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Intramolecular Alder Ene Approach to Stereochemical Control over Three Contiguous Stereogenic Centres : Synthesis of (±)-Methyl Cucurbate and (±)-Methyl Epijasmonate

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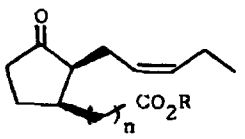
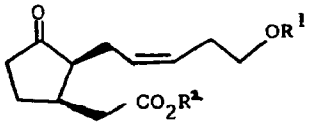
Abstract : **The total synthesis of epijasmonoids, (±)-methyl cucurbate and (±)-methyl epijasmonate is described starting from aldehyde 14, where the key step is a highly stereocontrolled 5- (3,4) ene cyclization 17 → 18.**

The epijasmonoid family of natural products featuring a *cis* -1, 2- disubstituted cyclopentane ring system includes methyl epijasmonate (1)[1] and its higher homologs 2-4,[2] methyl tuberonate (5),[3] β-D-glucopyranosyltuberonic acid (6)[3] and its methyl ester 7[3] as well as some of their reduction products namely, cucurbic acid (8)[4] and lactone 13.[5] These substances display a diversity of biological activities, such as strong jasmine note,[1a,b,c] plant growth regulation,[4] pheromone synergest[1b,c] and/or potato-tuber induction[3] and have been targets of intense synthetic interest in recent years.[6] Clearly, the turning point in jasmonoid research has been the discovery that the characteristic odour of jasmine oil is due to methyl epijasmonate (1) rather than the popularly known methyl jasmonate (10),[1d] and that the real metabolite in jasmonoid biosynthesis is epijasmonic acid (11) rather than jasmonic acid (12).[2]

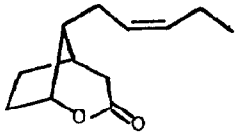
In this communication, we describe straightforward syntheses of the methyl ester 9[6a,b]



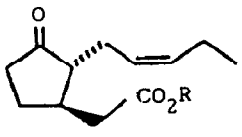
1 : n = 1 ; R = Me
2 : n = 3 ; R = H
3 : n = 5 ; R = H
4 : n = 7 ; R = H
11 : n = 1 ; R = H



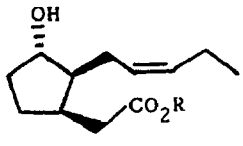
5 : R^1 = H; R^2 = Me
6 : R^1 = β-D-Glu; R^2 = H
7 : R^1 = β-D-Glu; R^2 = Me



13



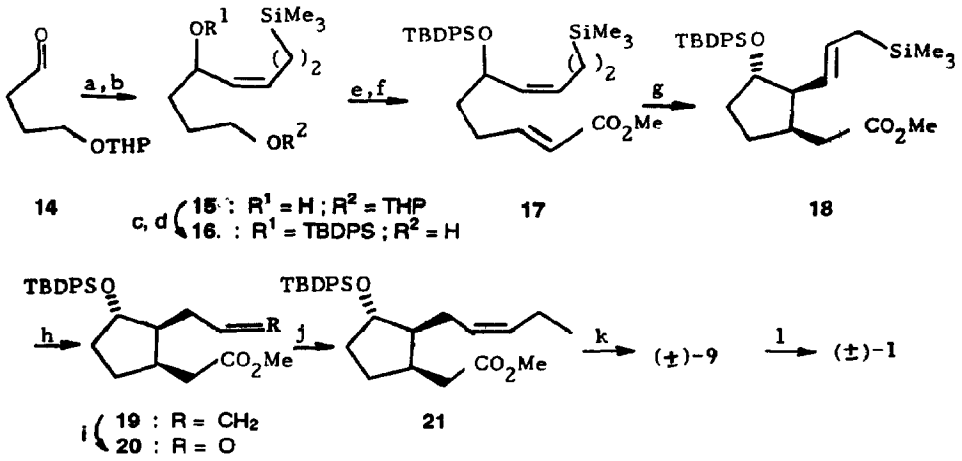
10 : R = Me
12 : R = H



8 : R = H
9 : R = Me

of (±)-cucurbic acid (8)[4], a potent plant growth inhibitor and (±)-methyl epijasmonate (1),[1,6] the queen of aroma, wherein a suitable building block for epijasmonoid synthesis, e.g. 20, was efficiently prepared in nine steps from 14 via a highly diastereoselective and diastereoface selective 5-(3,4) ene cyclization of a functionalized 1,6-diene 17 (Scheme).

Scheme [8]



(a) LiC≡C(CH$_2$)$_2$SiMe$_3$/THF-HMPA, -78° , 80%; (b) i-BuMgBr/Cp$_2$TiCl$_2$ (cat.), 85%; (c) t-BuPh$_2$SiCl/Im/DMF, 85%; (d) PPTS/EtOH, 97%; (e) DMSO, (COCl)$_2$,90%; (f) (MeO)$_2$P(O)CH(Li)CO$_2$Me, then purification by plc, 80%; (g) 235°C, 18hr, 95%; (h) HI/bz, 79%; (i) O$_3$, 88%; (j) Ph$_3$(Pr)PBr/NaN(SiMe$_3$)$_2$, -78° → r.t., 69%; (k) n-Bu$_4$NF, 89%; (l) H$_2$CrO$_4$/ether, 70%.

The aldehyde **14**[7] was converted to the ene educt **17** (31% overall) following our earlier developed protocol.[9] Heating a 5% solution of **17** in a sealed tube under argon at 235°C for 18 h smoothly effected carbocyclization to **18**[10] in almost quantitative yield. It should be noted that **18** contains most of the necessary stereochemical features of cucurbic acid (**8**). Protodesilylation[11] of **18** was best carried out in the presence of HI to give **19** (79%) which was oxidatively cleaved to **20** (88%). Wittig olefination (69%) under salt-free conditions followed by exposure of **21**[13] to n-Bu$_4$NF[12] gave (±)-cucurbic acid methyl ester (**9**) (89%) whose spectral properties were in accordance with those reported.[6b] Finally, oxidation of **9** with chromic acid under Brown's condition[14] yielded (±)- methyl epijasmonate (**1**)[15] (70%) identified by spectral comparison (^{1}H- & ^{13}C-NMR) with those of the authentic sample. Overall yields of **9** and **1** from **14** were 12.5% in 11 steps and 8.8% in 12 steps, respectively.

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8. All new compounds were characterized by IR, ^{1}H- & ^{13}C-NMR and MS.
9. See preceding paper. The isomeric purity of **15** (>99% Z) was determined as usual by GC-MS and NOE studies on the corresponding disilyl ether **18** (R^1 = R^2 = SiMe$_2$Bu^t).
10. GC-MS analysis of crude product indicated the presence of three isomers in a ratio of 89:10.5:0.5.
11. Other reagents (BF$_3$.2HOAc, conc. HCl etc.) were unrewarding.
12. The minor C1-β isomer (10.5%) carried over from **18** was eliminated at this stage presumably by lactone formation to **13**.
13. **21** is uncontaminated with any *E*-isomer.[6d]
14. Brown, H. C.; Garg, C. P.; Liu, K. T. *J. Org. Chem.* 1971, **36**, 387.
15. 90% pure with 10% of trans-epimer **10** as determined by ^{13}C NMR.[6b]

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