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Stereoselective Synthesis of Macrolactin A Analogues. Part 2: the C_1-C_{14} Fragment

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Abstract : *A synthetic approach to the C_1-C_{14} part of Macrolactin A analogues is presented. The sequence involving hydroboration-Pd° coupling reaction was found to be the most efficient in term of chemio- and stereo-selectivity to prepare the sensitive and functionalized E,Z diene unit.* Copyright © 1996 Elsevier Science Ltd

In the preceding paper, we outlined our strategy for the total synthesis of Macrolactin A analogues such as compound **1**.[1] According to the synthetic plan, we divided analogue **1** into two segments **2** and **3** (figure 1).

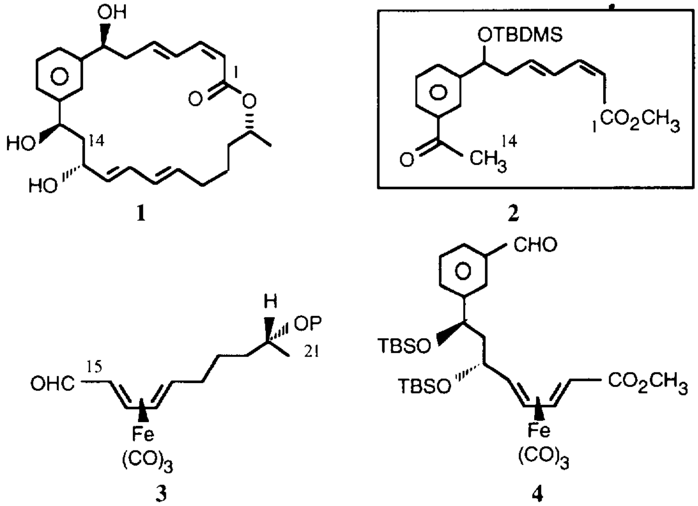
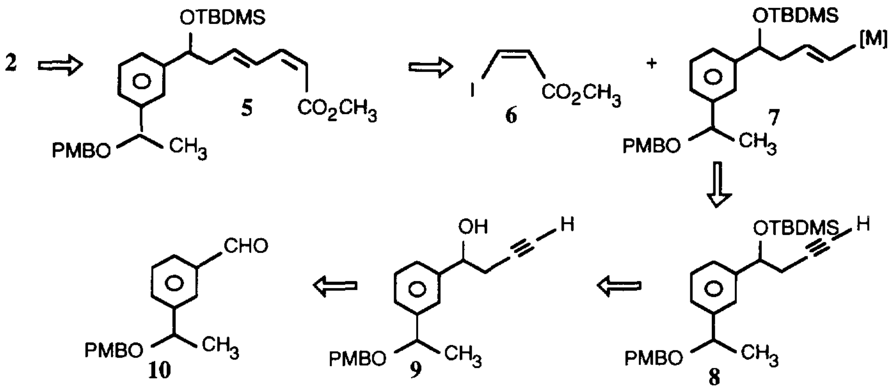


Figure 1

The synthesis of complex **3**, in optically pure form, has been reported earlier.[2] A tricarbonyliron complexed dienoate **4** was prepared following an aldol coupling/1,3 reduction methodology, thus providing a good model for the stereoselective construction of the anti 1,3-diol in C_{13}, C_{15} positions of macrolide **1**. In this second paper, we describe the synthesis of a C_1-C_{14} segment **2** which incorporates the sensitive electrophilic (E,Z) dienic moiety.

Our strategy for the synthesis of this C_1-C_{14} segment is summarized in Scheme 1. We proposed that the (E,Z) dienoate **5** could be prepared from the homopropargylic alcohol **8** through the use of a hydrometallation followed by a coupling with the known[3] (Z)-vinylic iodide **6**. Furthermore, alcohol **9** should be available *via* a propargylation reaction of aldehyde **10**.

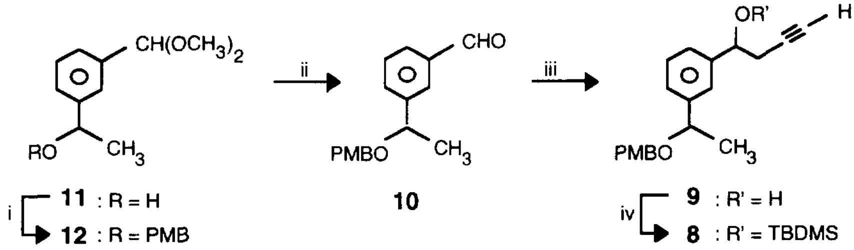


Scheme 1

Preliminary studies[4] have established that the paramethoxybenzyl (PMB) and the tertiobutyldimethylsilyl (TBDMS) are the most convenient protecting groups during the synthesis of ketone **2** and for the preparation of the Macrolactin A analogs.

HOMOPROPARGYLIC ALCOHOL 8

This intermediate **8** has been prepared in four steps with a high overall yield (70%) starting from alcohol **11**[1] (Scheme 2).



(i) NaH, DMF then; 4-CH_3O-C_6H_4-CH_2Br, (95%); (ii) SiO_2, 1% H_2SO_4, CH_2Cl_2; 89%; (iii) Al, $HgCl_2$, $BrCH_2$-$C{\equiv}CH$, THF, rt, 88%; (iv) $tBuMe_2SiCl$, imidazole, DMF,94%.

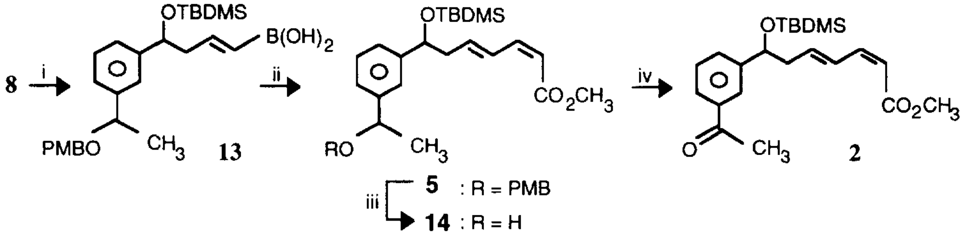
Scheme 2

During these preliminary studies, the reactions have been done only in racemic form. However, the enantioselective preparation of homopropargylic alcohols have been described recently: either chiral non racemic allenyl boranes[5], or allenyltri-n-butyl stannanes in the presence of a chiral Lewis acid[6], gave homopropargylic alcohols with high enantioselectivities. These results suggest that the control of the absolute configuration at the C_7 stereogenic center should be possible at this stage.

(E,Z) DIENE CONSTRUCTION USING A HYDROMETALLATION/COUPLING SEQUENCE

A coupling reaction between a vinyl metal **7** and the vinyl iodide **6**[3] appeared as the most direct and stereoselective methodology to build the sensitive (E,Z) diene fragment. However, the organometallic resulting from a hydrometallation of the alkyne must be compatible with ether and ester groups and it must give a good stereochemical control under mild conditions.

Preliminary studies have demonstrated that either hydroalumination or hydrozirconation were unsuccessful in our case.[4] Thus, the coupling reaction from vinylboranes[7] appeared as an attractive and efficient methodology as demonstrated for instance in Kishi in the palytoxin synthesis[8] or by Nicolaou in the preparation of diHETEs.[9] Such a sequence involving hydroboration followed by a Pd° coupling reaction was applied to alkyne **8** as shown in Scheme 3. Monohydroboration and hydrolysis of the corresponding vinylborane gave boronic acid **13** in high yield. The coupling reaction was carried out under Kishi's conditions using TPOH as a base and the p-methoxy benzyl group proved to be compatible with these hydroboration coupling conditions. The E,Z stereochemistry of diene **5** is easily established by ^1H NMR.



(i) catecholborane, 90°C, 2 hours, then r.t., H_2O, 12 hours, 98%;
(ii) (Z)-methyl-3-iodo-propen-1-oate, $Pd(PPh_3)_4$ (25 mol%), 60% (traces of debenzylated diene, 6%);
(iii) DDQ, 1.5 eq., CH_2Cl_2/H_2O (18/1), 76%; (iv) PDC, 2.3 eq., 4Å molecular sieves, CH_2Cl_2, 82%.
Scheme 3

The target ketone **2** was accessible in two steps from diene **5** (62% overall yield, scheme 4). Firstly, an oxidative removal of the p-methoxybenzyl group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in a 18/1 mixture of CH_2Cl_2/H_2O gave alcohol **14** without affecting silyl ether protective group at C7 position. The last stage involved the oxidation of **14** with pyridinium dichromate in the presence of 4Å molecular sieves. It is important to point out that during all these reactions the E,Z geometry of the diene unit was kept intact.

CONCLUSION

The C_1-C_{14} fragment of Macrolactin A analogue **1** was efficiently constructed by an hydroboration/Pd° coupling approach fully compatible with the presence of several functional groups such as ethers or esters and highly stereoselective to prepare the desired functionnalized E,Z diene unit. Furthermore, this synthesis should be adaptable to the preparation of optically pure intermediates thus offering a promising entry into total synthesis of Macrolactin A analogues and other polyenic macrolides.

EXPERIMENTAL SECTION

For general experimental details, see the preceding paper.

2-(3'-dimethoxymethyl)phenyl-2-p-methoxybenzyloxy-ethane (**12**)

To a solution of alcohol **11** (105 g, 5.35 mmol) in anhydrous DMF (20 mL), was added under nitrogen by small portions at 0°C, sodium hydride (NaH, 60% dispersion in mineral oil, 330 mg, 8.25 mmol). The reaction mixture was stirred at 0°C for one hour before adding dropwise 4-methoxybenzylbromide (1.5 g, 7.5 mmol) as a solution in anhydrous DMF (20 mL). After one hour at 0°C under stirring, the mixture was hydrolysed with water and extracted with methylene chloride. The organic layers were washed (H_2O), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using ether/

petroleum ether 1:9 to afford protected alcohol **12** (1.6 g, 95%, R_F= 0.46 with ether/petroleum ether 1:1) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.34 (m, 4 H), 7.23-6.86 (m, 4 H), 5.41 (s, 1H), 4.50 (q, 1H, J= 6.5 Hz), 4.38-4.20 (dd, 2H, J= 11.3 Hz), 3.81 (s, 3H), 3.35 (s, 6H), 1.46 (d, 3H, J= 6.5 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 159.1, 143.9, 138.3, 130.7 (ipso C), 129.2, 128.4, 126.0, 125.8, 124.8, 113.8 (8 aromatic C), 103.2 [$\underline{C}H(OCH_3)_2$], 76.9 (O$\underline{C}H_2$), 69.9 (C_2), 55.2 ($\underline{C}H_3$-C_6H_4), 52.7 [$CH(O\underline{C}H_3)_2$], 24.1 (C_1). This (NMR pure) product was used directly for the next step of the synthesis.

2-(3'-oxymethyl)phenyl-2-p-methoxybenzyloxy-ethane **(10)**

To a suspension of silica gel (30 g) in methylene chloride (80 mL) under rapid stirring, was added 25 drops of 1% aqueous sulfuric acid solution. When the mixture was again homogeneous, acetal **12** (1 g, 3.15 mmol) in CH_2Cl_2 (4 mL) was added. After stirring for one hour, the suspension was filtered and silica gel was rinsed with methylene chloride. The crude product, obtained after concentration in vacuo, was purified by flash chromatography on silica gel using ether/ petroleum ether 1:1 to afford aldehyde **10** (0.76 g, 89%, R_F= 0.43 with ether/petroleum ether 1:1) as a colorless oil. IR (neat): 1701 (CHO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.4 (s, 1H), 7.83-7.52 (m, 4 H), 7.23-6.86 (m, 4 H), 4.57 (q, 1H, J= 6.5 Hz), 4.41-4.25 (dd, 2H, J= 11.3 Hz), 3.80 (s, 3H), 1.48 (d, 3H, J= 6.5 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 191.9 ($\underline{C}$HO), 159.9, 145.2, 136.8, 132.2, 130.3, 129.2, 128.8, 127.3, 113.8 (12 aromatic C), 76.3 (O$\underline{C}H_2$), 70.2 (C_2), 55.0 (O$\underline{C}H_3$), 23.9 (C_1). Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53, H, 6.71. Found: C, 75.50; H, 6.76.

4-[3'-(2"-p-methoxybenzyloxy-ethane)phenyl]-4-hydroxy-but-1-yne **(9)**

To a suspension of aluminium powder (140 mg, 5.2 mmol) and mercuric chloride (13 mg, 0.06 mmol) in THF (4 mL) was added dropwise under rapid stirring and under nitrogen propargyl bromide (1.36 g, 11.2 mmol, 80 wt% solution in toluene) as a solution in anhydrous THF (10 mL). The mixture was cooled to -80°C and aldehyde **10** (0.85 g, 3.15 mmol) in THF (5 mL) was added dropwise. The mixture was stirred 30 minutes at -75°C and water (50 mL) was added followed by diethyl ether (2 x 50 mL). The organic layer was washed twice with water, dried over ($MgSO_4$) and concentrated in vacuo. Flash chromatography on silica gel using ether/ petroleum ether 2:3 afforded homopropargylic alcohol **9** (0.86 g, 88%, R_F= 0.29 with ether/petroleum ether 1:1) as a colorless oil. IR (neat): 3421 (OH), 3293 (C≡CH), 2112 (C≡C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 4H), 7.22 (d, 2H, J= 8.7 Hz), 6.86 (d, 2H, J= 8.7 Hz), 4.90 and 4.89 (t, 1H, J= 6.2 Hz), 4.49 (q, 1H), 4.39-4.21 (dd, 2H), 3.79 (s, 3H), 2.66 (dd, 2H, J= 6.2, 2.7 Hz), 2.07 and 2.06 (t, 1H), 1.45 (d, 3H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 159.1, 143.8, 143.2, 130.6, 129.3, 128.5, 125.7, 124.9, 124.0, 113.8 (aromatic C), 80.9 (C_2), 76.8 (O$\underline{C}H_2$), 72.2 (C_1), 70.9 (C_4), 69.9 ($CH_3\underline{C}HOCH_2$), 55.1 (O$\underline{C}H_3$), 29.2 (C_3), 24.1 ($\underline{C}H_3CHOCH_2$).This (NMR pure) product was used directly for the next step of the synthesis.

4-[3'(2"-p-methoxybenzyloxy-ethane)phenyl]-4-t-butyldimethylsilyloxy-but-1-yne **(8)**

To a stirred solution of homopropargylic alcohol **9** (0.8 g, 2.58 mmol) in anhydrous DMF (5 mL), was added under nitrogen imidazole (0.35 g, 5.16 mmol) and tert-butylchlorodimethylsilane (0.58 g, 3.87 mmol). The reaction mixture was stirred at room temperature for one hour followed by the addition of diethyl ether (20 mL). The organic layer was washed with a saturated aqueous Na_2CO_3 solution, water and dried over $MgSO_4$. After removal of the solvents, the residue was purified by flash chromatography on silica gel using ether/ petroleum ether 2:3 to afford silyl ether **8** (1 g, 94%, R_F= 0.51 with ether/petroleum ether 1:1) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 4H), 7.22 (d, 2H, J= 8.7 Hz), 6.86 (d, 2H , J= 8.7 Hz), 4.83 (t, 1H, J= 6.3 Hz), 4.47 and 4.46 (q, 1H), 4.36-4.18 (dd, 2H), 3.79 (s, 3H), 2.66-2.45 (m, 4H), 1.95 and 1.93 (t, 1H, J= 2.6 Hz), 1.45 and 1.44 (d, 3H, J= 6.5 Hz), 0.88 and 0.87 (2s, 18H), 0.09 to -0.07 (m, 12H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 159.1, 144.2, 143.7, 130.7, 129.3, 128.2, 125.7, 125.5, 125.1, 125.0, 124.0, 123.9, 113.8 (aromatic C), 81.6 (C_2), 76.9, 76.8 ($O\underline{C}H_2$,), 73.8 (C_1), 70.0, 69.9 (CH_3-$\underline{C}HOSi$, C_4), 55.2 ($O\underline{C}H_3$), 30.9 (C_3), 25.8 [$C(\underline{C}H_3)_3$], 24.3, 24.1 [$\underline{C}(CH_3)_3$, $\underline{C}H_3CHOCH_2$], -4.7 and -4.8 $(\underline{C}H_3)_2$. Anal. Calcd. for $C_{26}O_3H_{36}Si$: C, 73.54; H, 8.54. Found: C, 73.33; H, 8.20.

(2Z,4E)-methyl-7-[3'-(2"-p-methoxybenzyloxy-ethane)phenyl]-7-t-butyldimethylsilyloxy-hepta-2,4-dien-1-oate **(5)** *(as mixtures of diastereoisomers)*

a) - Hydroboration: Alkyne **8** (740 mg, 1.79 mmol) and catecholborane (813 mg, 6.7 mmol) was stirred for 24 hours at 90°C before adding 2.5 mL of water. The mixture was stirred overnight at room temperature. The organic compounds were extracted twice with pentane (2x5 mL) ; the organic layers were washed with water and dried over $MgSO_4$. After filtration and concentration in vacuo, we isolated boronic acid **13** (800 mg, 98%) as a colorless oil (mixtures of diastereoisomers). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-6.81 (m, 8H), 5.79 and 5.78 (d, 1H, J= 18 Hz), 4.80-4.50 (m, 2H), 4.34-4.18 (dd, 2H, $OC\underline{H}_2$), 3.79 (s, 3H, $OC\underline{H}_3$), 1.45 (d, 3H, J= 6.4 Hz), 0.88 (m, 9H), 0.10 to -0.09 (m, 6H). This (NMR pure) compound was used directly for the next coupling reaction.

b) - Aqueous 10% thallium hydroxide solution: To a solution of commercially available thallium ethoxide (0.225 mL, 3.6 mmol) cooled to 0°C under argon atmosphere, was added dropwise 0.225 mL water. A white precipitate appeared and was dried in vacuo to remove ethanol formed in the reaction ; 7 mL H_2O was then added to give a 10% thallium hydroxide solution.

c) - Pd ^{0} Coupling reaction: In a two necked-round bottom flask, a solution of (Z)-methyl-3-iodo-propen-1-oate (330 mg, 1.56 mmol) and tetrakis(triphenylphosphine)palladium (448 mg, 0.39 mmol) in 20 mL anhydrous THF was stirred for 30 minutes under nitrogen . In a second flask, 15.3 mL of aqueous 70% thallium hydroxide solution was added to a solution of boronic acid **13** (800 mg) dissolved in anhydrous THF (40 mL). The content of the first flask was then transferred into this boronic acid solution and the resulting mixture was stirred for one hour at room temperature. After quenching with water, extraction with ether, the organic layers were dried and concentrated *in vacuo*. A purification by flash-chromatography on silica gel using ether/ petroleum ether 10:90 afforded diene **5** (520 mg, 60%, R_F= 0.72 with ether/petroleum ether 1:1) as a colorless oil and traces of debenzylated diene (30 mg, 6% , R_F= 0.17 with ether/petroleum ether 1:1). IR (neat): 1719 (CO_2CH_3), 1641 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5H), 7.23-6.87 (m, 4H), 6.50 (t, 1H, J = 11.3 Hz), 6.05 (dt, 1H, J = 7.8 Hz), 5.57 (d, 1H, J = 11.4 Hz), 4.74 (t, 1H, J = 5.8 Hz), 4.46 (q, 1H), 4.35-4.17 (dd, 2H), 3.80 (s, 3H), 3.70 (s, 3H), 2.70-2.41 (m, 2H), 1.44 and 1.43 (d, 3H, J = 6.5 Hz), 0.88-0.87 (2s, 18H), 0.03 to -0.02 (m, 6H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 166.6 ($\underline{C}O_2CH_3$), 159.1 (ipso C), 145-0 (ipso C and C_3), 143.8 (ipso C), 141.4 (C_5), 130.7 (ipso C), 129.2, 129.1, 128.3, 125.4, 125.3, 124.9, 123.8 (aromatic C and C_4), 115.5 (C_2), 113.7 (aromatic C), 76.9, 76.8 ($O\underline{C}H_2$), 74.8 (C_7), 69.9, 65.8 ($CO_2\underline{C}H_3$), 55.1, 44.4 (C_6), 25.8 [$C(\underline{C}H_3)_3$], 24.2, 24.1 [$\underline{C}(CH_3)_3$, $\underline{C}H_3CHOCH_2$], -4.6, -4.8 [$\underline{C}H_3)_2$]. Anal. Calcd. for $C_{30}H_{42}O_5Si$: C, 70.55; H, 8.29. Found: C, 70.24; H, 8.35.

(2Z,4E)-methyl-7-(3'-ethan-2-ol)phenyl-7-t-butyldimethylsilyloxy-hepta-2,4-dien-1-oate **(14)** *(as mixtures of diastereoisomers)*

To a solution of diene **5** (400 mg, 0.8 mmol) in a 18/1 CH_2Cl_2/H_2O mixture (12.6 mL/0.7 mL) was added under stirring 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (273 mg, 1.2 mmol). The reaction mixture was stirred for one hour before being quenched by an aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layers were washed with water, brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2, ether/petroleum ether = 2:3). A mixture of alcohol **16** and anisaldehyde was isolated (300 mg). Anisaldehyde was then eliminated *via* a Kugelrhohr distillation (Bp 7 mbar= 130°C) to afford alcohol **14** (230 mg, 76%, R_F= 0.17 with ether/petroleum ether 1:1) as a colorless oil, (mixtures of diastereoisomers). IR (neat): 3424 (OH), 1703 (CO_2CH_3), 1639 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.38 (m, 5H), 6.52 (t, 1H, J= 11.3 Hz), 6.04 (dt, 1H, J= 7.4 Hz), 5.58 (d, 1H, J= 11.3 Hz), 4.96 and 4.89 (q, 1H, J= 6.4 Hz), 4.74 (dd, 1H, J= 7.1, 5.2 Hz), 3.70 (s, 3H), 2.68-2.45 (m, 2H), 1.48 (d, 3H, J= 6.5 Hz), 0.88, 0.87 (2s, 18H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 166.8 ($\underline{C}O_2CH_3$), 145.9, 145.8 (ipso C), 145.1 (C_3), 144.8 (ipso C), 141.4 (C_5), 128.9, 128.2, 124.7, 124.3, 124.1, 122.9, 122.7 (aromatic C and C_4), 115.6 (C_2), 74.7 (C_7), 70.2 ($CH_3\underline{C}HOH$), 44.3 (C_6), 25.7 [$C(CH_3)_3$], 25.2 [$\underline{C}H_3CHOH$ and $\underline{C}(CH_3)_3$], -4.7, -4.8 ($(\underline{C}H_3)_2$). Anal. Calcd. for $C_{22}H_{34}O_4Si$: C, 67.65; H. 8.77. Found: C, 67.36; H, 8.71.

(2Z,4E)-methyl-7-(3'-ethan-1-one)phenyl-7-t-butydimethylsilyloxy-hepta-2,4-dien-1-oate **(2)**

To a stirred solution of pyridinium dichromate (526 mg, 1.39 mmol) in anhydrous methylene chloride (5 ml) containing 3g activated molecular sieves (4Å powder) under nitrogen, was added alcohol **14** (230 mg, 0.6 mmol) as a solution in CH_2Cl_2 (2 mL). The mixture was stirred for 2 hours before being filtered through silica gel and the filtrate was concentrated *in vacuo*. Flash chromatography on silica gel using ether/ petroleum ether 2:3 afforded ketone **2** (190 mg, 82%, R_F= 0.47 with ether/petroleum ether 1:1) as a colorless oil. . IR (neat): 1718 (CO_2CH_3), 1688 ($COCH_3$), 1641 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88-7.29 (m, 5H), 6.49 (t, 1H, J= 11.4 Hz), 5.99 (dt, 1H, J= 7.4 Hz), 5.56 (d, 1H, J= 11.4 Hz), 4.78 (dd, 1H, J= 7.1, 5.2 Hz), 3.68 (s, 3H), 2.58 (s, 3H), 2,56 (m, 2H), 0.86 (s, 9H), 0.05 to -0.02 (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 198.0 ($\underline{C}OCH_3$), 166.8 ($\underline{C}O_2CH_3$), 145,7 (ipso C), 144.8 (C_3), 140,7 (C_5), 137,1 (ipso C), 130.8, 129.4, 128.5, 127.3, 125.9 (aromatic C and C_4), 115.9 (C_2), 74.3 (C_7), 51.1 ($CO_2\underline{C}H_3$), 44.3, 26.7 ($CO\underline{C}H_3$), 25.8 [$C(\underline{C}H_3)_3$], 18.2 [$\underline{C}(CH_3)_3$], -4.7, -4.9 ($(\underline{C}H_3)_2$). EIHRMS: the intensity of molecular ion m/z for $C_{22}H_{32}O_4Si$ was too low to be measured accurately. For $[M-C(CH_3)_3]^+$ calc. 331.1366, found 331.1364.

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