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Total Synthesis of (R,R)-Crinan via Regiospecific and Stereoselective Palladium Catalysed Cyclisation.

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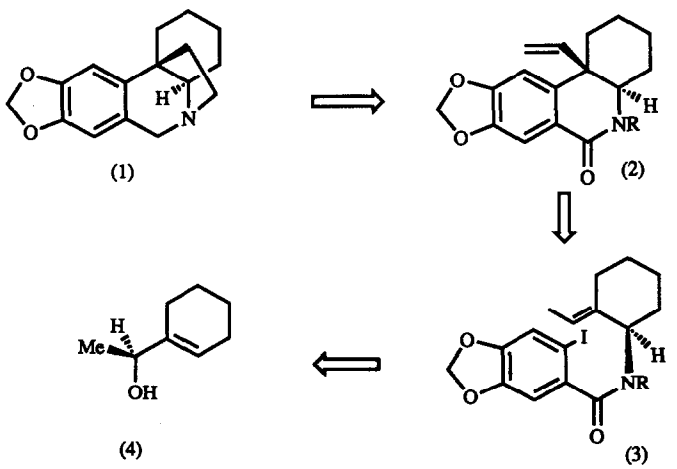
Abstract: The synthesis of (R,R)-crinan from (S)-1- cyclohexenylethan-1-ol is described. The key palladium catalysed step involves a regiospecific 6-exo trig cyclisation which proceeds with 20:1 stereoselectivity for the trans-ring junction over the cis-ring fusion. The ring junction stereochemistry is sensitive to solvent, phosphine and small amounts of water.

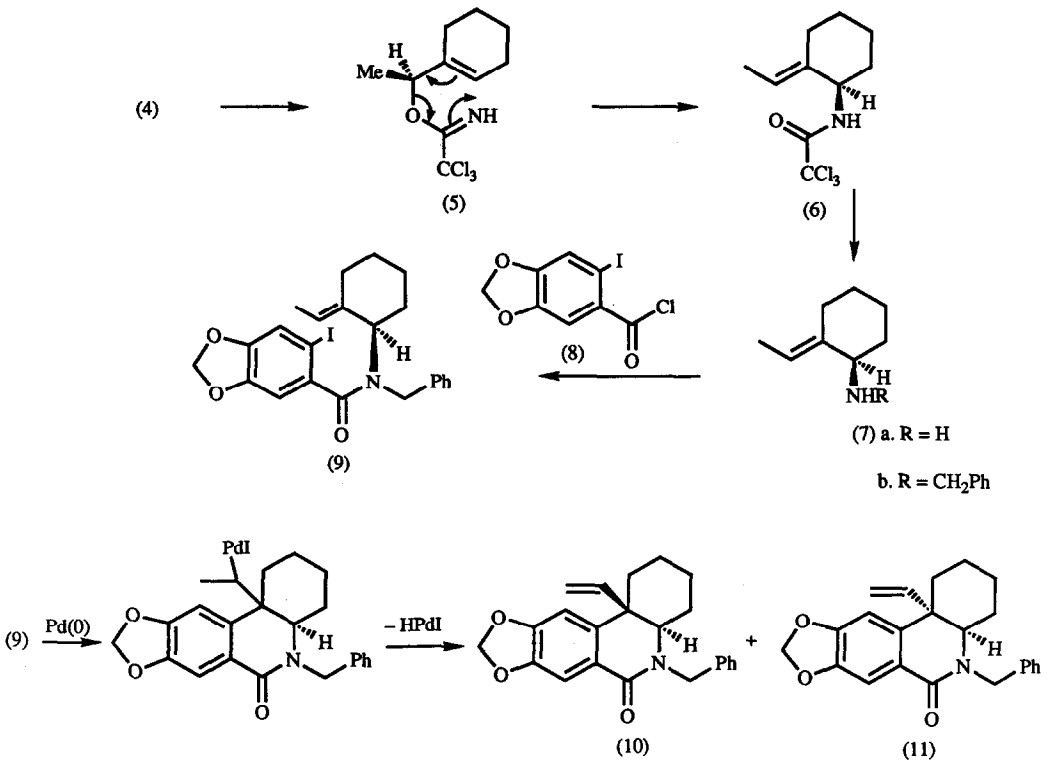
The *Amaryllidaceae* alkaloids have attracted considerable attention both from structural elucidation and synthetic viewpoints.[1] Many of these tyrosine derived alkaloids[2] incorporate a perhydroindole moiety in various structural skeletons. A wide range of approaches to the synthesis of the racemic alkaloids have been reported[3,4] but few enantioselective routes have been published.[5] Our interest in these alkaloids arose from our demonstration that intramolecular Heck reactions can be used to created fused-, bridged- and spiro-ring systems and tetrasubstituted carbon centres.[6] A suitable skeleton to test this methodology further and which would furnish interesting data with respect to the stereochemistry of ring junction(s) created in Heck-type processes was provided by (R,R)-crinan (1) (Scheme 1). Several syntheses of the racemic alkaloid have been reported.[4]



Scheme 1

The key palladium catalysed step (3) → (2) (Scheme 1) was of interest because although the regiochemistry of the cyclisation could be confidently predicted to be 6-exo trig rather than 7-endo trig, the resulting ring junction stereochemistry was less obvious. In our studies of chiral Heck-type cyclisations we had shown that cyclisations to homochiral products could be achieved when a trisubstituted carbon centre was created by use of a chiral auxiliary[7] but that tetrasubstituted centres were created with markedly less asymmetric induction. We therefore elected to utilise the homochiral alcohol (4) as our starting material. Recently much more efficient chiral induction in Heck-type processes have been reported by several authors although processes involving creation of tetrasubstituted carbon centres are still a problem.[8]

The homochiral (S)- alcohol (4) [$[\alpha]_D$-7.6($CHCl_3$)] was prepared (88%) by kinetic resolution of the racemic material using a Sharpless kinetic resolution involving (D)-diisopropyl tartrate.[9] Treatment of (4) with trichloroacetonitrile in ether at -5°C in the presence of a catalytic amount of sodium hydride gave the trichloroimidate (5) in good yield. This material was somewhat unstable and was subjected to Claisen rearrangement (Overman's protocol[10]) in boiling toluene without further purification. The product (6) was obtained in 75% yield and evaluation by chiral hplc (Chiralcel, 10% i-PrOH-hexane) confirmed that no racemisation had occurred. Hydrolysis of (6) followed by condensation of the amine (7a) with benzaldehyde and subsequent borohydride reduction gave the amine (7b). This amine was acylated with the acid chloride (8) to give enamide (9). Although small amounts of the intermediates between (4) and (9) were purified for microanalysis and to obtain spectroscopic data the reactions were carried out with crude material since pmr spectral analysis showed >90% purity in each case. The overall yield of pure enamide (9)[$[\alpha]_D$ + 67.7 ($CHCl_3$)] from alcohol (4) was 24.5%.



With the key enamide (9) to hand we investigated the palladium catalysed cyclisation to (10) or (11) under a variety of conditions (Table) using racemic (9) initially.

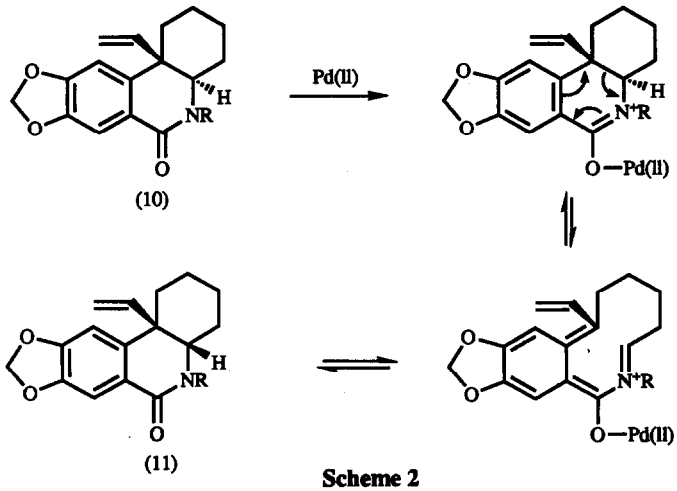
Table. Palladium catalysed cyclisation of (9) to (10) and (11).[a]

ENTRY	PHOSPHINE	ADDITIVE	REACTION CONDITIONS	RATIO (10) : (11) (YIELD %)
1	PPh_3	-	CH_3CN,80°C,36h	4:1 (63)
2	PPh_3	-	DMF,120°C,16h	4:1 (65)
3	$P(o\text{-}tol)_3$	-	DMF,120°C,16h	4.5:1
4	$P(2\text{-}MeOC_6H_4)_3$	-	DMF,120°C,16h	4.5:1
5	BINAP[b]	-	DMF,120°C,16h	4.5:1
6	PPh_3	NEt_4Cl,(1mol)	DMF,120°C,16h	3:1
7	PPh_3	Ag(OTf),(1mol)	DMF,120°C,16h	2.5:1
8	$P(o\text{-}tol)_3$	-	DMF,80°C,6h	4.5:1[c]
9	$P(o\text{-}tol)_3$	-	PhH,80°C,16h	4.5:1[c]
10	$P(o\text{-}tol)_3$	-	CH_3CN,80°C,24h	8.5:1
11	$P(o\text{-}tol)_3$	-	CH_3CN,70°C,72h	19:1[d]
12	$P(o\text{-}tol)_3$	H_2O[e]	CH_3CN,80°C,16h	12:1
13	$P(o\text{-}tol)_3$	H_2O[e]	CH_3CN,70°C,72h	18.5:1 (68)
14	$P(o\text{-}tol)_3$	H_2O[e]	CH_3CN,80°C,16h	20:1(68)[f]

a. The catalyst system comprised 10mol% $Pd(OAc)_2$, 20mol% PR_3 and K_2CO_3 (2mol).
b. 2,2′-Bis(diphenylphosphino)-1,1′binapthyl (10mol%).
c. 30-40% conversion.
d. 60% conversion.
e. 10:1 v/v CH_3CN-H_2O.
f. $Pd(OAc)_2$ replaced by 10mol% $Pd(dba)_2$. (dba=dibenzylidineacetone).

Using our standard cyclisation conditions and catalyst system we obtained a 4:1 mixture of the trans-(10)- and cis-(11)-isomers. Adding tetraethylammonium chloride or silver triflate (Table, entries 7 and 8) had a deleterious effect on the trans: cis ratio, whilst increasing the steric bulk of the phosphine (Table, entries 3-5, 8-11) was beneficial. Tri(o-tolyl)phosphine was particularly promising although the best conditions (Table, entry 11) led to only 60% conversion to products after 72h. However, addition of small amounts of water to the reaction resulted in a noticeable increase in rate (Table, entries 12 and 13) and at 70°C in acetonitrile led to complete conversion of (9) to an 18.5:1 mixture of (10) and (11). Finally replacing $Pd(OAc)_2$ by $Pd(dba)_2$ (Table, entry 14) afforded a further small increase in selectivity for the trans-isomer to 20:1 and these conditions were selected for processing homochiral-(9). Addition of more water had a deleterious effect on the reaction. Others have also noted the beneficial effect of water on palladium catalysed reactions[11]. When reactions of racemic (9) in acetonitrile were monitored at low conversions the cyclisation appeared to be stereospecific for the trans-isomer (10) with cis-isomer (11) appearing after longer reaction times suggesting that some trans → cis isomerisation might be occurring. Examination of molecular models indicates the most favourable conformation for ring formation involves a palladium complex of a chair cyclohexane with the bulky amide

substituent equatorial. Transition states leading to the cis-isomer (11) appear highly unfavoured on steric grounds. One attractive mechanism for such an interconversion is shown in Scheme 2.

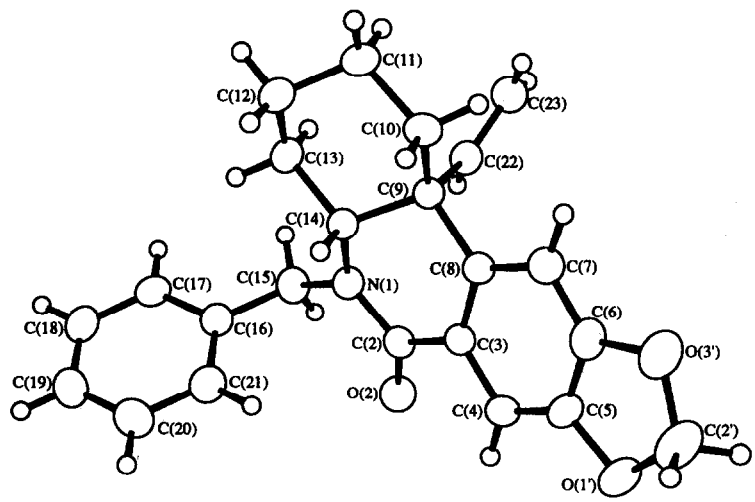


(10) (11)

Scheme 2

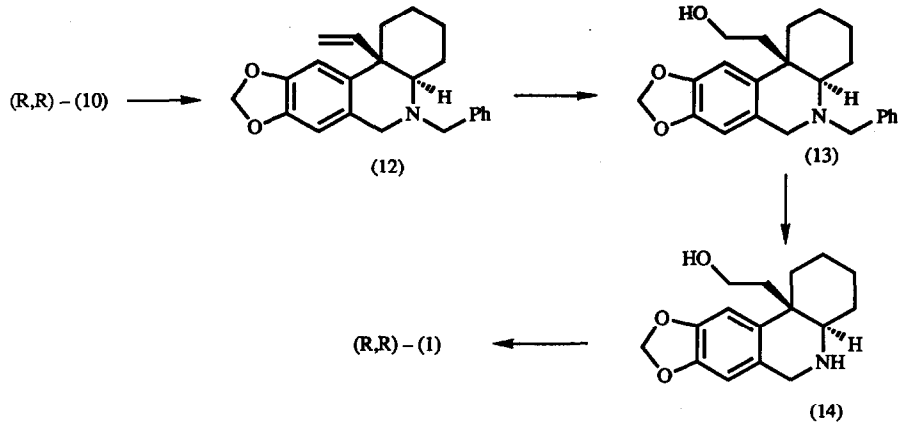
However, attempts to isomerise (10) to (11) in the presence of Pd(II) salts were unsuccessful and recycling (10) through the reaction conditions also failed to induce any isomerisation.

Palladium catalysed cyclisation of the (R)-enamide (9) using the conditions noted in the table (entry 14) gave a 20:1 mixture of (10) and (11).[12] Chromatographic purification of this mixture (SiO_2) followed by crystallisation from ether-petroleum ether gave homochiral (R,R)-(10) in 68% yield. The optical purity of (10) was confirmed by chiral hplc (Chiralcel, 1% i-PrOH-hexane) and the absolute configuration was established as (R,R)-(10) by X-ray crystallography (Figure). The X-ray data are summarised in the experimental section.



Figure

The final stages of the synthesis are summarised in Scheme 3.



Scheme 3

Lithium aluminium hydride reduction of the amide functionality of (10) proceeded in good yield in ether to afford (12)(80%). Hydroboration-oxidation of (12) to the terminal alcohol (13) could only be achieved in moderate (40%) yield due to interference by the adjacent tertiary amine. Racemic (13) was an intermediate in Ninomiya's synthesis of (+)-crinan[4]. Debenzylation of (R,R)-(13) using 20% Pearlman's catalyst and 5 atm hydrogen proceeded in quantitative yield. Finally ring closure of (14) to (R,R)-(1) was achieved in 40% yield using thionyl chloride at room temperature. Comparison of the optical rotation and melting point of the synthetic (R,R)-(1) with the reported values [$[\alpha]_D^{20}$-12.2, m.p. 96-98°C (synthetic),$[\alpha]_D^{20}$-12.7, m.p. 97-99°C (natural)[13]] confirmed their equivalence.

Experimental. General experimental details were as previously described.[6]

(S)-1-Cyclohexenylethan-1-ol (4). Powdered and activated 3Å molecular sieves (5g) were added to a solution of racemic 1-cyclohexenylethan-1-ol (34g, 0.27mol) and diisopropyl (D)-tartrate (9.36g, 0.04mol) in dry dichloromethane (1L). Titanium isopropoxide (7.7g, 0.027mol) was added to the stirred mixture, maintained at -10 to -20°C, and stirring continued for 30 min. t-Butylhydroperoxide (54ml, 3M solution in toluene) was then added and the mixture stirred at -20°C for 9h. The reaction was then quenched with an aqueous solution (300ml) of ferrous sulphate (90g) and citric acid (30g) at -20°C and the mixture stirred vigorously at room temperature for 30mins. The organic phase was separated and the aqueous layer extracted with ether (2x300ml). The combined organic layers were concentrated to ca. 1L, 30% aqueous sodium hydroxide (30ml) added and the mixture stirred for 1h. The organic layer was separated, washed with brine (50ml), and the solvent removed. The residue was purified by column chromatography eluting with 1:9 v/v ether-petroleum ether. The product (15g,88%) was obtained as colourless oil, $[\alpha_D]^{20}$-7.58(c.3.0, $CHCl_3$); δ 5.6 (br s,1H,=CH), 4.1(q,J 6.6 and 12Hz,1H,OCH), 2.42 (br s,1H,OH), 2.0-1.9(m,4H, 2xCH_2) and 1.2(s,3H, Me); m/z(%) 126 (M^+,100), 11(59), 97(46), 67(90) and 43(82).

(S)-(1-Cyclohexenylethan-1-yl)-2,2,2-trichloroethanimidate (5). A suspension of sodium hydride (0.48g, 50% dispersion in oil, 0.01mol) in dry ether (60ml) was added dropwise to a solution of (S)-1-cyclohexenylethan-1-ol (12.6g, 0.1mol) in ether (15ml). After the evolution of hydrogen ceased (5min), the reaction mixture was

cooled to -10°C. Trichloroacetonitrile (10ml, 0.1mol) was then added dropwise to the stirred solution while the temperature was maintained below - 5°C. The addition was completed within 15min., and the solution was allowed to warm to room temperature and was concentrated. Pentane (5ml) containing 1ml of methanol was added and the insoluble materials were removed by filtration and the residue was washed with pentane (5ml). The combined filtrates were concentrated to give the crude product as a brown liquid (20g) which was used for the following step without purification. δ 8.24(br s, 1H,NH), 5.79(br s,1H,=CH, 5.3(q, J 6.6 and 12.9Hz, 1H, CHO), 2.1 - 1.9 (m, 4H, 2xCH_2), 1.73 - 1.4(m, 4H, 2xCH_2) and 1.43 (d, J 6.6 Hz, 3H, Me); m/z(%) 271(M^++1, 0.7), 234(47), 109(99), 93(100), and 67(65).

(R)-2,2,2-trichloro-N-[(2-ethylidine)cyclohex-1-yl]acetamide (6). A solution of crude (S)-(1-cyclohexenylethan-1-yl)-2,2,2-trichloroethanimidate (20g, 0.074mol) in toluene (100ml) was boiled under reflux for 3h. The solvent was then removed and the residue crystallised from ether to afford the **product** (15g,75%) as colourless needles, m.p. 90-92°C, $[\alpha]_D^{20}$-5.3 (c3.0, $CHCl_3$). (Found: C, 44.15; H, 5.1; N, 5.15. $C_{10}H_{14}Cl_3NO$ requires C, 44.4; H, 5.2; N, 5.2%); δ 6.73-6.63 (br s, 1H, NH), 5.32 (q, J 6.6 and 13Hz, 1H=CH), 4.36-4.29(m, 1H, CHN), 2.54-2.04(m, 1H, CH), 2.0-1.3(m, 7H, cylohexane ring) and 1.63(d, J 6.6Hz, 3H, Me); m/z(%) 270(M^+, 1), 236(45), 234(67), 108(100), 79(51) and 44(76).

(R)-E-Ethylidine-2-cyclohexylamine (7a). A solution of (S)-(1-cyclohexenylethan-1-yl)-2,2,2-trichloroethanimidate (14.5g, 0.054mol) in absolute ethanol (200ml) was stirred vigorously with 6N aqueous sodium hydroxide (200ml) at room temperature for 36h. Dichloromethane (300ml) was then added, the organic layer separated and the aqueous layer extracted with dichloromethane (3x200ml). The combined extracts were dried ($MgSO_4$), the solvent removed under reduced pressure and the semisolid residue extracted with boiling hexane (3x200ml). The hexane solution was concentrated to leave a pale yellow liquid (5g, 75%) whose nmr spectrum showed it to comprise > 90% of (7a). This material was used for the following step without purification. A small sample was purified by preparative tlc and obtained as a colourless oil, $[\alpha]_D^{20}$ - 20.5 (c 2.0, $CHCl_3$); the hydrochloride salt had m.p. 173-178°C. [Found (hydrochloride salt): 59.45; H, 10.05; N, 8.5. $C_8H_{10}ClN$ requires C, 59.45, H, 10.0; N, 8.65%); δ 5.5 (q, J 13 and 6.6 Hz, 1H,=CH), 3.19 (m, 1H, CHN), 2.6-2.5 (m, 1H, cyclohexane ring), 1.9 - 1.7 (m, 7H, cyclohexane ring) and 1.6 (s, 3H, Me); m/z(%) 125(M^+,37) 110(100), 96(60), 82(59) and 36(42).

(R)-N-(2-Ethylidinecyclohexyl)benzylamine (7b). A solution of crude (R)-E-ethylidine-2-cyclohexylamine (above) (5g, 0.04mol) and benzaldehyde (4.2g, 0.04mol) in benzene (50ml) was boiled under reflux using a Dean-Stark trap for 2h. The solvent was then removed under reduced pressure and the residual oil dissolved in dry methanol (50ml). Sodium borohydride (2.88g, 0.08mol) was added to this solution portionwise with stirring over 10min. and the resulting mixture stirred at room temperature for 24h. The solvent was then removed under reduced pressure, the residue dissolved in ether (200ml) and washed with water (50ml). The aqueous layer was extracted with ether (2x50ml), the combined organic extracts dried ($MgSO_4$) and the solvent removed to leave a pale yellow oil (7g,81%) whose nmr spectrum showed it to comprise > 90% (7b) and which was used for the following step without purification. A small sample was purified by preparative tlc and obtained as colourless oil, $[\alpha]_D$-33.13 (c 1.66, $CHCl_3$); the hydrochloride salt had m.p. 130-133°C [Found (hydrochloride salt): C, 71.7; H, 9.1; N, 5.55. $C_{15}H_{22}ClN$ requires C, 71.55; H, 8.8; N, 5.55%); δ 7.3-7.2(m, 5H, ArH), 5.3(q,1H=CH), 3.7 and 3.6(2xd, AB, J 13.2Hz, 2x1H, NCH_2), 3.0(br s, 1H, NCH), 2.1-1.6(m, 8H, cyclohexane ring) and 1.6(d, J 6.7Hz, Me); m/z(%) 215(M^+,40), 200(79), 186(12), 172(14), 124(9) and 91(100).

(R)-N-(2-Ethylidinecyclohexyl)-N-benzyl-2-iodo-4,4-methylenedioxybenzamide (9). A solution of crude (R)-N-(2-ethylidinecyclohexyl)benzylamine (above) (4.5g, 0.02mol), triethylamine (2.32g, 0.023mol), and 2-iodopiperonylic acid chloride (5.33g, 0.02mol) in dry benzene (100ml) was boiled under reflux for 3h. The solvent was then removed, the residue dissolved in ether (100ml), washed with water (25ml) and the aqueous layer extracted with ether (2x25ml). The combined organic extracts were dried ($MgSO_4$), the solvent removed and the residue purified by column chromatography eluting with 1:1 v/v ether-petroleum ether. The **product** (5.6g, 55%) was obtained as colourless needles from ether-petroleum ether, m.p. 169-173°C (decomp), $[\alpha]_D^{20}$+ 67.7 (c 2.0, $CHCl_3$) (Found: C, 56.55; H, 4.65; I, 25.65; N, 2.8. $C_{23}H_{24}INO_3$ requires C, 56.45; H, 4.95; I, 25.95; N, 2.85%), δ 7.6 (d, J 7Hz, 2H, ArH), 7.3-7.2(m, 4H, ArH), 6.7 (s, 1H, ArH), 6.0 (d, J 8Hz, 2H, OCH_2O), 5.5 and 4.0 (2xd, AB, J 15.5Hz, 2x1H, NCH_2) 5.2(q, 1H, J 8.7 and 3Hz, 1H,=CH), 3.9(m,1H, NCH), 2.0 1.1(m, 8H, cyclohexane ring) and 1.7 (d, J 6Hz, 3H, Me); m/z(%) 489 (M^+,100), 398(99), 361(22), 275(81), 149(99) and 91(99).

(R,R)-trans-11b-Vinyl-5-benzyl-1,2,3,4,4a,11b-hexahydro[1,3]dioxolo[4,5-j]phenanthridine-6(5H)-one(10). A mixture of (9) (4.5g, 9mmol), palladium dibenzylidineacetone (0.52g, 0.09mmol), tri(o-tolyl)phosphine (0.54g, 0.18g) and potassium carbonate (2.48g, 27mmol) in acetonitrile (100ml) and water (10ml) was boiled under reflux for 16h. The solvent was then removed, the residue dissolved in dichloromethane (200ml) and washed with water (25ml). The aqueous layer was extracted with dichloromethane (2x50ml), the combined organic extracts dried ($MgSO_4$) and the solvent removed. The residue which comprised a 20:1 mixture of trans-(10)- and cis-(11)-isomers was purified by column chromatography eluting with 1:1 v/v petroleum ether-ether. The pure trans-isomer (10) (3g, 68%) was obtained as colourless prisms from ether-petroleum ether, m.p. 128-130°C, $[\alpha]_D^{20}$-47.5 (c 2.0, $CHCl_3$); (Found: C, 76.6; H, 6.65; N, 3.8. $C_{23}H_{23}NO_3$ requires C, 76.45; H, 6.4; N, 3.85%); δ 7.6 (s, 1H, ArH), 7.3 7.2(m, 5H, ArH), 6.8(s, 1H, ArH), 6.2-6.0(dd, J 17 and 11Hz, 1H, HC=), 6.0 (d, J 1Hz, 2H, OCH_2O), 5.4 and 4.5 (2xd, AB, J 16Hz, 2x1H, NCH_2), 5.1 (d,J 10Hz, 1H, HC=), 4.7 (d, J 10Hz, 1H, HC=), 3.7 (dd, J 12.5 and 3.5Hz, 1H, HCN), and 2.4-1.6(m, 8H, cyclohexane ring); m/z(%) 361(M^+,75), 317(39), 270(36), 242(54), 146(42) and 91(100).

(R,R)-trans-11b-Vinyl-5-benzyl-1,2,3,4,4a,11b-hexahydro[1,3]dioxolo[4,5-j]phenanthridine (12). Lithium aluminium hydride (0.65g, 7.6mmol) was added in small portions over 5min. to a stirred solution of (R,R)-(10) (2.75g, 7.6mmol) in dry ether (100ml) and stirring continued at room temperature for 3h. Water (25ml) was then added dropwise, the ether layer separated and the aqueous layer extracted with ether (2x50ml). The combined ether extracts were dried ($MgSO_4$), the solvent removed and the residue purified by column chromatography eluting with 4:1 v/v petroleum ether-ether. The **product** (2.1g, 80%) crystallised from ether-petroleum ether as colourless prisms m.p. 66-68°C, $[\alpha]_D^{20}$-78.3(c 2.0, $CHCl_3$) (Found: C, 79.5; H, 7.1; N, 4.05. $C_{23}H_{25}NO_2$ requires C, 79.5; H, 7.25; N, 4.05%); δ 7.4-7.2 (m, 5H, ArH), 6.8(s, 1H, ArH), 6.6-6.5(m, 1H, HC=), 5.8 (d, J 8Hz, 2H, OCH_2O), 5.1 (m,2H, H_2C=), 4.2 and 3.2 (2xd, AB, J 13Hz, 2x1H, NCH_2), 3.7 and 3.3 (2xd, AB, J 15Hz, 2x1H, NCH_2) and 2.5-1.3 (m, 8H, cyclohexane ring); m/z(%) 347(M^+,37) 304(13), 290(32), 256(20), 200(22), 108(49) and 91(100).

(R,R)-trans-5-Benzyl-2,3,4,4a,5,6-hexahydro-1H-[1,3]dioxolo[4,5-j]phenanthridine-11b-ethanol (13). Borane-dimethyl sulphide complex (10.8ml, 2M solution in THF) was added with stirring to a solution of (R,R)-(12)(1.59g, 4.3mmol) in dry THF at 0°C. The resulting solution was stirred at room temperature for 8h. Aqueous sodium hydroxide (2N, 5ml) was then added dropwise followed by hydrogen peroxide (30% v/v, 5ml)

and the mixture stirred at room temperature for 1h. Ether (100ml) was then added, the organic layer separated, and the aqueous layer extracted with ether (2x25ml). The combined organic extracts were dried ($MgSO_4$), the solvent removed, and the residue purified by column chromatography eluting with 1:1 v/v ether-petroleum ether. The **product** (0.6g, 40%) was obtained as colourless prisms from methanol, m.p. 192-193°C; $[\alpha]_D^{20}$-46.6(c 0.4, CH_2Cl_2) (Found: C, 75.45; H, 7.4; N, 3.75. $C_{23}H_{27}NO_3$ requires C, 75.6; H, 7.45; N, 3.85%); δ 7.3 (m,5H, ArH), 6.6 and 6.3 (2xs, 2x1H, ArH), 5.9 (d,J 6Hz, 2H, OCH_2O), 4.4 and 3.0 (2xd, AB, J 12Hz, 2x1H, NCH_2), 3.5 and 3.3 (2xd, AB, J 11.7Hz, 2x1H, NCH_2), 2.9 and 2.6 (2xt, 2x1H, OCH_2), 2.4 (dd, J 3 and 13Hz, 1H, NCH) and 2.7-1.3 (m, 8H, cyclohexane ring); m/z(%) 364(M^+-1,26), 321(65), 274(86), 230(87), 214(52), 200(13) and 91(100).

(R,R)-trans-2,3,4,4a,5,6,-Hexahydro-1H-[1,3]dioxolo[4,5-j]phenanthridine-11b-ethanol (14). A mixture of (R,R)-(13) (0.25g, 0.68mmol), 20% palladium hydroxide on carbon (0.06g) and conc. hydrochloric acid (4 drops) in methanol (20ml) was stirred at room temperature under 5atm pressure of hydrogen for 16h. Solid materials were filtered off, the solvent removed, the residue dissolved in chloroform (50ml) and washed with saturated aqueous potassium carbonate solution (2x10ml). The aqueous layer was extracted with chloroform (2x25ml), the combined organic extracts were dried ($MgSO_4$), and the solvent removed to give the **product** (0.18g, 98%) which crystallised from methanol, as colourless prisms m.p. 178°C, (Found: C, 69.75; H, 7.55; N, 5.05. $C_{16}H_{21}NO_3$ requires C, 69.8; H, 7.7; N, 5.1%); δ 6.7 and 6.65 (2xs, 2x1H, ArH), 5.9 (s, 2H, OCH_2O), 4.2 and 4.0 (2xd, AB, J 13.2Hz, 2x1H, NCH_2), 3.4 and 2.8 (2xd, AB, J 8.8Hz, 2x1H, OCH_2), 2.9 (t,1H, NCH), 2.5 (t,1H, cyclohexane ring), and 2.0-1.1 (m, 7H, cyclohexane ring); m/z(%) 275(M^+,28), 257(83), 228(100), 214(85), 200(56), 149(64), 115(43) and 57(76).

(R,R)-(-)-Crinan (1). Thionyl chloride (0.4ml, 53mmol) was added with stirring to a solution of (R,R)-(14) 0.36mmol (0.1g) in dry dioxan (20ml) at 0°C and stirring continued at room temperature for 16h. Water (10ml) was then added, the aqueous layer saturated with potassium carbonate, and the organic layer separated. The aqueous layer was extracted with ether (2x20ml), the combined organic extracts dried over anhydrous potassium carbonate and the solvent removed. The residue was purified by column chromatography eluting with 19:1 v/v ether-methanol. The **product** (0.35g, 40%) was obtained as colourless prisms from methanol. m.p. 96-98°C (lit.[13] 97-99°C), $[\alpha]_D^{20}$-12.2; (c 0.66, $CHCl_3$); (lit.[13]-12.7); δ 6.7 and 6.4 (2xs, 2x1H, ArH), 5.9 (s, 2H, OCH_2), 4.4 and 3.8 (2xd, AB, J 11.8Hz, 2x1H, NCH_2), 2.8 (t, 1H, NCH), 2.8 (m, 2H, NCH_2), 2.3 and 1.6 (2xd, AB, J 12Hz, 2x1H, CH_2) and 2.3 - 1.1 (m, 8H, cyclohexane ring).

Single crystal X-ray diffraction analysis of 10- All crystallographic measurements were carried out at 200 K on a Stoe STADI4 diffractometer using graphite monochromated Copper K_α X-radiation (λ = 1.54184 Å). Data (one complete unique set together with a large number of equivalent reflections) were collected in the range $4.0° < 2\theta < 130.0°$ using ω-θ scans with no significant variation observed in the intensities of three standard reflections. Lorentz and polarisation corrections were applied to the data-set together with a semi-empirical absorption correction which used azimuthal ψ-scans.

The structure was solved by direct methods using SHELXS[14]. The correct solution gave two molecules in the asymmetric unit. The corresponding bond lengths and angles of the two do not

differ significantly but there are slight differences between there overall orientations of the benzyl substituents (see the comparative dihedral in angles in Table C).

The structure was refined by full-matrix least-squares (based on F^2) using the SHELXL93[15] program system which uses all data in refinement. The weighting scheme used was $w = [\sigma^2(F_o^2) + (0.0446P)^2 + 1.2522P]^{-1}$ where $P=(F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were constrained to predicted positions (C-H = 0.98, 0.97 and 0.93Å, for primary, secondary and aromatic hydrogens respectively). Refinement included an isotropic extinction parameter x so that $F_c'' = k F_c [1 + 0.001 * x * F_c^2 * \lambda^3]^{-¼}$ where k is the overall scale factor. The absolute structure was confirmed by refinement of a 'Flack' parameter, x = 0.15(14)[16]. The parameters wR_2 and R_1, which are given below, are defined as $wR_2 = (\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[wF_o^4])^{½}$ and $R_1 = \Sigma| |F_o| - |F_c| | / |F_o|$. The latter is given for comparison with refinements based on F and uses reflections with $F_o > 4.0\ \sigma(F_o)$.

Crystal data - $C_{23}H_{23}NO_3$, 0.53 x 0.38 x 0.36 mm, M = 361.42, monoclinic, space group *I*2 (=*C*2), *a* = 19.916(2), *b* = 9.0806(8), *c* = 20.538(2) Å, β = 95.237(10)°, *U* = 3698.8(6) Å^3, *Z* = 8, D_x = 1.298 Mg m^{-3}, μ = 0.685 mm^{-1}, *F*(000) = 1536.

Data collection - Scan speeds 1.5 - 8.0° min^{-1}, ω scan widths 1.05° + α-doublet splitting, $4.0 < 2\theta < 130.0°$, 10899 Data collected 6098 of which were unique, R_{int} = 0.0331, R_{sig} = 0.0304. There were 6098 reflections with $F_o > 4.0\ \sigma(F_o)$.

Structure refinement - Number of parameters = 488, isotropic extinction paramter x = 0.00073(5), goodness of fit s = 1.052, wR_2 = 0.0857, R_1 = 0.0331.

Non-hydrogen atomic co-ordinates are listed in Table A. Since there are no significant differences in corresponding bond length for the two independant molecules in the interests of brevity only the bond lengths for one molecule have been listed in Table B. Table C lists comparative dihedral angles which show the differences between the two molecules.

Supplementary data has been deposited at the Cambridge Crystallographic Data Centre which includes hydrogen co-ordinates and all thermal parameters together with complete bond lengths and angles and is available on request.

Table A. Non-hydrogen atom co-ordinates for **10** with estimated standard deviations (e.s.d.'s) in parentheses.

	x	y	z
		Molecule 1	
N(1)	8387.8(7)	5949(2)	4472.5(7)
C(2)	8041.3(9)	7175(2)	4623.5(8)
O(2)	7928.7(7)	8199.3(14)	4238.2(6)
C(3)	7799.1(8)	7204(2)	5287.4(8)
C(4)	7590.7(8)	8576(2)	5509.5(8)
C(5)	7354.2(8)	8615(2)	6113.2(8)
O(1')	7035.2(7)	7684(2)	7054.4(6)
C(2')	6960.4(12)	9245(2)	7058.7(9)
O(3')	7115.8(7)	9807.5(14)	6436.1(6)
C(6)	7298.3(9)	7350(2)	6478.0(8)
C(7)	7481.8(8)	5992(2)	6263.3(8)
C(8)	7755.4(8)	5925(2)	5658.1(7)
C(9)	8004.2(8)	4470(2)	5387.9(8)
C(10)	8264.7(9)	3426(2)	5947.5(9)
C(11)	8631.8(10)	2073(2)	5715.9(11)
C(12)	9195.1(11)	2521(2)	5307.0(12)
C(13)	8937.3(10)	3503(2)	4740.0(10)
C(14)	8605.9(9)	4878(2)	4997.7(8)
C(15)	8636.6(9)	5873(2)	3821.8(8)
C(16)	9348.7(9)	6418(2)	3789.1(7)
C(17)	9769.7(9)	5734(2)	3373.0(8)
C(18)	10409.5(9)	6263(2)	3305.2(8)
C(19)	10651.5(10)	7479(2)	3658.3(8)
C(20)	10244.6(10)	8159(2)	4077.2(9)
C(21)	9598.3(10)	7639(2)	4143.9(8)
C(22)	7428.1(9)	3806(2)	4944.6(8)
C(23)	7046.0(9)	2680(2)	5078.3(10)
		Molecule 2	
N(1)	4932.8(7)	16239.5(15)	7207.0(6)
C(2)	5233.5(9)	17403(2)	6941.5(8)
O(2)	5324.7(7)	18589.8(14)	7227.1(6)
C(3)	5461.9(8)	17170(2)	6278.0(8)
C(4)	5623.2(9)	18435(2)	5928.3(8)
C(5)	5868.5(8)	18217(2)	5333.9(8)
O(1')	6067.8(6)	19263.0(14)	4905.1(5)
C(2')	6247.7(10)	18454(2)	4349.3(8)
O(3')	6246.4(7)	16918.1(14)	4509.8(5)
C(6)	5976.1(8)	16825(2)	5100.2(7)
C(7)	5830.8(8)	15577(2)	5433.8(7)
C(8)	5551.6(8)	15757(2)	6034.1(7)
C(9)	5342.7(8)	14433(2)	6432.9(7)
C(10)	5106.7(9)	13142(2)	5982.9(8)
C(11)	4775.3(10)	11897(2)	6336.9(9)
C(12)	4201.6(9)	12458(2)	6709.1(9)
C(13)	4440.5(9)	13698(2)	7174.7(8)
C(14)	4734.0(8)	14945(2)	6790.9(8)
C(15)	4699.6(9)	16406(2)	7860.9(8)
C(16)	3961.2(9)	16767(2)	7858.5(8)
C(17)	3571.9(11)	16133(2)	8311.7(9)
C(18)	2898.4(12)	16498(3)	8323.4(12)
C(19)	2603.3(12)	17479(3)	7877.8(13)
C(20)	2977.5(12)	18103(3)	7419.9(12)
C(21)	3655.2(10)	17763(3)	7416.2(9)
C(22)	5940.4(8)	14029(2)	6917.7(7)
C(23)	6359.0(9)	12929(2)	6873.3(9)

Table B. Bond lengths (pm) a for one of the two independent molecules of **10** with e.s.d.'s in parentheses

N(1)-C(14)	1.487(2)	C(2)-O(2)	1.228(2)
C(2)-C(3)	1.488(2)	C(3)-C(8)	1.396(2)
C(3)-C(4)	1.402(2)	C(4)-C(5)	1.367(2)
C(5)-O(3')	1.376(2)	C(5)-C(6)	1.382(3)
O(1')-C(6)	1.372(2)	O(1')-C(2')	1.426(3)
C(2')-O(3')	1.437(2)	C(6)-C(7)	1.370(2)
C(7)-C(8)	1.403(2)	C(8)-C(9)	1.533(2)
C(9)-C(22)	1.523(2)	C(9)-C(10)	1.543(2)
C(9)-C(14)	1.546(2)	C(10)-C(11)	1.528(3)
C(11)-C(12)	1.517(3)	C(12)-C(13)	1.518(3)
C(13)-C(14)	1.529(2)	C(15)-C(16)	1.509(2)
C(16)-C(21)	1.393(3)	C(16)-C(17)	1.396(2)
C(17)-C(18)	1.381(3)	C(18)-C(19)	1.383(3)
C(19)-C(20)	1.380(3)	C(20)-C(21)	1.389(3)

Table C. Selected comparative dihedral angles (°) illustrating the difference between the two independent molecules of **10**

Molecule 1		Molecule 2	
C(2)-N(1)-C(15)-C(16)	93.1(2)	C(2)-N(1)-C(15)-C(16)	97.2(2)
C(14)-N(1)-C(15)-C(16)	-75.7(2)	C(14)-N(1)-C(15)-C(16)	-71.3(2)
N(1)-C(15)-C(16)-C(17)	144.4(2)	N(1)-C(15)--C(16)-C(17)	140.3(2)
N(1)-C(15)-C(16)-C(21)	-38.5(2)	N(1)-C(15)--C(16)-C(21)	-41.2(2)

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