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Tetrahedron Letters 45 (2004) 2809–2811
Tetrahedron Letters

Syntheses of two cytotoxic polyunsaturated pyrrole metabolites of the marine sponge *Mycale micracanthoxea*

Trond Vidar Hansen[a,*] and Lars Skattebøl[b]

[a]*School of Pharmacy, Department of Medicinal Chemistry, University of Oslo, PO Box 1185, Blindern, N-0316, Oslo, Norway*
[b]*Department of Chemistry, University of Oslo, PO Box 1033, Blindern, N-0315, Oslo, Norway*

Received 5 December 2003; revised 23 January 2004; accepted 6 February 2004

Abstract—Starting from eicosapentaenoic acid (EPA) the marine, naturally occurring, pyrrole derivatives, mycalazol **5** and mycalazal **2** have been synthesized. The Stille coupling reaction is a key step in the syntheses.

Marine organisms have proved to be an abundant source of biologically interesting secondary metabolites.[1,2] In 1997 Salvá and co-workers[3] identified fourteen structurally related 2,5-disubstituted pyrroles from the northeastern Atlantic sponge *Mycale micracanthoxea*. The compounds exhibit interesting cytotoxic activity towards several cancer cell lines. The characteristic structural feature of the compounds is a C-16 or longer carbon chain attached to the 5-position of the pyrrole ring. Some of them contain several methylene interrupted *Z*-double bonds in the side chain. As part of an ongoing effort on the synthesis and biological testing of derivatives of eicosapentaenoic acid (**1**, EPA) and docosahexaenoic acid (**2**, DHA)[4–8] the present paper describes the first syntheses of two of the polyunsaturated pyrroles: mycalazol **5** (**3**) and mycalazal **2** (**4**) (Fig. 1).

The compounds **3** and **4** contain the same number of methylene interrupted double bonds as those present in EPA. Hence we decided on a synthetic strategy for both compounds in which one of the fragments contains all the double bonds and the other an appropriate pyrrole entity. For compound **3**, a five carbon chain extension of EPA leads to the acid **5**, as one of the fragments. The other fragment is the known stannylpyrrole **6**,[9] and we anticipated that a Stille coupling would combine the two fragments affording the target molecule after reduction. A similar strategy has been used successfully by Nabbs and Abell for the synthesis of some of the saturated mycalazols.[10]

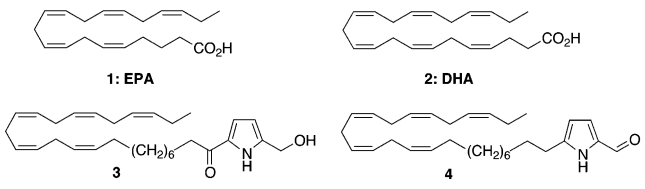

Figure 1.

The acid **5** was prepared as outlined in Scheme 1. Reduction of EPA with LAH in ether furnished the known alcohol **7**,[11] which was converted to the thioether **8** with $(PhS)_2$ and Bu_3P.[12] Oxidation of the sulfide with oxone in aqueous MeOH at 0 °C afforded the sulfone **9** (53% overall yield from EPA). Reaction of the α-sulfonyl carbanion, formed from **9** with LDA at −78 °C, with methyl 5-bromovalerate furnished the ester **10**. The phenylsulfonyl group was removed with sodium amalgam in the usual way,[13] and the resulting ester **11** was hydrolyzed with LiOH in aqueous MeOH to the acid **5**[14] (34% yield from **9**). The acid **5** was converted to the acid chloride **12** with $(COCl)_2$ in CH_2Cl_2 and the subsequent Stille coupling with the organotin derivative **6** furnished the pyrrole **13** in 81% yield (Scheme 2).[14] The synthesis was concluded by chemoselective reduction of the formyl group with $Zn(BH_4)_2$ in ether at 0 °C affording the target molecule **3** (76% yield) with spectral data in agreement with those reported for mycalazol **5**.[3]

It seemed obvious to transform the mycalazol **3** into the corresponding mycalazal derivative **4** using

Keywords: Pyrroles; Synthesis; Stille coupling.
* Corresponding author. Tel.: +47-2285-7450; fax: +47-2285-5947; e-mail: t.v.hansen@farmasi.uio.no

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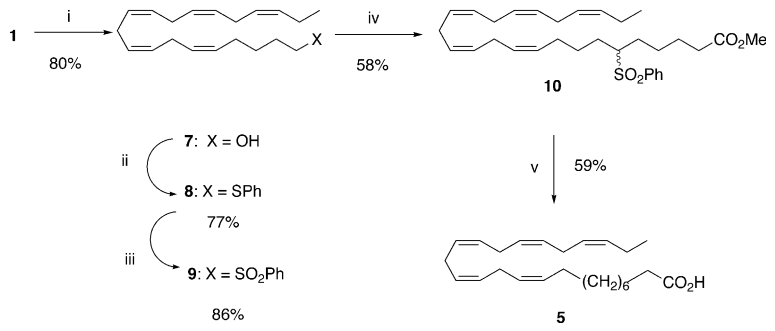
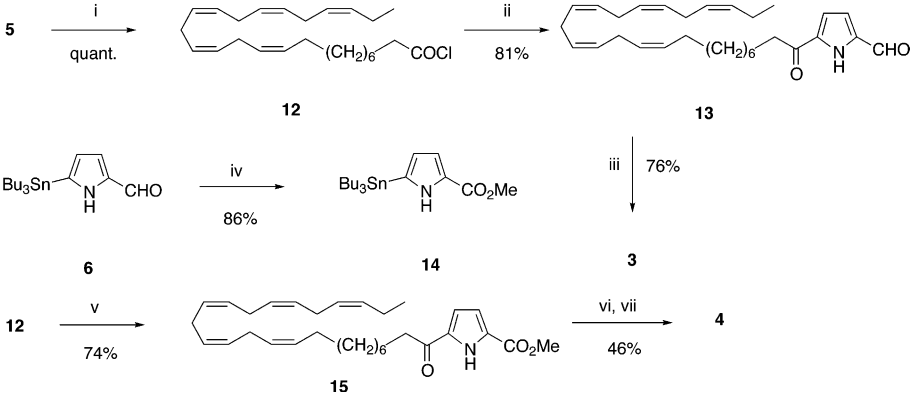
doi:10.1016/j.tetlet.2004.02.024



Scheme 1. Reagents and conditions: (i) $LiAlH_4$, ether, Δ; (ii) $(PhS)_2$, Bu_3P, THF; (iii) $KHSO_5$, MeOH, 0 °C; (iv) (a) LDA, THF, −78 °C, (b) methyl 5-bromovalerate, THF; (v) (a) Na(Hg), Na_2HPO_4, MeOH, −20 °C, (b) LiOH, H_2O, MeOH.



Scheme 2. Reagents and conditions: (i) $(COCl)_2$, CH_2Cl_2; (ii) **6**, $Pd(PPh_3)_4$ (10%), THF, Δ; (iii) $Zn(BH_4)_2$, THF, 0–25 °C; (iv) (a) NaCN, CH_2Cl_2, (b) MnO_2, MeOH; (v) **14**, $Pd(PPh_3)_4$ (10%), THF, Δ; (vi) $TsNHNH_2$, MeOH, (b) $NaB(CN)H_3$, MeOH; (vii) DIBAL-H, −78 °C, THF.

chemoselective reactions. However, some initial experiments were unsatisfactory, and we chose to prepare **4** by a similar route to that described above, viz. reaction of the stannylpyrrole **14** with the acid chloride **12** under Stille conditions, as outlined in Scheme 1. Transformation of the aldehyde function of **6** into a methyl carboxylate group using the one-pot cyanohydrin procedure reported by Corey et al.[15] provided the organotin derivative **14** in 86% yield.[14] It underwent Stille coupling with the acid chloride **12** to give the pyrrole **15**[14] (74% yield), the carbonyl function of which was transformed to a methylene group by reduction of the corresponding tosylhydrazone with $NaB(CN)H_3$. The ester thus obtained was finally reduced by DIBAL-H in THF to give **4** in 46% yield, which exhibited spectral data in agreement with those reported for mycalazal **2**.[3]

In conclusion, the syntheses of the naturally occurring pyrrole derivatives **3** and **4** confirmed the assigned structures and provided sufficient material for biological testing.

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14. Spectral data of selected compounds: (*all-Z*)-10,13,16,19,22-pentacosapentaenoic acid **5**: pale yellow oil; IR (film) 3300–3560, 1712 cm^{-1}; ^1H NMR (300 MHz): δ 0.94 (t, *J* 7.5 Hz, 3H), 1.20–1.90 (m, 10H), 2.00–2.06 (m, 4H), 2.26 (t, *J* 7 Hz, 2H), 2.65–2.85 (m, 10H), 5.24–5.40 (m, 10H), 11.72 (br s, 1H); ^{13}C NMR (75 MHz): δ 14.13 (CH_3), 22.74, 25.20, 25.44 (3×CH_2), 25.62 (3×CH_2), 26.15, 26.34, 26.42, 27.15, 28.52, 28.64, 32.43, (7×CH_2), 126.23, 128.41, 128.56, 128.61, 128.67, 128.73, 129.24, 129.31, 129.68, 129.79 (10×CH), 176.31 (C); HRMS calcd

for $C_{25}H_{40}O_2$ (M^+): 372.3028, found 372.3019; 5-((*all-Z*)-10,13,16,19,22-pentacosapentaenyl)pyrrole-2-carboxaldehyde **13**: colourless oil; IR (film) 1700, 1680 cm^{-1}; ^1H NMR (300 MHz): δ 0.97 (t, J 7.5 Hz, 3H), 1.22–1.70 (m, 12H), 2.00–2.14 (m, 4H), 2.48 (t, J 7.2 Hz, 2H), 2.84–2.95 (m, 8H), 5.29–5.41 (m, 10H), 6.86 (dd, J 2.5, 3.6 Hz, 1H), 6.92 (dd, J 2.5, 3.6 Hz, 1H), 9.68 (s, 1H), 9.91 (br s, 1H); ^{13}C NMR (75 MHz): δ 14.21 (CH_3), 20.64, 25.54, 27.39, 27.92, (4×CH_2), 29.31 (3×CH_2), 29.54 (3×CH_2), 29.66 (2×CH_2), 109.12 (CH), 122.28 (CH), 127.11, 127.51, 127.88, 128.12, 128.44, 128.78 (6×CH), 130.12, 132.13, 132.51 (6×CH), 135.24, 180.72, 191.20 (3×C); HRMS calcd for $C_{30}H_{45}NO_2$ (M^+): 449.3294, found 449.3270; Methyl 5-tributylstannylpyrrole-2-carboxylate **14**: pale yellow oil; IR (film) 3288, 1709 cm^{-1}; 0.88 (m, 9H), 1.18–1.70 (m, 18H), 3.82 (s, 3H), 6.33 (dd, J 2.5, 3.6 Hz, 1H), 6.96 (dd, J 2.5 Hz, 3.6 Hz, 1H) 9.88 (br s, 1H); ^{13}C NMR (75 MHz): δ 10.25 (3×CH_2), 13.58 (3×CH_3), 27.41 (3×CH_2), 29.09 (3×CH_2), 52.33 (CH_3), 120.91 (CH), 122.13 (CH), 136.41, 141.81, 177.81 (3×C); Methyl 5-((*all-Z*)-10,13, 16,19,22-pentacosapentaenoyl)pyrrole-2-carboxylate **15**: colourless oil, IR (film) 1690, 1722 cm^{-1}; ^1H NMR (300 MHz): δ 0.95 (t, J 7.5 Hz, 3H), 1.24–1.70 (m, 12H), 2.05–2.10 (m, 4H), 2.65 (t, J 7.2 Hz, 2H), 2.80–2.94 (m, 8H), 3.67 (s, 3H), 5.25–5.38 (m, 10H), 6.88 (dd, J 2.8, 3.8 Hz, 1H), 6.92 (dd, J 2.8, 3.8 Hz, 1H), 9.90 (br s, 1H); ^{13}C NMR (75 MHz): δ 14.26 (CH_3), 20.53, 22.06, 25.51, (3×CH_2), 25.58, (6×CH_2), 25.60, 25.62, 38.51 (4×CH_2), 52.08 (CH_3), 115.32, 119.56, 126.98, 127.84, 127.85, 127.97, 128.04, 128.05, 128.23, 128.26, 128.30, 132.02, (12×CH), 134.67, 135.24, 178.03, 180.74 (4×C); HRMS calcd for $C_{31}H_{45}NO_2$ (M^+): 479.3399, found 479.3381.

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