Double diastereodifferentiation in the Mukaiyama aldol reactions of π-allyltricarbonyliron lactone complexes: 1,7- *vs.* 1,2-asymmetric induction

Steven V. Ley,* Liam R. Cox and Julia M. Worrall

Department of Chemistry, University of Cambridge, Lensfield Rd, Cambridge, UK CB2 1EW

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The Mukaiyama aldol reactions of trimethylsilyl enol ether-substituted π-allyltricarbonyliron lactone complexes with chiral aldehydes under $BF_3{\cdot}OEt_2$ activation proceed with high levels of substrate control (1,7-induction), overriding possible 1,2-induction from the aldehyde stereogenic centre. When $TiCl_4$ is used as the Lewis acid with (*R*)- or (*S*)-2-benzyloxypropanal, however, chelation control (1,2-induction) is observed, overriding the templating effect of the iron complex.

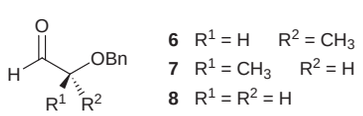
In the aldol reaction of an unsubstituted enolate or enolate equivalent with an aldehyde, asymmetric induction is achieved if the nucleophile preferentially recognises one face of the aldehyde. This can occur if the aldehyde is chiral, so that its faces are diastereotopic, or if it is achiral (so that its faces are enantiotopic) and interacts with a chiral environment in the course of the reaction.[1] In the Mukaiyama aldol reaction of a chiral aldehyde with an achiral silyl enol ether, the highest diastereofacial selectivities are usually observed when the aldehyde bears an α-heteroatom substituted stereogenic centre which is tethered to the carbonyl group *via* a chelating Lewis acid (Fig. 1a).[2] The diastereotopic faces of the resulting conformationally constrained electrophile are easily distinguishable. In contrast, lower selectivity is usually observed in the reactions of *linear* chiral aldehyde–Lewis acid complexes with achiral silyl enol ethers.[3] The Felkin-Anh model is useful for qualitatively predicting the stereochemical outcome of these reactions.[4] In this model both the relative sizes of substituents at the α-stereogenic centre and the energies of their σ* orbitals are considered. An alkoxy substituent takes the place of the "large" group in the model at the expense of an alkyl or phenyl group (Fig. 1b).

The possibility of double stereodifferentiation arises when both aldehyde and enol ether reactants are chiral entities.[5] The stereochemical preference of the aldehyde can then either oppose or reinforce that which the enol ether would express in a reaction with an achiral aldehyde. In the mismatched case, the stereoselectivity observed can provide an indication of the relative influence of the directing groups on each reactant.

The Mukaiyama aldol reactions of trimethylsilyl enol ether-substituted η^4-dienetricarbonyliron complexes have been extensively studied by Franck-Neumann *et al.* These complexes afforded low to moderate diastereoselectivity in their reactions with achiral aldehydes under $BF_3{\cdot}OEt_2$ or $TiCl_4$ activation.[6,7] Using enantiomerically enriched (*S*)-2-benzyloxypropanal under $TiCl_4$ activation, however, complete 1,2-induction (chelation control) from the aldehyde stereogenic centre was observed, the inherent chirality of the diene complex exerting no control over the reaction.[6,8] Use of a racemic η^4-diene complex in this reaction resulted in formation of only two of the four possible diastereoisomers, differing in the configuration of the metal–ligand attachment. Separation of the diastereoisomers therefore comprised a novel procedure for the resolution of the η^4-dienetricarbonyliron complexes (Fig. 2).

We have recently shown that trimethylsilyl enol ether groups appended to the allyl ligand of *endo*-substituted π-allyltricarbonyliron lactone complexes react with achiral aldehydes with excellent diastereoselectivity under $BF_3{\cdot}OEt_2$ activation.[9,10] The transition metal complex acts as a rigid scaffold, blocking one face of the silyl enol ether functionality while creating a chiral environment for recognition of the aldehyde on the other face (Fig. 3). We wondered whether this templating effect would be sufficiently powerful to override the normal stereochemical preference of an aldehyde bearing an α-stereogenic centre.

(*R*)-Trimethylsilyl enol ether **2** was prepared in greater than 96% enantiomeric excess from the known methyl ketone complex **1**[11] by treatment with TMSOTf in the presence of Et_3N in CH_2Cl_2 at 0 °C. This was reacted with both (*R*)- and (*S*)-2-benzyloxypropanals **6** and **7** according to our standard



procedure, under $BF_3{\cdot}OEt_2$ activation.[12] The resulting mixtures of TMS-protected and unprotected aldol products were desilylated using HF–pyridine during the work-up and the

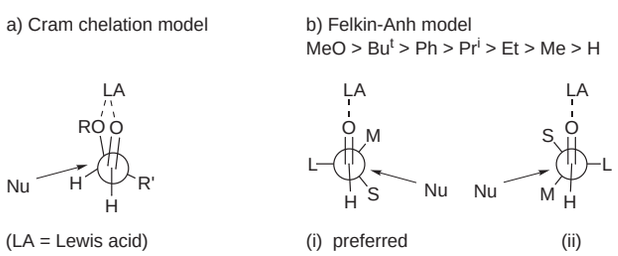


Fig. 1

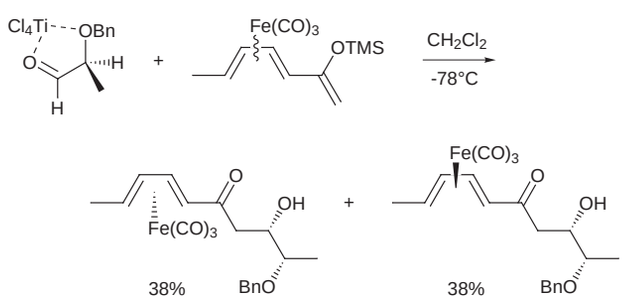
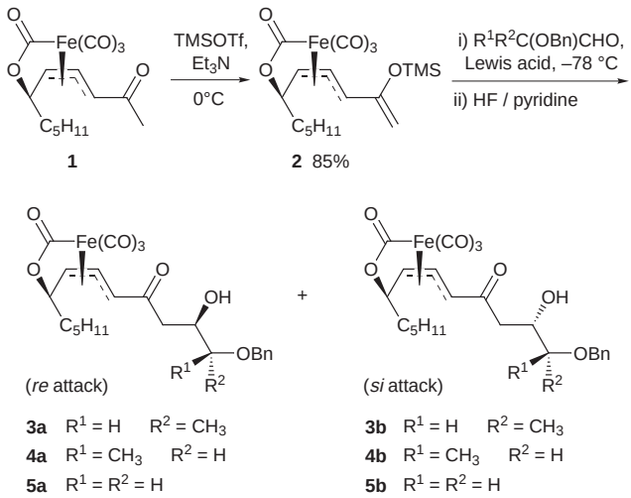


Fig. 2

Table 1 Reaction of silyl enol ether complex **2** with α-benzyloxy aldehydes



1 **2** 85%

3a $R^1 = H$ $R^2 = CH_3$
4a $R^1 = CH_3$ $R^2 = H$
5a $R^1 = R^2 = H$

3b $R^1 = H$ $R^2 = CH_3$
4b $R^1 = CH_3$ $R^2 = H$
5b $R^1 = R^2 = H$

Entry	Aldehyde	R^1	R^2	Lewis acid[a]	Major product	Yield (%)	De (%)[b]
1	**6** (*R*)	H	CH_3	$BF_3{\cdot}OEt_2$	**3a**	58	60
2	**7** (*S*)	CH_3	H	$BF_3{\cdot}OEt_2$	**4a**	69	51
3	**8**	H	H	$BF_3{\cdot}OEt_2$	**5a**	47	55
4	**6** (*R*)	H	CH_3	$TiCl_4$	**3a**	29	93
5	**7** (*S*)	CH_3	H	$TiCl_4$	**4b**	25	90
6	**8**	H	H	$TiCl_4$	—	22	0

[a] $BF_3{\cdot}OEt_2$-mediated reactions were carried out in a 4:1 Et_2O–CH_2Cl_2 mixture. $TiCl_4$-mediated reactions were performed in neat CH_2Cl_2. [b] Diastereoisomeric excess determined by comparison of integrals in the ^1H NMR spectrum of the crude reaction mixture.

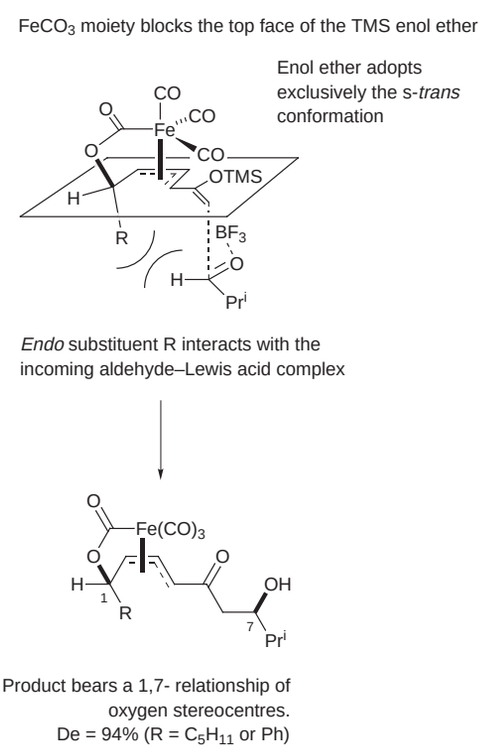


Fig. 3

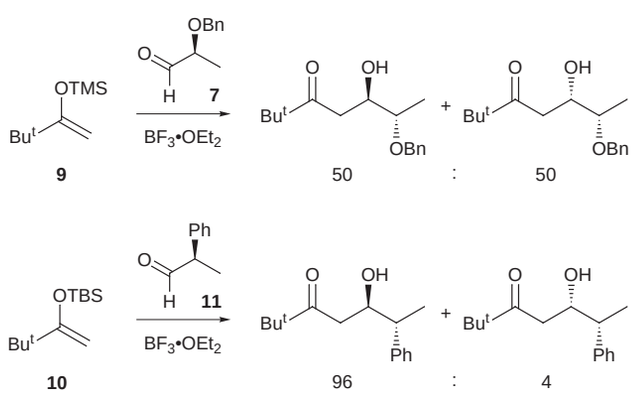


Fig. 4

diastereoisomeric excesses determined by comparison of integrals in the ^1H NMR (600 MHz) spectrum of the crude product (Table 1, entries 1 and 2).

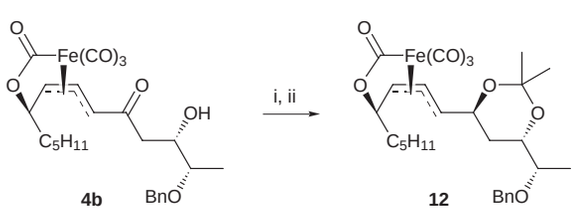
In both cases the major diastereoisomer obtained was that arising from *re* face attack on the aldehyde. These results are consistent with substrate-controlled reactions, reflecting the diastereofacial preference of the iron complex. Interestingly, the levels of stereocontrol were significantly lower than those obtained previously with achiral α-branched aldehydes.[9,12] Furthermore the reaction of the predicted mismatched pair (*R*)-**2** and **6** (based on the ordering of the substituents OBn > Me > H in the Felkin-Anh model) proceeded with slightly *better* diastereoselectivity than the predicted matched pair (*R*)-**2** and **7**.

A survey of the literature revealed an example in which 2-benzyloxypropanal failed to show a diastereofacial preference in a $BF_3{\cdot}OEt_2$-mediated Mukaiyama aldol reaction. Reaction with achiral silyl enol ether **9** generated a 1:1 mixture of diastereoisomers.[13] This result can be contrasted with the reaction of (*R*)-2-phenylpropanal **11** with the similar silyl enol ether **10**, which proceeded with 92% diastereoisomeric excess (Fig. 4).[14] Anh and Eisenstein have suggested that the two minimum energy conformations (i) and (ii) (Fig. 1b) are of comparable intrinsic energy and that stereodifferentiation arises from differential interactions of the attacking nucleophile with the small and medium substituents.[4b] In the aldehydes **7** and **11**, however, the small and medium substituents are the same (hydrogen and methyl respectively). This suggests that there may be an alternative reactive conformation of similar energy available to 2-benzyloxypropanal **7**.

In order to rule out the stereochemical bias of the chiral aldehydes as the origin of the relatively low diastereoselectivity, the achiral α-heterosubstituted aldehyde **8** was reacted with **2** for comparison (Table 1, entry 3). Once again, only moderate diastereoselectivity (55% de) was obtained. Aldehyde **8** is less sterically demanding than its chiral relatives **6** and **7** so reduced diastereoselectivity would be predicted on these grounds alone. However, the selectivity obtained also compares unfavourably with the reaction of the straight chain aliphatic aldehyde hexanal, which reacted with **2** in 82% diastereoisomeric excess.[9,12] The reduced selectivity in the reactions of aldehydes **6**–**8** would therefore appear to be caused by a steric or electronic effect of the α-benzyloxy group on the relative energies of competing transition states.

A more direct comparison of our system with the η^4-dienetricarbonyliron complexes studied by Franck-Neumann would require the reactions with (*R*)- and (*S*)-2-benzyloxypropanal to be carried out under $TiCl_4$ activation, with the potential for chelation control. We have previously found that the use of $TiCl_4$ in the Mukaiyama aldol reactions of π-allyltricarbonyliron lactone complexes results in low conversions and significant hydrolysis of the silyl enol ether starting material. Decomposition was found to occur over long reaction times or on raising the temperature above −78 °C. It was felt, however, that the presence of a coordinating α-oxygen substituent in the aldehyde might moderate the Lewis acidity of the titanium and improve the efficiency of the reaction. The addition of $TiCl_4$-complexed (*R*)- and (*S*)-2-benzyloxypropanals **6** and **7** to silyl enol ether **2** was therefore attempted (Table 1, entries 4 and 5).

The $TiCl_4$-mediated reactions proceeded very slowly and only around 25% conversion was achieved after several hours at −78 °C. Apparent hydrolysis of the silyl enol ether also occurred under the reaction conditions, resulting in the isolation of methyl ketone **1** as the major product. The aldol products in both cases were isolated in excellent diastereoisomeric excess. Interestingly, the diastereofacial preference of the addition was found to be governed almost entirely by the aldehyde, the inherent *re* face preference of the silyl enol ether having no significant effect. The relative stereochemistry of complex **4b** (entry 5) was confirmed as that arising from *si* attack by highly stereoselective reduction of the ketone group[15] and formation of the acetonide **12** (Scheme 1). Analysis of the



4b **12**

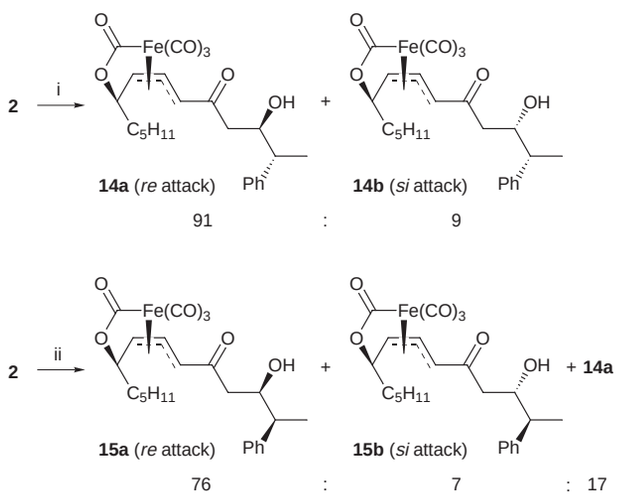
Scheme 1 *Reagents and conditions*: i. $AlBu^i_3$, CH_2Cl_2, 0 °C, 2 h; ii. PPTS, 2,2-dimethoxypropane, DMF, 25 °C, 4 h, 65% yield from **4b**.

^{13}C NMR spectrum of the acetonide revealed chemical shifts for the acetal carbon at 101.2 ppm and for the acetal methyl carbons at 23.7 and 24.8 ppm, which are characteristic of an *anti* diol.[16–18]

A number of different factors could contribute to the shift of stereochemical control from the iron lactone complex to the aldehyde. Firstly, the conformationally defined, cyclic aldehyde–Lewis acid complex has a very strong diastereofacial preference, as illustrated by the earlier work of Franck-Neumann. Also, *gauche* interactions and/or remote interactions of the *endo* substituent with the Lewis acid may be important for *re* face stereoselection in the BF_3-mediated reactions.[10,12] In the chelation controlled reactions, the Lewis acid is complexed to the oxygen lone pair *syn* to the aldehyde substituent, while non-chelating Lewis acids such as BF_3 occupy the *anti* lone pair for steric reasons.[19] This affects the shape of the Lewis acid–aldehyde complex and will therefore alter its interaction with the iron lactone template. Furthermore, the directing effect of the iron complex would appear to be weakened by the presence of an α-alkoxy substituent on the aldehyde (*vide supra*) and this could be exacerbated by Lewis acid complexation.

The reaction of **2** with the $TiCl_4$-complexed achiral aldehyde **8** (Table 1, entry 6) produced a roughly 1:1 mixture of diastereoisomeric aldol products. This suggests that it is not only the strong diastereofacial bias of the aldehyde which forces the *re* face preference of the iron lactone template to be overturned; this preference is already lost as a result of electronic and conformational differences in the $TiCl_4$-complexed aldehyde.

The aldol reactions of (*R*)-**2** with BF_3-complexed (*R*)- and (*S*)-2-phenylpropanals **11** and **13**, which have shown high levels of Felkin-Anh control in reactions with achiral nucleophiles (see Fig. 4), were also carried out. The (*R*)-aldehyde **11** prefers *re* face attack and is therefore the matched isomer, while the (*S*)-aldehyde **13** provides the mismatched case (Scheme 2). In the



Scheme 2 *Reagents and conditions*: i. premixed (*R*)-2-phenylpropanal (**11**) and $BF_3{\cdot}OEt_2$ (1:1, 1.5 equiv.), Et_2O–light petroleum 4:1, −78 °C, 6 h, then HF–pyridine, THF, 25 °C, 0.5 h, 59% combined yield; ii. premixed (*S*)-2-phenylpropanal (**13**) and $BF_3{\cdot}OEt_2$ (1:1, 1.5 equiv.), Et_2O–light petroleum 4:1, −78 °C, 6 h, then HF–pyridine, THF, 25 °C, 0.5 h, 53% combined yield.

matched case, the expected major diastereoisomer **14a** was obtained with 82% diastereoisomeric excess. As had been hoped, in the mismatched case similarly high diastereoselectivity (83% de) was obtained. The major diastereoisomer **15a** proved to be that resulting from 1,7-induction by the substrate, *i.e. re* face attack, while the minor isomer **15b** was that arising from *si* face attack in accordance with the Felkin-Anh model. A third product was also obtained from this reaction, which was spectroscopically identical to **14a** and was therefore attributed to isomerisation of the aldehyde prior to the aldol addition. Such isomerisation would allow the reaction to proceed in the matched sense and could be explained in terms of a kinetic resolution effect if the rate of the matched reaction is significantly greater than the rates of the mismatched reactions. Any racemisation of the aldehyde under the reaction conditions would then be amplified by the more rapid consumption of the (*R*)-2-phenylpropanal generated.

In summary, the Mukaiyama aldol reactions of silyl enol ether-functionalised *endo* π-allyltricarbonyliron lactone complexes with chiral aldehydes under $BF_3{\cdot}OEt_2$ activation have been shown to proceed with high levels of 1,7-asymmetric induction from the lactone tether stereocentre. The templating effect of the iron complex leads to selective attack on the *re* face

of the aldehyde, overriding where necessary the diastereofacial preference of the aldehyde as predicted by the Felkin–Anh model.

Aldehydes bearing an α-benzyloxy substituent react with lower diastereoselectivity than simple aliphatic or aromatic aldehydes. Activation of these aldehydes using $TiCl_4$ instead of BF_3 results in slower reactions on which the iron complex appears to exert no diastereocontrol. The asymmetry at the α-centre of the aldehyde is then the controlling factor and high diastereoselectivity is observed in accordance with the Cram chelation model. The breakdown in *re* face recognition by the iron lactone template may be partly attributed to the different shape and polarity of the chelated aldehyde–Lewis acid complex.

There are a number of other examples of aldol reactions in which chiral enolate equivalents have proved able to overturn the diastereofacial bias of chiral aldehydes.[20] Nevertheless, the results obtained with π-allyltricarbonyliron lactone complex **2** where the source of induction is so remote seem quite remarkable. The products of the aldol reaction can be decomplexed in a variety of ways, to afford stereodefined β- and δ-lactones,[21] (*E*,*E*)-dienes[21] or enediols,[22] so the reaction represents a powerful tool for the synthesis of highly functionalised organic molecules.

Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker DRX-600 or DPX-200 spectrometers and are reported as follows: chemical shift, δ (ppm), [number of protons, multiplicity, coupling constant J (Hz), and assignment]. Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used as the internal reference. ^{13}C NMR spectra were recorded in $CDCl_3$, at 150 or 50 MHz on Bruker DRX-600 or DPX-200 spectrometers, respectively, using the central resonance of $CDCl_3$ (δ_C = 77.0 ppm) as the internal reference. Infra-red spectra were recorded on Perkin-Elmer 983G or FTIR 1620 spectrometers. Mass spectra were obtained on a Kratos MS890MS spectrometer or a Bruker BIOAPEX 4.7 T FTICR spectrometer. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured with an Optical Activity AA-1000 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Flash column chromatography was carried out using Merck Kieselgel (230–400 mesh) unless otherwise indicated. Analytical thin layer chromatography (TLC) was performed using precoated glass-backed plates (Merck Kieselgel 60 F254) and visualised by UV, acidic ammonium molybdate(IV) or acidic potassium permanganate solutions. Petrol refers to petroleum ether bp 40–60 °C, which was distilled prior to use, and ether (Et_2O) refers to diethyl ether.

All reactions were carried out under an argon atmosphere in oven-dried glassware unless otherwise stated. Ether and THF were distilled from sodium benzophenone ketyl; CH_2Cl_2 from calcium hydride. Other reagents and solvents were purified using standard procedures.[23] Aqueous solutions are saturated unless otherwise specified.

Methyl ketone complex **1** (>96% ee) was prepared as previously described.[11]

[(3*E*,5*S*,6*R*)-6-(Carbonyloxy-κ*C*)-2-trimethylsilyloxy-(3,4,5-η)-undeca-1,3-dien-5-yl]tricarbonyliron 2

Et_3N (0.046 g, 0.46 mmol) and trimethylsilyl triflate (0.083 g, 0.37 mmol) were added sequentially to a cooled (0 °C) solution of methyl ketone complex **1** (0.100 g, 0.29 mmol) in CH_2Cl_2 (1 ml) and the reaction was stirred at 0 °C for 2 h. The reaction mixture was then directly subjected to flash column chromatography (Florisil; 20% Et_2O–petrol) to afford **2** as a silver grey crystalline solid (0.096 g, 80%). $[\alpha]_D^{26}$ −184.7 (*c* 1.00 in $CHCl_3$); mp 77–80 °C (Found: C, 51.38; H, 6.26. $C_{18}H_{26}FeO_6Si$ requires C, 51.17; H, 6.21%); ν_{max}(Nujol mull)/cm^{-1} 2922 (CH), 2853 (CH), 2077 (CO), 2011 (CO), 2002 (CO), 1685 (C=O), 1654 (C=C), 1605, 1462; δ_H(200 MHz) 0.25 (9H, s, $Si(CH_3)_3$), 0.89 (3H, t, *J* 6.0, 11-H × 3), 1.12–1.66 (8H, m, 7-H × 2, 8-H × 2, 9-H × 2, 10-H × 2), 4.26 (1H, apparent q, *J* 6.4, 6-H), 4.33–4.43 (2H, m, 1-H × 1, 3-H), 4.57–4.69 (2H, m, 1-H × 1, 5-H), 5.00 (1H, dd, *J* 11.9, 8.5, 4-H); δ_C(50 MHz) −0.3 ($Si(CH_3)_3$), 14.0 (CH_3), 22.5 (CH_2), 26.7 (CH_2), 31.6 (CH_2), 36.8 (CH_2), 76.2 (CH), 77.4 (CH), 79.4 (CH), 85.6 (CH), 94.3 (CH_2), 153.8 (quat. C), 204.3 (CO), 205.5 (CO), 206.2 (CO), 209.2 (CO); *m*/*z* (FAB) 445 [(M + Na)$^+$, 14%], 423 (MH, 100), 339 (MH − 3CO, 53), 311 (MH − 4CO, 88), 239 (18), 165 (13), 145 (77) [Found: (MH$^+$) 423.0947. $C_{18}H_{27}FeO_6Si$ requires *M*H, 423.0926].

General procedure for the Mukaiyama aldol reactions using BF_3·OEt_2; synthesis of complexes 3–5, 14 and 15

For a 0.20 mmol scale reaction: BF_3·OEt_2 (1.5 equiv.) was added to a stirred solution of the aldehyde (1.5 equiv.) in Et_2O (1 ml) at room temperature. After 1 minute, the solution was added dropwise to a cooled (−78 °C) solution of silyl enol ether **2** (1.0 equiv.) in Et_2O–CH_2Cl_2 (2 and 0.75 ml) and stirred at −78 °C for 3–24 h. Et_3N (1.5 equiv.) was then added with vigorous stirring. After 2 minutes the mixture was filtered through Celite eluting with Et_2O–CH_2Cl_2 (20 ml, 4 : 1) and then concentrated *in vacuo*. The residue was diluted with THF (0.4 ml) and treated with HF–pyridine (0.4 ml of a *ca.* 2.25 M soln. in THF) for 30 minutes at room temperature. The mixture was then poured into aqueous $NaHCO_3$ (5 ml) and extracted with Et_2O (3 × 5 ml), the organic fractions were washed with brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The de was determined by ^{1}H NMR analysis of the crude reaction mixture and subsequent flash chromatography afforded the non-silylated aldol products. In cases where an inseparable mixture of diastereoisomers was obtained, data is reported on the mixtures. Assignments for the minor diastereoisomer are primed (′).

[(8*E*,6*R*,7*S*,12*R*,13*R*)-13-Benzyloxy-6-(carbonyloxy-κ*C*)-12-hydroxy-10-oxo-(7,8,9-η)-tetradec-8-en-7-yl]tricarbonyliron 3a and [(8*E*,6*R*,7*S*,12*S*,13*R*)-13-benzyloxy-6-(carbonyloxy-κ*C*)-12-hydroxy-10-oxo-(7,8,9-η)-tetradec-8-en-7-yl]tricarbonyliron 3b. Prepared according to the general procedure using TMS enol ether **2** (0.074 g, 0.18 mmol), (*R*)-2-benzyloxypropanal and BF_3·OEt_2. After 9 h, the reaction was quenched with Et_3N and the products were desilylated with HF–pyridine. Flash chromatography (eluent: 20–70% Et_2O–petrol; gradient) afforded *aldol complexes* **3a** and **3b** as an inseparable mixture (**3a** : **3b** 80 : 20; 0.053 g, 58%); ν_{max}(film)/cm^{-1} 3456 (OH), 2930 (CH), 2085 (CO), 2028 (CO), 1681 (C=O), 1497; δ_H(600 MHz) 0.89 (3H, t, *J* 6.6, 1-H × 3), 1.19–1.51 {9H, m, [including 1.25 (2.4H, d, *J* 6.0, 14-H × 3), 1.23 (0.6H, d, *J* 6.4, 14-H′ × 3)], 2-H × 2, 3-H × 2, 4-H × 2, 14-H × 3}, 1.54–1.62 (2H, m, 5-H × 2), 2.75 (0.8H, d, *J* 3.5, OH), 2.77 (0.2H, d, *J* 6.2, OH′), 2.85 (2H, d, *J* 6.0, 11-H × 2), 3.56 (0.8H, apparent qn, *J* 5.7, 13-H), 3.58–3.63 (0.2H, m, 13-H′), 3.84 (0.2H, d, *J* 11.4, 9-H′), 3.90 (0.8H, d, *J* 11.2, 9-H), 4.11–4.16 (0.8H, m, 12-H), 4.16–4.20 (0.2H, m, 12-H′), 4.34 (1H, apparent q, *J* 5.9, 6-H), 4.46 (0.8H, d, *J* 11.6, C*H*HPh), 4.52 (0.2H, d, *J* 11.7, C*H*HPh′), 4.63 (0.2H, d, *J* 11.7, CH*H*Ph′), 4.67 (0.8H, d, *J* 11.6, CH*H*Ph), 5.01 (1H, dd, *J* 8.5, 4.5, 7-H), 5.54 (1H, dd, *J* 11.2, 8.5, 8-H), 7.27–7.38 (5H, m, Ph); δ_C(150 MHz) 13.9 (CH_3), 15.0 (CH_3), 15.1 (CH_3′), 22.4 (CH_2), 26.5 (CH_2), 31.5 (CH_2), 36.6 (CH_2), 45.0 (CH_2′), 46.0 (CH_2), 66.0 (CH), 70.6 (CH), 70.8 (CH′), 71.0 (CH_2), 76.7 (CH), 76.8 (CH), 84.5 (CH), 84.8 (CH′), 92.1 (CH), 127.8 (2 × CH, Ar), 128.5 (CH, Ar), 138.1 (quat. C, Ar), 199.7 (CO), 202.4 (CO), 202.5 (CO′), 203.2 (CO), 204.3 (CO′), 204.6 (CO), 204.9 (CO′), 207.8 (CO); *m*/*z* (FAB) 515 (MH$^+$, 9%), 487 (MH − CO, 6), 457 (10), 425 (11), 403 (MH − 4CO, 14), 385 (MH − 4CO − H_2O, 100), 295 (MH − 4CO − OH − CH_2Ph, 47), 237 (34) [Found: (MH$^+$ − 4CO − H_2O) 385.1481. $C_{21}H_{29}FeO_3$ requires *M*H − 4CO − H_2O, 385.1466].

[(8*E*,6*R*,7*S*,12*R*,13*S*)-13-Benzyloxy-6-(carbonyloxy-κ*C*)-12-hydroxy-10-oxo-(7,8,9-η)-tetradec-8-en-7-yl]tricarbonyliron 4a and [(8*E*,6*R*,7*S*,12*S*,13*S*)-13-benzyloxy-6-(carbonyloxy-κ*C*)-12-hydroxy-10-oxo-(7,8,9-η)-tetradec-8-en-7-yl]tricarbonyliron 4b. Prepared according to the general procedure using TMS enol ether **2** (0.075 g, 0.18 mmol), (*S*)-2-benzyloxypropanal and $BF_3{\cdot}OEt_2$. After 6.5 h, the reaction was quenched with Et_3N and the products were desilylated with HF–pyridine. Flash chromatography (eluent: 30–50% Et_2O–petrol; gradient) afforded *aldol complexes* **4a** and **4b** as an inseparable mixture (**4a**:**4b** 76:24; 0.062 g, 69%); ν_{max}(film)/cm^{-1} 3470 (OH), 2930 (CH), 2862 (CH), 2088 (CO), 2020 (CO), 1668 (C=O), 1497; δ_H(600 MHz) 0.88 (3H, t, *J* 6.9, 1-H × 3), 1.25 (3H, d, *J* 6.3, 14-H × 3), 1.26–1.60 (8H, m, 2-H × 2, 3-H × 2, 4-H × 2, 5-H × 2), 2.70 (0.76H, d, *J* 4.5, OH), 2.78 (0.24H, dd, *J* 16.2, 2.6, 11-H′ × 1), 2.84 (0.76H, dd, *J* 17.2, 9.5, 11-H × 1), 2.91 (0.24H, d, *J* 4.5, OH′), 2.93–2.98 {1H, m, [including 2.96 (0.76H, dd, *J* 17.2, 2.7)], 11-H × 1}, 3.53 (0.24H, apparent qn, *J* 5.7, 13-H′), 3.57 (0.76H, apparent qn, *J* 5.8, 13-H), 3.89 (1H, d, *J* 11.1, 9-H), 4.08–4.12 (0.24H, m, 12-H′), 4.18–4.22 (0.76H, m, 12-H), 4.35 (1H, apparent q, *J* 5.7, 6-H), 4.47 (0.24H, d, *J* 11.6, C*H*HPh′), 4.52 (0.76H, d, *J* 11.6, C*H*HPh), 4.65 (0.76H, d, *J* 11.6, CH*H*Ph), 4.68 (0.24H, d, *J* 11.6, CH*H*Ph′), 5.02 (1H, dd, *J* 8.7, 4.6, 7-H), 5.53–5.59 {1H, m, [including 5.57 (0.76H, dd, *J* 11.1, 8.7)], 8-H}, 7.27–7.38 (5H, m, Ph); δ_C(50 MHz) 13.9 (CH_3), 15.1 (CH_3), 22.4 (CH_2), 26.5 (CH_2), 31.4 (CH_2), 36.6 (CH_2), 45.7 (CH_2), 65.8 (CH), 70.2 (CH), 70.9 (CH_2), 76.7 (CH), 77.0 (CH), 84.6 (CH), 92.1 (CH), 127.7 (2 × CH, Ar), 128.4 (CH, Ar), 138.2 (quat. C, Ar), 199.6 (CO), 202.4 (CO), 203.8 (CO), 204.5 (CO), 207.8 (CO); *m*/*z* (FAB) 385 (MH − 4CO − H_2O, 24%), 295 (MH − 4CO − OH − CH_2Ph, 6), 133 (100) [Found: (MH − 4CO − H_2O) 385.1475. $C_{21}H_{29}FeO_3$ requires *M*H − 4CO − H_2O, 385.1466].

[(5*E*,2*R,7*S**,8*R**)-1-Benzyloxy-8-(carbonyloxy-κ*C*)-2-hydroxy-4-oxo-(5,6,7-η)-tridec-5-en-7-yl]tricarbonyliron 5a and [(5*E*,2*S**,7*S**,8*R**)-1-benzyloxy-8-(carbonyloxy-κ*C*)-2-hydroxy-4-oxo-(5,6,7-η)-tridec-5-en-7-yl]tricarbonyliron 5b.** Prepared according to the general procedure using *racemic* TMS enol ether **2**[12] (0.065 g, 0.15 mmol), benzyloxyacetaldehyde and $BF_3{\cdot}OEt_2$. After 4.5 h, the reaction was quenched with Et_3N and the products were desilylated with HF–pyridine. Flash chromatography (eluent: 40–60% Et_2O–petrol; gradient) afforded *aldol complexes* **5a** and **5b** as an inseparable mixture (**5a**:**5b** 77:23; 0.036 g, 47%); ν_{max}(film)/cm^{-1} 3406 (OH), 2927 (CH), 2094 (CO), 2046 (CO), 2029 (CO), 1672 (C=O); δ_H(600 MHz) 0.88 (3H, t, *J* 6.9, 13-H × 3), 1.23–1.51 (6H, m, 10-H × 2, 11-H × 2, 12-H × 2), 1.54–1.63 (2H, m, 9-H × 2), 2.80 (0.77H, d, *J* 3.8, OH), 2.82 (0.23H, d, *J* 3.6, OH′), 2.84–2.94 (1.77H, m, 3-H × 2, 3-H′ × 1), 2.98 (0.23H, dd, *J* 16.9, 8.6, 3-H′ × 1), 3.46–3.57 (2H, m, 1-H × 2), 3.85 (0.23H, d, *J* 11.0, 5-H′), 3.88 (0.77H, d, *J* 11.1, 5-H), 4.35 (1H, apparent q, *J* 5.7, 2-H), 4.36–4.41 (1H, m, 8-H), 4.55–4.60 (2H, AB system, J_{AB} 12.0, C*H*$_2$Ph), 5.03 (1H, dd, *J* 8.6, 4.6, 7-H), 5.54–5.58 {1H, m, [including 5.57 (0.77H, dd, *J* 11.1, 8.6)], 6-H}, 7.28–7.38 (5H, m, Ph); δ_C(50 MHz) 13.9 (CH_3), 22.4 (CH_2), 26.4 (CH_2), 31.4 (CH_2), 36.6 (CH_2), 46.5 (CH_2), 65.7 (CH), 66.7 (CH), 73.2 (CH_2), 73.4 (CH_2), 76.7 (CH), 84.6 (CH), 92.1 (CH), 127.7 (CH, Ar), 127.8 (CH, Ar), 128.4 (CH, Ar), 137.7 (quat. C, Ar), 199.5 (CO), 202.2 (CO), 203.2 (CO), 204.3 (CO), 207.7 (CO); *m*/*z* (FAB) 501 (MH$^+$, 23%), 473 (MH − CO, 6), 411 (M − CHPh, 11), 388 (M − 4CO, 11), 371 (MH − 4CO − H_2O, 100) [Found: (MH$^+$) 501.1255. $C_{24}H_{29}FeO_8$ requires *M*H, 501.1212].

[(8*E*,6*R*,7*S*,12*R*,13*R*)-6-(Carbonyloxy-κ*C*)-12-hydroxy-10-oxo-13-phenyl-(7,8,9-η)-tetradec-8-en-7-yl]tricarbonyliron 14a and [(8*E*,6*R*,7*S*,12*S*,13*R*)-6-(carbonyloxy-κ*C*)-12-hydroxy-10-oxo-13-phenyl-(7,8,9-η)-tetradec-8-en-7-yl]tricarbonyliron 14b. Prepared according to the general procedure using TMS enol ether **2** (0.044 g, 0.10 mmol), (*R*)-2-phenylpropanal and $BF_3{\cdot}OEt_2$. After 6 h, the reaction was quenched with Et_3N and the products were desilylated with HF–pyridine. Flash chromatography (eluent: 30–50% Et_2O–petrol; gradient) afforded *aldol complexes* **14a** and **14b** as an inseparable mixture (**14a**:**14b** 91:9; 0.029 g, 59%); ν_{max}(film)/cm^{-1} 3448 (OH), 2930 (CH), 2090 (CO), 2021 (CO), 1673 (C=O), 1495; δ_H(200 MHz) 0.87 (3H, t, *J* 6.4, 1-H × 3), 1.15–1.61 {11H, m, [including 1.40 (3H, d, *J* 6.9, 14-H × 3)], 2-H × 2, 3-H × 2, 4-H × 2, 5-H × 2, 14-H × 3}, 2.40 (0.09H, d, *J* 3.5, OH′), 2.57–2.93 (3.91H, m, 11-H × 2, 13-H, OH), 3.71 (0.91H, d, *J* 11.2, 9-H), 3.87 (0.09H, d, *J* 11.2, 9-H′), 4.17–4.37 (2H, m, 6-H, 12-H), 4.95–5.04 {1H, m, [including 4.99 (0.91H, dd, *J* 8.7, 4.4)], 7-H}, 5.46–5.61 {1H, m, [including 5.51 (0.91H, dd, *J* 11.2, 8.7)], 8-H}, 7.18–7.38 (5H, m, Ph); δ_C(150 MHz) 13.9 (CH_3), 17.5 (CH_3), 22.4 (CH_2), 26.5 (CH_2), 31.4 (CH_2), 36.6 (CH_2), 45.8 (CH), 48.3 (CH_2), 65.7 (CH), 72.1 (CH), 76.8 (CH), 84.7 (CH), 91.9 (CH), 126.8 (CH, Ar), 127.8 (CH, Ar), 128.7 (CH, Ar), 143.7 (quat. C, Ar), 199.7 (CO), 202.3 (CO), 204.3 (CO), 204.4 (CO), 207.8 (CO); *m*/*z* (FAB) 485 (MH$^+$, 34%), 400 (M − 3CO, 17), 373 (MH − 4CO, 19), 355 (MH − 4CO − H_2O, 100), 154 (32), 136 (40), 105 (60) [Found: (MH$^+$) 485.1265. $C_{24}H_{29}FeO_7$ requires *M*H, 485.1263].

[(8*E*,6*R*,7*S*,12*R*,13*S*)-6-(Carbonyloxy-κ*C*)-12-hydroxy-10-oxo-13-phenyl-(7,8,9-η)-tetradec-8-en-7-yl]tricarbonyliron 15a and [(8*E*,6*R*,7*S*,12*S*,13*S*)-6-(carbonyloxy-κ*C*)-12-hydroxy-10-oxo-13-phenyl-(7,8,9-η)-tetradec-8-en-7-yl]tricarbonyliron 15b. Prepared according to the general procedure using TMS enol ether **2** (0.096 g, 0.23 mmol), (*S*)-2-phenylpropanal and $BF_3{\cdot}OEt_2$. After 6 h, the reaction was quenched with Et_3N and the products were desilylated with HF–pyridine. Flash chromatography (eluent: 30–50% Et_2O–petrol; gradient) afforded *aldol complexes* **15a** and **15b** and *isomerisation product* **14a** as an inseparable mixture (**15a**:**15b**:**14a** 76:7:17; 0.058 g, 53%); ν_{max}(film)/cm^{-1} 3499 (OH), 3056 (CH), 2933 (CH), 2092 (CO), 2025 (CO), 1672 (C=O), 1495; δ_H(200 MHz) 0.88 (3H, t, *J* 6.5, 1-H × 3), 1.18–1.64 {11H, m, [including 1.34 (3H, d, *J* 7.1, 14-H × 3)], 2-H × 2, 3-H × 2, 4-H × 2, 5-H × 2, 14-H × 3}, 2.40 (0.76H, d, *J* 3.5, OH), 2.65–2.97 [3.24H, m, 11-H × 2, 13-H, OH′, OH (isom.)], 3.68 (0.07H, d, *J* 11.1, 9-H′), 3.71 [0.17H, d, *J* 11.1, 9-H (isom.)], 3.86 (0.76H, d, *J* 11.2, 9-H), 4.16–4.39 (2H, m, 6-H, 12-H), 4.95–5.05 {1H, m, [including 5.01 (0.76H, dd, *J* 8.7, 4.6)], 7-H}, 5.46–5.62 {1H, m, [including 5.55 (0.76H, dd, *J* 11.2, 8.7)], 8-H}, 7.15–7.38 (5H, m, Ph); δ_C(50 MHz) 13.9 (CH_3), 16.8 (CH_3), 22.4 (CH_2), 26.5 (CH_2), 31.5 (CH_2), 36.6 (CH_2), 45.3 (CH), 47.0 (CH_2), 65.9 (CH), 71.9 (CH), 76.7 (CH), 84.6 (CH), 92.0 (CH), 126.9 (CH, Ar), 128.1 (CH, Ar), 128.6 (CH, Ar), 142.5 (quat. C, Ar), 199.6 (CO), 202.5 (CO), 204.2 (CO), 204.4 (CO), 208.0 (CO); *m*/*z* (FAB) 485 (MH$^+$, 56%), 400 (M − 3CO, 16), 373 (MH − 4CO, 27), 355 (MH − 4CO − H_2O, 100), 221 (44), 190 (47), 105 (51) [Found: (MH$^+$) 485.1263. $C_{24}H_{29}FeO_7$ requires *M*H, 485.1263].

General procedure for the Mukaiyama aldol reactions using $TiCl_4$

For a 0.20 mmol scale reaction: $TiCl_4$ (1.8 equiv.) was added to a stirred solution of the aldehyde (2.0 equiv.) in CH_2Cl_2 (2 ml) at −78 °C. After 15–30 minutes, this solution was added by cannula to a cooled (−78 °C) solution of silyl enol ether **2** (1.0 equiv.) in CH_2Cl_2 (1 ml) and stirred at −78 °C for 3 h. The mixture was allowed to warm to 0 °C and poured into aqueous $NaHCO_3$ (5 ml, ice cold) and extracted with CH_2Cl_2 (3 × 5 ml). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The de was determined by ^{1}H NMR analysis of the crude reaction mixture and subsequent flash chromatography afforded the aldol products.

[(8*E*,6*R*,7*S*,12*S*,13*S*)-13-Benzyloxy-6-(carbonyloxy-κ*C*)-12-hydroxy-10-oxo-(7,8,9-η)-tetradec-8-en-7-yl]tricarbonyliron 4b. Prepared according to the general procedure using TMS enol ether **2** (0.097 g, 0.23 mmol), (*S*)-2-benzyloxypropanal and

$TiCl_4$. Work-up and flash chromatography (eluent: 40% Et_2O–petrol) afforded *methyl ketone complex* **1** (0.038 g, 48%), followed by *aldol complexes* **4a** and **4b** as an inseparable mixture (**4a**:**4b** 5:95; 0.030 g, 25%); ν_{max}(film)/cm^{-1} 3460 (OH), 2934 (CH), 2862 (CH), 2089 (CO), 2026 (CO), 1666 (C=O), 1497; δ_H(600 MHz) 0.88 (3H, t, *J* 6.6, 1-H × 3), 1.25 (3H, d, *J* 6.2, 14-H × 3), 1.26–1.61 (8H, m, 2-H × 2, 3-H × 2, 4-H × 2, 5-H × 2), 2.78 (1H, dd, *J* 16.2, 2.4, 11-H × 1), 2.92 (1H, br s, OH), 2.95 (1H, dd, *J* 16.2, 9.4, 11-H × 1), 3.54 (1H, apparent qn, *J* 5.8, 13-H), 3.89 (1H, d, *J* 11.1, 9-H), 4.08–4.12 (0.95H, m, 12-H), 4.18–4.22 (0.05H, m, 12-H′), 4.34 (1H, apparent q, *J* 5.3, 6-H), 4.47 (1H, d, *J* 11.6, C*H*HPh), 4.68 (1H, d, *J* 11.6, CH*H*Ph), 5.01 (1H, dd, *J* 8.4, 4.6, 7-H), 5.55 (1H, dd, *J* 11.1, 8.4, 8-H), 7.27–7.37 (5H, m, Ph); δ_C(50 MHz) 13.9 (CH_3), 15.1 (CH_3), 22.4 (CH_2), 26.5 (CH_2), 31.4 (CH_2), 36.6 (CH_2), 46.0 (CH_2), 66.1 (CH), 71.0 (CH_2), 71.1 (CH), 76.8 (CH), 77.0 (CH), 84.7 (CH), 92.1 (CH), 127.7 (2 × CH, Ar), 128.4 (CH, Ar), 138.1 (quat. C, Ar), 199.7 (CO), 202.2 (CO), 203.8 (CO), 204.9 (CO), 207.8 (CO); *m*/*z* (FAB) 515 (MH^+, 4%), 385 (MH − 4CO − H_2O, 23%), 295 (MH − 4CO − OH − CH_2Ph, 7), 133 (100) [Found: (MH^+) 515.1370. $C_{25}H_{31}FeO_8$ requires *M*H, 515.1368].

[(8*E*,6*R*,7*S*,10*S*,12*S*,13*S*)-13-Benzyloxy-6-(carbonyloxy-κ*C*)-10,12-(propane-2,2-diyldioxy)-(7,8,9-η)-tetradec-8-en-7-yl]tricarbonyliron 12. Triisobutylaluminium (1.0 M in toluene; 0.074 ml, 0.074 mmol) was added dropwise to a solution of aldol product **4b** (90% de; 0.019 g, 0.037 mmol) in benzene (1 ml) at 0 °C. After 1 h, aqueous NH_4Cl (5 drops) was added. The mixture was stirred for a further 5 minutes and then dried ($MgSO_4$) and filtered through Celite eluting with CH_2Cl_2 (10 ml). The solvent was removed under reduced pressure and the *crude diol* was used directly in the following reaction.

2,2-Dimethoxypropane (0.077 g, 0.74 mmol) and PPTS (cat.) were added to a solution of the *crude diol* in DMF (0.6 ml) at room temperature. After 3.5 h, H_2O (2 ml) was added and the mixture extracted with CH_2Cl_2 (3 × 2 ml). The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (eluent: 20% Et_2O–petrol) afforded *acetonide* **12** as a pale yellow oil (0.013 g, 65% from **4b**). Only one diastereoisomer was observed by NMR; ν_{max}(film)/cm^{-1}; 2932 (CH)], 2082 (CO), 2020 (CO), 1665 (C=O); δ_H(600 MHz) 0.89 (3H, t, *J* 6.9, 1-H × 3), 1.18 (3H, d, *J* 6.5, 14-H × 3), 1.25–1.62 {14H, m, [including 1.33 (3H, s, acetonide CH_3), 1.38 (3H, s, acetonide CH_3)] 2-H × 2, 3-H × 2, 4-H × 2, 5-H × 2, acetonide CH_3 × 2}, 1.89 (1H, ddd, *J* 12.9, 9.5, 6.0, 11-H × 1), 2.10 (1H, ddd, *J* 12.9, 10.0, 6.7, 11-H × 1), 3.54 (1H, apparent qn, *J* 6.2, 13-H), 3.92 (1H, dt, *J* 10.0, 6.0, 12-H), 3.95 (1H, dd, *J* 12.0, 3.0, 9-H), 4.23 (1H, dt, *J* 7.3, 5.2, 6-H), 4.36 (1H, ddd, *J* 9.5, 6.7, 3.0, 10-H), 4.59 (1H, dd, *J* 8.2, 4.7, 7-H), 4.61 (1H, d, *J* 12.0, C*H*HPh), 4.66 (1H, d, *J* 12.0, CH*H*Ph), 4.70 (1H, dd, *J* 12.0, 8.2, 8-H), 7.26–7.36 (5H, m, Ph); δ_C(150 MHz) 13.9 (CH_3), 15.4 (CH_3), 22.5 (CH_2), 23.7 (CH_3, acetonide), 24.8 (CH_3, acetonide), 26.7 (CH_2), 31.6 (CH_2), 35.2 (CH_2), 36.7 (CH_2), 65.8 (CH), 70.1 (CH), 71.8 (CH_2), 76.0 (CH), 76.2 (CH), 77.2 (CH), 85.0 (CH), 88.2 (CH), 101.2 (quat. C, acetonide), 127.5 (CH, Ar), 127.7 (CH, Ar), 128.3 (CH, Ar), 144.9 (quat. C, Ar), 4 × CO not observed; *m*/*z* (FAB) 557 (MH^+, 7%), 399 (7), 385 (8), 343 (9), 153 (29), 105 (100).

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