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Tetrahedron Letters 45 (2004) 133–135
Tetrahedron Letters

# Total synthesis of a dibromotyrosine alkaloid inhibitor of mycothiol S-conjugate amidase

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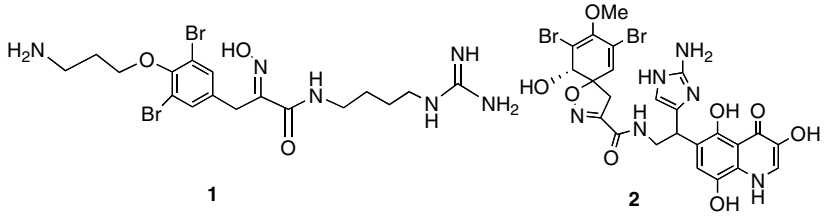
Received 5 September 2003; accepted 20 October 2003

**Abstract**—Two complementary synthetic sequences are described for the first total synthesis of a dibromotyrosine alkaloid (**1**) reported to inhibit a critical mycobacterial enzyme, mycothiol S-conjugate amidase. The *O*-benzyloxime of 4-hydroxyphenylpyruvic acid was dibrominated and successively linked to a 3-aminopropyl chain, then to a 4-aminobutylguanidine unit, followed by selective deprotections to yield alkaloid **1**. In an improved variant, the *O*-tetrahydropyranyloxime **12** was condensed with 4-aminobutylguanidine then dibrominated to phenol **14**, which upon Mitsunobu coupling to a 3-aminopropyl segment and deprotection produced the target **1**.


In 2001 Bewley et al. reported the isolation of two novel dibromotyrosine alkaloids from an Australian nonverongid sponge of the *Oceanapia* species.[1] These compounds, represented by structures **1** and **2**, showed significant inhibitory activity against the mycobacterial enzyme mycothiol S-conjugate amidase. Since this enzyme appears to play a critical role in protecting mycobacteria against alkylating agents and antibiotics,[2] alkaloids of this type are potentially useful therapeutic agents against *Mycobacterium tuberculosis* and related pathogens.

To confirm the NMR-based structure assignment for **1**, and to scale up the synthesis of **1** and its analogs, we have explored the total synthesis of this molecule using two complementary synthetic sequences. Retrosynthetic analysis reveals that the target **1** may be dissected into three units: the 'Western' propylamine tail (**3**), the central dibromo oxime acid unit (**4**), and the 'Eastern' 4-aminobutylguanidine chain (**5**).

Our first synthetic route (Scheme 1) proceeded from 4-hydroxyphenylpyruvic acid, which was converted to the *O*-benzyloxime, then methylated with diazomethane to give the oxime methyl ester **6**. Dibromination of **6** with 2.0 equiv of NBS in THF at room temperature gave the dibromo derivative **7**.[3] Careful hydrogenolysis of the *O*-benzyl group in 1:1 dioxane–acetic acid[4] produced the crystalline dibromoester oxime **8**, shown by X-ray crystallography to possess the *E*-configuration as shown.[5]




*Keywords*: mycothiol S-conjugate amidase; dibromotyrosine alkaloid; 4-hydroxyphenylpyruvamide oximes.

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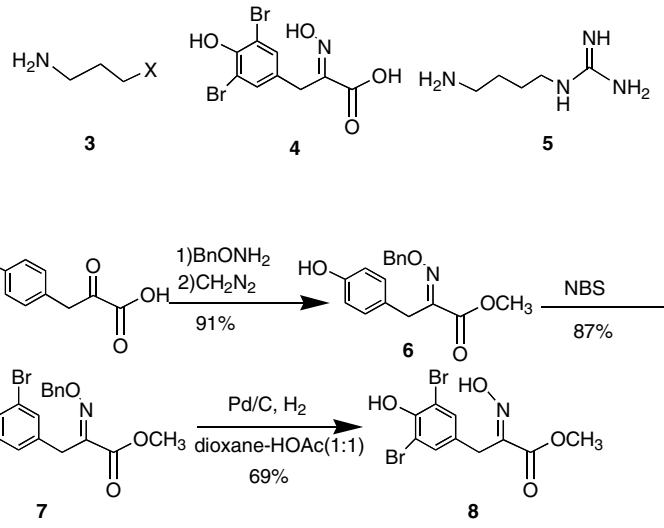
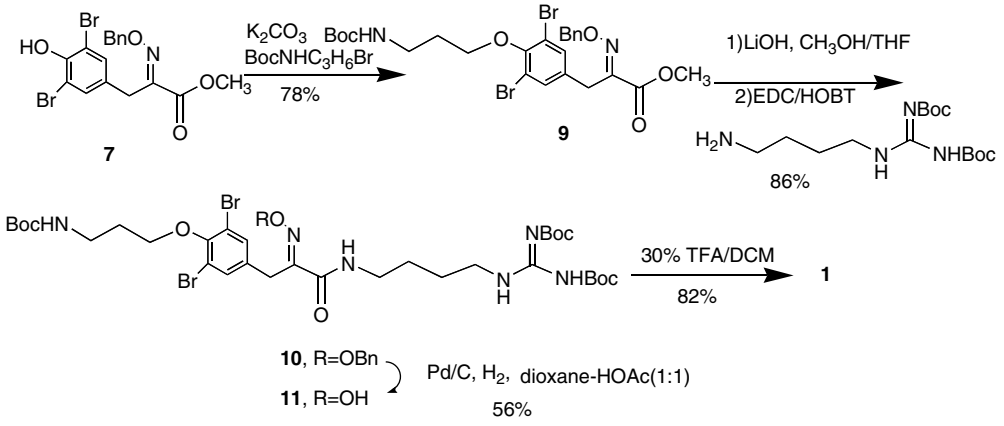
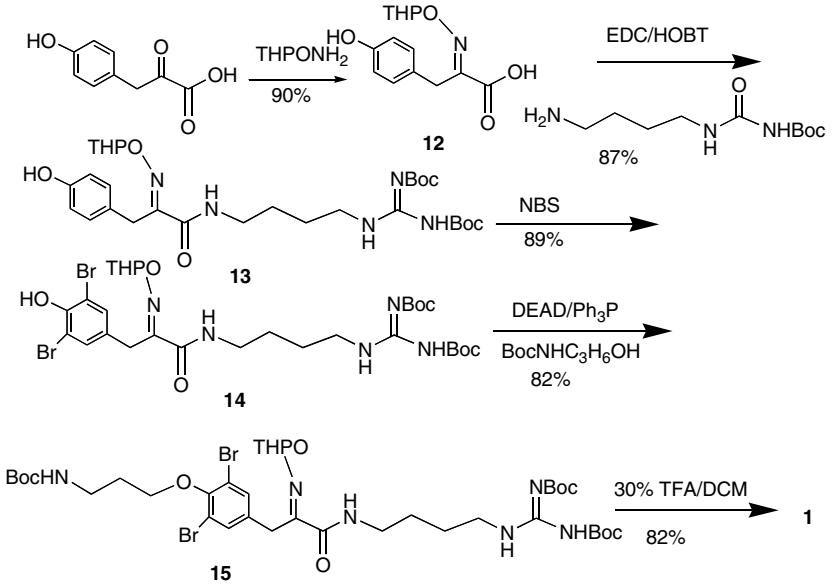
doi:10.1016/j.tetlet.2003.10.117




**Scheme 1.**




**Scheme 2.**




**Scheme 3.**

Direct *O*-alkylation[6] of the phenolic hydroxyl in **7** with $BocNH(CH_2)_3Br$ introduced the protected propylamine tail to give **9**.[7] Saponification of the ester followed by coupling of the resulting acid with a protected 4-aminobutylguanidine[8] established the Eastern chain to yield the amide **10**.[9] The delicate chemoselective catalytic debenzylation of **10** required use of the 1:1 dioxane–acetic acid solvent system described earlier, and led to the free oxime **11**[10] in only 56% yield. Removal of all Boc groups in **11** was achieved in 30% $CF_3CO_2H$ in dichloromethane to produce the target **1** as its bis trifluoroacetate salt in good yield (Scheme 2).

To enhance the chemoselectivity of the oxime deprotection step, the protecting group was switched from *O*-benzyl to *O*-tetrahydropyranyl.[11] In this second synthetic sequence, 4-hydroxyphenylpyruvic acid was converted to the THP-oxime acid **12**, which was coupled with the protected 4-aminobutylguanidine shown to install the Eastern chain as in **13**. Then **13** was dibrominated to the dibromophenol amide **14** (Scheme 3).[12] At this point, Mitsunobu coupling[13] of the phenolic hydroxyl with 3-(*t*-butoxycarbonylamino)propanol produced the fully elaborated system **15**. Removal of both the THP and all Boc groups by 30% $CF_3CO_2H$ in dichloromethane led smoothly to the target aminoguanidine **1** as its bis trifluoroacetate salt.

The proton and $^{13}C$ NMR of our synthetic alkaloid **1** as the bis trifluoroacetate salt and free base were in agreement with the corresponding spectra provided by Dr. Bewley.[14] This comprises the first total synthesis of the Bewley compound **1**, and provides reliable methodology for the synthesis of related structures which may act as inhibitors of mycothiol S-conjugate amidase.

## References and Notes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7. Spectroscopic data for compound **9**: mp 110–112 °C (hexane/dichloromethane). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.47 (s, 9H), 2.04 (m, 2H), 3.46 (m, 2H), 3.85 (s, 2H), 3.89 (s, 3H), 4.03 (t, $J = 5.8$ Hz, 2H), 4.98 (br s, 1H), 5.35 (s, 2H), 7.35–7.44 (m, 5H), 7.41 (s, 2H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 163.5, 156.0, 151.6, 149.4, 135.8, 134.4, 133.3, 128.7, 128.5 (2×C), 117.9, 79.0, 78.3, 71.2, 53.0, 38.0, 30.1, 30.0, 28.4 (3×C). MS (API-ES, pos.): 635(M+Na). Anal. Calcd for $C_{25}H_{30}Br_2N_2O_6$: C, 48.87; H, 4.92; N, 4.56. Found: C, 48.76; H, 4.89; N, 4.46%.
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9. Spectroscopic data for compound **10**: colorless oil. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.46 (s, 9H), 1.51 (s, 18H), 1.61 (m, 4H), 2.03 (m, 2H), 3.35 (m, 2H), 3.45 (m, 4H), 3.83 (s, 2H), 4.02 (t, $J = 5.8$ Hz, 2H), 5.01 (br s, 1H), 5.23 (s, 2H), 6.80 (t, $J = 6.0$ Hz, 1H), 7.31–7.45 (m, 5H), 7.44 (s, 2H), 8.35 (br s, 1H), 11.52 (s, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 163.4, 162.0, 156.1, 156.0, 153.3, 151.4, 151.2, 136.2, 134.8, 133.5, 128.6, 128.4, 128.2, 117.8, 83.1, 79.3, 79.0, 77.5, 71.2, 40.4, 39.1, 38.0, 29.9, 28.6, 28.4 (3×C), 28.2 (3×C), 28.0 (3×C), 26.8, 26.5. MS (API-ES, pos.): 911(M+H). HRMS calcd for $C_{39}H_{57}N_6O_9Br_2$: 911.2554; found: 911.2535.
10. Spectroscopic data for compound **11**: colorless oil. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.45 (s, 9H), 1.48 (s, 9H), 1.49 (s, 9H), 1.55 (m, 4H), 2.01 (m, 2H), 3.30 (m, 2H), 3.42 (m, 4H), 3.86 (s, 2H), 3.99 (t, $J = 5.6$ Hz, 2H), 4.93 (br s, 1H), 6.83 (t, $J = 6.0$ Hz, 1H), 7.49 (s, 2H), 8.42 (br s, 1H), 10.42 (br s, 1H), 11.49 (br s, 1H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 163.1, 162.9, 156.2, 156.1, 153.2, 151.20, 151.17, 135.4, 133.4, 117.7, 83.3, 79.6, 79.2, 71.1, 40.5, 38.9, 38.1, 31.5, 29.9, 28.4 (3×C), 28.2 (3×C), 28.0 (3×C), 26.7, 26.4. MS (API-ES, pos.): 821(M+H).
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12. Spectroscopic data for compound **14**: white foam. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.50 (s, 9H), 1.51 (s, 9H), 1.61 (m, 5H), 1.71–1.73 (m, 2H), 1.86 (m, 3H), 3.25–3.45 (m, 4H), 3.61–3.63 (m, 2H), 3.86 (AB, $J = 9.7$ Hz, 2H), 5.41 (s, 1H), 5.80 (br, 1H), 6.93 (br, 1H), 7.48 (s, 2H), 8.35 (br, 1H), 11.50 (br, 1H). MS (API-ES, pos.): 750(M+H).
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14. Spectroscopic data for synthetic **1** as the bis trifluoroacetate salt (white foam): $^1H$ NMR ($d_4$-MeOH, 400 MHz): $\delta$ 7.50 (s, 2H), 4.08 (t, $J = 5.6$ Hz, 1H), 3.84 (s, 2H), 3.27 (m, 2H), 3.25 (m, 2H), 3.17 (m, 2H), 2.18 (m, 2H), 1.57 (m, 4H). $^{13}C$ NMR (100 MHz): $\delta$ (in $d_6$-DMSO): 163.1, 156.7, 151.1, 150.5, 136.5, 132.9, 117.2, 70.4, 40.4, 38.3, 36.5, 28.0, 27.7, 26.3, 26.0. MS (API-ES, pos.): 521(M+H). We thank Dr. Bewley for providing original spectra of the natural alkaloid.