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Short Access to (+)-Lupinine and (+)-Epiquinamide via Double Hydroformylation†

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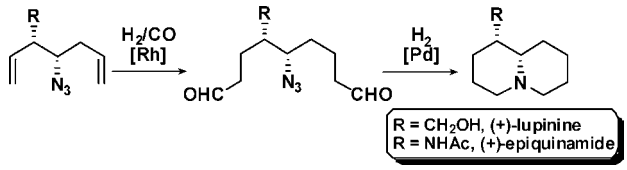
ABSTRACT



Short and efficient access to (+)-lupinine and (+)-epiquinamide by means of an unprecedented double hydroformylation of a bis-homoallylic azide followed by a tandem catalytic hydrogenation/reductive bis-amination is reported.

In recent years, synthetic strategies toward piperidine- and pyrolidine-containing alkaloids have often implemented transition-metal-catalyzed transformations. In this regard, the ring closing metathesis (RCM) has found its way for the construction of many alkaloids,[1] but a prerequisite for performing a RCM is the presence of two olefinic partners in the substrate to be heterocyclized, one of them being generally a homoallylamine. As an alternative, a homoallylamine could also be identified as an ideal substrate for performing a hydroformylation.[2] This atom-economic process[3] consists of a formal addition of H_2/CO across an olefin catalyzed by Rh(I) and has recently emerged as a powerful method in the synthesis of alkaloids.[4] Thus, if the introduction of the aldehyde function occurs regioselectively at the terminal carbon atom of the alkene function, the presence of the nucleophilic nitrogen atom in the allylamine will allow us to form an internal imine directly amenable to a six-membered N-heterocycle.

Combining hydroformylation and heterocycle syntheses, we recently disclosed the hydroformylation of homoallylic azides[5] as a highly efficient way to construct the piperidine nucleus thus offering a new tactic for the construction of alkaloids. Indeed, the reaction proceeded with a very good

† This paper is dedicated to Christian Marazano.
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(3) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

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catalyst-based regiocontrol in favor of the linear aldehyde employing a biphephos/rhodium(I) catalyst (see Scheme 1).[6] Additionally, we have recently shown that instead of the amine function one could employ as an amine surrogate the azido function. This functional group remains intact during the hydroformylation reaction thus enabling a range of subsequent chemoselective transformations (e.g., Schmidt rearrangement, aza-Wittig reaction, Staudinger reaction).[7] To further extend our strategy, the syntheses of naturally occurring quinolizidine alkaloids (+)-lupinine **1a** and (+)-epiquinamide **1b** have now been considered (Figure 1).

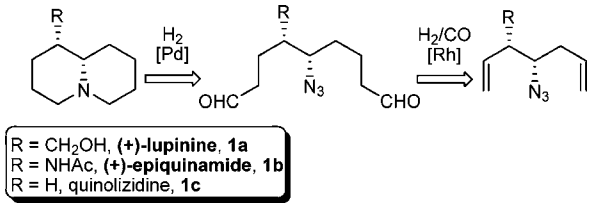
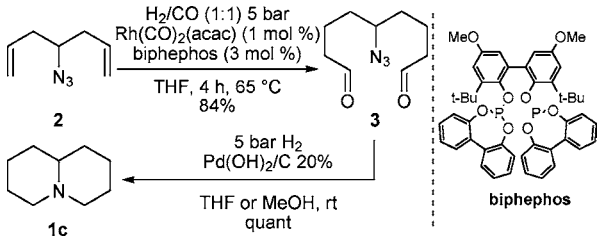


Figure 1. Strategy for the formation of quinolizidine alkaloids.

From a retrosynthetic point of view, the quinolizidine ring system is attainable by a double reductive amination of two equidistant aldehydes smoothly generated by a regioselective bidirectional hydroformylation of an appropriate chiral bis-homoallylic amine which might be generated in situ through catalytic reduction of the azide function.

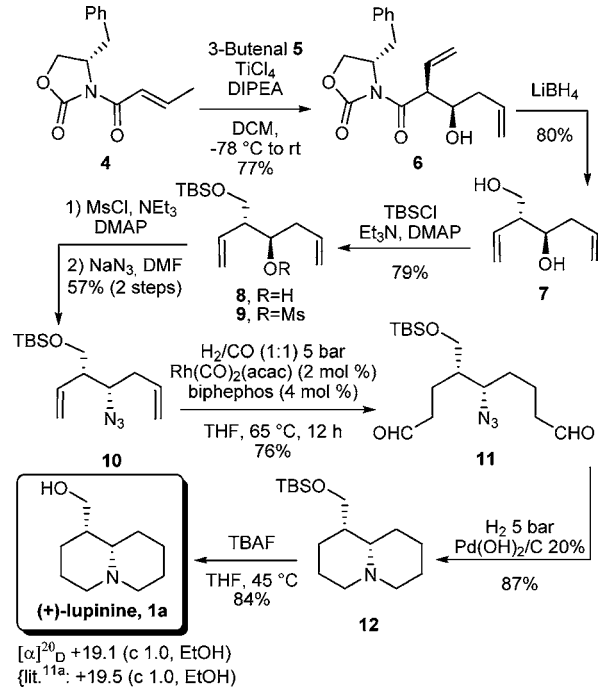
Scheme 1. Model Reaction



To explore the feasibility of this approach, we subjected the bis-homoallylic azide **2** to the conditions of a regioselective hydroformylation employing the biphephos/rhodium(I) catalyst (Scheme 1). The bisaldehyde **3** was formed smoothly in high regioselectivity and good yield. After subjection of the azide to the conditions of catalytic hydrogenation employing Pearlman's catalyst, a clean tandem azide reduction/reductive bis-amination process[8] took place to form the desired quinolizidine **1c** exclusively.[9]

Next, (+)-lupinine **1a** (Scheme 2), a quinolizidine alkaloid from *Lupinus* spp.,[10] was selected as a target to explore our new bidirectional hydroformylation/tandem hydrogenation−reductive bis-amination strategy. Previously, Ma et al.[11] reported the access to all four epimers of lupinine via a double RCM reaction of nitrogen-containing tetraenes.

Scheme 2. Synthesis of (+)-Lupinine, **1a**



Interestingly, a similar intermediate (**9**) could be used for our purposes. However, for the preparation of **9**, we chose a different path.

Our synthesis commenced with the Evans aldol reaction[12] between commercially available oxazolidinone **4** and freshly

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(9) ^{1}H NMR yield.

(10) (a) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. (c) Abdel Halim, O. B.; El Gammal, A. A.; Abdel Fatta, H.; Takeya, K. *Phytochemistry* **1999**, *51*, 5.

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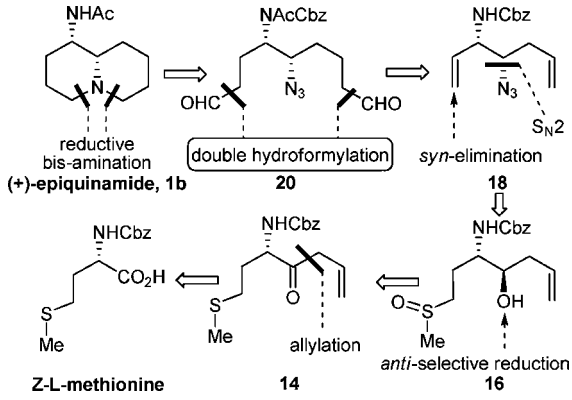
prepared 3-butenal[13] **5**. Employing DIPEA as the base to form the chlorotitanium enolate via soft enolization of **4**, the *syn*-aldol product **6** was obtained as a single diastereomer in 77% yield. Reductive removal of the chiral auxiliary with lithium borohydride, in THF with some methanol, furnished the diol **7** in 80% yield. The primary alcohol was protected as a TBS ether, and the secondary alcohol was activated as its mesylate and displaced with the azide function upon reaction with sodium azide in DMF to give the desired bis-homoallylic azide **10**. Subjection of **10** to the conditions of a hydroformylation employing the biphephos/rhodium system furnished the azido-bis-δ,δ'-aldehyde **11** in very good yield (76%). Azido and subsequent imine reduction gave in one pot the desired quinolizidine core **12** in 87% yield; treatment of compound **12** with TBAF resulted in the formation of (+)-lupinine **1a**. Finally, the present route to (+)-lupinine features 8 steps (from **4**) with an overall yield of 15%.

In a second part, we focused on the total synthesis of (+)-epiquinamide **1b** (Scheme 3), an alkaloid isolated from the rainforest frog *Epipedobates tricolor* along with Epibatidine and that has a relevant activity on nicotinic receptors.[14]

Scheme 3. Retrosynthetic Analysis for (+)-Epiquinamide

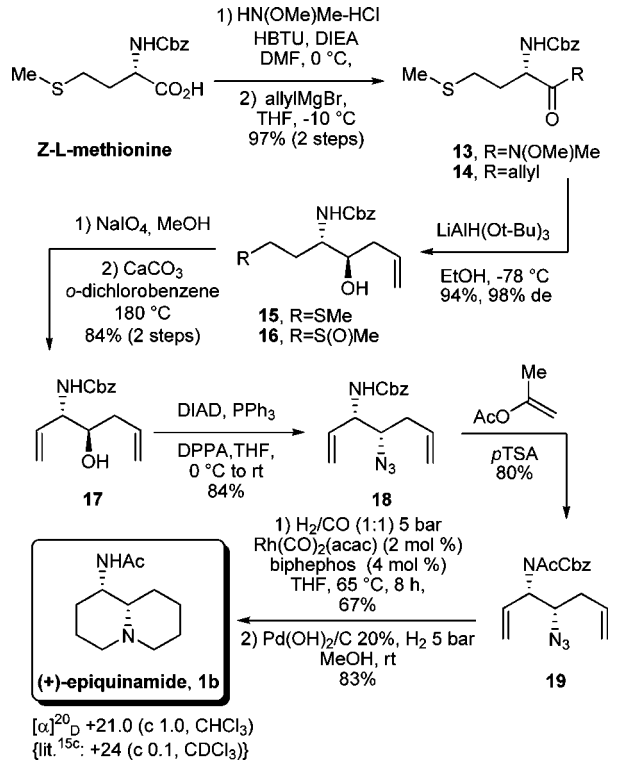


(+)-Epiquinamide **1b** has attracted considerable attention from the synthetic community. Interestingly, most of the reported strategies used RCM as the key reaction.[15]

Following our key strategy (Scheme 1), the access to the enantiopure bis-homoallylic azide **18** from the chiral pool has been envisaged. Indeed, one olefin (vide supra) may be obtained by *syn*-elimination of the corresponding sulfoxide **16** obtained from a former methionine derivative. The azido group can be introduced from a *anti*-1,2 amino alcohol **16** generated by chelation-controlled reduction of the corresponding homoallylic ketone **14**. The latter may be easily obtained from inexpensive amino acid Cbz-L-methionine via the Weinreb amide and an allyl-Grignard, introducing the second essential alkene function.

Initially, Cbz-L-vinylglycine was considered in our strategy, but as epimerization was a concern, the olefin was kept in its hidden form (dialkylsulfide) until reaching **17** (Scheme 4), a compound not prone to epimerization.[16]

Scheme 4. Synthesis of (+)-Epiquinamide, **1b**



It should be mentionned that the choice of the N-protecting group is not trivial as it is decisive for the chelation-controlled reduction. It must be stable for the thermal elimination and ideally removable during the final hydrogenolysis. As a consequence, we selected the benzylcarbamate (Cbz) as a suitable protecting group.

Practically, Weinreb amide **13** was obtained from Cbz-L-methionine using standard coupling conditions (Scheme 4), and subsequent treatment with allylmagnesium chloride afforded the corresponding homoallylic ketone **14** in excellent yields (97% over 2 steps) along with a negligible amount of isomerized product.[17] At this point, three reducing conditions were evaluated (see Supporting Information for details) to obtain the desired *anti* amino alcohol **15** with high diastereoselectivity. The best result was obtained with lithium

(13) See Supporting Information for the preparation of **5**.

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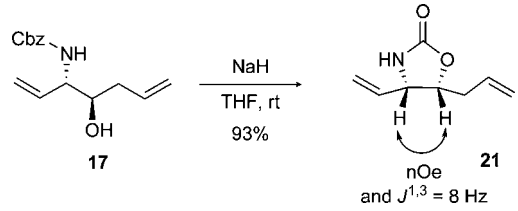
(17) Liu, J.; Ikemoto, N.; Petrillo, D.; Amstrong, J. D., III. *Tetrahedron Lett.* **2002**, *43*, 8223.

tris-*tert*-butoxy aluminum hydride furnishing the desired *anti* alcohol in excellent yield and diastereoselectivity.[18] Subsequent oxidation of the sulfide was achieved quantitatively with sodium *meta*-periodate producing a ~1:1 mixture of sulfoxide diastereomers (**16**). Thermal treatment of **16** in the presence of calcium carbonate[19] initiated a clean *syn*-elimination to yield the desired bis-homoallylic alcohol **17** in a very good overall yield. Noteworthy is that only two purification steps were needed from Cbz-L-methionine.

Scheme 5. Determination of the Relative Stereochemistry



Moreover, the *anti* relationship in **17** could be secured by NOE experiments performed on the corresponding cyclic carbamate **21** (Scheme 5). The observed vicinal coupling constant ($J = 8$ Hz) is consistent with a *cis* stereochemistry of oxazolidinone **21**.[20]

Next, a Mitsunobu reaction enabled the introduction of the azido function to give **18** in 84% yield setting the desired stereochemistry for **1b**.[21]

Anticipating a possible trapping of one aldehyde during the hydroformylation process with the secondary carbamate to form an enamide, acylation of intermediate **18** was decided to preclude cyclohydrocarbonylation.[22] In our hands, acylation under basic conditions was found to be problematic as only low conversions were obtained (LiHMDS, AcCl, THF, −10 to 0 °C, 14%, 89% based on recovered starting material, see Supporting Information). Gratifyingly, the reaction proceeded under mild acidic conditions with *p*TSA in isopropenylacetate[23] as solvent to yield the desired *N*-Cbz, *N*-acylated product **19** in 80% yield.

Finally, applying to **19** the previously developed hydroformylation conditions furnished the azido-bis-δ,δ'-aldehyde **20** in 67% yield. The latter was subjected to hydrogenation in the presence of Pearlman's catalyst allowing four reductive reactions in one pot: the azido group was converted into a free amine, two reductive aminations produced the bicyclic quinolizidine ring, and the cleavage of the Cbz protecting group afforded **1b** with consistent analytical data (NMR, HRMS, and optical rotation) in 83% yield.

In conclusion, we successfully realized the total syntheses of two quinolizidine alkaloids, (+)-lupinine **1a** (8 steps, overall yield 15% from **4**) and (+)-epiquinamide **1b** (9 steps, overall yield 29% from Cbz-L-methionine), using a bidirectional regioselective hydroformylation of chiral bis-homoallylic azides as a key step followed by a highly efficient tandem catalytic azide reduction/reductive bis-amination process. Taking advantage of the exceptional stability of azides during the hydroformylation process, the proposed methodology is well suited for the preparation of quinolizidine alkaloids. Moreover, the use of methylsulfide compounds as a hidden terminal alkene function may be an attractive strategy for subsequent hydroformylation. Applying the hydroformylation reaction in the synthesis of other alkaloids is currently underway in our laboratories.

In our group, we are currently applying this hydroformylation strategy for the synthesis of other alkaloids.

Acknowledgment. This work was supported by the Ministère délégué à l'Enseignement Supérieur et à la Recherche (EA, TS).

Supporting Information Available: Detailed experimental procedures and spectral and analytical data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Mesylation of alcohol **17** followed by treatment with sodium azide gave also compound **18** in 81% (over two steps).

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