211. Michael Addition of Lithio-α-(methyldiphenylsilyl)acetate to Cyclopentenone: A Direct Synthesis of (±)-Methyl Jasmonate[1])

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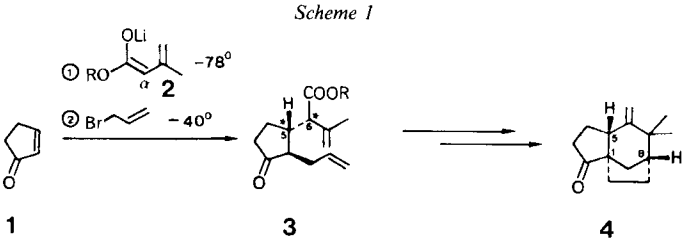
Summary

Aprotic 1,4-addition of a lithiated α-(methyldiphenylsilyl)acetate to cyclopentenone and *in situ* enolate alkylation provides a direct synthesis of (±)-methyl jasmonate *(Scheme 3)*.

Introduction. – The norsesquiterpene (±)-khusimone (**4**) has been prepared recently in 20% overall yield from 2-cyclopentenone (**1**, *Scheme 1*) [1]. In this synthesis the initial smooth conjugate addition of the ester dienolate **2** (R = Et) to **1** at −78° followed by trapping of the intermediate enolate with an electrophile permits the direct vicinal bifunctionalization **1**→**3**[2]). Simple ester enolates usually do not undergo 1,4-addition[3]). This problem has attracted widespread synthetic activity prompted by the importance of (±)-methyl jasmonate (**16**) as a perfumery constituent. Accordingly, considerable effort has been spent on α,β-difunctionalizations of cyclopentenones *(Scheme 2)*.

Scheme 1

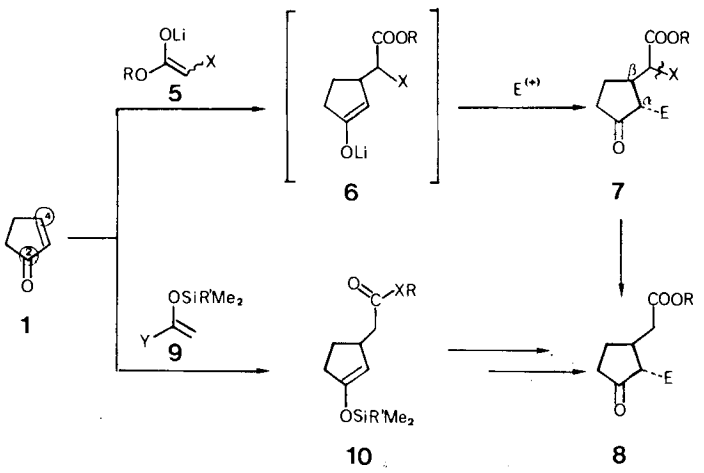


[1]) Presented *(W.O.)* at the 8th International Symposium 'Synthesis in Organic Chemistry', Cambridge, UK, July 1983.

[2]) An analogous asymmetric *Michael* addition of a dienolate **2** (R, chiral) was used for an enantioselective synthesis of (−)-khusimone, *cf.* Footnote 1.

[3]) Reviews [2] [5].

Scheme 2



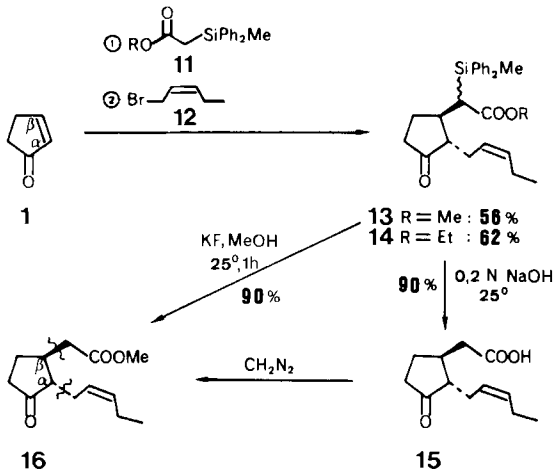
Indirect routes include the fluoride-catalyzed process **1** + **9**→**10** (R′ = Me, X = S, Y = S-*t*-Bu) which requires subsequent mercury ion promoted carbothioate hydrolysis [3]. A more recent report deals with the reaction **1** + **9**→**10** (R′ = *t*-Bu, X = O, Y = OMe) (proceeding at +55°) which is promising, although the final transformation **10**→(±)-**16** has been achieved in only 19% yield [4]. Another basic approach employs α-heterosubstituted enolates **5** which, as softer nucleophiles, should favor kinetic 1,4- over 1,2-addition[3]). However, at −78° in THF enolates **5** (X = SeMe, SePh and SMe) gave only 1,2-adducts with 2-cyclopentenone which, at higher temperatures and at longer reaction times, equilibrated with the conjugate addition products. By contrast, enolate **5** (X = SPh) added to **1** cleanly in a 1,4-fashion even at − 78° [6]. Exploiting this observation for a synthesis of quadrone, enolate **5** (X = SPh) has been added to an annulated cyclopentenone; *in situ* aldolization of the intermediate enolate and subsequent C,S-hydrogenolysis gave a vicinal disubstituted cyclopentanone (analogous to the sequence **1**→**7**→**8**) [7][4]).

Synthesis of (±)-Methyl Jasmonate (16). – Aiming at a direct conversion of 2-cyclopentenone (**1**) to methyl jasmonate (**16**)[5]), we chose a more suitable acetate enolate equivalent. Intrigued by the smooth C,Si-cleavage and the synthetic versatility of α-silylated carboxylates [8], the use of enolates **5** (X = SiR_3) was studied. Reactions of **5** (X = $SiMe_3$, R = Et or *t*-Bu) with conjugated enones and enals in THF were previously reported to give products derived from 1,2-addition and *Peterson* olefination [11]. However, it was encouraging to find that addition of **5** (X = $SiMe_3$, R = Me or Et) to **1** in THF/HMPA at −40°, followed by trapping of **6** with allyl bromide and fluoride promoted C,Si-cleavage gave the vicinally disubstituted cyclopentanone **8** (E = allyl) in 20 to 30% overall yield.

[4]) For 1,4-additions of malonate and propionate anions to 2-(phenylthio)-2-cyclopentenone see [9].

[5]) For isolation, structure and different syntheses of methyl jasmonate see [4] [10] and ref. cited therein.

Scheme 3



Under analogous reaction conditions the use of enolates **5** (X = $SiPh_2Me$) proved to be advantageous *(Scheme 2* and *3)*. Accordingly 2-cyclopentenone was added to lithiated methyl α-(methyldiphenylsilyl)acetate (prepared from **11** (R = Me) and lithium diisopropylamide (LDA)) in THF/HMPA (3.3:1) at −20°; addition of the intermediate enolate **6** to bromide **12** furnished **13** in 56% yield. Similarly the α-silylated ester **11** (R = Et) [14] furnished the desired disubstituted ketone **14** in 62% yield. The auxiliary silyl group was efficiently removed with KF in MeOH or on alkaline saponification to give in 90% yield either (±)-methyl jasmonate (**16**) or the free acid **15**, respectively. Treatment of the latter with diazomethane also furnished (±)-methyl jasmonate (**16**, 90%), identified by comparison with an authentic sample (IR, ^{1}H-NMR (360 MHz), Ms).

The utility of α-silylated ester enolates for enone-α,β-functionalizations is currently being explored in this laboratory.

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Experimental Part

General. All reactions were carried out with magnetic stirring under N_2 or Ar. The workup procedure consists of washing the org. extracts with H_2O followed by drying over anh. $MgSO_4$, filtration and removal of solvent by distillation *in vacuo* using a rotatory evaporator. CC was carried out using SiO_2 *(Merck, Kieselgel 60)*. GLC, retention time (t_R) in min, was carried out using a *Carlo Erba SS455* instrument, N_2-pressure 1 kg/cm^2, glass column, 3 m × 3 mm, 5% *OV-225* on *Chromosorb WAW 80/160* at 200°. IR spectra in CCl_4 unless otherwise specified $\tilde{\nu}_{max}$ in cm^{-1}. ^{1}H-NMR spectra in $CDCl_3$, standard TMS, δ (ppm) = 0. Mass spectra (MS): signals are given in *m/z* (rel.-%).

Methyl 2-(methyldiphenylsilyl)acetate (**11**, R = Me). Analogous to the preparation of **11** (R = Et) [12] a solution of methyldiphenylchlorosilane (4.66 g, 20 mmol) and methyl bromoacetate (3.8 g, 25 mmol) in dry benzene/Et_2O (1:1, 10 ml) was added over 30 min to Zn-wool (1.64 g, 25 mmol) and iodine (1 crystal) in benzene (25 ml) under gentle reflux. After 1 h the mixture was cooled to 0° and aq. 1N HCl (20 ml) was added over 15 min. The org. layer was washed successively with H_2O and aq. $NaHCO_3$ to give after workup, chromatography (hexane/EtOAc 9:1) and distillation, **11** (R = Me, oil, 4.19 g, 76%), b.p. 140–146°/0.2 Torr. IR: 1745, 1425. ^{1}H-NMR (60 MHz): 0.62 (*s*, 3 H); 2.45 (*s*, 2 H); 3.50 (*s*, 3 H); 7.15–7.7 (10 H).

(Z)-*1-Bromo-2-pentene* (**12**). *Lindlar* catalyst (400 mg) was added to a solution of 2-pentyn-1-ol (8 g) in hexane (150 ml). The mixture was stirred under H_2 (1 atm) at r.t. for 3 h to give after filtration and distillation (Z)-2-penten-1-ol (7.8 g, 95% yield, b.p. 48–49°/15 Torr). This alcohol was converted to bromide **12** without isomerization using the procedure of *Corey et al.* [13] as follows. Methyl sulfide (11.2 ml, 153 mmol) was added dropwise at 0° to a solution of *N*-bromosuccinimide (22.7 g, 127 mmol) in dry CH_2Cl_2 (40 ml) (420 ml). Then a solution of (Z)-2-penten-1-ol (6.8 g, 85 mmol) in CH_2Cl_2 (40 ml) was added dropwise at −20°. The mixture was stirred at 0° for 3 h, then diluted with pentane and poured into ice water (16 ml). The org. phase was washed with sat. aq. NaCl, filtered through SiO_2, dried and evaporated. Distillation of the residue furnished bromide **12** (oil, 7.5 g, 60% yield), b.p. 52°/40 Torr). IR (film): 3030, 2960, 2930, 2850, 1720, 1200, 960. ^{1}H-NMR (60 MHz): 0.98 (*t*, *J* = 7.5, 3 H); 1.7–2.35 (2 H); 3.6–4.2 (2 H); 5.2–5.9 (2 H). MS: 150 (5, $C_5H_9{}^{81}Br^+$), 69 (85), 53 (39), 41 (100), 39 (75).

Methyl trans-*2-{3-oxo-2-[(Z)-2-pentenyl]cyclopentyl}-2-(methyldiphenylsilyl)acetate* (**13**). A 1.5N solution of BuLi in hexane (1.1 ml, 1.65 mmol) was added to dry diisopropylamine (166 mg, 1.65 mmol) in dry THF (3 ml) at 0°. After 10 min at 0° methyl α-(methyldiphenylsilyl)acetate (**11**, R = Me; 405 mg, 1.5 mmol) was added over 3 min at −20°. After successive addition of HMPA (0.9 ml) and 2-cyclopentenone (**1**) (0.135 ml, 1.65 mmol) the mixture was stirred at −20° for 1 h and then slowly injected into a solution of the bromide **12** (1.05 ml, 7.5 mmol) in THF/HMPA (3.3:1, 1.9 ml) at −40°. Stirring the mixture at −40° for 1 h, followed by quenching with sat. aq. NH_4Cl (2 ml), extraction with pentane/Et_2O (1:1), workup and chromatography (hexane/EtOAc 9:1) gave **13** (1:1-diastereoisomeric mixture, 350 mg, 56% yield, oil). IR: 1743, 1715, 1427, 698. ^{1}H-NMR (360 MHz): 0.77 (*s*, 1.5 H); 0.82 (*s*, 1.5 H); 0.95 (*t*, *J* = 7.5, 1.5 H); 0.97 (*t*, *J* = 7.5, 1.5 H); 1.8–2.8 (11 H); 3.25 (*s*, 1.5 H); 3.45 (*s*, 1.5 H); 5.05–5.45 (2 H); 7.2–7.7 (10 H). MS: 420 (0.13, $C_{26}H_{32}O_3Si^+$), 255 (0.3), 214 (26), 199 (100), 181 (3), 150 (10), 137 (12), 121 (5), 82 (32).

Ethyl trans-*2-{3-oxo-2-[(Z)-2-pentenyl]cyclopentyl}-2-(methyldiphenylsilyl)acetate* (**14**). Following the procedure described for the preparation of **13** using LDA (1.65 mmol), ethyl α-(methyldiphenylsilyl)acetate [14] (**11**, R = Et; 426 mg, 1.5 mmol), 2-cyclopentenone (1.65 mmol) and bromide **12** (7.5 mmol) the ethyl ester **14** was obtained (oil, 1:1-diastereoisomeric mixture, 405 mg, 62%). IR (film): 1738, 1710, 1427, 1110, 698. ^{1}H-NMR (100 MHz): 0.78 (*s*, 1.5 H); 0.82 (*s*, 1.5 H); 0.8–1.1 (6 H); 1.7–3.1 (11 H); 3.3–4.2 (2 H); 4.9–5.8 (2 H); 7.2–7.9 (10 H). MS: 434 (62, $C_{27}H_{34}O_3Si^+$), 416 (19), 356 (36), 323 (30), 314 (39), 310 (37), 237 (48), 197 (100).

(±)-*Jasmonic acid* (**15**). A solution of the α-silylated ester **14** (260 mg, 0.6 mmol) in 0.67N NaOH (EtOH/H_2O 2:1, 36 ml) was stirred at r.t. for 16 h. After addition of aq. 1N HCl (6 ml) extraction of the mixture with $CHCl_3$, followed by workup and chromatography (hexane/EtOAc/HOAc 30:10:0.1) gave **15** (oil, 113 mg, 90%). IR: 3440–3000 br., 1745, 1710. ^{1}H-NMR (100 MHz): 0.97 (*t*, *J* = 7.5, 3 H); 1.35–3.0 (12 H); 5.1–5.75 (2 H); 7.3 (br., 1 H). MS: 210 (32, $C_{12}H_{18}O_3^+$), 192 (4), 181 (4), 163 (5), 151 (42), 142 (29), 133 (24), 109 (33), 83 (100), 69 (26).

(±)-*Methyl jasmonate* (**16**). a) *By Protodesilylation of* **13**. A mixture of the α-silylated methyl ester **13** (290 mg, 0.69 mmol) and KF (150 mg, 1.6 mmol) in MeOH/H_2O (4:1, 15 ml) was stirred at r.t. for 2 h. Evaporation of the mixture, trituration of the residue with Et_2O, workup and chromatography (hexane/EtOAc 9:1) furnished **16** (oil, 139 mg, 90%), GLC: t_R 12.8 min. IR: 1742. ^{1}H-NMR (360) MHz): 0.96 (*t*, *J* = 7.5, 3 H); 1.50 (*m*, 1 H); 1.90 (*m*, 1 H); 1.95–2.6 (9 H); 2.71 (*m*, 1 H); 3.70 (*s*, 3 H); 5.26 (*m*, 1 H); 5.45 (*m*, 1 H). MS: 224 (17, $C_{13}H_{20}O_3^+$), 193 (6), 151 (27), 133 (12), 121 (9), 109 (27), 83 (100), 67 (33), 55 (44). The above cited GLC behavior (coinjection), IR, ^{1}H-NMR and mass spectra are identical to those of an authentic sample of (±)-methyl jasmonate.

b) *By Esterification of* **15**. A 1N solution of CH_2N_2 in Et_2O (1.5 ml) was added slowly to a solution of **15** (100 mg, 0.48 mmol) in Et_2O (5 ml). Evaporation of the solution and chromatography of the residue gave (±)-**16** (96 mg, 90%) identified by comparison (GLC, IR, ^{1}H-NMR, MS) with an authentic sample.

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