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Stereoselective synthesis of the dolastatin units by organotrifluoroborates additions to α-amino aldehydes

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Abstract—Dolastatin units were synthesized from the 1,2-addition reactions of potassium allyl or crotyltrifluoroborate salts to aldehyde derivatives from natural amino acids. The reactions were carried out in presence of a phase-transfer catalyst in a biphasic medium at room temperature and excellent yields (>89–93%) and stereoselective (>90:10 to 98:2) were obtained. The dolastatin units **8** and **14a**–**b** were obtained after three steps in good overall yields (50–62%).

1. Introduction

Marine cyanobacteria has been shown to be a rich source of bioactive compounds, mainly peptides and depsipeptides.[1] Several of these compounds resemble dolastatins, which were originally isolated from the sea hare *Dolabella auricularia*.[2]

Since dolastatin **10** (**1**, Fig. 1)[3–6] is in human clinical trials for the treatment of cancer[7–9] its syntheses and that of its analogues (e.g., malevamide-D[6]) has become very attractive.

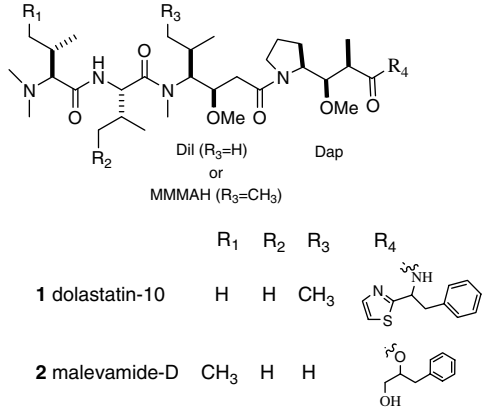

Figure 1. Dolastatin-10 and malevamide-D.

Unusual amino acids, such as (2*R*,3*R*,4*S*)-dolaproine (Dap), (3*R*,4*S*,5*S*)-dolaisoleuine (Dil), or 3-methoxy-5-methyl-4-(methylamino)hexanoic acid (MMMAH), are present in the structure of this dolastatins family, so their stereoselective syntheses are extremely important and have been shown by different research's groups.[10–19]

Potassium organotrifluoroborate salts are excellent substitute for boronic acids or esters.[20–23] Among their advantages we can highlight: (i) higher stability to air and moisture; (ii) easily prepared from inexpensive materials and; (iii) greater nucleophilicity. They are good partners to Suzuki–Miyaura and 1,2- or 1,4-addition reactions.

Herein, we wish to report a successful and mild approach for the total synthesis of the β-methoxy-γ-amino acids, using the 1,2-addition reaction between potassium allyl or crotyltrifluoroborate salts and aldehydes derived from natural amino acids in presence of a phase-transfer catalyst (PTC).

2. Results and discussion

The addition reactions were carried out in a biphasic system (dichloromethane and water) in presence of 10 mol % of tetra *n*-butylammonium iodide (*n*-Bu_4NI)

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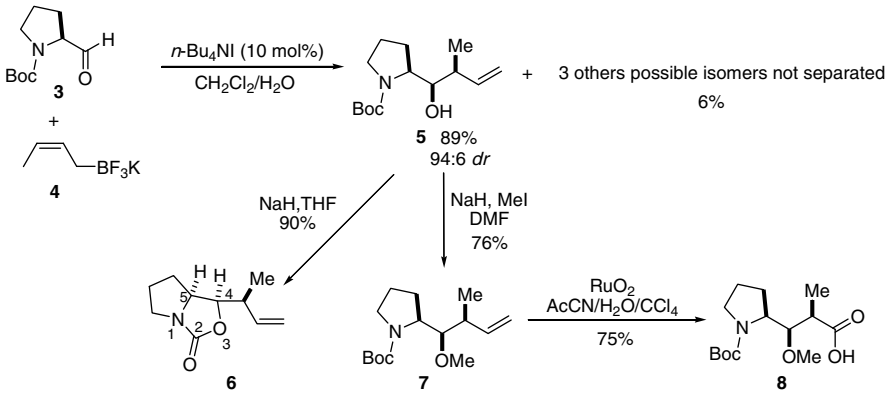


Scheme 1. Synthesis of *N*-Boc-dolaproine (Dap) from the *N*-Boc-prolinal.

in 20 min.[24–26] The *N*-Boc-Dap **8** was prepared from the crotylation of *N*-Boc-prolinal[27,28] **3** (Scheme 1). The addition products were obtained in 95% global yield (mixture of four possible diastereoisomers) and the desired (2*R*,3*R*,4*S*)-*syn* product **5**, precursor of dolaproine, was isolated in 89% yield (dr >94:6).

N-Boc-Dil **14a** and *N*-Boc-MMMAH **14b** were obtained from the allylation of *N*-Boc-isoleucinal **9a** and *N*-Boc-valinal **9b**, respectively (Scheme 2).[26] The *syn* alcohol **11a** derived from **9a** was obtained in 91% yield and dr >90:10, while the *syn* alcohol **11b** derived from **9b** was obtained in 93% yield and dr >98:2.

As in the case of *N*-Boc-Dap, the *syn*/*anti* stereochemistry was assigned on the basis of the corresponding 4,5-disubstituted oxazolidin-2-ones (**12a**–**b**).[29] The coupling constant J_{4-5} was measured and found to be 5.9 Hz in both compounds. In both cases, these values corresponding to the *cis* stereochemistry.[30]

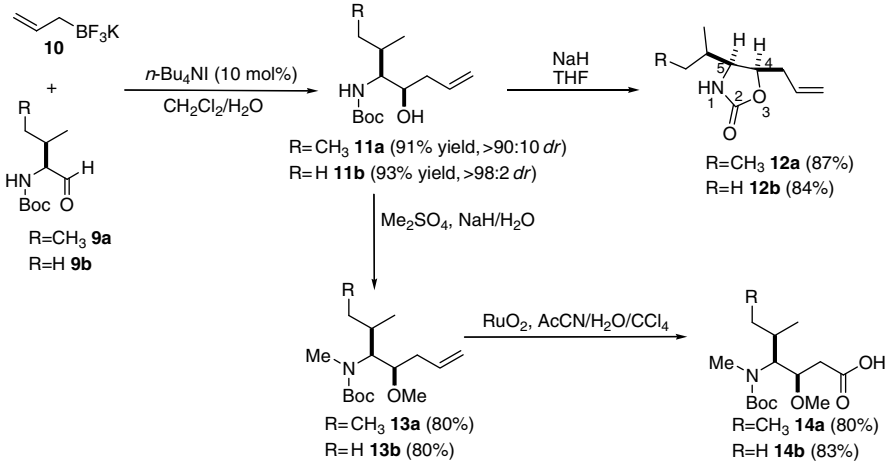
The *syn*/*anti* stereochemistry of product **5** was assigned on the basis of the corresponding 4,5-dissubstituted oxazolidin-2-one **6**. The coupling constant J_{4-5} was measured and found to be 6.9 Hz that corresponding to the *cis* stereochemistry.

There are in the literature several examples of chiral or achiral crotylboronate additions to *N*-Boc-prolinal.[15,31] However, these protocols involve a longer reaction period, and lower yields and stereoselectivity, as well as anhydrous solvents and unstable boron compounds are required.

Alcohol **5** was submitted to an O-methylation reaction with NaH and MeI, the O-methylated product **7** was obtained with 76% yield. The oxidative double-bond cleavage of **7**, in presence of RuO_2 yielded *N*-Boc-Dap **8** in 75% yield.[15] The oxidative cleavage was also carried out using $KMnO_4$ and $NaIO_4$.[32] However, a complex mixture was observed and the desired product was observed by HPLC in very small quantity. The synthesis of *N*-Boc-dolaproine **8** was achieved in three steps from *N*-Boc-prolinal, with an overall yield of 50%.

The allylation of *N*-Boc-valinal **9b** was also carried out in dichloromethane and $BF_3{\cdot}Et_2O$;[33,34] however, the addition product **11b** was obtained in a lower yield (50%) then the biphasic medium and *n*-Bu_4NI were used.

Alcohols **11a**–**b** were submitted to a N,O-dimethylation with Me_2SO_4 and NaH/H_2O.[35,36] Products **13a**–**b** were obtained in 80% yield in both cases. Despite the yield



Scheme 2. Syntheses of *N*-Boc-Dil and *N*-Boc-MMMAH.

of N,O-dimethylation using NaH and MeI is slightly higher,[14,15] we chose the NaH/H_2O system to avoid the excessive use of the methylating agent and due to economics, since Me_2SO_4 is cheaper than MeI.

Products **13a**–**b** were submitted to an oxidative cleavage in presence of RuO_2.[37] The *N*-Boc-Dil **14a** was obtained in 80% yield, while the *N*-Boc-MMMAH **14b** in 83% yield.

The syntheses of this *N*-Boc-γ-amino acids **14a**–**b** were achieved in three steps from the corresponding *N*-Boc-amino aldehydes, with an overall yield of 58% and 62%, respectively.

3. Conclusion

In summary, we present a mild protocol for the preparation of unique units present in the dolastatin-10 and its analogues. Allylation and crotylation of *N*-Boc-amino aldehydes were carried out in biphasic and aqueous media utilizing potassium allyl- and crotyltrifluoroborates.

The addition reactions showed excellent stereoselectivities (>90:10 to 98:2) and the products were achieved in high yields (>89%). This new methodology is an alternative to the use of chiral auxiliary or elaborate boronic esters.

Acknowledgments

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26. *Typical procedure to 1,2-addition reactions*: To a solution of the aldehyde (1.00 mmol) and tetra *n*-butylammonium iodide (36.9 mg, 0.10 mmol) in CH_2Cl_2 (3 mL) were added the potassium allyl or crotyltrifluoroborate salt (1.10 mmol) and water (3 mL). The biphasic reaction mixture was vigorously stirred for 20 min at rt. The reaction mixture was then diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated in vacuo to afford yellowish oil. This material was chromatographed in silica gel using EtOAc/hexane (2:8) as the eluant.
(S)-tert-Butyl 2-((1R,2S)-1-hydroxyl-2-methylbut-3-enyl) pyrrolidine-1-carboxylate (**5**): Product **5** was prepared from the crotylation of *N*-Boc-prolinal in 89% of yield. PF = 66–69 °C (lit.[3] 67–68 °C); $[\alpha]_D^{20}$ −64 (*c* 1, MeOH); ^1H NMR ($CDCl_3$) 1.04 (d, $J = 6.8$ Hz, 3H), 1.45 (s, 9H), 1.62–1.99 (m, 4H), 2.21–2.25 (m, 1H), 3.25–3.31 (m, 1H), 3.41–3.51 (m, 2H), 3.89–3.96 (m, 1H), 4.89 (broad, 1H), 4.97–5.05 (m, 2H), 5.88–5.97 (m, 1H). ESI-MS *m*/*z* (%): 278 (6, M+Na), 256 (8, M+1), 200 (100), 156 (36).
tert-Butyl (3R,4S,5R)-5-hydroxy-3-methyloct-7-en-4-ylcarbamate (**11a**): Product **11a** was prepared from the allylation of *N*-Boc-isoleucinal in 91% of yield. $[\alpha]_D^{20}$ +13 (*c* 1, MeOH); ^1H NMR ($CDCl_3$) 0.78–0.87 (m, 6H), 1.03–1.10 (m, 1H), 1.36 (s, 9H), 1.50–1.58 (m, 2H), 2.12–2.16 (m, 2H), 2.76 (broad, 1H), 3.15–3.22 (m, 1H), 3.75 (broad, 1H), 4.95–5.07 (m, 3H), 5.70–5.84 (m, 1H). ESI-MS *m*/*z* (%): 280 (100, M+Na), 202 (41), 158 (94).
tert-Butyl (3S,4R)-4-hydroxy-2-methylhept-6-em-3-ylcarbamate (**11b**): Product **11b** was prepared from the allylation of *N*-Boc-valinal in 93% of yield. $[\alpha]_D^{20}$ +15 (*c* 1, MeOH); ^1H NMR ($CDCl_3$) 0.94–0.98 (m, 6H), 1.45 (s, 9H), 1.80–1.89 (m, 1H), 2.21–2.28 (m, 2H), 2.69 (broad, 1H), 3.15–3.23 (m, 1H), 3.80–3.86 (m, 1H), 4.99 (d, $J = 9.8$ Hz, 1H), 5.10–5.16 (m, 2H), 5.78–5.92 (m, 1H). ESI-MS *m*/*z* (%): 266 (100, M+Na), 188 (30), 144 (75).

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31. *Typical procedure for the cyclisation of compounds* **5** *and* **11a–b**: To a solution of compound **5** (0.128 g, 0.5 mmol) in THF (2 mL) at −5 °C was added sodium hydride (60% dispersion in mineral oil, 40 mg, 1 mmol). The mixture was stirred overnight at room temperature and then was hydrolysed with aq 5% $KHSO_4$. After dilution with ethyl acetate (80 mL), the organic layer was washed with brine, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The cyclised product was purified by column chromatography on silica flash. *4-(1-Methyl-2-propenyl)-3,1-oxazabicyclo*[3.3.0]*octan-2-one* **6**: Compound **6** was prepared from compound **5** in 90% of yield. $[\alpha]_D^{20}$ +38 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) 1.21 (d, $J = 6.5$ Hz, 3H), 1.44–1.53 (m, 1H), 1.76–1.91 (m, 2H), 2.45–2.57 (m, 1H), 3.11–3.19 (m, 1H), 3.66–3.74 (m, 2H), 4.36 (dd, $J_1 = 10.6$ Hz $J_2 = 6.9$ Hz, 1H), 5.11–5.19 (m, 2H), 5.62–5.74 (m, 1H). GC–MS *m*/*z* (%): 181 (11, M^+), 126 (94), 82 (100), 55 (43).
(*4S,5R*)-*5-allyl-4-*((*R*)-*sec-butyl*)*oxazolidin-2-one* **12a**: Compound **12a** was prepared from compound **11a** in 87% of yield. $[\alpha]_D^{20}$ −5 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) 0.85–0.91 (m, 6H), 1.02–1.15 (m, 1H), 1.38–1.63 (m, 2H), 2.39–2.47 (m, 2H), 3.30–3.33 (m, 1H), 4.31 (dd, $J_1 = 10.4$ Hz $J_2 = 5.9$ Hz, 1H), 5.10–5.19 (m, 2H), 5.70–5.82 (m, 1H). GC–MS *m*/*z* (%): 183 (2, M^+), 142 (68), 126 (100), 86 (40), 57 (61), 43 (68).
(*4S,5R*)-*5-allyl-4-isopropyloxazolidin-2-one* **12b**: Compound **12b** was prepared from compound **11b** in 84% of yield. $[\alpha]_D^{20}$ +60 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) 0.90–0.95 (m, 6H), 1.65–1.76 (m, 1H), 2.43–2.47 (m, 2H), 3.24–3.28 (m, 1H), 4.32 (dd, $J_1 = 10.6$ Hz $J_2 = 5.9$ Hz, 1H), 5.16–5.22 (m, 2H), 5.73–5.87 (m, 1H). GC–MS *m*/*z* (%): 169 (1, M^+), 128 (77), 126 (92), 86 (20), 43 (75), 41 (100).

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tert-Butyl (*3R,4S,5R*)-*5-methoxy-3-methyloct-7-en-4-yl-*(*methyl*)*carbamate* **13a**: Product **13a** was obtained in 80% of yield. $[\alpha]_D^{20}$ −18 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) (two conformers, 50:50) 0.88–0.93 (m, 6H), 0.96–1.09 (m, 1H), 1.31–1.43 (m, 1H), 1.44 (s, 4.5H), 1.45 (s, 4.5H), 1.89–1.97 (m, 1H), 2.12–2.21 (m, 1H), 2.28–241 (m, 1H), 2.76 (s, 1.5H), 2.79 (s, 1.5H), 3.35 (s, 1.5H), 3.36 (s, 1.5H), 3.38–3.41 (m, 1H), 3.64–3.69 (m, 0.5H), 3.83–3.87 (m, 0.5H), 5.01–5.12 (m, 2H), 5.78–5.95 (m, 1H). ESI-MS *m*/*z* (%): 309 (5, M+Na), 286 (19, M+1), 230 (100), 186 (85).
tert-Butyl (*3S,4R*)-*4-methoxy-2-methylhept-6-en-3-yl-*(*methyl*)*carbamate* **13b**: Product **13b** was obtained in 80% of yield. $[\alpha]_D^{20}$ −18 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) (two conformers, 50:50) 0.85–0.88 (m, 3H), 0.96–1.00 (m, 3H), 1.47 (s, 9H), 2.12–2.21 (m, 2H), 2.32–2.39 (m, 1H), 2.79 (s, 1.5H), 2.82 (s, 1.5H), 3.36 (s, 1.5H), 3.38 (s, 1.5H), 3.37–3.44 (m, 1H), 3.58–3.62 (m, 0.5H), 3.78–3.82 (m, 0.5H), 5.04–5.14 (m, 2H), 5.84–5.93 (m, 1H). ESI-MS *m*/*z* (%): 294 (3, M+Na), 272 (13, M+1), 216 (91), 172 (100).
37. *Typical procedure to oxidative cleveage with* RuO_2: To a solution of alkenes **7** or **13a–b** (2.8 mmol) in a system $CH_3CN/H_2O/CCl_4$ (5:7.5:5 mL) were added $NaIO_4$ (2.5 g, 11.6 mmol) and RuO_2 (15.6 mg, 2.5 mol %) at room temperature and the mixture was stirred for 72 h at same temperature. Then it was diluted with ethyl acetate (100 mL) and successively washed with $Na_2S_2O_3$ (10%) and brine. The organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by silica flash chromatography using AcOEt/hexane/MeOH (4:4:2) as eluant.
(*2R,3R*)-*3-*((*S*)-*1-*(*tert-butoxycarbonyl*)*pyrrolidin-2-yl*)-*3-methoxy-2-methylpropanoic acid*; *N-Boc-Dap* **8**: The *N*-Boc-Dap **8** was prepared from compound **7** in 75% of yield. $[\alpha]_D^{20}$ −50 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) 1.19 (d, $J = 6.9$ Hz, 3H), 1.40 (s, 9H), 1.65–1.72 (m, 1H), 1.79–1.89 (m, 3H), 2.40–2.44 (m, 1H), 3.12–3.20 (m, 1H), 3.37 (s, 3H), 3.32–3.49 (m, 1H), 3.70–3.85 (m, 2H), 9.29 (s, 1H). ESI-MS *m*/*z* (%): 324 (32, M+K), 224 (5), 202 (100), 187 (15).
(*3R,4S,5R*)-*4-*(*tert-butoxycarbonyl*(*methyl*)*amino*)-*3-methoxy-5-methylheptanoic acid* **14a**: The *N*-Boc-Dil **14a** was prepared from compound **13a** in 80% of yield. $[\alpha]_D^{20}$ −3 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) (two conformers, 50:50) 0.77–0.88 (m, 3.5H), 0.94–1.03 (m, 3.5H), 1.22–1.33 (m, 1H), 1.40 (s, 4.5H), 1.43 (s, 4.5H), 1.88–1.98 (m, 1H), 2.43–2.64 (m, 2H), 2.76 (s, 1.5H), 2.77 (s, 1.5H), 3.33 (s, 1.5H), 3.37 (s, 1.5H), 3.72–3.76 (m, 0.5H), 3.80–3.86 (m, 0.5H), 3.95–3.98 (m, 1H), 7.70 (s, 1H). ESI-MS *m*/*z* (%): 326 (18, M+Na), 304 (9, M+1), 248 (100), 304 (67).
(*3R,4S*)-*4-*(*tert-butoxycarbonyl*(*methyl*)*amino*)-*3-methoxy-5-methylhexanoic acid* **14b**: The *N*-Boc-MMMAH **14b** was prepared from compound **14b** in 83% of yield. $[\alpha]_D^{20}$ −17 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$) (two conformers, 50:50) 0.83–0.85 (m, 3H), 0.99–1.04 (m, 3H), 1.42 (s, 4.5H), 1.45 (s, 4.5H), 2.11–2.17 (m, 1H), 2.40–2.72 (m, 2H), 2.78 (s, 1.5H), 2.80 (s, 1.5H), 3.35 (s, 1.5H), 3.37 (s, 1.5H), 3.95–3.98 (m, 0.5H), 3.76–3.80 (m, 0.5H), 3.95–4.08 (m, 1H), 9.63 (s, 1H). ESI-MS *m*/*z* (%): 312 (13, M+Na), 290 (6, M+1), 234 (100), 190 (72).