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Synthesis of the 4-methyl-1,2-oxazetidine-4-carboxylic acid moiety of the originally proposed halipeptin A and B structures

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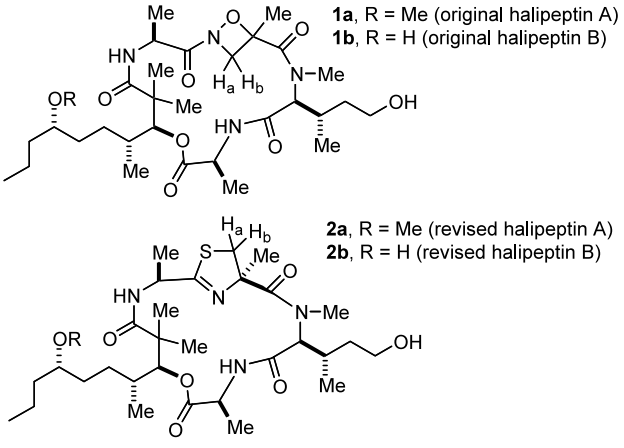
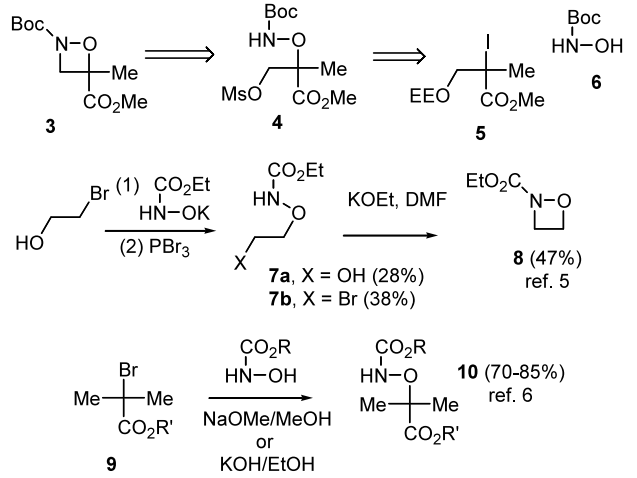
Abstract—*O*-Alkylation of *N*-hydroxycarbamate **6** with iodo ester **5** affords **15**, which was elaborated to mesylate **4**. Intramolecular *N*-alkylation affords methyl *N*-Boc-4-methyl-1,2-oxazetidine-4-carboxylate (**3**). The geminal coupling constant of the methylene protons is 8.5 Hz, which is much smaller than the 12.0 Hz reported for halipeptins A and B. This confirms that the halipeptins do not contain an oxazetidinecarboxylic acid as originally proposed in structure **1**, but a thiazoline as in the revised structure **2**. The unusual *O*-alkylation of **5** probably proceeds by an electron transfer mechanism.

Gomez-Paloma and co-workers recently reported the isolation of the novel depsipeptide halipeptins A and B (**1a** and **1b**) with potent anti-inflammatory activity from the sponge *Haliclona* species.[1] The most unusual feature of these molecules is the 4-methyl-1,2-oxazetidine-4-carboxylic acid. We were immediately suspicious of this structural assignment because of the geminal coupling constant between H_a and H_b of 12.0 Hz, while geminal coupling constants in azetidines are typically 5.5–7.0 Hz.[2]



We report here the synthesis of methyl *N*-Boc-4-methyl-1,2-oxazetidine-4-carboxylate (**3**) with a geminal coupling constant of 8.5 Hz providing evidence that the structure of the halipeptins was misassigned. After our work was completed, Gomez-Paloma, De Riccardis and co-workers published revised structures **2a** and **2b**, without the oxazetidine, based on their reinterpretation of the mass spectral data to indicate the presence of a sulfur and two fewer oxygens.[3]

The chemistry of 1,2-oxazetidines is not well-developed and there are no general methods for their preparation.[4] We envisioned that **3** could be prepared by intramolecular *N*-alkylation of mesylate **4**, which could be prepared by *O*-alkylation of iodo ester **5** with *tert*-butyl *N*-hydroxycarbamate (**6**) followed by functional group interchange as shown in Scheme 1.



Scheme 1. Retrosynthesis of **3** and literature precedents.

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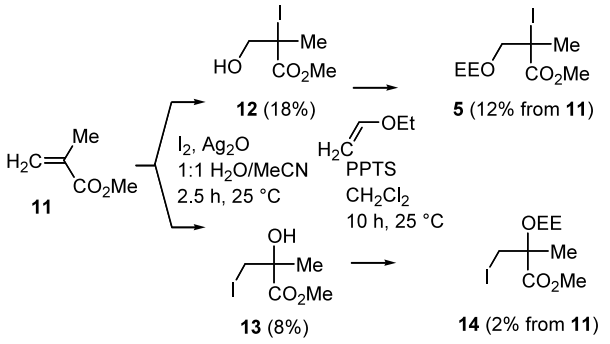
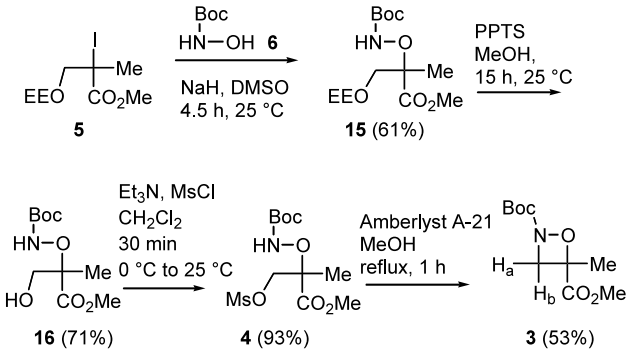


Scheme 2. Preparation of iodo ester **5**.



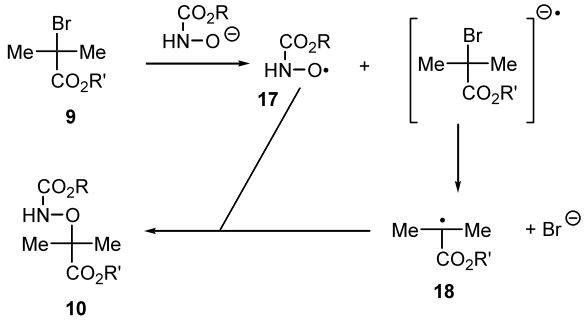
Scheme 3. Preparation of oxazetidinecarboxylate **3**.

Oxazetidine **8** has been prepared by intramolecular *N*-alkylation of bromide **7b**, which was prepared by *O*-alkylation of 2-bromoethanol with the potassium salt of ethyl *N*-hydroxycarbamate to give **7a**, followed by reaction with PBr_3 to introduce the bromide.[5] Alkylation of **6** with **5** should proceed readily even though the halide is tertiary since the analogous reaction of bromo ester **9** gives **10** cleanly.[6] We therefore turned our attention to the preparation of protected tertiary iodo ester **5**.

Reaction of methyl methacrylate (**11**) with 1 equiv. of I_2 and 1 equiv. of Ag_2O in 1:1 H_2O/MeCN afforded a difficultly separable 2:1 mixture of the desired iodo alcohol **12** and the regioisomer **13** in 26% yield as shown in Scheme 2.[7] This mixture was easily separated from the volatile starting material **11** and the volatile epoxide derived from cyclization of either **12** or **13**. Treatment of this mixture with 1 equiv. of ethyl vinyl ether and pyridinium tosylate (PPTS) in CH_2Cl_2 for 10 h protected the primary alcohol giving ethoxyethyl ether **5**, while leaving the more hindered tertiary alcohol of **13** largely unprotected, thus facilitating purification. Flash chromatography gave **5** in 12% overall yield from **11**. While the yield is modest, the starting materials and reagents are inexpensive and the byproducts are either volatile or much more polar so this procedure is suitable for preparation of multi-gram quantities of **5**.

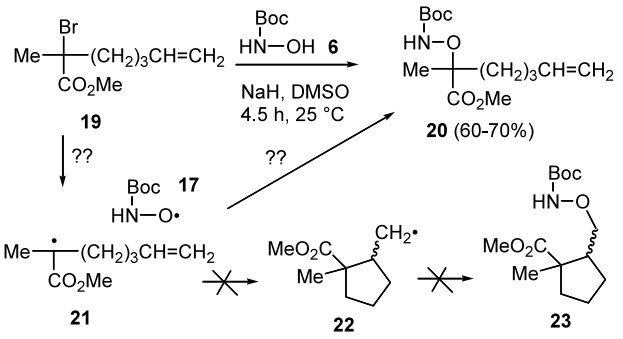
O-Alkylation of *tert*-butyl *N*-hydroxycarbamate (**6**) with iodo ester **5** using NaH in DMSO afforded 61% of **15** as shown in Scheme 3.[8] Less than 10% of **15** was formed using conditions reported for the preparation of **10** with alkoxide bases in alcohol.[6] Hydrolysis of the ethoxyethyl group of **15** with PPTS in MeOH for 15 h afforded 71% of alcohol **16**,[9] which was converted to 93% of mesylate **4**[10] with Et_3N and MsCl in CH_2Cl_2. Treatment of **4** with a variety of bases gave the desired oxazetidine **3**, which was hard to isolate from an aqueous workup. Fortunately, treatment of **4** with a weakly basic ion-exchange resin (Amberlyst A-21) in MeOH at reflux for 1 h, filtration through Celite, concentration and flash chromatography afforded 53% of pure **3**.[11] As expected, the geminal coupling constant decreased from 12.9 Hz in alcohol **16** and 11.0 Hz in mesylate **4** to 8.5 Hz in oxazetidine **3**. The formation of the four-membered ring was confirmed by the HMBC spectrum, which showed a cross peak between the methylene hydrogens and the Boc carbonyl carbon, as well as carbon-4, and the ester carbonyl and methyl carbons. These data confirm that halipeptins A and B do not contain a 1,2-oxazetidine-4-carboxylic acid.

The *O*-alkylation of tertiary halides **5** and **9** with *N*-hydroxycarbamate esters is unlikely to proceed through an S_N2 reaction. An electron transfer mechanism is more likely.[12] Transfer of an electron should give oxygen-centered radical **17**, which is stabilized by the adjacent nitrogen,[13] and tertiary radical **18**, which will combine to give **10** as shown in Scheme 4. Numerous examples of nucleophilic displacements on tertiary bromide **9** are known and they generally involve nucleophiles such as phenols, hydrazines and *N*-hydroxycarbamates that can form a stable radical by electron transfer.



Scheme 4. Electron transfer mechanism for *O*-alkylation of **9**.

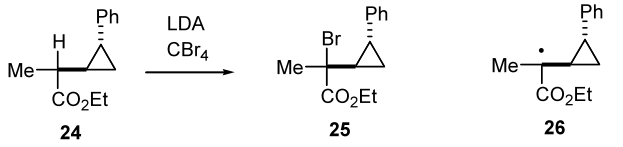
We briefly attempted to confirm the electron transfer mechanism for the substitution by preparing tertiary bromo esters that would lead to a rearrangement product if the alkylation proceeded through a radical. Bromination[14] of the enolate of methyl 2-methyl-6-heptenoate[15] with CBr_4 afforded 35% of **19**.[16] Alkylation of **6** with **19** afforded only unrearranged alkylation product **20** in 60–70% yield and none of cyclopentane **23** that would be formed by rearrangement of radical **21** to cyclopentanemethyl radical **22** and trapping with oxygen-centered radical **17** as shown in Scheme 5. However, radical **21** is known to rearrange more slowly



Scheme 5. Alkylation of **19** without rearrangement.

than most 5-hexenyl radicals with a rate constant of only 10^4 s^{-1}.[17] Therefore the absence of **23** does not preclude the intermediacy of radical **21** in the alkylation, since trapping with **17** could well be faster than rearrangement.

We then prepared bromide **25** by bromination[14] of the known ester **24**[18] since radical **26** is known to undergo ring opening very rapidly (see Scheme 6).[19] Unfortunately, bromide **25** was unstable and underwent ring opening on standing or silica gel chromatography.



Scheme 6.

In conclusion, we have prepared oxazetidinecarboxylate **3** using the *O*-alkylation of **6** with **5** to give **15** and the *N*-alkylative cyclization of **4** as the key steps. The geminal coupling constant of 8.5 Hz confirms that halipeptins A and B, with a 12.0 Hz coupling constant, do not contain an oxazetidinecarboxylate. The *O*-alkylation of tertiary halo esters **5** and **9** with *N*-hydroxycarbamates appears to proceed through an electron transfer mechanism, although the involvement of radical intermediates could not be established with substrates that give radicals prone to rearrangement.

Acknowledgements

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7. Reaction of methyl methacrylate with iodine and silver nitrate in MeOH gives a mixture of regioisomeric iodo methyl ethers. See: Kihara, N.; Ollivier, C.; Renaud, P. *Org. Lett.* **1999**, *1*, 1419–1422. Reaction of methyl methacrylate with iodine and silver nitrate in H_2O/MeCN afforded **12**, **13**, and the nitrate esters.
8. Methyl 2-[[[(1,1-dimethylethoxy)carbonyl]amino]oxy]-3-(1-ethoxyethoxy)-2-methylpropionate (**15**). *t*-Butyl *N*-hydroxycarbamate (**6**) (313 mg, 2.35 mmol) in dry DMSO (2 mL) was added to NaH (60% by weight in mineral oil, 96 mg, 2.4 mmol) in dry DMSO (2 mL) and the mixture was stirred for 5 min. Iodide **5** as a 1:1 mixture of diastereomers (742 mg, 2.35 mmol) in dry DMSO (2 mL) was added and the mixture was stirred for 4.5 h. The mixture was diluted with diethyl ether, washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and concentrated to give 700 mg of crude **15**. Flash chromatography (85:15 hexanes/EtOAc) gave 460 mg (61%) of pure **15** as a 1:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) 7.50 (s, 1×0.5, NH), 7.46 (s, 1×0.5, NH), 4.75 (q, 1×0.5, J=5.5 Hz), 4.74 (q, 1×0.5, J=5.5 Hz), 3.84 (d, 1×0.5, J=10.4 Hz), 3.79 (d, 1×0.5, J=10.4 Hz), 3.77 (s, 3), 3.73 (d, 1×0.5, J=10.4 Hz), 3.69 (d, 1×0.5, J=10.4 Hz), 3.67–3.57 (m, 1), 3.48–3.39 (m, 1), 1.50 (s, 3×0.5), 1.49 (s, 3×0.5), 1.46 (s, 9), 1.30 (d, 3×0.5, J=5.5 Hz), 1.28 (d, 3×0.5, J=5.5 Hz), 1.19 (t, 3×0.5, J=7.4 Hz), 1.18 (t, 3×0.5, J=7.4 Hz); ^{13}C NMR (172.3, 172.2), (156.62, 156.58), (99.8, 99.6), (86.2, 86.1), (81.6, 81.5), (68.1, 67.2), (61.2, 60.9), 52.3, 28.1 (3 C), (19.4, 19.3), 18.1, (15.14, 15.09); IR (neat) 3300, 1747; HRMS (FAB/DCM/NBA/NaCl) calcd for $C_{14}H_{27}NO_7Na$ (MNa^+) 344.1685, found 344.1681.
9. Data for **16**: mp 103–104°C; ^{1}H NMR ($CDCl_3$) 7.70 (s, 1, NH), 4.31 (br s, 1, OH), 3.88 (dd, 1, J=12.9, 3.7 Hz), 3.72 (s, 3), 3.61 (dd, 1, J=11.0, 12.9 Hz), 1.43 (s, 3), 1.42 (s, 9); ^{13}C NMR 172.2, 158.5, 86.7, 82.9, 61.8, 52.2, 28.0 (3 C), 18.7; IR (KBr) 3370, 3211, 1748, 1707.
10. Data for **4**: ^{1}H NMR ($CDCl_3$) 7.57 (s, 1, NH), 4.52 (d, 1, J=11.0 Hz), 4.45 (d, 1, J=11.0 Hz), 3.81 (s, 3), 3.10 (s, 3), 1.55 (s, 3), 1.47 (s, 9); ^{13}C NMR 170.4, 156.4, 84.5, 82.2, 69.9, 52.9, 37.8, 28.1 (3 C), 18.1; IR (neat) 3315, 1747.
11. Methyl 2-(1,1-dimethylethoxy)carbonyl-4-methyl-1,2-oxazetidine-4-carboxylate (**3**). Amberlyst A-21 was stirred in methanol for 0.5 h, filtered, and washed with MeOH to

remove soluble impurities. A mixture of washed Amberlyst A-21 (0.5 g) and **4** (70 mg) were refluxed in MeOH (4 mL) for 1 h. The mixture was cooled, filtered through Celite, and concentrated to give 46 mg of crude **3**. Flash chromatography (9:1 hexanes/EtOAc) gave 26 mg (53%) of pure **3**: ^{1}H NMR ($CDCl_3$) 4.68 (d, 1, $J=8.5$ Hz), 4.36 (d, 1, $J=8.5$ Hz), 3.85 (s, 3), 1.76 (s, 3), 1.52 (s, 9); ^{13}C NMR 171.5, 161.0, 83.3, 81.5, 61.5, 52.9, 28.0 (3 C), 23.0; IR (neat) 1744, 1714; HRMS (DCI/NH_3) calcd for $C_{10}H_{21}N_2O_5$ (MNH_4^+) 249.1450, found 249.1461.

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