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Amine-mediated tandem conjugative isomerization-bridging Michael addition: concise synthesis of 1-azabicyclo[3.3.1]nonanes

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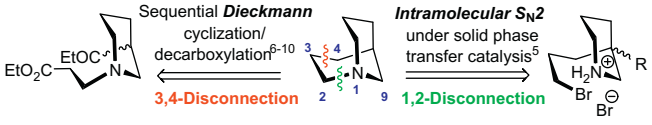
ABSTRACT

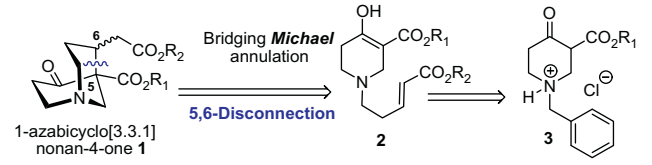
To reach densely functionalized 1-azabicyclo[3.3.1]nonane frameworks synthesis, a stereocontrolled bridging Michael addition involving an unexplored C-5/C-6 disconnection strategy was studied. 1-Azabicyclo[3.3.1]nonane scaffolds have been diastereoselectively elaborated in fairly good yields by two concise pathways implying pyrrolidine derivative organocatalyst or enantiopure 1-phenylethylamine.

Cinchona alkaloids represent the most famous example of polyfunctionalized 1-azabicyclic frames that are widely found in unnatural as well as natural biologically active compounds.[1–3] During the past decade, 1-azabicycloalkanes (so-called 'cage amines') have mobilized considerable attention of medicinal chemists notably in the design and synthesis of neuronal nicotinic acetylcholine receptor (nAChR) subtype-selective ligands.[3] In the context of developing new treatments of psychotic and neurodegenerative disorders including nicotine addiction, autism, schizophrenia and Parkinson and Alzheimer diseases, hetero-aromatic substituted 1-azabicyclo[3.3.1]nonanes have been recently prepared as nAChR-α7 subtype-selective ligands.[4,5] Therefore, intense efforts have been engaged in developing general synthetic routes to aza-bridged azabicyclic skeletons.[3]

In contrast to more constrained 1-azabicycloalkanes such as quinuclidine, the higher [3.3.1] homologues have been much less studied. A literature review underlines the lack of common methods for their synthesis and, to our knowledge, only two strategies have been exemplified until now (Scheme 1). Kohn and co-workers described the preparation of parent 8-substituted aza-bridged [3.3.1]bicyclic amines using a Dieckmann cyclization as the key step.[6] This Dieckmann route was firstly reported in 1952 by Sternbach and Kaisern.[7] Later, Martell,[8] Halpern,[9] King[10] and Feuerbach[4b] related the preparation of 1-azabicyclo[3.3.1]nonan-3-one derivatives according to the same strategy. More recently, Slowinski proposed an alternative multi-step sequence for the synthesis of bridgehead-substituted 1-azabicylo[3.3.1]nonanes: the azabicyclic



Scheme 1. Two main strategies for azabicyclo[3.3.1]nonane scaffold synthesis.



Scheme 2. 1-Azabicyclo[3.3.1]nonanone retrosynthesis through unexplored C(5)/C(6)-disconnection.

skeleton was built at the late stages by an intramolecular nucleophilic substitution using solid phase-transfer catalysis.[5b,c]

These two main strategies gave monosubstituted 1-azabicyclo-[3.3.1]nonanes without stereoselectivities.

Our group has earlier described the stereocontrolled synthesis of quinuclidine nucleus through asymmetric bridging annulation of chiral β-enamino ester derived from (*S*)-phenylethylamine.[11] In addition, whilst a resurgence of interest in organocatalysed Michael reaction, the synthesis of highly functionalized 1-azabicyclo[3.3.1]nonan-3-ones **1** through a stereoselective bridging Michael addition involving a C(5)/C(6)-disconnection remains still

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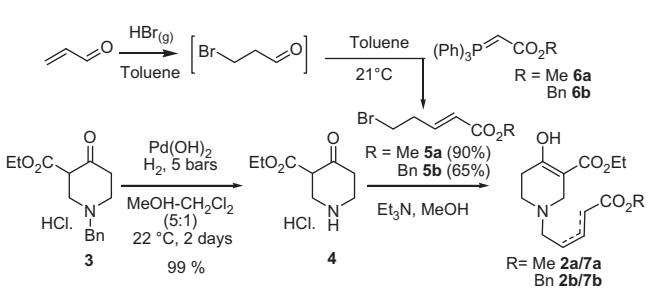
unexplored (Scheme 2). Indeed, over the last decade, a consistent theme among the catalytic amine-mediated conjugate addition was concentrated to the development of its intermolecular version.[12] To the best of our knowledge, the intramolecular process has received much less attention and the main investigations in this area were reported for the 1,4-addition of enols derived from aldehydes as reactive nucleophiles to potent electrophilic Michael acceptors such as enals, enones, vinylsulfones or alkylidene malonates.[13]

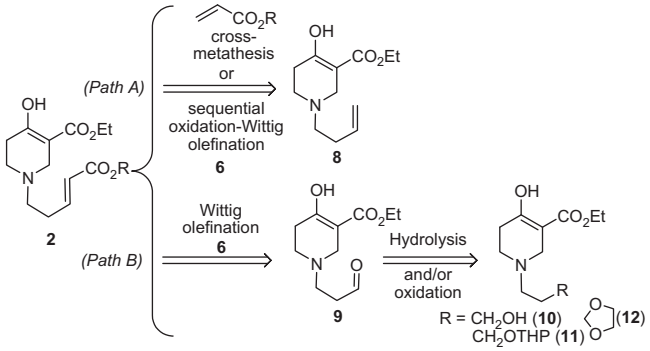
In this context, we envisaged to expand the scope of amine-mediated intramolecular Michael addition by studying the challenging construction of 1-azabicyclo[3.3.1]nonane frameworks via a bridging conjugate addition of the less nucleophilic β-ketoester moiety to the deactivated α,β-unsaturated ester as the electrophilic alkene. Amine-catalysed intramolecular Michael addition implying these both weakly reactive partners has never been studied up till now and still remains a great challenge. Indeed, an organocatalysed procedure will provide a particular attractive method for the synthesis of highly functionalized products in both step- and atom-economical manner (Scheme 2).

In the first part of this current work, considerable efforts have been made to optimize the synthesis of the cyclization precursors **2a** (methylester) and **2b** (benzylester) (Scheme 3). Their preparation was performed from the commercially available N-benzylated piperidin-4-one hydrochloride **3** (Scheme 3). The latter was first hydrogenolysed in the presence of Pearlman catalyst to afford the piperidin-4-one hydrochloride **4** in quantitative yield.[11] The following step was first envisaged through direct alkylation of the piperidine nitrogen-base by methyl or benzyl (*E*)-5-bromo-2-pentenoate **5a** or **5b**.[14] The latter have been prepared in excellent 90% and 65% yields, respectively with an exclusive *E*-selectivity according to a one-pot two-step procedure. This strategy involves in situ generation of 3-bromopropanal followed by Wittig olefination with methyl or benzyl (triphenylphosphoranylidene)acetates **6a** or **6b** respectively.[15] Under standard basic conditions, N-alkylation step afforded in poor yields a mixture of the expected precursor **2a** or **2b** as the minor product accompanied by its deconjugate isomer **7a** or **7b**, respectively (Scheme 3).

Next, confronted to this undesired deconjugation reaction, numbers of alternative synthetic routes have been explored and are summarized in the retrosynthetic Scheme 4. Piperidinone **4** has been alkylated by 4-bromo-but-1-ene in 75% yield (Scheme 4-Path A). The corresponding *N*-homoallyl derivative **8** has been then fruitlessly engaged in different synthetic sequences such as (1) cross-metathesis in the presence of titanium isopropylate and Grubbs II or Grubbs-Hoveyda catalyst;[16] (2) cross-metathesis in the presence of both previous catalysts from piperidine firstly quartenarized by the action of benzylbromide;[17] (3) oxidative cleavage (ozonolysis or OsO_4–$NaIO_4$[18]) followed by Wittig olefination using **6a** or **6b** (Scheme 4—Path A). Starting material was recovered unchanged except in the oxidative cleavage in which



Scheme 3. Synthesis of cyclization precursors.



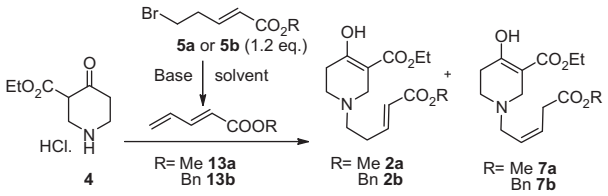
Scheme 4. Synthetic routes explored to prepare precursors **2**.

only degradation products were obtained. Degradation may be explained by the competitive oxidative cleavage of the enol ester function borne by the piperidine moiety. For this reason, preparation of the Wittig olefination precursor has been attempted by different strategies. Piperidinone **4** has been successfully alkylated by 2-(2-bromoethyl)-1,3-dioxolane, 3-bromopropoxy-tetrahydro-2*H*-pyran and 3-bromopropan-1-ol in roughly 70% yields (Scheme 4—Path B—compounds **12**, **11** and **10**). Nevertheless, neither acidic dioxolane cleavage of **12** nor oxidation of propanol derivative **10** followed or not by trapping with Wittig reagent allowed the respective access to the aldehyde intermediate **9** or to precursor **2** (Scheme 4—Path B). Only degradation has been observed. These results can be explained by the instability of the β-amino-aldehyde intermediate **9** that may auto-condense through aldolization or that may undergo retro-Michael reaction.

Due to these unsatisfactory results, the firstly envisaged N-alkylation procedure using 5-bromo-2-pentenoate **5** has been revisited. That was also sustained by the fact that the target compound **2** and its deconjugate isomer **7** were gratifyingly separated by flash chromatography on silica gel. The N-alkylation reaction was then followed by ^{1}H NMR: examination of the crude reaction mixture spectrum revealed the formation of alkyl penta-2,4-dienecarboxylate **13** resulting from base-mediated dehydrobromination of **5**.[19,20] As already known, N-alkylation proceeded, de facto, by an aza-1,6-conjugate addition producing both α,β- and β,γ-unsaturated adducts **2** and **7**, respectively:[21] the β,γ-unsaturated compounds **7** result from kinetic protonation of the intermediary enolate.[21b] To improve the reaction efficiency, solvent and base effects were explored and the more significant results were summarized in Table 1.

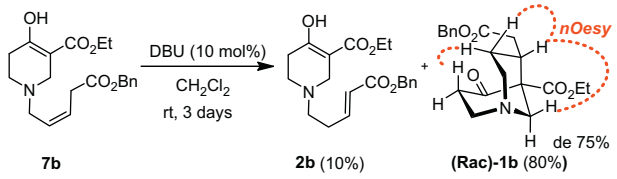
It was shown that reaction proceeded in poor yields using potassium carbonate or triethylamine considered separately (entries 1–4). Partial transesterification of the benzyl ester moiety occurred using methanol as the solvent (entry 1). Reactions performed at 25 °C using DMF were found optimal (entries 6–7). Modest yields of this N-alkylation reaction are explained by direct bridging annulation side-reaction of compound **2** occurring under basic conditions. Indeed, trials of DBU-catalysed conjugative isomerization[21d] of β,γ-unsaturated ester **7b** furnished the targeted α,β-unsaturated isomer **2b** in 50% yield after one day of reaction, accompanied by 10% of the Michael adduct **1b**. Prolonged reaction time (3 days) effected cyclization and led in excellent 85% yield a racemic mixture of 1-azabicyclononane **1b** with good diastereomeric excess (de 75%) measured by ^{1}H NMR (Scheme 5). The relative configuration of the major diastereomer **1b** was ascertained by 2D and NOESY NMR experiments (Scheme 5 and Supplementary data). Similar results of tandem conjugative isomerization-bridging Michael cyclization were observed starting from a mixture **7a**/**2a** or **7b**/**2b** in terms of selectivity and rate.

Table 1
Optimization of piperidin-4-one N-alkylation[a]

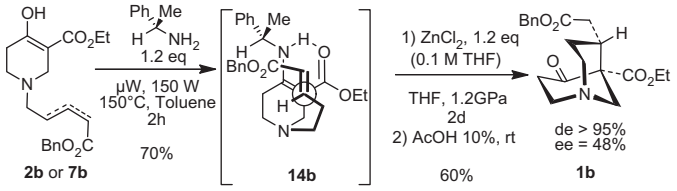


Entry	Base[a]	5	Solvent *T* (°C), t (d)	Yield[b] (%)
1	K_2CO_3 5 equiv	**5b**	MeOH 25 °C, 2d	**7a** (20)
2	K_2CO_3 5 equiv	**5b**	CH_2Cl_2/THF (1/1) 24 °C, 2d	**2b**/**7b** (10/10)
3	K_2CO_3 5 equiv	**5b**	AcCN/THF (3/1) 50 °C, 3d	—
4	Et_3N 6 equiv	**5b**	CH_2Cl_2/THF (2/1) 24 °C, 3d	**7b** (30)
5	K_2CO_3 5 equiv + *i*Pr_2Net 3 equiv	**5b**	CH_2Cl_2/THF (1/1) 24 °C, 3d	—
6	K_2CO_3 1,5 equiv + Et_3N 5 equiv	**5a**	DMF 24 °C, 7d	**7a**/**2a** (42/33)
7	K_2CO_3 1,7 equiv + Et_3N 3,6 equiv	**5b**	DMF 24 °C, 7d	**7b**/**2b** (40/32)

[a] The reaction was carried out starting from a molar solution of piperidin-4-one hydrochloride **4**.
[b] Isolated yield.



Scheme 5. DBU-induced tandem conjugative isomerization-bridging annulation.



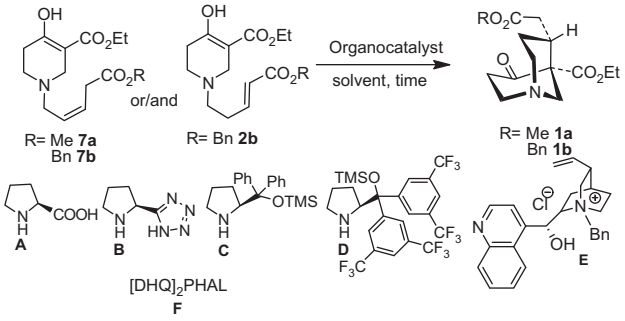
Scheme 6. Asymmetric Michael cyclization of chiral β-enaminoester.

Keenly encouraged by these results, we examined the asymmetric intramolecular Michael reaction using chiral β-enaminoester derived from (*S*)-(−)-phenylethylamine (Scheme 5).[22,13] Treatment of β-ketoester **2b** or **7b** by a slight excess of (*S*)-(−)-phenylethylamine in toluene under microwave irradiation promoted not only the formation of the chiral β-enaminoester (*S*)-**14b** in 70% yield but also the unexpected conjugate isomerization of the nitrogen-substituted lateral chain (Scheme 6).[23] It has been well established that Michael addition of chiral β-enaminoesters required further activation by addition of Lewis acid or high pressure in order to achieve reasonable yields and selectivity.[24,22c] Attempts to catalyse the cyclization of **14b** with $FeCl_3$, $ZnCl_2$ And $Cu(OAc)_2$ (0.1–1.2 equiv) not only under standard thermal conditions but also under microwave irradiations were unsuccessful. Only the combined effects of stoichiometric amount Lewis acid ($ZnCl_2$, 1.2 equiv) associated to high pressure (1.2 GPa) activations followed by hydrolytic work-up furnished diastereoselectively the desired Michael adduct **1b** in 60% yield (over two steps) and 48% ee (Scheme 6). The excellent diastereocontrol can be justified by a '*syn*-periplanar' approach of the two reactive parts with an '*endo*-arrangement' in which ester group of the acceptor part faced amine of the β-enaminoester part (Scheme 6).

Encouraged by the excellent diastereoselectivity and promising enantioselectivity and by recent reports on organocatalyst-mediated asymmetric Michael reaction,[25,26] we wish to study the straightforward synthesis of 1-azabicyclo[3.3.1]nonane skeletons by unexplored organocatalysed intramolecular Michael addition to α,β-unsaturated esters. The organocatalysed bridging conjugate addition was first investigated starting from **2b** using proline **A**, proline derivatives (**B**–**D**) and Cinchona alkaloid-derived catalysts **E** and **F** (Table 2). Whatever the reaction time (until 15 days) and protic (EtOH) or aprotic (CH_2Cl_2 or $CHCl_3$) conditions, organocatalysts **A**, **B**, **C** and **D** (10–30 mol %) were ineffective. Similarly, use of both cinchonidine derivative **E** and dihydroquinine derivative **F** (5–10 mol %) in basic phase-transfer catalysis (10 mol % of K_2CO_3 or CsOH) was unsuccessful. In all cases, at room temperature, starting material remained unmodified. Under refluxing conditions, only degradation was observed. Satisfyingly, use of the bi-functional catalyst proline-tetrazole **B**/piperidine led up to the expected azabicyclononane **1b** in 60% yield with total diastereoselectivity (entry 1). Furthermore, we have shown that piperidine used in stoichiometric amount did not allow access to cycloadduct **1b** starting from the conjugate precursor **2b** (entry 2). These results suggested that, under these reaction conditions, piperidine did favour neither intramolecular Michael addition contrary to DBU nor enamine formation. More gratifyingly, same reaction conditions applied to deconjugate substrate **7b** afforded diastereoselectively bicycle **1b** in 55% yield through a tandem conjugative isomerization-intramolecular Michael reaction (entry 3). Similarly, the bridged amine **1a** was obtained in 55% yield from **7a** (entry 6). Moreover, microwave irradiation (150 °C, 150 W) efficiently accelerated the tandem reaction without erosion of diastereoselectivity: reaction time was shortened from 10 days to 10 h (entry 4).

Chiral HPLC confirmed the excellent reaction diastereoselectivity but unfortunately showed the absence of enantioselectivity suggesting that the relative bulkiness of secondary-amine catalysts **A**–**D** may disfavour the formation of iminium ions with β-ketoesters. The absence of facial differentiation by the chiral organocatalyst was able to explain this lack of enantioselectivity. In conclusion, the secondary-amine catalysts, successfully used in the asymmetric Michael reactions by Jørgensen,[25] proved to be inefficient for the stereocontrol of the intramolecular Michael addition of poor nucleophilic β-ketoesters to less electrophilic α,β-unsaturated esters. The excellent diastereocontrol can be justified by the same approaches described previously starting from chiral β-enaminoester (Scheme 6). The proline-tetrazole **B**/piperidine catalyst might both stabilize the '*endo*-arrangement' by hydrogen-bonding and authorize the 1,4-addition by external hydrogen-transfer.

Table 2
Organocatalysed intramolecular Michael reaction screening



Entry	Compd	Catal.[a] (mol %)	Solvent *T* (°C), t (d)	Yield[b,c] (%)	de[d] (%)
1	**2b**	**B** (15)	Piperidine[e], $CHCl_3$ 22 °C, 7d	60[c]	>95
2	**2b**	/	Piperidine[e], $CHCl_3$ 22 °C, 7d	S.M.[f]	
3	**7b**	**B** (15)	Piperidine[e], $CHCl_3$ 22 °C, 10d	55[c]	>95
4	**7b**	**B** (15)	Piperidine[e], $CHCl_3$ μW[f] (150 °C), 10 h	50[c]	>95
5	**7b+2b**	**B** (15)	Piperidine[e], $CHCl_3$ 22 °C, 10d	63[c]	>95
6	**7a**	**B** (15)	Piperidine[e], $CHCl_3$ 22 °C, 10d	55[c]	>95

[a] Reactions were performed with substrate (0.5 mmol), catalyst and anhydrous solvent (0.1 mL).
[b] Isolated yield.
[c] 100% conversion monitored by ^1H NMR (disappearance of ethylenic proton).
[d] de values were determined by ^1H NMR and confirmed by chiral HPLC analysis.
[e] 0.5 mmol of piperidine was added.
[f] Starting material.

In conclusion, the present work provides the first diastereoselective synthesis of highly functionalized 1-azabicyclo[3.3.1]nonane skeletons by an amine-mediated tandem conjugative isomerization-intramolecular Michael addition. This concise strategy exemplifies the not yet explored C-5/C-6 disconnection. Moreover, we have shown that the combined use of ultra-high pressure and Lewis acid can circumvent the problems of substrate-dependency for the intramolecular asymmetric aza-Michael addition in terms of reactivity and steric hindrance.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.069.

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20. In the absence of additional base, treatment of piperidin-4-one amine base **4** with alkyl bromopentenoate **5a** or **5b** only gives alkyl penta-2,4-dienecarboxylate **8a** or **8b**.
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