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An expeditious convergent synthesis of a dibromotyrosine alkaloid inhibitor of mycothiol-*S*-conjugate amidase

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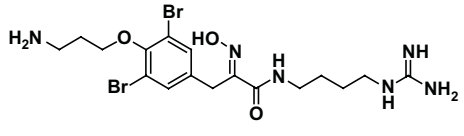
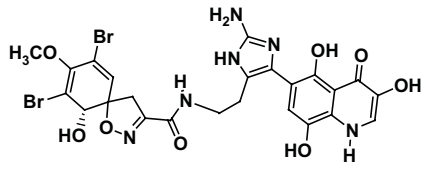
Abstract—A quick, economic synthesis of the alkaloid **1**, an inhibitor of mycothiol-*S*-conjugate amidase (MCA) is reported. Starting from low-cost, commercially available 4-hydroxybenzaldehyde, the nine-step synthesis involved dibromination and coupling with *N*-acetylglycine to give a stable methyloxazole intermediate **5** which was hydrolyzed, oximated and coupled to agmatine to yield the oxime in ~30% overall yield. It was not necessary to protect the oxime in the synthetic sequence thereby circumventing a deprotection step.

Two novel alkaloids **1** and **2** isolated[1] from an Australian non-verongid sponge of the *Oceanapia* species exhibit significant inhibitory activity against mycothiol-*S*-conjugated amidase (MCA). Due to the crucial role played by MCA, such alkaloids are marked as potentially useful therapeutic agents against *Mycobacterium tuberculosis* and related pathogens. As part of our ongoing programme on the total synthesis of biologically active natural products, we undertook the synthesis of **1** and the same is reported[2] in this letter.



1



2

Retrosynthetic analysis of **1** revealed that the synthesis of the alkaloid may be realized starting from inexpensive and commercially available 4-hydroxybenzaldehyde **3**. Thus dibromination of **3** with 2 equiv of NBS in DMF at room temperature gave the dibromo derivative in 93% yield. The latter was *O*-alkylated with 1,3-dibromopropane in K_2CO_3 and DMF at 80 °C for 4 h to furnish the tribromoaldehyde **4** in excellent yield. The stable, crystalline methyloxazolone intermediate[3] **5** was generated by condensation of **4** with *N*-acetylglycine in refluxing acetic anhydride and sodium acetate for 3 h in about 79% yield. Hydrolysis of the oxazole with 2 M HCl in THF at 70 °C for 12 h provided the pyruvic acid derivative **6** as a solid in 78% yield. Oximation of this tribromoketo acid with hydroxylamine in dioxane followed by conversion of the bromoether **7** to the azido ether[4] **8** proceeded smoothly in near quantitative yield. The crucial coupling reaction of **8** with *N*-Boc protected agmatine[5,6] **9** to give the intermediate **10** was effected with *N*-hydroxyphthalimide in DCC and dioxane at ambient temperature in 78% yield. Other reagents[7] were also tried for this coupling reaction but the yields obtained were not satisfactory and ranged between 50% and 55% (Scheme 1).

Further steps in the synthetic sequence involved reduction of the azidopropyl ether **10** to the corresponding aminopropyl ether **11**. This was achieved in 84% yield with Ph_3P in aqueous THF[8] and the oil obtained was fully characterized (see References and notes). Removal of the two Boc groups in **11** was achieved with 30%

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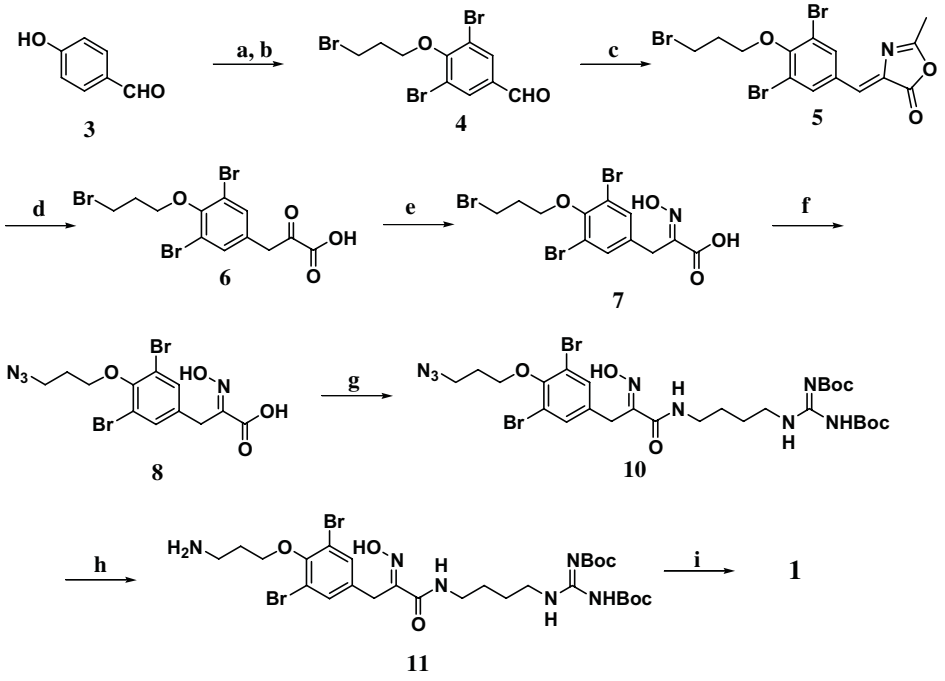

Scheme 1. Reagents and conditions: (a) NBS, DMF, 0–25 °C, 2 h, 93%; (b) K_2CO_3, DMF, $Br(CH_2)_3Br$, 70–80 °C, 4 h, 79%; (c) *N*-acetylglycine, Ac_2O, CH_3COONa, 150 °C, 3 h, 79%; (d) HCl–THF (1:3), 70 °C, 12 h, 78%; (e) $NH_2OH{\cdot}HCl$, $NaHCO_3$, dioxane, 25–30 °C, 4 h, 76%; (f) NaN_3, DMSO, 50 °C, 8 h, 89%; (g) *N*-hydroxyphthalimide, DCC, dioxane, *N*-Boc protected agmatine **9**, 25–30 °C, 6 h, 78%; (h) Ph_3P, THF–H_2O, 40 °C, 24 h, 84%, (i) 30% TFA–CH_2Cl_2, 25 °C, 1 h, quantitative.

CF_3COOH in dichloromethane to produce the target **1** as its bis-trifluoroacetate salt in quantitative yield (Scheme 1). The spectral data of synthetic **1** as the bis-trifluoroacetate salt was in full conformity with its structure (see References and notes).

While our synthesis was in progress, two reports appeared on the synthesis of **1**. The first total synthesis of **1** by Kende et al.[9] utilized 4-hydroxyphenylpyruvic acid as the starting material and involved *O*-benzylated hydroxylamine and *O*-THP protected hydroxylamine for oximation. In the former case, a careful chemoselective catalytic debenzylation was achieved in only 56% yield. In the second synthetic approach, Fetterolf and Bewley[10] utilized the expensive dibromotyrosine as the starting material and, via an unstable trifluoromethyl oxazolone intermediate, completed the synthesis. Debenzylation was not smooth and gave rise to the amine (instead of the oxime) as the major product. Finally, palladium black was used for this purpose, which also gave the amine as a minor product in addition to the required oxime as the major product.

In our approach to the synthesis of **1** we wished to retain the oxime **8** without protection and to realize this, we carried out the dibromination of 4-hydroxybenzaldehyde followed by *O*-alkylation with 1,3-dibromopropane as the first two steps of the synthetic scheme. Compared to 1-bromo-3-aminopropane, 1,3-dibromopropane is cheaper and hence, the latter was used. Also, by converting the bromoether **7** to the azido ether **8**, which was later reduced to the amino compound **11**, we avoided the protection and deprotection of the amino function with Boc functionality. Activation of the carboxylic group and coupling of **8** with *N*-Boc protected agmatine **9** could thus be achieved with the unprotected oxime. Our sequence thus avoided protection–deprotection of the hydroxyl group of the oxime as well as the amino group of the *O*-alkyl ether. All the intermediates in our synthetic sequence, except the azido **10** and the amino **11** compounds were stable crystalline solids with definite mps.[11–16]

Our ultimate goal in this project is to develop a solid phase combinatorial strategy so that a number of new entities can be synthesized. Therefore, all the reactions in our synthesis were carried out under homogenous and mild reaction conditions in high yields. We would like to use the hydroxyl group in the starting material for anchoring to a solid phase such as the bromo Wang polystyrene resin or the chlorosulfamyl resin by installing a suitable spacer.

In our opinion, the amidoxime and the guanidine moieties are the two prominent pharmacophores. It is therefore possible to synthesize new and small molecules analogous to **1** having only one of the two pharmacophores above so that the actual unit responsible for the anti-mycobacterial activity can be identified. Our results in this direction will be disclosed in due course.

In conclusion, our approach to the total synthesis of **1** gives a methodology amenable to scale up. The starting material is cheap and easily accessible; all the reactions lead to good to excellent yields of the products. This synthetic approach also offers methodology for the

synthesis of related analogues with equal/better activity as inhibitors of MCA.

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11. Spectroscopic data for compound **5**: white solid, mp 125–127 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.43 (m, 5H), 3.72 (t, $J = 6.4$ Hz, 2H), 4.18 (t, $J = 6.8$ Hz, 2H), 6.89 (s, 1H), 8.49 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.4, 29.4, 33.2, 80.0, 118.3, 126.6, 131.6, 133.6, 135.6, 154.4, 166.6, 167.2. FT IR (chloroform) ν_{max} 3019, 1808, 1660, 1216 cm^{-1}. FABMS (pos) 483.5 (M+H). Anal. Calcd for $C_{14}H_{12}Br_3NO_3$: C, 34.89; H, 2.51; N, 2.91. Found: C, 35.05; H, 2.62; N, 2.98.
12. Spectroscopic data for compound **6**: white solid, mp 147–149 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6, 200 MHz): δ 2.25 (m, 2H), 3.63–3.81 (m, 2H), 4.09 (m, 2H), 6.29 (s, 1H), 7.33 (br s, 1H), 7.85 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.7, 31.8, 68.6, 105.0, 116.3, 131.8, 133.0, 141.6, 149.8, 164.9. FT IR (Nujol) ν_{max} 3200, 2925, 1698, 1456, 1377 cm^{-1}. Anal. Calcd for $C_{12}H_{11}Br_3O_4$: C, 31.41; H, 2.42. Found: C, 31.59; H, 2.52.
13. Spectroscopic data for compound **7**: white solid, mp 170–172 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.23 (m, 2H), 3.70–3.83 (m, 4H), 4.04 (t, $J = 6$ Hz, 2H), 7.43 (s, 2H). ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz): δ 28.8, 29.5, 32.9, 69.4, 117.4, 133.1, 135.4, 150.9, 166.3. FT IR (chloroform) ν_{max} 3234, 3019, 1699, 1455 cm^{-1}. Anal. Calcd for $C_{12}H_{12}Br_3NO_4$: C, 30.41; H, 2.55; N, 2.96. Found: C, 30.54; H, 2.61; N, 3.14.
14. Spectroscopic data for compound **10**: colourless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.45 (s, 9H), 1.48 (s, 9H), 2.02 (t, $J = 6.7$ Hz, 2H), 3.40 (m, 4H), 3.79 (s, 2H), 4.00 (t, $J = 6.9$ Hz, 2H), 4.66 (s, 1H), 6.78 (t, $J = 4.3$ Hz, 1H), 7.40 (s, 2H), 8.29 (s, 1H), 11.5 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.5, 26.7, 28.0, 28.6, 29.5, 39.0, 40.4, 48.2, 69.7, 79.1, 83.0, 117.7, 133.5, 134.9, 151.4, 153.2, 156.0, 162.0. FT IR (chloroform) ν_{max} 3419, 3330, 3017, 2099, 1719, 1671, 1637 cm^{-1}. Anal. Calcd for $C_{27}H_{40}Br_2N_8O_7$: C, 43.33; H, 5.39; N, 14.97. Found: C, 43.55; H, 5.53; N, 15.08.
15. Spectroscopic data for compound **11**: colourless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.48 (s, 18H), 1.58 (m, 4H), 2.00 (br s, 2H), 2.18 (m, 2H), 3.00–3.42 (m, 6H), 3.80 (s, 2H), 4.02 (t, $J = 5.3$ Hz, 2H), 6.78 (t, $J = 3.9$ Hz, 1H), 7.41 (s, 2H), 8.31 (s, 1H), 11.47 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.1, 26.3, 27.5, 27.8, 28.2, 29.0, 29.1, 38.6, 39.9, 43.5, 69.3, 78.1, 82.6, 117.3, 133.0, 134.4, 150.8, 150.9, 152.8, 155.6, 161.6. FT IR (chloroform) ν_{max} 3673, 3419, 3330, 3018, 1720, 1672, 1633 cm^{-1}. Anal. Calcd for $C_{27}H_{42}Br_2N_6O_7$: C, 44.89; H, 5.86; N, 11.63. Found: C, 45.11; H, 5.69; N, 11.56.
16. Spectroscopic data for synthetic **1**: as the bis-trifluoroacetate salt (white foam). ^{1}H NMR (MeOH-d_4, 300 MHz): δ 1.59 (m, 4H), 2.17 (m, 2H), 3.20–3.33 (m, 6H), 3.84 (s, 2H), 4.1 (m, 2H), 7.46 (s, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 25.8, 25.9, 27.5, 28.3, 36.5, 39.7, 40.4, 69.9, 117, 132.9, 136.5, 149.8, 151.5, 156.7, 162.6. FT IR (Nujol) ν_{max} 3363, 2930, 1670, 1674, 1122 cm^{-1}. MS. 521.3 (M+H).