Natural Products Synthesis

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Total Synthesis of Halipeptins A and D and Analogues**

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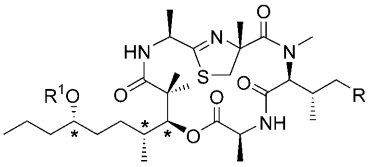
The halipeptins are a group of natural products whose structural identity and biological properties are still shrouded in mystery. In 2001 Gomez-Paloma et al. reported the isolation of halipeptins A and B from the marine sponge *Haliclona* sp. and showed that halipeptin A exhibits impressive antiinflammatory properties that exceed those of well-established drugs.[1] Their later isolation of halipeptin C prompted them to revise their structural assignment to that of thiazoline containing macrocycles as shown for halipeptins A–C (**1a–c**) in Scheme 1 leaving open the absolute configuration at the marked positions.[2] The isolation of a fourth member of this family of marine natural products, halipeptin D (**1d**, Scheme 1), by the group of Faulkner soon after,[3] did not reveal further stereochemical details but raised our interest in this class of natural products once halipeptin D (**1d**) was reported to exhibit strong inhibitory activity in vitro against different human cancer-cell lines.[4]



1a: R^1 = Me, R^2 = CH_2OH: halipeptin A
1b: R^1 = H, R^2 = CH_2OH: halipeptin B
1c: R^1 = H, R^2 = H : halipeptin C
1d: R^1 = Me, R^2 = Me : halipeptin D

Scheme 1. Structures of halipeptins A–D (**1a–d**). Positions of uncertain stereochemical assignment are marked *.

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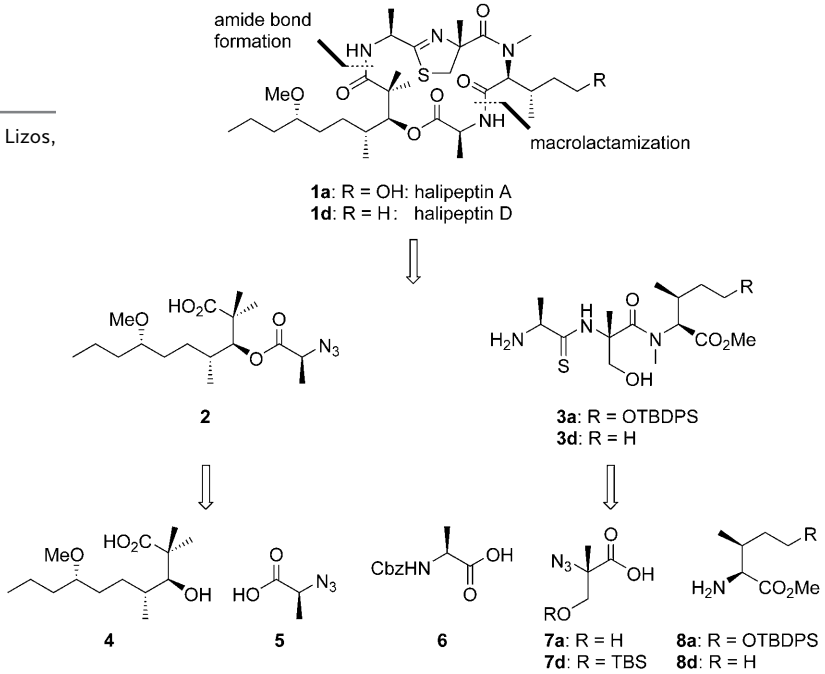
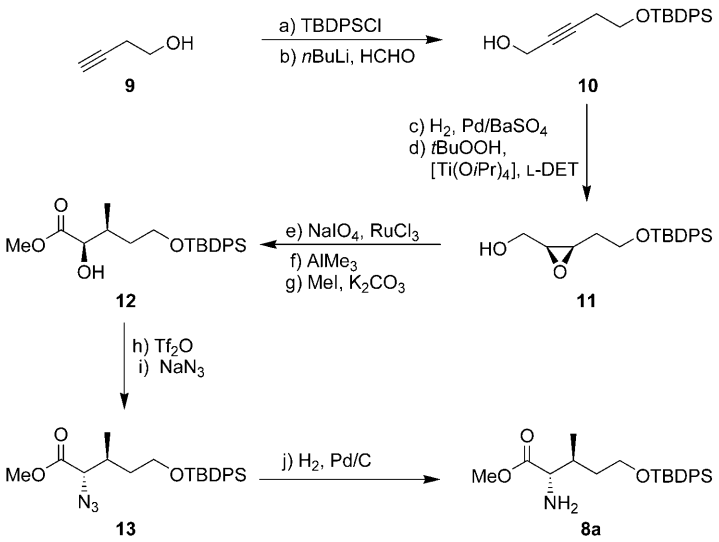
Determining their structural identity beyond any doubt[5] and rendering them available for further biological investigations were two reasons we undertook their total synthesis. There was a third motivation: their intriguing molecular architectures and the (subtle) challenge they posed for chemical synthesis. Indeed, these depsipeptides include in their molecular frameworks a novel, highly substituted peptide backbone connected to a hydroxylated carbon chain wrapped into a 16-membered macrolide ring. The entire C_{31} structure contains eight stereocenters (three of which are, in principle, epimerizable) and 11 methyl groups. The highly congested and conformationally rigid macrocyclic ring contains within its thread a Me-substituted thiazoline ring adjacent to an *N*-methyl-substituted amide, an arrangement that forces this linkage into a cisoid geometry, unlike the other two amide bonds that reside in their usual transoid forms. This highly substituted cisoid bond, postulated to persist even in open chain intermediates, is rare and was expected to present an unprecedented and adventurous challenge in the total synthesis of these molecules.

Our retrosynthetic analysis of halipeptins A (**1a**) and D (**1d**) (Scheme 2) relied on a retrolactamization to open the macrocycle and a subsequent retro amide-bond formation to dissect the generated chain into two key fragments, thioamides **3a** and **3d** as direct precursors for thiazoline formation, and alanine ester **2** within which are embedded both a 3-hydroxydecanoic acid domain and a masked L-alanine residue. This approach allows a late-stage construction of the thiazoline moiety, thus avoiding likely epimerization at its α position.[6] Further disconnection of these frag-



Scheme 2. Retrosynthetic analysis of halipeptins A (**1a**) and D (**1d**).

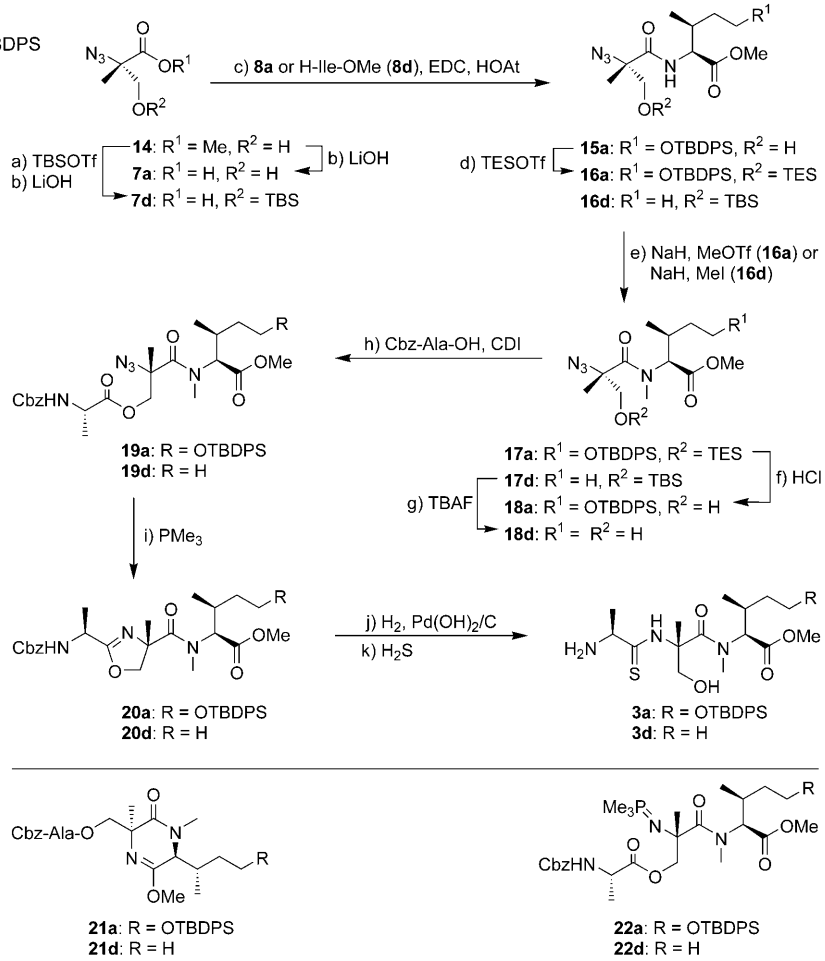


Scheme 3. Construction of TBDPS-protected δ-hydroxy-L-isoleucine methyl ester (**8a**). a) TBDPSCl (1.1 equiv), imidazole (2.2 equiv), CH_2Cl_2, 25 °C, 16 h, 99%; b) *n*BuLi (2.5 M in hexanes, 1.05 equiv), *p*-formaldehyde (1.1 equiv), Et_2O, −78→25 °C, 14 h, 72%; c) H_2 (1 atm), 5% Pd/$BaSO_4$ (7% by weight), quinoline (5% by weight), MeOH, 25 °C, 20 min, 98%; d) [Ti(O*i*Pr)$_4$] (0.3 equiv), L-DET (0.35 equiv), *t*BuOOH (2.0 equiv), M.S. (4 Å), CH_2Cl_2, −20 °C, 17 h, 99%; e) $NaIO_4$ (4.1 equiv), $RuCl_3 \cdot H_2O$ (2.2 mol%), $CCl_4/CH_3CN/H_2O$ (1:1:1.5), 25 °C, 2 h, 80%; f) $AlMe_3$ (3.0 equiv), hexanes, 25 °C, 30 h, 80%; g) MeI (1.3 equiv), K_2CO_3 (1.1 equiv), acetone, 25 °C, 18 h, 90%; h) Tf_2O (1.5 equiv), pyridine (10.0 equiv), CH_2Cl_2, 0 °C, 20 min; i) NaN_3 (1.5 equiv), DMF, 25 °C, 40 min, 75% (two steps); j) H_2 (1 atm), 10% Pd/C (30% by weight), EtOH, 25 °C, 2.5 h, 99%. DET = diethyl tartrate; DMF = *N*,*N*-dimethylformamide; M.S. = molecular sieves; TBDPS = *tert*-butyldiphenylsilyl; Tf = trifluoromethanesulfonyl.

ments led to the identification of building blocks **4**–**7** and **8a** for halipeptin A (**1a**), and **4**–**7** and **8d** for halipeptin D (**1d**), as shown in Scheme 2.

After having established[3] a stereochemically flexible route to hydroxydecanoic acid **4**,[5,7] our first objective towards the synthesis of halipeptin A (**1a**) was the construction of suitably protected δ-hydroxyisoleucine derivative[8] **8a** (Scheme 3). Silylation of homopropargylic alcohol **9** and trapping of the corresponding acetylide with formaldehyde gave propargylic alcohol **10** in 71% overall yield. Partial hydrogenation[9] of **10** with Lindlar catalyst gave the corresponding *Z* allylic alcohol (98% yield), which was subjected to Sharpless asymmetric epoxidation conditions to yield epoxy alcohol **11** in almost quantitative yield (99%). Compound **11** was then oxidized to the corresponding epoxy acid (80% yield), which was subsequently treated with $AlMe_3$[9] at ambient temperature to afford, upon methylation with MeI, hydroxyester **12** as a single isomer in 72% overall yield for the two steps. Treatment of **12** with triflic anhydride, followed by exposure of the resulting triflate to sodium azide furnished, with inversion of configuration, the orthogonally protected isoleucine derivative **13** in 75% overall yield. δ-Hydroxyisoleucine methyl ester **8a** was then obtained from **13** in quantitative yield by reduction of the azide group.

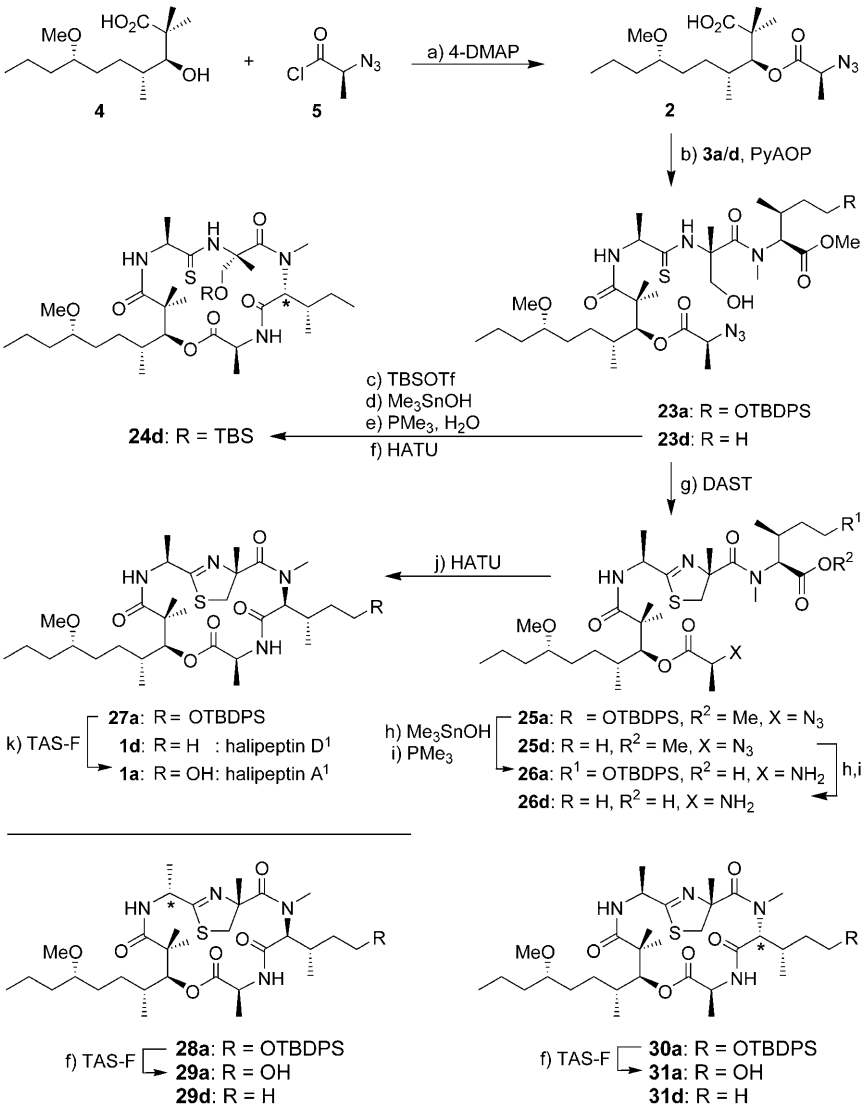
Initial attempts to obtain alanine–α-methylserine–*N*-methylisoleucine tripeptides as **3** (Scheme 2) by sequential peptide coupling failed as a result of cyclization of the dipeptide precursors upon activation (e.g. diketopiperazine formation upon reduction of azide **17d**). Instead, we devised a strategy to attach the N-terminal alanine unit that did not involve a free amino group as shown in Scheme 4. The *O*-silylated dipeptides **16a** and **16d** were obtained from α-methyl serine derivative **14**,[10] after suitable protection/deprotection steps and coupling to isoleucines **8a** and **8d**,



Scheme 4. Synthesis of thioamides **3a** and **3d**. a) TBSOTf (2.0 equiv), 2,6-lutidine (4.0 equiv), CH_2Cl_2, 0 °C, 1.5 h, 98%; b) LiOH·H_2O (3.0 equiv), MeOH/H_2O (4:1), 0→25 °C, 2 h, 100%; c) **8a** (1.0 equiv), EDC (1.2 equiv), HOAt (1.2 equiv), *i*Pr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 17 h, 55% (**15a**); **8d** (2.0 equiv), EDC (2.0 equiv), HOAt (2.0 equiv), *i*Pr_2NEt (3.0 equiv), CH_2Cl_2, 25 °C, 17 h, 91% (**16d**); d) TESOTf (1.3 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, 0 °C, 20 min, 85%; e) NaH (4.0 equiv), MeOTf (2.5 equiv), THF, 0 °C, 1 h, 83% (**17a**); NaH (3.0 equiv), MeI (4.0 equiv), DMF, 0 °C, 1 h, 96% (**17d**); f) aqueous HCl (1 N; 20 equiv), THF, 25 °C, 1 h, 100%; g) TBAF (3.0 equiv), THF, 25 °C, 2 h, 98%; h) CDI (4.0 equiv), Cbz-Ala-OH (4.0 equiv), CH_2Cl_2, 25 °C, 0.5 h; then **18a** or **18d**, 18 h, **19a**: 88%, **19d**: 96%; i) PMe_3 (1.0 M in THF; 1.8 equiv), toluene, 25 °C, 2 h, **20a**: 79%, **20d**: 83%; j) H_2 (1 atm), 20% Pd(OH)$_2$/C (30% by weight), EtOH, 25 °C, 1 h, 100%; k) H_2S (excess), MeOH/Et_3N (2:1), 25 °C, 48–72 h, complete conversion, product not isolated. Cbz = benzyloxycarbonyl; CDI = carbonyldiimidazole; EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HOAt = 1-hydroxy-7-azabenzotriazole; TBAF = tetra-*n*-butylammonium fluoride; TBS = *tert*-butyldimethylsilyl; TES = triethylsilyl.

respectively. Deprotonation of the amide with NaH allowed selective methylation with MeOTf (→**17a**) or MeI (→**17d**), and selective desilylation with HCl or TBAF furnished the desired azide fragment **18a** (HCl) or **18d** (TBAF), respectively, which were converted into their alanine ester counterparts, **19a** (88% yield) and **19d** (96% yield), by CDI-mediated couplings with Cbz-Ala-OH in preparation for the impending tripeptide construction. It was postulated[11] that reaction of the azide group of **19a** and **19d** with a suitable phosphine reagent would generate the corresponding azaylide (**22a** and **22d**, respectively) which, upon intramolecular collapse onto the closest ester grouping, could furnish the desired oxazolines **20a** and **20d**, respectively. Indeed, this much-anticipated cascade proceeded smoothly upon exposure of **19a** and **19d** to PMe_3 in benzene or toluene at ambient temperature to furnish oxazolines **20a** (79% yield) and **20d** (83% yield) accompanied by only small amounts of the undesired six-membered rings (that is, dihydropyrazinones **21a** (17%) and **21d** (16%)). The chromatographically purified **20a** and **20d** were then converted into thioamides **3a** and **3d**, respectively, by hydrogenolytic cleavage of their Cbz group (100% yield) followed by thiolysis of the oxazoline rings with H_2S–Et_3N.[12] After evaporation of the solvents, the products **3a** and **3d** were used directly in the next step without further purification.

In our first attempt to synthesize halipeptin D (**1d**) from thioamide **5d** we improvised for a last-stage construction of the thiazoline moiety due to fears of epimerization[6] of the adjacent stereocenter (Scheme 5). The sterically congested ester **2** was prepared in 94% yield from hydroxydecanoic acid **4** and excess acid chloride **5** (10 equiv, prepared in situ from the corresponding carboxylic acid[13] and oxalyl choride in DMF) in the presence of Et_3N and 4-DMAP at 50°C. It is noteworthy that no epimerization at the azide-bearing center was observed in this step despite the basic conditions employed, as confirmed by the synthesis and characterization of the alanine epimer of **2** from **4** and *ent*-**5**. Coupling of carboxylic acid **2** with amino fragments **3a** and **3d** was best achieved by PyAOP activation in the presence of iPr$_2$NEt (92% yield). Protection of **23d** as a TBS ether (99%), selective hydrolysis of the methyl ester with Me_3SnOH[14] (52%), followed by Staudinger reduction of the azide group within the resulting carboxylic acid, and direct macrolactamization (HATU, HOAt, iPr$_2$NEt) yielded macrocycle **24d** as the only product (38%) with complete epimerization of the C-terminal isoleucine unit.



Scheme 5. Completion of the total synthesis of halipeptins A (**1a**) and D (**1d**) and their epimers **29a**, **29d**, **31a**, and **31d**. a) **5** (10.0 equiv), 4-DMAP (0.5 equiv), Et_3N (12 equiv), DMF, 50°C, 2 h, 94%; b) **3a** (1.0 equiv), PyAOP (1.5 equiv), iPr$_2$NEt (2.0 equiv), DMF, 25°C, 17 h, 71% (**23a**); **3d** (2.0 equiv), PyAOP (2.5 equiv), iPr$_2$NEt (2.5 equiv), DMF, 25°C, 17 h, 92% (**23d**); c) TBSOTf (1.2 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 0°C, 0.5 h, 99%; d) Me_3SnOH (20 equiv), CH_2ClCH_2Cl, 80°C, 48 h, 52% at 79% conversion; e) PMe_3 (3.0 equiv), THF/H_2O (9:1), 25°C, 48 h; f) HATU (2.0 equiv), HOAt (2.0 equiv), iPr$_2$NEt (2.0 equiv), CH_2Cl_2 (0.5 mM), 25°C, 18 h, 38% (two steps); g) DAST (1.5 equiv), CH_2Cl_2, −78→−20°C, 1 h, **25a**: 85%; **25d**: 84%; h) Me_3SnOH (20 equiv), CH_2ClCH_2Cl, 90°C, 48–72 h, 82% from **25a**; 85% from **25d**; i) PMe_3 (2.5 equiv), THF/H_2O (9:1), 25°C, 2 h; j) HATU (2.0 equiv), HOAt (2.0 equiv), K_2CO_3 (10.0 equiv), CH_2Cl_2 (0.5 mM), 25°C, 24 h, **27a**: 31%, **28a**: 10%, **30a**: 14%; **1d**: 25%, **29d**: 5%, **31d**: 18%; k) TAS-F (5.0 equiv), DMF, 25°C, 24 h, **1a**: 85%; **29a**: 81%; **31a**: 85%. DAST = (diethylamino)sulfur trifluoride; 4-DMAP = 4-(dimethylamino)pyridine; HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; PyAOP = (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; TAS-F = tris(dimethylamino)-sulfur (trimethylsilyl)difluoride.

This problem was overcome by a detour, which adopted thiazoline formation prior to macrocyclization as shown in Scheme 5. Thus, exposure of thioamide intermediates **23a** and **23d** to DAST[15] in CH_2Cl_2 at −78°C led to thiazolines **25a** (85% yield) and **25d** (84% yield). Selective hydrolysis of the methyl esters of **25a** (82% yield) and **25d** (85% yield) was achieved by the mild action of Me_3SnOH,[14] delivering, upon Staudinger reduction with PMe_3/H_2O, amino acids **26a** and

26d, respectively. The latter were utilized without isolation in the macrocyclization experiments.

Initial attempts to cyclize **26d** to halipeptin D (**1d**) under the influence of HATU in the presence of HOAt and iPr$_2$NEt resulted in the predominant formation of, again, the isoleucine epimer **31d** (epimeric at the indicated (*) site, 17% yield from the corresponding azido carboxylic acid) which, however, this time was accompanied by the natural product, halipeptin D (**1d**, 13% from the corresponding azido carboxylic acid) and traces of **29d**, epimeric at the indicated (*) site adjacent to the thiazoline moiety. Changing the base to K_2CO_3 in the macrolactamization step increased both the yield and selectivity for the natural product (**1d**: 25% yield; **29d**: 5% yield; **31d**: 18% yield; Table 1). Owing to the profound differences in their R_f values, all isomers could be separated easily by preparative TLC (silica gel) by using hexane/EtOAc or CH_2Cl_2/acetone mixtures.

Under the HATU/HOAt/K_2CO_3 conditions for the macrolactamization step, amino acid **26a** was converted into halipeptin A TBDPS derivatives **27a** (31%; yield) and its epimers **28a** (10% yield) and **30a** (14% yield; Scheme 5). Exposure of these compounds to TAS-F liberated halipeptin A (**1a**, 86% yield) and its epimers **29a** (81% yield; Table 1) and **31a** (85% yield). Synthetic halipeptins A (**1a**) and D (**1d**) exhibited identical physical properties to those reported (**1a**,[1] **1d**[3]) for the natural products. Intriguingly, however, and despite previous reports regarding naturally derived halipeptin D,[4] synthetic halipeptin D (**1d**) and its synthesized epimers exhibited only weak toxicity against tumor cells (HCT-116 human colon carcinoma, IC_{50} values, **1d**: 32.5 μM; **29d**: 105.4 μM; **31d**: 111.4 μM).[16] Since natural halipeptin D (**1d**) was isolated from a marine species that contained several potent cytotoxic agents,[3] we attribute this discrepancy to contamination of the naturally derived material by one or more such contaminants.

The chemistry described herein confirmed the structures of halipeptins A (**1a**) and D (**1d**), highlighted their interesting chemical properties, and rendered them and their analogues readily available for further biological investigations.

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[1] a) A. Randazzo, G. Bifulco, C. Giannini, M. Bucci, C. Debitus, G. Cirino, L. Gomez-Paloma, *J. Am. Chem. Soc.* **2001**, *123*, 10870–10876.

[2] C. Della Monica, A. Randazzo, G. Bifulco, P. Cimino, M. Aquino, I. Izzo, F. De Riccardis, L. Gomez-Paloma, *Tetrahedron Lett.* **2002**, *43*, 5707–5710.

[3] The isolation and characterization, the construction of certain fragments used in the present synthesis, and the total synthesis of a number of oxazoline analogues of the halipeptins are reported elsewhere: K. C. Nicolaou, D. Schlawe, D. W. Kim, D. A. Longbottom, R. G. de Noronha, D. E. Lizos, R. Rao Manam, D. J. Faulkner, *Chem. Eur. J.* **2005**, *11*, in press (DOI: 10.1002/chem.200500624).

Table 1: Selected physical properties of **1d**, **29a**, **29d**, and **31d**.

1d: colorless oil; $R_f = 0.36$ (silica, hexanes/EtOAc 1:1); $[\alpha]_D^{32} = -19.1$ ($c = 0.46$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3435, 3331, 2966, 2931, 2782, 1749, 1671, 1637, 1514, 1455, 1401, 1373, 1261, 1155, 1091, 1038, 973, 808, 756, 585$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.20$ (d, $J = 7.7$ Hz, 1H), 7.01 (d, $J = 8.5$ Hz, 1H), 4.98 (d, $J = 10.3$ Hz, 1H), 4.84–4.74 (m, 2H), 4.68 (d, $J = 3.0$ Hz, 1H), 4.13 (d, $J = 12.1$ Hz, 1H), 3.28 (s, 3H), 3.27 (d, $J = 12.1$ Hz, 1H), 3.09–3.05 (m, 1H), 2.78 (s, 3H), 2.22–2.16 (m, 1H), 1.92–1.88 (m, 1H), 1.49 (d, $J = 7.4$ Hz, 3H), 1.44 (s, 3H), 1.39 (d, $J = 7.4$ Hz, 3H), 1.49–1.27 (m, 9H), 1.18 (s, 3H), 1.12 (s, 3H), 1.04–0.99 (m, 1H), 0.96–0.88 (m, 9H), 0.79 ppm (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 177.2, 173.6, 172.5, 169.6, 169.3, 83.9, 82.5, 80.6, 65.0, 56.5, 49.5, 48.5, 45.8, 44.3, 35.7, 34.2, 33.5, 31.9, 31.2, 30.7, 26.2, 25.0, 23.1, 22.3, 22.0, 18.5, 18.0, 17.7, 14.4, 14.3, 12.5$ ppm; HRMS (ESI TOF): calcd for $C_{31}H_{54}N_4O_6S$ [M+H$^+$]: 611.3837; found: 611.3836

29a: colorless oil; $R_f = 0.20$ (silica, EtOAc); $[\alpha]_D^{32} = -12.1$ ($c = 0.2$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3430, 2961, 2917, 2855, 1733, 1710, 1662, 1644, 1507, 1485, 1374, 1255, 1095$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.79$ (d, $J = 5.5$ Hz, 1H), 6.58 (d, $J = 8.5$ Hz, 1H), 5.39 (d, $J = 10.0$ Hz, 1H), 4.87–4.84 (m, 1H), 4.78–4.75 (m, 1H), 4.74 (d, $J = 1.9$ Hz, 1H), 4.03 (d, $J = 12.0$ Hz, 1H), 3.82–3.79 (m, 1H), 3.72–3.67 (m, 1H), 3.33 (d, $J = 12.0$ Hz, 1H), 3.27 (s, 3H), 3.09–3.07 (m, 1H), 2.78 (s, 3H), 2.55–2.51 (m, 1H), 2.17–2.08 (m, 1H), 1.43 (d, $J = 6.4$ Hz, 3H), 1.41 (s, 3H), 1.31 (d, $J = 7.1$ Hz, 3H), 1.22 (s, 3H), 1.52–1.14 (m, 10H), 1.09 (s, 3H), 1.08–1.02 (m, 1H), 1.02–0.96 (m, 6H), 0.68 ppm (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 176.9, 173.6, 172.8, 170.3, 169.2, 84.7, 82.2, 80.5, 64.4, 60.9, 56.4, 49.2, 49.1, 45.1, 43.3, 35.7, 32.9, 32.3, 31.1, 30.7, 29.7, 28.3, 24.3, 23.2, 22.9, 21.5, 19.5, 18.4, 18.2, 14.3, 14.2$ ppm; HRMS (ESI TOF): calcd for $C_{31}H_{54}N_4O_7S$ [M+H$^+$]: 627.3786; found: 627.3790

29d: colorless oil; $R_f = 0.36$ (silica, hexanes/EtOAc 1:1); $[\alpha]_D^{32} = -13.8$ ($c = 0.45$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2965, 2924, 2874, 1749, 1673, 1638, 1613, 1507, 1452, 1397, 1371, 1261, 1095, 1035, 970, 804, 668$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.79$ (d, $J = 5.5$ Hz, 1H), 6.58 (d, $J = 9.2$ Hz, 1H), 5.28 (d, $J = 10.3$ Hz, 1H), 4.87–4.81 (m, 1H), 4.77–4.72 (m, 1H), 4.71 (d, $J = 1.9$ Hz, 1H), 4.01 (d, $J = 12.2$ Hz, 1H), 3.32 (d, $J = 12.2$ Hz, 1H), 3.27 (s, 3H), 3.09–3.05 (m, 1H), 2.78 (s, 3H), 2.24–2.18 (m, 1H), 2.10–2.02 (m, 1H), 1.45 (d, $J = 6.6$ Hz, 3H), 1.43 (s, 3H), 1.32 (d, $J = 7.0$ Hz, 3H), 1.22 (s, 3H), 1.51–1.15 (m, 9H), 1.10 (s, 3H), 1.06–1.02 (m, 1H), 1.02–0.96 (m, 6H), 0.88 (t, $J = 7.1$ Hz, 3H), 0.66 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 176.9, 173.6, 172.7, 170.4, 169.3, 87.8, 82.1, 80.5, 64.8, 56.4, 49.1$ (2 peaks), $45.1, 43.4, 35.7, 33.4, 32.9, 32.3, 31.1, 30.6, 25.5, 24.3, 23.3, 22.8, 21.5, 19.5, 18.4, 17.5, 14.3, 14.1, 12.5$ ppm; HRMS (ESI TOF): calcd for $C_{31}H_{54}N_4O_6S$ [M+H$^+$]: 611.3837; found: 611.3833

31d: colorless oil; $R_f = 0.55$ (silica, hexanes/EtOAc 1:2); $[\alpha]_D^{32} = +6.0$ ($c = 0.15$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 3413, 3342, 2966, 2932, 2861, 1743, 1667, 1637, 1514, 1455, 1373, 1261, 1096, 1032, 961, 797, 750, 585$ cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, 3:1 ratio of conformers): $\delta = 7.17$ (d, $J = 5.3$ Hz, 1H), 7.11 (d, $J = 7.0$ Hz, 1H), 6.28 (minor d, $J = 6.5$ Hz), 6.02 (minor d, $J = 6.1$ Hz), 5.02 (d, $J = 1.7$ Hz, 1H), 4.93 (minor d, $J = 10.6$ Hz), 4.89 (minor d, $J = 2.2$ Hz), 4.84–4.83 (minor m), 4.74–4.70 (m, 1H), 4.62–4.56 (m, 1H), 4.53 (minor d, $J = 11.0$ Hz), 4.48 (d, $J = 10.9$ Hz, 1H), 3.50 (d, $J = 11.6$ Hz, 1H), 3.49 (d, $J = 11.6$ Hz, 1H), 3.27 (s, 3H), 3.24 (minor s), 3.09 (minor d, $J = 11.0$ Hz), 3.07–3.04 (m, 1H), 2.98 (s, 3H), 2.19–2.14 (m, 1H), 1.99–1.84 (m, 1H), 1.60 (d, $J = 7.0$ Hz, 3H), 1.50 (d, $J = 7.0$ Hz, 3H), 1.45 (s, 3H), 1.22 (s, 3H), 1.48–1.20 (m, 9H), 1.13 (s, 3H), 0.90–0.86 (m, 10H), 0.81–0.79 ppm (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, 3:1 ratio of confomers, only major peaks are shown): $\delta = 174.7, 174.3, 172.4, 169.6, 169.6, 84.8, 82.8, 80.6, 63.6, 56.5, 51.6, 47.9, 45.4, 44.5, 35.6, 34.4, 33.9, 31.5, 31.2, 30.8, 26.9, 26.4, 25.7, 22.3, 20.3, 19.5, 18.4, 15.5, 14.4, 14.3, 11.6$ ppm; HRMS (ESI TOF): calcd for $C_{31}H_{54}N_4O_6S$ [M+H$^+$]: 611.3837; found: 611.3844

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