Tetrahedron Vol. 48, No. 42, pp. 9373-9384, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

AN INTRAMOLECULAR COBALT CYCLISATION FOR THE CONSTRUCTION OF SUBSTITUTED PYRROLIDINES.

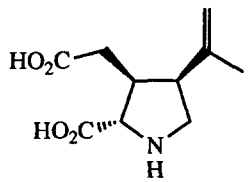
Jack E. Baldwin*, Mark G. Moloney and Andrew F. Parsons.

The Dyson Perrins Laboratory, University of Oxford,
South Parks Road, Oxford. OX1 3QY.U.K.

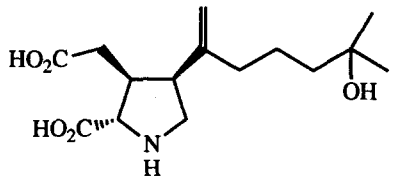
(*Received in UK* 29 *July* 1992)

Abstract: *Cobalt mediated cyclisations of a radical onto a substituted allylamine can be used to generate highly functionalised pyrrolidines. The facility of the ring closure depends on the nature of substituents on the alkene moeity. Dehydrocobaltation of the initially formed organocobalt(III) species is a competing reaction.*

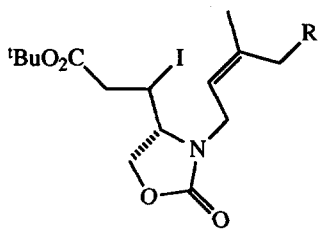
The application of cobalt-mediated radical carbon-to-carbon bond forming reactions has attracted considerable attention.[1] They are distinguished from most other radical-based methods (for example, those which use Bu_3SnH or R_3SiH[2]) in that, although they proceed via the intermediacy of radicals, the precursor radical is generated by the homolysis of a cobalt(III)-carbon bond, and the product radical is trapped by the resulting cobalt(II) species, to generate another organocobalt(III) species. This organometallic intermediate is able to undergo further transformations. Examples include dehydrocobaltation to generate an alkene, or interception with an added radical trapping agent, such as dioxygen, TEMPO or diphenyl diselenide.[1] Significantly, these organocobalt species provide access to unsaturated or more highly functionalised products, rather than simply the fully reduced ones, as for tributyltin hydride mediated radical reactions.



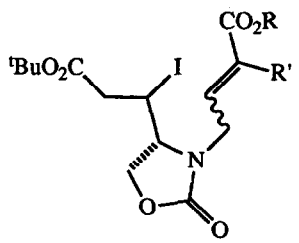
(1)



(2)



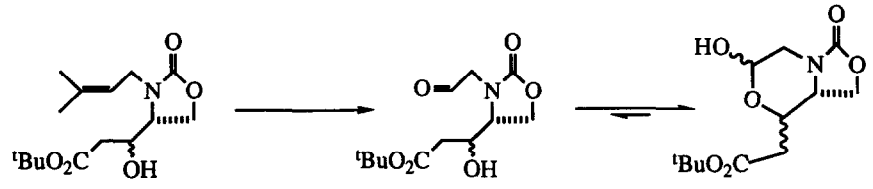
(3a) R =H
(3b) R = $(CH_2)_2CH{=}CMe_2$



(4)

Recently, we reported the synthesis of kainic acid (1) and a kainoid analogue (2), using a cobalt-mediated radical ring closure of iodides (3a) and (3b) respectively, as the key ring closure step.[3] It was observed that, in addition to the desired pyrrolidine ring formation in 36-44% yield, the reaction of (3a) and (3b) with cobaloxime(I) led to significant amounts (typically 26-31%) of non-ring closed by-products. These by-products resulted from either elimination of the starting iodide [under the basic conditions required to generate cobalt(I)], or more likely via dehydrocobaltation of the initially formed organocobaloxime(III) species. In an attempt to increase the efficiency of the cyclisation, we decided to investigate the use of electron deficient alkenes as radical acceptors, by preparing precursor iodides of type (4). This was prompted by our previous favourable experience in the synthesis of acromelic acid A.[4] Also recent work has shown that alkyl cobalt-mediated cyclisations occur *via* free radicals[5] and that free radical cyclisations are improved by matching radical philicity to the acceptor alkene.[6]

In an attempt to prepare substrates of type (4), the unsaturated oxazolidinone (5), prepared as previously described,[3] was oxidatively cleaved using osmium tetroxide/sodium periodate, to give aldehyde (6). From the proton n.m.r. spectrum, it was evident that this aldehyde (6) existed in equilibrium in which the lactol (7) was the predominant component. Homologation of this aldehyde(6)/lactol(7) mixture was attempted using a range of Wittig reagents (Table 1). The required phosphoranes were prepared from the bromide and carbethoxymethylene triphenylphosphorane (2 equiv.), using the Bestmann transylidation reaction.[7] The phosphorane (8) gave no reaction with the aldehyde(6)/lactol(7) mixture but ylides (9), (10) and (11)[8] gave very clean reactions, giving yields of 49, 54 and 78% respectively of the desired alkenes (12-14, X=OH), as a mixture of carbon-carbon double bond isomers (Table 1). The use of longer reaction times, and of tetrahydrofuran rather than dichloromethane as the solvent, did not significantly affect the yields.

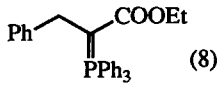
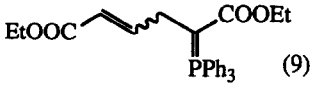
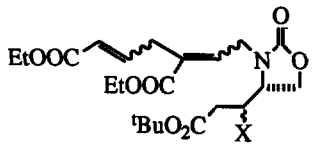
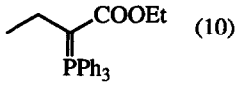
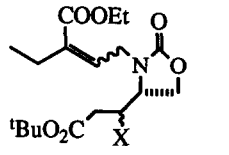
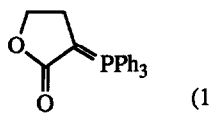
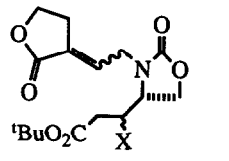


(5) (6) (7)

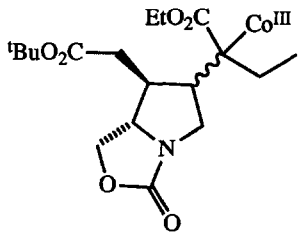
The alcohols (12-14, X=OH) were then converted to iodides (12-14, X=I) via the triflate in 63-74% yield (Table 2). On reaction of iodide (13, X=I) with cobaloxime(I) [generated from chlorocobaloxime(III) and sodium borohydride in methanol at 0°C using 0.8 equivalents of sodium hydroxide[9] for each equivalent of the iodide], an inseparable mixture of (Z) and (E) alkenes (15) was obtained in 69% yield. This represents a significantly more efficient ring closure compared to compounds of type (3). In addition, variable amounts of the α,β-unsaturated ester (16) were isolated (0-4%). The ratio of the two alkene double bond regioisomers (15) was approximately 1:1, as shown by ^1H n.m.r. spectroscopy, in contrast to the fact that earlier reports[10] suggested that a predominance of the *trans*- isomer would be expected on dehydrocobaltation. Each of the two double bond isomers was epimeric at C-4, with a similar diastereoselectivity[11] to that found in earlier investigations for substrates possessing an oxazolidinone ring.[3] The formation of the epimeric double bond isomers was thought to

involve the intermediacy of an organocobaloxime(III) species (17) which presumably undergoes dehydrocobaltation to form an equal mixture of the *cis*- and *trans*- double bond isomers. No dehydrocobaltation towards the tertiary centre to give the exocyclic product was evident from the n.m.r. spectra.

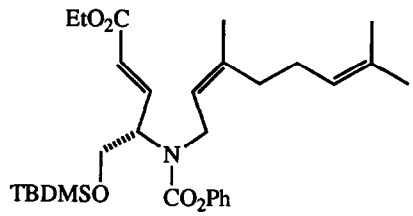
Table 1: Reaction of Various Wittig Reagents with Aldehyde (6):Lactol (7)

Wittig Reagent	Method	Product, [Yield%]
 (8)	A	(-)
 (9)	B	 (12, X=OH) [49%]
 (10)	C	 (13, X=OH) [54%]
 (11)	C	 (14, X = OH) [78%]

METHODS: A, THF, reflux, 12h; B, THF, reflux, 36h; C; CH_2Cl_2, reflux, 24h



(17)



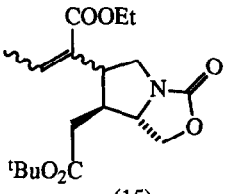
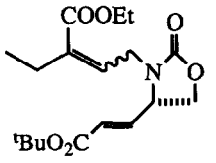
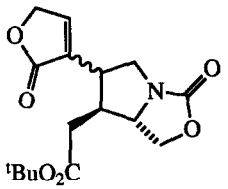
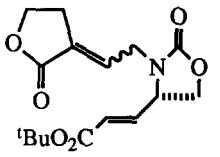
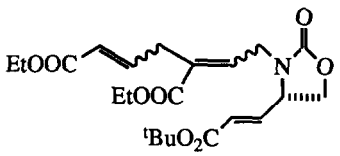
(21)

On reaction of iodide (14, X=I) with cobaloxime(I) under the same conditions, an inseparable mixture of pyrrolidine (18) and α,β-unsaturated oxazolidinone (19), in the ratio 17:1 in 71% overall yield was obtained.[12] However, under the conditions which had previously been described[13] (to minimise reduction of the cyclised α,β-unsaturated products) only direct elimination occurred to form the α,β-unsaturated ester (19). This ester (19) is

unreactive towards Michael addition of Co(I), which would generate the same organocobalt(III) intermediate as that derived from iodide (14, X=I), and which could lead to pyrrolidine ring formation.[14] Indeed it was found that the reaction of cobalt(I) (generated under alkaline or neutral conditions[15]) with similar α,β-unsaturated esters such as (21), did not occur, and this presumably is a result of steric hindrance at the β-position.

In contrast to iodides (13) and (14), iodide (12, X=I) gave only the direct elimination product (20) on reaction with cobalt(I) and no conditions could be found to obtain any of the desired cyclised product. This could be the result of a more sterically demanding side chain which slows the rate of cyclisation relative to the rate of elimination.

Table 2: Cobalt Mediated Reactions of Substrates

Substrate Alcohol	Iodide, % Yield	Products From Cobalt(I) Reaction
(13, X=OH)	(13, X=I), 74%	 (15)  (16)
(14, X=OH)	(14, X=I), 63%	 (18)  (19)
(12, X=OH)	(12, X=I), 65%	 (20)

This work has further demonstrated the importance of matching radical philicity to the acceptor alkene for high yielding cobalt-mediated oxidative cyclisations. As in reported tin-mediated cyclisations, efficient ring closure of the nucleophilic radical was observed when electron withdrawing substituents were present on the double bond. This has an important bearing on the efficient construction of the pyrrolidine ring by cobalt cyclisation, in for example, kainoid synthesis.

Experimental.

General

Melting points were determined with a Büchi 510 capillary apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter with a path-length of 10cm; concentrations are given in g/100cm^3. Infrared spectra were recorded on either a Perkin-Elmer 781 spectrophotometer or a Perkin-Elmer 1750 IR FT spectrometer; only selected resonances are reported and are reported as strong (s), medium (m), weak (w) or broad (br). ^{1}H n.m.r. spectra were recorded at 200MHz on a Varian Gemini 200 spectrometer, at 300 MHz on a Bruker WH 300 spectrometer and at 500MHz on a Bruker AM 500 spectrometer. Chemical shifts are quoted on the scale using residual solvent as an internal standard. Multiplicities are reported as broad (br), singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). ^{13}C n.m.r. spectra were recorded at 50MHz on a Varian Gemini 200 spectrometer or at 125MHz on a Bruker AM 500 spectrometer. Mass spectra were recorded on either a VG Micromass ZAB IF or a VG Mass lab 20-250 spectrometer using ammonia desorption chemical ionisation (DCI). Microanalyses were performed by the microanalytical service of the Dyson Perrins Laboratory. T.l.c. was performed on aluminium plates coated with Merck silica gel 60F$_{254}$. Compounds were visualised with iodine or a solution of dodeca-Molybdophosphoric acid in ethanol. Flash column chromatography was carried out using Sorbsil C60 40/60 flash silica gel. All solvents were distilled before use, following standard literature procedures.[16]

(4*R*)-3-(Oxoethyl)-4-[2-(*tert*-butyloxycarbonyl)-1-(hydroxy)ethyl]-2-oxazolidinone (6) : Lactol (7).

A mixture of alcohol (5) (0.5g, 1.67mmol) and osmium tetroxide (catalytic) in dioxane:water (2:1, 15ml) was stirred while sodium periodate (0.79g, 3.67mmol) was added portionwise over 0.5h. The mixture was then stirred at r.t. overnight, after which water and ethyl acetate was added. The organic layer was separated and the aqueous phase was extracted further (three times). The combined organic extracts were dried($MgSO_4$) and evaporated *in vacuo*. Chromatography of the residue on silica (ethyl acetate) afforded aldehyde (6):lactol (7) (0.38g, 83%) as a white waxy solid (in the ratio *c.a.* 1:3.8); Rf 0.36 (ethyl acetate); m.p. 126-136°C ; $[\alpha]_D^{20}$ +3.8° (c 0.53, $CHCl_3$); (Found: C, 52.23; H, 7.42; N 5.07. $C_{12}H_{19}NO_6$ requires C, 52.74; H, 7.01; N, 5.13%); υ_{max}($CHCl_3$) 3550-3250 (br, m), 3060-2960 (m), 1770-1680 (vs), 1475 (m), 1450-1400 (m), 1390 (w), 1370 (m), 1310 (w), 1260-1200 (m), 1155 (s), 1110 (m), 1075 (m), 1050 (m), 950 (w) and 840 (w) cm^{-1}. δ_H (300MHz; $CDCl_3$) 4.84-4.75 (1H, m, C<u>H</u>OH), 4.42-3.17 (6H, m, N-C<u>H</u>$_2$, N-CO$_2$C<u>H</u>$_2$, N-C<u>H</u> and O-C<u>H</u>), 2.45-2.15 (2H, m, C<u>H</u>$_2$CO$_2$), 1.97 (1H, br s, exchangeable , CHO<u>H</u>) and 1.44 (9H, s, CO$_2$C(C<u>H</u>$_3$)$_3$); δ_C (125MHz; $CDCl_3$) 170.5, 170.1 (<u>C</u>O$_2$C(CH$_3$)$_3$), 160.7, 159.7 (N-<u>C</u>O$_2$), 95.5, 95.3 (<u>C</u>H-OH), 81.8, 81.7 (CO$_2$<u>C</u>(CH$_3$)$_3$), 65.0, 64.5, 63.0, 62.6, 60.9, 60.5 (<u>C</u>H$_2$OCO, <u>C</u>H-NCO$_2$ and <u>C</u>HOCH), 47.7, 47.6 (N-<u>C</u>H$_2$), 37.5, 37.4 (<u>C</u>H$_2$CO$_2$) and 28.0 (CO$_2$C(<u>C</u>H$_3$)$_3$); m/z (DCI, NH_3) 291 ($M+NH_4^+$, 8%), 274 ($M+H^+$, 4), 235 (84), 218 (98), 200 (34) and 174 (100). The presence of the aldehyde was indicated from the ^{1}H n.m.r. spectrum [δ 9.62 (s, CH$_2$C<u>H</u>O)] and ^{13}C n.m.r. spectrum [δ 201.5 (CH$_2$<u>C</u>HO)].

Ethyl-(3-phenyl-2-triphenylphosphoranylidene)propionate (8).

To a boiling solution of (carbethoxymethylene)triphenylphosphorane (3.06g, 8.8mmol) in ethyl acetate (25ml) was added benzyl bromide (0.75g, 4.4mmol) while stirring. After refluxing for 3h, the solution was cooled to r.t. and the phosphonium bromide salt removed by filtration. The filtrate was then concentrated *in vacuo* to afford crude product. Recrystallisation (ethyl acetate) afforded phosphorane (8) (1.43g, 74%) as a pale yellow-white product which was contaminated with starting material; υ_{max} ($CHCl_3$) 3080-2950 (m), 1775-1690 (m), 1600 (s), 1480 (w), 1435 (m), 1370 (m), 1310 (m), 1250-1200 (m), 1155-1130 (m), 1100 (s) and 1085 (m) cm^{-1}; δ_H (200MHz; $CDCl_3$) 7.75-7.34 (15H, m, aromatics), 7.13-6.93 (5H, m, aromatics), 3.97 (2H, q, *J* 6.3 Hz, $CO_2C\underline{H}_2CH_3$), 3.40 (2H, d, *J* 17.0 Hz, $C\underline{H}_2$-C=P) and 1.05 (3H, t, *J* 6.3 Hz, $CO_2CH_2C\underline{H}_3$).

Reaction of Phosphorane (8) with Aldehyde (6) : Lactol (7).

A mixture of aldehyde (6):lactol (7) (0.18g, 0.7mmol) and phosphorane (8) (0.58g, 1.3mmol) in tetrahydrofuran (20ml) was refluxed under a nitrogen atmosphere for 12h. After cooling to r.t., the solvent was removed *in vacuo* to afford crude product. Column chromatography on silica (ethyl acetate) afforded a white crystalline compound (0.27g) [Rf 0.42 (ethyl acetate)] which from the ^1H n.m.r. and mass spectra indicated no alkene formation.

Ethyl-(2-triphenylphosphoranylidene)-5-(ethoxycarbonyl)-pent-4-enoate (9).

A mixture of ethyl bromocrotonate (1.0g, 5.2mmol) and (carbethoxymethylene)-triphenylphosphorane (3.03g, 8.7mmol) in ethyl acetate (30ml) was refluxed under a nitrogen atmosphere for 3h. After cooling, the resultant phosphonium salt was filtered off. The filtrate was then evaporated *in vacuo*. Diethyl ether (50ml) was then added to the oily residue and the mixture was stirred for 0.25h. The precipitate which resulted was then removed by filtration and the filtrate was evaporated *in vacuo* to afford crude phosphorane (9) (2.2g, 92%) as a red-brown oily residue which was used without further purification. δ_H (200MHz; $CDCl_3$) 7.68-7.39 (15H, m, aromatics), 6.95-6.80 (1H, m, O_2C-CH=C$\underline{H}$), 5.33 (1H, d, *J* 14 Hz, O_2C-C$\underline{H}$=CH), 4.13 (4H, q, *J* 7 Hz, 2 x $CO_2C\underline{H}_2CH_3$), 2.82 (2H, dd, *J* 16 and 6 Hz, =C-C$\underline{H}_2$-C) and 1.26 (6H, t, *J* 8 Hz, 2 x $CO_2CH_2C\underline{H}_3$); m/z (DCI, NH_3) 461 ($M+H^+$, 55%), 415 (14), 279 (79) and 262 (100).

(4*R*)-3-[3,6-(Diethoxycarbonyl)-hexa-2,5-dienyl]-4-[2-(*tert*-butyloxycarbonyl)-1-(hydroxy)ethyl]-2-oxazolidinone (12, X=OH).

A mixture of the aldehyde (6):lactol (7) (0.47g, 1.7mmol) and crude ylide (9) (2.1g, 4.6mmol) was refluxed in tetrahydrofuran (30ml) under a nitrogen atmosphere for 36h. The solvent was then removed *in vacuo* affording crude product. Column chromatography on silica (ethyl acetate-hexane, 2.3:1) afforded alcohol (12) (0.38g, 49%) as a pale brown oil as a mixture of isomers; Rf 0.41 (ethyl acetate-hexane, 2.3:1); υ_{max} (thin film) 3650-3200 (br, m), 3040-2850 (m), 1723 (vs), 1654 (m), 1478 (m), 1445 (m), 1394 (m), 1369 (s), 1276 (s), 1159 (s), 1097 (m), 1041 (m), 987 (w), 955 (w), 845 (w) and 763 (m) cm^{-1}; δ_H (200MHz; $CDCl_3$) 6.97-6.80 (2H, m, 2 x C=C$\underline{H}$-CH_2), 6.01 and 5.81 (1H, 2 x d, *J* 15.8 and 15.6 Hz, O_2C-C$\underline{H}$=C), 4.35-3.77 (10H, m, =C-$C\underline{H}_2$-N, $C\underline{H}_2OCO$, N-C$\underline{H}$, C$\underline{H}$-OH and 2 x $CO_2C\underline{H}_2CH_3$), 3.57 and 3.48 (1H, 2 x br s, =CH-C$\underline{H}$-C=), 3.33 (1H, d, *J* 6.3 Hz, =CH-C$\underline{H}$-C=), 2.37-2.32 (2H, m, $C\underline{H}_2CO_2$), 1.48 (9H, s, $CO_2C(C\underline{H}_3)_3$) and 1.35-1.23 (6H, m, 2 x $CO_2CH_2C\underline{H}_3$); δ_C (125MHz; $CDCl_3$) 171.2, 171.1 ($\underline{C}O_2$), 166.3, 166.1 ($\underline{C}O_2$), 158.1 (N-$\underline{C}O_2$), 144.7,

141.2, 137.5, 132.0, 124.0, 122.4 (HC=C and C=C), 82.3 ($CO_2C(CH_3)_3$), 67.0, 66.3, 62.8, 62.7, 61.2, 60.3, 58.1, 58.0 ($CO_2CH_2CH_3$, CH_2OCON, N-CH and CHOH), 43.5, 40.9, 37.1, 36.7 (CH_2CO_2, =C-CH_2-N and =C-CH_2-C=), 28.0 ($CO_2C(CH_3)_3$) and 14.2 (2 x $CO_2CH_2CH_3$); m/z (DCI, NH_3) 473 ($M+NH_4^+$, 16%), 456 ($M+H^+$, 4), 417 (20) and 400 (100).

Ethyl-(2-triphenylphosphoranylidene)butanoate (10).

A mixture of ethyl 2-bromobutyrate (3.5g, 18.0mmol) and triphenylphosphine (6.5g, 24.8mmol) in toluene (10ml) was refluxed for 0.5h, under an nitrogen atmosphere. The solvent was then decanted from the dark-brown solid, which was then washed with ethyl acetate (three times). The residue was dissolved in the minimum amount of ethanol (*c.a.* 50ml) and added dropwise with stirring to a solution of aqueous sodium hydroxide (10%, 100ml), at ice-bath temperature. The mixture was stirred for 0.5h, and then extracted with ethyl acetate (three times). The combined extracts were dried($MgSO_4$) and concentrated *in vacuo*. The dark brown residue was then treated with diethyl ether (70ml) and the mixture was stirred for 0.5h (some precipitate appeared). The solution was then filtered and then evaporated *in vacuo* to afford crude phosphorane (10) (3.3g, 49%) as a dark brown oily residue, which was used without further purification. δ_H (200MHz; $CDCl_3$) 7.73-7.42 (15H, m, aromatics), 4.14 (2H, q, *J* 7.4 Hz, CH_3CH_2-CO_2), 2.07-1.87 (2H, m, CH_3CH_2-C=P), 1.27 (3H, t, *J* 7.4 Hz, $CO_2CH_2CH_3$) and 0.87 (3H, t, *J* 7.5 Hz, CH_3CH_2-C=).

(4*R*)-3-[3-(Ethoxycarbonyl)pent-2-enyl]-4-[2-(*tert*-butyloxycarbonyl)-1-(hydroxy)ethyl]-2-oxazolidinone (13, X=OH).

A mixture of aldehyde (6):lactol (7) (0.1g, 0.37mmol) and phosphorane (10) (0.28g, 0.73mmol) in dichloromethane (10ml) was heated to reflux and stirred overnight under an nitrogen atmosphere. The solvent was then removed *in vacuo* affording crude product as a pale brown oil. Column chromatography on silica (ethyl acetate-hexane, 3:1 to ethyl acetate) afforded alkene (13, X=OH) (73mg, 54%) as a mixture of *cis*- and *trans*-isomers as a colourless viscous oil; Rf 0.62 (ethyl acetate); $[\alpha]_D^{25}$ -7.3° (c 0.79, $CHCl_3$); υ_{max} ($CHCl_3$) 3050-2910 (m), 1745 (vs), 1710 (s), 1650 (vw), 1475 (w), 1440 (m), 1370 (m), 1310 (w), 1250-1200 (s), 1190 (w), 1150 (s), 1110-1060 (w), 1035 (w) and 840 (w) cm^{-1}; δ_H (200MHz; $CDCl_3$) 6.61 and 5.90 (1H, 2 x t, *J* 7.4 and 7.5 Hz, *trans*- and *cis*- isomers respectively, C=CH-CH_2), 4.38-3.82 (8H, m, $CO_2CH_2CH_3$, =C-CH_2-N, NCO_2CH_2, OCON-CH and CH-OH), 3.57 and 3.54 (m, *cis*- isomer CH-OH), 2.44-2.30 (4H, m, CH_3CH_2-C= and $CH_2CO_2C(CH_3)_3$), 1.46 (9H, s, $CO_2C(CH_3)_3$), 1.30 (3H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$) and 1.04 (3H, t, *J* 7.6 Hz, =C-CH_2CH_3); δ_C (125MHz; $CDCl_3$) 171.1 (CO_2), 166.9 (CO_2), 158.2 (N-CO_2), 137.9 (=C-$CO_2CH_2CH_3$), 134.1 (CH_2-CH=C), 81.9 ($CO_2C(CH_3)_3$), 66.8 (N-CO_2CH_2), 62.7 (CHOH), 60.7 ($CO_2CH_2CH_3$), 58.3 (N-CH), 40.8 (N-CH_2-C=), 37.5 ($CH_2CO_2C(CH_3)_3$), 28.1 ($CO_2C(CH_3)_3$), 20.3 (CH_3CH_2-C=), 14.4 and 14.0 ($CO_2CH_2CH_3$ and CH_3CH_2-C=); m/z (DCI, NH_3) 389 ($M+NH_4^+$, 16%), 372 ($M+H^+$, 6), 333 (38) and 316 (100).

From the ^1H n.m.r. spectrum (500MHz; $CDCl_3$) the ratio of *cis*-:*trans*- isomers was 1:5.8.

α-(Triphenylphosphoranylidene)-γ-butyrolactone (11).

A mixture of α-bromo-γ-butyrolactone (5g, 30.3mmol) and triphenylphosphine (7.95g, 30.3mmol) in tetrahydrofuran (12ml) was refluxed for 20h to form an off-white coloured precipitate. Aqueous sodium

hydroxide (10%, 150ml) was then added dropwise to an aqueous slurry (50ml) of the precipitate. The solution was then extracted with chloroform (three times). The combined organic extracts were dried($MgSO_4$) and evaporated *in vacuo*, to afford crude product as a yellow-brown solid. Recrystallisation (chloroform) afforded the title compound (11) (7.9g, 75%) as a white solid; δ_H (200MHz; $CDCl_3$) 7.71-7.48 (15H, m, aromatics), 4.34 (2H, t, *J* 7.8 Hz, $CO_2C\underline{H}_2CH_2$) and 2.66 (2H, t, *J* 8.2 Hz, $CO_2CH_2C\underline{H}_2$); m/z (DCI, NH_3) 347 ($M+H^+$, 26%), 279 (38) and 263 (100).

(4*R*)-3-[α-(Butyrolactonylidenyl)ethyl]-4-[2-(*tert*-butyloxycarbonyl)-1-(hydroxy)ethyl]-2-oxazolidinone (14, X=OH).

A mixture of aldehyde (6):lactol (7) (0.29g, 1.1mmol) and phosphorane (11) (0.38g, 1.1mmol) was refluxed in tetrahydrofuran (30ml) overnight under a nitrogen atmosphere. The solvent was removed *in vacuo*, and the resulting residue was purified by column chromatography on silica (ethyl acetate) to afford the title compound (14, X=OH) (0.31g, 86%) as a sticky white solid; Rf 0.39 (ethyl acetate); $[\alpha]_D^{20}$ -3.3° (c 0.77, $CHCl_3$); υ_{max} ($CHCl_3$) 3600-3500 (m), 3080-2980 (m), 1755 (vs), 1521 (s), 1477 (m), 1424 (s), 1365 (w), 1209 (s), 1150 (m), 1105 (w), 1050-1000 (m), 925 (s) and 850 (m) cm^{-1}; δ_H (200MHz; $CDCl_3$) 6.66 and 6.30 (1H, 2 x m, *trans*- and *cis*- C$\underline{H}$=C isomers respectively), 4.44-4.19 and 4.03-3.80 (8H, m, $CO_2C\underline{H}_2$, =C-C$\underline{H}_2$-N, N-$CO_2C\underline{H}_2$, N-C$\underline{H}$ and C$\underline{H}$-OH), 3.01 (2H, br s, C-C$\underline{H}_2$-C=), 2.38-2.32 (2H, m, $C\underline{H}_2CO_2$) and 1.44 (9H, s, $CO_2C(C\underline{H}_3)_3$); δ_C (125MHz; $CDCl_3$) 171.1, 170.6 (2 x $\underline{C}O_2$), 158.3 (N-$\underline{C}O_2$), 132.7 (CH=$\underline{C}$), 129.4 ($\underline{C}$H=C), 82.2 ($CO_2\underline{C}(CH_3)_3$), 66.5, 65.7, 62.7, 58.4 (N-$CO_2\underline{C}H_2$, N-$\underline{C}$H, $\underline{C}$HOH and $CO_2\underline{C}H_2$), 41.9 (N-$\underline{C}H_2$-C=), 37.0 ($\underline{C}H_2CO_2$), 28.0 ($CO_2C(\underline{C}H_3)_3$) and 25.1 (C-$\underline{C}H_2$-C=); m/z (DCI, NH_3) 359 ($M+NH_4^+$, 63%), 342 ($M+H^+$, 5), 328 (23), 303 (100) and 286 (55).

Reaction of (6):(7) with (11) in dichloromethane (reflux, 24h) afforded (14) in 78% yield.

(4*R*)-3-[3,6-(Diethoxycarbonyl)-hex-2,5-dienyl]-4-[2-(*tert*-butyloxycarbonyl)-1-(iodo)ethyl]-2-oxazolidinone (12, X=I).

To a solution of the alcohol (12, X=OH) (0.32g, 0.70mmol) and pyridine (0.27ml, 3.3mmol) in dry dichloromethane (10ml) was added triflic anhydride (0.18ml, 1.1mmol) dropwise while stirring at -20°C. After stirring for 2.5h, sodium iodide in ethylene glycol dimethyl ether (1M, 7ml) was added and the solution was allowed to warm to r.t.. The solvent was then removed *in vacuo*, and ethyl acetate and water was added to the residue. The organic layer was separated, washed with saturated aqueous sodium thiosulphate solution, water, brine, dried($MgSO_4$) and evaporated *in vacuo* to afford crude product. Column chromatography (silica; hexane-ethyl acetate, 1.5:1) afforded iodide (12, X=I) (0.26g, 65%) as a pale yellow oil; Rf 0.38 (hexane-ethyl acetate, 1.5:1); δ_H (200MHz; $CDCl_3$) 6.99-6.73 (2H, m, 2 x C=C$\underline{H}$-CH_2), 5.98 and 5.81 (1H, 2 x d, *J* 15.8 and 15.8 Hz, O_2C-C$\underline{H}$=C), 4.52-4.05 (10H, m, =C-C$\underline{H}_2$-N, $C\underline{H}_2OCON$, N-C$\underline{H}$, C$\underline{H}$-I and 2 x $CO_2C\underline{H}_2CH_3$), 3.86-3.69 and 3.37-3.25 (2H, m, =C-C$\underline{H}_2$-C=), 2.93-2.64 (2H, m, $C\underline{H}_2CO_2$), 1.46 (9H, s, $CO_2C(C\underline{H}_3)_3$) and 1.33-1.21 (6H, m, 2 x $CO_2CH_2C\underline{H}_3$); δ_C (125MHz; $CDCl_3$) 168.9 ($\underline{C}O_2$), 166.0, 165.7 ($\underline{C}O_2$), 157.7, 157.6 (N-$\underline{C}O_2$), 144.2, 140.1, 136.1, 132.8, 124.6, 122.5 ($\underline{C}$=C and H$\underline{C}$=C), 82.3 ($CO_2\underline{C}(CH_3)_3$), 65.9, 61.3, 60.7, 60.3, 59.7, 59.5 ($\underline{C}H_2OCON$, N-$\underline{C}$H and 2 x $CO_2\underline{C}H_2CH_3$), 43.0, 40.1, 38.8 (=C-$\underline{C}H_2$-N, =C-$\underline{C}H_2$-C= and

$\underline{C}H_2CO_2$), 27.9 ($CO_2C(\underline{C}H_3)_3$), 22.9, 22.7 ($\underline{C}$H-I), 14.2 and 14.1 (2 x $CO_2CH_2\underline{C}H_3$); m/z (DCI, NH_3) 583 ($M+NH_4^+$, 100%), 566 ($M+H^+$, 5), 527 (40), 510 (44), 471 (46), 455 (36) and 415 (45).

Reaction of Iodide (12, X=I) with Cobaloxime (I) leading to (4*R*)-3-[3,6-(Diethoxycarbonyl)-hex-2,5-dienyl]-4-[2-(*tert*-butyloxycarbonyl)-1-ethenyl]-2-oxazolidinone (20).

To a suspension of chlorocobaloxime (III) (0.15g, 0.37mmol) in methanol (3ml) at 0°C was added aqueous sodium hydroxide (10M, 0.030ml) dropwise while stirring. The mixture was then stirred for 0.1h and then treated with the portionwise addition of sodium borohydride (0.03g, 0.8mmol). The resulting dark coloured solution was then stirred for 0.25h, after which a solution of iodide (12, X=I) (0.20g, 0.35mmol) in methanol (6ml) was added dropwise slowly. The solution was then stirred at 0°C for 0.5h followed by stirring overnight at r.t.. The solvent was then removed *in vacuo* and ethyl acetate and water was added to the residue. The organic layer was separated, washed with water, brine, dried($MgSO_4$) and evaporated under reduced pressure. Column chromatography (silica; hexane-ethyl acetate, 1.5:1) afforded alkene (20) (0.13g, 84%) as a colourless oil; Rf 0.22 (hexane-ethyl acetate, 1.5:1); υ_{max} ($CHCl_3$) 2940-2820 (m), 1762 (vs), 1713 (vs), 1657 (m), 1591 (w), 1573 (vw), 1457 (w), 1385 (m), 1368 (s), 1310 (s), 1153 (m), 1125 (m), 1094 (m), 1061 (m), 981 (m) and 889 (m) cm^{-1}; δ_H (200MHz; $CDCl_3$) 6.91-6.53 (3H, m, 2 x C=C$\underline{H}$-CH_2 and C=C$\underline{H}$-CHN), 5.99-5.70 (2H, m, 2 x O_2C-C$\underline{H}$=C), 4.55-3.97 (9H, m, =C-C$\underline{H}_2$-N, C$\underline{H}_2$OCON, N-C$\underline{H}$ and 2 x $CO_2C\underline{H}_2CH_3$), 3.79-3.60 and 3.34-3.10 (2H, m, =C-C$\underline{H}_2$-C=), 1.47 (9H, s, $CO_2C(C\underline{H}_3)_3$) and 1.32-1.21 (6H, m, 2 x $CO_2CH_2C\underline{H}_3$); m/z (DCI, NH_3) 455 ($M+NH_4^+$, 100%), 438 ($M+H^+$, 13), 399 (51), 382 (64) and 336 (18).

(4*R*)-3-[3-(Ethoxycarbonyl)pent-2-enyl]-4-[2-(*tert*-butyloxycarbonyl)-1-(iodo)ethyl]-2-oxazolidinone (13, X=I).

To a solution of the alcohol (13, X=OH) (0.11g, 0.3mmol) and pyridine (0.11ml, 1.4mmol) in dichloromethane (7.5ml) at 0°C was added triflic anhydride (0.07ml, 0.13g, 0.4mmol) dropwise while stirring under a nitrogen atmosphere. After stirring for 1.5h, sodium iodide in ethylene glycol dimethyl ether (1M, 5ml) was added dropwise. The solution was then slowly allowed to warm to r.t. and then stirred for 1h. The solvent was removed *in vacuo* and ethyl acetate and water was added to the residue. The organic layer was separated, washed with saturated aqueous sodium thiosulphate, water, brine, dried($MgSO_4$) and evaporated *in vacuo* to afford crude product as a yellow oil. Column chromatography (hexane-ethyl acetate, 1.5:1) on silica afforded iodide (13, X=I) (0.1g, 74%) as a yellow oil; Rf 0.5 (hexane-ethyl acetate, 1.5:1); $[\alpha]_D^{19}$ +38.2° (c 0.73, $CHCl_3$); υ_{max} ($CHCl_3$) 3050-2820 (w), 1750 (s), 1740-1690 (m), 1475 (w), 1450-1400 (m), 1370 (m), 1305 (m), 1280 (m), 1245-1200 (s), 1165 (m), 1060 (w), 1030 (w), 930 (w) and 840 (w) cm^{-1}; δ_H (200MHz; $CDCl_3$) 6.57 (1H, t, *J* 6.8 Hz, C=C$\underline{H}$-CH_2N), 4.53-4.18 and 3.90-3.78 (8H, m, =C-C$\underline{H}_2$-N, $CO_2C\underline{H}_2CH_3$, $NCO_2C\underline{H}_2$, OCON-C$\underline{H}$ and C$\underline{H}$-I), 2.97-2.67 (2H, m, C$\underline{H}_2CO_2$), 2.48-2.32 (2H, m, $CH_3C\underline{H}_2$C=), 1.48 (9H, s, $CO_2C(C\underline{H}_3)_3$), 1.32 (3H, t, *J* 7 Hz, $CO_2CH_2C\underline{H}_3$) and 1.07 (3H, t, *J* 7.4 Hz, $C\underline{H}_3CH_2$C=); δ_C (125MHz; $CDCl_3$) 168.9 ($\underline{C}O_2$), 166.7 ($\underline{C}O_2$), 157.5 (N-$\underline{C}O_2$), 138.7 (C=$\underline{C}$-$CO_2CH_2CH_3$), 132.7 (CH_2-$\underline{C}$H=C), 82.4 ($CO_2\underline{C}(CH_3)_3$), 65.9 (N-$CO_2\underline{C}H_2$), 60.9 ($CO_2\underline{C}H_2CH_3$), 59.6 (N-$\underline{C}$H), 40.0 (N-$\underline{C}H_2$-C=), 38.8 ($\underline{C}H_2CO_2C(CH_3)_3$), 28.0 ($CO_2C(\underline{C}H_3)_3$), 23.0 ($\underline{C}$H-I), 20.4 ($CH_3\underline{C}H_2$-C=), 14.2 and 13.9 ($CO_2CH_2\underline{C}H_3$ and $\underline{C}H_3CH_2$-C=); m/z (DCI, NH_3) 499 ($M+NH_4^+$, 60%), 482 ($M+H^+$, 8), 443 (65), 426 (79) and 379 (100).

Reaction of Iodide (13, X=I) with Cobaloxime (I).

To a suspension of chlorocobaloxime (III) (0.08g, 0.2mmol) in methanol (3ml) at 0°C was added aqueous sodium hydroxide (10N, 0.015ml) dropwise while stirring. The mixture was then stirred for 0.1h and then treated with sodium borohydride (0.015g, 0.4mmol). After stirring for 0.25h, a solution of iodide (13, X=I) (0.09g, 0.2mmol) in methanol (10ml) was added dropwise slowly. The solution was allowed to warm to r.t. and then stirred for 3h, after which the solvent was removed *in vacuo*. Ethyl acetate and water was then added to the residue, the organic layer separated, washed with water, brine, dried($MgSO_4$) and evaporated *in vacuo* to afford crude product. Column chromatography (silica; hexane-ethyl acetate, 1.9:1) afforded an inseparable mixture of pyrrolidines (15) and α,β-unsaturated ester (16) (9:9:1, 0.05g, 74%) [Rf 0.28 (hexane-ethyl acetate, 1.9:1)].

Major pyrrolidine double bond diastereoisomers (15): δ_H (200MHz; $CDCl_3$) 7.04 and 6.05 (1H, 2 x q, *J* 7.2 Hz, *trans*- and *cis*- C=C<u>H</u>-CH_3), 4.58-4.12 (5H, m, $CO_2C\underline{H}_2CH_3$, $C\underline{H}_2OCON$ and O_2C-N-C<u>H</u>), 4.01-3.63 (2H, m, N-$C\underline{H}_2$-CH), 3.46-3.11 (1H, m, C=C-C<u>H</u>-CH_2), 2.54-2.08 (3H, m, $C\underline{H}_2$-CO_2 and C<u>H</u>-CH_2CO_2), 1.99 and 1.83 (3H, d, *J* 7.2 Hz, C=CH-$C\underline{H}_3$), 1.48 and 1.46 (9H, 2 x s, $CO_2C(C\underline{H}_3)_3$) and 1.38-1.26 (3H, m, $CO_2CH_2C\underline{H}_3$); δ_C (125MHz; $CDCl_3$) 171.4 ($CH_2\underline{C}O_2$), 167.6, 167.1 ($\underline{C}O_2CH_2CH_3$), 161.3 (N-$\underline{C}O_2$), 142.2, 138.9 (<u>C</u>=CH), 133.5, 132.0 (C=<u>C</u>H), 81.4 ($CO_2\underline{C}(CH_3)_3$), 68.5, 67.9, 63.8, 63.4 (N-<u>C</u>H-CH_2 and $\underline{C}H_2OCON$), 60.7 ($CO_2\underline{C}H_2CH_3$), 49.9, 49.4, 44.0, 43.2, 39.1 (N-$\underline{C}H_2$-CH, C=C-<u>C</u>H and <u>C</u>H-CH_2CO_2), 34.7, 34.2 ($\underline{C}H_2CO_2$), 28.1 ($CO_2C(\underline{C}H_3)_3$), 16.0 and 14.4 ($\underline{C}H_3$-C=C) and 14.2 ($CO_2CH_2\underline{C}H_3$); m/z (GCMS) 371 ($M+NH_4^+$, 3%), 354 ($M+H^+$, 18), 298 (42), 282 (38), 210 (67) and 58 (100).

Minor pyrrolidine double bond diastereoisomers (15): The presence of the minor diastereomer was indicated by the ^1H n.m.r. spectrum δ(200MHz, $CDCl_3$) 6.55 and 6.26 (2 x q, *J* 6.7Hz, *trans*- and *cis*- C=C<u>H</u>CH_3).

α,β-Unsaturated Ester (16): The presence of this compound was indicated by the ^1H n.m.r. spectrum [δ (200MHz; $CDCl_3$) 6.63 (dd, *J* 7.4 and 16.2 Hz, O_2C-CH=C<u>H</u>) and 5.95 (d, *J* 16.0 Hz, O_2C-C<u>H</u>=CH).

(4*R*)-3-[α-(Butyrolactonylidenyl)ethyl]-4-[2-(*tert*-butyloxycarbonyl)-1-(iodo)ethyl]-2-oxazolidinone (14, X=I).

To a solution of the alcohol (14, X=OH) (0.18g, 0.53mmol) and pyridine (0.20ml, 2.5mmol) in dry dichloromethane (7.5ml) at -20°C was added triflic anhydride (0.14ml, 0.78mmol) dropwise while stirring under a nitrogen atmosphere. After stirring for 2.5h, a solution of sodium iodide in ethylene glycol dimethyl ether (1M, 5ml) was added dropwise. The solution was allowed to warm slowly to 0°C and then stirred for 1h. After warming to r.t., the solvent was evaporated *in vacuo*. Column chromatography (silica; ethyl acetate-hexane, 4:1) afforded iodide (14, X=I) (0.15g, 63%) as a white crystalline solid; Rf 0.47 (ethyl acetate-hexane, 4:1); m.p. 131-133°C (dec.); $[\alpha]_D^{20}$ +22.4° (c 0.72, $CHCl_3$); (Found: C, 42.38; H, 4.97; N, 3.32. $C_{16}H_{22}NO_6I$ requires C, 42.59; H, 4.91; N, 3.10%); υ_{max} ($CHCl_3$) 3060-2980 (m), 1750 (s), 1470 (w), 1420 (w), 1370 (m), 1280 (w), 1250-1200 (m), 1155 (m), 1070 (w), 1030 (m), 930 (w) and 840 (w) cm^{-1}; δ_H (500MHz; $CDCl_3$) 6.64 (1H, m, C<u>H</u>=C), 4.51-4.40 and 4.29-4.20 (7H, m, N-$CO_2C\underline{H}_2$, C<u>H</u>-I, N-$C\underline{H}_2$-C= and $CO_2C\underline{H}_2$), 3.83 (1H, dd, *J* 16 and 7 Hz, N-C<u>H</u>), 3.03 (2H, m, C-$C\underline{H}_2$-C=C), 2.91-2.73 (2H, m, $C\underline{H}_2CO_2$) and 1.48 (9H, s, $CO_2C(C\underline{H}_3)_3$); δ_C (125MHz; $CDCl_3$) 170.0, 169.0 (2 x $\underline{C}O_2$), 157.7 (N-$\underline{C}O_2$), 131.2 (<u>C</u>=CH), 130.2 (<u>C</u>H=C),

82.6 ($CO_2\underline{C}(CH_3)_3$), 66.0, 65.5, 59.9 ($CO_2\underline{C}H_2$, N-$\underline{C}H$ and N-$CO_2\underline{C}H_2$), 41.3 (N-$\underline{C}H_2$-C=), 39.0 ($\underline{C}H_2CO_2C$), 28.0 ($CO_2C(\underline{C}H_3)_3$), 25.3 (C-$\underline{C}H_2$-C=C) and 22.4 ($\underline{C}H$-I); m/z (DCI, NH_3) 469 ($M+NH_4^+$, 1%), 413 (8), 285 (21), 270 (54), 252 (48) and 226 (100).

Reaction of Iodide (14, X=I) with Cobaloxime(I).

To a suspension of chlorocobaloxime (III) (0.11g, 0.27mmol) in methanol (3ml) at 0°C was added aqueous sodium hydroxide (10N, 0.02ml) dropwise while stirring. After stirring for 0.1h, the mixture was treated with the portionwise addition of sodium borohydride (0.02g, 0.5mmol). The resulting dark coloured solution was then stirred for 0.25h after which a solution of iodide (14, X=I) (0.11g, 0.25mmol) in methanol (30ml) was added dropwise slowly. After stirring at 0°C for 0.5h, the solvent was evaporated *in vacuo*. Ethyl acetate and water was then added to the resulting residue. The organic layer was separated, washed with water, dried($MgSO_4$) and evaporated *in vacuo* to afford crude product. Column chromatography on silica (ethyl acetate-hexane, 9:1) afforded the butenolide (18) together with α,β-unsaturated ester (19) (17:1, 58mg, 71%) as a colourless oil; Rf 0.33 (ethyl acetate-hexane, 9:1); υ_{max} ($CHCl_3$) 3050-2900 (m), 1770-1710 (vs), 1600 (w), 1480 (w), 1390 (m), 1370 (m), 1350 (w), 1230-1200 (s), 1155 (s), 1080 (m), 1055 (m), 1025 (w) and 835 (w) cm^{-1}.

Butenolide (18): δ_H (200MHz; $CDCl_3$) 7.30 (1H, m, C$\underline{H}$=C), 4.87 (2H, s, $CO_2C\underline{H}_2$-C=), 4.55-2.95 (6H, m, C=C-C$\underline{H}$-C, N-$CO_2C\underline{H}_2$, N-C$\underline{H}$ and N-C$\underline{H}_2$), 2.68-1.98 (3H, m, C$\underline{H}_2$-CO_2 and N-CH-C$\underline{H}$) and 1.42 (9H, s, $CO_2C(C\underline{H}_3)_3$); δ_C (125MHz; $CDCl_3$) 173.2, 170.7 (2 x $\underline{C}O_2$), 161.1 (N-$\underline{C}O_2$), 148.5 ($\underline{C}$=CH), 145.2 ($\underline{C}$H=C), 81.5 ($CO_2\underline{C}(CH_3)_3$), 70.4, 67.8, 63.28 ($CO_2\underline{C}H_2$, N-$CO_2\underline{C}H_2$ and N-$\underline{C}$H), 49.5, 43.1, 39.4, 34.2 (N-$\underline{C}H_2$, C-$\underline{C}$H-C=C, N-CH-$\underline{C}$H and $\underline{C}H_2CO_2$) and 28.0 ($CO_2C(\underline{C}H_3)_3$); m/z (DCI, NH_3) 341 ($M+NH_4^+$, 18%), 324 ($M+H^+$, 54), 285 (17) and 268 (100).

α,β-Unsaturated Ester (19): The presence of this compound was indicated from signals in the ^1H n.m.r. spectrum [δ (200MHz; $CDCl_3$) 6.64 (m, O_2C-CH=C$\underline{H}$) and 5.99 (d, *J* 16.2 Hz, O_2C-C$\underline{H}$=CH)].

Acknowledgements: We thank the SERC for a studentship (to AFP).

References.

1. G.Pattenden, *Chem. Soc. Rev.*, 1988, **17**, 361-382.
2. B.Giese,'Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds', Pergamon, 1986.
3. J.E.Baldwin, M.G.Moloney and A.F.Parsons, *Tetrahedron*, **1990**, *46*, 7263-7282; J.E.Baldwin, M.G.Moloney and A.F.Parsons, *Tetrahedron*, **1991**, *47*, 155-172.
4. J.E.Baldwin and C-S. Li, *J. Chem. Soc., Chem. Commun.*, 1988, 261-263.
5. B.Giese, J.Hartung, J. He, O.Hüter and A.Koch, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 325-327. See also A.J.Clark and K.Jones, *Tetrahedron Letts.*, 1989, **30**, 5485-5488. For an example of dichotomous reactivity in stannane and cobalt-mediated radical cyclisations see M.J.Begley, H.Bhandal, J.H.Hutchinson and G.Pattenden, *Tetrahedron Letts.*, 1987, **28**, 1317-1320.

6. D.P.Curran, *Synthesis*, 1988, 417-439 and 489-513; B.Giese, *Angew. Chem. Int. Ed. Engl.*, 1983, **22**, 753-764.
7. H.J. Bestmann, *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 645-660.
8. G.A. Howie, P.E. Manni, and J.M. Cassady, *J. Med. Chem.*, 1974, **17**, 840-843; H. Zimmer and T. Pamplone, *J. Het. Chem.*, 1965, **2**, 95-96.
9. 0.8 equivalents of sodium hydroxide was used to minimise products resulting from base-induced elimination.
10. J.H. Grate and G.N. Shrauzer, *J. Am. Chem. Soc.*, 1979, **101**, 4601-4611.
11. In earlier work on related closures of compounds of type (3), the (4*S*):(4*R*) ratio was found to be 4:1. Careful analysis of the ^{1}H n.m.r. spectra of the crude product (15) was consistent with a similar product ratio, and on the basis of this precedent the major diastereomer is tentatively assigned the (4*S*) configuration.
12. The diastereoselectivity of this cyclisation at C-4 could not be determined from the ^{1}H n.m.r. spectrum.
13. The sodium borohydride solution [0.25 equivalents for each equivalent of (14, X=I), 1M in 2M aq. NaOH] was added dropwise to the mixture of (14, X=I), chlorocobaloxime(III) and sodium hydroxide in methanol at 0°C. See ref 3.
14. H.Bhandal, A.R.Howell, V.F.Patel and G.Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2709-2714. H.Bhandal and G.Pattenden, *J. Chem. Soc., Chem. Commun.*, 1988, 1110-1112.
15. G.N.Schrauzer and R.J.Windgassen, *J. Am. Chem. Soc.*, 1967, **89**, 1999-2007.
16. 'Purification of Laboratory Chemicals', Eds. D.D.Perrin and W.L.F.Armarego, Pergamon Press, 3rd Ed., 1988.