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Stereoselective 1,4-addition of Grignard reagents to chiral γ-alkoxy-α,β-unsaturated ketones

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Abstract: Copper-catalyzed conjugate addition reactions of Grignard reagents to γ-alkoxy-α,β-unsaturated ketones, derived from mandelic acid, have been studied. Diastereoselectivity is strongly dependent on the nature of the γ-alkoxy protection group. Bulky silyl protection gives poor stereoselectivities, whereas the ketone bearing benzyloxymethylene (BOM) protection reacts with excellent yields and stereoselectivities.
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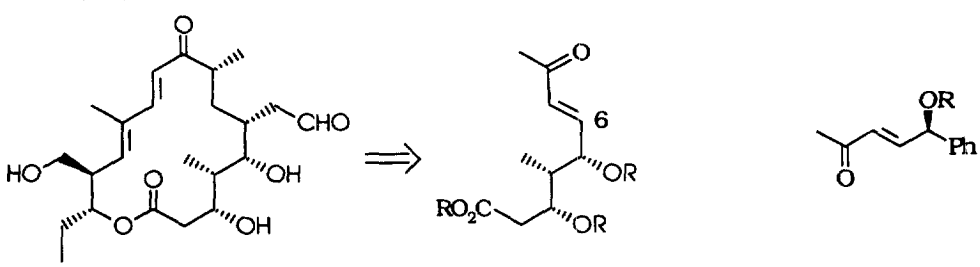
The stereoselective addition of organometallic reagents to α,β-unsaturated carbonyl compounds is a powerful method in the stereocontrolled synthesis.[1] The original catalytic reaction[2] often proceeds with no regioselectivity (1,2 versus 1,4 addition) and strongly depends on the structure of a substrate. In recent years, several research groups reported on the stereoselective conjugate addition of copper, lithium and magnesium reagents to γ-alkoxy-[3–10] and γ-amino-α,β-unsaturated[11–14] carbonyl compounds or sulfones.[15,16] The diastereoselectivity of this addition was generally dependent on the substrate and reagent structure, while in some cases opposite stereochemical results were observed.[17,18]

We are presently working on a total synthesis of tylonolide **1**, a 16-membered-ring aglycone of a macrolide antibiotic—tylosin. The proposed synthetic route (Scheme 1) requires the *anti*-stereoselective conjugate addition for introduction of C-6 stereogenic center. Therefore, we decided to investigate this reaction using a model compound **3** synthesized in a four-step reaction sequence from L-mandelic acid.



1 **2** **3**

Scheme 1.

Since the new stereogenic center generated should be *anti* to the alkoxy function, we have chosen the $SiPh_2Bu^t$ protection group for a model compound. We expected from the literature precedent that such a bulky group will enable the reagent to attack from the opposite side of the alkoxy substituent, according to the 'modified' Felkin–Anh model.[3] (5*R*)-5-(*O*-t-Butyldiphenylsilyl)-5-phenyl-pent-3-en-2-one **4** was prepared by the reaction of *O*-silylated mandelic aldehyde with acetylmethylene-triphenylphosphorane. Only the *E*-isomer was detected by NMR/HPLC methods.

For our studies, we have chosen the method described by Kuwajima *et al.* for the synthesis of *E*-enol silyl ethers.[19] This copper-promoted addition is strongly accelerated when TMSCl and

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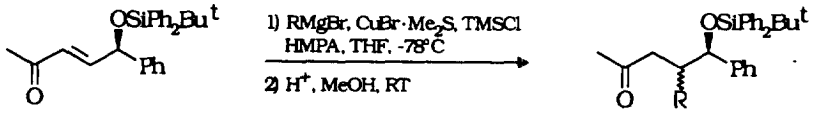
HMPA are added. The reaction was carried out using simple Grignard reagents: methyl-, phenyl- and vinylmagnesium bromides (Scheme 2).



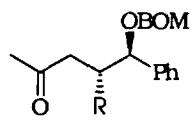
4 5

Scheme 2.

A mixture of very stable silylated enol ethers was formed, which was immediately subjected to deprotection under acidic conditions. The reaction proceeded smoothly, but without expected selectivity. We obtained a mixture of adducts unseparable by column chromatography or preparative HPLC, without pronounced stereoselectivity (Table 1).

Since the concept of application of silylated model compounds failed regarding the stereoselective course of the addition, we decided to use the benzyloxymethylene (BOM) group for protection of hydroxy functionality, very well known for its chelating abilities.[20] Using the same synthetic procedure, we have prepared enone **7** with 61% overall yield, starting from L-mandelic acid (Scheme 3).

The reaction was performed by slow addition of the substrate together with TMSCl to a solution containing the Grignard reagent, copper(I) bromide and HMPA in THF at −78°C and afforded, after deprotection of the TMS group, products of 1,4-addition of type **8** with excellent yields and stereoselectivities (Table 2).



8

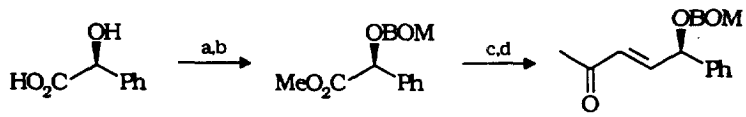
The diastereomeric ratio was determined by ^{1}H NMR methods and confirmed by HPLC. All diastereomers of this series were separable by column chromatography or preparative HPLC.

The configurational assignment was based on NOE difference measurements of hemiacetals, obtained by hydrogenolysis of the BOM protective group and subsequent methylation of the anomeric center. Substantial intensity enhancement of appropriate neighbouring protons clearly indicates the *anti* position of a new substituent (Scheme 4).

Diastereoselectivity of the conjugated addition to γ-alkoxy-α,β-unsaturated systems was investigated by several groups. Most of them suggested the 'modified' Felkin–Anh model for explanation of *anti*-selective addition of cuprates[3,5–8] and a chelation-controlled model for *syn*-selective reactions of lithium and Grignard reagents.[5,8] For some cuprates a formation of π-complexes was also proposed.[4] Apart from experimental results, some attempts of explanation for stereoselectivity through molecular

Table 1. Conjugate additions to ketone **4**

Compound	Yield [%]	Diastereomer ratio
5 a R=Me	85	62 : 38
5 b R=Ph	86	60 : 40
5 c R=$CHCH_2$	88	79 : 21



6 **7**

Scheme 3. Reagents and conditions: (a) MeOH, AcCl, RT, 2 h, 92%; (b) BOMCl, i-Pr_2EtN, CH_2Cl_2, RT, 20 h, 60°C, 3 h, 85%; (c) DIBAL, Et_2O, −78°C, 30 min; (d) $CH_3COCHPPh_3$, toluene, 50°C, 14 h, Σ 78%.

Table 2. Conjugate additions to ketone 7

Entry	Compound	T [°C]	Yield [%]	*anti / syn*
1	**8 a** R=Me	-78	92	93 : 7
2		-30	82	87 : 13
3		0	76	83 : 17
4		20	70[a]	75 : 25
5	**8 b** R=Ph	-78	84	94 : 6
6	**8 c** R=$CHCH_2$	-78	90	96 : 4

[a] Substantial amount of 1,2-addition products appeared with the increase of temperature.

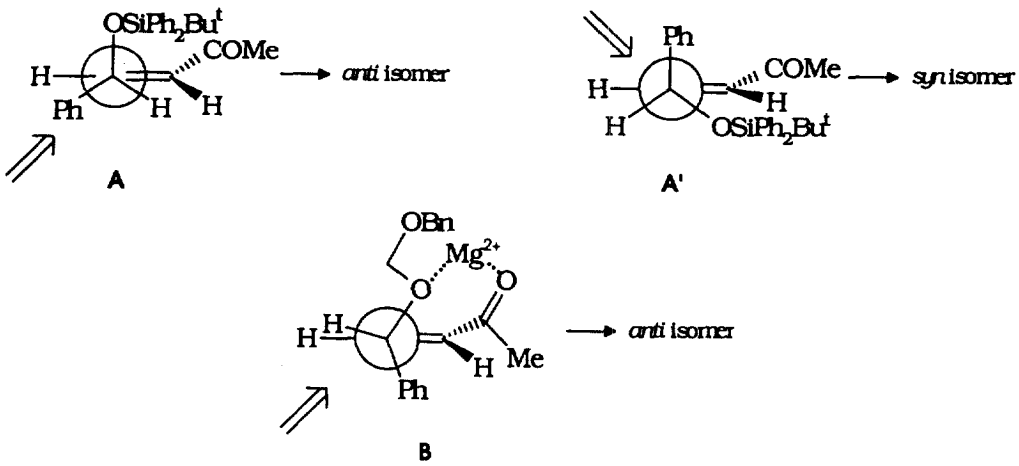
9 **10**

Scheme 4.

mechanics studies have appeared in the literature.[21] During their extensive studies on the conjugate addition of organocopper reagents, Yamamoto *et al.* observed similar diastereoselectivity for γ-benzyloxy and γ-*t*-butyldimethylsilyloxy substituted Michael acceptors and reported a lack of chelation effects.[4c] In our work the difference of stereoselectivity in reactions of γ-BOM and γ-silyl protected ketones indicates the existence of co-ordination interactions in the BOM series. Poor stereoselectivity in reactions of the γ-silyloxy compound **4** could be explained by competition between two proposed conformers A and A″. In both conformations the large substituent (silyloxy) prevents the opposite sides of π-system from nucleophilic attack (Scheme 5).

In the case of the BOM series, proposed by other authors,[4,5] conformer B is additionally stabilized by co-ordination of the magnesium cation to the carbonyl and γ-alkoxy oxygens. Further co-ordination with the benzyloxy oxygen (BOM protection) is likely.

In conclusion, the method described herein can be applied for introduction of a stereogenic center in excellent yield and with *anti*-stereoselectivity. Studies on the application of this method in the total synthesis of tylonolide are now in progress in our laboratory.



Scheme 5.

Experimental section

All reactions were carried out under argon atmosphere with anhydrous solvents that have been dried according to standard laboratory methods. ^1H and ^{13}C NMR spectra were measured on a Bruker AM-500 (500 and 125 MHz) and Varian Gemini (200 and 50 MHz) using residual $CHCl_3$ as internal reference. Mass spectra were carried out using an AMD-604 Intectra instrument. Optical rotations were measured on a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell. Infrared spectra were recorded on a Perkin–Elmer 1640 FT-IR. Melting points were determined with a Kofler hot stage apparatus and are uncorrected. HPLC was carried out on a Knauer system using a UV spectrophotometer for peak detection. Flash-column chromatography was performed according to Still *et al.* on silica gel (Kieselgel-60, Merck, 200–400 mesh). Grignard reagents (1 M solutions in THF) were purchased from Aldrich.

(E)-(5R)-5-(O-t-Butyldiphenylsilyl)-5-phenyl-pent-3-en-2-one **4**

To a stirred solution of methyl (*O*-t-butyl-diphenylsilyl)mandelate (4.50 g, 11,12 mmol) in dry ether (50 ml), under argon at −78°C, was added diisobutylaluminium hydride (1.3 eq., 1.5 M in toluene). After 15 min MeOH was added (5 ml) and the reaction mixture was poured into an aq. saturated solution of sodium–potassium tartrate (150 ml). After 2 h the aqueous layer was extracted with ethyl acetate (2×100 ml), the combined organic layers were dried ($MgSO_4$), evaporated to dryness and the residue was dissolved in 40 ml of dry toluene. Acetylmethylene-triphenylphosphorane (3.8 g, 11.94 mmol) was added and the reaction mixture was stirred for 14 h at 50°C. Water was added (40 ml), the aqueous layer was extracted with ethyl acetate (3×30 ml), the combined organic layers were dried ($MgSO_4$), evaporated to dryness and the residue was purified by flash chromatography (hexane:ethyl acetate 95:5→9:1) to give **4** (4.28 g, 93% yield) as a colourless oil: $[\alpha]_D$=25.2 (c 3.83, $CHCl_3$); ν_{max} (film, cm^{-1}) 2931, 2857, 1679, 1427, 1112, 700, 504; δ_H (200 MHz, $CDCl_3$) 7.69–7.62 (m, 2H, Ph), 7.49–7.15 (m, 13H, Ph), 6.67 (dd, $J_{3,4}$=15.9 Hz, $J_{4,5}$=5.4 Hz, 1H, 4-H), 6.15 (dd, $J_{3,4}$=15.9 Hz, $J_{3,5}$=1.4 Hz, 1H, 3-H), 5.27 (dd, $J_{3,5}$=1.4 Hz, $J_{4,5}$=5.4 Hz, 1H, 5-H), 2.13 (s, 3H, 1-Me), 1.08 (s, 9H, t-Bu); δ_C (50 MHz, $CHCl_3$) 198.7 (C-2), 148.4 (C-3), 141.1 (C-4), 135.8, 134.8, 133.3, 132.8, 129.9, 129.7, 128.5, 128.3, 127.7, 127.5, 126.4 (3×Ph), 75.2 (C-5), 27.0 (C-1), 26.9 (3×Me), 19.4 (CMe_3); m/z (LSIMS, NBA) 437 $(M+Na)^+$, 415 $(M+H)^+$; m/z (HRLSIMS) calculated for $C_{27}H_{31}O_2Si$ $(M+H)^+$ 415.2546, found 415.2090; Anal. Calculated for $C_{27}H_{30}O_2Si$: C, 78.22; H, 7.29. Found: C, 77.98; H, 7.27.

(E)-(5R)-5-(O-Benzyloxymethylene)-5-phenyl-pent-3-en-2-one 7

Prepared in 78% yield by the above method. Colourless oil: $[\alpha]_D$=61.8 (c 2.30, $CHCl_3$); ν_{max} (film, cm^{-1}) 3000, 2395, 1670, 1625, 1030, 1115, 650; δ_H (500 MHz, $CDCl_3$) 7.40–7.26 (m, 10H, Ph), 6.78 (dd, $J_{3,4}$=16.0 Hz, $J_{4,5}$=5.5 Hz, 1H, 4-H), 6.32 (dd, $J_{3,4}$=16.0 Hz, $J_{3,5}$=1.3 Hz, 1H, 3-H), 5.34 (dd, $J_{3,5}$=1.3 Hz, $J_{4,5}$=5.5 Hz, 1H, 5-H), 4.81 (d_{AB}, $J_{A,B}$=7.1 Hz, 1H, OCH_AH_BOBn), 4.75 (d_{AB}, $J_{A,B}$=7.1 Hz, 1H, OCH_AH_BOBn), 4.64 (d_{AB}, $J_{A,B}$=11.7 Hz, 1H, OCH_AH_BPh), 4.57 (d_{AB}, $J_{A,B}$=11.7 Hz, 1H, OCH_AH_BPh), 2.25 (s, 3H, 1-Me); δ_C (50 MHz, $CHCl_3$) 198.4 (C-2), 145.8 (C-3), 138.5, 137.4 (Ph), 129.7 (C-4), 128.7, 128.4, 127.9, 127.7, 127.3 (Ph), 92.1 (OCH_2OBn), 76.6 (C-5), 69.8 (OCH_2Ph), 27.1 (C-1); Anal. Calculated for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.75; H, 6.84.

General procedure for the addition of Grignard reagents to pent-3-en-2-ones 4 and 7

To a stirred suspension of $CuBr \cdot Me_2S$ (0.2 mmol, 41 mg) and HMPA (4 mmol, 0.7 ml) in THF (4 ml), under argon at −78°C was added a solution of Grignard reagent (4 mmol) followed by stirring for 10 minutes. To this mixture was added a precooled solution of the ketone (2 mmol) and TMSCl (3 mmol, 0.4 ml) in THF (2 ml). The reaction was stirred at −78°C and followed by disappearance of starting material in TLC (hexane:ethyl acetate=9:1). Aqueous NH_4Cl (10 ml) was added to the mixture, which was then extracted with ether (3×10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated. The residue was dissolved in 5 ml of MeOH, a catalytic amount of camphorsulfonic acid was added and the reaction mixture was stirred for 30 min at RT. The reaction was worked up by addition of brine (10 ml), extracted with ether (3×10 ml), dried over anhydrous $MgSO_4$ and purified by flash chromatography (hexane–ethyl acetate).

*(4RS,5R)-4-Methyl-5-(O-t-butyldiphenylsilyl)-5-phenyl-pent-2-one **5a** (62:38 mixture of diastereoisomers)*

Oil; ν_{max} (film, cm^{-1}) 2962, 2932, 2858, 1717, 1428, 1362, 1112, 1063, 702, 504; m/z (LSIMS, NBA) 453 $(M+Na)^+$; m/z (HRLSIMS) calculated for $C_{28}H_{34}O_2SiNa$ $(M+Na)^+$ 453.2229, found 453.2226; Anal. Calculated for $C_{28}H_{34}O_2Si$: C, 78.09; H, 7.96. Found: C, 77.97; H, 8.07.

Major diastereoisomer

δ_H (500 MHz, $CDCl_3$) 7.72–7.64 (m, 2H, Ph), 7.45–7.18 (m, 13H, Ph), 4.50 (d, $J_{4,5}$=6.1 Hz, 5-H), 2.53 (dd, $J_{3,3''}$=16.2 Hz, $J_{3,4}$=4.1 Hz, 3-H), 2.35–2.28 (m, 4-H), 1.95 (dd, $J_{3,3''}$=16.2 Hz, $J_{3'',4}$=9.4 Hz, 3-H″), 1.94 (s, 1-Me), 1.01 (s, t-Bu), 0.68 (d, J=6.6 Hz, 4-Me); δ_C (50 MHz, $CHCl_3$) 208.5 (C-2), 142.1, 141.9, 136.0, 135.9, 134.1, 133.5, 129.6, 129.4, 127.6, 127.5, 127.1, 127.0 (3×Ph), 79.1 (C-5), 47.1 (C-3), 37.1 (C-4), 30.1 (C-1), 27.0 (3×Me), 19.5 (CMe_3), 15.3 (C4-*Me*).

Minor diastereoisomer, remaining signals: δ_H

(500 MHz, $CDCl_3$) 4.63 (d, $J_{4,5}$=4.7 Hz, 5-H), 2.46 (dd, $J_{3,3''}$=16.6 Hz, $J_{3,4}$=4.2 Hz, 3-H), 1.91 (dd, $J_{3,3''}$=16.6 Hz, $J_{3'',4}$=10.5 Hz, 3-H″), 1.90 (s, 1-Me), 1.03 (s, t-Bu), 0.74 (d, J=7.0 Hz, 4-Me); δ_C (50 MHz, $CHCl_3$) 78.7 (C-5), 46.0 (C-3), 36.8 (C-4), 30.2 (C-1), 15.5 (C4-Me).

*(4RS,5R)-4-Phenyl-5-(O-t-butyldiphenylsilyl)-5-phenyl-pent-2-one **5b** (60:40 mixture of diastereoisomers)*

Oil; ν_{max} (film, cm^{-1}) 3030, 2932, 2858, 1719, 1428, 1112, 1069, 700, 503; m/z (LSIMS, NBA) 515 $(M+Na)^+$; m/z (HREIMS) calculated for $C_{29}H_{27}O_2Si$ $(M-C_4H_9)^+$ 435.1783, found 435.1780; Anal. Calculated for $C_{33}H_{36}O_2Si$: C, 80.44; H, 7.36. Found: C, 80.42; H, 7.57.

Major diastereoisomer: δ_H

(500 MHz, $CDCl_3$) 7.68–6.72 (m, 20H, Ph), 4.78 (d, $J_{4,5}$=6.9 Hz, 5-H), 3.48 (ddd, $J_{3,4}$=4.9 Hz, $J_{3'',4}$=9.9 Hz, $J_{4,5}$=6.9 Hz, 4-H), 2.88 (dd, $J_{3,3''}$=16.4 Hz, $J_{3,4}$=4.9 Hz, 3-H), 2.61 (dd, $J_{3,3''}$=16.4 Hz, $J_{3'',4}$=9.9 Hz, 3-H″), 1.85 (s, 1-Me), 1.00 (s, t-Bu); δ_C (50 MHz, $CHCl_3$) 207.6 (C-2), 141.8,

140.1, 136.1, 136.0, 133.9, 133.3, 129.6, 129.4, 129.0, 127.9, 127.8, 127.5, 127.3, 127.2, 127.0, 126.5 (4×Ph), 79.1 (C-5), 49.6 (C-4), 45.4 (C-3), 30.2 (C-1), 27.0 (3×Me), 19.4 (CMe_3).

Minor diastereoisomer, remaining signals

δ_H (500 MHz, $CDCl_3$) 4.82 (d, $J_{4,5}$=5.7 Hz, 5-H), 3.53–3.45 (m, 4-H), 2.65 (dd, $J_{3,3''}$=16.6 Hz, $J_{3,4}$=4.8 Hz, 3-H), 2.55 (dd, $J_{3,3''}$=16.6 Hz, $J_{3'',4}$=10.0 Hz, 3-H''), 1.79 (s, 1-Me), 0.96 (s, t-Bu); δ_C (50 MHz, $CHCl_3$) 79.3 (C-5), 48.9 (C-4), 44.0 (C-3), 30.2 (C-1), 19.3 (CMe_3).

(4RS,5R)-4-Vinyl-5-(O-t-butyldiphenylsilyl)-5-phenyl-pent-2-one ***5c*** *(79:21 mixture of diastereoisomers)*

Oil; ν_{max} (film, cm^{-1}) 3071, 2931, 2857, 1718, 1427, 1112, 1067, 701, 504; m/z (LSIMS, NBA) 465 $(M+Na)^+$; m/z (HRLSIMS) calculated for $C_{29}H_{34}O_2SiNa$ $(M+Na)^+$ 465.2216, found 465.2225; Anal. Calculated for $C_{29}H_{34}O_2Si$: C, 78.68; H, 7.74. Found: C, 78.62; H, 7.57.

Major diastereoisomer

δ_H (200 MHz, $CDCl_3$) 7.74–7.64 (m, 2H, Ph), 7.48–7.10 (m, 13H, Ph), 5.52 (ddd, J=8.0, 10.5, 17.2 Hz, 4-C*H*CH_2), 4.97–4.76 (m, 4-CHCH_2), 4.64 (d, $J_{4,5}$=5.8 Hz, 5-H), 3.01–2.74 (m, 4-H), 2.47 (dd_{AB}, $J_{3a,3b}$=16.0 Hz, $J_{3a,4}$=4.7 Hz, 3-H_A), 2.22 (dd_{AB}, $J_{3a,3b}$=16.0 Hz, $J_{3b,4}$=9.4 Hz, 3-H_B), 1.93 (s, 1-Me), 1.02 (s, t-Bu); δ_C (50 MHz, $CHCl_3$) 207.7 (C-2), 141.6 (4-*C*HCH_2), 137.0, 136.0, 134.0, 133.3, 129.7, 129.5, 127.6, 127.5, 127.3, 127.2, 127.1 (3×Ph), 116.8 (4-CH*C*H_2), 77.9 (C-5), 47.2 (C-4), 44.5 (C-3), 30.1 (C-1), 27.0 (3×Me), 19.4 (CMe_3).

Minor diastereoisomer, remaining signals

δ_H (200 MHz, $CDCl_3$) 4.75 (d, $J_{4,5}$=4.8 Hz, 5-H), 2.55 (dd_{AB}, $J_{3a,3b}$=15.9 Hz, $J_{3a,4}$=4.1 Hz, 3-H_A), 2.10 (dd_{AB}, $J_{3a,3b}$=15.9 Hz, $J_{3b,4}$=9.8 Hz, 3-H_B), 1.89 (s, 1-Me), 1.02 (s, t-Bu); δ_C (50 MHz, $CHCl_3$) 141.4 (4-*C*HCH_2), 117.1 (4-CH*C*H_2), 77.8 (C-5), 47.4 (C-4), 43.6 (C-3).

(4R,5R)-4-Methyl-5-(O-benzyloxymethylene)-5-phenyl-pent-2-one ***8a*** *(*anti *addition product)*

Oil; $[\alpha]_D$=94.7 (c 4.30, $CHCl_3$); ν_{max} (film, cm^{-1}) 3040, 2960, 2890, 1723, 1500, 1458, 160, 1102, 1040, 695; δ_H (500 MHz, $CDCl_3$) 7.40 7.25 (m, 10H, Ph), 4.67 (d_{AB}, J_{AB}=6.9 Hz, 1H, OC$H_A$$H_B$OBn), 4.65 ($d_{AB}$, J_{AB}=11.7 Hz, 1H, OC$H_A$$H_B$Ph), 4.57 ($d_{AB}$, J_{AB}=6.9 Hz, 1H, OCH_AH_BOBn), 4.46 (d_{AB}, J_{AB}=11.7 Hz, 1H, OCH_AH_BPh), 4.39 (d, $J_{4,5}$=7.5 Hz, 1H, 5-H), 2.78 (dd, $J_{3,3''}$=16.3 Hz, $J_{3,4}$=4.3 Hz, 1H, 3-H), 2.45 (m, 1H, 4-H), 2.30 (dd, $J_{3,3''}$=16.3 Hz, $J_{3'',4}$=8.8 Hz, 1H, 3-H''), 2.14 (s, 3H, 1-Me), 0.80 (d, J=6.8 Hz, 3H, 4-Me); δ_C (125 MHz, $CHCl_3$) 207.8 (C-2), 139.5, 137.6, 128.4, 128.3, 127.9, 127.7, 127.6, 127.5 (2×Ph), 92.6 (OCH2OBn), 79.9 (C-5), 69.8 (OCH2Ph), 47.0 (C-3), 37.4 (C-4), 30.2 (C-1), 15.5 (C4-Me); Anal. Calculated for $C_{20}H_{24}O_3$: C, 76.89; H, 7.75. Found: C, 77.09; H, 7.71.

(4S,5R)-4-Methyl-5-(O-benzyloxymethylene)-5-phenyl-pent-2-one ***8a*** *(*syn *addition product)*

Oil; $[\alpha]_D$=75.4 (c 2.30, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 7.40–7.25 (m, 10H, Ph), 4.72 (d_{AB}, J_{AB}=6.9 Hz, 1H, OC$H_A$$H_B$OBn), 4.70 ($d_{AB}$, J_{AB}=11.7 Hz, 1H, OC$H_A$$H_B$Ph), 4.60 ($d_{AB}$, J_{AB}=6.9 Hz, 1H, OCH_AH_BOBn), 4.54 (d, $J_{4,5}$=5.9 Hz, 1H, 5-H), 4.49 (d_{AB}, J_{AB}=11.7 Hz, 1H, OCH_AH_BPh), 2.53–2.40 (m, 2H, 3-H, 4-H), 2.23–2.12 (m, 1H, 3-H''), 2.03 (s, 3H, 1-Me), 0.97 (d, J=6.7 Hz, 3H, 4-Me); Anal. Calculated for $C_{20}H_{24}O_3$: C, 76.89; H, 7.75. Found: C, 76.95; H, 8.01.

(4R,5R)-4-Phenyl-5-(O-benzyloxymethylene)-5-phenyl-pent-2-one ***8b*** *(*anti *addition product)*

Colourless crystals, mp. 84–85°C (hexane–ether); $[\alpha]_D$=80.3 (c 2.90, $CHCl_3$); ν_{max} (KBr, cm^{-1}) 2995, 2880, 1715, 1488, 1447, 1190, 1027, 1012, 650;; δ_H (500 MHz, $CDCl_3$) 7.37–7.05 (m, 15H, Ph), 4.76 (d, $J_{4,5}$=7.4 Hz, 1H, 5-H), 4.65 (d_{AB}, J_{AB}=7.0 Hz, 1H, OC$H_A$$H_B$OBn), 4.57 ($d_{AB}$, J_{AB}=7.0 Hz, 1H, OCH_AH_BOBn), 4.45 (d_{AB}, J_{AB}=11.5 Hz, 1H, OC$H_A$$H_B$Ph), 4.33 ($d_{AB}$, J_{AB}=11.5 Hz, 1H, OCH_AH_BPh), 3.58 (ddd, $J_{3a,4}$=5.3 Hz, $J_{3b,4}$=9.1 Hz, $J_{4,5}$=7.4 Hz, 1H, 4-H), 3.05 (dd_{AB}, $J_{3a,3b}$=16.5 Hz, $J_{3a,4}$=5.3 Hz, 1H, 3-H_A), 2.94 (dd_{AB}, $J_{3a,3b}$=16.5 Hz, $J_{3b,4}$=9.1 Hz, 1H, 3-H_B), 2.04 (s, 3H, 1-Me);

δ_C (125 MHz, $CHCl_3$) 207.0 (C-2), 153.7, 152.5, 150.6, 141.3, 141.1, 140.9, 140.8, 140.6, 140.4, 140.3, 140.2, 139.4 (3×Ph), 92.6 (OCH_2OBn), 81.9 (C-5), 69.9 (OCH_2Ph), 48.4 (C-4), 45.2 (C-3), 30.3 (C-1); Anal. Calculated for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 80.32; H, 6.93.

(4S,5R)-4-Phenyl-5-(O-benzyloxymethylene)-5-phenyl-pent-2-one ***8b*** *(*syn *addition product)*

Colourless crystals mp. 75–77°C (hexane–ether); $[\alpha]_D$=108.0 (c 0.60, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.40–7.10 (m, 15H, Ph), 4.79 (d, $J_{4,5}$=8.2 Hz, 1H, 5-H), 4.44 (d_{AB}, J_{AB}=7.2 Hz, 1H, OCH_AH_BOBn), 4.48 (d_{AB}, J_{AB}=7.2 Hz, 1H, OCH_AH_BOBn), 4.08 (d_{AB}, J_{AB}=11.7 Hz, 1H, OCH_AH_BPh), 4.00 (d_{AB}, J_{AB}=11.7 Hz, 1H, OCH_AH_BPh), 3.59 (ddd, $J_{3a,4}$=9.4 Hz, $J_{3b,4}$=5.0 Hz, $J_{4,5}$=8.2 Hz, 1H, 4-H), 2.75 (dd_{AB}, $J_{3a,3b}$=16.6 Hz, $J_{3a,4}$=9.4 Hz, 1H, 3-H_A), 2.54 (dd_{AB}, $J_{3a,3b}$=16.6 Hz, $J_{3b,4}$=5.0 Hz, 1H, 3-H_B), 1.86 (s, 3H, 1-Me); Anal. Calculated for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 80.08; H, 7.13.

(4R,5R)-4-Vinyl-5-(O-benzyloxymethylene)-5-phenyl-pent-2-one ***8c*** *(*anti *addition product)*

Oil; $[\alpha]_D$=121.0 (c 3.30, $CHCl_3$); ν_{max} (film, cm^{-1}) 2970, 2893, 1710, 1490, 1448, 1355, 1195, 1027; δ_H (500 MHz, $CDCl_3$) 7.36–7.34 (m, 10H, Ph), 5.63 (ddd, J=8.2, 10.3, 16.9 Hz, 1H, 4-C*H*CH_2), 4.96 (d, J=10.3 Hz, 1H, 4-CHC*H*H″), 4.92 (d, J=16.9 Hz, 1H, 4-CHCH*H*″), 4.69 (d_{AB}, J_{AB}=7.0 Hz, 1H, OCH_AH_BOBn), 4.67 (d_{AB}, J_{AB}=11.6 Hz, 1H, OCH_AH_BPh), 4.59 (d_{AB}, J_{AB}=7.0 Hz, 1H, OCH_AH_BOBn), 4.59 (d, 5-H, overlap with OCH_AH_BOBn), 4.47 (d_{AB}, J_{AB}=11.6 Hz, 1H, OCH_AH_BPh), 3.08–3.01 (m, 1H, 4-H), 2.73 (dd_{AB}, $J_{3a,3b}$=16.2 Hz, $J_{3a,4}$=4.6 Hz, 1H, 3-H_A), 2.54 (dd_{AB}, $J_{3a,3b}$=16.2 Hz, $J_{3b,4}$=8.9 Hz, 1H, 3-H_B), 2.11 (s, 3H, 1-Me); δ_C (125 MHz, $CHCl_3$) 207.5 (C-2), 137.4 (4-*C*HCH_2), 139.6, 137.5, 128.3, 128.2, 127.8, 127.7, 127.6 (2×Ph), 116.8 (4-CH*C*H_2), 92.6 (OCH_2OBn), 80.7 (C-5), 70.0 (OCH_2Ph), 46.0 (C-4), 44.4 (C-3), 30.3 (C-1); Anal. Calculated for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.65; H, 7.36.

(4S,5R)-4-Vinyl-5-(O-benzyloxymethylene)-5-phenyl-pent-2-one ***8c*** *(*syn *addition product)*

Oil; $[\alpha]_D$=88.3 (c 1.90, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.34–7.25 (m, 10H, Ph), 5.76 (ddd, J=8.3, 10.4, 17.4 Hz, 1H, 4-C*H*CH_2), 5.08 (d, J=10.4 Hz, 1H, 4-CHC*H*H″), 5.02 (d, J=17.4 Hz, 1H, 4-CHCH*H*″), 4.71 (d_{AB}, J_{AB}=6.9 Hz, 1H, OCH_AH_BOBn), 4.69 (d_{AB}, J_{AB}=11.8 Hz, 1H, OCH_AH_BPh), 4.67 (d, $J_{4,5}$=6.0 Hz, 1H, 5-H) 4.59 (d_{AB}, J_{AB}=6.9 Hz, 1H, OCH_AH_BOBn), 4.48 (d_{AB}, J_{AB}=11.8 Hz, 1H, OCH_AH_BPh), 3.05-2.98 (m, 1H, 4-H), 2.50 (dd_{AB}, $J_{3a,3b}$=16.4 Hz, $J_{3a,4}$=5.0 Hz, 1H, 3-H_A), 2.39 (dd_{AB}, $J_{3a,3b}$=16.4 Hz, $J_{3b,4}$=8.5 Hz, 1H, 3-H_B), 2.01 (s, 3H, 1-Me); δ_C (125 MHz, $CHCl_3$) 207.5 (C-2), 137.6 (4-*C*HCH_2), 139.6, 137.8, 128.4, 128.2, 127.8, 127.7, 127.6 (2×Ph), 117.0 (4-CH*C*H_2), 92.7 (OCH_2OBn), 80.5 (C-5), 69.8 (OCH_2Ph), 45.8 (C-4), 44.9 (C-3), 30.5 (C-1); Anal. Calculated for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 78.12; H, 7.37.

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References

1. Reviews: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.*, **1992**, *92*, 771. (b) Leonard, J. *Contemp. Org. Synth.*, **1994**, *1*, 387. (c) Yamamoto, Y. In *Houben-Weyl*, Methods of Organic Chemistry; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E. *Eds.*; Thieme: Stuttgart, 1995: Vol. E 21b, 2041.
2. Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.*, **1941**, *63*, 2308.
3. (a) Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.*, **1983**, *24*, 2231; (b) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Chong, W. K. *J. Am. Chem. Soc.*, **1987**, *109*, 7575; (c) Roush, W. R.; Michaelides, M. R.; Tai, Lesur, B. M.; D. F.; Chong, W. K.; Harris, D. J. *J. Am. Chem. Soc.*, **1989**, *111*, 2984.

4. (a) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.*, **1987**, 464; (b) *ibid.*, **1987**, 1572; (c) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.*, **1992**, *114*, 7652.
5. (a) Leonard, J.; Ryan, G. *Tetrahedron Lett.*, **1987**, *28*, 2525; (b) Leonard, J.; Ryan, G.; Swain, P. A. *Synlett*, **1990**, 613; (c) Leonard, J.; Mohialdin, S.; Reed, D.; Jones, M. F. *Synlett*, **1992**, 741; (d) Leonard, J.; Mohialdin, S.; Reed, D.; Ryan, G.; Swain, P. A. *Tetrahedron*, **1995**, *51*, 12843.
6. Hanessian, S.; Sumi, K. *Synthesis*, **1991**, 1083.
7. Salomon, R. G., Miller, D. B., Raychaudhuri, S. R., Avasthi, K., Lal, K., Levison, B. S. *J. Am. Chem. Soc.*, **1984**, *106*, 8296.
8. Larchêveque, M.; Tamagnan, G.; Petit, Y. *J. Chem. Soc., Chem. Commun.*, **1989**, 31.
9. Nemoto, H.; Ando, M.; Fukumoto, H. *Tetrahedron Lett.*, **1990**, *31*, 6205.
10. (a) Dondoni, A.; Merino, P.; Orduna, P. *Tetrahedron Lett.*, **1991**, *32*, 3247; (b) Dondoni, A.; Boscarato, A.; Marra, A. *Synlett*, **1993**, 256.
11. (a) Reetz, M. T.; Rŝhring, D. *Angew. Chem.*, **1989**, *101*, 1732; *Angew. Chem., Int. Ed. Engl.*, **1989**, *28*, 1706. (b) Iako, I.; Uiber, P.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Tetrahedron Lett.*, **1990**, *31*, 1011.
12. (a) Bernardi, A.; Cardani, S.; Poli, G.; Scolastico, C. *J. Org. Chem.*, **1986**, *51*, 5041; (b) *ibid.*, **1988**, *53*, 1600; (c) Bernardi, A.; Cardani, S.; Scolastico, C.; Villa, R. *Tetrahedron*, **1990**, *46*, 1987.
13. Yoda, H., Shirai, T., Katagiri, T., Takabe, K., Kimata, K., Hosoya, K. *Chem. Lett.* **1990**, 2037.
14. Burgess, K., Cassidy, J., Henderson, I. *J. Org. Chem.*, **1991**, *56*, 2050.
15. (a) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.*, **1979**, *20*, 3465; (b) *ibid.*, **1980**, *21*, 4772; (c) Isobe, M.; Ichikawa, Y.; Funabashi, Y.; Mio, S.; Goto, T. *Tetrahedron*, **1986**, *42*, 2863.
16. (a) Alcaraz, C.; Carretero, J. C.; Dominguez, E. *Tetrahedron Lett.*, **1991**, *32*, 1385; (b) Dominguez, E.; Carretero, J. C. *Tetrahedron Lett.*, **1993**, *34*, 5803; (c) Carretero, J. C.; Dominguez, E. *J. Org. Chem.*, **1993**, *58*, 1596.
17. (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.*, **1981**, *103*, 1224; (b) *ibid.*, **1982**, *104*, 2027; (c) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.*, **1979**, *20*, 2327.
18. Ziegler, F. E.; Gilligan, P. J. *J. Org. Chem.*, **1981**, *46*, 3874.
19. (a) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, T. *Tetrahedron Lett.*, **1986**, *27*, 4025; (b) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, T. *Tetrahedron* , **1989**, *45*, 349.
20. Garvey, G. J.; Kimura, M. *J. Org. Chem.*, **1982**, *47*, 1982.
21. (a) Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.*, **1989**, *111*, 6524. (b) Bernardi, A.; Capelli, A. M.; Gennari, C.; Scolastico, C. *Tetrahedron: Asymmetry*, **1990**, 1, 21.

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