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AN EXPEDITIOUS SYNTHESIS OF DOLASTATIN 10

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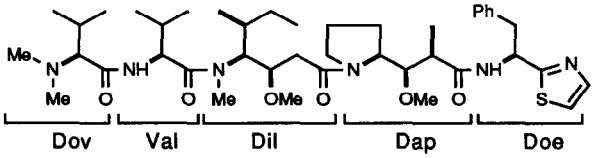
Summary: Total synthesis of dolastatin 10 (1) was completed by developing an efficient synthesis of two key amino acid components, Dil (6) and Dap (11), and subsequent stepwise coupling of five amino acid components from C-terminal Doe.

Naturally occurring pentapeptide (-)-dolastatin 10 (**1**) has been reported to exhibit the most potent antineoplastic activity known to date.[1] Recent total synthesis of (-)-**1** established the structure and absolute configuration of (-)-dolastatin 10.[2] The development of an efficient synthetic route to (-)-**1** and stereochemical analogues is expected to provide the opportunity for full assessment of biological properties. We herein report an expeditious synthesis of (3*R*,4*S*,5*S*)-dolaisoleuine (Dil) and (2*R*,3*R*,4*S*)-dolaproine (Dap), two amino acid components of (-)-**1**, by a stereoselective construction of the requisite asymmetric centers followed by a rapid *N* and *O* methylation. Stepwise coupling of five amino acids from Doe completed total synthesis of (-)-**1**.[3]



Dolastatin 10 (**1**)

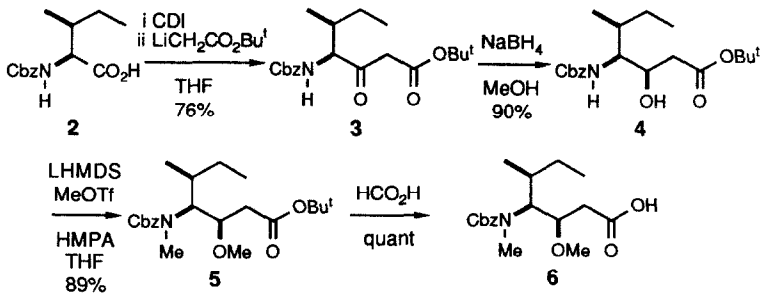
The most straightforward synthesis of Dil component involves a four-step conversion: (i) *N*-protected L-Ile (**2**) to a keto ester (**3**), (ii) reduction to **4**, (iii) *N*,*O*-dimethylation to **5**, and (iv) finally selective deprotection to **6**.[3a] Since a keto ester (**3**) synthesis[3a,4,5] and selective deprotection are the established technique, we focussed on reduction and methylation steps.

A keto ester (**3**, $[\alpha]_D^{25}$ +31.4 °(*c* 0.87, $CHCl_3$)) was prepared from **2**[6] (i. CDI / THF, ii. $LiCH_2CO_2Bu^t$)[4] in 76% yield.[7] Reduction of **3** with $NaBH_4$ in MeOH resulted in a production of the desired 3*R*-alcohol (**4**, mp 94-95 °C, $[\alpha]_D^{25}$ +6.65 °(*c* 1.11, $CHCl_3$)) as a major diastereomer in 90% yield.[8] On the other hand, reduction of the corresponding *N*-methylated ketone provided the reverse stereoselectivity,[9] producing 3*S*-alcohol in 72% yield. These reduction procedures established the stereoselective synthetic route to either **4** or the corresponding diastereomer, which would be useful for the synthesis of the stereochemical analogues of **1**.

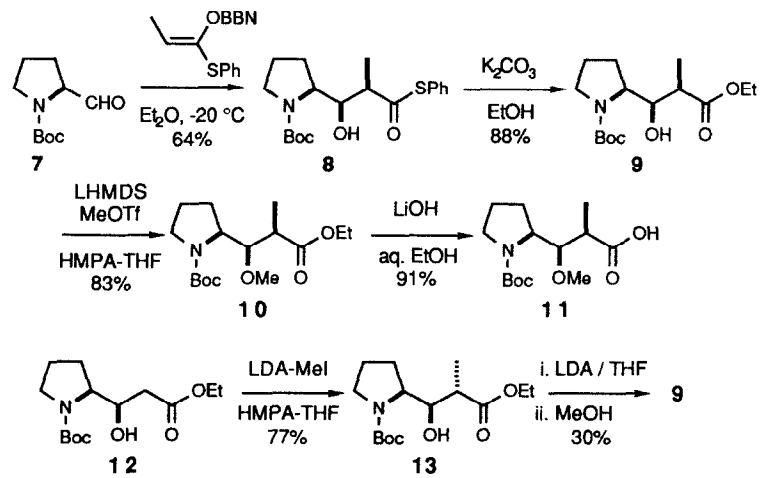
N,*O*-Dimethylation of **4** proved problematic. Standard methylation of **4** with Ag_2O-MeI[10] and CH_2N_2[11] did not afford **5**, giving *O*-methylation or elimination products, respectively. Appropriate combination of a lithium amide base and a methylating agent proved to be successful. It is important to use lithium hexamethyldisilazide (LHMDS) as a base and MeOTf as a rapid methylating agent to

provide **5** ($[\alpha]_D^{30}$ -14.7 °(*c* 4.17, $CHCl_3$); -15.5 °($CHCl_3$)[2]) in 89% yield.[12] Other combinations of LHMDS-MeI, LDA-MeOTf or -MeI proved to be unsatisfactory.[13]

Treatment of **5** with HCO_2H provided **6** ($[\alpha]_D^{25}$ -12.2 °(*c* 1.63, MeOH)) quantitatively.



Boc-(2*R*,3*R*,4*S*)-Dap (**11**) was prepared in four steps from *N*-Boc-L-prolinal (**7**).[14] Aldol reaction of **7** with a *Z*-boron enolate of thiophenyl propionate[15] stereoselectively provided **8** (mp 112-3 °C, $[\alpha]_D^{25}$ -83.3 °(*c* 1.30, $CHCl_3$)) in 64% yield, and other two diastereomers were obtained in 10 and 1% yields.[16] Ethanolysis of **8** (K_2CO_3 in EtOH) provided **9** ($[\alpha]_D^{30}$ -46.4 °(*c* 0.91, $CHCl_3$)) in 88% yield. A rapid *O*-methylation of **9** afforded **10** ($[\alpha]_D^{25}$ -49.2 °(*c* 3.50, $CHCl_3$)) in 83% yield. Hydrolysis (LiOH / aq. EtOH) of **10** provided **11** ($[\alpha]_D^{30}$ -63.0 °(*c* 2.06, MeOH); -40 °(MeOH)[2]) in 91% yield. Direct hydrolysis of the corresponding methyl ether of **8** provided a mixture of **11** and isomerized diastereomer.



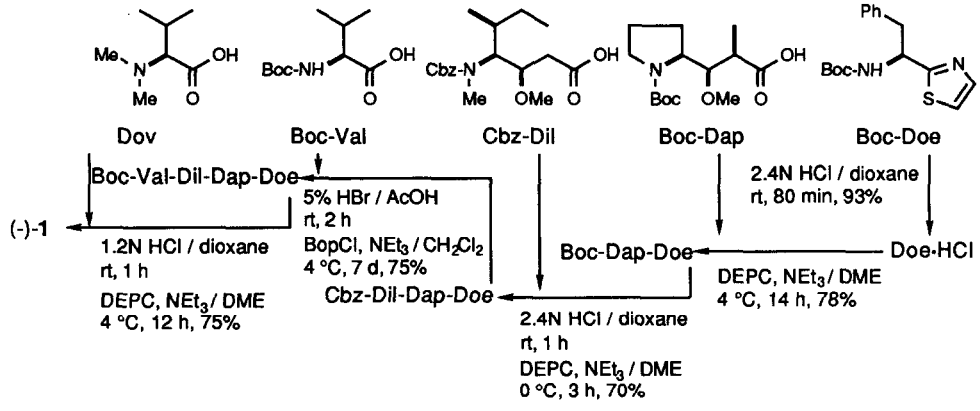
Stereochemistry of **8** was also confirmed as follows. The stereochemically known ester (**12**)[14] was subjected to stereoselective methylation reaction (LDA-MeI / HMPA-THF, -78 to -20 °C, 2.5 h)[18] to provide anti-**13**[19] in 77% yield, which was then isomerized through deprotonation-protonation sequence (i. LDA / THF, -20 °C, 1 h; ii. MeOH, -78 °C) to provide syn-**9**.[19]

Dov (*N*,*N*-dimethylvaline) was prepared by dimethylation of L-valine according to the reported procedure.[20] *N*-Protected Doe (Boc-Doe) was prepared from Boc-L-phenylalanine (i. B_2H_6 / THF,

81%; ii. SO_3-Py, DMSO, NEt_3 / CH_2Cl_2,[21] 91%; iii. $H_2N(CH_2)_2SH$ / benzene, quant.; iv. MnC column / dioxane, 19%[22]). Hydrochloride of Doe (mp 163-4 °C (EtOH-Et_2O), $[\alpha]_D^{25}$ +42.5 °(*c* 0.9 MeOH)) was prepared in 93% yield by treating Boc-Doe with 2.4N HCl in dioxane.

Sequential elongation from Doe hydrochloride to dolastatin 10 was carried out as shown Scheme I. Treatment of Doe hydrochloride and Boc-Dap (**11**) with DEPC[23]-NEt_3 in DME provid Boc-Dap-Doe (mp 135-6 °C (Et_2O-hexane), $[\alpha]_D^{25}$ -76.4°(*c* 1.64, MeOH)) in 78% yield. Deblockii and coupling with Cbz-Dil (**6**) provided Cbz-Dil-Dap-Doe ($[\alpha]_D^{25}$ -60.2°(*c* 1.13, MeOH)) in 70% tw step yield. Subsequent deblocking and coupling with Boc-Val[24] using BopCl procedure[25] provid Boc-Val-Dil-Dap-Doe ($[\alpha]_D^{25}$ -50.9°(*c* 0.685, $CHCl_3$)) in 75% two-step yield.[26] Final deblocking a coupling with Dov provided (-)-**1** (mp 107-8°C, $[\alpha]_D^{27}$ -68.8° (*c* 0.032, MeOH)) in 75% two-step yield

Scheme I



Melting point, optical rotation, UV, NMR (^1H, ^{13}C), MS of the synthetic (-)-**1** w indistinguishable with those reported for (-)-**1**.[1,2] Biological activity of (-)-**1** and synthe intermediates is currently under evaluation.

References and Notes

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(12) *N,O*-Dimethylation procedure for the synthesis of **5**: A solution of **4** (5.0 g, 13.7 mmol) in THF (50 ml) was added to a solution of LHMDS (34.3 mmol) in HMPA (7.1 ml, 41 mmol) and THF (50 ml) at -78 °C. After the mixture was stirred for 25 min, MeOTf (9.3 ml, 82.2 mmol) was added at -20 °C. After being stirred at -20 °C for an additional 15 min, the mixture was worked up as usual. Column chromatography (SiO_2, AcOEt/hexane=1/9) afforded **5** (4.79 g) in 89% yield.
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(16) The structures of isomers were confirmed to be (2*S*,3*S*,4*S*)- and (2*R*,3*S*,4*S*)-isomers, respectively, by the chemical conversion of the corresponding diastereomer of **12**.
(17) Aldol reaction of **7** with ethyl lithiopropionate in HMPA-THF at -78 °C provided **9**, **13**, and other two isomers in 38, 25, 8, and 8% isolated yields, respectively, and these isomers could be separated by silica gel column chromatography.
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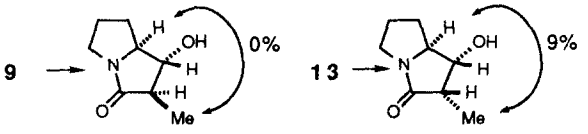

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