Intramolecular functionalisation by a methylene radical of a 1,2-diol and a vicinal amino alcohol: models for coenzyme B_{12}-dependent diol dehydratase and ethanolamine ammonia lyase

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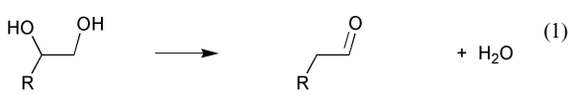
Coenzyme B_{12}-dependent diol dehydratase converts 1,2-diols (*e.g.* propane-1,2-diol) into the corresponding aldehyde and water. The similar enzyme ethanolamine ammonia lyase transforms vicinal aminoalcohols (*e.g.* 2-aminoethanol) into the corresponding aldehyde and ammonia. Model systems have been developed that replicate key features of the putative enzymatic mechanism, *i.e.* removal of a hydrogen atom from the CH_2OH group of a 1,2-diol or vicinal aminoalcohol by a methylene radical derived from an alkylcobalt compound, and conversion of a 1,2-diol or vicinal aminoalcohol into a carbonyl compound and water or ammonia triggered by such a methylene radical. The models are based on alkyl(pyridine)bis(dimethylglyoximato)cobalt complexes [alkyl(pyridine)cobaloximes, Cbx], which were synthesised from appropriate organic precursors using standard methodology. The complexes contain a 1,2-diol [as in 4,5-dihydroxy-2,2-dimethylpentyl(pyridine)cobaloxime] or vicinal aminoalcohol [as in 6-amino-5-hydroxy-2,2-dimethylhexyl(pyridine)cobaloxime] tethered to the cobalt by a carbon chain. Photolysis or thermolysis of 4,5-dihydroxy-2,2-dimethylpentyl(pyridine)cobaloxime at pH 3 or 9 gave 4,4-dimethylpentanal. It is proposed that homolysis of the Co–C bond of 4,5-dihydroxy-2,2-dimethylpentyl(pyridine)cobaloxime induced by photolysis or thermolysis affords the 1,2-dihydroxy-4,4-dimethyl-1-pentyl radical *via* a 1,5-H shift, which is converted into the 4,4-dimethyl-1-oxo-2-pentyl radical, and hence 4,4-dimethylpentanal. The pathway for formation of the aldehyde was diagnosed using the specifically deuteriated analogue [5,5-$^2H_2$]-4,5-dihydroxy-2,2-dimethylpentyl(pyridine)-cobaloxime, which gave [1,5-$^2H_2$]-4,4-dimethylpentanal accompanied by 3,3-dimethylbutanal on thermolysis or photolysis at pH 3. The protected model compound **2a** was hydrolysed to 6-amino-5-hydroxy-2,2-dimethylhexyl(pyridine)cobaloxime, which was heated at pH 3 or 9 to give 5,5-dimethylhexan-2-one and ammonia.

Introduction

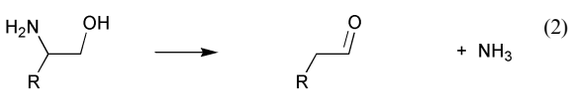
The coenzyme B_{12}-dependent enzymes propanediol dehydratase (EC 4.2.1.28 from *Klebsiella pneumoniae*),[1] glycerol dehydratase (EC 4.2.1.30, also from *K. pneumoniae*)[1d,2] and ethanolamine ammonia lyase (EC 4.3.1.7 from *Clostridia*)[3] perform similar reactions. The diol dehydratases catalyse the conversion of a 1,2-diol into the corresponding aldehyde and water [eqn. (1)],[1,2]



(1)

(*e.g.* R = H or Me)

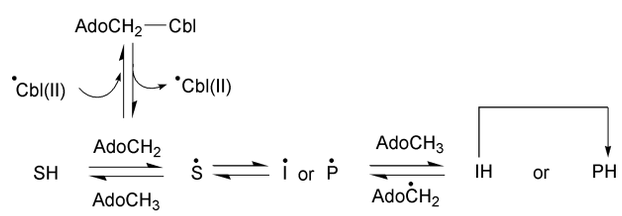
while ethanolamine ammonia lyase catalyses the conversion of a vicinal aminoalcohol into the corresponding aldehyde and ammonia [eqn. (2)].[3,4] These enzymes have been termed



(2)

(R = H or Me)

eliminases because the overall catalytic reaction is an elimination of either water (diol dehydratases) or ammonia (ethanolamine ammonia lyase) from a substrate molecule.[5] The diol dehydratases and ethanolamine ammonia lyase belong to a class of coenzyme B_{12}-dependent reactions[5,6] in which a substrate molecule (SH) is converted into an intermediate substrate-derived radical S$^\bullet$. A group X (OH, NH_2 or substituted carbon) is thereby activated, and migrates (1,2-shift) to the radical centre. This leads to an isomeric radical (I$^\bullet$ or P$^\bullet$, see Scheme 1) and hence to an intermediate (IH) or product (PH).



Scheme 1 General mechanistic scheme for coenzyme B_{12}-dependent enzymatic reactions [$AdoCH_2$-Cbl = coenzyme B_{12} (adenosylcobalamin), SH = substrate, IH = intermediate, PH = product; S$^\bullet$, I$^\bullet$ and P$^\bullet$ are the corresponding protein-bound radicals].

With the diol dehydratases and ethanolamine ammonia lyase, IH loses water or ammonia to give the end-product aldehyde. The sequence described (Scheme 1) is initiated by homolytic fission of the cobalt–carbon σ-bond of the B_{12} coenzyme (adenosylcobalamin, AdoCbl), leading to the 5′-deoxyadenosyl radical, which abstracts a hydrogen atom from SH to give S$^\bullet$ and 5′-deoxyadenosine. The latter gives up a hydrogen atom to I$^\bullet$ or P$^\bullet$ forming IH or PH and regenerating the 5′-deoxyadenosyl radical. According to the 'bound radical' hypothesis[7,8] all of the radicals described are 'anchored' to the protein throughout.

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Experimental support for the pathway described has come from spectroscopic studies (electron paramagnetic resonance, EPR) of the working enzymes, which detected intermediate radicals.[3b,9,10] Model studies pertaining to the diol dehydratases have shown the possibility of activation of a 1,2-diol by hydrogen atom abstraction from C-1, induced by a primary organic radical and leading, *via* a 1,2-dihydroxyalkyl radical, to a product aldehyde or ketone.[11,12] A critical issue in the context of the diol dehydratases is the mechanism of the conversion of the intermediate 1,2-dihydroxyalkyl radical into a 1,1-dihydroxy-2-alkyl radical. Insights into possible mechanisms[13] have been provided by *ab initio* molecular orbital calculations, which have indicated that the enzyme mediates a 1,2-hydroxy shift by 'partial protonation' of the migrating hydroxy group.[14] A recently determined crystal structure of diol dehydratase[15] supports this mechanism by showing that the substrate diol binds at a distance of *ca.* 10 Å from the cobalt of the cofactor, where it interacts with several amino acid residues and a potassium ion. The latter observation explains why diol dehydratase requires a monovalent cation for activity (preferably NH_4^+ or K^+).[16] Hence, the migration of the hydroxy group may be assisted either through its interaction with the Lewis acid K^+ or through partial protonation by NH_4^+. The enzyme also contains an active site carboxylate (Gluα170), which interacts with the non-migrating hydroxy group and assists the rearrangement in a 'push–pull' manner.[14,15]

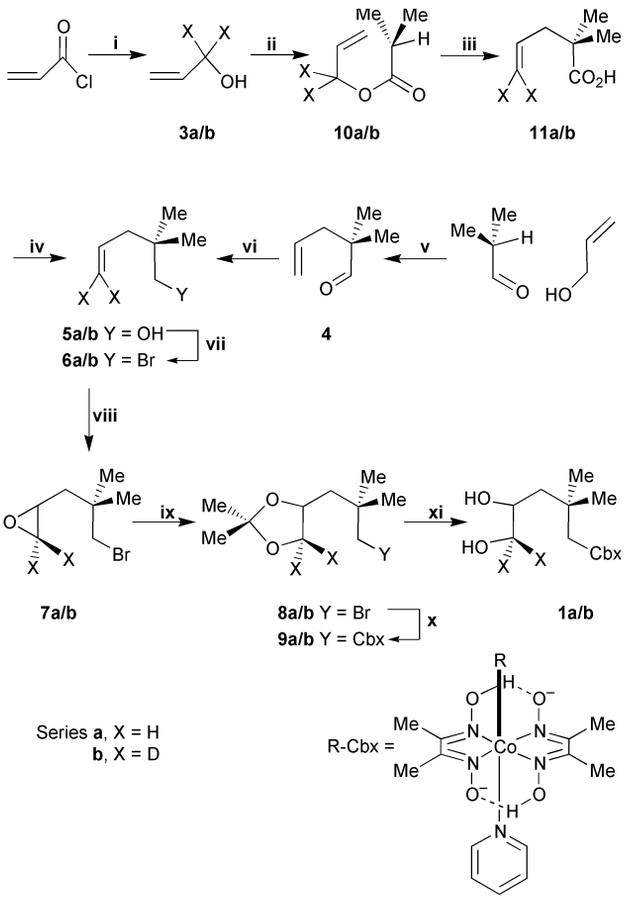
It was long ago suggested that the ethanolamine ammonia lyase reaction proceeds *via* intermediate radicals.[17] This conclusion was supported by EPR studies[10] and by the finding that the chiral methyl group in the ethanal derived from incubating either enantiomer of [2-^{2}H,2-^{3}H]-2-aminoethanol with ethanolamine ammonia lyase was racemic in each case.[18] We have sought to develop a model system that replicates two key features of the putative enzymatic mechanism: (i) regiospecific removal of a hydrogen atom from C*H*OH of a vicinal aminoalcohol by a methylene radical derived from an alkylcobalt compound, and (ii) conversion of a vicinal aminoalcohol into a carbonyl compound and ammonia triggered by such a methylene radical.

In a preliminary communication[11f] we described a model system for diol dehydratase in which regiospecific removal of a hydrogen atom from a 1,2-diol was achieved by a methylene radical derived from an alkylcobaloxime [4,5-dihydroxy-2,2-dimethylpentyl(pyridine)cobaloxime **1a**], with conversion of the 1,2-diol into an aldehyde. In this paper we provide full details of these studies and the results of further experiments with a specifically deuteriated diol substrate (**1b**), which supports the reaction pathway proposed.[5] We also describe the first model system for ethanolamine ammonia lyase, which replicates the two features defined above. This was achieved by a remarkable remote functionalisation initiated from the oxazolidinone **2a** of 6-amino-5-hydroxy-2,2-dimethylhexyl(pyridine)-cobaloxime **2b**. This model compound was used, rather than a direct analogue of **1a**, because of its synthetic accessibility. For both **1a** and **2b**, the critical path between the initially formed radical and the site that undergoes H-atom abstraction is such that a 1,5-H shift can occur. This has been shown to be favoured over a 1,4- or 1,6-H shift.[11d]

Results and discussion

Synthesis of model compounds for diol dehydratases

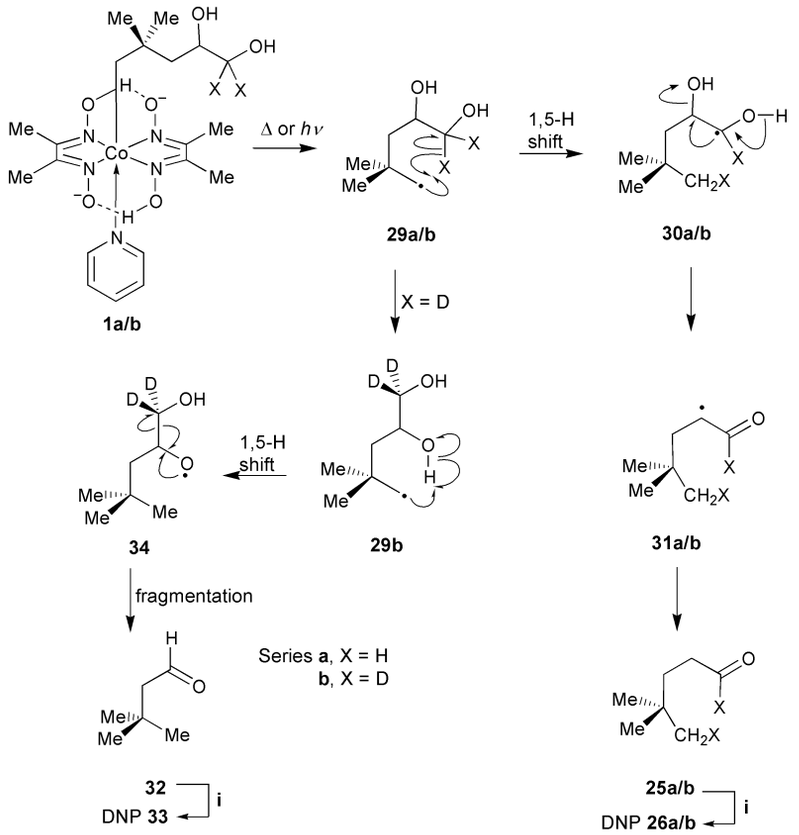
The synthetic route to the unlabelled model compound, 4,5-dihydroxy-2,2-dimethylpentyl(pyridine)cobaloxime **1a** starting from allyl alcohol **3a** and isobutyraldehyde, *via* the intermediates **4** and **5a**–**9a**, is shown in Scheme 2 (X = H). Photolysis or thermolysis of this compound at pH 3 or 9 gave 4,4-dimethylpentanal **25a** with yields in the range 15–45%, Scheme 3. Formation of the aldehyde is initiated by homolysis of the Co–C σ-bond of **1a**, with the resulting 4,5-dihydroxy-2,2-dimethyl-1-pentyl radical **29a** undergoing rearrangement to the 1,2-dihydroxy-4,4-dimethyl-1-pentyl radical **30a** by a 1,5-hydrogen shift (for further details see below). To support this hypothesis we synthesised the specifically deuteriated analogue **1b**, by a similar route to that used for **1a**, as shown in Scheme 2 (X = D). The main difference in the syntheses of **1a** and **1b** concerned the preparation of the intermediate 2,2-dimethylpent-4-en-1-ol, either unlabelled **5a** or dideuteriated at C-5, **5b**. In the unlabelled series this was obtained by acid-catalysed condensation of isobutyraldehyde with allyl alcohol, followed by an *in situ* Claisen rearrangement to afford **4**, which was reduced to **5a**. For the synthesis of the corresponding dideuteriated compound **5b**, reduction of acryloyl chloride with lithium aluminium deuteride gave [1,1-$^2H_2$]prop-2-en-1-ol **3b**,[19] which was converted into the corresponding ester **10b** by treatment with isobutyryl chloride. The ester was subjected to an Ireland-type Claisen rearrangement,[20] which afforded [5,5-$^2H_2$]-2,2-dimethylpent-4-enoic acid **11b**. Reduction of the acid gave the alcohol **5b**. The ^{1}H NMR spectral data for each deuteriated intermediate (**3b**, **5b**–**11b**, *cf.* Scheme 2) and for **1b** was compared with that for the corresponding unlabelled compound (**3a**, **5a**–**11a** and **1a**, respectively) and confirmed the integrity of the deuterium atoms throughout the synthesis.



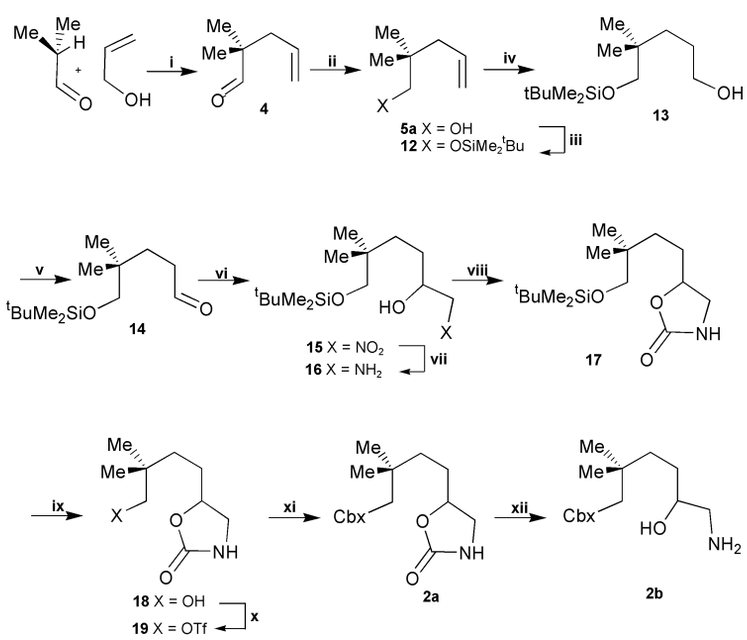
Scheme 2 Synthesis of model compounds (**1a/b**) for diol dehydratases. *Reagents and conditions*: **i** $LiAlD_4$, Et_2O, rt, 62%. **ii** Isobutyryl chloride, pyridine, 0 °C, 99%. **iii** Lithium isopropylcyclohexylamide, *n*-butyllithium, THF, then TMSCl, MeOH, −70 °C-reflux, 41%. **iv** $LiAlH_4$, Et_2O, rt, 80%. **v** *p*-Cymene, *p*-TsOH, reflux, 60%. **vi** $NaBH_4$, EtOH, NaOH, rt, 72%. **vii** CBr_4, PPh_3, MeCN, reflux, 91%. **viii** *M*CPBA, CH_2, rt, 73%. **ix** $BF_3{\cdot}Et_2O$, $(CH_3)_2CO$, −75 °C, 64%. **x** BrCbx, $NaBH_4$, EtOH, {→Cbx(I)}, 35%. **xi** HCl (aq.), rt, 82%.

Synthesis of a model compound for ethanolamine ammonia lyase

The protected model compound **2a** was synthesised from the same starting materials as used for **1a**, *via* intermediates **12**–**19** (see Scheme 4). Thus, 2,2-dimethylpent-4-en-1-ol **5a** was pro-



Scheme 3 Thermal and photochemical decomposition of the diol dehydratase model. *Reagents and conditions*: **i** 2,4-Dinitrophenylhydrazine, H_2SO_4 (aq.), rt.



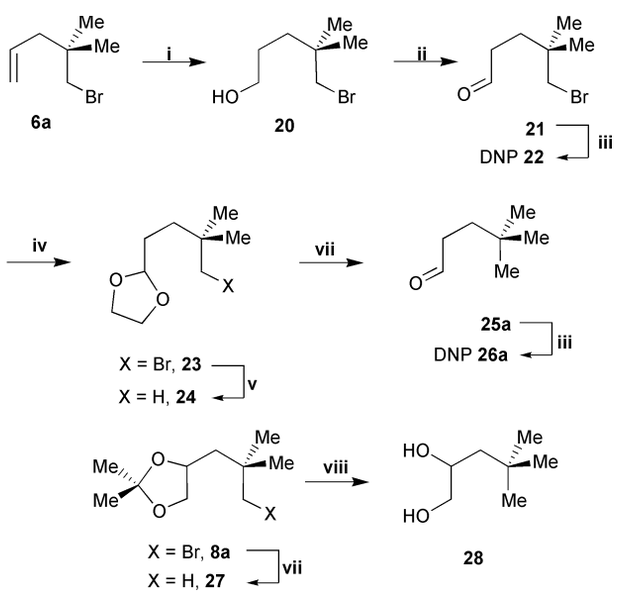
Scheme 4 Synthesis of a model compound (**2a/b**) for ethanolamine ammonia lyase. *Reagents and conditions*: **i** *p*-Cymene, *p*-TsOH, reflux, 60%. **ii** $NaBH_4$, EtOH, rt, 72%. **iii** $^tBuMe_2SiCl$, DMF, imidazole, rt, 100%. **iv** (i) 2-Methylbut-2-ene, BH_3·THF, THF, 0 °C; (ii) NaOH–H_2O_2, rt, 82%. **v** $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 53%. **vi** CH_3NO_2, NaOH, EtOH, 0 °C, 77%. **vii** Pd/C, H_2, EtOH, rt, 65%. **viii** (i) MeOCOCl, Et_3N, CH_2Cl_2, 0 °C; (ii) NaH, THF, rt, 75%. **ix** TBAF, THF, rt, 62%. **x** $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2, −75 °C, 100%. **xi** Cbx(I), EtOH, rt, 75%. **xii** LiOH, *in situ*, rt, 100%.

tected as its *tert*-butyldimethylsilyl ether **12**, which was converted into the aldehyde **14**, by hydroboration to alcohol **13**, followed by Swern oxidation. Base-promoted reaction of **14** with nitromethane (Henry reaction) gave **15**, which was reduced to **16**. The amino and hydroxy groups in **16** were protected by formation of oxazolidinone **17**. Removal of the silyl group from **17** gave **18**, which was activated by conversion into triflate **19**. Reaction of **19** with (pyridine)cob(I)aloxime gave cobaloxime **2a**, which was fully characterised spectroscopically. In particular, the ^1H and ^{13}C NMR data, including a COSY spectrum, were in complete accord with structure **2a**. Numerous attempts to isolate analytically pure 6-amino-5-hydroxy-2,2-dimethylhexyl(pyridine)cobaloxime **2b** from hydrolysis of **2a** were unsuccessful. For thermal degradation experiments it was found best to generate a solution of **2b** *in situ* by hydrolysis of **2a**, carefully monitored by TLC.

Thermolysis and/or photolysis of model compounds 1a/b and 2b

Thermolysis and photolysis of alkylcobaloximes cause homolysis of the Co–C bond and the release of the alkyl group as a radical.[21] The rates of these processes and the fates of both the alkyl radical and cob(II)aloxime moiety are pH-dependent. Early models for diol dehydratases used photolytic cleavage of the Co–C bond as this process occurs readily in aqueous media in contrast to the relatively harsh thermal conditions required.[11a–e,12] However, the initial homolysis proceeds from an excited state of the alkylcobaloxime and may be regarded as an imperfect model for the enzymatic reactions, which are non-photolytic. The *gem*-dimethyl group in compounds **1a**, **1b** and **2b** significantly lowers the temperature required to achieve thermal homolysis of the Co–C bond and also blocks a side-reaction observed with simpler model compounds [*e.g.* 4,5-dihydroxypentyl(pyridine)cobaloxime], whereby a β-elimination involving the 4,5-dihydroxypentyl radical diverts this radical from a 1,5-hydrogen shift towards the by-product 4,5-dihydroxypent-1-ene.[11d,e] This strategy was based on the observation of Grate and Schrauzer and others that the thermal stability of neopentylcobalamin is much lower than that of alkylcobalamins with primary alkyl groups.[22]

Following thermal or photochemical degradation of **1a**, **1b** and **2b**, aldehyde and/or ketone products were isolated, characterised (^{1}H NMR and MS analyses) and quantified (UV-VIS spectroscopy) as their 2,4-dinitrophenylhydrazones (DNPs). This method was validated for both **1a** and **2b** by independent analysis of the product aldehyde or ketone by GC. Authentic samples of 4,4-dimethylpentanal **25a** and its DNP derivative **26a** were independently synthesised (Scheme 5). All thermal



Scheme 5 Synthesis of authentic samples of the standards, 4,4-dimethylpentanal **25a** and its DNP **26a**, and 4,4-dimethylpentane-1,2-diol **28**. *Reagents and conditions*: **i** (i) BH_3·THF, 2-methylbut-2-ene, 0 °C. (ii) NaOH, H_2O_2, 5 °C, 62%. **ii** Pyridinium dichromate, CH_2Cl_2, rt, 75%. **iii** 2,4-Dinitrophenylhydrazine, H_2SO_4 (aq.), rt, 63%. **iv** $(CH_2OH)_2$, 2,6-*tert*-butyl-4-methyl-pyridinium tetrafluoroborate, benzene, reflux, 75%. **v** Ph_3SnH, AIBN, benzene, 45 °C, 67%. **vi** THF (aq.), DOWEX 50W, rt. **vii** Bu_3SnH, benzene, reflux, 81%. **viii** CH_3OH, MeCOCl, reflux, 90%.

and photochemical experiments were performed, at least in duplicate, with a deoxygenated solution (argon or nitrogen) of the alkylcobaloxime. It was shown for **1a** that admission of oxygen to reactions reduced the yield of aldehyde to zero.

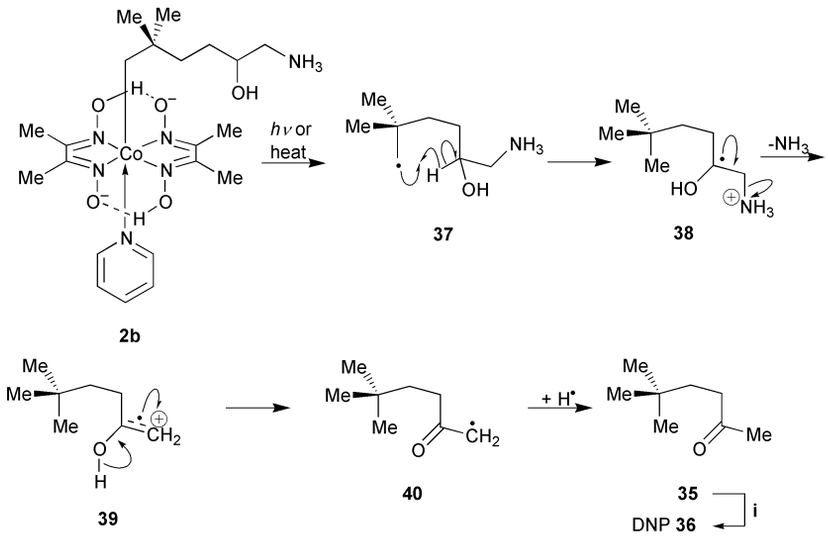
Heating **1a** in pH 3 aqueous acetic acid for 7 h at 100 °C caused complete decomposition of the alkylcobaloxime and gave 20–22% 4,4-dimethylpentanal **25a** according to both DNP and GC analysis. Thermal decomposition of **1a** at pH 9, 100 °C, gave 15–21% 4,4-dimethylpentanal (DNP and GC analysis). Photolytic degradation of **1a** gave 43–45% 4,4-dimethylpentanal at pH 3 and 20–25% aldehyde at pH 9 (DNP and GC analysis). The reaction mixtures were also analysed for the presence of 4,4-dimethylpentane-1,2-diol **28** (authentic sample obtained as shown in Scheme 5), because pentane-1,2-diol was a significant by-product in the photolysis of 4,5-dihydroxypentyl(pyridine)cobaloxime.[11d,e] However, no **28** was found, indicating the improved efficiency of the model resulting from *gem*-dimethyl substitution. Heating or photolysing **1b** at pH 3 using the procedures described for **1a** gave a mixture of two DNPs, which were identified as **26b** and **33** by comparison of the ^{1}H NMR of the mixture with data for authentic samples (*i.e.* non-deuteriated **26a** in the case of **26b**). For photolysis a ratio of *ca.* 1:1 was obtained for **26b**:**33**, whereas thermolysis gave predominantly **33**. The spectrum corresponding to **26b** showed a singlet at δ 0.93 (6H) for the *gem*-dimethyl group and a broad resonance at δ 0.92 (2H) assigned to the CH_2D group. The resonance observed at δ 7.57 corresponded to *ca.* 0.5H and was assigned to the hydrazone CH of **33**, there being no resonance from the deuterated hydrazone of **26a**.

The oxazolidinone group of the protected cobaloxime **2a** was hydrolysed using 1 M lithium hydroxide in water (7 days at room temperature, in darkness). This procedure had been previously developed for the hydrolysis of **17** to **16**. Monitoring the hydrolysis of **2a** using lithium hydroxide in D_2O by ^{1}H NMR showed the disappearance of the resonances at δ 3.35, 3.7 and 4.6 from the oxazolidinone ring and the appearance of new signals at δ 3.2 (assigned to C*H*OH of **2b**) and 3.35 and 3.7 (assigned to CH_2NH$_2$ of **2b**). After adjusting the pH of the alkaline solution of **2b** to 3 or 9 by addition of acetic acid and degassing with argon, it was heated at 100 °C until decomposition was complete, as shown by TLC monitoring. Thus, heating **2b** at pH 3 for 5 h caused complete decomposition of the alkylcobaloxime and gave 37% (average of two experiments) of 5,5-dimethylhexan-2-one **35**. The identity of the ketone was established by GC analysis of an ethereal extract of an aliquot of the reaction mixture, using an authentic sample of 5,5-dimethylhexan-2-one as a reference standard. Further confirmation of the identity of the ketone and its yield were obtained by conversion into its DNP derivative, which was also compared with an authentic sample. The DNP was obtained by adding the reaction mixture from a thermolysis of **2b** to aqueous acidic DNP reagent and extracting with ether. The thermal decomposition of **2b** at pH 9, 100 °C, gave 50% (average of two experiments) of 5,5-dimethylhexan-2-one (DNP **36** and GC analysis).

After extraction of 5,5-dimethylhexan-2-one DNP, the solution was basified and distilled to give an aqueous solution of ammonia, which was analysed using Nessler's reagent. This gave ammonia yields of 47% (pH 3 thermolysis of **2b**) and 67% (pH 9 thermolysis of **2b**). A control experiment was performed in which compound **16** was subjected to a sequence of thermolysis at pH 3, addition to DNP reagent, basification and distillation. The resulting distillate contained no ammonia.

Mechanism of thermal decomposition of 1a, 1b and 2b and photochemical decomposition of 1a and 1b

The decompositions of **1a** and **1b** under both thermal and photochemical conditions can be rationalised as in Scheme 3. The critical step following homolysis of the Co–C bond of **1a** to give **29a** is a 1,5-H shift, which affords the 1,2-dihydroxy-4,4-dimethyl-1-pentyl radical **30a**. This species is converted into the 4,4-dimethyl-1-oxo-2-pentyl radical **31a**, and hence 4,4-dimethylpentanal **25a**. The detailed mechanism of the pathway from **30a** to **25a** cannot be defined without further experimental information. In the light of recent *ab initio* molecular orbital calculations on the diol dehydratase reaction and the determination of the crystal structure of the enzyme (see Introduction), future model studies need to focus on the proton



Scheme 6 Thermal or photochemical decomposition of the ethanolamine ammonia lyase model compound.

transfer steps that may activate the migrating/eliminated hydroxy group in enzymatic and model reactions.

Following homolysis of the Co–C bond of **1b** to give **29b**, the type of 1,5-H shift proposed for **29a** is impeded by a primary kinetic isotope effect.[11d] Although an analogous 1,5-D shift occurs with **29b** to give **30b** and hence **25b** *via* **31b**, a competing 1,5-H shift occurs from the 2-hydroxy group leading to 3,3-dimethylbutanal **32**. Thus, it is proposed that **29b** gives **34**, which fragments to 3,3-dimethylbutanal **32** and the hydroxymethyl radical.

Thermolysis of **2b** proceeds in a similar manner to the thermolysis of **1a**. However, the 1,5-H shift in the initially formed radical **37** now leads *via* **38**–**40** to the ketone product **35** and ammonia (see Scheme 6).

Conclusions

The model experiments described in this paper support the proposed reaction pathways for propanediol dehydratase, glycerol dehydratase and ethanolamine ammonia lyase by showing that 1,2-diols and vicinal aminoalcohols can be converted into a carbonyl compound and water or ammonia, respectively, by reaction pathways in which radicals are likely intermediates. The model systems described replicate an important feature of the enzymatic reactions, *i.e.* the regioselective activation of a substrate molecule by a hydrogen atom abstraction induced by a primary organic radical. However, the detailed mechanisms of rearrangement of the radicals can only be determined by further investigations.

Experimental

Materials and methods

Unless otherwise stated gas chromatography (GC) was performed on a Pye 104 machine fitted with an 8″ ov17 column of 4 mm inner diameter with a nitrogen flow rate of 55 cm^3 min^{-1}, and a temperature gradient of 12 °C min^{-1} from 100 °C. Water for analytical purposes was obtained from a Purite still plus HP. Light petrol refers to the fraction boiling between 40 and 60 °C. Petrol refers to the fraction boiling between 60 and 80 °C. For other purification procedures and details of instruments *etc.* see ref. 23. All alkylcobaloximes were protected from light. *J* values are given in Hz.

2,2-Dimethylpent-4-enal 4[24]

The aldehyde **4** was prepared as described by Brannock.[24] Fractional distillation of the reaction mixture yielded 2,2-dimethylpent-4-enal (53.6 g, 48%), with a further 15 g contaminated with *p*-cymene (total yield 60%).

2,2-Dimethylpent-4-en-1-ol 5a[24]

2,2-Dimethylpent-4-enal **4** (11.2 g, 0.1 mol) in aq. ethanol was reduced with sodium borohydride (1.4 g, 0.037 mol) in 0.2 M aq. NaOH. Fractional distillation of the crude product gave 2,2-dimethylpent-4-en-1-ol **5a** (8.2 g, 72%), bp 54 °C (22 mmHg) or 154 °C (760 mmHg).[25]

5-Bromo-4,4-dimethylpent-1-ene 6a[25,26]

2,2-Dimethylpent-4-en-1-ol **5** (6.6 g, 58.0 mmol), was treated with carbon tetrabromide (20.0 g, 60.5 mmol) and triphenylphosphine (15.9 g, 60.5 mmol) in acetonitrile (150 cm^3) using the procedure of Hooz and Gilani.[26] The crude product was purified by column chromatography (light petrol) to give 5-bromo-4,4-dimethylpent-1-ene **6a** (11.6 g, 91% by ^{1}H NMR analysis) contaminated with bromoform.

2-(3-Bromo-2,2-dimethylpropyl)oxirane 7a

5-Bromo-4,4-dimethylpent-1-ene **6a** (9.3 g, 52.6 mmol) was oxidised with *m*-chloroperoxybenzoic acid (11.8 g, 58 mmol) in DCM (150 cm^3) over 15 h at room temp. The excess of peracid was destroyed with sodium sulfite. The crude product was purified by column chromatography (light petrol : ether, 8 : 1) to give a colourless syrup. This was flash distilled (bp 42 °C at 0.3 mmHg) to yield *2-(3-bromo-2,2-dimethylpropyl)oxirane* **7a** (5.4 g, 73%) as a viscous, colourless oil (Found: C, 43.71; H, 6.86; $C_7H_{13}BrO$ requires C, 43.54; H, 6.79%); ν_{max} (film)/cm^{-1} 3050, 1261 and 666 (s); δ_H (200 MHz; $CDCl_3$), 3.78 (1H, d, CH_2Br, *J* 10.1), 3.70 (1H, d, CH_2Br, *J* 10.1), 3.28–3.34 (1H, dddd, CHOC, *J* 4.0, 4.6, 7.2 and 5.1), 3.09–3.15 (1H, dd, CH_2O, *J* 4.0 and 2.7), 2.76–2.84 (1H, dd, CH_2O, *J* 2.7 and 5.1), 2.02–2.09 (1H, dd, CH_2, *J* 4.6 and 14.3), 1.75–1.85 (1H, dd, CH_2, *J* 7.2 and 14.3), 1.50 (6H, s, Me_2); δ_C (50 MHz; $CDCl_3$), 48.8 (t, CH_2Br), 46.4 (t, CH_2O), 46.2 (t, CH_2), 42.6 (d, CH), 34.8 (s, CMe_2), 26.1 (q, Me_2); *m*/*z* (EI) 177 (10%, $M^+ - Me$), 135 (60), 113 (10), 55 (100), 41 (95).

4-(3-Bromo-2,2-dimethylpropyl)-2,2-dimethyl-1,3-dioxolane 8a

A solution of 2-(3-bromo-2,2-dimethylpropyl)oxirane (2.01 g, 10.4 mmol) in acetone (8 cm^3) was flushed with dry nitrogen for 15 min and cooled to −75 °C. Boron trifluoride–diethyl ether (300 μl) was added and the resulting solution was stirred at −75 °C for 5 h. A solution of 0.1 M NaOH (15 cm^3) was added and, after vigorous agitation, the acetone was removed under

reduced pressure. Ether (15 cm^3) was added and the organic layer was separated, washed with 0.1 M NaOH solution, water and brine, dried (K_2CO_3) and the solvent removed. The product was purified by column chromatography (light petrol : ether, 8 : 1) to give *4-(3-bromo-2,2-dimethylpropyl)-2,2-dimethyl-1,3-dioxolane* **8a** (1.66 g, 64%) as a colourless oil (Found: C, 47.75; H, 7.29; $C_{10}H_{19}BrO_2$ requires C, 47.82; H, 7.62%); ν_{max} (film)/cm^{-1} 1380, 1155 and 656; δ_H (200 MHz; $CDCl_3$) 4.09–4.19 (1H, m, CH, *J* 5.8, 7.6, 7.8 and 4.0), 4.05 (1H, dd, CH_2O, *J* 5.8 and 7.6), 3.46 (1H, t, CH_2O, *J* 7.6), 3.40 (1H, d, CH_2Br, *J* 10.0), 3.35 (1H, d, CH_2Br, *J* 10.0), 1.64 (1H, dd, CH_2, *J* 14.4 and 7.8), 1.60 (1H, dd, CH_2, *J* 14.4 and 4.0), 1.39 (3H, s, Me), 1.34 (3H, s, Me), 1.09 (3H, s, Me), 1.07 (3H, s, Me); δ_C (50 MHz; $CDCl_3$) 108.9 (s, O_2CMe_2), 73.1 (d, CH), 70.4 (d, CH_2O), 46.8 (t, CH_2Br), 43.2 (t, CH_2), 34.4 (s, CMe_2), 27.0 (q, Me), 26.8 (q, Me), 26.1 (q, Me), 26.0 (q, Me); *m/z* (EI) 251 (10%, MH^+), 235 (80), 175 (20), 135 (20), 95 (100).

4,5-Dihydroxy-2,2-dimethyl-4,5-di-*O*-isopropylidenepentyl-(pyridine)bis(dimethylglyoximato(1−)-*N*,*N*′)cobalt 9a

Bromo(pyridine)bis(dimethylglyoximato(1−)-*N*,*N*′)cobalt (0.52 g, 1.2 mmol) was suspended in ethanol (40 cm^3) in a Schlenk tube, degassed and flushed with nitrogen for 1 h. Sodium borohydride (0.13 g, 3.4 mmol) was added as a suspension in ethanol (2 cm^3) and the mixture was stirred for 1 h until a homogeneous dark brown–green solution was obtained. To this solution, 4-(3-bromo-2,2-dimethylpropyl)-2,2-dimethyl-1,3-dioxolane **8a** (0.16 g, 0.6 mmol) was added, and the resultant solution was protected from light and stirred at room temp. for 12 h. Air was bubbled through the clear orange solution for 30 min before water (100 cm^3) was added and the product alkylcobaloxime was extracted into ethyl acetate. The combined organic extracts were dried (K_2CO_3) and the solvent removed. The residue was dissolved in a minimum amount of DCM and purified by column chromatography (96 : 3 : 1 DCM–methanol–pyridine). Product-containing fractions were combined and the solvent was removed. The residue was subjected to high vacuum to remove traces of pyridine. *Alkylcobaloxime* **9a** (0.12 g, 35%) was isolated as an orange–yellow crystalline solid (Found: C, 51.05; H, 6.81; N, 12.78; $C_{23}H_{38}CoN_5O_6$ requires C, 51.20; H, 7.10; N, 12.98%); ν_{max} (disc)/cm^{-1} 3150 (br) and 1234 (s); δ_H (200 MHz; $CDCl_3$) 8.47 (2H, d, α-pyr, *J* 4.9), 7.65 (1H, t, γ-pyr, *J* 6.0), 7.25 (2H, t, β-pyr, *J* 4.2), 3.93–4.05 (2H, m, CH_2O), 3.30 (1H, t, CH, *J* 9.9), 2.06 (6H, s, $dmgMe_2$), 2.05 (6H, s, $dmgMe_2$), 1.77 (1H, d, $CoCH_2$, *J* 9.0), 1.45 (1H, d, $CoCH_2$, *J* 9.0), 1.36 (2H, m, CH_2), 1.28 (3H, s, Me), 1.25 (3H, s, Me), 0.73 (3H, s, Me), 0.69 (3H, s, Me); δ_C (50 MHz; $CDCl_3$) 150.2 (C=N), 150.1 (C=N), 149.4 (α-pyr), 137.5 (γ-pyr), 125.1 (β-pyr), 107.7 (O_2CMe_2), 73.9 (CHO), 70.9 (CH_2O), 46.1 (CH_2), 42.2 ($CoCH_2$), 38.5 (CMe_2), 28.8 (Me), 28.5 (Me), 27.1 (Me), 26.1 (Me), 12.1 ($dmgMe_4$); *m/z* (FAB) 540 (MH^+), 539, 461, 290 (100%).

4,5-Dihydroxy-2,2-dimethylpentyl(pyridine)bis(dimethylglyoximato(1−)-*N*,*N*′)cobalt 1a

4,5-Dihydroxy-2,2-dimethyl-4,5-di-*O*-isopropylidenepentyl-(pyridine)bis(dimethylglyoximato(1−)-*N*,*N*′)cobalt **9a** (0.16 g, 0.3 mmol) was dissolved in ethanol (3 cm^3) and 2 M HCl (0.45 cm^3) was added. The solution was stirred in the dark at room temp for 5 h. The solvent was removed and the residue was subjected to column chromatography (90 : 9 : 1, DCM–methanol–pyridine). After removal of the solvent, traces of pyridine were removed under high vacuum to give the *diolcobaloxime* **1a** (0.11 g, 82%) as an orange crystalline solid (Found: C, 48.61; H, 6.57; N, 13.80; $C_{20}H_{34}CoN_5O_6$ requires C, 48.10; H, 6.86; N, 14.02%); ν_{max} (disc)/cm^{-1} 3406 br, 2910–2950 and 1560; δ_H (200 MHz; $CDCl_3$) 8.46 (2H, d, α-pyr), 7.68 (1H, t, γ-pyr), 7.27 (2H, t, β-pyr), 3.59 (1H, m, C*H*OH), 3.48 (1H, dd, CH_2OH, *J* 11.0 and 3.3), 3.30 (1H, dd, CH_2OH, *J* 11.0 and 7.9), 2.09 (6H, s, $dmgMe_2$), 2.07 (6H, s, $dmgMe_2$), 1.98 (1H, d, $CoCH_2$, *J* 8.9), 1.57 (1H, d, $CoCH_2$, *J* 8.8), 1.46 (1H, dd, CH_2, *J* 14.8 and 6.1), 1.18 (1H, dd, CH_2, *J* 14.5 and 4.3), 0.73 (3H, s, Me), 1.05 (1H, s, OH), 1.01 (1H, s, OH), 0.63 (3H, s, Me); δ_C (50 MHz; $CDCl_3$) 151.1 (C=N), 150.7 (C=N), 149.5 (α-pyr), 137.6 (γ-pyr), 125.2 (β-pyr), 69.9 (CHOH), 68.4 (CH_2OH), 45.2 (CH_2), 42.0 ($CoCH_2$), 38.7 (CMe_2), 29.6 (Me), 29.2 (Me), 12.3 ($dmgMe_2$), 12.2 ($dmgMe_2$); *m/z* (FAB) 500 (10%, MH^+), 421, 420, 368, 290 (100), 289 (94).

Prop-2-enyl 2-methylpropionate 10a[27]

Prop-2-enyl 2-methylpropionate was prepared from allyl alcohol **3a** (3.00 g, 3.51 cm^3, 0.05 mol) and isobutyryl chloride (5.54 g, 5.48 cm^3, 0.05 mol) according to the procedure of Arnold and Kulenovic:[27] colourless oil (6.77 g, 99%); ν_{max} (film)/cm^{-1} 2978, 1738 and 1650; δ_H (200 MHz; $CDCl_3$) 5.78–5.97 (m, 1H, =CH-), 5.14–5.32 (m, 2H, CH_2=), 4.51–4.55 (2H, m, CH_2), 2.53 (1H, quintet, CH, *J* 7.0), 1.14 (6H, d, Me_2, *J* 7.0); δ_C (50 MHz; $CDCl_3$) 176.8 (COO), 132.4 (=CH), 117.8 (=CH_2), 64.9 (CH_2O), 34.0 (CH), 19.0 (Me_2); *m/z* (EI) 128.085 (M^+, $C_7H_{12}O_2$ requires 128.084) 128 (10%, M^+), 71 (20), 57 (40).

[1,1-$^2H_2$]Prop-2-en-1-ol 3b[27]

[1,1-$^2H_2$]Prop-2-en-1-ol was prepared[19] by reduction with lithium aluminium deuteride (5.0 g, 0.2 mmol) of acryloyl chloride (16.2 g, 0.2 mmol) to give the deuteriated *allyl alcohol* **3b** (6.7 g, 62%), which was used without further purification; ν_{max} (film)/cm^{-1} 3370, 2964, 2934 and 1035; δ_H (200 MHz; $CDCl_3$) 5.8–6.1 (1H, m, =CH), 5.0–5.3 (2H, m, =CH_2), 2.0–2.2 (1H, br s, OH); δ_C (50 MHz; $CDCl_3$) 137.3 (CH), 115.4 (CH_2), 63.2 (t, CD_2).

[1,1-$^2H_2$]Prop-2-enyl 2-methylpropionate 10b

[1,1-$^2H_2$]Prop-2-enyl 2-methylpropionate **10b** was prepared from [1,1-$^2H_2$]prop-2-en-1-ol **3b** in the same manner as **10a**. The *title compound* **10b** was obtained as a colourless oil (6.61 g, 88%); ν_{max} (film)/cm^{-1} 2976, 1736 and 1645; δ_H (200 MHz; $CDCl_3$) 5.67–5.96 (1H, m, =CH-), 5.15–5.33 (m, 2H, CH_2=), 2.45–2.70 (1H, quintet, CH, *J* 7.0), 1.16 (6H, d, Me_2, *J* 7.0), the methylene multiplet at δ 4.5 was not present; δ_C (50 MHz; $CDCl_3$) 176.7 (COO), 132.4 (=CH), 118.0 (=CH_2), 64.9 (CD_2O), 34.0 (CH), 19.0 (Me_2); *m/z* (EI) 130.0963 (M^+, $C_{12}H_{10}{}^2H_2O_2$ requires 130.0962), 130 (15%), 71 (100), 43 (100).

2,2-Dimethylpent-4-enoic acid 11a[20,28]

Prop-2-enyl 2-methylpropionate **10a** (1.28 g, 10 mmol, 1.4 cm^3) was subjected to a Claisen rearrangement according to the procedure of Ireland *et al.*,[20] to yield the carboxylic acid **11a** (0.53 g, 41%) as a colourless oil; δ_H (200 MHz; $CDCl_3$), 11.4–11.6 (1H, br s, COOH), 5.60–5.80 (1H, m, vinylic CH), 4.95–5.06 (2H, m, =CH_2), 2.20–2.25 (2H, dt, CH_2, *J* 7.4 and 0.9), 1.12 (6H, s, Me_2).

[5,5-$^2H_2$]-2,2-Dimethylpent-4-enoic acid 11b

[5,5-$^2H_2$]-2,2-Dimethylpent-4-enoic acid **11b** was prepared from [1,1-$^2H_2$]prop-2-enyl 2-methylpropionate **10b** in the same manner as **11a** yielding the *title compound* (2.63 g, 40%) as a pale yellow oil; ν_{max} (film)/cm^{-1} 3100, 1703 and 1603; δ_H (200 MHz; $CDCl_3$) 11.25–11.6 (1H, br s, COOH), 5.6–5.7 (1H, br t, =CH), 2.4–2.6 (2H, m, =CH_2), 2.1 (2H, d, -CH_2, *J* 7.4), 1.1 (6H, s, Me_2); δ_C (50 MHz; $CDCl_3$) 184.6 (COOH), 133.7 (CH=), 44.3 (CH_2), 33.9 (CMe_2), 24.6 (Me_2); *m/z* (EI) 130.0982 (M^+, $C_7H_{10}{}^2H_2O_2$ requires 130.0962), 130.1 (7%), 115 (25), 85 (100), 43 (60).

[5,5-$^2H_2$]-2,2-Dimethylpent-4-en-1-ol 5b

[5,5-$^2H_2$]-2,2-Dimethylpent-4-enoic acid **11b** (2.65 g, 20.3

mmol) in ether (20 cm^3) was reduced with lithium aluminium hydride (2.40 g, 63 mmol) in ether (80 cm^3) to yield the *alcohol* **5b** (1.9 g, 80%) as a colourless oil; ν_{max} (film)/cm^{-1} 3400 and 1050; δ_H (200 MHz; $CDCl_3$) 5.73–5.83 (1H, br t, =CH), 3.27 (2H, s, CH_2O), 1.96 (2H, d, CH_2), 1.88 (1H, br s, OH), 0.84 (6H, s, Me_2); *m*/*z* (EI) 117.1241 (MH^+, $C_7H_{13}{}^2H_2O$ requires 117.1248), 117 (15%), 116 (5), 73 (100), 43 (95).

[1,1-$^2H_2$]-5-Bromo-4,4-dimethylpent-1-ene 6b

This compound was synthesised from [5,5-$^2H_2$]-2,2-dimethylpent-4-en-1-ol **5b** in the manner of **6a** (1.9 g, 50% by NMR analysis); ν_{max} (film)/cm^{-1} 2924 and 1653; δ_H (200 MHz; $CDCl_3$) 5.69–5.78 (1H, br t, =CH), 3.25 (2H, s, CH_2Br), 2.07 (2H, d, CH_2, *J* 7.5), 0.99 (6H, s, Me_2); *m*/*z* (EI) 178 (5%, M^+), 135 (60), 99 (64), 55 (100).

[3,3-$^2H_2$]-2-(3-Bromo-2,2-dimethylpropyl)oxirane 7b

[3,3-$^2H_2$]-2-(3-Bromo-2,2-dimethylpropyl)oxirane **7b** was synthesised from [1,1-$^2H_2$]-5-bromo-4,4-dimethylpent-1-ene **6b** in the manner of **7a**. Distillation under reduced pressure (bp 42 °C at 0.3 mmHg) yielded the *deuteriated bromo epoxide* **7b** (1.1 g, 52%) as a colourless oil; ν_{max} (film)/cm^{-1} 3046, 1267 and 663; δ_H (200 MHz; $CDCl_3$) 3.37 (1H, d, CHBr, *J* 10.1), 3.32 (1H, d, CH'Br, *J* 10.1), 2.93 (1H, dd, CHO, *J* 4.7 and 7.2), 1.6–1.75 (1H, dd, CH, *J* 4.7 and 14.3), 1.45 (1H, dd, CH′, *J* 7.2 and 14.3), 1.1 (6H, s, Me_2); δ_C (50 MHz; $CDCl_3$) 48.2 (CH_2Br), 46.4 (CH_2), 42.7 (CH), 34.6 (CMe_2), 26.2 (Me_2).

[5,5-$^2H_2$]-4-(3-Bromo-2,2-dimethylpropyl)-2,2-dimethyl-1,3-dioxolane 8b

This was synthesised from [3,3-$^2H_2$]-2-(3-bromo-2,2-dimethylpropyl)oxirane **7b** in the manner of **8a** to yield the *deuteriated bromo acetal* **8b** (0.84 g, 53%) as a colourless oil; δ_H (200 MHz; $CDCl_3$) 4.1 (1H, dd, CHO), 3.3 (2H, s, CH_2Br), 1.6–1.8 (1H, dd, CH_2, *J* 14.2 and 7.8), 1.4–1.6 (1H, dd, CH_2, *J* 14.2 and 4.0), 1.35 (3H, s, Me), 1.30 (3H, s, Me), 1.1 (3H, s, Me), 1.06 (3H, s, Me); δ_C (50 MHz; $CDCl_3$) 108.9 (O_2CMe_2), 73.1 (CH), 46.8 (CH_2Br), 43.2 (CH_2), 34.4 (CMe_2), 27.0 (Me), 26.8 (Me), 26.1 (Me), 26.0 (Me).

[5,5-$^2H_2$]-4,5-Dihydroxy-2,2-dimethyl-4,5-di-*O*-isopropylidenepentyl(pyridine)bis(dimethylglyoximato(1−)-*N*,*N*′)cobalt 9b

This was synthesised from [5,5-$^2H_2$]-4-(3-bromo-2,2-dimethylpropyl)-2,2-dimethyl-1,3-dioxolane **8b** in the manner of **9a** to yield the *deuteriated alkyl-cobaloxime* **9b** (0.12 g, 35%) as orange plates; ν_{max} (disc)/cm^{-1} 2955 and 1240; δ_H (200 MHz; $CDCl_3$) 8.5 (2H, m, α-pyr), 7.65 (1H, t, γ-pyr), 7.25 (2H, t, β-pyr), 3.31 (1H, s, CHO), 2.07 (6H, s, $dmgMe_2$), 2.06 (6H, s, $dmgMe_2$), 1.92 (1H, d, $CoCH_2$, *J* 8.8), 1.55 (1H, d, $CoCH_2$, *J* 8.8), 1.4 (2H, m, CH_2), 1.34 (3H, s, Me), 1.30 (3H, s, Me), 0.77 (3H, s, Me), 0.73 (3H, s, Me); δ_C (50 MHz; MeOH) 150.7 (C=N), 149.1 (α-pyr), 139.8 (γ-pyr), 126.9 (β-pyr), 110.4 (O_2CMe_2), 75.6 (CHO), 45.2 (CH_2), 35.5 (CMe_2), 27.7 (Me), 27.4 (Me), 26.7 (Me), 26.6 (Me), 12.7 ($dmgMe_4$) [NB the expected resonance for CD_2OH was not identified]; *m*/*z* (FAB) 542 (MH^+), 541, 463, 290.

[5,5-$^2H_2$]-4,5-Dihydroxy-2,2-dimethylpentyl(pyridine)bis(dimethylglyoximato(1−)-*N*,*N*′)cobalt 1b

This compound was prepared from **9b** in the manner of **1a** to give the *deuteriated diol-cobaloxime* **1b** (75 mg, 57%) as orange plates; ν_{max} (disc)/cm^{-1} 3410 br, 2928, 1562, 1446 and 1237; δ_H (500 MHz; $CDCl_3$) 8.5–8.55 (2H, d, α-pyr), 7.75 (1H, t, γ-pyr), 7.25 (2H, t, β-pyr), 3.5 (1H, br t, C*H*OH, *J* 5.1), 2.22 (6H, s, $dmgMe_2$), 2.15 (6H, s, $dmgMe_2$), 2.07–2.10 (1H, d, CH-Co, *J* 11.0), 1.45–1.55 (1H, d, CH′-Co, *J* 11.0), 1.4 (1H, m, CH_2), 1.2 (1H, m, CH'_2), 0.8 (3H, s, CH_3), 0.65 (3H, s, CH_3); δ_C (120 MHz; $CDCl_3$) 150.1 (C=N), 149.3 (α-pyr), 137.5 (γ-pyr), 125.1 (β-pyr), 69.6 (CHOH), 44.6 (CH_2), 42.0 (br, $CoCH_2$), 38.5 (CMe_2), 29.9 (Me), 29.8 (Me), 12.2 ($dmgMe_2$), 12.1 ($dmgMe_2$) [NB the expected resonance for CD_2OH was not identified]; *m*/*z* (FAB) 502 (MH^+), 423, 422, 368, 290 (100%), 289.

1-[*tert*-Butyl(dimethyl)silyloxy]-2,2-dimethylpent-4-ene 12

2,2-Dimethylpent-4-en-1-ol **5a** (13.7 g, 0.1 mol), *tert*-butyldimethylsilyl chloride (25.0 g, 0.2 mol) and imidazole (11.3 g, 0.2 mol) in dimethylformamide (100 cm^3) were stirred under a nitrogen atmosphere overnight (18 h). Work-up was carried out in the usual manner.[29] The crude product was purified by flash column chromatography (light petrol) and the solvent was removed to yield the *title compound* **12** (27.4 g, 100%) as a colourless liquid; ν_{max} (film)/cm^{-1} 2957, 1641 and 1257; δ_H (200 MHz; $CDCl_3$) 5.68–5.89 (1H, m, RCH=), 4.92–4.97 (2H, m, $=CH_2$), 3.20 (2H, s, CH_2O), 1.96 (2H, dt, CH_2, *J* 4.3 and 1.10), 0.87 (9H, s, ^tBu), 0.80 (6H, s, Me_2), 0.07 (6H, s, $SiMe_2$); δ_C (50 MHz; $CDCl_3$) 135.8 (R*C*=), 116.7 ($=CH_2$), 71.3 (CH_2O), 43.2 (CH_2), 35.6 (CMe_2), 26.0 ($SiCMe_3$), 24.0 (Me_2), 18.3 ($SiCMe_3$), −5.5 ($SiMe_2$); *m*/*z* (EI) 228 (10%, M^+), 97 (45).

1-[*tert*-Butyl(dimethyl)silyloxy]-2,2-dimethylpentan-5-ol 13[30,31]

Hydroboration of 1-[*tert*-butyl(dimethyl)silyloxy]-2,2-dimethylpent-4-ene **12** (2.05 g, 9.0 mmol) in tetrahydrofuran (10 cm^3) was achieved with disiamylborane (1,2-dimethylpropylborane).[30] Work-up and oxidation was carried out using the procedure of Brown *et al*.[31] The crude product was purified by flash column chromatography (CH_2Cl_2) to yield the *alcohol* **13** (1.7 g, 82%) as a colourless oil; δ_H (200 MHz; $CDCl_3$) 3.59 (2H, t, CH_2OH, *J* 6.7), 3.22 (2H, s, CH_2OSi), 1.67 (1H, br s, OH), 1.50–1.61 (2H, m, CH_2), 1.11–1.48 (2H, m, CH_2), 0.87 (9H, s, ^tBu), 0.81 (6H, s, Me_2), 0.00 (6H, s, $SiMe_2$); δ_C (50 MHz; $CDCl_3$) 71.4 (CH_2OH), 63.9 (CH_2OSi), 35.0 (CMe_2), 34.5 (CH_2), 27.4 (CH_2), 25.9 (Me_2), 24.1 (^tBu), 18.3 ($SiCMe_3$), −5.5 ($SiMe_2$).

5-[*tert*-Butyl(dimethyl)silyloxy]-4,4-dimethylpentanal 14

Swern oxidation of 1-[*tert*-butyl(dimethyl)silyloxy]-2,2-dimethylpentan-5-ol **13** (3.78 g, 15.4 mmol) in DCM (10 cm^3) with oxalyl chloride (2.2 g, 1.5 cm^3, 17 mmol) and dimethyl sulfoxide (2.6 g, 2.4 cm^3, 34 mmol) in DCM (45 cm^3) at −78 °C,[32] followed by flash column chromatography (CH_2Cl_2) of the crude product, yielded the *aldehyde* **14** (2.0 g, 53%) as a colourless oil; ν_{max} (film)/cm^{-1} 2930 and 1713; δ_H (200 MHz; $CDCl_3$) 9.73 (1H, br t, CHO), 3.22 (2H, s, CH_2O, 2.33–2.40 (2H, m, CH_2CH_2CHO), 1.5–1.7 (2H, t, CH_2CH_2CHO, *J* 8.2), 0.86 (9H, s, ^tBu), 0.82 (6H, s, Me_2), −0.01 (6H, s, $SiMe_2$).

1-[*tert*-Butyl(dimethyl)silyloxy]-5-hydroxy-2,2-dimethyl-6-nitrohexane 15[33]

5-[*tert*-Butyl(dimethyl)silyloxy]-4,4-dimethylpentanal **14** (2.01 g, 8.2 mmol) and nitromethane (0.50 g, 8.2 mmol) in ethanol (4 cm^3) were cooled in an ice bath and sodium hydroxide solution (0.9 cm^3, 10 M, 9 mmol) was added dropwise over 30 min. The reaction mixture was stirred for 3 h on an ice bath then acetic acid solution (10 cm^3, 1 M) was added. The ethanol was removed under reduced pressure and the aq. residue was extracted with ethyl acetate. The combined organic extracts were washed with sodium hydroxide solution (0.1 M), brine, and dried. Removal of the solvent and purification of the residue by flash column chromatography (CH_2Cl_2) gave the *nitro alcohol* **15** (1.8 g, 77%) as a colourless oil; ν_{max} (film)/cm^{-1} 3435, 2955, 1556, 1363 and 1099; δ_H (200 MHz; $CDCl_3$) 4.3–4.5 (2H, m, CH_2NO_2), 4.1–4.3 (1H, m, CHOH), 3.2 (2H, s, CH_2OSi), 2.4 (1H, br s, OH), 1.2–1.6 (4H, m, CH_2CH_2), 0.89 (9H, s, ^tBu), 0.88 (6H, s, Me_2), 0.02 (6H, s, $SiMe_2$); δ_C (50 MHz; $CDCl_3$) 80.6 (CH_2NO_2), 71.1 (CH_2OH), 69.5 (CH_2OSi), 35.0 (CMe_2), 33.9 ($CHOHCH_2$), 28.5 ($CHOHCH_2CH_2$), 25.9 (OSi-

C*Me*$_3$), 24.2 (C*Me*$_2$) , 24.0 (C*Me*$_2$), 18.3 (Si*C*Me$_3$), −5.5 (Si*Me*$_2$); *m/z* (EI) 306.211 (MH$^+$, $C_{14}H_{32}NO_4Si$ requires 306.210), 306 (20%).

6-Amino-1-[*tert*-butyl(dimethyl)silyloxy]-5-hydroxy-2,2-dimethylhexane 16

To a solution of 1-[*tert*-butyl(dimethyl)silyloxy]-5-hydroxy-2,2-dimethyl-6-nitrohexane **15** (6.31 g, 21.8 mmol) in ethanol (125 cm^3) was added a slurry of palladium supported on charcoal (10%, 3.0 g, 14 mol%) in ethanol (80 cm^3). The reaction mixture was degassed by stirring under water pump vacuum, then the vacuum was replaced by a hydrogen atmosphere at atmospheric pressure. The reaction mixture was stirred for 24 h, after which time the hydrogen atmosphere was removed. Filtration of the crude reaction mixture through Celite, removal of the solvent and flash column chromatography (DCM–methanol–aq. ammonia, 8:1:0.1) of the crude product yielded the *amino alcohol* **16** (3.5 g, 65%) as a viscous oil; ν_{max} (film)/cm^{-1} 3354, 2955, 2930, 1591, 1473 and 1099; δ_H (200 MHz; $CDCl_3$), 3.5 (1H, br s, OH), 3.3 (2H, br s, NH_2), 3.2 (2H, s, CH_2OSi), 2.9 (1H, br s, C*H*-NH_2), 2.6 (1H, br s, C*H*-NH_2), 1.1–1.5 (4H, m, CH_2CH_2), 0.9 (9H, s, ^{t}Bu), 0.8 (6H, s, Me_2), 0.0 (6H, s, $SiMe_2$); δ_C (50 MHz; $CDCl_3$) 72.1 (CHOH), 71.1 (CH_2OSi), 46.9 (CH_2NH_2), 35.0 (*C*Me$_2$), 34.5 (CHOH*C*H$_2$CH$_2$), 29.3 (CHOHCH$_2$*C*H$_2$), 25.9 (SiC*Me*$_3$), 24.3 (Me), 23.9 (Me), 18.3 (Si*C*Me$_3$), −5.4 ($SiMe_2$); *m/z* (EI) 276.2361 (MH$^+$, $C_{14}H_{34}NO_2Si$ requires 276.2354), 276 (25%), 245 (40), 218 (60).

5-{4-[*tert*-Butyl(dimethyl)silyloxy]-3,3-dimethylbutyl}-1,3-oxazolidin-2-one 17

A solution of 6-amino-1-[*tert*-butyl(dimethyl)silyloxy]-5-hydroxy-2,2-dimethylhexane **16** (1.27 g, 4.6 mmol) and triethylamine (3.7 g, 5.13 cm^3, 37 mmol, 8 mol equiv.) in DCM (12 cm^3) was cooled in an ice bath. To this a solution of methyl chloroformate (2.16 g, 2.13 cm^3, 27.6 mmol, 6 mol equiv.) was added dropwise over a period of 30 min, then the mixture was stirred at room temperature overnight. The reaction mixture was poured into dilute hydrochloric acid (1 M, 50 cm^3), the organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with 1 M hydrochloric acid, sodium bicarbonate solution, water, brine, and dried. Removal of the solvent yielded the intermediate *1-[tert-butyl(dimethyl)silyloxy]-5-hydroxy-2,2-dimethyl-6-(methoxycarbonylamino)hexane* (1.2 g, 75%). A small portion of the crude product was purified by flash column chromatography (petrol–ethyl acetate, 3:1) to give a colourless oil which was characterised by ^{1}H NMR; δ_H (200 MHz; $CDCl_3$), 5.1 (1H, br s, NH), 3.6 (3H, s, OMe), 3.2–3.6 (2H, m, CH_2N), 3.2 (2H, s, CH_2OSi), 2.9–3.1 (1H, m, CH_2OH), 1.1–1.5 (4H, m, CH_2CH_2), 0.9 (9H, s, ^{t}Bu), 0.8 (6H, s, Me_2), 0.0 (6H, s, $SiMe_2$).

To a solution of 1-[*tert*-butyl(dimethyl)silyloxy]-5-hydroxy-2,2-dimethyl-6-(methoxycarbonylamino)hexane (1.2 g, 3.5 mmol) in tetrahydrofuran (10 cm^3) was added sodium hydride (0.2 g, 7.0 mmol). The reaction mixture was stirred under a nitrogen atmosphere for 4 h. Saturated ammonium chloride solution (20 cm^3) was added cautiously, then the organic layer was separated, dried ($MgSO_4$) and the solvent was removed. The crude product was purified by flash column chromatography (petrol–ethyl acetate, 2:1) to yield the *oxazolidinone* **17** (0.8 g, 75%) as a colourless solid, mp 85 °C; ν_{max} (disc)/cm^{-1} 3242, 3159, 2959, 1740 and 1097; δ_H (200 MHz; $CDCl_3$), 6.25 (1H, br s, NH), 4.4–4.5 (1H, m, CHO, *J* 7.9), 3.64 (1H, t, CHNH, *J* 8.4), 3.20 (1H, t, CH′NH, *J* 7.9), 3.20 (2H, s, CH_2OSi), 1.5–1.9 (2H, m, CHOC*H*$_2$CH$_2$), 1.1–1.5 (2H, m, CHOCH$_2$C*H*$_2$), 0.9 (9H, s, ^{t}Bu), 0.8 (6H, s, Me_2), 0.0 (6H, s, $SiMe_2$); δ_C (50 MHz; $CDCl_3$), 160.4 (C=O), 77.9 (CHO), 71.2 (CH_2OSi), 46.0 (CH_2NH), 34.9 (*C*Me$_2$), 33.1 (CHO*C*H$_2$CH$_2$), 29.6 (CHOCH$_2$*C*H$_2$), 25.9 (SiC*Me*$_3$), 24.2 (Me), 24.0 (Me), 18.3 (Si*C*Me$_3$), −5.5 ($SiMe_2$); *m/z* (EI) 302.2161 (MH$^+$, $C_{15}H_{32}NO_3Si$ requires 302.2154) 302 (10%, MH$^+$), 286 (10), 244 (80).

5-(4-Hydroxy-3,3-dimethylbutyl)-1,3-oxazolidin-2-one 18

To 5-{4-[*tert*-butyl(dimethyl)silyloxy]-3,3-dimethylbutyl}-1,3-oxazolidin-2-one **17** (2.64 g, 8.8 mmol) in tetrahydrofuran (50 cm^3) was added tetrabutylammonium fluoride[29] as a solution in tetrahydrofuran (1.1 M, 15 cm^3, 16.5 mmol) and the reaction mixture was stirred for 24 h, after which time TLC showed the absence of starting material. Water (5 cm^3) was added and the tetrahydrofuran was removed. The aqueous component was extracted into DCM and the organic extracts were washed with water, brine and dried ($MgSO_4$). The crude product was purified by flash column chromatography (ethyl acetate) to yield the *alcohol* **18** (1.01 g, 62%) as a colourless solid, mp 72 °C; ν_{max} (disc)/cm^{-1} 3317, 2957, 2872 and 1745; δ_H (200 MHz; $CDCl_3$) 6.5 (1H, br s, NH), 4.5–4.7 (1H, m, CHO, *J* 7.9), 3.65 (1H, t, CHNH, *J* 8.4), 3.3 (2H, s, CH_2OH), 3.25 (1H, t, CH′NH, *J* 7.9), 2.9 (1H, br s, OH), 1.5–1.9 (2H, m, CHOC*H*$_2$CH$_2$), 1.1–1.5 (2H, m, CHOCH$_2$C*H*$_2$), 0.95 (6H, s, Me_2); δ_C (50 MHz; $CDCl_3$), 160.6 (C=O), 77.9 (CHO), 71.1 (CH_2OH), 46.0 (CH_2NH), 34.7 (*C*Me$_2$), 32.9 (CHO*C*H$_2$CH$_2$), 29.5 (CHOCH$_2$*C*H$_2$), 24.0 (Me), 23.8 (Me); *m/z* (EI) 188.1279 (MH$^+$, C_9 H_{18} NO_3 requires 188.1286) 188 (50%), 156 (40), 95 (90), 56 (100).

5-[3,3-Dimethyl-4-(trifluoromethylsulfonyloxy)butyl]-1,3-oxazolidin-2-one 19

A solution of 5-(4-hydroxy-3,3-dimethylbutyl)-1,3-oxazolidin-2-one **18** (52.0 mg, 0.28 mmol) and triethylamine (30.9 mg, 52 µl, 0.31 mmol) in DCM (5 cm^3) was cooled to −75 °C. To this solution was added trifluoromethanesulfonic anhydride (86.3 mg, 51 µl, 0.31 mmol). The reaction was allowed to stir at this temperature for 15 min, then allowed to warm to room temperature. The reaction mixture was washed quickly with 0.1 M hydrochloric acid solution and dried ($MgSO_4$) to yield the *triflate* **19** (89 mg, 100%) which was used without further purification; δ_H (200 MHz; $CDCl_3$) 6.2–6.4 (1H, br s, NH), 4.5–4.7 (1H, br m, CHO), 4.2 (2H, s, CH_2OTf), 3.6–3.8 (1H, br t, CHNH), 3.1–3.3 (1H, br t, CH′NH), 1.5–1.8 (2H, br m, CHOC*H*$_2$CH$_2$), 1.2–1.5 (2H, br m, CHOCH$_2$C*H*$_2$), 1.0 (6H, s, Me_2).

2,2-Dimethyl-4-(2-oxo-1,3-oxazolidin-5-yl)butyl(pyridine)bis(dimethylglyoximato(1−)-*N*,*N*′)cobalt 2a

The title compound **2a** was synthesised from bromo(pyridine)bis(dimethylglyoximato(1−)-*N*,*N*′)cobalt (0.25 g, 0.56 mmol), dimethylglyoxime (100 mg), sodium borohydride (63 mg, 1.7 mmol) and 5-[3,3-dimethyl-4-(trifluoromethylsulfonyloxy)-butyl]-1,3-oxazolidin-2-one **19** (89 mg, 0.23 mmol) in ethanol (20 cm^3) in the same manner as **9a**. The product was extracted into DCM and the extracts were washed with water, brine, and dried (K_2CO_3). Removal of the solvent and flash column chromatography (DCM–methanol–pyridine, 95:2.5:0.1) of the residue, followed by exposure to high vacuum (0.5 mmHg) to remove traces of pyridine, gave the *alkylcobaloxime* **2a** as a red solid (110 mg, 75%); ν_{max} (disc)/cm^{-1} 3306, 2924 and 1751; δ_H (500 MHz; $CDCl_3$) 18.3 (2H, br s, H bonded dmgOH), 8.55 (2H, dd, α-pyridine, *J* 1.2 and 6.35), 7.72 (1H, tt, γ-pyridine, *J* 1.5 and 7.6), 7.32 (2H, m, β-pyridine, *J* 1.2 and 7.5), 5.34 (1H, br s, NH), 4.65–4.60 (1H, m, CHO, *J* 6.8 and 7.3), 3.68 (1H, t, CHNH, *J* 8.3), 3.33 (1H, t, CH′NH, *J* 7.9), 2.143 (6H, s, dmgMe_2), 2.136 (6H, s, dmgMe_2), 1.79 (2H, s, $CoCH_2$), 1.61–1.68 (1H, m, COC*H*$_2$CH$_2$), 1.48–1.55 (1H, m, COC*H*′$_2$CH$_2$), 1.28 (1H, m, COCH$_2$C*H*$_2$), 1.16 (1H, dt, COCH$_2$C*H*′$_2$, *J* 4.4 and 13.0), 0.74 (6H, s, Me_2); δ_C (125 MHz; $CDCl_3$) 159.8 (C=O), 149.3 (α-pyr), 137.4 (γ-pyr), 125.2 (β-pyr), 78.3 (CHO), 45.7 (CH_2NH), 41.7 ($CoCH_2$), 36.6 (CHO*C*H$_2$CH$_2$), 28.2 (Me_2), 12.1 (dmgMe_4), 9.7 (CHOCH$_2$*C*H$_2$).

Thermolysis and photolysis of cobaloximes 1a and 1b

Reactions at pH 3 were carried out in 0.1 M aq. acetic acid, whilst reactions at pH 9 were performed in 0.01 M aq. sodium tetraborate. Samples for photolysis and thermolysis were prepared by dissolving the cobaloxime (50 mg) in the appropriate solvent (50 cm^3) and deoxygenated by bubbling nitrogen through the solution for 30 min.

Photolysis. The reaction flask was transferred to a water bath (15 °C) and photolysed at a distance of 2 cm from the light source (Hanovia medium pressure mercury lamp). Completion of photolysis at pH 3 was indicated by the absence of any yellow colour in the solution (about 20 min). Photodecomposition at pH 9 took considerably longer (about $4\frac{1}{2}$ h) and was monitored to completion by TLC.

Thermolysis. The solution was heated at 100 °C for 7 h, when TLC analysis indicated the absence of starting material.

Analysis. Following photolysis or thermolysis the solution was cooled. For some experiments starting from **1a** the solution was extracted with ether and analysed by GC (comparison with authentic 4,4-dimethylpentanal **25a**). In other experiments (starting from **1a** or **1b**) the reaction mixture was poured into acidic 0.4% 2,4-dinitrophenylhydrazine solution[34] (50 cm^3) and stirred for 30 min. The DNP-derivative(s) was extracted into DCM (3 × 50 cm^3). The combined extracts were dried and evaporated to dryness to give a residue that was purified by column chromatography on silica (20 g, elution with 2:1 petrol–CH_2Cl_2). The yellow band of aldehyde-DNP **26a** was collected and the solvent was removed. The residue was taken up in spectroscopic grade ethanol and the absorbance of the solution was measured at 359.1 nm (ε 16 000 $dm^3\ mol^{-1}\ cm^{-1}$) to give the yield of the DNP. Starting from **1a**, the DNP was identified as 4,4-dimethylpentanal 2,4-dinitrophenylhydrazone **26a** by comparison (^{1}H NMR and TLC) with an authentic sample. Starting from **1b**, the DNP was identified as a mixture of [1,5-$^2H_2$]-4,4-dimethylpentanal 2,4-dinitrophenylhydrazone **26b** and 3,3-dimethylbutanal 2,4-dinitrophenylhydrazone **33** by comparison (^{1}H NMR and TLC) with authentic samples of **33** and the unlabelled compound **26a**.

Hydrolysis of the oxazolidinone-cobaloxime 2a and thermolysis of 2b

Oxazolidinone-cobaloxime **2a** (50 mg, 0.09 mmol) was taken up in aq. lithium hydroxide (1 M, 10 cm^3) and stirred in the dark for 7 days, after which time TLC showed the absence of **2a**. The pH of the solution was adjusted to either 3 or 9 with acetic acid (1 M), measured with a standardised pH meter, and the volume was made up to 50 cm^3 with water. The solution was degassed by bubbling with argon for 1 h and processed further in the manner described for **1a** and **1b**. The yield of *ketone hydrazone* **36** was calculated from the weight of the 2,4-dinitrophenylhydrazone produced after removal of solvent *in vacuo* (0.1 mmHg). The DNP was identified as 5,5-dimethylhexan-2-one 2,4-dinitrophenylhydrazone **36** by comparison (NMR and TLC) with an authentic sample.

The aqueous layer from preparation of 2,4-dinitrophenylhydrazone was basified to pH 14 and distilled. The distillate was made up to a known volume of water and aliquots were analysed for ammonia using the Nessler method,[35] by measuring the absorbance at 525 nm.

5-Bromo-4,4-dimethylpentan-1-ol 20

The borane-tetrahydrofuran complex was assayed prior to use by reaction with glycerol in a gas burette.

Hydroboration of 5-bromo-4,4-dimethylpent-1-ene **6a** (0.78 g, 4.5 mmol) in tetrahydrofuran (4 cm^3) was prepared in the manner of **13**.[30,31] The crude product was purified by column chromatography (petrol–ethyl acetate, 10:1 to 5:1) to give the *bromo alcohol* **20** (0.52 g, 62%) as a colourless oil (Found: C, 43.41; H, 7.94; $C_7H_{15}OBr$ requires C, 43.09; H, 7.75%); ν_{max} (film)/cm^{-1} 3550–3200, 2975, 1475, 1390, 1370, 1250 and 1060; δ_H (300 MHz; $CDCl_3$) 3.63 (2H, t, CH_2OH, *J* 6.4), 3.87 (2H, s, CH_2Br), 1.88 (1H, br s, OH), 1.44–1.54 (2H, m, CH_2), 1.33–1.41 (2H, m, CH_2), 0.99 (6H, s, CMe $_2$); δ_C (74.5 MHz; $CDCl_3$) 63.4 (CH_2OH), 46.5 (CH_2Br), 36.02 (CH_2), 34.4 (CH_2), 27.5 (*C*Me_2), 25.8 (Me_2); *m*/*z* (EI) 195/197 (MH^+), 177/179, 115, 97 (100).

5-Bromo-4,4-dimethylpentanal 21

5-Bromo-4,4-dimethylpentan-1-ol **20** (0.4 g, 2.0 mmol) was subjected to a pyridinium dichromate oxidation using the standard procedure.[34] Filtration of the residue through a bed of $MgSO_4$–silica (1:1) and removal of the solvent yielded the *bromo aldehyde* **21** (0.3 g, 75%) as a colourless oil; ν_{max} (film)/cm^{-1} 2970, 2740, 1730, 1390, 1370, 1255 and 655; δ_H (60 MHz; CCl_4) 9.90 (1H, t, CHO), 3.05 (2H, s, CH_2Br), 2.30–2.00 (2H, m, CH_2), 1.10–1.60 (2H, m, CH_2), 1.00 (6H, s, CMe_2); *m*/*z* (EI) 193 (35%, MH^+), 177 (10), 135 (50), 97 (50), 55 (100), 41 (100). The aldehyde was characterised more fully as the 2,4-dinitrophenylhydrazone.

5-Bromo-4,4-dimethylpentanal 2,4-dinitrophenylhydrazone 22

An acidic solution of 2,4-dinitrophenylhydrazine (0.4 M, 50 cm^3) was added to 5-bromo-4,4-dimethylpentanal **21** (20 mg, 0.1 mmol). After stirring at room temperature for 5 h the derivative was extracted into ethyl acetate (2 × 20 cm^3). The solvent was removed and the DNP derivative purified by column chromatography (petrol–ethyl acetate, 2:1) to give the *hydrazone* **22** as an orange crystalline solid (24 mg, 63%); ν_{max} (disc)/cm^{-1} 3600–3400, 3300, 2850, 1640, 1600, 1540, 1360, 1320, 1260 and 1140; δ_H (200 MHz; $CDCl_3$) 11.03 (1H, br s, NH), 9.10 (1H, d, Ph-H, *J* 2.6), 8.30 (1H, dd, Ph-H, *J* 2.6 and 9.6), 7.92 (1H, d, Ph-H, *J* 9.6), 7.56 (1H, t, CH, *J* 5.2), 3.32 (2H, s, CH_2), 1.09 (6H, s, CMe_2); δ_C (50 MHz; $CDCl_3$) 152.1, 145.2, 138.1, 130.1, 129.1 and 123.6 (Ph), 116.7 (CH), 45.7 (CH_2Br), 36.1 (CH_2), 34.6 (CH_2), 27.8 (*C*Me_2), 25.9 (C*Me*$_2$).

2-(4-Bromo-3,3-dimethylbutyl)-1,3-dioxolane 23

5-Bromo-4,4-dimethylpentanal **21** (0.9 g, 4.7 mmol), ethane-1,2-diol (1.2 cm^3, 18.6 mmol) and 2,6-di-*tert*-butyl-4-methylpyridinium tetrafluoroborate (2 mol%) were heated in refluxing benzene (12 cm^3) under a Dean–Stark trap for 24 h.

The reaction mixture was cooled and the benzene removed under reduced pressure. The residue was dissolved in water (50 cm^3) and extracted with ether (2 × 25 cm^3). The ether layer was washed with water (25 cm^3), dried ($MgSO_4$) and the solvent removed. The residue was purified by column chromatography (petrol–ethyl acetate, 10:1) to give the *bromo acetal* **23** (0.8 g, 75%) as a colourless oil (Found: C, 45.98; H, 7.26; $C_9H_{17}O_2Br$ requires C, 45.75; H, 7.25%); ν_{max} (film)/cm^{-1} 2965, 2880, 1470, 1410, 1390, 1370, 1230, 1140, 1050 and 1030; δ_H (300 MHz; $CDCl_3$) 4.77 (1H, t, CH, *J* 4.6), 3.90 and 3.79 (4H, 2 m, OCH_2-CH_2O), 3.22 (2H, s, CH_2Br), 1.52–1.57 (2H, m, CH_2), 1.37–1.43 (2H, m, CH_2), 0.95 (6H, s, CMe_2); δ_C (75.5 Hz; $CDCl_3$) 104.7 (CH), 64.9 (CH_2O), 46.2 (CH_2Br), 34.1 (CH_2), 33.8 (CH_2), 27.8 (*C*Me_2), 25.6 (*CMe*$_2$); *m*/*z* (EI) 235.0342 ($M - H^+$, $C_9H_{16}O_2{}^{79}Br$ requires 235.0334) 235/237, 209/211, 135/137, 73 (100%).

2-(3,3-Dimethylbutyl)-1,3-dioxolane 24

2-(4-Bromo-3,3-dimethylbutyl)-1,3-dioxolane **23** (0.1 g, 0.4 mmol), triphenyltin hydride (0.2 cm^3, 0.8 mmol) and a trace of AIBN were dissolved in d_6-benzene (0.3 cm^3) and sealed in an NMR tube under nitrogen. The tube was placed in a water bath at 45 °C and the reaction monitored by the disappearance

of the CH_2Br resonance at 3.20 ppm in the ^1H NMR spectrum (60 MHz).

After $5\frac{1}{2}$ h the reaction mixture was poured into water (10 cm^3) and the product extracted into petrol (2 × 5 cm^3). The residue was purified by column chromatography (petrol–ethyl acetate, 10:1) to give the *acetal* **24** (45 mg, 67%) as a colourless oil; ν_{max} (film)/cm^{-1} 2957, 2868, 1475, 1394, 1365, 1298, 1209, 1047 and 988; δ_H (300 MHz; $CDCl_3$) 4.74 (1H, t, CH, *J* 4.8), 3.85–3.93 (2H, m, CH_2O), 3.76–3.80 (2H, m, CH_2O), 1.53–1.60 (2H, m, CH_2), 1.21–1.26 (2H, m, CH_2), 0.82 (9H, s, CMe_3); δ_C (75.5 MHz; $CDCl_3$) 105.5 (CH), 65.0 (CH_2O), 38.0 (CH_2), 30.1 (CH_2), 29.4 (CMe_3), 29.3 (CMe_3); *m*/*z* (EI) 159 ($M\text{-}H^+$), 115, 97, 73, 59 (100%).

4,4-Dimethylpentanal 25a

2-(3,3-Dimethylbutyl)-1,3-dioxolane **24** (0.1 g, 0.6 mmol) was dissolved in aq. THF (0.4 cm^3 THF, 0.6 cm^3 H_2O) and Dowex 50W ion-exchange resin added. The mixture was stirred at room temperature for 24 h.

TLC indicated the absence of starting material and the formation of a DNP positive product. The reaction mixture was extracted with ether (2 × 1 cm^3) and the ether removed by careful distillation through a Vigreux column, followed by distillation of the product. GC analysis of the distillate and residue indicated a clean formation of 4,4-dimethylpentanal. The aldehyde was further characterised by the preparation of the 2,4-dinitrophenylhydrazone **26a** in the manner of **22**; δ_H (200 MHz; $CDCl_3$) 11.01 (1H, br s, NH), 9.14 (1H, d, Ph-H, *J* 2.6), 8.30 (1H, dd, Ph-H, *J* 2.6 and 9.6), 7.96 (1H, d, Ph-H, *J* 9.6), 7.57 (1H, t, CH, *J* 5.2), 2.40–2.50 (2H, m, CH_2), 1.40–1.50 (2H, m, CH_2), 0.96 (9H, s, CMe_3); *m*/*z* (EI) 294.1315 (M^+, $C_{13}H_{18}N_4O_4$ requires 294.1328), 278, 180 (100%).

4-(2,2-Dimethylpropyl)-2,2-dimethyl-1,3-dioxolane 27

Under a nitrogen atmosphere, tributyltin hydride (1.2 cm^3, 4.5 mmol) was added to a solution of 4-(3-bromo-2,2-dimethylpropyl)-2,2-dimethyl-1,3-dioxolane (0.51 g, 2.0 mmol) in benzene (5 cm^3) and the solution was heated at reflux for 20 h. The solvent was removed and the reaction mixture was distilled under reduced pressure to yield *acetal* **27** as a colourless oil (0.28 g, 81%); ν_{max} (film)/cm^{-1} 2870–2986 s, 1157 and 1067; δ_H (300 MHz; $CDCl_3$) 4.15 (1H, m, CH), 4.04 (1H, dd, CH_2O, *J* 7.8 and 5.7), 3.42 (1H, t, CH_2O, *J* 7.8 and 7.8), 1.65 (1H, dd, CH_2, *J* 14.0 and 5.9), 1.40 (1H, dd, CH_2, *J* 14.0 and 8.1), 1.39 (3H, s, Me), 1.36 (3H, s, Me), 0.94 (9H, s, CMe_3); δ_C (50 MHz; $CDCl_3$) 108.2 (CMe_2), 73.9 (CH), 70.9 (CH_2O), 47.4 (CH_2), 30.1 (CMe_2), 30.0 (Me_3), 27.1 (Me), 26.1 (Me); *m*/*z* (EI) 173 (MH^+), 158, 157, 142.

4,4-Dimethylpentane-1,2-diol 28[36]

A solution of 4-(2,2-dimethylpropyl)-2,2-dimethyl-1,3-dioxolane (0.17 g, 1.0 mol) in methanol (10 cm^3) and acetyl chloride (0.35 cm^3) was protected from moisture and heated at reflux for 4 h. The extent of reaction was followed by TLC. Removal of the solvent yielded sufficiently pure diol **28** (0.12 g, 90%). A small amount was distilled for analysis using a Kugelrohr distillation apparatus; bp 90 °C at 0.4 mmHg (lit.[37] bp 83–86 °C at 0.1 mmHg); ν_{max} (film)/cm^{-1} 3360 br, 2870–2950, 1160 and 1089; δ_H (200 MHz; $CDCl_3$) 3.84 (1H, br m, C*H*OH), 3.54 (1H, br m, CH_2OH), 3.40 (1H, br m, CH'_2OH), 1.32 (2H, br m, CH_2), 0.96 (9H, s, Me_3); δ_C (50 MHz; $CDCl_3$) 70.1 (CHOH), 68.1 (CH_2OH), 46.9 (CH_2), 30.1 (CMe_3), 30.1 (Me_3); *m*/*z* (EI) 265 (M_2H^+), 133, 115, 101, 57 (100%).

3,3-Dimethylbutanal 32[37]

3,3-Dimethylbutan-1-ol was subjected to a pyridinium dichromate oxidation using the standard procedure[34] to give the aldehyde **32** which was converted into its 2,4-dinitrophenylhydrazone **33** in the manner of **22** for spectroscopic identification;[37] δ_H (200 MHz; $CDCl_3$) 11.30 (*cis*) and 11.08 (*trans*) (1H, br s, NH), 9.15 (1H, d, Ph-H, *J* 2.7), 8.32 (1H, dd, Ph-H, *J* 2.3 and 9.5), 7.98 (*cis*) and 7.96 (*trans*) (1H, d, Ph-H, *J* 9.5), 7.59 (*trans*, *J* 6.29) and 7.09 (*cis*, *J* 5.89) (1H, t, CH), 2.34 (*trans*, *J* 6.27) and 2.29 (*cis*, *J* 5.98) (2H, d, CH_2), 1.12 (*cis*) and 1.05 (*trans*) (9H, s, Me_3).

5,5-Dimethylhexan-2-one 35[38]

Grignard coupling[38,39] of *tert*-butyl chloride (23.5 g, 0.3 mmol) to methyl vinyl ketone (7.0 g, 0.1 mol) in ether (40 cm^3), followed by fractional distillation through a short Vigreux column at 35 mmHg gave the ketone **35** (1.8 g, 14%); bp 69 °C (35 mmHg) (lit.[38] 71–72 °C at 35 mmHg); ν_{max} (film)/cm^{-1} 2957, 2868, 1718 and 1365; δ_H (200 MHz; $CDCl_3$) 2.34 (2H, t, CH_2CO, *J* 8.1), 2.10 (3H, s, Me), 1.42 (2H, t, Me_3CH_2 *J* 8.1), 0.83 (9H, s, Me_3); δ_C (50 MHz; $CDCl_3$) 209 (C=O), 39.5 (CH_2CO), 37.4 (Me), 29.9 (Me_3CH_2), 29.1 (Me_3); *m*/*z* (EI) 128.1199 (M^+, $C_8H_{16}O$ requires 128.1201), 128 (18%).

The corresponding hydrazone **36**[37] was synthesised from **35** in the manner of **22**; ν_{max} (disc)/cm^{-1} 3323, 3109, 2957, 2866, 2108, 1628, 1506 and 1336; δ_H (200 MHz; $CDCl_3$) 11.2 (*trans*) and 11.0 (*cis*) (1H, br s, NH), 9.12 (1H, d, Ph-H, *J* 2.6), 8.27 (1H, dd, Ph-H, *J* 2.2 and 9.6), 7.95 (1H, d, Ph-H, *J* 9.6), 7.48 (*trans*) and 6.91 (*cis*) (1H, t, CH, *J* 5.37), 2.31–2.42 (2H, m, CH_2CN), 2.13 (*cis*) and 2.05 (*trans*) (3H, s, Me), 1.40–1.45 (2H, m, Me_3CH_2), 0.99 (*cis*) and 0.95 (*trans*) (9H, s, Me_3); *m*/*z* (EI) 308.1489 (M^+, $C_{14}H_{20}N_4O_4$ requires 308.1484), 380 (26%, M^+) 251 (35), 237 (5).

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References

1 (*a*) R. H. Abeles, A. M. Brownstein and C. H. Randles, *Biochem. Biophys. Acta*, 1960, **41**, 531; (*b*) T. Tobimatsu, T. Sakai, Y. Hashida, N. Mizoguchi, S. Miyoshi and T. Toraya, *Arch. Biochem. Biophys.*, 1997, **347**, 132; (*c*) T. A. Bobik, Y. Xu, R. M. Jeter, K. E. Otto and J. R. Roth, *J. Bacteriol.*, 1997, **179**, 6633; (*d*) T. Toraya, in *Chemistry & Biochemistry of B_{12}*, ed. R. Banerjee, Wiley-Interscience, New York, 1999, ch. 31, p. 783; (*e*) T. Toraya, *Cell. Mol. Life Sci.*, 2000, **57**, 106.

2 (*a*) T. Tobimatsu, M. Azuma, H. Matsubara, H. Takatori, T. Niida, K. Nishimoto, H. Satoh, R. Hayashi and T. Toraya, *J. Biol. Chem.*, 1996, **271**, 22352; (*b*) L. Macis, R. Daniel and G. Gottschalk, *FEMS Microbiol. Lett.*, 1998, **164**, 21.

3 (*a*) B. M. Babior, in *B_{12}*, ed. D. Dolphin, Wiley, New York, 1982, vol. 2, p. 263; (*b*) V. Bandarian and G. H. Reed, in *Chemistry & Biochemistry of B_{12}*, ed. R. Banerjee, Wiley-Interscience, New York, 1999, ch. 32, p. 811.

4 B. M. Babior, *BioFactors*, 1988, **1**, 21.

5 B. T. Golding and W. Buckel, in *Comprehensive Biological Catalysis*, ed. M. L. Sinnott, Academic Press, New York, 1998, ch. 33, p 239.

6 R. Banerjee, *Chem. Biol.*, 1997, **4**, 175.

7 (*a*) R. G. Finke, D. A. Schiraldi and B. J. Mayer, *Coord. Chem. Rev.*, 1984, **54**, 1; (*b*) R. G. Finke, in *Molecular Mechanisms in Bioorganic Processes*, eds. C. Bleasdale and B. T. Golding, Royal Society of Chemistry, 1990, 281.

8 B. T. Golding, in *B_{12}*, ed. D. Dolphin, Wiley-Interscience, New York, 1982, ch. 15, 543.

9 G. Gerfen, in *Chemistry & Biochemistry of B_{12}*, ed. R. Banerjee, Wiley-Interscience, New York, 1999, ch. 31, p. 783.

10 S. A. Cockle, H. A. O. Hill, R. J. P. Williams, S. P. Davies and M. A. Foster, *J. Am. Chem. Soc.*, 1972, **94**, 275.

11 (*a*) B. T. Golding, T. J. Kemp, E. Nocchi and W. P. Watson, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 813; (*b*) B. T. Golding, C. S. Sell and P. J. Sellars, *J. Chem. Soc., Chem. Commun.*, 1976, 773; (*c*) B. T. Golding, T. J. Kemp, C. S. Sell, P. J. Sellars and W. P. Watson, *J. Chem. Soc., Perkin Trans. 2*, 1978, 839; (*d*) B. T. Golding, C. S. Sell and P. J. Sellars, *J. Chem. Soc., Perkin Trans. 2*, 1980, 961; (*e*) R. M. Dixon, B. T. Golding, S. Mwesigye-Kibende and D. N. Ramakrishna Rao, *Philos. Trans. R. Soc. London, Ser. A*, 1985, **311**,

531; (*f*) R. J. Anderson, S. Ashwell, R. M. Dixon and B. T. Golding, *J. Chem. Soc.*, *Chem. Commun.*, 1990, 70; (*g*) B. T. Golding, R. J. Anderson, S. Ashwell, C. H. Edwards, I. Garnett, F. Kroll and W. Buckel, *Proceedings of the 4th European Symposium on Vitamin B_{12}*, eds. B. Kräutler, D Arigoni and B. T. Golding, Verlag Chemie, Innsbruck, 1998, p. 201.
12 P. Müller and J. Rétey, *J. Chem. Soc.*, *Chem. Commun.*, 1983, 1342.
13 B. T. Golding and L. Radom, *J. Am. Chem. Soc.*, 1976, **98**, 6331.
14 D. M. Smith, B. T. Golding and L. Radom, *J. Am. Chem. Soc.*, 1999, **121**, 5700.
15 N. Shibata, J. Masuda, T. Tobimatsu, T. Toraya, K. Suto, Y. Morimoto and N. Yasuoka, *Structure*, 1999, **7**, 997.
16 T. Toraya and S. Fukui, in B_{12}, ed. D. Dolphin, Wiley, New York, 1982, vol. 2, 233.
17 (*a*) J. Halpern, *Ann. N.Y. Acad. Sci*, 1974, **239**, 2; (*b*) B. T. Golding and L. Radom, *J. Chem. Soc.*, *Chem. Commun.*, 1973, 939.
18 C. J. Suckling, D. Arigoni and B. M. Babior, *J. Biol. Chem.*, 1974, **249**, 6359.
19 R. D. Scheutz and F. W. Millard, *J. Org. Chem.*, 1959, **24**, 297.
20 R. E. Ireland, R. H. Mueller and A. K. Willard, *J. Am. Chem. Soc.*, 1976, **98**, 2866.
21 (*a*) B. T. Golding, T. J. Kemp, P. J. Sellars and E. Nocchi, *J. Chem. Soc.*, *Dalton Trans.*, 1977, 1266; (*b*) B. T. Golding, T. J. Kemp and H. H. Sheena, *J. Chem. Res. (M)*, 1981, 334.
22 (*a*) J. H. Grate and G. N. Schrauzer, *J. Am. Chem. Soc.*, 1979, **101**, 4601; (*b*) J. M. Pratt, in B_{12}, ed. D. Dolphin, Wiley, New York, 1982, vol. 1, ch. 10, p. 325.
23 (*a*) A. P. Henderson, J. Riseborough, C. Bleasdale, W. Clegg, M. R. J. Elsegood and B. T. Golding, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 3407; (*b*) B. T. Golding, A. Mitchinson, W. Clegg, M. R. J. Elsegood and R. J. Griffin, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 349.
24 K. C. Brannock, *J. Am. Chem. Soc.*, 1959, **81**, 3379.
25 (*a*) E. A. Hill, D. C. Link and P. Donndelinger, *J. Org. Chem.*, 1981, **46**, 1177; (*b*) A. L. J. Beckwith, C. J. Easton, T. Lawrence and A. K. Serelis, *Aust. J. Chem.*, 1983, **36**, 545.
26 J. Hooz and S. S. H. Gilani, *Can. J. Chem.*, 1968, **46**, 86.
27 R. T. Arnold and S. T. Kulenovic, *J. Org. Chem.*, 1978, **43**, 3087.
28 (*a*) H. J. Günther, E. Guntrum and V. Jäger, *Liebigs Ann. Chem.*, 1984, 15; (*b*) M. Kawashima, T. Sato and T. Fujisawa, *Tetrahedron*, 1989, **45**, 403; (*c*) S. A. Glover and A. L. J. Beckwith, *Aust. J. Chem.*, 1987, **40**, 701.
29 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.
30 M. Negishi and H. C. Brown, *Synthesis*, 1974, 77.
31 G. Zweifel, N. R. Ayyanger and H. C. Brown, *J. Am. Chem. Soc.*, 1963, **85**, 2072.
32 K. Omura and D. Swern, *Tetrahedron*, 1978, **34**, 1651; A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
33 R. H. Wollenberg and S. J. Miller, *Tetrahedron Lett.*, 1978, **19**, 3219.
34 E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.
35 A. Vogel, in *Quantitative Organic Synthesis*, 4th edn., Longman, New York, 1978, 730.
36 R. S. Edmundson and C. I. Forth, *Phosphorus Sulfur*, 1980, **8**, 315.
37 F. C. Whitmore and A. H. Homeyer, *J. Am. Chem. Soc.*, 1933, **55**, 4555.
38 E. H. Man, F. C. Frostick, Jnr. and C. R. Hauser, *J. Am. Chem. Soc.*, 1952, **74**, 3228.
39 K. V. Baker, J. M. Brown, N. Hughes, A. J. Skarnulis and A. Sexton, *J. Org. Chem.*, 1991, **56**, 698.