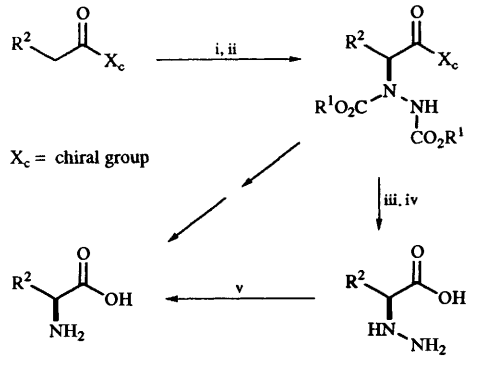
Synthesis of chiral diazanedicarboxylate and diazenedicarboxylate esters: electrophilic amination reactions of achiral ester and amide enolates

Joanna M. Harris, Evon A. Bolessa, Aubrey J. Mendonca, Sheng-Chu Feng and John C. Vederas*
Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

A series of chiral dialkyl (bornyl, isobornyl, menthyl) diazenedicarboxylates **4a–c** were prepared by conversion of the corresponding alcohols into chloroformates, condensation with hydrazine, and oxidation of the corresponding dialkyl diazanedicarboxylates **3a–c** with *N*-bromosuccinimide and pyridine (50–90% yield). Their reaction with achiral enolates of esters and *N*,*N*-dimethyl amides at −78 °C gave α-hydrazino acid derivatives with little or no stereoselectivity. Analogous aminations of chiral oxazolidinone (Evans enolate) anions were highly selective, but were controlled exclusively by enolate geometry.

Introduction

Simple dialkyl diazenedicarboxylates† (*e.g.*, diethyl diazenedicarboxylate)[1] are essential reagents for Mitsunobu reactions[2–4] and see increasing use as electrophilic nitrogen donors in amination reactions[5–11] and as potent Diels–Alder dienophiles[12] or participants in ene reactions[13] for the construction of nitrogen-containing systems. Condensation of achiral diazenedicarboxylate esters with chiral enolates[5–10] proceeds rapidly at −78 °C with high diastereoselectivity to give aminated derivatives which can be easily converted into the corresponding optically pure α-hydrazino acids or, if desired, the α-amino acids (Scheme 1).[14] It is surprising that the synthesis of chiral diazenedicarboxylate reagents has not been reported‡ despite their potential for double diastereoselection with chiral enolates or for asymmetric reaction with achiral anions. The present study investigates the preparation of chiral dialkyl diazenedicarboxylates and their use as electrophilic enolate amination reagents.



Scheme 1 *Reagents*: i, Base; ii, $R^1O_2C–N=N–CO_2R^1$; iii, LiOH; iv, H_3O^+; v, H_2, Pt or RaNi

Results and discussion

Since optically pure monoterpene alcohols are inexpensive and readily available, their diazenedicarboxylate esters allow a rapid test of possible stereoselectivity in amination reactions. Thus, condensations of (+)-menthol **1a**, (−)-borneol **1b**, or (−)-isoborneol **1c** with phosgene generate the chloroformates **2a–c** (80–95% yield), which react with 0.5 molar equivalents of hydrazine to form the corresponding dialkyl diazanedicarboxylates **3a–c** (41–55% yield) (Scheme 2). Standard oxidation with *N*-bromosuccinimide (NBS) in pyridine[16] affords the diazenedicarboxylate esters **4a–c** in good yield (77–91%).

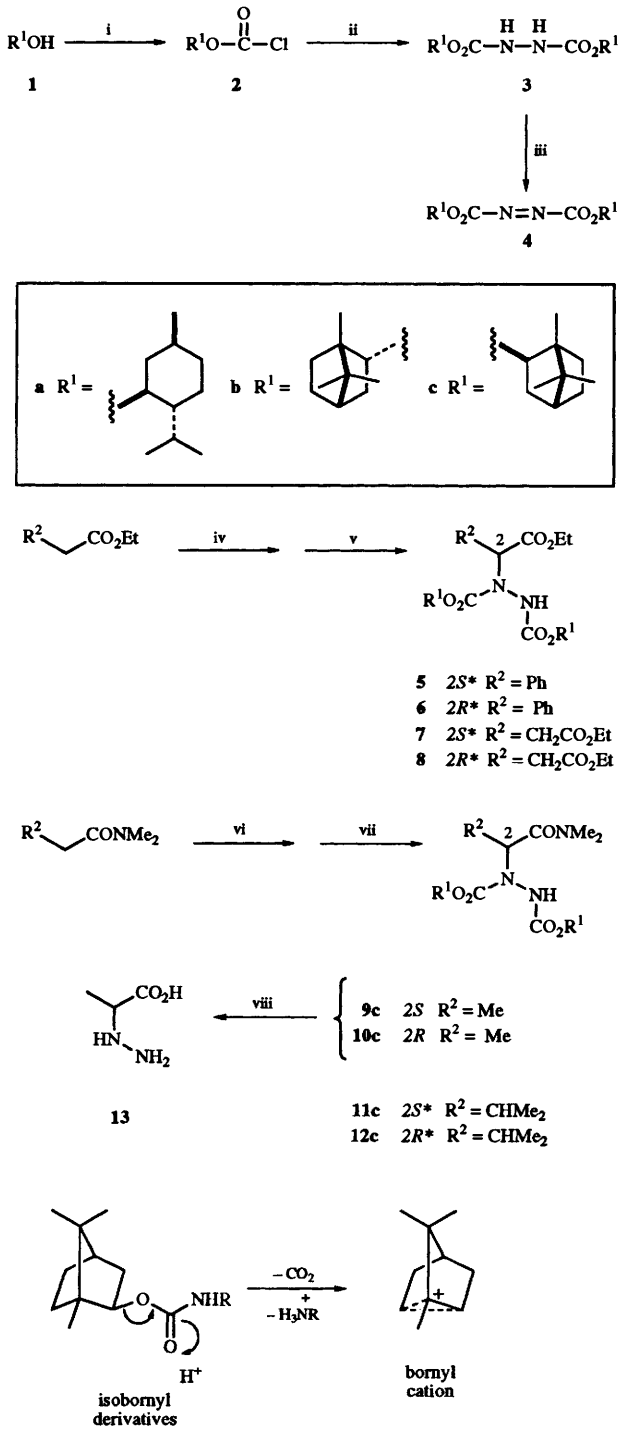
Amination of simple non-chelating ester enolates, which can exist as both *E* and *Z* isomers,[17] with compounds **4a–c** would not be expected to give good stereoselection, but it does provide insight into the overall reactivity and properties of these reagents. Thus, treatment of ethyl phenylacetate with lithium hexamethyldisilylamide (LHMDS) followed by addition of di-(+)-menthyl diazenedicarboxylate **4a** gave a 2:1 mixture of diastereoisomers **5a** and **6a** in 59% yield (Table 1). Diethyl succinate, under similar conditions, afforded a 1:1 mixture of diastereoisomers **7a** and **8a** in low (13%) yield. Similar reactions of ethyl phenylacetate or diethyl succinate with di-(−)-bornyl diazenedicarboxylate **4b** or with di-(−)-isobornyl diazenedicarboxylate **4c** also display little if any stereoselectivity. The chromatographic separation of these diastereoisomers is generally quite difficult, although during isolation of compound **5b/6b** one of the isomers could readily be obtained in pure form. Owing to hindered rotation at the amide bonds, the ^{1}H NMR spectra of all of these aminated products are broad and complex unless acquired at high temperature (*e.g.*, 100 °C) in toluene. The menthyl (**a**) and bornyl (**b**) carbamate moieties in products **5**, **6**, **7** and **8** proved to be very stable and difficult to remove, even with prolonged reflux in 6 mol dm^{-3} HCl or conc. HBr, and the corresponding α-hydrazino acids cannot be

Table 1 Aminations of enolates by chiral dialkyl diazenedicarboxylates

Substrate	Diazenedicarboxylate ester	Product (ratio, yield/%)[a]
$PhCH_2CO_2Et$	**4a**	**5a/6a** (2:1, 59%)
	4b	**5b/6b** (1:1, 57%)
	4c	**5c/6c** (1:1, 42%)
$(CH_2CO_2Et)_2$	**4a**	**7a/8a** (1:1, 13%)
	4b	**7b/8b** (1:1, 49%)
	4c	**7c/8c** (1:1, 41%)
$EtCONMe_2$	**4c**	**9c/10c** (1:1, 72%)
$Pr^iCH_2CONMe_2$	**4c**	**11c/12c** (1:1, 87%)
14	**4c**	**16** (56%)[b]
15	**4c**	**17** (88%)[b]

[a] Yields were not optimized and are given for the mixture of isomers separated from all other impurities. [b] Only single isomer was detected by ^{1}H NMR spectroscopy before purification.

† Previously called azodicarboxylates.
‡ For a reaction in which a chiral diazenedicarboxylate may be an intermediate see ref. 15.

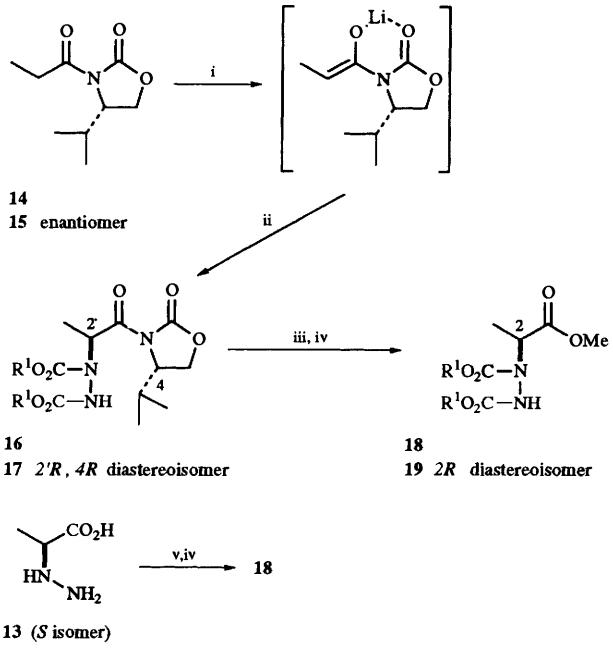


Scheme 2 *Reagents and conditions*: i, $COCl_2$; ii, N_2H_4; iii, NBS, pyridine; iv, LHMDS, −78 °C; v, **4**; vi, LDA, −78 °C; vii, **4c**; viii, aq. HCl, sealed tube, 100 °C

obtained in reasonable yield. However, the isobornyl (**c**) analogues hydrolyse readily because the correct alignment of the carbon–oxygen bond (*exo*) assists formation of the stabilized bornyl cation (Scheme 2).[18]

In contrast to ester enolates, anions generated from tertiary amides are known to assume the *Z* configuration preferentially,[17] thereby limiting stereochemical outcomes due to electrophilic attack on enolates of different geometry. However, reaction of *N*,*N*-dimethylpropionamide or *N*,*N*-dimethylisovaleramide with lithium diisopropylamide (LDA) followed by addition of di-(−)-isobornyl diazenedicarboxylate **4c** gave in each case a 1:1 ratio of diastereoisomers (**9c**/**10c** and **11c**/**12c**, respectively), as determined by high-temperature (100 °C) ^{1}H NMR analysis. The complete lack of stereoselectivity was confirmed by hydrolysis of the 1:1 mixture of products **9c** and **10c** to racemic α-hydrazinopropionic acid (*RS*)-**13** (75% yield).

In order to test the possibility of double diastereoselection with chiral enolates of defined geometry, the enantiomeric oxazolidinones **14** and **15** were aminated at −78 °C using the standard procedure[5,6] with the same di-(−)-isobornyl diazenedicarboxylate **4c** to give products **16** and **17**, respectively (Scheme 3). In both cases, only one diastereoisomer could be



Scheme 3 *Reagents and conditions*: i, LDA, −78 °C; ii, **4c**; iii, LiOH, H_2O_2; iv, CH_2N_2; v, **2c**

detected using high-temperature ^{1}H NMR spectrometry. Removal of the oxazolidinone auxiliary from compounds **16** and **17** by using lithium hydroperoxide[19] followed by acidification and treatment with diazomethane generated the corresponding diastereoisomeric methyl esters **18** and **19** (each in 87% yield), both of which bear (−)-isobornyl groups but which have opposite configurations at C-2. These could also be distinguished by high-temperature ^{1}H NMR analysis. Reaction of optically pure (2*S*)-2-hydrazinopropionic acid (L-hydrazinoalanine) (*S*)-**13**[20] with (−)-isobornyl chloroformate **2c** followed by esterification with diazomethane afforded pure compound **18**, thereby confirming the stereochemical assignment at C-2. Amination of either compound **14** or **15** with dibenzyl diazenedicarboxylate gave a 9:1 ratio of diastereoisomers with the same relative stereochemical outcome being favoured.[5] Comparison with the present results shows that the geometry of the Evans enolate completely controls the sense of diastereoselection and that the effect of the isobornyl moieties is solely to increase steric bulk and enhance the ratio.

It appears that the conformational mobility of diazenedicarboxylates **4a–c** around the single bonds to oxygen and the equal accessibility of both faces of their azo moiety to electrophilic attack prevent control of amination stereochemistry by these simple chiral diazenedicarboxylate esters. Since both azo nitrogens can be attacked (each from either face) a number of stereochemically different reaction pathways are likely to have very similar or identical energy profiles. The following paper

examines the possibility of generating bridged chiral diazenedicarboxylates with one face shielded and each nitrogen in a different steric environment.

Experimental

General procedures

All reactions were done under dry Ar. All solvents were purified and distilled according to Perrin *et al.*[21] Progress of reactions was monitored by TLC on commercial silica gel plates (Merck 60F-254 or Merck RP-8F_{254}S) using either UV absorption, I_2 staining, ninhydrin (amino acids), Bromocresol Green (acids), or *p*-(dimethylamino)benzaldehyde (hydrazino acids) spray for visualization. Flash chromatography employed Merck type 60 silica gel, 230–420 mesh. Normal-phase medium-pressure liquid chromatography (MPLC) was done using Merck type 60H silica gel. Mps were determined on either a Thomas Hoover or a Büchi apparatus using open-end capillary tubes, and are uncorrected. NMR spectra were recorded on Bruker WP80, WH200, AM300, WM360 or AM400 instruments. The *J* values are given in Hz. IR spectra were determined with a Nicolet 7199 FT-IR spectrometer. Mass spectra (MS) were recorded with an ionizing voltage of 70 eV on a Kratos AEI MS50 instrument for electron impact (EI) ionization, on an MS12 for chemical ionization (CI), and on an MS-9 for fast-atom bombardment (FAB). All literature compounds had ^{1}H NMR, IR and MS spectra consistent with assigned structures. Optical rotations were measured on a Perkin-Elmer 241 or 141 polarimeter with a micro cell (100 mm; 0.9 cm^3) or a standard cell (100 mm; 8 cm^3), respectively. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. Microanalyses were completed at the University of Alberta Microanalytical Laboratory. (−)-Isoborneol **1c** was prepared by reduction of (+)-camphor with sodium boranuide in methanol: mp 214–216 °C; $[\alpha]_D$ −34.8 (*c* 1, MeOH).

Preparation of chloroformates 2a–c

Since phosgene is highly toxic, all operations must be conducted in an efficient hood with test strips for detection prepared by soaking filter paper in a CCl_4 solution (10%) of equal parts of *p*-(dimethylamino)benzaldehyde and diphenylamine.[22] The dried strips turn from yellow to deep orange upon exposure to phosgene. All excess of phosgene and residues containing it were destroyed by venting onto or washing with aq. ammonia. In a typical procedure, phosgene (15.2 cm^3, 220 mmol; *d* 1.432) was added *via* a cannula to a solution of (+)-menthol **1a** (31.2 g, 200 mmol) in dry THF (75 cm^3) at 20 °C, and the mixture was stirred for 45 min. Triethylamine (31.7 cm^3, 220 mmol) was added dropwise and a white precipitate formed, which was stirred overnight at 20 °C. The solid was filtered off and the filtrate was concentrated to give *chloroformate* **2a** (41.3 g, 95%) (Found: C, 60.7; H, 8.7. $C_{11}H_{19}ClO_2$ requires C, 60.40; H, 8.76%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1775 (C=O); δ_H(300 MHz; $CDCl_3$) 4.74 (1 H, dt, *J* 4.0 and 10.0), 2.14 (1 H, m), 1.95 (1 H, m), 1.76–1.64 (2 H, m), 1.58–1.39 (2 H, m), 1.22–0.84 (9 H, m) and 0.81 (3 H, d, *J* 6.0); *m/z* (CI-NH_3) 236 (MNH_4^+).

(−)-Borneol **1b** (10.0 g, 65.0 mmol), phosgene (4.94 cm^3, 71.0 mmol) and triethylamine (9.07 cm^3, 65.0 mmol) gave crude chloroformate **2b** which was used directly: ν_{max} $(CHCl_3)/cm^{-1}$ 2960 and 1775 (C=O); *m/z* (CI-NH_3) 234 (MNH_4^+).

(−)-Isoborneol **1c** (10.0 g, 65.0 mmol), phosgene (4.93 cm^3, 71.0 mmol) and triethylamine (9.98 cm^3, 71 mmol) gave *chloroformate* **2c** (11.2 g, 80%) (Found: M^+, 216.0904. $C_{11}H_{17}ClO_2$ requires M, 216.0917); $\nu_{max}(CHCl_3)/cm^{-1}$ 1776 (C=O); δ_H(200 MHz; $CDCl_3$) 4.75 (1 H, dd, *J* 3.5 and 7.5), 1.93 (1 H, m), 1.80 (1 H, m), 1.72 (2 H, m), 1.12 (2 H, m), 1.03 (1 H, s), 0.98 (3 H, s), 0.96 (3 H, s) and 0.84 (3 H, s).

Preparation of diazane-1,2-dicarboxylate esters

Di-(+)-menthyl diazane-1,2-dicarboxylate 3a. A solution of triethylamine (28.6 cm^3, 205 mmol) in dry THF (100 cm^3) at 0 °C was treated with hydrazine hydrate (2.95 cm^3, 93 mmol), and then was stirred until it became cloudy. Chloroformate **2a** (40.6 g, 186 mmol) was added and the mixture was stirred at 0 °C for 45 min and then at 20 °C for 24 h. The precipitate was filtered off and the solid was recrystallized from $CHCl_3$ to give *diazanedicarboxylate* **3a** (15.1 g, 41%), mp 108–110 °C (Found: C, 66.7; H, 10.1; N, 7.0. $C_{22}H_{40}N_2O_4$ requires C, 66.63; H, 10.17; N, 7.06%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3283 (NH) and 1707 (C=O); δ_H(300 MHz; $CDCl_3$) 6.32 (2 H, br s), 4.63 (2 H, dt, *J* 4.0 and 9.0), 2.06 (2 H, m), 1.92 (2 H, m), 1.67 (4 H, m), 1.47 (2 H, m), 1.33 (2 H, m), 1.04 (6 H, m), 0.91 (6 H, d, *J* 6.5), 0.88 (6 H, d, *J* 6.5) and 0.79 (6 H, d, *J* 7.0); *m/z* (CI-NH_3) 414 (MNH_4^+).

Di-(−)-bornyl diazane-1,2-dicarboxylate 3b. The above procedure with chloroformate **2b** (14.3 g, 69.0 mmol), triethylamine (10.7 cm^3, 76.0 mmol) and hydrazine hydrate (1.10 cm^3, 35 mmol) produced a liquid, which was purified by flash chromatography [$CHCl_3$–MeOH (98:2)] to give *diazanedicarboxylate* **3b** (7.50 g, 55%) as a solid, mp 140–143 °C (from ethyl acetate–hexane) (Found: C, 67.3; H, 9.3; N, 6.9. $C_{22}H_{36}N_2O_4$ requires C, 67.32; H, 9.24; N, 7.14%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3290 (NH) and 1718 (C=O); δ_H(360 MHz; $CDCl_3$) 6.70 (2 H, s), 4.88 (2 H, m), 2.34 (2 H, m), 1.88 (2 H, m), 1.70 (4 H, m), 1.25 (4 H, m), 1.09 (2 H, m) and 0.92–0.79 (18 H, m); *m/z* (CI-NH_3) 410 (MNH_4^+).

Di-(−)-isobornyl diazane-1,2-dicarboxylate 3c. The above procedure with chloroformate **2c** (12.0 g, 56.0 mmol), triethylamine (8.51 cm^3, 61.0 mmol) and hydrazine hydrate (0.881 cm^3, 28 mmol) produced a liquid, which was purified by flash chromatography [$CHCl_3$–MeOH (98:2)] to give *diazanedicarboxylate* **3c** (6.05 g, 55%) (Found: C, 67.5; H, 8.9; N, 7.2%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3283 (NH) and 1715 (C=O); δ_H(400 MHz; $CDCl_3$) 6.72 (2 H, br s), 4.65 (2 H, br s), 1.80 (3 H, m), 1.69 (6 H, m), 1.51 (2 H, m), 1.12 (3 H, m), 1.01 (3 H, s), 0.94 (3 H, s), 0.90 (3 H, s), 0.86 (3 H, s) and 0.85 (6 H, d, *J* 4.5); *m/z* (CI-NH_3) 410 (MNH_4^+).

Diazenedicarboxylate esters

Di-(+)-menthyl diazenedicarboxylate 4a. The oxidation method of Carpino *et al.* was adapted.[23] Diazanedicarboxylate **3a** (2.38 g, 6.00 mmol) as a solution in THF (130 cm^3) was treated with pyridine (0.730 cm^3, 9.00 mmol), cooled to 0 °C, and NBS (1.28 g, 7.20 mmol) was added. The mixture was protected from light and stirred at 20 °C for 22 h. It was washed successively with water (100 cm^3) and 10% aq. K_2CO_3 (2 × 100 cm^3). The organic phase was dried ($MgSO_4$), and concentrated under reduced pressure to a solid, which was purified by flash chromatography [$CHCl_3$–MeOH (98:2)] to give *diazenedicarboxylate* **4a** (2.04 g, 86%) as a yellow solid; mp 66–69 °C (Found: C, 66.7; H, 9.9; N, 7.0. $C_{22}H_{38}N_2O_4$ requires C, 66.97; H, 9.71; N, 7.10%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1771 (C=O); δ_H(300 MHz; $CDCl_3$) 4.63 (2 H, dt, *J* 5.0 and 11.0), 2.17 (2 H, m), 1.98 (2 H, m), 1.72 (4 H, m), 1.54 (4 H, m), 1.14 (6 H, m), 0.95 (6 H, d, *J* 8.5), 0.92 (6 H, d, *J* 8.5) and 0.82 (6 H, d, *J* 7.0); *m/z* (CI-NH_3) 412 (MNH_4^+).

Di-(−)-bornyl diazenedicarboxylate 4b. The above procedure with diazanedicarboxylate **3b** (0.392 g, 1.00 mmol) in CH_2Cl_2 (20 cm^3), pyridine (0.121 cm^3, 1.50 mmol), and NBS (0.214 g, 1.20 mmol) gave *diazenedicarboxylate* **4b** (0.299 g, 77%) as a yellow solid; mp 93–96 °C (Found: C, 67.65; H, 8.6; N, 7.1. $C_{22}H_{34}N_2O_4$ requires C, 67.66; H, 8.78; N, 7.17%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1770 (C=O); δ_H(400 MHz; $CDCl_3$) 5.17 (2 H, m), 2.49 (2 H, m), 1.95 (2 H, m), 1.78 (4 H, m), 1.41–1.20 (6 H, m), 0.95 (6 H, s), 0.94 (6 H, s) and 0.91 (6 H, s); *m/z* (CI-NH_3) 408 (MNH_4^+).

Di-(−)-isobornyl diazenedicarboxylate 4c. The above procedure with diazanedicarboxylate **3c** (2.80 g, 7.14 mmol), pyridine (0.890 cm^3, 11.0 mmol), and NBS (1.52 g, 8.60 mmol) gave *diazenedicarboxylate* **4c** (2.53 g, 91%) as a yellow oil (Found: C, 67.4; H, 8.6; N, 7.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1777 (C=O); δ_H(400 MHz; $CDCl_3$) 4.90 (2 H, dd, *J* 3.5 and 7.5), 1.93 (4 H, m), 1.82 (2 H, m), 1.74 (2 H, m), 1.64 (2 H, m), 1.15 (4 H, m), 0.96 (3 H, s), 0.95 (3 H, s), 0.94 (3 H, s), 0.91 (3 H, s) and 0.86 (6 H, d); *m/z* (CI-NH_3) 408 (MNH_4^+).

Di-(+)-menthyl *N*-[(*S*)-ethoxycarbonyl(phenyl)methyl]-diazane-1,2-dicarboxylate 5a and its (*R*)-isomer 6a

The methods of Trimble and Vederas,[5] and Evans *et al.*[24] were adapted. To a solution of hexamethyldisilazane (HMDS) (0.232 cm^3, 1.10 mmol) in THF (5 cm^3) at −78 °C was added a solution of BuLi (1.49 mol dm^{-3} in hexane; 0.67 cm^3, 1.00 mmol). To LHMDS thus formed was added ethyl phenylacetate (0.159 cm^3, 1.00 mmol) dropwise and the solution was stirred at −78 °C for 15 min. A solution of diazenedicarboxylate **4a** (0.394 g, 1.00 mmol) in THF (2 cm^3) was added over a period of 5 min and the reaction mixture was stirred for 2 min. The reaction was quenched at −78 °C with acetic acid (0.057 cm^3, 1.00 mmol) and the mixture was allowed to warm to 20 °C over a period of 1 h. Water (15 cm^3) was added and the resulting solution was extracted with CH_2Cl_2 (3 × 15 cm^3). The organic phase was dried ($MgSO_4$), and concentrated under reduced pressure to a yellow liquid, which was purified by flash chromatography [hexane–ethyl acetate (85:15)] to give *phenylacetates* **5a** and **6a** (0.327 g, 59%) as an oily 2:1 mixture of diastereoisomers (Found: C, 69.2; H, 9.1; N, 5.0. $C_{32}H_{50}N_2O_6$ requires C, 68.79; H, 9.02; N, 5.01%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3230 (NH), 1737 (C=O) and 1713 (C=O); δ_H(400 MHz; [$^2H_8$]toluene; 373 K) (major diastereoisomer) 7.40–7.07 (5 H, m), 6.59 (1 H, s), 6.04 (1 H, s), 4.75 (1 H, m), 4.44 (1 H, m), 4.01 (2 H, q, *J* 7.0), 2.17 (1 H, m), 2.05 (1 H, m), 1.93 (1 H, br), 1.76 (1 H, br), 1.53 (4 H, m), 1.34 (2 H, m), 1.17 (2 H, m), 1.02 (4 H, m), 0.95 (3 H, d, *J* 7.0), 0.91 (3 H, d, *J* 7.0), 0.89–0.69 (14 H, m) and 0.66 (3 H, d, *J* 7.0) (minor diastereoisomer) 7.40–7.07 (5 H, m), 6.62 (1 H, s), 6.09 (1 H, s), 4.75 (1 H, m), 4.44 (1 H, m), 4.01 (2 H, q, *J* 7.0), 2.17 (1 H, m), 2.05 (1 H, m), 1.93 (1 H, br), 1.76 (1 H, br), 1.53 (4 H, m), 1.34 (2 H, m), 1.17 (2 H, m), 1.02 (4 H, m), 0.95 (3 H, d, *J* 7.0), 0.91 (3 H, d, *J* 7.0), 0.89–0.69 (14 H, m) and 0.66 (3 H, d, *J* 7.0); *m/z* (CI-NH_3) 559 (MH^+).

Di-(−)-bornyl *N*-[(*S*)- and (*R*)-ethoxycarbonyl(phenyl)-methyl]diazane-1,2-dicarboxylate 5b, 6b

The above procedure with ethyl phenylacetate (0.080 cm^3, 0.500 mmol), HMDS (0.116 cm^3, 0.550 mmol), BuLi (1.6 mol dm^{-3} in hexane; 0.312 cm^3, 0.500 mmol), THF (2.5 cm^3) and diazenedicarboxylate **4b** (0.195 g, 0.51 mmol), followed by purification by flash chromatography [hexane–ethyl acetate (80:20)] gave phenylacetates **5b** and **6b** (0.158 g, 57%) as an oily 1:1 mixture of diastereoisomers; $\nu_{max}(CHCl_3)/cm^{-1}$ 3330 (NH), 1734 (C=O) and 1719 (C=O); δ_H(400 MHz; [$^2H_8$]toluene; 373 K) 7.40–7.09 (5 H, m), 6.78 (1 H, s), 6.11 (1 H, s), 5.07 (1 H, m), 4.78 (1 H, m), 4.00 (2 H, q, *J* 7.0), 2.34 (1 H, m), 2.09 (2 H, m), 1.82 (1 H, m), 1.66 (2 H, m), 1.52 (1 H, m), 1.46 (1 H, m), 1.28 (3 H, m), 1.15 (3 H, m), 0.96 (3 H, t, *J* 7.0), 0.89 (3 H, s), 0.81 (3 H, s), 0.77 (6 H, s), 0.73 (3 H, s) and 0.69 (3 H, s); *m/z* (CI-NH_3) 555 (MH^+).

Di-(−)-isobornyl *N*-[(*S*)- and (*R*)-ethoxycarbonyl(phenyl)-methyl]diazane-1,2-dicarboxylate 5c and 6c

The above procedure with ethyl phenylacetate (0.096 cm^3, 0.600 mmol), HMDS (0.139 cm^3, 0.660 mmol), BuLi (1.34 mol dm^{-3} in hexane; 0.492 cm^3, 0.660 mmol), THF (5 cm^3) and diazenedicarboxylate **4c** (0.258 g, 0.660 mmol), followed by purification by flash chromatography [hexane–ethyl acetate (80:20)] gave solid *phenylacetates* **5c** and **6c** (0.138 g, 42%) as a 1:1 mixture of diastereoisomers, mp 57–59 °C (from ethyl acetate–hexane) (Found: C, 69.1; H, 8.2; N, 5.0. $C_{32}H_{46}N_2O_6$ requires C, 69.29; H, 8.36; N, 5.05%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3320 (NH), 1734 (C=O) and 1716 (C=O); δ_H(400 MHz; [$^2H_8$]toluene; 373 K) (Isomer A) 7.36–7.02 (5 H, m), 6.57 (1 H, s), 6.04 (1 H, s), 4.76 (1 H, m), 4.49 (1 H, m), 3.96 (2 H, m), 1.86 (2 H, m), 1.71 (2 H, m), 1.58–1.41 (6 H, m), 1.41–1.18 (4 H, m), 1.01 (3 H, s), 0.96–0.90 (6 H, m), 0.83 (3 H, s), 0.74 (3 H, s), 0.69 (3 H, s) and 0.68 (3 H, s) (Isomer B) 7.36–7.02 (5 H, m), 6.56 (1 H, s), 6.04 (1 H, s), 4.76 (1 H, m), 4.38 (1 H, m), 3.96 (2 H, m), 1.86 (2 H, m), 1.71 (2 H, m), 1.58–1.41 (6 H, m), 1.41–1.18 (4 H, m), 1.01 (3 H, s), 0.96–0.90 (6 H, m), 0.83 (3 H, s), 0.74 (3 H, s), 0.69 (3 H, s) and 0.68 (3 H, s); *m/z* (CI-NH_3) 572 (MNH_4^+).

Diethyl (2*S*)- and (2*R*)-{*N*,*N*′-bis-[(+)-menthyloxycarbonyl]-hydrazino}succinate 7a and 8a

The above procedure with a solution of diethyl succinate (0.166 cm^3, 1.00 mmol) in THF (2 cm^3), HMDS (0.232 cm^3, 1.10 mmol), BuLi (1.49 mol dm^{-3} in hexane; 0.67 cm^3, 1.00 mmol), THF (5 cm^3) and a solution of diazenedicarboxylate **4a** (0.394 g, 1.00 mmol) in THF (5 cm^3) gave hydrazinosuccinates **7a** and **8a** (0.072 g, 13%) as an oily 1:1 mixture of diastereoisomers, $\nu_{max}(CHCl_3)/cm^{-1}$ 3310 (NH) and 1740 (C=O); δ_H(400 MHz; [$^2H_8$]toluene; 373 K) (Isomer A) 6.44 (1 H, s), 5.45 (1 H, t, *J* 6.5), 4.73 (2 H, m), 4.09–3.94 (4 H, m), 3.02 (2 H, d, *J* 7.0), 2.04 (2 H, m), 1.55 (4 H, m), 1.33 (4 H, m), 1.08 (3 H, m), 1.02 (6 H, m), 0.99–0.86 (15 H, m) and 0.86–0.77 (8 H, m) (Isomer B) 6.44 (1 H, s), 5.39 (1 H, t, *J* 6.5), 4.73 (2 H, m), 4.09–3.94 (4 H, m), 3.01 (2 H, d, *J* 7.0), 2.04 (2 H, m), 1.55 (4 H, m), 1.33 (4 H, m), 1.08 (3 H, m), 1.02 (6 H, m), 0.99–0.86 (15 H, m) and 0.86–0.77 (8 H, m); *m/z* (CI-NH_3) 586 (MNH_4^+).

Diethyl (2*S*)- and (2*R*)-{*N*,*N*′-bis-[(−)-bornyloxycarbonyl]-hydrazino}succinate 7b and 8b

The above procedure with a solution of diethyl succinate (0.083 cm^3, 0.500 mmol) in THF (1 cm^3), HMDS (0.116 cm^3, 0.550 mmol), BuLi (1.6 mol dm^{-3} in hexane; 0.312 cm^3, 0.500 mmol), THF (2.5 cm^3) and a solution of diazenedicarboxylate **4b** (0.195 g, 0.510 mmol) in THF (2.5 cm^3) gave hydrazinosuccinates **7b** and **8b** (0.139 g, 49%) as an oily 1:1 mixture of diastereoisomers, $\nu_{max}(CHCl_3)/cm^{-1}$ 3300 (NH) and 1739 (C=O); δ_H(400 MHz; [$^2H_8$]toluene; 373 K) (Isomer A) 6.56 (1 H, s), 5.35 (1 H, t, *J* 6.5), 5.01 (1 H, m), 4.97 (1 H, m), 4.02–3.91 (4 H, m), 2.98 (2 H, d, *J* 6.5), 2.27 (2 H, m), 1.99 (2 H, m), 1.64 (2 H, m), 1.49 (2 H, m), 1.29–1.03 (6 H, m), 1.01–0.95 (9 H, m), 0.83 (6 H, t, *J* 7.0) and 0.76–0.69 (9 H, m) (Isomer B) 6.56 (1 H, s), 5.34 (1 H, t, *J* 6.5), 5.01 (1 H, m), 4.97 (1 H, m), 4.02–3.91 (4 H, m), 2.96 (2 H, d, *J* 6.5), 2.27 (2 H, m), 1.99 (2 H, m), 1.64 (2 H, m), 1.49 (2 H, m), 1.29–1.03 (6 H, m), 1.01–0.95 (9 H, m), 0.83 (6 H, t, *J* 7.0) and 0.76–0.69 (9 H, m); *m/z* (CI-NH_3) 582 (MNH_4^+).

Diethyl (2*S*)- and (2*R*)-{*N*,*N*′-bis-[(−)-isobornyloxycarbonyl]-hydrazino}succinate 7c and 8c

The above procedure with a solution of diethyl succinate (0.085 cm^3, 0.510 mmol) in THF (1 cm^3), HMDS (0.118 cm^3, 0.560 mmol), BuLi (1.34 mol dm^{-3} in hexane; 0.380 cm^3, 0.510 mmol), THF (2.5 cm^3) and a solution of diazenedicarboxylate **4c** (0.199 g, 0.510 mmol) in THF (2.5 cm^3) gave *hydrazinosuccinates* **7c** and **8c** (0.117 g, 41%) as an oily 1:1 mixture of diastereoisomers (Found: C, 63.6; H, 8.9; N, 4.7. $C_{30}H_{48}N_2O_8$ requires C, 63.81; H, 8.57; N, 4.96%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3300 (NH) and 1737 (C=O); δ_H(400 MHz; [$^2H_8$]toluene; 373 K) (Isomer A) 6.44 (1 H, s), 5.35 (1 H, m), 4.75–4.64 (2 H, m), 4.03–3.89 (4 H, m), 2.96 (2 H, d, *J* 7.0), 1.84 (3 H, m), 1.67 (3 H, m), 1.53 (5 H, m), 1.39 (3 H, m), 1.00–0.96 (6 H, m), 0.92 (3 H, s), 0.91–0.88 (6 H, m) and 0.73 (6 H, s) (Isomer B) 6.42 (1 H, s), 5.35 (1 H, m), 4.75–4.64 (2 H, m), 4.03–3.89 (4 H, m), 2.96 (2 H, d, *J* 7.0), 1.84 (3 H, m),

1.67 (3 H, m), 1.53 (5 H, m), 1.39 (3 H, m), 1.00–0.96 (6 H, m), 0.92 (3 H, s), 0.91–0.88 (6 H, m) and 0.73 (6 H, s); *m/z* (CI-NH_3) 582 (MNH_4^+).

Di-(−)-isobornyl *N*-[1-(dimethylcarbamoyl)ethyl]diazane-1,2-dicarboxylate 9c, 10c

Following the procedure of Trimble and Vederas,[5] a solution of 0.8 mol dm^{-3} lithium diisopropylamide in THF (1.5 cm^3) [2.4 mol dm^{-3} BuLi in hexane (0.67 cm^3) and diisopropylamine (0.224 cm^3)] at −78 °C was added dropwise to a stirred solution of *N,N*-dimethylpropionamide (0.126 g, 1.25 mmol) in THF (18 cm^3) at −78 °C. The mixture was stirred at −78 °C for 40 min, after which a solution of diazenedicarboxylate **4c** (0.627 g, 1.60 mmol) in THF (1.5 cm^3) was added over a period of 2 min. After being stirred for 2 min the reaction mixture was quenched with 5% NH_4Cl (10 cm^3) and warmed to room temp. The solution was extracted with CH_2Cl_2 (4 × 25 cm^3). The organic phase was dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography [hexane–ethyl acetate (55:45)] gave hydrazinopropionamides **9c** and **10c** (0.442 g, 72%) as an oily 1:1 mixture of diastereoisomers, ν_{max}($CHCl_3$)/cm^{-1} 3280 (NH), 1733 (C=O), 1709 (C=O) and 1649 (C=O); δ_H(400 MHz; [$^2H_8$]toluene; 373 K) (Isomer A) 7.14 (1 H, br s), 5.08 (1 H, br), 4.71 (2 H, m), 2.53 (3 H, s), 2.52 (3 H, s), 1.85 (2 H, m), 1.69 (3 H, m), 1.53 (5 H, m), 1.38 (4 H, m), 1.28 (3 H, d, *J* 7.0), 1.03 (3 H, s), 0.99 (3 H, s), 0.95 (3 H, s), 0.89 (3 H, s), 0.75 (3 H, s) and 0.73 (3 H, s) (Isomer B) 7.14 (1 H, br s), 5.08 (1 H, br), 4.71 (2 H, m), 2.53 (3 H, s), 2.52 (3 H, s), 1.85 (2 H, m), 1.69 (3 H, m), 1.53 (5 H, m), 1.38 (4 H, m), 1.26 (3 H, d, *J* 7.0), 1.03 (3 H, s), 0.99 (3 H, s), 0.95 (3 H, s), 0.89 (3 H, s), 0.75 (3 H, s) and 0.73 (3 H, s); *m/z* (CI-NH_3) 492 (MH^+).

Di-(−)-isobornyl *N*-[1-(dimethylcarbamoyl)-2-methylpropyl]-diazane-1,2-dicarboxylate 11c and 12c

The above procedure with *N,N*-dimethylisovaleramide (0.161 g, 1.25 mmol), diisopropylamine (0.224 cm^3, 1.60 mmol), BuLi (2.4 mol dm^{-3} solution in hexane; 0.67 cm^3, 1.60 mmol) and diazenedicarboxylate **4c** (0.627 g, 1.60 mmol) in THF (1.5 cm^3) gave hydrazinoisovaleramides **11c** and **12c** (0.566 g, 87%) as an oily 1:1 mixture of diastereoisomers, ν_{max}($CHCl_3$)/cm^{-1} 3280 (NH), 1709 (C=O) and 1640 (C=O); δ_H(400 MHz; [$^2H_8$]toluene; 373 K) (Isomer A) 4.86 (1 H, d, *J* 9.0), 4.73 (2 H, m), 2.75 (6 H, br), 2.32 (1 H, m), 1.84 (5 H, m), 1.53 (6 H, m), 1.39 (3 H, m), 1.03 (3 H, s), 1.00 (3 H, s), 0.94 (3 H, s), 0.87 (3 H, s) and 0.74 (12 H, m) (Isomer B) 4.82 (1 H, d, *J* 9.0), 4.73 (2 H, m), 2.75 (6 H, br), 2.32 (1 H, m), 1.84 (5 H, m), 1.53 (6 H, m), 1.39 (3 H, m), 1.03 (3 H, s), 1.00 (3 H, s), 0.91 (3 H, s), 0.87 (3 H, s) and 0.74 (12 H, s); *m/z* (CI-NH_3) 520 (MH^+).

α-Hydrazinopropionic acid 13

Following the procedure of Ito *et al.*[25] the diastereoisomeric mixture **9c**/**10c** (0.038 g, 0.08 mmol) in 6 mol dm^{-3} HCl (2.0 cm^3) was heated in a sealed tube at 100 °C for 41 h. After cooling to room temp. the solution was repeatedly extracted with diethyl ether (6 × 5 cm^3). The aqueous phase was concentrated under reduced pressure and then applied to the H^+ form of a column of AG-50X8 cation-exchange resin. The column was eluted with, successively, 1, 2 and 6 mol dm^{-3} HCl and fractions containing product were combined to give acid **13** (9 mg, 75%) as its HCl salt; ν_{max}($CHCl_3$)/cm^{-1} 2778 (OH) and 1728 (C=O); δ_H(400 MHz; D_2O) 3.80 (1 H, q) and 1.45 (3 H, d); *m/z* (FAB$^+$) 105.16 (MH^+).

(2′*S*,4*S*)-3-{2-[*N,N*′-Bis-(−)-isobornyloxycarbonylhydrazino]-propionyl}-4-isopropyloxazolidin-2-one 16

The procedure described for hydrazinopropionamide **9c**/**10c** above, with (*S*)-4-isopropyl-3-propionyloxazolidin-2-one **14** (0.463 g, 2.50 mmol), diisopropylamine (0.448 cm^3, 3.20 mmol), BuLi (2.5 mol dm^{-3} in hexane; 1.28 cm^3, 3.2 mmol) and diazenedicarboxylate **4c** (1.25 g, 3.20 mmol), followed by purification by flash chromatography [hexane–ethyl acetate (68:32)] gave the *oxazolidinone* **16** (0.810 g, 56%) as a solid, mp 82–84 °C (Found: C, 64.8; H, 8.7; N, 7.0. $C_{31}H_{49}N_3O_7$ requires C, 64.67; H, 8.58; N, 7.30%); ν_{max}($CHCl_3$)/cm^{-1} 3340 (NH), 1786 (C=O), 1719 (C=O) and 1699 (C=O); δ_H(400 MHz; [$^2H_8$]toluene; 373 K) 6.65 (1 H, br), 5.95 (1 H, q, *J* 7.0), 4.74 (2 H, dt, *J* 8.0 and 4.0), 3.86 (1 H, dd, *J* 8.5 and 4.0), 3.55 (1 H, dd, *J* 9.0 and 3.0), 3.46 (1 H, t, *J* 9.0), 2.20 (1 H, m), 1.86 (2 H, m), 1.71 (2 H, m), 1.54 (3 H, d, *J* 7.0), 1.52 (4 H, m), 1.39 (2 H, m), 1.05 (3 H, s), 1.02 (1 H, m), 0.99 (3 H, s), 0.96 (1 H, m), 0.93 (3 H, s), 0.92 (1 H, m), 0.90 (3 H, s), 0.85 (1 H, m), 0.74 (6 H, d, *J* 3.5), 0.69 (3 H, d, *J* 7.0) and 0.54 (3 H, d, *J* 7.0); *m/z* (CI-NH_3) 593 (MNH_4^+).

(2′*R*,4*R*)-3-{2-[*N,N*′-Bis-(−)-isobornyloxycarbonyl)hydrazino]-propionyl}-4-isopropyloxazolidin-2-one 17

The above procedure with (*R*)-4-isopropyl-3-propionyloxazolidin-2-one **15** (0.463 g, 2.50 mmol), diisopropylamine (0.448 cm^3, 3.20 mmol), BuLi (2.5 mol dm^{-3} in hexane; 1.28 cm^3, 3.2 mmol) and diazenedicarboxylate **4c** (1.25 g, 3.20 mmol) gave the *oxazolidinone* **17** (1.26 g, 88%) as a solid, mp 79–81 °C (Found: C, 64.6; H, 8.6; N, 7.0%); ν_{max}($CHCl_3$)/cm^{-1} 3330 (NH), 1785 (C=O) and 1705 (C=O); δ_H(400 MHz; [$^2H_8$]toluene; 373 K) 6.73 (1 H, br), 6.01 (1 H, br m), 4.78 (2 H, dt, *J* 8.5 and 4.0), 4.69 (1 H, br m), 3.86 (1 H, m), 3.60 (1 H, dd, *J* 3.0 and 9.0), 3.53 (1 H, dd, *J* 4.0 and 10.0), 2.21 (1 H, m), 1.83 (2 H, m), 1.71 (2 H, m), 1.53 (3 H, d, *J* 7.0), 1.52 (4 H, m), 1.37 (2 H, m), 1.04 (3 H, s), 1.01 (1 H, m), 0.98 (3 H, s), 0.94 (1 H, m), 0.90 (6 H, s), 0.85 (1 H, m), 0.73 (6 H, s), 0.70 (3 H, d, *J* 7.0) and 0.57 (3 H, d, *J* 7.0); *m/z* (CI-NH_3) 593 (MNH_4^+).

Di-(−)-isobornyl *N*-[(*S*)-1-(methoxycarbonyl)ethyl]diazane-1,2-dicarboxylate 18

A 0.05 mol dm^{-3} solution of the oxazolidinone **16** (0.050 g, 0.090 mmol) in (3:1) THF–water cooled to 0 °C was treated with hydrogen peroxide (13.0 mm^3, 0.430 mmol), followed by aq. lithium hydroxide (0.007 g, 0.170 mmol in 0.70 cm^3). The reaction mixture was stirred at 0 °C for 1 h. Diethyl ether (2 cm^3) was added, followed by dropwise addition of 10% formic acid (39.0 mm^3, 0.85 mmol). The cooled mixture was treated with an ethereal solution of freshly prepared diazomethane[26] until the evolution of nitrogen ceased and the colour of the solution was a pale yellow. The resulting solution was concentrated under reduced pressure to give a substance (0.059 g), which was purified on normal TLC (5 × 10 cm) plates [$CHCl_3$–MeOH (95:5)] to give *hydrazinopropionate* **18** (0.036 g, 86%) as an oil (Found: C, 65.1; H, 8.7; N, 5.6. $C_{26}H_{42}N_2O_6$ requires C, 65.25; H, 8.84; N, 5.85%); ν_{max}($CHCl_3$)/cm^{-1} 3320 (NH), 1740 (C=O) and 1715 (C=O); δ_H(400 MHz; [$^2H_8$]toluene; 373 K) 6.37 (1 H, br s), 4.89 (1 H, br), 4.72 (2 H, m), 3.30 (3 H, s), 1.82 (3 H, m), 1.70 (3 H, m), 1.52 (5 H, m), 1.43 (3 H, d, *J* 7.5), 1.36 (3 H, m), 0.99 (3 H, s), 0.97 (3 H, s), 0.92 (3 H, s), 0.89 (3 H, s) and 0.73 (6 H, s); *m/z* (CI-NH_3) 496 (MNH_4^+).

Di-(−)-isobornyl *N*-[(*R*)-1-(methoxycarbonyl)ethyl]diazane-1,2-dicarboxylate 19

A 0.05 mol dm^{-3} solution of the oxazolidinone **17** (0.100 g, 0.170 mmol) in (3:1) THF–water was treated with hydrogen peroxide (27.0 mm^3, 0.870 mmol), followed by aq. lithium hydroxide (0.015 g, 0.350 mmol in 1.30 cm^3). The reaction mixture was stirred at 0 °C for 1 h, then was warmed to room temp. and the reaction was quenched with a 10% excess of 1.5 mol dm^{-3} Na_2SO_3. The mixture was buffered to pH 10 with aq. $NaHCO_3$. The THF was evaporated off and the resulting solution was extracted with CH_2Cl_2 (3 × 15 cm^3). The organic phase was dried ($MgSO_4$), and concentrated under

reduced pressure to give a foam (0.092 g). A solution of this foam (0.046 g) in diethyl ether (3 cm^3) was treated with formic acid (10.0 mm^3) and the resulting solution was cooled to 0 °C. An ethereal solution of freshly prepared diazomethane[26] was added until the evolution of N_2 had ceased and the colour of the solution was a pale yellow. The resulting solution was concentrated under reduced pressure to give a substance (0.044 g), which was purified on normal TLC plates (5 × 10 cm) [$CHCl_3$–MeOH (95:5)] to give hydrazinopropionate **19** (0.034 g, 87%) as an oil; $\nu_{max}(CHCl_3)/cm^{-1}$ 3320 (NH), 1741 (C=O) and 1718 (C=O); δ_H(400 MHz; [$^2H_8$]toluene; 373 K) 6.42 (1 H, br s), 4.90 (1 H, br), 4.75 (2 H, m), 3.32 (3 H, s), 1.83 (3 H, m), 1.79 (3 H, m), 1.52 (5 H, m), 1.44 (3 H, d, *J* 7.5), 1.36 (3 H, m), 0.99 (3 H, s), 0.97 (3 H, s), 0.90 (3 H, s), 0.88 (3 H, s), 0.74 (3 H, s) and 0.72 (3 H, s); *m/z* (CI-NH_3) 496 (MNH_4^+).

Acknowledgements

These investigations were supported by the Natural Sciences and Engineering Research Council of Canada.

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Paper 5/00483G
Received 27*th January* 1995
Accepted 3*rd April* 1995