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Synthesis of Aza-Muricatacin : an Analogue of the Bioactive Muricatacin an Acetogenin of Annonaceae

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Abstract : Muricatacin is a hydroxy butanolide extracted from *Annona muricata*, and has shown cytotoxic activity. The *threo* and *erythro* aza-analogues, namely the hydroxy pyrrolidones have been synthesized through two different routes . © 1997 Elsevier Science Ltd.

Muricatacin [(4*S**, 5*S**)-5-hydroxy-heptadecan-4-olide] has been isolated from *Annona muricata* (Annonaceae), as a quasi-racemic mixture and has shown interesting *in vitro* cytotoxic activity[1]. Since its isolation and characterization in 1991, several syntheses of (+) or (-)-muricatacin, as well as *epi*-muricatacin have been described in the literature[2a-e,3]. In this letter we wish to report the stereoselective preparation of both *threo* and *erythro* diastereomers of its aza-analogue, the corresponding hydroxy pyrrolidones (Fig. 1), by two different routes.

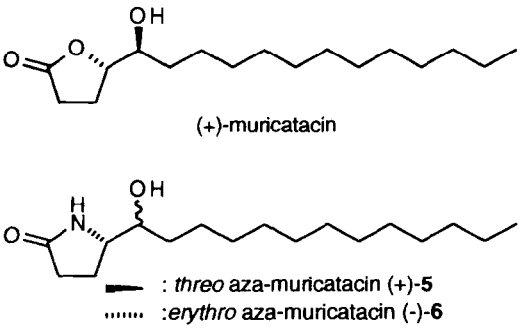
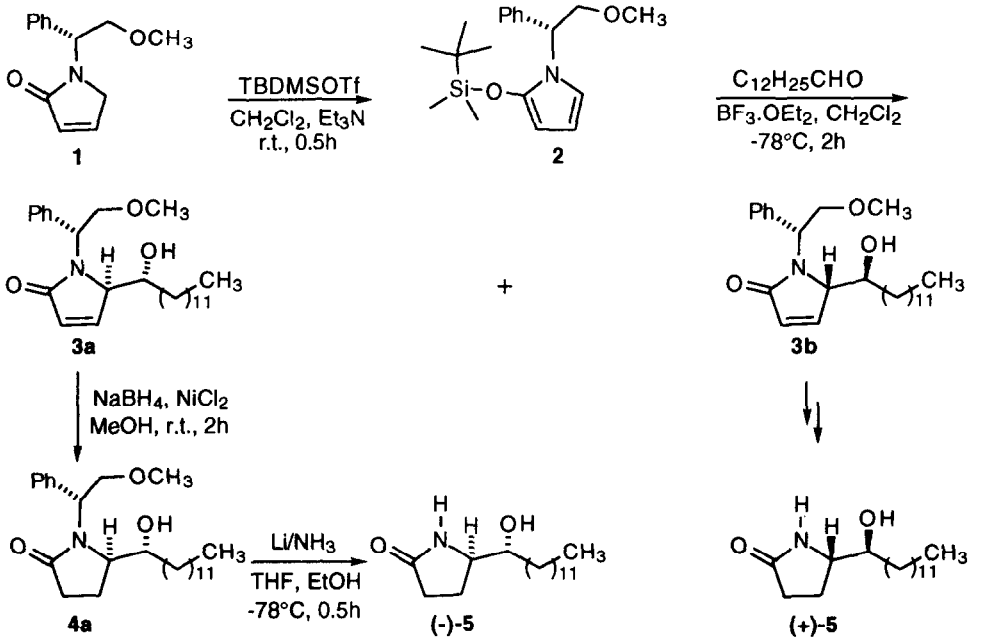


Figure 1

Both enantiomers of the *threo* isomer of aza-muricatacin were stereoselectively synthesized through the condensation of a chiral silyloxypyrrole with an achiral aldehyde, a methodology recently studied in one

of our laboratories[4]. The synthesis is described in Scheme 1. Chiral silyloxypyrrole **2** (prepared in one step and 90% yield from lactam **1**) was treated with tridecanal in the presence of $BF_3.OEt_2$ (CH_2Cl_2, -78°C) to give the aldol adducts **3** as a mixture of the two *threo* diastereomers (3:1 ratio in favor of the 4*R*, 5*R* isomer **3a**). The configurations of these compounds were established on the basis of previous studies[4]. Both diastereomers **3a** and **3b** were readily separated by flash chromatography on silica gel and isolated in 60 and 22 % yield respectively.[5] Each diastereomer was then separately treated : the reduction of the double bond was obtained by treatment with $NaBH_4$ (5 equiv.) in the presence of $NiCl_2$ (0.5 equiv.) in methanol[6] to give **4** in good yield (**4a** : 88% , **4b** : 47% after extensive purification[5]). The cleavage of the chiral auxiliary was eventually achieved by reduction with Li in liquid ammonia (THF, 10 equiv. EtOH, -78°C, 30 min.) to give the target compounds **(-)-5**[7] ($[\alpha]_D$ = -4.8 (c 2.7, $CHCl_3$), 72% yield from **4a**) and **(+)-5**[7] ($[\alpha]_D$ = +5.9 (c 2.6, $CHCl_3$), 81% yield from **4b**) (Scheme 1).

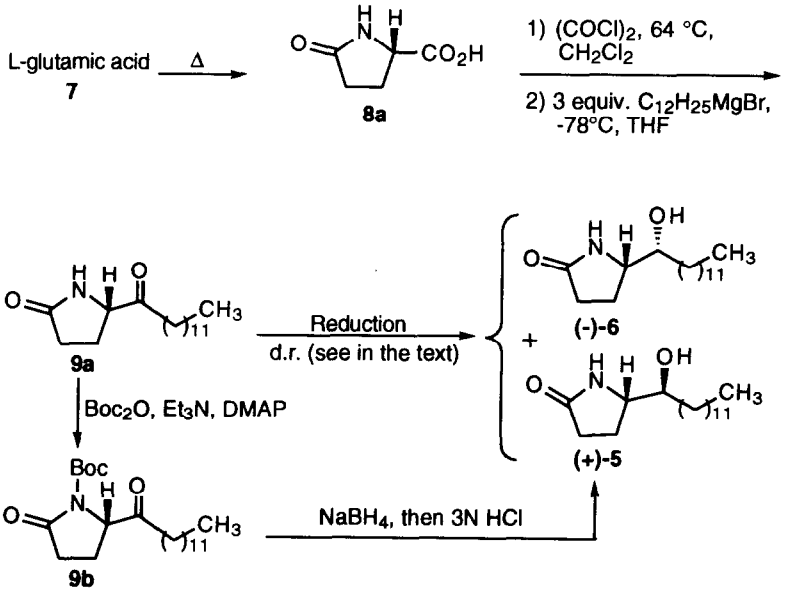


Scheme 1

The epimeric *erythro* 4*S*, 5*R* isomer **(-)-6** was alternatively prepared from L-glutamic acid through an acylation-reduction sequence (Scheme 2).

L-glutamic acid **7** was first heated up to give the corresponding (+)-pyroglutamic acid **8a** which was directly treated at 64 °C with 10 equiv. of oxalyl chloride for 2 hours. After evaporation of the volatils, THF was added in the crude reaction mixture, cooled to -78°C, before addition of 3 equiv. of dodecylmagnesium bromide. After stirring at -78°C for 2h and hydrolysis, the keto-pyrrolidone **9a** ($[\alpha]_D$ = -2.4 (c 1.44, $CHCl_3$)),was obtained in moderate yield (40 %). Then reduction of the latter with two equivalents of L-Selectride® at -78 °C in THF afforded the inseparable *erythro:threo* mixture (33:66 ratio) of hydroxy

pyrrolidones (-)-**6** and (+)-**5** in low yield (23 %). The use of $NaBH_4$ in THF/MeOH (99:1) at -10 °C gave rise to (-)-**6**[7] as the major isomer with 63:37 ratio (*erythro:threo*), but in 68 % yield (Scheme 2). It is noteworthy that the reduction with $NaBH_4$ in the presence of 1 equiv. of $MnCl_4Li_2$ at -10 °C in THF/MeOH (99/1) afforded the major *erythro* compound (-)-**6** (d.r. = 74:26) in 85 % yield[8]. When the reduction ($NaBH_4$ in the presence of 1 equiv. of $MnCl_4Li_2$) is performed at -40 °C, the major isomer (-)-**6** is now formed with a 82:18 (*erythro:threo*) ratio and in 80 % yield. We then decided to protect **9a** as its N-Boc derivative **9b** under usual conditions (Boc_2O, DMAP, Et_3N, r.t., 44 % yield) prior the $NaBH_4$ reduction at -10 °C. The mixture of the expected alcohols was directly treated by 3N HCl in AcOEt at 20 °C for 1 hour, to remove the N- Boc protecting group, leading to the major isomer (+)-**5** ((-)-**6**:(+)-**5** = 5:95) in 65 % yield for the last two steps. Indeed, such effect of the protecting group on the nitrogen atom was already observed by Soai *et all.* in the proline series[9]. The *erythro* selectivity in the unprotected case **9a** can be rationalized by the Cram's chelation model, whereas for the N-Boc derivative **9b** the Cram's open chain model may be applied to explain the *threo* selectivity[9].



Scheme 2

The synthesized aza-analogues of muricatacin were then tested against KB (and Vero cells for two of them), the results were reported in the Table.

It can be seen that all isomers exhibited interesting and similar cytotoxicity in the same range as the parent muricatacin.[3]

Table: *In vitro* cytotoxicity of muricatacin and aza-muricatacin isomers (KB and Vero cells)

cytotoxicity of IC_{50} (µg/mL)	(+)-muricatacin	(+)-**5**	(-)-**5**	(-)-**6**
KB	5.5	2.7	3.7	7.2
Vero	11	-	7	12

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References and notes

1 Rieser, M. J.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; *Tetrahedron Lett.*, **1991**, *32*, 1137-1140.

2 a) Figadère, B.; *Acc. Chem. Res.*, **1995**, *28*, 359-366, and references therein; b) Somfai, P.; *J. Chem. Soc. Perkin Trans I*, **1995**, 817-819; c) Bonini, C.; Federici, C.; Rossi, L.; Righi, G.; *J. Org. Chem.*, **1995**, *60*, 4803-4812; d) van Aar, M. P. M.; Thijs, L.; Zwanenburg, B.; *Tetrahedron* , **1995**, *51*, 11223-11234; e) Quayle, P.; Rahman, S.; *Tetrahedron Lett.*, **1995**, *36*, 8037-8038.

3 Figadère, B.; Harmange, J.-C.; Laurens, A.; Cavé, A.; *Tetrahedron Lett.*, **1991**, *32*, 7539-7542.

4 Baussanne, I.; Royer, J.; *Tetrahedron Lett.*, **1996**, *37*, 1213-1216

5 **3b** was only 90% pure and contained some epimeric compound **3a.** Complete separation of diastereomers was obtained on purification on the next step.

6 Abe, N.; Fujisaki, F.; Sumoto, K.; Miyano, S.; *Chem. Pharm. Bull.* **1991**, *39*, 1167-1170.

7 Spectroscopic data of *threo* **5** : ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) : 0.9 (t, J=7Hz, 3H), 1.3 (m, 22H), 1.8 (m, 1H), 2.1 (m, 1H), 2.35 (m, 2H), 3.33 (bs, 1H), 3.52 (dd, J=J'=6.7Hz , 1H), 4.35 (bs, 1H), 7.50 (bs, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ (ppm) : 14.4, 23.6, 24.5, 26.6, 30.3, 30.6 (several C), 31.3, 32.9, 34.1, 60.8, 75.4, 180.9.

Spectroscopic data of *erythro* (-)-**6** (from a 82:18 mixture of **(-)-6:(+)-5**) : $[\alpha]_D$ = -3.3 (c 1.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.88 (t, J=7Hz, 3H), 1.26 (m, 20H), 1.47 (m, 2H), 1.65 (m, 1H), 2.07 (m, 1H), 2.22 (m, 1H), 2.37 (m, 1H), 3.67 (m, 2H), 6.67 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) : 14.1, 20.3, 22.9, 25.7, 26.8, 29.6, 32.4, 59.1, 72.3, 177.7, 179.5; MS-CI (NH_4^+) m/z : 284 (MH^+).

8 For the use of $MnCl_2$ in $NaBH_4$ reductions of 3-keto-2-methyl esters, see : Fujii, H.; Oshima, K.; Utimoto, K.; *Tetrahedron Lett.*, **1991**, *32*, 6147-6150.

9 Ookawa, A.; Soai, K.; *J. Chem. Soc. Perkin Trans I*, **1987**, 1465-1471.

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