

# Stereoselective Construction of the 5-Hydroxy Diazabicyclo[4.3.1]decane-2-one Scaffold, a Privileged Motif for FK506-Binding Proteins

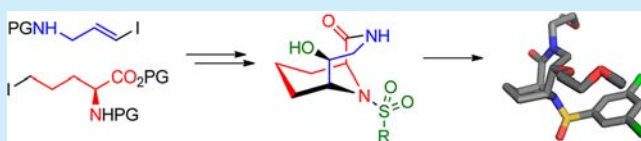
Matthias Bischoff,<sup>†</sup> Claudia Sippel,<sup>†</sup> Andreas Bracher,<sup>‡</sup> and Felix Hausch\*<sup>†</sup>

<sup>†</sup>Max Planck Institute of Psychiatry, Kraepelinstr. 2, 80804 München, Germany

<sup>‡</sup>Max Planck Institute of Biochemistry, Am Klopferspitz 18, 82152 Martinsried, Germany

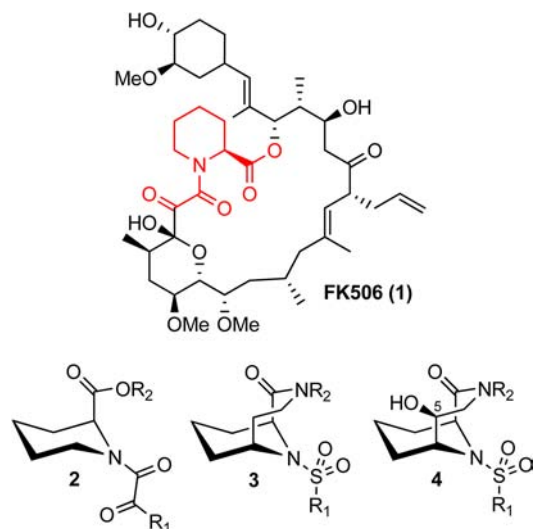
**S** Supporting Information

**ABSTRACT:** A stereoselective synthesis of a derivatized bicyclic [4.3.1]decane scaffold based on an acyclic precursor is described. The key steps involve a Pd-catalyzed  $sp^3$ – $sp^2$  Negishi-coupling, an asymmetric Shi epoxidation, and an intramolecular epoxide opening. Representative derivatives of this novel scaffold were synthesized and found to be potent inhibitors of the psychiatric risk factor FKBP51, which bound to FKBP51 with the intended molecular binding mode.



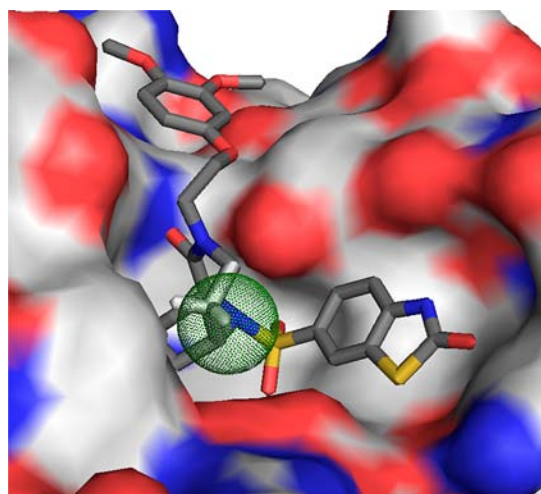
FK506-binding proteins (FKBPs) bind to the natural products FK506 and rapamycin and enable their immunosuppressive properties.<sup>1</sup> In addition, these proteins have emerged as potential targets for neurodegenerative or psychiatric disorders.<sup>2</sup>

In the course of our ongoing effort toward the rational structure-based design of novel, drug-like ligands for FKBPs,<sup>3</sup> we have recently identified [4.3.1] bicyclic sulfonyl aza-amides **3** as a privileged, conformationally preorganized class of FKBP ligands that have substantially improved ligand efficiencies compared to FK506 or monocyclic analogs thereof such as **2** (Figure 1).<sup>3f</sup>



**Figure 1.** FK506 (**1**), monocyclic **2**, and bioisosteric, bicyclic [4.3.1] scaffolds **3** and **4** derived thereof.

To further optimize the [4.3.1] scaffold, we first analyzed the cocrystal structure of ligands from type **3** in complex with FKBP51 (Figure 2).



**Figure 2.** Cocrystal structure of a representative [4.3.1] bicycle **3** in complex with the FK506-binding domain of FKBP51.<sup>3f,4</sup>

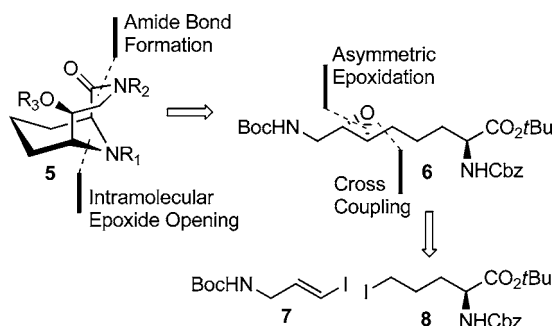
This revealed that a polar substituent in the pro-S configuration at the C-5 position (**4**, Figure 1) such as a hydroxyl group would fit into the binding pocket and might further improve the affinity through additional contacts with the protein. We therefore set out for a stereoselective route to 5-OH substituted diazabicyclo[4.3.1]decane-2-ones, taking orthogonal protecting groups for the amino and hydroxyl functionalities ( $R_1$ ,  $R_3$ ) into account in order to have three

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independent attachment points for subsequent chemical derivatization (Scheme 1).

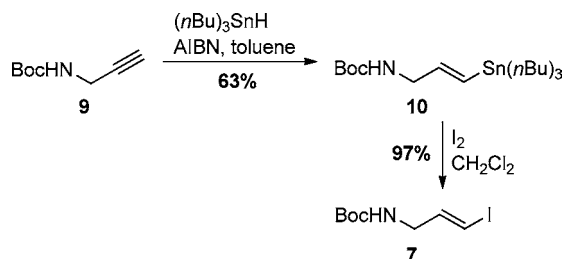
### Scheme 1. Retrosynthesis of the 5-OH Substituted Diazabicyclo[4.3.1]decane-2-one Motif 5



The retrosynthetic analysis of **5** (Scheme 1) can be traced back to a vinyl iodide building block **7** and the  $\delta$ -iodinated amino acid derivative **8**, which were intended for a Pd-catalyzed cross-coupling reaction. An asymmetric epoxidation of the resulting alkene with subsequent intramolecular epoxide opening of **6** would then pave the way for the 2,6-*cis*-substituted piperidine with the required *S* configuration of the hydroxyl substituent. Finally, an intramolecular lactamization would lead to the target core structure **5**.

Toward the building block **7**, *N*-Boc-propargylamine (**9**) was hydrostannylated to give the corresponding vinyl stannane as an *E/Z* mixture of **6:1** (Scheme 2). The desired *E*-isomer **10** could be separated by column chromatography in 63% yield. Iododestannylation then furnished vinyl iodide **7** in 97% yield.<sup>5</sup>

### Scheme 2. Synthesis of Vinyl Iodide Building Block 7

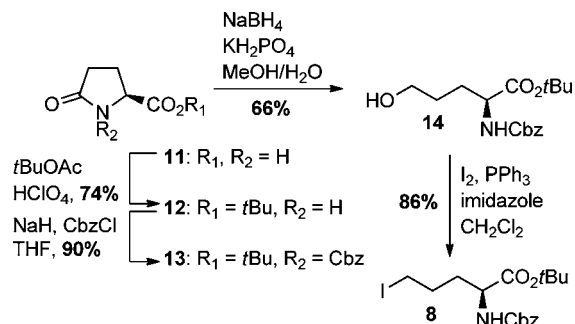


For the synthesis of the second building block *L*-pyroglutamic acid (**11**) was first protected at the carboxyl group as *tert*-butyl ester and then protected at the amide function using NaH and CbzCl to give **13** according to known procedures (Scheme 3).<sup>6</sup> A chemoselective reduction of the amide carbonyl group to alcohol **14** employing NaBH<sub>4</sub> in MeOH, EtOH, or *t*BuOH as solvent afforded **14** only in poor yields accompanied by the respective ester as a side product. The use of KH<sub>2</sub>PO<sub>4</sub> as a buffer in a MeOH/H<sub>2</sub>O solvent mixture proved to be an effective method for a clean conversion to the alcohol in 66% yield.<sup>7</sup> A final Appel reaction under standard conditions provided **8** in 86% yield.<sup>8</sup>

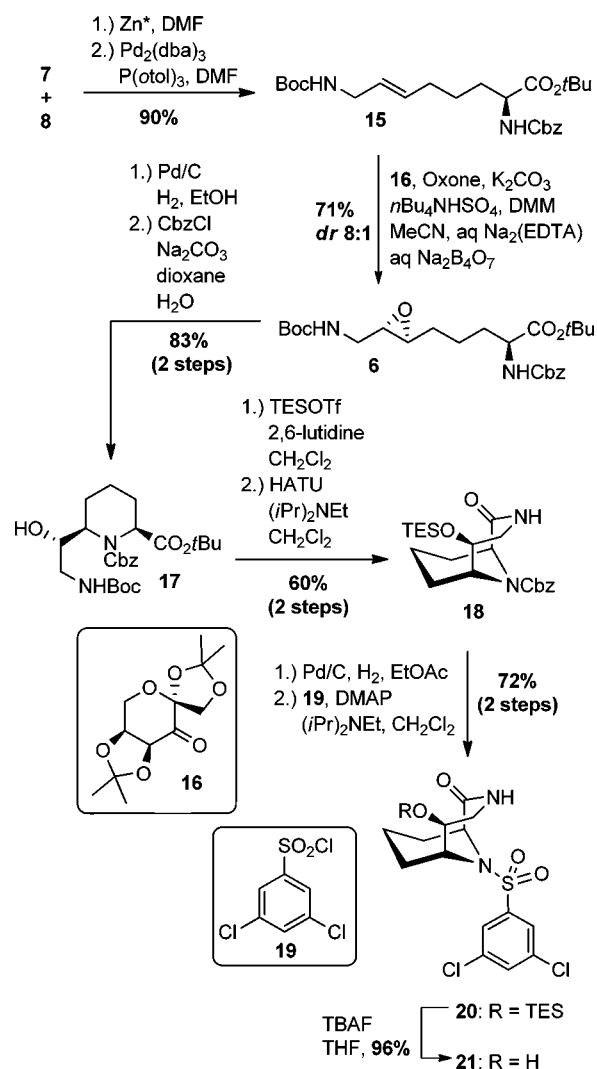
With these two building blocks in hand we were pleased that the Pd-catalyzed sp<sup>3</sup>-sp<sup>2</sup> Negishi coupling between the amino acid derived organozinc compound prepared in situ from **8** and vinyl iodide **7** proceeded in excellent yield (Scheme 4).<sup>9</sup>

The resulting alkene **15** was subjected to an asymmetric epoxidation by using the *L*-fructose-derived Shi ketone<sup>10</sup> **16**,

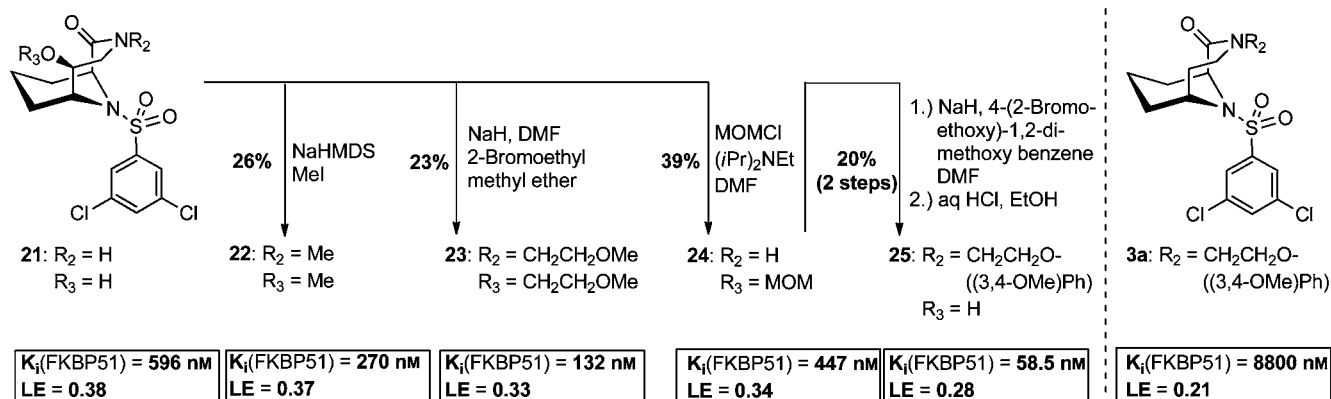
### Scheme 3. Synthesis of Alkyl Iodide Building Block 8



### Scheme 4. Synthesis of the 5-OH Substituted Diazabicyclo[4.3.1]decane-2-one Scaffold



which was synthesized in five steps from *L*-sorbose,<sup>11</sup> providing the epoxide **6** in good yield and diastereomeric excess of 8:1. Hydrogenolysis of the Cbz-group triggered 6-*exo*-trig cyclization to the *cis*-piperidine core, which was directly reprotected with CbzCl to afford **17** in 83% yield. At this point it was possible to separate the diastereomerically pure compound from the minor diastereomer formed in the epoxidation step. In order to set the stage for the intramolecular lactamization it was necessary to protect the hydroxyl group in **17** and to deprotect the amino and carboxyl group. Initial attempts involved TBS

Scheme 5. Synthesis and  $K_i$ -Values of Representative Derivatives 21–25 and Unsubstituted Bicycle 3a

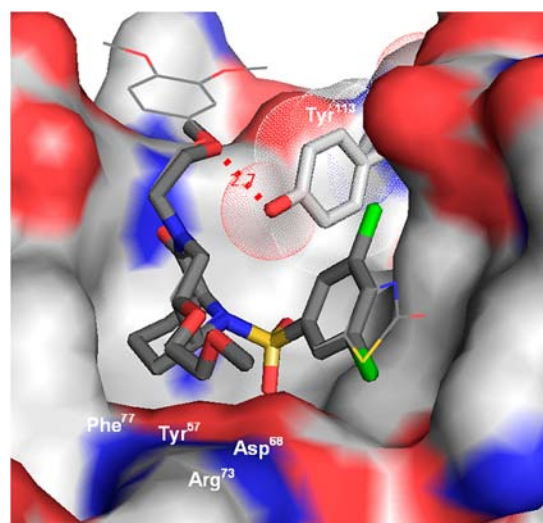
protection of the hydroxyl group and subsequent acidic deprotection of the Boc- and *t*Bu-groups. However, it turned out that the acid could not be released without concomitant cleavage of the silyl ether. Eventually, it was found that the hydroxyl group could be protected with simultaneous deprotection of the Boc- and *t*Bu-groups in a single step, by employing excess TESOTf and 2,6-lutidine.<sup>12</sup> The so formed amino acid was then cyclized under high dilution conditions ( $5 \times 10^{-3} \text{ M}$ ) using HATU to afford the orthogonally protected bicycle **18** in 60% yield over two steps. Finally, to elaborate the core structure of the bicycle, the Cbz-group was cleaved and the 3,5-dichlorobenzenesulfonyl moiety was introduced as an exemplary sulfonamide which had previously shown superior affinity for FKBP51.<sup>3e,f</sup> Subsequently, the TES-group was cleaved with TBAF to give **21** in a 70% overall yield over three steps.

With the core structure **21** in hand we tested its binding affinity to the FK506-binding protein 51, a promising novel target for stress-related disorders. Using a fluorescence polarization assay<sup>3a</sup> we were pleased to observe an affinity of 596 nM, making **21** the most efficient FKBP51 ligand known so far.<sup>13</sup>

To further explore the binding properties of the novel scaffold in more detail we prepared representative derivatives. Compound **21** was reacted with NaHMDS and iodomethane to give the N,O-dimethylated derivative **22** accompanied by an inseparable mixture of the two respective monomethylated products (Scheme 5). Likewise, alkylation of **21** with 2-bromoethyl methyl ether afforded the bis-alkylated derivative **23**. We also installed a 2-(3,4-dimethoxyphenoxy)ethyl subunit, a preferred  $R_2$  substituent for FKBP51, to allow a direct comparison between type 3 and type 4 bicyclic ligands (Figure 1). Toward this end, alcohol **21** was MOM-protected to give **24** followed by alkylation with 4-(2-bromoethoxy)-1,2-dimethoxybenzene and acidic cleavage of the protecting group to give **25**. Compounds **22** to **25** all potently bound to FKBP51, with **25** exceeding the affinity of the prototypical FKBP ligand FK506 ( $K_i(\text{FKBP51}) = 104 \text{ nM}$ ,  $\text{LE} = 0.17$ ).<sup>3a</sup> Compound **25** also allows a direct comparison with a corresponding unsubstituted analog **3a**,<sup>3f</sup> which shows that the additional hydroxyl group in the C5-position, enabled by the new synthetic approach, enhances the affinity for FKBP51 by more than 100-fold.

To determine the molecular binding mode of the novel FKBP ligands we solved the cocrystal structure of **23** with the FK506-binding domain of FKBP51 at a resolution of 1.0 Å.<sup>3b,14</sup> The [4.3.1] bicyclic core nearly perfectly superimposed with

corresponding atoms of the precursor scaffold **3** (Figure 3). The *N*-methoxyethyl substituent of **23** closely mimicked the



**Figure 3.** Cocrystal structure of **23** in complex with the FK506-binding domain of FKBP51. The position of a superimposed unsubstituted [4.3.1] bicycle **3** from Figure 2 is indicated as thin lines.<sup>4</sup>

conformation of the larger (dimethoxyphenoxy)ethyl residue in **3** and serves as a hydrogen bond acceptor for Tyr<sup>113</sup>. The additional *O*-methoxyethyl substituent of **23** extends in a staggered/*gauche* conformation and engages in van der Waals interactions with Tyr<sup>57</sup>, Asp<sup>68</sup>, Arg<sup>73</sup>, and Phe<sup>77</sup>.

In summary, we have developed a concise and stereoselective procedure for the construction of the C5-hydroxy derivatized diazabicyclo[4.3.1]decane-2-one scaffold. Additional substituents in the 5-position substantially enhance affinity and ligand efficiency for FKBP51.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, spectroscopic data, and NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [hausch@mpipsykl.mpg.de](mailto:hausch@mpipsykl.mpg.de).

## Notes

The authors declare the following competing financial interest(s): M.B., A.B., and F.H. have filed patent applications on FKBP inhibitors.

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- (14) Diffraction data and coordinates are available through the wwPDB under accession code 4TX0.