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New Piperidine Scaffolds via Nucleophilic Reactivity of (−)-Phenyloxazolopiperidine

Erwan Poupon,[†] David François,[‡] Nicole Kunesch,[‡] and Henri-Philippe Husson*[,‡]

Laboratoire de Pharmacognosie Associé au CNRS, UMR 8076 (BioCIS), Centre d'Études Pharmaceutiques, Université Paris-Sud 11, 5, Rue Jean-Baptiste Clément, 92296 Châtenay-Malabry CEDEX, France, and Laboratoire de Chimie Thérapeutique et Laboratoire de Pharmacognosie, Faculté des Sciences Pharmaceutiques et Biologiques, UMR 8638 Associée au CNRS et à l'Université René-Descartes (Paris 5), 4, Avenue de l'Observatoire, 75256 Paris CEDEX 06, France

henri-philippe.husson@univ-paris5.fr

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The present work illustrates the power of compound **2** as a chiral, nonracemic, and stable 2-piperideine (enamine) equivalent in the rapid and efficient construction of 3-substituted piperidines (carbon−carbon and carbon−sulfur bonds) such as 3-spiropiperidines. This methodology offers a new route to such systems that could compete with previously reported strategies.

Introduction

Functionalized piperidine structures embody some of the key features found in numerous natural products, biologically active compounds, and drugs. Synthesis of such compounds often requires the use of stereoselective methods involving carbon−carbon bond-forming reactions, and in this regard, enamines have proved to be useful intermediates.[1] Recently, we have reported the easy preparation of **2** from building block **1** via a mild reductive decyanation (Scheme 1).[2] Compound **2** is an equivalent of 2-piperideine, which itself has proved to be unstable and exist in the monomeric form in equilibrium with the trimeric one.[3] Moreover, 1-alkyl 2-piperideine leads to dimerization products.[4]

Hence, problems associated with 2-piperideine chemistry do not arise so much in the production of tetrahydropyridines, but rather in their exploitation for syntheses. Thus, compound **2** overcomes the problems mentioned above. We have therefore examined the reactivity of this compound and showed its usefulness both in methodology developments[2] and in total synthesis.[5] As depicted in

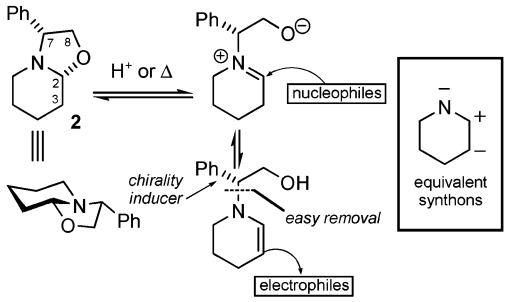

FIGURE 1. Synthetic potentialities of building block **2**.

Figure 1, our preliminary studies suggest that its remarkable reactivity can be explained by the equilibrium between the bicyclic system **2** and its opened enamine-iminium ion tautomeric form. Thus, the latter offers dual properties, which should permit access to substituted piperidines at the C-2 or C-3 positions by means of electrophilic or nucleophilic attacks, respectively. Moreover, one can expect that the presence of the chiral appendage would discriminate between the two faces of the iminium or enamine during the course of such reactions. Finally, elimination of the chiral appendage would allow further substitutions on the nitrogen atom.

As part of our continuing work on endocyclic enamine reactivity study, we have elected to turn our attention to the nucleophilic properties of **2** and, in the present paper, report how various chiral nonracemic structures can be easily obtained in one or two steps from this new starting material by exploitation of its enamine reactivity.[6] In particular, we investigated the condensation of Michael acceptor, namely, methyl vinyl ketone (MVK), together with mono- and dialdehydes with **2**.

* To whom correspondence should be addressed. Phone: +33-1 53 73 97 54. Fax: +33-1 43 29 14 03.
[†] Université Paris-Sud 11.
[‡] Université René-Descartes (Paris 5).

(1) For some elegant examples of natural product synthesis featuring tetrahydropyridines as nucleophilic key intermediates, see: Nicolaou, K. C.; Nevalainen, M.; Safina, B. S.; Zak, M.; Bulat, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1941−1945; Jakubowicz, K.; Ben Abdelgelil, K.; Herdemann, M.; Martin, M.-T.; Gateau-Olesker, A.; Al Mourabit, A.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 7381−7387. Wanner, M. J.; Koomen, G.-J. *J. Org. Chem.* **1995**, *60*, 5634−5637.

(2) For preliminary results, see: François, D.; Poupon, E.; Lallemand, M.-C.; Kunesch, N.; Husson, H.-P. *J. Org. Chem.* **2000**, *65*, 3209−3212.

(3) (a) Schöpf, C.; Arm, H.; Braun, F. *Chem. Ber.* **1952**, *85*, 937−948. (b) De Kimpe, N.; Stevens, C. *J. Org. Chem.* **1993**, *58*, 2904−2906.

(4) (a) Martinez, S. J.; Joule, J. A. *Tetrahedron* **1978**, *34*, 3027−3036. (b) Beeken, P.; Fowler, F. W. *J. Org. Chem.* **1980**, *45*, 1336−1338.

(5) Poupon, E.; Kunesch, N.; Husson, H.-P. *Ang. Chem., Int. Ed.* **2000**, *39*, 1493−1495.

(6) General and versatile asymmetric methods for synthesizing 3-substituted piperidines are by far less numerous compared to methodologies for access to 2-subsituted systems.

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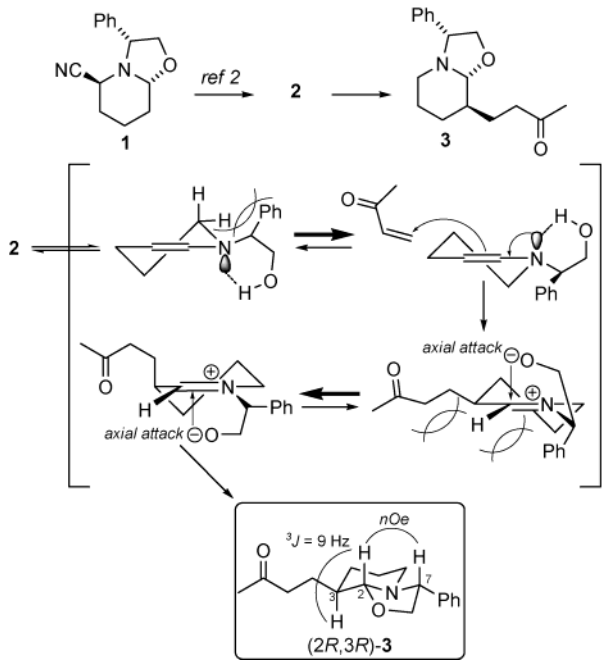
SCHEME 1. Diastereoselective Monoalkylation[a]



[a] Reagents and conditions: MVK (1 equiv), MeOH, reflux, 4 h or room temperature, 5 days (60−63%).

Results and Discussion

The preparation of enantiopure compound **2** was achieved via a high-yielding reductive decyanation with Raney nickel starting from **1**.[7] This reaction can be carried out on a multigram scale with a satisfying 90% yield and without any racemization of the oxazolidine ring.[8] The most interesting advantage of this new process is the ease of the protocol, which makes this reaction more feasible in comparison with the existing methods such as Na in liquid ammonia. With this compound in hand, we herein report new expedient entries into the rich chemistry of tetrahydropyridine systems.

Monoalkylation with Michael Acceptor. MVK is a Michael acceptor that has been widely used in enamine alkylation.[9] This reaction appeared to be a simple test to determine the diastereoselectivity control imposed by the chiral appendage borne at the nitrogen atom, keeping in mind that the synthetic applications of alkylated intermediates could be of great interest, for example, in natural product synthesis. Reaction of **2** with 1 equiv of MVK in a boiling protic solvent such as MeOH provided Michael adduct (2*R*,3*R*)-**3** in acceptable yield (63%) with a satisfactory level of diastereomeric induction (de = 92%, inseparable compounds). At room temperature, the same reaction was slower, occurring over a period of a few days. However, it gave similar results both in terms of yield and stereoselectivity (Scheme 1). Furthermore, the structural assignment of **3** was made on the basis of NMR analysis.

The stereochemical outcome thus observed can be accounted for by both stereoelectronic and steric effects.[10] As depicted in Scheme 1, stereoelectronic effects imply a preferred alkylation on the same face as the nitrogen lone electronic pair; conjointly, the presence of the phenylethanol moiety imposes a transition state with a highly hindered face. Finally, formation of the oxazolidine is stereoelectronically controlled according to a model often discussed in the chemistry of iminiums (i.e., equatorial position of the oxygen atom, cis position for H-2 and H-7).[10] It is interesting to note that the Mannich derivatives between the potential iminium salt and the methyl ketone were not formed.

Access to 3-Spiropiperidines. It is worth noting that 3-spiropiperidines have attracted some attention because of their unique structure found only in a few natural products[11] (e.g., nitramine, serratezomine A, gymnodimine) and also due to their particular biological profile. Recently, studies of different spiropiperidine systems have resulted in a novel 3-spiropiperidine series of potent growth hormone secretagogues.[12] Conformationally restricted GABA and Gabapentin analogues, in which the 3-spiropiperidine pattern is found, have also been prepared as well as GABA-uptake inhibitors.[13] Furthermore, this spirocyclic skeleton is found not only in some applications in the pharmaceutical field but also in agrochemistry, as exemplified by the discovery of insect repellent molecules.[14]

To successfully achieve our goal and in order to continue our investigations into the chemistry of 3-spiropiperidines, upon which we had embarked a few years ago,[15] compound **2** was reacted with an excess of MVK to give rise to the formation of the Michael-type bisadduct **4**. Subsequent acidic treatment of **4** with concentrated hydrochloric ethanol gave a 1:1 mixture of two isomeric spirocyclic compounds **5** and **6**, which were easily and totally separable by flash chromatography. This sequence formally proceeds by an initial attack of a thermodynamic enol of a side chain at C-3 on the carbonyl function of the other side chain tethered to C-3. As shown in Scheme 2, the crotonization followed the two

(7) For a comprehensive review on the CN(*R*,*S*) strategy see: Husson, H.-P.; Royer, J. *Chem. Soc. Rev*. **1999**, *28*, 383−394.

(8) See Supporting Information for an improved synthesis of building block **2**.

(9) See inter alia: (a) Asymmetric Michael addition reactions involving chiral imines, reviews: Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed*. **2003**, *42*, 1688−1690. Christoffers, J. *Chem. Eur. J*. **2003**, *9*, 4862−4867. D'Angelo, J.; Desmaële, D.; Dumas, F.; Guinguant, A. *Tetrahedron*: *Asymmetry* **1992**, *3*, 459−505. (b) Michael additions involving piperideines: Stevens, R. V.; Hrib, N. *J. Chem. Soc., Chem. Commun*. **1983**, 1422−1424. (c) Mitch, C. H. *Tetrahedron Lett*. **1988**, *29*, 6831−6834. (d) Vázquez, E.; Galindo, A.; Gnecco, D.; Bernès, B. *Tetrahedron: Asymmetry* **2001**, *12*, 2099−2102.

(10) For a leading reference, see: Stevens, R. V. *Acc. Chem. Res*. **1984**, *17*, 7, 289−296.

(11) Nitramine: see ref 15 and references therein. Serratezomine A: Morita, H.; Arisaka, M.; Yoshida, N.; Kobayashi, J. *J. Org. Chem*. **2000**, *65*, 6241−6245. Gymnodimine: Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H. F.; Yasumoto, T. *Tetrahedron Lett*. **1995**, *36*, 7093−7096. For the construction of the spirocyclic moiety: Yang, J.; Cohn, S. T.; Romo, D. *Org. Lett*. **2000**, *2*, 763−766. For racemic synthesis of the key pharmacophoric spirocyclic imine, see: Trzoss, M.; Brimble, M. A. *Synlett* **2003**, 2042−2046.

(12) Yang, L.; Morriello, G.; Prendergast, K.; Cheng, K.; Jacks, T.; Chan, W. W.-S.; Schleim, K. D.; Smith, R. G.; Patchett, A. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 107−112.

(13) (a) GABA analogues: Bendl, M.; Eder, M.; Langhammer, I.; Urban, E. *Heterocycles* **2000**, *53*, 115−126. (b) Gabapentin analogues: Receveur, J.-M.; Bryans, J. S.; Field, M. J.; Singh, L.; Horwell, D. C. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 2329−2334. (c) GABA-uptake inhibitors: Fleischhacker, W.; Lauritz, S.; Urban, E.; Baurmann, P.; Bittiger, H. *Eur. J. Med. Chem*. **1995**, *30*, 707−713.

(14) (a) Smolanoff, J. U.S. Patent 4 374 991, 1983. (b) Smolanoff, J. U.S. Patent 4 400 512, 1983.

(15) François, D.; Lallemand, M.-C.; Selkti, M.; Tomas, A.; Kunesch, N.; Husson, H.-P. *Ang. Chem., Int. Ed*. **1998**, *37*, 104−105.

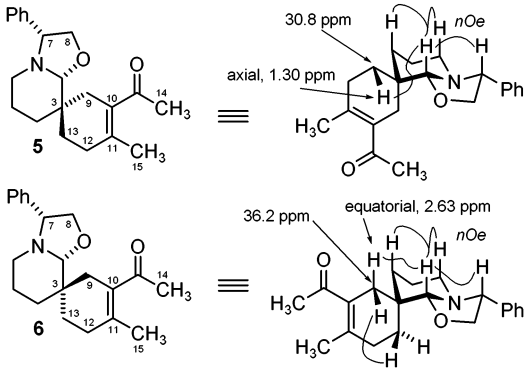
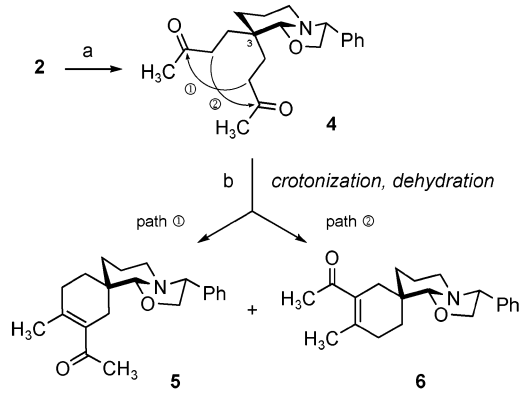


FIGURE 2. Selected NMR data for compounds **5** and **6**.

SCHEME 2. Two-Step Access to Spiropiperidines via a Double Alkylation/Crotonization Sequence[a]



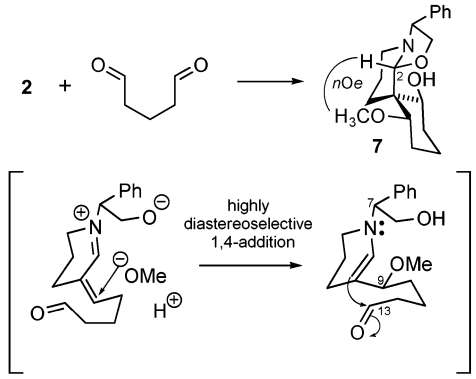
[a] Reagents and conditions: (a) MVK (10 equiv), MeOH, rt, 2 days (60%); (b) MeOH, HCl, reflux, 0.5 h (60%, **5**/**6** = 1).

possible pathways 1 and 2, and respectively led to two quaternary alcohols, which *in situ* underwent a dehydration to yield the corresponding α,*β*-unsaturated derivatives **5** and **6**.

Despite similar analytical data, the structure elucidation of these two compounds was achieved unambiguously by extensive two-dimensional NMR studies (see selected NMR data in Figure 2). For instance, NOE correlations between axial H-2 and axial H-13 or equatorial H-9 in compounds **5** and **6**, respectively, were observed. These two 3-spiropiperidine systems represent a strong example of the degree of complexity and diversity reachable from **2** through the use of two easy and well-known reactions. Moreover, **5** and **6** are also ideal templates because of their high level of rigidity (bicyclic spiro core) and their diverse chemical potential (ketone, double bond, potential iminium). It is noteworthy that reductive opening of the oxazolidine ring and/or concomitant debenzylation of **5** and **6** would lead to enantiomeric compounds. They can be subjected to a variety of organic transformations and will be the basis for the generation of a library of small molecules. As described for compound **3**, no Mannich reaction onto the potential iminium was observed.

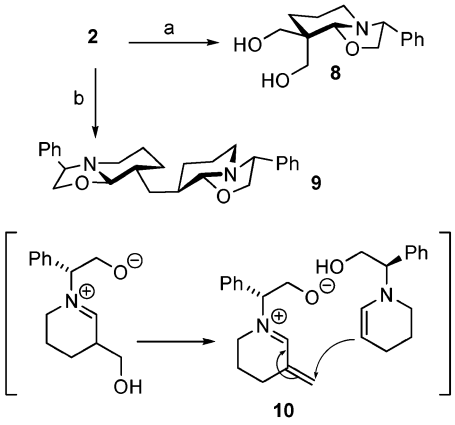
Another example of efficient access to a 3-spiropiperidine was demonstrated when **2** was treated with glutaraldehyde in boiling methanol (Scheme 3). Spirocompound **7** was obtained as a single diastereomer. The first step consisted of the reaction of the enamine **2** with

SCHEME 3. Synthesis of Spiropiperidine 7 and Plausible Mechanism[a]



[a] Reagents and conditions: glutaraldehyde (4 equiv), MeOH, reflux, 18 h (50%).

SCHEME 4. Reactions with Formaldehyde[a]

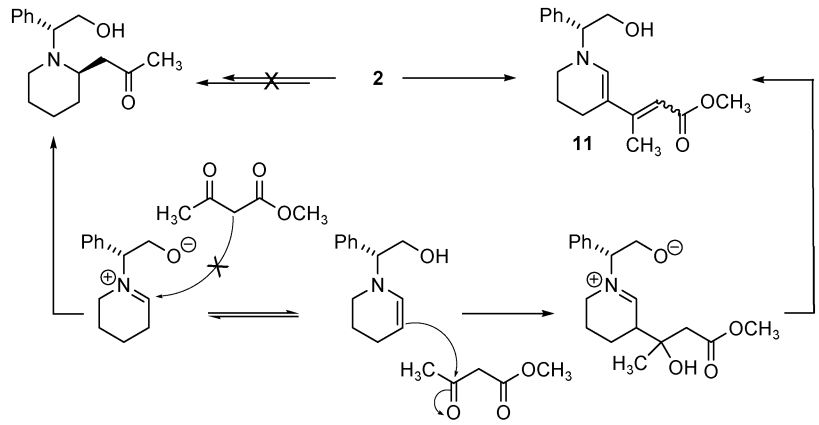


[a] Reagents and conditions: (a) $(HCHO)_n$ (5 equiv), MeOH, rt, 2 days (82%); (b) $(HCHO)_n$ (1 equiv), MeOH, molecular sieves 4 Å, rt, 6 days (20%).

glutaraldehyde followed by dehydration of the formed alcohol. A methanol molecule then acted as a nucleophile in a stereocontrolled 1,4-addition, thereby creating a new stereogenic center. A second enamine reaction on the remaining aldehyde function gave rise, after residual iminium trapping, to compound **7** with acceptable yield. Stereochemistry was unambiguously established by two-dimensional NMR and by the observation of NOE correlation between methoxy protons and axial H-2. Trapping of the intermediate with other nucleophiles can be envisaged. The result of this reaction is to be compared to previous work from our laboratory.[15]

Reactions with Carbonyls. These first examples constitute a new and straightforward route for the construction of 3-spiropiperidines. To extend the scope of this reaction, we tested the behavior of **2** toward formaldehyde used either in excess or default. In the first case, a double addition was observed and diol **8** was obtained with good yield (Scheme 4). Among the few aldehydes tested only formaldehyde gave double addition.[17] When used in default, in dehydrating conditions, the only isolated compound was the unsymmetrical dimer **9**, obtained as a pure diastereomer in low yield. Once again, trapping of the putative α,*β*-unsaturated iminium **10** by a nucleophile, in this case a second molecule of the

SCHEME 5. Reaction with Malonic-Type Nucleophile: Enamine vs Iminium[a]



[a] Reagents and conditions: methylacetoacetate (4 equiv), MeOH/H_2O (7:3), reflux, 2 days (60%).

enamine form of **2**, can explain the stereocontrolled formation of **9**.

Finally, to illustrate the primacy of the enamine reactivity in mild conditions versus iminium electrophilic reactivity, compound **11**, a stable bis-vinylogous amide, was synthesized as a 93:7 mixture of *E*/*Z* isomers by treatment of **2** with an excess of methylacetoacetate in a mixture of water and methanol at reflux. A likely mechanism involves an initial attack of the enamine on the ketone followed by dehydration of the quaternary alcohol and isomerization of the iminium into the enamine. No reaction on the iminium could be detected, which could have led to a pelletierine-type compound after decarboxylation (Scheme 5).

Carbon−Sulfur Bond Formation and Access to a New Azabicyclic System. We then studied the possibility of creating a carbon−heteroatom bond from **2**. We chose to use sulfur-containing electrophiles for at least two reasons. First, 3-thiopiperidines have been seldom described in the literature,[18] and second, on the basis of the experience gained from MVK studies, a double addition could conceivably provide access to a precursor of a ketone function as represented in Figure 3. Such target compounds could presumably give us a synthetic pathway to 4-substituted piperidines after deprotonation and alkylation.

We decided to use *S*-methylmethanethiosulfonate as an electrophilic thiolating agent. When used in default (0.5 equiv) at room temperature in methanol, monosubstituted compound **12** was formed in 70% yield (Scheme 6). If used in excess, a 1:1 mixture of compound **12** and disubstituted **13** was obtained. Changes in experimental conditions never made the sole obtention of **13** possible, even when a large excess of reagent was engaged.

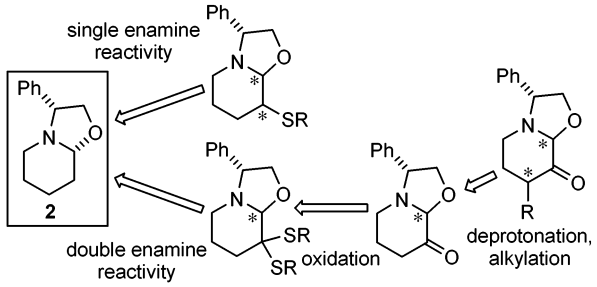


FIGURE 3. Retrosynthetic plans concerning sulfur substitutions.

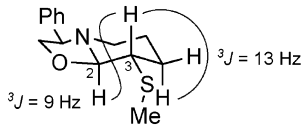
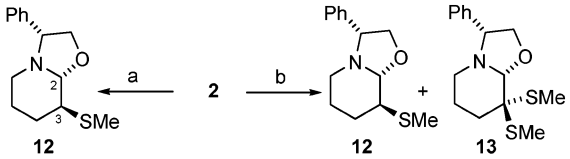


FIGURE 4. Selected NMR data for compounds **12**.

SCHEME 6. Carbon−Sulfur Bond Formation[a]



[a] Reagents and conditions: $MeSO_2SMe$ (0.5 equiv), MeOH, rt, 3 days (70%, based on $MeSO_2SMe$); (b) $MeSO_2SMe$ (10 equiv), MeOH, rt, 5 days (**12**, 30%; **13**, 30% based on **1**).

Fortunately, both compounds were completely separable by flash chromatography. Concerning diastereoselectivity during the formation of **12**, it appeared to be better than the one observed with the MVK system (de 95%). Stereochemistry at the C-2 and C-3 positions on the piperidine ring was deduced from NMR studies (Figure 4). For example, a trans diaxial coupling constant of 13 Hz was measured between H-3 and axial H-4.

We then investigated further transformations of compound **13** into 3-oxopiperidine. By means of oxidative conditions, we attempted to convert this dithioketal into the corresponding ketone using bis-trifluoroacetoxyiodobenzene (BTIB) as described by Stork and Coll.[19] This method led not to the desired target molecule but rather

(16) For recent examples of spirocyclic compounds constructed by the means of an enamine/Michael and aldol sequence, see: Christoffers, J.; Kreidler, B.; Oertling, H.; Unger, S.; Frey, W. *Synlett* **2003**, 493−496. Christoffers, J.; Kreidler, B.; Unger, S.; Frey, W. *Eur. J. Org. Chem.* **2003**, 2845−2853.

(17) See ref 5 for examples.

(18) For examples, see the following. (a) For the preparation of racemic 3-thiopiperidines: Ibarra, C. A.; Cuervo, R.; Fernández-Monreal, M. C.; García, M.; Ruiz, M. P.; Elliel, E. L. *J. Chem. Soc., Perkin Trans 1* **1991**, 1473−1477. (b) For enantioselective strategy starting from a lactam derived from (*R*)-(−)-phenylglycinol, see: Forns, P.; Montserrat Fernández, M.; Diez, A.; Rubiralta, M.; Cherrier, M.-P.; Bonin, M.; Quirion, J.-C. *Synthesis* **1999**, 258−263.

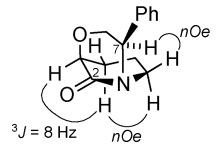


FIGURE 5. Selected NMR data for compounds **14**.

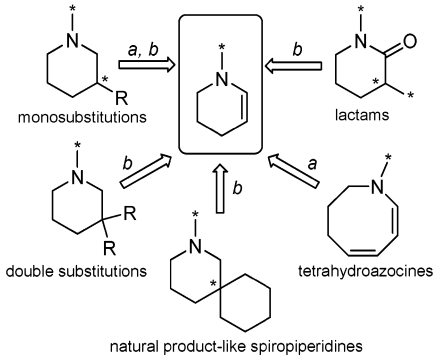
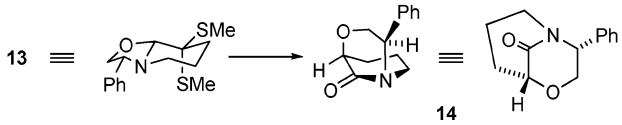


FIGURE 6. Diverse structures from **2**. (a) Ref 2, (b) this work.

SCHEME 7. Oxidative Rearrangement of 13 into Lactam 14[a]



[a] Reagents and conditions: $(CF_3CO_2)_2IPh$ (2 equiv), CH_3CN/H_2O (9:1), rt, 2 h (60%).

to the rearranged original lactam **14**, obtained as a single diastereomer in a very clean reaction (Scheme 7).[20]

Compound **14**, sharing the same mass with the initial target, constituted a chiral, nonracemic, unprecedented bicyclic morpholinone-based scaffold that was fully and unambiguously ascertained by two-dimensional NMR (see Figure 5). An 8 Hz coupling constant between H-3 and axial H-4 was observed, indicating a cis equatorial/axial relationship consistent with an axial position of the oxygen at the C-3 position.

Recently, mild conditions of conversion of dithioketals into the corresponding ketone function using Dess–Martin periodinane have been reported.[21] Starting from **13**, similar conditions were disappointing, resulting in the formation of a complex mixture of compounds.

Conclusion

In conclusion, the present work illustrates the power of compound **2** as a chiral and stable enamine equivalent in the rapid and efficient construction of 3-subsituted piperidines.

We aimed to demonstrate through this series of examples that readily available stable tetrahydropyridine surrogate **2** can lead to diverse and complex frameworks. Noteworthy were these molecules that can be rapidly assembled using short sequences (maximum of two) of simple transformations usually carried out in protic solvents at room temperature (Figure 6). This work is intended to show how diversity-oriented chemistry, using simple starting materials, can lead to enantiopure drug-like and/or natural product-like compounds.[22]

Experimental Section[23]

4-[(3*R*,8a*R*)-8-(3-Oxo-butyl)-3-phenyl-hexahydro-oxazolo-[3,2-*a*]pyridin-8-yl]-butan-2-one 4. A solution of phenyloxazolopiperidine **2**[8] (500 mg, 2.46 mmol) and MVK (1.724 g, 2 mL, 24.6 mmol, 10 equiv) in MeOH (20 mL) was stirred at room temperature for 6 days. The mixture was concentrated under reduced pressure and the crude mixture submitted to purification by flash chromatography on silica gel (cyclohexane/ether 6:4) to afford **3** as a colorless oil: $C_{21}H_{29}NO_3$, R_f = 0.2 (cyclohexane/ether 6:4); $[\alpha]^{28}_D = -71$ (*c* 1, $CHCl_3$); IR (film, $CHCl_3$) 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (td, ^2J ^3J = 14 Hz, ^3J = 5 Hz, 1 H), 1.34 (br d, ^3J = 13 Hz, 1 H), 1.45−1.65 (m, 4 H), 1.91 (td, ^2J ^3J = 10 Hz, ^3J = 3 Hz), 1.98 (t, ^3J = 8.5 Hz), 2.11 (s, 3 H), 2.14 (s, 3 H), 2.25−2.50 (m, 3 H), 2.62 (dd, ^3J = 13 Hz, ^3J = 6 Hz, 1 H), 2.75 (m, 1 H), 3.35−3.45 (m, 2 H), 3.48 (s, 1 H), 4.04 (t, ^2J ^3J = 7 Hz, 1 H), 7.1−7.3 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 21.2, 29.9, 30.6, 32.8, 37.8, 38.3, 47.9, 66.7, 73.0, 101.1, 127.6, 128.4, 138.8, 209.0, 209.4; MS (CI, NH_3), *m*/*z* $(M + H)^+$ 344; HRMS (CI, CH_4) *m*/*z* $(M + 1)^+$ calcd for $C_{21}H_{30}NO_3$ 344.2225, found 344.2227.

(1*R*,6*R*)-8-Acetyl-9-methyl-(3*R*-phenyl-5*H*-oxazolo[3,2-*a*])-2-aza-spiro[5.5]undec-8-ene 5 and (1*R*,6*S*)-8-Acetyl-9-methyl-(3*R*-phenyl-5*H*-oxazolo[3,2-*a*])-2-aza-spiro[5.5]-undec-8-ene 6. Diketone **4** (172 mg, 0.98 mmol) was diluted in concentrated hydrochloric EtOH (5 mL) and refluxed for 30 min. The reaction mixture was then brought to pH 9 by addition of an aqueous solution of $NaHCO_3$ and extracted (4 times) with CH_2Cl_2 (20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 98:2) to give in the order of elution **5** (48 mg, 30%) and **6** (49 mg, 30%) as colorless oils. **Spiropiperidine 5**: $C_{21}H_{27}NO_2$, R_f = 0.6 (cyclohexane/ether 6:4); $[\alpha]^{20}_D$ = −33 (*c* 1, $CHCl_3$); IR ($CHCl_3$, film) 1685, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (td, ^2J ^3J = 13.5 Hz, ^3J = 5.5 Hz), 1.25−1.35 (m, 1 H), 1.38−1.50 (m, 1 H), 1.58−1.72 (m, 1 H), 1.72−1.85 (m, 2 H), 1.86 (s, 3 H), 2.0 (td, ^2J ^3J = 12 Hz, ^3J = 3 Hz, 1 H), 2.08−2.20 (m, 2 H), 2.31 (s, 3 H), 2.43, 2.54 (2 d (AB), ^2J = 17.5 Hz), 2.83 (dd, ^2J = 12 Hz, ^3J = 4.5 Hz), 3.4−3.6 (m, 3 H), 4.16 (t, ^2J ^3J = 7 Hz), 7.2−7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 21.2, 26.9, 29.5, 29.7, 30.0, 30.8, 48.0, 67.2, 73.4, 101.0, 127.6, 128.4, 132.3, 138.1, 138.7, 205.1; MS (CI, NH_3), *m*/*z* $(M + 1)^+$ 326; HRMS (CI, CH_4) *m*/*z* $(M + 1)^+$ calcd for $C_{21}H_{28}NO_2$ 326.2120, found 326.2120. **Spiropiperidine 6**: $C_{21}H_{27}NO_2$, R_f = 0.5 (cyclohexane/ether 6:4); $[\alpha]^{20}_D$ = −20 (*c* 1, $CHCl_3$); IR ($CHCl_3$, film) 1683, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (td, ^2J ^3J = 13.5 Hz, ^3J = 4 Hz), 1.35−1.45 (m, 1 H), 1.65 (m, 3 H), 1.88 (s, 3 H), 2.05 (ddd, ^2J = 14 Hz, ^3J = 11.5 Hz, ^3J = 3 Hz, 1 H), 2.1−2.2 (m, 2 H), 2.23 (s, 3 H), 2.63 (ddd, ^2J = 16 Hz, ^3J = 2.5 Hz, ^3J = 2 Hz), 2.85 (ddd, ^2J = 11.5 Hz, ^3J = 4 Hz, ^3J = 2.5 Hz), 3.53 (m, 1 H), 3.65 (br s, 1 H), 4.14 (t, ^2J ^3J = 11.5 Hz, 1 H), 7.2−7.5 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 21.2, 21.3, 29.5, 30.1, 30.6, 36.2, 48.0, 67.1, 73.3, 99.9, 127.6, 128.4, 130.8, 139.0, 140.7, 203.7;

(19) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, 30, 287−290. Conditions as used in ref 18b.

(20) Mechanistic considerations for the ready formation of this 4-oxo-1-azabicyclo[3.3.1]nonane derivative are discussed in Supporting Information.

(21) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 575−578.

(22) Recent reviews in the field of piperidines and piperidones: (a) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989. (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701−1729.

(23) See ref 2 for general methods. All compounds were fully characterized by IR, MS, HRMS, ^1H NMR, ^{13}C NMR, COSY, HETCOR and, when needed, NOESY experiments.

MS (CI, NH_3), *m/z* $(M + 1)^+$ 326; HRMS (CI, CH_4) *m/z* $(M + 1)^+$ calcd for $C_{21}H_{28}NO_2$ 326.2120, found 326.2135.

(1*R*,6*S*,7*R*,11*S*)-11-Methoxy-(3*R*-phenyl-5*H*-oxazolo[3,2-*a*])-2-aza-spiro[5.5]undecan-7-ol 7. A solution of **2** (100 mg, 0.49 mmol) and glutaraldehyde (192 mg, 1.96 mmol, 0.8 mL of a 25% aqueous solution) in MeOH (10 mL) was refluxed for 18 h. The cooled mixture was diluted with a saturated solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The dried (Na_2SO_4), combined organic layers were concentrated under reduced pressure and purified by flash chromatography on silica gel (cyclohexane/ether 7:3) to afford spiropiperidine **7** as a colorless oil (77 mg, 50%): $C_{19}H_{27}NO_3$, R_f = 0.3 (cyclohexane/ether 1:1); $[\alpha]^{20}_D = -3$ (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.2−2.2 (m, 11 H), 2.86 (br d, ^3J = 5.5 Hz, 1 H), 3.11 (dd, ^3J = 12.5 Hz, ^3J = 3.5 Hz), 3.34 (s, 3 H), 3.49 (t, ^2J ^3J = 8.5 Hz), 3.78 (t, ^2J ^3J = 8.5 Hz), 4.1−4.2 (m, 1 H), 4.24 (s, 1 H), 4.27 (t, ^2J ^3J = 8.5 Hz, 1 H), 7.2−7.4 ppm (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 20.6, 22.4, 24.5, 28.6, 44.8, 47.9, 57.5, 68.1, 71.8, 72.8, 79.8, 96.3, 127.6, 128.5, 128.7, 137.3 ppm; MS (CI, NH_3), *m/z* $(M + 1)^+$ 318; HRMS (CI, CH_4) *m/z* $(M + 1)^+$ calcd for $C_{19}H_{28}NO_3$ 318.2069, found 318.2072.

[(3*R*,8a*R*)-8-Hydroxymethyl-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridin-8-yl]-methanol 8. A mixture of **2** (200 mg, 0.98 mmol) and paraformaldehyde (150 mg, 4.92 mmol, 5 equiv) in MeOH (10 mL) was stirred at room temperature for 2 d. After concentration under reduced pressure, the crude material was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 97:3) to furnish diol **8** as a colorless oil (213 mg, 82%); $C_{15}H_{21}NO_3$, R_f = 0.3 (CH_2Cl_2/MeOH 9:1); $[\alpha]^{20}_D$ = −37 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.9−2.0 (m, 4 H), 2.05 (td, ^2J ^3J = 13 Hz, ^3J = 4 Hz), 2.9 (dd, ^2J = 13 Hz, ^3J = 4 Hz), 3.3−4.0 (m, 6 H), 3.8 (s, 1 H), 4.2 (t, ^2J ^3J = 9 Hz), 7.1−7.5 ppm (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.5, 28.4, 42.4, 47.8, 63.6, 66.7, 67.9, 73.3, 99.2, 127.6, 128.0, 128.6, 137.9 ppm; MS (CI, NH_3), *m/z* $(M + 1)^+$ 264; HRMS (CI, CH_4) *m/z* $(M + 1)^+$ calcd for $C_{15}H_{22}NO_3$ 264.1600, found 264.1608.

(3*R*,8*R*,8a*R*)-8-[(3*R*,8*R*,8a*R*)-8-(3-Phenyl-hexahydro-oxazolo[3,2-*a*]pyridine)]-methyl-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine 9. A mixture of **2** (200 mg, 0.98 mmol) and paraformaldehyde (27 mg, 0.88 mmol, 0.9 equiv) in MeOH was stirred at room temperature for 6 days in the presence of 1 g of molecular sieves (4 Å). After filtration and washing with CH_2Cl_2, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/ether 9:1) to give **9** (39 mg, 20%, recovered **2** = 11 mg): colorless oil; $C_{27}H_{34}N_2O_2$, R_f = 0.3 (cyclohexane/ether 8:2); $[\alpha]^{18}_D$ = −51 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.0−2.2 (m, 7 H), 2.85 (br d, ^2J = 10.5 Hz), 3.4 (d, ^3J = 10 Hz, 1H), 3.53 (t, ^3J = 7 Hz), 3.64 (td, ^2J ^3J = 7 Hz, ^3J = 1.5 Hz, 1 H), 4.16 (t, ^2J ^3J = 7 Hz, 1 H), 7.2−7.4 ppm (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 28.1, 33.0, 37.5, 47.7, 67.4, 72.8, 99.1, 127.7, 128.4, 138.4 ppm; MS (CI, NH_3), *m/z* $(M + 1)^+$ 419; HRMS (CI, CH_4) *m/z* $(M + 1)^+$ calcd for $C_{27}H_{35}N_2O_2$ 419.2699, found 419.2695.

3-[1-(2-Hydroxy-1*R*-phenyl-ethyl)-1,4,5,6-tetrahydro-pyridin-3-yl]-but-2-enoic Acid Methyl Ester 11. A solution of **2** (1 g, 4.92 mmol) and methylacetoacetate (2.28 g, 2.12 mL, 19.70 mmol, 4 equiv) in a (7:3) MeOH/H_2O mixture (25 mL) was refluxed for 2 days. The cooled mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the oily residue by flash chromatography (CH_2Cl_2/MeOH 99:1) afforded **11** as a yellowish oil (892 mg, 60%). **11** (93:7 mixture of *E*/*Z* isomers): $C_{18}H_{23}NO_3$, R_f = 0.3 (CH_2Cl_2/MeOH 97:3); $[\alpha]^{20}_D$ = −91 (*c* 1, $CHCl_3$); IR (film, $CHCl_3$) 3384, 1553, 1162, 1136 cm^{-1}; ^{1}H NMR (major diastereomer) (300 MHz, $CDCl_3$) δ 1.80−1.90 (m, 2 H), 2.15−2.25 (m, 2 H), 2.37 (s, 3 H), 2.90−3.00 (m, 1 H), 3.00−3.10 (m, 1 H), 3.65 (s, 3 H), 4.00−4.20 (m, 2 H), 4.35 (dd, ^3J = 5.5 Hz, ^3J = 5 Hz, 1 H), 5.41 (s, 1 H), 7.05 (s, 1 H), 7.15−7.45 ppm (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 21.6, 22.1, 43.8, 50.3, 62.0, 69.0, 103.0, 107.2, 126.9, 127.6, 127.8, 128.4, 128.6, 137.5, 139.5, 155.5, 168.9 ppm; MS (CI, NH_3), *m/z* $(M + 1)^+$ 302; HRMS (CI, CH_4) *m/z* $(M + 1)^+$ calcd for $C_{18}H_{24}NO_3$ 302.1756, found 302.1760.

(3*R*,8*S*,8a*R*)-8-Methylsulfanyl-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine 12. A mixture of phenyloxazolopiperidine **2** (50 mg, 0.24 mmol) and methylmethanethiosulfonate (15 mg, 0.12 mmol, 0.5 equiv) in MeOH (5 mL) was stirred at room temperature for 3 days. After concentration under reduced pressure, the crude oily residue was submitted to purification by flash chromatography on silica gel (cyclohexane/ether 96:4) to afford thiopiperidine **12** as a colorless oil (15 mg, 50% based on thiosulfonate, recovered **2** = 20 mg): $C_{14}H_{19}NOS$, R_f = 0.4 (cyclohexane/ether 96:4); $[\alpha]^{25}_D$ = −20 (*c* 1, $CHCl_3$); IR (film, $CHCl_3$) 2886 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35−1.60 (m, 1 H), 1.7−1.9 (m, 2 H), 1.9−2.2 (m, 2 H), 2.41 (s, 3 H), 2.85 (ddd, ^3J = 4 Hz, ^3J = 9 Hz, ^3J = 13 Hz), 2.95 (br d, ^2J = 10 Hz, 1 H), 3.65−3.85 (m, 3 H), 4.2 (t, ^2J ^3J = 7.5 Hz, 1 H), 7.2−7.4 ppm (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 25.4, 29.8, 47.2, 66.7, 73.0, 99., 127.6, 127.8, 128.4, 138.7 ppm; MS (CI, NH_3), *m/z* $(M + 1)^+$ 250; HRMS (CI, CH_4) *m/z* $(M + 1)^+$ calcd for $C_{14}H_{20}NOS$ 250.1266, found 250.1265.

(3*R*,8a*R*)-8,8-Bis-methylsulfanyl-3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine 13. A solution of phenyloxazolopiperidine **2** (100 mg, 0.49 mmol) and an excess of methylmethanethiosulfonate (621 mg, 0.51 mL, 4.90 mmol, 10 equiv) in MeOH (10 mL) was stirred at room temperature for 3 days. After concentration under reduced pressure, the crude oily residue was submitted to purification by flash chromatography on silica gel (cyclohexane/ether 96:4) to afford bis-thiopiperidine **13** as a colorless oil (43 mg, 30%), which crystallizes slowly, followed by monothiopiperidine **12** (36 mg, 30%). **13**: $C_{15}H_{21}NOS_2$, R_f = 0.5 (cyclohexane/ether 96:4); $[\alpha]^{25}_D$ = −1.5 (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.4−1.55 (m, 2 H), 1.95−2.2 (m, 3 H), 2.07 (s, 3 H), 2.28 (s, 3 H), 2.85 (br d, ^3J = 6 Hz, 1 H), 3.51 (t, ^3J = 8 Hz), 3.62 (dd, ^2J = 8 Hz, ^3J = 7.5 Hz, 1 H), 4.1 (s, 1 H), 4.17 (t, ^2J ^3J = 8 Hz, 1 H), 7.2−7.5 ppm (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.4, 22.0, 32.8, 47.3, 62.4, 66.0, 73.5, 102.7, 127.7, 128.5, 138.5 ppm; IR (film, $CHCl_3$) 2886 cm^{-1}; MS (CI, NH_3), *m/z* $(M + 1)^+$ 296; HRMS (CI, CH_4) *m/z* $(M + 1)^+$ calcd for $C_{15}H_{22}NOS_2$ 295.1065, found 295.1067.

(2*R*,5*R*)-2-Phenyl-4-oxa-1-aza-bicyclo[3.3.1]nonan-9-one 14. Bis-thiopiperidine **13** (54 mg, 0.13 mmol) was dissolved in a mixture of acetonitrile and water (9:1, 10 mL). Bis-trifluoroacetoxyiodobenzene (146 mg, 0.27 mmol, 2 equiv) was then added at once. After 2 h of stirring at room temperature, the reaction mixture was diluted with an aqueous saturated solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give an oily residue that was purified by flash chromatography (CH_2Cl_2/MeOH 99:1) to afford lactam **14** (29 mg, 60%) as a colorless oil: $C_{13}H_{15}NO_2$, R_f = 0.3 (CH_2Cl_2/MeOH 99:1); IR (film, $CHCl_3$) 1676 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.7−1.9 (m, 2 H), 2.2−2.35 (m, 2 H), 2.35−2.5 (m, 1 H), 2.9−3.1 (m, 1 H), 2.9−3.1 (m, 1 H), 3.78 (t, ^3J = 7 Hz), 4.08 (t, ^3J = 7.5 Hz,), 4.35 (d, ^3J = 7 Hz), 7.2−7.7 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 23.9, 53.8, 58.8, 63.9, 71.8, 127.2, 127.7, 127.8, 128.1, 128.6, 138.2, 173.5 ppm; MS (ESI), *m/z* $(M + K)^+$ 256; HRMS (ESI) *m/z* $(M + K)^+$ calcd for $C_{13}H_{15}NO_2K$ 256.0740, found 256.0738.

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Supporting Information Available: Improved procedure for the preparation of **2**, ^{1}H and ^{13}C NMR spectra for all new compounds (**4**−**9**, **11**−**14**), and mechanistic considerations for the formation of **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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