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Synthesis and Ene Reactions of Di-(-)-menthyl Diazenedicarboxylate

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Abstract: The preparation di-(-)-menthyl diazendicarboxylate **3** is described. Reaction of hydrazine with excess (-)-menthyl chloroformate **1** afforded dimenthyl diazanedicarboxylate **2** which was then oxidized to the azo-enophile **3**. The azo-ene reactions of **3** with the alkenes *trans*-3-hexene **4**, *trans*-4-octene **6**, cyclohexene **8** and cyclopentene **10** were carried out using the Lewis acid catalyst tin tetrachloride. *Trans*-3-hexene **4** and *trans*-4-octene **6** afforded the ene adducts **5** (80%) and **7** (70%) with a diastereomeric excess of 2.5:1 and 2:1 respectively. Use of cyclohexene **8** and cyclopentene **10** afforded the ene adducts **9** and **11** in 81% and 88% yield, however, no diastereomeric excess was observed. Finally use of conjugated aromatic acyclic alkenes **12** and **14** afforded the chlorides **13** and **15** in 93% and 56% yield respectively. In these latter cases an ionic addition proceeded rather than a pericyclic ene reaction. Attempted removal of the chiral menthyl ester auxiliary from the ene adduct **5** proved difficult.

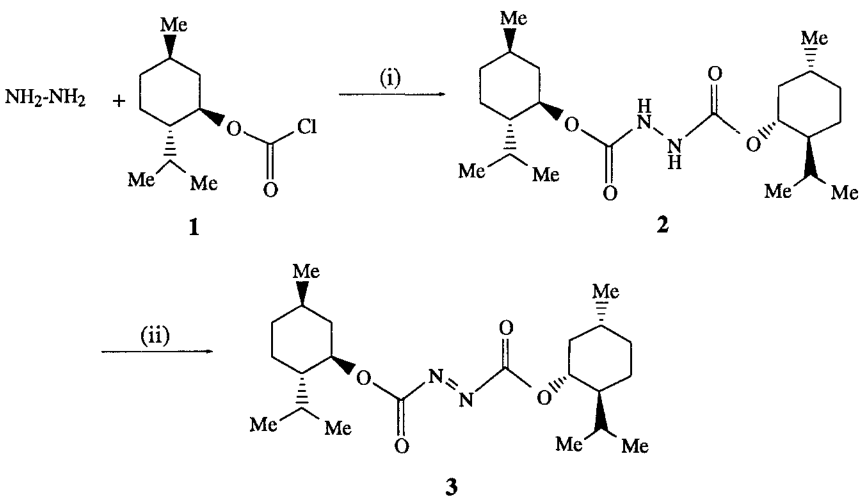
The ene reaction[1] plays an important role in organic synthesis in that it provides a method for C-C bond formation with concomitant activation of an allylic C-H bond. Intramolecular versions[2] of the ene reaction have adopted an important role in synthesis and various functionalised carbon skeletons can be constructed due to the range of enophiles which can be used. Thus, acetylenes react with simple alkenes to give 1,4-dienes,[3] carbonyl compounds give homoallylic alcohols[4] and imino derivatives of aldehydes form homoallylic amines.[5] A number of Lewis acid promoters have now also been developed which have resulted in milder conditions and significant rate enhancements thereby extending the scope of the ene reaction.[6]

The azo-ene reaction involves treatment of an alkene with an azo-diester to afford a diacyl hydrazine which upon cleavage to a carbamate, provides an alternative method to effect allylic amination of alkenes. The preparation of allylic amines has been limited to the use of sulfur diimido compounds,[7] *N*-sulfonylimines,[8] *N*-phenyltriazoline-3,5-diones,[9] acylnitroso compounds[10] or *N*-sulfinylbenzenesulfonamide.[11] We have recently reported[12] the use of tin tetrachloride as a promoter for the azo-ene reaction of diethyl diazenedicarboxylate (DEAD) with alkenes thereby eliminating the formation of diadducts which were often observed in the harsher thermal reactions.[13] This Lewis acid mediated azo-ene reaction offers an alternative to the use of the more reactive enophile bis(2,2,2-trichloroethyl)azodicarboxylate used by Leblanc *et al.*[14] Cleavage of the N-N bond was effected using zinc in acetic acid in the latter case whereas lithium in liquid ammonia was effective in our case.[12]

The use of asymmetric ene reactions has been reviewed by Mikami and Shimizu,[15] with emphasis to date focusing predominantly on development of an asymmetric carbonyl-ene reaction. Whitesell *et al.*[16] have

reported excellent asymmetric induction in carbonyl-ene reactions using 8-phenylmenthyl glyoxalates with a stoichiometric quantity of tin tetrachloride. Similarly, Mikami *et al.*[17] reported high diastereoselectivity in imine-ene reactions of 1,1-disubstituted alkenes with chiral α-imino-esters bearing a 8-phenylmenthyl auxiliary. Mikami *et al.*[18] have also explored catalyst-based enantiofacial control in the reactions of achiral ene and enophile components. These authors have developed efficient asymmetric catalysis of the glyoxylate-ene reaction affording α-hydroxy esters of biological and synthetic importance. The successful catalyst was prepared from diisopropoxytitanium dihalide and enantiomerically pure binaphthol in the presence of molecular sieves (MS 4A).

We now wish to report our initial studies directed towards development of an asymmetric azo-ene reaction. The work reported herein focuses on the use of an azo-enophile bearing a chiral ester auxiliary that can be used to transfer chirality to the newly formed stereogenic centre. This strategy therefore offers a potential method to effect asymmetric allylic amination. Given the successful use of menthyl ester derived chiral auxiliaries in the carbonyl-ene and imine-ene reactions described above, it was decided to investigate the level of asymmetric induction in the reaction of the chiral azo-enophile di-(-)-menthyl diazenedicarboxylate **3** with simple alkenes under Lewis acid catalysis.



Reagents and Conditions: (i) -10°C - 0°C, EtOH, aq. Na_2CO_3, 85%; (ii) $PhI(OCOCF_3)_2$ CH_2Cl_2, room temp., 24 h., 97%.

Scheme

At the outset of this work, di-(-)-menthyl diazenedicarboxylate **3** had not been reported in the literature, however, during the course of this work Vederas *et al.*[19] reported the preparation of the opposite enantiomer and its reaction with amide and ester enolates. Vederas *et al.*[19] prepared di-(+)-menthyl diazanedicarboxylate **2** in 41% yield from (+)-menthyl chloroformate **1** and hydrazine in THF using triethylamine as the base. Our procedure involved addition of two equivalents of hydrazine to one equivalent of (-)-menthyl chloroformate in ethanol at 0°C followed by the simultaneous addition of a second equivalent of (-)-menthyl chloroformate with a solution of aqueous Na_2CO_3 (Scheme). This afforded diacyl hydrazine **2** in 85% yield with a higher melting point than that reported by Vederas *et al.*[19] Oxidation of diacyl hydrazine **2** to the azo compound **3** was then

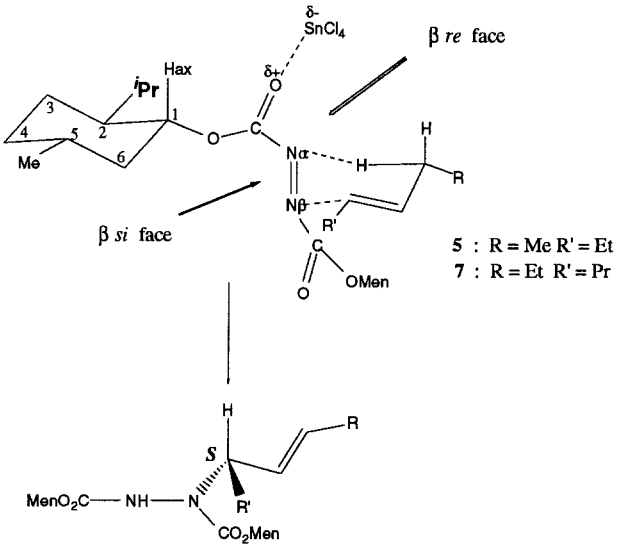
effected in 97% yield using [bis(trifluoroacetoxy)iodo]benzene[20] in dichloromethane at room temperature. This procedure afforded higher yields than the use of *N*-bromosuccinimide as reported by Vederas *et al.*[19] and was superior to the use of fuming nitric acid which gave variable yields in our hands.

With a successful synthesis of azo-enophile **3** in hand, attention then focused on the Lewis acid promoted azo-ene reaction (Table). Initially alkenes which could afford only one regioisomeric ene adduct were used as the ene component. Given that tin tetrachloride had been found to be the optimum Lewis acid to use in the azo-ene reactions of diethyl diazenedicarboxylate with various alkenes,[12] it was decided to investigate this asymmetric variant of the ene reaction using the same Lewis acid.

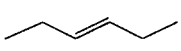
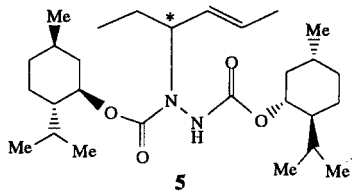
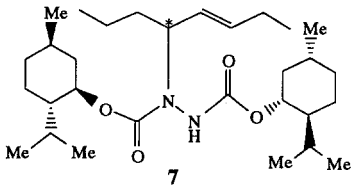
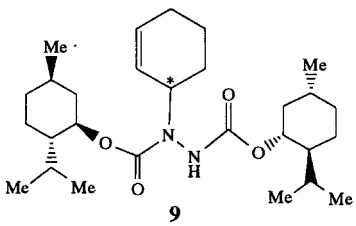
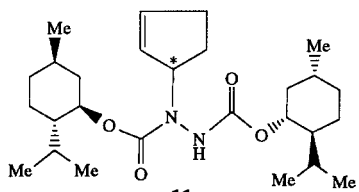
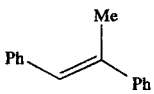
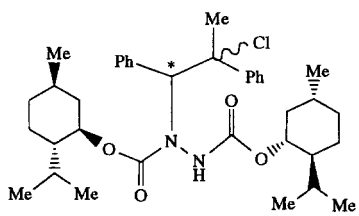
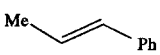
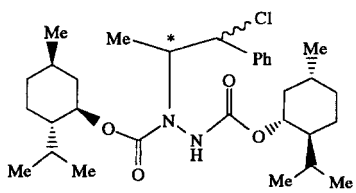
Addition of tin tetrachloride (2 equiv.) to a solution of di-(-)-menthyl diazenedicarboxylate **3** and *trans*-3-hexene **4** (2.5 equiv.) in dichloromethane at -60°C afforded the ene adduct **5** in 80% yield after purification by flash chromatography. Due to hindered rotation about the amide bond and the formation of diastereomers arising from generation of an additional stereogenic centre at C-4', the ^{1}H NMR spectrum of the adduct **5** was very broad and complex. Attempts to improve the resolution by using variable temperature ^{1}H NMR and several different solvents were fruitless. Better resolution was also not achieved using the chiral shift reagent (+)-*t*-butylphenylphosphinothioic acid.

Due to the poor resolution obtained in the ^{1}H n.m.r. spectrum of the ene adduct **5**, high prformance liquid chromatography (HPLC) was used to resolve the diastereomers. Using a Whatman Partisil 5 normal phase silica column run at 25°C and 3.5% ethyl acetate in hexane as eluant two peaks were observed in the chromatogram at R_t = 16.92 min and at R_t =19.53 min. Integration of these peaks afforded a 2.5:1 ratio of the two diastereomers.

Use of *trans*-4-octene **6** as the alkene component under similar conditions afforded ene adduct **7** in 70% yield and as a 2:1 mixture of diastereomers. Examination of a transition state model (Figure) for the ene reaction using *trans*-3-hexene **4** and *trans*-4-octene **6** may allow a prediction of which diastereomer should be the favoured product.



Figure

Table :	Reaction of Azo-enophile 3 with Alkenes using $SnCl_4$	
 **4**	 **5**	80% 2.5 : 1
 **6**	 **7**	70% 2.0 : 1
 **8**	 **9**	81% 1 : 1
 **10**	 **11**	88% 1 : 1
 **12**	 **13**	93% 1 : 1
 **14**	 **15**	56% 1 : 1

The menthyl group adopts a chair conformation with the methyl and isopropyl group in equatorial positions. Complexation of the carbonyl group to the Lewis acid affords the more stable *S trans* conformation about the C-N sigma bond (Figure). In this conformation the isopropyl group shields the Nβ-*re*-face, therefore the alkene approaches the enophile from the less hindered Nβ-*si*-face and the ene reaction occurs *via* a six membered transition state to afford the (*S*)-diastereomer of the ene adduct.

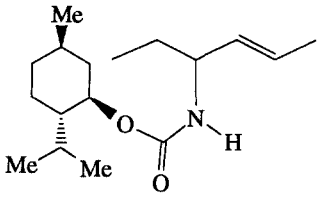
Having examined the ene reaction of azo-enophile **3** with symmetrical acyclic alkenes it was decided to investigate the use of cyclic alkenes as the ene component. Addition of di-(-)-menthyl diazenedicarboxylate **3** to cyclohexene **8** and cyclopentene **10** at -60°C followed by the addition of tin tetrachloride resulted in the formation of the ene adducts **9** (81%) and **11** (88%) respectively. HPLC analysis of the ene adducts established that 1:1 mixtures of diastereomers had formed in both cases. Thus, no diastereomeric excess was observed for these cyclic alkenes.

Disappointed with the lack of asymmetric induction in the ene reaction using cyclic alkenes, it was then decided to examine the use of acyclic alkenes conjugated to an aromatic system as the ene component. Azo-enophile **3** was added to *trans*–α-methylstilbene **12** in dichloromethane at -60°C followed by the addition of tin tetrachloride (1 equiv.). In this case only one major product formed in the reaction which was established to be chloride **13** (93%). The product analysed corrrectly for $C_{37}H_{53}N_2O_4Cl$ thus, clearly chloride had been incorporated into the product. No terminal vinylic protons were observed in the ^1H NMR spectrum as required for formation of the ene prouct. The ^1H NMR spectrum was complex due to the due to the presence of several diastereomers arising from creation of two new stereogenic centres at C-1' and C-2'. The regiochemistry of the product was established by the presence of a methine carbon at δ 60.0, characteristic of a CHN carbon (C-1') and a quaternary carbon at δ 83.0 assigned to C-2'.

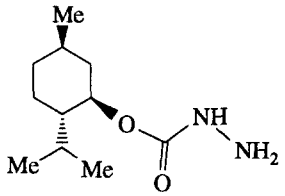
Clearly in this system an ionic mechanism involving a stepwise reaction with a carbonium ion intermediate is operative rather than a pericyclic mechanism. This situation has been observed in related imine-ene reactions.[5] Use of only 0.25 equivalents of the tin tetrachloride in an attempt to form the ene adduct rather than the chloride **13**, led only to incomplete formation of the chloride **13** (20%) and recovered starting material. Thus, one equivalent of the Lewis acid is required to effect complete reaction of alkene **12** with azo-enophile **3** and only the addition product **13** is formed.

Reaction of an alternative aromatic alkene, *trans*-β-methylstyrene **14** with azo-enophile **3** under similar conditions [tin tetrachloride (1 equiv.) at -60°C] also only afforded the addition product **15** in 56% yield. Attempts to form the ene product using less Lewis acid were unsuccessful.

Having established that the ene reaction of azo-enophile **3** with *trans*-3-hexene **4** mediated by tin tetrachloride afforded the ene adduct **5** with a 2.5:1 ratio of diastereomers, it was decided to examine cleavage of the N-N bond of the ene adduct to the carbamate **16**. Lithium in liquid ammonia had been used successfully to claeve the N-N bond of the ene adducts formed using diethyl diazenedicarboxylate.[12] Treatment of azo-ene adduct **5** with lithium in liquid ammonia however, resulted in formation of acyl hydrazine **17** and menthol. Thus, clearly, fragmentation of the C5'-N bond had occurred followed by cleavage of the carbomenthoxy group to form **17** and menthol. Use of other one electron reductants eg. samarium iodide and lithium naphthalenide, to effect the desired N-N cleavage were also unsuccessful.



16



17

Attempts were then made to remove the menthyl auxiliary groups from ene adduct **5** *via* hydrolysis. Treatment of ene adduct **5** with concentrated potassium hydroxide in methanol and isopropanol under reflux for 30 hours only afforded unreacted **5**. Use of concentrated hydrochloric acid was not feasible due to the lability of the double bond. Upon completion of this work, it was reported by Vederas *et al.*[19] that removal of the menthyl group from related carbamates proved problematic in that attempted hydrolysis of menthyl carbamates by heating under reflux in concentrated hydrochloric acid for 2 days afforded only recovered starting material.

In summary, whilst the azo-enophile **3** can be readily prepared, it exhibited only modest levels of asymmetric induction in Lewis acid catalysed ene reactions with symmetrical acyclic alkenes. Use of cyclic alkenes and activated aromatic alkenes were disappointing affording 1:1 mixtures of the diastereomeric ene products in the former case and addition products in the latter case. The menthyl ester auxiliary group proved difficult to remove, thus alternative chiral auxiliaries need to be evaluated for use in an asymmetric azo-ene reaction.

EXPERIMENTAL

General Details

Melting points were determined using a Reichert Kofler block and are uncorrected. Optical rotations were measured using a Perkin Elmer 241 polarimeter in CH_2Cl_2 at the indicated concentrations. Infrared absorption spectra were recorded using Perkin Elmer 1600 Series FTIR spectrometer as Nujol Mulls or thin films between sodium chloride plates. ^1H NMR spectra were obtained using either a Bruker AM 400 or Bruker AC 200 Spectrometer. ^{13}C NMR data were recorded using a Bruker AM 400 or Bruker AC 200 Spectrometer. ^{13}C NMR spectra were interpreted with the aid of DEPT 135 and DEPT 90 experiments. Low resolution mass spectra were recorded using a VG 70-SE spectrometer operating at an accelerating voltage of 70eV. High resolution mass spectra were recorded at a nominal resolution of 5000 or 10000 as appropriate. Elemental analyses were performed at the Microanalytical Laboratory, University of New South Wales, Sydney. Flash chromatography was performed using Merck Kieselgel 60 (230-400 Mesh) with the indicated solvents. High performance chromatography (HPLC) was performed using Waters and Associates HPLC instrumentation fitted with a Whatman Partisil 5 normal phase silica column with a flow rate of 1.5 cm^3/min. using 3.5% ethyl acetate in hexane as eluant.

Di-(-)-menthyl diazane-1,2-dicarboxylate **2**

To a solution of (-)-menthyl chloroformate **1** (2 cm^3, 9.1 mmol) in 95% ethanol (10 cm^3) was added hydrazine hydrate (0.44 cm^3, 9.2 mmol) whilst maintaining the temperature at 0-5°C (ice/salt bath). After 10 min., (-)-menthyl chloroformate **1** (2 cm^3, 9.14 mmol) was added simultaneously with a solution of Na_2CO_3 (485 mg) in H_2O (6 cm^3). The (-)-menthyl chloroformate was added ahead of the Na_2CO_3 solution ensuring

the temperature did not rise above 20°C and that there was always an excess of (-)-menthyl chloroformate present. The reaction mixture was filtered and the colourless precipitate washed with water (20 cm^3) and extracted into ethyl acetate (3x30 cm^3). The ethyl acetate extract was dried (Na_2SO_4) and the solvent removed at reduced pressure. The crude product was recrystallized from hexane / ethyl acetate (9:1) to give the *title compound* **2** (3.05 g, 85%) as a colourless solid, m.p. 119-121 °C (lit.[19] m.p. 108-110 °C); $[\alpha]_D^{20}$ -76.7 (c, 0.62, CH_2Cl_2); (Found: C, 67.0; H, 10.2; N, 7.1. $C_{22}H_{40}N_2O_4$ requires C, 66.6; H, 10.2; N, 7.1%); υ_{max} (thin film)/cm^{-1} 3290br (NH) and 1705s (C=O); δ_H (200 MHz; $CDCl_3$) 0.78 [6 H, d, *J* 6.8, 2xCH_3], 0.88 [6 H, d, *J* 6.6, CH($C\underline{H}_3$)2], 0.89 [6 H, d, *J* 6.6, CH($C\underline{H}_3$)2], 0.97-1.15 (6 H, m), 1.31-1.40 (2 H, m), 1.42-1.51 (2 H, m), 1.60-1.72 (4 H, m), 1.86-1.92 (2 H, m), 2.00-2.12 (2 H, m), 4.63 (2 H, ddd, $J_{1'ax,2'ax}$ 10.7, $J_{1'ax,6'ax}$ 10.7, $J_{1'ax,6'eq}$ 4.0, 1'-H), 6.19 (2 H, br s, NH); δ_C (50 MHz; $CDCl_3$) 20.7 (5'-CH_3), 21.9 [$CH_3(^iPr)$], 21.9 [$CH_3(^iPr)$], 23.5 (CH_2, C-4'), 26.1 [$CH(^iPr)$], 31.3 (CH, C-5') 34.1 (CH_2, C-3'), 41.0 (CH_2, C-6'), 47.1 (CH, C-2'), 76.3 (CHO), 156.5 (quat, C=O); *m/z* (%) 396 (M^+, 43), 381 (M-CH_3, 11), 259 (M-$C_{10}H_{17}$, 20), 154 (M-$C_{12}H_{22}N_2O_3$, 11), 139 (M-$C_{12}H_{21}N_2O_4$, 100).

Di-(-)-menthyl diazene-1,2-dicarboxylate 3

(a) Using [bis(trifluoroacetoxy)iodo]benzene as the oxidant.

To a solution of di-(-)-menthyl diazane-1,2-dicarboxylate **2** (218 mg, 0.5 mmol) in dichloromethane (10 cm^3) was added [bis(trifluoroacetoxy)iodo]benzene (290 mg, 0.6 mmol) and the reaction mixture stirred for 24h. The solvent was removed under reduced pressure to afford a yellow oil, which was purified by flash chromatography using hexane to hexane / ethyl acetate (6:4) as eluant to give the *title compound* **3** (210 mg, 97%) as pale yellow needles on standing; mp 72-73 °C (lit.[19] m.p. 66-69°C); $[\alpha]_D^{20}$ -77.4 (c, 0.63, CH_2Cl_2); (Found: C, 66.6; H, 9.7; N, 6.9. $C_{22}H_{38}N_2O_4$ requires C, 67.0; H, 9.6; N, 7.1%); υ_{max} (thin film)/cm^{-1} 1705s (C=O) and 1640s (N=N); δ_H (200 MHz; $CDCl_3$) 0.82 (6 H, d, *J* 7.0, 2xCH_3), 0.91 [6 H, d, *J* 7.1, CH($C\underline{H}_3$)2], 0.95 [6 H, d, *J* 7.1, CH($C\underline{H}_3$)2], 1.05-1.14 (6 H, m), 1.06-1.25 (2 H, m), 1.49-1.60 (2 H, m), 1.68-1.78 (4 H, m), 1.93-2.01 (2 H, m), 2.15-2.20 (2 H, m), 4.90 (2 H, ddd, $J_{1'ax,2'ax}$ 11.0, $J_{1'ax,6'ax}$ 11.0, $J_{1'ax,6'eq}$ 4.5, 1'-H); *m/z* (%) 394 (M^+, 42), 351 (M-$CH(CH_3)_2$, 49), 307 (M-C_6H_{15}, 27), 239 (M-$C_{10}H_{19}O$, 9), 139 (M-$C_{12}H_{19}N_2O_4$, 100).

(b) Using fuming nitric acid as the oxidant.

To a solution of di-(-)-menthyl diazane-1,2-dicarboxylate **2** (400 mg, 1.0 mmol) in nitric acid (2 cm^3, 70%) at 0-5°C was added fuming nitric acid (4 cm^3, 90%) and the resultant mixture stirred at -20--5°C for 2.5h. The reaction mixture was poured onto ice/water (20 cm^3), extracted with CH_2Cl_2 (3x30 cm^3) and washed with water (2x20 cm^3). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure affording a yellow oil, which was purified by flash chromatography [hexane / ethyl acetate (9:1)] to give the *title compound* **3** (215 mg, 54%) as pale yellow needles on standing, m.p. 72-73°C.

Di-(-)-menthyl (E)-1-(2'-hexen-4'-yl)-1,2-diazanedicarboxylate 5

To a solution of di-(-)-menthyl diazene-1,2-dicarboxylate **3** (406 mg, 1.03 mmol) and *trans*-3-hexene **4** (0.19 cm^3, 1.54 mmol) in CH_2Cl_2 (10 cm^3) cooled to -60°C under N_2 was added $SnCl_4$ (0.24 cm^3, 2.06mmol). After 5 min. the yellow solution turned colourless and water (10 cm^3) was added. After extraction with CH_2Cl_2 (3 x 40 cm^3) the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resultant oil was purified by flash chromatography using hexane / ethyl acetate (6:4) as eluant to afford the *ene adduct* **5** (388 mg, 80%), as a colourless solid and as a 2.5:1 mixture of diastereomers, mp 72-73°C; (Found: C, 70.1; H, 10.7; N, 5.8. $C_{28}H_{50}N_2O_4$ requires C, 70.3; H, 10.5; N, 5.9%); υ_{max} (thin film)/

cm^{-1} 3270br (NH) and 1715s (C=O); δ_H (200 MHz; $CDCl_3$) (major diastereomer) 0.80 (3 H, t, *J* 6.4, 6'-H), 0.90 [12 H, d, *J* 6.8, 2xCH(C<u>H</u>3)2], 1.00-1.02 (8 H, m, 2xCH_3 and 5'-H), 1.02-2.00 [21 H, m, 6xCH_2, 1'-H, 2"-H, 2'"-H, 5"H, 5'"-H, and 2xC<u>H</u>$(CH_3)_2$], 4.30-4.71 (3 H, m, CHN, 2xCHO), 5.31-5.50 (1 H, m, 3'-H) 5.58-5.76 (1 H, m, 2'-H) 6.19 (1 H, br s, NH); *m/z* (%) 478 (M^+, 2), 396 (M-C_6H_{10}, 10), 259 (M-$C_{16}H_{27}$, 8), 139 (M-$C_{18}H_{31}N_2O_4$, 79), 83 (M-$C_{22}H_{39}N_2O_4$, 100).

Di-(-)-menthyl (E)-1-(3'-octen-5'-yl)-1,2-diazanedicarboxylate 7

To a solution of di-(-)-menthyl diazene-1,2-dicarboxylate **3** (181 mg, 0.46 mmol) and *trans*-4-octene **6** (0.07 cm^3, 0.46 mmol) in CH_2Cl_2 (10 cm^3) cooled to -60°C under N_2 was added $SnCl_4$ (0.05 cm^3, 0.46mmol). After 5 min. the yellow solution turned colourless and water (10 cm^3) was added. After extraction with CH_2Cl_2 (3x40 cm^3) the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resultant oil was purified by flash chromatography using hexane / ethyl acetate (6:4)as eluant to afford the *ene adduct* **7** (163 mg, 70%) as a colourless oil and as a 2:1 mixture of diastereomers (Found: C, 70.1; H, 10.9; N, 5.5. $C_{30}H_{54}N_2O_4$ requires C, 70.1; H, 10.9; N, 5.5%); υ_{max} (thin film)/cm^{-1} 3268br (NH) and 1710s (C=O); δ_H (200 MHz; $CDCl_3$) (major diastereomer) 0.75 (6 H, t, *J* 6.3, 1'-H and 8'-H), 0.87 [12H, d, *J* 6.4, 2xCH(C<u>H</u>3)2], 0.92-1.20 (10 H, m, 2xCH_3, 6'-H and 7'-H), 1.20-2.15 [20 H, m, 6xCH_2, 2'-H, 2"-H, 2'"-H, 5"H, 5'"-H, and 2xC<u>H</u>$(CH_3)_2$], 4.40-4.70 (3 H, m, CHN, 2xCHO), 5.29-5.45 (1 H, m, 4'-H) 5.51-5.71 (1 H, m, 3'-H) 6.10 (1 H, br s, NH); δ_C (50 MHz; $CDCl_3$) 13.4 (CH_3, C-8'), 13.8 (CH_3, C-1') 19.4 (CH_2, C-7'), 20.8 (CH_3, CH_3-5"/CH_3-5'"), 22.0 [$CH_3(^iPr)$], 23.4 (CH_2, C-4"/C-4'"), 25.4 (CH_2, C-6'), 26.2 [$CH(^iPr)$], 31.3 (CH, C-5"/C-5'"), 33.9 (CH_2, C-2'), 34.2 (CH_2, C-3"/C-3'"), 41.1 (CH_2, C-6"/C-6'"), 47.2 (CH, C-2"/C-2'"), 59 .2 (CHN), 75.6 (CHO), 126.9 (CH, C-4'), 135.0 (CH, C-3'), 155.8 (quat, C=O); *m/z* (%) 506 (M^+, 5), 396 (M-C_8H_{14}, 5), 157 (M-$C_{20}H_{33}N_2O_3$, 18), 139 (M-$C_{20}H_{35}N_2O_4$, 79), 83 (M-$C_{24}H_{43}N_2O_4$, 100).

Di-(-)-menthyl 1-(2'-cyclohexen-1'-yl)-1,2-diazanedicarboxylate 9

To a solution of di-(-)-menthyl diazene-1,2-dicarboxylate **3** (201 mg, 0.51 mmol) and cyclohexene **8** (0.08 cm^3, 0.76 mmol) in CH_2Cl_2 (10 cm^3) cooled to -60°C under N_2 was added $SnCl_4$ (0.12 cm^3, 1.02 mmol). After 5 min. the yellow solution turned colourless and water (10 cm^3) was added. After extraction with CH_2Cl_2 (3x40 cm^3) the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resultant oil was purified by flash chromatography using hexane / ethyl acetate (6:4) as eluant to afford the *ene adduct* **9** (198 mg, 81%) as a colourless oil and a 1:1 mixture of diastereomers (Found: $[M-H]^+$, 475.3548. $C_{28}H_{48}N_2O_4$ requires $[M-H]^+$, 475.3613); υ_{max} (thin film)/cm^{-1} 3309br (NH) and 1714s (C=O); δ_H (200 MHz; $CDCl_3$), 0.79 (6 H, d, *J* 6.6, 2xCH_3), 0.80-0.92 [12 H, m, 2xCH(C<u>H</u>3)2], 0.92-1.12 (4 H, m, 5'-H, 6'-H), 1.12-2.31 [20 H, m, 6xCH_2, 4'-H, 2"-H, 2'"-H, 5"-H, 5'"-H, and 2xC<u>H</u>$(CH_3)_2$], 4.48-4.89 (3 H, m, CHN, 2xCHO), 5.40-5.62 (1 H, m, 3'-H) 5.70-5.90 (1 H, m, 2'-H), 6.29 (1 H, br s, NH); *m/z* (%) 476 (M^+, 2), 396 (M-C_6H_8, 43), 352 (M-C_9H_{16}, 44), 156 (M-$C_{18}H_{28}N_2O_3$, 38), 139 (M-$C_{18}H_{29}N_2O_4$, 77), 83 (M-$C_{22}H_{37}N_2O_4$, 100).

Di-(-)-menthyl 1-(2'-cyclopenten-1'-yl)-1,2-diazanedicarboxylate 11

To a solution of di-(-)-menthyl diazene-1,2-dicarboxylate **3** (228 mg, 0.58 mmol) and cyclopentene **10** (0.08 cm^3, 0.87 mmol) in CH_2Cl_2 (10 cm^3) cooled to -60°C under N_2, was added $SnCl_4$ (0.13 cm^3, 1.16 mmol). After 5 min. the yellow solution turned colourless and water (10 cm^3) was added. After extraction with CH_2Cl_2 (3x40 cm^3) the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resultant oil was purified by flash chromatography using hexane / ethyl acetate (6:4) as eluant to

afford the *ene adduct* **11** (236 mg, 88%), as a colourless solid and a 1:1 mixture of diastereomers, m.p. 64-65°C; (Found: C, 69.7; H, 9.7; N, 5.9. $C_{27}H_{46}N_2O_4$ requires C, 70.1; H, 9.9; N, 6.1%); υ_{max} (thin film)/cm^{-1} 3320br (NH) and 1715s (C=O); δ_H (200 MHz; $CDCl_3$), 0.80 (6 H, d, *J* 6.4, 2xCH_3) , 0.90-1.02 [12H, m, 2xCH(C<u>H</u>3)2], 1.02-1.25 (2 H, m, 5'-H), 1.25-2.50 [20 H, m, 6xCH_2, 4'-H, 2"-H, 2'"-H, 5"-H, 5'"-H, and 2xC<u>H</u>$(CH_3)_2$], 4.50-4.80 (2 H, m, 2xCHO), 5.15-5.42 (1 H, m, CHN) 5.50-5.70 (1 H, m, 3'-H) 5.85-6.05 (1 H, m, 2'-H), 6.30 (1 H, br s, NH); *m/z* (%) 462 (M^+, 2), 396 (M-C_5H_6, 5), 352 (M-C_8H_{14}, 1), 139 (M-$C_{17}H_{27}N_2O_4$, 83), 83 (M-$C_{21}H_{35}N_2O_4$, 100).

Di-(-)-menthyl 1-(2'-chloro-1',2'-diphenyl)prop-1'-yl-1,2-diazanedicarboxylate ***13***

To a solution of di-(-)-menthyl diazene-1,2-dicarboxylate **3** (162 mg, 0.41 mmol) and *trans*-α-methylstilbene **12** (159 mg, 0.82 mmol) in CH_2Cl_2 (10 cm^3) cooled to -60°C under N_2 was added $SnCl_4$ (0.05 cm^3, 0.41 mmol). After 5 min. the yellow solution turned colourless and water (10 cm^3) was added. After extraction with CH_2Cl_2 (3x40 cm^3) the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resultant oil was purified by flash chromatography using hexane / ethyl acetate (2:1) as eluant to afford the *chloride* **13** (224 mg, 93%) as a colourless solid and a 1:1 mixture of diastereomers, m.p. 90-92°C; υ_{max} (thin film)/cm^{-1} 3278br (NH) and 1722s (C=O); δ_H (200 MHz; $CDCl_3$), 0.70 (6 H, d, *J* 6.9, 2xCH_3), 0.80-0.96 [12H, m, 2xCH(C<u>H</u>3)2], 1.00-1.20 (3 H, m, 3'-CH_3), 1.20-2.40 [18 H, m, 6xCH_2, 2"-H, 2'"-H, 5"-H, 5'"-H, and 2xC<u>H</u>$(CH_3)_2$], 4.25-4.47 (1 H, m, CHN), 4.50-4.80 (2 H, m, 2xCHO), 5.75 (1 H, br s, NH), 7.01-7.51 (10 H, m, 2xPh); δ_C (50 MHz; $CDCl_3$), 20.8 (CH_3), 20.9 (CH_3), 22.0 [$CH_3(^iPr)$], 23.6 (CH_2, C-4"/C-4'"), 26.9 [$CH(^iPr)$], 32.0 (CH, C-5"/C-5'"), 34.2 (CH_2, C-3"/C-3'"), 41.3 (CH_2, C-6"/C-6'"), 47.2 (CH, C-2"/C-2'"), 60.0 (CHN), 78.3 (CHO), 83.0 (quat, C-2'), 124.3 (CH, ArC), 127.9 (CH, ArC), 128.2 (CH, ArC), 138.4 (quat, ArC), 143.2 (quat, C=O); *m/z* (%) 589 [(M-Cl)$^+$, 34], 451 [M-Cl-$C_{10}H_{18}$, 30], 407 [M-Cl-$C_{13}H_{26}$, 18], 313 [M-Cl-$C_{20}H_{36}$, 100].

Di-(-)-menthyl 1-(1'-chloro-1'-phenyl)prop-2'-yl-1,2-diazanedicarboxylate ***15***

To a solution of di-(-)-menthyl diazene-1,2-dicarboxylate **3** (175 mg, 0.44 mmol) and *trans*-β-methylstyrene **14** (0.12 cm^3, 0.88 mmol) in CH_2Cl_2 (10 cm^3) cooled to -60°C under N_2, was added $SnCl_4$ (0.05 cm^3, 0.44 mmol). After 5 min. the yellow solution turned colourless and water (10 cm^3) was added. After extraction with CH_2Cl_2 (3x40 cm^3) the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The resultant oil was purified by flash chromatography using hexane / ethyl acetate (2:1) as eluant affording the *chloride* **15** (126 mg, 56%) as a colourless solid and a 1:1 mixture of diastereomers, m.p. 43-44°C; (Found: C, 67.7; H, 9.1; N, 4.8; Cl, 6.4. $C_{31}H_{49}N_2O_4Cl$ requires C, 67.8; H, 9.0; N, 5.1; Cl, 6.5%); υ_{max} (thin film)/cm^{-1} 3292br (NH) and 1716s (C=O); δ_H (200 MHz; $CDCl_3$), 0.83 (6 H, d, *J* 6.8, 2xCH_3), 0.90-0.95 [12H, m, 2xCH(C<u>H</u>3)2], 1.02-1.11 (3 H, m, 3'-H), 1.12-2.20 [18 H, m, 6xCH_2, 2"-H, 2'"-H, 5"-H, 5'"-H, and 2xC<u>H</u>$(CH_3)_2$], 4.50-4.78 (3 H, m, CHCL, 2xCHO), 4.78-4.90 (1 H, m, 2'-H), 6.30 (1 H, br s, NH), 7.26-7.38 (5 H, m, Ph); δ_C (50 MHz; $CDCl_3$), 21.0 (CH_3), 21.1 (CH_3), 22.6 [$CH_3(^iPr)$], 23.2 (CH_2, C-4"/C-4'"), 26.7 [$CH(^iPr)$], 32.0 (CH, C-5"/C-5'"), 34.4 (CH_2, C-3"/C-3'"), 42.0 (CH_2, C-6"/C-6'"), 47.9 (CH, C-2"/C-2'"), 60.0 (CHN), 66.1 (CHCl), 77.2 (CHO), 124.3 (CH, ArC), 128.3 (CH, ArC), 129.5 (CH, ArC), 139.2 (quat, ArC), 158.2 (quat, C=O); *m/z* (%) 548 (M^+, 7), 533 (M-CH_3, 63), 512 (M-HCl, 9), 423 (M-C_7H_6Cl, 12), 139 (M-$C_{23}H_{41}N_2O_4$, 45), 118 (M-$C_{22}H_{39}N_2O_4Cl$, 37), 103 (M-$C_{23}H_{42}N_2O_4Cl$, 100).

(-)-Menthyl diazane-1-carboxylate ***17***

To a solution of the ene adduct **5** (77 mg, 0.16 mmol) in liquid ammonia (15 cm^3) was added lithium metal (20 mg, 2.9 mmol) and the reaction mixture stirred under a dry-ice / acetone condenser for 2h under N_2.

Ammonium chloride (200 mg, 3.74 mmol) was then added, followed by saturated NH_4Cl solution (3 cm^3). The product was then extracted into ether (3x50 cm^3) and dried (Na_2SO_4). The combined organic extracts were then concentrated under reduced pressure and the resultant oil was purified by flash chromatography [hexane-ethylacetate (9:1)] to afford the *title compound* **17** (31 mg, 90%), as a colourless solid m.p. 102-103°C (lit.[21] m.p. 101.5-102°C); $[\alpha]_D^{20}$ -71.2 (c, 0.46, CH_2Cl_2); υ_{max} (thin film)/cm^{-1} 3412br (NH) and 1731s (C=O); δ_H (200 MHz; $CDCl_3$) 0.82 (3 H, d, *J* 6.2, CH_3), 0.90 [6 H, d, *J* 6.5, $CH(\underline{CH_3})_2$], 0.99-1.20 (3 H, m), 1.20-1.43 (1 H, m), 1.43-1.60 (1 H, m), 1.60-1.75 (2 H, m), 1.92-2.00 (1 H, m), 2.00-2.15 (1 H, m), 4.62 (1 H, ddd, $J_{1'ax,2'ax}$ 10.2, $J_{1'ax,6'ax}$ 10.2, $J_{1'ax,6'eq}$ 5.1, 1'-H), 6.35 (3 H, br s, NH, NH_2); *m/z* (%) 214 (M^+, 100), 171 (M-$CH(CH_3)_2$, 50), 155 (M-C_3H_9N, 15).

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