Synthesis of Macrocyclic Pyrrolizidine Alkaloid Analogues from (−)-(7*R*,8*R*)-1-Chloromethyl-1,2-didehydro-7-hydroxypyrrolizidinium Chloride

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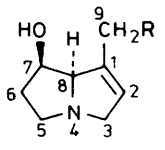
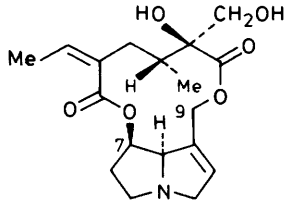
Treatment of the (−)-hydrochloride of (7*R*,8*R*)-1-chloromethyl-1,2-didehydro-7-hydroxypyrrolizidine (**2**) with a series of aromatic and unsaturated anhydrides at room temperature gave the corresponding macrocyclic diesters of retronecine (**1**). The reaction probably takes place by initial formation of the 7-monoesters of the allylic chloride (**2**), followed by intramolecular nucleophilic substitution of the chlorine by carboxylate anion. A range of ten-membered [(**6**)—(**12**)] macrocyclic diesters of retronecine (**1**), and one example each of an 11-membered, (**13**), and 12-membered pyrrolizidine alkaloid analogue, (**14**), have been prepared.

Pyrrolizidine alkaloids have attracted much attention because of their widespread distribution and because of the hepatotoxicity exhibited by many of these alkaloids.[1,2] The most toxic alkaloids contain (+)-retronecine (**1**) as base portion of a macrocyclic diester system. Pyrrolizidine alkaloids with ring

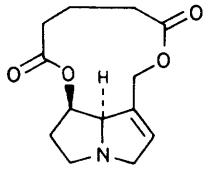


(**1**) R = OH
(**2**) R = Cl

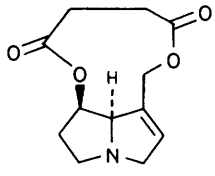


(**3**)

sizes of 11, 12, 13, and 14 have been isolated. The structural features necessary for hepatotoxicity to be observed are the presence of a 1,2-double bond in the pyrrolizidine nucleus and esterification at C-9. Increased toxicity is normally associated with acylation at C-7 and with the presence of a macrocyclic ring as in retrorsine (**3**).[3] Most of the synthetic effort in this area is still directed towards the base portion of the alkaloids (necines).[1] The only macrocyclic pyrrolizidine alkaloids prepared so far are (+)-dicrotaline,[4] (±)-integerrimine,[5] (±)-fulvine,[6] (±)-crispatine,[6] and the *O*-acetyl derivative of crobarbatine.[7] We have sought to prepare macrocyclic pyrrolizidine alkaloids and analogues to study their biological activity in order to obtain a better understanding of the relationship between the structure and toxicity of these compounds. Thus a series of 11-membered analogues containing (+)-retronecine (**1**), including compound (**4**), was prepared in good yield



(**4**)



(**5**)

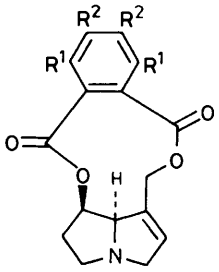
by treatment of retronecine (**1**) with glutaric anhydride followed by Corey–Nicolaou lactonisation *via* the pyridine-2-thiol esters.[8] Recently, the first ten-membered pyrrolizidine alkaloid analogues containing (+)-retronecine, including compounds (**5**) and (**6**), were prepared by the same method in 79 and 16% yield, respectively.[9] The poor yield obtained for the latter analogue containing an aromatic diacid portion prompted us to develop a different route to analogues containing aromatic rings or unsaturation in the acid moiety.

The (−)-hydrochloride of (7*R*,8*R*)-1-chloromethyl-1,2-didehydro-7-hydroxypyrrolizidine (**2**) was first prepared by Adams and Van Duuren from (+)-retronecine (**1**).[10] Culvenor and coworkers developed a method for selective esterification of retronecine at C-9 by preparing the allylic chloride (**2**) hydrochloride and heating it with the sodium salts of various acids in aqueous ethanol for several hours.[11] This reaction has now been developed for use in an intramolecular fashion to generate new dilactones derived from (+)-retronecine.

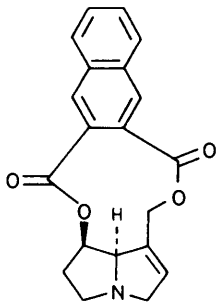
Results and Discussion

Retrorsine (**3**) is the major alkaloidal constituent of *Senecio isatideus* plants. These plants are used in our biosynthetic work.[12] A supply of (+)-retronecine (**1**) was obtained by alkaline hydrolysis of retrorsine. Conversion of (+)-retronecine into the (−)-hydrochloride of (7*R*,8*R*)-1-chloromethyl-1,2-didehydro-7-hydroxypyrrolizidine (**2**) was achieved in improved yields (89—93%) by treatment with thionyl chloride. Preliminary experiments on the formation of the known[9] macrocyclic dilactone (**6**) were carried out by treatment of the allylic chloride (**2**) hydrochloride with phthalic anhydride in the presence of various bases. Use of potassium hydroxide in *NN*-dimethylformamide (DMF) even in the presence of crown ethers gave very low yields of the cyclised product (**6**). With tributylamine as base, the reaction mixture was left for 24 h at room temperature in DMF. After purification of the reaction products by column chromatography on basic alumina a low yield (9%) of the phthalate diester (**6**) was obtained. Some improvement in the yield (to 16%) was achieved using the same conditions but with Hunig's base (*NN*-di-isopropylethylamine) present. The use of 2 equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base in DMF produced a significant improvement in the yield of the pyrrolizidine alkaloid analogue (**6**) to 57%. A limited amount of lactonisation was found to occur even in the absence of any base, but the reaction could only be completed by the addition of 2 equiv. of DBU.

The scope of this new lactonisation procedure was examined. Three readily available phthalic anhydride derivatives (4,5-dichloro, 3,4,5,6-tetrachloro, and 3,4,5,6-tetrabromo) were tested. The symmetrical substitution was chosen to avoid problems with the formation of diastereoisomers. The electron-withdrawing effect of the halogens was expected to increase the rate of monoester formation with the allylic chloride (**2**) if



(6) $R^1 = R^2 = H$
(7) $R^1 = H$, $R^2 = Cl$
(8) $R^1 = R^2 = Br$
(9) $R^1 = R^2 = Cl$



(10)

steric effects were not important. Three new ten-membered pyrrolizidine alkaloid analogues (7)—(9) were formed rapidly from the halogeno anhydrides and the hydrochloride of (2) in good yields with DBU as base. Lower yields were obtained with Hunig's base (Table). An accurate measurement on the dichloro analogue (7), $[\alpha]_D^{18}$ +264°, gave a molecular formula of $C_{16}H_{13}{}^{35}Cl_2NO_4$. The mass spectral fragmentation pattern of the free base was typical for a macrocyclic dilactone containing (+)-retronecine,[8,9] with peaks at *m/z* 357, 355, 353 (M^+, Cl isotopes), 137, 136, 120, 119, 94, 93, and 80. The key feature in the ^1H n.m.r. spectrum of compound (7) taken in deuteriochloroform is an AB system at δ_H 4.27 and 5.55 (*J* 12 Hz) due to the protons at C-9. The chemical-shift difference ($\Delta\delta$) between these protons (1.28 p.p.m.) is the same as that for the phthalate diester (6), and is similar to the value observed for the succinate diester (5) (1.34 p.p.m.[9]). The structures of the two other analogues (8) and (9) were established by analogous spectroscopic and analytical data. The methylene protons at C-9 of compounds (8) and (9) displayed $\Delta\delta$ values of 0.94 and 1.05 p.p.m. in their ^1H n.m.r. spectra, respectively. Previous attempts to prepare the ten-membered analogues (7) and (8) by the Corey–Nicolaou route had been unsuccessful (Table). Formation of the 9-monoester from (+)-retronecine (1) and the tetrahalogeno anhydrides occurred smoothly, but little thiol ester formation was observed and lactonisation failed to occur.

Reaction of the (−)-hydrochloride of (2) with naphthalene-2,3-dicarboxylic anhydride also occurred readily in the presence of DBU to give a 50% yield of the naphthalene derivative (10) which showed a large $\Delta\delta$ of 1.31 p.p.m. for the C-9 protons in its ^1H n.m.r. spectrum.

Monitoring the formation of the macrocyclic products [(6)—(10)] by t.l.c. indicated rapid production (few minutes) of the cyclised material, and no evidence was obtained for the presence of the expected 7-monoester intermediates. The lactonisation step is presumably rapid. The reactions were routinely left for 24 h to ensure completion.

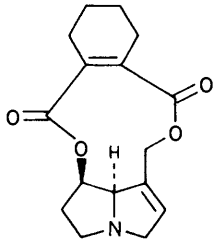
Treatment of glutaric and succinic anhydrides with the (−)-hydrochloride of the allylic chloro compound (2) using DBU as base did produce the macrocyclic dilactones (4) and (5) but cyclisation was considerably slower than with the aromatic anhydrides. Some decomposition of the allylic chloride (2) was also evident (t.l.c.), which reduced the yields of the cyclised products. The Corey–Nicolaou route is preferred for the formation of the analogues (4) and (5).[8,9]

We had desired for some time to prepare ten-membered analogues with a double bond in the acid portion of the macrocyclic ring. However, the reaction of cyclohexene-1,2-dicarboxylic anhydride and maleic anhydride with retronecine did not lead to cyclised material under Corey–Nicolaou conditions. Lactonisation between the two unsaturated anhydrides and the (−)-hydrochloride of compound (2) occurred with DBU as base to afford the new pyrrolizidine alkaloid analogues (11) and (12) containing a double bond in the acid portion of the macrocyclic ring. Much lower yields of the cyclised products (11) and (12) were obtained when Hunig's base was employed (Table). The $\Delta\delta$ values of 1.26 and 1.29 p.p.m. observed for the analogues (11) and (12) in their ^1H n.m.r. spectra are similar to those found for the other ten-membered analogues.

Table. Formation of pyrrolizidine alkaloid analogues

Analogue	Yield (%) Method A[a]	Method B[b]	Method C[c]	Δδ/p.p.m. (for C-9 protons)
(6)	57	16	16	1.28
(7)	73	54	<1	1.28
(8)	65	21	0	0.94
(9)	71	48		1.05
(10)	50			1.31
(11)	42	2	<1	1.26
(12)	25	8	0	1.29
(13)	61			0.40
(14)	15			0.97

[a] Reaction of (7*R*,8*R*)-1-chloromethyl-1,2-didehydro-7-hydroxypyrrolizidine (2) hydrochloride with DBU as base. [b] Reaction of (2) hydrochloride with Hunig's base. [c] Corey–Nicolaou route.[7,8]



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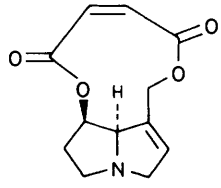
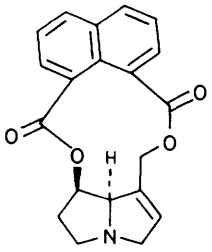


(12)

All of the ten-membered-ring pyrrolizidine alkaloid analogues produced so far have large $\Delta\delta$ values of 0.94—1.34 p.p.m. for the methylene protons at C-9 in the n.m.r. spectra (Table).[9] This range of values is much higher than that recorded for 11-membered-ring pyrrolizidine alkaloids ($\Delta\delta$ 0.0—0.92 p.p.m., except for dicrotaline, $\Delta\delta$ 1.24 p.p.m.[4]), but is similar to the range of values observed for 12-membered diesters containing retronecine. Large values of $\Delta\delta$ are believed to arise when one of the C-9 protons lies close to both the plane of the double bond in the five-membered ring and the plane of the ester carbonyl group, resulting in a large deshielding effect for that proton. *X*-Ray studies have supported these ideas and have shown that 12-membered alkaloids have ester carbonyl groups that are anti-parallel, whereas most 11-membered alkaloids have ester carbonyl groups that are syn-parallel and directed below the plane of the macrocycle.[2] The ten-membered succinate analogue (5) was recently shown by us to have ester carbonyl groups that are anti-parallel.[13] It seems likely from consideration of ^1H n.m.r data that the other ten-membered analogues [(6)—(12)] have similar conformations of the macrocyclic rings. (The conformations of pyrrolizidine alkaloids in solution and in the solid state are believed to be similar.[14])

Treatment of the (−)-hydrochloride of compound (2) with naphthalene-1,8-dicarboxylic anhydride and DBU produced an 11-membered analogue (13) in 61% yield. The most interesting spectral feature of this new pyrrolizidine alkaloid analogue is a $\Delta\delta$ value of 0.40 p.p.m. for the protons at C-9 in the ^1H n.m.r.

spectrum. This value is much less than for the ten-membered analogues but is in the usual range found for 11-membered pyrrolizidine alkaloids containing a retronecine moiety. This suggests that the ester carbonyl groups in this analogue may be syn-parallel.



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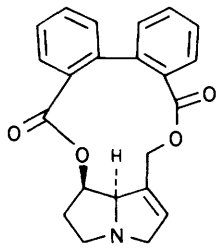

(14)

Finally, reaction of the allylic chloride (**2**) with diphenic (biphenyl-2,2′-dicarboxylic) anhydride and DBU gave the 12-membered analogue (**14**) in low yield (15%). The reaction was slow and appreciable decomposition of the allylic chloride (**2**) occurred. The ^{1}H n.m.r. spectrum of compound (**14**) showed a $\Delta\delta$ value of 0.97 p.p.m., which is within the range reported for 12-membered-ring pyrrolizidine alkaloid diesters containing retronecine.

Treatment of various aromatic and unsaturated anhydrides with (−)-9-chloro-9-deoxyretronecine (**2**) hydrochloride in the presence of various bases gave a range of new pyrrolizidine alkaloid analogues. Better yields were obtained with DBU than with Hunig's base. Lactonisation is rapid and efficient with the more rigid monoesters derived from aromatic and unsaturated acids, where the number of degrees of freedom is reduced. This lactonisation method therefore provides a complementary route to the Corey–Nicolaou conditions, which work better with saturated anhydrides. Further studies will be carried out to establish the conformations and to determine the toxicity of these new pyrrolizidine alkaloid analogues.

Experimental

M.p.s were measured with a Kofler hot-stage apparatus. N.m.r. spectra were recorded with a Bruker WP-200 SY spectrometer operating at 200 MHz (δ_H) or 50 MHz (δ_C). Spectra were recorded in either deuteriochloroform with residual chloroform (δ_H 7.25; δ_C 77.0) as internal standard, or in hexadeuteriodimethyl sulphoxide (δ_H 2.44; δ_C 39.5). Mass spectra were obtained with A.E.I. MS 12 or 902 spectrometers. Optical rotations were measured with an Optical Activity Ltd. AA-100 polarimeter. I.r. spectra were obtained on a Perkin-Elmer 580 and u.v. spectra with a Pye-Unicam SP-100 spectrophotometer. T.l.c. of the bases was carried out on Kieselgel G plates of 0.25 mm thickness developed with chloroform–methanol–conc. ammonia (85:14:1), and the bases were located by oxidation with *o*-chloranil, followed by treatment with Ehrlich's reagent.[15] DMF was dried with 3Å molecular sieves as detailed by Burfield and Smithers.[16]

(−)-1-*Chloromethyl*-1,2-*didehydro*-7β-*hydroxy*-8α-*pyrrolizidine* [(−)-9-*Chloro*-9-*deoxyretronecine*] (**2**) *Hydrochloride*.—(+)-Retronecine[9] (720 mg, 4.64 mmol) was added in portions to stirred thionyl chloride (2.2 ml, *ca.* 28 mmol) at −5 °C. After the addition was complete the solution was allowed to warm to +5 °C during *ca.* 2 h. Thionyl chloride was removed under reduced pressure at 20 °C. The resulting amber foam was taken up in the minimum amount of hot 95% ethanol, and diethyl ether was added until the solution became slightly opaque. (−)-9-Chloro-9-deoxyretronecine (**2**) hydrochloride (773 mg, 79%) crystallised as short off-white needles which were analytically pure. Additional crystals of (**2**) hydrochloride (92 mg, 10%) which were pure enough for further use were obtained from the filtrate. This gave a total yield of 865 mg (89%) (lit.,[10] 50%); m.p. 151—152 °C (from ethanol–diethyl ether) (lit.,[10] 152—153 °C); $[\alpha]_D^{18}$ −46° (*c* 0.69 in EtOH) (lit.,[10] $[\alpha]_D^{36}$ −64.7°); R_F 0.18; $\nu_{max.}$(KBr) 3 265 and 2 550 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.98 (2 H, m, 6-H_2), 3.16 (1 H, m, 5-H), 3.65 (1 H, m, 5-H), 3.87 (1 H, m, 3-H), 4.20 (1 H, m, 3-H), 4.33 (1 H, m, 9-H), 4.48 (2 H, complex, 9- and 7-H), 4.70 (1 H, br s, 8-H), 5.45 (1 H, br s, OH), 5.90 (1 H, s, 2-H), and 12.30 (1 H, br s, NH); δ_C[$(CD_3)_2SO$] 35.4 (C-6), 40.1 (C-9), 53.1 (C-5), 59.6 (C-3), 68.4 (C-7), 77.1 (C-8), 124.3 (C-2), and 133.8 (C-1); *m/z* 175, 173 (M^+, 9%), 138, 129, 94, (100), and 80 (Found: M^+, 173.0615. Calc. for $C_8H_{12}{}^{35}ClNO$: *M*, 173.0607) (Found: C, 45.7; H, 6.3; Cl, 33.6; N, 6.6. Calc for $C_8H_{13}Cl_2NO$: C, 45.7; H, 6.2; Cl, 33.75; N, 6.7%).

(+)-7,9-O,O-(4,5-*Dichlorophthaloyl*)*retronecine* (**7**).—4,5-Dichlorophthalic anhydride (56.4 mg, 0.260 mmol) was added to a stirred solution of (−)-9-chloro-9-deoxyretronecine hydrochloride (52.0 mg, 0.248 mmol) in DMF (2 ml) under argon at ambient temperature. After 5 min, DBU (75 μl, 0.50 mmol) was added dropwise by syringe. The solvent was removed under reduced pressure after 24 h to give a clear oil. The oil was dissolved in dichloromethane (5 ml) and the solution was washed with saturated brine (5 ml) containing conc. ammonia (2 ml). The aqueous layer was washed with dichloromethane (2 × 5 ml), and the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on basic alumina, with 20% v/v chloroform in dichloromethane as eluant, to yield (+)-7,9-O,O-(4,5-*dichlorophthaloyl*)*retronecine* (**7**) (64 mg, 73%) as small needles, m.p. 196—199 °C (from hexane); $[\alpha]_D^{18}$ +264° (*c* 0.36 in $CHCl_3$); R_F 0.63; $\nu_{max.}$(CCl_4) 1 730 cm^{-1}; $\lambda_{max.}$(EtOH) 275 (ε 760), 287 (745), and 296sh nm; δ_H($CDCl_3$) 2.02 and 2.15 (2 H, m, 6-H_2), 2.61 (1 H, m, 5β-H), 3.22 (1 H, m, 5α-H), 3.47 (1 H, m, 3β-H), 3.87 (1 H, m, 3α-H), 4.27 (1 H, ABq, *J* 12 Hz, 9-H), 4.50 (1 H, m, 8-H), 5.55 (1 H, ABq, *J* 12 Hz, 9-H), 5.77 (1 H, m, 7-H), 6.09 (1 H, br s, 2-H), and 7.84 and 7.85 (2 H, d, $J < 1$ Hz, 16- and 19-H); δ_C($CDCl_3$) 37.7 (C-6), 53.7 (C-5), 60.4 and 61.3 (C-3 and -9), 75.9 and 77.4 (C-7 and -8), 131.2 and 131.4 (C-1, -12, and -13), 131.6 and 131.7 (C-16 and -19), 135.8 (C-2), 136.4 and 136.6 (C-17 and -19), and 165.8 and 165.9 (C-11 and -14); *m/z* 357, 355, 353 (M^+, 10%), 137, 136, 120, 119, 94, 93 (100), and 80 (Found: M^+, 353.0221. $C_{16}H_{13}{}^{35}Cl_2NO_4$ requires *M*, 353.0221) (Found: C, 54.2; H, 3.6; N, 3.9. $C_{16}H_{13}Cl_2NO_4$ requires C, 54.25; H, 3.7; N, 3.95%).

The same procedure was used for the preparation of the pyrrolizidine alkaloid analogues [(**6**)—(**14**)].

(+)-7,9-O,O-*Phthaloylretronecine* (**6**).—By use of phthalic anhydride the phthalate diester (**6**) (57%) was obtained as prisms, m.p. and mixed m.p. 145—146 °C (from hexane) (lit.,[9] 145—146 °C); $\lambda_{max.}$(EtOH) < 204 (ε > 30 000) and 284 nm (2 200) (Found: C, 67.2; H, 5.2; N, 5.0. Calc. for $C_{16}H_{15}NO_4$: C, 67.4; H, 5.3; N, 4.9%).

(+)-7,9-O,O-(3,4,5,6-*Tetrabromophthaloyl*)*retronecine* (**8**).—By use of 3,4,5,6-tetrabromophthalic anhydride the *tetrabromophthalate diester* (**8**) (65%) was obtained as plates, m.p. 211—213 °C (decomp.) (from hexane); $[\alpha]_D^{13}$ +216° (*c* 1.17 in $CHCl_3$); R_F 0.65; $\nu_{max.}$(KBr) 1 738 and 1 724 cm^{-1}; $\lambda_{max.}$(EtOH) 230 (ε 27 000), 300sh, and 308 nm (950); δ_H($CDCl_3$) 2.04 and 2.16 (2 H, m, 6-H_2), 2.69 (1 H, m, 5β-H), 3.18 (1 H, m, 5α-H), 3.51 (1 H, m, 3β-H), 3.87 (1 H, m, 3α-H), 4.45 (1 H, ABq, *J* 12 Hz, 9-H), 4.50 (1 H, m, 8-H), 5.39 (1 H, ABq, *J* 12 Hz, 9-H), 5.93 (1 H, m, 7-H), and 6.16 (1 H, br s, 2-H); δ_C($CDCl_3$) 32.8 (C-6), 53.5

(C-5), 60.8 and 62.3 (C-3 and -9), 75.8 and 77.1 (C-7 and -8), 123.3, 124.3, 133.1, 133.5, 133.9, and 136.1 (C-12, -13, -16, -17, -18, and -19), 130.6 (C-1), 138.0 (C-2), and 163.4 and 164.2 (C-11 and -14); *m/z* 601 (M^+, 11%), with a cluster of isotope peaks, 137, 136 (100), 120, 119, 94, 93, and 80 (Found: M^+, 600.7407. $C_{16}H_{11}{}^{79}Br_2{}^{81}Br_2NO_4$ requires *M*, 600.7381) (Found: C, 31.8; H, 1.6; N, 2.2. $C_{16}H_{11}Br_4NO_4$ requires C, 32.0; H, 1.85; N, 2.3%).

(+)-7,9-O,O-(3,4,5,6-*Tetrachlorophthaloyl*)*retronecine* (**9**).—By use of 3,4,5,6-tetrachlorophthalic anhydride the *tetrachlorophthalate diester* (**9**) (71%) was obtained as needles or diamond-shaped plates, m.p. 188—190 °C (decomp.) (from hexane); $[\alpha]_D^{18}$ +295° (*c* 0.23 in $CHCl_3$); R_F 0.67; $\nu_{max.}$(KBr) 1 740 cm^{-1}; $\lambda_{max.}$(EtOH) 227 (ε 32 000), 298 (1 090), and 308 nm (1 140); δ_H($CDCl_3$) 1.96 and 2.09 (2 H, m, 6-H_2), 2.62 (1 H, m, 5β-H), 3.12 (1 H, m, 5α-H), 3.44 (1 H, m, 3β-H), 3.82 (1 H, m, 3α-H), 4.34 (1 H, ABq, *J* 12 Hz, 9-H), 4.45 (1 H, m, 8-H), 5.39 (1 H, ABq, *J* 12 Hz, 9-H), 5.92 (1 H, m, 7-H), and 6.10 (1 H, br s, 2-H); δ_C($CDCl_3$) 32.8 (C-6), 53.4 (C-5), 60.7 and 62.2 (C-3 and -9), 76.4 and 77.7 (C-7 and -8), 129.7, 130.7, 132.0, 133.0, 136.5, and 137.0 (C-12, -13, -16, -17, -18, and -19), 130.4 (C-1), 137.8 (C-2), 162.1 and 162.9 (C-11 and -14); *m/z* 423 (M^+, 8%), with a cluster of isotope peaks, 137, 136, 120, 119, 118, 106, 94, 93 (100), and 80 (Found: M^+, 422.9432. $C_{16}H_{11}{}^{35}Cl_3{}^{37}ClNO_4$ requires *M*, 422.9412) (Found: C, 45.5; H, 2.6; N, 3.2. $C_{16}H_{11}Cl_4NO_4$ requires C, 45.4; H, 2.6; N, 3.3%).

(+)-7,9-O,O-(*Naphthalene*-2,3-*dicarbonyl*)*retronecine* (**10**).—By use of naphthalene-2,3-dicarboxylic anhydride, (*naphthalene*-2,3-*dicarbonyl*)*retronecine* (**10**) (50%) was produced as hexagonal plates, m.p. 192—194 °C (from hexane); $[\alpha]_D^{14}$ +288° (*c* 0.24 in $CHCl_3$); R_F 0.59; $\nu_{max.}$(KBr) 1 725 and 1 717 cm^{-1}; $\lambda_{max.}$(EtOH) 221 (ε 42 400), 324 (1 200), 337 (1 670), and 357 nm (165); δ_H($CDCl_3$) 2.04 and 2.18 (2 H, m, 6-H_2), 2.63 (1 H, m, 5β-H), 3.18 (1 H, m, 5α-H), 3.50 (1 H, m, 3β-H), 3.85 (1 H, m, 3α-H), 4.29 (1 H, ABq, *J* 12 Hz, 9-H), 4.50 (1 H, m, 8-H), 5.60 (1 H, ABq, *J* 12 Hz, 9-H), 5.87 (1 H, m, 7-H), 6.12 (1 H, br s, 2-H), 7.61 (2 H, m, 18- and 21-H, or 19- and 20-H), 7.93 (2 H, m, 19- and 20-H, or 18- and 21-H), and 8.29 and 8.31 (2 H, s, 16- and 23-H); δ_C($CDCl_3$) 33.6 (C-6), 53.7 (C-5), 60.7 and 61.5 (C-3 and -9), 75.7 and 77.4 (C-7 and -8), 128.3 (C-12 or -13), 128.7 and 128.8 (C-18, -19, -20, -21, and -13 or -12), 131.2 (C-16 and -23), 132.0 (C-1), 133.6 and 133.7 (C-17 and -22), 135.7 (C-2), and 168.0 (C-11 and -14); *m/z* 335 (M^+, 31%), 206, 198, 137, 136, 126, 120, 119 (100), 118, 117, 94, 93, and 80 (Found: M^+, 335.1162; C, 71.4; H, 5.0; N, 4.2. $C_{20}H_{17}NO_4$ requires *M*, 335.1158; C, 71.6; H, 5.1; N, 4.2%).

(+)-7,9-O,O-(3,4,5,6-*Tetrahydrophthaloyl*)*retronecine* (**11**).—Use of 3,4,5,6-tetrahydrophthalic anhydride gave the *tetrahydrophthalate diester* (**11**) (42%) as an oil, $[\alpha]_D^{20}$ +19.5° (*c* 0.37 in $CHCl_3$); R_F 0.62; $\nu_{max.}$(CCl_4) 1 720s and 1 642w cm^{-1}; $\lambda_{max.}$(EtOH) 248 (ε 1 940) and 288 nm (970); δ_H($CDCl_3$) 1.45—1.80 (4 H, complex, 17- and 18-H_2), 1.88—2.30 (4 H, complex, 6- and 16- or 19-H_2), 2.44—2.76 (3 H, complex, 5β-H and 19- or 16-H_2), 3.30 (1 H, m, 5α-H), 3.50 (1 H, m, 3β-H), 3.92 (1 H, m, 3α-H), 4.11 (1 H, ABq, *J* 12 Hz, 9-H), 4.57 (1 H, m, 8-H), 5.37 (1 H, ABq, *J* 12 Hz, 9-H), 5.68 (1 H, m, 7-H), and 5.96 (1 H, br s, 2-H); δ_C($CDCl_3$) 21.1 (C-17 and -18), 25.7 and 26.2 (C-16 and -19), 33.4 (C-6), 53.6 (C-5), 60.1 and 60.3 (C-3 and -9), 73.9 and 77.4 (C-7 and -8), 131.4 (C-1), 134.1 (C-2), 135.7 and 137.3 (C-12 and -13), and 168.2 and 168.4 (C-11 and -14); *m/z* 289 (M^+, 22%), 137, 136, 120, 119, 108, 94, 93 (100), 80, and 79 (Found: M^+, 289.1318. $C_{16}H_{19}NO_4$ requires *M*, 289.1314).

(+)-7,9-O,O-*Maleoylretronecine* (**12**).—By use of maleic anhydride the *maleate diester* (**12**) (25%) was obtained as prisms, m.p. 140—141 °C (from hexane); $[\alpha]_D^{17}$ +112° (*c* 0.28 in $CHCl_3$); R_F 0.58; $\nu_{max.}$(KBr) 1 730s, 1 710s, and 1 618w cm^{-1}; $\lambda_{max.}$(EtOH) < 204 nm (ε > 18 300); δ_H($CDCl_3$) 2.03 and 2.15 (2 H, m, 6-H_2), 2.63 (1 H, m, 5β-H), 3.22 (1 H, m, 5α-H), 3.49 (1 H, m, 3β-H), 3.83 (1 H, m, 3α-H), 4.16 (1 H, ABq, *J* 12 Hz, 9-H), 4.43 (1 H, m, 8-H), 5.45 (1 H, ABq, *J* 12 Hz, 9-H), 5.55 (1 H, m, 7-H), 6.00 (1 H, br s, 2-H), and 6.28 and 6.29 (2 H, ABq, *J* 12 Hz, 12- and 13-H); δ_C($CDCl_3$) 33.8 (C-6), 53.9 (C-5), 60.7 (C-3 and -9), 75.3 and 77.7 (C-7 and -8), 130.7 and 130.9 (C-12 and -13), 131.6 (C-1), 135.2 (C-2), and 165.1 and 165.4 (C-11 and -14); *m/z* 235 (M^+, 21%), 137, 136, 120, 119, 94, 93 (100), and 80 (Found: M^+, 235.0848; C, 61.0; H, 5.6; N, 5.9. $C_{12}H_{13}NO_4$ requires *M*, 235.0845; C, 61.3; H, 5.6; N, 6.0%).

(−)-7,9-O,O-*Naphthaloylretronecine* (**13**).—By use of naphthalic (naphthalene-1,8-dicarboxylic) anhydride the *naphthalate diester* (**13**) was obtained as the hydrate (61%), colourless needles, m.p. 92—95 °C (from hexane); $[\alpha]_D^{20}$ −104° (*c* 0.11 in $CHCl_3$); R_F 0.59; $\nu_{max.}$(KBr) 3 620, 3 390, 3 180, 1 728, and 1 700 cm^{-1}; $\lambda_{max.}$(EtOH) 226 (ε 13 800) and 286 nm (2 840); δ_H($CDCl_3$) 2.22 (2 H, m, 6-H_2), 2.85 (1 H, m, 5β-H), 3.34 (1 H, m, 5α-H), 3.46 (1 H, m, 3β-H), 3.90 (1 H, m, 3α-H), 4.57 (1 H, ABq, *J* 12 Hz, 9-H), 4.61 (1 H, m, 8-H), 4.97 (1 H, ABq, *J* 12 Hz, 9-H), 5.94 (1 H, m, 2-H), 7.51 (2 H, m, 18- and 22-H), 7.77 (1 H, m, 17- or 23-H), 7.96 (2 H, m, 19- and 21-H), and 8.08 (1 H, m, 23- or 17-H); δ_C($CDCl_3$) 33.6 (C-6), 54.3 (C-5), 59.8 and 61.1 (C-3 and -9), 73.2 and 79.0 (C-7 and -8), 124.9, 125.5, 128.1, 131.6, 131.9, and 132.8 (C-17, -18, -19, -21, -22, and -23), 127.2, 128.5, 130.4, 132.1, and 134.1 (C-1, -12, -13, -14, and -20), 136 (C-2), and 168.0 and 169.1 (C-11 and C-14); *m/z* 335 (M^+, 11%), 198, 155, 154, 137, 136, 127, 126, 120, 119 (100), 94, 93, and 80 (Found: M^+, 335.1175. $C_{20}H_{17}NO_4$ requires *M*, 335.1158) (Found: C, 68.1; H, 5.1; N, 4.1. $C_{20}H_{17}NO_4{\cdot}H_2O$ requires C, 68.0; H, 5.4; N, 4.0%).

(−)-7,9-O,O-*Diphenoylretronecine* (**14**).—By use of diphenic (biphenyl-2,2′-dicarboxylic) anhydride the *diphenate diester* (**14**) (15%) was obtained as an oil, $[\alpha]_D^{18}$ −43° (*c* 0.43 in $CHCl_3$); R_F 0.59; $\nu_{max.}$(CCl_4) 1 744 (1 722sh), 1 691, and 1 652 cm^{-1}; $\lambda_{max.}$(EtOH) < 210 (ε > 36 700) and 278 (2 660); δ_H($CDCl_3$) 2.13 (2 H, m, 6-H_2), 2.74 (1 H, m, 5β-H), 3.42 (2 H, m, 3β-H and 5α-H), 3.93 (1 H, m, 3α-H), 4.34 (1 H, m, 8-H), 4.36 (1 H, ABq, *J* 12 Hz, 9-H), 5.33 (1 H, ABq, *J* 12 Hz, 9-H), 5.39 (1 H, m, 7-H), 5.84 (1 H, m, 2-H), and 7.30—7.64 (8 H, complex, 18-, 19-, 20-, 21-, 22-, 23-, 24-, and 25-H); δ_C($CDCl_3$) 34.6 (C-6), 53.9 (C-5), 62.2 and 62.8 (C-3 and -9), 74.8 and 77.0 (C-7 and -8), 126.6, 127.4, 127. 5, 128.7, 129.6, 130.5, 130.7, 130.8, and 131.3 (C-12, -18, -19, -20, -21, -22, -23, -24, and -25), 132.2, 132.4, 133.6, 139.3, and 140.0 (C-1, -12, -13, -14, and -15), and 167.5 and 167.8 (C-11 and -16); *m/z* 361 (M^+, 39%), 317, 316, 181, 180, 153, 152, 151, 137, 136, 120, 119 (100), 118, 117, 106, 94, 93, and 80 (Found: M^+, 361.1320. $C_{22}H_{19}NO_4$ requires *M*, 361.1314).

Preparation of (+)-7,9-O,O-(3,4,5,6-*Tetrachlorophthaloyl*)-*retronecine* (**9**) *using Hunig's Base*.—Tetrachlorophthalic anhydride (66.0 mg, 0.231 mmol) was added to a stirred solution of (−)-9-chloro-9-deoxyretronecine (**2**) hydrochloride (46.2 mg, 0.220 mmol) in DMF (2 ml) under argon at ambient temperature. After 5 min Hunig's base (*NN*-di-isopropylethylamine) (77 μl, 0.442 mmol) was then added dropwise by syringe. After the solution had been stirred for 24 h the solvent was evaporated off under reduced pressure to produce a clear brown oil. The oil was dissolved in dichloromethane (5 ml) and the solution was washed with saturated brine (5 ml) containing conc. ammonia (2 ml). The aqueous layer was washed with additional dichloromethane (2 × 5 ml), and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford the cyclised product (**9**) as an oil which crystallised with

time (45 mg, 48%). This compound was identical in all respects with the product obtained by use of DBU as base.

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