JOC The Journal of Organic Chemistry

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Metal-Free Decarboxylative Hetero-Diels–Alder Synthesis of 3-Hydroxypyridines: A Rapid Access to *N*-Fused Bicyclic Hydroxypiperidine Scaffolds

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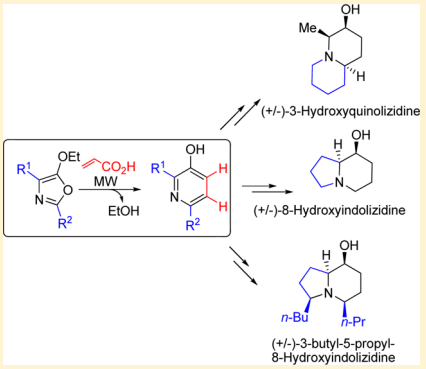
Supporting Information

ABSTRACT: A complete experimental and theoretical study of the thermally controlled metal-free decarboxylative hetero-Diels–Alder (HDA) reaction of 5-alkoxyoxazoles with acrylic acid is reported. This strategy offers a new entry to valuable 2,6-difunctionalized 3-hydroxypyridines from readily available 2- and 4-disubstituted 5-alkoxyoxazoles. The reaction conditions proved compatible with, among others, ketone, amide, ester, ether, and nitrile groups. The broad functional group tolerance of the protocol allows a rapid and versatile access to both hydroxyindolizidine and hydroxyquinolizidine derivatives via a pyridine dearomatization strategy.



INTRODUCTION

3-Hydroxypiperidine systems are widely present in natural products and exhibit a large panel of biological activities including antibiotic, anesthetic,[1] and antifungal effects.[2] Among them, *N*-fused bicyclic hydroxypiperidines such as hydroxyindolizidines or hydroxyquinolizidines have attracted increasing interest over the past 10 years, in particular due to their challenging structural features (Figure 1).[3] As examples, it is worth noting the hydroxylated alkaloid swainsonine, isolated from *Rhizoctonia leguminicola*, that displays important anticancer or glycosidase inhibitory activity.[4] Moreover, other interesting *N*-bridgehead hydroxypiperidines were reported such as the representative alkaloids 209H, pumiliotoxin 251D,[5] or more recently, the 3-butyl-5-propyl-8-hydroxyindolizidine[6] extracted from frog skin or found in the venom of the ant *Myrmicaria melanogaster*, respectively.

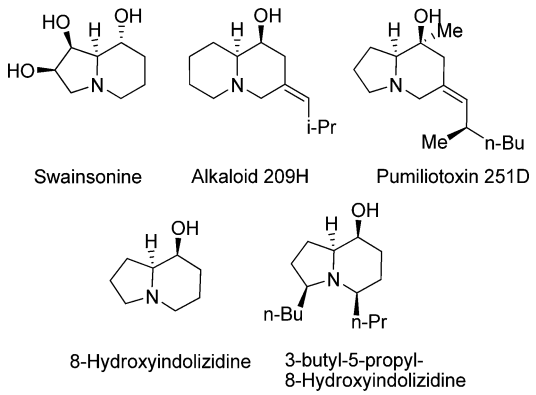


Figure 1. Naturally occurring *N*-fused bicyclic hydroxypiperidine derivatives.

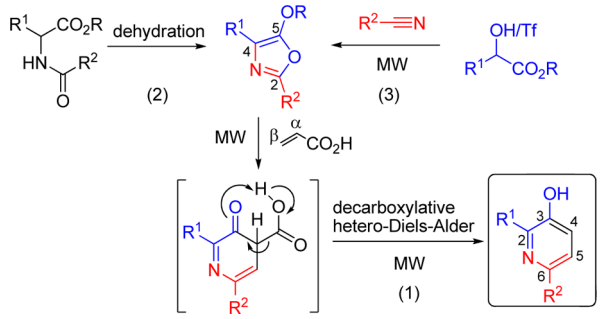
These bicyclic hydroxypiperidine scaffolds are usually prepared through piperidine ring-closure strategies (lactamization,[7] *N*-alkylation,[8] reductive amination,[9] conjugate addition,[10] or metathesis[11]). In addition, efficient tools to dearomatize pyridine ring systems into their corresponding piperidine derivatives have become available.[12] For example, Charette et al. have recently reported an elegant intramolecular pyridine activation–dearomatization strategy.[13] Furthermore, stereoselective heterogeneous catalytic hydrogenation of pyridines has been shown to efficiently lead to piperidine derivatives.[14] Despite these notable recent advances, the pyridine dearomatization approach to access functionalized bicyclic 3-hydroxypiperidine alkaloids is still underexplored. This can be partly explained by the requirement of suitably prefunctionalized 2,6-disubstituted 3-hydroxypyridine precursors that often demand several synthetic steps.

Indeed, few straightforward constructions of the 3-hydroxypyridine pattern are exposed in the literature.[15] To cover this gap, Wang et al. recently developed a spectacular cascade [1 + 5] cycloaddition of isonitriles to provide highly substituted 4-acylamino-5-acyloxypyridines.[16] In this context, our laboratory

Received: December 9, 2013
Published: January 15, 2014

recently communicated a complementary route to less functionalized 3-hydroxypyridine derivatives through a metal-free decarboxylative [4 + 2] cycloaddition process involving 5-alkoxyoxazoles and acrylic acid (Scheme 1, path 1).[17] This

Scheme 1. Convergent Approach to 2,6-Difunctionalized 3-Hydroxypyridines through Thermally Controlled Decarboxylative HDA Reaction of Alkoxyoxazoles with Acrylic Acid

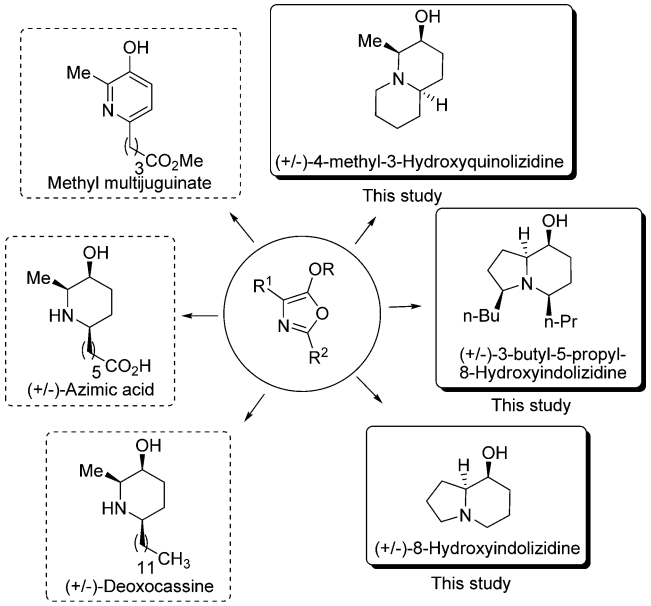


method aims at covering a limitation of the Kondrat'eva reaction[18] that does not allow a general access to weakly functionalized 3-hydroxypyridines because of the requirement of electron-withdrawing groups on the olefin partner to complete the HDA step. Advantageously, this single-step HDA/alcohol elimination/removal of the electron-withdrawing group−aromatization strategy tolerates a range of different functional groups.

In addition, the starting 5-alkoxyoxazoles are traditionally prepared via intramolecular cyclodehydration reaction of α-amido esters (Scheme 1, path 2). Alternatively, intermolecular processes that enable a rapid access to a range of 5-alkoxyoxazoles have been recently reported.[19] In this context, we have recently published an expedient and versatile access to diversely substituted 5-alkoxyoxazoles from the corresponding α-triflyloxy- or α-hydroxyl esters and nitriles under microwave conditions (Scheme 1, path 3).[20]

In our previous paper, the decarboxylative HDA reaction has shown to be a valuable synthetic tool to prepare efficiently a naturally occurring 3-hydroxypyridine and 3-hydroxypiperidines (Scheme 2). Herein, we wish to report a full account of our investigations regarding specific requirements, scope, and limitations of the decarboxylative HDA reaction. Furthermore, the first use of this methodology for the elaboration of challenging scaffolds such as bicyclic alkaloids hydroxyindolizidines and hydroxyquinolizidines via a pyridine dearomatization/ring closure strategy is also disclosed. Finally, a thorough theoretical analysis of the reaction mechanism is presented in order to explain the observed regioselectivity and to cast the light on the role of substituents. In particular, the reaction key steps will be rationalized using a concerted DFT−conceptual DFT[21]−QTAIM[22] analysis, a framework that combines three important theories based on the same primary ingredient, the electron density, which is the fundamental observable in quantum chemistry. A special emphasis will notably be put on Pendás' interacting quantum atoms (IQA) approach,[23] which constitute, from our viewpoint, a method of choice to study bond-breaking and -forming processes.

Scheme 2. Application of the Decarboxylative HDA Reaction to the Synthesis of Natural Alkaloids



RESULTS AND DISCUSSION

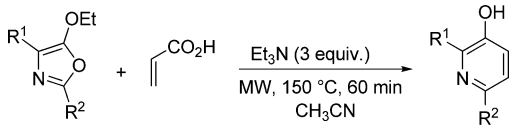
An exhaustive exemplification of the reaction scope and limitations is reported in Table 1. First, aliphatic 2- and/or 4-substituted 5-alkoxyoxazoles generally reacted with the acrylic acid in good yields (40−70%, entries 1−7). Furthermore, phenyl substituents on the alkoxyoxazole rings led to the corresponding 2- or 6-phenyl-3-hydroxypyridines in useful yields (60−66%, entries 8−10). Satisfyingly, the methodology also proved to be effective with substrates bearing various functionalities. Ester derivatives at either position 2 or 4 on the oxazole ring gave good yields regardless their chain length (42−70%, entries 11−15). Gratifyingly, the developed conditions were tolerant of sensitive functional groups such as ketones with 69% and 56% yield obtained from **1p** and **1q**, respectively (entry 16 and 17). Interestingly, the sulfone-containing 5-alkoxyoxazole **1r** provided the product of elimination **2r** in useful 50% yield (entry 18). Ether derivatives were formed in moderate yields (41 and 50%, entry 19 and 20). Nitrogen-containing functional groups such as nitrile and amide gave the 3-hydroxypyridines in convenient 40−79% yield (entries 21−23). Nonetheless, the challenging amine-bearing oxazole **1x** furnished the desired 3-hydroxypyridine **2x** in 23% yield. Finally, alcohol derivatives furnished the desired pyridines in low 27−36% yields (entries 25 and 26).

Taking advantage of the fact that both the Ritter-mediated synthesis of 5-alkoxyoxazoles and their subsequent decarboxylative cycloaddition into the corresponding 3-hydroxypyridines were optimized in nitrile-base solvents, a microwave-mediated one-pot process was serendipitously investigated (Scheme 3).

First, the reaction was run with ethyl *O*-trifluoromethanesulfonyl-2-hydroxypropanoate in acetonitrile playing both the role of reagent (first step) and solvent (second step). To our delight, the corresponding 3-hydroxypyridine **2aa** was obtained in satisfying 56% yield. This consecutive microwave-assisted pyridine synthesis was also successfully extended to butyronitrile and benzonitrile to afford **2b** and **2c** in 50% and 58% yield, respectively. Although useful yields and a substantial gain of

dx.doi.org/10.1021/jo402729a | J. Org. Chem. 2014, 79, 1303−1319

Table 1. Full Scope of the Decarboxylative HDA Reaction[a]



1a-z 2a-z

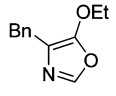
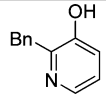
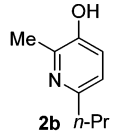
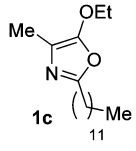
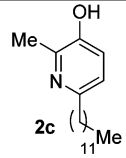
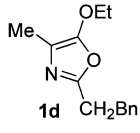
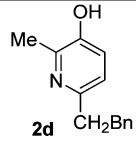
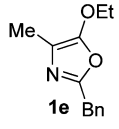
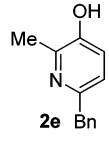
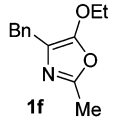
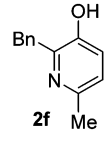
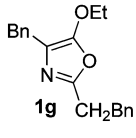
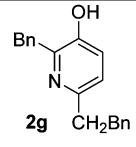
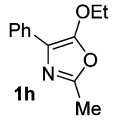
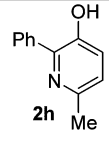
entry	substrate	product	yield (%)[b]
1	 1a	 2a	63
2	 1b *n*-Pr	 2b *n*-Pr	40
3	 1c	 2c	42
4	 1d	 2d	70
5	 1e	 2e	58
6	 1f	 2f	67
7	 1g	 2g	64
8	 1h	 2h	63

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Table 1. continued

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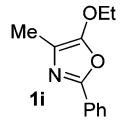
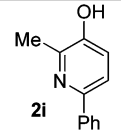
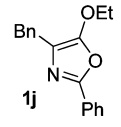
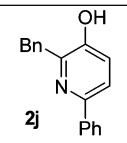
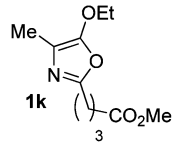
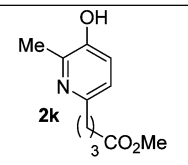
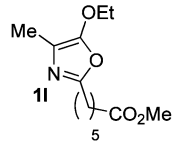
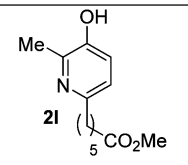
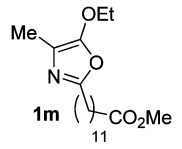
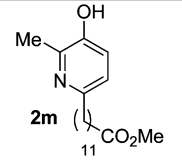
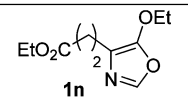
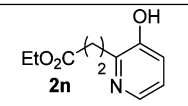
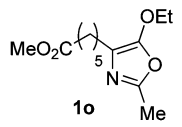
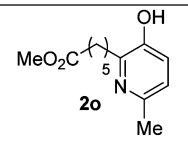
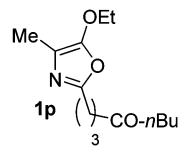
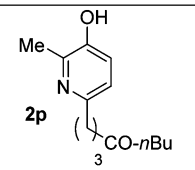
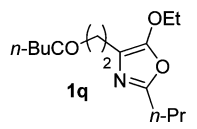
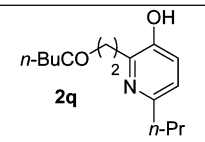
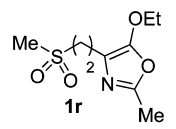
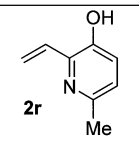
9			66
10			60
11			70
12			59
13			52
14			56
15			42
16			69
17			56
18			50

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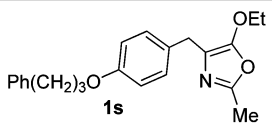
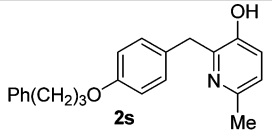
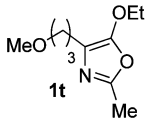
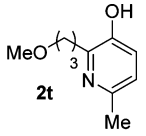
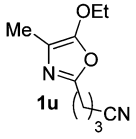
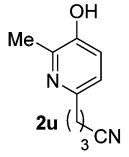
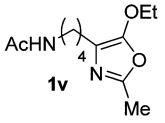
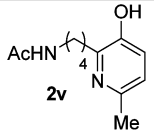
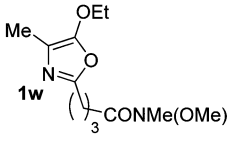
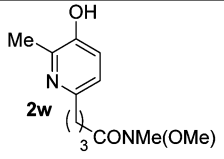
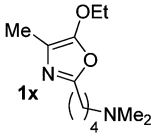
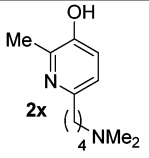
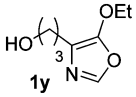
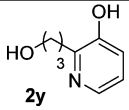
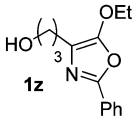
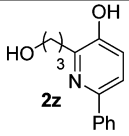
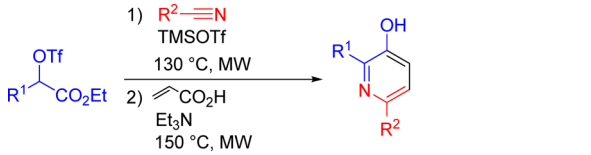
Table 1. continued

entry	substrate	product	yield (%)[b]
19	 **1s**	 **2s**	41
20	 **1t**	 **2t**	50
21	 **1u**	 **2u**	79
22	 **1v**	 **2v**	40
23	 **1w**	 **2w**	59
24	 **1x**	 **2x**	23
25	 **1y**	 **2y**	27
26	 **1z**	 **2z**	36

[a]Reaction conditions: alkoxyoxazole **1** (1.2 mmol) and acrylic acid (2.4 mmol, 2 equiv), Et_3N (3.6 mmol, 3 equiv) in CH_3CN (3 mL) at 150 °C for 60 min, under microwave conditions. [b]Isolated yield.

Scheme 3. One-Pot Synthesis of 3-Hydroxypyridines from α-Triflyloxy Esters



56% **2aa** (R^1 = Me, R^2 = Me)
50% **2b** (R^1 = Me, R^2 = *n*-Pr)
58% **2c** (R^1 = Me, R^2 = Bn)
19% **2ab** (R^1 = *i*-Bu, R^2 = Me)

time were provided with the one-pot compared to the two-pot process, this method was not as generalizable with a range of nitrile and triflyloxy derivatives as observed for compound **2ab** obtained in low 19% yield.

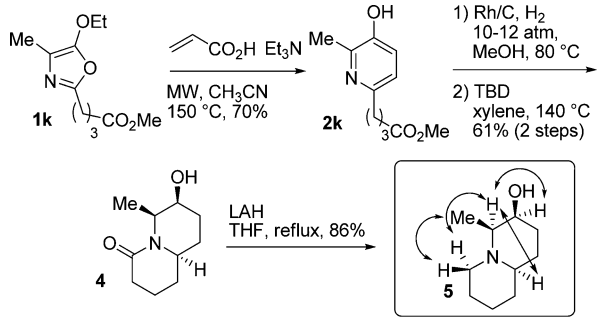
Since the decarboxylative HDA process is tolerant of a variety of functional groups including esters, these latter should serve as cyclization precursors to build up the nitrogen-fused bicyclic ring systems after dearomatization of the pyridine into the corresponding piperidine derivatives. This flexible process should allow the construction of either hydroxyindolizidines or hydroxyquinolizidines depending on the carbon atom chain length separating the ester group from the pyridine ring. Moreover, the location of the ester, i.e., at either position 2 or 6

dx.doi.org/10.1021/jo402729a | J. Org. Chem. 2014, 79, 1303−1319

on the 3-hydroxypyridine, would also govern the relative position of the hydroxyl group on the piperidine moiety on the final *N*-fused bicyclic system.

In order to investigate this versatile approach to hydroxylated bicyclic piperidines, the preparation of the 4-methyl-3-hydroxyquinolizidine **5** was first considered (Scheme 4). The

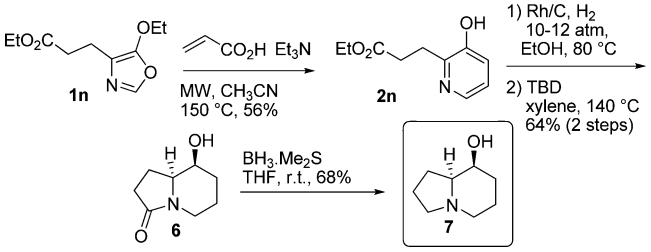
Scheme 4. Synthesis of the (±)-4-Methyl-3-hydroxyquinolizidine 5



hydroxypyridine **2k** was effectively generated from **1k** and acrylic acid in good 70% yield, under optimized microwave-assisted conditions. Next, catalytic hydrogenation of **2k** in the presence of Rh/C delivered diastereoselectively with *all-cis* stereochemistry[24] the corresponding 3-hydroxypiperidine, which subsequently led to the bicyclic amide **4** in 61% over two steps after intramolecular aminolysis promoted by TBD.[25] Final reduction of **4** with $LiAlH_4$ provided the desired 3-hydroxyquinolizidine **5** in 86% yield, its relative configuration being confirmed by a NOESY experiment.[26]

Next, the dearomatization/lactamization strategy was applied to the construction of the known 8-hydroxyindolizidine **7**.[27] This synthesis was undertaken from the readily available 2-substituted 5-alkoxyoxazole **1n** (Scheme 5). Then, the

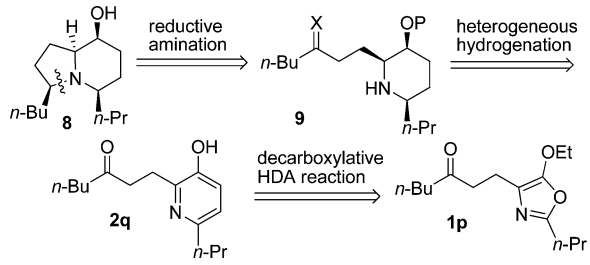
Scheme 5. Synthesis of the (±)-8-Hydroxyindolizidine 7



decarboxylative cycloaddition of **1n** with acrylic acid provided the corresponding pyridine **2n** in convenient 56% yield. Catalytic diastereoselective hydrogenation of **2n** and its subsequent lactamization afforded the bicyclic lactame **6** in a *cis*/*trans* ratio of 9:1 and 64% yield over two steps. To complete the synthesis, the reduction of the lactam group gave the 8-hydroxyindolizidine **7** in 68% yield. It should be stressed that the minor *trans*-isomer was easily removed at this stage by column chromatography. Both ^1H and ^{13}C NMR analyses were consistent with previously reported values.[27a]

After establishing a viable route to hydroxyquinolizidine and hydroxyindolizidine derivatives through a pyridine dearomatization/lactamization strategy, the diastereoselective synthesis of the natural 8-hydroxyindolizidine **8**, bearing four stereogenic centers, was next investigated through a pyridine dearomatization/reductive amination ring-closure approach (Scheme 6). Thus, the required piperidine **9** would be envisioned from the

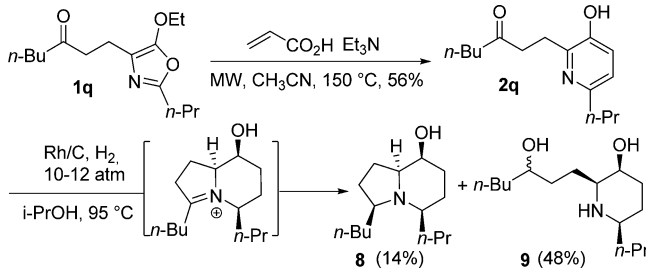
Scheme 6. Retrosynthetic Analysis of the Ant Venom Alkaloid 8



pyridine **2q**, which would be provided via the developed microwave-assisted decarboxylative hetero-Diels–Alder cyclization of the keto-oxazole **1q**.

Satisfyingly, the key HDA step involving the 5-alkoxyoxazole **1q** and acrylic acid afforded the expected pyridine **2q** in 56% yield under microwave conditions (Scheme 7). At this stage, we

Scheme 7. Synthetic Route to the (±)-8-Hydroxyindolizidine 8



took advantage of having the keto-3-hydroxypypridine **2q** in hand to attempt an ambitious stereoselective cascade hydrogenation/reductive amination sequence to furnish directly the final bicyclic alkaloid **8**. To the best of our knowledge, such a stereoselective sequence has never been reported with electron-rich 3-hydroxypyridines.[28] Indeed, for this approach to succeed, the pyridine ring hydrogenation and subsequent intramolecular imination should proceed while avoiding the ketone reduction. While this transformation conducted to the formation of the unwanted hydroxypiperidine **9** as one would expect in 48% yield, it is worth mentioning that the desired hydroxyindolizidine **8**, bearing four new stereogenic centers, was stereoselectively obtained out of eight possible diastereoisomers, albeit with a low 14% yield.[29] All reductions proceeded with high level of diastereoselectivities without the need of an external chiral auxiliary, the final stereoselectivity for the iminium reduction step being controlled by the bowl shape of the bicyclic iminium intermediate.

In order to define an exclusive pathway to the bicyclic alkaloid **8**, both the ketone and the hydroxyl group of **2q** were protected before the hydrogenation step, providing **10** in good 72% yield over two steps (Scheme 8).[30] Then, the heterogeneous catalytic hydrogenation of **10** afforded the functionalized piperidine **11** in convenient 66% yield. After the protecting group was removed from the ketone, the reductive amination was carried out directly on the crude material in the presence of Pearlman's catalyst to afford the *N*-fused bicyclic

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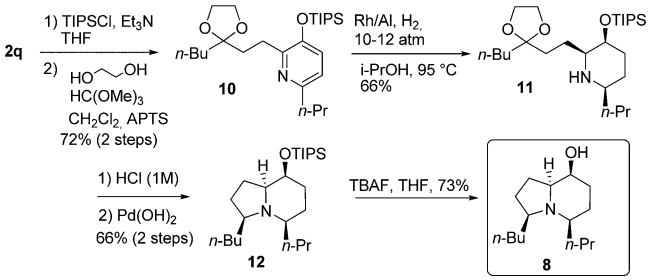
Scheme 8. Selective Route to 8



system **12** as one single isomer. Final removal of the silyl ether protecting group gave the desired alkaloid **8** in 73% yield.

In order to get more insight into the factors governing the selectivity and the efficiency of such a chemical process, density functional theory calculations were carried out using the computational protocol designed in ref 17 for the reaction involving compound **1b**. Scheme 9 offers a simplified representation of the investigated reaction pathway.

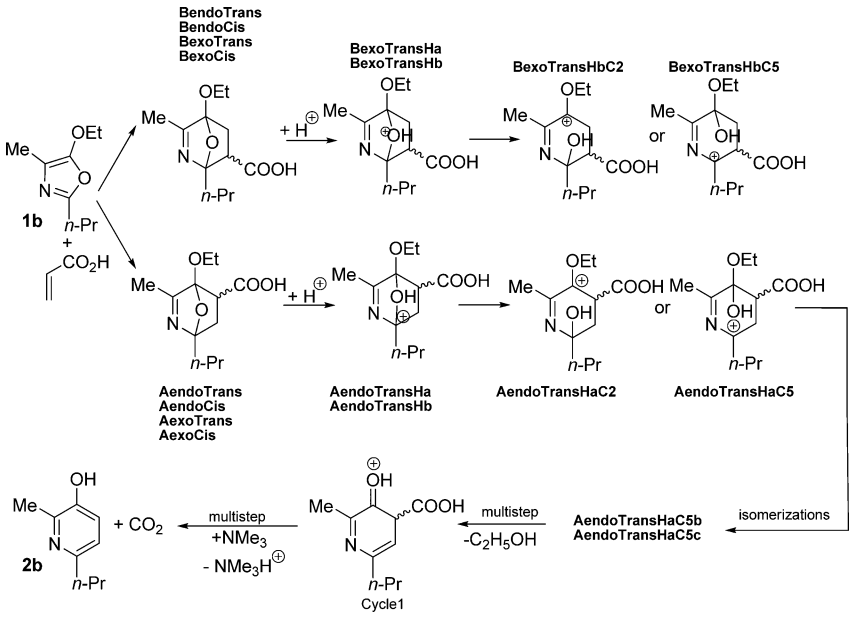
The first step is the HDA cyclization between oxazole and acrylic acid. If many theoretical studies have been devoted for several decades to Diels–Alder reactions,[31] the rationalization of HDA transformations by quantum chemistry has been conversely the subject of very few studies.[32] For this reason, we will consider all various adducts that can be possibly formed. The COOH group of acrylic acid can indeed come on the same side as the oxazole's OEt substituent, forming products labeled A, while B refers to cases where OEt and COOH are positioned oppositely. For these two classes, both *endo* and *exo* approaches are possible. Lastly, COOH can adopt two orientations with OH pointing "down" (the C=O and C=C bonds then adopt a relative s-*trans* conformation) or "up" (s-*cis*). The resulting eight possibilities (**AendoTrans**, **AendoCis**, **AexoTrans**, **AexoCis**, **BendoTrans**, **BendoCis**, **BexoTrans**, and **BexoCis**) are represented in Figure S1 (Supporting Information). As HDA reactions are known to be under kinetic control, the products ratios will mainly depend on the activation barriers leading to them. The corresponding values (at 150 °C) are respectively equal to 19.3, 19.6, 21.7, 21.1, 21.0, 20.9, 19.4, 20.5 kcal/mol.

These values show that for A-type orientation, *endo* approaches are slightly kinetically favored, while *exo* ones are predicted to react faster in B cases. Importantly, the lowest activation free enthalpies for A and B are almost equal (19.3 and 19.4 kcal/mol), so that both approaches are identically probable. In all cases, the cycloaddition is asynchronous (see Table 1 for the atoms numbering): C^5-C_α = 2.41 Å and C^2-C_β = 1.98 Å for the **AendoTrans** transition state (TS), and C^5-C_β = 1.98 Å and C^2-C_α = 2.36 Å for **BexoCis**. The fact that these two activation energies are almost equal can seem surprising since only products stemming from the first orientation are observed. One can thus wonder whether these energies can be rationalized in terms of the intrinsic reactivity of the reactants. Toward this goal, we invoke conceptual DFT[21] and notably the recently developed state specific dual descriptors (eq S1, Supporting Information),[33] which can be seen as a conceptual DFT extension of frontier orbitals theory.

First, we scrutinize the atomic values of the first state specific descriptor, Δf_1, for the two carbons of acrylic acid (Figure S2): they are both positive, thus corresponding to overall electrophilic regions. As for oxazole, positions C^4 and C^5 are, as expected, mainly nucleophilic, featuring negative atomic values. On the contrary, the first state-specific dual descriptors give positive values for C^2 and N^3, contrary to the expected reactivity. We are here facing a case where higher order state-specific dual descriptors should be examined.[33] Interestingly, Δf_2 enables recovery of the nucleophilic character of C^2 and N^3 with negative atomic values. From them, we define (eqs S3–4, Supporting Information) new quantities aiming at discriminating the two approaches: *Pref*Δf (A) = −0.003 au and *Pref*Δf (B) = −0.010 au, so that the formation of **BexoTrans** is favored.

But, philicity is only one facet of reactivity, linked to "orbital control". For its counterpart, the "charge control", two descriptors based on atomic charges (accounting for electrostatics at first order), are also built (eqs S5–6, Supporting Information) to distinguish the two pathways: *Pref*Q(A) = −0.031 au, *Pref*Q(B) = −0.025 au. The **AendoTrans** approach

Scheme 9. Studied Reaction Pathway



dx.doi.org/10.1021/jo402729a | J. Org. Chem. 2014, 79, 1303–1319

is thus favored from this point of view. All in all, the two antagonist effects qualitatively explain why the two activation barriers are close.

The influence of temperature can also be briefly discussed. The same activation barriers are, for instance, equal to 16.5 (**AendoTrans**) and 16.6 (**BexoTrans**) kcal/mol at 25 °C. A temperature increase does not modify the energy ranking but only increases the barriers, as expected for a step that is entropically disfavored. The corresponding bicycle products are more stable than the reactants (from, respectively, −6.4 and −9.0 kcal/mol), the addition being, however, still reversible at the experimental temperature (the forward activation barrier is, for instance, equal to 25.7 kcal/mol for **AendoTrans**). Then the products must undergo the protonation of the C−O−C bridge in order to open it. Several protonated products are possible, depending on the H orientation (pointing toward N, "Ha", or in direction of the COOH, "Hb"), as represented in Figure S3 (Supporting Information).

The relative Gibbs energies are respectively equal to 0.0 (**AendoTransHa**), 3.2 (**AendoTransHb**), 2.4 (**BexoTransHa**), and −4.0 kcal/mol (**BexoTransHb**). For each subgroup (**AendoTransH** and **BexoTransH**), the favored products are those where the differences between the two C−O bond lengths are the lowest. As for the highest stability of **BexoTransHb**, it can be accounted for by the creation of a hydrogen bond between the oxonium and carboxylic acid groups (O−H, 1.04 Å and H···O, 1.54 Å). In the following, only **AendoTransHa** and **BexoTransHb** will be further investigated. Two acidic species are present in the medium to form them: acrylic acid and the HDA products themselves. The energies for first molecule path are equal to 42.2 (**AendoTrans**) and 40.9 kcal (**BexoTrans**), while the autoprotolysis of the bicyclic products, respectively, requires 37.9 and 39.9 kcal/mol, so that it may be privileged. Then, the opening of the bridges can occur in two ways, depending on which carbon center the positive charge is formally created. When it is generated on C^2 (respectively C^5), the corresponding carbocations will be denoted "C2" (respectively "C5"), as shown in Figure S4 (Supporting Information).

The relative Gibbs energies (with **AendoTransHa** as reference) equal −0.3 (**AendoTransHaC2**), −6.4 (**AendoTransHaC5**), −6.0 (**BexoTransHbC5**), and −3.5 kcal/mol (**BexoTransHbC2**), while the associated activations barriers are 2.3, 5.6, 4.4, and 3.3 kcal/mol, respectively, being almost insensitive to temperature since this step is a pure intramolecular rearrangement. The hydrogen bonds in **BexoTransHbC5** and **BexoTransHbC2** can be compared: O−H = 0.97 Å and H···O = 1.99 Å, O−H = 0.97 Å, and H···O = 2.01 Å, respectively, a possible qualitative reason for the greater stability of first compound. Interestingly, **AendoTransHaC5** can undergo a series of isomerizations (Figure S4, Supporting Information): first, the rotation (requiring 5.0 kcal/mol) of the OH bond around the C−O bond, leading to **AendoTransHaC5b** (see Figure S5, Supporting Information) and affording a product that is only 0.7 kcal/mol higher in energy. Then, the alcohol group can flip to form a hydrogen bond with the carboxylic group (O−H = 0.97 Å, H···O = 2.02 Å) at a low energetic cost (7.0 kcal/mol), giving **AendoTransHaC5c**, which is 2.3 kcal/mol higher in energy than **AendoTransHaC5b**.

Even if **AendoTransHaC5b** is not the most stable product, it is the only one that can reasonably lead to the rearomatization of the six-membered ring. Actually, as shown in Figure S5 (Supporting Information), the oxygen atom and one of the CH_2 hydrogens are on the same cycle side and almost on the same bonding plane ($\angle OC^5C_\beta H^6 = 15°$). In addition, $O\cdots H^6$ is only 2.56 Å, so that this conformation (that is hold locked by the hydrogen bond between OH and COOH, which "pushes" the OEt in axial position) is prone to endure a hydrogen shift from carbon to oxygen, a prelude to the planarization of the hexacycle. The corresponding optimized TS (**TSshift**) is represented in Figure S6 (Supporting Information) as well as the local minimum that is connected to it (**ProductShift**) where C_2H_5OH still strongly interacts with the cycle (C^5-O = 1.60 Å). The corresponding Gibbs activation barrier is equal to 17.6 (25 °C) and 18.2 kcal/mol (150 °C), while **ProductShift** is only 2.6 kcal/mol (at 150 °C) higher in energy than the initial **AendoTransHa** product.

In order to account for this proton move, Bader's atoms-in-molecules theory (QTAIM)[22] is invoked, and in particular Pendás' interacting quantum atoms (IQA) approach,[23] which enables rigorous estimation of the interatomic interaction energies (IEs). First, we compare those for the two $C_\beta-H$ bonds: −147.8 kcal/mol for $C_\beta-H^6$, −151.7 kcal/mol for $C_\beta-H^7$, proving that the interaction of H^6 with oxygen weakens the $C_\beta-H^6$ bond, a fact that is corroborated by a smaller electron accumulation in the bonding region (lower electron density value at the characteristic bond critical point: 0.289 au vs 0.296 au, less negative laplacian values: −1.106 au vs −1.153 au) and which also reflects in smaller bond orders (0.90 vs 0.92). As expected, the $O\cdots H^6$ interaction is stabilizing and mainly of electrostatics character (83%), and its energy equals −15.2 kcal/mol.

At the transition state, the situation is reversed: the forming $O-H^7$ bond becomes the most energetic one (IE equal to −163.1 kcal/mol) with an increasing covalency character (representing 31%), while the IE between the two atoms forming the breaking $C_\beta-H^6$ bond equals −86.2 kcal/mol, the bond becoming partly of electrostatic nature (25%). It is also worth noting that the C^5-O bond remains very strong (IE = −400 kcal/mol), so that ethanol elimination is scarcely initiated at this step.

The release of ethanol and **Cycle1** (Figure S7, Supporting Information) is a multistep process: from **ProductShift**, a TS (where C−O = 2.05 Å) leads to a minimum where C−O = 2.42 Å. The activation barrier is lower than 2.4 kcal/mol at any temperature and is strongly entropically favored. Determining this pathway is thus irrelevant. Conversely, it is pertinent to look at the whole **AendoTransHa->Cycle1** + C_2H_5OH process: the Gibbs reaction energy equals 3.0 kcal/mol at 25 °C, 0.8 kcal/mol at 150 °C, and −2.0 kcal/mol at 250 °C. This equilibrium can be more displaced in presence of a base like NMe_3, the proton exchange between **Cycle1** and NMe_3 affording **Cycle2** (Figure S6, Supporting Information) that is strongly thermodynamically favored (−35.5 kcal/mol). It also induces a simultaneous transfer of the hydrogen of the alcohol group to the carboxylic group. Finally, the decarboxylation can occur, as described in our previous paper: the C−H bond comes into the plane and the C−C simultaneously elongates, as evidenced in Figure S8 (Supporting Information). The corresponding barrier is equal to 11.7 kcal/mol, while the final products (hydroxypyridine + CO_2 + NMe_3H^+) are 29.3 kcal/mol lower in energy than **Cycle2**. This final step is accordingly at the same time kinetically affordable and strongly thermodynamically favored.

dx.doi.org/10.1021/jo402729a | J. Org. Chem. 2014, 79, 1303−1319

In summary, four main activation barriers drive the process: the HDA cycloaddition (for which the *exo* and *endo* approaches feature very close activation energies), the oxygen protonation (which is the rate determining step if the medium is not enough acidic), the hydrogen shift leading to ethanol elimination, and the final rearomatization with CO_2 release. Having determined the favored pathway, we aim now at unravelling the role of oxazole substituents. To this purpose, we computed the corresponding activation energies for the **Aendo1** path when *n*Pr is substituted by Ph (compound **1i**) and H. The corresponding TSs states are represented below in Figure 2 for this last family.

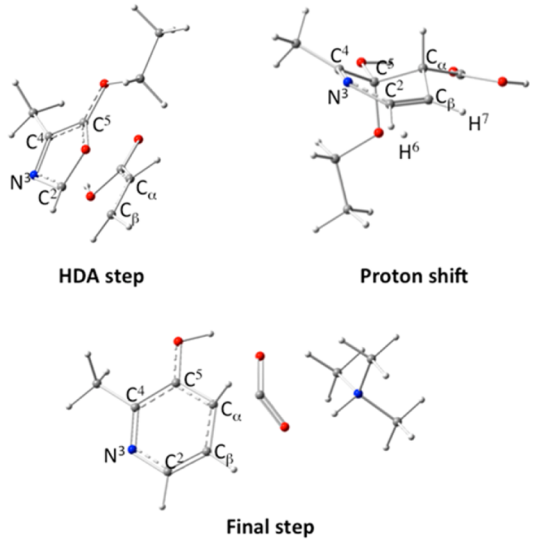


Figure 2. Views of the main transition states along the reaction path for the H family. Key: H, white; C, gray; N, blue; O, red.

As for the first step, the following activation Gibbs energies ranking was obtained at 150 °C: 18.9 (H), 19.3 (*n*Pr), 20.1 (Ph) kcal/mol. Interestingly, this hierarchy can be qualitatively justified by using the previously designed reactivity descriptors. Indeed, from an electrostatic point of view, the three reactants are expected to be equally reactive, the values for $Pref\,Q(A)$ being equal to −0.030 au (H) and −0.031 au (*n*Pr and Ph). On the contrary, a clear discrimination appears in terms of $S^2 Pref\Delta f(A)$ (note that the global softness has little influence by itself), following the energetic trend −0.075 au (H), −0.051 au (*n*Pr), −0.028 au (Ph). The substituents thus mainly modulate the oxazole nucleophilicity.

We next turned our attention to the hydrogen shift. The computed Gibbs activation energies are equal to 14.1 kcal/mol (H), 18.3 (*n*Pr), and 22.3 (Ph) kcal/mol. Interestingly, this consequent variability can be justified from the IQA point of view by inspecting IEs in the corresponding **AendoTransHaC5c** precursors. For the C_β–H^6 bond, we obtained −147.1 kcal/mol in the H case and −147.8 for the *n*Pr compound. Concerning the O···H^6 interaction, the related IEs are respectively equal to −15.8 (H) and −15.2 (*n*Pr) kcal/mol. It follows that for the H compound two cumulative factors favor the proton shift with respect to the *n*Pr case: a stronger O···H^6 interaction and a weaker C_β–H^6 bond. The same kind of analysis can be conducted to explain the higher activation barrier for the Ph compound: the C_β–H^6 IE is almost equal as the one for *n*Pr (−147.5 vs 147.8 kcal/mol), but the IE for the O···H^6 interaction, which is fundamental to produce the proton shift, is consequently lower in absolute value (−13.8 to compared to −15.2 kcal/mol), providing an energetic hint for the higher activation barrier for the Ph compound.

Lastly, the activation energies for the full rearomatization through CO_2 release are almost independent of the substituents, and the ranking slightly depends on temperature: 12.0 (*n*Pr) < 12.2 (H) < 12.3 (Ph) at 0 K and 11.7 (*n*Pr) < 13.3 (Ph) < 14.1 (H) kcal/mol at 150 °C. The fact that these energies are all close to one another can be ascribed to the fact that the varied substituents have almost no contribution to the energy of the C–C breaking bond. This can be measured in terms of the source function (eq S7, Supporting Information) that measures how many electrons atoms bring to a specific region. We found that for the H compound the contribution of H to the electron density at the C–C breaking bond critical point is equal to 0.0013 au, representing 0.5% of the total density at this point. Similarly, we obtained that *n*Pr contributes for 0.0018 au (0.7%), and Ph for 0.0019 au (0.8%). In each case, these sources are positive, meaning that these substituents tend to enrich in electrons the bonding zone, but these contributions are too small to strongly influence the considered activation barrier.

In conclusion, this theoretical study showed that the energy profile for this one-pot reaction is complex, many conformations being close in energy with low corresponding interconversion energies. The regioselectivity (route A preferred rather than route B) may stem not from the HDA step but from the fact that an intermediate compound (**AendoTransHaC5b**, whose geometry is locked by an intramolecular hydrogen bond) in the first path can undergo a proton shift leading to a favored ethanol elimination. Importantly, it was shown that all key intermediates feature specific intramolecular interactions that govern the final selectivity of the reaction.

The influence of the substituents was subsequently studied and was shown to vary along the reaction path: very small for the final rearomatization process but not negligible for the HDA step, and more considerable for the proton shift. These effects were rationalized in the framework of conceptual DFT and Bader's theory, two approaches deeply rooted in physics and which share the same primary ingredient (the electron density) as DFT. From this viewpoint, we suggest the use of consistent combined DFT (to determine the energetic profile)–conceptual DFT (to characterize the intrinsic reactivity of reactants)–QTAIM (in particular in its IQA flavor, to quantify interatomic interactions) strategy in organic chemistry.

■ CONCLUSION

In summary, a complete joint experimental and theoretical study (defining a framework that could be generally applied in computational organic chemistry) of the decarboxylative HDA reaction between readily available 5-alkoxyoxazoles and acrylic is reported. The synthetic method is general and compatible with a plethora of functional groups, affording a rapid route to functionalized 3-hydroxypyridine derivatives. Furthermore, this process offers an original and versatile route to *N*-fused bicyclic hydroxypiperidine systems such as hydroxyquinolizidine or hydroxyindolizidine through a dearomatization/ring closure strategy.

dx.doi.org/10.1021/jo402729a | J. Org. Chem. 2014, 79, 1303–1319

EXPERIMENTAL SECTION

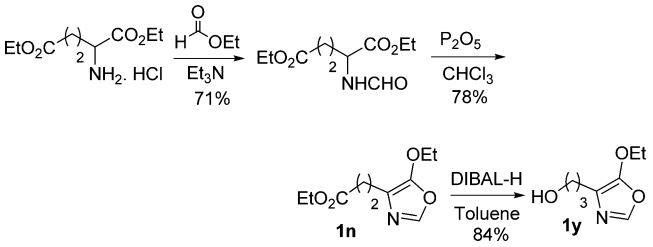
General Information. All solvents were dried following standard procedures: CH_2Cl_2, CH_3CN, triethylamine, distillation over CaH_2; DMF, MeOH, and xylene, dried over 3 Å MS; THF, distillation over Na/benzophenone. $CHCl_3$ was washed with water to remove ethanol, dried over $MgSO_4$, and distilled over P_2O_5. Acrylic acid was distilled prior to use. Commercially available reagents were used without further purification. HRMS were obtained using the electrospray ionization (ESI) technique and a time-of-flight (TOF) analyzer. ^1H and ^{13}C NMR chemical shifts are expressed in parts per million (ppm) from $CDCl_3$ (δ_H = 7.26, δ_C = 77.00), DMSO-d_6 (δ_H= 2.50, δ_C = 39.43), MeOD-d_4 (δ_H = 3.31, δ_C = 49.05), CD_3CN-d_3 (δ_H = 1.94, δ_C = 1.9). Multiplicities are describedd as s (singlet), d (doublet), dd, ddd, etc. (doublet of doublets, doublet of doublets of doublets, etc.), t (triplet), q (quadruplet), quin (quintuplet), sext (sextuplet), sept (septuplet), dt (doublet of triplets), td (triplet of doublets), m (multiplet), b (broad). Coupling constants, J, are reported in hertz.

High-pressure hydrogenations were carried out in a Berghof reactor BR 25. Microwave reactions were performed using a CEM Focused Microwave Synthesis System TM apparatus, Model Discover. The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. All the reactions were performed in special 10 mL glass vessels under an atmosphere of argon. Reaction mixture temperatures were measured during microwave heating with an IR surface sensor located in the base of the Discover. For 5-alkoxyoxazoles synthesis, the temperature fixed to 130 °C was maintained for 3 min (i.e., hold time: time the system maintains the control parameters) and was usually reached within 1 min (i.e., run time: maximum run time for the method for situations where the control point is not reached). For 3-hydroxypyridine synthesis, the temperature fixed to 150 °C was maintained for 60 min and was usually reached within 1 min.

The oxazoles **1a−l,p,u,w,z** were prepared according to known procedures.[17] The other 5-alkoxyoxazoles were prepared as described below.

Methyl 13-((1-Ethoxy-1-oxopropan-2-yl)amino)-13-oxotridecanoate. To a solution of the 12-(methoxycarbonyl)dodecanoic acid (1.50 g, 5.81 mmol) in dry THF (50 mL) under inert atmosphere, at 0 °C, were added dropwise and successively *N*-methylmorpholine (0.70 mL, 6.39 mmol, 1.1 equiv) and isobutyl chloroformate (0.76 mL, 5.81 mmol, 1 equiv). The mixture was then stirred at 0 °C for 30 min. Then ethyl alaninate hydrochloride (1.07 g, 6.97 mmol, 1.2 equiv) and *N*-methylmorpholine (0.77 mL, 6.97 mmol, 1.2 equiv) were successively added. The reaction was stirred at 0 °C for 1 h and then was allowed to stir at room temperature. The reaction was monitored by TLC for consumption of the starting material. The solution was quenched with a solution of satd aq $NaHCO_3$ (20 mL), and the resulting mixture was extracted with AcOEt (2 × 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (AcOEt/cyclohexane 3:7) to give the desired product as a white solid (1.04 g, 2.90 mmol, 50%). Mp: 76−78 °C. IR (neat): 3325, 2910, 2853, 1739, 1736, 1641, 1527, 1470, 1202, 1169, 1023. ^1H (300 MHz, $CDCl_3$): δ 5.99 (d, J = 6.6 Hz, 1H), 4.59 (quin, J = 7.1 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.67 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 2.20 (t, J = 6.0 Hz, 2H), 1.65−1.58 (m, 4H), 1.40 (d, J = 7.2 Hz, 3H), 1.33−1.23 (m, 14H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 174.3, 173.2, 172.6, 61.3, 51.4, 47.9, 36.5, 34.1, 29.4, 29.4, 29.3, 29.2, 29.1, 25.5, 24.9, 18.5, 14.1. HRMS (ESI+): calcd for $C_{19}H_{36}NO_5$ 358.2593, found 358.2597.

Methyl 12-(5-Ethoxy-4-methyloxazol-2-yl)dodecanoate (1m). It was prepared according to the procedure described in the literature[17] using methyl 13-((1-ethoxy-1-oxopropan-2-yl)amino)-13-oxotridecanoate (600 mg, 1.68 mmol), CaO (471 mg, 8.40 mmol, 5 equiv), Celite (120 mg, 20% by weight relatively to the starting amido ester), and P_2O_5 (954 mg, 6.72 mmol, 4 equiv) in dry $CHCl_3$ (25 mL). The resulting mixture was hydrolyzed by a solution of satd aq $NaHCO_3$. The crude product was finally purified by chromatography on silica gel (100% AcOEt) to give the product as a colorless oil (371 mg, 1.09 mmol, 65%). IR (neat): 2918, 2853, 1739, 1674, 1577, 1437, 1327, 1243, 1094. ^1H (300 MHz, $CDCl_3$): δ 4.09 (q, J = 7.0 Hz, 2H), 3.65 (s, 3H), 2.57 (t, J = 7.7 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 1.98 (s, 3H), 1.72−1.54 (m, 4H), 1.37−1.22 (m, 14H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 174.1, 155.7, 153.3, 112.2, 70.1, 51.3, 34.0, 29.4, 29.3, 29.2, 29.1, 29.0, 29.0, 28.4, 26.8, 24.9, 14.9, 9.9. HRMS (ESI+): calcd for $C_{19}H_{34}NO_4$ 340.2488, found 340.2491.



***N*-Formylglutamic Acid Diethyl Ester.** To a mixture of glutamic acid diethyl ester hydrochloride (2.0 g, 8.4 mmol) and ethyl formate (4.20 mL, 52.0 mmol, 6.2 equiv) under inert atmosphere were added triethylamine (1.24 mL, 9.2 mmol, 1.1 equiv). The reaction was stirred at 60 °C for 12 h, filtered through Celite, and washed with ethyl acetate and the filtrate concentrated. The residue was purified by chromatography on silica gel (cyclohexane/AcOEt 1:1), to give the product as a colorless oil (1.38 g, 6 mmol, 71%). IR (neat): 3320, 2984, 1733, 1669, 1522. ^1H (300 MHz, $CDCl_3$): δ 8.22 (s, 1H), 6.34 (d, J = 5.7 Hz, 1H), 4.70 (tq, J = 5.1, 7.8 Hz, 1H), 4.22 (qd, J = 1.2, 7.2 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 2.50−2.19 (m, 3H), 2.08−1.96 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 6.9 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 172.6, 171.3, 160.8, 61.7, 60.6, 50.2, 30.1, 27.2, 14.0, 13.9. HRMS (ESI+): calcd for $C_{10}H_{18}NO_5$ 232.1185, found 232.1185.

Ethyl 3-(5-Ethoxyoxazol-4-yl)propanoate (1n). Compound **1n** was prepared according to the procedure described in the literature[17] using *N*-formylglutamic acid diethyl ester (800 mg, 3.46 mmol), CaO (970 mg, 17.30 mmol, 5 equiv), Celite (160 mg, 20% by weight relatively to the starting amidoester), and P_2O_5 (1.96 g, 13.9 mmol, 4 equiv) in dry $CHCl_3$ (30 mL). The resulting mixture was hydrolyzed by a solution of satd aq $NaHCO_3$. The crude product was finally purified by chromatography on silica gel (100% AcOEt) to give the product as an orange oil (578 mg, 2.71 mmol, 78%). IR (neat): 2985, 2923, 1731, 1669, 1516, 1376, 1332, 1262. ^1H (300 MHz, $CDCl_3$): δ 7.37 (s, 1H), 4.17 (q, J = 7.0 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 2.77−2.71 (m, 2H), 2.65−2.60 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 172.5, 154.0, 142.1, 114.3, 69.9, 60.0, 32.6, 19.8, 14.7, 13.9. HRMS (ESI+): calcd for $C_{10}H_{15}NO_4Na$ 236.0899, found 236.0902.

3-(5-Ethoxyoxazol-4-yl)propan-1-ol (1y). To a solution of the ester **1n** (450 mg, 2.11 mmol) dissolved in dry THF (10 mL) under inert atmosphere at −78 °C was added diisobutylaluminum hydride (7.0 mL, 8.4 mmol, 4 equiv, C = 1.2 mol/L into toluene) dropwise. The resulting reaction mixture was warmed to 0 °C over 4 h. The solution was carefully quenched with a solution of satd aq Rochelle's salt (10 mL) and stirred for 1 h at room temperature. The resulting solution was extracted with AcOEt (2 × 30 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (AcOEt/cyclohexane 8:2) to give the desired product as a colorless oil (304 mg, 1.8 mmol, 84%). IR (neat): 3350, 2941, 1663, 1513. ^1H (300 MHz, $CDCl_3$): δ 7.41 (s, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.70 (t, J = 5.7 Hz, 2H), 2.55 (t, J = 6.9 Hz, 2H), 2.15 (b, 1H), 1.85 (q, J = 6.0 Hz, 2H), 1.37 (t, J = 6.9 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 153.9, 142.2, 115.5, 70.0, 61.5, 31.1, 20.8, 14.7. HRMS (ESI+): calcd for $C_8H_{13}NO_3Na$ 194.0793, found 194.0786.

Methyl 6-(5-Ethoxy-2-methyloxazol-4-yl)hexanoate (1o). Compound **1o** was prepared according to the procedure described in the literature[17] using the 1-ethyl 8-methyl 2-acetamidooctanedioate[34] (400 mg, 1.46 mmol), CaO (410 mg, 7.32 mmol, 5 equiv), Celite (80 mg, 20% by weight relatively to the starting amido ester), and P_2O_5 (831 mg, 5.85 mmol, 4 equiv) in dry $CHCl_3$ (12 mL). The

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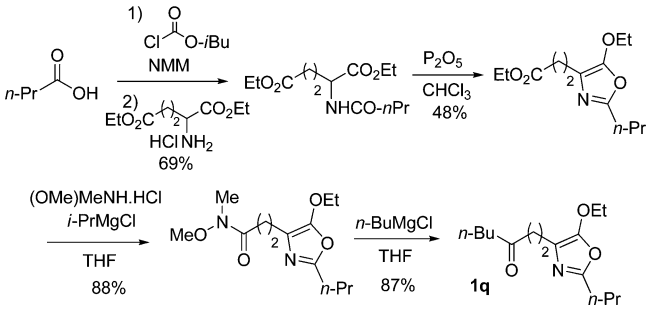
reaction was monitored by TLC for consumption of the starting material. The resulting mixture was hydrolyzed by a solution of satd aq $NaHCO_3$. The crude product was finally purified by chromatography on silica gel (100% AcOEt) to give the product as a yellow oil (281 mg, 1.10 mmol, 75%). IR (neat): 2937, 2857, 1737, 1667, 1583, 1440, 1377, 1263, 1200. ^1H (200 MHz, $CDCl_3$): δ 4.08 (q, J = 7.1 Hz, 2H), 3.66 (s, 3H), 2.37−2.26 (m, 4H), 2.23 (s, 3H), 1.72−1.52 (m, 4H), 1.42−1.24 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H), ^{13}C (75 MHz, $CDCl_3$): δ 173.9, 153.3, 152.0, 116.4, 70.1, 51.1, 33.7, 28.5, 28.0, 24.5, 24.2, 14.8, 14.0, HRMS (ESI+): calcd for $C_{13}H_{21}NO_4Na$ 278.1377, found 278.1368.



***N*-Butanoylglutamic Acid Diethyl Ester.** The compound was prepared according to the procedure described above using *n*-butanoic acid (0.78 mL, 8.54 mmol), *N*-methylmorpholine (1.03 mL, 9.39 mmol, 1.1 equiv), and isobutyl chloroformate (1.12 mL, 8.54 mmol, 1 equiv) in dry THF (30 mL). Subsequently, diethyl 2-aminopentanedioate hydrochloride (2.46 g, 10.3 mmol, 1.2 equiv) and *N*-methylmorpholine (1.13 mL, 10.3 mmol, 1.2 equiv) were successively added. The crude product was finally purified by chromatography on silica gel (pentane/AcOEt 7:3), to give the product as a white solid (1.62 g, 5.9 mmol, 69%) with a low melting point (below 40 °C). IR (neat): 3319, 2963, 2878, 1745, 1719, 1644, 1527, 1384. ^1H (200 MHz, $CDCl_3$): δ 6.17 (d, J = 8.0 Hz, 1H), 4.61 (td, J = 7.5 Hz, J = 8.0 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 2.44−2.33 (m, 2H), 2.29−2.11 (m, 3H), 2.06−1.92 (m, 1H), 1.66 (sext, J = 7.5 Hz, 2H), 1.34−1.21 (m, 6H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C (50 MHz, $CDCl_3$): δ 173.0, 172.7, 171.9, 61.2, 60.4, 51.3, 38.0, 30.2, 27.0, 18.8, 13.9, 13.9, 13.4. Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.87; H, 8.89; N, 5.19.

Ethyl 3-(5-Ethoxy-2-propyloxazol-4-yl)propanoate. The compound was prepared according to the procedure described in the literature[17] using diethyl 2-butyramidopentanedioate (1.50 g, 5.4 mmol), CaO (1.54 g, 27.5 mmol, 5 equiv), Celite (300 mg, 20% by weight relatively to the starting amidoester), and P_2O_5 (3.12 g, 22.0 mmol, 4 equiv) in dry $CHCl_3$ (30 mL). The resulting mixture was hydrolyzed by a solution of satd aq $NaHCO_3$. The crude product was finally purified by chromatography on silica gel (100% CH_2Cl_2) to give the product as a yellow oil (673 mg, 2.64 mmol, 48%). IR (neat): 2968, 2929, 1733, 1670, 1375, 1179, 1141, 1090, 1021. ^1H (200 MHz, $CDCl_3$): δ 4.12 (q, J = 7.2 Hz, 2H), 4.11 (q, J = 7.1 Hz, 2H), 2.74−2.53 (m, 6H), 1.81−1.63 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C (50 MHz, $CDCl_3$): δ 172.6, 155.5, 153.2, 114.5, 70.0, 60.0, 32.8, 30.2, 20.1, 20.0, 14.7, 13.9, 13.3. HRMS (ESI+): calcd for $C_{13}H_{22}NO_4$ 256.1549, found 256.1539.

3-(5-Ethoxy-2-propyloxazol-4-yl)-*N*-methoxy-*N*-methylpropanamide. To a solution of ethyl 3-(5-ethoxy-2-propyloxazol-4-yl)propanoate (557 mg, 2.18 mmol) dissolved in dry THF (8 mL) under inert atmosphere at −10 °C were added successively *N*,*O*-dimethylhydroxylamine hydrochloride (447 mg, 4.58 mmol, 2.1 equiv) and isopropyl magnesium chloride (4.6 mL, 9.16 mmol, 4.2 equiv, C = 2.0 mol/L into THF) dropwise. The reaction was stirred for 1.5 h and monitored by TLC for consumption of the starting material. The mixture was then quenched with a solution of satd aq NH_4Cl (10 mL), and the resulting mixture was extracted with AcOEt (2 × 25 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (100% AcOEt, R_f = 0.4) to give the product as a pale yellow oil (519 mg, 1.92 mmol, 88%). IR (neat): 2966, 2905, 1668, 1442, 1376, 1258. ^1H (300 MHz, $CDCl_3$): δ 4.12 (q, J = 7.2 Hz, 2H), 3.67 (s, 3H), 3.17 (s, 3H), 2.77−2.67 (m, 4H), 2.58 (t, J = 7.5 Hz, 2H), 1.72 (sext, J = 7.5 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H). ^{13}C (50 MHz, $CDCl_3$): δ 173.2, 155.3, 153.1, 114.9, 69.9, 60.8, 31.9, 30.3, 30.1, 20.1, 19.4, 14.6, 13.3. HRMS (ESI+): calcd for $C_{13}H_{23}N_2O_4$ 271.1658, found 271.1651.

1-(5-Ethoxy-2-propyloxazol-4-yl)heptan-3-one (1q). To a solution of 3-(5-ethoxy-2-propyloxazol-4-yl)-*N*-methoxy-*N*-methylpropanamide (519 mg, 1.92 mmol) dissolved in dry THF (8 mL) under inert atmosphere was added dropwise *n*-butylmagnesium chloride (4.8 mL, 9.6 mmol, 5 equiv, C = 2.0 mol/L into THF) at room temperature. The reaction was stirred for 30 min and then quenched with a solution of satd aq NH_4Cl (10 mL), and the resulting mixture was extracted with AcOEt (2 × 25 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (pentane/AcOEt 8:2) to give the product as a pale yellow oil (1.67 mmol, 446 mg, 87%). IR (neat): 2966, 2928, 2882, 1713, 1668, 1457, 1376, 1258. ^1H (200 MHz, $CDCl_3$): δ 4.11 (q, J = 7.0 Hz, 2H), 2.77−2.69 (m, 2H), 2.65−2.53 (m, 4H), 2.40 (t, J = 7.4 Hz, 2H), 1.81−1.64 (m, 2H), 1.62−1.47 (m, 2H), 1.35 (t, J = 7.0 Hz, 3H), 1.29−1.19 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C (50 MHz, $CDCl_3$): δ 210.4, 155.9, 153.4, 115.1, 70.4, 42.7, 41.1, 30.5, 26.0, 22.4, 20.5, 18.9, 15.1, 13.9, 13.7. HRMS (ESI+): calcd for $C_{15}H_{26}NO_3$ 268.1913, found 268.1911.

***N*-Acetylmethionine Sulfone Ethyl Ester.** To a solution of methionine sulfone (2.00 g, 11 mmol) in dry ethanol (60 mL) under inert atmosphere at 0 °C was added thionyl chloride (2.4 mL, 33 mmol, 3 equiv) dropwise. The resulting solution was stirred at reflux for 6 h and concentrated. The residue was taken up into diethyl ether, and the resulting white solid was filtrated. The solid was washed with two portions of diethyl ether to afford the corresponding pure ethyl ester hydrochloride (2.68 g, 10.9 mmol). To a solution of the previously prepared ethyl ester hydrochloride (2.68 g, 10.9 mmol) in dry dichloromethane (30 mL) at 0 °C were successfully added triethylamine (3.7 mL, 26.6 mmol, 2.4 equiv) and acetic anhydride (1.08 mL, 11.6 mmol, 1.06 equiv). The solution was stirred at room temperature for 2 h and quenched with a solution of satd aq $NaHCO_3$ (15 mL), and the resulting mixture was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (100% AcOEt, then 2% EtOH) to give the product as a white solid (2.172 g, 8.6 mmol, 79%). Mp: 100−102 °C. IR (neat): 3321, 2934, 1724, 1642, 1544, 1241. ^1H (300 MHz, $CDCl_3$): δ 6,53 (d, J = 7.5 Hz, 1H), 4.65 (td, J = 4.8 Hz, 8.1 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.20−2.98 (m, 2H), 2.91 (s, 3H), 2.46−2.34 (m, 1H), 2.24−2.08 (m, 1H), 2.02 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 170.9, 170.3, 62.0, 51.0, 50.6, 40.7, 25.3, 22.9, 14.0. HRMS (ESI+): calcd for $C_9H_{18}NO_5S$ 252.0906, found 252.0904.

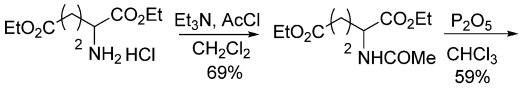
5-Ethoxy-2-methyl-4-(2-(methylsulfonyl)ethyl)oxazole (1r). It was prepared according to the procedure described in the literature[17] using ethyl 2-acetamido-4-(methylsulfonyl)butanoate (380 mg, 1.51 mmol), CaO (423 mg, 7.55 mmol, 5 equiv), Celite (76 mg, 20% by weight relatively to the starting amidoester), and P_2O_5 (857 mg, 6.04 mmol, 4 equiv) in dry $CHCl_3$ (13 mL). The resulting mixture was hydrolyzed by a solution of satd aq $NaHCO_3$. The crude product was finally purified by chromatography on silica gel (100% AcOEt) to give the product as a colorless oil (317 mg, 1.36 mmol, 90%). IR (neat): 2960, 2929, 1671, 1586, 1444, 1378, 1286, 1266, 1216. ^1H (300 MHz, $CDCl_3$): δ 4.15 (t, J = 7.1 Hz, 2H), 3.33−3.28 (m, 2H), 2.94−2.86 (m, 2H), 2.88 (s, 3H), 2.32 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 153.3, 152.1, 111.7, 69.8, 52.5, 40.2, 17.7, 14.4, 13.6. HRMS (ESI+): calcd for $C_9H_{15}NO_4NaS$ 256.0619, found 256.0611.

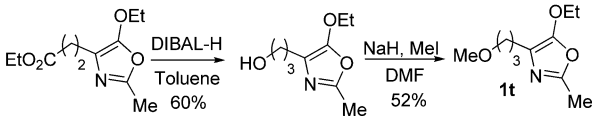
(*O*-Phenylethyl)-*N*-acetyltyrosine Ethyl Ester. To a solution of *N*-acetyltyrosine ethyl ester (1.79 g, 7.1 mmol) in dry DMF (10 mL) under inert atmosphere were added successively K_2CO_3 (2.95 g, 21.4 mmol, 3 equiv) and 1-bromo-3-phenylpropane (1.84 mL, 14.2 mmol, 2 equiv). The solution then was allowed to stir at 50 °C for one night.

dx.doi.org/10.1021/jo402729a | J. Org. Chem. 2014, 79, 1303−1319

The solution was quenched with a solution of satd aq $NaHCO_3$ (15 mL), and the resulting mixture was extracted with AcOEt (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (AcOEt/cyclohexane 1:1) to give the desired product as a white solid (577 mg, 1.56 mmol, 22%). Mp: 88−90 °C. IR (neat): 3343, 2993, 2945, 2927, 2866, 1745, 1648, 1528, 1516, 1449, 1377, 1244, 1220. ^{1}H (300 MHz, $CDCl_3$): δ 7.32−7.17 (m, 5H), 7.00 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 5.88 (d, J = 7.8 Hz, 1H), 4.85−4.78 (m, 1H), 4.18 (dq, J = 7.2, 0.8 Hz, 2H), 3.93 (t, J = 6.3 Hz, 2H), 3.12−3.00 (m, 2H), 2.81 (t, J = 7.5 Hz, 2H), 2.14−2.05 (m, 2H), 1.99 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 171.8, 169.6, 158.2, 141.5, 130.3, 128.5, 128.5, 127.8, 126.0, 114.6, 66.9, 61.5, 53.3, 37.1, 32.2, 30.9, 23.2, 14.2. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.13; H, 7.27; N, 3.81.

5-Ethoxy-2-methyl-4-(4-(3-phenylpropoxy)benzyl)oxazole (1s). Compound **1s** was prepared according to the procedure described in the literature[17] using (*O*-phenylethyl)-*N*-acetyltyrosine ethyl ester (937 mg, 2.54 mmol), CaO (712 mg, 12.70 mmol, 5 equiv), Celite (187 mg, 20% by weight relatively to the starting amido ester), and P_2O_5 (1.44 g, 10.2 mmol, 4 equiv) in dry $CHCl_3$ (30 mL). The resulting mixture was hydrolyzed by a solution of satd aq $NaHCO_3$. The crude product was finally purified by chromatography on silica gel (AcOEt/cyclohexane 1:1) to give the product as an orange oil (415 mg, 1.18 mmol, 47%). IR (neat): 2929, 2859, 1672, 1611, 1580, 1511, 1454, 1371, 1241. ^{1}H (300 MHz, $CDCl_3$): δ 7.30−7.14 (m, 7H), 6.82−6.76 (d, J = 8.7 Hz, 2H), 4.08 (q, J = 7.1 Hz, 2H), 3.93 (t, J = 6.2 Hz, 2H), 3.63 (s, 2H), 2.79 (t, J = 7.7 Hz, 2H), 2.30 (s, 3H), 2.12−2.03 (m, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 157.4, 153.7, 152.2, 141.4, 131.4, 129.3, 128.4, 128.2, 125.7, 116.1, 114.4, 77.5, 77.1, 76.7, 70.2, 66.7, 32.0, 30.7, 30.0, 14.9, 14.2. HRMS (ESI+): calcd for $C_{22}H_{25}NO_3Na$ 374.1732, found 374.1727, calcd for $C_{22}H_{26}NO_3$ 352.1913, found 352.1903.





***N*-Acetylglutamic Acid Ethyl Ester.** To a solution of glutamic acid diethyl ester hydrochloride (1.0 g, 4.9 mmol) in dry CH_2Cl_2 (10 mL) under inert atmosphere, at 0 °C, were added dropwise and successively triethylamine (2.1 mL, 14.7 mmol, 3 equiv) and acetyl chloride (380 μL, 5.39 mmol, 1.1 equiv). The reaction was stirred at 0 °C for 1 h and then was allowed to stir for one night at room temperature. The solution was quenched with a solution of satd aq $NaHCO_3$, and the resulting mixture was extracted with AcOEt (×2). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (Petroleum ether/AcOEt 8:2), to give the product as a white solid with a low melting point (below 40 °C) (828 mg, 3.38 mmol, 69%). IR (neat): 3313, 2987, 2939, 1721, 1648, 1528, 1365, 1208. ^{1}H (300 MHz, $CDCl_3$): δ 6.20 (d, J = 6.6 Hz, 1H), 4.64−4.58 (m, 1H), 4.23−4.09 (m, 4H), 2.48−2.14 (m, 3H), 2.04−1.93 (m, 1H), 2.02 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 173.0, 172.1, 170.0, 61.8, 60.8, 51.8, 30.4, 27.5, 23.3, 14.3, 14.2. ^{1}H NMR spectrum was in accordance with literature data.[35]

Ethyl 3-(5-Ethoxy-2-methyloxazol-4-yl)propanoate. The compound was prepared according to the procedure described in the literature[17] using *N*-acetylglutamic acid ethyl ester (586 mg, 2.39 mmol), CaO (670 mg, 11.95 mmol, 5 equiv), Celite (120 mg, 20% by weight relatively to the starting amido ester), and P_2O_5 (1.36 g, 9.6 mmol, 4 equiv) in dry $CHCl_3$ (10 mL). The resulting mixture was heated during 3 h at 75 °C and then was hydrolyzed by a solution of satd aq $NaHCO_3$. The crude product was finally purified by chromatography on silica gel (AcOEt/CH_2Cl_2 5:95, R_f = 0.3) to give the product as a yellow oil (1.42 mmol, 323 mg, 59%). IR (neat): 2981, 1733, 1678, 1588, 1443, 1377, 1256. ^{1}H (300 MHz, $CDCl_3$): δ 4.10 (q, J = 7.2 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 2.68−2.63 (m, 2H), 2.59−2.53 (m, 2H), 2.27 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 184.5, 172.3, 159.4, 155.0, 63.2, 60.8, 29.4, 29.1, 24.2, 14.3, 14.0. HRMS (ESI+): calcd for $C_{11}H_{18}NO_4$ 228.1236, found 228.1233.

3-(5-Ethoxy-2-methyloxazol-4-yl)propan-1-ol. To a solution of ethyl 3-(5-ethoxy-2-methyloxazol-4-yl)propanoate (800 mg, 3.52 mmol) dissolved in dry THF (8 mL) under inert atmosphere at −78 °C was added diisobutylaluminum hydride (8.80 mL, 10.56 mmol, 3 equiv, C = 1.2 mol/L into toluene) dropwise. The resulting reaction mixture was warmed to 0 °C over 4 h. The solution was carefully quenched with a solution of satd aq Rochelle's salt (15 mL) and stirred for 1 h at room temperature. The resulting solution was extracted with AcOEt (2 × 20 mL), and the combined organic layers were washed with brine (8 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (AcOEt/cyclohexane 7:3) to give the desired product as a colorless oil (390 mg, 2.11 mmol, 60%). IR (neat): 3347, 2929, 2868, 1667, 1580, 1441, 1371, 1267, 1245. ^{1}H (300 MHz, $CDCl_3$): δ 4.11 (q, J = 7.1 Hz, 2H), 3.69 (t, J = 6.0 Hz, 2H), 2.49 (t, J = 6.9 Hz, 2H), 2.31 (s, 3H), 1.82 (quin, J = 6.4 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 153.5, 152.5, 116.1, 70.5, 62.2, 31.4, 21.5, 15.0, 14.3. HRMS (ESI+): calcd for $C_9H_{16}NO_3$ 186.1130, found 186.1130.

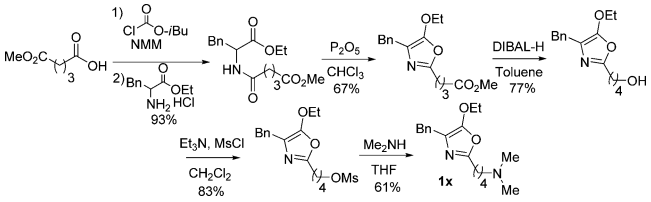
5-Ethoxy-4-(3-methoxypropyl)-2-methyloxazole (1t). To a solution of 3-(5-ethoxy-2-methyloxazol-4-yl)propan-1-ol (390 mg, 2.11 mmol) dissolved in dry DMF (4 mL) under inert atmosphere was added NaH (92 mg, 2.32 mmol, 1.1 equiv) at 0 °C. After 30 min at room temperature, iodomethane (143 μL, 2.36 mmol, 1.1 equiv) was added. The solution was then stirred for one night at room temperature. The reaction mixture was quenched with water (15 mL) and extracted with AcOEt (2 × 20 mL). The combined organic layers were washed with brine (8 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (AcOEt/cyclohexane 3:7) to give the desired product as a colorless oil (1.10 mmol, 220 mg, 52%). IR (neat): 2927, 2866, 1666, 1588, 1449, 1383, 1268, 1250, 1118, 1087, 1027, ^{1}H (300 MHz, $CDCl_3$): δ 4.10 (q, J = 7.0 Hz, 2H), 3.39 (t, J = 6.5 Hz, 2H), 3.33 (s, 3H), 2.42 (t, J = 7.5 Hz, 2H), 2.31 (s, 3H), 1.85 (quin, J = 7.4 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), ^{13}C (75 MHz, $CDCl_3$): δ 153.5, 152.0, 116.0, 71.7, 70.1, 58.2, 28.2, 21.0, 14.8, 14.0, HRMS (ESI+): calcd for $C_{10}H_{18}NO_3$ 200.1287, found 200.1287.

***N*,*N*-Diacetyllysine Ethyl Ester.** To a solution of lysine ethyl ester dihydrochloride (2.00 g, 8.0 mmol) in dry dichloromethane (40 mL) at 0 °C were successfully added triethylamine (4.58 mL, 33.0 mmol, 4.15 equiv) and acetic anhydride (1.56 mL, 16.5 mmol, 2.05 equiv). The solution was stirred at room temperature for 2 h and quenched with a solution of satd aq $NaHCO_3$ (10 mL), and the resulting mixture was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (from 5 to 20% EtOH/AcOEt) to give the product as a white solid (1.58 g, 6.1 mmol, 75%). Mp: 82−84 °C. IR (neat): 3301, 2937, 1724, 1640, 1544. ^{1}H (300 MHz, $CDCl_3$): δ 6.70 (d, J = 7.8 Hz, 1H), 6.40 (t, J = 4.8 Hz, 1H), 4.42 (td, J = 4.8, 8.1 Hz, 1H), 4.10 (q, J = 6.9 Hz, 2H), 3.17−3.10 (m, 2H), 1.95 (s, 3H), 1.89 (s, 3H), 1.81−1.58 (m, 2H), 1.50−1.41 (m, 2H), 1.34−1.26 (m, 2H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 172.3, 170.4, 170.2, 61.1, 51.8, 38.6, 31.5, 28.6, 22.9, 22.7, 22.2, 13.9. HRMS (ESI+): calcd for $C_{12}H_{23}N_2O_4$ 259.1658, found 259.1661.

***N*-(4-(5-Ethoxy-2-methyloxazol-4-yl)butyl)acetamide (1v).** To a solution of *N*,*N*-diacetyllysine ethyl ester (300 mg, 1.16 mmol) dissolved in dry $CHCl_3$ (2 mL) under inert atmosphere in a sealed glass tube were added successively Celite (20 mg) and P_2O_5 (659 mg, 4.64 mmol, 4 equiv). The reaction mixture was heated at 95 °C during 3 h, and an additional 4 equiv of P_2O_5 was added. The reaction

dx.doi.org/10.1021/jo402729a | J. Org. Chem. 2014, 79, 1303−1319

mixture was then stirred at 95 °C for 6 h. The solution mixture was hydrolyzed at 0 °C by a solution of satd aq $NaHCO_3$ (30 mL) and extracted by AcOEt (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (NH_4OH/EtOH/CH_2Cl_2 1:10:89), to give the product as a colorless oil (100 mg, 0.42 mmol, 36%). IR (neat): 3286, 3085, 2929, 2868, 1650, 1554, 1441, 1376, 1267, 1241. ^1H (300 MHz, $CDCl_3$): δ 5.65 (s, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.26 (q, J = 6.3 Hz, 2H), 2.37 (t, J = 7.1 Hz, 2H), 2.31 (s, 3H), 1.96 (s, 3H), 1.67−1.53 (m, 4H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 170.2, 153.5, 152.2, 116.1, 70.3, 39.3, 28.7, 25.8, 23.9, 23.1, 14.9, 14.1. HRMS (ESI+): calcd for $C_{12}H_{21}N_2O_3$ 241.1552, found 241.1554.



Methyl 5-(1-Ethoxy-1-oxo-3-phenylpropan-2-ylamino)-5-oxopentanoate. To a solution of the corresponding carboxylic acid and the 5-methoxy-5-oxopentanoic acid (1.275 g, 8.72 mmol) in dry THF (30 mL) under inert atmosphere, at 0 °C, were added dropwise and successively *N*-methylmorpholine (1.05 mL, 9.59 mmol, 1.1 equiv) and isobutyl chloroformate (1.14 mL, 8.72 mmol, 1 equiv). The mixture was then stirred at 0 °C for 30 min. Then ethyl 2-amino-3-phenylpropanoate hydrochloride (2.40 g, 10.46 mmol, 1.2 equiv) and *N*-methylmorpholine (1.15 mL, 10.46 mmol, 1.2 equiv) were successively added. The reaction was stirred at 0 °C for 1 h and then was allowed to stir at room temperature. The reaction was monitored by TLC for consumption of the starting material. The solution was quenched with a solution of satd aq $NaHCO_3$ (20 mL), and the resulting mixture was extracted with AcOEt (2 × 30 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (AcOEt/cyclohexane 3:7) to give the desired product as a pale yellow oil (8.10 mmol, 2.603 g, 93%). IR (neat): 3303, 2972, 2946, 1737, 1650, 1532, 1437, 1376, 1241, 1201. ^1H (300 MHz, $CDCl_3$): δ 7.29−7.21 (m, 3H), 7.08 (dd, J = 7.5, 1.8 Hz, 2H), 5.90 (d, J = 6.9 Hz, 1H), 4.84 (m, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.64 (s, 3H), 3.16−3.02 (m, 2H), 2.31 (t, J = 7.1 Hz, 2H), 2.21 (t, J = 7.2 Hz, 2H), 1.90 (quin, J = 7.3 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 173.5, 171.7, 136.0, 129.3, 128.5, 127.0, 61.5, 53.1, 51.5, 38.0, 35.1, 32.9, 20.7, 14.1. HRMS (ESI+): calcd for $C_{17}H_{24}NO_5$ 322.1654, found 322.1655.

Methyl 4-(4-Benzyl-5-ethoxyoxazol-2-yl)butanoate. The compound was prepared according to the procedure described in the literature[17] using methyl 5-((1-ethoxy-1-oxo-3-phenylpropan-2-yl)amino)-5-oxopentanoate (800 mg, 2.49 mmol), CaO (698 mg, 12.45 mmol, 5 equiv), Celite (160 mg, 20% by weight relatively to the starting amidoester), and P_2O_5 (1.41 g, 9.96 mmol, 4 equiv) in dry $CHCl_3$ (30 mL). The resulting mixture was hydrolyzed by a solution of satd aq $NaHCO_3$. The crude product was finally purified by chromatography on silica gel (100% CH_2Cl_2) to give the product as a colorless oil (505 mg, 1.67 mmol, 67%). IR (neat): 3033, 2981, 2955, 1737, 1663, 1580, 1493, 1454, 1437, 1376, 1354, 1319, 1249, 1210. ^1H (300 MHz, $CDCl_3$): δ 7.31−7.15 (m, 5H), 4.07 (q, J = 7.1 Hz, 2H), 3.72 (s, 2H), 3.66 (s, 3H), 2.67 (t, J = 7.4 Hz, 2H), 2.39 (t, J = 7.4 Hz, 2H), 2.04 (quin, J = 7.4 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 173.1, 154.5, 153.9, 139.3, 128.3, 128.2, 125.9, 115.4, 70.1, 51.3, 32.9, 30.8, 27.6, 22.0, 14.8. HRMS (ESI+): calcd for $C_{17}H_{21}NO_4Na$ 326.1368, found 326.1371.

4-(4-Benzyl-5-ethoxyoxazol-2-yl)butan-1-ol. To a solution of methyl 4-(4-benzyl-5-ethoxyoxazol-2-yl)butanoate (451 mg, 1.49 mmol) dissolved in dry toluene (4.5 mL) under inert atmosphere at −78 °C was added diisobutylaluminum hydride (3.73 mL, 4.47 mmol, 3 equiv, C = 1.2 mol/L into toluene) dropwise. After 3 h at −78 °C, the solution was carefully quenched with a solution of satd aq Rochelle's salt (15 mL) and stirred for 1 h at room temperature. The resulting solution was extracted with AcOEt (2 × 20 mL), and the combined organic layers were washed with brine (8 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (AcOEt/cyclohexane 1:1 then 100% AcOEt, R_f = 0.2 AcOEt/cyclohexane 1:1) to give the desired product as a yellow oil (315 mg, 1.14 mmol, 77%). IR (neat): 3361, 2933, 2860, 1666, 1582, 1498, 1449, 1371. ^1H (300 MHz, $CDCl_3$): δ 7.31−7.16 (m, 5H), 4.07 (q, J = 7.1 Hz, 2H), 3.72 (s, 2H), 3.61 (t, J = 6.2 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 1.80 (quin, J = 7.4 Hz, 2H), 1.60 (quin, J = 6.9 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 155.8, 153.9, 139.3, 128.4, 128.3, 126.0, 115.2, 70.3, 61.4, 31.9, 30.8, 28.0, 22.9, 14.9. HRMS (ESI+): calcd for $C_{16}H_{21}NO_3Na$ 298.1419, found 298.1424.

4-(4-Benzyl-5-ethoxyoxazol-2-yl)butyl Methanesulfonate. To a solution of 4-(4-benzyl-5-ethoxyoxazol-2-yl)butan-1-ol (257 mg, 0.93 mmol) in dry dichloromethane (5 mL) under inert atmosphere at 0 °C were added successively and dropwise triethylamine (0.16 mL, 1.12 mmol, 1.2 equiv) and methanesulfonyl chloride (79 μL, 1.02 mmol, 1.1 equiv). The solution then was allowed to stir for 2 h at room temperature. The solution was quenched with a solution of satd aq $NaHCO_3$ (10 mL), and the resulting mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (AcOEt/cyclohexane 1:1) to give the desired product as a yellow oil (273 mg, 0.77 mmol, 83%). IR (neat): 2937, 2763, 2806, 1667, 1576, 1454, 1380, 1249, 1140. ^1H (300 MHz, $CDCl_3$): δ 7.30−7.15 (m, 5H), 4.25 (t, J = 6 Hz, 2H), 4.06 (q, J = 7.1 Hz, 2H), 3.71 (s, 2H), 2.97 (s, 3H), 2.63 (t, J = 7.7 Hz, 2H), 1.87−1.78 (m, 4H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 154.9, 154.0, 139.2, 128.4, 128.3, 126.1, 115.3, 70.4, 69.4, 37.1, 30.7, 28.3, 27.6, 22.7, 14.9. HRMS (ESI+): calcd for $C_{17}H_{24}NO_5S$ 354.1375, found 354.1391.

4-(4-Benzyl-5-ethoxyoxazol-2-yl)-*N*,*N*-dimethylbutan-1-amine (1x). To a solution of 4-(4-benzyl-5-ethoxyoxazol-2-yl)butyl methanesulfonate (425 mg, 1.2 mmol) under inert atmosphere was added dimethylamine (6.0 mL, 12 mmol, 10 equiv, C = 2 mol/L into THF). The solution then was allowed to stir for 60 h at room temperature. The solution was quenched with a solution of satd aq $NaHCO_3$ (10 mL), and the resulting mixture was extracted with AcOEt (2 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (NH_4OH/EtOH/AcOEt 0.5:9.5:90) to give the desired product as a yellow oil (220 mg, 0.73 mmol, 61%). IR (neat): 2984, 2937, 1666, 1577, 1491, 1452, 1348, 1247, ^1H (300 MHz, $CDCl_3$): δ 7.28−7.14 (m, 5H), 4.06 (q, J = 6.0 Hz, 2H), 3.71 (s, 2H), 2.63 (t, J = 6.0 Hz, 2H), 2.26 (t, J = 6.0 Hz, 2H), 2.19 (s, 6H), 1.77−1.68 (m, 2H), 1.55−1.45 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 155.4, 153.8, 139.4, 128.3, 128.1, 125.9, 115.3, 70.1, 59.1, 45.3, 30.8, 28.3, 26.9, 24.7, 14.8. HRMS (ESI+): calcd for $C_{18}H_{27}N_2O_2$ 303.2073, found 303.2070.

General Procedure for the Synthesis of 3-Hydroxypyridines 2a−z. To the corresponding 5-alkoxyoxazole (1.2 mmol) dissolved in acetonitrile (3 mL) under inert atmosphere in a microwave vial, equipped with a magnetic stirrer bar, were successively added triethylamine (0.49 mL, 3.6 mmol, 3 equiv) and acrylic acid (0.16 mL, 2.4 mmol, 2 equiv). The vial was quickly sealed, and the reaction was performed in a microwave during 60 min (holding time) at 150 °C with a power of 300 W. The solution was concentrated under reduced pressure, quenched with satd aq $NaHCO_3$ (15 mL), and extracted with AcOEt (2 × 20 mL). The organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by trituration (1 × 2 mL of pentane/0.2 mL AcOEt at 0 °C, then 2 × 1 mL pentane at room temperature) and then purified by chromatography on silica gel (AcOEt/EtOH 9:1) to give the product as a solid. The solid was dissolved before the chromatography in the eluent system at 40 °C.

dx.doi.org/10.1021/jo402729a | J. Org. Chem. 2014, 79, 1303−1319

The characterization data for 3-hydroxypyridines **2a−d,f−l,p,u,w,z** have been reported previously.[17] The characterizations of other 3-hydroxypyridines are reported below.

*6-Benzyl-2-methylpyridin-3-ol (**2e**).* 136 mg, 0.70 mmol, 58%. Pale brown solid. Mp: 198−200 °C. IR (neat): 3059, 2927, 2460, 1729,1575, 1484, 1456, 1347, 1284, 1262. ^{1}H (300 MHz, MeOD-d_4): δ 7.32−7.15 (m, 5H), 7.07 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 4.01 (s, 2H), 2.41 (s, 3H). ^{13}C (75 MHz, MeOD-d_4): δ 151.6, 151.3, 146.7, 141.4, 129.8, 129.4, 127.2, 123.9, 123.0, 43.4, 18.2. HRMS (ESI+): calcd for $C_{13}H_{14}NO$ 200.1075, found 200.1075.

*Methyl 12-(5-Hydroxy-6-methylpyridin-2-yl)dodecanoate (**2m**).* 201 mg, 0.63 mmol, 52%. Pale yellow solid. ^{1}H (300 MHz, $CDCl_3$): δ 7.00 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 3.67 (s, 3H), 2.67 (t, J = 7.8 Hz, 2H), 2.48 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 1.67−1.54 (m, 4H), 1.29−1.23 (m, 14H). ^{13}C (75 MHz, $CDCl_3$): δ 174.4, 150.9, 150.6, 145.8, 123.2, 121.0, 51.4, 36.4, 34.0, 30.5, 29.5, 29.4, 29.4, 29.3, 29.2, 29.1, 24.9, 17.9. The ^{1}H NMR spectrum was in accordance with literature data.[14a]

*Ethyl 3-(3-Hydroxypyridin-2-yl)propanoate (**2n**).* The compound was prepared according to the procedure described above except for the purification step. The crude solid was first purified by chromatography on silica gel and then triturated. 131 mg, 0.67 mmol, 56%. White solid. Mp: 102−104 °C. IR (neat): 3272, 2930, 1729, 1636, 1575, 1457, 1448, 1365, 1281, 1172, 1110. ^{1}H (300 MHz, $CDCl_3$): δ 8.12 (dd, J = 4.8 Hz, J = 1.5 Hz, 1H), 7.21 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H), 7.07 (dd, J = 8.1 Hz, J = 4.5 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.10−3.05 (m, 2H), 2.89−2.84 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1H (300 MHz, MeOD-d_4): δ 7.90 (dd, J = 4.8 Hz, J = 1.5 Hz, 1H), 7.18−7.07 (m, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.08 (t, J = 7.8 Hz, 2H), 2.69 (t, J = 7.8 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C (75 MHz, MeOD-d_4): δ 174.8, 153.4, 149.1, 139.9, 124.0, 123.5, 61.5, 33.2, 28.4, 14.4. The ^{1}H NMR spectrum was in accordance with literature data.[36]

*2-(3-Hydroxypropyl)pyridin-3-ol (**2y**).* The compound was prepared according to the procedure described above except for the purification step. The crude solid was only purified by chromatography on silica gel. 50 mg, 0.33 mmol, 27%. Pale yellow oil. IR (neat): 3133, 2940, 2871, 2346, 1577, 1455, 1289, 1170, 1017. ^{1}H (300 MHz, MeOD-d_4) δ 7.90 (dd, J = 4.7,1.4 Hz, 1H), 7.18−7.07 (m, 2H), 3.59 (t, J = 6.8 Hz, 2H), 2.85 (t, J = 7.7 Hz, 2H), 1.89 (quin, J = 7.2 Hz, 2H). ^{13}C (75 MHz, MeOD-d_4) δ 153.5, 150.8, 139.6, 123.7, 123.6, 62.7, 32.3, 29.5. HRMS (ESI+): calcd for $C_8H_{12}NO_2$ 154.0868, found 154.0875.

*Methyl 6-(3-Hydroxy-6-methylpyridin-2-yl)hexanoate (**2o**).* Compound **2o** was prepared according to the procedure described above except for the purification step. The crude solid was first purified by chromatography on silica gel and then triturated. 119 mg, 0.50 mmol, 42%. Pale yellow solid. Mp: 88−90 °C. IR (neat): 2946, 2921, 2855, 1733, 1570, 1497, 1467, 1436, 1424, 1370, 1327, 1273. ^{1}H (300 MHz, MeOD-d_4): δ 7.05 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 3.64 (s, 3H), 2.75 (t, J = 7.7 Hz, 2H), 2.39 (s, 3H), 2.32 (t, J = 7.4 Hz, 2H), 1.70−1.60 (m, 4H), 1.44−1.35 (m, 2H). ^{13}C (75 MHz, MeOD-d_4): δ 175.8, 151.0, 150.3, 148.3, 124.3, 122.9, 51.9, 34.6, 32.7, 30.0, 29.5, 25.8, 22.5. HRMS (ESI+): calcd for $C_{13}H_{20}NO_3$ 238.1443, found 238.1435.

*1-(3-Hydroxy-6-propylpyridin-2-yl)heptan-3-one (**2q**).* 168 mg, 0.67 mmol, 56%. Yellow solid. Mp: 144−146 °C. IR (neat): 2958, 2931, 2862, 2474, 1830, 1708, 1575, 1432, 1363, 1272. ^{1}H (200 MHz, MeOD-d_4): δ 7.09 (d, J = 8.2 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 3.05−2.98 (m, 2H), 2.86−2.77 (m, 2H), 2.63 (t, J = 7.6 Hz, 2H), 2.53 (t, J = 7.3 Hz, 2H), 1.73−1.38 (m, 4H), 1.27−1.24 (m, 2H), 0.98−0.89 (m, 6H). ^{13}C (50 MHz, MeOD-d_4): δ 213.4, 152.6, 151.1, 148.4, 124.3, 122.7, 43.1, 41.6, 39.5, 27.3, 27.0, 24.6, 23.3, 14.2, 14.0. HRMS (ESI+): calcd for $C_{15}H_{24}NO_2$ 250.1807, found 250.1807.

*6-Methyl-2-vinylpyridin-3-ol (**2r**).* Compound **2r** was prepared according to the procedure described above except for the purification step. The crude product was directly purified by chromatography on silica gel (100% AcOEt) to give the desired product as a pale yellow solid (81 mg, 0.60 mmol, 50%). Mp: 172−174 °C. IR (neat): 3023, 2921, 2848, 2493, 1865, 1733, 1576, 1492, 1401, 1274, 1250. ^{1}H (300 MHz, MeOD-d_4): δ 7.10 (d, J = 8.4 Hz, 1H), 7.08−6.96 (dd, J = 17.6 Hz, J = 11.3 Hz, 1H), 6.98 (d, J = 8.1 Hz, 1H), 6.24 (dd, J = 17.6 Hz, J = 2.3 Hz, 1H), 5.42 (dd, J = 11.4 Hz, J = 2.1 Hz, 1H), 2.41 (s, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 151.1, 149.1, 143.4, 132.8, 125.3, 124.3, 118.8, 22.7. HRMS (ESI+): calcd for $C_8H_{10}NO$: 136.0762, found 136.0757.

*6-Methyl-2-(4-(3-phenylpropoxy)benzyl)pyridine-3-ol (**2s**).* Compound **2s** was prepared according to the procedure described above except for the purification step. The crude solid was first purified by chromatography on silica gel and then triturated first with a mixture of AcOEt/pentane 1:1 (2 mL) and then with diethyl ether (4 mL). 164 mg, 0.49 mmol, 41%. White solid. Mp: 150−152 °C. IR (neat): 3023, 2939, 2860, 2486, 1606, 1576, 1516, 1347, 1280, 1238, 1172, 1118, 1033. ^{1}H (300 MHz, MeOD-d_4): δ 7.27−7.11 (m, 7H), 7.09 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 8.7 Hz, 2H), 4.02 (s, 2H), 3.90 (t, J = 6.3 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2H), 2.40 (s, 3H), 2.07−1.98 (m, 2H). ^{13}C (75 MHz, MeOD-d_4) δ 158.7, 151.0, 149.2, 148.7, 142.9, 133.1, 130.6, 129.5, 129.3, 126.8, 124.7, 123.4, 115.2, 67.9, 37.8, 33.1, 32.2, 22.5. HRMS (ESI+): calcd for $C_{22}H_{24}NO_2$ 334.1807, found 334.1794.

*2-(3-Methoxypropyl)-6-methylpyridin-3-ol (**2t**).* 108 mg, 0.60 mmol, 50%. White solid. Mp: 150−152 °C. IR (neat): 2919, 2818, 1575, 1502, 1421, 1367, 1264, 1279, 1202. ^{1}H (300 MHz, $CDCl_3$): δ 7.52 (b, 1H), 7.07 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 3.43 (s, 3H), 3.39 (t, J = 5.9 Hz, 2H), 2.91 (t, J = 6.6 Hz, 2H), 2.45 (s, 3H), 2.02 (quin, J = 6.2 Hz, 2H). ^{13}C (75 MHz, $CDCl_3$): δ 149.7, 148.5, 147.9, 124.1, 122.2, 71.4, 58.5, 28.3, 28.2, 23.0. HRMS (ESI+): calcd for $C_{10}H_{16}NO_2$ 182.1181, found 182.1181.

*N-(4-(3-Hydroxy-6-methylpyridin-2-yl)butyl)acetamide (**2v**).* Compound **2v** was prepared according to the procedure described above except for the purification step. The crude solid was first purified by chromatography on silica gel and then triturated first with a mixture of AcOEt/pentane 1:1 (2 mL) then with diethyl ether (4 mL). 106 mg, 0.48 mmol, 40%. White solid. Mp: 126−128 °C. IR (neat): 3277, 3068, 2929, 2868, 2580, 1633, 1554, 1498, 1428, 1371, 1275, 1175, 1127, 1062. ^{1}H (300 MHz, MeOD-d_4): δ 7.06 (d, J = 8.1 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 3.20 (t, J = 6.9 Hz, 2H), 2.78 (t, J = 7.5 Hz, 2H), 2.40 (s, 3H), 1.93 (s, 3H), 1.73−1.62 (m, 2H), 1.60−1.50 (m, 2H). ^{13}C (75 MHz, MeOD-d_4): δ 173.1, 151.0, 150.0, 148.4, 124.4, 123.0, 40.3, 32.4, 30.1, 27.3, 22.5. HRMS (ESI+): calcd for $C_{12}H_{19}N_2O_2$ 223.1447, found 223.1438.

*Methyl 6-(3-Hydroxy-6-methylpyridin-2-yl)hexanoate (**2x**).* Compound **2x** was prepared according to the procedure described above except for the purification step. The crude solid was first purified by chromatography on silica gel (EtOH/AcOEt/NH_4OH 10/89/1) and then triturated. 80 mg, 0.28 mmol, 23%. White solid. Mp: 96−98 °C. IR (neat): 3030, 2933, 2855, 2818, 2764, 1570, 1491, 1455, 1430, 1346, 1273. ^{1}H (300 MHz, MeOD-d_4): δ 7.26−7.16 (m, 4H), 7.13−7.08 (m, 2H), 6.98 (d, J = 8.4 Hz, 1H), 4.11 (s, 2H), 2.71 (t, J = 7.5 Hz, 2H), 2.33 (t, J = 7.8 Hz, 2H), 2.20 (s, 6H), 1.72−1.61 (m, 2H), 1.55−1.45 (m, 2H). ^{13}C (75 MHz, MeOD-d_4): δ 152.6, 151.4, 149.0, 141.1, 129.7, 129.1, 126.8, 124.6, 122.9, 60.3, 45.2, 38.7, 37.3, 29.3, 27.6. HRMS (ESI+): calcd for $C_{18}H_{25}N_2O$: 285.1967, found 285.1965.

One-Pot Procedure for the Synthesis of 3-Hydroxypyridines. To the corresponding triflate (1.2 mmol) in acetonitrile (0.92 mL, 15 equiv) or in the functionalized nitrile (4.5 mmol, 5 equiv) under inert atmosphere in a microwave vial, equipped with a magnetic stirrer bar, was added trimethylsilyl trifluoromethanesulfonate (22 μL, 0.12 mmol, 0.1 equiv). The vial was sealed, and the reaction was performed in a microwave during 3 min (holding time) at 130 °C with a maximum power of 100 W. Then, triethylamine (0.73 mL, 5.4 mmol, 4.5 equiv) and acrylic acid (160 μL, 2.4 mmol, 2 equiv) were successively added to the reaction mixture under inert atmosphere. The vial was quickly sealed, and the reaction was performed in a microwave during 60 min (holding time) at 150 °C with a power of 300 W. The solution was quenched with satd aq $NaHCO_3$ (10 mL) and extracted with AcOEt (2 × 20 mL). The organic phases were washed with a phosphate buffer (pH = 5.80, 8 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude solid product was finally purified by chromatography on silica gel (cake, CH_2Cl_2 100%, then AcOEt 100%, and finally AcOEt/EtOH

9:1) followed by a trituration (2 × 2 mL of diethyl ether) to give the product as a solid.

*2,6-Dimethylpyridin-3-ol (**2aa**).*[37] 83 mg, 0.67 mmol, 56%. Pale yellow solid. Mp: 194−196 °C. IR (neat): 3461, 2997, 2923, 2560, 1931, 1738, 1574, 1472, 1250, 1233, 1160, 1041, ^{1}H (300 MHz, MeOD-d_4): δ 7.05 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 2.38 (s, 3H), 2.37 (s, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 151.5, 147.7, 146.2, 124.3, 123.0, 22.2, 17.9.

*2-Methyl-6-propylpyridin-3-ol (**2b**).* 91 mg, 0.60 mmol, 50%.

*2-Methyl-6-benzylpyridin-3-ol (**2c**).* 140 mg, 0.70 mmol, 58%.

*2-Isobutyl-6-methylpyridin-3-ol (**2ab**).* 38 mg, 0.23 mmol, 19%. Pale yellow solid. Mp: 174−176 °C. IR (neat): 2963, 2923, 2112, 1914, 1574, 1477, 1267, 1156, 1137, 1035, ^{1}H (300 MHz, MeOD-d_4): δ 7.05 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 2.63 (d, J = 7.2 Hz, 2H), 2.39 (s, 3H), 2.07 (sept, J = 6.9 Hz, 1H), 0.90 (d, J = 6.9 Hz, 3H), ^{13}C (75 MHz, MeOD-d_4): δ 151.5, 149.7, 148.1, 124.4, 122.9, 41.5, 29.5, 22.8, 22.4. HRMS (ESI+): calcd for $C_{10}H_{16}NO$ 166.1232, found 166.1224.[38]

Synthesis of (±)-4-Methyl-3-hydroxyquinolizidinol 5. *(±)-(6S*,7S*,9aR*)-7-Hydroxy-6-methylhexahydro-1H-quinolizin-4(6H)-one (**4**).* A solution of 3-hydroxypyridine **2k** (30 mg, 0.14 mmol) in dry methanol (1.5 mL) and Rh/C (5% w/w, 30 mg, 0.03 mmol, 0.1 equiv) was stirred in a Berghof reactor under 10 bar of hydrogen at 80 °C for 5 h. After the reactor was cooled to room temperature, the reaction mixture was filtered through Celite using CH_2Cl_2/EtOH/NH_4OH (9:1:0.5) as solvent and the filtrate concentrated under vacuum to give 30 mg of crude piperidine methyl ester as a clear oil that was used without purification. ^{1}H (300 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.55 (s, 1H), 2.75 (qd, J = 6.6 Hz, J = 1.4 Hz, 1H), 2.61−2.52 (m, 1H), 2.32 (t, J = 7.4 Hz, 2H), 1.93−1.87 (m, 1H), 1.72−1.61 (m, 3H), 1.55−1.30 (m, 4H), 1.10 (d, J = 6.6 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 174.0, 67.8, 56.7, 55.7, 51.5, 36.3, 34.0, 32.0, 25.8, 21.2, 18.6. The hydroxypiperidine (30 mg, 0.14 mmol) was dissolved in xylene (0.5 mL), and solid TBD (7 mg, 0.05 mmol, 0.35 equiv) was added.[25] The resulting solution was heated at 140 °C for 3 h, and then the solution was cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, EtOAc/EtOH from 95:5 to 90:10). The corresponding product was further triturated with Et_2O to afford the desired bicyclic amide **4** (16 mg, 0.087 mmol, 61% yield over two steps) as a white solid. Mp: 106−108 °C. IR (neat): 3374, 2946, 2872, 1606, 1465, 1348. ^{1}H (300 MHz, $CDCl_3$): δ 4.19−4.08 (m, 2H), 3.47−3.37 (m, 1H), 3.13 (b, 1H), 2.46−2.23 (m, 2H), 1.99−1.61 (m, 7H), 1.27 (d, J = 6.6 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 170.7, 67.2, 54.1, 53.4, 32.4, 30.7, 27.9, 25.9, 19.8, 14.5, HRMS (ESI+): calcd for $C_{10}H_{18}NO_2$ 184.1338, found 184.1343.

(±)-(3S,4S*,9aR*)-4-Methyloctahydro-1H-quinolizin-3-ol (**5**).* To a solution of **4** (20 mg, 0.11 mmol) in dry THF (1.5 mL) under an atmosphere of argon at 0 °C was carefully added $LiAlH_4$ (16 mg, 0.42 mmol). The solution was stirred at reflux for 6 h and then quenched by the addition of water (30 μL), aq 15% NaOH (30 μL), and water (60 μL). The gray suspension was stirred for 1 h, filtered through Celite, and washed with Et_2O/EtOH (9:1) and the filtrate concentrated under vacuum. The crude residue was purified by flash column chromatography (SiO_2, EtOAc/EtOH/NH_4OH 90:10:1) to afford **5** (16 mg, 0.094 mmol, 86%) as a white solid. Mp: 92−94 °C, IR (neat): 3189, 2931, 2790, 1444, 1046, ^{1}H (300 MHz, CD_3CN) δ 3.47 (b, 1H), 3.08−3.02 (m, 1H), 2,63 (b, 1H), 2.06 (qd, J = 1.8, 6.6 Hz, 1H), 1.82−1.18 (m, 12H), 1.07 (d, J = 6.3 Hz, 3H), ^{13}C (75 MHz, CD_3CN) δ 71.9, 64.0, 63.4, 52.5, 35.2, 33.1, 29.4, 27.8, 25.9, 18.8. HRMS (ESI+): calcd for $C_{10}H_{20}NO$ 170.1545, found 170.1539.

Synthesis of (±)-8-Hydroxyindolizidine (7). *(±)-(8S*,8aS*)-8-Hydroxyhexahydroindolizin-3(5H)-one (**6**).* A solution of 3-hydroxypyridine **2n** (150 mg, 0.77 mmol) in dry ethanol (7.5 mL) and Rh/C (5% w/w, 140 mg, 0.15 mmol, 0.2 equiv) was stirred in a Berghof reactor under 10 bar of hydrogen at 80 °C for 5 h. After the reactor was cooled to room temperature, the reaction mixture was filtered through Celite using CH_2Cl_2/EtOH/NH_4OH (9:1:0.5) as solvent and the filtrate concentrated under vacuum. The crude residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/EtOH 95:5, R_f = 0.3 CH_2Cl_2/EtOH 90:10) to afford the piperidine (102 mg, 0.51 mmol, 66%) as a white solid. Major Diastereoisomer (*cis*). ^{1}H (300 MHz, $CDCl_3$): δ 4.17−4.11 (m, 2H), 3.83 (b, 1H), 3.72 (q, J = 7.1 Hz, 2H), 3.58−3.52 (m, 1H), 2.71−2.62 (m, 1H), 2.50−2.26 (m, 2H), 2.14−1.97 (m, 3H), 1.79−1.61 (m, 4H), 1.55−1.49 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 174.7, 66.0, 61.0, 39.9, 30.8, 30.4, 19.3, 17.7. The piperidine (90 mg, 0.45 mmol) was dissolved in xylene (3.0 mL) and solid TBD (22 mg, 0.16 mmol, 0.35 equiv) was added. The resulting solution was heated at 140 °C for 3 h, then the solution was cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, EtOAc/EtOH 95:5) to afford the desired bicyclic amide **6** (68 mg, 0.44 mmol, 97% yield) as a white solid and as a mixture of diastereoisomers (*cis*/*trans* 9:1). Major Diastereoisomer (*cis*): ^{1}H (300 MHz, $CDCl_3$): δ 4.18−4.10 (m, 2H), 3.85−3.81 (m, 1H), 3.58−3.52 (m, 1H), 2.71−2.61 (m, 1H), 2.29−2.26 (m, 2H), 2.14−1.96 (m, 4H), 1.79−1.64 (m, 2H), 1.55−1.48 (m, 1H). ^{13}C (75 MHz, $CDCl_3$): δ 174.8, 66.4, 61.0, 40.0, 30.4, 30.3, 19.4, 17.8. The ^{1}H NMR spectrum was in accordance with literature data.[39]

*(8S,8aS)-Octahydroindolizin-8-ol (**7**).* A solution of **6** (29 mg, 0.19 mmol) in dry THF (0.5 mL) at 0 °C was added borane dimethyl sulfide complex 94% (71 μL, 0.75 mmol, 4 equiv). The solution was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched by dropwise addition of ethanol (1 mL). The solvent was evaporated and the crude residue dissolved in ethanol (1.5 mL) and heated to reflux for 3 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (SiO_2, pentane/Et_2O 1:1) to give **7** (18 mg, 0.13 mmol, 68%) as a white solid and single isomer. ^{1}H (300 MHz, $CDCl_3$): δ 4.47−4.40 (m, 1H), 3.37−3.30 (m, 1H), 3.24−3.17(m, 1H), 3.13−3.05(m, 1H), 2.78(dt, J = 3.9, 12.3 Hz, 1H), 2.58 (td, J = 3.3, 12.0 Hz, 1H), 2.26−1.45 (m, 8H). The ^{1}H NMR spectrum was in accordance with literature data.[27a]

Synthesis of (±)-3-Butyl-5-propyl-8-hydroxyindolizidine 8. *Synthetic Route A.* Direct access from the pyridine **2q**:

(±)-(3S,5R*,8S*,8aS*)-3-Butyl-5-propyloctahydroindolizin-8-ol (**8**).* A solution of **2q** (110 mg, 0.44 mmol) in dry THF (8 mL) and Rh/C (5% w/w, 110 mg, 0.05 mmol, 0.12 equiv) was stirred in a Berghof reactor under 10−12 bar of hydrogen at 80 °C (temperature in the oil bath) for 3 h. After the reactor was cooled to room temperature, the reaction mixture was filtered through Celite using EtOAc/EtOH/NH_4OH (9:1:0.2) as solvent and the filtrate concentrated under vacuum. The crude residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/EtOH/NH_4OH from 50:1:0.2 to 50/4/1) to afford the 8-hydroxyindolizidine **8** (14 mg, 0.058 mmol, 14%) and the hydroxypiperidinol **9** (55 mg, 0.21 mmol, 48% yield) as a colorless oils. **8**. IR (neat): 3487, 2956, 2873, 1467, 1378. ^{1}H (300 MHz, $CDCl_3$): δ 3.76 (s, 1H), 2.75 (apparent t, J = 7.2 Hz, 1H), 2.40 (apparent dd, J = 4.8, 10.8 Hz, 1H), 2.29−2.23 (m, 1H), 1.86−1.71 (m, 3H), 1.66−1.16 (m, 15H), 0.94−0.87 (m, 6H). ^{13}C (75 MHz, $CDCl_3$): δ 70.2, 65.4, 64.2, 60.6, 39.2, 37.6, 32.1, 28.9, 28.6, 26.5, 25.8, 22.8, 19.0, 14.3, 14.1, MS(ESI+): m/z 240 (100) $[M + H]^+$. **9**. ^{1}H (300 MHz, $CDCl_3$): δ 3.63 (b, 1H), 3.57−3.53 (m, 0.42H), 3.47−3.43 (m, 0.58H), 3.13 (s, 2H), 2.57−2.46 (m, 2H), 1.90−1.84 (m, 1H), 1.73−1.23 (m, 17H), 0.89−0.84 (m, 6H). ^{13}C (75 MHz, $CDCl_3$): δ 71.9, 70.9, 67.2, 66.1, 60.9, 60.0, 56.4, 56.1, 39.1, 39.0, 37.5, 37.0, 36.1, 33.4, 32.0, 31.9, 28.5, 28.1, 28.0, 26.1, 25.9, 22.8, 22.7, 19.0, 18.9, 14.1, 14.0. HRMS (ESI+): calcd for $C_{15}H_{32}NO_2$ 258.2433, found 258.2439.

Synthetic Route B. *1-(6-Propyl-3-(triisopropylsilyloxy)pyridin-2-yl)heptan-3-one.* To a solution of **2p** (60 mg, 0.24 mmol) in dry THF (1.5 mL) were added dropwise and successively triethylamine (65 μL, 0.48 mmol, 2 equiv) and triisopropylsilyl chloride (56 μL, 0.26 mmol, 1.1 equiv). The mixture was stirred at room temperature for 12 h. The solution was quenched with a solution of satd aq $NaHCO_3$ (5 mL), and the resulting mixture was extracted twice with AcOEt (2 × 10 mL). The combined organic layers were washed with brine (4 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (cyclohexane/AcOEt from 95:5 to 90:10) to give the desired product

dx.doi.org/10.1021/jo402729a | J. Org. Chem. 2014, 79, 1303−1319

as a colorless oil (78 mg, 0.19 mmol, 80%). IR (neat): 2945, 2868, 1717, 1576, 1457, 1279. ^{1}H (300 MHz, $CDCl_3$): δ 6.92 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 3.09 (t, J = 6.9 Hz, 2H), 2.80 (t, J = 7.5 Hz, 2H), 2.60 (t, J = 7.5 Hz, 2H), 2.48 (t, J = 7.2 Hz, 2H), 1.72−1.52 (m, 4H), 1.37−1.21 (m, 5H), 1.12−1.06 (m, 18H), 0.91 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.5 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 210.7, 153.0, 150.6, 147.8, 124.2, 120.1, 42.6, 40.0, 39.4, 26.9, 25.9, 23.2, 22.3, 17.9, 13.8, 13.8, 12.8. HRMS (ESI+): calcd for $C_{24}H_{44}NO_2Si$ 406.3141, found 406.3139.

*2-(2-(2-Butyl-1,3-dioxolan-2-yl)ethyl)-6-propyl-3-(triisopropylsilyloxy)pyridine (**10**).* To a solution of the ketopyridine (71 mg, 0.18 mmol) in dry CH_2Cl_2 (2.5 mL) were added successively ethylene glycol (100 μL, 1.8 mmol, 10 equiv), methyl orthoformate (98 μL, 0.87 mmol, 5 equiv), and *p*-toluenesulfonic acid monohydrate (43 mg, 0.22 mmol, 1.25 equiv). The resulting mixture was stirred at room temperature for 4 h and quenched with a solution of satd aq $NaHCO_3$ (5 mL), and the resulting mixture was extracted with AcOEt (2 × 10 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was finally purified by chromatography on silica gel (cyclohexane/AcOEt 95:5) to give the desired product as a colorless oil (70 mg, 0.16 mmol, 90%). IR (neat): 2945, 2868, 1574, 1458, 1277. ^{1}H (300 MHz, $CDCl_3$): δ 6.93 (d, J = 8.1 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 3.98−3.93 (m, 4H), 2.92−2.86 (m, 2H), 2.65 (t, J = 7.5 Hz, 2H), 2.04 −1.98 (m, 2H), 1.76−1.62 (m, 6H), 1.40−1.25 (m, 5H), 1.12−1.09 (m, 18H), 0.94 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$): δ 153.2, 152.2, 147.7, 124.3, 119.9, 111.7, 64.9, 39.4, 37.2, 35.6, 27.3, 25.8, 23.2, 22.9, 17.9, 14.0, 13.8, 12.9. HRMS (ESI+): calcd for $C_{26}H_{48}NO_3Si$ 450.3403, found 450.3392.

(±)-(2S,3S*,6R*)-2-(2-(2-Butyl-1,3-dioxolan-2-yl)ethyl)-6-propyl-3-(triisopropylsilyloxy)piperidine (**11**).* A solution of **10** (70 mg, 0.16 mmol) in dry isopropyl alcohol (4 mL) and Rh/Al (5% w/w, 60 mg, 0.029 mmol, 0.18 equiv) was stirred in a Berghof reactor under 10−12 bar of hydrogen at 95 °C (temperature in the oil bath) for 48 h. After the reactor was cooled to room temperature, the reaction mixture was filtered through Celite using EtOAc/EtOH/NH_4OH (9:1:0.2) as solvent and the filtrate concentrated under vacuum. The crude residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/EtOH/NH_4OH 50:1.5:0.1) to afford the piperidine **11** (47 mg, 0.10 mmol, 66% yield) as a colorless oil. IR (neat): 2941, 2866, 1741, 1464. ^{1}H (300 MHz, $CDCl_3$): δ 3.89 (s, 4H), 3.83 (b, 1H), 2.56−2.45 (m, 2H), 1.96−1.94 (m, 2H), 1.78−1.23 (m, 20H), 1.07 (s, 18H), 0.91−0.85 (m, 6H). ^{13}C (75 MHz, $CDCl_3$): δ 111.9, 67.5, 64.9, 61.1, 56.2, 39.2, 37.1, 34.0, 32.5, 27.2, 26.3, 25.9, 19.0, 18.2, 18.2, 14.1, 13.9, 12.9. HRMS (ESI+): calcd for $C_{26}H_{54}NO_3Si$ 456.3876, found 456.3880.

(±)-(3S,5R*,8S*,8aS*)-3-Butyl-5-propyl-8-(triisopropylsilyloxy)-octahydroindolizine (**12**).* To a solution of **11** (47 mg, 0.10 mmol) in THF (3 mL) was added a solution of 1 M aq HCl (1 mL, 1 mmol, 10 equiv). After being stirred for 36 h at room temperature, the solution was quenched with a solution of satd aq $NaHCO_3$ (5 mL), and the resulting mixture was extracted with AcOEt (2 × 10 mL). The combined organic layers were washed with brine (1 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Next, the crude amino-ketone was dissolved in dry isopropyl alcohol (3.5 mL), and $Pd(OH)_2$ (20% w/w, 14 mg, 0.02 mmol, 0.2 equiv) was added. The resulting reaction mixture was stirred under hydrogen atmosphere for 12 h and filtered through Celite using EtOAc/EtOH/NH_4OH (9.5:0.5:0.05) as solvent and the filtrate concentrated under vacuum. The crude residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/EtOH/NH_4OH 50:3:0.2) to afford the indolizidine **12** (27 mg, 0.068 mmol, 66% yield over two steps) as a colorless oil. IR (neat): 2942, 2865, 1465, 1380. ^{1}H (300 MHz, $CDCl_3$): δ 3.99 (s, 1H), 2.65 (apparent t, J = 7.8 Hz, 1H), 2.24 (dd, J = 3.3, 10.2 Hz, 1H), 2.13 (apparent t, J = 11.4 Hz, 1H), 1.90−1.18 (m, 21H), 1.07 (s, 18H), 0.89 (m, 6H). ^{13}C (75 MHz, $CDCl_3$): δ 70.7, 67.3, 64.3, 60.3, 39.2, 37.8, 33.1, 29.1, 28.2, 27.0, 26.6, 23.0, 19.0, 18.2, 18.2, 14.5, 14.2, 12.7, HRMS (ESI+): calcd for $C_{24}H_{50}NOSi$ 396.3662, found 396.3654.

(±)-(3S,5R*,8S*,8aS)-3-Butyl-5-propyloctahydroindolizin-8-ol (**8**).* To a solution of **12** (27 mg, 0.07 mmol) in THF (0.8 mL) was added a solution of TBAF (1 M in THF, 0.21 mmol, 3 equiv). After being stirred for 24 h at room temperature, the solution was quenched with a solution of satd aq $NaHCO_3$ (2 mL), and the resulting mixture was extracted with AcOEt (2 × 6 mL). The combined organic layers were washed with brine (1 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, CH_2Cl_2/MeOH/NH_4OH 50:1:0.2) to afford the indolizidine **8** (12 mg, 0.05 mmol, 73%) as a colorless oil. IR (neat): 3487, 2956, 2873, 1467, 1378. ^{1}H (300 MHz, $CDCl_3$): δ 3.76 (s, 1H), 2.78 (apparent t, J = 7.8 Hz, 1H), 2.42 (apparent dd, J = 4.5, 10.5 Hz, 1H), 2.22−2.35 (m, 1H), 1.87−1.73 (m, 3H), 1.66−1.14 (m, 15H), 0.94−0.87 (m, 6H). ^{13}C (75 MHz, $CDCl_3$): δ 70.2, 65.4, 64.2, 60.6, 39.2, 37.6, 32.1, 28.9, 28.6, 26.5, 25.8, 22.8, 19.0, 14.3, 14.1.

General Computational Details. All DFT calculations were performed with the Gaussian09 software,[40] using the M05-2X exchange-correlation functional[41] and the 6-311++G(2d,2p) basis set. All geometries were fully optimized in the singlet spin state using a polarizable continuum model in the latest IEFPCM implementation with default parameters for acetonitrile,[42] including the effects of the solute−solvent dispersion interaction, solute−solvent repulsion interaction energy, and solute cavitation energy.[43] The nature of the stationary points was checked by vibrational analyses. TSs were in particular identified by their unique imaginary frequency and by performing intrinsic reaction coordinate[44] calculations. Entropies in solution were estimated following $S_{corr} = S_{vibrational} + 0.60\ (S_{translational} + S_{rotational})$, as assessed in ref 17. All Bader's QTAIM calculations were carried out with AIMAll,[45] the quality of basin integrations being monitored by checking at integrated laplacian values. Additional information about the theoretical calculations is provided in the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra for all compounds and theoretical complementary details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the FEDER (33885 and 33887) and CNRS for financial support to L.-A.J. and for a Chaire d'Excellence to V.T., respectively, A. Marcual and M. Hubert-Roux (CNRS) and E. Petit (INSA de Rouen) for HRMS and elemental analyses, respectively, and the CRIHAN for computational resources. We also thank L. Truong (CNRS) and C. Antheaume (Université de Strasbourg) for helpful discussions.

■ REFERENCES

(1) Gnamm, C.; Brödner, K.; Krauter, C. M.; Helmchen, G. *Chem.—Eur. J.* **2009**, *15*, 10514−10532.

(2) For a review on the synthesis of 3-hydroxypiperidines, see: Wijdeven, M. A.; Willemsen, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2010**, 2831−2844.

(3) For a review on the synthesis of indolizidines and quinolizidines, see: Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139−165.

(4) Goss, P. E.; Reid, C. L.; Bailey, D.; Dennis, J. W. *Clin. Cancer Res.* **1997**, 1077−1086.

(5) Pinho, V. D.; Procter, D. J.; Burtoloso, A. C. B. *Org. Lett.* **2013**, *15*, 2434−2437.

(6) Jones, H.; Voegtle, H. L.; Miras, H. M.; Weatherford, R. G.; Spande, T. F.; Garraffo, H. M.; Daly, J. W.; Davidson, D. W.; Snelling, R. R. *J. Nat. Prod.* **2007**, *70*, 160−168.
(7) Bernardim, B.; Pinho, V. D.; Burtoloso, A. C. B. *J. Org. Chem.* **2012**, *77*, 9926−9931.
(8) (a) Fan, G.-J.; Wang, Z.; Wee, A. G. H. *Chem. Commun.* **2006**, 3732−3734. (b) Guo, H.; O'Doherty, G. A. *Tetrahedron* **2008**, *64*, 304−313. (c) Wee, A. G. H.; Fan, G.-J.; Bayirinoba, H. M. *J. Org. Chem.* **2009**, *74*, 8261−8271. (d) Dhand, V.; Draper, J. A.; Moore, J.; Britton, R. *Org. Lett.* **2013**, *15*, 1914−1917.
(9) (a) Toyooka, N.; Zhou, D.; Nemoto, H.; Tezuka, Y.; Kadota, S.; Jones, T. H.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Synlett* **2008**, *12*, 1894−1896. (b) Lina, G.-J.; Huang, P.-Q. *Org. Biomol. Chem.* **2009**, *7*, 4491−4495.
(10) de Vicente, J.; Arrayás, R. G.; Cañada, J.; Carretero, J. C. *Synlett* **2000**, 53−56.
(11) (a) Song, L.; Duesler, E. N.; Mariano, P. S. *J. Org. Chem.* **2004**, *69*, 7284−7293. (b) Ceccon, J.; Greene, A. E.; Poisson, J.-F. *Org. Lett.* **2006**, *8*, 4739−4742.
(12) Tite, T.; Jacquelin, F.; Bischoff, L.; Fruit, C.; Marsais, F. *Tetrahedron: Asymmetry* **2010**, *21*, 2032−2036 and references therein.
(13) Barbe, G.; Pelletier, G.; Charette, A. B. *Org. Lett.* **2009**, *11*, 3398−3401.
(14) (a) Hasseberg, H.-A.; Gerlach, H. *Liebigs Ann. Chem.* **1989**, 255−261. (b) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171−4175. (c) Maegawa, T.; Akashi, A.; Yaguchi, K.; Iwasaki, Y.; Shigetsura, M.; Monguchi, Y.; Sajiki, H. *Chem.—Eur. J.* **2009**, *15*, 6953−6963.
(15) (a) Kondrat'eva, G. Ya. *Khim. Nauka Prom-st.* **1957**, *2*, 666. (b) Firestone, R. A.; Pfister, K.; Boettcher, R. R.; Cross, F. J.; Currie, R. B.; Monaco, M.; Peterson, E. R.; Reuter, W. *J. Org. Chem.* **1962**, *27*, 2705. (c) Fletcher, M. D.; Hurst, T. E.; Miles, T. J.; Moody, C. J. *Tetrahedron* **2006**, *62*, 5454. (d) Lu, J.-Y.; Arndt, H.-D. *J. Org. Chem.* **2007**, *72*, 4205−4212. (e) Lu, J.-Y.; Keith, J. A.; Shen, W.-Z.; Schürmann, M.; Preut, H.; Jacob, T.; Arndt, H.-D. *J. Am. Chem. Soc.* **2008**, *130*, 13219−13221. (f) Yoshida, K.; Kawagoe, F.; Hayashi, K.; Horiuchi, S.; Imamoto, T.; Yanagisawa, A. *Org. Lett.* **2008**, *11*, 515−518. (g) Yoshida, K.; Kawagoe, F.; Hayashi, K.; Horiuchi, S.; Imamoto, T.; Yanagisawa, A. *Org. Lett.* **2009**, *11*, 515−518.
(16) (a) Lei, C.-H.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *J. Am. Chem. Soc.* **2013**, *135*, 4708−4711. (b) Lei, C.-H.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *Chem.—Eur. J.* **2013**, *50*, 16981−16987.
(17) Jouanno, L.-A.; Tognetti, V.; Joubert, L.; Sabot, C.; Renard, P.-Y. *Org. Lett.* **2013**, *15*, 2530−2533.
(18) For recent advances on this reaction, see: (a) Sabot, C.; Oueis, E.; Brune, X.; Renard, P.-Y. *Chem. Commun.* **2012**, *48*, 768−770. (b) Lehmann, J.; Alzieu, T.; Martin, R. E.; Britton, R. *Org. Lett.* **2013**, *15*, 3550−3553. (c) Uosis-Martin, M.; Dan Pantoş, G.; Mahon, M. F.; Lewis, S. E. *J. Org. Chem.* **2013**, *78*, 6253−6263.
(19) (a) Doyle, K. J.; Moody, C. J. *Tetrahedron* **1994**, *50*, 3761−3772. (b) Ducept, P. C.; Mardsen, S. P. *Synlett* **2000**, *5*, 692−694. (c) Thalhammer, A.; Mecinović, J.; Schofield, C. J. *Tetrahedron Lett.* **2009**, *50*, 1045−1047. (d) Lai, P.-S.; Taylor, M. S. *Synthesis* **2010**, *9*, 1449−1452. (e) Lalli, C.; Bouma, M. J.; Bonne, D.; Masson, G.; Zhu, J. *Chem.—Eur. J.* **2011**, *17*, 880−889. (f) El Kaïm, L.; Grimaud, L.; Patil, P. *Synlett* **2012**, *23*, 1361−1363.
(20) Jouanno, L.-A.; Sabot, C.; Renard, P.-Y. *J. Org. Chem.* **2012**, *77*, 8549−8555. Correction: Jouanno, L.-A.; Sabot, C.; Renard, P.-Y. *J. Org. Chem.* **2013**, *78*, 1706.
(21) (a) Chermette, H. *J. Comput. Chem.* **1999**, *20*, 129. (b) Geerlings, P.; De Proft, F.; Langenaeker, W. *Chem. Rev.* **2003**, *103*, 1793.
(22) Bader, R. F. W. *Atoms in Molecules: A Quantum Theory*; Oxford University Press: Oxford, 1990.
(23) (a) Blanco, M. A.; Pendás, A. M.; Francisco, E. *J. Chem. Theory Comput.* **2005**, *1*, 1096. (b) Pendás, A. M.; Blanco, M. A.; Francisco, E. *J. Chem. Phys.* **2004**, *120*, 4581.
(24) The *cis*-hydrogenation of pyridines catalyzed by rhodium is well established. For some examples, see ref 14a and: Snider, B. B.; Neubert, B. J. *Org. Lett.* **2005**, *7*, 2715−2718.
(25) Sabot, C.; Kumar, K. A.; Meunier, S.; Mioskowski, C. *Tetrahedron Lett.* **2007**, *48*, 3863−3866.
(26) See the Supporting Information.
(27) For examples of synthesis of **7**, see: (a) Lee, H. K.; Chun, J. S.; Pak, C. S. *J. Org. Chem.* **2003**, *68*, 2471−2474. (b) Fan, G.-J.; Wang, Z.; Wee, A. G. H. *Chem. Commun.* **2006**, 3732−3734. (c) Wee, A. G. H.; Fan, G.-J.; Bayirinoba, H. M. *J. Org. Chem.* **2009**, *74*, 8261−8271. (d) Kumar, R. S. C.; Reddy, G. V.; Babu, K. S.; Rao, J. M. *Tetrahedron Lett.* **2011**, *52*, 4382−4384. (e) Bernardim, B.; Pinho, V. D.; Burtoloso, A. C. B. *J. Org. Chem.* **2012**, *77*, 9926−9931.
(28) For an example with quinolines, see: Rueping, M.; Hubener, L. *Synlett* **2011**, *9*, 1243−1246.
(29) Both ^{1}H and ^{13}C NMR analyses were consistent with values reported in the literature.
(30) The protection of the ketone group has revealed to be difficult without prior protection of the hydroxyl group.
(31) For some recent examples, see: (a) Morell, C.; Ayers, P. W.; Grand, A.; Gutiérrez-Olica, S.; Toro-Labbé, A. *Phys. Chem. Chem. Phys.* **2008**, *10*, 7239. (b) Saha, S.; Roy, R. K.; Pal, S. *Phys. Chem. Chem. Phys.* **2010**, *12*, 9328. (c) Black, K.; Liu, P.; Xu, L.; Doubleday, C.; Houk, K. N. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 12860. (d) Liu, F.; Paton, R. S.; Kim, S.; Liang, Y.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 15642.
(32) (a) Domingo, L. R.; Picher, M. T.; Sáez, J. A. *J. Org. Chem.* **2009**, *74*, 2726. (b) Lodewyk, M. W.; Kurth, M. J.; Tantillo, D. J. *J. Org. Chem.* **2009**, *74*, 4804. (c) Zhang, W.; Zhu, Y.; Wei, D.; Li, Y.; Tang, M. *J. Org. Chem.* **2012**, *77*, 10729. (d) Uosis-Martin, M.; Dan Pantoş, G.; Mahon, M. F.; Lewis, S. E. *J. Org. Chem.* **2013**, *78*, 6253.
(33) Tognetti, V.; Morell, C.; Ayers, P. W.; Joubert, L.; Chermette, H. *Phys. Chem. Chem. Phys.* **2013**, *15*, 14465.
(34) Pham, R.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 3676.
(35) Conde, S.; López-Serrano, P.; Fierros, M.; Biezma, M. I.; Martínez, A.; Rodríguez-Franco, M. I. *Tetrahedron* **1997**, *53*, 11745.
(36) Desideri, N.; Galli, A.; Sestili, I.; Stein, M. L. *Arch. Pharm. (Weinheim)* **1992**, *325*, 29.
(37) Kuo, Y.-H.; Shih, K.-S. *Chem. Pharm. Bull.* **1991**, *39*, 181−183.
(38) Calo, N.; Desideri, N.; Manna, F.; Stein, M. L. *Gazz. Chim. Ital.* **1984**, *114*, 211.
(39) Pham, R.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 3676.
(40) Frisch, M. J. et al. Gaussian09, Revision B.01, Gaussian, Inc., Wallingford, CT, 2010.
(41) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 364.
(42) Scalmani, G.; Frisch, M. J. *J. Chem. Phys.* **2010**, *132*, 114110.
(43) (a) Florsi, F.; Tomasi, J.; Pascual-Ahuir, J. L. *J. Comput. Chem.* **1991**, *12*, 784. (b) Pierotti, R. A. *Chem. Rev.* **1976**, *76*, 717.
(44) (a) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363. (b) Hratchian, H. P.; Schlegel, H. B. *J. Chem. Phys.* **2004**, *120*, 9918.
(45) Keith, T. A. *AIMAll*, TK Gristmill Software, Overland Park, KS, 2012 (aim.tkgristmill.com).