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A highly selective monoalkylation of *tert*-butyl 3,4-dihydroxy-4-phenylpiperidine-1-carboxylate under phase transfer conditions

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ABSTRACT

Liquid–liquid phase transfer conditions have been found to provide highly selective monoalkylation of *tert*-butyl 3,4-dihydroxy-4-phenylpiperidine-1-carboxylate, a transformation for which many other common alkylation protocols proved inadequate. The high preference for 3-*O*-alkylation in the phase transfer alkylation is emphasised by the absence of diether formation even in the presence of a large excess of reagents.

We have recently described the discovery of PF-00446687 (Fig. 1), a potent and selective small-molecule agonist of the melanocortin-4 (MC4) receptor, which showed efficacy in a pilot clinical study of male erectile dysfunction, thereby providing the first evidence that selective MC4 receptor activation may be sufficient to elicit pro-erectile effects in humans.[1]

A key structure–activity relationship (SAR) observed during the optimization of the chemical series was the profound potency enhancement resulting from the addition of methyl substituents at C3 and C5 of the piperidine ring. To investigate more fully the SAR in this region, we wished to prepare analogues containing alkoxy substituents at C3/C5. We identified the piperidine diol **2**/*ent*-**2** as a key potential intermediate, attracted by its straightforward preparation via Sharpless asymmetric dihydroxylation of a protected tetrahydropyridine **1** (Scheme 1).[2]

Despite the simple accessibility of such enantiopure piperidine 3,4-diols, there have been remarkably few reports of their selective mono-*O*-alkylation. The few successful examples have been limited to benzylations,[3,4] and the only previous monomethylation of which we are aware proceeded in very low yield with significant quantities of starting material recovered.[5] In our own hands, a similar protocol based on deprotonation with sodium hydride provided a quantitative yield of the diether **3** when excess reagents were employed (Table 1, entry 1),[6] but attempts to achieve monoalkylation by limiting either the base or iodomethane to stoichiometric quantities were unsuccessful: the crude reaction mixtures were found to contain a mixture of unreacted diol and all three possible alkylation products (diether **3** and each of the monoethers). Separation of the components on a preparative scale proved difficult, and variations in the quantities of reagents used or in the reaction procedure provided inadequate alteration of the product ratios. Consequently, we sought an alternative method for achieving the desired monoalkylation.

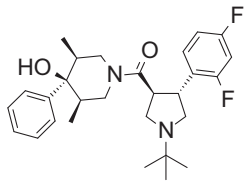
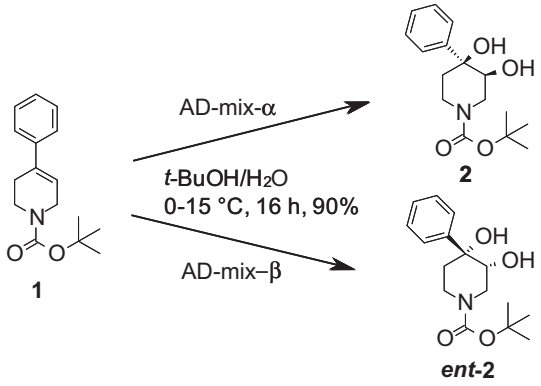


Figure 1. Structure of PF-00446687.



Scheme 1.

In parallel with our attempts to identify a direct monoalkylation protocol, we also explored the potential of employing a protecting group strategy. Whilst ultimately unsuccessful in terms of providing access to the desired targets, these efforts yielded a useful insight into the relative reactivity of the two hydroxyl groups. For example, it was found that good selectivity can be achieved

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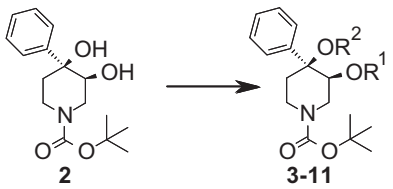
Table 1
Reagents and conditions for attempted selective derivatisation of diol **2**



Entry	Reagent	Conditions[a]	R^1	R^2	Product	Yield[b]
1	MeI (3 equiv)	NaH (3 equiv), THF, 4 h	Me	Me	**3**	100%
2	Ac_2O (2.5 equiv)	Et_3N, CH_2Cl_2, 16 h	Ac	H	**4**	89%
			Ac	Ac	**5**	5%
3	TMSCl (4 equiv)	Et_3N, CH_2Cl_2, 16 h	TMS	H	**6**	100%
4	TMSCl (4 equiv)	Imidazole, DMF, 16 h	TMS	TMS	**7**	87%
5	Me_3OBF_4 (4 equiv)	Proton sponge (4 equiv), CH_2Cl_2, 72 h	Me	Me	**3**	10%
			Me	H	**8**	80%
			H	Me	**9**	Trace
6	MeI (10 equiv)	KOH(s) (10 equiv), DMSO, 5 min	Me	Me	**3**	Trace[c]
			Me	H	**8**	Major product[c]
7	MeI (10 equiv)	KOH(s) (10 equiv), DMSO, 15 min	Me	Me	**3**	Major product[c]
			Me	H	**8**	Not detected[c]
8	MeI (20 equiv)	K_2CO_3(s) (10 equiv), MeCN, reflux, 72 h	Me	Me	**3**	Not detected
			Me	H	**8**	10%
9	MeI (20 equiv)	NaOH (20 equiv), Bu_4NHSO_4 (1 equiv), H_2O/PhMe (1:1), 16 h	Me	Me	**3**	Trace
			Me	H	**8**	96%
			H	Me	**9**	1.5%
10	EtI (20 equiv)	NaOH (20 equiv), Bu_4NHSO_4 (1 equiv), H_2O/PhMe (1:1), 16 h	Et	H	**10**	92%
11	BnBr (2 equiv)	NaOH (10 equiv), Bu_4NHSO_4 (0.5 equiv), H_2O/PhMe (1:1), 16 h	Bn	H	**11**	93%

[a] All reactions carried out at 20 °C unless otherwise stated.
[b] Isolated yields after chromatography unless otherwise stated.
[c] Judged by TLC.

by direct reaction of the diol with acetic anhydride in the absence of prior alkoxide generation, producing only 5% of diacetate **5** even in the presence of excess reagent over an extended reaction time (Table 1, entry 2).

However, it also became clear that the extent of selectivity was in some cases highly dependent on the choice of reaction conditions. For example, reaction with excess chlorotrimethylsilane in the presence of triethylamine in dichloromethane provided monosilylether **6** with complete selectivity even after an extended reaction time (Table 1, entry 3), whereas exposure to the same excess of reagent in the presence of imidazole in DMF produced smooth formation of the disilylether **7** in the same time period (Table 1, entry 4).

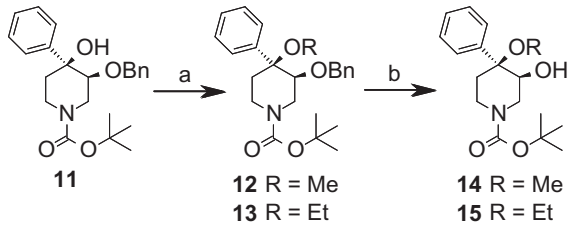
These results encouraged an examination of the methods for achieving monoalkylation not dependent on complete formal alkoxide formation. Numerous methods based on the activation by silver(I) salts[7] were found to be unsuccessful owing to impractically slow or incomplete conversion or, under more forcing conditions, substrate decomposition. Our attention then turned to metal-free conditions promoted by Evans[8] as useful alternatives to standard alkoxide procedures, relying on particularly active alkylating agents. Disappointingly, no reaction was obtained with methyl triflate in the presence of 2,6-di-*tert*-butylpyridine at room temperature, and at elevated temperatures only decomposition of the diol was observed. Much more encouraging was the reaction with trimethyloxonium tetrafluoroborate in the presence of proton sponge (Table 1, entry 5). This delivered by far the cleanest monoalkylation seen by us at that point, providing the desired monoether **8** in 80% yield.

Despite this significant step forward, further improvements remained desirable. Not only was the reaction very slow (the mass balance in this reaction at three days comprised ~10% unreacted **2**), but also there was still sufficient formation of dialkylated product **3** to complicate purification of the targeted 3-*O*-monoalkylated product **8** (the two compounds having very similar retention times on silica). As a consequence, examination of alternative alkylation conditions continued, the focus now moving to those under which alkylation occurs via the intermediacy of an alkoxide, but without complete deprotonation prior to exposure to the electrophile. Use of powdered potassium hydroxide in DMSO[9] provided in principle the necessary selectivity (Table 1, entry 6), but subsequent progression to the dialkylated product occurred too rapidly to be of practical use (Table 1, entry 7; no attempt was made to limit the quantities of reagents or reduce the temperature, owing to the more favourable results described below). The selectivity similarly offered by use of potassium carbonate in acetonitrile at reflux[10] was, in contrast, rendered impractical by the very slow progression of the reaction (Table 1, entry 8).

The desired balance of reaction rate versus selectivity was finally obtained with the use of liquid–liquid phase transfer conditions. Such conditions are well known for alkylation of alcohols with benzylic and allylic halides, but they have been relatively seldom used for simple alkyl halides. In the present case, reaction of the diol with excess iodomethane at room temperature in a rapidly stirred two-phase water/toluene system containing sodium hydroxide and a stoichiometric quantity of a phase transfer catalyst provided an excellent product profile within a reasonable reaction time (Table 1, entry 9).

Most significantly, only a trace of dialkylated product **3** was generated, which enabled vastly simpler purification of the desired mono-3-*O*-methylated product **8** (the presence of mono-4-*O*-methylated by-product **9** is less problematic for purification owing to a larger polarity difference). The high selectivity for monoalkylation is particularly notable given the large excess of electrophile used in this reaction.

Reaction with iodoethane (Table 1, entry 10) occurs equally smoothly under these conditions. In the case of benzyl bromide (Table 1, entry 11), reduced quantities of reagents may be employed without detriment to the yield or rate of reaction.



Scheme 2. Reagents and conditions: (a) RI (2 equiv), KOH(s) (4 equiv), DMSO, 20 °C, 72 h, 98% for **12**, 66% for **13**; (b) 15 wt % of 20 wt % $Pd(OH)_2$/C, 1-methylcyclohexa-1,4-diene, EtOH, reflux, 1.5 h, 100% for **14**, 100% for **15**.

Access to mono-4-*O*-alkylated compounds was provided by derivatisation of benzyl ether **11** with haloalkanes in DMSO in the presence of powdered potassium hydroxide,[9] followed by benzyl-deprotection of the resulting diethers **12** and **13** under transfer hydrogenation conditions (Scheme 2).

The *O*-alkylated piperidines **3**, **8**–**11**, **14** and **15** shown above were all cleanly Boc-deprotected (4 M hydrogen chloride in 1,4-dioxane (10 equiv), dichloromethane, 20 °C, 30–60 min) to give quantitative yields of the corresponding amines as their hydrogen chloride salts.

In conclusion, we have identified that a convenient phase transfer alkylation protocol[6,11] provides high selectivity in the derivatisation of diol **2**, a challenging setting in which many other common conditions for hydroxyl alkylation have proven inadequate. The MC4 agonist activity of compounds analogous to PF-00446687 derived from such 3- and 4-*O*-alkylated piperidines will be described in detail elsewhere.

Acknowledgement

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11. *Representative experimental procedure*. A solution of NaOH (544 mg, 13.6 mmol) in H_2O (3.4 mL) was added to a solution of *tert*-butyl (3*S*,4*S*)-3,4-dihydroxy-4-phenylpiperidine-1-carboxylate (**2**) (200 mg, 0.68 mmol) in PhMe (3.4 mL) followed by MeI (0.85 mL, 13.6 mmol) and Bu_4NHSO_4 (231 mg, 0.68 mmol). The mixture was stirred vigorously at 20 °C for 16 h, then diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in vacuo. The residual oil was purified by column chromatography on silica gel (pentane/EtOAc 1:0–7:3 gradient elution) to give methyl ether **8** as a colourless oil (200 mg, 96%). ^{1}H NMR (CD_3OD, 400 MHz) δ 1.50 (s, 9H), 1.68 (dt, J = 2.4, 14.2 Hz, 1H), 1.93 (td, J = 4.7, 13.3, 13.5 Hz, 1H), 3.03 (br s, 1H), 3.11 (s, 3H), 3.17 (br s, 1H), 3.57 (dd, J = 4.9, 10.5 Hz, 1H), 3.85–3.90 (m, 1H), 4.19 (br s, 1H), 7.23 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.7 Hz, 2H), 7.51 (d, J = 7.7 Hz, 2H); ^{13}C NMR (CD_3OD, 500 MHz) δ 28.7, 39.5, 54.8, 58.5, 75.0, 81.3, 81.8, 126.2, 127.8, 129.1, 147.3, 156.5; LRMS (APCI) m/z 208 $[MH - Boc]^+$. HRMS (ESI^+) found m/z 330.1687 (calculated for $C_{17}H_{25}N_1Na_1O_4$ = 330.167579).