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Selective Chemical Oxidation of Risperidone: A Straightforward and Cost-Effective Synthesis of Paliperidone

Renata Riva,*[a] Luca Banfi,[a] Graziano Castaldi,[b] Diego Ghislieri,[b] Luciana Malpezzi,[c] Francesca Musumeci,[a] Roberto Tufaro,[b] and Marcello Rasparini*[b]

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A very short and cost-effective synthesis of the commercial drug paliperidone has been achieved starting from its parent compound risperidone, through a thoroughly optimized oxidation with air under basic conditions.

Introduction

Atypical antipsychotics are gradually replacing typical antipsychotics in the treatment of schizophrenia because of the decreased propensity to cause extrapyramidal signs and symptoms (EPS) and the absence of sustained prolactin elevation. These drugs act as dual dopamine-serotonin antagonists. The reasons for reduced extrapyramidal activity in these drugs are not yet fully understood. The reduction may be linked to the dual activity against D_2 and serotonin receptors (mainly 5-HT_2 and 5-HT_7). However, it was shown that the kinetics of binding to dopamine D_2 receptors differ among antipsychotic compounds, and therefore it was proposed that fast-off kinetics (high k_{off}) may be associated with lower liability for extrapyramidal side effects (EPS).[1,2] Thus, a loose binding with D_2 receptors may be the distinctive mark of atypical antipsychotics.

Risperidone (**2**) is an antipsychotic widely used in clinical practice for the treatment of schizophrenia, autism, and bipolar disorders. Though generally considered an atypical antipsychotic, there is still some debate about that classification. In fact, in vitro experiments showed a dissociation time of 27 min, more similar to that of older "typical" antipsychotics.

The major route for elimination of **2** is hepatic oxidation to both enantiomers of 9-hydroxyrisperidone (paliperidone, **1**).[3–5] It has been suggested that the extent of extrapyramidal symptoms during risperidone treatment depends on the proportion of **2** to **1** in the patient.[2] Actually, paliperidone (**1**) is characterized by a very fast 50% dissociation from D_2 (only 60 s), and thus it definitely is an atypical antipsychotic. This knowledge has prompted the development of **1** as a separate antipsychotic drug. Paliperidone (**1**) is generally regarded as an improved drug compared to its parent not only because of its reduced side effects, but also because of its better pharmacokinetic properties, that is, having a longer elimination half-life in the brain. For these reasons, notwithstanding its higher price, it has recently been successfully commercialized on the drug market as the racemate[6] and is sold as Invega®.

In continuation of our research focused on the efficient synthesis of pharmaceutically active principles, we decided to search for an original and scalable synthetic route for this important drug.

The first synthesis of paliperidone was described by its discoverers at Janssen,[7] and the route is very similar to the one previously employed for risperidone (Scheme 1). The key intermediates are compounds **4**, which in turn are synthesized from protected pyridopyrimidinone **5** by hydrogenation of the pyridine ring (R = benzyl) or by simultaneous hydrogenation and hydrogenolysis (R = H). This procedure is not fully satisfactory. Compared to the industrial risperidone synthesis, the need to include an extra oxygen leads to diminished yields for both the formation of **5** from aminopyridine **6**, as well as for the formation **4** from the hydrogenation of **5**. In our hands these steps were found to be troublesome, and the purification steps were rather difficult. A possible alternative is represented in the synthesis of **4** by nitrosation of **9**, a key intermediate in the risperidone synthesis. This approach was recently reported in a patent,[8] after the completion of the present work, and involves oxidation of **9** with isoamyl nitrite. Unfortunately, conversion of the resulting oxime **8** into the key intermediate **4** required a multi-step sequence, using a stoichiometric amount of $TiCl_3$, making this approach not very attractive.

[a] Department of Chemistry and Industrial Chemistry, University of Genova,
Via Dodecaneso 31, 16146 Genova, Italy
Fax: +39-010-3536118
E-mail: riva@chimica.unige.it
[b] Chemessentia Srl,
Via Bovio 6, 28100 Novara, Italy
Fax: +39-0321-479200
E-mail: Marcello.Rasparini@chemessentia.it
[c] Politechnic of Milan, Department of Chemistry, Materials and Industrial Chemistry,
Via Mancinelli 7, 20131 Milan, Italy

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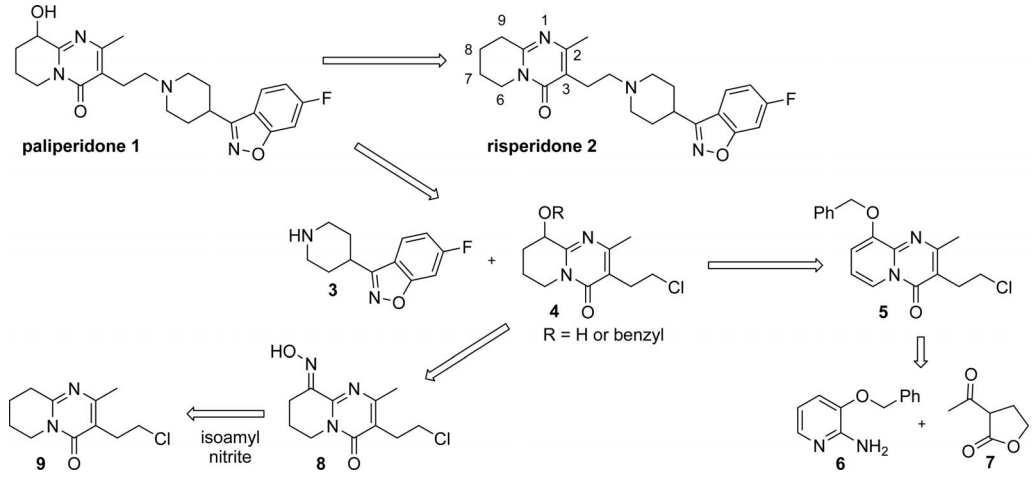
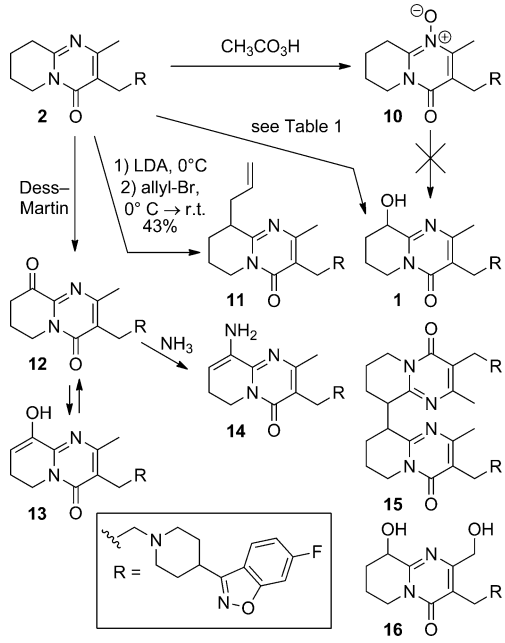


Scheme 1.

Due to these problems, the market price of paliperidone (**1**) was expected to be more than four times higher than that of risperidone (**2**). Thus, we reasoned that the direct oxidation of **2** to **1**, in one step, would lead to a synthesis of **1** which was more convenient than those previously known. Though simple in theory, this approach was not expected to be trivial in practice, because risperidone (**2**) possesses several oxidizable sites. Indeed, it can form *N*-oxides at N-1 or at the piperidine nitrogen, and it can be oxidized at five different positions activated by being α to heteraromatic systems (benzylic positions). For example, it is well known that in the liver the oxidation at C-9 is accompanied by oxidation at C-6.

Although biological oxidation of **2** to **1** seems the most obvious approach, as paliperidone is a natural metabolite of risperidone, the use of cytochromes to convert **2** into **1** on a preparative scale was found to be inefficient by other researchers in the field.[9] Furthermore, we could find in the literature very few examples of biological oxidations of benzylic carbons in nitrogen heterocycles.[10] For these reasons we decided to concentrate our efforts on chemical methodologies.



Scheme 2.

Results and Discussion

We first tried some neutral oxidizing agents. The oxidations at benzylic positions of electron-rich arenes by a variety of oxidants are well known, but in our case, the electron-poor nature of the pyrimidinone ring made all attempts unsuccessful. In general the reaction was very difficult, and in all cases, the nitrogens tended to be oxidized first. For example no reaction occurred with *meta*-chloroperbenzoic acid, whereas slow formation of the *N*-oxide at N-1 to give **10** was observed (Scheme 2) with peracetic acid (generated in situ from acetic acid and hydrogen peroxide). Unfortunately, the reaction was not clean, because of concurrent formation of the *N*-oxide on the piperidine ring, and the yield of **10** was poor. Nevertheless we tried to convert this *N*-oxide into **1** by way of the Boekelheide rearrangement,[11,12] but this was unsuccessful.

Other reagents, such as the Dess–Martin periodinane,[13] directly afforded 9-oxo-risperidone (**12**), and no intermediate alcohol **1** was observed. At first sight the formation of **12** may be considered useful in view of possible reduction to **1**. However, as already anticipated by a study on a model compound,[14] reduction of **12** to **1** with $NaBH_4$ or other reducing agents (for example, diisobutylaluminum hydride) proceeded poorly, because of concomitant reduction of the pyrimidinone ring.

Therefore we realized that the best strategy would be to exploit the electron-poor nature of the pyrimidone and to convert the benzylic proton at C-9 into an anion to facilitate oxidation. As already stated above, **2** has five benzylic positions, and at least two of them may form resonance stabilized anions, that is, at C-9 and the methyl group. Thus, to have an idea of possible selectivity and to check the compatibility of the whole molecule with strong bases, we first

studied the allylation of **2**. Although **2** was found to be unstable in the presence of NaH, we succeeded in obtaining the 9-allyl derivative **11** in 43% yield by deprotonation of **2** with LDA (lithium diisopropylamide) followed by reaction with allyl bromide. Although a diallylated side product was detected, NMR clearly showed that it was diallylated at C-9. Although this reaction was not optimized, this encouraging result demonstrated that kinetic deprotonation at C-9 was favored with LDA and prompted us to treat the same carbanion with oxidizing agents. Probably the most versatile and convenient reagent for the hydroxylation of enolates derived from ketones and esters is Davis' 3-phenyl-2-(phenylsulfonyl)oxaziridine,[15,16] which has also been used on large scale syntheses of active principles.[17] Although to the best of our knowledge it was not previously employed in benzyl anions oxidations, we tried to trap the LDA derived carbanion of **2** with this reagent, but this was unsuccessful.

Among the rare examples of benzylic oxidations of nitrogen heterocycles, the oxidation of deoxyquinine with dioxygen under basic conditions performed by Uskokovic[18] and Stork[19] during their total synthesis of quinine caught our attention. Indeed, it is a benzylic oxidation of a quinoline derivative within a quite complex structure containing, as in our case, a tertiary cyclic aliphatic amine. Thus we decided to treat the LDA derived anion with dioxygen.[20] We were delighted to find that treatment of **2** with LDA followed by bubbling O_2 at 0 °C followed by a reductive work-up (Table 1, Entry 1) gave the desired product **1**. However, the reaction was largely incomplete, the isolated yield was poor (10%), and various side products were detected. The most important one was ketone **12**, which was formed in equal amounts with **1**. In $CDCl_3$, this compound is a mixture of ketone **12** and enol **13** (82:18) and is not very stable, slowly decomposing at –20 °C in the dry state. Interestingly ketone **12** was completely converted into the corresponding stable enamine **14** when chromatography of the crude product was carried out in the presence of ammonia. Apart from this ketone, other more polar impurities were present. Two of them were identified by HPLC-MS. The first one, with $[M + H]^+ = 819$, was proposed to be dimer **15**. The structure of the second one, with $[M + H]^+ = 443$, was more difficult to assign. It is clearly a product of dioxygenation, but the second oxidation could in principle have occurred at N-1, at the piperidine nitrogen, or at one of the other four benzylic positions. As described below, the structure **16** was later unambiguously assigned to this impurity by crystallographic methods. Other unidentified polar impurities were also present.

Identification of the impurities allowed us to draw a possible mechanism for this reaction (Scheme 3).[21] Among the five possible benzylic positions, it is likely that two are more

Table 1. Optimization of conversion of **2** into **1**.

Entry	Base[a]	Solvent	Conc. [M]	Additive[b]	Oxidant[c]	Temp.	Time [h]	Work-up[d]	Yield [%] Main products[e]		
									1	**2**	**12**
1	LDA	THF	0.0244	none	O_2	0 °C	3.25	A	10	39	10
2	*t*BuOK	THF	0.0244	none	O_2	–10 °C	3.75	–		no reaction	
3	KHMDS	THF	0.0244	none	O_2	0 °C	2	–		no reaction	
4	LiHMDS	THF	0.0244	none	O_2	–10 °C	0.75	B	25	3	9
5	LiHMDS	THF	0.0244	none	O_2	–30 °C	3.5	B	20	46	4
6	LiHMDS	DMF/THF[e]	0.0244	none	O_2	–10 °C	6	–		no reaction	
7	LiHMDS	CH_2Cl_2/Et_2O[e]	0.0244	none	O_2	–10 °C	3	B	18	16	45
8	LiHMDS	toluene	0.0244	none	O_2	–10 °C	3.5	B	11	18	34
9	LiHMDS	CH_2Cl_2/toluene[f]	0.0244	none	O_2	–10 °C	4	B	40	28	14
10	LiHMDS	CH_2Cl_2/toluene[f]	0.122	none	O_2	–10 °C	0.6	B	34	0	19
11	LiHMDS	CH_2Cl_2/toluene[f]	0.122	$P(OEt)_3$	O_2	–10 °C	0.75	B	40	0	6
12	LiHMDS	CH_2Cl_2/toluene[f]	0.122	$P(OEt)_3$	O_2	–40 °C	3	B	36	18	25
13	LiHMDS	CH_2Cl_2/toluene[f]	0.122	$P(OMe)_3$	O_2	–40 °C	1.25	B	60	0	10
14	LiHMDS	CH_2Cl_2/toluene[f]	0.122	$P(OMe)_3$	air	–40 °C	2.5	B	61	0	7
15	LiHMDS	CH_2Cl_2/toluene[f]	0.122	$P(OMe)_3$	air	–78 °C	7	B	66	0	8
16	LiHMDS	toluene	0.122	$P(OMe)_3$	O_2	–30 °C	3	B	56	0	17
17	LiHMDS	Diglyme/toluene[e]	0.122	$P(OMe)_3$	O_2	r.t.	4.5	–		no reaction	
18	*t*BuONa	*t*BuOH/DMF	0.122	$P(OEt)_3$	O_2	r.t.	3	B	0	14	5
19	*t*BuOK	*t*BuOH/DMF	0.122	$P(OEt)_3$	O_2	r.t.	5	B	5	18	0
20	NaH	DMF	0.122	$P(OMe)_3$	O_2	r.t.	4.3	B		no reaction	
21[g]	LiHMDS	CH_2Cl_2/THF	0.244	$P(OMe)_3$	air	–78 °C	5	C	70	0	8

[a] 1.5 equiv. of base were always used. HDMS is bis(trimethylsilyl)amide. [b] 1.15 equiv. of the additive were always used. [c] In all cases bubbling of O_2 or air into the reaction mixture was started 5 min after addition of the appropriate base. [d] Work-up conditions: (**A**) quenching the reaction mixture with MeOH/H_2O, aqueous KI, and AcOH, and then extraction with CH_2Cl_2; (**B**) quenching with aqueous NH_4Cl and extraction with CH_2Cl_2 after adjusting the pH to 10 with K_2CO_3; and (**C**) quenching with H_2O followed by overnight stirring, and then extraction with CH_2Cl_2. [e] The crude product was fractionated by chromatography affording a fraction containing unseparated **1**, **2**, and **12**. Then NMR was used to establish the relative ratio of these three compounds. [f] In these cases, a solution of LiHMDS in THF, Et_2O, or toluene was added to the solution of **1** in the first solvent. [g] Reaction was carried out on 10 g scale. For details, see Exp. Sect.

easily deprotonated thanks to possible resonance stabilization, that is, at C-9 and the methyl group. The preferential hydroxylation at C-9 indicates that deprotonation at C-9 to give **17** is favored. This enolate can undergo a Single Electron Transfer (SET) process with triplet oxygen, giving the radical **18**, which accounts for the formation of dimer **15**,[22] and the superoxide anion. Combination of these two radicals generates **19**, which is probably in equilibrium with **20**. Anion **19** can in turn react with a reducing agent to give alkoxide **21**. The nature of the reducing agent is unclear according to the literature precedents. A likely possibility is that one molecule of **19** interacts in a redox process with one molecule of anion **17** to give two molecules of alkoxide **21**.[23]

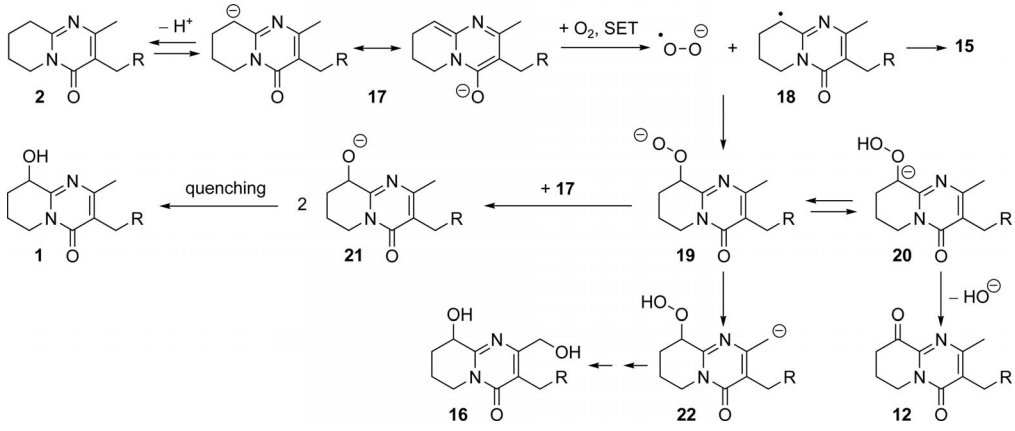
On the other hand, elimination of a hydroxide anion from **20** gives ketone **12**. This ketone could in principle be derived from **1** (or **21**) by a second oxygenation process. However, a control experiment showed that paliperidone (**1**) is not converted into **12** under the same reaction conditions.

Finally anion **19** can also undergo an intramolecular proton transfer to form **22** which can then react with a second oxygen molecule to eventually lead to **16**, analogous to the conversion of **17** to **1**. Diol **16** could also be derived from an initial hydroxylation of the methyl group followed by a second hydroxylation at C-9. In this case, the product of the single hydroxylation at the methyl site should have been formed as well, but it was never detected it in the crude reaction mixtures.

In this scenario, the reduction of **19** to **21** seems to be the most critical step. This reaction is probably slow, as demonstrated in the literature that dioxygen oxidation of enolates may be stopped, under appropriate circumstances, at the hydroperoxide level.[23–26] The low reduction rate of **19** allows, through an intramolecular process, the conversion to ketone **12**. As already stated, **12** is not a useful intermediate. When the crude mixtures obtained from the oxidation reaction were treated with $NaBH_4$ prior to purification, the yields of **1** turned out to be lower, due to decomposition processes involving the two heterocyclic rings of both **1** and **12**. The partial conversion was a problem too, because separation of **1** from unreacted **2** was rather difficult.

Therefore we tried to optimize the reaction (see Table 1) to reach a full conversion, to minimize formation of ketone **12**, and to maximize the yield of **1** (Table 1). We first noticed that the reductive work-up was not necessary, as we obtained the same yields without it. Thus the hydroperoxide species seemed to be completely converted under the reaction conditions to afford either **1** or **12**. With LDA in THF (tetrahydrofuran), the conversions were always low and increasing the reaction times was not beneficial. Thus we screened various combinations of bases and solvents. The solvent was particularly critical, because of the poor solubility of risperidone (**2**) in most of them, and was reflected in a low active concentration of the substrate. Risperidone (**2**) was sufficiently soluble at low temperatures only in THF, CH_2Cl_2, and alcohols. As shown by Entries 1–9, the best results (40% yield) were obtained by addition of lithium bis(trimethylsilyl)amide (LiHMDS) in toluene to a solution of **2** in CH_2Cl_2 (Entry 9). However, there was still partial conversion, and substantial amounts of ketone **12** were present. A real breakthrough occurred with an increase of substrate concentration, which led to full conversion (Entry 10). Unfortunately, the ratio of **1/12** was still unacceptably low.

To increase this ratio, we should accelerate the conversion of hydroperoxide anion **19** into **21**, compared to the disproportionation leading to ketone **12**. We reasoned that the introduction of a reducing agent in the reaction media could be the ideal solution. For example, this reducing agent could be a sulfide, a phosphane, or a phosphite.[27,28] For practical reasons we chose a phosphite, because of its lower cost and the possibility of easily eliminating the resulting phosphates by extraction. This hypothesis proved to be correct. A comparison of Entry 10 with Entry 11 shows that the ratio **1/12** increases from 1.8:1 to 6.7:1. A further improvement in the isolated yield of **1** and in the **1/12** ratio was achieved by using $P(OMe)_3$, instead of $P(OEt)_3$, and by



Scheme 3.

lowering the reaction temperature (Entries 13–15). Moreover we noticed that the reaction worked similarly by bubbling air instead of oxygen, with obvious advantages from the procedural safety point of view. Under the best conditions (Entry 15), an isolated yield of 66% of **1** was obtained, with a **1/12** ratio higher than 8:1. This high ratio also makes purification of **1** by chromatography easier, because **1** and **12** have similar polarities.

Having found benefits in the use of phosphites, we also checked if these additives could improve the reactions with other base/solvent combinations, but this was unsuccessful (Entries 16–20).

The conditions for Entry 15 were used substantially for scaling-up the methodology. We were able to carry out the reaction on a 10 g scale (Entry 21), increasing even further the concentration, and attain an isolated yield of pure **1** (after chromatography) of 70%. However, working in a more concentrated solution required the substitution of toluene (solvent for the base) with THF to avoid the partial precipitation of **2** at low temperature. In this procedure we also isolated ketone **12** (8%) and detected, by HPLC analysis of the crude product, the presence of 3–4% of diol **16**. Preliminary results have shown that pure **1** can also be obtained, with only a slight decrease in yield, by crystallization of the crude product without the need for chromatography.

Although it was very difficult to obtain a pure sample of **16**, after several chromatographic purifications and preparative TLC plates, we finally succeeded in isolating a few milligrams of crystals. This made the X-ray diffraction analysis feasible and allowed us to unambiguously establish the molecular structure of **16** (Figure 1). The OH group linked to C-9 was found to be disordered over the two possible positions, with occupation factors of 0.8 and 0.2 for O-3 and O-3′ atoms, respectively.

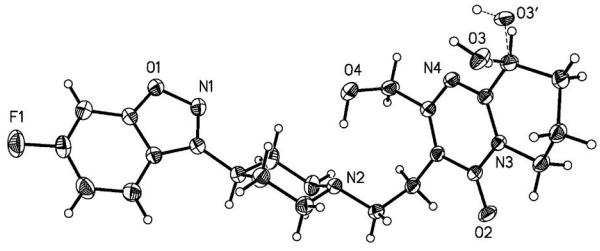


Figure 1. X-ray structure of **16** and selected atom labelling. ORTEP view at the 30% probability level.

In conclusion, careful optimization of the hydroxylation of **2** with dioxygen (or air) under basic conditions led to an efficient synthesis of highly valuable paliperidone from its cheaper parent risperidone in one step. Moreover, we feel that the optimization study described in this paper will also be helpful in future synthetic approaches involving autooxidations of heterocyclic benzylic positions under basic conditions. Indeed, this methodology has been used very seldom so far, notwithstanding its great potential for the synthesis of biologically active compounds.[18–20,22,29–31]

Experimental Section

NMR spectra were recorded at 300 MHz (^{1}H), and 75 MHz (^{13}C) with tetramethylsilane (^{1}H NMR in $CDCl_3$: δ = 0.000 ppm) or $CDCl_3$ (^{13}C in $CDCl_3$: δ = 77.16 ppm) as the internal standard. Chemical shifts are reported in ppm (δ scale). Peak assignments were made with the aid of gCOSY (gradient-selected COSY) and gHSQC (gradient-selected heteronuclear single quantum correlation) experiments. LRMS data were recorded with an Agilent 6310 instrument. Flash column chromatography was done using 220–400 mesh silica.

General Procedure for the Small Scale Oxidation of 2 (Table 1, Entries 10–15): A solution of risperidone (**1**, 500 mg, 1.22 mmol) in dry CH_2Cl_2 (10 mL) was cooled under an Ar atmosphere to the appropriate temperature. Then (in the case of Entries 11–15), trimethyl or triethyl phosphite (1.58 mmol) was added. LiHDMS (0.68 M in toluene, 2.69 mL, 1.83 mmol), freshly prepared from bis(trimethylsilyl)amine and *n*BuLi (1.6 M in hexanes), was added during 2 min. After 5 min, dioxygen or air (chromatographic grade) was bubbled into the solution (about 1 bubble per second) for the appropriate time always maintaining the solution at the same temperature. At the end, after stopping the gas flow, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) and saturated aqueous K_2CO_3 (5 mL). After checking that the pH was between 10 and 11, and adjusting it if needed, the mixture was extracted with CH_2Cl_2 (3×), and the organic extracts were washed with brine and dried with Na_2SO_4. The solvents were evaporated to dryness, and the crude product was purified by chromatography (CH_2Cl_2/MeOH, from 90:10 to 85:15) to give a single fraction containing, in the order of elution, **2**, **12**, and **1**. After evaporation to dryness, this fraction was weighed and examined by using ^{1}H NMR to determine the molar ratio of the three compounds. The yields reported in Table 1 were determined from this ratio and from the weight of the mixture.

Preparative Scale Synthesis of Paliperidone (1) from Risperidone (2): A solution of risperidone (**1,** 10.0 g, 24.4 mmol) in dry CH_2Cl_2 (100 mL) was cooled to –78 °C under a N_2 atmosphere and treated with trimethyl phosphite (3.31 mL, 28.06 mmol, 1.15 equiv.). Then, LiHDMS (1.0 M in THF, 25.6 mL, 1.05 equiv., commercially available from Chemetall) was slowly added so that the temperature did not exceed –70 °C. After 5 min from the end of the base addition, air (chromatographic grade) was slowly bubbled into the cooled solution through a sintered steel plug until the disappearance of the risperidone (**2**), as monitored by TLC (CH_2Cl_2/MeOH/satd. NH_4OH, 95:5:1, visualized with UV and ninhydrin) for 5 h typically. The mixture was quenched with water (50 mL) and stirred overnight to destroy the excess phosphite. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). Evaporation to dryness gave a crude foam which was purified by chromatography (CH_2Cl_2/MeOH, from 90:10 to 80:10) to give first ketone **12** (820 mg, 8%) and then **1** (7.29 g, 70%) as a foam, which was pure according to TLC and NMR. The tail fractions weighed 1.56 g. HPLC analysis of the crude product showed that it contained about 3–4% of the diol **16**. An analytically pure sample of **1** was obtained by crystallization from ethyl acetate/*n*-hexane (m.p. 162.2–162.4 °C) or by crystallization from dimethylacetamide [m.p. 186.2 °C, differential scanning calorimetry (DSC)]. ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 1.76 (ddt, J_d = 4.3, 12.9 Hz, J_t = 9.5 Hz, 1 H, 8-H), 1.89–2.04 (m, 1 H), 2.07–2.21 (m, 6 H), 2.25–2.42 (m, 2 H, C*H*HN of piperidine), 2.36 (s, 3 H, CH_3), 2.55 (m_c, 2 H, CH_2CH$_2$-N), 2.79 (m_c, 2 H, CH_2CH$_2$-N), 3.10 (m_c, 1 H, CH-isoxazolyl), 3.18 (br. d, J = 11.4 Hz, C*H*HN of piperidine), 3.87–4.03 (m, 2 H, 6-H), 4.42 (s, 1 H, OH), 4.51 (dd, J = 6.3, 10.2 Hz,

1 H, 9-H), 7.07 (dt, J_d = 2.2 Hz, J_t = 8.8 Hz, 5-H of benzoisoxazole), 7.25 (dd, J = 2.2, 9.0 Hz, 7-H of benzoisoxazole), 7.72 (dd, J = 5.4, 9.0 Hz, 4-H of benzoisoxazole) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 18.5 (CH_2), 21.2 (CH_3), 24.0 (CH_2), 27.1 (CH_2), 30.7 (2 CH_2), 34.7 (CH), 42.5 (CH_2), 53.5 (2 CH_2), 56.7 (CH_2), 67.1 (CH), 97.5 (d, J = 27.0 Hz, CH), 112.4 (d, J = 25.3 Hz, CH), 117.4 (C_{quat}), 120.6 (C_{quat}), 122.7 (d, J = 11.5 Hz, CH), 157.5 (C_{quat}), 157.9 (C_{quat}), 161.2 (C_{quat}), 162.1 (C_{quat}), 163.9 (d, J = 13.2 Hz, C_{quat}), 164.0 (d, J = 248.5 Hz, C_{quat}) ppm. FT-IR: $\tilde{\nu}_{max}$ = 3287, 2934, 2783, 2754, 1616, 1535, 1413, 1338, 1269, 1183, 1143, 1130, 996, 955, 868, 853, 817, 792, 758, 698 cm^{-1}. LRMS (ESI, ion trap, 70 V): m/z (%) = 427 (9) $[M + H]^+$, 209 (100). $C_{23}H_{27}FN_4O_3$ (426.48): calcd. C 64.77, H 6.38, F 4.45, N 13.14; found (sample crystallized from dimethylacetamide) C 64.84, H 6.48, F 4.49, N 13.21. A small amount (few milligrams) of compound **16** was obtained after several chromatographic purifications and preparative TLCs of the tail fractions. A crystal suitable for single-crystal X-ray diffraction was selected and used to determine the molecular and crystal structure of the compound.

Crystal Data and Structure Refinement for 16: Colorless monoclinic crystal of $C_{23}H_{27}FN_4O_4$ (0.78 × 0.40 × 0.04 mm in size), molecular weight 442.5 g/mol, space group $P2_1/n$, a = 6.9000(2) Å, b = 21.9314(9) Å, c = 13.8711(6) Å, β = 92.212(1), V = 2097.5(2) Å^3, Z = 4, D_c = 1.401 g cm^{-3}, room temperature. A total of 19923 reflections {independent 3284 [R(int) = 0.0248]} was collected by using graphite monochromated Mo-K_α radiation (λ = 0.71069 Å) with a SMART-APEX CCD area detector diffractometer. The structure was solved by direct methods and refined by a full-matrix least-squares procedure with anisotropic temperature factors for non-hydrogen atoms. The hydrogen atoms were located in calculated positions and refined in the riding model. Final R values were: R_1 = 0.0380 and wR_2 = 0.0958 for 308 refined parameters and 2932 observed reflections.

CCDC-801682 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Independent Synthesis of Ketone 12 from Paliperidone (1): A solution of paliperidone (**1**, 1.00 g, 2.44 mmol) in glacial acetic acid (12 mL) and acetonitrile (3 mL) was cooled to 0 °C and treated with aqueous NaOCl (15%, 2 mL). After stirring for 1 h at 0 °C, the mixture was diluted with water (150 mL) and neutralized with $NaHCO_3$ (pH = 7). The reaction mixture was extracted with CH_2Cl_2 (3×) and dried with Na_2SO_4. Evaporation of solvent followed by purification of the crude product by chromatography (CH_2Cl_2/MeOH, between 100:0 and 90:10) gave pure **12** as a foam (453 mg, 45%). An 82:18 mixture of ketone and enol was present in the ^{1}H NMR sample. ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 2.00–2.15 (m, 4 H), 2.18–2.40 (m, 4 H), 2.47 (s, 3 H, CH_3), 2.48–2.63 (m, 2 H), 2.78–2.90 (m, 4 H), 3.02–3.22 (m, 3 H), 4.11 (dt, J_d = 5.1 Hz, J_t = 7.5 Hz, 0.18 H, 6-H of enol), 4.19 (t, J = 5.8 Hz, 0.82 H, 6-H of ketone), 5.68 (t, J = 4.6 Hz, 0.18 H, C*H*=C of enol), 7.04 (dt, J_d = 2.1 Hz, J_t = 8.8 Hz, 5-H benzoisoxazole), 7.22 (dd, J = 2.0, 8.6 Hz, 7-H of benzoisoxazole), 7.68 (dd, J = 5.1, 8.6 Hz, 4-H of benzoisoxazole) ppm. Only the signals of the ketone are reported in the ^{13}C NMR data. ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 20.5 (CH_2), 21.6 (CH_3), 24.5 (CH_2), 30.6 (2 CH_2), 34.5 (CH), 37.1 (CH_2), 42.4 (CH_2), 53.4 (2 CH_2), 56.2 (CH_2), 97.4 (d, J = 26.5 Hz, CH), 112.3 (d, J = 25.1 Hz, CH), 117.3 (C_{quat}), 122.6 (d, J = 11.1 Hz, CH), 126.6 (C_{quat}) 145.6 (C_{quat}), 158.7 (C_{quat}), 161.1 (C_{quat}), 161.2 (C_{quat}), 163.8 (d, J = 13.3 Hz, C_{quat}), 164.1 (d, J = 249.0 Hz, C_{quat}), 189.5 (C_{quat}) ppm. LRMS (ESI, ion trap): m/z = 425.3 $[M + H]^+$. $C_{23}H_{25}FN_4O_3$ (424.47): calcd. C 65.08, H 5.94, F 4.48, N 13.20; found C 65.21, H 6.02, F 4.48, N 13.18.

Enamine 14: Ketone **12** was also characterized by converting it to enamine **14**. When the crude product, derived from risperidone oxidation under the conditions of Entry 10, was purified by chromatography with CH_2Cl_2/MeOH/saturated NH_4OH, ketone **12** was quantitatively converted into enamine **14**. (With high quantities of **12**, it was difficult to separate **12** from **1** using only CH_2Cl_2/MeOH). Enamine **14** was easier to characterize by NMR, because of the lack of the keto-enol equilibrium, that is, there was no evidence of the imine. ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 1.68 (br. s, 2 H, NH_2), 2.02–2.17 (m, 3 H), 2.20–2.36 (m, 3 H), 2.34 (s, 3 H, CH_3), 2.43 (dt, J_d = 4.8 Hz, J_t = 7.2 Hz, 2 H, 7-H), 2.49–2.62 (m, 2 H), 2.72–2.90 (m, 2 H), 3.01–3.23 (m, 3 H), 4.11 (t, J = 7.2 Hz, 2 H, 6-H), 5.49 (t, J = 4.8 Hz, 8-H), 7.05 (dt, J_d = 2.0 Hz, J_t = 9.0 Hz, 5-H benzoisoxazole), 7.24 (dd, J = 1.5, 8.4 Hz, 7-H of benzoisoxazole), 7.72 (dd, J = 5.1, 8.4 Hz, 4-H of benzoisoxazole) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 21.0 (CH_2), 21.6 (CH_3), 24.2 (CH_2), 30.6 (2 CH_2), 34.7 (CH), 39.4 (CH_2), 53.5 (2 CH_2), 56.7 (CH_2), 97.5 (d, J = 26.8 Hz, CH), 104.3 (C_{quat}), 112.4 (d, J = 25.1 Hz, CH), 117.4 (C_{quat}), 121.5 (C_{quat}), 122.8 (d, J = 11.1 Hz, CH), 135.0 (C_{quat}), 147.9 (C_{quat}), 158.1 (C_{quat}), 161.2 (C_{quat}), 161.8 (C_{quat}), 164.0 (d, J = 13.7 Hz, C_{quat}), 164.2 (d, J = 249.0 Hz, C_{quat}) ppm. $C_{23}H_{26}FN_5O_2$ (423.48): calcd. C 65.23, H 6.19, N 16.54; found C 65.05, H 6.11, N 16.39.

Allylated Risperidone 11: A solution of LDA was freshly prepared from *n*BuLi (1.6 M in *n*-hexane, 4 mL, 6.40 mmol) and diisopropylamine (995 μL, 7.04 mmol) in THF (8 mL). A solution of risperidone (**2**, 101.8 mg, 248 μmol) in dry THF (5 mL) was cooled under argon to 0 °C and treated with the solution of lithium diispropylamide (0.49 M in THF/*n*-hexanes, 755 μL, 372 μmol). At the end of the addition, the cooling bath was removed. After 15 min, allyl bromide (27.5 μL, 322 μmol) was added. After stirring for 15 min at room temp., the reaction was quenched with saturated aqueous NH_4Cl, and the pH was adjusted to 11 with saturated aqueous K_2CO_3. The mixture was extracted with Et_2O, and the organic extracts were washed with brine and dried with Na_2SO_4. Evaporation of the solvent gave a crude product which was purified by chromatography (CH_2Cl_2/MeOH, from 97:3 to 92:8) to give pure **11** (34.9 mg, 31%). The 9,9′-diallylated product (9.9 mg, 8%) and recovered **2** (28.2 mg) were also isolated. The yield of **11** based on recovered starting material was 43%. ^{1}H NMR (300 MHz, $CDCl_3$, 297 K): δ = 1.60–1.74 (m, 1 H), 1.80–2.20 (m, 7 H), 2.24–2.46 (m, 3 H), 2.33 (s, 3 H, CH_3), 2.55 (m, 2 H, C*H*$_2$CH$_2$-N), 2.72–2.93 (m, 4 H, C*H*$_2$CH$_2$-N and C*H*-C*H*H-CH=CH$_2$), 3.09 (m, 1 H, CH-isoxazolyl), 3.19 (br. d, J = 11.1 Hz, C*H*HN of piperidine), 3.85–4.01 (m, 2 H, 6-H), 5.02–5.20 (m, 2 H, C*H*$_2$=CH), 5.80 (dddd, J = 6.0, 7.8, 10.2, 17.7 Hz, C*H*=CH$_2$), 7.06 (dt, J_d = 2.0 Hz , J_t = 8.8 Hz, 5-H benzoisoxazole), 7.24 (dd, J = 2.0, 8.7 Hz, 7-H of benzoisoxazole), 7.72 (dd, J = 5.1, 8.7 Hz, 4-H of benzoisoxazole) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 297 K): δ = 20.0 (CH_2), 21.5 (CH_3), 23.9 (CH_2), 24.0 (CH_2), 30.6 (2 CH_2), 34.7 (CH), 38.3 (CH_2), 39.9 (CH), 42.9 (CH_2), 53.5 (2 CH_2), 56.8 (CH_2), 97.5 (d, J = 26.5 Hz, CH), 112.4 (d, J = 25.4 Hz, CH), 117.4 (C_{quat}), 117.6 (CH_2), 119.1 (C_{quat}), 122.8 (d, J = 11.1 Hz, *C*H), 135.8 (*C*H), 158.4 (C_{quat}), 158.6 (C_{quat}), 161.2 (C_{quat}), 162.8 (C_{quat}), 164.0 (d, J = 13.3 Hz, C_{quat}), 164.2 (d, J = 249.0 Hz, C_{quat}) ppm. LRMS (ESI, ion trap): m/z = 451.1 $[M + H]^+$. $C_{26}H_{31}FN_4O_2$ (450.55): calcd. C 69.31, H 6.94, N 12.44; found C 69.57, H 6.95, N 12.27.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR, ^{13}C NMR, IR, LRMS, HPLC and DSC of compound **1**; ^{1}H NMR and ^{13}C NMR of compounds **11** and **12**.

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