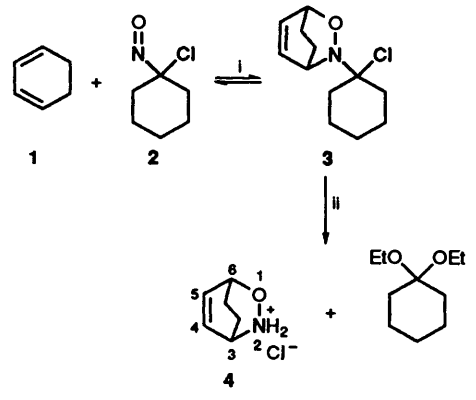
Asymmetric Induction in the Diels–Alder Reactions of α-Hydroxy Acyl Nitroso Compounds

Gordon W. Kirby* and Muhammad Nazeer
Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, UK

The hydroxamic acids **7**, derived from a series of α-hydroxy acids **5**, have been oxidised with periodate to form transient, chiral acyl nitroso compounds **8**, which were trapped *in situ* with cyclopentadiene and cyclohex-1,3-diene to give mixtures of diastereoisomeric, Diels–Alder cycloadducts **9** and **10**, respectively. Cycloaddition at 0 °C occurred with moderate stereoselectivity, *e.g.* both the mandeloyl nitroso compound **8a** with cyclopentadiene and the *tert*-butylglycoloyl nitroso compound **8d** with cyclohexadiene gave *ca.* 5:1 mixtures of diastereoisomers. Much higher diastereoselectivities (cycloadduct ratios *ca.* 10:1 for **9a**, **9d** and **10d**) were observed at −78 °C. The mandeloyl nitroso compound **8a**, which can form an intramolecular hydrogen bond between the hydroxy and nitroso groups, showed higher stereoselectivities than its *O*-methyl ether **8b**. The major cycloadduct **13a** of the (*S*)-mandeloyl nitroso compound **12** and cyclohexadiene was degraded to the bicyclic oxazine **15** of known absolute configuration. Formation of the cycloadduct **13a** as the major product is consistent with preferential *endo* addition of the hydrogen bonded nitroso compound **12** from the face *anti* to the phenyl group.

The Diels–Alder cycloaddition reactions of *C*-nitroso compounds and conjugated dienes provide, by reduction of the resulting dihydrooxazines, synthetically useful routes to 4-amino alcohols.[1] However, primary and secondary aliphatic *C*-nitroso compounds generally exist as the corresponding dimers, while the monomeric, tertiary compounds react slowly, if at all, with dienes. Until recently, for these reasons, only nitrosoarenes and geminal chloro- or bromo-nitroso compounds had found much synthetic use as dienophiles. For example (Scheme 1), the



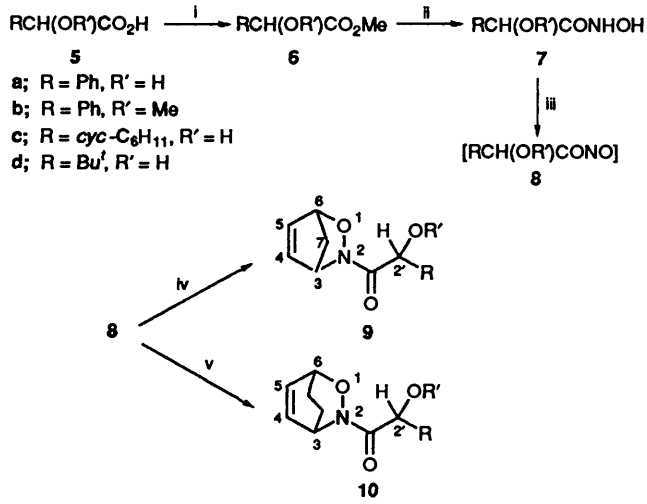
Scheme 1 *Reagents and conditions:* i, 20 °C; ii, catalytic amount of HCl in EtOH

cycloadduct **3** of cyclohexadiene **1** and 1-chloro-1-nitrosocyclohexane **2**, formed slowly in ethanol, solvolyses *in situ* to give the bridged dihydrooxazine **4** in good yield.[2]

Acyl nitroso compounds,[3] XCONO (X = R, RO, or RR'N), readily generated as transient dienophiles by oxidation of the corresponding hydroxamic aicds, XCONHOH, may be trapped *in situ* by conjugated dienes. The resulting cycloadducts are usually obtained in high yield; moreover, the urethanes[4] derived from *C*-nitroso formate esters, ROCONO, may be converted into the parent dihydrooxazines by standard, selective methods.

Optically pure, chiral dihydrooxazines may be required for the total synthesis of natural products or pharmaceuticals. With this in mind, Kresze *et al.* studied asymmetric induction with various geminal chloro nitroso compounds having the nitroso group attached directly to a chiral centre. For example, a chloro nitroso derivative of a mannofuranose[5] gave the bicyclic oxazine **4** predominantly as the 1*S* enantiomer (≥95% e.e.), and a 17-chloro-17-nitrosoandrostane[6] gave mainly the corresponding 1*R* enantiomer **15** (≥95% e.e.). Efficient chiral induction is, in principle, more difficult to achieve with acyl nitroso compounds, because the nitroso group must necessarily be separated from any chiral centre by at least 2 single bonds. However, we pointed out[7] that acyl nitroso compounds derived from chiral α-hydroxy or α-amino acids might form intramolecular hydrogen bonds, which would prevent rotation of the dienophilic group and facilitate stereoselective attack on a diene. We report here[8] studies on acyl nitroso compounds derived from mandelic acid **5a** and other chiral α-hydroxy acids **5**.

The racemic hydroxamic acid **7a**, prepared[9] from methyl (±)-mandelate **6a** and hydroxylamine, was oxidised at 0 °C with sodium periodate, in the usual way, in the presence of cyclopentadiene, to give a mixture of the racemic, diastereoisomeric cycloadducts **9a**, in good yield (Scheme 2). The dia-



Scheme 2 *Reagents and conditions:* i, MeOH–HCl, or CH_2N_2 for **5d**; ii, $HONH_3Cl$–NaOH in EtOH; iii, $NaIO_4$ at 0 °C or Et_4NIO_4 at −78 °C; iv, cyclopentadiene; v, cyclohex-1,3-diene

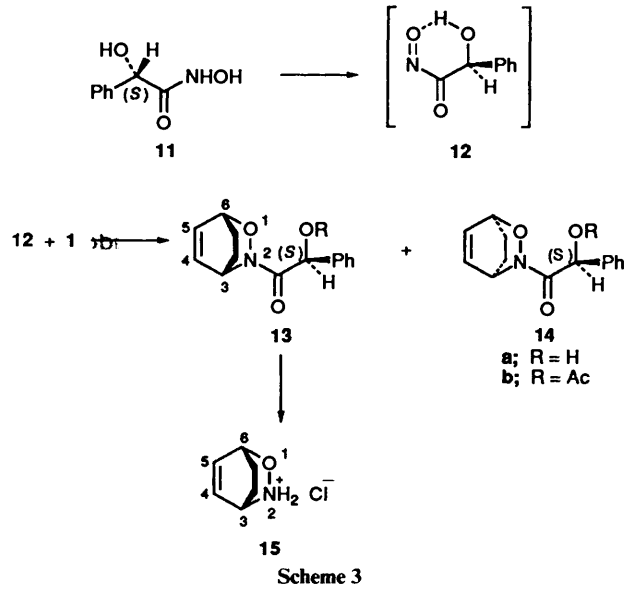
Table 1 Asymmetric induction in the cycloaddition of the acylnitroso compounds **8** with cyclopentadiene and cyclohexadiene

Product	T/°C	Ratio of diastereoisomeric cycloadducts a	b	c	d
9	0	5.1	2.6	3.6	3.4
9	−78	*ca.* 10	3.5	6.3	*ca.* 10
10	0	3.5	2.1	2.5	4.6
10	−78	6.1	3.3	5.1	*ca.* 11

stereoisomers could not be separated by TLC on silica, nor could their ratio be determined accurately by ^{1}H NMR spectroscopy owing to the overlap of diagnostic signals. The mixture was therefore treated with acetic anhydride in pyridine to form the corresponding *O*-acetyl derivatives **9** (R = Ph, R′ = Ac). Again, these were not separable by TLC, but integration of the NMR signals for the olefinic protons and 2′-H indicated a 5.1:1 ratio of diastereoisomers (d.e. 67%). An advantage of the use of acyl nitroso compounds in synthesis, not previously exploited, arises from the high rates of their formation and subsequent trapping by conjugated dienes. Consequently, cycloadducts may be formed at low temperatures, with a resulting increase in stereoselectivity. Thus, (±)-mandelohydroxamic acid **7a** was oxidised with tetraethylammonium periodate, in the presence of cyclopentadiene, in homogeneous solution (methanol–dichloromethane) at, notionally, −78 °C.* The diastereoisomeric cycloadducts **9a** were obtained in the ratio† *ca.* 10:1, as determined again from the ^{1}H NMR spectrum of the mixture of their *O*-acetates. Similarly, oxidation of (±)-mandelohydroxamic acid in the presence of cyclohexa-1,3-diene **1** gave a mixture of the diastereoisomeric adducts **10a**. These were acetylated, as before, to allow the determination by ^{1}H NMR spectroscopy of the ratio, 3.5:1, of the acetates **10** (R = Ph, R′ = Ac). On this occasion, the acetates, but not the parent adducts **10a** were separable by chromatography on silica plates. Again, the ratio of the diastereoisomers **10a**, 6.1:1, was greater when the reaction was carried out at −78 °C. The ratios observed from the foregoing and following experiments are collected in Table 1.

To test whether intramolecular hydrogen bonding (see later) significantly enhanced chiral induction, as predicted, experiments were carried out with the (±)-*O*-methylmandelohydroxamic acid **7b**. The diastereoisomeric cycloadducts of cyclopentadiene **9b** and cyclohexadiene **10b** were obtained in ratios 2.6:1 and 2.1:1, respectively, from the reactions at 0 °C. Only a small increase in the ratios, to 3.5:1 and 3.3:1 respectively, was observed for reactions at −78 °C. Intramolecular hydrogen-bonding in the mandeloyl nitroso compound **8a** might well account for the lower asymmetric inductions shown by the methyl ether **8b**, although the greater size of the methoxy group, compared with the hydroxy group, could cause a similar effect.

Similar studies were carried out with the acyl nitroso compounds derived from (±)-hexahydromandelic acid **5c** and (±)-2-hydroxy-3,3-dimethylbutanoic acid **5d**. The former acid was obtained by catalytic hydrogenation of (±)-mandelic acid,[10] and the latter from pinacolone by successive oxidation[11] and reduction with sodium borohydride. The compositions of the mixtures of the cycloadducts **9c**, **10c**, **9d** and **10d** were determined, as before, by ^{1}H NMR spectroscopy. No high precision is claimed for the ratios (Table 1) of diastereoisomers measured in this way, but they suffice to illustrate the relative merits of the chiral dienophiles **8**. Overall, only moderate asymmetric induction was achieved at 0 °C for the α-hydroxy derivatives **8a**, **c** and **d**, the highest ratio of diastereoisomers (*ca.* 5:1, d.e. *ca.* 60%) being observed for the mandelic derivatives of cyclopentadiene **9a** and the *tert*-butylglycolic derivatives of cyclohexadiene **10d**. However, at −78 °C, ratios of *ca.* 10:1 (d.e. *ca.* 82%) were obtained for the 3 sets of cycloadducts **9a**, **9d** and **10d**. Since mandelic acid **5a** is readily available in racemic form and as the individual enantiomers, it is suitable for exploratory work with conjugated dienes generally. The following experiments with the (*S*)-mandelic derivative **11** were carried out to determine the relative stereochemistry of the cyclohexadiene adducts **13a** and **14a** (Scheme 3).



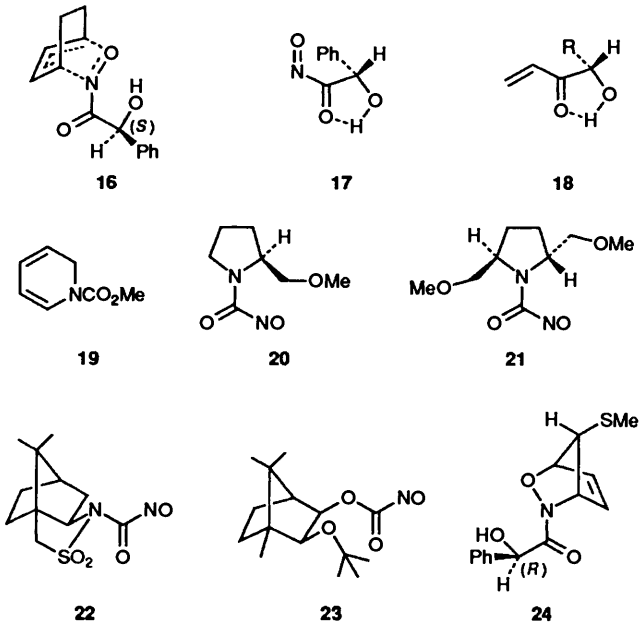
Scheme 3

(*S*)-(+)-Mandelohydroxamic acid‡ **11**, prepared as before from methyl (*S*)-(+)-mandelate, was oxidised at 0 °C in the presence of cyclohexadiene **1** to give a *ca.* 3.5:1 mixture of the cycloadducts **13a** and **14a**, which were separated by TLC as the corresponding *O*-acetyl derivatives **13b** and **14b**. The major diastereoisomer **13b** was then cleaved with sodium methoxide in methanol to give the corresponding oxazine, which was isolated as the known, crystalline hydrochloride **15**. The optical rotation of this salt, $[\alpha]_D$ −24, agreed well with that reported for a sample having an unambiguously determined absolute configuration.[6] The configuration of the major, diastereoisomeric product **13** is that expected on the basis of the following assumptions; that (a) the nitroso dienophile reacts mainly in the hydrogen bonded form **12**, (b) cycloaddition occurs preferentially in the *endo* mode **16** and (c) the diene adds selectively to the face of the nitroso group opposite to that occupied by the phenyl group. Structure **12**, with a 6-membered, hydrogen-bonded ring, is likely to be more stable than the alternative **17** with a 5-membered ring. Not only is the ring size less favourable in the conformation **17**, but, if dipole–dipole repulsion between the carbonyl and nitroso groups caused the latter to adopt the *anti* orientation, as drawn, steric repulsion from the phenyl group would result. Nevertheless, certain chiral hydroxyenones[12] are believed to undergo Diels–Alder reactions preferentially in the conformations **18**.

* This was the temperature of the acetone–carbon dioxide cooling bath, not of the reaction mixture.

† Ratios of this magnitude could not be determined with any great precision by integration of ^{1}H NMR spectra.

‡ The optical rotation of this hydroxamic acid **11** was incorrectly reported in our preliminary communication.[8] This error was courteously brought to our attention by Mr. S. B. King (Cornell University). We checked the rotation of a freshly prepared specimen of the (*R*)-(−)-enantiomer and obtained a value, $[\alpha]_D$ −63, in agreement with his.



Defoin *et al.*[13] employed *C*-nitrosoformate esters, ROCONO, in the synthesis of diaminodideoxylyxose derivatives. As part of a wider study, they observed that cycloaddition of the *O*-methyl (*R*)-mandeloyl derivative **8b** with the dihydropyridine **19** at 0 °C gave diastereoisomeric adducts in a ratio of 1.5:1. However, the corresponding hydroxy dienophile **8a** was not investigated. To our knowledge, this was the first reported example of the use of a chiral acyl nitroso compound in synthesis.

Following our preliminary publication, Miller *et al.*[14] reported independent studies on the cycloaddition of the mandelic nitroso compound **8a** with cyclopentadiene and cyclohexadiene. Their findings agreed generally with our own, but additionally they showed that cycloaddition with cyclopentadiene occurred, as with cyclohexadiene, by preferential *endo* attack *anti* to the phenyl group (*cf.* **16**). Molecular mechanical calculations[15] indicated that the hydrogen-bonded, *anti* conformation **12** was strongly favoured energetically.

The Diels–Alder reactions of other chiral acyl nitroso compounds have recently been described. Brouillard-Poichet *et al.*[16] studied dienophiles derived from proline. Best results were obtained with the methoxy derivative **20**, which gave cycloadducts of cyclohexadiene in the ratio 84:16. The corresponding alcohol was less selective (cycloadduct ratio, 76:24). However, intramolecular hydrogen bonding (*cf.* **12**) would require an 8-membered ring involving the nitroso group, or a 7-membered ring involving the carbonyl group. Notwithstanding the statement by these authors,[16] their finding does not, therefore, contradict our original proposal.[7,8] In contrast, Gouverneur and Ghosez[17a] showed that much higher diastereoselectivities (*e.g.* ≥98% d.e. with cyclohexadiene) were obtainable with the related dienophile **21** possessing C_2 symmetry. Defoin *et al.*[17b] have reported similarly high stereoselectivities with a *trans*-2,5-dimethylpyrrolidine derivative. The *C*-nitrosoformamide **21** was then used for the asymmetric amination of carboxylic acids, to give enantiomerically pure amino acids.[18] Similarly, the chiral auxiliaries developed by Oppolzer[19] have been exploited successfully in the synthesis of chiral acyl nitroso compounds. Thus, the transient dienophiles **22**[20] and **23**[21] both added to typical cyclic and acyclic dienes with high diastereoselectivity.

A range of readily accessible, chiral *C*-, *N*- and *O*-nitrosocarbonyl compounds is now available for use in asymmetric synthesis, especially of nitrogen-containing natural products. Even when the diastereoisomeric excess is not high, separation of an enriched mixture of cycloadducts can lead to an enantiomerically pure product. For example, King and Ganem[22] developed an elegant, short synthesis of mannostatin A from the 2.6:1 mixture of cycloadducts of 5-methylthiocyclopenta-1,3-diene and the (*R*)-mandelic dienophile **8a**. The major cycloadduct **24**, which was separated by chromatography and crystallisation, had the stereochemistry expected from the foregoing discussion (*cf.* **16**).

Experimental

General.—NMR spectra were recorded with Perkin-Elmer R-32 and Bruker WP 200 spectrometers. *J* Values are in Hz. IR spectra were recorded with either Perkin-Elmer 580 or 257 spectrometers. Mass spectra were obtained by EI at 70 eV with AEI MS 12 and MS 9 spectrometers. TLC was carried out on Merck silica gel GF_{254} plates. Column chromatography employed Merck silica HF_{254}, the solvent flow being assisted with a water pump. Organic solutions were dried over anhydrous magnesium sulfate and evaporated in a Büchi rotary evaporator. Light petroleum refers to the fraction b.p. 60–80 °C. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}.

Preparation of the Hydroxamic Acids **7**.—Generally, the corresponding methyl esters **6** were treated, in ethanol, with an excess of hydroxylamine prepared *in situ* from hydroxylamine hydrochloride and 10 mol dm^{-3} aqueous sodium hydroxide, according to a published method.[9] The esters **6** were prepared from the acids **5** with methanolic hydrogen chloride or, for the derivative **6d**, with diazomethane. The acids **5b**,[23] **5c**[10] and **5d**[11,24]* were prepared by literature methods.

(R)-(−)-*Mandelohydroxamic acid* (R)-**7a**. The (R)-*hydroxamic acid* **7a** had m.p. 137–139 °C (from ethyl acetate–light petroleum) (Found: C, 57.55; H, 5.4; N, 8.4. $C_8H_9NO_3$ requires C, 57.6; H, 5.4; N, 8.4%); $[\alpha]_D^{17}$ −63 (*c* 1.6 in H_2O); ν_{max}(KBr)/cm^{-1} 3480, 3300, 1675 and 1630; δ(90 MHz; CD_3OD) 4.80 (3 H, br s, NH and OH giving CD_3OH), 4.90 (s, OCH) and 7.45 (m, Ph); δ[90 MHz; $(CD_3)_2SO$; standard CHD_2SOCD_3, δ 2.49] 4.90 (s, C*H*OH), 5.90 (s, CHO*H*), 7.45 (m, Ph) and 8.70 and 10.65 (2 × s, NH and OH).

(S)-(+)-*Mandelohydroxamic acid* (S)-**7a**. The (S)-*hydroxamic acid* **7a** had m.p. 138–139 °C (from ethyl acetate–light petroleum) (Found: C, 57.6; H, 5.4; N, 8.2. $C_8H_9NO_3$ requires C, 57.5; H, 5.4; N, 8.4%); $[\alpha]_D$ +63 (*c* 2.5 in H_2O); ν_{max}(KBr)/cm^{-1} 3420, 3300, 1675 and 1630; δ(90 MHz; CD_3OD) 4.80 (3 H, br s, NH and OH giving CD_3OH), 4.90 (s, OCH) and 7.45 (m, Ph).

(±)-O-*Methylmandelohydroxamic acid* **7b**. The *hydroxamic acid* **7b** had m.p. 139–140 °C (from ethyl acetate–light petroleum) (Found: C, 59.85; H, 6.05; N, 7.7. $C_9H_{11}NO_3$ requires C, 59.7; H, 6.1; N, 7.8%); ν_{max}(KBr)/cm^{-1} 3180, 1660 and 1640; δ(90 MHz; CD_3OD) 3.35 (s, OMe), 4.68 (s, OCH), 4.80 (2 H, br s, NH and OH giving CD_3OH) and 7.40 (m, Ph).

(±)-*Hexahydromandelohydroxamic acid* **7c**. The *hydroxamic acid* **7c** had m.p. 181–182 °C (from ethyl acetate–light petroleum) (Found: C, 55.4; H, 8.8; N, 8.0%; M$^+$, 173.1054. $C_8H_{15}NO_3$ requires C, 55.5; H, 8.7; N, 8.1%; *M*, 173.1052; ν_{max}(KBr)/cm^{-1} 3458 and 1630; δ(90 MHz; CD_3OD) 1.0–2.0 (m, cyclohexyl-H), 3.85 (d, *J* 4, OCH) and 4.90 (3 H, br s, NH and OH giving CD_3OH).

(±)-3,3-*Dimethyl*-2-*hydroxybutanohydroxamic acid* **7d**. The *hydroxamic acid* **7d** had m.p. 134–135 °C (from ethyl acetate–

* We treated a mixture of 3,3-dimethyl-2-oxobutanoic acid and pivalic acid, obtained by oxidation[11] of pinacolone, with sodium borohydride in methanol. The acid **5d** was obtained by crystallisation of the reaction mixture.

light petroleum) (Found: C, 49.0; H, 8.7; N, 9.5%; M^+, 147.0889. $C_6H_{13}NO_3$ requires C, 49.0; H, 8.8; N, 9.5%; *M*, 147.0895); ν_{max}(KBr)/cm^{-1} 3235 and 1630; δ(90 MHz; $CDCl_3$) 1.00 (s, Bu^t), 3.70 (s, OCH) and 4.80 (3 H, br s, NH and OH giving CD_3OH).

Preparation of the Cycloadducts **9** *and* **10**: *General Methods.*—Cyclopentadiene and cyclohexa-1,3-diene were freshly distilled before use. For convenience, aqueous sodium periodate was used as oxidant at 0 °C, although tetraethylammonium periodate was required at −78 °C. Generally, equimolecular amounts of reactants were employed, although an excess of the diene may be advantageously used to improve yields. Typically, the diene (3 mmol) in ethyl acetate (50 cm^3), and sodium periodate (3 mmol) in 0.5 mol dm^{-3} aqueous sodium acetate (50 cm^3) adjusted to pH 6 with hydrochloric acid, were stirred vigorously at 0 °C. The hydroxamic acid **7** (3 mmol) was added to the mixture in small portions during 10 min. After 0.5 h, the layers were separated and the aqueous layer was extracted with ethyl acetate. The combined ethyl acetate solutions were washed successively with 5% aqueous sodium thiosulfate, aqueous sodium hydrogen carbonate and water, and were then dried and evaporated. The resulting oily mixture of diastereoisomeric cycloadducts was chromatographed on a short silica column eluted with chloroform (separation of the diastereoisomers was *not* desired initially). The ratio of diastereoisomers was determined at this stage by ^{1}H NMR spectroscopy.

Alternatively, the hydroxamic acid **7** in methanol–dichloromethane (1:1) was added dropwise to the diene and tetraethylammonium periodate[25] in dichloromethane with stirring and cooling in an acetone–solid carbon dioxide bath (bath temperature *ca.* −78 °C). After 1 h, the mixture was allowed to warm up to room temp. The resulting cycloadducts were isolated and purified as before.

The ratios of diastereoisomeric cycloadducts are given in Table 1.

Cycloadducts **9a** *of Cyclopentadiene and the* (±)-*Mandeloyl Nitroso Compound* **8a**.—Prepared at 0 °C, the mixture of racemic, diastereoisomeric 2-*mandeloyl*-3,6-*dihydro*-3,6-*methano*-2H-1,2-*oxazines* **9a** formed a gum (68%) (Found: C, 67.5; H, 5.7; N, 5.9%; M^+, 231.0905. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.6; N, 6.1%; *M*, 231.0895); ν_{max}(CHCl$_3$)/cm^{-1} 3420 and 1650; δ(90 MHz; $CDCl_3$) 1.72 (d, *J* 9, 7-H), 1.91 (d, *J* 9 with fine splitting, 7-H), 4.15 (br s, OH, exch. with D_2O), 5.05–5.40 (m, 3-, 2′- and 6-H), 5.70 and 6.25 (2 × m, 4- and 5-H) and 7.30 (m, Ph). The mixture did not separate by TLC. Owing to the overlap of ^{1}H signals, the ratio of cycloadducts was not determined at this stage.

The mixture of cycloadducts **9a** was treated with acetic anhydride in pyridine at room temperature overnight. After addition of water, to decompose any acetic anhydride, the usual work-up gave the corresponding mixture of O-*acetyl derivatives* **9** (R = Ph, R′ = Ac) as a gum (Found: M^+, 273.0989. $C_{15}H_{15}NO_4$ requires *M*, 273.1001); ν_{max}(CHCl$_3$)/cm^{-1} 1740 and 1675; δ(200 MHz; $CDCl_3$) 1.74 (d, *J* 8.7, 7-H), 2.00 (dt, *J* 8.7 and 1.9, 7-H), 2.12 (s, Ac in the minor component), 2.15 (s, Ac in the major component), 5.17, 5.28 and 5.32 (3 × br s, 3- and 6-H), 5.73 (m, 4- or 5-H in the major component), 5.97 (s, 2′-H in the minor component), 6.10 (s, 2′-H in the major component), 6.25 (m, 4- or 5-H in the major component), 6.42 and 6.60 (2 × m, 4- and 5-H in the minor component) and 7.32 and 7.50 (2 × m, Ph in the major and minor components, respectively). Again, these acetyl derivatives were not separable by TLC. However, integration of the 2′-, 4- and 5-H signals gave a measure of the diastereoisomeric ratio (Table 1). The mixture **9a** prepared at −78 °C (yield 71%) was treated similarly.

Cycloadducts **10a** *of Cyclohexadiene and the* (±)-*Mandeloyl Nitroso Compound* **8a**.—Prepared at 0 °C, the mixture of racemic, diastereoisomeric 2-*mandeloyl*-3,6-*dihydro*-3,6-*ethano*-2H-1,2-*oxazines* **10a** formed a gum (55%) (Found: M^+, 245.1014. $C_{14}H_{15}NO_3$ requires *M*, 245.1052); ν_{max}(CHCl$_3$)/cm^{-1} 3470 and 1655; δ(90 MHz; $CDCl_3$) 1.35, 1.48, 2.10 and 2.20 (4 × m, 7- and 8-H_2), 4.15 (br s, OH, exch. with D_2O), 4.55 (br s, 3- or 6-H), 5.25 (br s, 3- or 6-H), 5.30 (s, 2′-H), 6.00 and 6.40 (2 × t, *J* 7, 4- and 5-H) and 7.35 (m, Ph). The mixture did not separate by TLC and the overlap of ^{1}H signals prevented the determination of composition by integration.

The mixture of cycloadducts was treated with acetic anhydride in pyridine, as described for the cycloadducts **9a**. The resulting mixture of *O*-acetyl derivatives **10** (R = Ph, R′ = Ac) was separated on TLC plates developed with light petroleum–diethyl ether (1:1), the major component having the higher R_f value. The mixture showed δ(200 MHz; $CDCl_3$) 1.40, 1.80 and 2.20 (3 × m, 7- and 8-H_2), 2.13 (s, Ac in the minor component), 2.16 (s, Ac in the major component), 4.61 (m, 3- or 6-H in the major component), 4.71 (m, 3- or 6-H in the minor component), 5.15 (m, 3- or 6-H), 6.11 (ddd, *J* 8.0, 5.5 and 1.5, 4- or 5-H in the major component), 6.11 (s, 2′-H in the minor component), 6.21 (s, 2′-H in the major component), 6.41 (ddd, *J* 8.0, 6.5 and 1.5, 4- or 5-H in the major component), 6.59 (m, 4- and 5-H in the minor component), 7.34 (m, Ph in the major component) and 7.49 (m, Ph in the minor component). The ratio of cycloadducts was measured by integration of the signals for 4- and 5-H and 2′-H. The mixture was separated by preparative TLC to give the *O*-acetyl cycloadducts **10** (R = Ph, R′ = Ac) in a ratio *ca.* 3.5:1, essentially the same as that determined from the ^{1}H spectra. The *major component* formed a gum (Found: M^+, 287.1137. $C_{16}H_{17}NO_4$ requires *M*, 287.1158); ν_{max}(CHCl$_3$)/cm^{-1} 1738 and 1655; δ(90 MHz; $CDCl_3$) 1.36, 1.46 and 2.20 (3 × m, 7- and 8-H_2), 2.16 (s, Ac), 4.66 and 5.16 (2 × br s, 3- or 6-H), 6.15 (t, *J* 7, 4- or 5-H), 6.25 (s, 2′-H), 6.45 (t, *J* 7, 4- or 5-H) and 7.35 (m, Ph). The *minor component* also formed a gum (Found: M^+, 287.1149. $C_{16}H_{17}NO_4$ requires *M*, 287.1158); ν_{max}(CHCl$_3$)/cm^{-1} 1738 and 1655; δ(90 MHz; $CDCl_3$) 1.40 and 1.80 (2 × m, 7- and 8-H_2), 2.12 (s, Ac), 4.71 and 5.21 (2 × br s, 3- and 6-H), 6.15 (s, 2′-H), 6.59 (m, 4- and 5-H) and 7.40 (m, Ph).

The mixture of cycloadducts **10** prepared at −78 °C (yield 53%) was similarly analysed by ^{1}H NMR spectroscopy (200 MHz) after conversion into the corresponding *O*-acetates.

Cycloadducts **9b** *of Cyclopentadiene and the* (±)-O-*Methylmandeloyl Nitroso Compound* **8b**.—Prepared at 0 °C, the mixture of racemic, diastereoisomeric 2-[2′-*methoxy*(*phenylacetyl*)-3,6-*dihydro*-3,6-*methano*-2H-1,2-*oxazines* **9b** formed a gum (65%) (Found: M^+, 245.1088. $C_{14}H_{15}NO_3$ requires *M*, 245.1052); ν_{max}(CHCl$_3$)/cm^{-1} 1655; δ(200 MHz; $CDCl_3$) 1.76 and 1.96 (2 × m, 7-H_2), 3.37 (s, OMe in the minor component), 3.45 (s, OMe in the major component), 4.93 (s, 2′-H in the minor component), 4.98 (s, 2′-H in the major component), 5.15–5.45 (m, 3- and 6-H), 5.60–6.70 (m, 4- and 5-H) and 7.35 (m, Ph). Separation could not be achieved by TLC. The diastereoisomeric ratio was determined by integration of the *O*-methyl and 2′-H signals. The mixture of cycloadducts **9b** prepared at −78 °C (yield 63%) was analysed similarly.

Cycloadducts **10b** *of Cyclohexadiene and the* (±)-O-*Methylmandeloyl Nitroso Compound* **8b**.—Prepared at 0 °C, the mixture of racemic, diastereoisomeric 2-[2′-*methoxy*(*phenylacetyl*)]-3,6-*dihydro*-3,6-*ethano*-2H-1,2-*oxazines* **10b** formed a gum (59%) (Found: M^+, 259.1205. $C_{15}H_{17}NO_3$ requires *M*, 259.1209); ν_{max}(CHCl$_3$)/cm^{-1} 1652; δ(200 MHz; $CDCl_3$) 1.20–2.30 (m, 7- and 8-H_2), 3.34 (s, OMe in the minor component), 3.37 (s, OMe in the major component), 4.60 (m, 3- or 6-H), 4.70 (m, 3-

or 6-H), 5.00 (s, 2'-H in the minor component), 5.06 (s, 2'-H in the major component), 5.20 (m, 3- or 6-H), 6.00 and 6.34 (2 × m, 4- and 5-H in the major component), 6.52 and 6.63 (2 × m, 4- and 5-H in the minor component) and 7.30 and 7.50 (2 × m, Ph). The mixture was not separable by TLC. The ratio of components was determined by integration of the signals for 2'-H. The corresponding mixture prepared at −78 °C (54%) was analysed similarly.

Cycloadducts **9c** *of Cyclopentadiene and the* (±)-*Hexahydro Mandeloyl Nitroso Compound* **8c**.—Prepared at 0 °C, the mixture of racemic, diastereoisomeric 2-(cyclohexylglycoloyl)-3,6-dihydro-3,6-methano-2*H*-1,2-oxazines **9c** formed a gum (80%); δ(90 MHz; $CDCl_3$) 0.50–2.10 (m, cyclohexyl-H and 7-H_2), 3.25 (br s, OH, exch. with D_2O), 3.80 (d, *J* 3, 2'-H in the minor component), 4.05 (d, *J* 2, 2'-H in the major component), 5.30 (br s, 3- and 6-H) and 6.30 and 6.45 (2 × m, 4- and 5-H). The ratio of components was determined by integration of the signals for 2'-H. The mixture was separated on silica gel plates by multiple elution with diethyl ether–light petroleum (1:1). The *major cycloadduct* **9c**, which had the lower R_f value, formed a gum (Found: M, 237.1355. $C_{13}H_{19}NO_3$ requires *M*, 237.1365); $\nu_{max}(CHCl_3)/cm^{-1}$ 3495 and 1640; δ(90 MHz; $CDCl_3$) 0.50–2.00 (m, cyclohexyl-H and 7-H_2), 3.10 (br s, OH, exch. with D_2O), 4.05 (d, *J* 2, 2'-H), 5.30 (br s, 3- and 6-H) and 6.30 and 6.50 (2 × m, 4- and 5-H). The *minor cycloadduct* **9c** also formed a gum (Found: M^+, 237.1365. $C_{13}H_{19}NO_3$ requires *M*, 237.1365); $\nu_{max}(CHCl_3)/cm^{-1}$ 3495 and 1640; δ(90 MHz; $CDCl_3$) 0.75–2.00 (m, cyclohexyl-H and 7-H_2), 3.05 (br d, *J* 6, OH, exch. with D_2O), 3.90 (d, *J* 3, after D_2O exch., 2'-H), 5.30 (br s, 3- and 6-H) and 6.32 and 6.58 (2 × m, 4- and 5-H). The corresponding mixture **9c** prepared at −78 °C (83%) was similarly analysed by ^1H NMR spectroscopy but was not separated into its components.

Cycloadducts **10c** *of Cyclohexadiene and the* (±)-*Hexahydro Mandeloyl Nitroso Compound* **8c**.—Prepared at 0 °C, the mixture of racemic, diastereoisomeric 2-(*cyclohexylglycoloyl*)-3,6-*dihydro*-3,6-*ethano*-2H-1,2-*oxazines* **10c** formed a gum (55%) (Found: M^+, 251.1514. $C_{14}H_{21}NO_3$ requires *M*, 251.1521); $\nu_{max}(CHCl_3)/cm^{-1}$ 3490 and 1635; δ(90 MHz; $CDCl_3$) 0.90–2.40 (cyclohexyl-H and 7- and 8-H_2), 3.30 (br s, OH, exch. with D_2O), 4.03 (d, *J* 3, 2'-H in the minor component), 4.20 (d, *J* 2, 2'-H in the major component), 4.80 and 5.25 (2 × m, 3- and 6-H) and 6.50–6.80 (m, 4- and 5-H). The ratio of components was determined by integration of the signals for 2'-H. The mixture was not separable by TLC. The mixture **10c** formed at −78 °C (yield 56%) was analysed similarly.

Cycloadducts **9d** *of Cyclopentadiene and the* (±)-3,3-*Dimethyl-2-hydroxy Butanoyl Nitroso Compound* **8d**.—Prepared at 0 °C, the mixture of racemic, diastereoisomeric 2-(*tert*-butylglycoloyl)-3,6-dihydro-3,6-methano-2*H*-1,2-oxazines **9d** formed a gum (75%); δ(90 MHz; $CDCl_3$) 0.90 (s, Bu^t in the major component), 0.95 (s, Bu^t in the minor component), 1.80–2.00 (m, 7-H_2), 3.90 (s, after D_2O exch., 2'-H in the minor component), 4.05 (s, after D_2O exch., 2'-H in the major component), 4.25 (br s, OH, exch. with D_2O), 5.30–5.50 (m, 3- and 6-H) and 6.30–6.70 (m, 4- and 5-H). The ratio of components was determined by integration of the signals for 2'-H and the *tert*-butyl group. The mixture was separated on silica gel plates by multiple elution with diethyl ether–light petroleum (1:1). The *major cycloadduct* **9d**, which had the lower R_f value, formed a gum (Found: M^+, 211.1219. $C_{11}H_{17}NO_3$ requires *M*, 211.1208); $\nu_{max}(CHCl_3)/ cm^{-1}$ 3500 and 1625; δ(90 MHz; $CDCl_3$) 0.90 (s, Bu^t), 1.92 (m, 7-H_2), 3.05 (br s, OH, exch. with D_2O), 4.05 (s, after D_2O exch., 2'-H), 5.30–5.60 (m, 3- and 6-H) and 6.30–6.60 (m, 4- and 5-H). The *minor cycloadduct* **9d** also formed a gum (Found: M^+, 211.1195. $C_{11}H_{17}NO_3$ requires *M*, 211.1208); $\nu_{max}(CHCl_3)/ cm^{-1}$ 3500 and 1626; δ(90 MHz; $CDCl_3$) 0.95 (s, Bu^t), 1.92 (m, 7-H_2), 3.15 (br s, OH, exch. with D_2O), 3.90 (s, after D_2O exch., 2'-H), 5.35 (br s, 3- and 6-H) and 6.25–6.40 (m, 4- and 5-H). The mixture **9d** formed at −78 °C (yield 70%) was analysed similarly by ^1H NMR spectroscopy but was not separated into its components.

Cycloadducts **10d** *of Cyclohexadiene and the* (±)-3,3-*Dimethyl-2-hydroxy Butanoyl Nitroso Compound* **8d**.—Formed at 0 °C, the mixture of racemic, diastereoisomeric 2-(*tert-butylglycoloyl*)-3,6-*dihydro*-3,6-*ethano*-2H-1,2-*oxazines* **10d** formed a gum (58%) (Found: M^+, 225.1372. $C_{12}H_{19}NO_3$ requires *M*, 225.1365); $\nu_{max}(CHCl_3)/cm^{-1}$ 3500 and 1622; δ(200 MHz; $CDCl_3$) 0.80 (s, Bu^t in the major component), 0.89 (s, Bu^t in the minor component), 1.44 and 2.13 (2 × m, 7- and 8-H_2), 3.00 (br s, OH, exch. with D_2O), 3.95 (s, after D_2O exch., 2'-H in the minor component), 4.05 (s, after D_2O exch., 2'-H in the major component), 4.71 and 5.28 (2 × br s, 3- and 6-H) and 6.53 (m, 4-and 5-H). The mixture was not separable by TLC. The ratio of components was determined by integration of the signals for 2'-H. The mixture **10d** formed at −78 °C (yield 60%) was analysed similarly.

Cycloadducts **13a** *and* **14a** *of Cyclohexadiene and the* (S)-*Mandeloyl Nitroso Compound* **12**; *Degradation to Form the Bicyclic Oxazine* **15**.—A mixture of the cycloadducts **13a** and **14a** was prepared at 0 °C, as described for the corresponding racemates **10a**. The derived *O*-acetyl derivatives **13b** and **14b** were separated on silica gel plates by multiple elution with diethyl ether–light petroleum (1:1). The *major* O-*acetate* **13**, which had the higher R_f value, formed a gum (Found: M^+, 287.1148. $C_{16}H_{17}NO_4$ requires *M*, 287.1158); $[\alpha]_D$ +32 (*c* 0.75 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1738 and 1653; δ(90 MHz; $CDCl_3$) 1.36, 1.45 and 2.20 (3 × m, 7- and 8-H_2), 2.16 (s, Ac), 4.66 and 5.15 (2 × br s, 3- and 6-H), 6.15 (t, *J* 7, 4- or 5-H), 6.25 (s, 2'-H), 6.45 (t, *J* 7, 4- or 5-H) and 7.35 (m, Ph). The *minor* O-*acetate* **14b** also formed a gum (Found: M^+, 287.1155. $C_{16}H_{17}NO_4$ requires *M*, 287.1158); $[\alpha]_D$ +62 (*c* 0.15 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1738 and 1653; δ(90 MHz; $CDCl_3$) 1.40 and 1.80 (2 × m, 7- and 8-H_2), 2.10 (s, Ac), 4.71 and 5.20 (2 × br s, 3- and 6-H), 6.15 (s, 2'-H), 6.60 (m, 4- and 5-H) and 7.40 (m, Ph).

The major *O*-acetyl derivative **13b** (201 mg, 0.70 mmol) was kept in 2 mol dm^{-3} methanolic sodium methoxide (0.70 cm^3, 1.40 mmol) at room temp. overnight. The mixture was acidified with methanolic hydrogen chloride and then evaporated to dryness. The residue was stirred with water and chloroform and the aqueous layer was extracted with chloroform [the chloroform layer contained methyl (*S*)-mandelate]. The aqueous layer was made alkaline with saturated aqueous sodium hydrogen carbonate and then extracted 3 times with chloroform. The combined extracts were washed with water and then dried and evaporated. The residue was dissolved in 0.1 mol dm^{-3} methanolic hydrogen chloride and the solution was evaporated to yield the 3,6-dihydro-3,6-ethano-2H-1,2-oxazin-2-ium chloride **15** (31 mg, 30%), m.p. 161–162 °C (lit.,[6] 163 °C), $[\alpha]_D$ −24 (*c* 1.00 in MeOH) (lit.,[6] −24).

Acknowledgements

We thank the Government of Pakistan and the SERC for financial support, Mr. P. Snedden for preparing a fresh sample of (*R*)-(−)-mandelohydroxamic acid,‡ and Professor B. Ganem and Mr. S. B. King (Cornell University) for helpful correspondence.‡

References

1 J. Hamer and M. Ahmad, 1,4-*Cycloaddition Reactions*, ed. J. Hamer, Academic Press, New York, 1967, ch. 12.
2 O. Wichterle and J. Novak, *Collect. Czech. Chem. Commun.*, 1950, **15**, 309.
3 G. W. Kirby and J. G. Sweeny, *J. Chem. Soc., Chem. Commun.*, 1973, 704; G. W. Kirby, *Chem. Soc. Rev.*, 1977, **6**, 1; G. W. Kirby and J. G. Sweeny, *J. Chem. Soc., Perkin Trans. 1*, 1981, 3250.
4 G. W. Kirby, H. McGuigan, J. W. M. Mackinnon, D. McLean and R. P. Sharma, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1437.
5 H. Felber, G. Kresze, H. Braun and A. Vasella, *Tetrahedron Lett.*, 1984, **25**, 5381.
6 M. Sabuni, G. Kresze and H. Braun, *Tetrahedron Lett.*, 1984, **25**, 5377.
7 C. C. Christie, G. W. Kirby, H. McGuigan and J. W. M. Mackinnon, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2469.
8 Preliminary communication, G. W. Kirby and M. Nazeer, *Tetrahedron Lett.*, 1988, **29**, 6173.
9 S. R. Sandler and W. Karo, *Organic Functional Group Preparations*, Academic Press, New York, 1972, vol. III, p. 419.
10 J. H. Stocker, *J. Org. Chem.*, 1962, **27**, 2288.
11 C. Glücksmann, *Monatsh. Chem.*, 1889, **10**, 770; 1891, **12**, 356.
12 W. Choy, L. A. Reed III and S. Masamune, *J. Org. Chem.*, 1983, **48**, 1137.
13 A. Defoin, H. Fritz, C. Schmidlin and J. Streith, *Helv. Chim. Acta*, 1987, **70**, 554.
14 A. Miller, T. McC. Paterson and G. Procter, *Synlett*, 1989, **1**, 32.
15 A. Miller and G. Procter, *Tetrahedron Lett.*, 1990, **31**, 1041.
16 A. Brouillard-Poichet, A. Defoin and J. Streith, *Tetrahedron Lett.*, 1989, **30**, 7061.
17 (*a*) V. Gouverneur and L. Ghosez, *Tetrahedron Asymm.*, 1990, **1**, 363; (*b*) A. Defoin, J. Pires, I. Tissot, T. Tschamber, D. Bur, M. Zehnder and J. Streith, *Tetrahedron Asymm.*, 1991, **2**, 1209.
18 V. Gouverneur and L. Ghosez, *Tetrahedron Lett.*, 1991, **32**, 5349.
19 W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 876.
20 V. Gouverneur, G. Dive and L. Ghosez, *Tetrahedron Asymm.*, 1991, **2**, 1173.
21 S. F. Martin, M. Hartmann and J. A. Josey, *Tetrahedron Lett.*, 1992, **33**, 3583.
22 S. B. King and B. Ganem, *J. Am. Chem. Soc.*, 1991, **113**, 5089.
23 W. Reeve and I. Christoffel, *J. Am. Chem. Soc.*, 1950, **72**, 1480.
24 T. Tanabe, S. Yajima and M. Imaida, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 2178.

Paper 3/01570J
Received 18*th March* 1993
Accepted 2*nd April* 1993