One-pot synthesis of (R)-convolutamydine A involving in situ chiral organocatalyst formation

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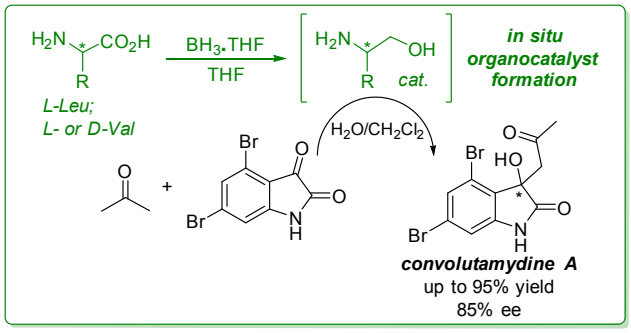
Abstract: The application of a convenient one-pot synthetic strategy, utilizing an *in situ* formed organocatalyst, to the enantioselective synthesis of anti-leukaemia agent *(R)-convolutamydine A* has been demonstrated.



Keywords: chiral drug synthesis, organocatalysis, one-pot reactions, amino alcohols, reduction, aldol reaction

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1 Introduction

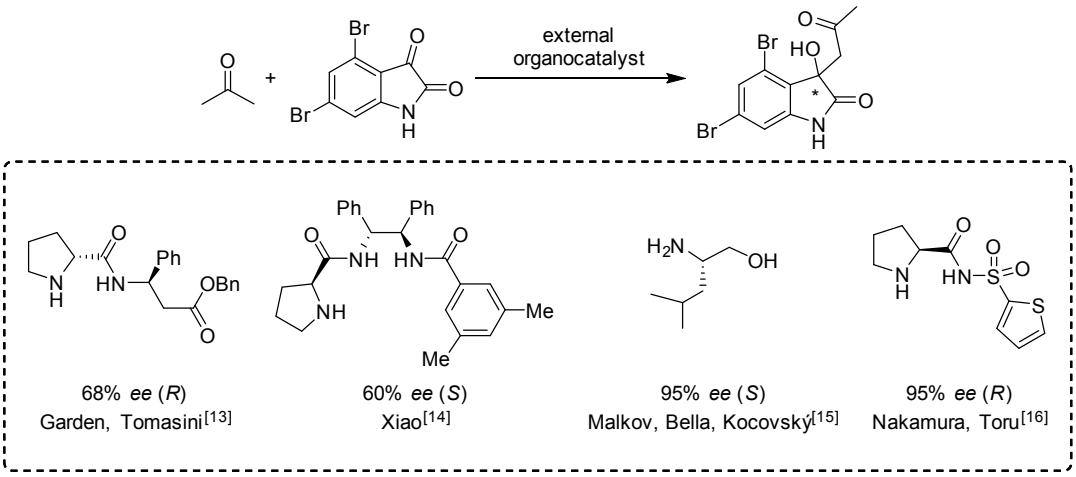
The combination of one-pot multi-step operations and organocatalysis is an elegant, economically attractive method, which has gained considerable attention in modern synthetic chemistry [1-10]. Such synthesis usually relies on the use of organocatalysts prepared in advance [5-10].

Recently, we disclosed a new one-pot synthetic approach employing organocatalysts, prepared *in situ* via one-pot transformations and subsequently used for enantioselective synthesis of 1,2-amino alcohol derived chiral drugs [11]. According to our new approach, not only the target chiral compound, but also the organocatalyst required for its enantioselective formation can be synthesized in a one-pot procedure without intermediate isolation or purification steps, leading to the reduction of costs, saving of materials, time, effort and contributing further to the sustainability of the one-pot process.

To extend this concept further and to demonstrate its generality, we present here the application of our approach to the synthesis of *convolutamydine A*, which involves a two-step one-pot sequence, namely *in situ* organocatalyst formation (through reduction of amino acids *L*-Leu **1a** or *L*-Val **1b** to catalytically active amino alcohols) and addition of acetone to 4,6-dibromoisatin. (*R*)-*Convolutamydine A* is a member of the oxindole subfamily, which exhibits a potent inhibitory activity on the differentiation of HL-60 human leukaemia cells [12].

The most convenient synthetic pathway towards enantiopure *convolutamydine A* is the direct aldol reaction of acetone with 4,6-dibromoisatin. Few chiral organocatalysts have been developed for the preparation of *convolutamydine A* using this aldol addition in moderate to high enantioselectivities (Scheme 1) [13-16].

Nonetheless, the reported synthetic methodologies towards *(R)-convolutamydine A* employ external organocatalysts (Scheme 1), prepared in advance which require isolation and purification. To meet the basic needs of the pharmaceutical chemistry, synthetic methods towards synthesis of chiral drugs must be simple, straightforward



Scheme 1: Known chiral organocatalysts for the aldol reaction of acetone with 4,6-dibromoisatin.

and environmentally friendly [17]. Thus, finding a new facile and direct access to (*R*)-*convolutamydine A* under mild reaction conditions and without intermediary workup and purification steps is highly attractive.

2 Results and Discussion

Following our previous work on organocatalytic aldol reactions[18,19] and applying our expertise in the research fields of the organocatalytic construction of quaternary carbon centers[20-22] we decided to study the direct aldol reaction of acetone with 4,6-dibromoisatin.

Since amino alcohols **2a** and **2b** have already been reported by one of us as active external catalysts for the aldol addition of acetone to 4,6-dibromoisatin (entries 1 and 2, Table 1) [15], we were interested in exploring whether selected amino alcohols **2c-2f** would perform as well as or even better than catalysts **2a** and **2b** in the same aldol addition. Reactions were run at room temperature in CH_2Cl_2 under conditions employing 20 mol% of amino alcohols and water (100 mol%) as an additive (Table 1). The use of (*S*)-proline derived catalyst **2c** gave the *S*-configured product in high yield (93%), but with only 4% ee (entry 3).

Interestingly, without water additive the carene derived catalyst **2d** provides the (*S*)-*convolutamydine A* with 44% yield and 51% ee (entry 4), while addition of 100 mol% of water additive leads to the opposite enantiomer (*R*)-*convolutamydine A* with 23% yield and 13% ee (entry 5). It seems that the enantioselectivity of the monoterpene based catalyst **2d** can be reversed in the presence of water additive. Further studies are required to obtain more insight into the observed unusual switch in the enantioselectivity. Notably, in 2011 Wennemers and co-workers reported another intriguing example of reversal of enantioselectivity by changing the nature of the reaction medium in the tripeptide catalyzed aldol reaction of cyclohexanone and 4-nitrobenzaldehyde [23].

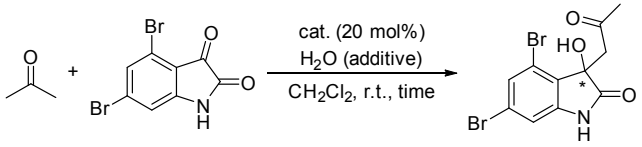
Next, application of two diastereoisomeric amino alcohols **2e** and **2f** gave the same *R*-configured product with similar results (entries 6 and 7, Table 1) regarding yields (90% und 98%, respectively) and enantioselectivities (77% ee and 78% ee, correspondingly). These observations demonstrate that the dominating influence on the absolute configuration of the resulting product *convolutamydine A* resides in the stereogenic carbon center of the chiral catalyst adjacent to the amine group. These results also suggest the involvement of enamine activation mechanism.

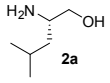
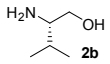
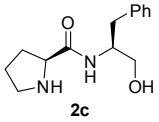
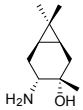
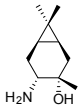
Thus, under the same reaction conditions catalysts **2c-2f**, as alternatives of **2a** and **2b**, promoted a less-stereoselective aldol transformation to afford the *S*- or *R*-configured *convolutamydine A* (entries 3-7 *vs.* entries 1 and 2, Table 1). Therefore, chiral amino alcohols **2a** and **2b** were selected as catalysts for further studies. Commercially available and cheap amino acids *L*-Leu **1a** and *L*-Val **1b** were used as starting materials for the *in situ* formation of selected chiral organocatalytic amino alcohols *L*-leucinol (**2a**) and *L*-valinol (**2b**).

For *in situ* generation of the corresponding vicinal amino alcohols (Table 2), we decided to apply previously optimized borane reduction of the amino acids employing BH_3-THF (1.5 equiv.) in THF under reflux conditions [11]. No racemisation of the corresponding amino alcohols **2a** and **2b**/**2b'** was observed under the selected reaction conditions.

Starting with *L*-Leu **1a** and carrying out the proposed one-pot reaction without any additive, we isolated the product, *convolutamydine A* in 30% yield in racemic

Table 1: Synthesis of convolutamydine A using external chiral amino alcohols as catalysts.



Entry	Catalyst	Water additive (mol%)	Time, h [a]	Yield (%)[b]	ee (%)[c]
1[d]	 **2a**	100	36	98	95 (*S*)
2[d]	 **2b**	100	36	84	95 (*S*)
3	 **2c**	100	48	93	4 (*S*)
4	 **2d**	0	36	44	51 (*S*)[e]
5	 **2d**	100	48	23	13 (*R*)[f]
6	 **2e**	100	144	90	77 (*R*)
7	 **2f**	100	48	98	78 (*R*)

[a] Reaction time required for complete conversion. [b] Yields of isolated products. [c] Determined by chiral phase HPLC analysis and compared with authentic racemic material. [d] Yields and ee-values have been previously reported [15]. [e] $[\alpha]_D$ = +25.2 (*c* 0.29, MeOH). [f] $[\alpha]_D$ = -6.36 (*c* 0.015, MeOH).

form (entry 1, Table 2). Further optimisation of the two-step one-pot sequence revealed the necessity of presence of water as an additive in the aldol reaction step. Increasing the amount of water led to improved yield and enantioselectivity of *(S)-convolutamydine A* (Table 2). We found that the addition of 5.0 equiv. of water resulted in 84% yield and 80% enantioselectivity (entry 4, Table 2) after a relatively short reaction time.

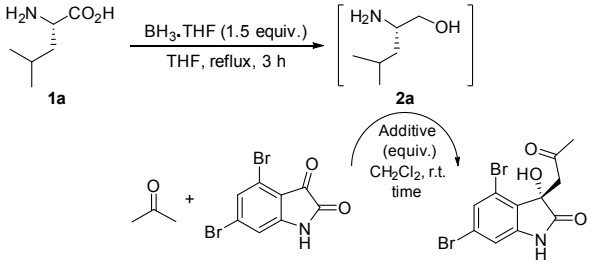
Interestingly, larger amounts of water (e.g., 208.0 equiv.) resulted in decreased yield without loss of selectivity (65%, 85% ee, Table 2, entries 5-7).

Notably, a plausible transition state model was suggested for this aldol reaction catalyzed by external leucinol [15], which fits well with the experimental data, but does not include an explicit molecule of water. Therefore, it can be reasoned, that the presence of water in our one-pot reaction leads to an increase in the active catalyst **2a** concentration, facilitating the enamine mechanism proposed previously [15]. Indeed, water might favour the release of the catalytically active free 1,2-amino

alcohol **2a** from the oxazaborolidine intermediate, which could be formed after the reduction step.

The decrease of reaction selectivity and yield at very high levels of water may be due to interference of water molecules with the hydrogen bond between the OH-group of the catalyst and the keto group of dibromoisatin in the transition state. This agrees with the decrease of selectivity observed in protic solvents like methanol [15].

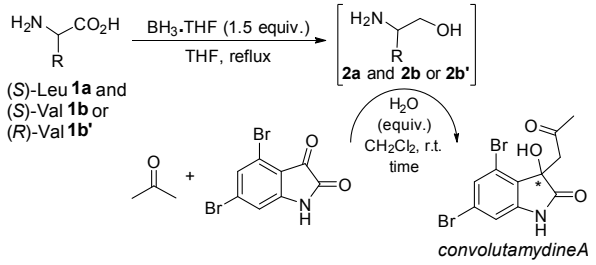
Table 2: Pre-optimisation of reaction conditions for one-pot synthesis of convolutamydine A.



Entry	Additive (equiv.)	Time, h	Yield (%)[a]	ee (%)[b] (S)
1	-	36	30	rac
2	H_2O (1.0)	24	70	75
3	H_2O (3.0)	36	60	79
4	H_2O (5.0)	18	84	80
5	H_2O (7.0)	18	79	85
6	H_2O (9.0)	18	75	80
7	H_2O (208.0)	18	65	85

[a]Yields of isolated products. [b]Determined by chiral phase HPLC analysis and compared with authentic racemic material.

Table 3: One-pot organocatalyst / convolutamydine A sequential synthesis.



Entry	Amino acid	Time, h	Yield (%)[a]	ee (%)[b]
1	(*S*)-Leu **1a**[c]	18	84	80 (*S*)
2	(*S*)-Leu **1a**[c]	18	80	75 (*S*)
3	(*R*)-Val **1b'**[d]	18	95	70 (*R*)
4	(*S*)-Val **1b**[d]	18	82	77 (*S*)
5	(*R*)-Val **1b'**[d]	16	92	73 (*R*)

[a]Yields of isolated products. [b]Determined by chiral phase HPLC analysis and compared with authentic racemic material. [c]Reduction of **1a** under reflux for 3 h. [d]d Reduction of **1b** and **1b'** under reflux for 17 h.

Based on the pre-optimisation with *L*-leucine shown in Table 2, we next studied the reproducibility of the two-step one-pot synthesis using two different amino acids, namely *L*-leucine **1a** and *D*-valine **1b'**. In general, *L*-amino acids preferentially afford the (*S*)-enantiomer (entries 1, 2 and 4, Table 3), while *D*-amino acids (e.g. (*R*)-**1b'**, entries 3 and 5) gave the desired (*R*)-configured *convolutamydine A*.

Consequently, we optimized the synthesis of the natural product *convolutamydine A* in a one-pot reaction over two steps. We obtained the product in reproducible high yields and good *ee*-values (80-95% yields and 73-80% ees, entries 1-5, Table 3). Leucine **1a** gave better *ee*-values than valine **1b**. Further improvement of the ee-values of *convolutamydine A* with respect to the value determined directly from the crude reaction mixture should be possible by means of crystallization [15].

3 Conclusions

In summary, the synthesis of an anti-leukaemia agent *convolutamydine A* via a two-step one-pot transformation involving *in situ* chiral organocatalyst formation from commercially available inexpensive starting materials (α-amino acids) has been investigated. The advantages of such one-pot reactions are the reduction of work-up and purification steps, resulting in lower costs, material and labor input, which makes the multi-step sequential synthesis even more efficient, atom economical and environmentally friendly.

4 Experimental Section

4.1 General

Solvents were purified by standard procedures and distilled prior to use. Reagents purchased from commercial sources were used without further purification. TLC chromatography was performed on pre-coated aluminium silica gel ALUGRAM® SIL G/UV254 plates (Macherey-Nagel GmbH&Co.). Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on *Bruker Avance 400 NMR* spectrometer using the solvent as internal standard. The enantiomeric excess of products was determined by chiral HPLC analysis (using chiral column: Daicel Chiralpak IA) in comparison with authentic

racemic material. HPLC measurements were performed using Agilent Technologies 1200 Series equipment. A PerkinElmer 341 polarimeter was used for optical rotation measurements.

4.2 One-pot procedure for the synthesis of (*R*)-convolutamydine A:

To a stirred solution of *D*-Valine (32 mg, 0.27 mmol) in dry THF (0.41 mL) at 0°C, was added BH_3·THF (0.41 mL, 1.0 M in THF) via syringe. The reaction mixture was then stirred for 17 h under reflux. The conversion was followed by TLC. The reaction mixture was cooled to room temperature and CH_2Cl_2 (6.57 mL) and water (5 equiv., 0.086 mL) were added slowly, After 1 minute, 4,6-dibromoisatin (1 equiv., 0.96 mmol, 290.73 mg) and acetone (30 equiv., 28.2 mmol, 2.11 mL) were then added. The reaction mixture was stirred at room temperature for additional 16 h, and was then washed with water and dried over Na_2SO_4. The organic solvents were removed under reduced pressure and the residue was purified by flash chromatography on SiO_2 (ethyl acetate / petrolether 1:1) to give (*R*)-convolutamydine A as a white solid (317 mg, 92% yield, 73% ee).

The enantiomeric excess was determined by chiral HPLC analysis (Daicel Chiralpak IA column, λ = 210 nm, mobile phase n-hexane/*i*PrOH 85:15, flow 0.95 mL/min). $[\alpha]^{25}_{D}$ +43.9 (*c* 0.33, MeOH) [lit. [15] +48.9 (*c* 0.33, MeOH)]; ^{1}H NMR (300 MHz, DMSO-d6): δ = 2.03 (s, 3H), 3.12 (d, *J* = 16.8 Hz, 1H), 3.76 (d, *J* = 17.7 Hz, 1H), 6.22 (br s, 1H, OH), 6.94 (d, *J* = 1.2 Hz, 1H), 7.28 (d, *J* = 1.2 Hz, 1H), 10.64 (s, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d6): δ = 205.3, 177.3, 146.4, 128.7, 126.7, 122.4, 119.6, 111.8, 73.7, 48.3, 30.0 ppm; $IR_{(neat)}$: ν = 3313, 3226, 1703, 1605, 1578, 1432, 1358, 1317, 1166, 1076, 845, 677 cm^{-1}. MS (MALDI) spectrum showed molecular ions $[M+Na]^+$ at m/z 384, 386 and 388 respectively $[M+K]^+$ at m/z 400, 402 and 404 in the ratio 1:2:1.

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