SYNTHESIS OF 4-AZATRICYCLO[4,4,0,$0^{3,8}$]DECAN-5-ONE A LACTAM WITH A NON-PLANAR *cis*-AMIDE GROUP — AND RELATED COMPOUNDS*

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The synthesis of racemic, as well as optically active, 4-azatricyclo[4,4,0,$0^{3,8}$]decan-5-one (4-aza-twistan-5-one), its N-methyl derivative, 4-azatricyclo[4,4,0,$0^{3,8}$]decane and 4-azatricyclo-[4,3,1,$0^{3,7}$]decan-5-one, from the corresponding bicyclo[2,2,2]octane derivatives is described. The absolute configuration of all the optically active compounds was derived unequivocally from the known absolute configuration of the starting compounds.

Recently, there is a still growing number of data indicating that amide groups in peptides and related compounds may not necessarily be planar, as was previously (with much simplification) inferred from the original Pauling's concepts[2,3] (for a review see ref.[4]). Convenient models for studying non-planar amide groups have been found among lactams (*e.g.*[5,6]) and cyclopeptides[7,8]. The presence of a non-planar amide group in optically active amides, lactams and peptides deserves particular attention. The usual chromophore in these compounds which absorbs in the measurable UV-region of the spectrum – the amide group – is symmetrical in its planar arrangement (having a plane of symmetry) and its chiroptical properties are determined by the chirality, induced by its environment. On the contrary, a non-planar amide group necessarily represents an inherently chiral chromophore. According to the common experience[9], the dichroic electronic transitions in inherently chiral chromophores exhibit substantially higher rotational strengths than the analogous transitions in chromophores with induced chirality. Therefore, even relatively small deviations from planar arrangement of the amide group could manifest themselves expressively in the chiroptical properties, even though these deviations have almost no influence on other chemical or physical properties. Similar marked differences could exist also in biochemical interactions with other chiral molecules.

Systematic study of these effects requires suitable model compounds of known

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absolute configuration and conformation of the amide group. Further, such models must exhibit certain conformational stability in order to enable the interpretability of the results, and finally, they have to be accessible. Necessarily – at least in the beginning of our studies – we have to select models with a rigid structure. We have suggested[1] the 4-azatwistane lactam *I* as a suitable model in which the non-planarity of the amide group is guaranteed by the geometry of the rigid molecule. The present communication describes the synthesis of this and related compounds. The three-dimensional structure of the crystalline compound *Ia* has been determined by X-ray diffraction by Venkatesan and collaborators[10]. We studied the infrared[11] and CD spectra[12] of this lactam and carried out also some quantum chemical calculations[13].

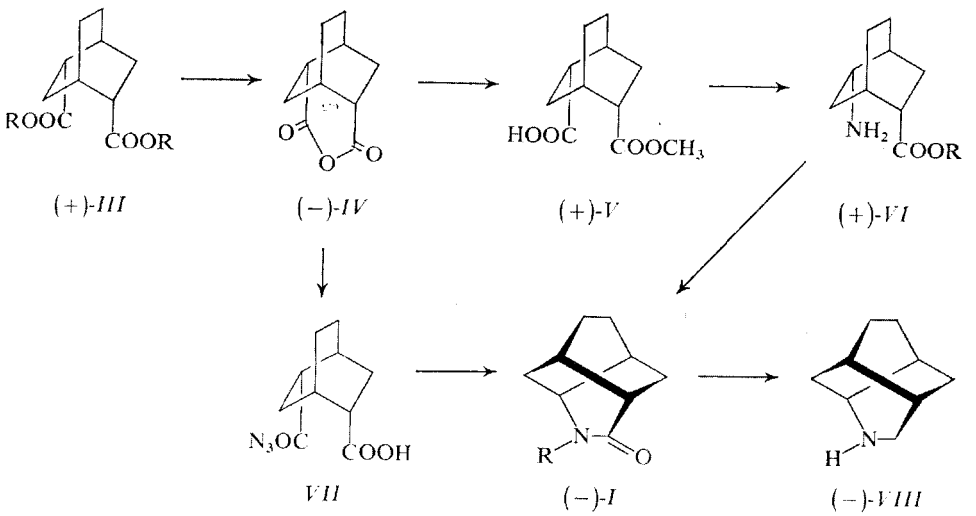
As models with a planar amide group – though as a part of a five-membered ring – we synthesized derivatives of 4-azatricyclo[4,3,1,$0^{3,7}$]decane the molecular skeleton of which is similar to that of the 4-azatwistane derivatives.

The 4-azatricyclo[4,4,0,$0^{3,8}$]decane (azatwistane) system was synthesized by cyclisation of *endo,endo*-2-aminobicyclo[2,2,2]octane-5-carboxylic acid (*VIa*) which in turn was prepared in good yield from *endo,endo*-bicyclo[2,2,2]octane-2,5-dicarboxylic acid (*IIIa*) as shown in Scheme 1. The method of choice was the cyclisation of the chloride hydrochloride of *VIa*, prepared *in situ* in dimethylformamide; the alternative cyclisation of the amino ester *VIb* or the direct pyrolysis of the amino acid *VIa* gave very poor yields. Also, the attempted thermal decomposition of the monoazide *VII* prepared *via* the anhydride *IV*, gave only very low yields of the product. The lactam *Ia* was methylated to the N-methyl derivative *Ib* using sodium hydride and methyl iodide in dimethylformamide. Reduction of *Ia* with lithium aluminium hydride afforded 4-azatwistane *VIII*.

The same reactions were used in the synthesis of optically active derivatives. Since the absolute configuration of the starting (+)-bicyclo[2,2,2]octane-2,5-dicarboxylic acid, (+)-*IIIa*, is already known[14] to be 2*S*, 5*S*, we can assign the absolute configuration also to all optically active azatwistane derivatives prepared in this study (Scheme 1).

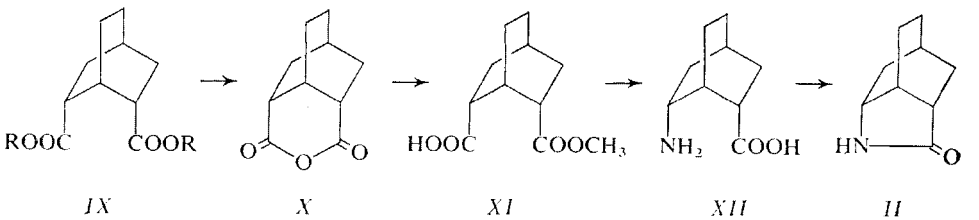
The 4-azatricyclo[4,3,1,$0^{3,7}$]decane system was built by cyclisation of 2-aminobicyclo[2,2,2]octane-6-carboxylic acid (*XII*), prepared from *endo,endo*-bicyclo[2,2,2]octane-2,6-dicarboxylic acid (*IXa*) (ref.[15]), analogously to the 4-azatwistane series (Scheme 2). In this case a simple pyrolysis of the free acid *XII* was satisfactory. Due to an error, the acid *IXa* was previously reported[15] to melt at 227–229°C; its correct melting point is 242–243°C.

The optically active lactam (+)-*II* was synthesized from (−)-(2*R*)-bicyclo[2,2,2]-octane-2-carboxylic acid, (−)-*XIII*, of known absolute configuration[14,16]. The acid (−)-*XIII* was converted *via* its chloride into the azide *XIV* which was then photolyzed to give the optically active lactam (+)-*II* in 11% yield, besides great amount of the corresponding isocyanate (Scheme 3). A control experiment has shown that under



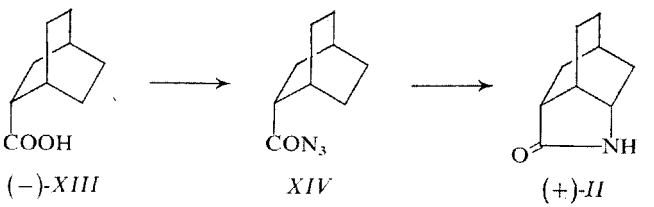
SCHEME 1

In formulae: *a*, R = H; *b*, R = CH_3. The absolute configuration, as represented by formulae, corresponds to the given signs of optical rotation.



SCHEME 2

In formulae: *a*, R = H; *b*, R = CH_3



SCHEME 3

The absolute configuration, as represented by the formulae, corresponds to the given signs of optical rotation.

the conditions used (0°C) for the conversion of (−)-*XIII* into *XIV* no epimerisation took place. Since it is unlikely that the photochemical cyclisation would involve racemisation we may assume that the lactam (+)-*II* obtained in this way is optically pure or nearly so.

EXPERIMENTAL

endo,endo-Bicyclo[2,2,2]octane-2,5-dicarboxylic Anhydride (*IV*)

A solution of the acid *IIIa* (4·0 g) in acetic anhydride (20 ml) was refluxed for 2 h. The volatile parts were distilled off under normal pressure, then at 10 Torr and the residue was sublimed *in vacuo* (0·1 Torr) at bath temperature 200—260°C. The sublimate was sublimed once more, residues from both the sublimations were combined, boiled again with acetic anhydride and worked up as described above. The total yield of *IV* was 3·2 g (89%), m.p. 217—220°C. For $C_{10}H_{12}O_3$ (180·2) calculated: 66·65% C, 6·71% H; found: 66·60% C, 6·71% H.

endo,endo-2-Methoxycarbonylbicyclo[2,2,2]octane-5-carboxylic Acid (*V*)

A solution of the anhydride *IV* (3·1 g) in methanol (70 ml) was refluxed for 2 h, the solvent was removed and the product distilled at 130—131°C/0·1 Torr, m.p. 79—81°C (in bulk), yield 3·05 g (85%). For $C_{11}H_{16}O_4$ (212·2) calculated: 62·25% C, 7·60% H; found: 62·40% C, 7·61% H.

endo,endo-2-Aminobicyclo[2,2,2]octane-5-carboxylic Acid (*VIa*)

A mixture of the monomethyl ester *V* (2·95 g) and thionyl chloride (9·8 g; 6 ml) was stirred for 1·5 h at room temperature. The thionyl chloride was distilled off *in vacuo* at room temperature. A small sample of the remaining ester-chloride was converted into *IIIb* which was pure according to gas–liquid chromatography. The ester-chloride was dissolved in dimethylformamide (15 ml) and after stirring at 0°C for 1 h freshly activated[17,18] dry sodium azide (3 g) was added. The mixture was stirred for 2 h at 0°C, diluted with water and the product was taken into benzene (5 × 25 ml). The combined benzene extracts were washed with water, dried and concentrated to about 40 ml. The solution was refluxed until the nitrogen evolution ceased (45 min). A sample taken from the mixture (b.p. 74—75°C/0·1 Torr) proved to be methyl *endo,endo*-5-isocyanatobicyclo[2,2,2]octane-2-carboxylate; IR spectrum: 2270 cm^{-1} (NCO). For $C_{11}H_{15}NO_3$ (209·2) calculated: 63·14% C, 7·23% H, 6·69% N; found: 63·03% C, 7·26% H, 7·07% N. The crude reaction mixture was refluxed under stirring with concentrated hydrochloric acid (50 ml) for 2 h, the benzene was distilled off, the aqueous solution was refluxed for 2 h and evaporated. The residue was dissolved in water, extracted twice with ether, the aqueous layer treated with charcoal, filtered and taken to dryness, affording 2·65 g (92·8%) of the hydrochloride of *VIa* which was precipitated from an ethanolic solution with ether; m.p. 215—229°C. The attempts to narrow the melting point range were unsuccessful. The free amino acid *VIa* was liberated from the hydrochloride using Amberlite IR-4B and on recrystallisation from water it melted at 296—300°C under decomposition. For $C_9H_{15}NO_2$ (169·2) calculated: 63·88% C, 8·94% H, 8·28% N; found: 63·58% C, 8·99% H, 8·52% N.

Methyl ester (*VIb*), b.p. 129—129·5°C/0·1 Torr, was prepared by the Fischer esterification of *VIa*. For $C_{10}H_{17}NO_2$ (183·2) calculated: 65·54% C, 9·35% H, 7·64% N; found: 65·69% C, 9·58% H, 7·37% N.

4-Azatricyclo[4,4,0,$0^{3,8}$]decan-5-one (*Ia*)

A) A solution of the hydrochloride of *VIa* (2·0 g) in thionyl chloride (40 ml) was stirred for 2 h at room temperature. The excess reagent was distilled off *in vacuo* and the residue was dissolved in dimethylformamide (100 ml). Triethylamine (0·98 g) was added under cooling, the mixture was stirred for 0·5 g and further triethylamine was added in three portions (3 × 0·49 g). After 2 hours' stirring the mixture was set aside overnight, diluted with water and extracted several times with dichloromethane. The combined extracts were washed twice with water, dried and taken down. The residue was sublimed *in vacuo* (bath temperature 130—230°C) and the product upon crystallisation from ethyl acetate melted at 203—203·5°C; yield 0·65 g (45%). Mass spectrum: calculated for $C_9H_{13}NO$: M^+ 151·0997, found: 151·0997. For $C_9H_{13}NO$ (151·2) calculated: 71·49% C, 8·67% H, 9·25% N; found: 71·77% C, 8·77% H, 9·24% N.

B) The amino acid *VIa* (0·52 g) was heated with a free flame in a flask into which a sublimation finger was inserted, first at normal pressure and then *in vacuo*. The material which sublimed was further purified by two sublimations and two crystallisations from ethyl acetate, affording 14·9 mg (3·2%) of the lactam *Ia*, m.p. 203—203·5°C.

C) A solution of *VIb* (162 mg) in xylene (40 ml) was heated to 190°C in an autoclave for 16 h. The solvent was distilled off and the residue chromatographed on a silica gel column (50 g, methanol–ether 1 : 10). Sublimation and crystallisation from ethyl acetate afforded 4 mg (3%) of the desired lactam *Ia*, m.p. 202—203°C. Heating *VIb* without solvent led only to polymers.

D) Finely powdered anhydride *IV* (1·4 g) was dissolved at 0°C under stirring in 100% hydrazine hydrate (4·5 ml), the hydrazine hydrate was distilled off *in vacuo*, the residue diluted with water (30 ml) and allowed to pass through a Zerolit FF column. This was washed with CO_2-free water until the eluate was neutral. The retained monohydrazide of the acid *IIIa* was liberated from the column by elution with 3% sodium hydroxide (500 ml). The eluate was made acid by adding hydrochloric acid and extracted twice with ether. The stirred aqueous layer was treated at 0°C with sodium nitrite (0·75 g) and the stirring was continued for 1 h. The product was then taken up into ether (4 × 50 ml), the combined ethereal extracts were washed with water, dried and taken down, leaving 0·54 g (31%) of the impure monoazide *VII* which decomposed at 85—87°C. IR spectrum: 1704 cm^{-1} (COOH), 2140 cm^{-1} (CON_3). For $C_{10}H_{13}N_3O_3$ (223·2) calculated: 53·80% C, 5·87% H, 18·83% N; found: 54·27% C, 6·06% H, 17·17% N. A solution of the crude *VII* (0·3 g) in toluene (30 ml) was refluxed for 2 h. The reaction mixture was filtered, taken down and the residue pyrolyzed in a sublimation apparatus, first under normal pressure and then *in vacuo*. The sublimate was twice sublimed at 0·1 Torr (bath 130—230°C) and purified by two crystallisations from ethyl acetate, affording 12·9 mg (6·4%) of the lactam *Ia*, m.p. 201—203°C.

4-Aza-4-methyltricyclo[4,4,0,$0^{3,8}$]decan-5-one (*Ib*)

A solution of the lactam *Ia* (103·4 mg) in dimethylformamide (20 ml) was added to a suspension of sodium hydride (48 mg) in benzene and the mixture was stirred for 2 h at room temperature. Freshly distilled methyl iodide (1 ml) was added and the mixture was again stirred for 2 h. The next day the mixture was diluted with water, the product extracted with dichloromethane (4×), the combined extracts washed with water, dried, and taken down. Chromatography on a silica gel column (50 g, methanol–ether 1 : 10) afforded 50·2 mg (44%) of the product, b.p. 146 to 147°C/10 Torr. Mass spectrum: 165 (M^+), M—15, M—28, M—29, M—42. For $C_{10}H_{15}NO$ (165·2) calculated: 72·69% C, 9·15% H, 8·48% N; found: 72·25% C, 9·34% H, 8·64% N.

4-Azatricyclo[4,4,0,$0^{3,8}$]decane (*VIII*)

A solution of the lactam *Ia* (205 mg) and lithium aluminium hydride in tetrahydrofuran (0·78 g in 20 ml) was refluxed for 8 h under stirring. The mixture was decomposed by addition of water (0·8 ml), 15% sodium hydroxide solution (0·8 ml) and again water (3·2 ml). The precipitated hydroxides were filtered off, washed with ether and the filtrate was twice extracted with dilute (1 : 5) hydrochloric acid. The combined aqueous layers were washed with ether, taken to dryness and the residue crystallized from 2-propanol, affording 101 mg (43%) of the hydrochloride of *VIII*, m.p. 307–311°C (sealed capillary). For $C_9H_{16}ClN$ (173·7) calculated: 62·23% C, 9·28% H, 8·06% N; found: 61·89% C, 9·36% H, 8·13% N. The base *VIII* was liberated in 75% yield from the hydrochloride by treatment with concentrated potassium hydroxide solution; the sublimed product melted at 175–177°C (sealed capillary). Mass spectrum: for $C_9H_{15}N$ calculated: M^+ 137·1204, found: 137·1201. The compound formed very rapidly a carbonate.

(+)-(2*S*,5*S*)-Bicyclo[2,2,2]octane-2,5-dicarboxylic Acid ((+)-*IIIa*)

This enantiomer was prepared either by crystallisation of its brucine salt as already described[14], or by crystallisation of its salt with (+)-dehydroabietylamine according to the following procedure. The mother liquors from the crystallisation of brucine salt of the (−)-enantiomer were decomposed with hydrochloric acid to give the acid, enriched in the (+)-enantiomer, $[\alpha]_D^{25}$ +96° (*c* 0·5, methanol). This material (15·9 g) was dissolved in acetone and treated with an equimolar amount (23 g) of (+)-dehydroabietylamine in acetone. Two crystallisations of the precipitated salt from 2-propanol afforded 10·4 g of the salt, m.p. 203–204°C. For $C_{30}H_{25}NO_4$ (483·7) calculated: 74·49% C, 9·38% H, 2·90% N; found: 74·20% C, 9·61% H, 2·79% N. Decomposition of the salt afforded (+)-*IIIa*, m.p. 198–199°C (water), $[\alpha]_D^{25}$ +125·8° (*c* 0·5, methanol).

(+)-(2*S*,5*S*)-2-Aminobicyclo[2,2,2]octane-5-carboxylic Acid ((+)-*VIa*)

The acid (+)-*IIIa*, $[\alpha]_D^{25}$ +125·8°, was transformed into its anhydride, m.p. 233–238°C, $[\alpha]_D^{25}$ −64·2° (*c* 0·5, benzene) in 84% yield. For $C_{10}H_{12}O_3$ (180·2) calculated: 66·65% C, 6·71% H; found: 66·25% C, 6·77% H. This afforded the monomethyl ester (+)-*V*, b.p. 141°C/0·1 Torr, $[\alpha]_D^{25}$ +102·4° (*c* 0·87, methanol), in 83% yield; this was converted into the hydrochloride of (+)-*VIa*, m.p. 205–230° (2-propanol) in 94% yield. The free amino acid (+)-*VIa* decomposed at 327–329°C (water); $[\alpha]_D^{25}$ +29·9° (*c* 0·5, 6M-HCl). For $C_9H_{15}NO_2$ (169·2) calculated: 63·88% C, 8·93% H, 8·28% N; found: 64·14% C, 9·08% H, 8·14% N. All the synthetic procedures were analogous to that described for the racemic compounds.

(−)-(3*S*)-4-Azatricyclo[4,4,0,$0^{3,8}$]decan-5-one ((−)-*Ia*)

This compound was prepared from the hydrochloride of (+)-*VIa* as described for the racemic material (procedure *A*); m.p. 204·5–205°C (ethyl acetate); $[\alpha]_D^{20}$ −324·3° (*c* 0·5, methanol). For $C_9H_{13}NO$ (151·2) calculated: 71·49% C, 8·67% H, 9·26% N; found: 71·41% C, 8·74% H, 9·40% N.

(−)-(3*S*)-4-Aza-4-methyltricyclo[4,4,0,$0^{3,8}$]decan-5-one ((−)-*Ib*)

The title compound was prepared from the lactam (−)-*Ia* (101·3 mg) exactly as described for the racemic derivative; yield 62·4 mg of the product boiling at 145–147°C/10 Torr. Mass spectrum: for $C_{10}H_{15}NO$ calculated M^+ 165.1154: found: 165.1147, C_7H_9NO 123.0682. $[\alpha]_D^{20}$ −485° (*c* 0·066, methanol).

(−)-(3*S*)-4-Azatricyclo[4,4,0,$0^{3,8}$]decane ((−)-*VIII*)

Prepared as described for the racemate; hydrochloride m.p. 304−305°C (sealed capillary). For $C_9H_{16}ClN$ (173·7) calculated: 62·23% C, 9·28% H, 8·06% N; found: 62·22% C, 9·41% H, 8·17% N. The sublimed amine melted at 174−177°C (sealed capillary), $[\alpha]_D^{20}$ −423·6° (*c* 0·3, ethanol). Mass spectrum: for $C_9H_{15}N$ calculated: M^+ 137·1204, found: 137·1207.

endo,endo-Bicyclo[2,2,2]octane-2,6-dicarboxylic Acid (*IXa*)

A solution of the dimethyl ester *IXb* (13 g) in methanol (55 ml) was refluxed with a 15% potassium hydroxide solution (55 ml) for 30 min. The potassium salt, which precipitated during the saponification, was dissolved by addition of water (100 ml). The isolation afforded 9·2 g (83%) of the crude acid. Two crystallisations from water gave 5·4 g (48%) of material, melting at 242 to 242·5°C, pure according to gas–liquid chromatography of its dimethyl ester. The acid of the same m.p. was obtained by hydrolysis of the anhydride *X* and also by periodate oxidation of a diol as already described in ref.[15]. The mixed m.p.'s of the samples prepared in these ways did not exhibit depressions.

Bicyclo[2,2,2]octane-2,6-dicarboxylic Anhydride (*X*)

A solution of the acid *IXa* (0·5 g) in acetic anhydride (2·5 ml) was refluxed for 1·5 h, taken to dryness *in vacuo*, the residue sublimed and the product crystallised from methylcyclohexane, m.p. 200−202°C, yield 0·3 g (65%). For $C_{10}H_{12}O_3$ (180·2) calculated: 66·65% C, 6·71% H; found: 66·73% C, 6·66% H.

endo,endo-2-Methoxycarbonylbicyclo[2,2,2]octane-6-carboxylic Acid (*XI*)

The anhydride *X* (2·0 g) in methanol (40 ml) was refluxed for 6 h. The solution was taken down and distilled, b.p. 135−137°C/0·1 Torr, yield 1·9 g (81%). Crystallisation of a sample from ligroin gave the product, m.p. 80−82°C. The dimethyl ester, prepared by treatment with diazomethane, proved to be pure (gas–liquid chromatography). For $C_{11}H_{16}O_4$ (212·2) calculated: 62·25% C, 7·60% H; found: 62·77% C, 7·50% H.

endo,endo-2-Aminobicyclo[2,2,2]octane-6-carboxylic Acid (*XII*)

The monomethyl ester *XI* (1·9 g) was converted into the title compound as described for the isomeric amino acid *VIa*. The procedure afforded 1·0 g (54%) of the hydrochloride, decomposition at 242−245°C. For $C_9H_{16}ClNO_2$ (205·7) calculated: 52·54% C, 7·84% H, 6·91% N; found: 52·58% C, 7·77% H, 6·81% N. The free amino acid *XII* melted at 224−226°C (water). For $C_9H_{15}NO_2$ (169·2) calculated: 63·88% C, 8·94% H, 8·28% N; found: 63·35% C, 8·89% H, 8·12% N.

4-Azatricyclo[4,3,1,$0^{3,7}$]decan-5-one (*II*)

A) The acid *XII* (330 mg) was pyrolyzed in a sublimation apparatus at bath temperature 220−240°C, first under normal pressure and then *in vacuo*. The sublimate was resublimed at 0·1 Torr. Two crystallisations from ethyl acetate afforded 247 mg (81%) of the lactam *II*, m.p. 174−175°C. Molecular weight 151 (mass spectrum). For $C_9H_{13}NO$ (151·2) calculated: 71·49% C, 8·67% H, 9·26% N; found: 71·44% C, 8·76% H, 9·07% N.

B) A solution of *XIII* (3·0 g) in thionyl chloride (7 ml) was stirred at 0°C for 1·5 h. The reagent was distilled off *in vacuo* and the residue dissolved under cooling in dimethylformamide (15 ml). After stirring for 20 min, activated[17,18] sodium azide (3·0 g) was added at 0°C to this solution, the mixture was stirred at this temperature for 2 h, diluted with water and the product was taken up into pentane. The pentane layer was washed with sodium hydrogen carbonate solution and with water, dried and taken down. The residue was dissolved in cyclohexane (350 ml) irradiated under cooling (internal temperature 10°C) in a forced-circulation apparatus equipped with a Hanau TQ 150 high-pressure mercury lamp. After 1·5 h thin-layer chromatography showed absence of the starting azide. The mixture was taken down, the residue dissolved in benzene and the solution allowed to pass through a silica gel column (20 g). The isocyanate (1·2, strong band in the infrared at 2270 cm^{-1}) was eluted with benzene. Subsequent elution with methanol gave a crystalline mixture which on further chromatography on a silica gel column (60 g; ether–methanol 10 : 1) afforded the crude lactam *II*. Sublimation *in vacuo* followed by two crystallisations from ethyl acetate gave 102 mg (3·5%) of pure *II*, m.p. 172—174°C, identical with the specimen prepared according to the procedure *A*).

(+)-(3*S*)-4-Azatricyclo[4,3,1,$0^{3,7}$]decan-5-one ((+)-*II*)

This compound was prepared from (−)-(2*R*)-bicyclo[2,2,2]octane-2-carboxylic acid (−)-*XIII*, $[\alpha]_D^{20}$ −58·3° (*c* 0·5, methanol) following the procedure *B*) described for the racemic compound. Thus, 2·5 g of (−)-*XIII* afforded 282 mg (11·5%) of (+)-*II*, m.p. 175·5°C (ethyl acetate), $[\alpha]_D^{20}$ +14·8° (*c* 0·5, methanol). For $C_9H_{13}NO$ (151·2) calculated: 71·49% C, 8·67% H, 9·26% N; found: 71·24% C, 8·74% H, 8·93% N.

In a control experiment, a solution of (−)-*XIII*, $[\alpha]_D^{25}$ −58·3° (150 mg) in thionyl chloride (1·5 ml) was stirred for 2 h at 0°C. The reagent was distilled off *in vacuo*, dimethylformamide (2 ml) was added at 0°C to the residue, and the solution was stirred for 3 h at 0°C. The mixture was decomposed with water at 0°C, the acid taken into pentane, washed twice with water, dried and the solvent distilled off, affording the acid (−)-*XIII*, $[\alpha]_D^{25}$ −58·0° (*c* 0·5, methanol).

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