Tetrahedron Letters 49 (2008) 6631–6634

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Catalytic asymmetric synthesis of the docetaxel (Taxotere) side chain: organocatalytic highly enantioselective synthesis of esterification-ready α-hydroxy-β-amino acids

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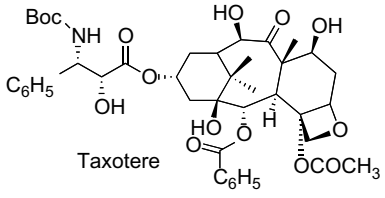
ARTICLE INFO

Article history:
Received 3 August 2008
Revised 26 August 2008
Accepted 5 September 2008
Available online 11 September 2008

ABSTRACT

A highly enantioselective catalytic route to protected β-amino-α-hydroxy acids, such as the side chain of Taxotere, is presented. The organocatalytic asymmetric reactions between unmodified protected α-oxyaldehydes and *N*-Boc-protected aryl imines give the corresponding compound with up to >19:1 dr and 99–99% ee.

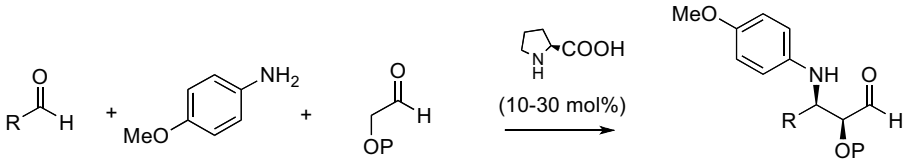
The β-amino-α-hydroxy acid moiety is a common structural component in a vast group of naturally occurring as well as pharmaceutically active molecules.[1] In this context, docetaxel (Taxotere), a synthetic derivative of paclitaxel (Taxol), which is one of the most outstanding cancer chemotherapeutic substances, contains a (2*R*,3*S*)-phenylisoserine side chain.[2]



The importance of α-hydroxy-β-amino acid derivatives has inspired chemists to develop a number of methods for their preparation.[1,3] Among them, Shibasaki and co-workers reported a four-step synthesis of the Taxotere side chain based on a direct zinc organometallic complex-catalyzed Mannich reaction between an *N*-Boc imine and 2-hydroxy-2'-methoxyacetophenone.[4]

Recently, organocatalysis was added to the synthetic repertoire of the direct Mannich reaction.[5–7] For example, we have reported amino acid-catalyzed Mannich reactions between protected α-oxyaldehydes, *para*-anisidine, and aldehydes (Eq. 1).[8]

The corresponding *N*-*p*-methoxyphenyl (PMP)-protected α-oxy-β-amino aldehydes are excellent precursors for the synthesis of α-hydroxy-β-amino acids. However, removal of the PMP group requires oxidative conditions, can be low yielding, and requires Boc protection as an additional step. Enders recently reported elegant examples of Mannich-type reactions between ketones and Boc imines.[9] List[10] and our group[11] have also reported that aldehydes can be employed as donors in organocatalytic reactions with Boc imines. Moreover, we recently showed that proline catalyzes the highly enantioselective addition of α,β-unsaturated aldehydes to Boc imines.[12] Based on our previous results and retro-synthetic analysis, we envisioned a short route to the important Taxotere side chain via an amino acid-catalyzed direct Mannich-type



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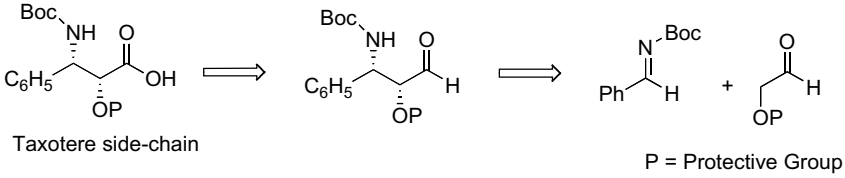
doi:10.1016/j.tetlet.2008.09.038

reaction between protected α-oxyaldehydes and *N*-Boc-protected benzaldimine (Eq. 2).



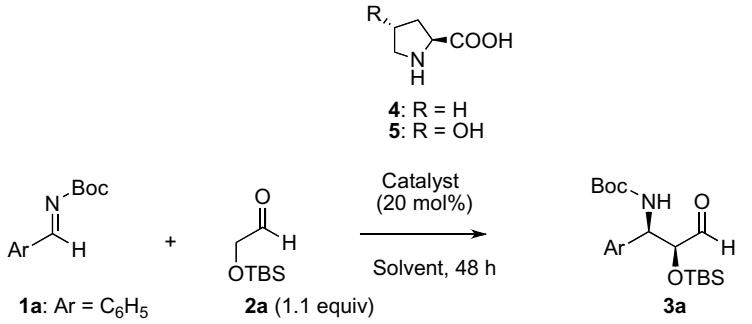
(2)

Herein, we report a highly enantioselective synthesis of the esterification-ready side chain of Taxotere (>19:1 dr, 99% ee). The reaction is a direct route to Boc-protected α-hydroxy-β-aminoaldehydes.

In an initial screen, we found that (*S*)-proline **4** and hydroxyproline **5** catalyzed the reaction between phenyl *N*-Boc-imine **1a** (0.25 mmol) and *tert*-butyldimethylsilyl (TBS)-protected α-oxyaldehyde **2a** (0.27 mmol) with high stereoselectivity to give the corresponding α-oxy-β-amino aldehyde **3a** in poor to good yields but with excellent diastereomeric ratios and ees (Table 1).[13]

(*S*)-Proline-catalyzed the formation of protected α-oxy-β-amino aldehyde **3a** in 12–36% yield with >19:1 dr (*syn*:*anti*) and 99–99% ee in DMF, NMP, and CH_3CN, respectively, at 4 °C (entries 1–3). The optically active aldehyde **3a** was quite stable but was stored at −20 °C. The highest yield was obtained when CH_3CN was used as the solvent. Performing the catalytic reaction at room temperature increased the yield of **3a** to 48% without affecting the stereoselectivity (entry 6). Inspired by these excellent results, we decided

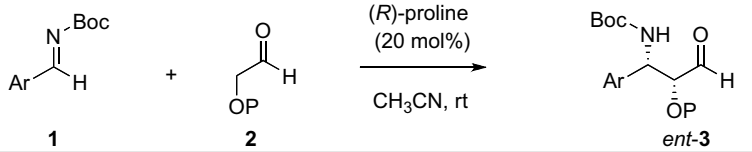
Table 1
Catalyst screen for the enantioselective reactions between **1a** and **2a**[a]



Entry	Catalyst	Time (h)	Solvent	Temperature (°C)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**4**	48	DMF	4	12	>19:1	99
2	**4**	48	CH_3CN	4	36	>19:1	>99
3	**4**	48	NMP	4	24	>19:1	99
4	**4**	48	$CHCl_3$	4	Trace	n.d.	n.d.
5	**4**	48	CH_2Cl_2	4	Trace	n.d.	n.d.
6	**4**	16	CH_3CN	rt	48	>19:1	99
7	**5**	16	CH_3CN	rt	6	>19:1	95
8	**4**	48	Toluene	4	Trace	n.d.	n.d.

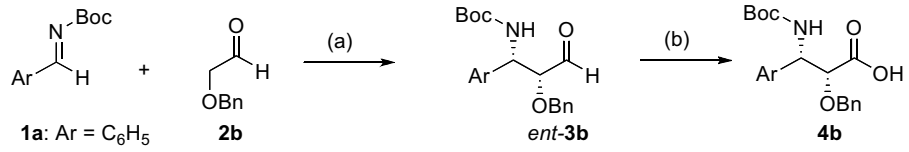
[a] Experimental conditions: A mixture of **1a** (0.25 mmol), aldehyde **2a** (0.50 mmol), and catalyst (20 mol %) in 1.0 mL of solvent was stirred under the conditions displayed in the table.
[b] Isolated yield of pure compound **3a**.
[c] Determined by ^1H NMR of the crude reaction mixture.
[d] Determined by chiral-phase HPLC analysis. n.d. = not determined. TBS = *tert*-butyldimethylsilyl.

Table 2
Direct organocatalytic asymmetric Mannich reactions between *N*-Boc-protected imines **1** and α-oxyaldehydes **2**[a]



Entry	Ar	X	Product	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	Ph	TBS	*ent*-**3a**	40	56	>19:1	99
2	Ph	Bn	*ent*-**3b**	5	60	>19:1	99
3	4-MeC_6H_4	Bn	*ent*-**3c**	16	56	3:1	99
4	4-$MeOC_6H_4$	Bn	*ent*-**3d**	16	52	9:1	99

[a] Experimental conditions: A mixture of **1a** (0.25 mmol), α-oxyaldehyde **2** (0.27 mmol), and (*R*)-proline (20 mol %) in 1.0 mL of CH_3CN was stirred at room temperature.
[b] Isolated yield of pure compound **3**.
[c] *syn*/*anti* ratio determined by ^1H NMR analysis.
[d] Determined by chiral-phase HPLC analyses. TBS = *tert*-butyldimethylsilyl. Bn = benzyl.

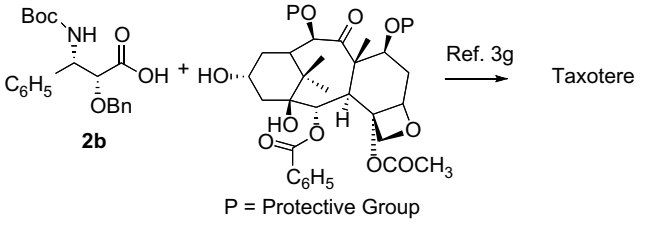


Scheme 1. Reagents and conditions: (a) (*R*)-proline (20 mol %), CH_3CN, rt, 16 h, 60%; (b) $NaClO_2$, *iso*-butene, $KHPO_4$, *t*-BuOH/H_2O 2:1, 85%.

to investigate the catalytic asymmetric Mannich reaction between various *N*-Boc-protected imines **1** and different α-oxyaldehydes **2** (Table 2).[14] In order to achieve the same configuration (2*R*,3*S*) as that of the Taxotere side chain, (*R*)-proline was selected as the organocatalyst.

The (*R*)-proline-catalyzed Mannich reactions proceeded with excellent enantioselectivity, and the corresponding α-oxy-β-amino aldehydes *ent*-**3a**–*ent*-**3d** were obtained in good yields with 99% ee. To our delight, the reaction was highly *syn*-selective (>19:1 dr) when imine **1a** was used as the acceptor (entries 1 and 2). In fact, this is the key transformation for the synthesis of the Taxotere side chain (Eq. 2). For example, (*R*)-proline-catalyzed the asymmetric reaction between imine **1a** and benzyl-protected α-oxyaldehyde **2b** with high diastereo- and enantioselectivity to give the corresponding orthogonally protected α-oxy-β-amino aldehyde *ent*-**3b**[14] in 60% yield with >19:1 dr and 99% ee (entry 2). Moreover, the reactions were readily scaled up. Next, the α-oxy-β-amino aldehyde *ent*-**3b** was oxidized to the corresponding (2*R*,3*S*)-phenylisoserine (Taxotere) side chain **4b**[3g] in high yield (Scheme 1).[15] This reaction can also be performed as a one-pot operation.

Notably, the benzyl-protected β-amino-α-hydroxy acid **4b** is esterification-ready for reaction with 10-deacetylbaccatin III, an abundant natural product obtained from the yew tree, which after deprotection gives Taxotere (Eq. 3).[3g]



(3)

On the basis of the absolute configuration, we propose transition-state model **I** to account for the diastereo- and enantioselectivity of the (*R*)-proline-catalyzed formation of α-oxy-β-amino aldehydes **3** (Fig. 1). Hence, the (*R*)-proline forms an enamine with the aldehyde, which is attacked by the *N*-Boc-protected imine from its *Re*-face providing (2*R*,3*S*)-β-amino-α-hydroxy acid derivatives. This is in accordance with the opposite established transition states of previously reported (*S*)-proline-catalyzed Mannich reactions[5,6] with α-oxyaldehydes.[8]

In summary, we have reported a simple, highly enantioselective, organocatalytic asymmetric Mannich-type reaction with α-oxyaldehydes as nucleophiles and Boc-protected imines as acceptors. The corresponding orthogonally protected α-oxy-β-aminoaldehydes were formed in good yields with 99% ee. The importance of this transformation as an entry to the synthesis of α-hydroxy-β-amino acids was further exemplified by the highly stereoselective (>19:1 dr, 99% ee) synthesis of the esterification-ready Taxotere side chain. Further elaboration of this novel transformation in total synthesis as well as mechanistic studies is ongoing in our laboratory.

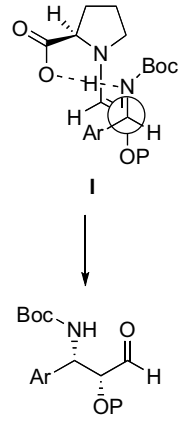


Figure 1. Transition-state model evoked to account for the enantioselectivity of the (*R*)-proline-catalyzed reactions.

Acknowledgments

We gratefully acknowledge the Swedish National Research Council and Carl-Trygger Foundation for financial support.

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13. *Typical experimental procedure*: To a stirred solution of imine **1a** (1.0 equiv, 0.25 mmol) and aldehyde **2a** (1.1 equiv, 0.27 mmol) in solvent (1.0 mL) at 4 °C was added (*S*)-proline (20 mol %), and the resulting reaction mixture was stirred vigorously for the reported time. Next, the reaction mixture was directly loaded onto a silica-gel column and immediate chromatography (pentane/EtOAc-mixtures or toluene/EtOAc-mixtures) furnished the corresponding aldehyde **3a**: colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (br s, 1H), 7.36–7.24 (m, 5H), 5.43 (d, J = 8.0 Hz, 1H), 5.21 (d, J = 8.0 Hz, 1H), 4.22 (br s, 1H), 1.41 (s, 9H), 0.78 (s, 9H), −0.14 (s, 3H), −0.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 201.7, 155.2, 139.5, 128.7, 127.8, 126.6, 81.7, 80.3, 55.6, 28.5, 25.8, −5.1, −5.5; HRMS (ESI): calcd for [M+Na] ($C_{20}H_{33}NO_4SiNa$) requires m/z 402.2071, found 402.2074. The enantiomeric excess was determined by HPLC with an AD column *n*-hexane/*i*-PrOH = 98:2, λ = 220 nm), 0.5 mL/min; major enantiomer t_R = 16.6 min, minor enantiomer = 24.1 min; $[\alpha]_D^{25}$ −10.5 (*c* 1.0, $CHCl_3$).
14. *Typical experimental procedure*: To a stirred solution of imine **1a** (1.0 equiv, 0.25 mmol) and aldehyde **2b** (1.1 equiv, 0.27 mmol) in CH_3CN (1.0 mL) at room temperature was added (*R*)-proline (20 mol %). The reaction mixture was stirred vigorously for the reported time. Next, the reaction mixture was directly loaded on a silica-gel column, and immediate chromatography (pentane/EtOAc-mixtures or toluene/EtOAc-mixtures) furnished the corresponding aldehyde. *ent*-**3b**: colorless oil. ^{1}H NMR (400 MHz): δ 9.73–9.72 (m, 1H), 7.37–7.23 (m, 8H), 7.10–7.06 (m, 2H), 5.52 (br s, 1H), 5.24 (br s, 1H), 4.60 (d, J = 11.6 Hz, 1H), 4.39 (d, J = 11.6 Hz, 1H), 4.04 (br s, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz): 201.2, 155.2, 139.4, 136.7, 128.8, 128.7, 128.4, 128.3, 127.9, 126.8, 86.0, 80.3, 73.6, 54.3, 28.5; HRMS (ESI): calcd for [M+Na] ($C_{21}H_{25}NO_4Na$) requires m/z 378.1676, found 378.1671. The enantiomeric excess was determined by HPLC with an AD column (*n*-hexane/*i*-PrOH = 90:10, λ = 220 nm), 0.5 mL/min; major enantiomer t_R = 15.9 min, minor enantiomer = 28.2 min; $[\alpha]_D^{25}$ +29.0 (*c* 1.0, $CHCl_3$).
15. *Preparation of acid* **4b:** To a solution of *ent*-**3b** (0.1 mmol) in chloroform (1 mL), isobutene (0.1 mL), *tert*-butanol (0.4 mL), H_2O (0.2 mL), KH_2PO_4 (54.4 mg, 4.0 mmol), and $NaClO_2$ (36 mg, 4.0 mmol) were added sequentially at room temperature. After 16 h, the crude product was purified by column chromatography (pentane/EtOAc-mixtures) to afford 32 mg (85%) of the desired acid **4b**; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.19 (m, 8H), 7.04–7.00 (m, 2H), 5.80 (d, J = 8 Hz, 1H), 5.30 (d, J = 8.8 Hz, 1H), 4.70 (d, J = 10 Hz, 1H), 4.32 (d, J = 10 Hz, 1H), 4.20 (br s, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.4, 155.9, 139.5, 136.6, 128.8, 128.6, 128.2, 128.0, 127.8, 126.9, 80.6, 80.1, 73.2, 56.0, 28.5; HRMS (ESI): calcd for [M+Na] ($C_{21}H_{25}NO_5Na$) requires m/z 394.1625, found 394.1635. $[\alpha]_D^{25}$ +19.0 (*c* 1.0, $CHCl_3$).