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Antagonists of human CCR5 receptor containing 4-(pyrazolyl)piperidine side chains. Part 2: Discovery of potent, selective, and orally bioavailable compounds

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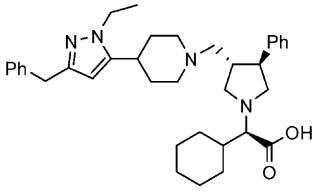
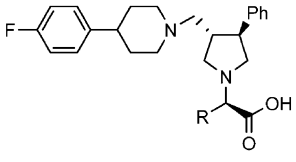
Dedicated to Professor Orville L. Chapman on the occasion of his 71st birthday

Abstract—Modifications of the alkyl acetic acid portion and the phenyl on pyrrolidine in our lead pyrazole compound **1** afforded the isopropyl compound **9**. This compound is a potent CCR5 antagonist showing good in vitro antiviral activity against HIV-1, an excellent selectivity profile, and good oral bioavailability in three animal species. During this investigation, a new method for the preparation of α-(pyrrolidin-1-yl)-α,α-dialkyl acetic acid from a pyrrolidine and α-bromo-α,α-dialkyl acetic acid using silver triflate was discovered. This allowed us to prepare compounds such as **24** and **25** for the first time. A novel Pd-mediated *N*-dealkylation of α-(pyrrolidin-1-yl)acetic acid was also uncovered.

The discovery that the chemokine receptor CCR5 is a co-receptor with CD4 for HIV-1 cell entry has sparked widespread interest in small molecule CCR5 antagonists as potential agents for the treatment and prevention of HIV-1 infection.[1–12] Previous reports from these laboratories have described 1-amino-2-aryl-4-(piperidin-1-yl)butanes,[1,2,12] 1,3,4-trisubstituted pyrrolidines,[2–7] and related compounds[11] as potent CCR5 antagonists. Some of these displayed very good antiviral activity against HIV-1 in vitro and reasonable oral bioavailability in animal species.





	1	**2**, R = c-Hex	**3**, R = i-Pr
CCR5 IC_{50}, nM	1.2	4	36
HeLa (BAL) IC_{90}, nM	0.4	100	>100
PBMC (BAL) IC_{95}, nM	< 8		>3000

In the preceding paper, the incorporation of a heteroaryl ring into the piperidine side-chain in the 1,3,4-trisubstituted pyrrolidine series afforded compounds such as **1** with potent CCR5 binding and in vitro antiviral activities.[13] However, this and related compounds did not have the required pharmacokinetic profile or off-target

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selectivity for further development. Herein we detail our continued SAR studies in this series leading to potent, selective, and orally bioavailable compounds.

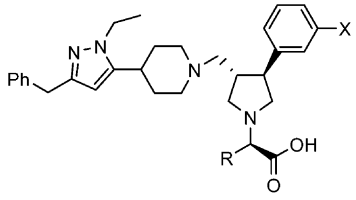
Results from some related 4-(4-fluorophenyl)piperidines such as **2** and **3** have shown that the nature of the alkyl group attached to the acetic acid portion of the molecule can have a profound effect on their pharmacokinetic (PK) profiles.[4] For example, the isopropyl compound **3** is bioavailable in several animal species although its CCR5 binding and antiviral activities were modest. In contrast, cyclohexyl compound **2** showed similar PK profile in the rat as **1**.[14] This result inspired us to prepare a set of alkyl derivatives of **1** at that position. These compounds were prepared using the methods reported previously.[5,13] Since a 3-fluorophenyl moiety was one of the few replacements of the phenyl group on the pyrrolidine that preserve CCR5 binding activity,[4] analogues having this 3-fluorophenyl were also prepared (Table 1).

Our results showed that the simple addition of a fluorine on compound **1** to give **4** did not consistently affect its activity or pharmacokinetic profile. The cycloalkylmethylene compounds **5** and **6** possessed similar activity and PK profiles as **1**. Replacing the cyclohexyl in **1** with an isobutyl as in **7** resulted in some improvements in the Cl_p and AUC values, but with about a 10-fold loss of antiviral activity in the cell culture HIV-1 infectivity assay using HeLa cells (HeLa assay). More dramatic improvements in PK were observed when the isopropyl group was introduced in compound **8**. However, there was a further loss of antiviral activity. Adding a fluorine to compound **8** afforded **9** and produced further improvements in the PK profile and some restoration of antiviral activity. The sensitivity of the PK profile to the substitutions at these positions was most dramatically illustrated by the comparison of **9** and **10**. The addition of a single methylene group and deletion of a fluorine increased the clearance of compound **10** by almost 20-fold compared to compound **9**.

Due to its improved PK profile and antiviral activity in the HeLa assay, compound **9** was investigated in more detail. In an HIV-1 infectivity inhibition assay, using peripheral blood mononuclear cells against the BAL-1 strain (the PBMC assay),[17] it gave an average IC_{95} of 22 ± 16 nM ($n = 26$). The decreases in clearance of compounds **8** and **9** compared to other in Table 1 parallel a decline in their volumes of distribution (Vd_{ss}). Therefore, it may be attributed to increases in plasma protein binding. Indeed, compound **9** was 99.90% and 99.96% protein bound in human and rat plasma, respectively. Therefore, the PBMC assays were repeated in the presence of 50% normal human serum. Under these more stringent conditions, **9** gave IC_{95} of 350 ± 320 nM ($n = 14$). The other four compounds in Table 1 showed higher activity in the PBMC assay, indicating that larger alkyl groups enhance potency in this crucial measure of antiviral activity.

In addition to its excellent binding activity on the CCR5 receptor, our lead compound **1** also showed multiple submicromolar activities against other targets including the L-type Ca^{2+} channel where it showed an IC_{50} of 225 nM. To our surprise, compound **9** was very selective, showing no activity (IC_{50} or $K_i > 10{,}000$ nM) in the L-type Ca^{2+} channel or on a panel of about 150 other

Table 1. CCR5 binding affinity, antiviral activity, and pharmacokinetic profile in the rat of pyrazole compounds with various alkylacetic acids



Compd	R =	X =	CCR5 IC_{50} (nM)[a]	HeLa IC_{90} (nM)[c]	Cl_p, (mL/min/kg)	$AUCN_{po}$ (μM·h/dose)	Vd_{ss} (L/kg)	$t_{1/2}$, h	F (%)	PBMC IC_{95} (nM)[f]	PBMC IC_{95} 50% NHS (nM)
1	*c*-Hex	H	1.2, 2.0[b]	0.4,0.4	64	0.02	3.4	0.82	4.1	<8 ($n=2$)	<8, 31
4	*c*-Hex	F	1.6	0.4	84	0.01	3.9	0.83	3	ND[d]	ND[d]
5	*c*-Bu-CH_2	F	1.2	0.4	46[e]	0.05	1.4	0.71	7.3	<0.8 ($n=3$)	35 ± 44 ($n=4$)
6	*c*-Pr-CH_2	F	1.2	0.4	81[e]	0.03	1.2	0.25	8.1	<8	31
7	*i*-Bu	H	2.9[b]	3.7	43	0.13	2.1	1.2	17	<8	125
8	*i*-Pr	H	2.8[b]	11	12.6[e]	0.45	0.50	5.6	17	ND[d]	ND[d]
9	*i*-Pr	F	1.5	3.7	3.2	1.1	0.28	1.4	11	22 ± 16 ($n=26$)	350 ± 320 ($n=14$)
10	*c*-Bu	H	1.6	3.7	60[e]	0.06	1.0	1.0	11	ND[d]	ND[d]

[a] IC_{50}'s reported are averages of triplicate measurements whose standard errors were normally $<15\%$ in a given assay. Assay to assay variability was within ± 2-fold based on a standard compound. Unless otherwise noted, data from displacement of [^{125}I]-labeled MIP-1α from the CCR5 receptor expressed on CHO cell membranes. See ref 3 footnote 20 for assay protocol.

[b] Data from GP120-membrane assay. See ref 15 for assay protocol.

[c] Cell culture infectivity assay by HIV-1 in HeLa cells. See ref 16 for assay conditions.

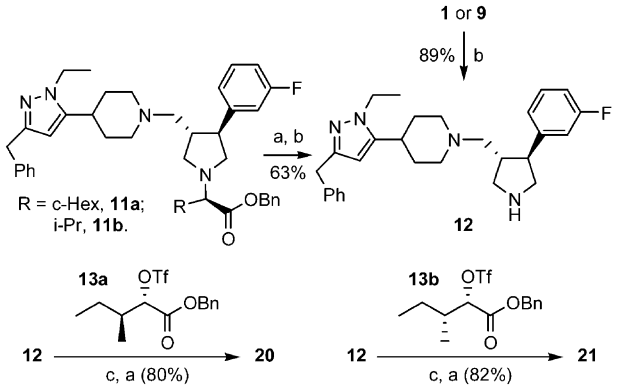
[d] Not determined.

[e] All compounds were dosed at 0.5 mpk IV and 2.0 mpk po. These compounds were dosed as a mixture of five compounds. Mixture dosing can inflate AUC_{po} and %F compared to single dosing; increases of 2- to 3-fold were common for compounds discussed here. Values of Cl_p usually did not change significantly in cases where comparisons are available.

[f] Inhibition of HIV-1 infectivity in human donor PBMCs over a 7-day period. Results under the heading of 50% NHS were obtained in the presence of 50% normal human serum. See ref 17 for assay protocol.

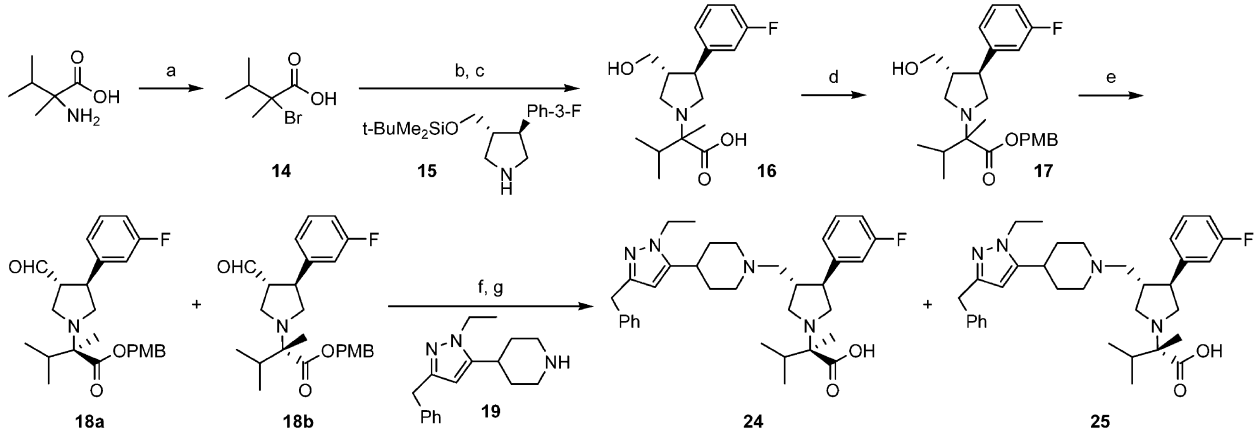
receptors and enzymes (data not shown). Compound **9** was also a true antagonist without any agonist activity based on a microphysiometer assay.[18] At 1 and 10 μM, it showed 0% of the initial response of MIP-1α at its EC_{50} (1–2 nM).

It was clear from the data presented in Table 1 that only minor structural changes could be tolerated in **9** without jeopardizing its PK profile. Therefore, additional close analogues of **9** were investigated in an effort to improve antiviral activity while preserving its PK profile (Table 2). Compound **23** was prepared using the methods reported earlier.[5,13] Synthesis of compounds **20** and **21** took advantage of our observation of a novel dealkylation process. During the catalytic hydrogenolysis of benzyl or *p*-methoxybenzyl (PMB) esters such as **11** to generate compounds such as **1** or **9**, exposure of the reaction mixtures to air for any length of time before the Pd/C catalyst was filtered resulted in the rapid formation of a side-product. This side-product was identified as pyrrolidine **12**. Exposing the reaction mixture to air for a few hours after finishing hydrogenolysis without filtering out the catalyst resulted in complete conversion to **12**. Alternatively, stirring methanol solutions of **1** or **9** in the presence of Pd/C catalyst and air gave **12** as the only product by HPLC. No hydrogen pretreatment was required for this reaction to proceed. Similar treatment of **11a** or **b** resulted in no change. No intermediates were observed by HPLC during the transformation of **9** to **12**.[19] Although a number of other reagents, such as Ph-$I(OAc)_2$,[20] $H_2O_2/H_2SO_4/100\,°C$,[21] anodic oxidation,[22] and Mn^{3+} complexes,[23] are known to decarboxylate similar amino acids, this Pd/C/air method offer simplicity and potential chemoselectivity. Reacting **12** with isomeric triflates **13a** and **b** afforded compounds **20** and **21**, respectively, after hydrogenolysis (Scheme 1).



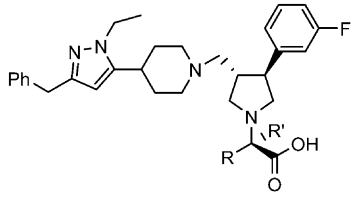
Scheme 1. Reagents: (a) H_2, Pd/C, MeOH; (b) Pd/C, exposure to air, MeOH; (c) DIEA, MeCN, rt.

The displacement of triflates by pyrrolidine during the preparation of compound **22** required the use of the purified triflate in DMF at 50 °C versus DCM at room temperature for less sterically hindered cases. The method used to couple the triflate and pyrrolidine described before was not suitable for the introduction of dialkyl acetate groups as required in **24** and **25**. Although there were several reports for preparing similar compounds,[24–26] they failed in our case. After considerable experimentation, a method was found for the preparation of this type of compound as shown in Scheme 2.[27] Diazotization of α-methylvaline in the presence of hydrobromic acid and potassium bromide gave bromo acid **14** in a low yield.[28] Side-products included the corresponding hydroxy acid and trimethyl acrylic acid and 2-isopropyl acrylic acid from elimination. The bromo acid **14** hydrolyzes partially on silica gel. Therefore, a semi-crude mixture containing about 50% **14** was used in the next step. Slow addition of a THF solution of silver triflate to a mixture of **14**, excess pyrrolidine **15**,[29] and four equivalents of DIEA in THF followed by quenching with KBr gave a mixture of isomeric silyl compounds. The mixture was desilylated during purification on preparative HPLC using MeCN and water with 0.1% TFA. The alcohols **16** were converted to PMB esters **17**. The isomeric PMB esters can be separated on silica gel. They were converted to isomeric aldehydes **18a** and **18b** separately using Swern oxidation. Reductive amination with pyrazolylpiperidine **19**[13] and debenzylation gave the final compounds **24** and **25**. The identity of **24** and **25** were assigned based on comparison of proton NMR of **18a** and **18b** with those of the corresponding isopropyl compounds (the aldehyde precursor to **11b** and its diastereomer).



Scheme 2. Reagents: (a) $NaNO_2$, KBr, HBr, H_2O, 5%; (b) AgOTf, 4 equiv DIEA, THF, rt; (c) preparative RP-HPLC ($MeCN/H_2O$/0.1% trifluoroacetic acid), 60%; (d) 4-methoxybenzyl chloride, Cs_2CO_3, DMF, rt, 52%; (e) oxalyl chloride, dimethyl sulfoxide, Et_3N, dichloromethane, −78 °C to rt, 88–100%; (f) $NaBH(OAc)_3$, DIEA, 1,2-dichloroethane; (g) 96% formic acid, rt, 71–89% (two steps).

Table 2. CCR5 binding affinity, antiviral activity, and pharmacokinetic profile in the rat of compound **9** analogues



	Compd R =	R′ =	CCR5 IC_{50}, (nM)[a]	HeLa IC_{90}, (nM)[b]	Cl_p, (mL/min/kg)	$AUCN_{po}$, (μM·h/dose)	Vd_{ss} (L/kg)	$t_{1/2}$ (h)	F (%)
20	(*S*)-s-Bu	H	0.8	<0.14	25	0.16	0.64	0.54	13
21	(*R*)-s-Bu	H	0.9	0.4	ND[c]	ND	ND	ND	ND
22	*t*-Bu	H	0.8	<0.14	5.7[d]	3.7	0.24	0.79	71
23	3-Pentyl	H	0.9	0.4	19[d]	0.80	0.49	0.59	52
24	*i*-Pr	Me	1.6	300	ND[c]	ND	ND	ND	ND
25	Me	*i*-Pr	5.5	>300	10	0.62	0.43	0.74	21

[a] See footnote a of Table 1.
[b] See ref 16 for assay conditions.
[c] Not determined.
[d] See footnote e of Table 1.

Addition of a methyl group to the isopropyl region of **9** afforded compounds **20**–**22** with good CCR5 binding affinity and antiviral activity as measured in the HeLa assay (Table 2). Compound **23**, with the addition of two methyl groups, conformed to the same trend. However, only the *t*-Bu compound **22** showed improvements in its PK profile in the rat over **9**, especially in oral AUCN. Modifications leading to α,α-dialkyl analogues **24** and **25** yielded a considerable loss of antiviral activity and some deterioration in the rat PK profile of **25** compared to **9**.

Compound **22** showed an IC_{95} of <8 nM in the HIV-1 PBMC infectivity inhibition assay ($n=3$). In the presence of 50% normal human serum, its IC_{95} was 40 ± 28 nM ($n=3$). Therefore, addition of the methyl group to **9** restored antiviral activity of **22** back to the level of our initial lead compound **1**. However, its selectivity profile was not as good as compound **9**. For example, **22** had an IC_{50} of 3.5 μM at the type 2 Na^+ channel.

Based on their overall properties, compounds **9** and **22** were further evaluated in dog and rhesus monkey for their pharmacokinetic profiles (Table 3). Unfortunately, the improvement of the PK profile of **22** over **9** observed in the rat was not realized in the dog. When **9** was dosed at 10 mpk po in the rat, it showed a significant increase in dose-normalized AUC and %F to 3.14 and 31.7%, respectively, compared with 1.05 and 10.6% at 2 mpk. That suggested that its oral bioavailability might improve at higher doses in larger animals as well.

Table 3. Pharmacokinetic profiles of CCR5 antagonists **9** and **22** in dog and rhesus monkey[a]

	Compd	**9**	**22**
Dog	Cl_p (mL/min/kg)	3.5	13
	$AUCN_{po}$ (μM·h/dose)	1.9	1.0
	Vd_{ss} (L/kg)	0.61	0.50
	$t_{1/2}$ (h)	3.4	0.64
	F (%)	20	44
Monkey	Cl_p (mL/min/kg)	20	
	$AUCN_{po}$ (μM·h/dose)	0.08	
	Vd_{ss} (L/kg)	1.2	
	$t_{1/2}$ (h)	1.3	
	F (%)	4.7	

[a] Compounds were dosed at 0.5 mpk iv and 2.0 mpk po. Compound **22** was not tested in monkey.

In summary, modifications in the α-alkyl acetic acid region and addition of a 3-fluoro substitution to the phenyl group on pyrrolidine in our lead pyrazole compound **1** have resulted in the isopropyl compound **9**. It is a potent CCR5 antagonist with good in vitro antiviral activity against HIV-1, excellent selectivity versus a large panel of receptors, enzymes, transporters and ion channels, and oral bioavailability in several animal species. During this investigation, a new method for the introduction of α-(pyrrolidin-1-yl) group onto α,α-dialkylacetic acid via the bromo acid was discovered. A novel Pd-mediated *N*-dealkylation of α-(pyrrolidin-1-yl)acetic acid was also uncovered. Additional SAR studies focusing on the benzyl portion of compound **9** and its analogues will be the subject of our next report.

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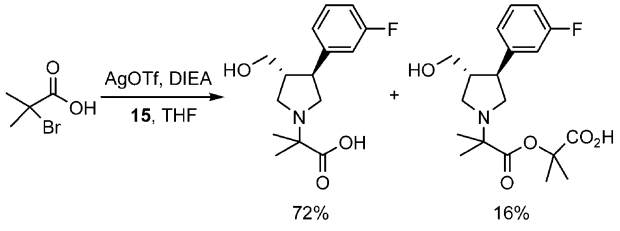
References and notes

1. Finke, P. E.; Oates, B.; Mills, S. G.; MacCoss, M.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Carella, A.; Carver, G.; Holmes, K.; Danzeisen, R.;

Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Schlief, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2475 and references cited therein.
2. Willoughby, C. W.; Berk, S. C.; Rosauer, K. G.; Delgrado, S.; Chapman, K. T.; Gould, S. L.; Springer, M. S.; Malkowitz, L.; Schlief, W. A.; Hazuda, D.; Miller, M.; Kessler, J.; Danzeisen, R.; Holmes, K.; Lineberger, J.; Carella, A.; Carver, G.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3137.
3. Hale, J. J.; Budhu, R. J.; Mills, S. G.; MacCoss, M.; Malkowitz, L.; Siciliano, S.; Gould, S. L.; DeMartino, J. A.; Springer, M. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1437.
4. Hale, J. J.; Budhu, R. J.; Holson, E. B.; Finke, P. E.; Oates, B.; Mills, S. G.; MacCoss, M.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Siciliano, S.; Malkowitz, L.; Schlief, W. A.; Hazuda, D.; Miller, M.; Kessler, J.; Danzeisen, R.; Holmes, K.; Lineberger, J.; Carella, A.; Carver, G.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2741.
5. Lynch, C. L.; Hale, J. J.; Budhu, R. J.; Gentry, A. L.; Mills, S. G.; Chapman, K. T.; MacCoss, M.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J.; Cascieri, M. A.; Carella, A.; Carver, G.; Holmes, K.; Schlief, W. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3001 and references cited therein.
6. Willoughby, C. W.; Rosauer, K. G.; Hale, J. J.; Budhu, R. J.; Mills, S. G.; Chapman, K. T.; MacCoss, M.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J.; Cascieri, M. A.; Carella, A.; Carver, G.; Holmes, K.; Schlief, W. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 427.
7. Lynch, C. L.; Willoughby, C. W.; Hale, J. J.; Holson, E. J.; Budhu, R. J.; Gentry, A. L.; Rosauer, K. G.; Caldwell, C. G.; Chen, P.; Mills, S. G.; MacCoss, M.; Berk, S.; Chen, L.; Chapman, K. T.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J.; Cascieri, M. A.; Carella, A.; Carver, G.; Holmes, K.; Schlief, W. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 119.
8. Baba, M.; Nishimura, O.; Kanzaki, N.; Okamoto, M.; Sawada, H.; Iizawa, Y.; Shiraishi, M.; Aramaki, Y.; Okonogi, K.; Ogawa, Y.; Meguro, K.; Fujino, M. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 5698.
9. Tagat, J. R.; Steensma, R. W.; McCombie, S. W.; Nazareno, D. V.; Lin, S.-I.; Neustadt, B. R.; Cox, K.; Xu, S.; Wojcik, L.; Murray, M. G.; Vantuno, N.; Baroudy, B. M.; Strizki, J. M. *J. Med. Chem.* **2001**, *44*, 3343 and references cited therein.
10. For a review, see: Kazmierski, W.; Bifulco, N.; Yang, H.; Boone, L.; DeAnda, F.; Watson, C.; Kenakin, T. *Bioorg. Med. Chem.* **2003**, *11*, 2663.
11. Lynch, C. L.; Gentry, A. L.; Hale, J. J.; Mills, S. G.; MacCoss, M.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J.; Cascieri, M. A.; Doss, G.; Carella, A.; Carver, G.; Holmes, K.; Schlief, W. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 677.
12. Kim, D.; Wang, L.; Caldwell, C. G.; Chen, P.; Finke, P. E.; Oates, B.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Danzeisen, R.; Carver, G.; Carella, A.; Holmes, K.; Lineberger, J.; Schlief, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3099 and 3103.
13. Shen, D.-M.; Shu, M.; Mills, S. G.; Chapman, K. T.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J.; Kwei, G. Y.; Carella, A.; Carver, G.; Holmes, K.; Schleif, W. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M. D.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, preceding paper in this issue. doi:10.1016/j.bmcl.2003.12.004.
14. This trend was not always observed. In the related 4-(3-phenylpropyl)piperidine series, the isopropyl compound has similar pharmacokinetic profile as the cyclohexyl compound with diminished CCR5 binding and antiviral activities (ref 5).
15. Siciliano, S. J.; Kuhmann, S. E.; Weng, Y.; Madani, N.; Springer, M. S.; Lineberger, J. E.; Danzeisen, R.; Miller, M. D.; Kavanaugh, M. P.; DeMartino, J. A.; Kabat, D. *J. Biol. Chem.* **1999**, *274*, 1905.
16. Hazuda, D. J.; Felock, P.; Witmer, M.; Wolfe, A.; Stillmock, K.; Grobler, J. A.; Espeseth, A.; Gabryelski, L.; Schleif, W.; Blau, C.; Miller, M. D. *Science* **2000**, *287*, 646.
17. Saag, M. S.; Emini, E. A.; Laskin, O. L.; Douglas, J.; Lapidus, W. I.; Schleif, W. A.; Whitley, R. J.; Hildebrand, C.; Byrnes, V. W.; Kappes, J. C.; Anderson, K. W.; Massari, F. E.; Shaw, G. M. *New Engl. J. Med.* **1993**, *329*, 1065.
18. See note 20 of ref 3 for assay protocol.
19. We have not studied the mechanism or scope of this transformation, although it appears to be general to compounds reported here. During a discussion with Prof. Barry M. Trost, he suggested a Pd-mediated oxidative decarboxylation of compounds such as **1** and **9** to an iminium intermediate followed by hydrolysis as a possible pathway.
20. Boto, A.; Hernandez, R.; Suarez, E. *J. Org. Chem.* **2000**, *65*, 4930 and references cited therein.
21. Barsukov, A. V.; Yaroshenko, G. F.; Lastovskii, R. P.; Dyatlova, N. M. *J. Gen. Chem. USSR (Engl. Transl.)* **1983**, *53*, 1109.
22. Hashiguchi, S.; Maeda, Y.; Kishimoto, S.; Ochiai, M. *Heterocycles* **1986**, *24*, 2273.
23. Gangopadhyay, S.; Ali, M.; Saha, S. K.; Banerjee, P. *J. Chem. Soc., Dalton Trans.* **1991**, 2729.
24. Carrell, D. P.; Cragoe, E. J. WO 9640104, 1996.
25. Guziec, F. S. J.; Torres, F. F. *J. Org. Chem.* **1993**, *58*, 1604.
26. Kahovec, L.; Hohlrausch, K. W. F. *Monatsh. Chem.* **1943**, *74*, 104.
27. As a model reaction, simultaneous slow addition (syringe pump) of THF solutions of 1.1 equivalents each of silver triflate and commercially available 2-bromo-isobutyric acid to pyrrolidine **15** in the presence of 4 equiv of DIEA followed by HPLC purification ($MeCN/H_2O$, 0.1% TFA) with concurrent loss of the silyl group gave 72% of alcohol product and 16% of a side product having two units of isobutyric acid incorporated. For another application of this reaction, see Zhang, F., et al. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2573. Slow addition of silver triflate or the bromo acid alone gave 60 and 65% of the desired product, respectively. Ag_2O/toluene with or without sonication gave much lower conversions. Silver trifluoroacetate gave similar results as silver triflate.



28. Petit, Y.; Larcheveque, M. *Org. Synth.* **1997**, *75*, 37.
29. About 2-fold excess of **15** was used to minimize the bis-alkylation product discussed in footnote 27 above.