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An easy and stereoselective synthesis of *N*-Boc-dolaproine via the Baylis–Hillman reaction

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Abstract—In this communication we report a stereoselective total synthesis of *N*-Boc-dolaproine (Dap), an amino acid residue of the antineoplastic pentapeptide Dolastatin 10. Our strategy is based on a Baylis–Hillman reaction between *N*-Boc-prolinal and methyl acrylate, followed by a diastereoselective double bond hydrogenation and hydrolysis of the ester function.

Dolastatin 10 (**1**, Fig. 1) has been reported to exhibit a remarkable antineoplastic activity[1] and is now in Phase II human cancer clinicals trials.[2] Its structure and absolute configuration were ascertained by total synthesis some years ago.[3a] The unusual β-methoxy-γ-amino acid dolaproine (Dap) comprises the most complex unit of the pentapeptide **1**, and has been synthesized by several groups employing aldol condensation,[3a–c] addition of a crotylboronate to *N*-Boc-prolinal[3e,f] and a cobalt-catalyzed Reformatsky reaction.[4] More recently, Genet et al.[5] reported a new strategy based on a dynamic kinetic resolution of a β-keto ester derivative.

In an ongoing research program focused on the utilization of Baylis–Hillman adducts[6] for the total synthesis of biologically active products,[7] we decided to propose an alternative strategy for the preparation of this important non proteinogenic amino acid.

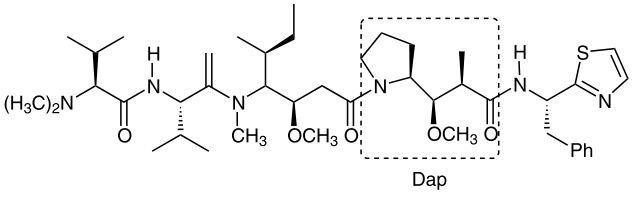

Figure 1. Dolastatin 10.

A careful search of the literature pointed out that Drewes and Roos[8] have already reported that chiral α-amino aldehydes such as L-prolinal provided a moderate *anti* diastereoselectivity in the Baylis–Hillman reaction with methyl acrylate, but the specific rotation of the product is low (ca. 1°), suggesting that racemization of the starting aldehyde had occurred.

It seems likely that under extended period of reaction DABCO is sufficiently basic to abstract the α carbonyl proton thus leading to a loss of chirality. Besides this, the presence of a strong electron-attracting *N*-protecting groups (*p*-nitrobenzoyl or sulfonyl) should contribute to increase the acidity of the α hydrogen. Our interest was to overcome the problem of racemization by shortening the reaction time and changing the *N*-protecting group.

In a recent report, we demonstrated that the use of ultrasound radiation significantly decreases the Baylis–Hillman reaction time.[9] It is worth mentioning that other alternatives to accelerate the Baylis–Hillman reaction time have already been related, such as the use of Lewis acid (alone)-catalyzed or -promoted reaction,[10] microwaves,[11] salts and metals,[12] ionic liquids[13] and an aqueous medium.[14]

Then, we decided to apply ultrasound radiation to the DABCO-catalyzed coupling between *N*-Boc-prolinal (**3**) and an acrylate (**4** or **5**). If it was possible to achieve good control in the racemization reaction, a subsequent diastereoselective hydrogenation of intermediates **6** or **7** should guarantee access to our target (Scheme 1).

Keywords: dolaproine; Baylis–Hillman; hydrogenation; amino aldehydes.

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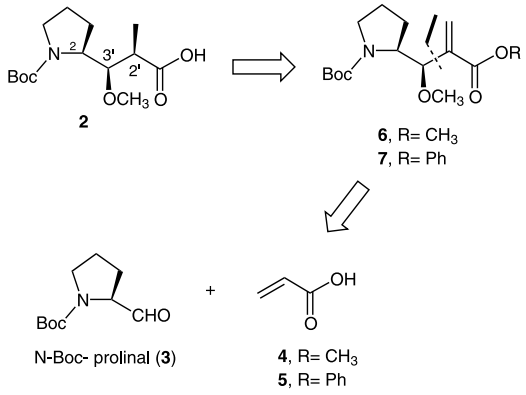


Scheme 1. Retrosynthetic analysis for *N*-Boc-dolaproine (**2**).

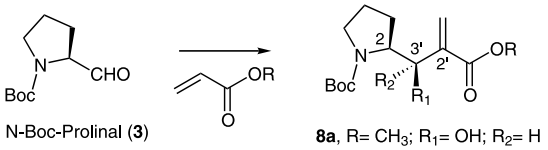
In this communication, we report a successful and simple approach for the total synthesis of *N*-Boc-dolaproine (**2**), employing a Baylis–Hillman reaction as the key step. *N*-Boc-prolinal was prepared following a well established procedure described in the literature.[15]

For the two acrylates examined (**4** and **5**), the Baylis–Hillman reactions we performed without and with sonication. The results obtained are summarized in Table 1.

As expected, the reactions with an aromatic acrylate were faster than those in which methyl acrylate was used. From Table 1, it is clear that the ultrasound technique has a significant effect on the time of reaction; however, the nature of acrylate moiety has a major effect on both the reaction time and the stereoselectivity (entry 4).

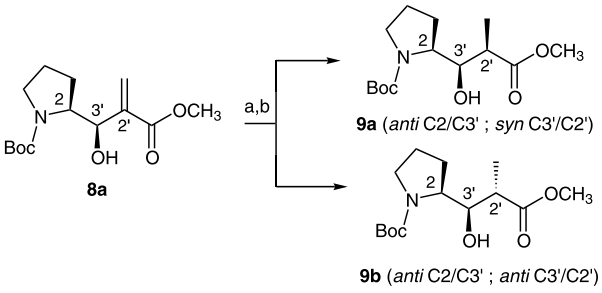
Diastereoisomers obtained from methyl acrylate (**8**) were chromatographically separable and the stereochemistry of the major one, determined by ^{1}H NMR and proved to be *anti* (**8a**, Scheme 2), as expected.[7] The *anti* diastereoselectivity may be rationalized in terms of the Felkin–Ahn open-chain model.[16] The α_D value of

Table 1. Baylis–Hillman reaction of *N*-Boc-prolinal



Entry	Acrylate	Conditions	Time (% yield)	Ratio[d]
1	Methyl	Standard[b]	7 days (70)	3:1
2	Methyl	Ultrasound[c]	5 days (75)	3:1
3	Phenyl[a]	Standard	4 days (65)	8:1
4	Phenyl	Ultrasound	2 days (70)	8:1

[a] **CAUTION**: Phenyl acrylate is both an irritant and toxic.
[b] Room temperature, CH_2Cl_2; DABCO/aldehyde (equimolar ratio) and 4-fold excess of the acrylate.
[c] Ultrasonic cleaner, 1000 W, 40 kHz.
[d] Determined by CG–MS.



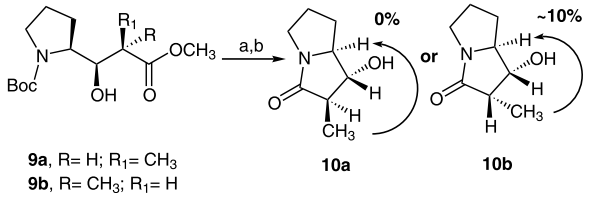
Scheme 2. Diastereoselective hydrogenation of **8a**. *Reagents and conditions*: (a) H_2, Pd/C 5%; EtOAC, rt, atmospheric pressure, 91% of a 83:17 diastereoisomeric mixture; (b) flash chromatography (EtOAc–hexane 1:9; major isomer: 79% yield).

the methyl derivative **8a** was measured (–32.5°, *c* 1, MeOH) and strongly suggested that the Baylis–Hillman reaction had occurred without extensive racemization (Scheme 2).

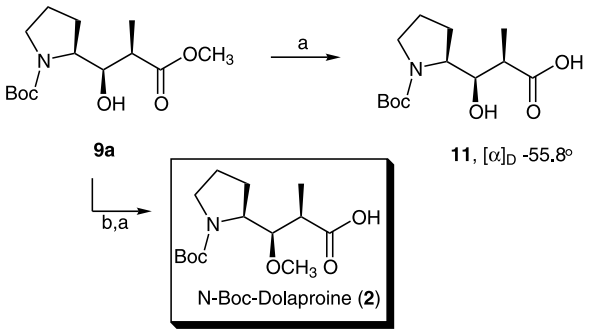
Unfortunately, the relative stereochemistry of the phenyl derivative was uncertain (**8c** and **8d**, see Table 1). The diastereoisomers could not be easily separated on a silica gel chromatographic column and their ^{1}H NMR spectra were undistinguishable. The planned synthetic pathway was followed subjecting only **8a** (*anti* methyl derivative, enantiomerically enriched) to the hydrogenation step (Scheme 2).

Ester **9** was obtained in a 83:17 diastereomeric ratio determined by GC–MS of the crude product. To define the stereochemistry of the major isomer, after purification by flash chromatography, ester **9** was subjected to deprotection and a cyclization sequence to yield lactam **10** (Scheme 3).[11] NOE experiments supported the stereochemical assignment: the cyclic product did not show increment of signals, suggesting a *trans* C*H*–C*H*$_3$ relationship (lactam **10a**). Similarly, the same experiment on the lactam derived from the minor diastereoisomer showed a signal increment of ~10%, suggesting a *cis* C*H*–C*H*$_3$ relationship. These observations confirmed the *anti–syn* (C2–C3′–C2′, Scheme 3) configuration of ester **9a**.

Then, ester **9a** was subjected to the next synthetic step. To confirm, as quickly as possible, if we were in the right direction, we decided, in this stage of the work, to



Scheme 3. Relative stereochemistry determination of **9a**. *Reagents and conditions*: (a) CF_3CO_2H/CH_2Cl_2, 68% yield; (b) K_2CO_3/MeOH, overnight (**9a→10a**: 82% yield; **9b→10b**: 71% yield).



Scheme 4. Synthesis of *N*-Boc-dolaproine (**2**). *Reagents and conditions*: (a) LiOH/THF, rt, 16 h, 87%; (b) Me_3OBF_4, CH_2Cl_2, proton sponge, rt, 18 h, 70%.

transform **9a** into a compound with well established relative and absolute configurations. Thus, treatment of ester **9a** with LiOH–H_2O/THF, at room temperature, gave *N*-Boc-nordolaproine (**11**) in 87% yield (Scheme 4).

The α_D value of **11** (−55.8°, *c* 0.71, MeOH) was nearly identical to that reported in literature[17] and, therefore, confirmed that the absolute configuration had been retained in all steps.

Then, the synthesis of *N*-Boc-dolaproine was achieved in two subsequent steps from ester **9a**. First, *O*-methylation of the hydroxy moiety with MeO_3BF_4 and proton sponge afforded the methoxy ester **6** in 70% yield. Saponification of the methyl ester function with LiOH in THF/H_2O led to *N*-Boc-protected dolaproine (**2**) in 86% yield.[18] Since the removal of Boc protective group is well documented in literature,[1] the preparation of dolaproine has been formally achieved from a Baylis–Hillman adduct.

The synthesis of *N*-Boc-dolaproine **2** was achieved in four steps from *N*-Boc-prolinal, with an overall yield of 27%.[19] Despite moderate selectivities, this simple and efficient synthetic strategy, associated with the ready chromatographic separation of the diastereoisomers, provided a new entry to *N*-Boc-dolaproine. As far as we know this is the first report concerning the asymmetric total synthesis of a dolaproine derivative from a Baylis–Hillman adduct. Our results demonstrate clearly that it is possible to retain the configuration of the α-carbonyl center in *N*-Boc-prolinal, using a Baylis–Hillman coupling carried out in the presence of ultrasound.[20,21]

In summary, this reaction sequence is very easy to implement and did not require anhydrous solvents, a temperamental boron enolate or a low reaction temperature. Additional studies focusing on the generalization of this method for other chiral α-amino aldehydes using other activated acrylates are ongoing in our laboratory and will be reported in due course.

Acknowledgements

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18. Ref. 3g: $[\alpha]_D^{26} = -56.8°$ (*c* 0.52, MeOH); Ref. 3i: $[\alpha]_D^{25} = -57.0°$ (*c* 0.81, MeOH); Ref. 3b: $[\alpha]_D^{27} = -54.5°$ (*c* 1, MeOH).
19. All spectral data were compatible with those related previously for *N*-Boc-dolaproine (**2**). A colorless viscous oil, which crystallize on standing. Recrystallization (twice) from acetone–hexane produced needles: mp 138–142°C; $[\alpha]_D^{25} = -60.2°$ (*c* 0.5, CH_3OH); (lit.[9] $[\alpha]_D^{25} = -61.4°$ (*c* 0.5, CH_3OH); lit. $[\alpha]_D^{25} = -57.0°$ (*c* 2.08, CH_3OH); EIMS *m*/*z* 287 (M+), 255, 214, 170, 114, 70; IR (KBr, λ_{max}): 3084, 2978, 2938, 2884, 1736, 1696, 1402, 1167, 1167, 1099 cm^{-1}; ^1H NMR (500 MHz, CD_3CN, 50°C) δ 3.80 (m, 2H), 3.44 (m, 1H), 3.39 (s, 3H, OCH_3), 3.16 (m, 1H), 2.47 (m, 1H), 1.96–1.82 (m, 4H), 1.72 (m, 1H), 1.44 (s, 9H), 1.18 (d, 3H, $J = 7$ Hz).
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