Synthesis of (±)-Methyl 2,5-Dimethyl-3-vinylhex-4-enoate (Methyl Santolinate)

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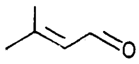
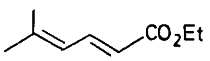
Summary Racemic methyl santolinate (**5c**) was synthesized stereoselectively in five steps from 3-methylbut-2-enal *via* the Claisen rearrangement of the allyl siloxyvinyl ether (**4**).

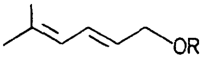
Recently the structure and stereochemistry of methyl santolinate (**5c**), a novel non-head-to-tail monoterpene from the sagebrush, *Artemesia tridentada tridentada*, was reported.[1] We now report the stereoselective synthesis of racemic (**5c**). 3-Methylbut-2-enal[2] (**1**) was converted into ethyl 5-methyl-hexa-2,4-dienoate (**2**) (96% *E*-isomer) in 85% isolated yield by the Wadsworth–Emmons modification of the Wittig reaction.[3] The *E* stereochemistry was confirmed by measuring the n.m.r. coupling constants (*J* 15 Hz) of the appropriate olefinic protons of a sample of (**2**) isolated by g.l.c. Reduction of (**2**) with LiAlH$_4$ gave (*E*)-5-methyl hexa-2,4-dien-1-ol (**3a**) in 88% yield.



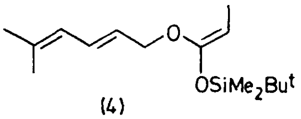
(1)



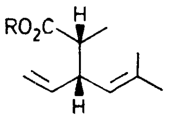
(2)



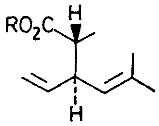
(3)
a; R = H
b; R = C(O)Et



(4)



(5)
a; R = SiMe$_2$Bu^t
b; R = H
c; R = Me



(6)
a; R = SiMe$_2$Bu^t
b, R = H
c; R = Me

The allyl siloxyvinyl ether modification[4] of the Claisen rearrangement provided a stereoselective approach to the desired (**5c**). Esterification of (**3a**) with propionic anhydride in pyridine gave (**3b**) in 89% yield. Treatment of (**3b**) in tetrahydrofuran (THF) at −78 °C with 1·05 equiv. of lithium isopropylcyclohexylamide gave the lithium enolate of (**3b**) which, on addition of an excess of Me$_2$Bu^{t}SiCl in hexamethylphosphoric triamide–THF, produced the enol silyl ether (**4**). The slight excess of base was neutralized with saturated NaCl at 0°C since failure to do so results in a lowering of the stereoselectivity of the final products from 8 : 1 to 5 : 1. Heating (**4**) at 65 °C for 3 h resulted in the Claisen rearrangement products (**5a**) and (**6a**). Dilute acetic acid hydrolysis of the silyl esters gave the corresponding acids (**5b**) and (**6b**) which were directly converted into their methyl esters† with diazomethane before isolation. The esters (**5c**) and (**6c**) were obtained in 53% yield (g.l.c. relative to internal standard) based on starting ester (**3b**) in an 8 : 1 ratio. Both esters had identical properties (g.l.c. and i.r. and n.m.r. spectra) when compared with authentic samples isolated from sagebrush. This reaction gives similar diastereomeric ratios to those produced in the acid-catalysed Claisen rearrangement of 1-dimethylamino-1-methoxyprop-1-ene with allyl alcohols and suggests that the *O*-silyl keten acetal (**4**) should be almost exclusively the *EE*-isomer.[5]

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† Equilibration of methyl santolinate in methanol with 1 mol. equiv. of NaOMe at 66 °C gives a 1 : 1 mixture of (**5c**) and its epimer, (**6c**).

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