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Synthesis of Chiral N-Protected α-Amino-β-Diketones from α-Diazoketones Derived from Natural Amino Acids

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Abstract: α-Diazoketols, prepared by condensation of aldehydes or ketones with lithiated optically active α-diazoketones derived from natural amino acids, rearrange to homochiral α-amino-β-diketones on treatment with rhodium(II) acetate.

The methine hydrogen atom of terminal α-diazocarbonyls, $RCOCHN_2$, is sufficiently acidic to be readily removed by a suitable base to furnish a nucleophilic anion capable of undergoing aldol type addition to aldehydes and ketones.[1] In early work Wenkert et. al.[2] used potassium hydroxide in methanol for the reaction. More recent studies suggest that LDA is the base of choice when high yields of aldol product are required and there are now several examples of formation of diazo lithioesters,e.g. ethyl diazo(lithio)acetate, and diazo lithioketones and their subsequent addition to aldehydes and ketones. Interest in this diazo-aldol reaction is derived largely from the chemical properties of the adduct formed. In particular, these β-hydroxy-α-diazocarbonyls are prone to loss of nitrogen with concomitant hydrogen or alkyl shifts to form β-dicarbonyl products. Although there have not been many reports dealing with the chemistry of α-diazo-β-hydroxyl carbonyl compounds, some representative examples have established the synthetic versatility of this diazo-aldol reaction. The formation of a β-ketoester *via* the diazo aldol reaction served as an important intermediate in Corey's total synthesis of (±)-atractyligenin[3]. The same methodology was employed by Pellicciari and co-workers to construct β-damascone[4], (22S)-22-hydroxy bile acid[5] and D-homo-steroid derivatives.[6]

As part of a programme directed towards the use of chiral diazoketones for homochiral group transfer in synthesis, in particular of diazoketones derived from readily available natural amino acids, we have applied the diazo aldol reaction and the subsequent rhodium-catalysed rearrangement to the preparation of novel α-amino β-dicarbonyl compounds from α-amino diazoketones.

Results and Discussions

The L-amino acids in **Scheme 1** were studied with N-protection in the form of ethoxycarbonyl or butoxycarbonyl(BOC) derivatives. These N-protected amino acids were converted into α-diazoketones *via* the acid chloride or the mixed anhydride by treatment with etheral diazomethane(**Scheme 1**). Chromatography afforded pure α-diazoketones in good yield(**Table 1**). The mixed anhydride method is particularly suitable for preparing the corresponding α-diazoketones from the acid sensitive N-BOC amino acids. These two methods of making α-diazoketones derived from N-protected amino acids have previously been shown to proceed without racemisation by chiral shift NMR studies[7]. The N-protected amino acid-derived diazoketone could be

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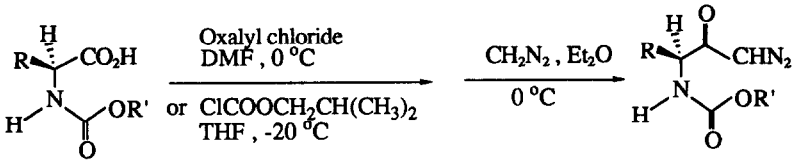
Dedicated to Professor C.W. Rees on the occasion of his 65th birthday

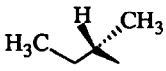
easily metallated by addition to a solution of LDA in tetrahydrofuran at -84 °C. The resulting solution was treated with aldehyde or ketone to form the diazoketols. The aldehydes and ketones employed were

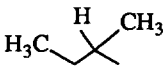


1. R = CH_3, R' = CH_2CH_3

2. R = $(CH_3)_2CH$, R' = CH_2CH_3

4. R = $PhCH_2$, R' = $C(CH_3)_3$

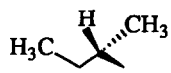
5. R =  , R' = $C(CH_3)_3$

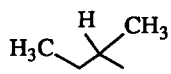
6. R =  , R' = $C(CH_3)_3$

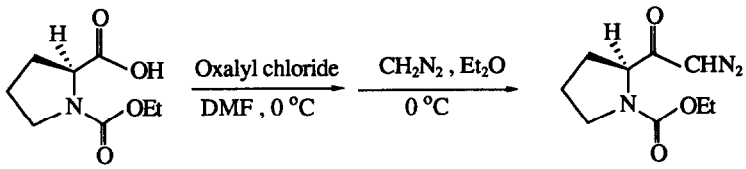
10. R = CH_3, R' = CH_2CH_3

11. R = $(CH_3)_2CH$, R' = CH_2CH_3

13. R = $PhCH_2$, R' = $C(CH_3)_3$

14. R =  , R' = $C(CH_3)_3$

15. R =  , R' = $C(CH_3)_3$



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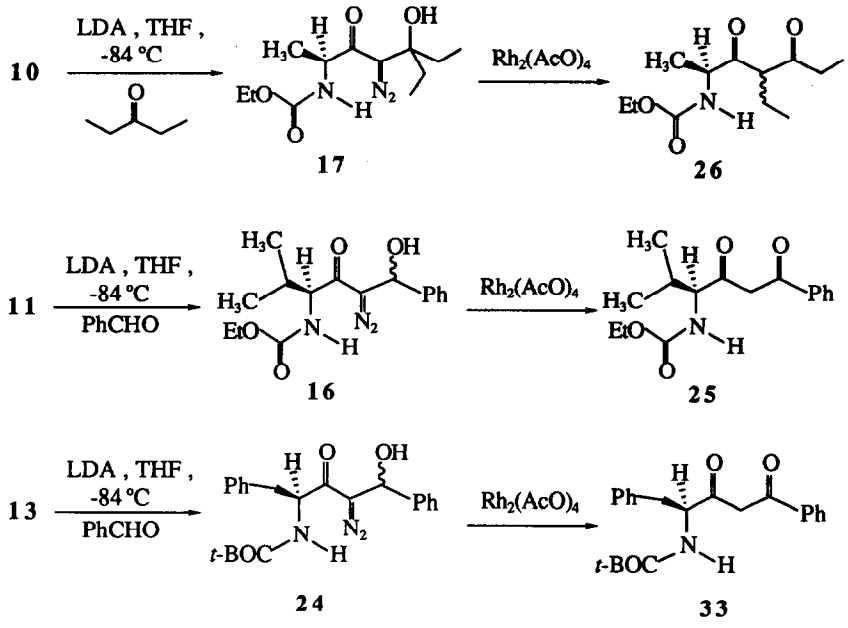
Scheme 1

Table 1 α-Diazoketone derived from N-protected amino acid

α-diazo ketone	Yield %	$[\alpha]_D^{20}$
10	88	-48.5° (c, 5.0 in CH_2Cl_2)
11	78	-34.3° (c, 3.43 in CH_2Cl_2)
12	76	-138.3° (c, 7.1 in CH_2Cl_2)
13	80	-39.6° (c, 1.8 in CH_3OH)
14	80	-20.3° (c, 0.94 in CH_2Cl_2)
15	79	——



Scheme 2

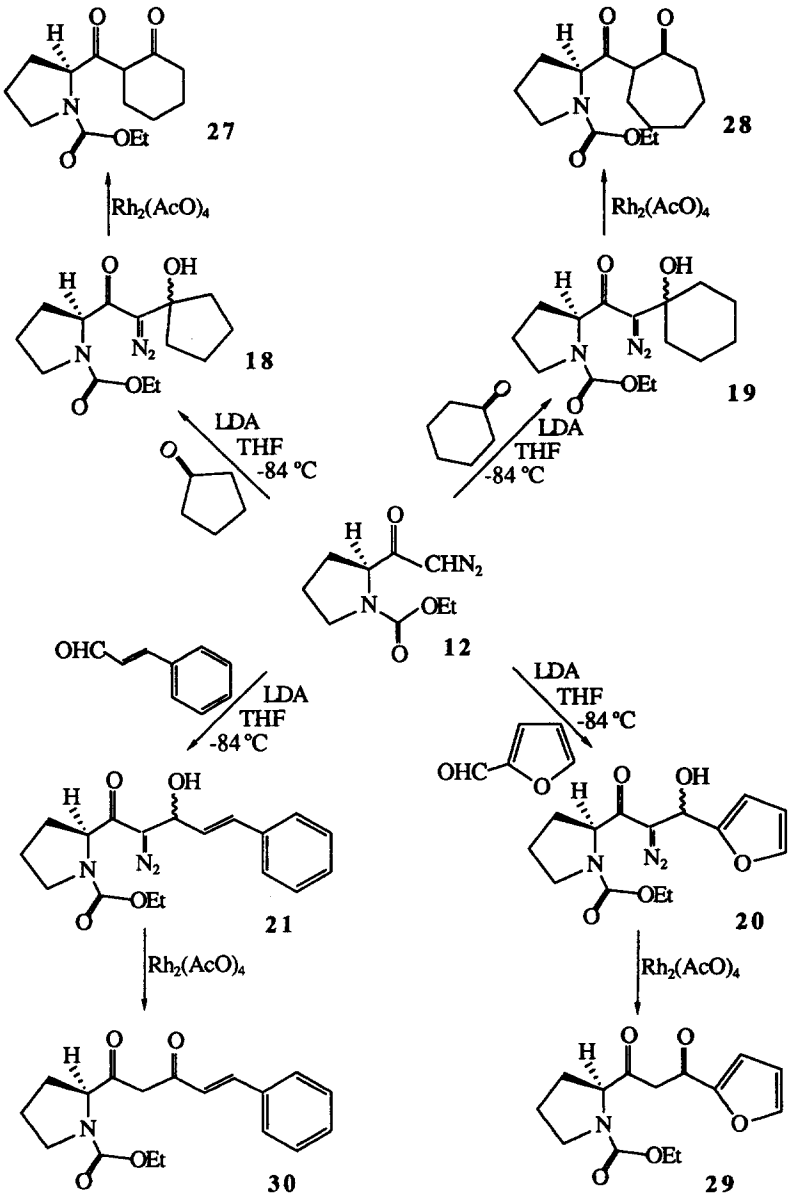
Table 2 Synthesis of α-diazoketols

α-diazoketol	Yield %	α-diazoketol	Yield %
16	65	**21**	75
17	76	**22**	55
18	67	**23**	52
19	76	**24**	91*
20	82		

* The reaction was quenched by aqueous ammonium chloride solution

benzaldehyde,cinnamaldehyde, diethyl ketone, cyclopentanone and cyclohexanone. The reaction mixture was quenched by the addition of acetic acid or aqueous ammonium chloride solution followed by standard aqueous workup. In general, the crude products were purified by chromatography to afford mixtures of diastereoisomers of the α-diazoketol in moderate to good yields(**Scheme2,3,4.Table2**). No attempt was made to separate the diastereoisomers, since the new chiral centre was destined to be destroyed in the next step. We found that acetic acid, the quenching reagent formerly used for this type of reaction, was not always satisfactory. Its use as quenching reagent in the preparation of α-diazoketol **24** resulted in a complex mixture of products, and the yield of the desired α-diazoketol was extremely low. However, when aqueous ammonium

chloride was employed, a high yield (up to 91%) of pure α-diazoketol **24** was obtained. Also acid catalysed decomposition of diazo compounds is well known. Therefore it would appear that aqueous ammonium chloride is more appropriate than acetic acid as quenching reagent in these reactions. Earlier work by Kim and coworkers[8] showed that the transformation of α-diazoketols to the corresponding β-dicarbonyls can be catalysed by various Lewis acids and metal salts. As Pellicciari[4] pointed out, rhodium(II) acetate is a more

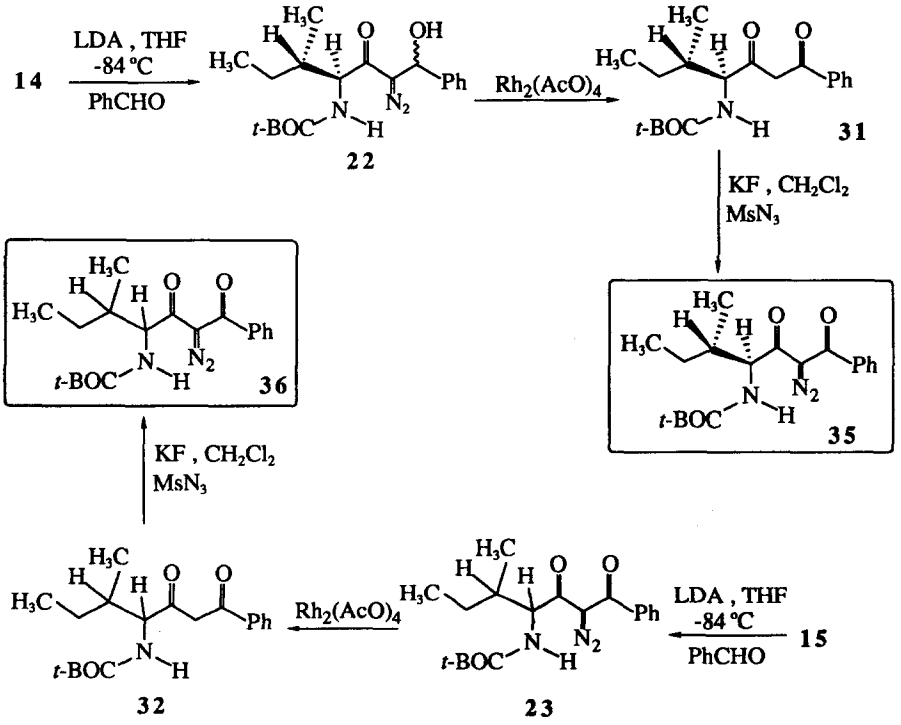


Scheme 3

efficient catalyst for this type of transformation.To complete the synthesis, α-diazoketols **16-20** derived from the corresponding N-protected amino acid were converted to β-diketones when treated with a catalytic amount of rhodium(II) acetate (0.5-1.0 mol %) in methylene chloride at room temperature (**Scheme2,3,4.**

Table 3 Synthesis of β-diketones

β-diketone	Yield %	$[\alpha]_D^{20}$
25	60	-14.1° (c, 3.57 in CH_2Cl_2)
26	62	+15.3° (c, 4.0 in CH_2Cl_2)
27	79	-51.1° (c, 7.0 in CH_2Cl_2)
28	57	-26.6° (c, 7.0 in CH_2Cl_2)
29	61	-119.6° (c, 3.1 in CH_2Cl_2)
30	63	-135.2° (c, 3.85 in CH_2Cl_2)
31	72	+1.42° (c, 7.0 in CH_2Cl_2)
32	75	——



Scheme 4

Table3). Moderate to good yields of β-diketone products, as can be seen from **Table 3**, were obtained after purification. Possible competitive side reactions, e.g. N-H insertion, C-H insertion and carbonyl ylide formation were not observed, indicating that the 1,2-hydrogen or alkyl shift is the perferred pathway for the Rh(II) catalysed reaction of these diazo ketols. Although the structures in the Schemes illustrate keto forms only, with the exception of **26**, all of the β-diketones were isolated as mixtures of keto and enol forms with the enols (2 isomers possible in each case) predominating. It was desirable to establish beyond doubt that this two-step synthesis of α-amino β-dicarbonyl systems from α-amino acids was racemization-free. The fact that the products were prototropic mixtures rendered difficult the direct application of ^1H NMR chiral shift reagents. However we found that a simple modification of the product **31** derived from isoleucine provided a solution. The methylene group between the β-dicarbonyl functions in **31** and its racemic counterpart **32** can be easily transformed into a diazo group(**Scheme 4**). In these cases, to avoid the possibility of partial racemization during diazo transfer we used potassium fluoride[9] as the base instead of triethylamine, which is the more commonly used base in diazo transfer processes. The final 2-diazo-1,3-diketones **35** and **36** both contain two chirality centres. By simply comparing the ^1H and ^{13}C NMR spectra of **35** with **36**, which consists of two diastereoisomers, it was clearly established that no epimerization/racemization occurred when forming **35** (for the appropriate ^1H and ^{13}C NMR data.see experimental section). The results not only confirmed that racemisation- free β-diketone formation can be effected by this approach, they also indicate that the synthesis of 2-diazo-1,3-diketones from N-protected amino acids occurs with complete homochirality transfer.

In summary, the present results offer an efficient approach to the synthesis of β-diketones and 2-diazo-1,3-diketones derived from N-protected natural amino acids with homochirality transfer. Extension of the synthetic potential of this type of reaction to modified small peptides leading to potential protease inhibitors is being investigated.

Experimental Section

General Procedures. Reactions requiring anhydrous conditions were performed in flame-dried glassware under a positive pressure of nitrogen. Reaction mixtures were stirred magnetically . Air- and moisture-sensitive liquids and solutions were transfered *via* syringe or cannula into the reaction vessels through rubber septa. Flash column chromatography was performed using Rhone-Poulenc silica gel C60-H(40-60μm).

Materials. Commercial grade solvents were used without futher purification except as indicated below. Tetrahydrofuran was distilled from sodium benzophenone dianion. Dichloromethane was distilled from P_2O_5. Lithium diisopropylamide mono(tetrahydrofuran), 1.5M solution in cyclohexane, was purchased from Aldrich. Methanesulfonyl chloride was purified by distillation. All ketones and aldehydes were purified by distillation prior to use. The hexane and ethyl acetate used for chromatography were purified by distillation.

Instrumentation. Infrared spectra were obtained using a Perkin-Elmer 983G grating spectrophotometer. ^1H NMR(300MHz) and ^{13}C NMR(75MHz) spectra were recorded with a GE-300 spectrometer. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane. Elemental analyses were determined on a Perkin-Elmer 2400 CHN micro analyser. Optical rotations were measured on a Perkin-Elmer 241 polarimeter using a path length of 10cm. Melting points were determined on a Reichert microscope hot stage apparatus and are uncorrected. Preparative thin layer chromatography(p.t.l.c.). was performed on silica Gel $60PF_{254}$ (Merck 7747); analytical thin layer chromatography (t.l.c.) was performed on Merck Kieselgel $60F_{254}$ plates

visualising the components using a Hanovia Chromatolite ultraviolet lamp or iodine.

Synthesis of N-Protected α-Amino Acids

General procedure for N-ethoxycarbonyl protection [10]

N-Ethoxycarbonyl-L-alanine **1**.

To a solution of L-alanine (5.0 g, 56.1 mmol) in 1N sodium hydroxide (56ml) was added ethyl chloroformate (4.6 ml, 105 mol%) dropwise at room temperature over 1hr while intermittent addition of 1N sodium hydroxide was used to maintain the solution pH between 9-10. Two hours after the addition of ethyl chloroformate, the solution was cooled to 0°C and washed with ether (2 x 25ml). The solution was acidified to a pH 1 by dropwise addition of 3M phosphoric acid. The product was then extracted with dichloromethane (3 x 40ml) and the extract was dried and evaporated to afford **1** (7.5 g, 91%) as a white crystalline solid, m.p. 79-80 °C (from acetone-hexane) (lit.[11] 80-81 °C); $[\alpha]_D^{20}$ -15.4° (c, 5.0 in CH_2Cl_2) (lit.,[10] -15.3° in CH_2Cl_2); υ_{max} (KBr) 3423(NH), 3500-2400(COOH), 1711cm^{-1} br(carbonyls) ; δ_H ($CDCl_3$): 1.29(3H, t, CH_3CH_2O), 1.44(3H, d, J = 7.6Hz, CH_3CH), 4.15(2H, q, CH_3CH_2O), 4.25(1H, m, C*H*(N)COOH), 5.22(1H, br d, J = 5.6Hz, N*H*), 11.05(1H, br s, COO*H*).

N-Ethoxycarbonyl-L-valine **2**

L-Valine (10.0 g, 85.3 mmol) was protected according to the same procedure employed to procure **1**. The product **2** (15.8 g, 98%) was obtained as a viscous colourless oil, $[\alpha]_D^{20}$ -1.63° (c, 2.64 in CH_2Cl_2); υ_{max}(neat) 3500-2500 (NH and COOH), 1739cm^{-1} br (carbonyls); δ_H ($CDCl_3$): 0.93(3H, d, J = 6.8Hz, CH_3), 1.25(3H, t, J = 7.1Hz CH_3CH_2O), 2.22(1H, m, CH_3CHCH_3), 4.14(2H, q, J = 7.1Hz CH_3CH_2O), 4.33(1H, m, C*H*(N)COOH), 5.34(br d), 6.44(br d) (1H, N*H*) 10.83(1H, br s, COO*H*).

N-Ethoxycarbonyl-L-proline **3**

L-Proline (10.0g, 86.9mmol) was protected by the procedure employed to procure **1**. The product **3** (14.8 g, 91%) was obtained as a white microcrystalline solid following trituration with hexane, m.p. 61-62 °C (lit.[12], 62-63 °C); $[\alpha]_D^{20}$ -68.14° (c, 4.21 in CH_3OH); (lit.[12] -66.2° in MeOH); υ_{max}(KBr) 3600-2500 (NH and COOH), 1740cm^{-1} br(carbonyls); δ_H ($CDCl_3$): 1.29(3H, t, J = 7.1Hz CH_3CH_2O), 1.99(2H, m, CH_2), 3.50(2H, m, CH_2), 4.19(2H, q, J = 7.1Hz CH_3CH_2O), 4.40(1H, dd J_1 = 8.7Hz, J_2 = 8.1 Hz CH_2CH(N)COOH), 9.00(1H, br s, COO*H*).

General procedure for N-*tert*-butoxycarbonyl protection

N-*tert*-Butoxycarbonyl-L-phenylalanine **4** [13]

L-Phenylalanine (10.0 g, 60.5 mmol) and sodium hydroxide (2.7 g, 67.0 mmol) were dissolved in a *tert*-butanol-water mixture (75ml, 1:1, v/v). To this solution at a pH of 8-9 di-*tert*-butyldicarbonate (14.6 g, 67.0 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 16hrs. The excess of di-*tert*-butyldicarbonate was then removed by ethyl acetate extraction (2 x 50ml). The aqueous layer was treated with aqueous acetic acid (3.8 ml in 20 ml H_2O) and then extracted with ethyl acetate (4 x 70ml). The combined extracts were washed with water, dried and the solvent removed under reduced pressure. The crude product was recrystallised from ethyl acetate-hexane to afford **4** (15.0 g, 94%) as a white crystalline solid,

m.p. 87-88 °C (lit.,[14] 87-88°C); $[\alpha]_D^{20}$ -4.0° (c, 3.0 in AcOH) (lit,[14] -4.0° in AcOH); υ_{max}(KBr) 3306(NH), 3500-2500(COOH), 1705(COOH), 1643cm^{-1} ($NHCO_2C(CH_3)_3$); δ_H ($CDCl_3$): (1:2 mixture of rotamers) 1.28(3H, s, $C(CH_3)_3$), 1.42(6H, s, $C(CH_3)_3$), 2.93(m), 3.17(m) (1H, $PhCH_2$), 3.21(1H, m. $PhCH_2$) 4.41 (br m), 4.62(br m) (1H, CH(N)CO), 4.98(br d), 6.53(br d) (1H, NH) 7.26(5H, m, Ar-H), 9.04(1H, br s, COOH).

(3S,4S)-N-tert-Butoxycarbonyl-isoleucine **5**

(3S,4S)-isoleucine (8.0 g, 61.0 mmol) was protected according to the procedure employed to procure **4**. The crude product was recrystallised from ethyl acetate-hexane to afford **5** as a white crystalline solid (13.7 g, 97%), m.p. 70-71 °C (Lit.[15], 70-71 °C); $[\alpha]_D^{20}$ +2.49° (c, 2.0 in AcOH) (Lit.[15], 2.5° in AcOH); υ_{max}(KBr) 3309(NH), 3500-2500(COOH), 1706(COOH), 1642cm^{-1} ($NHCO_2C(CH_3)_3$); δ_H ($CDCl_3$): (1:2 mixture of rotamers) 0.93(3H, t, J = 7.4Hz, $CHCH_3$); 0.97(3H, d, J = 7.1Hz, CH_2CH_3), 1.25(1H, m, CH_2CH_3), 1.44(1H, m, CH_2CH_3), 1.45(9H, s, $C(CH_3)_3$), 2.06(1H, m, CH_2CHCH_3), 4.09(m), 4.32(m) (1H, CH(N)CO), 5.11(br d), 6.20(br d) (1H, NH), 11.27(1H, br s, COOH).

(±)-N-tert-Butoxycarbonyl-isoleucine **6**

(±)-isoleucine (5.0 g, 38.1mmol)was protected according to the procedure employed to procure **4**. The crude product was recrystallised from ethyl acetate-hexane to afford **6** (8.5 g, 96%) as a white crystalline solid with broad melting point; υ_{max}(KBr) 3309(NH), 3500-2500(COOH), 1706(COOH), 1642cm^{-1} ($NHCO_2C(CH_3)_3$); δ_H ($CDCl_3$): (1:1 mixture of diastereoisomers) 0.86-1.0(6H, m, $CHCH_3$, CH_2CH_3), 1.12-1.33(1H, m, CH_2CH_3), 1.37-1.50(1H, m, CH_2CH_3), 1.44(s), 1.45(s) (9H, $C(CH_3)_3$), 2.04(1H, m, CH_2CHCH_3), 4.10-4.40(1H, m, CH(N)CO), 5.00-5.20(br d), 6.25-6.30(br d) (1H, NH), 10.7(1H, br s, COOH).

Synthesis of N-protected amino acid chlorides

General procedure[16]

To a solution of the N-protected amino acid (1 equiv.) in dichloromethane (0.52M) at 0 °C were added oxalyl chloride (1.2 equiv.) and DMF (2 drops, catalytic) *via* a septum in a dry nitrogen atmosphere. The solution was then stirred over 3h allowing it to warm to room temperature. The solution was then concentrated under reduced pressure to afford the crude acid chloride which was used directly without further purification.

N-Ethoxycarbonyl-L-alanyl chloride **7**

N-Ethoxycarbonyl-L-alanine **1** (3.0 g, 18.6mmol) was converted by general procedure to give the title compound **7** (3.2 g, 97%) as a yellow oil, υ_{max}(film) 3321(NH), 1785(COCl), 1700 cm^{-1}($NHCO_2Et$); δ_H ($CDCl_3$): 1.36(3H, t, CH_3CH_2O), 1.65 (3H, d, J = 8.4Hz, CH_3CH), 4.44(2H, q, CH_3CH_2O), 5.30(1H, m, CHCNCO).

N-Ethoxycarbonyl-L-valyl chloride **8**

N-Ethoxycarbonyl-L-valine **2** (10.0 g, 52.9 mmol) was converted by general procedure to give the title compound **8** (10.8 g, 98%) as an colorless oil , υ_{max}(film) 3305(NH), 1788(COCl), 1705cm^{-1} (CO_2Et); δ_H ($CDCl_3$): 0.93(3H, d, J, 6.8Hz, CH_3CHCH_3), 1.00(3H, d, J, 6.8Hz, CH_3CHCH_3), 1.25(3H, t, J = 7.1Hz,

CH_3CH_2O), 2.22(1H, m, CH_3CHCH_3), 4.13(2H, q, J = 7.1Hz, CH_3CH_2O), 4.33(1H, m, CH(N)COOH), 5.34(1H, br. d, NH), 10.83(1H, br. s, COOH).

N-Ethoxycarbonyl-L-prolyl chloride **9**

N-Ethoxycarbonyl-L-proline **3** (11.0 g, 58.8 mmol) was converted by the general procedure to give the title compound **9** (11.8 g, 98%) as a colourless oil, υ_{max} (film) 1785(COCl) and 1700 cm^{-1} (NCOOEt); δ_H ($CDCl_3$): 1.25 (3H, t, J = 7Hz,OCH_2CH_3),1.70-2.50 (4H, m, CH_2), 3.48 (2H, t, J = 6Hz, CH_2N), 4.09 (2H, q, J = 7Hz, OCH_2CH_3), 4.60-4.90 (1H, m, CH(N)COCl).

Synthesis of α-diazoketones

Preparation of diazomethane

Etheral diazomethane was prepared from Diazald according to the literature procedure.[17]

General procedure for α-diazoketone preparations

(a) Preparation from acid chlorides [18]

The acid chloride (1 equiv.) in a solution of ether or THF was added *via* a pressure equalized dropping funnel to a freshly prepared ethereal diazomethane solution (3-4 equiv.) over 1h at 0°C under a dry nitrogen atmosphere. The reaction solution was then allowed to warm to room temperature over 3-4 h. The solvent was removed under reduced pressure to yield the crude α-diazoketone which was purified by silica gel chromatography. (ethyl acetate-hexane 2:8-3:7)

(b) Preparation *via* mixed anhydrides [19]

The N-protected amino acid (27.0 mmol) in dry ether (60 ml) and THF (60 ml) was stirred at -20 °C under a dry nitrogen atmosphere. To this solution triethylamine (3.8 ml, 1 equiv.) followed by isobutyl chloroformate (3.7 ml, 1 equiv.) were added. The solution was stirred for half an hour and then allowed to warm to -10 °C. At this temperature ethereal diazomethane (2 equiv.) was added *via* a pressure equalised dropping funnel over half an hour. The solution was stirred for a further 3h allowing it to reach room temperature. It was then evaporated to a third of its original volume using a rotatory evaporator with an acetic acid trap to destroy residual diazomethane. The solution was diluted with ether (50 ml) and washed with water (50 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and brine (50 ml). It was then dried and evaporated to give the crude α-diazoketone which was purified by silica gel chromatography.(ethyl acetate-hexane 2:8-3:7)

N-Ethoxycarbonyl-L-alanyl diazomethane **10**

The acid chloride **7** (3.2 g, 17.8 mmol) was converted by general method (a) to give the title compound **10**. Purification using ethyl acetate-hexane as eluant funished the diazoketone **10** (2.9 g, 88%) as a pale yellow solid, m.p. 48-50 °C; $[\alpha]_D^{20}$ -48.5° (c, 5.0 in CH_2Cl_2); υ_{max}(film) 3300(NH), 2100(CHN_2), 1700($NHCO_2Et$), 1640 cm^{-1}($COCHN_2$); δ_H ($CDCl_3$): 1.18(3H, d, J = 7.5Hz, CH_3CH), 1.35(3H, t, CH_3CH_2O), 3.92-4.27(3H, m, CH_3CH_2O & CH(N)CO), 5.68(1H, br s, CHN_2), 5.94(1H, br d, NH).

N-Ethoxycarbonyl-L-valyl diazomethane **11**

The acid chloride **8** (10.0 g, 48.2 mmol) was converted by general procedure (a) to obtain the title compound **11**. Purification using ethyl acetate-hexane as eluant funished the pure diazoketone **11**(8.0 g, 78%)

as a yellow oil, $[\alpha]_D^{20}$ -34.3° (c, 3.43 in CH_2Cl_2); υ_{max}(KBr) 3325(NH), 2100(CN_2), 1710(CO_2Et), 1632cm^{-1} ($COCHN_2$); δ_H ($CDCl_3$): 0.90(3H, d, J = 6.8Hz, C*H*$_3$), 0.99(3H, d, J = 6.7Hz, C*H*$_3$),1.25(3H, t, J = 7.1Hz, C*H*$_3$CH$_2$O), 2.10(1H, m, CH$_3$C*H*CH$_3$), 4.12(2H, q, J = 7.1Hz, CH$_3$C*H*$_2$O, 1H, m, C*H*(N)COCHN$_2$), 5.29(1H, br. d, N*H*), 5.42(1H, s, C*H*N$_2$).

N-Ethoxycarbonyl-L-prolyl diazomethane **12**

The acid chloride **9** (10.2 g, 49.6 mmol) was converted by general procedure (a) to the title compound **12**. Purification using ethyl acetate-hexane as eluant funished the pure diazoketone **12** (8.0 g, 76%) as a yellow oil, $[\alpha]_D^{20}$ -138.3° (c, 7.1 in CH_2Cl_2); Anal. Calcd. for $C_9H_{13}N_3O_3$ C, 51.18; H, 6.20; N, 19.89% Found: C,51.42; H, 6.18; N,19.89; υ_{max} (neat) 2106(CHN_2), 1696(CO_2Et), 1632cm^{-1} ($COCHN_2$); δ_H ($CDCl_3$): 1.26 (3H, t, J = 7Hz, OCH$_2$C*H*$_3$), 1.91(2H, m, C*H*$_2$), 2.05(2H, m, C*H*$_2$), 3.54 (2H, m, C*H*$_2$N), 4.15 (2H, q, J = 7Hz, OC*H*$_2$CH$_3$), 4.20 (1H, m, C*H*(N)COCHN$_2$). 5.42(br s), 5.52(br s) (1H, br s C*H*N$_2$).

N-tert-Butoxycarbonyl-L-phenylalanyl diazomethane **13** [20]

The N-protected acid **4** (6.0 g, 22.6 mmol) was converted by general procedure (b) to obtain the crude product which was purified by flash chromatography to afford the pure title compound **13** (5.2 g, 80%) as a pale yellow solid, m.p. 78.5-81.0 °C; (lit.[20], 83.5-85 °C); $[\alpha]_D^{20}$ -39.6° (c, 1.8 in MeOH), (lit.[20], -40° in MeOH); υ_{max}(KBr) 3319(NH), 2102(CN_2), 1679(NHCO$_2$(CH)$_3$), 1635cm^{-1} ($COCHN_2$); δ_H ($CDCl_3$): 1.41(9H, s, (C*H*$_3$)$_3$CH), 3.03(2H, d, J = 6.6Hz, PhC*H*$_2$), 4.42(1H, m, C*H*(N) CO), 5.11(1H, br d, N*H*), 5.22(1H, s, C*H*N$_2$), 7.18-7.33(5H, m, Ar*H*).

(3S,4S)-N-tert-Butoxycarbonylisoleucinyl diazomethane **14**

The N-protected acid **5** (5.0 g, 22.0 mmol) was converted by general procedure(b) to obtain the crude product which was purified by flash chromatography to afford the pure title compound **14** (4.4 g, 80%)as a pale yellow solid, m.p. 86-87 °C; (lit.[21], 87-88 °C); $[\alpha]_D^{20}$ -20.3° (c, 0.94 in CH_2Cl_2). υ_{max}(KBr) 3359(NH), 2107(CN_2), 1672(NHCO$_2$C(CH$_3$)$_3$), 1634cm^{-1} ($COCHN_2$); δ_H ($CDCl_3$): 0.91(3H, t, J = 7.3Hz, CHC*H*$_3$) , 0.954(3H, d, J = 6.8Hz, CH$_2$C*H*$_3$), 1.15(1H, m, C*H*$_2$CH$_3$), 1.44(9H, s, C(C*H*$_3$)$_3$), 1.50(1H, m, C*H*$_2$CH$_3$), 1.82(1H, m, CH$_2$C*H*CH$_3$), 4.10(1H, br s, C*H*(N)C(O)CHN$_2$), 5.13(1H, br s, N*H*), 5.43(1H, br s, C*H*N$_2$).

(±)-N-tert-Butoxycarbonylisoleucinyl diazomethane **15**

The N-protected acid **6** (5.0 g, 22 mmol) was converted by general procedure(b) to obtain the crude product which was purified by flash chromatography to afford the pure title compound **15** (4.3 g, 79%) as a pale yellow solid with broad meting point, υ_{max}(KBr) 3735(NH), 2103(CN_2), 1704(NHCO$_2$(CH)$_3$), 1630cm^{-1} ($COCHN_2$); δ_H ($CDCl_3$): 0.83-0.98(6H, m, CHC*H*$_3$, CH$_2$C*H*$_3$), 1.20-1.40(1H, m, C*H*$_2$CH$_3$), 1.40-1.51(1H, m, C*H*$_2$CH$_3$) 1.44(9H, s, C(C*H*$_3$)$_3$), 1.85(1H, m, CH$_2$C*H*CH$_3$), 4.09-4.27(1H, m, C*H*(N)C(O)CHN$_2$), 5.16(1H, br s, N*H*), 5.46(1H, br. s, C*H*N$_2$).

Synthesis of α-diazoketols

General procedure.

N-Ethoxycarbonyl-L-valyl-2-hydroxy-2-phenyl-diazoethane **16**

A cold solution of lithium di-isopropylamide (LDA), (1.25 ml of 1.5M solution in cyclohexane, 1.88

mmol) was added over 15 min to a stirred solution of diazoketone **11** (200 mg, 0.94 mmol) in THF (20 ml) at -84 °C. A solution of benzaldehyde (200 mg, 1.88 mmol) in THF (10ml) was then added dropwise over 10 min. and the mixture was stirred at -84 °C for 1 hour, after which acetic acid (107 µl, 1.88 mmol) in 5ml THF was added. The mixture was allowed to warm to room temperature and water (20 ml) was added. It was then concentrated under vacuum. Extracted with three 50ml portions of ether. The combined organic extracts were then washed with saturated aqueous sodium bicarbonate and brine, dried and evaporated under reduced pressure to give a brown oil. Purification by preparative thin layer chromatography on silica gel using ethyl acetate-hexane (3:7) as eluant funished the pure title compound **16** (184 mg, 65%) as a colourless oil, υ_{max}(KBr) 3600-3300(OH,NH), 2091(CN_2), 1693(CO_2Et), 1623 ($COCN_2$), 1518cm^{-1} (Ph); δ_H ($CDCl_3$): 0.88-0.96(6H, m, CH_3CHCH_3), 1.23(3H, t, J = 7.0Hz, CH_3CH_2O), 2.00(1H, m, CH_3CHCH_3), 4.09(2H, q, J = 7.0Hz, CH_3CH_2O, 1H, br s, O*H*), 4.35 (1H, m, C*H*(N)CO), 5.62(1H, br d, N*H*), 6.05(1H, s, *CH*OH), 7.30-7.39(5H, m, Ar*H*)

N-Ethoxycarbonyl-L-alanyl-2-ethyl-2-hydroxy-diazobutane **17**

Diazoketone **10** (400 mg, 2.16 mmol) was lithiated according to the procedure employed for **16** and then treated with 3-pentanone to afford the compound **17**. Purification by preparative thin layer chromatography on silica gel using ethyl acetate-hexane as eluant funished pure **17** (443 mg, 76%) as a pale yellow oil, υ_{max}(neat) 3530-3300(OH, NH), 2093(CN_2), 1686($NHCO_2Et$), 1618 cm^{-1}($COCN_2$); δ_H ($CDCl_3$): 0.86-0.95(6H, m, 2 x CH_3CHC), 1.26-1.28(3H, m, CH_3CH_2O), 1.36(3H, d, J = 7Hz, CH_3CHNH), 1.71-1.82(4H, m, 2 x CH_3CH_2C), 4.10-4.13(2H, m, CH_3CH_2O), 4.27(1H, s, O*H*), 4.63(1H, m,CH_3CHNH) C*H*(N)CO), 5.72(1H, br d, N*H*).

N-Ethoxycarbonyl-L-prolyl-(1-hydroxy)cyclopentyl diazomethane **18**

Diazoketone **12** (230 mg, 1.09 mmol) was lithiated according to the procedure employed for **16** and then treated with cyclopentanone to afford compound **18**. Purification by preparative thin layer chromatography on silican gel using ethyl acetate-hexane as eluant funished pure **18** (215 mg, 67%) as a pale yellow oil, υ_{max} (neat) 3600-3300(OH), 2077(CN_2), 1682(NCO_2Et), 1633cm^{-1} ($COCN_2$); δ_H ($CDCl_3$): 1.19-1.29 (3H, m, OCH_2CH_3), 1.66-1.83(4H, m, $CH_2CH_2CH_2COH$), 1.83-2.26(8H, m, $CH_2C(OH)CH_2$, $NCH_2CH_2CH_2$), 3.47-3.56(2H, m, NCH_2CH_2), 3.90(1H,br. s, OH), 4.10-4.20 (2H, m, OCH_2CH_3), 4.48-4.63 (1H, m, C*H*(N)$COCN_2$).

N-Ethoxycarbonyl-L-prolyl-(1-hydroxy)-cyclohexyl diazoethane **19**

Diazoketone **12** (260 mg 1.23 mmol) was lithiated according to the procedure employed for **16** and then treated with cyclohexanone to afford compound **19**. Purification by preparative thin layer chromatography on silica gel using ethyl acetate-hexane as eluant funished the pure title compound **19** (290 mg, 76%) as a pale yellow oil, υ_{max} (neat) 3600-3300(OH), 2075(CN_2), 1692(NCO_2Et), 1630cm^{-1} ($COCN_2$); δ_H ($CDCl_3$): 1.19-1.39(3H, m, OCH_2CH_3), 1.45-1.82(8H, m, $CH_2CH_2CH_2CH_2COH$), 1.87-2.26(6H, m, CH_2COH, $NCH_2CH_2CH_2$), 3.48-3.53(2H, m, NCH_2CH_2), 4.07-4.16(2H, m, OCH_2CH_3), 4.27(1H, s, O*H*), 4.48-4.62 (1H, m, C*H*(N)$COCN_2$).

N-Ethoxycarbonyl-L-prolyl-2-(2-furyl)-2-hydroxy-diazoethane **20**

Diazoketone **12** (230 mg, 1.09 mmol) was lithiated according to the procedure employed for **16** and then treated with 2-furaldehyde to afford compound **20**. Purification by preparative thin layer chromatography on silica gel using ethyl acetate-hexane as eluant funished pure **20** (273 mg, 82%) as a pale yellow oil, υ_{max} (neat) 3600-3300(OH), 2084(CN_2), 1675(NCO_2Et), 1641cm^{-1} ($COCN_2$); δ_H ($CDCl_3$): 1.21-1.28 (3H, m, OCH_2CH_3), 1.90-2.21(4H, m, $NCH_2CH_2CH_2$), 3.48-3.53(2H, m, NCH_2CH_2), 4.04-4.18 (2H, m, OCH_2CH_3), 4.20-4.60 (1H, m, CH(N)$COCN_2$), 5.93-6.01(1H, br s, CHOH), 6.34-6.44(2H, m, furyl-*H*), 7.39(1H, br s, furyl-*H*).

N-Ethoxycarbonyl-L-prolyl-2-hydroxy-3-ene-4-phenyl-diazobutane **21**

Diazoketone **12** (260 mg, 1.23 mmol) was lithiated according to the procedure employed for **16** and then treatted with cinnamaldehyde to afford the compound **21**. Purification by preparative thin layer chromatography on silica gel using ethyl acetate-hexane as eluant funished the pure **21** (318 mg, 75%) as a pale yellow oil, υ_{max} (neat) 3600-3300(OH), 2081(CN_2), 1679(NCO_2Et), 1637cm^{-1} ($COCN_2$); δ_H ($CDCl_3$): 1.21-1.29 (3H, m, OCH_2CH_3), 1.86-2.31(4H, m, $NCH_2CH_2CH_2$), 3.50-3.63(2H, m, NCH_2CH_2), 4.07-4.18 (2H, m, OCH_2CH_3), 4.51-4.63 (1H, m, CH(N)$COCN_2$), 5.56-5.58(1H, br. d, CHOH), 6.20-6.29(1H, m, CH=CHPh), 6.78-6.87(1H, br d, CH=CHPh), 7.29-7.47(5H, m, Ar-*H*).

(3S,4S)-N-Butoxycarbonylisoleucinyl-2-hydroxy-2-phenyl-diazoethane **22**

Diazoketone **14** (200 mg, 0.78 mmol) was lithiated according to the procedure employed for **16** and then treated with benzaldehyde to afford the compound **22**. Purification by preparative thin layer chromatography on silica gel using ethyl acetate-hexane as eluant funished the pure **22** (156 mg, 55%) as a pale yellow oil, Anal. Calcd. for $C_{19}H_{27}N_3O_4$ C, 63.14; H, 7.53; N, 11.63 Found: C, 62.95; H, 7.80; N, 11.55. υ_{max}(neat) 3600-3300(OH, NH), 2087(CN_2),1695($NHCO_2C(CH_3)_3$),1619cm^{-1} ($COCHN_2$), 1491(ArH); δ_H ($CDCl_3$): 0.84-0.96(6H, m, $CHCH_3$, CH_2CH_3), 1.11-1.24(1H, m, CH_2CH_3), 1.30-1.64(1H, m, CH_2CH_3), 1.43(9H, s, $C(CH_3)_3$), 1.73(1H, m, CH_2CHCH_3), 3.86(1H, br s, O*H*), 4.36(1H, br t, CH(N)C(O)CHN_2), 5.33(1H, br d, N*H*), 6.10(1H, br s, CH(OH)Ph), 7.30-7.48(5H, m, Ar*H*).

(±)-N-Butoxycarbonylisoleucinyl-2-hydroxy-2-phenyl-diazoethane **23**

Diazoketone **15** (200 mg, 0.78 mmol) was lithiated according to the procedure employed for **16** and then treated with benzaldehyde to afford the compound **23**. Purification by preparative thin layer chromatography on silica gel using ethyl acetate-hexane as eluant funished the pure **23** (148mg, 52%) as a pale yellow oil, υ_{max}(neat) 3600-3300(OH, NH), 2087(CN_2), 1695($NHCO_2C(CH_3)_3$), 1619cm^{-1} ($COCHN_2$), 1491(ArH); δ_H ($CDCl_3$): (1:1 mixture of diastereoisomers) 0.84-0.96(6H, m, $CHCH_3$, CH_2CH_3), 1.10-1.60(2H, m, CH_2CH_3), 1.44(9H, s, $C(CH_3)_3$), 1.73(1H, m, CH_2CHCH_3), 3.79(1H, br s, O*H*), 4.33-4.58(1H, m, CH(N)C(O)CHN_2), 5.29-5.32(1H, br d, N*H*), 6.04(1H, br s, CH(OH)Ph), 7.30-7.54(5H, m, Ar*H*).

N-Butoxycarbonyl-L-phenylalanyl-2-hydroxy-2-phenyl-diazoethane **24**

Diazoketone **13** (150 mg, 0.52 mmol) was lithiated according to the procedure employed for **16** and then treated with benzaldehyde and the reaction quenched by ammonium chloride aqueous solution (instead of acetic acid THF solution) to afford the compound **24**. Purification by preparative thin layer chromatography on silica gel using ethyl acetate-hexane as eluant funished a pure separable mixture of the two isomeric diazoketols **24**

(186 mg, 91%) as a pale yellow oil, (isomer ratio 70/30), Major isomer: υ_{max}(neat) 3600-3300(OH, NH), 2101(CN_2), 1692($NHCO_2C(CH_3)_3$), 1621cm^{-1} ($COCHN_2$), 1491(ArH); δ_H ($CDCl_3$): 1.39(9H, s, $C(CH_3)_3$), 2.92-3.06(2H, m, $PhCH_2$), 4.10(1H, br. s, O*H*), 4.40(m) 4.60(m) (1H, C*H*(N)CO), 5.24(1H, m, N*H*), 5.51(m), 5.90(m)(1H, C*H*(OH)Ph), 7.10-7.40(10H, m, ArH); minor isomer: υ_{max}(neat) 3600-3300(OH, NH), 2092(CN_2), 1687($NHCO_2C(CH_3)_3$), 1615cm^{-1} ($COCHN_2$), 1491(ArH); δ_H ($CDCl_3$): 1.44(9H, s, $C(CH_3)_3$), 3.02-3.08(2H, m, $PhCH_2$), 3.26(1H, br. s, O*H*), 4.69(m), 4.89(m)(1H, m, C*H*(N)CO), 5.34(1H, m, N*H*), 5.63(m), 5.97 (m)(1H, C*H*(OH)Ph), 7.10-7.40(10H, m, Ar*H*).

Synthesis of β-diketone derived from amino acid

General precedure

The α-diazoketol in dry dichloromethane (0.01M) was treated with rhodium(II) acetate (0.5 mol%) under nitrogen at room temperture for 1h. The solvent was removed under vacuo and the remaining oil was purified by preparative thin layer chromatography eluting with ethyl acetate-hexane (4:6) to yield the pure product.

(N-Ethoxycarbonyl-L-valyl)-methyl phenyl ketone **25**

α-Diazoketol **16** (115 mg, 0.40 mmol) afforded pure **25** (70 mg, 60%), (predominantly in enol form) as an oil, $[\alpha]_D^{20}$ -14.1° (c, 3.57 in CH_2Cl_2); Anal. Calcd. for $C_{16}H_{21}NO_4$ C, 65.96; H, 7.27; N, 4.81. Found: C, 65.83; H, 7.36; N, 4.59; υ_{max}(neat) 3334(NH) 2961-2871(OH), 1703(NCO_2Et), 1602 (OCCH=C), 1570cm^{-1} (Ph); δ_H ($CDCl_3$): 0.93(3H, d, J = 7.0Hz, CH_3CHCH_3), 1.03(3H, d, J = 7.0Hz, CH_3CHCH_3), 1.26(3H, t, J = 7.0Hz, CH_3CH_2O), 2.17(1H m, CH_3CHCH_3), 4.10-4.17(2H, J = 7.0Hz, CH_3CH_2O), 4.32 (1H, m, C*H*(N)CO), 5.40 (1H, br d, N*H*), 6.25 (1H, s, OCC*H*=C(OH)Ph), 7.40-7.60 (3H, m, Ar*H*), 7.88 (2H, d, J = 7.4Hz, Ar*H*), 15.75(1H, br s, OCCH=C(O*H*)Ph).

4-N-Ethoxycarbonyl-L-alanyl-3-hexanone **26**

α-Diazoketol **17** (407 mg, 1.50 mmol) afforded pure **26**(225 mg, 62%) as an oil, $[\alpha]_D^{20}$ +15.3° (c, 4.0 in CH_2Cl_2); Anal. Calcd. for $C_{12}H_{21}NO_4$ C, 59.24; H, 8.70; N, 5.76. Found: C, 59.28; H, 8.66; N, 5.70; υ_{max}(neat) 3347(NH), 1697 br. (carbonyl); δ_H ($CDCl_3$): 0.89(3H, t, J = 7.3Hz, CH_3CH_2CH), 1.04(3H, t, J = 7.2Hz, $OCCH_2CH_3$), 1.25(3H, t, J = 7Hz, CH_3CH_2O), 1.34(3H, d, J = 7.1Hz, $CH_3CH(N)$), 1.90(2H, m, CH_3CH_2CH), 2.53(2H, q, J = 7.2Hz, $OCCH_2CH_3$), 3.79(1H, q, J = 7Hz, $CHCH_2CH_3$), 4.12(2H, q, J = 7Hz, CH_3CH_2O), 4.37(1H, m, C*H*(N)CO), 5.32(1H, br d, N*H*).

2-N-Ethoxycarbonyl-L-prolyl-cyclohexanone **27**

α-Diazoketol **18** (210 mg, 0.71 mmol) afforded pure **27** (150 mg, 79%) (predominantly in enol form) as an oil, $[\alpha]_D^{20}$ - 51.1° (c, 7.0 in CH_2Cl_2); Anal. Calcd. for $C_{14}H_{21}NO_4$ C, 62.90; H, 7.92; N, 5.24. Found: C, 62.93; H, 7.68; N, 5.45. υ_{max}(neat) 2973-2831(OH), 1696(NCO_2Et), 1611 (OCC=C); δ_H ($CDCl_3$): 1.14(t), 1.26(t) (3H, t, J = 7.1Hz, CH_3CHO), 1.70(4H, m, $C=CH_2CH_2CH_2$ or $O=CH_2CH_2CH_2$) 1.80-2.03(4H, m, $NCH_2CH_2CH_2$), 2.18-2.53(4H, m, $CH_2C=C$, $CH_2C=O$), 3.47-3.63(2H, m, NCH_2CH_2 , 1H, m, OCC*H*CO), 4.10-4.15(2H, m, CH_3CH_2O), 4.65-4.74(1H, m, C*H*(N)C=O), 15.61(1H, br s, C=CO*H*).

2-N-Ethoxycarbonyl-L-prolyl-cycloheptanone **28**

α-Diazoketol **19** (250 mg, 0.81 mmol) afforded pure **28** (129 mg, 57%) (predominantly in enol form) as an oil, $[\alpha]_D^{20}$ - 26.6° (c, 7.0 in CH_2Cl_2); Anal. Calcd. for $C_{15}H_{23}NO_4$ C, 64.04; H, 8.24; N, 4.98. Found: C, 64.33; H, 8.58; N, 5.22; υ_{max}(neat) 2973-2853(OH), 1696(NCO_2Et), 1592 (OCC=C); δ_H ($CDCl_3$): 1.12-1.30(3H, m, CH_3CHO), 1.50-2.25(10H, m, $C=CH_2CH_2CH_2CH_2$ & $NCH_2CH_2CH_2$), 2.39-2.61(4H m, $CH_2C=C$, $CH_2C=O$), 3.43-3.62(2H, m, NCH_2CH_2, 1H, m, OCCHCO), 4.42-4.46(m), 4.69-4.73(m) (1H, $NCHC=O$), 15.49(s), 16.53(s) (1H, $C=COH$).

(N-Ethoxycarbonyl-L-prolyl)-methyl-2-furyl ketone **29**

α-Diazoketol **20** (210 mg, 0.68 mmol) afforded pure **29** (116 mg, 61%) (predominantly in enol form) as an oil, $[\alpha]_D^{20}$ -119.6° (c, 3.1 in CH_2Cl_2); Anal. Calcd. for $C_{14}H_{17}NO_5$ C, 60.21; H, 6.14; N, 5.02. Found: C, 60.20; H, 6.34; N, 5.28; υ_{max}(neat) 2973-2853(OH), 1696(NCO_2Et), 1592 (OCC=C); δ_H ($CDCl_3$): 1.17(t, J = 7Hz), 1.29(t, J = 7Hz) (3H, CH_3CH_2O), 1.92-2.26(4H, m, $NCH_2CH_2CH_2$), 3.50-3.62(2H, m, NCH_2CH_2), 4.07-4.21(2H, m, OCH_2CH_3), 4.36-4.40(m), 4.45-4.49(m) (1H, m, $NCHC=O$), 6.09(s), 6.14(s) (1H, $C(O)CH=COH$), 6.55(1H, s, furyl-*H*), 7.17(1H, s, furyl-*H*), 7.58(1H, s, furyl-*H*), 15.40(1H, br s, $C(O)CH=COH$)

(N-Ethoxycarbonyl-L-proyl)-methyl-1-ene-2-phenyl-ethyl ketone **30**

α-Diazoketol **21**(285 mg, 0.83 mmol) afforded pure **30** (165 mg, 63%) (predominantly in enol form) as an oil, $[\alpha]_D^{20}$ -135.2° (c, 3.85 in CH_2Cl_2); Anal. Calcd. for $C_{18}H_{21}NO_4$ C, 68.55; H, 6.71; N, 4.44. Found: C, 68.67; H, 6.94 ; N, 4.61; υ_{max}(neat) 2975(OH), 1696(NCO_2Et), 1634 (OCC=C); δ_H ($CDCl_3$): 1.15-1.35(3H, m, CH_3CH_2O), 1.87-2.18(4H, m, $NCH_2CH_2CH_2$), 3.49-3.63(2H, m, NCH_2CH_2), 4.06-4.21(2H, m, OCH_2CH_3), 4.27-4.34(m), 4.42-4.46(m) (1H, $NCHC=O$), 5.68(s), 5.73(s) (1H, $C(O)CH=CHOH$), 6.49(1H, d, J = 16Hz $HC=CHPh$), 7.36-7.66(1H, m, $HC=CHPh$, 5H, m, Ar*H*), 14.97(1H, br. s, $C(O)CH=COH$)

{(3S,4S)-N-Butoxycarbonylisoleucinyl}-methyl-phenyl ketone **31**

α-Diazoketol **22** (145 mg, 0.40 mmol) afforded pure **31** (96 mg, 72%) (predominantly in enol form) as an oil which formed a crystalline solid (from ether-hexane), m.p. 106-107 °C; $[\alpha]_D^{20}$ +1.42° (c, 1.06 in CH_2Cl_2); Anal. Calcd. for $C_{19}H_{27}NO_4$ C, 68.44; H, 8.16; N, 4.20. Found: C, 68.35 ; H, 8.11; N, 4.22; υ_{max}(neat) 3348(NH), 2970-2850(OH), 1680($NHCO_2C(CH_3)_3$), 1593cm^{-1} (OCC=C), 1491(ArH); δ_H ($CDCl_3$): 0.92(3H, t, J = 7.3Hz, $CHCH_2CH_3$), 0.98(3H, d, J = 6.8Hz,, $CHCH_3$), 1.14-1.21(1H, m, $CHCH_2CH_3$), 1.40-1.46(1H, m, $CHCH_2CH_3$), 1.45(9H, s, $C(CH_3)_3$), 1.88-1.90(1H, m, $CHCH_3$), 4.26-4.31(1H, m, CH(N)CO), 5.19(1H, br d, N*H*), 6.25(1H, s, $C(O)CH=COH$), 7.43-7.56(3H, m, Ar*H*), 7.88(2H, d, J = 7.3Hz, Ar*H*), 15,84(1H, br s, $C(O)CH=COH$).

{(±)-N-Butoxycarbonylisoleucinyl}-methyl-phenyl ketone **32**

α-Diazoketol **23** (148 mg, 0.41 mmol) afforded pure **32** (102 mg, 75%) (predominantly in enol form) as an oil which formed a crystalline solid (from ether-hexane) with broad meting point, υ_{max}(neat) 3348(NH), 2970-2850(OH), 1680($NHCO_2C(CH_3)_3$), 1593cm^{-1} (OCC=C), 1491(ArH); δ_H ($CDCl_3$): (1:1 mixture of diastereoisomers) 0.85-0.99(6H, m, $CHCH_2CH_3$, $CHCH_3$), 1.14-1.57(2H, m, $CHCH_2CH_3$), 1.46(9H, s,

C(C*H*$_3$)$_3$), 1.89-1.93(1H, m, C*H*CH$_3$), 4.27-4.32(m), 4.41-4.46(m) (1H, C*H*(N)C=O), 5.22(1H, br d, N*H*), 6.25(1H, br. s, C(O)C*H*=COH), 7.43-7.56(3H, m, Ar*H*), 7.88(2H, d, J = 7.3Hz, Ar*H*), 15,84(1H, br. s, C(O)CH=CO*H*).

(N-Butoxycarbonyl-L-phenylalanyl)-methyl phenyl ketone **33**

α-Diazoketol **24** (180 mg, 0.46 mmol) afforded pure **33** (96 mg, 57%) (predominantly in enol form) as an oil which formed a crystalline solid, m.p. 142.5-143.5 °C; (from ether-hexane), $[\alpha]_D^{20}$ -43.5° (c, 1.19 in CH_2Cl_2); Anal. Calcd. for $C_{22}H_{25}NO_4$ C, 71.91; H, 6.86; N, 3.81. Found: C, 71.89 ; H, 6.78 ; N, 3.75; υ_{max}(neat) 3370(NH), 1674(NHCO$_2$C(CH$_3$)$_3$), 1596cm^{-1} (OCC=C), 1515(ArH); δ_H (CDCl$_3$): 1.44(9H, s, C(C*H*$_3$)$_3$), 3.12(2H, d, J = 6.3Hz, PhC*H*$_2$), 4.66(H, d, J = 7Hz, C*H*(N)C=O), 5.27(1H, br d, N*H*), 6.08(1H, br s, C(O)C*H*=COH), 7.20-7.36(5H, m, Ar*H*), 7.40-7.78(5H, m, Ar*H*), 15.65(1H, s, C(O)CH=CO*H*).

Synthesis of 2-diazo-1,3-diketones 35 and 36

Methanesulfonyl azide **34**

The compound, prepared according to Danheiser's modification of Boyer method[22] in greater than 90% yield, was used for diazo transfer reaction without further purification.

(3S,4S)-N-Butoxycarbonylisoleucinyl-2-oxo-2-phenyldiazo ethane **35**

To a mixture of powered KF (61 mg, 1.05 mmol) and MsN_3 (31 mg, 0.25 mmol) in dichloromethane (40 ml) was added β-diketone **31** (70 mg, 0.21 mmol) in dichloromethane in one portion. The mixture was protected from light and was stirred at room temperature until reaction was complete (by TLC). After filteration through a layer of silica gel.(1 cm) the filtrate was washed with water (3 x 10ml). dried over Na_2SO_4, then concentrated to give crude **35**. Chromatography afforded the pure compound (69 mg, 91%) as a yellow wax; Anal. Calcd. for $C_{19}H_{25}N_3O_4$ C, 63.49; H, 7.01; N, 11.69. Found: C, 63.67 ; H, 6.87 ; N, 11.50; $[\alpha]_D^{20}$ -7.97° (c, 4.69in CH_2Cl_2); υ_{max}(neat) 3500-3300(NH), 2118(CN$_2$), 1710(NHCO$_2$C(CH$_3$)$_3$), 1645(COCN$_2$), 1492cm^{-1}(ArH); δ_H (CDCl$_3$): 0.89(3H, t, J = 7.3Hz, CHCH$_2$C*H*$_3$), 1.09(3H, d, J = 6.7Hz, CHC*H*$_3$), 1.30-1.50(2H, m, CHC*H*$_2$CH$_3$), 1.45(9H, s, C(C*H*$_3$)$_3$), 1.90(1H, m, C*H*CH$_3$), 5.29(1H, m, C*H*(N)C=O, 1H, N*H*), 7.40-7.66(5H, m, Ar*H*). δ_C (CDCl$_3$): 11.47(*C*H$_3$CH$_2$CH), 16.12(*C*H$_3$CH), 22.96(CH$_3$*C*H$_2$CH), 28.09(OC(*C*H$_3$)$_3$), 36.77(CH$_3$*C*H), 61.16(*C*H(N)), 79.40(O*C*(CH$_3$)$_3$), 82.72(*C*N$_2$), 127.13(*C*H of Ph), 128.67(*C*H of Ph), 132.50(*C*H of Ph), 137.00(*C* of Ph), 155.57(N*C*OOC(CH$_3$)$_3$), 184.17(*C*=O), 192.47(*C*=O).

(±)-N-Butoxycarbonylisoleucinyl-2-oxo-2-phenyl diazoethane **36**

This compound was prepared from the corresponding β-diketone **32** (110mg, 0.33mmol) as described above for **35**. Chromatography afforded pure **36** (107mg, 90%) as a yellow wax, υ_{max}(neat) 3500-3300(NH), 2118(CN$_2$), 1710(NHCO$_2$C(CH$_3$)$_3$), 1645(COCN$_2$), 1492cm^{-1}(ArH); δ_H (CDCl$_3$): (1:1 mixture of diastereoisomers) 0.803(d, J = 7.0Hz), 1.09(d, J = 6.7Hz) (3H,CHC*H*$_3$), 0.89(d, J = 7.3Hz) 1.012(t, J = 7.3Hz) (1H, CHCH$_2$C*H*$_3$), 1.29-1.61(2H, m, CHC*H*$_2$CH$_3$), 1.45(9H, s, C(C*H*$_3$)$_3$), 1.91(1H, m, C*H*CH$_3$), 5.23-5.27(m), 5.40-5.44(m) (1H, C*H*(N)C=O), 5.27(1H, br. s, N*H*), 7.37-7.65(5H, m, Ar*H*). δ_C (CDCl$_3$): 11.47, 13.08(*C*H$_3$CH$_2$CH), 16.11(*C*H$_3$CH), 23.00(CH$_3$*C*H$_2$CH), 27.82, 28.10(OC(*C*H$_3$)$_3$),

35.91, 36.79(CH_3CH), 59.89, 61.37($CH(N)$), 79.39($OC(CH_3)_3$), 82.49(CN_2), 127.11(*CH* of Ph), 128.66(*CH* of Ph), 132.47(*CH* of Ph), 137.01(*C* of Ph), 155.57($NCOOC(CH_3)_3$), 184.00, 184.15(*C*=O), 192.45, 201.34(*C*=O).

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