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A concise synthesis of AG5473/5507 utilizing *N*-acyliminium ion chemistry

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Abstract

FKBP-12 inhibitors AG5473 and AG5507 were resynthesized through a more efficient 11-step sequence. The key steps involved propargyl trimethylsilane addition to an *N*-acyliminium ion, ozonolysis of the allene and acid-catalyzed cyclization. A mild protocol for introducing a formaldehyde moiety to an anomeric center was established. The synthetic materials were evaluated in the FKBP rotamase assay.

Immunosuppressants, such as FK506, rapamycin and cyclosporin A (CsA), have attracted intensive research interest from the late 1980s to early 1990s.[1] Hundreds of small molecules were designed and synthesized to inhibit FKBP-12, the FK506 binding protein. These compounds were studied biologically and aimed at understanding the mechanism of the immunologic effect of FK506 and searching for better immunosuppressive drugs.[2] Both FKBP-12 and cyclophilin (CsA binding protein) possess a PPIase (*cis–trans* peptidyl-prolyl isomerase or rotamase) domain. However, inhibition of the catalytic isomerization activity is not directly related to immunosuppression (Scheme 1).[2] Instead, the 'effector region' plays an important role by interacting with calcineurin, a downstream target. In 1994, Soloman Snyder's group[3] and Bruce Gold's group[4] reported independently that FK506 and rapamycin can promote neurite outgrowth in PC-12 cells and in rat sensory ganglia at very low concentration (1–10 nM). These findings immediately drew significant attention and renewed research enthusiasm in the FKBP-12 inhibitors, some of which have the potential to penetrate the brain–blood barrier.[5]

In our previous immunophilin program, a class of polycyclic azamides was found to inhibit the isomerization activity of FKBP-12. AG5473 and AG5507 were among the more potent inhibitors selected for resynthesis and evaluation of their nerve regeneration activity. The original synthetic route for AG5473/5507 requires 20 steps including several low yielding reactions.[6] To prepare

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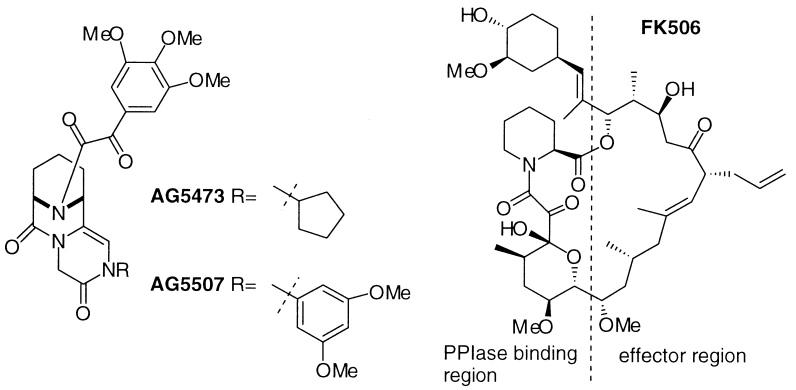
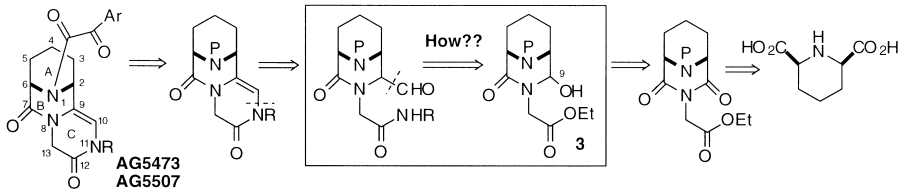


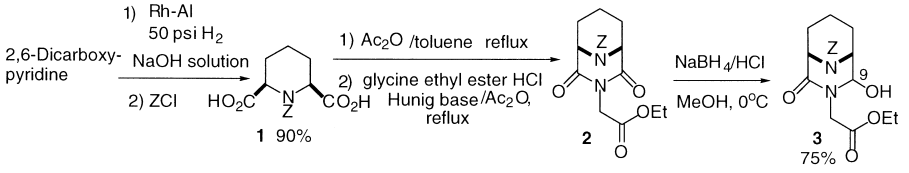
Scheme 1.

sufficient material for neurite outgrowth assays in a timely fashion, we decided to pursue a more efficient synthesis. As shown in Scheme 2, introduction of an aldehyde moiety to C-9 is the key for constructing the dihydropyrizinone ring C. A variety of reactions can be tested on the aminal **3** in order to achieve the desired carbonyl homologation.



Scheme 2.

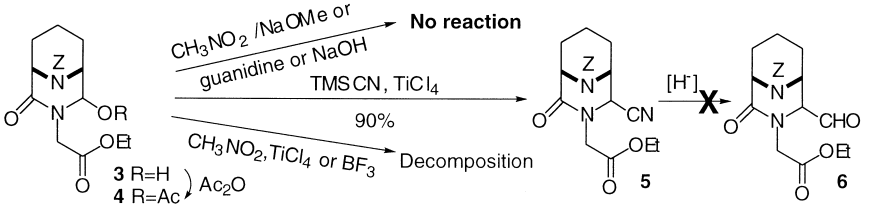
In the event, commercially available 2,6-dicarboxypyridine was hydrogenated and quenched with CBzCl, affording *N*–*Z*-piperidine-*cis*-2,6-dicarboxylic acid **1** in 90% yield (Scheme 3).[7] The reduction was performed under a 50 psi H_2 atmosphere in the presence of rhodium on aluminum.[8] Dehydration of dicarboxylic acid **1** provided a cyclic acid anhydride, which was condensed in situ with glycine ethyl ester. The crude acetamide **2** was subsequently treated with $NaBH_4$ in cold acidic methanol, leading to the key aminal **3** in 75% yield from **1**.



Scheme 3.

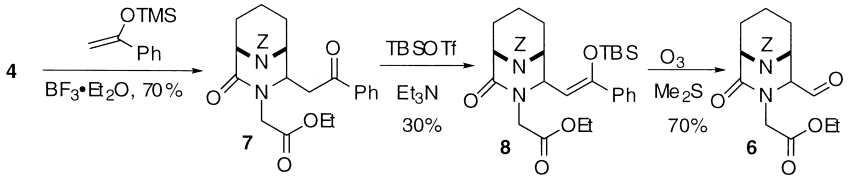
In our efforts to introduce an aldehyde equivalent, addition of nitromethane to C-9 in **3** was first examined (Scheme 4). Nitromethane was proven unreactive towards the acylaminal **3** under either basic[9] or neutral[10] conditions. Attempts involving acid or Lewis acid to generate a reactive

N-acyliminium ion only caused slow decomposition. In methylene chloride, the *N*-acyliminium ion promoted by $TiCl_4$ smoothly reacted with TMSCN to yield the cyano adduct **5** (90%). However, efforts to reduce the nitrile to aldehyde **6** were fruitless. We then screened conditions for intermolecular addition of vinyl trimethylsilane to *N*-acyliminium ion, inspired by Heitz and Overman's work in their indolizidine synthesis.[11] Catalysts such as $TiCl_4$, $BF_3{\cdot}Et_2O$ and TFA were tested. Since initial trials on aminal **3** were discouraging, the starting material **3** was converted into more reactive acetoxyamide **4**.[12] No reaction was observed even with excess vinyl trimethylsilane at elevated temperature (~70°C).



Scheme 4.

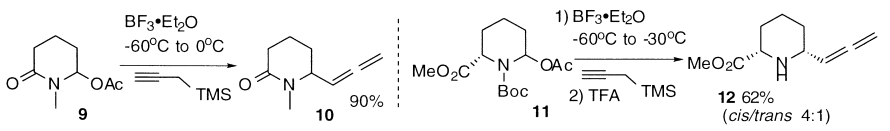
To evaluate the reactivity of the *N*-acyliminium ion, nucleophile 1-phenyl-1-(trimethyl-silyloxy)-ethylene was tested. Upon treatment with $BF_3{\cdot}Et_2O$, the corresponding adduct **7** was obtained in good yield (70%).[15] Attempts to transform the phenyl ketone (**7**) into aldehyde via re-enolation (**8**) and ozonization (**9**) were somewhat encouraging (21% for two steps, Scheme 5).



Scheme 5.

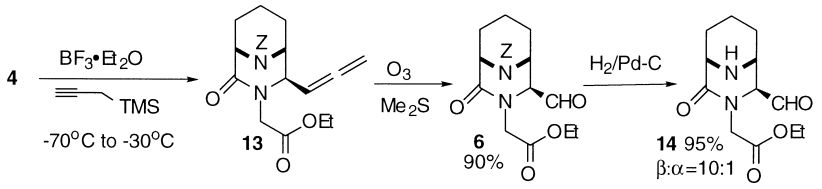
The three-step sequence was not adopted because it is intrinsically lengthy and low yielding. Still the partial success led to further investigation into the use of other nucleophiles for *N*-acyliminium ion trapping. Among them, propargyl trimethylsilane[13] is more attractive because the expected adduct may be ozonized to the desired aldehyde.

In our model study, both cyclic (**9**) and acyclic (**11**) acyliminium ion underwent the allene addition in good yield (Scheme 6). To our delight, the propargyl trimethylsilane addition to acetoxyamide **4** gave the desired allene **13**, which underwent smooth ozonolysis[14] to the aldehyde



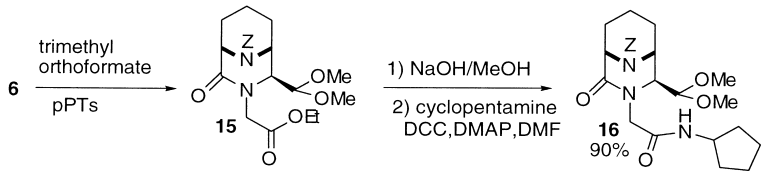
Scheme 6.

6 in excellent yield (90% for two steps, Scheme 7). The CBz group was removed by hydrogenation in order to avoid rotameric effect and thereby simplify stereochemical analysis. By ^{1}H NMR, the ratio of β:α aldehydes was 10:1,[15] suggesting that the nucleophilic propargyl prefers to approach from the more open β-face.



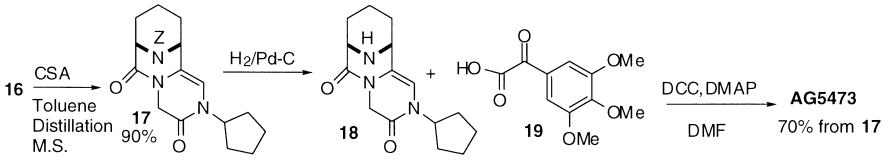
Scheme 7.

After the aldehyde (**6**) was protected as its dimethylacetal (**15**, Scheme 8), the ethyl ester was hydrolyzed. The resulting carboxylic acid was coupled with cyclopentamine in the presence of DCC/DMAP yielding the key amide **16** without isolation of intermediates (90% for three steps).



Scheme 8.

In order to furnish the dihydropyrizinone ring (C), acid-catalyzed condensation was tested. No reaction occurred with weaker acids such as pPTs, while the starting materials decomposed upon treatment of TFA. In the presence of (±)-camphor sulfonic acid (CSA), the cyclization was so sluggish that only 15% of the desired tricyclic product was obtained after prolonged reflux in toluene (48 h). Fortunately, removal of the by-product MeOH by 4 Å molecular sieve drove the cyclization to completion (90% yield, Scheme 9). The final steps, involving hydrogenation (**18**)[16] and amide formation, were uneventful to provide AG5473 in 70% yield. Analog AG5507 was also synthesized in a similar manner from the common intermediate **6**.



Scheme 9.

In summary, polycyclic azamides were prepared via an 11-step sequence. An efficient protocol for introducing an aldehyde moiety was established so that the tricyclic diazamide core can be assembled concisely. The synthetic materials were tested in FKBP-12 rotamase assay, and binding constants (Ki) for AG5473 and 5507 were found to be 84 nM and 54 nM, respectively. Further study on the nerve regeneration and protection effects of these compounds is ongoing.

Acknowledgements

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7. All compounds were characterized by satisfying proton NMR, MS and HRMS. Carbon-13 NMR spectra of some of the compounds were also recorded when necessary for structure assignment.
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12. Upon scale-up, intermediate **4** was prepared from crude **3** in quantitative yield. No purification is necessary for transformations from **1** to **4** besides routine workups.
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15. Although the stereochemistry of **6** was assigned by NOE experiments on **14β** (major), it is not crucial for our synthesis of the targets.
16. Resolution of the two enantiomers of the amines similar to **18** is being actively pursued.