Asymmetric Synthesis of β-Phenylserines by Condensation of Benzaldehyde with Zinc(II) and Copper(II) Complexes of (1*R*)-3-Hydroxymethylenebornan-2-one Glycine Imines

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The condensation between benzaldehyde and the zinc(II) and copper(II) complexes of the glycine imines of (1*R*)-3-hydroxymethylenebornan-2-one in the presence of strong bases has been studied. The diastereo- and enantio-selectivity of the reaction together with the spectroscopic characterization of the metal complexes and the corresponding enolate intermediates are reported.

The condensation of aldehydes on the methylene group of metal co-ordinated glycine imines represents a method of potential preparative interest for the synthesis of β-hydroxy amino acids.[1–4] Such interest is related particularly to the possibility of performing an asymmetric synthesis by employing suitable chiral auxiliary residues or resolved metal complexes, since the number of diastereo- and enantio-selective methods available for this important group of compounds is still rather limited.[4–6] We have recently reported a new method for the asymmetric synthesis of *threo* and *erythro* β-phenylserines which is based on the condensation of benzaldehyde with the metal enolates of the chiral imines derived from the condensation of alkyl esters of glycine with the easily available (+)-ketopinic acid.[7] An interesting aspect of the reaction is that the stereochemical outcome of the reaction depends markedly on the nature of the metal ion involved. Since we believe that the role played by metal ions in metal-dependent asymmetric syntheses is generally underestimated we thought it of interest to extend our investigation to other related systems. In this paper we wish to report the results of our stereochemical studies on the condensation between benzaldehyde and the zinc(II) and copper(II) complexes with the ligands obtained from the condensation of glycine and (1*R*)-3-hydroxymethylenebornan-2-one [(1*R*)-3-(hydroxymethylene)camphor] (hmb). The synthesis and stereochemical properties of a series of complexes of this type with various L-amino acid residues has been reported previously.[8–9]

Results and Discussion

In a previous investigation it was shown that the zinc(II) complexes formed between the condensation product of (1*R*)-3-hydroxymethylenebornan-2-one (hmb) and amino acids are obtained as mixtures of enolimine and ketoenamine forms.[9] Since optically active amino acids were employed a complex set of diastereoisomeric complexes was formed. These gave rise to a complicated patterm of NMR signals that were difficult to assign to the various forms. With the glycine complex reported here the situation appears simpler since the ^{1}H NMR spectrum in [$^2H_6$]DMSO shows the presence of three species that we identify as (**1**)–(**3**); L is a water or solvent molecule.

The doublet signal near δ 6.80 (*J* 12.6 Hz) and the multiplet near δ 6.40 are assigned to the =C–H and N–H protons of the ketoenamine form (**3**), respectively, as shown by decoupling experiments. The NH proton is further coupled with the glycine methylene group. The other signals near δ 7.80 and 7.40 are due to the enamine proton of (**2**) and the imine proton of (**1**) but their assignment to the two species is uncertain (Figure 1).

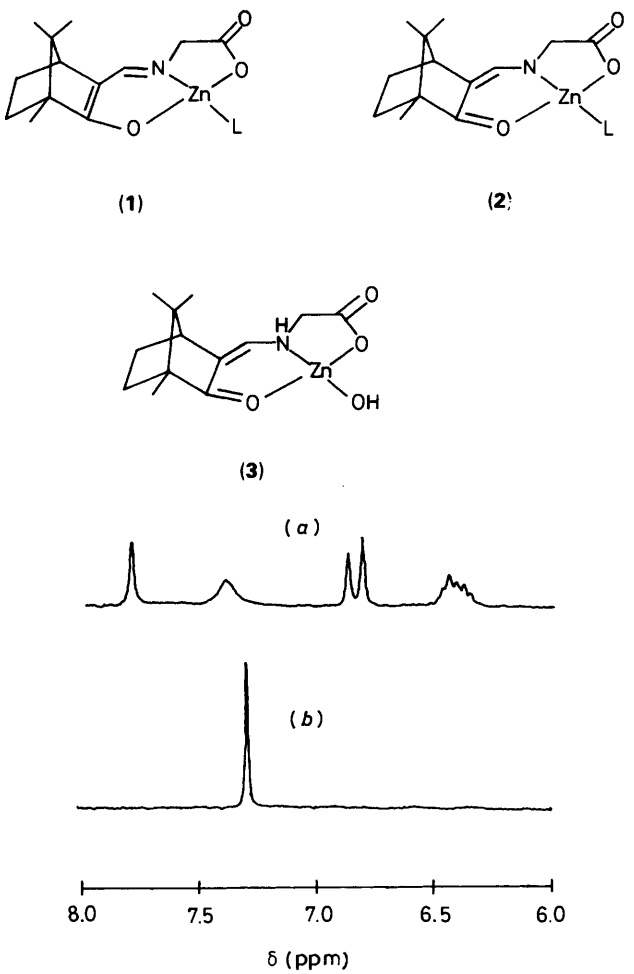


Figure 1. ^{1}H NMR spectra of the zinc(II) complex of the glycine imine in [$^2H_6$]DMSO: (*a*) before and (*b*) after the addition of excess potassium t-butoxide.

The addition of increasing amounts of solid potassium t-butoxide to a deuteriated DMSO solution of the zinc(II) complex simplifies the NMR spectrum progressively. A singlet signal grows in the alkenic region (Figure 1) and interestingly,

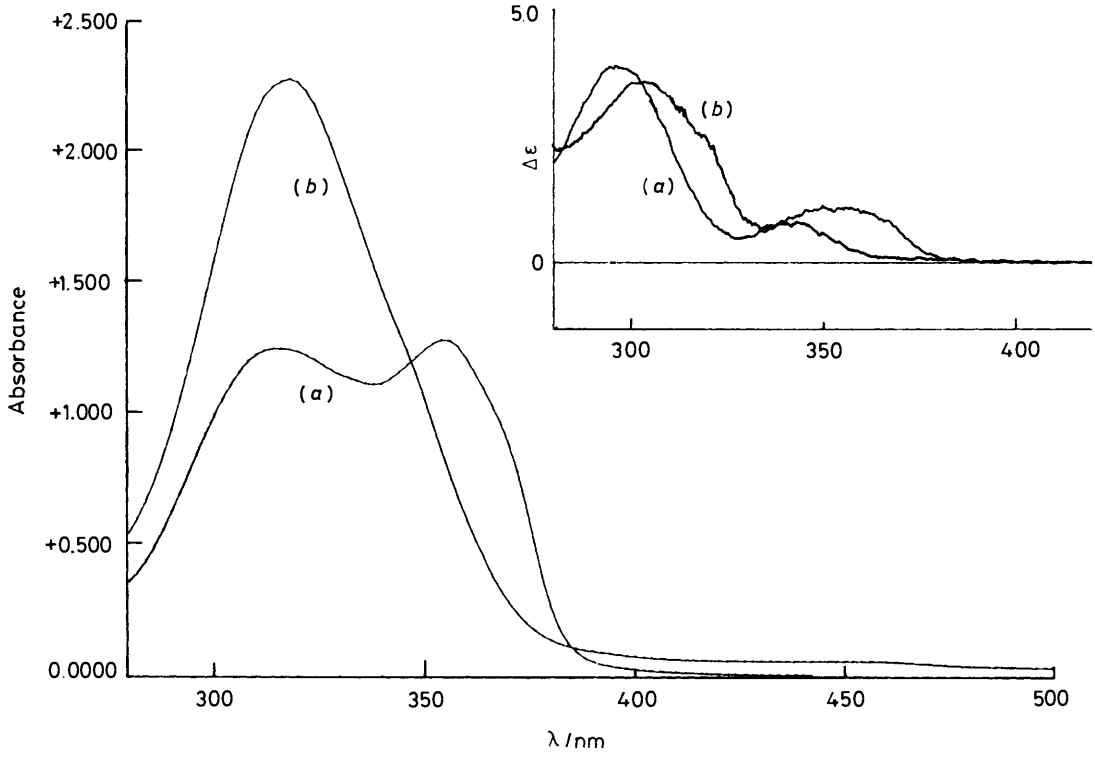


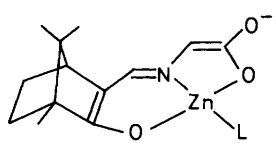
Figure 2. Electronic and circular dichroism (insert) spectra of a DMSO solution of the zinc(II) complex of the glycine imine: (*a*) before and (*b*) after the addition of excess potassium t-butoxide. [complex], 2.06 × 10^{-3} mol dm^{-3}; cell path length, 0.1 cm.

a new singlet signal of comparable intensity appears near δ 4.30. This replaces the multiplet signals in the range δ 3.30–4.00 attributed to the methylene group of the glycine residue of (**1**)–(**3**). In addition, the three narrow doublets between δ 2.20 and 2.60, due to the 4-H proton of the camphor moieties of (**1**)–(**3**), are replaced by a single doublet near δ 2.20. We attribute the three new signals at δ 7.30, 4.30, and 2.20 to the imine proton, the alkenic proton and the 4-H proton of the enolate species (**4**) produced by t-butoxide.

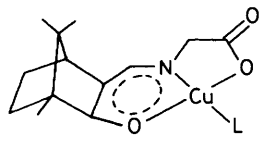
The electronic spectrum of the zinc(II) complex displays two bands of moderate intensity (ε *ca.* 6 000 dm^3 mol^{-1} cm^{-1}) in the near UV region, at 316 and 354 nm, due to π–π* transitions of the ligand chromophore for the various tautomeric forms of the complex. In the presence of an excess of potassium t-butoxide the optical spectrum changes giving a prominent bond of increased intensity at 318 nm (ε *ca.* 11 000 dm^3 mol^{-1} cm^{-1}) with a shoulder near 350 nm (Figure 2). The circular dichroism spectrum also undergoes some changes on formation of the metal enolate as shown in Figure 2.

The copper(II) complexes of amino acid imines derived from (1*R*)-3-hydroxymethylenebornan-2-one do not present problems connected with the existence of various tautomeric forms. The marked tendency toward square-planar co-ordination of the metal ion in this case prevents protonation of the nitrogen atom to give the ketoenamine form corresponding to (**3**). The X-ray structural determination of the copper(II) complex derived from L-phenylalanine and (1*R*)-3-hydroxymethylenebornan-2-one shows, in fact, that the six-membered chelate ring is planar, with extended π-delocalization involving also the copper(II)–ligand bonds.[10] A better representation of the copper(II) complex derived from glycine studied here is therefore given by structure (**5**).

The electronic spectrum of this compound displays two bands of moderate intensity in the near UV region (at 300 and 356 nm), which are essentially due to π–π* transitions localized



(**4**)



(**5**)

within the extended π-system of the ligand chromophore (Figure 3) and a weaker, broad absorption centred at 665 nm encompassing the metal d–d transitions. Additional weak absorptions between 400 and 450 nm, probably due to charge-transfer transitions from the ligand to Cu^{II}, are better resolved in the CD spectrum of the complex and are also reported in Figure 3.

The addition of potassium t-butoxide to the DMSO solution of the copper(II) complex produces optical changes in the near UV region that are very similar to those described above for the zinc(II) complex. Hence a similar species is likely to be formed in the two cases. As shown in Figure 3 the near UV spectrum of the anionic complex is dominated by an intense band near 330 nm (ε *ca.* 15 000 dm^3 mol^{-1} cm^{-1}), while the lower intensity band at 454 nm (ε *ca.* 900 dm^3 mol^{-1} cm^{-1}) is probably due to a charge-transfer transition from the enolate ligand to Cu^{II}. The weaker d–d transitions are partially obscured by this absorption but the centre of the d–d envelope is clearly shifted to higher energy, in agreement with the increased ligand field strength of the enolate ligand. The near UV circular dichroism spectrum of the copper(II) complex undergoes a change similar to that in the absorption spectrum on addition of t-butoxide; interestingly, the broad negative band near 430 nm becomes positive and red shifted in the enolate complex. It is important to note that the CD spectra of the enolate complexes are practically unaffected when a solution in DMSO has stood for one day at room temperature.

Table 1. Diastereoisomeric ratio and enantiomeric excess (ee) of *N*-benzoyl-β-phenylserine methyl esters from the reaction between benzaldehyde and the copper(II) complex.

Base (solvent)	Molar ratio[a]	*T*/°C	Yields[b] (%)	*threo*:*erythro*[c]	ee (*threo*)[d]	ee (*erythro*)[d]
LDA (THF)	1:1	−78	20	1:1.8	0	9
LDA (THF)	1:2	−78	42	1:1.4	3	4
Bu^{t}OK (THF)	1:1	20	35	2:1	20	9
Bu^{t}OK (THF)	1:2	20	65	5:1	27	32
KOH (PEG 400)	1:5	20	50	9:1	18	20

[a] Molar ratio metal complex/base. [b] Total yields evaluated on the mixture of *threo* and *erythro* diastereoisomers. [c] Evaluated by ^{1}H NMR spectroscopy of the crude reaction mixture after benzoylation and methylation. [d] Evaluated by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as a chiral shift reagent.

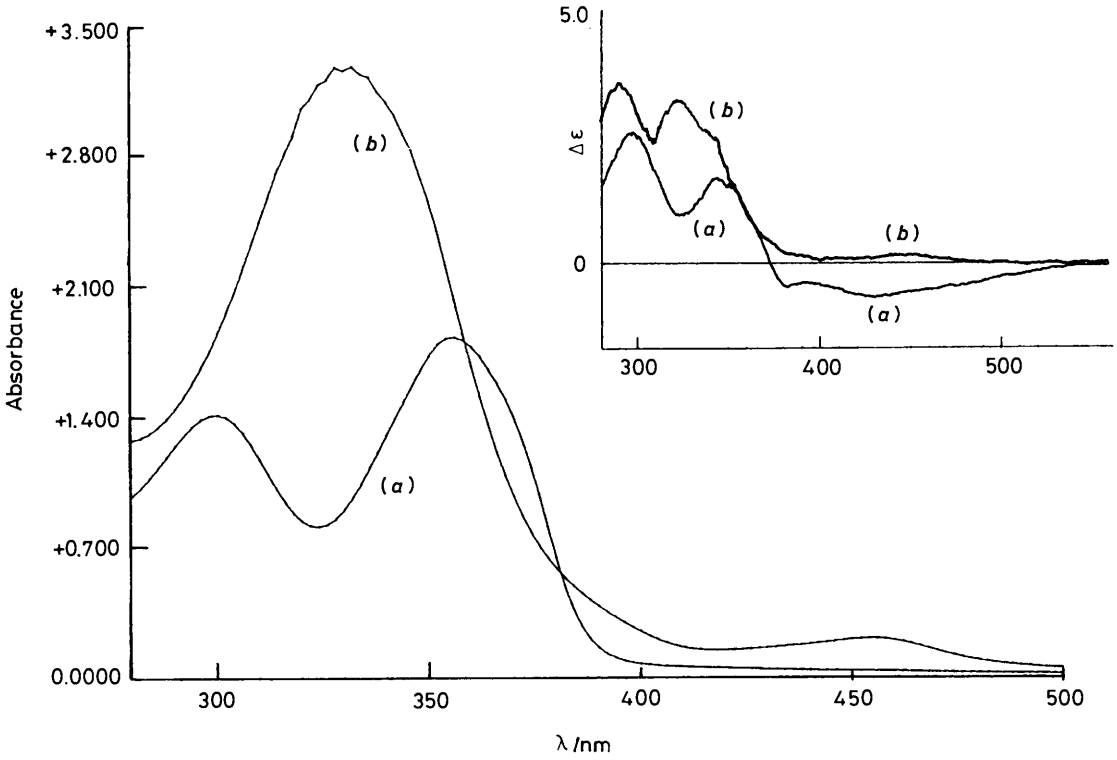


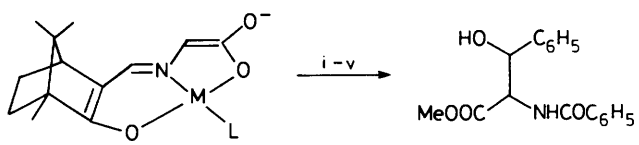
Figure 3. Electronic and circular dichroism (insert) spectra of a DMSO solution of the copper(II) complex of the glycine imine: (*a*) before and (*b*) after the addition of excess potassium t-butoxide. [complex], 2.18 × 10^{-3} mol dm^{-3}; cell path length, 0.1 cm.

This shows that the complexes are optically stable in the presence of moderate amounts of strong base.

The condensation of benzaldehyde with the zinc(II) and copper(II) complexes was performed under various experimental conditions in order to ascertain possible variations in the stereochemical outcome of the reaction. As already reported[7] the transformation of β-phenylserines into the corresponding *N*-benzoyl alkyl esters allows the diastereoisomeric and enantiomeric excesses to be determined. In fact, the ^{1}H NMR signals of the α-CH group occur as a doublet of doublets at δ 5.07 for the *threo* and δ 5.22 for the *erythro* diastereoisomers. This assignment was confirmed by an analysis of the derivatives of pure *threo*- and *erythro*-β-phenylserine samples. The enantiomeric excess for the two diastereoisomers was determined by ^{1}H NMR experiments using Eu(hfc)$_3$, which produces a clear separation of the ester methyl resonances. The preparation of the derivatives (**7**) was performed following the steps indicated in the Scheme.

The results in terms of diastereoisomeric ratios and enantiomeric excesses are collected in Table 1 and 2. Preliminary experiments run on the zinc(II) and copper(II) complexes showed that weak bases like pyridine or triethylamine, even at a large excess and in reflux conditions (acetonitrile or pyridine) were unable to promote the condensation of the aldehyde at reasonable rates. Therefore, much stronger bases such as potassium t-butoxide (Bu^{t}OK) or lithium diisopropylamide (LDA) had to be used. Potassium hydroxide in polyethylene glycol was also tested in order to ascertain conditions of more practical applicability.

The nature of the base plays an important role in the stereochemical outcome of the reaction. In general, potassium



(**6**) (**7**)

Scheme. *Reagents*: i, PhCHO; ii, H_3O^+; iii, H_2S; iv, PhCOCl, KOH; v, CH_2N_2.

Table 2. Diastereoisomeric ratio and enantiomeric excess (ee) of *N*-benzoyl-β-phenylserine methyl esters from the reaction between benzaldehyde and the zinc(II) complex.

Base (solvent)	Molar ratio[a]	*T*/°C	Yield (%)[b]	*threo*:*erythro*[c]	ee (*threo*)[d]	ee (*erythro*)[d]
LDA (THF)	1:1	−78			no reaction	
LDA (THF)	1:2	−78	10	1:1	0	4
LDA (THF)	1:3	−78	25	1:1.9	2	9
Bu^{t}OK (THF)	1:3	20	45	1.3:1	0	9
KOH (PEG 400)	1:5	20			no reaction	

[a] Molar ratio metal complex:base. [b] Total yields evaluated on the mixture of *threo* and *erythro* diastereoisomers. [c] Evaluated by ^{1}H NMR spectroscopy of the crude reaction mixture after benzoylation and methylation. [d] Evaluated by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as a chiral shift reagent.

t-butoxide gives much better diastereo- and enantio-selectivity in comparison with lithium di-isopropylamide and is also superior in terms of the chemical yields of the β-phenylserines produced. These differences may be due to the presence of co-ordination equilibria between the added base and the metal complex; it seems difficult to assume that the t-butoxide anion can co-ordinate to the negatively charged metal complex, whereas this possibility should not be precluded for the di-isopropylamine formed during the deprotonation step by LDA since the amine is a good donor ligand for either copper(II) or zinc (II).

The copper(II) complex shows higher reactivity and stereoselectivity with respect to the zinc(II) complex. This is particularly true for the reactions carried out with potassium t-butoxide as a base. It is also interesting to note that the reaction with potassium hydroxide leads to the highest diastereoisomeric excess with non-negligible enantiomeric enrichment in the two forms.

It is useful to compare the stereochemical outcome of this reaction with that reported for a similar condensation on the glycine residue using (+)-ketopinic acid as chiral auxiliary.[7] In that case higher enantioselectivities but lower diastereoselectivities were observed. It is likely that the methylene group of the glycine residue can approach somewhat more closely the chiral centres of the bicyclic skeleton in the ketopinic than in the hmb imine complex. Better ligand systems which take into account this factor are currently under development in our laboratories.

Experimental

Elemental analyses were carried out in the microanalytical laboratory of our Departments using a Perkin-Elmer 240 instrument. IR spectra were recorded on a Nicolet MX-1E FT instrument. Electronic and circular dichroism spectra were obtained on a HP 8452 A diode array spectrophotometer and a Jasco J-500 C dichrograph, respectively. ^{1}H NMR spectra were measured in [$^2H_6$]DMSO with a Bruker 200 AC spectrometer operating at 200 MHz. All reagents were of the highest grade commercially available and used as received. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride. Medium pressure chromatography was carried out with Merck Kieselgel 60 (0.040–0.062 mm, 230–400 mesh ASTM). (1*R*)-3-Hydroxymethylenebornan-2-one (hmb) was synthesized according to a literature procedure.[11] The zinc(II) and copper(II) complexes were prepared from equimolar amounts of hmb, glycine and the metal acetate in ethanol–water following essentially the general method of preparation of this type of imine complexes.[9]

Copper(II) *Complex*.—(Found: 49.52; H, 5.76; N, 4.54. Calc. for $C_{13}H_{17}NO_3Cu\cdot H_2O$: C, 49.28; H, 6.00; N, 4.42%). IR (Nujol ν_{max} 3 300 br (OH), 1 630 s, 1 622 s (C=N), (COO), 1 576 sh, 1 496 s (ring), and 1 430 m cm^{-1} (COO).

Zinc(II) *Complex*.—(Found: C, 48.21; H, 5.52; N, 4.19. Calc. for $C_{13}H_{17}NO_3Zn\cdot H_2O$: C, 48.99; H, 5.96; N, 4.39%). IR (Nujol ν_{max} 3 350 br (OH), 1 604 vs, br (C=N), (COO), (C=C), 1 540 m, 1 505 s (ring), and 1 411 m cm^{-1} (COO).

Condensation between Benzaldehyde and Metal Complexes. General Procedure.—The copper(II) and zinc(II) complexes were previously refluxed in benzene using a Dean–Stark apparatus in order to remove water. To a suspension of the complex (1 mmol) in anhydrous THF (7 cm^3) was added the appropriate quantity of potassium t-butoxide (Tables 1 and 2) and benzaldehyde (3 mmol) at room temperature and the mixture was stirred at this temperature for 10 h. The solvent was evaporated, the residue taken up with water (10 cm^3) and acidified with aqueous HCl (1 mol dm^{-3}) to pH 1 in order to hydrolyse the Schiff base. The metal ion was removed by precipitation with hydrogen sulphide at pH 1 for copper(II) and pH 4 for zinc(II). The mixture was filtered and the filtrate, after neutralization with an aqueous 5% $NaHCO_3$ solution, was extracted with diethyl ether (3 × 20 cm^3) in order to remove the hmb residue. To the aqueous solution was added potassium hydroxide (2 mmol) and benzoyl chloride (2 mmol) and the mixture was stirred overnight at room temperature. Aqueous sulphuric acid (3 cm^3; 0.5 mol dm^{-3}) was added and the reaction mixture was extracted with ethyl acetate (3 × 15 cm^3). The organic phase was dried over sodium sulphate and evaporated under reduced pressure. The residue was dissolved in diethyl ether (5 cm^3) and treated with an ethereal solution of diazomethane until a permanent light yellow colour persisted. After evaporation of the solvent, the residue was purified by medium pressure chromatography with a gradient of light petroleum–ethyl acetate from 7:3 to 1:1 (v/v). The *threo*- and *erythro*-*N*-benzoyl-β-phenylserine methyl esters could be obtained in a pure form.[12]

When lithium di-isopropylamide was used as a base the reaction between the metal complex (1 mmol) and benzaldehyde (3 mmol) in dry THF (7 cm^3) was carried out at −78 °C under a nitrogen atmosphere for 2 h. The subsequent procedures were as described above. When potassium hydroxide was used as a base, the metal complex (1 mmol) was dissolved in anhydrous polyethylene glycol (PEG 400, 6 cm^3). To this solution was added anhydrous potassium hydroxide (5 mmol) and benzaldehyde (3 mmol) and the mixture was stirred at room temperature for 4 days. The subsequent operations were performed as above.

The ^{1}H NMR data ($CDCl_3$) for the diastereoisomeric β-phenylserine derivatives (7) are as follows: *threo* form: δ 7.72–7.65 (2 H, m), 7.50–7.25 (8 H, m), 6.95 (1 H, d, *J* 8.5 Hz), 5.39 (1 H, d, *J* 3.1 Hz), 5.07 (1 H, dd, *J* 8.5, 3.1 Hz), and 3.75 (3 H,

s); *erythro* form: δ 7.79–7.70 (2 H, m), 7.54–7.27 (8 H, m), 6.90 (1 H, d, *J* 7.5 Hz), 5.38 (1 H, *J* 3.6 Hz), 5.22 (1 H, dd, *J* 7.5, 3.6 Hz), and 3.77 (3 H, s).

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