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The Synthesis of 1-Oxaquinolizidines *via* the Mercury (II) Acetate Mediated Cyclisation of Piperidine Alcohols

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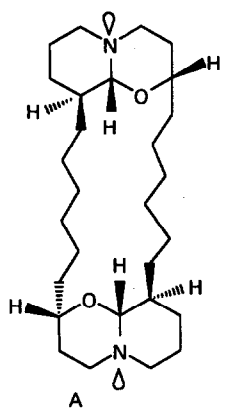
Abstract: The oxidation of (S)-3-piperidinyl-1-phenyl-1-propanols with mercury (II) acetate results in the formation of *trans* and *cis* decalin isomers of 1-oxaquinolizidines.

Recently a new class of macrocyclic 1-oxaquinolizidines (pyrido[2,1-b][1,3]oxazines), xestospongins have been isolated from the Australian sponge *xestospongia exigua*.[1] Our interest in these novel classes of macrocycles arose from their vasodilative properties and also from the challenging synthetic problems that are presented for their synthesis since the heterocyclic ring junction is at the aldehyde oxidation level and any strategy that is employed must cater for this lability of the system.



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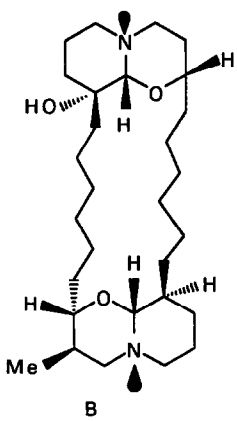

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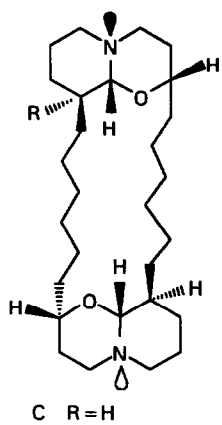
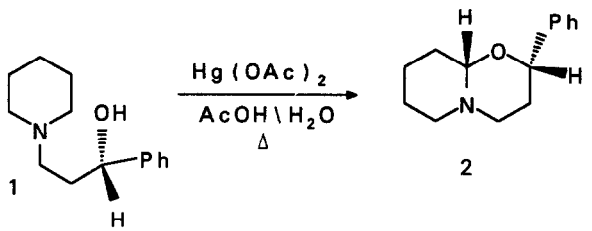


C R=H
D R=OH

The high degree of symmetry in the structure of xestospongin A[2] should allow its synthesis to be attained from common intermediates. A further consideration that we bore in mind was the desire for a chiral construction where the intermediates should also be capable of being readily utilised for the synthesis of analogues. Our initial target was to establish the methodology that would provide ready access to the parent heterocycles in which the correct relative stereochemistry is readily established making use of the substituent's preference to reside in an equatorial arrangement. As a prelude to this we undertook a review of the literature which indicated the 1-oxaquinolizidine ring system to be accessible by ring closure of an N-alkylated piperidine substituted propanol with mercury (II) acetate.[3]

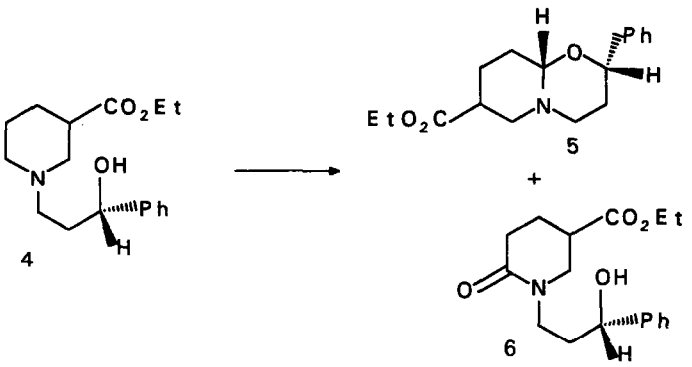
With these thoughts in the forefront we chose to examine the chemistry of (S)-3-piperidinyl-1-phenyl-1-propanol(1).[4] This was readily available as a pale yellow crystalline material by the action of piperidine on 3-chloro-1-phenyl-1-propanol (3) in 90-95% yield, $[\alpha]_D$ = - 34.2° (c= 4.33, $CHCl_3$); m.p. 41-43°. With the chiral (1) in hand we studied its cyclisation to the 1-oxaquinolizidine (2). This was smoothly effected using an excess of mercury (II) acetate in aqueous acetic acid. The bicyclic compound (2) was produced as a pale yellow clear oil, in 62% yield; $[\alpha]_D$ = -53° (c= 2.68, $CHCl_3$), which proved to be unstable towards silica gel chromatography, but it could be readily distilled or chromatographed using Florisil without extensive decomposition.



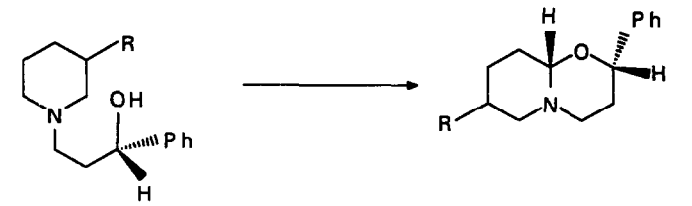
Analysis of the ^1H (400MHz) and ^{13}C n.m.r. spectra confirmed that (2) existed exclusively in the *trans* decalin form, as evidenced by the signals at δ 4.45 for H-2 (dd, J= 11.50, 2.51Hz) and δ 3.67 for H-9a (dd, J= 8.78, 2.73Hz); the resonance for the ring junction carbon (C9a) occurred at δ 92.60. We were unable to detect any of the *cis* isomer. If the reaction was left for longer time periods then the corresponding amide was formed as *ca* 50% of the total isolated yield; this presumably arises by over oxidation by mercury acetate.

With this success we turned our attention to the synthesis of chiral piperidines bearing a 3-substituent that would be capable of functioning as precursors for xestospongin synthesis. Thus treatment of the 3-carboethoxypiperidine with the chloropropanol (3) afforded the N-alkylated product (4) in 77-80% yield, as *ca.* 1:1 mixture of crystalline diastereoisomers; $[\alpha]_{Ddia}$ = -33.3° (c= 2.94, $CHCl_3$), m.p. 54-56°.

Oxidation of the mixture of diastereoisomers (4) for 18h with mercury (II) acetate led predominantly to the formation of an amide. We tentatively assign its structure as being (6) on the basis of its spectral data and by analogy with the compounds discussed below. Shortening of the reaction time to two hours led to the isolation of the mixture of isomers (5) in 63% yield, along with 10% of the amide (6), after chromatography, $[\alpha]_{Ddia}$ = -23.0° (c= 1.59, $CHCl_3$); m/z = 289 (M^+). Examination of the ^1H and COSY nmr spectra allowed a stereochemical assignment to be made, which shows that (6) is formed as a *ca.* 60:40 mixture of *trans* and *cis* decalin ring systems with the ester substituent being equatorial in both isomers. Evidence for this included the clear triplet of H-7_{eq} at δ 2.28 for the *trans* decalin, whilst in the *cis* decalin structure this is observed at δ 3.31



In the ^{13}C nmr spectrum resonances at δ 87.53 and 92.60 were observed for the *cis* and *trans* decalin type ring junction carbons. Reduction of the ethyl ester (5) with lithium aluminium hydride afforded the alcohol (7) as a mixture of decalins, in 77% yield, as a mixture of *cis* and *trans* decalin structures. Reduction of the ester (4) gave the corresponding diol in 83% yield as a light yellow oil, $[\alpha]_{D}^{dia}$ = -23.9° (c= 5.67, $CHCl_3$). This diol was subjected to the cyclisation conditions and afforded the alcohol (7) in 66 - 77% yield in a similar ratio for the decalin structures. However when the cyclisation was conducted on a one gram scale, small amounts (8mg), of the acyclic aldehyde derived from the oxidation of the primary alcohol were observed.



8 R= CH_2OH 7 R= CH_2OH

9 R= CH_3 10 R= CH_3

The alcohol (9) was prepared by the action of 3-methyl piperidine on (3) in 95% yield as a 1:1 mixture of diastereoisomers, this when subjected to mercury (II) acetate resulted in the smooth cyclisation to the quinolizidines (10) in 76% yield,$[\alpha]_{D}$dia = -50° (c= 0.83, $CHCl_3$), which could be purified by distillation; however extensive decomposition was observed in this case. The nmr spectra for (10) indicated that once again the oxaquinolizidine had been formed with the anticipated stereochemistry for the ring junction and that the methyl group occupied the equatorial position. Analysis of the COSY nmr spectrum confirmed that the major isomer (60:40), on this occasion had the *cis* decalin structure compared to *trans* for the minor isomer. This was evident by the observation that protons *cis* to the nitrogen lone pair have lower chemical shifts than those *trans* to the lone pair, exemplified by the fact that the signal for the H-1 proton occurs at δ 4.46 ppm in the *cis* decalin form whilst in the *trans* form it is observed at δ 3.49 ppm. This general difference in chemical shift for the isomers is also found in the case of the methylene protons

either side of the ring nitrogen.The resonances for the ring junction carbon atom were observed at δ 93.56 and 87.50 ppm respectively.

The formation of mixtures of *cis* and *trans* decalin ring systems for these compounds suggests that the energy difference between the two isomeric forms is negligible so that no discrimination occurs under the reaction conditions employed. The extra energy of stabilisation due to the anomeric effect in the *cis* decalin isomers is likely to afford these with additional stabilisation, and this is sufficient to offset the steric interactions that may occur in the transition state.

It is worth noting that the cyclisations with mercury acetate proceed readily with complete regioselectivity. Furthermore excellent control over the newly created chiral centre is observed.

EXPERIMENTAL

IR spectra were recorded on a Perkin Elmer 1600 FT spectrometer. Mass spectrometry was performed with a VG micromass 16F and AEI MS 902 spectrometers using an ionisation energy of 70 ev. NMR spectra were recorded on Jeol EX 90 and Bruker WH 400 spectrometers using deuteriochloroform as solvent. Melting points were determined using a Reichert apparatus in open capillaries and are uncorrected. Absorption chromatography was carried out using Kieselgel 7734 and on florisil, 60-100 mesh. All air sensitive reactions were performed in flame dried apparatus under an argon atmosphere.Optical rotations were detrmined with a Bellingham Stanley P20 polarimeter.

(S)-3-N-Piperidinyl-1-phenyl-1-propanol(1)
Piperidine (2.04g, 24mmol) and sodium iodide (0.09g, 0.6mmol) in ethanol (12.5ml) was treated with (S)-3-chloro-1-phenyl-1-propanol (1.03g, 6mmol) and the resulting solution heated at reflux for 18h. The mixture was cooled to room temperature to which was added sodium ethoxide (0.41g, 6mmol) in ethanol (10ml). The resulting solution was stirred at room temperature (RT) for 1h. The mixture was filtered and the solvent removed *in vacuo.* The resulting solid was dissolved in ether(30ml),filtered, dried ($MgSO_4$), and the solvent removed *in vacuo*, to yield a yellow crystalline solid. Recrystallisation from ether / petrol afforded the title compound as a white needles (1.25g 95%), m.p. 41-43°, $[\alpha]_D$ = -34.2° (C = 4.33, $CHCl_3$).ν_{max}, ($CHCl_3$), 3238, 1600, 762 cm^{-1}; δ_H (90 MHz), 1.35-1.84 (8H, m), 2.31 - 2.58 (5H, m), 2.76 (1H, m), 4.85 (1H, t, J 5.7Hz), 5.52 (1H, OH), 7.25 (5H, m, Ph); δ_C (22.4 MHz) 24.32, 26.18, 33.82, 54.76, 57.87, 75.77, 125.68, 126.90, 128.28, 145.31; m/z 219(M^+, 20), 77(100).
(Found C, 76.5; H, 9.7; N, 6.3; $C_{14}H_{21}NO$ requires C, 76.7; H, 9.6; N, 6.4%).

2-(S)-Phenyl-pyrido[2,1-b][1,3]oxazine(2)
The alcohol (1) (2.0g, 9.1mmol) in 5% acetic acid(50ml) was treated with mercury (II) acetate (14.52g, 5 equivelents) and the mixture heated at 94° for 1h.The precipitated mercury (I) acetate was filtered, washed with 5% acetic acid (washings added to filtrate). The filtrate was saturated with hydrogen sulphide and the mercury sulphide removed by filtration through a pad of celite. The filtrate was basified ,with solid K_2CO_3, added in small portions,with cooling in an ice bath. When evolution of of carbon dioxide had ceased the solution was extracted with ether (5 x 100ml). The combined organic extracts were dried with $MgSO_4$. Removal of the solvent in vacuo afforded a yellow oil. Chromatography on florisil(chloroform / methanol, 98:2), afforded the title compound (1.23g, 62%). A small sample was distilled using a kugelrhor (180°, 2mm Hg), for microanalysis, $[\alpha]_D$ = -53° (C = 2.68, $CHCl_3$). ν_{max} ($CHCl_3$) 2939, 1605, 762 cm^{-1}; δ (400 MHz), 1.4 (1H, m, H-3_{ax}), 1.58 - 1.86 (6H, m), 2.05 (1H, qd(d), H-6_{ax}, J 16.27, 12.03, 4.32, 0.97 Hz), 2.15 (1H, td, H-4_{ax}, J 14.25, 11.05, 3.32), 2.54 (1H, td, H-4_{eq}, J 14.25, 11.07, 2.87), 2.9 (1H, m, H-3_{eq}), 3.03 (1H, td, H-6_{eq}, J 11.8, 4.32, 2.26 Hz), 3.67 (1H, dd, H-9a, J 8.78, 2.48 Hz), 4.45 (1H, dd, H-2, J 11.50, 2.51 Hz),

7.37 (5H, m, Ph); δ_C (22.4 MHz), 22.40, 25.03, 31.41, 32.63, 52.42, 53.73, 79.39, 92.60, 125.87, 127.36, 128.23, 142.22.
(Found, C, 77.2; H, 8.5; N, 6.1; $C_{14}H_{19}NO$ requires C, 77.4; H, 8.8; N, 6.45%).

(1S, 3'R and S)-3-N-(3-Carboethoxy)piperidinyl-1-phenyl-1-propanol(4)
Ethyl nipecotate (3.14g, 20mmol) and S-3-chloro-1-propanol (1.71g, 10mmol) in ethanol (15ml) were treated with sodium iodide (0.17g, 1.2mmol). The resulting solution was heated at reflux for 18h. The mixture was cooled to RT and treated with sodium ethoxide (0.68g). Stirring was continued for 1h and the suspension filtered, the resulting filtrate was removed *in vacuo* and gave a yellow oil. Chromatography, silica, (chloroform / methanol; 98:2) gave the title compounds as a mixture of diastereoisomers in 2.32g, (80%) yield, $[\alpha]_{D}^{dia}$ = -33.3° (C = 2.94, $CHCl_3$) m.p. 54-56°. ν_{max} 3224, 1729, 1603 cm^{-1} ,δ_H (400MHz) 1.26 (3H, 2xt), 1.49 (1H, bm), 1.60 (1H, m), 1.73-1.97 (3H, m), 1.95 (1.5H, bd), 2.15 (1H, bm), 2.31 (0.5H, bm), 2.53-2.70 (3H, m), 2.82 (1H,bm), 2.93 (1H, bm), 3.07-3.15 (1H, bm), 4.13 (2H, m), 4.91 (1H, m), 6.57 (1H, b, OH), 7.21 (1H, m), 7.23-7.37 (3H, m),δ_C (22.4 MHz), 14.22, 24.48, 24.69, 26.90, 27.34, 33.97, 41.67, 41.90, 53.15, 54.34, 54.94, 56.22, 57.30, 60.22, 60.46, 75.32, 125.56, 126.87, 128.19, 144.98, 173.74, m/z 291 (M^+, 20), 170 (100), 142 (34). (Found C, 70.0, H, 8.7, N, 4.8,$C_{17}H_{25}NO_3$ requires C, 70.1, H, 8.6, N, 4.8%).

2(S)-Phenyl-3(R and S)-carboethxoy pyrido[2,1-b][1,3]oxazine (5)
The mixture of diastereomeric esters (4) (0.5g, 1.7mmol) in 5% acetic acid (10ml) was treated with mercury (II) acetate (2.74g, 5eq). The resulting mixture was heated at 82-85° for 2h. Workup as above afforded the title compound as a pale yellow oil in 0.36g (63%) yield, $[\alpha]_{D}^{dia}$ = -23.0° (C = 1.59, $CHCl_3$).ν_{max} 2950, 1730, 687 cm^{-1}, δ_H (400 MHz) 1.27 (3H, 2xt), 1.41-2.14 (8H, m), 2.28 (0.5H, t, J 11.4 Hz), 2.48 (0.5H, dt, J 11.94, 2.85),2.71 (1.5H, m), 3.04-3.17 (2H, m), 3.32 (0.5H, t, 10.15Hz), 3.60 (0.5H, dd, J 9.25, 3.03 Hz), 4.15 (2H, m), 4.39 (0.5H, m), 4.45 (0.5H, dd, J 11.80, 2.4 Hz), 4.59 (0.5H, dd, J 11.55, 2.66 Hz), 7.24-7.39 (5H, m),
δ_C (22.4 MHz), 14.11, 22.10, 25.68, 28.16, 29.65, 30.49, 33.17, 41.17, 41.47, 48.24, 52.62, 53.73, 54.15, 60.35, 79.42, 79.68, 87.59, 92.54, 125.69, 125.93, 127.42, 127.54, 128.32, 141.86, 142.70, 173.55, 173.87, m/z 289 (M^+, 9), 183 (33), 91 (20), 55(100). (Found M^+ 289.168 $C_{17}H_{23}NO_3$ requires 289.168).

(1S, 3'R and S)-3-N-(3-Hydroxymethyl)piperidinyl-1-phenyl-1-propanol(8)
The alcohol ester(4) (2g, 6.9mmol) in THF(10ml) was added dropwise to a suspension of lithium aluminium hydride (0.52g, 2eq) in THF (15 ml), at 0° under argon. The mixture was allowed to warm to RT over 1h. and stirred for a further 1h at RT, after which time tlc indicated consumption of starting material. The mixture was diluted with ethyl acetate (100ml) and treated with saturated ammonium chloride (40ml). The two phase system was stirred at RT for 1.25h The two phases were separated and the aqueous phase extracted with ethyl acetate (40 ml). The combined organic layers were dried ($MgSO_4$) and removed *in vacuo*. Chromatography, silica, gave the title compounds as a pale yellow oil 1.71g (73%), $[\alpha]_{D}^{dia}$ = -23.9° (C = 5.67, $CHCl_3$). ν_{max} 3356, 1603, 750 cm^{-1}, δ_H (90 MHz) 1.10 (1H, m), 1.62 - 2.10 (8H, m), 2.51 - 2.57 (1H, m), 2.61 - 3.08 (2H, m), 3.44 (2H, d, J 6.15 Hz), 4.89 (1H, t, J 5.71 Hz), 4.51 (2H, b), 7.32 (5H, m); m/z 249 (M^+ , 10), 129 (100). (Found M^+ 249.173 $C_{15}H_{23}NO_2$ requires 249.173)

2(S)-Phenyl-9(R and S)-hydroxymethyl pyrido[2,1-b][1,3]oxazine (7)
The diol (8) (0.89g, 3.6mmol) in 5% acetic acid (25ml) was treated with mercury (II) acetate (5.69g, 5eq) and the mixture heated at 88° for 1h.Workup as for (2) afforded the title compound as a yellow oil which was chromatographed on florisil ($CHCl_3$ / MeOH, 98:2 increasing to 90:10). This afforded the title compound as a pale yellow oil 0.59g, (66%), $[\alpha]_D$ = -23.0° (C = 1.59, $CHCl_3$), along with the aldehyde as a result of oxidation of the primary alcohol function (4mg).ν_{max} 3400, 1604, 750 cm^{-1}, δ_H (400MHz) 0.86 (0.45H, m), 1.16 (0.55H, m), 1.24(1H, s), 1.67 (1.5H, m), 1.79-2.09 (5H, m), 2.44 (0.55H, dt, J 3.0, 11.76 Hz), 2.55 (0.45H, dd, J 3.76, 11.13 Hz), 2.91-3.07 (2H, m), 3.11-3.34 (1.5H, m), 3.46 (0.5H, m), 3.57 (0.9H, m), 3.68 (1.1H, m), 4.18 (0.5H, m), 4.45 (0.45H, dd, J 2.48, 11.45Hz), 4.56 (0.55H, dd, J 2.65, 11.48 Hz), 7.34 (5H, m);δ_C (22.4 MHz) 23.03, 25.65, 29.09, 29.32, 29.53, 30.64, 33.11(2C), 37.26, 38.16, 50.98, 52.80(2C), 53.82,

56.24, 65.34, 65.93, 70.02, 78.43, 79.39, 89.26, 93.38, 125.54, 125.66, 125.93, 126.91, 127.45, 128.26, 141.83, 142.34, m/z 247 (M^+, 30), 77(100). (Found M^+ 247.155 $C_{15}H_{21}NO_2$ requires 247.157).

(1S, 3'R and S)-3-N-(3-Methylpiperidinyl)-1-phenyl-1-propanol(9)
3-Methyl piperidine (1.98g, 20mmol) in ethanol (20ml) was treated with 3-chloro-1(S)-phenyl-1-propanol (0.85g, 5mmol), and sodium iodide (0.03g). The resulting mixture was heated at reflux for 18h , cooled and treated with sodium ethoxide (0.68g, 10mmol).Stirring was continued for 1h and the suspension filtered, the resulting filtrate was removed *in vacuo* and gave a yellow oil. Chromatography, silica, (chloroform / methanol; 98:2) gave the title compounds as a mixture of diastereoisomers, 1.11g (95%) as yellow crystals, m.p. 103-105°. A small amount was recrystallised (ether) for microanalysis, $[\alpha]_D$ = -32.7° (C = 1.22, $CHCl_3$). ν_{max} (KBr) 3427, 1625, 705 cm^{-1}, δ_H (90MHz) 0.95 (3H, d, J 5.5Hz), 1.86 (9H, m), 2.63 (2H, m), 2.96 (2H, m), 4.97 (1H, t, J 5.65 Hz), 7.34 (6H, bs);δ_C (22.4MHz) 19.54, 25.36, 31.41, 32.76, 33.68, 53.28, 54.92, 57.49, 61.07, 62.74, 75.60, 125.54, 126.77, 128.14, 145.17, m/z 233(M^+, 10), 125 (100). (Found C, 77.4; H, 9.9; N, 6.0; $C_{15}H_{23}NO$ requires C, 77.3; H, 9.9; N, 6.0 %).

2(S)-Phenyl-9(R and S)-methyl pyrido[2,1-b][1,3]oxazine (10)
The mixture of diastereomeric piperidinyl alcohols (9) (0.8g, 3.4mmol) in 5% acetic acid (20ml) was treated with mercury (II) acetate (5.43g, 5eq). The resulting mixture was heated at 90° for 0.5h. Workup as above afforded the title compound as a pale yellow oil in 76% (0.6g) yield. Distallation, on this ocassion resulted in extensive decompostion of the product, $[\alpha]_D$ = -50° (C = 0.83, $CHCl_3$). ν_{max} 2947, 1604 724 cm^{-1}; δ_H (400MHz) *cis* decalin type ring junction (60% of total) 0.97 (3H, d, J 6.64Hz), 1.41 (2H, m, H-3β, H-8α), 1.52 (1H, m, H-8β), 1.79(1H, m, H-9β), 1.80 (1H, m, H-7β), 1.88 (1H, m, H-9α), 1.98 (1H, m, H-3α), 2.44 (1H, ddd, J 9.58, 3.7, 1.2 Hz, H-6β), 2.80 (1H, t, J 10.38, H-6α), 3.03 (1H, m, H-4α), 3.24 (1H, dt, 9.3, 3.35 Hz, H-4β), 4.47 (1H, t, J 3.27 Hz, H-9a), 4.61 (1H, dd, J 11.53, 2.71 Hz, H-2), 7.33 (5H, m);
trans decalin type ring junction (40% of total) 0.87 (3H, d, J 6.10Hz), 1.05 (2H, m, H-6β, H-8β), 1.72 (2H, m, H-7α, H-9α), 1.78 (2H, m, H-3β, H-8α), 1.85 (1H, m, H-9β), 2.10(1H, m, H-3α), 2.36 (1H, dt, J 12.05, 3.05 Hz, H-4β), 2.78 (1H, dt, J 2.78, 5.24, 7.92 Hz, H-6α), 3.03 (1H, dd, J 1.71, 12.05 Hz, H-4α), 3.49 (1H, dd, J 3.22, 9.82 Hz, H-9a), 4.43 (1H, dd, J 2.52, 11.47 Hz, H-2) 7.33 (5H, m);
δ_C (22.4MHz) 19.12, 19.51, 27.44, 27.68, 30.25, 30.52, 30.86, 31.50, 31.62, 33.56, 52.51, 53.79, 61.31, 79.48, 79.66, 87.50, 93.56, 125.66, 126.02, 127.33, 127.48 (2C), 142.13, 143.08; m/z 231(M^+, 22), 125(100). (Found C, 77.6; H, 8.9; N, 5.7; $C_{15}H_{23}NO$ requires C, 77.9; H, 9.2; N 6.1%).

Acknowledgements

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References and Notes

1 (a) Nakagawa, M.; Endo, N.; Tanaka, N.; Lee, G.P.; *Tetrahedron Lett.* **1984**, 25, 3227;
(b) Kobayashi, M.; Kawazoe, K.; Kitagawa, I.; *Tetrahedron Lett.* **1989**, 30, 4149;
(c) Kobayashi, M.; Kawazoe, K.; Kitagawa, I.; *Chem. Pharm. Bull.* **1989**, 37, 1676.

2 For recent approaches to the synthesis of xestospongins see:
(a) Hoye, T. R.; North, J.T.; *Tetrahedron Lett.* **1990**, 31, 4281;
(b) Ahn, K.H.; Lee, S.J.; *Tetrahedron Lett.* **1992**, 33, 507.

3 (a) Leonard, N.J.; Musker, W. K.; *J. Amer. Chem. Soc.* **1960**, 82, 5148.
(b) Winterfeldt, K.; Michael, H.; *Arch. Pharm.* **1961**, 294, 65.

4 The (R) enantiomer of this is also avilable, xestospongins have the (R) absolute stereochemistry