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Stereocontrol of the Horner–Wadsworth–Emmons Reaction: Application to the Synthesis of HIV-1 Protease Inhibitors

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A systematic study on the Horner–Wadsworth–Emmons (HWE) reaction has shown that ethyl diphenylphosphonoacetate and methyl diphenylphosphonoacetate give a high excess of (*Z*)-alkenes. These reaction conditions were then used to prepare (*Z*)-ethyl-5-phenylpent-2-enoate, the corresponding (*E*)-isomer being prepared by standard Wittig chemistry. Reduction of each allylic ester, with diisobutylaluminium hydride (DIBAL), gave the allylic alcohols (15) and (19), respectively. Epoxidation of (15) and (19), under Sharpless conditions, gave separate samples of all four stereoisomers of 2,3-epoxy-5-phenylpentan-1-ol. Esterification of each isomer with Cbz-valine, under Mitsunobu conditions, provided (9)–(12) which were assayed against HIV protease. The *cis* series (9)–(10) proved to be significantly more potent than the *trans* (11)–(12) and, within each of these series, the isomers derived from L-diisopropyltartrate [(9) and (11)] were the most active.

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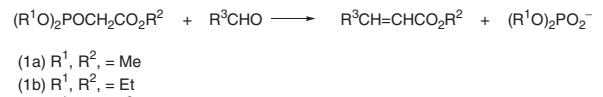
Introduction

The Horner–Wadsworth–Emmons (HWE) reaction of a resonance-stabilized phosphonate carbanion (1) and an aldehyde (2), or ketone, is a well established method for the introduction of carbon–carbon double bonds (see Scheme 1).[1,2] The utility of this reaction is facilitated by the fact that its stereochemical outcome can be controlled; for example, the structure of the phosphonate, the nature of the base, the structure of the carbonyl reagent and the reaction temperature all influence the *E*-to-*Z* product ratios.[1–6] However, most of the work published in this area is rather fragmented so that there are comparatively few systematic studies[6] addressing these issues. In this paper we present a detailed study of the effect of some of these reaction parameters on the outcome of reactions of phosphonates (1) with a range of aldehydes. The optimum conditions for the formation of the (*Z*)-alkene were then used to synthesize some epoxide-based inhibitors of HIV protease which were assayed against the enzyme.



(1a) R^1, R^2, = Me
(1b) R^1, R^2, = Et
(1c) R^1 = Ph, R^2 = Me
(1d) R^1 = Me, R^2 = Et
(1e) R^1 = Et, R^2 = Me
(1f) R^1 = Pr^i, R^2 = Me
(1g) R^1 = 4-$MeOC_6H_4$, R^2 = Me
(1h) R^1 = 3-$MeOC_6H_4$, R^2 = Me

Scheme 1

Results and Discussion

Model Studies

We initially investigated reactions of the phosphonates [(1a–c), see Scheme 1] with three types of aldehyde, (2a–b), (2c–f), (2g–j), where R^3 is conjugated to the carbonyl, is unbranched aliphatic, and is α-branched aliphatic, respectively. This was done in an attempt to ascertain the effect of aldehyde structure on the stereochemical outcome of HWE reactions (see Table 1). In this study, the aldehydes were reacted at either room temperature or –78°C with the anion derived from the phosphonate. The anion itself was generated from a tetrahydrofuran (THF) solution of the phosphonate at 0°C, on treatment with n-butyllithium. The *E*-to-*Z* ratio of products was determined by integration of the alkene protons in the ^{1}H nuclear magnetic resonance (NMR) spectrum of the crude reaction mixtures. The product alkenes were then isolated and characterized.

The reactions of the conjugated aldehydes benzaldehyde (2a) and cinnamaldehyde (2b) with the anion derived from trimethyl phosphonoacetate (1a) at –78°C gave a very strong preference for formation of the (*E*)-isomer. For both aldehydes the *E*-to-*Z* product ratio was greater than 19 : 1 (see Table 1). This selectivity has been noted previously in related studies.[7,8] Similarly, reactions of (1a) with the unbranched aliphatic aldehydes (2c–f) gave a strong preference for the (*E*)-alkene at both room temperature and –78°C (see Table 1). However, it is interesting to note that the preference for the (*E*)-isomer, in these reactions, decreases somewhat with

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Table 1. HWE reactions of phosphonates (1a–c) with aldehydes (2)

$(R^1O)_2POCH_2CO_2R^2$ + R^3CHO ⟶ $R^3CH{=}CHCO_2R^2$
(1) (2) (3)

	Aldehyde (2) R^3	Phosphonates (E:Z) (1a); $R^1 = R^2 = Me$ Room temp.	–78°C	(1b); $R^1 = R^2 = Et$ Room temp.	–78°C	(1c); $R^1 = Ph$, $R^2 = Me$ –78°C
(2a)	Ph	—	>19:1	—	>19:1	—
(2b)	PhCH=CH	—	>19:1	—	—	—
(2c)	Me	11:1	8:1	—	—	—
(2d)	Et	7:1	3.6:1	>19:1	9.3:1	1:1.3
(2e)	$Me(CH_2)_5$	5.5:1	2:1	>19:1	9.4:1	1:7
(2f)	$Me(CH_2)_9$	5.7:1	2:1	—	—	—
(2g)	Me_2CH	4.5:1	1:2.8	13:1	1.5:1	1:3.3
(2h)	$Me(CH_2)_8CHMe$	3.8:1	1:2.8	—	—	1:5.7
(2i)	cyclohexyl	3.4:1	1:3	—	—	—
(2j)	Et_2CH	3.6:1	1:5	12:1	1.5:1	1:3.8

Table 2. Effect of R^1 and R^2 on the outcome of HWE reactions at –78°

$(R^1O)_2POCH_2CO_2R^2$ + R^3CHO ⟶ $R^3CH{=}CHCO_2R^2$
(1) (2) (3)

Phosphonate (1)			E-to-Z ratio of alkenes (3) obtained on reaction of the indicated aldehyde (2)		
	R^1	R^2	(2a); $R^3 = Ph$	(2e); $R^3 = Me(CH_2)_5$	(2g); $R^3 = Me_2CH$
(1a)	Me	Me	>19:1	2:1	1:2.8
(1b)	Et	Et	>19:1	9.4:1	1.5:1
(1d)	Me	Et	>19:1	1.2:1	1:2.9
(1e)	Et	Me	>19:1	6.7:1	2.4:1
(1f)	iPr	Me	>19:1	>19:1	10:1

increasing chain length of R^3. By contrast, reactions of the more sterically hindered α-branched aliphatic aldehydes (2g–j), with the anion of (1a) at –78°C, gave a predominance of the (*Z*)-alkene (Table 1), the extreme case being the reaction of (2j) at –78°C where an *E*-to-*Z* ratio of 1:5 was observed (cf. (2g) which gave an *E*-to-*Z* ratio of 1:2.8 under the same conditions). A preference for the (*E*)-alkene remained in the equivalent reactions at room temperature.

The anion derived from triethyl phosphonoacetate (1b) was also reacted with the aldehydes (2d), (2e), (2g) and (2j) to ascertain the generality of these observations (see Table 1). Here, again, we found that the amount of (*Z*)-isomer formed increased with the increasing bulk of the R^3 group. However, unlike the reactions of (1a), the (*E*)-isomer still predominated in the reactions of aldehydes (2g) and (2j) at –78°C. Again we noted, as have others,[6] that a lower reaction temperature favours the formation of the (*Z*)-alkene.

The results of the reactions of a selection of aldehydes with a third phosphonate (1c), where R^1 is aromatic,[9] are also summarized in Table 1. In this case all aldehydes gave a predominance of the (*Z*)-alkene with the sterically most demanding examples again giving the greatest excess, in general. From the studies presented in Table 1 it appears that the nature of R^1 and R^2 of the phosphonate (1) has a significant effect on the stereochemical outcome of these reactions where the amount of the (*Z*)-alkene was greatest for reactions involving (1c) followed by (1a) and (1b).

The reactions of the anions derived from the phosphonates (1d–f) were studied to determine which of R^1 or R^2 was most important to the stereochemical outcome of these reactions (see Table 2). From these results it is clear that the nature of the phosphonate has little effect on reactions with aromatic aldehydes such as (2a), where an *E*-to-*Z* ratio of > 19:1 was observed in all cases. However, the nature of R^1 does appear to be important for the stereochemical outcome in reactions of the other aldehydes. For example, reaction of (2e) or (2g) with phosphonates (1a) and (1e), both of which have R^2 = Me but R^1 = Me and Et, respectively, gave products with a significantly different *E*-to-*Z* ratio. The formation of (*Z*)-alkene is favoured when R^1 is small, i.e. Me.[10] The phosphonate (1f), which contains a large isopropyl group at R^1, gave the poorest (*Z*)-selectivity in reactions with (2a), (2e) and (2g). A similar trend is evident on comparing the outcomes of the reactions of (1b) and (1d). The nature of R^2 seems to be comparatively unimportant for the stereochemical outcome of these reactions (cf. reactions of (1a)–(1d) and (1b)–(1e) in Table 2).

In the last series of reactions we considered the effect of the electronic properties of the phenyl group in phosphonates of the type (1c). We had already observed that (1c) led to elevated levels of the (*Z*)-alkene relative to the other phosphonates (see Table 1). Two new phosphonates were prepared and studied, one bearing a *para*-methoxy substituent (1g) and the other a *meta*-methoxy substituent (1h) (see Scheme 1).* Reaction of the phosphonate (1g) with (2e) and (2g) at –78°C gave a significant increase in the amount of (*E*)-alkene produced (an *E*-to-*Z* ratio of 1:4.2 and 1:2.1 for (2e) and (2g), respectively) relative to the equivalent reactions of (1c) (an *E*-to-*Z* ratio of 1:7 and 1:3.3 for (2e) and (2g), respectively, see Table 1). By contrast, the reaction of (1h) with the same aldehydes gave equivalent results to reactions of (1c) (an *E*-to-*Z* ratio of 1:7.2 and 1:3.3 for (2e) and (2g), respectively). From these results it is

* These phosphonates were chosen due to the availability of the starting materials used in their synthesis[9] and due to the differing electronic properties of *meta* and *para* substitution.

apparent that (*E*)-alkene formation is favoured by using phosphonates that have an electron-rich aryl group at R^1.

Synthesis of HIV-1 Protease Inhibitors

A number of epoxide-based inhibitors of HIV protease are known. For example, 1,2-epoxy-3-(*p*-nitrophenoxy)propane (EPNP) [(4),[11] see Fig. 1] is a relatively weak irreversible inhibitor (k_{inact} 11 mM), where the nitrophenoxy group is thought to reside in the S_1 pocket† of the enzyme's active site. Modifications to the structure of EPNP led to the development of the tripeptidomimetic epoxide (5) (k_{inact} 20 μM), which spans the S_3–S_1' subsites of the enzymes active site.[12] C_2-Symmetric epoxides such as compound (6) are reversible HIV-1 protease inhibitors (K_i 75 nM),[13] while the non-peptidic epoxide (7) is an irreversible inhibitor of HIV-1 protease (K_{inact} 65 μM).[14] Previous work in our laboratories led to the development of the peptidomimetic irreversible inhibitor (8) (K_{inact} 1.8 μM).[15] We now report the synthesis and assay of a series of epoxide-based HIV-1 protease inhibitors (9)–(12) (see Fig. 2). These compounds

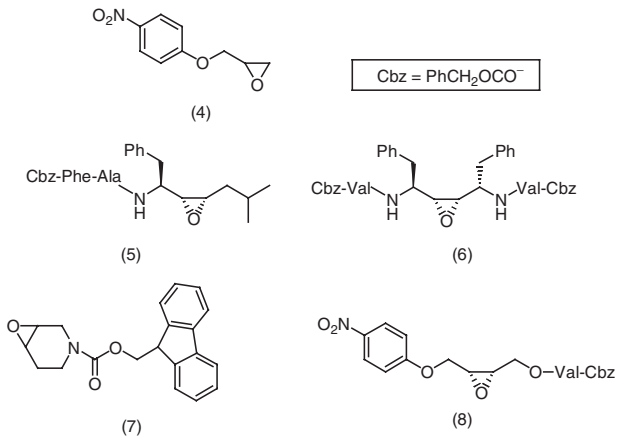


Fig. 1. Structures of a number of epoxide-based inhibitors of HIV protease.

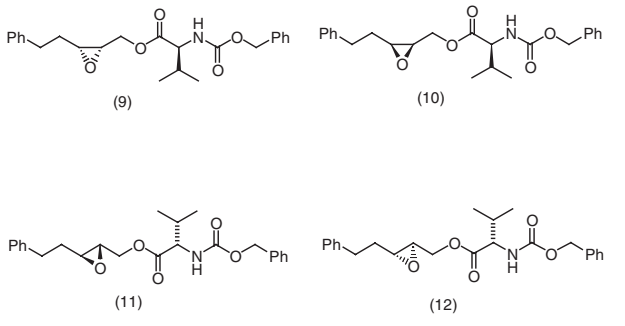
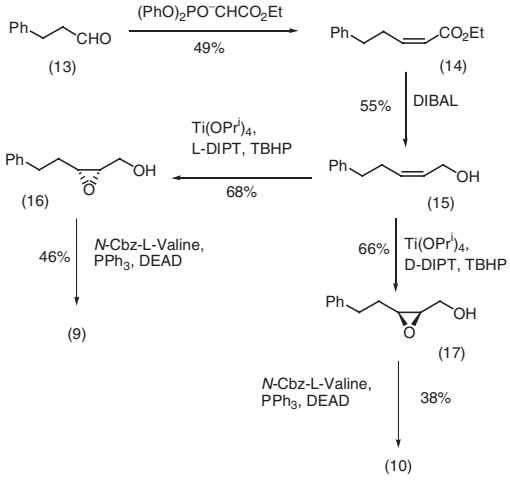
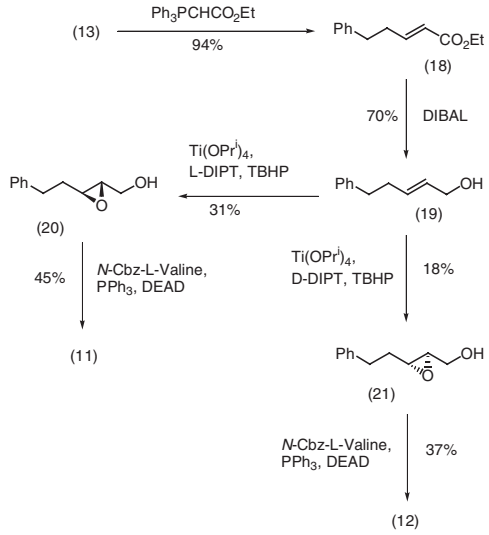


Fig. 2. Structures of the epoxide-based HIV-1 protease inhibitors (9)–(12) synthesized here.



Scheme 2



Scheme 3

were prepared to probe the effect of extending the peptide sequence of (4) in the C-direction and also the effect of the configuration of the epoxide on inhibitory activity. The strategy for the synthesis of these compounds was based upon key HWE and Wittig preparations of (14) and (18). Subsequently, epoxidation under Sharpless conditions gave the four isomeric epoxides which were elaborated into the target compounds (see Schemes 2 and 3).‡

A HWE reaction of hydrocinnamaldehyde (13) with the anion of ethyl diphenylphosphonoacetate,§ generated by n-butyllithium in THF at –78°C, gave the (*Z*)-allylic ester (14) in 49% yield, the crude mixture contained the (*Z*) and (*E*) isomers in a ratio of 8:1 [cf. results for (1c) in Table 1]. Reduction of (14) with diisobutylaluminium hydride

† Note the use of Schechter–Berger nomenclature (I. Schechter, A. Berger, *Biochem. Biophys. Res. Commun.* **1967**, *27*, 157). The residues on the amino-terminal side of the peptide bond that is to be cleaved are denoted P_1–P_n, and those on the carboxy-terminus are denoted P_1'–P_n'. In turn, the corresponding subsites on the enzyme are denoted S_n–S_n'.

‡ A phenyl group was chosen in place of the nitrophenoxy group of (7) because the synthetic precursor is commercially available and the nitrophenoxy group interferes with the HIV protease inhibitory assay.

§ Ethyl diphenylphosphonoacetate was used in place of methyl diphenylphosphonoacetate (1c) in these reactions because it was at hand and since we had already demonstrated that the nature of R^2 is comparatively unimportant to the stereochemical outcome.

Table 3. Inhibition of HIV Protease

Compound	Inhibition (%)[A]
(8)[B]	88[C]
(9)	100
(10)	26
(11)	16
(12)	9

[A] Assay conditions: after 1 min, pH 6.5, 37°C, [S] 50 μM, [I] 200 μM. [B] Reference 15. [C] [I] 20 μM.

(DIBAL) gave the corresponding (*Z*)-allylic alcohol (15) in 55% yield. Separate samples of this were then epoxidized under Sharpless conditions, using both L-diisopropyltartrate (L-DIPT) and D-DIPT, to give (16) and (17) respectively. These were then treated with *N*-Cbz-L-valine and diethylazodicarboxylate (DEAD)/PPh_3 to give the compounds (9) and (10) in 46 and 38% yields, respectively. The remaining stereoisomers (11) and (12) were prepared by an analogous route using the (*E*)-alkene (18), which was prepared using standard Wittig chemistry (see Scheme 3). Here, the key Wittig reaction gave a 14:1 ratio of (*E*)- to (*Z*)-alkenes.[16] The required (*E*)-alkene (18), isolated in 94% yield, was then reduced and used in the subsequent Sharpless chemistry as detailed in Scheme 3.

It is interesting to note that the ^{13}C NMR spectra of the isomeric pairs (9)–(10) and (11)–(12) show some diagnostic features. The spectra of (11) and (12) are essentially identical with the following exceptions: (i) one of the epoxide carbon resonances was observed at δ 55.9 and 56.0 for (11) and (12), respectively; (ii) the epoxide-CH_2O resonance was observed at δ 65.0 and 65.4 for (11) and (12) respectively; (iii) (11) revealed seven aromatic resonances while (12) showed only six; (iv) the carbobenzyloxy (Cbz) carbonyl resonance was observed at δ 156.2 and 159.4 for (11) and (12), respectively. The spectra of (9) and (10) reveal similar trends: (i) the epoxide carbon resonance differed (δ 53.6 and 53.8 for (9) and (10), respectively); (ii) the epoxide-CH_2O resonance differed (δ 63.3 and 63.4 for (9) and (10) respectively); (iii) (9) revealed seven aromatic resonances while (10) showed only six; (iv) the carbobenzyloxy (Cbz) carbonyl resonance differed (δ 156.1 and 155.7 for (9) and (10), respectively). Some other minor differences were also observed for (9) and (10), see experimental section for details.

Assay Against HIV Protease

Compounds (9)–(12) were assayed against HIV protease as previously detailed.[15,17] The first thing to note from the results presented in Table 3 is that, as expected, all compounds assayed in the current study were less active than (8),[15] where this compound contains a more optimum *para*-nitrophenoxy group as found in EPNP (4).[11] However, what is critical is that the *cis* series, (9)–(10), was significantly more active[18] than the *trans*, (11)–(12). In addition, it is apparent that within each series, the two isomers derived from L-DIPT [(9) and (11)] are the most active.

Conclusions

In summary, an investigation of the HWE reaction has led to the determination of experimental conditions to optimize the formation of (*E*)- and (*Z*)-alkenes. We have shown, as have others, that the nature of the aldehyde and R^1 in the phosphonate have a significant influence on the stereochemical outcome. The optimum phosphonate for (*Z*)-alkene formation, namely ethyl diphenylphosphonoacetate or methyl diphenylphosphonoacetate, was then used to prepare a series of isomeric epoxide-based HIV protease inhibitors that reveal some interesting structure–activity trends.

Experimental

NMR spectra were recorded on either a Varian Unity 300 or XL-300 spectrometer, and are reported in ppm relative to Me_4Si. Mass spectrometry (MS) was performed on a Kratos MS80RFA spectrometer. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8201PC spectrophotometer. Optical rotations were measured on a JASCO J-20C recording spectropolarimeter and $[\alpha]_D$ values are given in units of 10^{-1} ° cm^2 g^{-1}, with the concentration (*c*) given in units of mg cm^{-3}. Microanalyses were performed at the Department of Chemistry, University of Otago, Dunedin, New Zealand. Radial chromatography was performed on a Harrison and Harrison Chromatotron using 1 and 2 mm plates. Column chromatography was performed using 230–400 mesh Merck Silica Gel 60 under positive air pressure. Light petroleum refers to the fraction with a boiling point of 50–70°C. The starting phosphonates (1) were either purchased or prepared using standard methods.[9]

General Procedure for Reactions of the Phosphonates (1)

A stirred solution of the phosphonate (1) (1.4 mmol) in dry THF (2.5 mL) was cooled to 0°C under a nitrogen atmosphere and n-butyllithium (1.4 mmol of a 1.6 M solution in hexane) was added dropwise. After 10 min, the solution was brought to the desired temperature, and the aldehyde (2) (1.22 mmol) was added dropwise. The resultant mixture was stirred for 1.5 h and then quenched with water (3 mL) and ether (5 mL). The organic phase was washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by evaporation under reduced pressure. The residue was analysed by ^1H NMR spectroscopy and finally purified by column chromatography on silica. The NMR spectra of the simple alkenes (2) were compared with literature data.[19]

(Z)-Ethyl-5-phenylpent-2-enoate (14)

The general procedure was adopted using ethyl diphenylphosphonoacetate (1.74 g, 5.43 mmol), dry THF (15 mL), n-butyllithium (4.2 mL of a 1.6 M solution in hexane, 6.7 mmol), a temperature of –78°C and the aldehyde (13) (610 mg, 4.55 mmol). The residue was purified by column chromatography (90% light petroleum, 10% ethyl acetate) to give (14) (457 mg, 49%) and (18) (53 mg, 6%).[16]

(Z)-5-Phenylpent-2-en-1-ol (15)

A solution of (14) (321 mg, 1.6 mmol) in dry CH_2Cl_2 (20 mL) was cooled to –78°C under a nitrogen atmosphere, and diisobutylaluminium hydride (DIBAL, 6.1 mL of a 1 M solution in CH_2Cl_2, 6.1 mmol) was added dropwise. The resultant solution was stirred for 3 h at –78°C, and water (1 mL) was then added over 5 min, followed by 10% aqueous potassium sodium tartrate (10 mL). The mixture was then warmed to room temperature and the aqueous layer was separated and extracted three times with CH_2Cl_2. The combined organic extracts were washed with water, dried over anhydrous $MgSO_4$, and the solvent was removed by evaporation under reduced pressure. The residue was purified by radial chromatography on silica (70% light petroleum, 30% ethyl acetate) to give (15) as a *colourless oil* (140 mg, 55%) (Found: 162.1045. $C_{11}H_{14}O$ requires 162.1045). ^1H NMR ($CDCl_3$) δ 7.17–7.32, 5H, m, ArH; 5.59,

2H, m, CH; 4.00, 2H, d, *J* 5.9 Hz, C**H**$_2$OH; 2.69, 2H, t, *J* 7.3 Hz, PhC**H**$_2$; 2.40, 2H, q, *J* 7.3 Hz, CH_2; 1.23, br s, 1H, OH. ^{13}C NMR ($CDCl_3$) δ 141.5; 128.6; 128.3; 126.0; 131.5; 129.3; 58.3; 35.6; 29.2.

(2S,3R)-2,3-Epoxy-5-phenylpentan-1-ol (16)

A solution of titanium tetraisopropoxide (701 mg, 2.5 mmol) and 4Å molecular sieves (250 mg) in dry CH_2Cl_2 (25 mL) was cooled to –25°C under a nitrogen atmosphere. A solution of L-(+)-diisopropyl tartrate (L-DIPT, 691 mg, 3.0 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise, followed by (15) (395 mg, 2.5 mmol) in dry CH_2Cl_2 (4 mL). The resultant solution was stirred for 30 min, t-butylhydroperoxide (TBHP, 1 mL of a 4.8 M solution in CH_2Cl_2, 4.8 mmol) was added and the resultant solution was stored at –20°C for 20 h. The reaction was quenched with 10% aqueous tartaric acid (25 mL), the organic phase was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic fractions were dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by evaporation under reduced pressure. Excess peroxide was removed by azeotropic distillation with CCl_4 and the crude mixture was purified by radial chromatography on silica (60% light petroleum, 40% ethyl acetate) to give (16) as a *colourless oil* (303 mg, 68%) (Found: 160.0888. $C_{11}H_{12}O$ requires $[M-H_2O]^+$ 160.0888). IR (thin film) 3422(br), 3026, 2928, 2860, 1603 cm^{-1}. $[\alpha]_D^{23}$ –1.9 (*c*, 10.9 in $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.19–7.34, 5H, m, Ar**H**; 3.57, 2H, d, *J* 5.4 Hz, C**H**$_2$OH; 3.11, 2H, m, 2xCHO; 2.88, 1H, m, PhC**H**$_2$; 2.73, 1H, m, PhC**H**$_2$; 2.01, 1H, m, CH_2; 1.81, 1H, m, CH_2; 1.34, 1H, br s, OH. ^{13}C NMR ($CDCl_3$) δ 140.4; 128.0; 127.9; 125.7; 60.0; 56.6; 56.1; 32.2; 29.2.

*(2S,3R)-*N*-Cbz-L-Valine 2,3-Epoxy-5-phenylpentyl Ester (9)*

To a solution of (16) (15 mg, 0.08 mmol) in dry THF (1.5 mL) was added *N*-Cbz-L-valine (46 mg, 0.19 mmol) and triphenylphosphine (46 mg, 0.18 mmol). After stirring the mixture for 5 min, DEAD (31 mg, 0.18 mmol) was added dropwise, and the resultant solution was stirred at room temperature for 3 h, after which CH_2Cl_2 was added. The crude mixture was washed three times with saturated aqueous $NaHCO_3$, the organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent was removed by evaporation under reduced pressure. The residue was purified by radial chromatography on silica (80% light petroleum, 20% ethyl acetate) to give (9) as a *colourless oil* (16 mg, 46%) (Found: 411.2049. $C_{24}H_{29}NO_5$ requires 411.2046). IR ($CHCl_3$) 3436, 2968, 1722, 1511 cm^{-1}. $[\alpha]_D^{23}$ –6.1 (*c*, 16.0 in $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.19–7.35, 10H, m, Ar**H**; 5.25, 1H, d, *J* 8.8 Hz, CHN**H**; 5.11, 2H, br s, CO_2C**H**$_2$Ph; 4.36, 1H, dd, *J* 4.4, 8.8 Hz, C**H**NH; 4.19, 1H, dd, *J* 4.4, 12.2 Hz, CHC**H**$_2$O; 4.05, 1H, dd, *J* 6.3, 12.2 Hz, CHC**H**$_2$O; 3.14, 1H, m, C**H**CH$_2$O; 3.06, 1H, m, CH_2CH_2C**H**; 2.72–2.89, 2H, m, PhC**H**$_2$CH$_2$; 2.18, 1H, m, C**H**(Me)$_2$; 1.87, 2H, m, PhCH$_2$C**H**$_2$; 0.98, 3H, d, *J* 6.9 Hz, Me; 0.90, 3H, d, *J* 6.9 Hz, Me. ^{13}C NMR ($CDCl_3$) δ 171.8; 156.1; 140.6; 128.52; 128.50; 128.4; 128.2; 128.1; 126.2; 67.0; 63.3; 59.0; 55.9; 53.6; 32.6; 31.2; 29.8; 18.9; 17.5.

(2R,3S)-2,3-Epoxy-5-phenylpentan-1-ol (17)

The reaction was performed as described for (16) using Ti(OPr^i)$_4$ (113 mg, 0.40 mmol), D-(–)-diisopropyl tartrate (105 mg, 0.45 mmol), 4 Å molecular sieves (50 mg) (15) (58 mg, 0.36 mmol) and t-butylhyroperoxide (TBHP) in CH_2Cl_2 (0.24 mL of a 3 M solution, 0.72 mmol). Workup and purification gave (17) as a colourless oil (42 mg, 66%), with identical ^{1}H NMR data to (16).

*(2R,3S)-*N*-Cbz-L-Valine 2,3-Epoxy-5-phenylpentyl Ester (10)*

The preparation was performed as described for (9) using (17) (16 mg, 0.09 mmol). Purification of the residue by radial chromatography on silica (75% light petroleum, 25% ethyl acetate) gave (10) as a *colourless oil* (14 mg, 38%) (Found: 411.2051. $C_{24}H_{29}NO_5$ requires 411.2046). ^{1}H NMR ($CDCl_3$) δ 7.19–7.36, 10H, m, Ar**H**; 5.28, 1H, d, *J* 8.8 Hz, CHN**H**; 5.11, 2H, br s, CO_2C**H**$_2$Ph; 4.34, 1H, dd, *J* 4.9, 9.3 Hz, C**H**NH; 4.15, 1H, dd, *J* 3.9, 11.7 Hz, CHC**H**$_2$O; 4.05, dd, 1H, *J* 6.8, 11.7 Hz, CHC**H**$_2$O; 3.16, 1H, m, C**H**CH$_2$O; 3.07, 1H, m, CH_2CH_2C**H**; 2.87, 1H, m, PhC**H**$_2$CH$_2$; 2.74, 1H, m, PhC**H**$_2$CH$_2$; 2.19, 1H, m, C**H**(Me)$_2$; 1.87, 2H, m, PhCH$_2$C**H**$_2$; 0.98, 3H, d, *J* 6.8 Hz, Me; 0.90, 3H, d, *J* 6.8 Hz, Me. ^{13}C NMR ($CDCl_3$) δ 171.9; 155.7; 140.6; 128.5; 128.4; 128.2; 128.1; 126.3; 67.1; 63.4; 59.0; 55.9; 53.8; 32.7; 31.2; 29.8; 19.0; 17.5.

(2S,3S)-2,3-Epoxy-5-phenylpentan-1-ol (20)

The preparation was performed as described by the procedure for (16) using Ti(OPr^i)$_4$ (429 mg, 1.5 mmol), 4 Å molecular sieves (150 mg), and L-diisopropyl tartrate (421 mg, 1.8 mmol) (19)[16,20] (245 mg, 1.5 mmol), and TBHP in CH_2Cl_2 (1 mL of a 3 M solution, 3 mmol) was added. Purification of the residue by column chromatography (60% light petroleum, 40% ethyl acetate) gave (20) as a colourless oil (84 mg, 31%). The ^{1}H NMR, ^{13}C NMR and HRMS data of the product (20) were identical to those published.[20]

*(2S,3S)-*N*-Cbz-L-Valine 2,3-Epoxy-5-phenylpentyl Ester (11)*

The preparation was performed as described for (9) using (20) (23 mg, 0.13 mmol). Purification of the residue by column chromatography (80% light petroleum, 20% ethyl acetate) gave (12) as a *colourless oil* (24 mg, 45%) (Found: C, 70.0; H, 7.2; N, 3.5. $C_{24}H_{29}NO_5$ requires C, 70.0; H, 7.1; N, 3.4%). ^{1}H NMR ($CDCl_3$) δ 7.17–7.37, m, 10H, m, Ar**H**; 5.25, 1H, d, *J* 8.8 Hz, CHN**H**; 5.11, s, 2H, CO_2C**H**$_2$Ph; 4.31–4.41, 2H, m, CHC**H**$_2$O and C**H**NH; 3.96, 1H, dd, *J* 5.9, 12.2 Hz, CHC**H**$_2$O; 2.72–2.92, 4H, m, 2×–CHO–, PhC**H**$_2$CH$_2$; 2.17, 1H, m, C**H**(Me)$_2$; 1.88, 2H, m, PhCH$_2$C**H**$_2$; 0.98, 3H, d, *J* 6.8 Hz, Me; 0.90, 3H, d, *J* 6.8 Hz, Me. ^{13}C NMR ($CDCl_3$) δ 171.8; 156.2; 140.8; 128.54; 128.5; 128.4; 128.2; 128.1; 126.2; 67.1; 65.0; 59.0; 55.9; 55.2; 33.2; 32.1; 31.3; 18.9; 17.5.

(2R,3R)-2,3-Epoxy-5-phenylpentan-1-ol (21)

The preparation was performed as described for (16) using Ti(OPr^i)$_4$ (113 mg, 0.40 mmol), 4 Å molecular sieves (50 mg), D-diisopropyl tartrate (112 mg, 0.48 mmol) (19)[16,20] (64 mg, 0.40 mmol), and TBHP in CH_2Cl_2 (0.25 mL of a 3 M solution, 0.75 mmol). Purification of the residue by column chromatography (60% light petroleum, 40% ethyl acetate) gave (21) as a colourless oil (13 mg, 18%). The ^{1}H NMR and ^{13}C NMR spectra of the product (21) were identical to those published[21] and reported for (20).

*(2R,3R)-*N*-Cbz-L-Valine 2,3-Epoxy-5-phenylpentyl Ester (12)*

The preparation was performed as described for (9) using (21) (13 mg, 0.07 mmol). Purification of the residue by column chromatography (80% light petroleum, 20% ethyl acetate) gave (11) as a *colourless oil* (11 mg, 37%) (Found: C, 69.9; H, 6.9; N, 3.6. $C_{24}H_{29}NO_5$ requires C, 70.0; H, 7.1; N, 3.4%). ^{1}H NMR ($CDCl_3$) δ 7.18–7.38, 10H, m, Ar**H**; 5.29, 1H, d, *J* 9.3 Hz, CHN**H**; 5.12, 2H, s, CO_2C**H**$_2$Ph; 4.34, 2H, m, CHC**H**$_2$O and C**H**NH; 3.96, 1H, dd, *J* 6.3, 12.2 Hz, CHC**H**$_2$O; 2.70–2.95, 4H, m, 2×–CHO–, PhC**H**$_2$CH$_2$; 2.18, 1H, m, C**H**(Me)$_2$; 1.89, 2H, m, PhCH$_2$C**H**$_2$; 0.98, 3H, d, *J* 6.8 Hz, Me; 0.90, 3H, d, *J* 6.8 Hz, Me. ^{13}C NMR ($CDCl_3$) δ 171.8; 159.4; 140.8; 128.5; 128.4; 128.2; 128.1; 126.2; 67.1; 65.4; 59.0; 56.0; 55.2; 33.2; 32.1; 31.2; 18.9; 17.5.

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