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Asymmetric Biochemical Reduction, Acylation and Hydrolysis in the (Diene)Fe(CO)3 Series: Experimental Results and Molecular Modelling Studies

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Abstract: Asymmetric reduction using bakers yeast and asymmetric acyl transfer using porcine pancreatic lipase may be used in the kinetic resolution and desymmetrization of acyclic (diene)Fe(CO)3 complexes bearing CHO and CH_2OH substituents respectively. The results may be interpreted in terms of current active site models for these biotranformations.

Introduction. The use of organometallic transition metal complexes in organic synthesis has developed considerably in recent years; perhaps those which have received most attention are those based on the (arene)Cr(CO)3 and (diene)Fe(CO)3 series.(1) Suitably substituted, these compounds possess a planar chirality. To date, access to homochiral materials in the (diene)Fe(CO)3 series has relied mainly on classical methods involving diastereoisomer formation. (2) The availability of simpler, selective methods capable of use on a larger scale would greatly aid in the application of these homochiral materials to the synthesis of increasingly complex target molecules.

Enzymes exhibit a remarkable tolerance towards non-natural systems, perhaps a reflection of their great flexibility as catalysts in biological systems such as detoxification esterases, monooxygenases in the manufacture of metabolisable hydrocarbons, lipases in the cleavage of fatty acid esters and yeasts in their adaption to a variety of culture conditions. Biotransformation represents an increasingly common methodology for the synthesis of homochiral organic molecules, and adaption of this approach to organometallic π-complexes provides a logical extension, despite the difference in type of chirality (planar as opposed to carbon-centred), sensitivity to photo-oxidation and general lack of compatibility with aqueous media. Though several examples of kinetic resolutions now exist in the (arene)Cr(CO)3 series,(3) we are aware of only one example in the (diene)Fe(CO)3 series, namely the enantioselective hydrolysis of (2-ethoxycarbonylbutadiene)Fe(CO)3 using pig liver esterase.(4)

Two types of enzymes or microorganism seem most promising at this stage, namely lipase enzymes and bakers yeast respectively. Lipase enzymes do not require the regeneration of a cofactor and are easily used in

nonaqueous media, while bakers yeast (saccharomyces cerevisiae) is inexpensive, easily accessible and reactive with a variety of substrates.[5] The use of whole cells in this respect does not appear to be disadvantageous; we have recently shown [6] that organometallic fragments are completely compatible with penetration of modified steroids into whole cells.

We present here our results on bakers yeast reduction and use of esterolytic and lipolytic enzymes in the (diene)Fe(CO)3 series:[7]. Additionally, we show that the modelling of enzyme substrate interactions which has been used with success for organic substrates may be extended to modelling of organometallic substrates possessing planar chirality.

Results and Discussion

(a) Synthesis. For determination of enantiomeric excesses, all chiral complexes were prepared non-enzymatically as racemates. Complexes (1) and (6) were prepared by ultrasound reaction of $Fe_2(CO)_9$ with the free ligand;[8] complex (2) was the gracious gift of Professor René Grée (Université de Rennes). Reaction of $Fe_2(CO)_9$ with dimethylmuconate is not clean, and (8) was best prepared by reaction with $Fe(CO)_5$ in the presence of Me_3NO.[9] DIBAL reduction of (8) gave (10) which on Swern oxidation yielded the aldehyde (13). Complexes (3), (4) and (14) were prepared by $NaBH_4$ reduction of (1), (2) and (13) respectively.[10] Acylation of (3) and (10) to give (5), (11) and (12) was accomplished using pyridine/acetic anhydride. Methanolic hydrolysis of (6) and (8) gave the acids (7) and (9).

(1) R = Me

(2) R = CO_2Me

(3) X = H, R = Me

(4) X = H, R = CO_2Me

(5) X = COMe, R = Me

(6) X = Me

(7) X = H

(8) X = Me

(9) X = H

(10) X = Y = H

(11) X = H, Y = COMe

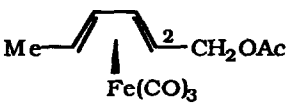
(12) X = Y = COMe

(13)

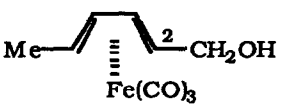
(14)

(b) *Enzymatic Acyl Transfer.* Though both kinetic resolutions and asymmetric acyl transfer to meso substrates have been reported in the (arene)$Cr(CO)_3$ and ferrocene series,[2a,c,11] we are aware of no

examples in the (diene)$Fe(CO)_3$ series. Acyl transfer to complex (3) from vinyl acetate in toluene using porcine pancreatic lipase (PPL) followed by workup at 53% completion provides (-)-(2R)-(5) in 70% e.e together with recovered (+)-(2S)-(3) in 76% e.e. The absolute configurations shown are based on assignments detailed in section (d). Enzymatic acylation of the meso-diol (10) provides the hemiacetate (11) in 56% e.e. whose absolute configuration is at present unknown. This last result is somewhat disappointing in terms of enantiomeric excess, and we are currently assessing a range of other lipase enzymes, together with enzymatic hydrolysis of the easily prepared meso diacetate (12). Nevertheless, the results are sufficient to allow some modelling of the enzyme-substrate interations in these systems.

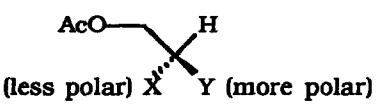


(5) (-)-(2R)

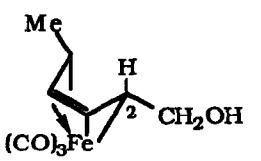


(3) (+)-(2S)

Active site models for PPL have been presented by Jones et al.,[12] Seebach et al., [13] and most recently by Wimmer.[14] The model of Wimmer (A) which appears to be most consistent with literature data is based on the orientation of groups X and Y in terms of relative polarity with relative size being of lesser importance. Site H is occupied by the smallest substituent which may be hydrogen or a small alkyl group.

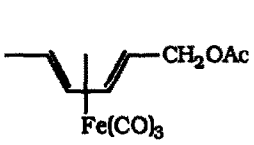


(A)

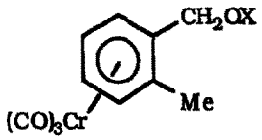


(B)

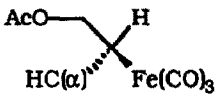
If C2 is regarded as having tetrahedral coordination in the alternative valence bond description (B), acyl transfer to the (2R) enantiomer is consistent with model (A), assuming the $Fe(CO)_3$ moiety has a higher relative polarity than the diene fragment. The kinetic resolution of (15a) which yields the (1R,2S) acetate (15b) [3a] and asymmetric acyl transfer to the meso alcohols (16a) and (17a) to give (16b) and (17b)[11] also fit this model, provided the unsubstituted C(α) carbon occupies site H. It may be noted that these latter reactions are not accomplished with PPL, but nevertheless with enzymes which give products of the same configuration as PPL. [3d]

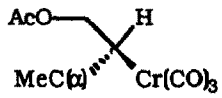


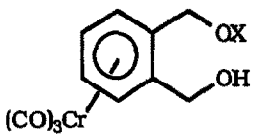
(4)

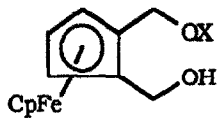


(15a) X = H
b X = COMe



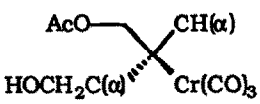


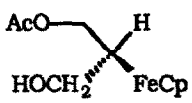




(16a) X = H
b X = COMe

(17a) X = H
b X = COMe

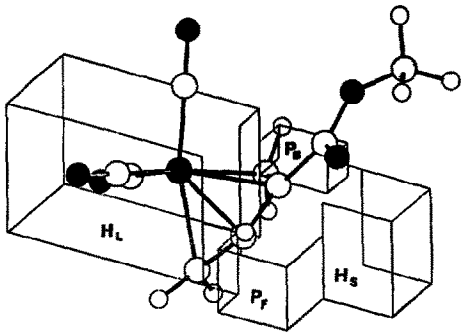




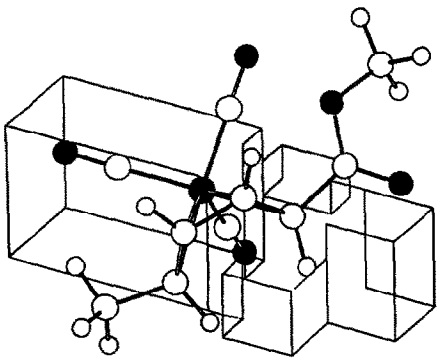
Assignment of the metal fragment as the substituent of higher polarity is consistent with dipole moment measurements on (benzene)$Cr(CO)_3$ and (butadiene)$Fe(CO)_3$.[15]

(c) *Enzymatic Hydrolysis*. Enzymatic desymmetrization of meso diesters in the ferrocene and (arene)$Cr(CO)_3$ series using pig liver esterase (PLE) have recently been reported. [16]

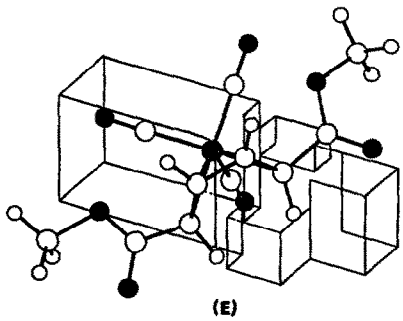
In view of the efficient hydrolysis reported for (2-ethoxycarbonylbuta-1,3-diene)$Fe(CO)_3$[4], we were surprised to observe that both esters (6) and (8) were unreactive to PLE under standard conditions (pH 7.2, phosphate buffer) even though the acids (7) and (9) can be prepared easily via methanolic hydrolysis. In a recent study,[17] Jones et al. have proposed an active site model to interpret and predict the specificity of PLE. The model is based on an arrangement of five cubic regions of space; H_L and H_S represent two hydrophobic zones of volumes 33 $Å^3$ and 5.5 $Å^3$ respectively. These pockets may accommodate weakly polar heteroatoms such as halogen or ether or ketal oxygen if necessary . Two other sectors (P_B and P_F) accept strongly polar or hydrophilic fragments. The essential catalytic region involves the serine residue near P_B which initiates hydrolysis by attack at the reactive ester group. Model (C) shows clearly that the 2-methoxycarbonyl derivative adapts well to the active site in the correct orientation, placing the ester close to P_B, with only one of the two basal carbonyls projecting through the open face of H_L. In contrast, models (D) and (E) show that the correct placement of acetate for complexes (6) and (8) entails a displacement of the other terminal substituent outside of the active site. We are currently examining other hydrolase enzymes to improve the generality of enzymatic hydrolysis.



(C)



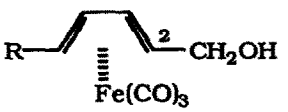
(D)



(E)

(d) *Bakers Yeast Reduction.* Though this method has been applied to kinetic resolutions in the (arene)$Cr(CO)_3$ series, [3b] we are aware of no examples in the (diene)$Fe(CO)_3$ series. Asymmetric reduction of 1,2-diformylferrocene using horse liver alcohol dehydrogenase/NADH has been reported. [16a,18]

Reduction of (1) using bakers yeast to approximately 60% completion provides the homochiral laevorotatory aldehyde (1) (>99% e.e.) together with the dextrorotatory alcohol (3) of 78% e.e. The absolute configuration of (1) was assigned by comparison of the CD spectrum of its crystalline $Fe(CO)_2PPh_3$ derivative prepared via Me_3NO substitution to that of the $Fe(CO)_2PPh_2$(neomenthyl) derivative of known absolute configuration.[19]. The assignments of absolute configuration in section (b) follow from this. Reduction of the meso complex (13) proceeds in good yield and 90% e.e. to give the hemialcohol (14) whose absolute configuration was assigned by comparison with the CD spectrum of a sample prepared inter alia by resolution of (14) using (-)-ephedrine.[20] Complex (2) may itself be selectively reduced using bakers yeast to give the aldehyde of (2R) configuration in 90% e.e. and the (2S) alcohol (4) in 76% e.e. These results may be compared with the excellent enantioselectivities observed recently in the asymmetric allylboration of complexes (1), (2) and (13).[21]



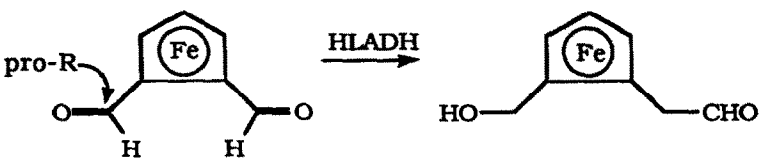
(3) R = Me (+)-(2S)

(1) R = Me (-)-(2R)

(4) R = CO_2Me (-)-(2S) (2) R = CO_2Me (+)-(2R)

(14) (-)-(2R)

The selectivity of bioreductions in many systems may be rationalized using Prélog's rule.[22] Thus, in the reduction using horse liver alcohol dehydrogenase (HLADH) of (1,2-diformyl) ferrocene[18], it is proposed that the reaction proceeds stereospecifically via delivery of hydride opposite to the metal at the re-face of the aldehyde which is exposed in the pro-R formyl group of the most stable aldehyde conformation.[18,23]



(18) (19)

An extension of this model to our results on (1) and (2) implies that reduction occurs via delivery of hydride to the re-face of the aldehyde exposed in the trans conformer of (2S)-(1).

(trans) (cis)

Variable temperature nmr studies show that in solution at low temperature (-115°C), cis and trans isomers are approximately equally populated.[24] We are currently addressing this question of stereoselectivity via enzymatic reduction of (1-deuteriosorbaldehyde)Fe(CO)3.

Conclusions

Our results and those of others cited herein indicate the increasing utility of enzymes in asymmetric synthesis using organometallic complexes. The excellent molecular recognition observed may also have potential use in the design of organometallic suicide substrates and in enzyme functionalization as an aid in three dimensional structure analysis.

Acknowledgments

We thank the British Council (Alliance Programme) and the CNRS for support of this work.

Experimental. Methyl sorbate and dimethylmuconate were prepared by literature procedures.[25] Reactions involving organometallic compounds were conducted under nitrogen. Bakers yeast was either obtained locally or from Sigma (YSC-II). Optical purities by HPLC were determined using a Chiralcel O.J. column on a Beckman System Gold apparatus using 99:1 isopropanol:heptane as solvent. The chiral shift reagent used in nmr studies was tris[3-(heptafluorohydroxymethylene)-(+)-camphorato]Eu(III). Enantiomeric excesses were determined against racemic compounds. Preparations of racemates and meso complexes are given below, together with details of biotransformation reactions. NMR data are collected in Table 1.

1. Complex (8) To degassed benzene (30 ml) was added Me_3NO (1.31 g, 11.8 mmol) and dimethylmuconate (0.5 g, 2.94 mmol). The mixture was cooled in an ice bath and $Fe(CO)_5$ (0.77 ml, 5.88 mmol) added dropwise. After stirring for 30 minutes, the mixture was refluxed for 2.5 hours to give a deep red solution. Evaporation of solvent and recrystallization from 60-80 petroleum ether gave the product (0.35 g, 39%) (m.p. 74-75°C; infrared (hexane): 2075, 2015, 2003 cm^{-1}). Microanalysis : calc. C-42.6, H-3.25%, found C-42.9, H-3.15%.

2. Complex (10). Under nitrogen, complex (8) (1g, 3.2 mmol) was dissolved in dry degassed thf (40 ml) and cooled to -78°C. DIBAL (15 ml, 1.0 M in hexanes) was added dropwise through a syringe with stirring. After warming to room temperature, ethanol (40 ml) and water (150 ml) were added and the aqueous layer extracted with diethyl ether (4 x 80 ml). Drying over $MgSO_4$ and removal of solvent followed by crystallization from ethyl acetate gave (10)(0.8 g, 88%) (m.p. 123-124°C; infrared (CH_2Cl_2): 2045, 1971 cm^{-1}). Microanalysis : calc. C-42.6, H-3.97%, found C-94.6, H-4.11%.

3. Complex (13). Oxalyl chloride (0.8 ml, 9 mmol) was added to dry distilled CH_2Cl_2 (6 ml) at -78°C. Dimethyl sulfoxide (1.1 ml, 15 mmol) was added and the mixture stirred at -78°C for 10 minutes. Complex (10) (0.76 g, 3 mmol) in CH_2Cl_2 (8 ml) was added and the mixture stirred for 25 minutes at -78°C. Triethylamine (0.8 ml, 5.7 mmol) was added and the mixture allowed to warm to room temperature. Water (75 ml) was added and the aqueous layer extracted with CH_2Cl_2 (3 x 75 ml). After drying with $MgSO_4$ and removal of solvent, the material was purified by chromatotron (eluant 3:1 pentane/ethyl acetate) to give (13) (0.4 g, 54%) (m.p. 93-94°C; infrared (CH_2Cl_2): 2075, 2019 cm^{-1}). Microanalysis : calc. C-43.2 H-2.42%, found C-43.5, H-2.39%.

4. Complexes (5), (11) and (12). Complex (10) (0.8 g, 3.2 mmol) was added to dry pyridine (2 ml); acetic anhydride (0.3 ml, 3.2 mmol) was added and the reaction monitored by tlc to complete disappearance of starting material. Pyridine was removed and the residue was purified by chromatotron (eluant 8:2 60-80 petroleum ether/ethyl acetate) to give (11) (0.42 g, 45%) (oil; infrared (hexane): 2051, 1987, 1979 cm^{-1}) and (12) (0.32 g, 30%) (m.p. 47-48°C; infrared (hexane): 2051, 1991, 1979 cm^{-1}). Microanalysis : (11) calc. C-44.6, H-4.09%, found C-44.8, H-4.22% (12) calc. C-4.06%, H-4.18%, found C-46.0, H-4.06%.

Complex (5) was prepared in the same way as an orange oil (infrared (hexane): 2047, 1983, 1975 cm^{-1}). Microanalysis : calc. C-47.1, H-4.29%, found C-46.9, H-4.01%.

5. Complex (14). Complex (13) (0.2 g, 0.8 mmol) was dissolved in methanol (5 ml) and $NaBH_4$ (0.03 g, 0.8 mmol) added slowly with stirring. The reaction was monitored by tlc to complete disappearance of starting material. Water (10 ml) was added and the aqueous layer extracted with diethyl ether (3 x 10 ml). After drying with $MgSO_4$ and removal of solvent, the product was purified by chromatotron (eluant 7:3 60-80 petroleum ether/ethyl acetate) to give (14) (0.1 g, 50%) which was crystallized from ethyl acetate/60-80 petroleum ether (m.p. 67-68°C; infrared (CH_2Cl_2): 2059, 1987 cm^{-1}), together with 50 mg of the dialcohol (10). Microanalysis : calc. C-46.6, H-3.45%, found C-46.7, H-3.6%.

6. Complex (9). Complex (8) (0.66 g, 2.14 mmol) was dissolved in methanol (10 ml). After addition of NaOH (1.08 ml of 1.99 M solution, 2.14 mmol), the solution was stirred at 30°C for 10 hours. Methanol was removed and water (10 ml) added to the residue which was then extracted with diethyl ether (3 x 10 ml) to remove unreacted diester.

The aqueous layer was acidified to pH 4 using 8.5% H_3PO_4 and extracted with diethyl ether (3 x 20 ml). Drying with $MgSO_4$ and removal of solvent gave (9) (0.52 g, 96%) which was recrystallized from diethyl ether/60-80 petroleum ether (m.p. 150-152°C; infrared (hexane): 2079, 2023 cm^{-1}). Microanalysis : calc. C-40.7, H-2.72%, found C-40.6, H-2.65%.

Complex (7) was prepared in 95% yield in the same way (m.p. 201-202°C; infrared (CH_2Cl_2): 2059, 1987 cm^{-1}). Microanalysis : calc. C-46.6, H-3.45%, found C-46.8, H-3.21%.

7. Enzymatic acylation of (3). Complex (3) (0.48 g, 2 mmol) was added to degassed toluene (16 ml) at 34°C; PPL (4 g) (Sigma Type II) and vinyl acetate (7 ml) were added and the reaction monitored by tlc until approximately 50% conversion (3.5 hours). The mixture was filtered through celite and evaporated to dryness. Purification by chromatotron (eluant 2:8 ethyl acetate/ 60-80 petroleum ether) yielded (5) 0.23 g, 41%, $[\alpha]_D$ -128, c=1.25, CH_2Cl_2, 70% e.e. by nmr) and recovered alcohol (3) (0.17 g, 36%, $[\alpha]_D$ +10, c=1.0, CH_2Cl_2, 76% e.e. by HPLC).

8. Enzymatic acylation of (10). Complex (10) (0.5 g, 2 mmol) dissolved in diethylether (3 ml) was added to degassed toluene (16 ml) at 34°C. Vinyl acetate (7 ml) and PPL (4 g) were added and the reaction monitored by tlc to first appearance of the diacetate (12) (1.5 hours). Work up as above yielded the monoacetate (11) (0.23 g, 38%, $[\alpha]_D$ -16, c=1.0, CH_2Cl_2, 56% e.e. by nmr).

9. Biochemical reduction of (1). To degassed water (100 ml) was added bakers yeast (10 g) and glucose (2.5 g). After equilibration at 25°C for 30 minutes, complex (1) (0.28 g, 1.2 mmol) dissolved in absolute ethanol (2 ml) was added. The reaction was monitored by tlc to approximately 50% completion (1.5 hours). After extraction with diethyl ether (5 x 200 ml), drying with $MgSO_4$ and removal of solvent, purification by chromatotron (eluant 2:8 ethylacetate/hexane) gave the alcohol (3) (0.15 g, 53%, $[\alpha]_D$ +10, c=1, CH_2Cl_2, 78% e.e. by HPLC) together with recovered aldehyde (1) (0.09 g, 32%, $[\alpha]_D$ -112, c=1, $CHCl_3$, >99% e.e. by nmr). For purposes of assignment of absolute configuration by CD, complex (1) was converted

to the $Fe(CO)_2PPh_3$ derivative by standard techniques.[24] CD:[$\lambda_{max}(\Delta\varepsilon)$]320(-14),375(+2.5)(c= $5x10^{-4}$,CH_3CN).

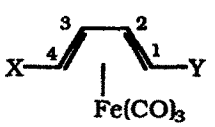
Complex (2) was reduced in the same way using 1,4-dioxane as solvent for the substrate to give (4) (36%, $[\alpha]_D$ -245, c=2.3, CH_2Cl_2, 76% e.e. by nmr) and recovered aldehyde (2) (36%, $[\alpha]_D$ +10, c=2.0, CH_2Cl_2, 90% e.e. by nmr).

10. Biochemical reduction of (13). To degassed water (100 ml) was added bakers yeast (10 g) and glucose (2.5 g). After equilibration at 25°C for 30 minutes, complex (13) (0.25g, 1 mmol) dissolved in 2:1 ethanol/dioxane (3 ml) was added. The reaction was monitored by the tlc and stopped at first appearance of the dialcohol (10). After work up as above, purification by chromatotron yielded the monoalcohol (14) (0.2 g, 80%, 90% e.e. by nmr). A single recrystallisation from 60-80 petroleum ether yielded homochiral material ($[\alpha]_D$ -28, c=1 x 10^{-3}, CH_3CN; CD: [$\lambda_{max}(\Delta\varepsilon)$]350(-1.5), 390(+2.0), c=1 x 10^{-4}, CH_3CN).

11. Attempted hydrolysis of (6). Complex (6) (20 mg, 0.09 mmol) in ethanol (2ml) was added to phosphate buffer (pH. 7.2, 20 ml) at 25°C. After addition of PLE (40µl of a suspension in 3.2M $(NH_4)_2SO_4$, Sigma ED 3.1.1.1), the mixture was stirred for 24 hours. After acidification and extraction with diethylether, only unchanged ester was recovered. Treatment of (8) in the same way yielded identical results.

12. Molecular modelling of enzymatic hydrolysis. The (diene)$Fe(CO)_3$ structures were generated from the structure of the amide of (+)-(2-carboxy-1,3-butadiene)$Fe(CO)_3$ with (-)-α–methylbenzylamine[4] recovered from the Cambridge Crystallographic Data Base. Substrate-active site fitting was estimated visually using MolView.[26]

Table 1 NMR Spectral Data[a]



	Position				
	1	2	3	4	Other
1	54.5(0.66)	81.2/89.5(5.08)	81.2/89.5(4.26)	60.3(0.83)	Me 19.1(0.88) CHO 196.1(8.99*)
2	55.5(0.60)	85.1/88.3(5.09)	85.1/88.3(5.36)	48.1(0.96)	CO_2Me 52.2, 171.9(3.25) CHO 196.4(8.89*)
3	82.4/86.3(0.70)	58.2/59.9(4.50)	58.2/59.9(4.31)	82.4/86.3(0.70)	CH_2 64.6(3.16,3.30) Me 19.0 (1.01)
4	64.2/64.3(0.76)	84.6/87.0(4.52)	84.6/87.0(5.46)	46.7(0.86)	CH_2 64.2/64.3(3.08)

					CO_2Me 52.1,172.1(3.31*)
5	54.1(0.6-0.8)	83.0/86.6(4.58)	83.0/86.6(4.28)	58.4(0.6-0.8)	CH_2 66.0(3.79,3.99) Me 19.1(0.96) OAc 20.9,170.7(1.69*)
6	45.1(0.81)	82.9/83.4(5.45)	82.9/83.4(4.28)	59.7(0.71)	Me 19.1(0.88) CO_2Me 51.7,172.8(3.32)
7	44.2(0.89)	83.1/88.9(5.71)	83.1/88.9(5.19)	60.1(1.40)	Me 19.2(1.45) CO_2H 179.4
8	46.9(0.87)	86.9(5.39)	b	c	CO_2Me 52.1,172.1(3.26) CO 212.2,205.8
9	45.7,47.1(0.7-0.9)	87.0/87.2(5.30)	87.0/87.2(5.30)	45.7/47.1(0.7-0.9)	CO_2Me 52.1,171.9(3.24) CO_2H 178.5
10	64.1/64.2(1.38)	84.5(5.35)	b	c	CH_2 64.1/64.2(4.56,4.70)
11	55.2(0.8-0.9)	84.0/84.3(4.4-4.6)	84.0/84.3(4.4-4.6)	61.4(0.8-0.9)	CH_2OH 64.3/65.8(3.13) CH_2OAc 64.3/65.8(3.79,4.00) OAc 20.7, 170.7(1.69*)
12	55.4(0.72)	84.6(4.50)	b	c	CH_2 65.5(3.70,3.96) OAc 20.7,170.5(1.68) CO 214.5, 208.7
13	55.3(0.70)	86.2(5.03)	b	c	CHO 196.3(8.88) CO 211.0,205.2
14	54.7(0.71)	82.6/87.2(5.09)	82.6/87.2(4.50)	63.5/63.7(0.88)	CH_2 63.5/63.7(3.06) CHO 196.9(8.97*)

a ^{13}C chemical shifts with ^1H values in parentheses (ppm from TMS). ^1H spectra in d^6-benzene except for (10)(d^6-acetone and (7)($CDCl_3$); major couplings are in the range J(1-2), J(3-4) 6.3-8.9 Hz, J(2,3) 4.9-5.3 Hz, J(4-Me) 5.8-6.3 Hz, J(1-CHO) 2.9-3.7 Hz, J(1-CH_2) 5.8-7.6 Hz, J(gem,CH_2) 12.0-

12.2. Hz. Resonances which are used in the assignment of enantiomeric excess are marked with an asterisk. ^{13}C spectra in CD_2Cl_2 solvent; spectra for which M-CO chemical shifts are given were run at -50°C.

b symmetrical; see position 2

c symmetrical; see position 1

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