation by means of pyridinium chlorochromate gave rise to ketone **7**[13] [mp 37 °C. IR: 1618 and 1753. ^{1}H-NMR: 5.79 (1H, d, *J*=8.6 Hz)] in 71% yield from **4.**

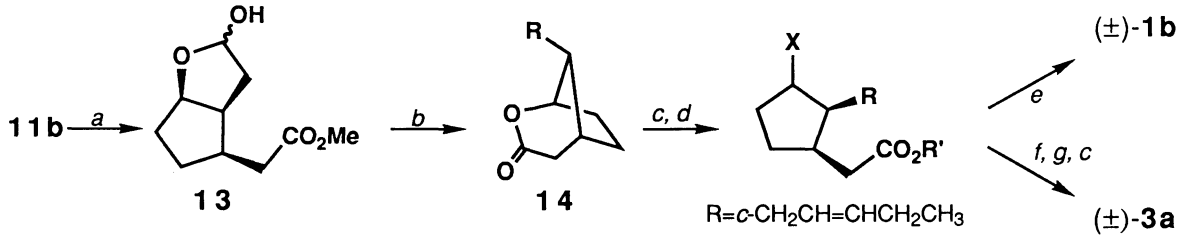
Hydrolytic conversion of **7** to acid **8**[13] [mp 35-37 °C. ^{13}C-NMR: 23.5, 27.7, 32.2,and 40.2 (each t), 37.6, 45.0, and 53.3 (each d), 176.2 and 217.8 (each s)] was quite smoothly attained in 97% yield by treatment with 95% sulfuric acid at room temperature for 2 days. To our knowledge, this is the first example of the acid hydrolytic conversion of 2,2-dichlorovinyl group to acetic acid moiety, though that of vinylhalides to ketones or aldehydes is well-known as a useful tool in organic synthesis.[6]

Highly regioselective ring opening of **8** was best conducted by treatment with 2.5 equiv. of 30% hydrogen peroxide and 0.5 equiv. of sulfuric acid in methanol at room temperature for 1 day.[7] Then, as a result of a sequence of reactions; Baeyer-Villiger oxidation, intramolecular recombination of lactone ring of the initially formed bridged lactone **10** and esterification, the γ-lactone **11b**[8,13] [mp 36-37 °C. IR: 1738 and 1777. ^{1}H-NMR: 3.69 (3H, s), 5.06 (1H, m)] was obtained directly in 82% yield along with a small amount of δ-lactone **12b**[13] [2.2%; mp 49-51 °C. IR: 1740 and 1760. ^{1}H-NMR: 3.70 (3H, s), 3.94 (1H,. d/d, *J*=11.4 and 10.1 Hz), 4.32 (1H, d/d, *J*=11.4 and 6.2 Hz)].

Interestingly, the regiochemical outcome of this Baeyer-Villiger oxidation is in a distinct contradiction to those reported on some 7-*syn*-methylnorbornanones so far, whose secondary carbon atom preferentially rearranged rather than tertiary one, which had been attributed to sterically less hindered *endo* attack of oxidant on ketone function.[9] Our result with the 7-*syn*-

hydroxycarbonylmethylnorbornanone (**8**) may be explained reasonably by the *exo* attack of oxidant through an initially formed peracid **9** or a hydrogen bonding between oxidant and C_7-acetic acid moiety, which is followed by migration of tertiary carbon atom *via* a chair-like transition state.[9]

Then, the compound **11b** was converted straightforwards into (±)-methyl epijasmonate (**1b**) by the following sequence of reactions. After reduction of **11b** with 2 equiv. of diisobutyl aluminum hydride [toluene THF, -78 °C], the obtained crystalline crude hemiacetal **13**[10,13] [94% crude yield, a 9:1 epimeric mixture regarding the hemiacetal hydroxy group. ^{1}H-NMR: 3.63 (3H, s), 4.41-4.79 (1H),. 5.38 (0.1H, d/d, *J*=5.1 and 3.5 Hz), 5.54 (0.9H, d, *J*=4.4 Hz)] was subjected to Wittig reaction under salt-free conditions [3 equiv. of salt-free *n*-propylidenetriphenylphosphorane, THF,-78 °C→r.t.] to give the bridged lactone **14**[13] [oil, 400MHz-^{1}H-NMR: 0.97 (3H, t, *J*=7.6 Hz), 1.68-1.84 (2H), 1.89 -2.43 (9H), 2.75 (1H, d/d/d, *J*=18.8, 5.1, 2.2 Hz), 4.60 (1H, m), 5.44 (1H, d/t/t, *J*=10.8, 7.3, 1.5 Hz), 5.37 (1H, d/t/t, *J*=10.8, 7.3, 1.5 Hz)] in 92% yield as a result of spontaneous lactonization of the Wittig product, a hydroxy anion of **15.** Alkaline hydrolysis of **14** with potassium hydroxide in aqueous methanol [r.t., 1 day] and subsequent esterification of a hydroxy acid **15** with diazomethane [Et_2O, 0 °C] yielded an ester **16**,[13] which on oxidation [PCC, 4Å-molecular sieve, CH_2Cl_2, 0 °C, 1.5 h] gave the oily (±)-methyl epijasmonate (**1b**)[13] in 84% yield from **14** after purification with column chromatography. Obtained **1b** was identical with an authentic material and free from the *trans*-isomer **2b** based on the HPLC analysis.[11]



a; DIBAL (2 equiv.), toluene-THF, -78 °C.
b; salt-free *n*-propylidinetriphenylphosphorane (3 equiv.), THF, -78 °C→r.t. *c;* aq. KOH, MeOH, r.t. *d;* CH_2N_2, Et_2O.
e; PCC, 4 Å-molecular sieve, CH_2Cl_2, 0 °C, 1.5 h. *f;* MsCl (1.2 equiv.), Et_3N (1.6 equiv.), CH_2Cl_2, 0 °C, 2 h. *g;* CsOAc (3.2 equiv.), 18-crown-6 (0.75 equiv.), benzene, reflux, 2 h.

Scheme 2.

Furthermore, the compound **16** could be easily converted to (±)-cucurbic acid (**3a**) *via* inversion of stereochemistry of hydroxy group according to Ikegami's procedure.[12] After mesylation of **16**, the resulting crude mesylate **17**[13] was treated with 3.2 equiv. of cesium acetate and 0.75 equiv. of 18-Crown-6 in the refluxing benzene for 2 h, yielding acetate **18**[13] in 63% yield from **16**. Acetate **18** was subjected to alkaline hydrolysis, resulting in oily (±)-cucurbic acid (**3a**)[13] quantitatively. The spectral data of methyl ester **3b** derived from **3a** [CH_2N_2, Et_2O] were in accordance with those reported[3b]. Overall yields of **1b** and **3a** from norbornene (**4**) were 41% in 10 steps and 29% in 12 steps, respectively.

In summary, this route to epijasmonoids is short and simple, and completely stereocontrolled. Further, because of the intermediate **11b** possessing suitable functional groups at the right positions, this approach would be applied to the synthesis of not only epijasmonoid analogues having modified side chains but also cyclic fatty acids reported as metabolites of linolenic acid,[2] which are currently of plant-physiological interest.

We thank Shiono Koryo Co., Ltd., for generous supply of (±)-methyl jasmonate.

References

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5) H. Fritz, C. D. Weis, and T. Winkler, *Helv. Chim. Acta.*, **58**, 1345 (1975).
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7) Oxidations of **8** under other acidic conditions using *m*-CPBA/CH_2Cl_2 or $K_2S_2O_5$-50% H_2SO_4 gave a mixture of acids, **11a**[13] [mp 87.5 °C] and **12a**[13] [mp 131 °C], in high yield but in low regioselectivity [**11a**:**12a**=4.5-5.5:1]. On contrary, oxidation under basic conditions [30% H_2O_2, aq. KOH] followed by treatment with 95% H_2SO_4, giving a 1:5 mixture of **11a** and **12a** in moderate yield.
8) This intermediate has been detected by Torii *et al.* as an undesired oily by-product during work on the total synthesis of **1b** and **2b**, see Ref. 3a. All spectral data were in good concordance with those reported.
9) G. R. Krow, *Tetrahedron*, **37**, 2697 (1981).
10) This compound had been already converted to **1b** *via* **14**, **15**,and **16** by Torii *et al.*, but this earlier route was somewhat lengthy (7 steps) with subsequent loss of overall yield (*ca.* 32%). See Ref. 3a.
11) The authentic (±)-**1b** was obtained from commercial methyl jasmonate according to Acree's separation procedure. See, R. Nishida, T. E. Acree, and H. Fukami, *Agric. Biol. Chem.*, **49**, 769 (1985).
12) T. Torisawa, H. Okabe, and S. Ikegami, *Chem. Lett.*, **1984**, 1555.
13) All compounds were fully characterized by ^{1}H-NMR, ^{13}C-NMR, IR, and mass spectra. Unless otherwise stated, ^{1}H-NMR (90 MHz) and ^{13}C-NMR (22.5 MHz) spectra were recorded in a $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in δ. IR spectra were taken in a $CHCl_3$ solution and are given in cm^{-1}.

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