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SYNTHESES OF (4*R*, 5*S*)- AND (4*S*, 5*R*)-MURICATACINS, AND (4*S*, 5*R*)-AZA-MURICATACIN, UNNATURAL ANALOGUES OF THE ANNONACEOUS ACETOGENIN

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Abstract – (4*R*, 5*S*)- and (4*S*, 5*R*)-Muricatacins, and (4*S*, 5*R*)-aza-muricatacin, unnatural analogues of the Annonaceous acetogenin, were prepared from (-)-muricatacin *via* Mitsunobu inversion or Weinreb amidation as the key step.

(-)-Muricatacin [(4*R*, 5*R*)-**1**, (4*R*, 5*R*)-5-hydroxyheptadecan-4-olide] was isolated as a quasi-racemic mixture (-25% ee) by McLaughlin *et al.* from seeds of the tropical fruit, *Annona muricata*; it showed interesting *in vitro* cytotoxicity.[1] (-)-Muricatacin [(4*R*, 5*R*)-**1**] is one of the simplest compounds in the Annonaceous acetogenins family, showing a broad spectrum of potent biological activity; it displays cytotoxicity, antitumor activity, and pesticidal, antifeedant, and antiinfective properties.[2] Action of these compounds partially comprises inhibition of mitochondrial complex I (NADH-ubiquinone oxidoreductase).[3-5] Synthetic study of these compounds was needed to prepare acetogenin analogue data addressing the relationship of structure-activity with inhibition of mitochondrial complex I.

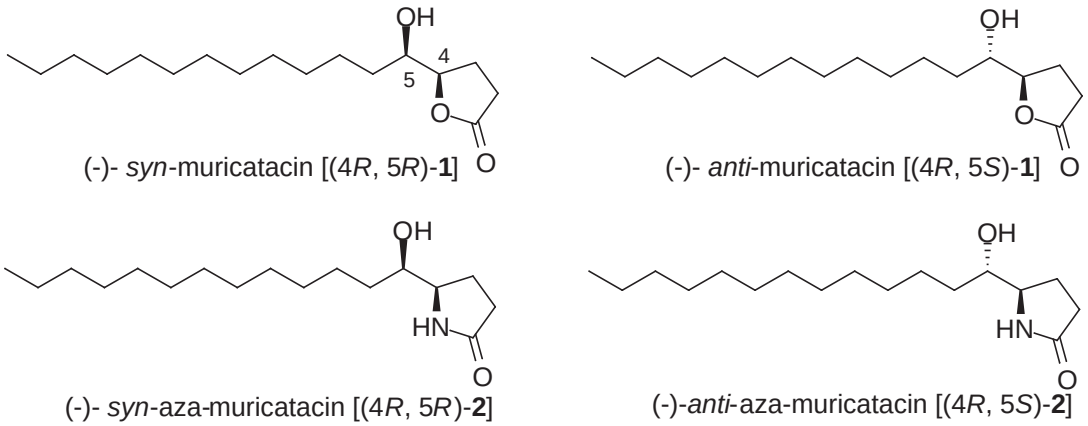
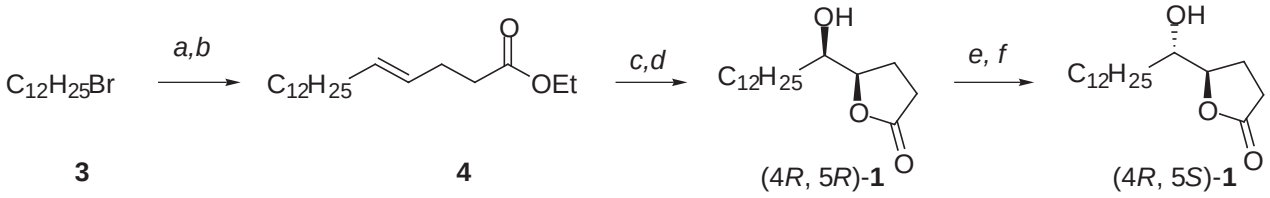


Figure 1

Although several syntheses of (+)- and (-)-muricatacins (**1**) have been disclosed in the literature,[6] one additional synthesis of four diastereoisomers has only been reported by the Yoon group.[7] Syntheses of *syn*- and *anti*-aza-muricatacins (**2**) have also appeared by efforts of the Royer group in 1997,[8] and the Andres group in 2001.[9] Royer and colleagues reported that *syn*- and *anti*-aza-muricatacins (**2**) showed unusually stronger cytotoxicity than muricatacin in the same range.[8] Thus it is possible to develop a more powerful inhibitor from this group.[10] Alternatively, aza-muricatacins can be useful synthetic precursors of nitrogen-containing acetogenins such as aza-solamin and diaza-bullatacin. Herein, we report stereocontrolled syntheses of (4*R*, 5*S*)-*anti*- and (4*S*, 5*R*)-*anti*-muricatacins and (4*S*, 5*R*)-*anti*-aza-muricatacin based on Sharpless asymmetric dihydroxylation.

Synthesis of (-)-muricatacin [(4*R*, 5*R*)-**1**] was followed by the method described by Wang *et al.*[11] We commenced synthesis using lauryl bromide (**3**). Grignard reaction of laurylmagnesium bromide with acrolein followed by Johnson Claisen rearrangement of the resulting allyl alcohol with triethyl orthoacetate gave ethyl ester (**4**) in 83% yield. Sharpless' asymmetic dihydroxylation of the ethyl ester (**4**) gave enantiomerically-pure muricatacin [(4*R*, 5*R*)-**1**; >99% ee from (*R*)-(+)-MTPA ester] after recrystallization. Treatment of (-)-muricatacin [(4*R*, 5*R*)-**1**] under Mitsunobu reaction conditions led to generate (-)-*anti*-muricatacin [(4*R*, 5*S*)-**1**] after hydrolysis in 30% yield.[6,14] (**Scheme 1**)

Scheme 1. Synthesis of (4*R*, 5*S*)-*anti*-muricatacin

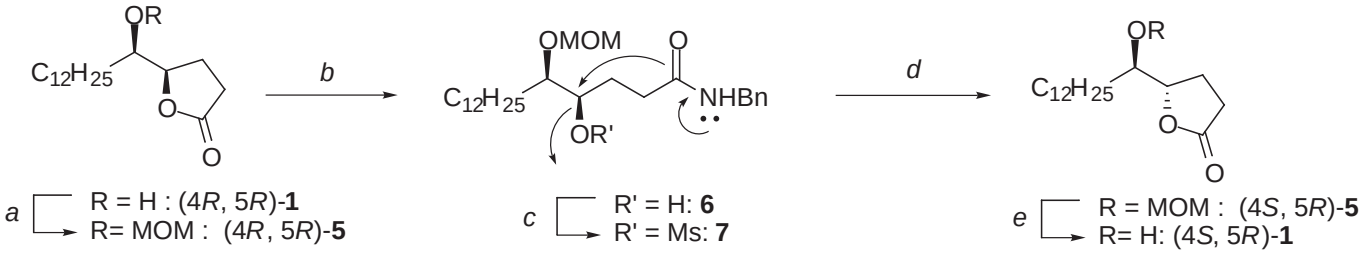


Reagents and conditions: (a) Mg, ether; then acrolein, 89%. (b) triethyl orthoacetate, phenol, 120°C, 92%. (c) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH-H_2O, 0°C. (d) recrystallization from hexane, 87% in two-steps, >98% ee. (e) PPh_3, DEAD, *p*-NO_2PhCO_2H, THF, 40°C. (f) K_2CO_3, MeOH, 30% in two-steps.

Next we attempted to convert (-)-muricatacin [(4*R*, 5*R*)-**1**] to *anti*-aza-muricatacin [(4*S*, 5*R*)-**2**]. Protection of the hydroxy group of (-)-muricatacin [(4*R*, 5*R*)-**1**] with MOMCl and Hunig's base afforded MOM ether [(4*R*, 5*R*)-**5**] in 98% yield. Treatment of MOM ether [(4*R*, 5*R*)-**5**] with benzylamine and trimethylaluminum[12] gave benzyl amide (**6**) in 95% yield. In this step, convertion of the hydroxyl group to azido group was tried using Mitsunobu reaction conditions (DPPA, DEAD, PPh_3, THF), however this reaction did not proceed. We then turned to two-step synthesis *via* mesylate. Although desired azide was formed in a trace amount by DeShong's method ($TMSN_3$, TBAF, THF, reflux),[13] a major product was MOM protected *anti*-muricatacin [(4*S*, 5*R*)-**5**] in 80% yield. Treatment of mesyl compound with DBU in benzene or THF reflux conditions also gave (4*S*, 5*R*)-**1** as a major product. This mechanism of cyclization

could be explained as the following: the mesyloxy group was displaced by the amide oxygen, and then the corresponding benzylimine was hydrolysed to give the lactone. We guess that displacement of the amido oxygen is faster than the nitrogen because benzyl protected secondary amide forms benzylimino alcohol easily. Treatment of (4*S*, 5*R*)-**5** with conc. HCl in MeOH gave (+)-*anti*-muricatacin [(4*S*, 5*R*)-**1**]. Spectral data of this compound were in good agreement with those previously reported.[7] **(Scheme 2)**

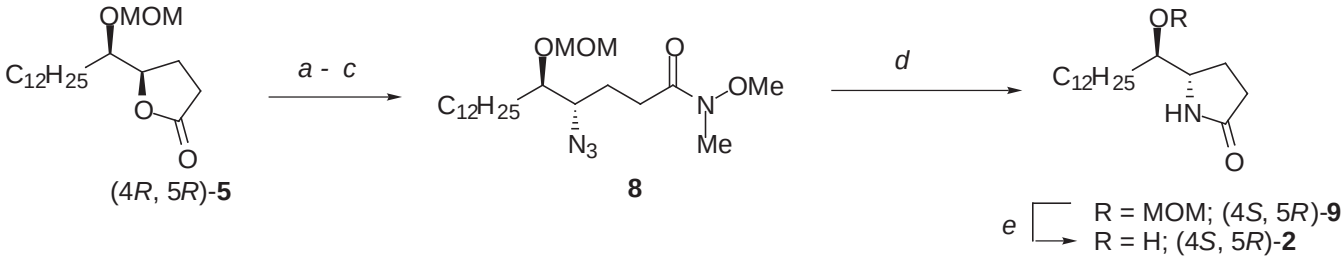
Scheme 2. Synthesis of (4*S*, 5*R*)-*anti*-muricatacin



Reagents and conditions: (a) MOMCl, *i*Pr_2NEt, CH_2Cl_2, 98%. (b) Me_3Al, $BnNH_2$, CH_2Cl_2, 95%. (c) MsCl, Et_3N, CH_2Cl_2. (d) THF, reflux, 12 h, 85% in two-steps. (e) HCl, MeOH, 90%.

In an attempt to improve efficiency of lactamization using tertiary amide, *N*-methyl-*N*-methoxyamine was chosen for Weinreb amidation. Treatment of the MOM ether [(4*R*, 5*R*)-**5**] with *N*-methyl-*N*-methoxyamine and trimethylaluminum in CH_2Cl_2 afforded tertiary amide in 95% yield.[12] On sequential mesylation and azidation of the resulting hydroxy group by DeShong's protocol,[13] the tertiary amide gave azido-amide (**8**) in 60% yield without forming *anti*-muricatacin. Hydrogenolysis of **8** in the presence of catalytic 10% Pd-C in MeOH and spontaneous cyclization afforded the desired pyrrolidone (**9**) in 65% yield. Finally, the pyrrolidone (**9**) was exposed to conc. HCl in MeOH to give aza-muricatacin [(4*S*, 5*R*)-**2**] in 84% yield. Spectral data of this compound were in good agreement with those previously reported.[9,14] **(Scheme 3)**

Scheme 3. Synthesis of (4*S*, 5*R*)-aza-muricatacin



Reagents and conditions: (a) Me_3Al, MeONHMe, CH_2Cl_2, 95%. (b) MsCl, Et_3N, CH_2Cl_2, 99%. (c) $TMSN_3$, TBAF, THF, reflux, 36 h, 80% (d) H_2, 10% Pd-C, MeOH, 65%. (e) conc. HCl, MeOH, 84%.

In summary, we synthesized (4*R*, 5*S*)-*anti*- and (4*S*, 5*R*)-*anti*-muricatacins using unnatural lactonization.

In addition, (4*R*, 5*S*)-*anti*-aza-muricatacin was prepared as a muricatacin analogue and a useful synthetic precuesor for other acetogenins.

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14. (4*R*, 5*S*)-**1**: mp 71-72°C; $[\alpha]_D$ +12.8° (*c* = 1.0, $CHCl_3$); IR (KBr): 3431, 2937, 2872, 1770, 1463,

1209, 1012 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.89 (3H, t, *J* = 6.6 Hz), 1.23 (20H, m), 1.42 (2H, m), 1.83 (1H, br s, OH), 2.1-2.32 (2H, m), 2.48-2.64 (2H, m), 3.92 (1H, m), 4.42 (1H, m) ; ^{13}C-NMR ($CDCl_3$): δ 14.2, 22.1, 22.7, 25.7, 28.8, 29.4, 29.6, 29.7, 32.0, 32.1, 71.3, 83.1, 177.8; MS m/z 285 (100%), 267, 249, 199, 86; HRMS: calcd $C_{17}H_{33}O_3$ (M^++H) 285.2431, Found 285.2428. (4*S*, 5*R*)-**2**: mp 80-81°C; $[\alpha]_D$ +5.8° (*c* = 0.3, $CHCl_3$); IR (KBr): 3332, 2923, 2853, 1681, 1462, 1278, 1075 cm^{-1}; ^{1}H-NMR (CD_3OD): δ 0.88 (3H, t, *J* = 6.6 Hz), 1.26 (26H, m), 1.50 (2H, m), 2.06 (2H, m), 2.33 (2H, m), 3.54 (1H, m), 3.60 (1H, m); ^{13}C-NMR (CD_3OD) : δ 14.5, 22.1, 23.8, 27.1, 29.6, 30.5, 30.8, 30.9, 31.3, 33.1, 34.3, 60.7, 73.8, 181.3; MS m/z 284 (100%), 282, 266, 178, 129, 84; HRMS: calcd $C_{17}H_{34}NO_2$ (M^++H) 284.2591, Found 284.2596.