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An Expeditious Synthesis of the MDM2−p53 Inhibitor AM-8553

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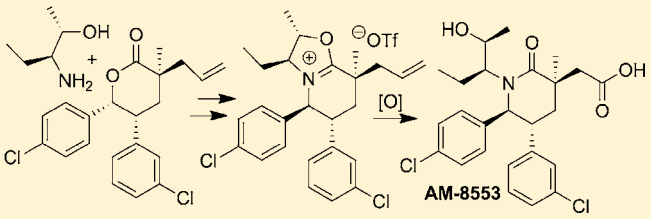
Supporting Information

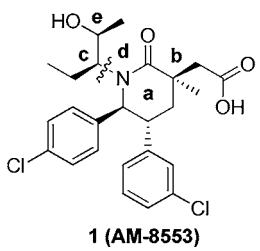
ABSTRACT: The development of the structurally complex MDM2/p53 inhibitor AM-8553 was impeded by the low yield of the initial synthesis. A second generation synthesis is described that features a Noyori dynamic kinetic resolution, a highly diastereoselective allylation, and a novel oxazoline-assisted piperidinone forming reaction to provide AM-8553 in 35.6% yield and 11 steps.



INTRODUCTION

Over the past decade, there has been considerable interest in the discovery of molecules that disrupt the protein−protein interaction between p53 and MDM2 as a potential treatment for human cancer.[1] In the presence of cellular stress, the tumor suppressor protein p53 is known to play a pivotal role in controlling cell cycle arrest, DNA repair, senescence, and apoptosis.[2] The MDM2 protein is transcriptionally activated by p53 and, once expressed, serves as a master regulator of p53 by controlling its activity and degradation.[3] Molecules which bind to MDM2 and neutralize the MDM2−p53 protein−protein interaction can disrupt the autoregulatory feedback loop between the two proteins, leading to increased p53 concentration and, eventually, tumor growth inhibition and apoptosis in cancer cells containing wild-type p53.[4]

We recently described a class of high-affinity inhibitors of the MDM2−p53 interaction, exemplified by piperidinone AM-8553 (**1**),[5] a 0.4 nM (K_d) inhibitor with demonstrated efficacy in xenograft studies. As our interest in AM-8553 grew, it became clear that further development of this compound would be limited by our ability to secure it on scale. The initial synthesis of AM-8553 comprised 17 steps and 0.37% overall yield and suffered from a number of deficiencies as outlined in Figure 1. In our previous synthetic route, the *trans*-aryl piperidone core was prepared as a racemate (Figure 1a) and required chiral chromatography to obtain the desired enantiomer. The installation of the quaternary center (Figure 1b) occurred with modest 3.9:1 diastereoselectivity, while the installation of the side chain (Figure 1c) did not show any diastereoselectivity. The use of the piperidinone as a nucleophile to install the side-chain fragment (Figure 1d) required the use of strong electrophiles. Lastly, our initial co-crystal structures of AM-8553 and MDM2 were not able to unequivocally distinguish between the oxygen and methyl group at the secondary alcohol (Figure 1e), rendering the configuration at that site ambiguous.



Issues:
a.) Racemic synthesis of core
b.) 3.9:1 *d.r.*
c.) 1:1 *d.r.*
d.) Difficult bond formation
e.) Ambiguous stereochemistry

Figure 1. Key issues from the first generation synthesis of AM-8553.

Our retrosynthesis for an improved route to **1** is shown in Scheme 1. Key to our approach was the desire to replace the difficult intermolecular amide alkyation (Figure 1, issues c,d) with a more facile intramolecular N−C6 bond-forming reaction (Scheme 1). Bicyclic iminium ether **2**, an intermediate similar to that employed by Aubé for lactam synthesis via the intramolecular Schmidt reaction,[6] was proposed to accomplish this goal. In our approach, it was conceived that a transient side-chain-derived oxazoline would render the amide of **3** nucleophilic at nitrogen, resulting in the displacement of a simultaneously activated C6 benzylic alcohol to assemble the lactam framework. The amide **3**, bearing a fully elaborated side chain, was envisioned to arise from a simple ring-opening of a *cis*-aryl lactone **4** with a readily available chiral amino alcohol. Furthermore, the cis disposition of aryl groups in lactone **4** serves to enable a highly diastereoselective installation of the quaternary center at C3. Ultimately, we hoped to arrive at lactone **4** as a single stereoisomer from the hydrogenolytic dynamic kinetic resolution of ketone **5** using Noyori's Ru BINAP/diamine catalyst system.[7]

RESULTS AND DISCUSSION

Inspired by the application of the Noyori catalyst system for a dynamic kinetic resolution (DKR) in Merck's taranabant

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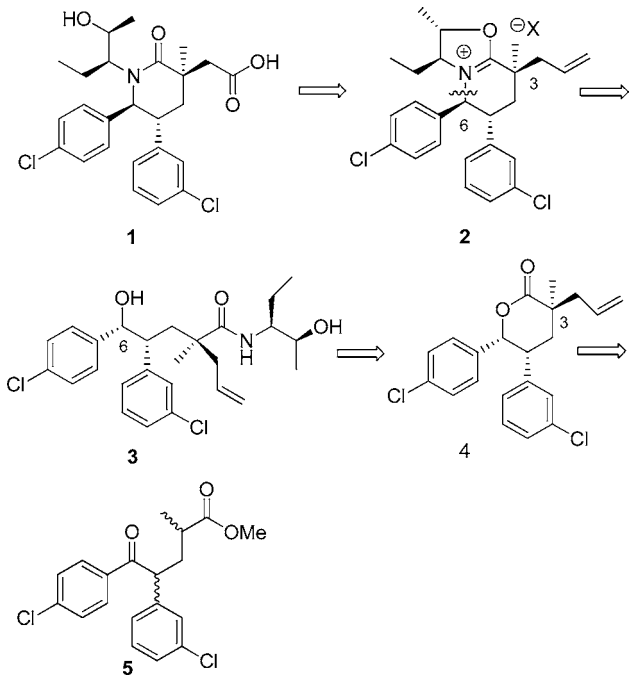
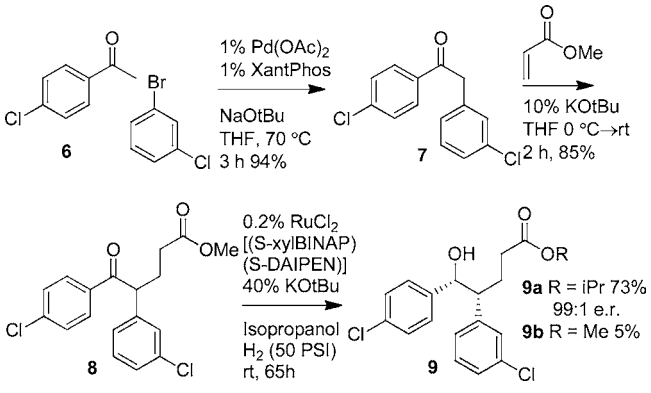
Scheme 1. Retrosynthesis of AM-8553 (1)



synthesis,[8] we sought to employ these conditions to set the relative and absolute stereochemistry of the aryl groups necessary for lactone **4**. To avoid complicating our initial investigation of the DKR process with diastereomers resulting from the C3 methyl group in **5**, we began our work with the desmethyl variant as depicted in Scheme 2. Application of

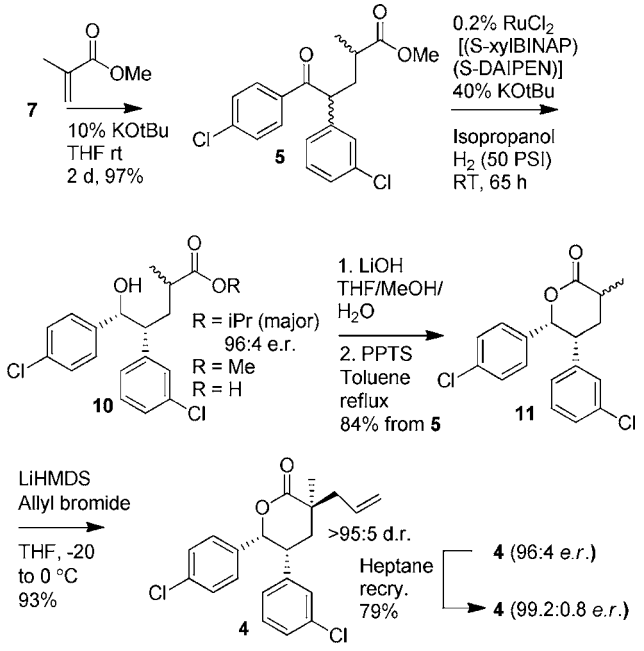
Scheme 2. Initial Exploration of the Dynamic Kinetic Resolution



Buchwald's ketone α-arylation conditions[9] to acetophenone **6** facilitated the synthesis of ketone **7** in 94% yield. Conjugate addition of **7** to methyl acrylate afforded the desmethyl DKR substrate **8**. Gratifyingly, catalytic hydrogenation in the presence of 0.2% $RuCl_2$[(*S*-xyl-BINAP)(S-DAIPEN) with 40% potassium *tert*-butoxide in isopropanol afforded compound **9** as a single diastereomer in 99:1 er, predominantly as the transesterifed isopropyl ester **9a**, with small amounts of methyl ester **9b** isolated as well. Lower er results were obtained using either higher pressure (500 psi, 92:8 er), methanol as a solvent (98:2 er), or use of Noyori's $RuCl_2$(S-BINAP)(S-DAIPEN) catalyst (92:8 er).[10] Lowering the temperature of the reaction to 0 °C resulted in unacceptably long reaction times.

The synthesis of key lactone **4** using this methodology is described in Scheme 3. Synthesis of methylated DKR substrate

Scheme 3. Synthesis of Lactone 4



5 was achieved in 99% yield from Michael addition of ketone **7** to methyl methacrylate. The higher yield of this reaction as compared to the desmethyl case (**8**) is attributed to the slower reaction rate, and ultimately, the absence of double-Michael adduct. Application of the optimized Noyori conditions yielded an inconsequential yet complex mixture of diastereomers and carboxyl functionality. A purified aliquot showed that the isopropyl ester product **10** was obtained in 96:4 er.[11] To maximize yields, the crude mixture was taken directly through a two-step hydrolysis/lactonization sequence to converge on lactone **11** as a 3:1 mixture of epimers at C3.

At this point we were ready to address a key deficiency of the previous route—the diastereoselectivity of the allylation at C3. We hypothesized that the enolate derived from **11** would react predominately from the more sterically accessible β-face as shown in Figure 2.

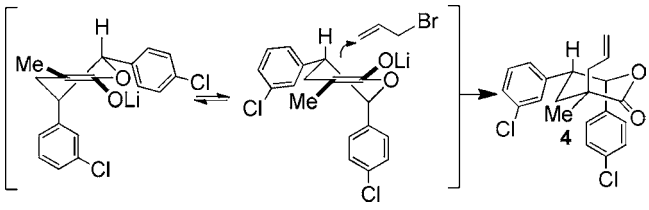


Figure 2. Diastereoselective allylation of **11**.

Diastereoselective alkylations of *cis*-5,6 disubstituted δ-lactones are well precedented to result in the C3 trans-alkylated product,[12] although little precedent exists for C3 alkyl-substituted lactones such as **11**.[13] Allylation of **11** using LiHMDS and allylbromide afforded lactone **4** in 93% yield. Analysis of the crude reaction mixture by ^{1}H NMR indicated that allylation had occurred in >95:5 dr and the crystalline

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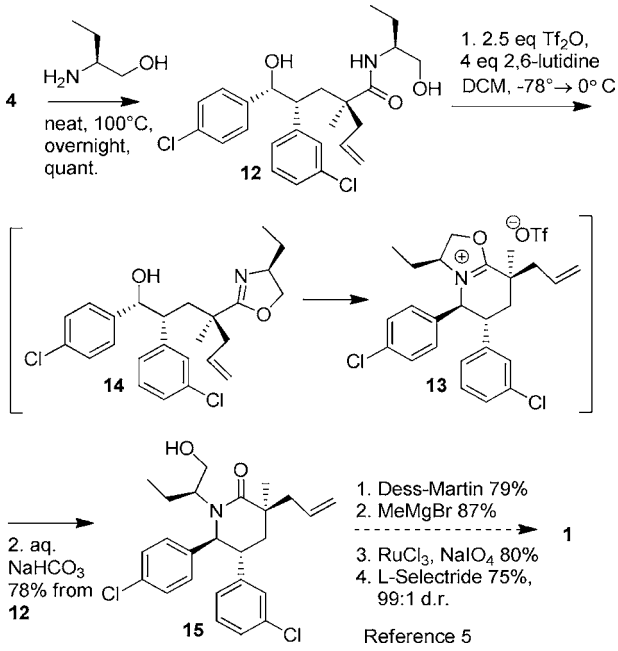
lactone **4** could be recrystallized from heptane to improve the er from 96:4 to 99.2:0.8 if desired.

With lactone **4** in hand we could turn our attention toward the proposed oxazoline-assisted piperidinone synthesis. Initially, we chose to avoid the ambiguity surrounding the stereochemistry of the secondary hydroxyl in **1** (Figure 1, issue e) by intercepting our previous route to **1** at a late stage and installing the hydroxyl as in our previous synthesis (Scheme 4).[5] The

Scheme 4. Oxazoline-Assisted Cyclization and Formal Synthesis of 1

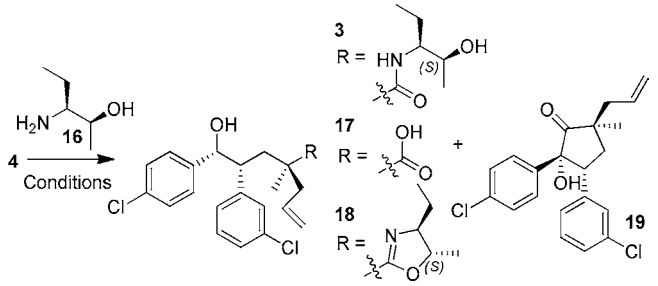


necessary amide **12** was obtained in quantitative yield by simply heating **4** with commercially available (*S*)-(+)-2-amino-1-butanol. Treatment of **12** with triflic anhydride and 2,6 lutidine at −78 °C resulted in the rapid formation of the desired bicylic iminium ether **13** upon warming past −50 °C.[14] Analysis of the reaction performed with substoichiometric amounts of triflic anhydride or less active sulfonylating agents such as nosylfluoride show that oxazoline **14** is formed first. Addition of a second equivalent of triflic anhydride activates the benzylic alcohol to nucleophilic displacement with inversion by the oxazoline nitrogen. The resulting iminium ether triflate salt **13** is stable to chromatography but is typically hydrolyzed with aqueous base to the piperidinone **15**. At this point, due to the amplification of er afforded by the covalent linking of two highly enantioenriched fragments, the product **15** was obtained as essentially enantiopure after silica gel chromatography.[15] AM-8553 (**1**) can be obtained from compound **15** in 4 steps according to our previously published route, completing a formal synthesis of AM-8553 (**1**) in 13 steps and 23% overall yield.

Next, we sought to expand our synthetic route to obtain the entirety of the side chain of **1** from a 3-amino-2-pentanol building block. However, as the configuration of the secondary hydroxyl in the side chain of **1** was originally obtained via a substrate-directed ketone reduction using L-Selectride, the stereochemistry was uncertain. Thus, we devised a sequence to afford both possible diastereomers from a single amino alcohol of known configuration, (2*S*,3*S*)-3-aminopentan-2-ol **16**.[16,17] We hoped that an understanding of the reaction mechanism of the lactam-forming sequence would serve to elucidate the absolute configuration of the side chain in **1**.

Contrary to the relative ease with which 2-amino-1-butanol opened the lactone **4** with simple heating, the freebase of (2*S*,3*S*)-3-aminopentan-2-ol (**16**) required extended reaction times and did not surpass 50% conversion even after 5 days at 100 °C (table 1). Addition of sodium hydride to a THF solution of **16** prior to the addition of lactone **4** rapidly yielded the product **3** in an optimized 78% yield, however, extreme care must be taken to minimize adventitious water that leads to significant formation of seco-acid **17**. Moving to a strong anhydrous base such as *n*-butyllithium likewise greatly accelerated the rate of reaction, but promoted a competitive ring contraction to afford ketone **19**. Treatment of lactone **4** with a strong, non-nucleophilic base such as LiHMDS in the absence of amino alcohol **16** could effect this rearrangement in reasonable yields.[18] The most practical synthesis of **3** was achieved by heating lactone **4** directly with the hydrochloride salt of **16** using triethylamine as base for 4 days at 100 °C, a process which required no freebasing of **16** and was highly reproducible.

Table 1. Opening of Lactone 4 under Various Conditions; All Yields Are Isolated except Where Noted



base	equiv **16**	*t*	*T* °C	**3** (%)	**17** (%)	**18** (%)	**4** (%)	**19** (%)
none	3	5 d	100	<50[a]				
6 equiv Et_3N	3[b]	4 d	100	76	2.5	3.2		
3.1 equiv NaH	1.5	0.5 h	23	78	12			
2.8 equiv *n*-BuLi	1.5	1 h	0−23	47			16	18
1.2 equiv Li-HMDS	0	14 h	23−30					68

[a]Not isolated. [b]HCl salt of **16** was used.

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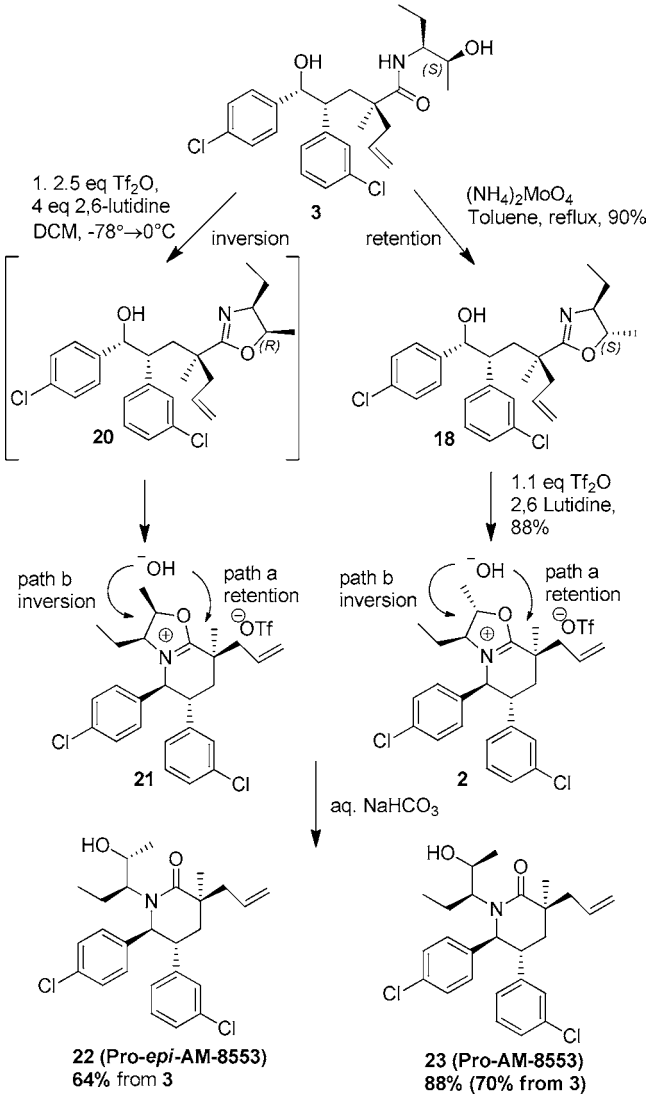
When amide **3** was subjected to triflic anhydride and 2,6 lutidine, (Scheme 5) the intermediate oxazoline **20** was formed

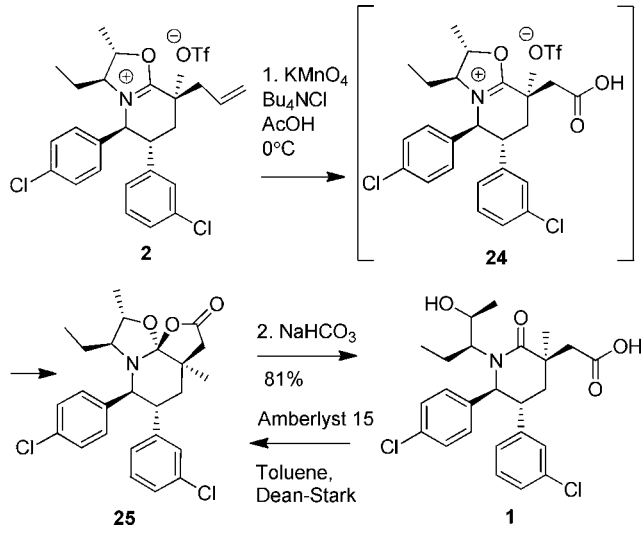
Scheme 5. Oxazoline-Assisted Cyclization Utilizing 2° Hydroxyl Amino Alcohols



with inversion of stereochemistry[19] (*vide infra*) at the secondary hydroxyl prior to the second cyclization to form iminium ether **21**. Upon basic hydrolysis of **21**, the undesired epimer **22** was obtained exclusively. Alternatively, formation of oxazoline **18** by azeotropic dehydration in the presence of a catalytic amount of $(NH_4)_2MoO_4$[20] occurs with retention of stereochemistry. Activation of the benzylic alcohol in **18** with triflic anhydride/2,6-lutidine afforded iminium ether **2** and desired piperidinone **23** upon hydrolysis.

To complete our synthesis of **1**, only an oxidative cleavage of the allyl group in **23** was formally required. We had anticipated having to employ a hydroxyl protecting group or other multistep sequence to avoid concomitant oxidation of the side chain in **23** to arrive at **1**. However, we ultimately chose to investigate the possibility of leveraging the iminium ether for this purpose and directly oxidize **2** to afford **1** after hydrolysis as shown in Scheme 6. By subjecting iminium ether **2** to $KMnO_4$ oxidation, we expected to observe intermediate **24** en route to **1**. However, the spectral characteristics[21] of a purified aliquot

Scheme 6. Bicyclic Iminium Ether 2 As a Hydroxyl Protecting Group and the Synthesis of 1



suggest structure **25** instead, where the newly formed carboxylic acid moiety has trapped the iminium ether. Hydrolysis of the crude oxidation product **25** with sodium bicarbonate afforded **1** in 81% overall yield. The readily hydrolyzed adduct **25** can be regenerated from **1** in the presence of acid.

With an expeditious and high-yielding (11 steps, 35.6% overall yield) approach to **1** accomplished, we turned our attention to determining the absolute stereochemistry of the side-chain hydroxyl in **1**. While the stereochemical outcome of the two oxazoline-forming protocols in Scheme 5 was confirmed by NOE studies on iminium ethers **21** and **2**, a detailed understanding of the mechanism of iminium ether hydrolysis was necessary to address the ambiguity of the absolute stereochemistry of hydrolysis products **22** and **23**, and ultimately, **1**. Aubé and co-workers have previously dealt with the ambident electrophilicity of these systems,[22] and they found through the use of ^{18}O-labeling studies that hydroxide would be expected to react via path A (retention), whereas nucleophiles such as azide, cyanide, and benzenethiolate should react via path B (inversion) (Scheme 5). However, the sterically encumbered nature of our bicyclic iminium ether system[23] warranted confirmation of these results.

Two ^{18}O-labeling experiments were performed as shown in Scheme 7. Ring-opening of 50% ^{18}O-labeled lactone **4** (see Supporting Information) with (*S*,*S*)-amino alcohol **16** led to 50% labeled amide **3**. When amide **3** was treated with triflic anhydride/2,6-lutidine to form iminium ether **21** and then hydrolyzed with unlabeled water, the ^{18}O was transferred from the carbonyl carbon of **3** to the hydroxyl position of **22** as evidenced by an additional upfield signal at ~71.1 ppm in the ^{13}C NMR.[24] Separately, unlabeled intermediate **21** was hydrolyzed with ~50% ^{18}O-labeled aqueous $NaHCO_3$ solution, and in this case the label was clearly incorporated at the carbonyl position of **22** (178.6 ppm). These results led us to conclude that configuration of the side-chain hydroxyl is inverted only once during the course of this sequence (oxazoline formation) and the absolute configuration of undesired epimer **22** is *R*. Subsequently, a small-molecule crystal structure of compound **22** (Figure 3) confirmed our assignment by this method.[25]

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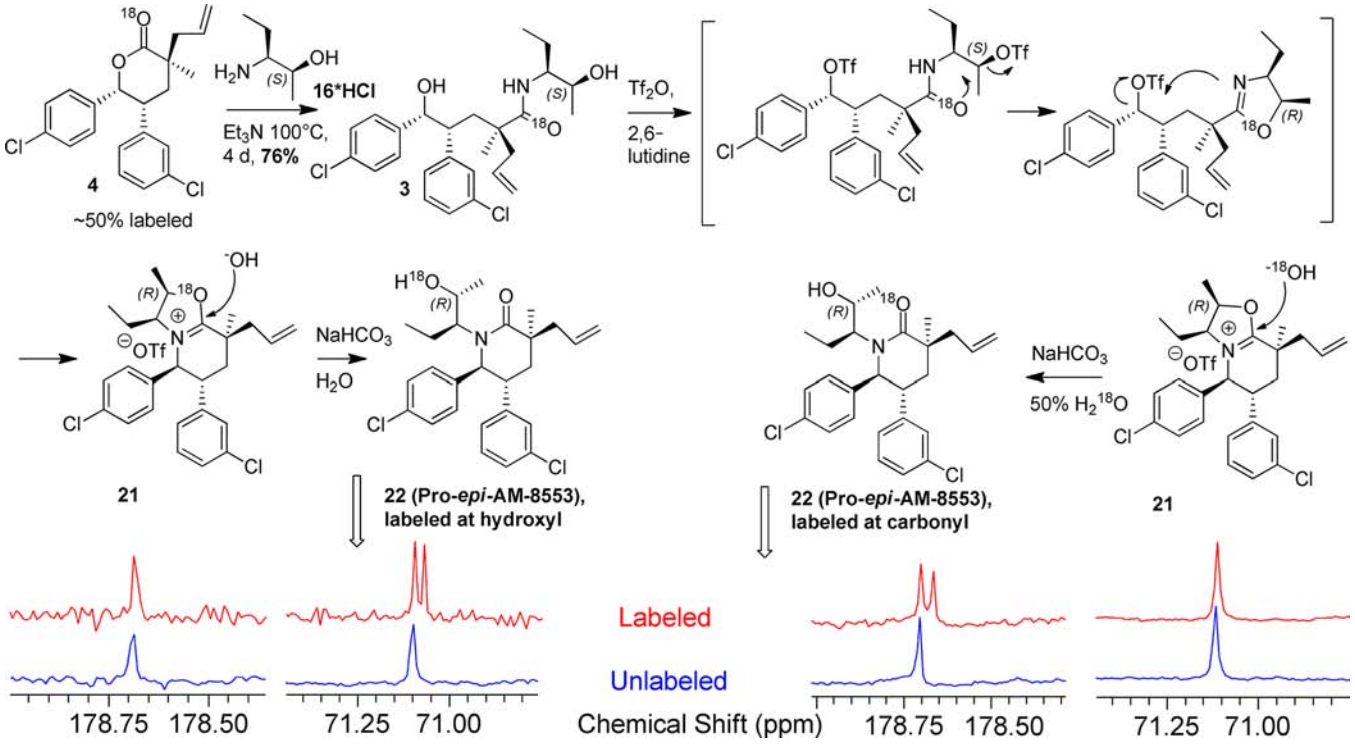
Scheme 7. ^{18}O-Labeling Studies To Determine Stereochemical Outcome of the Iminium Ether Formation and Hydrolysis



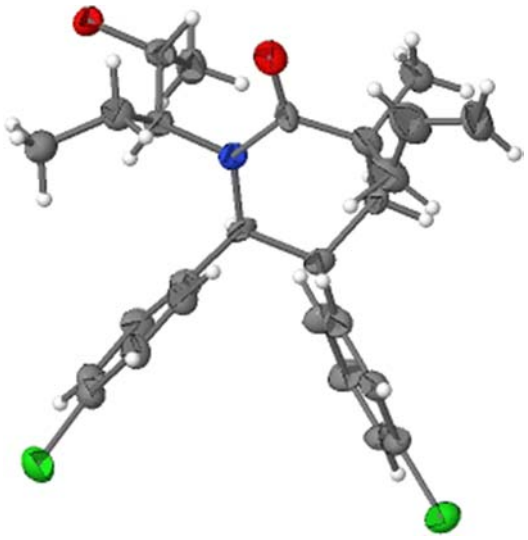


Figure 3. Crystal Structure of **22**.

CONCLUSION

The densely functionalized and stereochemically rich piperidinone AM-8553 necessitated the development of a high-yielding synthetic approach to evaluate this biologically intriguing molecule. An enantio- and diastereo-selective DKR was used to set the relative and absolute stereochemistry of the aryl groups of a δ-lactone, which in turn was used to effect the highly diastereoselective installation of the quaternary center at C3. The lactone was opened to an intermediate amide that underwent a facile double-cyclization to afford a key bicyclic iminium ether that, when hydrolyzed, led to the desired lactam core with all five stereogenic centers correctly set. An understanding of the mechanism of iminium ether formation and hydrolysis was used to elucidate the stereochemistry of the side chain of AM-8553. The iminium ether was also shown to be a competent alcohol protecting group that was stable to oxidative conditions to complete an 11-step synthetic route to AM-8553 in 35.6% overall yield. We expect to describe the large-scale application of this iminium ether lactam synthesis in due course.

ASSOCIATED CONTENT

Supporting Information

Detailed synthetic procedures, characterization data, and images of ^{1}H and ^{13}C spectra for compounds **1**–**5**, **7**–**15**, **18**–**19**, **21**–**23**, and **25**; syntheses and ^{13}C spectra of ^{18}O-labeled **3**, **4**, **21**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) The product is a ∼60:40 mixture of methyl epimers. The average er is 96:4. See Supporting Information for specific dr and er data.

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(14) The entire sequence can be run at −50 °C with comparable results. The reactions are typically warmed to 0 °C to avoid freezing of the aqueous quench.

(15) The minor diastereomers formed from the combination of lactone **4** and commerically available >97% ee S-2-amino-1-butanol are readily separable from **15** using hexanes /ethyl acetate chromatography ($\Delta R_f \approx 0.2$). Assuming no diastereoselection, the combination of 96:4 er lactone **4** and 98.5:1.5 er S-2-amino-1-butanol should afford **15** with >99.94:0.06 er.

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(21) The bicyclic iminium ethers **2**, **13**, and **21** exhibit several diagnostic spectral features: A characteristic downfield shift (∼1 ppm) for protons close to the positively charged nitrogen in ^{1}H NMR, a ∼180 ppm ^{13}C signal for the quaternary iminium ether carbon, and an IR stretch at ∼1610−1650 cm^{-1}. The product of the oxidation (**25**) exhibits no large downfield shifts in ^{1}H NMR, a single quaternary ^{13}C signal at 172.5 ppm and an additional quaternary ^{13}C signal at 122.6 ppm. A single strong C═O stretch at 1776 cm^{-1} in the IR spectrum is indicative of a five-membered ring lactone (see Hall, H. K.; Zbinden, R. J. *Am. Chem. Soc.* **1958**, *80*, 6428).

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(23) The significant difference in the observed rate of hydrolysis of the iminium ethers **2** and **21** derived from 2° alcohols when compared to **13** (from 1° alcohol) led us to suspect involvement of path b.

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(25) Single crystal X-ray diffraction data for compound **22** were collected using copper radiation. Structure determination of **22** was initiated in space group $P2_12_12_1$ as indicated from the observed metric constants, intensity statistics, and systematic absences. Subsequent structure solution and refinement confirmed the choice of space group (a = 10.4852(9) Å, b = 13.3205(11) Å, c = 17.2875(17) Å; V = 2414.5(4) Å^3, Z = 4, R = 6.6%). All non-hydrogen atoms were refined using anisotropic displacement parameters. Hydrogen atoms were placed in calculated positions. The Flack parameter showed a value very close to zero (0.02 (3)), indicating the correctness of the absolute structure (assignment of the hydroxyl center being (*R*)). As a further check, least-squares refinement was carried out on the epimeric structure (*S*, **23**), but a much higher *R*-factor (7.7%) was obtained with an unsatisfactory Flack parameter value (0.96(3)).