Synthetic Studies of Trichloroleucine Marine Natural Products. Michael Addition of $LiCCl_3$ to *N*-Crotonylcamphor Sultam

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Trichloro aminonitriles 6a-d: The procedure by Inaba[1] was followed except equimolar mixtures of (*R*)-α-methylbenzylamine and 3-methyl, 4,4,4-trilchlorobutanal were reacted. Reaction provided 4 diastereomers in 93 % yield which were purified by silica flash chromatography (15:85 EtOAc/ *n*-hexane) followed by HPLC (silica Microsorb, 25 ∞ 250 mm, 1:9 EtOAc / *n*-hexane, 13 mL/min.). Isomers **7b**, **7c**, **7a** and **7d** eluted with retention times of 9.6, 10.8, 11.0, 14.0 minutes and recovered ratios of :25:17:44:14, respectively.

(2*R*,4*S*)-2-(*N*-((1'*R)*-1'-phenylethyl)amino-5,5,5-trichloro-4-methylpentanenitrile (**7a**): $C_{14}H_{17}Cl_3N_2$; rt = 11.0 minutes; solid; mp 90-91 ^{o}C; $[\alpha]_D$ +87.3^{o} (*c* 0.65, $CHCl_3$); UV (*n*-hexane) λ 209 (11282), 251 (818), 257 (ε 813) nm; IR (NaCl) ν 3321, 2225 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 5H), 4.13 (q, 1H, *J* = 6.5 Hz), 3.29 (dd, 1H, *J* = 9.6, 6.2 Hz), 2.72 (dqd, 1H, *J* = 9.4, 6.5, 2.5 Hz), 2.45 (ddd, 1H, *J* = 13.7, 9.6, 2.5 Hz), 1.80 (ddd, 1H, *J* = 13.7, 9.3, 6.2 Hz), 1.40 (d, 3H, *J* = 6.5 Hz), 1.27 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 142.7 (s, C1), 128.7 (2C, d), 127.7 (d), 126.6 (2C, d), 119.3 (s, C8), 104.7 (s, C7), 56.5 (d, C2), 51.8 (d, C5), 46.9 (d, C3), 37.2 (t, C4), 24.8 (q, C9), 16.9 (q, C6); HRCIMS obsd *m/z* 319.0543 [M+H]$^+$, $C_{14}H_{17}Cl_3N_2H$ requires 319.0536.

(2*R*,4*R*)-2-(*N*-((1'*R)*-1'-phenylethyl)amino-5,5,5-trichloro-4-methylpentanenitrile (**7b**): $C_{14}H_{17}Cl_3N_2$; rt = 9.6 minutes; solid; mp. 80-81° C; $[\alpha]_D$ +135.9° (*c* = 0.75, $CHCl_3$); UV (MeOH) 209 (10570), 251 (556), 257 (ε 590) nm; IR (NaCl) ν 3301, 2229 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 5H), 4.11 (q, 1H, *J* = 6.5 Hz), 3.18 (dd, 1H, *J* = 11.6, 3.9 Hz), 2.94 (dqd, 1H, *J* = 10.1, 6.5, 2.1 Hz), 2.46 (ddd, 1H, *J* = 13.9, 11.6, 2.2 Hz), 1.78 (ddd, 1H, *J* = 14.0, 10.1, 3.9 Hz), 1.42 (d, 3H, *J* = 6.4 Hz), 1.06 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 142.7 (C1), 128.7 (2C, d), 127.9 (d), 126.9 (2C, d), 120.0 (C8), 105.2 (C7), 56.5 (C2), 50.5 (C5), 45.5 (C3), 36.9 (C4), 24.6 (C9), 15.4 (C6); HRCIMS obsd *m/z* 319.0541 [M+H]$^+$, $C_{14}H_{17}Cl_3N_2H$ requires 319.0536.

(2*S*,4*S*)-2-(*N*-((1'*R)*-1'-phenylethyl)amino-5,5,5-trichloro-4-methylpentanenitrile (**7c**): $C_{14}H_{17}Cl_3N_2$; rt= 10.8 minutes; solid; mp 70-71° C; $[\alpha]_D$ -34.6° (*c* 0.41, $CHCl_3$); UV (*n*-hexane) λ 205 (ε 5000), 252 (ε 2000) nm; IR (NaCl) ν 3301, 2218 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 5H), 4.09 (q, 1H, *J* = 6.4 Hz), 3.73 (dd, 1H, *J* = 11.0, 4.6 Hz), 2.94 (dqd, 1H, *J* = 9.7, 6.5, 2.7 Hz), 2.46 (ddd, 1H, *J* = 13.8, 11.0, 2.7 Hz), 1.89 (ddd, 1H, *J* = 14.2, 9.7, 4.5 Hz), 1.38 (d, 6H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 144.2 (s, C1), 128.7 (2C, d), 127.8 (d), 126.6 (2C, d), 119.7 (s, C8), 105.1 (s, C7), 56.0 (d, C2), 50.9 (d, C5), 45.7 (d, C3), 37.0 (t, C4), 21.8 (q, C9), 15.9 (q, C6); HRCIMS obsd *m/z* 319.0538 [M+H]$^+$, $C_{14}H_{17}Cl_3N_2H$ requires 319.0536.

(2*S*,4*R*)-2-(*N*-((1'*R)*-1'-phenylethyl)amino-5,5,5-trichloro-4-methylpentanenitrile (**7d**): $C_{14}H_{17}Cl_3N_2$; rt = 14.0 minutes; solid; mp 101-102 ^{o}C; $[\alpha]_D$ +14.6° (*c* 0.55, $CHCl_3$); UV (*n*-hexane) λ 211 (ε 23200), 252 (511), 257 (ε 539) nm; IR (NaCl) ν 3309, 2214 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 5H), 4.14 (q, 1H, *J* = 6.5 Hz), 3.81 (dd, 1H, *J* = 9.7, 6.1 Hz), 2.83 (dqd, 1H, *J* = 9.4, 6.5, 2.7 Hz), 2.44 (ddd, 1H, *J* = 13.7, 9.7, 2.7 Hz), 1.82 (ddd, 1H, *J* = 13.7, 9.4, 6.1 Hz), 1.38 (d, 6H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 144.0 (s, C1), 128.7 (2C, d),

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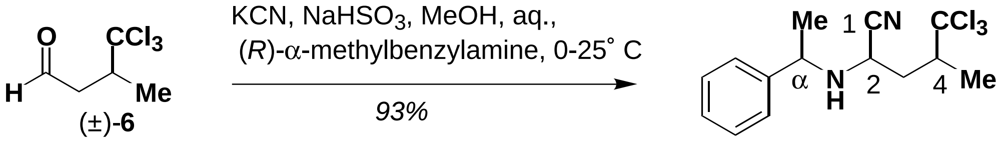
[1] Inaba, T.; Fujita, M.; Ogura, K. *J. Org. Chem.* **1991**, *56*, 1274-1279.

127.8 (d), 126.6 (2C, d), 119.0 (s, C8), 104.8 (s, C7), 56.2 (d, C2), 51.9 (d, C5), 46.8 (d, C3), 37.1 (t, C4), 22.1 (q, C9), 16.9 (q, C6); HRCIMS obsd *m / z* 319.0549 $[M+H]^+$), $C_{14}H_{17}Cl_3N_2H$ requires 319.0536.

Determination of Stereochemistry of 7a-d NMR spectral comparison of separated isomers **7a-d** reveals characteristic trends for chemical shifts influenced mainly by the newly created stereocenter, C-2 and the benzylic carbon.

The modified Strecker synthesis of (±)-**6** with (*R*)-α-methylbenzylamine[1] gave **7a-d** in 44: 25:17:14 % ratio respectively. It is well known that (*R*)-α-methylbenzylamine with 3-methylbutanal and KCN, under the similar equilibrium conditions, provides the (*R*)-amino nitrile as the major diastereomer.[1] Table *i* compares the H-2 proton chemical shifts of compounds **7a-d.** It is also documented that the ^{1}H NMR chemical shift of H-2 for similar (2*R*)-aminonitriles occurs upfield from the corresponding (*S*) epimer by approximately 0.5 ppm. Thus, from comparison of H NMR chemical shifts the pairs of diastereomers with the 2*R* configuration are major isomer **7a** and lesser isomer **7b** and the pairs **7c** and **7d** have the (2*S*) configuration. This was supported by comparison of ^{13}C NMR spectra (Table *ii*) which showed upfield shifts of the α-CH benzylic methine and C-1' phenyl ring carbon (~Δδ +2 ppm) with respect to the 2*S* pair.

The C-4 configurational assignments were revealed after the Strecker reaction was repeated with partially resolved aldehyde (*R*)-(+)-**6** (85% optical purity) which provided the major amino nitriles (2*R*, 4*R*)-**7b** and (2*S*, 4*R*)-**7d** in a 1.7:1 ratio.



	α, C2, C4	*ratio*
7a	*R, R, S*	44
7b	*R, R, R*	25
7c	*R, S, S*	17
7d	*R, S, R*	14

Table ***i*****:** $[\alpha]_D$ and ^{1}H NMR Chemical Shifts at H-2 (δ, $CDCl_3$)

Compound	$[\alpha]_D$ ($CHCl_3$)	δ H-2	Configuration at C2,4
7a	+87.3°	3.29	2*R*, 4*S*
7b	+135.9°	3.18	2*R*, 4*R*
7c	-34.6°	3.73	2*S*, 4*S*
7d	+14.6°	3.81	2*S*, 4*R*

Table ***ii*****:** ^{13}C NMR Chemical Shifts (δ, $CDCl_3$) of Compounds **7a-d**

C #	**7a**	**7b**	**7c**	**7d**
1	119.31	119.98	119.73	119.07
2	46.91	45.49	45.67	46.84
3	37.16	36.89	37.00	37.09
4	51.77	50.53	50.83	51.85
5	104.69	105.17	105.06	104.78
α	56.54	56.52	56.04	56.24
5-Me	16.91	15.38	15.87	16.93
α-Me	24.79	24.62	21.79	22.13
1'	142.71	142.74	144.19	144.02
2'-6'	126.64	126.90	126.64	126.63
	127.70	127.89	127.77	127.78
	128.73	128.74	128.72	128.72