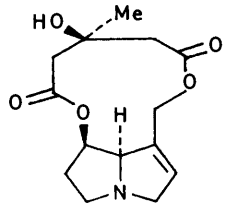
Pyrrolizidine Alkaloid Analogues. Synthesis of Macrocyclic Diesters of (±)-Synthanecine A Containing 12- to 16-Membered Rings

Robert H. Barbour and David J. Robins *
Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

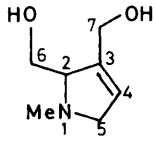
The first macrocyclic diesters of 2,3-bis(hydroxymethyl)-1-methyl-2,5-dihydropyrrole (**2**) [(±)-synthanecine A] with ring sizes of 12 to 16 have been prepared. Esterification of the imidazolide (**6**) of phenyl hydrogen adipate with (±)-synthanecine A was achieved at the 6-position. Treatment of the phenyl ester (**7**) with 1-(trimethylsilyl)imidazole and a catalytic quantity of sodium phenoxide produced the corresponding imidazolide and resulted in silylation of the free hydroxy group to afford the synthanecine A derivative (**8**). Attempted desilylation of the activated ester (**8**) followed by lactonisation failed and mixtures of oligomers were probably formed. In the successful route, treatment of (±)-synthanecine A (**2**) with thionyl chloride afforded (±)-3-chloromethyl-2-hydroxymethyl-1-methyl-2,5-dihydropyrrolium chloride (3). Nucleophilic displacement of the allylic chloride was carried out with adipic (**9a**), pimelic (**9b**), suberic (**9c**), azelaic (**9d**), and sebacic (**9e**) acids in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene to yield the 7-monoesters (**10a—e**) of synthanecine A. Lactonisation of these monoesters was achieved *via* the pyridine-2-thiol esters to give the new macrocyclic diesters (**4c—g**) with ring sizes of 12 to 16 in low overall yield (12—16%). Improved yields (25—30%) of the dilactones (**4c—g**) were obtained after rigorous purification and crystallisation of the allylic chloride hydrochloride (**3**).

Pyrrolizidine alkaloids have a wide distribution in plants, and cause problems for grazing livestock because many of the alkaloids are hepatotoxic.[1,2] The most toxic of these alkaloids are macrocyclic diesters of (+)-retronecine; one example is dicrotaline (**1**) which has an 11-membered ring.[3] Pyrrolizidine alkaloids with ring sizes of 11—14 are known[4] and analogues with 11-[5] and 10-membered[6] rings containing (+)-retronecine have been prepared. The key structural feature required in these compounds for the toxic action is an allylic ester function occurring as part of a 3-pyrroline (3,4-didehydropyrrolidine) system [as in structure (**1**)]. The toxic action is believed to involve dehydrogenation of the 1,2-unsaturated pyrrolizidine nucleus by hepatic oxidase enzymes to the corresponding pyrrole derivatives which can act as bifunctional alkylating agents.[2]

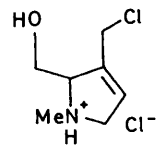
A monocyclic analogue of retronecine is 2,3-bis(hydroxymethyl)-1-methyl-2,5-dihydropyrrole (**2**) [(±)-synthanecine A]. Mattocks showed that ester derivatives of synthanecine A produce toxic effects similar to those caused by the corresponding esters of retronecine.[7] We considered that macrocyclic pyrrolizidine alkaloid analogues containing synthanecine A would be easier to prepare than natural macrocyclic pyrrolizidine alkaloids. These analogues would increase the range of compounds available for a detailed study of the relationships between structure, metabolism, and toxicity in this area.



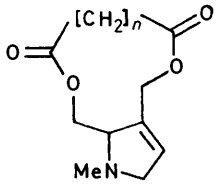
(1)



(2)



(3)



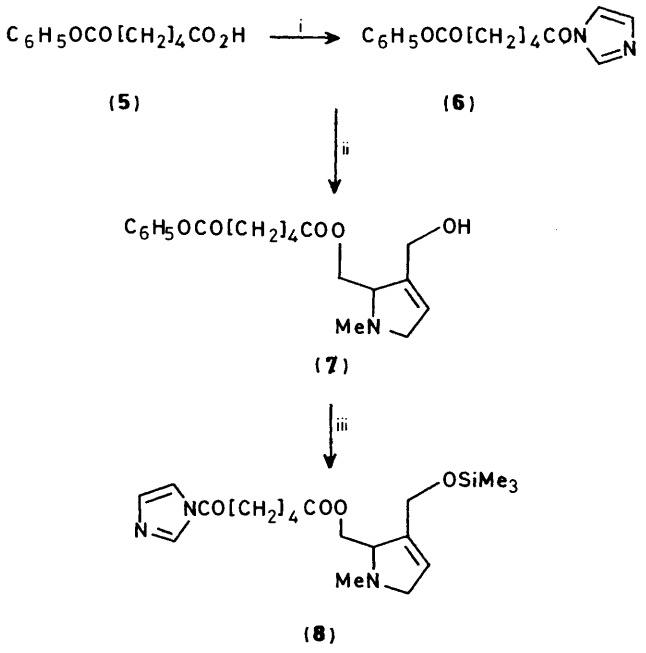
(4) a; $n = 2$
b; $n = 3$

At the start of this programme, a number of 11-[8] and 10-membered[9] macrocyclic diesters of (±)-synthanecine A (**2**) such as (**4a** and **b**) were prepared. Thus, treatment of the diol (**2**) with glutaric or succinic anhydride derivatives yielded the corresponding monoesters, which were lactonised *via* the pyridine-2-thiol esters.[10] In order to extend the range of analogues available for biological evaluation, an alternative route was developed. Synthanecine A (**2**) was converted into the allylic chloride (**3**) using thionyl chloride. Treatment of this product with succinic and glutaric anhydride derivatives in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave dilactones such as (**4**) directly.[11] Initial esterification of synthanecine A was followed by intramolecular nucleophilic substitution of the allylic chlorine by carboxylate anion to produce the 10- and 11-membered pyrrolizidine alkaloid analogues in good yield.

The use of succinic and glutaric anhydride derivatives in both these procedures restricts the formation of analogues to 10- and 11-membered rings. We were keen to prepare macrocyclic dilactones containing synthanecine A with larger rings for evaluation of their biological activity. The development of such a route might facilitate the preparation of macrocyclic pyrrolizidine alkaloids with ring sizes of 12 and 13.

Results and Discussion

Our initial strategy for construction of a macrocyclic diester of synthanecine A with a ring size of 12 is shown in Scheme 1. It was decided to prepare the phenyl ester (**7**), and then make use of the procedure of Masamune and co-workers for the conversion of phenyl esters into *N*-acylimidazoles.[12] Lactonis-



Scheme 1. *Reagents:* i, *N,N'*-carbonyldi-imidazole; ii, (±)-synthanecine A (**2**); iii, 1-(trimethylsilyl)imidazole, sodium phenoxide

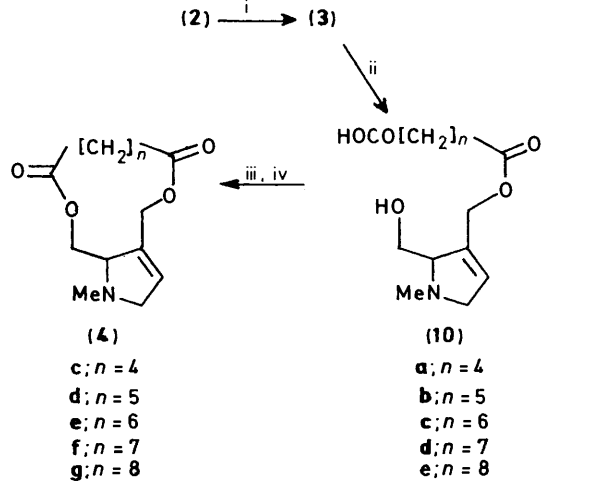
ation of the activated ester would complete the synthesis. Phenyl hydrogen adipate (**5**) was most conveniently prepared by treatment of adipic acid with phenol under Dean–Stark conditions using conc. sulphuric acid as catalyst. The reaction mixture was extracted at pH 8 to remove diphenyl adipate, then phenyl hydrogen adipate (44%) was separated from unchanged adipic acid by extraction at pH 5. The free acid group in phenyl hydrogen adipate (**5**) was activated by formation of the *N*-acylimidazole (**6**) in 85% yield. The imidazolide reacted selectively at C-6 of (±)-synthanecine A (**2**)[13] at room temperature to afford compound (**7**) in 49% yield after column chromatography. The ^{1}H n.m.r. spectrum of the synthanecine derivative (**7**) displayed a downfield shift of 0.4 p.p.m. for the C-6 protons, whereas the position of the C-7 protons was unchanged compared with that in synthanecine A (**2**). When the phenyl ester (**7**) was treated with 1 equiv. of 1-(trimethylsilyl)-imidazole and a catalytic amount of sodium phenoxide,[12] the trimethylsilyl ether of the alcohol (**7**) was formed. When 2 equiv. of 1-(trimethylsilyl)imidazole were employed, the *N*-acylimidazole (**8**) was probably formed, although this material was unstable and could not be purified. Accordingly, the crude reaction product was used directly in the next stage. However, attempts to form a lactone after cleavage of the silyl ether with fluoride under a variety of conditions (including high dilution) resulted in a mixture of products (t.l.c. data). The components of this mixture showed similar spectroscopic properties. In particular, the ^{1}H n.m.r. spectrum of the mixture showed downfield shifts for both C-6 and C-7 protons of *ca.* 0.4 p.p.m. In the mass spectrum of the mixture, fragment ions were observed at $M + 1$ and $M - 1$ (where M is the molecular ion calculated for the dilactone). From these data, it is likely that oligomers of synthanecine A and adipic acid have been formed.

In an alternative approach, the 6-adipoyl monoester of (±)-synthanecine A (**2**) was prepared *via* the *N*-acylimidazole, but this monoester could not be lactonised *via* the pyridine-2-thiol ester (Corey–Nicolaou procedure[10]).

It was desirable to make use of the greater nucleophilic character of the 6-hydroxy group of synthanecine A in the lactonisation step. This would require the preparation of the 7-monoester (**10**) of synthanecine A. This successful strategy,

Table. Yields of synthanecine A dilactones and chemical-shift differences for the C-6 and C-7 protons

Dilactone	Yield (%)	Δδ 6-H (p.p.m.)	Δδ 7-H (p.p.m.)
(**4a**)	(Ref. 9)	0.42	0.68
(**4b**)	(Ref. 8)	0.07	0.0
(**4c**)	12	0.76	0.72
(**4d**)	16	0.47	0.16
(**4e**)	10	0.73	0.21
(**4f**)	15	0.54	0.14
(**4g**)	15	0.30	0.08



Scheme 2. *Reagents and conditions:* i, $SOCl_2$; ii, $HO_2C[CH_2]_nCO_2H$ (**9a—e**), DBU, DMF; iii, 2,2'-dithiodipyridine, triphenylphosphine, DME; iv, high dilution, reflux

shown in Scheme 2, is a combination of two previously used routes to make macrocyclic diesters of synthanecine A.[8,11] (±)-Synthanecine A (**2**) was converted into the allylic chloride (**3**). This was treated with adipic acid (**9a**) and 2 equiv. of DBU in dry *N,N*-dimethylformamide (DMF) at room temperature for 2 days. A highly polar product was isolated and shown to be the expected 7-monoester (**10a**) of synthanecine A. The ^{1}H n.m.r. spectrum of this monoester (**10a**) showed a downfield shift of *ca.* 0.4 p.p.m. for the C-7 protons. The monoester (**10a**) was suspended in 1,2-dimethoxyethane (DME) and it gradually dissolved (formation of the pyridine-2-thiol ester) after the addition of 2,2'-dithiodipyridine and triphenylphosphine. The precipitated DBU·HCl was removed and the solution was diluted prior to effecting lactonisation by heating the mixture at reflux for 10 h. Purification of the dilactone was achieved by column chromatography on basic alumina. The 12-membered macrocyclic diester (**4c**) was obtained as an oil in *ca.* 12% yield, and was characterised as the picrolonate. The high-resolution mass spectrum of the free base (**4c**) contained a molecular ion corresponding to $C_{13}H_{19}NO_4$ with fragment ions typical for a dilactone of (±)-synthanecine A.[8,11] Ester carbonyl absorption for the free base (**4c**) was observed in its i.r. spectrum at 1 735 cm^{-1}. In the ^{1}H n.m.r. spectrum of the dilactone (**4c**), the diastereotopic pairs of protons at C-6 and C-7 both have large chemical-shift differences (Table). Both sets of signals were shifted downfield relative to the corresponding signals in the ^{1}H n.m.r. spectrum of synthanecine A (**2**). These data are convincing evidence for the formation of the 12-membered pyrrolizidine alkaloid analogue (**4c**).

In a similar fashion, new dilactones containing synthanecine

A with 13-, 14-, 15-, and 16-membered rings were prepared using pimelic (**9b**), suberic (**9c**), azelaic (**9d**), and sebacic (**9e**) acids, respectively. All of these macrocyclic diesters (**4d—g**) were obtained as oils, and solid derivatives were obtained for bases (**4d**) and (**4e**). All of the free bases showed ester carbonyl absorption at 1 735 cm^{-1} in their i.r. spectra. Correct accurate mass data were obtained for the four free bases (**4d—g**). The ^1H n.m.r. spectra of the free bases all showed downfield shifts of the C-6 and C-7 protons relative to synthanecine A. The chemical-shift differences for these sets of diastereotopic protons are recorded in the Table, with the values for the succinate (**4a**) and glutarate (**4b**) dilactones for comparison. A wide range of values was observed which may be a result of the different conformations adopted by the macrocyclic rings in these dilactones. An *X*-ray crystal structure analysis of the 10-membered dilactone (**4a**) has been carried out.[11] This showed that the ester carbonyl groups are antiparallel with the oxygen of the saturated ester carbonyl on the same side as the bridgehead hydrogen (2-H). Similar conformations have been established for the succinate diester of (+)-retronecine,[14] and for all the 12-membered macrocyclic pyrrolizidine alkaloids whose *X*-ray structures have been analysed.[4]

One of the major problems in developing the successful synthetic route was the purification of the allylic chloride (**3**). This was recently obtained crystalline and an *X*-ray crystal structure analysis was performed to confirm the structure.[15] The use of crystalline material in the synthesis of the macrocyclic diesters (**4d—g**) resulted in improved yields (25—30%).

The metabolism and toxicity of some of the 10- and 11-membered macrocyclic dilactones incorporating (±)-synthanecine A (**2**) were recently investigated.[16] Further studies with the new macrocyclic diesters (**4d—g**) are now in progress.

Experimental

M.p.s were measured with a Kofler hot-stage apparatus and are uncorrected. Organic solutions were dried with anhydrous $MgSO_4$, and solvents were evaporated off under reduced pressure below 40 °C. ^1H N.m.r. spectra were recorded with a Bruker WP-200SY spectrometer operating at 200 MHz. Spectra were recorded for solutions in deuteriochloroform with tetramethylsilane as internal standard, and they were subjected to first-order analysis in order to obtain *J* values. Mass spectra were obtained with A.E.I. MS 12 or 902 spectrometers. 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) unless otherwise stated, and the unsaturated bases were located by oxidation with *o*-chloranil, followed by treatment with Ehrlich's reagent.[17] DME was dried by distillation from potassium hydroxide and then from sodium–benzophenone under argon immediately prior to use. DMF was dried using 3 Å molecular sieves as described by Burfield and Smithers.[18]

Phenyl Hydrogen Adipate (**5**).—Adipic acid (**9a**) (50 g, 0.34 mol), phenol (32 g, 0.34 mol), and conc. sulphuric acid (1 ml) were added to toluene (350 ml). The solution was heated at reflux until the correct amount of water (*ca.* 6 ml) had collected in a Dean–Stark apparatus (*ca.* 30 h). Some of the toluene (150 ml) was removed by distillation and the resulting solution was allowed to cool before it was added, slowly, to a flask containing stirred saturated aqueous sodium hydrogen carbonate (350 ml). When effervescence had subsided the aqueous solution was washed with diethyl ether (3 × 350 ml) and acidified with 2M hydrochloric acid to pH 5. The acidic solution was extracted with chloroform (3 × 400 ml) and the combined chloroform extracts were dried ($MgSO_4$). Removal of the solvent gave *phenyl hydrogen adipate* (**5**) (33 g, 44%), m.p. 96—97 °C [from benzene–light petroleum (b.p. 60—80 °C)]; R_F 0.5 [ethyl acetate–light petroleum (b.p. 60—80 °C) (1:1)]; $\nu_{max.}$(KBr) 3 040, 1 758, 1 695, and 1 130 cm^{-1}; δ_H(90 MHz) 1.80 (4 H, m, 3- and 4-H_2), 2.44 (2 H, t, *J* 6 Hz, 5-H_2), and 2.59 (2 H, t, *J* 6 Hz, 2-H_2), and 7.00—7.50 (5 H, m, Ph); δ_C(25 MHz) 24.0 and 24.2 (C-3 and -4), 33.6 and 33.9 (C-2 and -5), 121.6 (C-3′ and -5′), 125.8 (C-4′), 129.4 (C-2′ and -6′), 150.7 (C-1′), 171.8 (C-1), and 179.7 (C-6); *m/z* 222 (M^+), 129, 111, 101, 94, 83, and 77 (Found: M^+, 222.0899; C, 64.8; H, 6.3%. $C_{12}H_{14}O_4$ requires *M*, 222.0893; C, 64.85; H, 6.35%).

Phenyl 5-(Imidazol-1-ylcarbonyl)valerate (**6**).—*N,N′*-Carbonyldi-imidazole (1.75 g, 11 mmol) was added to a solution of phenyl hydrogen adipate (**5**) (2 g, 9 mmol) in dry DME (45 ml) under argon. When effervescence had subsided (*ca.* 20 min) the solvent was removed under reduced pressure and the resulting white solid was dissolved in dichloromethane (40 ml). The organic solution was washed with water (3 × 40 ml) to remove imidazole, dried ($MgSO_4$), and concentrated at reduced pressure to give the imidazolide (**6**) (2.45 g, 85%) as a white solid; $\nu_{max.}$(KBr) 3 122, 1 760, 1 730, and 1 130 cm^{-1}; δ_H(90 MHz) 1.90 (4 H, m, 2 × CH_2CH_2CO), 2.63 (2 H, t, *J* 6 Hz, CH_2CO), 2.65 (2 H, t, *J* 6 Hz, CH_2CO), 7.00—7.50 (5 H, m, Ph), 7.19 (1 H, s, Im), 7.48 (1 H, s, Im), and 8.16 (1 H, s, Im); δ_C(25 MHz) 23.3 and 24.1 (C-3 and -4), 33.9 and 34.8 (C-2 and -5), 116.0 (Im), 121.5 (C-3′ and -5′), 125.9 (C-4′), 129.4 (C-2′ and -6′), 131.1 (Im), 136.1 (Im), 150.7 (C-1′), 169.0 (C=O) and 171.6 (C=O); *m/z* 205 (M^+ − Im), 177, 159, 135, 111, 94, 87, and 77.

Phenyl Ester (**7**) *of 6-O-Adipoylsynthanecine A*.—Synthanecine A (**2**) (300 mg, 2.1 mmol) was dissolved in dry DME (20 ml) under argon and the *N*-acylimidazole (**6**) (510 mg, 2.1 mmol) was added. The reaction mixture was stirred at room temperature. After 48 h the solvent was removed under reduced pressure and the resulting brown oil was dissolved in dichloromethane (20 ml). The organic solution was washed with water (3 × 20 ml) to remove imidazole, dried ($MgSO_4$), and filtered. After removal of the solvent under reduced pressure, the residual oil was purified by column chromatography [basic alumina; chloroform–dichloromethane (1:5)]. This afforded the *phenyl ester* (**7**) of 6-O-*adipoylsynthanecine A* (360 mg, 49%); R_F 0.47; $\nu_{max.}$(CCl_4) 3 460, 2 780, 1 760, 1 740, and 1 130 cm^{-1}; δ_H(90 MHz) 1.75 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.39 (2 H, m, $CH_2CO_2CH_2$), 2.48 (3 H, s, NMe), 2.56 (2 H, m, CH_2CO_2Ph), 2.83 (1 H, br s, OH), 3.25 (1 H, m, 5-H), 3.59 (1 H, m, 2-H), 3.81 (1 H, m, 5-H), 4.16 (1 H, s, 7-H_2), 4.18 (1 H, d, *J* 5 Hz, 6-H_2), 5.71 (1 H, br s, 4-H), and 7.00—7.50 (5 H, m, Ph); δ_C(25 MHz) 24.2 (2 × $CH_2CH_2CO_2$), 33.8 (2 × CH_2CO_2), 41.8 (NMe), 59.5 and 61.4 (C-5 and -6), 65.2 (C-7), 70.7 (C-2), 121.5 (2 s, Ph), 124.0 (C-4), 125.7 (Ph), 129.4 (2 s, Ph), 141.2 (C-3), 150.7 (Ph), 171.8 (C=O), and 173.2 (C=O); *m/z* 347 (M^+, 254, 222, 124, 111, 108, 94, and 82 (Found: M^+, 347.1732. $C_{19}H_{25}NO_5$ requires *M*, 347.1732).

Attempted Lactonisation of Phenyl Ester (**7**).—To a stirred solution of the phenyl ester (**7**) (100 mg, 0.29 mmol) in dry tetrahydrofuran (THF) (1.4 ml) under argon was added 1-(trimethylsilyl)imidazole (93 μl, 0.64 mmol). After 5 min at room temperature sodium phenoxide (catalytic) was added. The mixture was stirred for 2 h and then the solvent was removed under reduced pressure to leave the trimethylsilyl ether (**8**) as a clear oil; δ_H(90 MHz) 0.02 (9 H, s, Me_3Si), 1.75 (4 H, m, 2 × CH_2CH_2CO), 2.35 (4 H, m, CH_2CO), 2.52 (3 H, s, NMe), 3.27 (1 H, m, 5-H), 3.65 (1 H, m, 2-H), 3.83 (1 H, m, 5-H), 4.23 (2 H, s, 7-H_2), 4.23 (2 H, d, *J* 5 Hz, 6-H_2), 5.78 (1 H, br s, 4-H), 7.18 (1 H, s, Im), 7.48 (1 H, s, Im), and 8.17 (1 H, s, Im), plus signals

for imidazole and phenol. This mixture was immediately treated with anhydrous potassium fluoride (37 mg, 0.64 mmol) and 18-crown-6 (catalytic). After a further 5 h at room temperature the solvent was removed under reduced pressure. The oily residue was dissolved in dichloromethane (10 ml) and the organic solution was washed successively with aqueous potassium chloride (1M) (3 × 8 ml) to remove imidazole and 18-crown-6, and then with dil. aqueous sodium hydroxide (8 ml) and water (2 × 8 ml) to remove phenol. The organic solution was dried ($MgSO_4$), filtered, and concentrated to give an oil (69 mg); R_F 0.4, 0.5, and 0.6; $\nu_{max.}(CHCl_3)$ 2 950, 2 870, and 1 730 cm^{-1}; δ_H(90 MHz) 1.65 (4 H, m, 2 × $CH_2CH_2CO_2$), 2.34 (4 H, m, 2 × CH_2CO_2), 2.50 (3 H, s, NMe), 3.27 (1 H, m, 5-H), 3.60 (1 H, m, 2-H), 3.84 (1 H, m, 5-H), 4.16 (2 H, d, *J* 5 Hz, 6-H_2), 4.65 (2 H, s, 7-H_2), and 5.81 (1 H, br s, 4-H); δ_C(50 MHz) 24.3 (2 × $CH_2CH_2CO_2$), 33.7 (2 × CH_2CO_2), 41.8 (NMe), 60.5 and 61.4 (C-5 and -6), 65.0 (C-7), 70.6 (C-2), 127.2 (C-4), 136.0 (C-3), 172.8 and 173.0 (2 × C=O); *m/z* 254, 252, 199, 123, 107, and 94 [expected M^+ for (±)-6,7-*O*,*O*′-adipoylsynthanecine A (**4c**) is *m/z* 253].

Synthesis of Macrocyclic Diesters of Synthanecine A. General Procedure.—The diacid (0.5 mmol) and DBU (1.05 mmol) were added to a solution of the allylic chloride (**3**)[11] as a brown oil (0.5 mmol) in dry DMF (3 ml) under argon. The mixture was stirred at room temperature until the starting material had reacted (t.l.c.) (*ca.* 48 h). The DMF was removed under reduced pressure (3 mmHg) and dry DME (35 ml) was added to the resulting oily residue. 2,2′-Dithiodipyridine (1.06 mmol) and triphenylphosphine (1.06 mmol) were added and the reaction mixture was stirred vigorously at room temperature, under argon, until thiol ester formation was complete (t.l.c., R_F *ca.* 0.3) (*ca.* 48 h); a yellow solution containing a suspended white solid was observed. The white solid was allowed to settle out before the yellow solution was taken up in a syringe. This solution was added dropwise during 2 h to dry DME (70 ml) heated at reflux, under argon. Heating at reflux was continued until lactonisation was complete (t.l.c., R_F 0.6—0.7) (*ca.* 10 h). The solution was concentrated under reduced pressure to afford an oil. The oil was extracted with 1M citric acid (3 × 4 ml). The combined acid extracts were washed with chloroform (6 × 12 ml), then basified with conc. ammonia to pH 10, and extracted with chloroform (4 × 15 ml). The chloroform extracts were dried, filtered, and concentrated to afford an oil. Purification was achieved on basic alumina, elution being with increasing proportions of chloroform in dichloromethane.

(±)-6,7-O,O′-*Adipoylsynthanecine A* (**4c**).—The reaction of adipic acid (**9a**) (73 mg, 0.5 mmol) with the allylic chloride (**3**) (100 mg, 0.5 mmol) was carried out as described in the general procedure to yield the 12-*membered dilactone* (**4c**) (15 mg, 12%) as an oil, R_F 0.68; $\nu_{max.}(CCl_4)$ 2 940, 2 780, 1 735, 1 260, 1 170, 994, and 908 cm^{-1}; δ_H(200 MHz) 1.70 (4 H, m, 11- and 12-H_2), 2.30 (4 H, m, 10- and 13-H_2), 2.50 (3 H, s, NMe), 3.25 (1 H, m, 5-H), 3.61 (1 H, m, 2-H), 3.76 (1 H, dd, J_{gem} 11, J_{vic} 7 Hz, 6-H), 3.81 (1 H, m, 5-H), 4.52 (1 H, dd, J_{gem} 11, J_{vic} 2.6 Hz, 6-H), 4.31 (1 H, d, J_{gem} 12 Hz, 7-H), 5.03 (1 H, d, J_{gem} 12 Hz, 7-H), and 5.86 (1 H, br, s, 4-H); δ_C(50 MHz) 23.7 and 23.8 (C-11 and -12), 33.7 and 33.8 (C-10 and -13), 41.25 (NMe), 61.0 and 61.2 (C-5 and -6), 65.2 (C-7), 70.3 (C-2), 129.6 (C-4), 136.5 (C-3), and 173.0 and 173.4 (C-9 and -14); *m/z* 253 (M^+), 251, 123, 107, 94, and 55 (Found: M^+, 253.1316. $C_{13}H_{19}NO_4$ requires *M*, 253.1314). The *picrolonate* had m.p. 207—209 °C (from EtOH); *m/z* 264 (picrolonic acid), 253 (M^+), 111, 108, 107, 94, and 80 (Found: M^+, 253.1320. $C_{13}H_{19}NO_4$ requires *M*, 253.1314) (Found: C, 53.6; H, 5.4; N, 13.4. $C_{23}H_{27}N_5O_9$ requires C, 53.38; H, 5.26; N, 13.53%).

(±)-6,7-O,O′-*Pimeloylsynthanecine A* (**4d**).—Treatment of the allylic chloride (**3**) (166 mg, 0.84 mmol) with pimelic acid (**9b**) (134 mg, 0.84 mmol) was performed as described in the general procedure to afford the 13-*membered dilactone* (**4d**) (35 mg, 16%) as an oil; R_F 0.69; $\nu_{max.}(CCl_4)$ 2 940, 2 780, 1 735, 1 260, 1 160, and 1 060 cm^{-1}; δ_H(200 MHz) 1.20—1.90 (6 H, m, 11-, 12-, and 13-H_2), 2.35 (4 H, m, 10- and 14-H_2), 2.50 (3 H, s, NMe), 3.25 (1 H, m, 5-H), 3.50 (1 H, m, 2-H), 3.81 (1 H, m, 5-H), 3.88 (1 H, dd, J_{gem} 11.5, J_{vic} 7.5 Hz, 6-H), 4.35 (1 H, dd, J_{gem} 11.5, J_{vic} 2 Hz, 6-H), 4.54 (1 H, d, J_{gem} 12 Hz, 7-H), 4.70 (1 H, d, J_{gem} 12 Hz, 7-H), and 5.88 (1 H, br s, 4-H); δ_C(50 MHz) 23.8 and 24.1 (C-11 and -13), 27.1 (C-12), 34.2 and 36.0 (C-10 and -14), 40.9 (NMe), 60.6 and 60.8 (C-5 and -6), 64.9 (C-7), 70.6 (C-2), 130.3 (C-4), 136.9 (C-3), and 173.7 and 173.8 (C-9 and -15). The *picrolonate* had m.p. 186—187 °C (from EtOH); *m/z* 267 (M^+), 264 (picrolonic acid), 234, 156, 124, 123, 111, 108, 107, and 94 (Found: M^+, 267.1468. $C_{14}H_{21}NO_4$ requires *M*, 267.1470) (Found: C, 54.1; H, 5.4; N, 13.1. $C_{24}H_{29}N_5O_9$ requires C, 54.23; H, 5.50; N, 13.8%).

(±)-6,7-O,O′-*Suberoylsynthanecine A* (**4e**).—In a similar fashion, suberic acid (**9c**) (87 mg, 0.5 mmol) was treated with the allylic chloride (**3**) (100 mg, 0.5 mmol) to afford the 14-*membered dilactone* (**4e**) (14 mg, 10%) as an oil; R_F 0.73; $\nu_{max.}(CCl_4)$ 2 940, 2 785, 1 735, 1 250, 1 168, and 910 cm^{-1}; δ_H(200 MHz) 1.30 (4 H, m, 12- and 13-H_2), 1.70 (4 H, m, 11- and 14-H_2), 2.33 (4 H, m, 10- and 15-H_2), 2.54 (3 H, s, NMe), 3.29 (1 H, m, 5-H), 3.60 (1 H, m, 2-H), 3.74 (1 H, dd, J_{gem} 11, J_{vic} 3.6 Hz, 6-H), 3.80 (1 H, m, 5-H), 4.47 (1 H, dd, J_{gem} 11, J_{vic} 2 Hz, 6-H), 4.54 (1 H, d, J_{gem} 12 Hz, 7-H), 4.75 (1 H, d, J_{gem} 12 Hz, 7-H), and 5.88 (1 H, br s, 4-H); δ_C(50 MHz) 24.4 and 24.5 (C-12 and -13), 25.7 and 25.8 (C-11 and -14), 32.6 and 32.9 (C-10 and -15), 41.2 (NMe), 60.8 and 61.1 (C-5 and -6), 66.3 (C-7), 70.2 (C-2), 130.6 (C-4), 137.2 (C-3), 173.8 and 174.0 (C-9 and -16). The *picrolonate* had m.p. 191—193 °C (from EtOH); *m/z* 281 (M^+), 264 (picrolonic acid), 248, 111, 108, 107, and 94 (Found: M^+, 281.1632. $C_{15}H_{23}NO_4$ requires *M*, 281.1627) (Found: C, 55.1; H, 5.5; N, 12.6. $C_{25}H_{31}N_5O_9$ requires C, 55.04; H, 5.73; N, 12.84%).

(±)-6,7-O,O′-*Azelaoylsynthanecine A* (**4f**).—Treatment of the allylic chloride (**3**) (250 mg, 1.26 mmol) with azelaic acid (**9d**) (237 mg, 1.26 mmol) as described above afforded the 15-*membered dilactone* (**4f**) (56 mg, 15%) as an oil; R_F 0.68; $\nu_{max.}(CCl_4)$ 2 940, 2 785, 1 735, 1 242, and 1 162; δ_H(200 MHz) 1.30 (6 H, m, 12-, 13-, and 14-H_2), 1.60 (4 H, m, 11- and 15-H_2), 2.35 (4 H, m, 10-and 16-H_2), 2.51 (3 H, s, NMe), 3.28 (1 H, m, 5-H), 3.52 (1 H, m, 2-H), 3.80 (1 H, m, 5-H), 3.88 (1 H, dd, J_{gem} 11, J_{vic} 7.5 Hz, 6-H), 4.42 (1 H, dd, J_{gem} 11, J_{vic} 3 Hz, 6-H), 4.59 (1 H, d, J_{gem} 12 Hz, 7-H), 4.73 (1 H, d, J_{gem} 12 Hz, 7-H), and 5.88 (1 H, br s, 4-H); δ_C(50 MHz) 23.5 and 23.6 (C-12 and -14), 26.0 (C-13), 26.9 and 27.1 (C-11 and -15), 33.9 and 34.1 (C-10 and -16), 41.1 (NMe), 60.6 and 61.1 (C-5 and -6), 65.5 (C-7), 70.6 (C-2), 130.0 (C-4), 137.1 (C-3), 173.6 and 173.7 (C-9 and -17); *m/z* 295 (M^+), 217, 123, 107, 94, 82, and 67 (Found: M^+, 295.1785. $C_{16}H_{25}NO_4$ requires *M*, 295.1784). The picrate and picrolonate salts could not be prepared.

(±)-6,7-O,O′-*Sebacoylsynthanecine A* (**4g**).—The allylic chloride (**3**) (200 mg, 1 mmol) and sebacic acid (**9e**) (204 mg, 1 mmol) reacted together as described in the general procedure, to yield the 16-*membered dilactone* (**4g**) (47 mg, 15%) as an oil; R_F 0.68; $\nu_{max.}(CCl_4)$ 2 940, 2 780, 1 735, 1 260, and 1 168 cm^{-1}; δ_H(200 MHz) 1.31 (8 H, m, 12-, 13-, 14-, and 15-H_2), 1.65 (4 H, m, 11- and 16-H_2), 2.33 (4 H, m, 10- and 17-H_2), 2.53 (NMe), 3.32 (1 H, m, 5-H), 3.60 (1 H, m, 2-H), 3.83 (1 H, m, 5-H), 4.00 (1 H, dd, J_{gem} 11, J_{vic} 5 Hz, 6-H), 4.30 (1 H, dd, J_{gem} 11, J_{vic} 4 Hz, 6-H), 4.60 (1 H, d, J_{gem} 13 Hz, 7-H), 4.68 (1 H, d, J_{gem} 13 Hz, 7-H), and

5.86 (1 H, br s, 4-H); δ_C(50 MHz) 23.9, 24.0, 26.1, 26.4, 26.8 (× 2) (C-11, -12, -13, -14, -15, and -16), 33.9 and 34.3 (C-10 and -17), 41.8 (NMe), 60.7 and 61.5 (C-5 and -6), 65.4 (C-7), 70.5 (C-2), 128.0 (C-4), 136.0 (C-3), 173.5 and 173.8 (C-9 and -18); *m/z* 309 (M^+), 218, 124, 108, 107, 94, 78, and 67 (Found: M^+, 309.1965. $C_{17}H_{27}NO_4$ requires *M*, 309.1940). The picrolonate could not be prepared.

(±)-3-Chloromethyl-2-hydroxymethyl-1-methyl-2,5-dihydropyrrolium chloride (**3**) was originally obtained as a purple oil.[11] Purification of the oil by repeated treatment with activated charcoal produced a pale brown oil which eventually crystallised from ethanol–acetone as prisms, m.p. 135 °C.[11] When the synthesis of the macrocyclic dilactones was repeated with this crystalline material, improved yields (25—30%) were obtained.

Acknowledgements

We thank the S.E.R.C. and the M.R.C. for a CASE studentship (to R. H. B.) and we are grateful to Dr. A. R. Mattocks, M.R.C. Toxicology Unit, Carshalton, Surrey, for helpful discussions.

References

1 D. J. Robins, *Fortschr. Chem. Org. Naturst.*, 1982, **41**, 115.
2 A. R. Mattocks, 'Chemistry and Toxicology of Pyrrolizidine Alkaloids.' Academic Press, London, 1986.
3 K. Brown, J. A. Devlin, and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1819.
4 D. J. Robins, *Nat. Prod. Rep.*, 1984, **1**, 235; 1985, **2**, 213; 1986, **3**, 297.
5 J. A. Devlin, D. J. Robins, and S. Sakdarat, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1117.
6 M. Burton and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1985, 611.
7 H. E. Driver and A. R. Mattocks, *Chem.-Biol. Interact.*, 1984, **51**, 201.
8 R. H. Barbour and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2475.
9 R. H. Barbour, A. A. Freer, and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2069.
10 E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1974, **96**, 5614.
11 R. H. Barbour and D. J. Robins, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1169.
12 G. S. Bates, J. Diakur, and S. Masamune, *Tetrahedron Lett.*, 1976, 4423.
13 A. R. Mattocks, *J. Chem. Soc., Perkin Trans. 1*, 1974, 707; 1978, 896.
14 M. Burton, A. A. Freer, and D. J. Robins, *Acta Crystallogr., Sect. C*, 1985, **41**, 944.
15 A. A. Freer and D. J. Robins, *Acta Crystallogr., Sect. C*, 1987, **43**, 2240.
16 A. R. Mattocks, H. E. Driver, R. H. Barbour, and D. J. Robins, *Chem.-Biol. Interact.*, 1986, **58**, 95.
17 H. J. Huizing, F. DeBoer, and T. M. Malingré, *J. Chromatogr.*, 1980, **195**, 407; R. J. Molyneux and J. N. Roitman, *ibid.*, p. 412.
18 D. R. Burfield and R. H. Smithers, *J. Org. Chem.*, 1978, **43**, 3966.

Received 6th October 1987; *Paper* 7/1786