ORGANIC LETTERS

2011
Vol. 13, No. 14
3678–3681

Asymmetric Organocatalytic Synthesis of Complex Cyclopenta[*b*]quinoline Derivatives

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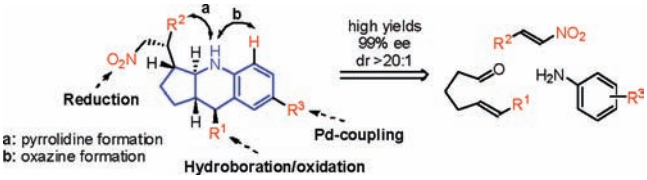
Received May 17, 2011

ABSTRACT



An efficient one-pot procedure that provides a direct access to polycyclic hexahydrocyclopenta[*b*]quinoline derivatives having five stereogenic centers has been developed. The system displays great tolerance toward different aldehydes, anilines, and nitroalkenes. The products are obtained in high yields and excellent enantio- and diastereoselectivities.

Multicomponent reactions have the potential to provide the high molecular diversity needed in the combinatorial approaches for the preparation of bioactive compounds.[1] In recent years, asymmetric organocatalytic domino and cascade reactions have been utilized for the synthesis of complex enantiomerically enriched molecules having multiple stereocenters.[2] In comparison to traditional stepwise approaches, the uninterrupted sequence of reactions in one flask reduces the number of manual operations, thereby saving time, effort, and production costs.

Nitrogen-containing heterocycles form an indispensible class of compounds, which are important in the fields of biochemistry, pharmaceutics, and material science.[3] Among these, the hexahydro-cyclopenta[*b*]quinoline core[4] is a virtually unexplored structure that is found in natural products such as isoschizogaline and isoschizogamine[5] as well as steroid alkaloids (Figure 1).[6]

The cyclopenta[*b*]quinoline core structure may be accessed *via* an intramolecular aza-Diels–Alder reaction

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10.1021/ol201328s
Published on Web 06/10/2011

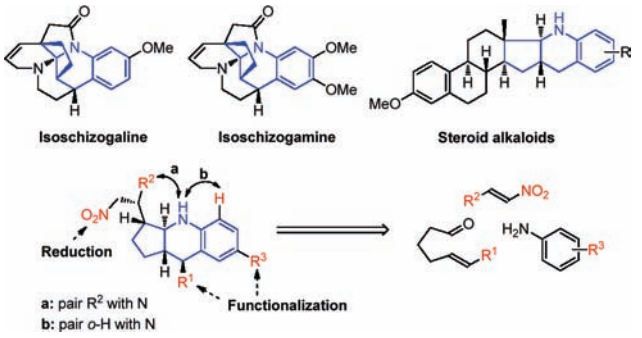


Figure 1. Synthetic outline for the formation of cyclopenta[*b*]quinoline derivatives and possible sites of modification.

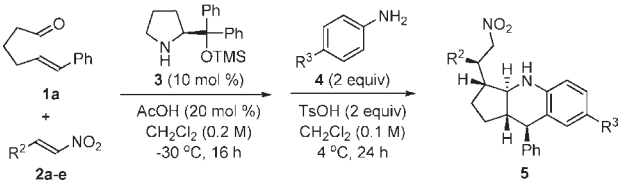
from a δ,ε-unsaturated aldehyde. Upon condensation with an aniline derivative, the resulting intermediate will undergo a cycloaddition/rearomatization (the Povarov reaction)[7] sequence, affording the tricycle.[2n] To the best of our knowledge, no catalytic, asymmetric approaches to these interesting and important N-heterocyclic structures have been described to date. Therefore, we imagined a route (Figure 1), in which the introduction of a stereocenter in the α-position of the aldehyde utilizing aminocatalysis would provide a suitable intermediate for the following condensation/cyclization cascade. Ideally, the initially formed stereocenter would direct the subsequent cycloaddition, thereby controlling the formation of the optically active cyclopenta[*b*]quinoline with high enantio- and diastereoselectivity.

We envisioned that employment of nitroalkenes in the initial organocatalytic step would furnish structures that allow for further expansion of molecular complexity and diversity by selective functional group manipulations. For example, reduction of the nitro group, and functionalizations at R^1 and R^3, depending on the chosen substituents at these positions, should be possible. Furthermore, selective pairing of the R^2 substituent and the aniline nitrogen could furnish a tetracyclic alkaloid structure, whereas pairing of the nitrogen with the *ortho*-hydrogen in another hetero-Diels–Alder reaction could afford a differently constructed polycyclic scaffold.

Herein, we present a simple and straightforward asymmetric strategy to provide cyclopenta[*b*]quinoline derivatives with high yields and excellent stereoselectivities. The procedure applies simple starting materials under mild reaction conditions, and significant possibilities for further structural diversification are demonstrated by various transformations.

We initiated our studies by performing the initial Michael reaction between (*E*)-6-phenylhex-5-enal (**1a**) and nitroalkene **2a**. The reaction was conducted employing

Table 1. Aniline and Nitroalkene Scope for the Formation of **5**[a]



entry	R^2	R^3	yield (%)[b]	ee (%)[c]	dr[d]
1	Ph	H	**5a** - 82	99	>20:1
2	Ph	Br	**5b** - 72	99	>20:1
3	Ph	NO_2	**5c** - 75	99	>20:1
4	Ph	CO_2Et	**5d** - 83	99	>20:1
5	Ph	COMe	**5e** - 70	99	>20:1
6	Ph	Me	**5f** - 79	99	>20:1
7	Ph	OMe	**5g** - 79	99	>20:1
8	4-Br-C_6H_4	H	**5h** - 85	99	>20:1
9	4-OMe-C_6H_4	H	**5i** - 66	99	>20:1
10	3-NO_2-C_6H_4	H	**5j** - 75	99	>20:1
11	2-Cl-C_6H_4	H	**5k** - 73	99	>20:1
12	2-furanyl	H	**5l** - 78	99	19:1
13[e]	CO_2Me	H	**5m** - 73	99	19:1

[a] For reaction conditions, see Supporting Information. [b] Yield after flash chromatography. [c] Determined by HPLC on a chiral stationary phase. [d] Determined by ^1H NMR spectroscopy of the crude reaction mixture after workup. [e] 20 mol % of catalyst was employed.

10 mol % of (*S*)-2-(diphenyl(trimethylsilyloxy)methyl)-pyrrolidine **3**[8] in CH_2Cl_2 at −30 °C, and after 16 h full and clean conversion to the Michael adduct was observed (dr > 20:1).[2j] The anticipated condensation/cycloaddition reaction was then evaluated by treating the adduct with aniline in the presence of TFA, which afforded the desired product **5a** with full conversion as an 87:13 mixture of diastereoisomers.[9] In order to achieve a higher selectivity in the cyclization step a series of Brønsted acids were investigated. (+)-CSA and TsOH afforded the product in excellent diastereoselectivity (dr > 20:1); however, full conversion was not achieved at −30 °C. By increasing the temperature to 4 °C and employing TsOH the product was isolated in 82% yield and with excellent stereoselectivities (99% ee and dr > 20:1). With these conditions in hand, the generality of the reaction was investigated (Table 1).

The developed reaction concept displayed great tolerance toward a number of aniline derivatives. All the reactions evaluated gave full conversion to the products **5a**–**g** with high yields ranging from 83 to 70% and excellent stereoselectivities (99% ee and > 20:1 dr). The electronic nature of the aniline had little effect on the reaction outcome as both electron-poor (Table 1, entries 2–5) and electron-rich (Table 1, entries 6–7) anilines were

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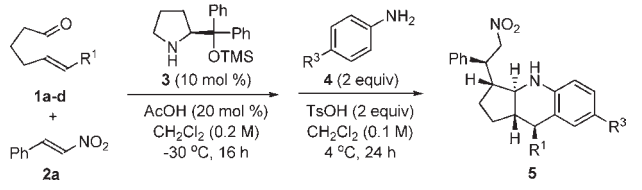
(9) The Michael adduct **12** epimerizes via iminium-ion-enamine tautomerization prior to the aza-Diels–Alder reaction; see Supporting Information.

successfully applied. Interestingly, no side products were observed when 4-aminoacetophenone was employed (entry 5), despite the presence of a ketone functionality. When the reaction was attempted using 4-ethynylaniline, hydration of the alkyne during workup afforded the ketone product **5e**.

Further examination of the reaction scope focused on the nitroalkene part, and a series of cyclopenta[*b*]quinoline derivatives were synthesized from neutral aniline **4a** in good yields (85−66%) and excellent enantioselectivities (99% ee). In general, the position and electronic properties of the aromatic ring had little or no effect on the outcome (Table 1, entries 8−11). Nitroalkenes bearing furanyl and ester moieties were also investigated affording the products with slightly reduced diastereoselectivities (19:1) arising from the initial organocatalyzed Michael reaction (Table 1, entries 12−13).

Next, a series of aldehydes were evaluated in combination with (*E*)-(2-nitrovinyl)benzene (**2a**) and different aniline derivatives (Table 2). Aldehydes with methyl- and bromo-substituents in the *para*-position were successfully applied affording good to high yields (55−79%) and excellent stereoselectivities (99% ee and dr >20:1). Furthermore, a vinyl substituted aldehyde could be implemented, furnishing products **5s**−**u** in good yields with excellent enantio- and diastereoselectivities (Table 2, entries 6−8). The vinyl group is a useful moiety for further functionalization of the products.

Table 2. Aldehyde and Aniline Scope for the Formation of **5**[a]



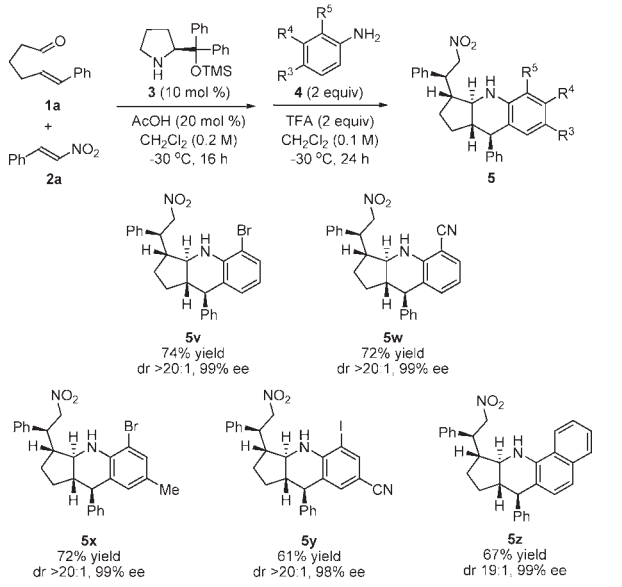
entry	R^1	R^3	yield (%)[b]	ee (%)[c]	dr[d]
1	4-Me-C_6H_4	H	**5n** - 79	99	>20:1
2	4-Me-C_6H_4	Br	**5o** - 77	99	>20:1
3	4-Me-C_6H_4	NO_2	**5p** - 55	99	>20:1
4	4-Br-C_6H_4	H	**5q** - 69	99	>20:1
5	4-Br-C_6H_4	CO_2Et	**5r** - 73	99	>20:1
6	vinyl	H	**5s** - 76	99	>20:1
7	vinyl	Br	**5t** - 67	99	>20:1
8	vinyl	CO_2Et	**5u** - 72	99	19:1

[a] For reaction conditions, see Supporting Information. [b] Yield after flash chromatography. [c] Determined by HPLC on a chiral stationary phase. [d] Determined by ^1H NMR spectroscopy of the crude reaction mixture after workup.

To further evaluate the methodology, a number of anilines with different substitution patterns were studied. Disappointingly, when *ortho*-bromoaniline **4h** was submitted to the developed reaction conditions using TsOH as the Brønsted acid, compound **5v** was obtained as a 4:1 mixture of diastereoisomers. This prompted us to study different acids, and to our delight, the product **5v** could be obtained as a single diastereoisomer in 74% yield (99% ee) when TFA was employed at −30 °C (Scheme 1). *ortho*-Cyanoaniline and two disubstituted anilines were successfully applied affording the products **5w**−**y** in good yields (72−61%) and excellent stereoselectivities (≥98% ee and dr >20:1). Finally, 1-aminonaphthalene was studied and, interestingly, TsOH gave the better result furnishing the product in 67% yield with good selectivities (99% ee, dr 19:1).

To demonstrate the synthetic utility of this protocol a number of transformations leading to more complex polycyclic structures were performed (Scheme 2). Treating **5b**,**5f** with formaldehyde in the presence of TFA resulted in condensation between the aniline and formaldehyde followed by a hetero-Diels−Alder/rearomatization sequence to yield two tetracyclic oxazine products **6** and **7** in 75% yield. When compound **5m**, having a methyl ester moiety as R^2, was subjected to borane, a reductive cyclization occurred, forming pyrrolidine product **8** in 74% yield, hereby creating a different tetracyclic alkaloid scaffold. The vinyl substituent in compound **5t** enables the introduction of various new functionalities, exemplified by the conversion into a primary alcohol **9** *via* a hydroboration−oxidation reaction in 64% yield. Furthermore, a Suzuki coupling was performed introducing a phenyl substituent on the cyclopenta[*b*]quinoline core structure in 82% yield.

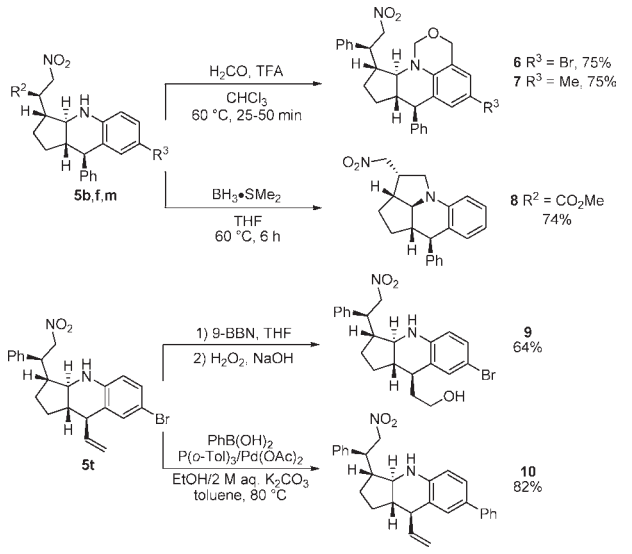
Scheme 1. Examples of *Ortho*- and Di-Substituted Anilines[a]



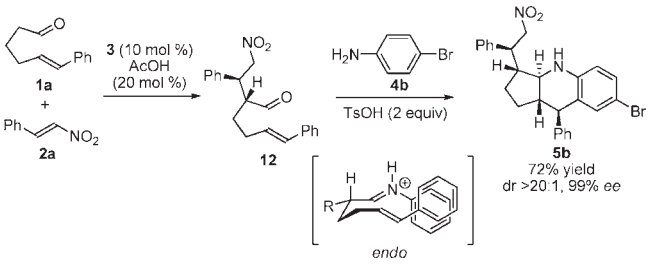
[a] **5z** was synthesized employing TsOH.

Finally, reduction of the nitro group with Zn/AcOH was achieved on **5k** in quantitative yield (not shown; see Supporting Information). These transformations clearly show the diverse possibilities of scaffold and functional group manipulations allowing access to structurally more complex molecules.

Scheme 2. Functionalization of the Cyclopenta[*b*]quinoline Derivatives



Scheme 3. Rationalization of Observed Stereochemistry



The absolute stereochemistry was unambiguously established by X-ray crystallography of compound **5b**.[10] A rationale for the observed stereochemistry is presented in Scheme 3. The initial Michael addition product **12** is formed with high *syn*-selectivity. The diastereoselectivity of the following cyclization can be explained by an *endo*-transition state. The intermediate adopts a conformation in which the substituent of the α-stereocenter is placed in a *pseudo*-equatorial position dictating the formation of the *trans*-product.

In conclusion, we have developed an efficient one-pot procedure that provides a direct access to almost enantiopure polycyclic hexahydrocyclopenta[*b*]quinoline derivatives having five stereogenic centers. The system displays great tolerance toward different aldehydes, anilines, and nitroalkenes. The synthetic usefulness of the products was demonstrated through a number of transformations introducing increased molecular complexity. The strategy might also be implemented for the construction of the corresponding cyclohexa-[*b*]quinoline derivatives (octahydroacridines) by extension of the aldehyde carbon chain. Furthermore, the compounds accessed by the described protocol could eventually demonstrate their usefulness in medicinal chemistry.

(10) See Supporting Information for crystal structure. CCDC 822137 (**5b**) contains the supplementary data for this paper.

Acknowledgment. This work was made possible by grants from OChemSchool (K.A.J.) and the Carlsberg Foundation (K.A.J.). Thanks are expressed to Dr. Jacob Overgaard for performing X-ray analysis.

Supporting Information Available. Detailed experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.