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# Synthetic Studies on Maduropeptin Chromophore 2. Synthesis of the Madurosamine Aryl Amide and the C1'-C9' Fragments

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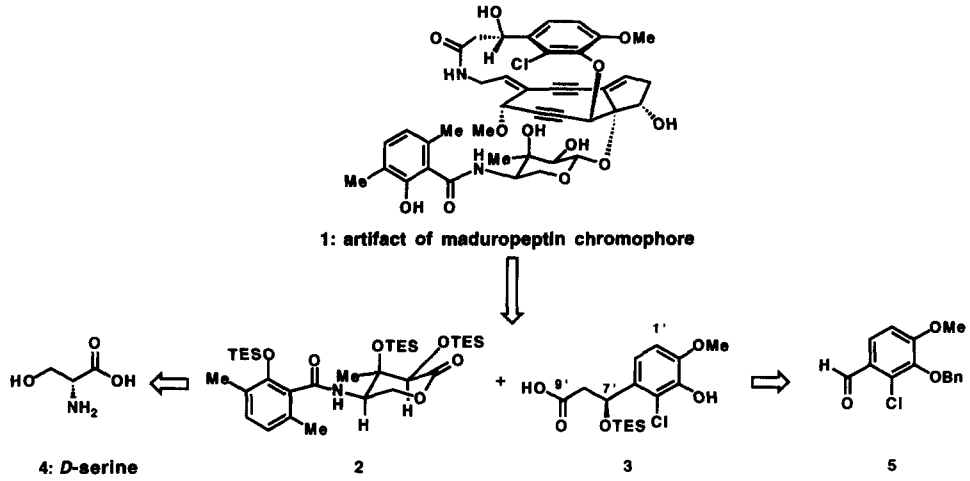
***Abstract***: *A retrosynthetic analysis (Scheme 1) of maduropeptin chromophore artifact 1 defined compounds 2 and 3 as required building blocks. The construction of 2 was achieved starting from the 2,5-dimethyl derived aromatic acid 8 and the D-serine derived δ-lactone 12 (Scheme 2), whereas the synthesis of 3 utilized an Evans's aldol condensation reaction between aldehyde 13 and chiral auxiliary 14 (Scheme 3).* © 1997 Elsevier Science Ltd.

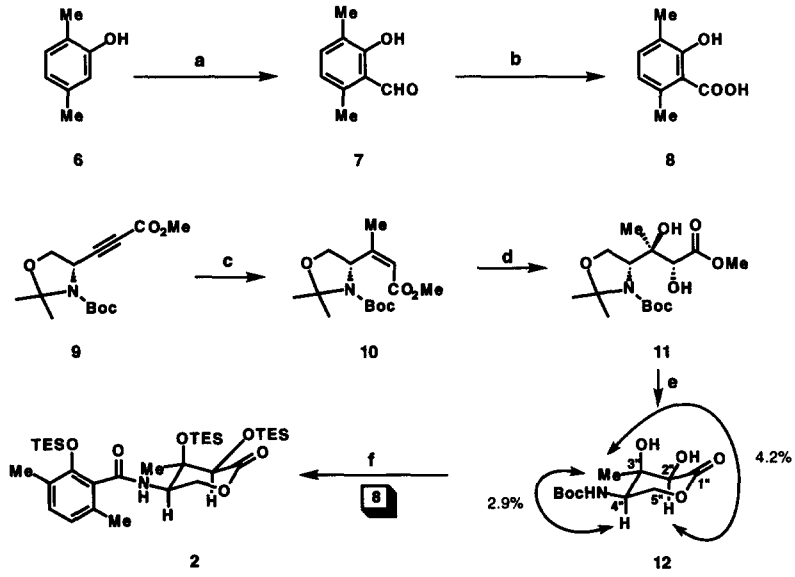
In the preceding paper[1], we described model studies directed towards the construction of the enediyne core of the maduropeptin artifact **1**. In this letter, we describe the synthesis of fragments **2** and **3**, required for the projected total synthesis of **1** (Scheme 1). As indicated in the Scheme 1, these building blocks (**2** and **3**) were traced, retrosynthetically, back to *D*-serine **4** and aryl aldehyde **5**, respectively.




**Scheme 1. Structures of maduropeptin chromophore artifact compound 1, madurosamine derivative 2, and C1'-C9' carboxylic acid fragment 3.**

The synthesis of the protected madurosamine aryl amide fragment **2** is shown in Scheme 2. Thus, treatment of commercially available 2,5-dimethyl phenol **6** with $TiCl_4$ and dichloromethyl methyl ether ($Cl_2CHOMe$) afforded aryl aldehyde **7** in 38% yield. Oxidation of **7** with $NaClO_2$-$NaH_2PO_4$ provided carboxylic acid **8** in 41% yield.

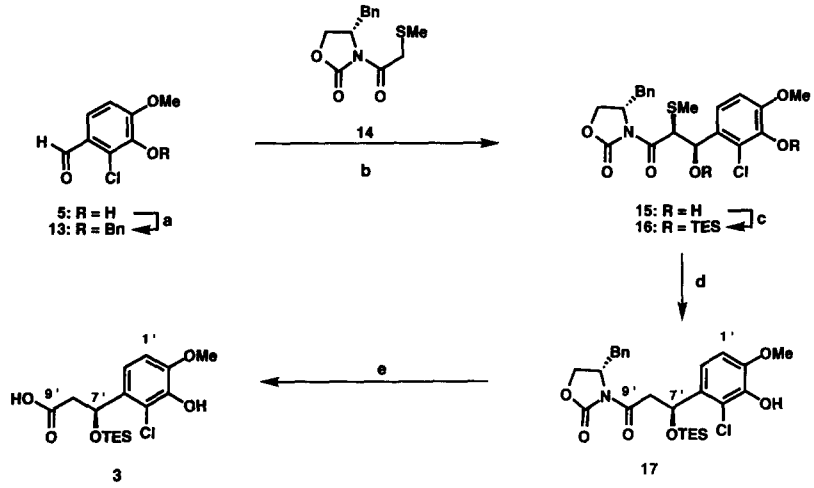
The second required fragment, madurosamine derivative **12**, was constructed as summarized in Scheme 2. Thus, the D-serine derived intermediate **9**[2,3] reacted smoothly with lithiumdimethyl cuprate to afford, stereoselectively, enoate **10** in 71% yield.[4] Dihydroxylation of **10** with catalytic $OsO_4$ and *N*-methylmorpholine *N*-oxide (NMO) in $Me_2CO$/ $^tBuOH/H_2O$ proceeded diastereoselectively to afford, in 71% yield, diol **11** as the major product (*ca* 12:1 ratio with its diastereoisomer). The observed stereoselectivity in this reaction is presumably a consequence of both steric and electronic effects and follows Kishi's pioneering work in this field.[5] Interestingly, switching to MeCN/ $^tBuOH/H_2O$ as the solvent for this dihydroxylation reaction led to reduced stereoselectivity (*ca* 3:1 in favor of **11**). The stereochemistry of compound **11** was confirmed by NOE experiments on lactone **12** (see Scheme 2) which was obtained from **11** on exposure to camphorsulfonic acid (CSA) in MeOH (84% yield). Removal of the Boc group from **12** (TFA, $CH_2Cl_2$), followed by coupling with carboxylic acid **8** in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole hydrate (HOBT) and *N*-methylmorpholine (NMM), and subsequent silylation (TESOTf, $Et_3N$), furnished the targeted intermediate **2** in 41% overall yield from **12**.




**Scheme 2. Synthesis of madurosamine lactone derivative 2. *Reagents and conditions*: (a) $Cl_2CHOMe$ (1.8 equiv), $TiCl_4$ (2.5 equiv), $CH_2Cl_2$, -50 → 0°C, 38%; (b) $NaClO_2$ (3 equiv), $NaH_2PO_4$ (3 equiv), $Me_2C$=CHMe, 25°C, 41%; (c) 1.2 equiv of $Me_2CuLi$, $Et_2O$, -78 °C, 1 h, 71%; (d) 0.1 equiv of $OsO_4$, 1.5 equiv of *N*-methylmorpholine *N*-oxide, acetone:$^tBuOH$:$H_2O$ (4:1:1), 25°C, 3 days, 67% (diastereoselectivity *ca* 12:1); (e) 3 mol% of camphorsulfonic acid (CSA), MeOH, 25 °C, 24 h, 84%; (f) (i) $CH_2Cl_2$:TFA (8:1), 0 °C , 10 h (ii) 8, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1-hydroxybenzotriazole hydrate (HOBT), *N*-methylmorphline (NMM) (iii) TESOTf, $Et_3N$, 41% (3 steps). Boc = $CO_2{}^tBu$; NOE values: C-3"-Me/C-4"-H (2.9%); C-3"-Me/C-5"-H (4.2%).**

The synthesis of the aryl fragment **3** is summarized in Scheme 3. Thus, aryl aldehyde **5**, prepared according to a literature procedure from 3-hydroxy-4-methoxybenzaldehyde,[6] was treated with benzyl bromide in the presence of $K_2CO_3$ to afford benzyl ether **13** in 93% yield. Reaction of **13** with the boron enolate derived from Evans's oxazolidinone **14**[7] and $^nBu_2BOTf$ afforded **15** diastereoselectively, and in 95% yield. Protection of the hydroxy group in **15** as a TES ether (TESCl, imidazole, 90% yield), followed by exposure to Raney Ni, resulted in desulfurization with concomitant debenzylation, furnishing compound **17** (78% yield). Hydrolysis of the amide group in **17** was accomplished by the action of LiOH in the presence of $H_2O_2$ in THF:MeOH:$H_2O$ at 0°C leading to the desired carboxylic acid **3** in 81% yield.

The described chemistry in this and the preceding paper[1] may facilitate the total synthesis of target **1** and related systems.[8]




**Scheme 3. Synthesis of C1'-C9' carboxylic acid fragment 3. *Reagents and conditions*: (a) 1.5 equiv of $K_2CO_3$, 1.1 equiv of $PhCH_2Br$, DMF, 25 °C, 2 h, 93%; (b) 14, 1.0 equiv of $^nBu_2BOTf$, 1.1 equiv of $Et_3N$, $CH_2Cl_2$, -78 → 0 °C, 40 min; then 1.0 equiv of 13, -78 °C, 45 min then 0 °C, 10 min, 95%; (c) 2.0 equiv of TESCl, 2.5 equiv of imidazole, THF, 0 → 25 °C, 1 h, 90%; (d) excess Raney Ni, acetone:EtOH (1:1.5), Δ, 5 h, 78%; (e) 4.0 equiv of LiOH, 6.0 equiv of $H_2O_2$, THF:MeOH:$H_2O$ (3:1:1), 0 °C, 3 h, 81%. Bn = $CH_2Ph$, TES = $SiEt_3$.**

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8. Selected physical data for compounds **3**, **12** and **2**. **3**: $R_f = 0.50$ (40% EtOAc in petroleum ether); $[\alpha]^{21}_D$ = -107.5° (*c* = 0.69, $CHCl_3$); IR (thin film): $\nu_{max}$ = 3500 (broad, O-H), 1712 (C=O), 1492, 1280, 1234, 1101, 1046, 739 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.12 (d, *J* = 8.6 Hz, 1 H, $C_5$-H), 6.82 (d, *J* = 8.6 Hz, 1 H, $C_{4'}$-H), 5.53 (dd, *J* = 9.0, 3.1 Hz, 1 H, $C_{7'}$-H), 3.92 (s, 3 H, $OCH_3$), 2.74 (dd, *J* = 15.1, 3.1 Hz, 1 H, $C_{8'}$-H), 2.59 (dd, *J* = 15.1, 9.0 Hz, 1 H, $C_{8'}$-H'), 0.88 (t, *J* = 8.0 Hz, 9 H, $Si(CH_2CH_3)_3$), 0.56 (q, *J* = 8.0 Hz, 6 H, $Si(CH_2CH_3)_3$); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 175.9, 146.4, 141.5, 134.0, 117.7, 116.7, 109.0, 67.9, 56.3, 44.0, 6.7, 4.7; FAB HRMS: calcd for $C_{16}H_{25}ClO_5SiNa$ ($M+Na^+$): 383.1058, found: 383.1069. **12**: $R_f$ = 0.25 (ether); $[\alpha]^{21}_D$ = +38.0° (*c* = 0.40, $CHCl_3$); IR (thin film): $\nu_{max}$ = 3377 (broad, O-H), 1747 (C=O), 1701 (C=O), 1523, 1370, 1162 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 5.05 (d, *J* = 8.9 Hz, 1 H, NH), 4.38 (dd, *J* = 10.8, 5.9 Hz, 1 H, $C_{5''}$-$H_{equatorial}$), 4.20 (dd, *J* = 10.8, 9.6 Hz, 1 H, $C_{5''}$-$H_{axial}$), 4.12 (ddd, *J* = 9.6, 8.9, 5.9 Hz, 1 H, $C_{4''}$-H), 4.04 (s, 1 H, $C_{2''}$-H), 3.53 (bs, 1 H, OH), 2.78 (bs, 1 H, OH), 1.46 (s, 9 H, $^t$Bu), 1.43 (s, 3 H, $C_{3''}$-$CH_3$); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 172.9, 155.5, 80.5, 72.8, 72.3, 68.3, 50.5, 28.2, 22.4; FAB HRMS: calcd for $C_{11}H_{19}NO_6Na$ ($M+Na^+$): 284.1110, found: 284.1114. **2**: $R_f$ = 0.30 (10% EtOAc in hexanes); IR (thin film): $\nu_{max}$ = 3429, 1766, 1669, 1577, 1495, 1413, 1275, 1229, 1153, 1132, 1038, 1007, 811 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 9.0 Hz, 1 H), 6.73 (d, *J* = 9.0 Hz, 1 H), 5.76 (d, *J* = 12.0 Hz, 1 H, NH), 4.44 (m, 2 H), 4.17 (m, 1 H), 4.12 (s, 3 H, $C_{2''}$-H), 2.27 (s, 3 H), 2.21 (s, 3 H), 1.43 (s, 3 H, $C_{3''}$-$CH_3$), 0.76 (m, 45 H); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 170.3, 168.8, 150.6, 133.2, 131.5, 129.5, 126.5, 123.4, 77.6, 76.5, 75.4, 67.4, 51.7, 22.9, 19.3, 17.2, 7.0, 6.9, 6.8, 6.3, 5.4, 4.8; FAB HRMS: calcd for $C_{33}H_{61}Si_3NO_6Cs^+$ ($M+Cs^+$): 784.2831, found: 784.2835.


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