ENANTIOSELECTIVE TOTAL SYNTHESIS OF IRNIINE AND BGUGAINE, BIOACTIVE 2-ALKYLPYRROLIDINE ALKALOIDS

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Abstract - An asymmetric total synthesis of the 2-(*R*)-alkylpyrrolidines, (-)-irniine (**1a**) and (-)-bgugaine (**1b**), toxic and antibiotic components of the tubers of *Arisarum vulgare*, and (+)-(*S*)-irniine (**1c**), was carried out by condensation of the corresponding 4-oxoalkanoic acid (**9**) with chiral phenylglycinol. Acids (**9**) were prepared from a hetero-organocuprate (I) complex, generated by reaction of methylcopper (I) with alkylmagnesium bromides and methyl chlorocarbonyl-propionate. Alkaloids (**1a**, **1b** and **1c**) displayed anti Gram(+) bacterial (MIC 12.5 - 50 μg/ml) and antifungal (MIC 6.25 - 50 μg/ml) activities.

(-)-(*R*)-Irniine (**1a**) and (-)-(*R*)-bgugaine (**1b**) are optically active 2-alkylpyrrolidines isolated from the tubers of *Arisarum vulgare*, a toxic Araceae responsible of human and animal poisonings in Morocco.[1-3] These alkaloids display antibacterial activity against Gram positive bacteria and antimycotic activity against some *Candida* and *Cryptococcus* strains.[3] The lipophilic nature as well as the stereochemistry of the alkaloids may be of importance in view of biological activity. This prompted us to determine the absolute configuration by way of a synthetic approach. A number of methods have been reported for asymmetric synthesis of 2-substituted pyrrolidines.[4,5] The double condensation of 3-acylpropionic acids with (-)-(*R*)-phenylglycinol is a key step for the construction of a chiral oxazololactam ring, and a subsequent three step reaction furnishes, in high enantiomeric purity, the (-)-2-alkylpyrrolidines.[4] 3-Acylpropionic acids were previously prepared either by reaction of a Grignard reagent with an α-silyl-γ-butyrolactone, followed by oxidation with Jones' reagent,[6] or by coupling an acid chloride with a bromide *via* copper/triphenylphosphine reagent.[7] Reported herein is a preparation of 3-acylpropionic acids *via* reaction of a Grignard reagent derived alkyl methylcuprate (I) complex with methyl chlorocarbonylpropionate, and the following asymmetric total synthesis of (-)-(*R*)-irniine (**1a**), (+)-(*S*)-irniine (**1c**) and (-)-(*R*)-bgugaine (**1b**) from the corresponding 3-acylpropionic acids and chiral phenylglycinol.

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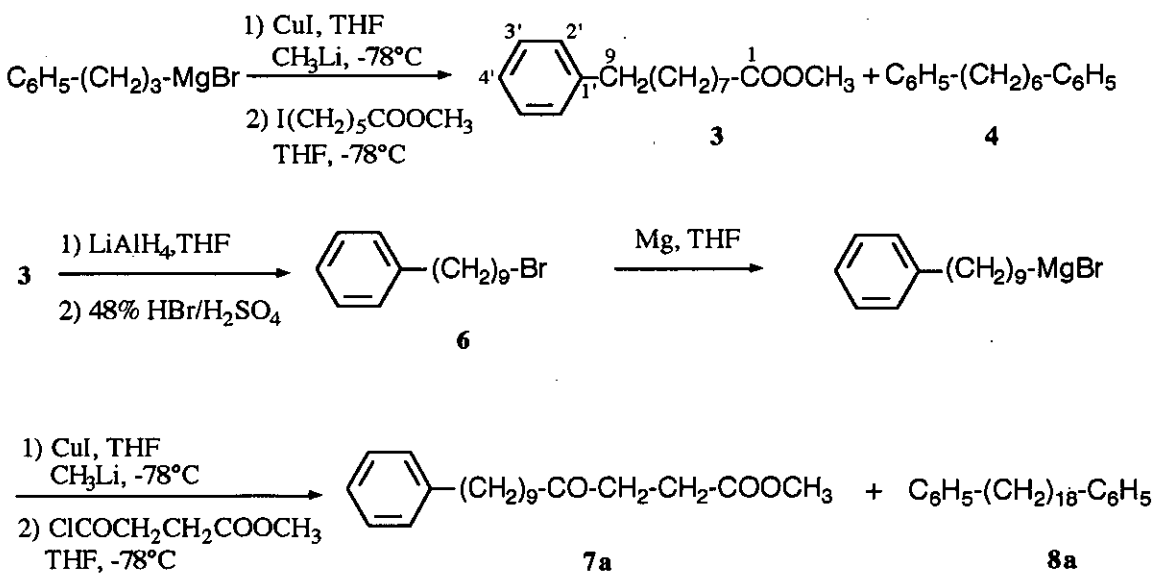
In order to synthesize 3-(9-phenyldecanoyl)propionic acid (**9a**), we designed a procedure involving selective cross-coupling of an organometallic reagent with an acid chloride bearing an ester group. The desired coupling group was thus easily introduced into the heterocuprate (I) complex by means of a Grignard reagent. The cross-coupling reaction was first applied for the preparation of the intermediate methyl 9-phenylnonanoate (**3**) (Scheme 1): 3-phenylpropylmagnesium bromide (1 equiv.) reacted with methylcopper (I) (1 equiv.), prepared from cuprous iodide and methyllithium at -78°C in THF, to form the 3-phenylpropyl methylcuprate (I) magnesium bromide complex. This complex was coupled at -78°C with methyl iodohexanoate **2** (1 equiv.), to produce methyl 9-phenylnonanoate (**3**) in 65 % purified yield along with a small amount (14 %) of the dimeric by-product, 1,6-diphenylhexane (**4**).

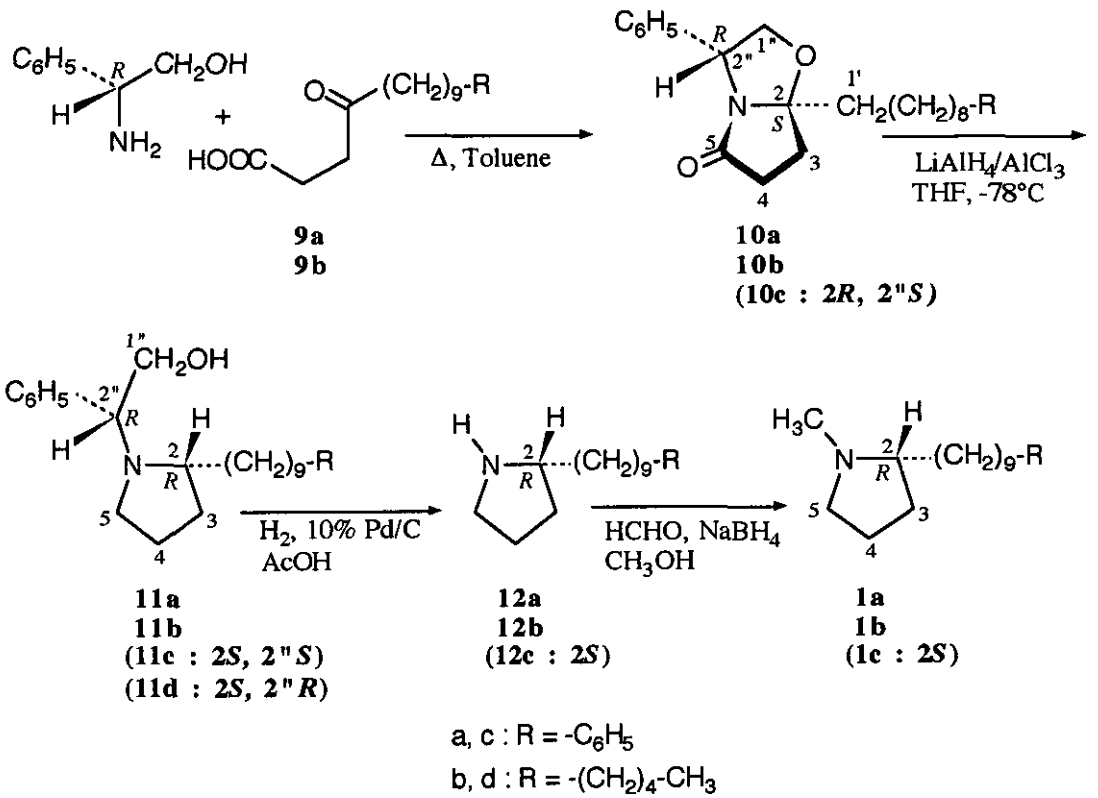
9-Phenylnonylmagnesium bromide, prepared from bromide (**6**), reacted with methylcopper (I) to generate a mixed cuprate (I) complex. 9-Phenylnonyl bromide (**6**) was obtained by reduction of the methyl ester (**3**) into alcohol (**5**) with $LiAlH_4$, followed by halogenation. The cuprate (I) complex was coupled with methyl chlorocarbonylpropionate to form the bifunctional methyl 3-(9-phenyldecanoyl)propionate (**7a**) in 65 % yield together with 1,18-diphenyloctadecane (**8a**), a by-product. One equivalent of iodohexanoate (**2**) or acid chloride was sufficient for coupling with the cuprate complex. An excess of halide [8,9] did not give higher yield and rather disturbed purification, by interferring with the final product in the course of the chromatography. However, the yield was increased by overnight stirring of the reaction mixture at room temperature, before workup.



Scheme 1 : Preparation of methyl 3-acylpropionate (**7a**).

An equimolar mixture of 3-acylpropionic acid (**9a**) and (-)-(*R*)-phenylglycinol was condensed to form (2*S*, 2"*R*)-oxazololactam (**10a**) by refluxing in toluene (Scheme 2). Treatment with $LiAlH_4$-$AlCl_3$ (AlH_3),[10] at -78°C, cleaved the oxazole ring of **10a** with simultaneous reduction of the lactam carbonyl,[4] to afford

(2*R*, 2"*R*)-benzylpyrrolidine (**11a**). This compound (**11a**) could not be separated from the neutral products by extraction with an aqueous acid, due to its strongly hydrophobic alkyl chain, and was therefore purified by silica gel chromatography. The *N*-benzyl substituent of **11a** was removed by 10 % Pd/C catalytic hydrogenation in AcOH [5] under 4 bars. Finally, *N*-methylation by HCHO condensation followed by $NaBH_4$ reduction of the pyrrolidine (**12a**) produced (-)-(*R*)-*N*-methyl-2-(9-phenylnonyl)pyrrolidine (**1a**), identical with natural (-)-(*R*)-irniine.[2]



Scheme 2 : Asymmetric synthesis of irniine (**1a**) and bgugaine (**1b**)

The enantiomeric (+)-(*S*)-irniine (**1c**) was similarly prepared by condensation of 3-acylpropionic acid (**9a**) with (+)-(*S*)-phenylglycinol, followed by reduction and *N*-methylation as described above. (*R*)-*N*-Methyl-2-tetradecylpyrrolidine (**1b**): (-)-(*R*)-bgugaine,[3] was synthesized by condensation of (-)-(*R*)-phenylglycinol with 4-oxooctadecanoic acid (**9b**). Compound (**9b**) was prepared by reacting tetradecyl methylcuprate (I) magnesium bromide complex with methyl chlorocarbonylpropionate. Reduction at -40°C of (2*S*, 2"*R*)-tetradecyloxazololactam (**10b**) provided 5.4 % of the epimeric (2*S*, 2"*R*)-benzylpyrrolidine (**11d**) in addition to the (2*R*, 2"*R*)-isomer (**11b**) (74.7 %) ($[\alpha]_D$ -79.8°, MeOH). Epimerization took place in small amounts, in this case, *via* formation of an iminium species.[11]

Table 1. ^{1}H Nmr data for **10a**, **11a**, **12a** and **1a** ($CDCl_3$, 300 MHz; δ ppm, *J* Hz).

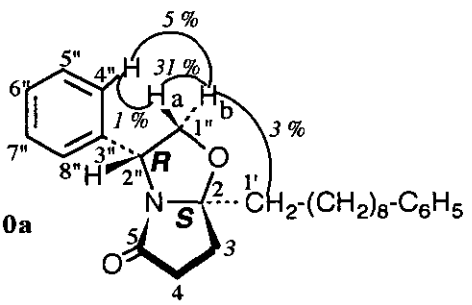
	10a		**11a**		**12a**		**1a**	
H	δ	*J*	δ	*J*	δ	*J*	δ	*J*
2	-		2.60 *m*		3.52 *m*		1.95 *m*	
3a	2.36 *ddd*	13.4,9.8,2.5	1.77 *m*		2.15 *m*		1.87 *m*	
3b	2.18 *ddd*	13.4,10.1,10.1	1.39 *m*		1.72 *m*		1.49 *m*	
4a	2.84 *ddd*	17.3,10.1,9.8	1.72 *m*		2.11 *m*		1.77 *m*	
4b	2.60 *ddd*	17.3,10.1,2.5	1.49 *m*		1.94 *m*		1.61 *m*	
5a	-		2.92 *ddd*	8.0,8.0,2.5	3.43 *m*		3.04 *ddd*	8.5,8.5,2.2
5b	-		2.21 *ddd*	9.0,9.0,7.5	3.33 *m*		2.09 *ddd*	8.5,8.5,8.5
1'a	1.68 *m*		1.84 *m*		1.99 *m*		1.62 *m*	
1'b	1.55 *m*		1.33 *m*		1.73 *m*		1.21 *m*	
2'	1.24 *m*		1.35 *m*		1.43 *m*		1.25 *m*	
3'-7'	1.24 *m*		1.37 *m*		1.32 *m*		1.27 *m*	
8'	1.62 *m*		1.67 *m*		1.62 *m*		1.27 *m*	
9'	2.61 *t*	6.9	2.65 *t*	7.5	2.62 *t*	7.7	2.58 *t*	7.7
11',15'	7.16-7.38 *m*		7.15-7.40 *m*		7.19 *m*		7.15 *m*	
12',14'	7.16-7.38 *m*		7.15-7.40 *m*		7.28 *m*		7.24 *m*	
13'	7.16-7.38 *m*		7.15-7.40 *m*		7.18 *m*		7.14 *m*	
1"a	4.64 *dd*	8.5,8.5	4.00 *dd*	11.0,10.0	-		-	
1"b	4.09 *dd*	8.5,7.7	3.68 *dd*	10.0,4.7	-		-	
2"	5.20 *dd*	8.5,7.7	4.09 *dd*	11.0,4.7	-		-	
4",8"	7.17 *m*		7.15-7.40 *m*		-		-	
5",7"	7.16-7.38 *m*		7.15-7.40 *m*		-		-	
*N*Me	-		-		-		2.30 *s*	
*N*H	-		-		7.39 *s*		-	
*O*H	-		3.26 br *s*		-		-	

All the compounds synthesized were analyzed by 2D-nmr, ^{1}H-^{1}H COSY, ^{1}H-^{13}C COSY and ^{1}H-^{13}C long range COSY; nmr data are summerized in Tables 1 - 3.

The stereochemical relationships of the two asymmetric centers of the (2*S*, 2"*R*)-oxazololactam (**10a**) were examined by NOE difference experiments (Scheme 3). Irradiation of the proton at δ 4.09 (H-1"b) enhanced the signal of the protons at δ 1.68 (H-1'a : 3 %) and at δ 7.17 (phenyl H-4" : 5 %), whereas irradiation of H-1"a, at δ 4.64, only slightly enhanced H-4" (1 %) and did not affect the signal of the proton H-1'. These results indicated the spatial proximities of the phenyl at 2", H-1"b, and H-1'a on the same side of the oxazololactam ring. Since the absolute configuration at C-2" was *R*, that of C-2 must be *S*.

Table 2. ^{1}H Nmr data for **10b**, **11b**, **11d**, **12b** and **1b** ($CDCl_3$, 300 MHz; δ ppm, *J* Hz).

	10b			**11b**			**11d**	**12b**	**1b**		
H	δ		*J*	δ		*J*	δ	δ	δ		*J*
2	-			2.48	*m*		2.71 *m*	3.27 *m*	1.95	*m*	
3a	2.29	*ddd*	13.3,10.0,2.1	1.20	*m*		1.61 *m*	2.02 *m*	1.91	*m*	
3b	2.09	*ddd*	13.0,10.2,10.0	1.20	*m*		1.37 *m*	1.54 *m*	1.43	*m*	
4a	2.75	*ddd*	17.3,10.0,10.0	1.61	*m*		1.56 *m*	1.96 *m*	1.77	*m*	
4b	2.51	*ddd*	17.2,10.2,2.1	1.92	*m*		1.64 *m*	1.82 *m*	1.61	*m*	
5a	-			2.81	*m*		2.92 *m*	3.21 *m*	3.05	*ddd*	8.4,8.4,2.2
5b	-			2.09	*ddd*	8.0,8.0,8.0	2.64 *m*	3.07 *m*	2.10	*ddd*	9.3,9.3,8.4
1'a	1.60	*m*		1.73	*m*		1.30 *m*	1.79 *m*	1.64	*m*	
1'b	1.53	*m*		1.19	*m*		1.00 *m*	1.55 *m*	1.17	*m*	
2'	1.33	*m*		1.20	*m*		1.10 *m*	1.31 *m*	1.26	*m*	
3'-11'	1.20	*m*		1.19	*m*		1.18 *m*	1.21 *m*	1.25	*m*	
12'	1.20	*m*		1.19	*m*		1.18 *m*	1.21 *m*	1.25	*m*	
13'	1.20	*m*		1.19	*m*		1.18 *m*	1.21 *m*	1.25	*m*	
14'	0.84	*t*	6.4	0.84	*t*	6.7	0.80 *m*	0.82 *m*	0.86	*t*	6.7
1"a	4.55	*dd*	8.5,7.5	3.88	*dd*	10.4,10.1	3.82 *m*	-	-		
1"b	4.00	*dd*	8.5,7.5	3.54	*dd*	10.1,4.2	3.72 *m*	-	-		
2"	5.12	*dd*	7.5,7.5	3.97	*dd*	10.4,4.2	3.69 *m*	-	-		
4",8"	7.17	*m*		7.08	*m*		7.25 *m*	-	-		
5",7"	7.26	*m*		7.24	*m*		7.25 *m*	-	-		
6"	7.16	*m*		7.24	*m*		7.25 *m*	-	-		
*N*Me	-			-			-	-	2.24	*s*	
*N*H	-			-			-	7.25 br *s*	-		
*O*H	-			3.25	br *s*	-	-	-	-		



Scheme 3 :
NOE difference measurements of **10a**

Table 3. ^{13}C Nmr data for compounds **10-12** and **1** ($CDCl_3$, 75 MHz; δ ppm) ; * may be reversed in the same column.

C	**10a**	**11a**	**12a**	**1a**	**10b**	**11b**	**11d**	**12b**	**1b**
2	102.7	58.9	60.4	66.4	102.6	59.0	59.8	59.6	66.5
3	30.9	29.9	30.0	30.7	30.8	29.8	30.0	30.6	30.8
4	33.3	22.0	23.3	21.7	33.2	22.1	23.0	23.5	21.8
5	179.5	45.5	44.4	57.2	179.1	45.4	52.5	44.2	57.4
1'	36.2	34.0	31.9	33.7	36.1	34.1	34.9	32.7	33.8
2'	23.8	26.0	26.7	26.6	27.8	26.1	26.6	27.0	26.7
3'	29.5	29.7	29.1*	29.9	29.5*	30.0*	30.0	29.6*	30.0
4'	29.3	29.6*	29.3	29.5*	29.5	29.7*	29.6	29.6	29.6
5'	29.3	29.5*	29.3	29.4*	29.5	29.7	29.6	29.6	29.6
6'	29.3	29.4*	29.3*	29.4*	29.5	29.7	29.6	29.6	29.6
7'	29.2	29.3	29.1*	29.2*	29.5	29.7	29.6	29.6	29.6
8'	31.4	31.4	31.3	31.4	29.5	29.7	29.6	29.6	29.6
9'	35.9	35.9	35.8	35.9	29.4*	29.7	29.6	29.5*	29.6
10'	142.8	142.8	142.7	142.8	29.3*	29.7	29.6	29.4*	29.6
11'	128.3	128.3	128.2	128.3	29.2	29.4	29.6	29.3	29.3
12'	128.1	128.1	128.0	128.1	31.8	31.9	31.9	31.9	31.9
13'	125.5	125.5	125.3	125.4	22.5	22.7	22.6	22.6	22.7
14'	128.1	128.1	128.0	128.1	14.0	14.1	14.1	14.0	14.1
15'	128.3	128.3	128.2	128.3	-	-	-	-	-
1"	72.8	60.9	-	-	72.6	61.0	63.3	-	-
2"	57.5	62.0	-	-	57.4	62.1	67.7	-	-
3"	140.1	135.3	-	-	140.1	135.3	139.1	-	-
4",8"	128.6	129.2	-	-	128.5	129.3	128.9	-	-
5",7"	127.3	128.0	-	-	127.2	128.1	128.2	-	-
6"	125.4	127.6	-	-	125.3	127.7	127.6	-	-
*N*Me	-	-	-	40.3	-	-	-	-	40.4

The enantiomeric purity of the pyrrolidines was measured by ^1H, ^{13}C and ^{19}F nmr studies of the Mosher's amide derivatives.[12] (+)-(*R*)-α-Methoxy-α-trifluoromethylphenylacetamides (MTPA) (**13a**, **13c** and **13b**) of (-)-(*R*)-**12a**, (+)-(*S*)-**12c** and (-)-(*R*)-**12b** pyrrolidines displayed the methoxy signals at δ 3.62 (^1H nmr spectra) and in the ^{13}C nmr spectra, at δ 55.09, δ 54.84 and δ 55.16, respectively. The trifluoromethyl signals were at δ -5.79, -6.39 and -5.71, respectively, in the ^{19}F nmr spectra ($CDCl_3$, extern. TFA = δ 0.00).

Noteworthy was that a chiral auxiliary group on *N*-1 strongly influenced the ^{1}H nmr shift of CH_2-5 in (2*R*, 2"*R*)-benzylpyrrolidines : Hb-5 of (2*R*, 2"*R*)-benzylpyrrolidines (**11a**) and (**11b**) were shielded at δ 2.21 and 2.09, by positive anisotropy of the benzene ring, as well as in (2*R*, 2"*R*)-MTPA amides (**13a**) and (**13b**), at δ 2.40. Ha-5 was out of the anisotropic field shifting at δ 2.64 in (2*S*, 2"*R*)-benzylpyrrolidine (**11d**), and at δ 2.80 in (2*S*, 2"*R*)-MTPA amide (**13c**). Magnetic nonequivalence of C-5 protons was thus Δδ 0.7 ppm for (2*R*, 2"*R*)-benzylpyrrolidine, Δδ 0.9-1.1 ppm for (2*R*, 2"*R*)-MTPA amides, and Δδ 0.3 ppm for (2*S*, 2"*R*)-benzyl derivative as well as for MTPA amides. CH-2 shift was not influenced. The two diastereoisomers were clearly distinguished in ^{1}H nmr, too. The absence of diastereomeric signals in the ^{1}H and ^{19}F nmr spectra indicated the optical purity of each alkaloid to be higher than 98 %ee. Specific rotations were -55.0° (MeOH) for synthetic (*R*)-irniine (**1a**), -35.0° (CH_2Cl_2) for natural irniine and +50.7° (MeOH) for synthetic (*S*)-irniine (**1c**), -45.0° (MeOH) for synthetic (*R*)-bgugaine (**1b**) and -48.0° (MeOH) for natural bgugaine. Stereochemistry of the synthesized compounds was thus controlled at each reaction step.

Alkaloids (**1a**) and (**1b**) inhibited the growth of Gram (+) bacteria, *Streptococcus aureus* and *Micrococcus luteus* with MIC 12.5 - 25.0 μg/ml, and *Bacillus cereus* with MIC 50 and 25μg/ml, respectively (Table 4). The 2*S* isomer (**1c**) was less active than the 2*R* isomer against the three strains of Gram (+) bacteria (MIC 50 μg/ml). Alkaloids (**1a**, **1b** and **1c**) showed similar activities against *Candida albicans* and *C. tropicalis* (MIC 25 - 50μg/ml). Compound (**1b**) displayed stronger inhibition of the proliferation of *Cryptococcus neoformans* (MIC 6.3 μg/ml) than **1a** and **1c**.

Table 4. Antibacterial and antifungal activities, *in vitro*.

	M.I.C. (μg/ml)			
	1a	**1c**	**1b**	
Gram (+) bacteria				Chloramphenicol
Staphylococcus aureus I.P.	25.0	50.0	12.5	12.5
Micrococcus luteus I.P.5345	12.5	50.0	12.5	12.5
Bacillus cereus	50.0	50.0	25.0	12.5
Yeasts				Ketoconazol
Candida albicans I.P. 4872	25.0	25.0	25.0	3.0
Candida tropicalis	50.0	25.0	25.0	50.0
Cryptococcus neoformans	50.0	25.0	6.3	0.2

EXPERIMENTAL

General. Thin layer chromatography was performed on precoated plates (silica gel 60 F_{254}, Merck). Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Nmr were recorded on a Bruker AC 300 (300 MHz) spectrometer with tetramethylsilane as an internal standard. EI mass spectra were measured on a Kratos MS-80 mass spectrometer.

Methyl 6-iodohexanoate (**2**). - 6-Bromohexanoic acid (25.0 g, 0.128 mol) and NaI (35.0 g, 0.23 mol) in acetone (150 ml) were refluxed for 7 h.[8] Solvent was evaporated and the residual mixture poured into water and extracted with CH_2Cl_2. The residue of this extract was crystallized from methanol, and yielded 6-iodo-1-hexanoic acid (27.1 g), mp 32-33°C. The acid (24.2 g) in methanol (50 ml) was esterified by freshly distilled diazomethane in ether solution. Removing of the solvents afforded the methyl ester (**2**) 25.3 g as a viscous oil.

6-Iodohexanoic acid : ^{1}H Nmr ($CDCl_3$) δ: 3.17 (2H, t, 6.9, H_2-6) ; 2.35 (2H, t, 7.4, H_2-2) ; 1.83 (1H, tt, 7.4, 6.9, H_2-5) ; 1.64 (2H, quint., 7.4, H_2-3) ; 1.44 (2H, quint., 7.4, H_2-4). ^{13}C Nmr ($CDCl_3$) δ : 179.9 (C-1) ; 33.8 (C-2) ; 33.0 (C-5) ; 29.8 (C-4) ; 23.5 (C-2) ; 6.3 (C-6). **2** : EIms: *m/z* 256 ($M^{+\bullet}$). ^{1}H Nmr ($CDCl_3$) δ, (*J*, Hz) : 3.61 (3H, s, OCH_3) ; 3.13 (2H, t, 7.0, H_2-6), 2.27 (2H, t, 7.3, H_2-2) ; 1.79 (2H, quint., 7.3, H_2-5), 1.60 (2H, quint., 7.6, H_2-3) ; 1.38 (2H, quint., 7.5, H_2-4). ^{13}C Nmr ($CDCl_3$) δ : 173.8 (C-1) ; 51.5 (OMe) ; 33.8 (C-2) ; 33.1 (C-5) ; 29.9 (C-4) ; 23.8 (C-3); 6,5 (C-6). Anal. Calcd for $C_7H_{13}O_2$: C, 32.81; H, 5.12. Found: C, 32.70; H, 5.15.

Methyl 9-phenylnonanoate (**3**). - 3-Phenylpropylmagnesium bromide was prepared from 1-bromo-3-phenylpropane (32.85 g, 0.165 mol) and magnesium turnings (4.50 g, 0.185 mol) in anhydrous THF (120 ml). Cuprous iodide (32.38 g, 0.170 mol) and 300 ml of THF were placed under argon in a flame-dried, 1 l round-bottomed flask equipped with a magnetic stirrer. To the suspension cooled at -78°, a 1.5 M ether solution of methyllithium (107 ml, 0.160 mol) was added with a syringe. The solution of 3-phenylpropylmagnesium bromide in THF was added to the resulting suspension of methylcopper at -78°C with a syringe. The reaction mixture was stirred at -78°C for another hour and warmed (10°C) until a clear solution was obtained. The purple solution was immediately cooled to -78°C, and methyl 6-iodohexanoate (**2**) (40.46 g, 0.158 mol) in THF (50 ml) was added with a syringe. The suspension was stirred for 1 h at -78°C, then allowed to warm to room temperature and stirred for 20 h. The reaction mixture was quenched by pouring into a saturated aq. NH_4Cl solution. The THF solution was separated and the aqueous phase extracted with CH_2Cl_2. The combined organic fractions were washed once with 200 ml of saturated NaCl, then dried over Na_2SO_4 and the solvent evaporated. Chromatography of the crude residual product (38.25 g) on a silica gel column, eluted by cyclohexane/ether (9/1) afforded methyl 9-phenylnonanoate (**3**) (25.35 g, 65 %), 1,6-diphenylhexane (**4**) (5.56 g, 14 %) and unreacted **2** (4.34 g). **3** : colorless oil ; EIms: *m/z* 248 ($M^{+\bullet}$). ^{1}H Nmr ($CDCl_3$) : 7.25 (2H, m, H-3',5'); 7.18 (1H, m, H-4'); 7.17 (2H, m, H-2',6'); 3.65 (3H, s, OMe); 2.60 (2H, t, 7.7, H_2-9); 2.29 (2H, t, 7, H_2-2); 1.64 (2H, m, H_2-3); 1.59 (2H, m, H_2-8); 1.31 (8H, br s, CH_2-4 to 7). ^{13}C Nmr ($CDCl_3$) : 174.0 (C-1); 142.7(C-1'); 128.2 (C-2',6'); 128.1(C-3',5') ; 125.4 (C-4'); 51.2 (OMe); 35.9 (C-9); 33.9 (C-2); 33.1 (C-8); 29.00, 29.2, 29.1 and 29.0 (C-4-7); 24.8 (C-3). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.42; H, 9.68. Found: C, 77.32; H, 9.77.

1-Bromo-9-phenylnonane (**6**). - 9-Phenylnonanol (**5**) (18.44 g, 84 mmol), prepared in 95 % yield from ester (**3**) by $LiAlH_4$ reduction, 25 ml of aq. HBr (48 %) and 4.58 ml of conc. H_2SO_4 were refluxed for 3 h, then cooled and poured on ice. The water insoluble layer was extracted with CH_2Cl_2, the organic phase washed with water, dried over Na_2SO_4 and the solvent evaporated. The crude extract (22.39 g) was

purified by chromatography on a silica gel column, eluted with cyclohexane/ether (95/5) and pure **6** was obtained as a colorless oil (19.64 g, 83 %). **5**: EIms: *m/z* 220 ($M^{+\bullet}$), $C_{15}H_{24}O$. ^1H nmr ($CDCl_3$) :7.27 (2H, m, H-3',5'); 7.20 (2H, m, H-2',6'); 7.19 (1H, m, H-4'); 3.61 (2H, t, 6.7, H_2-1); 2.62 (2H, t, 7.7, H_2-9); 2.31 (1H, br s, OH); 1.64 (2H, m, H_2-8); 1.56 (2H, m, H_2-2); 1.33 (10H, m, H_2-3 to -7). ^{13}C Nmr ($CDCl_3$) :142.8 (C-1'); 128.3 (C-2',6'); 128.1 (C-3',8); 125.4 (C-4'); 62.7 (C-1); 35.89 (C-9); 32.6 (C-2); 31.4 (C-8); 29.4, 29.3, 29.3 and 29.2 (C-4 to -7); 25.7 (C-3). **6 :** EIms: *m/z* 282 and 284 ($M^{+\bullet}$) ; ^1H nmr ($CDCl_3$) : 7.31 (2H, m, 3',5'); 7.24 (3H, m, 2',4',6'); 3.43 (2H, t, 6.9, H_2-1); 2.66 (2H, m, 7.7, H_2-9); 1.89 (2H, quint., 7.5, H_2-2); 1.66 (2H, m, H_2-8); 1.37 (10 H, br s, H_2-3 to -7). ^{13}C Nmr ($CDCl_3$) : 142.7 (C-1'); 128.3 (C-2',6'); 128.1 (C-3',5'); 125.5 (C-4'); 35.9 (C-9) ; 33.8; 32.7; 31.4; 29.3; 29.2; 28.7; 28.6. Anal. Calcd for $C_{15}H_{23}Br$: C, 63.60; H, 8.13. Found: C, 63.85; H, 8.15.

Methyl 4-oxo-13-phenyltridecanoate (7a). - The reaction was carried out as for compound (**3**), starting from CuI (13.90 g, 73 mmol), THF (150 ml) and 48.1 ml (77 mmol) of a 1.6 M solution of MeLi in ether, the solution of 9-phenylnonylmagnesium bromide, prepared from bromide (**6**) (20.60 g, 73 mmol) and Mg turnings (1.97 g, 81 mmol) in THF (60 ml), and 3-carbomethoxypropionyl chloride (11.22 g, 73 mmol) in THF (45 ml). The chromatography of the crude product (30 g) on a silica gel column eluted with CH_2Cl_2 yielded the keto ester (**7a**) (15.11 g, 65 %) and, a by-product, 1,18-diphenyl-octadecane (**8a**) (5.11 g, 17 %), mp 45-49°C(CH_2Cl_2). **7a**: EIms: *m/z* 318 ($M^{+\bullet}$). ^1H Nmr ($CDCl_3$) : 7.24 (2H, m, H-3',5'); 7.16 (1H, m, H-4'); 7.15 (2H, m, H-2',6'); 3.65 (OMe) ; 2.69(2H, t, 6.8, H_2-2) ; 2.58 (2H, t, 7.2, H_2-13); 2.56 (2H, t, 6.8, H_2-3); 2.41 (2H, t, 7.4, H_2-5); 1.59 (2H, m, H_2-12); 1.55 (2H, m, H_2-6); 1.26 (10H, br s, H_2-7 to -11). ^{13}C Nmr ($CDCl_3$) : 208.9 (C-4); 173.1 (C-1); 142.7 (C-1'); 128.3 (C-2',6'); 128.1 (C-3',5'); 125.4 (C-4'); 51.6 (OMe); 42.6 (C-5); 36.8 (C-3); 35.8 (C-13); 31.3 (C-12); 29.3, 29.2, 29.1, 29.1 and 29.0 (C-7 to -11); 27.6 (C-2); 23.7 (C-6). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.42; H, 9.50. Found: C, 75.50; H, 9.44.

4-Oxo-13-phenyltridecanoic acid (9a). - The ester (**7a**) (13.70 g, 43 mmol) was dissolved in a mixture of methanol (150 ml) and water (20 ml) containing 21 g (375 mmol) of KOH and stirred at 20°C for 20 h. The methanol was evaporated *in vacuo*, the mixture acidified with 10 % H_2SO_4 and extracted with CH_2Cl_2 several times. The organic extracts were combined, dried over Na_2SO_4 and the solvent evaporated to yield the crystalline acid (**9a**) (11.68 g, 89 %) recrystallized from methanol, mp 84-85°C. EIms: *m/z* 304 ($M^{+\bullet}$). Anal. Calcd for $C_{19}H_{28}O_3$: C, 75.00; H, 9.21. Found: C, 74.97; H, 9.36.

(2*S*,2"*R*)-2"-Phenyl-2-(9-phenylnonyl)oxazololactam (10a) :(3*R*,7a*S*)-3-phenyl-7a-(9-phenylnonyl)tetrahydro-5*H*-pyrrolo[2,1-*b*]oxazol-5(6*H*)-one . - The 4-oxo acid (**9a**) (9.46 g, 31 mmol) and (*R*)-phenylglycinol (4.27 g, 31 mmol) in toluene (200 ml) were refluxed for 15 h, with azeotropic elimination of water produced. The solvent was evaporated *in vacuo* and the residue was purified by silica gel column chromatography eluted with CH_2Cl_2/MeOH (98/2) to afford pure compound

10a, 12.10 g (96%) as a colorless oil. **10a** : $[\alpha]_D^{20}$ -106.4° (*c* 1, MeOH) ; EIms: *m/z* 369 ($M^{+\bullet}$). Anal. Calcd for $C_{24}H_{35}NO_2$: C, 78.05; H, 9.49; N, 3.79. Found: C, 78.11; H, 9.35; N, 3.58.

(2*R*,2"*R*)-*N*-[2"-(Hydroxymethyl)benzyl]-2-(9-phenylnonyl)pyrrolidine (11a). - $AlCl_3$ (3.08 g, 23 mmol) was added to THF (50 ml) at -78°C under argon with stirring. $LiAlH_4$ (2.66 g, 70 mmol) was added at -78°C, followed by **10a** (10.39 g, 25.6 mmol) in THF (20 ml). The reaction mixture was stirred for 1 h at -78°C, decomposed by acetone and water and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and the solvent evaporated to yield a residue (10.26 g) which afforded the benzyl-(*R*)-phenylnonylpyrrolidine (**11a**) (8.72 g, 87%), mp 57-59°C by silica gel chromatography, eluted with cyclohexane / acetone / 20 % aq. ammonia (80/20/0.5). **11a**: $[\alpha]_D^{20}$ -84.5° (*c* 1, MeOH). EIms: *m/z* 383 ($M^{+\bullet}$). Anal. Calcd for $C_{27}H_{29}NO$: C, 84.60; H, 7.57; N, 3.66. Found: C, 84.61; H, 7.37; N, 3.58.

(*R*)-2-(9-Phenylnonyl)pyrrolidine (12a). - The benzylpyrrolidine (**11a**) (4.00 g, 10 mmol) was added to a suspension of 1.00 g of 10 % Pd/C in 30 ml of AcOH. The reaction mixture was shaken under H_2 (4 bars) for 48 h at 20°C. After filtration, alkalization by 10 % aq. ammonia and evaporation to dryness, an oily residue (2.8 g), was obtained. Chromatography of the crude residue on a silica gel column (MeOH / CH_2Cl_2 / 20 % aq. ammonia : 85/15/0.5) afforded 2.57 g (90%) pure (*R*)-2-(9-phenylnonyl)pyrrolidine (**12a**), mp 90-93°C (MeOH), $[\alpha]_D^{20}$ -11.5° (*c* 1, MeOH). EIms: *m/z* 273 ($M^{+\bullet}$). HRms *m/z* 273.2440, calcd for $C_{19}H_{31}N$: 273.2457.

(2*R*)-*N*-Methyl-2-(9-phenylnonyl)pyrrolidine (1a) : irniine. - (*R*)-Pyrrolidine (**12a**) (1.00 g, 3.7 mmol) in MeOH (30 ml) was stirred for 1 h with 37 % aq. HCHO (8 ml), and then an excess of $NaBH_4$ (10 g) was added by portions. The solvent was evaporated, the residue extracted by CH_2Cl_2, and the extract purified by silica gel column chromatography (eluent MeOH/CH_2Cl_2/20 % aq. ammonia : 90/10/1) to afford 0.95 g (90 %) of pure (*R*)-*N*-methylpyrrolidine (**1a**) as a colorless oil, $[\alpha]_D^{20}$ -55.0° (*c* 1, MeOH). EIms: *m/z* 287 ($M^{+\bullet}$). HRms *m/z* 287.2595, calcd for $C_{20}H_{33}N$: 287.2613.

Methyl 4-oxooctadecanoate (7b). - 4-Oxo ester (**7b**) was synthesized as described above for compound (**7a**), from tetradecyl bromide (20.24 g, 73 mmol), Mg (1.97 g, 81 mmol), CuI (13.90 g, 73 mmol) and MeLi (48.1 ml of 1.6 M ether solution, 77 mmol), and 3-carbomethoxypropionyl chloride (11.22 g, 73 mmol) in THF (45 ml). Silica gel chromatography of the crude product furnished 13.10 g (57 %) of the pure ester (**7b**) (mp 46-48°C) and 3.50 g (15 %) of a dimeric alkyl byproduct, CH_3-$(CH_2)_{26}$-CH_3 (**8b**). **7b**: ^1H Nmr ($CDCl_3$) δ: 3.62 (3H, s, OMe) ; 2.67 (2H, t, 6.3, H_2-2) ; 2.53 (2H, t, 6.3, H_2-3) ; 2.39 (2H, t, 7.4, H_2-5) ; 1.53 (2H, t, 7.1, H_2-6) ; 1.21 (22H, br s, H_2-7 to -17) ; 0.83 (3H, t, 6.5, H_3-18). ^{13}C Nmr ($CDCl_3$) δ : 208.9 (C-4) ; 173.2 (C-1) ; 51.6 (OMe) ; 42.7 (C-5) ; 36.9 (C-3) ; 31.9 (C-14) ; 29.6 (6C), 29.4 (1C), 29.3 (1C), 29.2 (1C) (C-7 to -15); 27.7 (C-2) ; 23.8 (C-6) ; 22.6 (C-17); 14.0 (C-18). EIms: *m/z* 312 ($M^{+\bullet}$). Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.01; H, 11.62. Found: C, 73.12; H, 11.62.

4-Oxooctadecanoic acid (9b). - The ester (**7b**), (10.00 g) was hydrolyzed by a solution of KOH (15 g) in MeOH (100 ml) at 20°C for 20 h and treatment as for **9a** furnished 9.38 g (98 %) of pure **9b**, mp 96-97°C (MeOH). EIms: *m/z* 298 ($M^{+\bullet}$). Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.48; H, 11.41. Found: C, 72.54; H, 11.49.

(2*S*, 2"*R*)-2"-Phenyl-2-(tetradecyl)oxazololactam (10b) : (3*R*, 7a*S*)-3-phenyl-7a-tetradecyltetrahydro-5*H*-pyrrolo[2,1-*b*]oxazol-5(6*H*)-one . - Compound (**10b**) was prepared from **9b** (3.27 g, 10.9 mmol) and (*R*)-phenylglycinol (1.50 g, 10.9 mmol) in toluene (100 ml) as described for **10a**. After purification by silica gel chromatography, 3.95 g of pure **10b** (89 %) were obtained as a viscous oil, $[\alpha]_D^{20}$ -109.9° (*c* 1.1, MeOH). EIms: *m/z* 399 ($M^{+\bullet}$). Anal. Calcd for $C_{26}H_{41}NO_2$: C, 78.20; H, 10.28; N, 3.51. Found: C, 78.36; H, 10.35; N, 3.38.

***N*-(*R*)-α-(Hydroxymethyl)benzyl-2-(*R*)-tetradecylpyrrolidine (11b) and *N*-(*R*)-α-(hydroxymethyl)benzyl-2-(*S*)-tetradecylpyrrolidine (11d).** - **10b** (3.27 g, 8 mmol) in THF (7 ml) was reduced and cleaved to the corresponding pyrrolidine by $LiAlH_4$ -$AlCl_3$ in dry THF (0.9 g: 23 mmol, 1.0 g: 8 mmol, 16 ml) at -40°C and treated as usual. Silica gel chromatography of the crude product provided (2*R*, 2"*R*)-benzylpyrrolidine (**11b**), (2.37 g, 75 %), mp 73-74°C, $[\alpha]_D^{20}$ -79.8° (*c* 1.2, MeOH), EIms: *m/z* 387 ($M^{+\bullet}$) and (2*S*, 2"*R*)-benzylpyrrolidine (**11d**) (0.17 g, 5.4 %), $[\alpha]_D^{20}$ +8.5° (*c* 1.5, MeOH), as colorless oils. EIms: *m/z* 387 ($M^{+\bullet}$). Anal. Calcd for $C_{26}H_{45}NO$ (**11b**): C, 80.62; H, 11.63; N, 3.62. Found: C, 80.59; H, 11.58; N, 3.56.

(2*R*)-Tetradecylpyrrolidine (12b). - The (2*R*, 2"*R*)-benzylpyrrolidine (**11b**) (2.00 g, 52 mmol) in AcOH (40 ml) was reduced by H_2 (4 bars) with 10% Pd/C (1 g) at 25°C for 20 h. The silica gel chromatography of crude product furnished 1.26 g (91 %) of 2-(*R*)-tetradecylpyrrolidine (**12b**), mp 56-58°C, $[\alpha]_D^{20}$ -7.1° (*c* 1.1, MeOH). EIms: *m/z* 267 ($M^{+\bullet}$). Hrms *m/z* 267.2909, calcd for $C_{18}H_{37}N$: 267.2927.

(2*R*)-*N*-Methyl-2-tetradecylpyrrolidine (1b) : bgugaine. - **12b** was methylated as described for **1a** and afforded **1b**, as a colorless oil, $[\alpha]_D^{20}$ -45.0° (*c* 1.2, MeOH), identical to natural bgugaine (co-tlc, nmr, ms). EIms: *m/z* 281 ($M^{+\bullet}$). Hrms *m/z* 281.3102, calcd for $C_{19}H_{39}N$: 281.3083.

(2*S*)-*N*-Methyl-2-(9-phenylnonyl)pyrrolidine (1c). - **1c** was prepared from (*S*)-(+)-2-phenylglycinol and 4-oxo-13-phenyltridecanoic acid, as described for **1a**. Optical activities were the following : (2*R*,2"*S*)-oxazololactam (**10c**), $[\alpha]_D^{20}$ +88.1° (*c* 1.0, MeOH); (2*S*,2"*S*)-benzylpyrrolidine (**11c**), $[\alpha]_D^{20}$ +68.2° (*c* 1.0, MeOH) ; (2*S*)-2-(9-phenylnonyl)pyrrolidine (**12c**), $[\alpha]_D^{20}$ +8.2° (*c* 1.1, MeOH) ; (2*S*)-*N*-methyl-2-(9-phenylnonyl)pyrrolidine (**1c**), $[\alpha]_D^{20}$ +50.7° (*c* 1.8, MeOH). HRms *m/z* 287.2601, calcd for $C_{20}H_{33}N$: 287.2613.

Mosher's amides. - Pyrrolidine (**12a**), (27 mg, 0.1 mmol), undistilled (+)-(*R*)-MTPA-Cl (38 mg, 0.15 mmol), Et_3N (3 drops) and DMAP (4 crystals) in $CHCl_3$ (2 ml) were stirred under argon at 20°C for 20 h. The reaction mixture was washed with aq. 5 % HCl and then aq. 5 % NaOH. The crude product was isolated by extraction with CH_2Cl_2, drying and evaporating the solvent. Purification by tlc (SiO_2 gel, CH_2Cl_2/MeOH : 95/5) furnished the amide (49 mg, 97 %). **13a**: (*R*)-MTPA amide of **12a**, $[\alpha]_D^{20}$+62.6° (*c* 1.0, MeOH). ^{19}F Nmr ($CDCl_3$): -5,78. ^1H Nmr ($CDCl_3$): 1.10 - 2.10 (10 CH_2), 2.40 m (Ha-5), 2.60 t (CH_2-9'), 3.48 m (Hb-5), 3.62 s (OCH_3), 4.17 m (H-2), 7.10 - 7.60 (12 H). **13b** : (*R*)-MTPA amide of **12b**, $[\alpha]_D^{20}$+68.9° (*c* 1.0, MeOH). ^{19}F Nmr ($CDCl_3$): -5,71. ^1H Nmr ($CDCl_3$): 1.10 - 2.10 (15 CH_2), 2.40 m (Ha-5), 2.60 t (CH_2-9'), 3.35 m (Hb-5), 3.60 s (OCH_3), 4.17 m (H-2), 7.30 - 7.60 (6 H). **13c**: (*R*)-MTPA amide of **12c**, $[\alpha]_D^{20}$+105.1° (*c* 1.0, MeOH). ^{19}F Nmr ($CDCl_3$): -6.39. ^1H Nmr ($CDCl_3$): 1.10 - 2.10 (10 CH_2), 2.80. m (Ha-5), 2.56 t (CH_2-9'), 3.14 m (Hb-5), 3.62 s (OCH_3), 4.17 m (H-2), 7.10 - 7.60 (12 H).

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