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Approaches to installing a *N-gem*-dimethylmethylene-2-oxazolyl group and application to the synthesis of a second generation HIV protease inhibitor

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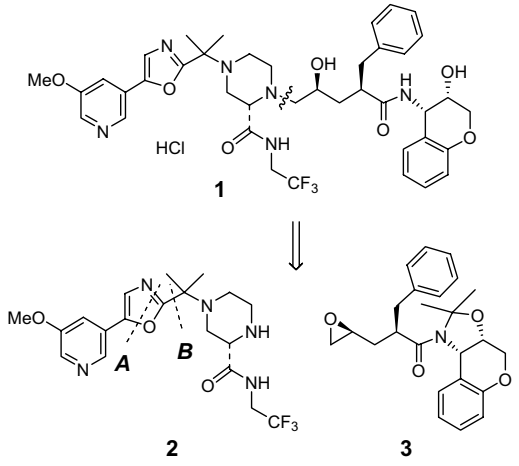
Abstract—Two syntheses of the title compound **1** were developed based on different approaches for installing the oxazole ring moiety. Formation and dehydration of ketoamide was initially used and scaled up to afford **1** on several kilogram scale, then oxazolyl anion/iminium coupling reaction was developed for a more convergent approach.

The HIV protease inhibitors, such as indinavir sulfate, have offered valuable therapies in controlling the progression of AIDS in HIV infected patients.[1–3] However, due to the fast emergence of resistant viral strains of HIV[4,5] and the rapid metabolism and clearance of drug from the body, more effective second generation analogs were sought with improved potency against resistant strains and improved pharmacokinetic profiles. Compound **1** showed superior properties versus indinavir and was chosen as a developmental candidate.[6–9] A scaleable synthesis of **1** was thus needed to prepare several kilograms of bulk drug to support a highly accelerated program. For greatest convergency, the disconnection in Scheme 1 was adopted involving coupling of a previously reported epoxide **3**[10] and the oxazole ring containing biarylpiperazine **2**. The synthesis of the latter posed a challenge due to sterically demanding linkage of the piperazine and oxazole moieties via a *gem*-dimethylmethylene group.[11] Ultimately, two disconnections of **2** were realized (at bonds ***A*** and ***B***), which are summarized in this report.



Scheme 1. Retrosyntheses of **1**.

Disconnection ***A*** started with conversion of 3,5-dibromopyridine **4** to 3-bromo-5-methoxypyridine **5** at 90–100 °C in DMF with 1.2 equiv of $NaOCH_3$. The reaction mixture after aqueous workup was filtered through a pad of silica gel, and the solution in MTBE was solvent switched to THF and treated with 2*M* *i*-PrMgCl/THF to generate Grignard **6**, which was converted to Boc-aminoketone **8** via reaction with

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Boc-glycine Weinreb amide reagent **7** in 75% overall isolated yield. Pre-treatment of **7** with *i*-PrMgCl to deprotonate the acidic NH group[12] allowed for the use of only 1 equiv of Grignard **6** versus 2 equiv without pre-treatment for this coupling. The Boc-aminoketone **8** was crystallized after workup and isolated in high purity. A total of 9 kg of **8** was prepared using this sequence (Scheme 2).

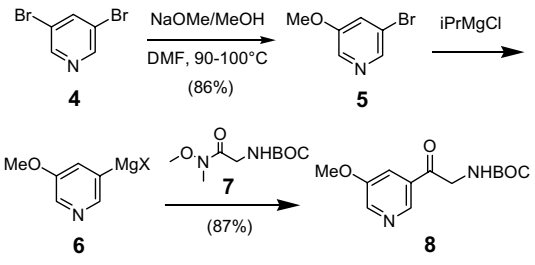
This ketone was used to prepare the ketoamide **13** precursor to the oxazole **2**. The previously reported chiral Boc-piperazine amide **9** (Ref. 10) was converted to the N1-Alloc derivative **10**, and the *gem*-dimethylmethylene moiety was installed via a silver mediated[13] *N*-alkylation with bromo-*gem*-dimethylacetic acid.[9] Ketone **8** was deprotected with aqueous HCl to afford aminoketone salt **12** and was coupled with acid **11** via EDC/HOBT activation. Due to the large steric bulk of the *gem*-dimethyl group, the coupling to **13** was slow and incomplete using the standard catalytic HOBT procedure. However, by using stoichiometric HOBT to first form the activated acid/HOBT adduct (rt, 1 h) and then adding the aminoketone salt **12** and Hünig's base, good conversion and yield of **13** were achieved. The ketoamide **13** was isolated as the bis-sulfate salt in 84% overall yield from BOC-aminoketone **8** (98.5% ee).

Cyclization and deprotection of the ketoamide **13** to afford oxazole **2** was best accomplished using a strongly dehydrating reagent, neat 30% fuming sulfuric acid (oleum) at 40 °C. Milder reagents (e.g., $POCl_3$, $POCl_3$/PCl_5, TFA/TFAA, PCl_5/MSA, $POCl_3$/MSA, $POCl_3$/H_2SO_4, or PCl_5/H_2SO_4) did not effect this cyclization, although P_2O_5/H_2SO_4 did produce some oxazole in lower yields. A significant racemization problem was observed, however, with 30% oleum, affording oxazole **2** with typically <90% ee at full conversion. Halting the reaction at lower conversions gave less racemization but at the expense of lower yields.

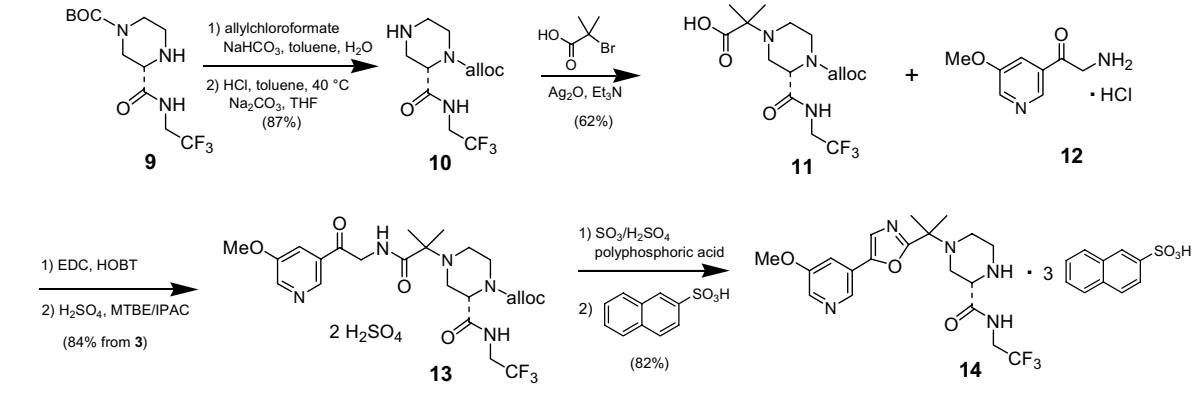
It was observed that the product **2** from the P_2O_5/H_2SO_4 reaction condition was obtained with no loss in optical purity (~98.7% ee), although the yield was only 50–60% due to formation of impurities. Addition of P_2O_5 to the 30% oleum reaction mixture did not suppress racemization and **2** was isolated with only 87% ee at 81% yield. Suspecting that more water or a different, more hydrated form of P_2O_5 was required in the reaction mixture to suppress racemization, polyphosphoric acid (PPA)/30% oleum combination was tried instead, and happily **2** was obtained with 96% ee at >85% yield. Scale-up under these conditions (2.5 vol of 30% oleum, 3 equiv of PPA, 6–7 h at 40–45 °C), in two batches generated 5 kg of oxazole **2** in 84% yield with 95% ee purity. (*Caution*: Oleum is highly corrosive. Also, the aqueous quench is highly exothermic and needs to be performed slowly and with adequate cooling.)

An upgrade in optical purity for **2** was, however, still required, and various salt forms of **2** were screened for crystallization since **2** as the free base could not be crystallized. A crystalline form of tris-2-naphthalenesulfonic acid (NSA)[14] salt **14** was identified that was capable of upgrading **2** to 99% ee from 87% ee via crystallization from acetonitrile/water. By forming this salt, 4.4 kg of **2** was purified to 99% ee from the initial 95% ee. A salt break with KOH/methanol and removal of K-NSA salt then afforded the free base **2** with 97% recovery without loss of optical purity (Scheme 3).

With pure biarylpiperazine **2** in hand, coupling with epoxide **3** was investigated. Among a wide range of solvents (alcohols, amides, DMSO, HOAc, water, etc., including mixtures) the optimized yield of 80% was achieved by heating in *tert*-amyl alcohol at 55 °C[15] for 4 days. Variation of reactant stoichiometries and concentrations had a negligible effect on the yield. Addition of a wide variety of Lewis acids[16] also failed to improve the yield (and in most cases was detrimental).



Scheme 2. Synthesis of Boc-aminoketone **8**.

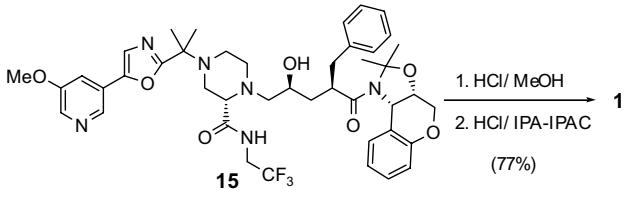


Scheme 3. Synthesis of oxazole intermediate **14**.

While the above coupling gave an acceptable yield it also generated several low level impurities, one of which was difficult to reject via crystallization. A highly productive HPLC separation[17] was employed to remove this impurity and afford 5.6 kg of purified product **15** in 80% overall yield from **2**. Subsequent removal of the acetonide was best performed with gaseous HCl in methanol (TFA/THF, HCl/IPA, MeOH/concd HCl were all notably slower). Isolation of **1** by crystallization as an HCl salt (isopropylacetate, IPA, concd HCl) provided the desired product with high purity in 79% yield from **15**. Therefore, to support this highly accelerated program, the development and execution of this scaleable synthesis was achieved in six months to prepare several kilograms of the candidate HIV protease inhibitor **1** (Scheme 4).

However, for a longer term synthesis of **1**, a more efficient synthesis of the biarylpiperazine **2** was desired that did not rely on a stoichiometric silver catalyzed *N*-alkylation and dehydration of ketoamide **13** using a very corrosive reagent. Thus, in a parallel study with the development of the above process, an alternative route to **2** was investigated and was ultimately successful (Scheme 5).

In this approach, the Grignard **6** was prepared and quenched with DMF to afford the aldehyde **16**, which was then converted to the oxazole **17** with tosylmethyl isocyanide reagent (TosMIC) in 82% overall yield.[18] Then, the acetonide of piperazine amide **19** was prepared from piperazine amide salt **18** (a precursor to **9**) (Ref. 9) and converted to the acetone iminium salt **20** by heating in dimethoxypropane in 90% overall yield. Replacement with anions other than triflate gave noncrystalline salts of **19**. Formation of the C2 anion of oxazole **17** with *i*-PrMgCl followed by the addition of iminium **20** afforded the protected biarylpiperazine **21** in good yield. Deprotection of the acetonide group and formation of the tris-salt **14** could then be achieved in one pot via heating in NSA/acetonitrile in 90% yield. This process, which was demonstrated successfully on 100 g scale, has the advantage of greater convergency and efficiency and is likely the more scaleable and practical route.

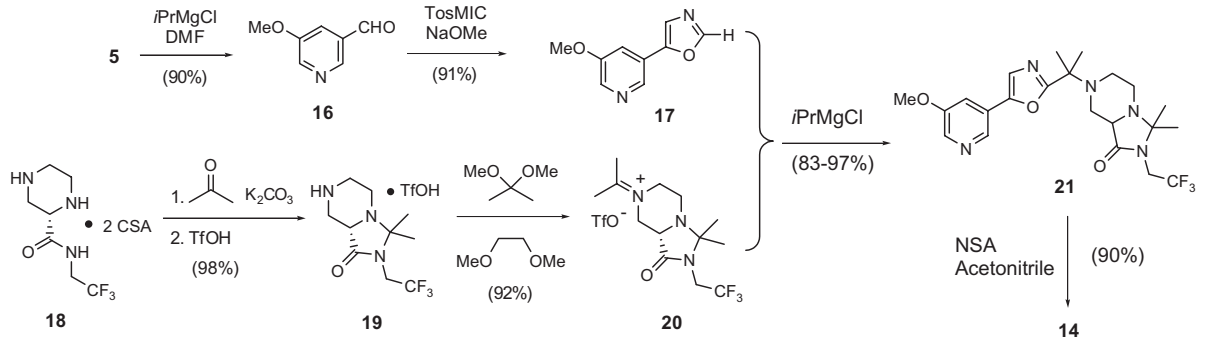


Scheme 4. Penultimate and conversion to product **1**.

The development of a more scaleable synthesis of **1** also needed to address the requirement for chromatographic purification. The problematic impurity was identified as an oxidative byproduct[17] and therefore the addition of antioxidants/reductants to the coupling reaction was screened. BHT, BHA, various silanes, sodium formate, sodium thiosulfate, potassium sulfite, and potassium thiosulfate were all ineffective. In contrast addition of 0.20 equiv of sodium metabisulfite almost completely suppressed the formation of the oxidative byproduct. Epoxide opening under these conditions, followed by the previously described deprotection and HCl salt formation, gave a 64% overall yield of **1** from **2** in the required purity without the need for chromatographic purification.

Thus, the synthesis of a second generation HIV protease inhibitor was achieved employing two different approaches to install the challenging *N-gem*-dimethylmethylene-2-oxazolyl group. The initial approach involving formation and dehydration of the ketoamide enabled a rapid synthesis of several kilograms of inhibitor **1** to support the rapid-paced program. The utility of polyphosphoric acid to suppress racemization during the oleum-mediated dehydration was demonstrated and two novel and possibly general purification protocols of 2-naphthalenesulfonic acid[14] were devised. As a successful strategy to rapid drug development for application to longer term synthesis, a more convergent disconnection was pursued in parallel and resulted in a highly efficient process involving oxazole anion addition to the piperazine iminium salt.

Characterization data—**8**: mp 112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 (s, 9H), 3.90 (s, 3H), 4.65 (d, 4.6 Hz, 2H), 5.50 (br s, 1H), 7.68 (dd, 2.9, 1.7 Hz, 1H), 8.50 (d, 2.9 Hz, 1H), 8.75 (d, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 47.8, 55.7, 80.0, 117.5, 130.5, 141.2, 143.5, 155.6, 155.9, 193.7.



Scheme 5. Alternative route to oxazole intermediate **14**.

13 (free base): $[\alpha]_D^{25}$ −44 (*c* 0.41, MeOH); ^{1}H NMR (400 MHz, DMSO): δ 8.76 (s, 1H), 8.65 (t, 1H), 8.53 (d, 2.3 Hz, 1H), 7.79 (s, 1H), 7.61 (t, 1H), 5.91 (m, 1H), 5.22 (m, 2H), 4.80 (dd, 6.2, 18.6 Hz, 1H), 4.55 (m, 5H), 3.90 (s, 3H+2H), 3.83 (d, 12.4 Hz, 1H), 3.38 (m, 2H), 2.81 (m, 1H), 2.41 (d, 11 Hz, 1H), 2.20 (t, 11 Hz, 1H), 1.12 (s, 3H), 1.08 (s, 3H).

14: mp 201 °C; $[\alpha]_D^{25}$ −8 (*c* 0.51, MeOH); ^{1}H NMR (400 MHz, DMSO): δ 1.57 (s, 6H), 2.49–2.51 (m, 2H), 3.00–3.03 (m, 2H), 3.35 (d, 12.6 Hz, 1H), 3.46 (d, 11.0 Hz, 1H), 3.97 (s, 3H), 3.97–4.07 (m, 3H), 7.49–7.54 (m, 6H), 7.71 (dd, 1.4, 8.5 Hz, 3H), 7.85 (d, 8.5 Hz, 3H), 7.86–7.93 (m, 3H), 7.94–7.97 (m, 3H), 7.99 (s, 1H), 8.05 (t, 2.1 Hz, 1H), 8.1–8.4 (broad, 3H), 8.50 (d, 2.6 Hz, 1H), 8.73 (d, 1.5 Hz, 1H), 8.8–8.9 (broad, 1H), 9.1–9.2 (broad, 1H), 9.29 (t, 6.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO): δ 24.3, 24.7, 43.0, 43.7, 47.1, 56.5, 57.7, 59.3, 123.2, 124.2, 124.7, 124.9 (q, 279 Hz), 126.9, 127.1, 127.3, 127.4, 127.9, 128.0, 128.9, 131.1, 131.8, 132.6, 133.4, 145.4, 146.4, 157.8, 166.4, 167.5.

17: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (m, 1H), 8.25 (s, 1H), 7.95 (s, 1H), 7.45 (s, 1H), 7.38 (m, 1H), 3.9 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 151.1, 148.7, 138.0, 137.6, 124.4, 123.0, 115.6, 55.7.

19: ^{1}H NMR (400 MHz, CD_3CN): δ 7.2 (br s, 2H), 3.93 (q, J = 9.4 Hz, 2H), 2.7–3.7 (m, 7H), 1.38 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 168.8, 124.1 (q, J = 279.5 Hz), 121.1 (q, J = 319.5 Hz), 78.9, 55.0, 45.0, 44.6, 41.0 (q, J = 35.7 Hz), 40.4, 24.1, 16.9.

20: ^{1}H NMR (500 MHz, CD_2Cl_2): δ 4.61 (m, 1H), 4.45 (m, 1H), 3.7–3.95 (m, 2H), 3.45–3.65 (m, 3H), 3.17 (dt, J = 11.3, 3.2 Hz, 1H), 3.01 (td, J = 11.3, 2.8 Hz, 1H), 2.65 (s, 3H), 2.64 (s, 3H), 1.45 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (126 MHz, CD_2Cl_2): δ 191.9, 169.4, 124.2 (q, J = 279.9 Hz), 79.5, 57.3, 53.9, 53.8, 42.7, 41.9 (q, J = 36 Hz), 26.5, 26.4, 24.7, 19.3.

1: mp 205 °C; ^{1}H NMR (400 MHz, CD_3OD): δ 8.50 (d, 1.5 Hz, 1H), 8.25 (d, 2.7 Hz, 1H), 7.70 (s, 2H), 7.32–7.17 (m, 5H), 7.16 (d, J = 7.6 Hz, 1H), 7.09 (m, 1H), 6.86 (m, 1H), 6.40 (d, 8.1 Hz, 1H), 5.17 (d, 4.0 Hz, 1H), 4.84 (s, 4H), 4.21 (br s, 1H), 4.17–3.98 (m, 4H), 3.96 (s, 3H), 3.97–3.75 (m, 3H), 3.40 (br s, 1H), 3.32–3.13 (m, 2H), 3.07 (br s, 1H), 3.03–2.93 (m, 2H), 2.85–2.62 (m, 3H), 1.90 (m, 1H), 1.68 (s, 6H), 1.53 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 177.8, 169.0, 167.5, 158.0, 155.7, 150.1, 140.5, 138.0, 137.9, 130.4, 130.0, 129.8, 129.6, 127.6, 126.6, 125.8 (q, 278 Hz), 125.0, 122.4, 122.0, 117.9, 117.4, 69.4, 66.6, 65.5, 62.2, 59.9, 56.8, 54.0, 49.7, 49.1, 46.1, 45.5, 41.5 (q, 34.9 Hz), 40.5, 38.6, 24.6, 24.3.

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13. The silver containing waste stream was forwarded to an outside vendor for metal recovery.
14. Since bulk commercial NSA was only available with low purity (~65–80 wt % and <90 A% purity), novel and practical purification procedures were devised to upgrade this acid to the required >99 A% purity. Method 1: Crude NSA is dissolved in toluene/acetonitrile at 80 °C, the bottom dark layer is cut, and the top layer containing the NSA is saturated with water and cooled to crystallize the NSA hydrate in 98–99 A% purity. Recrystallization from acetonitrile/toluene affords >99 A% purity (57% overall recovery). Method 2: The toluene layer after the cut is extracted with water. The aqueous layer is evaporated and solvent switched to acetonitrile. Toluene is added and heated to form a clear solution. Seeding with NSA and cooling generates a slurry, which is filtered, rinsed with toluene and dried to afford NSA with 99.5 A% purity (66% recovery).

15. Higher temperatures lead to lower product yields and purity while lower temperatures unacceptably increased the time required for complete conversion.
16. $Al(O\text{-}iPr)_3$, $LiClO_4$, LiCl, $LiBF_4$, $NaClO_4$, $Ti(O\text{-}iPr)_4$, $MgBr_2$, $Mg(OH)_2$, $Mg(ClO_4)_2$, $Sc(Otf)_3$, $Cu(Otf)_2$, $Zn(Otf)_2$, $La(O\text{-}iPr)_3$.
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