JOC The Journal of Organic Chemistry

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Diastereoselective Syntheses of (3*R**,4*R**)- and (3*R**,4*S**)-4-Aryl-3-methyl-4-piperidinemethanol and Fluoro Analogues

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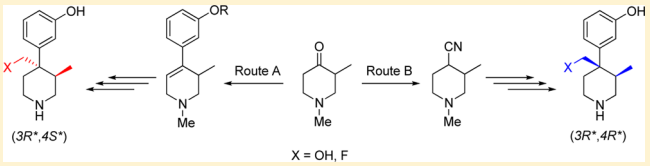
Supporting Information

ABSTRACT: Two concise and high-yielding diastereoselective syntheses of 4-aryl-3-methyl-4-piperidinemethanols were realized from 1,3-dimethyl-4-piperidinone. The key reactions to control the C3−C4 relative stereochemistry were the alkoxymethylation of a metalloenamine generated from 4-aryl-3-methyl-1,2,3,6-tetrahydropyridine that afforded the (3*R**,4*S**)-form and the nucleophilic substitution of a fluoroarene with deprotonated 3-methyl-4-piperidinenitrile giving the (3*R**,4*R**)-isomer. The corresponding fluoromethyl analogues were subsequently obtained through the fluorination of the piperidinemethanols using DAST.



INTRODUCTION

In recent years, 4-aryl-4-piperidinemethanols **1** have become attractive as versatile molecular frameworks for drug discovery programs (Scheme 1). The importance of piperidines **1** in medicinal chemistry is highlighted by their growing utility as key intermediates for the synthesis of more advanced structures and also by the presence of these structures in novel patented pharmaceutical agents targeting central nervous system disorders and cancers. For illustration, the coupling of piperidines **1** with a bromocyanopyridinone gave access to *N*-substituted piperidines **2** functioning as positive allosteric modulators of metabotropic glutamate receptors subtype 2 (mGluR2).[1] In this series, a further substitution of the hydroxy group by a fluorine led to compounds with an increased mGluR2 inhibition. The conversion of alcohols **1** into appropriate ethers **3** afforded inhibitors of neurokinin-1 and serotonin (5-hydroxytryptamine 5-HT) reuptake receptors,[2] and the transformation of **1** to spirodihydrobenzofurans **4** provided an efficient route to antagonists of CCR2 chemokine receptors.[3] Finally, piperidinemethanols **1** can also be the subject of other transformations such as a ring contraction to provide 3-disubstituted pyrrolidines **5** and **6** as a new class of compounds with potential pharmacotherapeutic interest.[4] Derivatives containing a backbone **6** have already been investigated as selective dopamine D3 receptor antagonists.[5]

The reported products **1**−**4** contain a symmetrical 3-desalkylpiperidine moiety, but SAR studies on other piperidine-based drugs identified that methyl substitution at position 3 on the ring improved potency and bioavailability. Typically, the 3-methylpiperidine unit has been identified as an attractive pharmacophore when embedded within spirocyclic CCR2 antagonists **7**[3] and **8**,[6] opioid ligands **9**,[7] and DPP-4 (dipeptidyl peptidase IV) inhibitors **10**[8] (Figure 1). In the case of 3,4-polysubstituted piperidines, the configuration at the C-3 and C-4 positions can be critical for the intrinsic biological activity. However, the structural specificity of the antagonist activity has only been demonstrated for opioid ligands **9**.

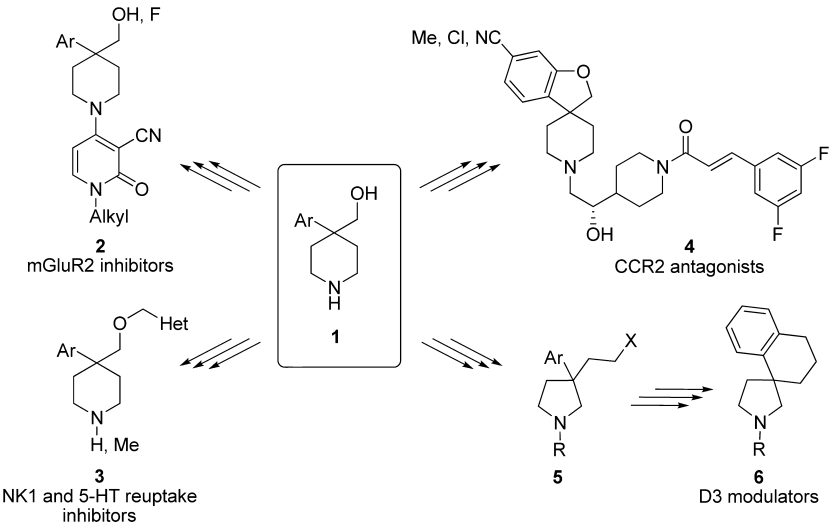
Considering the biological and synthetic importance of 3-methylpiperidines on one hand and of 4-aryl-4-piperidinemethanols on the other hand, we considered the 4-aryl-3-methyl-4-piperidinemethanols **11** to represent attractive tools for the development of original drug analogues (Scheme 2), for pharmaceutical optimization, and for understanding of binding mechanisms with the molecular targets. To date, the chemistry of such a building block remains relatively unexplored. Only one synthesis is reported in a patent and involves the sequential alkylation of an arylacetonitrile with the bis-mesylate of (*R*)-*N*-Boc-2-hydroxyethyl-2-hydroxypropylamine.[3] This approach led to a mixture of (3*R*,4*S*) and (3*R*,4*R*) diastereoisomers in a 7:3 ratio in rather poor yields (<20%).

Over the course of our program concerning preparation of 3,4-trisubstituted piperidines,[9] we set out to develop straightforward and diastereoselective synthetic routes to (3*R**,4*S**)- and (3*R**,4*R**)-4-aryl-3-methyl-4-piperidinemethanols **11a** and **11b** (Scheme 2). By analogy with the 4-arylpiperidine template in opioid ligands **9**, a phenol moiety was selected as the aryl group. Our strategy for the preparation

Received: October 23, 2012

   dx.doi.org/10.1021/jo302303h | *J. Org. Chem.* XXXX, XXX, XXX−XXX

Scheme 1. 4-Aryl-4-piperidinemethanols as Building Blocks for the Synthesis of Pharmacologically Active Molecules



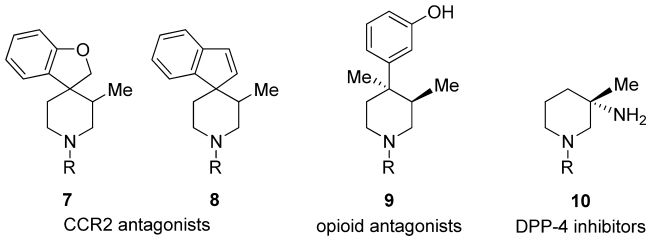
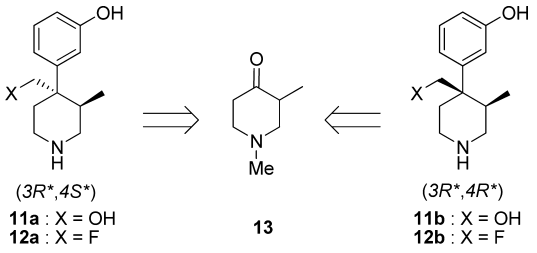


Figure 1. Structures of pharmacologically active 3-methylpiperidines **7**–**10**.

Scheme 2

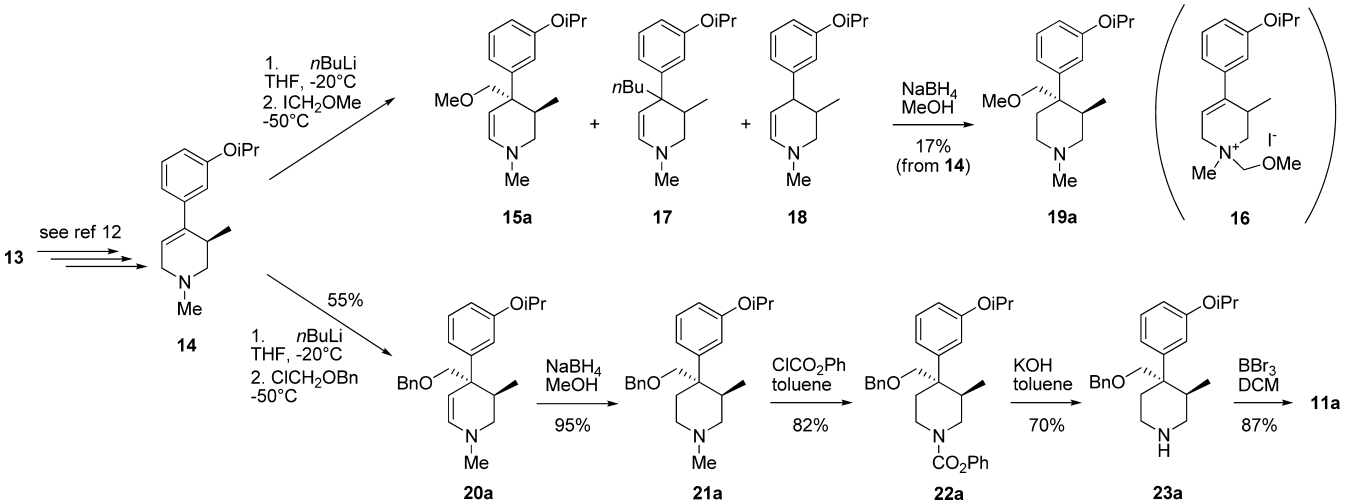


of piperidines **11a,b** was based on the use of the commercially available *N*-methyl-3-methyl-4-piperidinone **13** as the common starting material. Construction of the quaternary center at C4 was central to the syntheses of target compounds. The general approach involved sequential introduction of the aryl moiety and the hydroxymethyl equivalent, where control of the C3–C4 relative stereochemistry was directly related to the order of introduction of these groups. As the addition of fluorine at specific positions in drug-like molecules has successfully led to improvements in a variety of properties including enhanced binding interaction, brain penetration, metabolic stability, and extended biological half-life,[10] we also targeted fluorine-containing 4-aryl-3,4-dimethypiperidines. Knowing that conversion of the piperidinemethanol moiety present in mGluR2 inhibitors into their fluoromethyl derivative led to enhanced potency,[1] we focused on the diastereoselective preparation of fluoro compounds **12a** and **12b**.

RESULTS AND DISCUSSION

For the synthesis of **11a**, we envisioned an approach based on the alkylation reaction of the metalloenamine generated from the tetrahydropyridine **14** (Scheme 3).[11−14] Tetrahydropyr-

Scheme 3. Synthesis of Piperidine 11a



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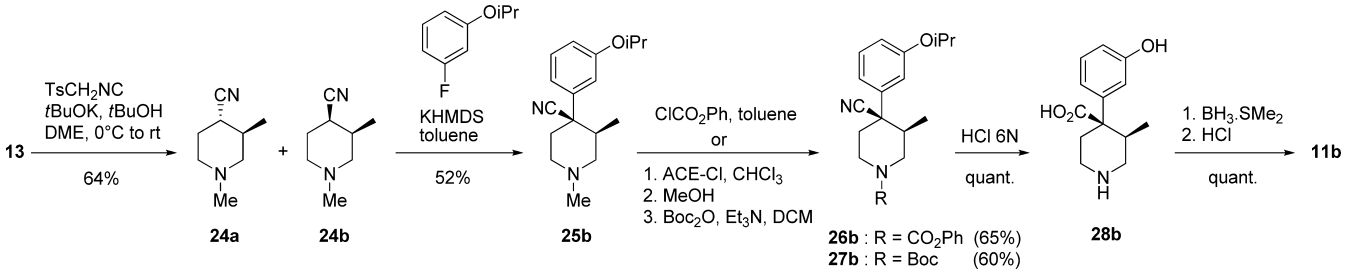
Scheme 4. Synthesis of Piperidine 11b



idine **14** was easily accessed from piperidinone **13** via aryllitihum addition followed by regioselective dehydration as described in the literature.[12] The metalloenamine alkylation methodology from 3-alkyl-4-aryltetrahydropyridines was previously reported with methylating,[11,12] propylating,[13] and allylating[14] agents in the context of the synthesis of morphinoid alkaloids. Alkylation was shown to be highly regioselective in favor of the 3-position and to occur exclusively *trans* to the C3-substituent. The *trans* diastereoselectivity was explained by the C3-substituent preferentially adopting a pseudoaxial orientation in the flattened metalloenamine, thus impeding alkylation from the β-face. Our attention was turned to the introduction of an alkoxymethyl group as a protected hydroxymethyl equivalent. In the event, treatment of tetrahydropyridine **14** with *n*-BuLi (1−1.5 equiv) in THF followed by iodomethoxymethane (1−2 equiv) did not provide an efficient access to the 4-methoxymethyltetrahydropyridine **15a** due to concurrent *N*-alkylation giving ammonium **16** and butylation of tetrahydropyridine **14** resulting in 4-butyltetrahydropyridine **17**. The *des*-alkyltetrahydropyridine **18**, formed by protonation of the metalloenamine was also detected as side product in significant amounts. Under a variety of conditions, a mixture of products **15a**/**16**/**17**/**18** was obtained in a ratio of about 34:34:21:11 (estimated from the ^{1}H NMR spectrum of the crude products). Tetrahydropyridines **15a**, **17**, and **18** were not easily separable by chromatography, and reduction with $NaBH_4$ was performed from a mixture enriched in **15a** to afford methoxymethylpiperidine **19a** in only 17% yield from tetrahydropyridine **14**.

Changing the hydroxymethylating equivalent to benzyloxymethyl chloride (BOM − Cl) proved more rewarding; treatment of the tetrahydropyridine **14** with *n*-BuLi in THF at −20 °C followed by addition of BOM − Cl at −50 °C afforded the pure benzyloxymethyltetrahydropyridine **20a** in 55% yield. No traces of side products **17**, **18**, and the corresponding ammonium were detected by ^{1}H NMR analysis of the crude product, and the diastereoisomer **20a** was the sole alkylation product isolated. Enamine **20a** was reduced with $NaBH_4$ to give piperidine **21a** in 95% yield. The anticipated *trans* diasteroselectivity of the metalloenamine alkylation was confirmed by ^{1}H NMR analysis of compound **21a** (and also of **19a**) with the signal attributed to the methyl group in position 3 in the form of a unique doublet at 0.85 ppm.[12] Compound **21a** was then subjected to successive deprotection steps to yield the target product **11a**. Treatment of *N*-methylpiperidine **21a** with phenyl chloroformate in refluxing toluene led to the *N*-phenylcarbamate **22a** in 82% yield. Basic hydrolysis of carbamate **22a** gave piperidine **23a** in 70% yield. Finally, liberation of the aliphatic alcohol and phenol functionalities was carried out using BBr_3 in DCM to produce hydroxymethylpiperidine **11a** in 87% yield.

The route envisaged for the preparation of hydroxymethylpiperidine **11b** involved 4-cyano-3-methylpiperidine **24** as the key intermediate (Scheme 4). Indeed, the α-arylation of a secondary aliphatic nitriles with aryl halides provides a valuable entry to tertiary benzylic nitriles, which are precursors of hydroxymethyl derivatives.[15−20] Single-step transformation of piperidinone **13** to the nitrile intermediate **24** was carried out using tosylmethyl isocyanide and *t*-BuOK in DME in 64% yield,[21] giving mixture of diastereoisomers **24a** and **24b** in a 70/30 ratio. Structural identification of the major isomer **24a** was achieved through a combination of NMR spectroscopic analyses (COSY, HSQC, and NOE) from a pure fraction isolated by chromatography.[22] On the basis of the COSY and HSQC spectra, we were able to assign a well-resolved signal at 2.85 ppm to the C4-H(CN) proton of the product. NOE experiments further confirmed the stereochemical relationship between C3 and C4 substituents on the basis of observed correlation for C3-H/C4-Me (see the Supporting Information). This result indicated that the newly introduced nitrile and the methyl group possess a *trans* relationship.

A variety of methods have been developed to carry out α-arylation of substituted nitriles with direct nucleophilic aromatic substitution (S_NAr) providing an attractive approach.[16,17] Classically, this method suffers from the use of harsh conditions unless an activated heteroaryl halide is employed.[16] The palladium-catalyzed arylation of nitriles has recently emerged as a promising methodology.[18−20] The applicability of this method to cyclohexanecarbonitriles has recently been addressed, but the use of the starting nitrile in excess (nitrile/aryl halide ratio of 1.5 to 2/1) reduces the attractiveness of the reported procedure in the present work.[20] Although underexploited to date, an improved procedure for direct S_NAr arylation of the potassium salts of secondary nitriles with aryl fluorides has been described by Caron and co-workers.[17] The potassium salts of nitrile derivatives of tropinone were shown to react with fluoroarenes from a less hindered α-equatorial direction. However, we are not aware of any reported examples of S_NAr arylation reactions of simple piperidinenitrile derivatives. From nitrile **24**, we anticipated that arylation will result in the (3*R**,4*R**) isomer as the major product. Nucleophilic substitution of (3-isopropoxy)fluorobenzene was realized using the 70/30 mixture of nitriles **24a** and **24b** in the presence of KHMDS in toluene at 120 °C for 24 h to give the desired benzylic nitrile **25b** in 52% yield as a single diastereoisomer. *N*-Methylpiperidine **25b** was converted to the phenyl and *tert*-butyl carbamates **26b** (65% yield) and **27b** (60% yield) by reaction with phenyl chloroformate in refluxing toluene or sequential *N*-demethylation and Boc protection, respectively. The crystal structure of *N*-Boc compound **27b** established the (3*R**,4*R**) configuration (see the Supporting Information). The high diastereoselectivity observed for the

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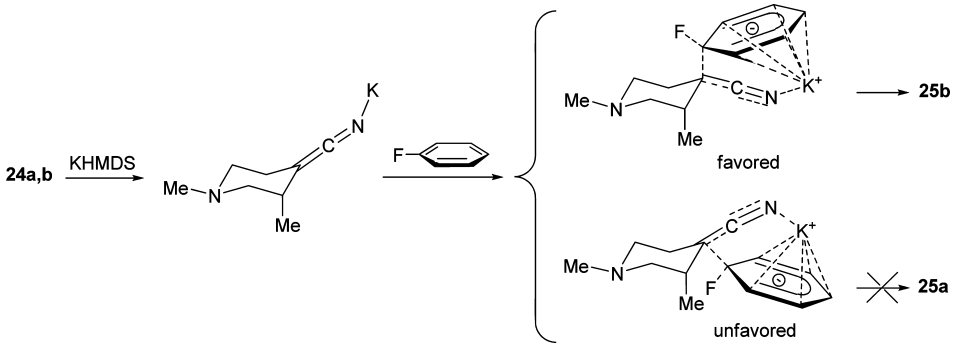
Scheme 5. Proposed Mechanism for the Formation of Nitrile 25b

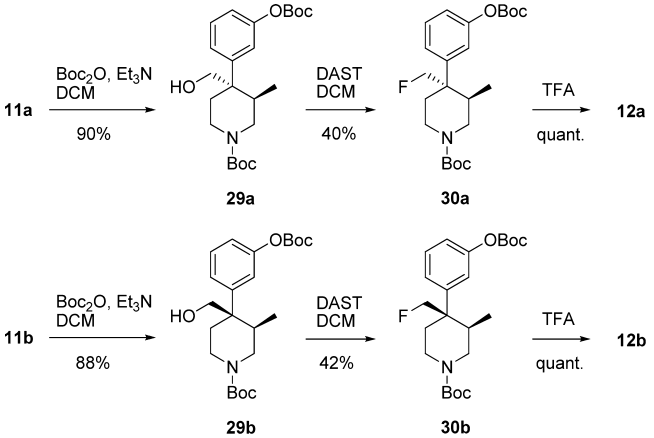


synthesis of nitrile **25b** can be rationalized on the basis of the proposed transition-state arrangement for the fluoroarene substitution process (Scheme 5). Following formation of the potassium ketenimine generated by deprotonation of nitriles **24a** and **24b**, arylation proceeds via potassium coordination with the developing negative charge on the aromatic ring. As observed for the alkylation reactions, addition *trans* to the C3-methyl is favored due to the steric hindrance of the pseudoaxially oriented methyl group at the adjacent position.

Heating of both nitriles **26b** and **27b** in HCl 6 N at reflux for 3 weeks led to *N*,*O*-deprotected piperidine carboxylic acid **28b** in quantitative yields. Despite the prolonged reaction time, the transformation was remarkably selective, although more forcing conditions such as refluxing H_2SO_4 (50%) or KOH (1 M) led to substantial degradation, and reaction with DIBAL afforded the corresponding aldehyde in less than 20% yield. Reduction of **28b** with borane−dimethyl sulfide in THF at reflux afforded the key hydroxymethylpiperidine **11b** quantitatively.

The targeted fluoromethylpiperidine derivatives **12a** and **12b** were synthesized by reaction of (diethylamido)sulfur trifluoride (DAST)[23] with an appropriate piperidinemethanol precursor. *N*-Methyl- and *N*-phenyloxycarbonylpiperidinemethanol failed to give access to **12a** and **12b** due to either unsuccessful fluorination (in case of *N*-methyl) or deprotection conditions incompatible with the presence of fluorine (in case of *N*-benzyloxycarbonyl, data not shown). Thus, syntheses of fluoromethylpiperidines **12a** and **12b** started from the previously prepared hydroxymethylpiperidines **11a** and **11b** (Scheme 6). Piperidines **11a** and **11b** were converted to *N*,*O*-di-Boc piperidines **29a** and **29b**, respectively, using $(Boc)_2O$ and Et_3N in CH_2Cl_2 in 88−90% yields. Fluorination of **29a** and **29b** with DAST afforded the fluoro analogues **30a** and **30b** in 40−42% yields, and deprotection with TFA produced the desired fluoromethylpiperidines **12a** and **12b** quantitatively.[24]

Scheme 6. Synthesis of Fluoromethylpiperidines 12a and 12b from Hydroxymethylpiperidines 11a and 11b



CONCLUSION

In summary, starting from 1,3-dimethyl-4-piperidinone **13**, (3*R**,4*S**)- and (3*R**,4*R**)-4-aryl-3-methyl-4-piperidinemethanols **11a** and **11b** were prepared in high yields and diastereoselectivities by two straightforward efficient synthetic protocols. The fluoro analogues **12a** and **12b** were subsequently obtained through fluorination with DAST. The procedures reported here pave the way for the preparation of novel structures as chemical tools for drug development.

EXPERIMENTAL SECTION

(3*R,4*S**)-4-(Benzyloxymethyl)-4-(3-isopropoxyphenyl)-1,3-dimethyl-1,2,3,4-tetrahydropyridine (20a).** To a solution of tetrahydropyridine **14**[12] (5.00 g, 20.4 mmol) in THF (50 mL) was added dropwise *n*-BuLi (1.6 M in hexanes, 19.1 mL, 30.6 mmol) while the temperature was maintained between −10 and −20 °C. When the addition was complete, the reaction mixture was stirred for 30 min at −20 °C and then cooled to −50 °C. Benzyloxymethyl chloride (75%, 5.8 mL, 30.6 mmol) was added dropwise to the reaction medium at −50 °C. The reaction mixture was stirred for 30 min at −50 °C. After addition of a dilute solution of aqueous NH_4OH (6%, 30 mL) and heptanes (25 mL), the reaction mixture was stirred for 1.5 h at rt and then concentrated. The residue was purified by chromatography on silica gel (DCM/MeOH from 100/0 to 96/4) to give the title compound as an orange oil (4.10 g, 55%): R_f 0.32 (DCM/MeOH 95/5); ^{1}H NMR ($CDCl_3$, 400.0 MHz) δ 0.50 (d, $^3J_{H-H}$ = 8.1 Hz, 3H), 1.26−1.33 (m, 6H) 2.17−2.22 (m, 1H), 2.44−2.52 (m, 2H), 2.50 (s, 3H), 3.39 and 3.57 (AB, d, $^2J_{A-B}$ = 7.1 Hz, 2H), 4.21 (sept, $^3J_{H-H}$ = 6.1 Hz, 1H), 4.28 (d, $^3J_{H-H}$ = 10.0 Hz, 1H), 4.30 (s, 2H), 6.01 (d, $^3J_{H-H}$ = 10.0 Hz, 1H), 6.71−6.75 (m, 2H), 6.93−6.99 (m, 2H), 7.20−7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.4, 22.2, 33.8, 42.2, 45.2, 48.5, 65.4, 69.8, 73.3, 109.7, 113.1, 117.7, 121.9, 127.0, 127.6, 128.6, 139.0, 144.6, 157.0; IR (neat) ν 2973, 2930, 1670, 1600, 1485, 1245, 1113. ESI$^+$/MS/MS (*m*/*z*) 366.2 ([M($C_{24}H_{31}NO_2$) + H]$^+$, 100), 288.2 (20), 141.0 (10); ESI$^+$/HRMS (QTOF) calcd for $C_{24}H_{32}NO_2$ 366.2433, found 366.2417.

(3*R,4*S**)-4-(Benzyloxymethyl)-4-(3-isopropoxyphenyl)-1,3-dimethylpiperidine (21a).** To a solution of tetrahydropyridine **20a** (1.00 g, 2.8 mmol) in MeOH (15 mL) at 0 °C was added $NaBH_4$ (160 mg, 4.4 mmol). When the addition was complete, the reaction mixture was stirred for 3 h at rt. The reaction was quenched by addition of acetone (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) then concentrated. The residue was dissolved in EtOAc (50 mL) and water (50 mL). After separation and extraction with EtOAc, the combined organic fractions were washed with water, dried, and concentrated. The residue was purified by chromatography on silica gel (AcOEt/

dx.doi.org/10.1021/jo302303h | J. Org. Chem. XXXX, XXX, XXX−XXX

MeOH from 100/0 to 95/5) to give the title compound as a yellow oil (955 mg, 95%): R_f 0.26 (AcOEt/MeOH 95/5); ^{1}H NMR ($CDCl_3$, 400.0 MHz) δ 0.85 (d, $^3J_{H-H}$ = 7.0 Hz, 3H), 1.31−1.33 (m, 6H), 2.04−2.08 (m, 2H), 2.16−2.18 (m, 2H), 2.26 (s, 3H), 2.45−2.53 (m, 2H), 2.76−2.81 (m, 1H), 3.57 and 3.79 (AB, d, $^2J_{A-B}$ = 9.3 Hz, 2H), 4.29−4.37 (m, 2H), 4.51 (sept, $^3J_{H-H}$ = 6.0 Hz, 1H), 6.73 (dd, $^3J_{H-H}$ = 1.6, 2.2 Hz, 1H), 6.75−6.89 (m, 2H), 7.11 (dd, $^3J_{H-H}$ = 1.6, 6.2 Hz, 1H), 7.18−7.23 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 15.9, 21.9, 26.3, 34.2, 42.3, 46.5, 52.1, 58.7, 69.5, 72.9, 74.6, 112.5, 115.2, 118.9, 127.0, 127.9, 128.4, 138.5, 147.9, 157.4; IR (neat) ν 2972, 2892, 1601, 1382, 1113, 1028; ESI$^+$/MS/MS (m/z) 368 ([M($C_{24}H_{33}NO_2$) + H]$^+$, 100), 260 ([M − BnO]$^+$, 80); ESI$^+$/HRMS (QTOF) calcd for $C_{24}H_{34}NO_2$ 368.2590, found 368.2599.

(3*R,4*S**)-Phenyl-4-(benzyloxymethyl)-4-(3-isopropoxyphenyl)-3-methylpiperidine-1-carboxylate (22a).** To a solution of *N*-methylpiperidine **21a** (500 mg, 1.36 mmol) in toluene (5 mL) was added dropwise phenyl chloroformate (200 μL, 1.56 mmol) at 85 °C. The mixture was refluxed for 3 h. After the mixture was cooled to 45 °C, aqueous NaOH (5%, 1.7 mL) was added, and the mixture was allowed to cool to rt under stirring. After separation, the organic layer was washed three times with MeOH/HCl (1 N) 1:1, then once with MeOH/NaOH (1 N) 1:1, and finally with water. The solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (pentane/diethyl ether from 90/10 to 70/30) to give the title compound as a yellow oil (526 mg, 82%): R_f 0.35 (pentane/diethyl ether 70/30); ^{1}H NMR ($CDCl_3$, 400.0 MHz): δ 0.76−0.80 (m, 3H), 1.32−1.34 (m, 6H), 2.08−2.16 (m, 2H), 2.25−2.30 (m, 1H), 3.15−3.47 (m, 2H), 3.66−3.70 (m, 1H), 3.86−3.97 (m, 2H), 4.21−4.26 (m, 1H), 4.36−4.38 (m, 2H), 4.53 (sept, J = 6.1 Hz, 1H), 6.78 (dd, $^4J_{H-H}$ = 1.3 Hz, $^3J_{H-H}$ = 7.8 Hz, 1H), 6.80−6.90 (m, 2H), 7.07−7.33 (m, 11H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.2, 22.2, 25.5, 34.3, 40.9, 43.3, 46.9, 69.8, 73.3, 74.3, 113.0, 115.0, 118.7, 121.8,125.2, 127.5, 128.3, 128.9, 129.3, 138.4, 151.6, 154.4, 157.8; IR (neat) ν 1713, 1595, 1488, 1426, 1198, 1114; ESI$^+$/MS/MS (m/z) 474.4 ([M($C_{30}H_{35}NO_4$) + H]$^+$, 100), 456.4 (30), 432.4 (50), 414.3 ([M − OiPr]$^+$, 35), 366.3 ([M − BnO]$^+$, 40), 324.3 (20), 320.3 (20), 272.3 (30), 246.3 ([M − $BnOCO_2Ph$ + H]$^+$, 20), 230.2 (40%); ESI$^+$/HRMS (QTOF) calcd for $C_{30}H_{36}NO_4$ 474.2644, found 474.2624.

(3*R,4*S**)-4-(Benzyloxymethyl)-4-(3-isopropoxyphenyl)-3-methylpiperidine (23a).** A mixture of phenyl carbamate **22a** (1.5 g, 3.17 mmol) and KOH (800 mg, 14.3 mmol) in toluene (50 mL) was refluxed for 24 h and then cooled to rt. After addition of water (50 mL) followed by extraction with EtOAc, the organic layer was washed with NaOH (1 N) and then with water, dried, and concentrated to give the title compound as a yellow oil which was used without further purification (800 mg, 70%): ^{1}H NMR (MeOD, 300.0 MHz) δ 0.75 (d, $^3J_{H-H}$ = 7.3 Hz, 3H), 1.28 (d, $^3J_{H-H}$ = 5.9 Hz, 6H), 1.97−2.12 (m, 3H), 2.64−2.69 (m, 1H), 2.79−2.99 (m, 2H), 3.07 (dd, $^3J_{H-H}$ = 3.7 Hz, 13.5 Hz, 1H), 3.65 and 3.94 (AB, d, $^2J_{A-B}$ = 9.1 Hz, 2H), 4.28−4.38 (m, 2H), 4.54 (sept, $^3J_{H-H}$ = 5.9 Hz, 1H), 6.74−6.77 (m, 1H), 6.86−6.90 (m, 2H), 7.09−7.11 (m, 2H), 7.17−7.26 (m, 4H); ^{13}C NMR (MeOD, 75.5 MHz) δ 13.4, 20.8, 20.9, 33.6, 41.3, 42.8, 49.3, 69.4, 72.5, 74.4, 112.6, 114.7, 118.5, 126.9, 127.1, 127.7, 128.3, 138.4, 147.9, 157.6; IR (neat) ν 3028, 2931, 1601, 1579, 1486, 1452, 1187, 1145, 1027; ESI$^+$/MS/MS (m/z) 354.3 ([M($C_{23}H_{31}NO_2$) + H]$^+$, 20), 246.2 ([M − BnO]$^+$, 100), 187.1 ([M − BnOOiPr]$^+$, 10), 159.1 (10), 96.1 (15); ESI$^+$/HRMS (QTOF) calcd for $C_{23}H_{32}NO_2$ 354.2433, found 354.2431.

(3*R,4*S**)-4-Hydroxymethyl-4-(3-hydroxyphenyl)-3-methylpiperidine Hydrochloride (11a).** To a solution of diether **23a** (580 mg, 1.64 mmol) in DCM (6 mL) at −78 °C was added BBr_3 (1 M in DCM, 16.4 mL, 16.4 mmol). The reaction mixture was stirred at −78 °C for 3 h, and EtOH (2 mL) was added dropwise. The mixture was warmed to rt and concentrated. The residue was dissolved in wate, and the pH was adjusted to 8 with NaOH (1 N). After the residue was washed with ethyl acetate, the aqueous layer was concentrated. The resulting residue was purified by chromatography on silica gel (DCM/MeOH 85/15) to give the title compound as a yellow solid (315 mg, 87%): R_f 0.24 (DCM/MeOH 85/15); mp 320−330 °C; ^{1}H NMR (MeOD, 300.0 MHz) δ 0.81 (d, $^3J_{H-H}$ = 7.3 Hz, 3H), 2.22−2.27 (m, 2H), 2.41−2.46 (m, 1H), 3.04 (dd, $^3J_{H-H}$ = 4.0 Hz, 13.2 Hz, 1H), 3.34−3.38 (m, 2H), 3.38 (dd, $^3J_{H-H}$ = 3.6, 13.2 Hz, 1H), 3.76 and 4.02 (AB, d, $^2J_{A-B}$ = 11.5 Hz, 2H), 6.68 (dd, $^4J_{H-H}$ = 2.3 Hz, $^3J_{H-H}$ = 8.0 Hz, 1H), 6.79−6.84 (m, 2H), 7.19 (t, $^3J_{H-H}$ = 8.0 Hz, 1H); ^{13}C NMR (D_2O, 75.5 MHz) δ 13.5, 31.7, 40.0, 42.9, 45.9, 48.8, 65.6, 113.5, 133.8, 118.9, 129.9, 145.2, 155.6; IR (neat) ν 3260, 2852, 1584, 1488, 1443, 1220, 1152, 1018; ESI$^+$/MS/MS (m/z) 464.2 (2[M-($C_{13}H_{19}NO_2$) + Na, 40), 222.2 ([M($C_{13}H_{19}NO_2$) + H]$^+$, 100), 152.2 (30); ESI$^+$/HRMS (QTOF) calcd for $C_{13}H_{20}NO_2$ 222.1494, found 222.1493.

(3*R,4*S**)- and (3*R**,4*R**)-1,3-Dimethylpiperidine-4-carbonitrile (24a and 24b).** To a solution of 1,3-dimethylpiperidin-4-one **13** (1 mL, 7.46 mmol) and tosylmethyl isocyanide (1.67 g, 14.9 mmol) in DME (24 mL) was added dropwise at 0 °C a solution of *t*-BuOK (1.67 g) in DME (12 mL) and *t*-BuOH (12 mL). The reaction mixture was stirred for 45 min at 0 °C then for 2 h at rt, and water (20 mL) was added. After extraction with diethyl ether, the combined organic fractions were dried and concentrated. The residue was purified by chromatography on silica gel (DCM/MeOH 100/0 to 95/5) to give a first fraction containing a mixture of **24a** and **24b** in a 7/3 ratio as a yellow oil (1.10 g, 55%) and a second fraction as pure **24a** (30 mg, 2%), R_f 0.32 for **24b** and 0.28 for **24a** (DCM/MeOH 94/6). Analysis of the mixture of **24a** and **24b**: ^{1}H NMR ($CDCl_3$, 400.0 MHz) δ 1.08−1.09 (m, 4.3H, 2a, 2b), 1.58 (t, $^3J_{H-H}$ = 10.8 Hz, 1H, 2a), 1.82−2.07 (m, 8.1H, 2a, 2b), 2.24 (s, 3H, 2a), 2.28−2.31 (m, 1.6H, 2b), 2.67−2.86 (m, 3.3H, 2a, 2b); ^{13}C NMR ($CDCl_3$, 100.4 MHz) attributed to **24b** δ 17.8, 29.2, 34.2, 34.3, 46.1, 54.3, 62.3, 121.5; ESI$^+$/MS/MS m/z 139.2 ([M($C_8H_{14}N_2$) + H]$^+$, 100), 122.1 (10), 112.2 ([M − CN]$^+$, 5), 107.1 (20); ESI$^+$/HRMS (QTOF) calcd for $C_8H_{15}N_2$ 139.1235, found 139.1230. Analysis for **24a**: ^{1}H NMR ($CDCl_3$, 400.0 MHz) δ 1.09 (d, $^3J_{H-H}$ = 6.4 Hz, 3H), 1.94−2.08 (m, 4H), 2.28−2.33 (4H), 2.70−2.80 (m, 2H), 2.83−2.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.1, 28.2, 32.1, 32.3, 46.1, 51.4, 59.2, 119.8; IR (neat) ν 2934, 2787, 2337, 1059.

(3*R,4*R**)-1,3-Dimethyl-4-(3-isopropoxyphenyl)piperidine-4-carbonitrile (25b).** To a 7/3 mixture of nitriles **24a** and **24b** (460 mg, 2.98 mmol) and fluoro-3-isopropoxybenzene (1.7 g, 11.9 mmol) was added dropwise a solution of KHMDS (0.5 M in toluene, 11.9 mL, 5.96 mmol) at rt. The reaction mixture was stirred at 120 °C for 24 h and cooled to rt. After addition of saturated aqueous solution of NH_4Cl and then extraction with EtOAc, the resulting organic layer was washed with water, dried, and concentrated. The residue was purified by chromatography on silica gel (DCM/MeOH from 100/0 to 98/2) to give the title compound as a brown oil (430 mg, 52%): R_f 0.29 (DCM/MeOH 96/4); ^{1}H NMR ($CDCl_3$, 400.0 MHz) δ 0.81 (d, $^3J_{H-H}$ = 6.5 Hz, 3H), 1.33 (d, $^3J_{H-H}$ = 6.0 Hz, 6H), 2.03 (dt, $^3J_{H-H}$ = 2.5, 13.8 Hz), 2.17−2.30 (m, 3H), 2.38 (s, 3H), 2.47 (dt, $^3J_{H-H}$ = 2.2, 12.0 Hz), 2.86−2.96 (m, 2H), 4.55 (sept, $^3J_{H-H}$ = 6.0 Hz, 1H), 6.82−6.83 (m, 1H), 7.02−7.05 (m, 2H), 7.23 (t, $^3J_{H-H}$ = 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.7, 22.0, 38.4, 39.1, 45.9, 49.4, 52.9, 60.1, 70.0, 114.0, 115.2, 118.0, 120.1, 130.0, 140.3, 158.3; IR (neat) ν 2973, 2791, 1603, 1581, 1466, 1254, 1114; ESI$^+$/MS/MS (m/z) 273.2 ([M($C_{17}H_{24}N_2O$) + H]$^+$, 100); ESI$^+$/HRMS (QTOF) calcd for $C_{17}H_{25}N_2O$ 273.1967, found 273.1974. Anal. Calcd for $C_{17}H_{24}N_2O$ C, 74.96; H, 8.88; N, 10.28. Found: C, 74.92; H, 9.11; N, 10.15.

(3*R,4*R**)-Phenyl-4-cyano-4-(3-isopropoxyphenyl)-3-methylpiperidine-1-carboxylate (26b).** To a solution of *N*-methylpiperidine **25b** (1.8 g, 6.60 mmol) in toluene (20 mL) was added dropwise phenyl chloroformate (1 mL, 7.92 mmol) at 85 °C, and the mixture was refluxed for 3 h. After cooling to 45 °C and addition of aqueous NaOH (5%, 4.5 mL), the mixture was cooled to rt under stirring. The organic and aqueous layers were separated, and the organic layer was washed three times with MeOH/HCl (1 N) 1:1 and then once with MeOH/NaOH (1 N) 1:1 and finally with water. The solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (pentane/diethyl ether from 100/0 to 70/30) to give the title compound as a yellow oil (1.6 g, 65%): R_f 0.67 (pentane/diethylether 70/30); ^{1}H NMR ($CDCl_3$, 400.0 MHz) δ 0.90 (d, $^3J_{H-H}$ = 6.8 Hz, 3H), 1.37 (d, $^3J_{H-H}$ = 6.0 Hz, 6H), 2.12−2.16 (m, 2H), 2.21−2.27 (m, 1H), 3.97−3.15 (m, 1H), 3.32−3.47 (m, 1H),

dx.doi.org/10.1021/jo302303h | J. Org. Chem. XXXX, XXX, XXX−XXX

4.33−4.47 (m, 2H), 4.61 (sept, $^3J_{H-H}$ = 6.0 Hz, 1H), 6.89 (dd, $^4J_{H-H}$ = 1.8 Hz, $^3J_{H-H}$ = 7.8 Hz, 1H), 7.03−7.07 (m, 2H), 7.15−7.17 (m, 2H), 7.24−7.27 (m, 1H), 7.33 (t, $^3J_{H-H}$ = 8.0 Hz, 1H), 7.38−7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (doubling of some signals due to rotamers) δ 14.1, 22.0, 37.8, 38.4, 38.9, 39.4, 41.8, 42.3, 59.1, 70.1, 114.3, 114.9, 117.9, 119.5, 121.7, 125.5, 129.4, 130.2, 139.6, 151.3, 153.4, 158.5; IR (neat) ν 2976, 1715, 1581, 1228, 1114, 1070; ESI$^+$/MS/MS (m/z) 401.1 (100). ESI$^+$/HRMS (QTOF) calcd for $C_{23}H_{26}N_2O_3Na$ 401.1841, found 401.1856.

(3*R,4*R**)-*tert*-Butyl 4-Cyano-4-(3-isopropoxyphenyl)-3-methylpiperidine-1-carboxylate (27b).** To a solution of *N*-methylpiperidine **25b** (1.5 g, 5.5 mmol) in $CHCl_3$ (20 mL) was added dropwise 1-chloroethyl chloroformate (1.2 mL, 11.0 mmol) at rt. The reaction mixture was refluxed for 4.5 h, cooled to rt, and concentrated under vacuum. The residue was dissolved in MeOH (20 mL). The solution was refluxed for 2 h, cooled to rt, and concentrated under vacuum. The residue was dissolved in DCM (25 mL), and Et_3N (1.3 mL, 8.8 mmol) and di-*tert*-butyl dicarbonate (1.8 g, 8.3 mmol) were added. The reaction mixture was stirred at rt for 4 h and then washed with brine. The organic layer was dried and concentrated. The residue was purified by chromatography on silica gel (hexane/diethyl ether from 80/20 to 70/30) to give the title compound as a white solid (1.2 g, 60%): mp 85−86 °C; R_f 0.47 (hexane/diethyl ether 70/30); ^{1}H NMR (DMSO, 300.0 MHz) δ 0.69 (d, $^3J_{H-H}$ = 6.6 Hz, 3H), 1.26 (d, $^3J_{H-H}$ = 5.9 Hz, 6H), 1.43 (s, 9H), 1.96−2.10 (m, 2H), 2.18−2.26 (m, 1H), 2.51−2.66 (m, 1H), 2.89−3.07 (m, 1H), 4.04−4.14 (m, 2H), 4.66 (sept, $^3J_{H-H}$ = 5.9 Hz, 1H), 6.89−6.93 (m, 1H), 7.02−7.08 (m, 2H), 7.33 (t, $^3J_{H-H}$ = 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.0, 21.9, 28.4, 33.5, 38.1, 38.9, 47.5, 70.0, 80.1, 114.1, 114.8, 117.9, 119.6, 130.0, 139.9, 154.4, 158.3; IR (neat) ν 1691, 1608, 1581, 1448, 1244, 1133; ESI$^+$/MS/MS (m/z) 381.2 ([M($C_{21}H_{30}N_2O_3$) + Na]$^+$, 30), 325 (100); ESI$^+$/HRMS calcd for $C_{21}H_{30}N_2NaO_3$ 381.2154, found 381.2156. Anal. Calcd for $C_{21}H_{30}N_2O_3$: C, 70.36; H, 8.44; N, 7.81. Found: C, 70.79; H, 8.65; N, 7.96.

(3*R,4*R**)-4-(3-Hydroxyphenyl)-3-methylpiperidine-4-carboxylic Acid Hydrochloride (28b).** A solution of nitrile **27b** (600 mg, 1.68 mmol) in HCl (6 N, 6 mL) was refluxed for 4 weeks, cooled to rt, and then concentrated to give the title compound as beige solid (455 mg, quant) which was used without further purification: mp 280−285 °C; ^{1}H NMR (MeOD, 400.0 MHz) δ 0.89 (d, $^3J_{H-H}$ = 6.7 Hz, 3H), 2.37−2.48 (m, 2H), 2.58−2.61 (m, 1H), 3.16−3.30 (m, 4H), 6.75 (ddd, $^4J_{H-H}$ = 0.8 Hz, $^4J_{H-H}$ = 2.3 Hz, $^4J_{H-H}$ = 3.1 Hz, 1H), 6.83−6.87 (m, 2H), 7.23 (t, $^3J_{H-H}$ = 8.0 Hz); ^{13}C NMR (MeOD, 100.6 MHz) δ 145, 36.6, 42.9, 47.9, 51.2, 53.8, 114.8, 115.3, 118.5, 130.7, 142.7, 158.8, 175.7; IR (neat) ν 3350, 2794, 1713, 1584, 1496, 1447, 1272, 1103; ESI$^+$/MS/MS 236.2 ([M($C_{13}H_{17}NO_3$) + H]$^+$, 30), 190.2 (100); ESI$^+$/HRMS (QTOF) calcd for $C_{13}H_{18}NO_3$ 236.1287, found 236.1293.

(3*R,4*R**)-4-Hydroxymethyl-4-(3-hydroxyphenyl)-3-methylpiperidine Hydrochloride (11b).** To a solution of carboxylic acid **28b** (440 mg, 1.68 mmol) in THF (5 mL) was added dropwise $BH_3{\cdot}SMe_2$ (1 M in THF, 10.1 mL, 10.1 mmol). The mixture was refluxed for 3 h. After cooling to rt and addition of MeOH (2 mL), the solvent was removed under reduced pressure. The residue was dissolved in a 1:1 MeOH/HCl (6 N) mixture (10 mL) and the solution refluxed for 1 h. The solvent was removed under reduced pressure to give the title compound as a beige solid (203 mg, 48%): mp 110−115 °C; ^{1}H NMR (MeOD, 400.0 MHz) δ 0.96 (d, $^3J_{H-H}$ = 7.2 Hz, 3H), 2.13−2.15 (m, 2H), 2.57−2.62 (m, 1H), 3.13−3.20 (m, 4H), 3.83 and 3.94 (AB, d, $^2J_{A-B}$ = 11.4 Hz, 2H), 6.38 (ddd, $^4J_{H-H}$ = 0.9 Hz, $^3J_{H-H}$ = 2.2 Hz, $^3J_{H-H}$ = 8.1 Hz), 6.92−6.96 (m, 2H), 7.18−7.23 (m, 1H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 13.0, 26.3, 35.4, 41.4, 41.5, 44.0, 46.8, 62.4, 113.9, 115.3, 118.7, 130.1, 147.3, 158.4; IR (neat) ν 3056, 1672, 1587, 1455, 1200, 1136; ESI$^+$/MS/MS (m/z) 222.2 ([M($C_{13}H_{19}NO_2$ + H)]$^+$, 100), 204.2 ([M − H_2O]$^+$, 30); ESI$^+$/HRMS (QTOF) calcd for $C_{13}H_{20}NO_2$ 222.1494, found 222.1489.

(3*R,4*S**)-1-(*tert*-Butoxycarbonyl)-4-(3-*tert*-butoxycarbonyloxyphenyl)-4-(hydroxymethyl)-3-methylpiperidine (29a).** To a solution of alcohol **11a** (130 mg, 0.59 mmol) and Et_3N (0.40 mL, 2.95 mmol) in DMF (1.5 mL) was added di-*tert*-butyl dicarbonate (643 mg, 2.95 mmol). The mixture was stirred overnight at rt and then concentrated. The residue was dissolved in DCM (2 mL) and water (2 mL). After separation and extraction with DCM, the combined organic fractions were washed with water, dried, and concentrated to give the title compound as a beige solid (223 mg, 90%): mp 50−55 °C; R_f 0.43 (pentane/EtOAc 70/30); ^{1}H NMR (MeOD, 400.0 MHz) δ 0.66 (d, $^3J_{H-H}$ = 7.0 Hz, 3H), 1.45 (s, 9H), 1.52 (s, 9H), 1.92−2.02 (m, 2H), 2.15−2.19 (m, 1H), 3.09−3.34 (m, 2H), 3.77−3.82 (m, 2H), 4.03−4.09 (m, 2H), 6.97−6.99 (m, 1H), 7.07−7.09 (m, 1H), 7.21 (d, $^3J_{H-H}$ = 8.0 Hz, 1H), 7.34 (t, $^3J_{H-H}$ = 8.0 Hz, 1H); ^{13}C NMR (MeOD, 100.6 MHz) δ 14.6, 27.5, 28.6, 35.2, 40.3, 41.3, 45.5, 47.2, 66.7, 80.8, 84.2, 119.8, 120.8, 125.2, 129.9, 149.1, 152.6, 153.6, 56.9; IR (neat) ν 3450, 1755, 1686, 1609, 1584, 1246, 1137; ESI$^+$/MS/MS (m/z) 444.5 ([M($C_{23}H_{35}NO_6$) + Na]$^+$, 30), 388.4 (40), 344.4 ([M − Boc+Na]$^+$, 100), 288.3 (30); ESI$^+$/HRMS (QTOF) calcd for $C_{23}H_{35}NO_6Na$ 444.2362, found 444.2362.

(3*R,4*R**)-1-(*tert*-Butoxycarbonyl)-4-(3-*tert*-butoxycarbonyloxyphenyl)-4-(hydroxymethyl)-3-methylpiperidine (29b).** To a solution of alcohol **11b** (200 mg, 0.78 mmol) and Et_3N (0.40 mL, 2.95 mmol) in DCM (5 mL) was added di-*tert*-butyl dicarbonate (643 mg, 2.95 mmol). The mixture was stirred overnight at rt, and then water (5 mL) was added. After separation and extraction with DCM, the combined organic fractions were washed with water, dried, and concentrated. The residue was purified by chromatography on silica gel (pentane/EtOAc from 90/10 to 70/30) to give the title compound as a beige solid (223 mg, 68%): mp 60−65 °C; R_f 0.48 (pentane/EtOAc 70/30); ^{1}H NMR (MeOD, 400.0 MHz) δ 0.95 (m, 3H), 1.45 (s, 9H), 1.53 (s, 9H), 1.88−1.93 (m, 2H), 2.40−2.42 (m, 1H), 3.19−3.22 (m, 1H), 3.44−3.48 (m, 1H), 3.64−3.79 (m, 3H), 6.99−7.01 (m, 1H), 7.24−7.5 (m, 1H), 7.37−7.38 (m, 2H); ^{13}C NMR (MeOD, 100.6 MHz) δ 13.5, 27.9, 28.7, 34.8, 36.1, 38.3, 41.2, 46.2, 70.8, 80.9, 84.3, 120.1, 121.9, 126.1, 130.3, 152.8, 153.7, 157.0; IR (neat) ν 3452, 1727, 1691, 1608, 1583, 1251, 1148. ESI$^+$/MS/MS (m/z) 444.5 ([M($C_{23}H_{35}NO_6$) + Na]$^+$, 25), 388.4 (40), 344.4 ([M − Boc + Na]$^+$, 100), 288.3 (40); ESI$^+$/HRMS (QTOF) calcd for $C_{23}H_{35}NNaO_6$ 444.2362, found 444.2358.

(3*R,4*S**)-1-(*tert*-Butoxycarbonyl)-4-(3-*tert*-butoxycarbonyloxyphenyl)-4-(fluoromethyl)-3-methylpiperidine (30a).** To a solution of alcohol **29a** (50 mg, 0.11 mmol) in DCM (0.5 mL) at −50 °C was added DAST (23 μL, 0.19 mmol). The mixture was stirred at −50 °C for 2 h and then at rt overnight and cooled to −78 °C. After addition of saturated aqueous solution of $NaHCO_3$ (0.5 mL) at −78 °C, the mixture was allowed to warm to rt. After extraction with DCM, the organic layer was washed with water, dried, and concentrated. The residue was purified by chromatography on silica gel (pentane/diethyl ether from 95/5 to 90/10) to give the title compound as a colorless oil (20 mg, 40%): R_f 0.60 (pentane/diethyl ether 80/20); ^{1}H NMR ($CDCl_3$, 400.0 MHz) δ 1.05−1.08 (m, 3H), 1.42 (s, 9H), 1.52 (s, 9H), 1.72−1.87 (m, 2H), 2.73−2.97 (m, 2H), 3.20−3.23 (m, 1H), 3.57−3.84 (m, 2H), 6.99−7.04 (m, 2H), 7.09−7.15 (m, 1H), 7.28−7.30 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) (some doubling of signals due to rotamers) δ 11.8, 27.7, 28.5, 31.4, 33.8, 38.4, 43.5, 47.4, 80.9 and 81.0, 84.1, 97.6 (d, $^2J_{C-F}$ = 174.1 Hz), 120.3, 120.4, 124.3, 124.4, 128.9, 129.0, 129.8, 129.9, 138.7, 139.0, 152.2, 152.3, 153.23, 153.3, 156.2, 156.7; ^{19}F NMR ($CDCl_3$) δ -(154.9−155.5) (m); IR (neat) ν 1755, 1689, 1613, 1588, 1235, 1138, 1046; ESI$^+$/MS/MS (m/z) 446.4 ([M($C_{23}H_{34}FNO_5$) + Na]$^+$, 35), 390.3 (100), 346.3 (60), 326.3 (20), 290.2 (20), 270.2 (10); ESI$^+$/HRMS (QTOF) calcd for $C_{23}H_{34}FNNaO_5$ 446.2319, found 446.2300.

(3*R,4*R**)-1-(*tert*-Butoxycarbonyl)-4-(3-*tert*-butoxycarbonyloxyphenyl)-4-(fluoromethyl)-3-methylpiperidine (30b).** To a solution of alcohol **29b** (100 mg, 0.22 mmol) in DCM (1 mL) at −50 °C was added DAST (46 μL, 0.38 mmol). The mixture was stirred at −50 °C for 2 h, then at rt for 20 h, and cooled to −78 °C. After addition of saturated aqueous solution of $NaHCO_3$ (1 mL) at −78 °C, the mixture was allowed to warm to rt. After extraction with DCM, the organic layer was washed with water, dried, and concentrated. The residue was purified by chromatography on silica gel (pentane/diethyl ether from 95/5 to 90/10) to give the title compound as a colorless oil (40 mg, 40%): R_f 0.38 (pentane/diethyl ether 90/10); ^{1}H NMR

dx.doi.org/10.1021/jo302303h | J. Org. Chem. XXXX, XXX, XXX−XXX

(MeOD, 400.0 MHz) δ 1.02−1.06 (m, 3H), 1.42 (s, 9H), 1.52 (s, 9H), 1.71−1.83 (m, 2H), 2.73−3.15 (m, 3H), 319−3.23 (m, 2H), 3.57−3.80 (m, 2H), 6.99−7.03 (m, 2H), 7.09−7.15 (m, 1H), 7.28−7.32 (m, 1H); ^{13}C NMR (MeOD, 100.6 MHz) (some doubling of signals due to rotamers) δ 12.0, 27.9, 28.6, 31.7, 38.6, 38.7 (d, $^{2}J_{C-F}$ = 46.3 Hz), 43.4, 81.0, 81.1, 84.2, 84.3, 96.2 (d, $^{1}J_{C-F}$ = 178.8 Hz), 97.7 (d, $^{1}J_{C-F}$ = 178.8 Hz), 120.5, 124.5, 129.0, 129.2, 129.9, 130.1, 138.8, 139.2, 152.4, 152.4, 153.4, 153.5, 156.3, 156.9; ^{19}F NMR (MeOD, 376.5 MHz) δ -(150.9−151.6) (m); IR (neat) ν 1755, 1688, 1612, 1587, 1234, 1137, 1046; ESI$^+$/MS (m/z) 224.2 ([M − 2Boc]$^+$, 100), 204.2 ([M − 2Boc-F]$^+$, 70); ESI$^+$/HRMS (QTOF) calcd for $C_{23}H_{34}FNNaO_5$ 446.2319, found 446.2306.

(3*R,4*R**)-4-Fluoromethyl-4-(3-hydroxyphenyl)-3-methylpiperidinium Trifluoroacetate (12a).** A solution of piperidine **30a** (20 mg, 0.05 mmol) in TFA (0.5 mL) was stirred for 30 min at rt and then concentrated to give the title compound as an orange oil (16 mg, 95%): ^{1}H NMR (MeOD, 400.0 MHz) δ 1.17−1.20 (m, 3H), 1.75−2.23 (m, 3H), 2.77−2.97 (m, 2H), 3.08−3.13 (m, 1H), 3.17−3.22 (m, 2H), 3.35−3.38 (m, 1H), 6.68−6.74 (m, 3H), 7.09−7.14 (m, 1H); ^{13}C NMR (MeOD, 100.6 MHz) δ 13.5, 29.0 (d, $^{3}J_{C-F}$ = 22.7 Hz), 36.3 (d, $^{3}J_{C-F}$ = 23.5 Hz), 41.5 (d, $^{2}J_{C-F}$ = 64.4 Hz), 47.4, 95.6 (d, $^{2}J_{C-F}$ = 176.2 Hz), 114.9, 118.5, 122.8, 130.3, 137.5, 158.4; ^{19}F NMR (MeOD, 376.5 MHz) δ −(151.8−152.9) (m, 1F), −76.8 (s, 3F); IR (neat) ν 3400, 1670, 1587, 1456, 1184, 1133, 1041; ESI$^+$/MS/MS (m/z) 224.3 ([M($C_{13}H_{18}$NOFN) + H]$^+$, 10), 204.3 ([M − F]$^+$, 100), 159.2 (10), 96.1 (10); ESI$^+$/HRMS (QTOF) calcd for $C_{13}H_{19}$FNO 224.1451, found 224.1456.

(3*R,4*R**)-4-Fluoromethyl-4-(3-hydroxyphenyl)-3-methylpiperidinium Trifluoroacetate (12b).** A solution of piperidine **30b** (30 mg, 0.07 mmol) in TFA (0.5 mL) was stirred for 30 min at rt then concentrated to give the title compound as an orange oil (15 mg, quantitative yield): ^{1}H NMR (MeOD, 400.0 MHz) δ 1.14−1.71 (m, 3H), 1.75−2.17 (m, 3H), 2.74−2.94 (m, 2H), 3.03−3.10 (m, 1H), 3.14−3.23 (m, 2H), 3.31−3.37 (m, 1H) 6.65−6.71 (m, 3H), 7.07−7.10 (m, 1H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 13.5, 31.1 (d, $^{3}J_{C-F}$ = 30.6 Hz), 35.8 (d, $^{3}J_{C-F}$ = 24.4 Hz), 40.8 (d, $^{2}J_{C-F}$ = 73.3 Hz), 43.1, 46.8, 114.6, 118.3, 122.4, 30.0, 137.6, 158.1; ^{19}F NMR (MeOD, 376.5 MHz) δ -(152.9−153.3) (m, 1F), −77.3 (s, 3F); IR (neat) ν 2989, 1669, 1587, 1459, 1198, 1132, 1041; ESI$^+$/MS (m/z) 446.4 ([2M($C_{13}H_{18}$FNO]$^+$, 80), 158.1 (100); ESI$^+$/HRMS (QTOF) calcd for $C_{13}H_{19}$FNO 224.1451, found 224.1446.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds, chiral HPLC chromatograms for **12a,b**, and X-ray crystallographic data for **27b** (CIF). This material is free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this research from the MERNT (Ministère de la Recherche et des Nouvelles Technologies), CNRS (Centre National de la Recherche Scientifique), CEA (Commissariat à l'Energie Atomique), the "CRUNCH" Network (Pôle Universitaire Normand de Chimie Organique), the "Région Basse-Normandie", and the European Union (FEDER funding) and for a studentship from the European Regional Development Fund (ERDF, ISCE-Chem & INTERREG IVa program 4061) is acknowledged.

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