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Structure−Activity Relationship Study of Ionotropic Glutamate Receptor Antagonist (2*S*,3*R*)-3-(3-Carboxyphenyl)pyrrolidine-2-carboxylic Acid

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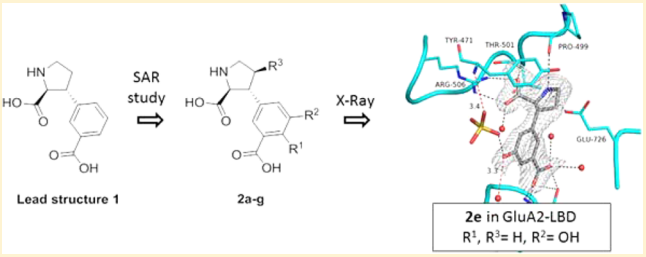
Supporting Information

ABSTRACT: Herein we describe the first structure−activity relationship study of the broad-range iGluR antagonist (2*S*,3*R*)-3-(3-carboxyphenyl)pyrrolidine-2-carboxylic acid (**1**) by exploring the pharmacological effect of substituents in the 4, 4′, or 5′ positions and the bioisosteric substitution of the distal carboxylic acid for a phosphonic acid moiety. Of particular interest is a hydroxyl group in the 4′ position **2a** which induced a preference in binding affinity for homomeric GluK3 over GluK1 (K_i = 0.87 and 4.8 μM, respectively). Two X-ray structures of ligand binding domains were obtained: **2e** in GluA2-LBD and **2f** in GluK1-LBD, both at 1.9 Å resolution. Compound **2e** induces a D1−D2 domain opening in GluA2-LBD of 17.3−18.8° and **2f** a domain opening in GluK1-LBD of 17.0−17.5° relative to the structures with glutamate. The pyrrolidine-2-carboxylate moiety of **2e** and **2f** shows a similar binding mode as kainate. The 3-carboxyphenyl ring of **2e** and **2f** forms contacts comparable to those of the distal carboxylate in kainate.



INTRODUCTION

In the mammalian central nervous system (CNS), (*S*)-glutamate (Glu) functions as the major excitatory neurotransmitter (Table 1).[1] The glutamatergic neurotransmitter system is involved in a vast number of basic neurophysiological processes such as memory and cognition as well as neuronal plasticity and development.[2−7] Thus, psychiatric diseases or neurological disorders such as depression,[8,9] anxiety,[10] addiction,[11] migraine,[12,13] and schizophrenia[14−16] may be directly related to disordered glutamatergic neurotransmission. Moreover, elevated synaptic Glu levels or excessive Glu signaling are neurotoxic and will ultimately cause neuronal death.[17−19] Thus, it is believed that neurodegenerative diseases such as Alzheimer's,[20−22] Huntington's,[23] amyotrophic lateral sclerosis (ALS),[24] cerebral stroke,[25] and epilepsy[26] may be due to malfunction of the glutamatergic neurotransmitter system, which may be overturned by action of small molecule Glu ligands.[1] Once released from the presynaptic neuron into the synapse, Glu activates a number of pre- and postsynaptic Glu receptors. On the basis of their pharmacological profile and ligand selectivity, the Glu receptors have been grouped in two main classes: the fast-acting ionotropic Glu receptors (iGluRs) comprising three groups, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (subunits GluA1−4), kainate (KA) receptors (subunits GluK1−5),[27] and *N*-methyl-D-aspartate (NMDA) receptors (subunits GluN1, GluN2A-D, and GluN3A,B),[28] and the G-protein coupled metabotropic Glu receptors (mGluRs, subunits mGluR1−8),[29] which produce a slower signal transduction through second messenger systems.

Summarizing the field of the iGluR antagonists (Table 1), AMPA/KA antagonists are well-known, as e.g., (*S*)-2-amino-3-[5-*tert*-butyl-3-(phosphonomethoxy)-4-isoxazolyl]propionic acid (ATPO)[31] and (*S*)-4-((3-(2-amino-2-carboxyethyl)-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)methyl)benzoic acid (UBP282).[32] In contrast, only subtype selective antagonists have been reported for GluK1, e.g., (3*S*,4a*R*,6*S*,8a*R*)-6-(((*S*)-2-carboxy-4,4-difluoropyrrolidin-1-yl)methyl)decahydroisoquinoline-3-carboxylic acid (LY466195)[13] and (*S*)-3-((3-(2-amino-2-carboxyethyl)-5-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2*H*)-yl)methyl)thiophene-2-carboxylic acid (UBP310).[30] Thus, there is a striking unmet need for the discovery of selective antagonists for the GluA1−4 and GluK2−5 subunits, as such compounds serve as pharmacological tools for studying the role and function of the iGluRs under both physiological and pathological conditions. On the basis of conformational analysis of known iGluR antagonists and the vast structural information on the GluA2-LBD and GluK1-LBD, (2*S*,3*R*)-3-(3-carboxyphenyl)pyrrolidine-2-carboxylic

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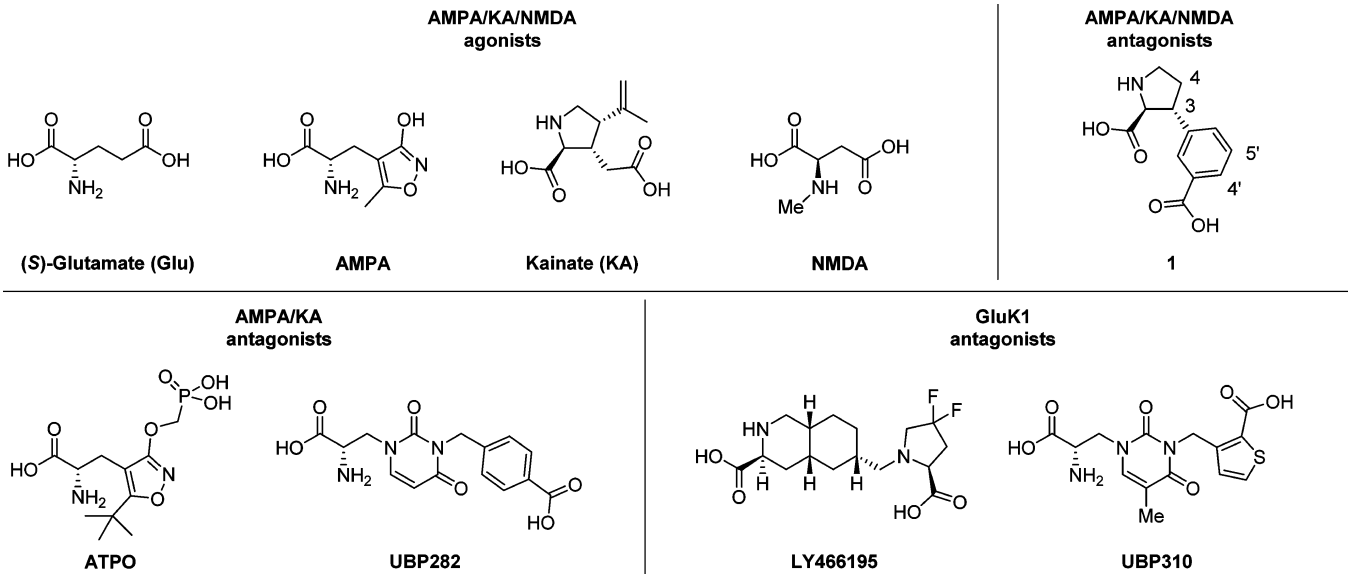
Table 1. Chemical Structures of Glu, iGluR Group-Defining Agonists AMPA, KA, and NMDA, Rationally Designed iGluR Antagonist 1, and Reported iGluR Antagonists (All Values in μM)



	native iGluRs (synaptosomes)			cloned homomeric iGluRs			
	AMPA IC_{50}	KA IC_{50}	NMDA K_i	GluA2 K_i	GluK1 K_i	GluK2 K_i	GluK3 K_i
1[a]	51	22	6.0	67	4.3	>100	8.1
ATPO	16[b]	>100[b]	>100[b]	60 ± 5	2.6 ± 0.4	>100	>1000
UBP282[c]	13	>200	--	--	9.25 (func)	>100	--
LY466195[d]	--	--	--	269	0.05	--	8.9
UBP310	--	--	--	>100	0.022 ± 0.005	>100	0.93 ± 0.12

[a]From ref 30. [b]From ref 31. [c]From ref 32. [d]From ref 13. Radioligands used for synaptosomal binding: AMPA, [^{3}H](*RS*)-AMPA; KA, [^{3}H]KA; NMDA, [^{3}H]CGP 39653. Recombinant receptor binding: presented are mean values ± SEM of at least three experiments, conducted in triplicate at 12−16 drug concentrations. Radioligands used: GluA2, [^{3}H](*RS*)-AMPA; GluK1−3, [^{3}H](2*S*,4*R*)-4-methyl Glu (SYM2081). Hill coefficients were not different from unity. --, not available.

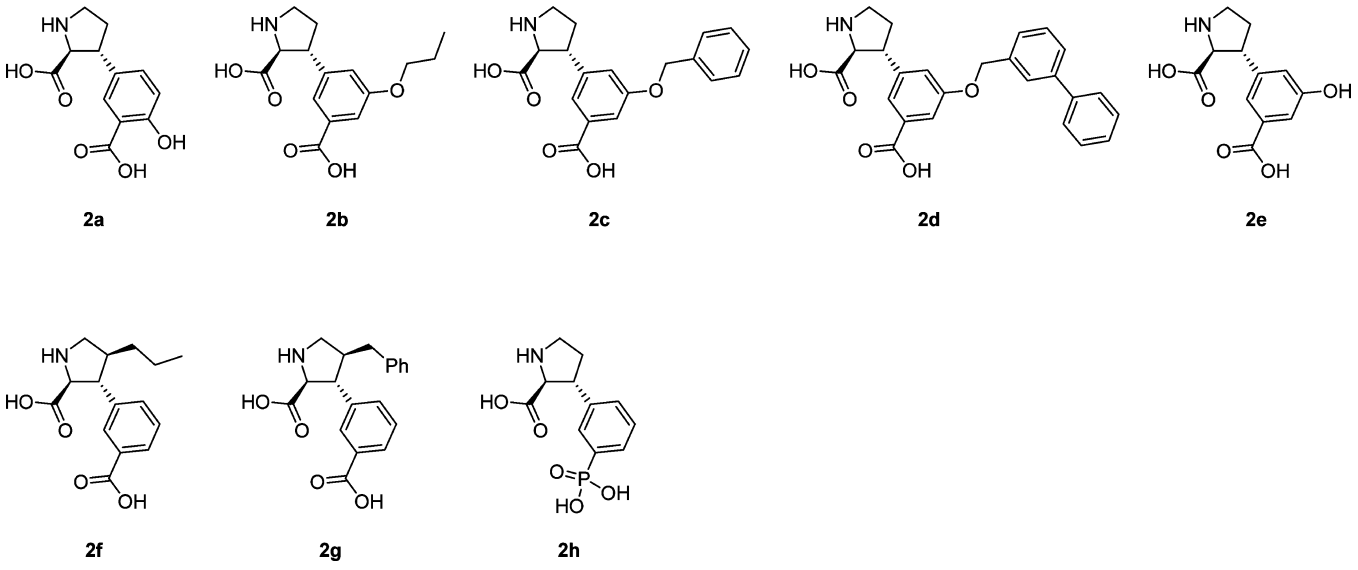


Figure 1. Chemical structures of rationally designed analogues **2a−h** of lead structure **1**.

acid (**1**) (Figure 1 and Table 1) was designed as a broad-acting iGluR antagonist.[30] Completing its synthesis, pharmacological characterization of **1** disclosed low-to-medium micromolar binding affinity to AMPA, KA, and NMDA receptors and functioned as an antagonist in a nondesensitizing functional GluK1 assay.[30] Thus, the design of antagonist **1** was successful and it defined a new lead structure for the discovery of subunit selective iGluR antagonists. Herein, we describe the first structure−activity relationship (SAR) study of broad-acting iGluR antagonist **1** together with X-ray crystallographic structures of **2e** in GluA2-LBD and **2f** in GluK1-LBD.

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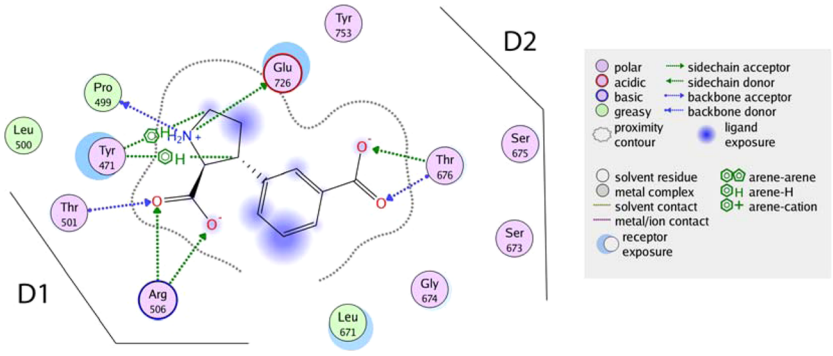
Table 2. Docking of 1 into the Structure of GluA2-LBD in Complex with the Antagonist ATPO (PDB ID: 1N0T) and Listing of GluA1−4 and GluK1−5 Amino Acid Residues (*Homo sapiens*), Which Define the D1−D2 Domain Ligand Binding Pocket (Highlighted in Green) As Well As Additional Residues within 4.5 Å Radius[a]



GluA1	GluA2	GluA3	GluA4	GluK1	GluK2	GluK3	GluK4	GluK5
	Ile421					Val		
	Glu423							
	Tyr426					Phe		
	Cys446							
	Lys470						Val	Leu
	Tyr471							
	Gly472							
	Trp481							
	Asn482						Thr	Thr
	Gly483							
	Met484							
	Ala496							
	Ala498							
	Pro499						Gly	Ala
	Leu500							Phe
	Thr501				Ala			
	Ile502							
	Thr503							
	Leu504			Tyr	Tyr	His	Ala	Ala
	Val505						Glu	Glu
	Arg506							
	Glu507							
	Glu508			Lys	Lys	Lys	Lys	Lys
	Val509					Ala		
	Ile510							
	Phe512							
	Pro515							
	Phe516							
	Met517							
	Ser518			Thr	Thr	Thr	Thr	Thr
	Leu519							
	Gly520							
	Ile521					Val		
	Ser522							
	Ile523							
	Met524			Leu	Leu	Leu	Leu	Leu
	Thr670			Ala	Ala	Ala		
	Leu671			Val	Val	Val	Ile	Ile
Glu	Asp672			Arg	Glu	Lys	His	His
Ala	Ser673			Asp	Asp	Asp	Gly	Ala
	Gly674							
	Ser675				Ala	Ala		
	Thr676						Ser	
	Lys677			Met	Met	Met	Met	Met
	Glu678			Thr	Thr	Thr	Thr	Thr
	Phe679							
	Phe680							
	Arg681			Lys	Lys	Lys	Gln	Gln
	Arg682			Lys	Lys	Lys	Asn	Asn
	Trp692							
Lys	Arg696	Lys	Arg	Ser	Ser	Ser	Tyr	Gln
	Phe703			Leu	Leu	Leu		
	Val704	Thr	Thr					
	Arg705	Lys			Lys	Lys	Lys	Lys
	Thr706			Asn	Ser	Asn	Ser	Ser
	Thr707			Ser	Asn	Asn	Thr	Thr
Met	Val711			Ile	Ile	Ile	Ile	Ile
	Tyr723	Phe	Phe	Leu	Phe	Leu	Phe	Phe
	Leu724							
	Leu725			Met	Met	Met		
	Glu726							
	Ser727							
	Thr728							
	Met729			Ser	Thr	Thr		
	Asn730			Ile	Ile	Ile		
	Lys751							
	Gly752							
	Tyr753							
	Gly754							
	Ala756			Gly	Gly	Gly	Gly	Gly

[a]Residues of differentiation to GluA2 are highlighted in grey.

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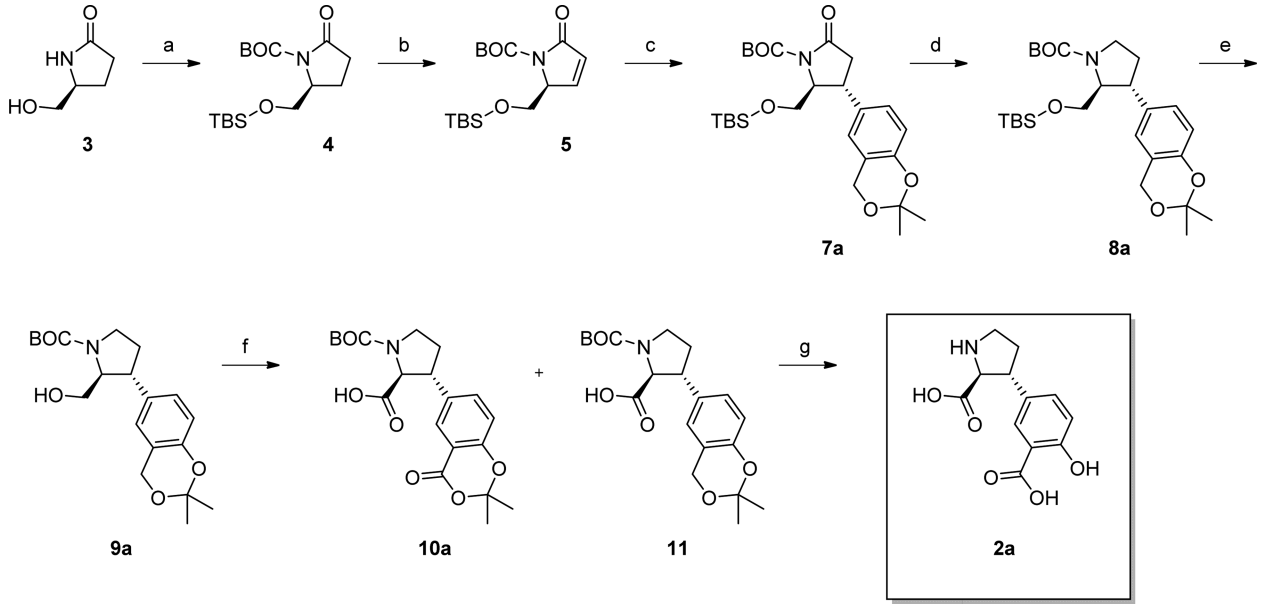
Scheme 1. Synthesis of 2a[a]



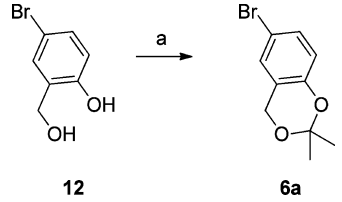
[a]Reagents and conditions: (a) TBSCl, imidazole, DCM, rt, 24 h, aq workup, then BOC_2O, DMAP, CH_3CN, rt, 16 h (two steps, 91%); (b) LHMDS, PhSeCl, THF, −78 °C, then 30% H_2O_2, EtOAc, 0 °C to rt (two steps, 64%); (c) **6a**, *tert*-BuLi, CuCN, Et_2O, −78 to −42 °C (70%); (d) BH_3·THF, THF, reflux, 3.5 h, then H_2O, NaOH, H_2O_2, rt, 3.5 h (46%); (e) TBAF, THF, rt, 2 h (87%); (f) $NaIO_4$, $RuCl_3$, 0 °C, 1.5 h (**10a**, 22%; **11**, 40%); (g) **10a** only, TFA:H_2O (1:1), rt, 16 h (59%).

RESULTS AND DISCUSSION

It is well-known that AMPA/KA receptors are highly dynamic in nature and that the degree of closure of the ligand binding domain (LBD) is connected to agonist vs antagonist function.[33−35] The apo (unbound) form of the LBD adopts an open cleft conformation. Antagonists have been shown to stabilize this open cleft form, whereas agonists induce cleft closure to various extents. On the design of analogues of antagonist **1**, we were faced with two challenges: (a) synthetic feasibility and (b) ligand−receptor interactions probing for iGluR subunit selectivity. In terms of (a), the 2,4-*cis* position as well as the 4′- and 5′-positions appeared accessible based on synthetic methodology already described for this class of compounds. In terms of (b), the in silico predicted binding mode of antagonist **1** in the X-ray structure of GluA2-LBD with ATPO (PDB ID: 1N0T) (Table 2)[30] suggests that a substituent in the 4′-position is directed into an area of the receptor presenting extensive hydrogen bonding capabilities, e.g., Ser673, Ser675, and Thr676 (GluA2 numbering with signal peptide), including harboring of a changing number of water molecules across the D1 and D2 domains. This area of the receptor is similar among the four GluA1−4 subunits but differs from and in between the five GluK1−5 subunits (Table 2). We therefore designed ligands **2a** and **2e** for improved hydrogen bonding capabilities. We were also interested in investigating the effect of substituting the 3′-carboxylic acid with a phosphonic acid functionality, **2h**. Such substitution has previously led to selectivity for native AMPA receptors over KA and NMDA receptors, e.g., for antagonist ATPO.[31] On the other hand, a substituent in the 5′-position of the phenyl ring is guided into a spacious conically shaped cleft between the D1 and D2 domains. Here, we envisaged that a lipophilic group could disrupt the water matrix and/or displace water molecules from the ligand binding pocket, thereby enhancing entropy contribution to ligand binding. This strategy gave rise to the synthesis of ligands **2b−d**. Finally, the analysis disclosed that a substituent in the 2,4-*cis* position is directed into a rigid area of the receptor, defined by the residues Glu423, Tyr471, and Pro499 (GluA2 numbering). Residues Glu423 and Tyr471 are conserved throughout GluA1−4 and GluK1−5, whereas Pro499 is different in GluK4,5. To investigate how the different receptor subtypes would respond, a small and larger lipophilic group were introduced, providing ligands **2f,g**.

Chemistry. The synthesis of compound **2a** commenced with double protection of commercially available optically pure (*S*)-5-(hydroxymethyl)-2-pyrrolidinone (**3**) to give **4** in high yield (Scheme 1). Subsequently, introduction of the double bond was carried out under standard selenylation conditions to give enone **5**. For target compound **2a**, the synthesis of suitably protected phenyl bromide **6a** was synthesized starting from commercially available phenolic alcohol **12** (Scheme 2).[30] Reduction of the lactam functionality by borane gave pyrrolidinone **8a** in low-to-acceptable yield (32−46%), with the byproduct being reductive opening of the isopropylidene group (determined by LC-MS). At this stage, a shortcut was attempted: full deprotection of pyrrolidinone **8a** in *p*-TsOH/MeOH at room temperature (rt) gave the expected phenolic diol **13** in high yield (Scheme 3). However, oxidation to the corresponding diacid **14**

Scheme 2. Synthesis of Bromide 6a[a]



[a]Reagents and conditions: (a) 2,2-dimethoxypropane, $ZnCl_2$, acetone, 40 °C, 1.5 h (88%).

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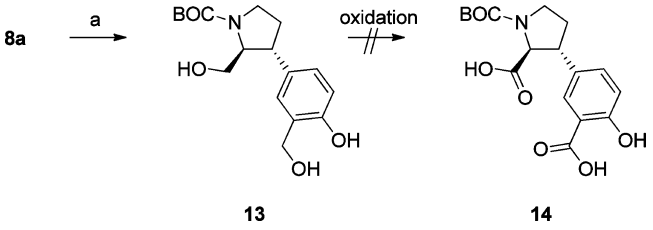
Scheme 3. Attempted Oxidation of Phenolic Diol 13[a]

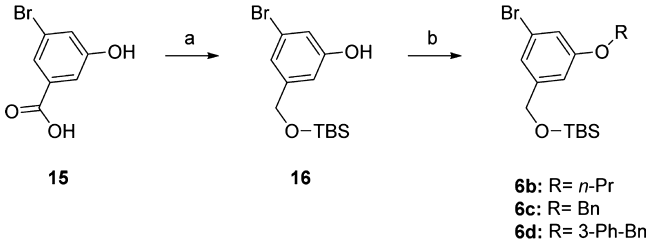


[a]Reagents and conditions: (a) *p*-TsOH, MeOH, rt, 5 h (71%).

was unsuccessful although several conditions were tried: $RuCl_3$–$NaIO_4$, TEMPO–NaOCl–$NaClO_2$, Pd–C/O_2/$NaBH_4$, PDC in DMF, and $KMnO_4$ in acetone (Scheme 3). Instead, a ruthenium-catalyzed oxidation of pyrrolidinone **8a** gave the desired acid-lactone **10a**, together with acid **11** as the side product in a 1:2 ratio (Scheme 1). The two products were easily separated by flash chromatography, after which acid-lactone **10a** was fully deprotected in TFA/H_2O to give target compound **2a**.

The synthesis of target structures **2b–e** (Scheme 4) followed the strategy described for compound **2a** with only few changes. First, suitably protected phenyl bromides **6b–d** were prepared starting from commercially available acid **15** in two steps (Scheme 5). Because of the bulkiness of the phenyl bromides **6b–d**, conjugate addition to enone **5** was carried out by use of a mixed-cyano Gilman cuprate, as previously described by us to be advantageous for this specific enone.[36] Reduction of the lactam functionality gave pyrrolidinones **8a–d** in acceptable yields (51–60%), and fluoride facilitated removal of the TBS groups provided the free diols **9b–d** in high yield. Subsequent ruthenium-catalyzed oxidation to give diacids **10b–d** was carried

Scheme 5. Synthesis of Substituted Phenylbromides 6b–d[a]

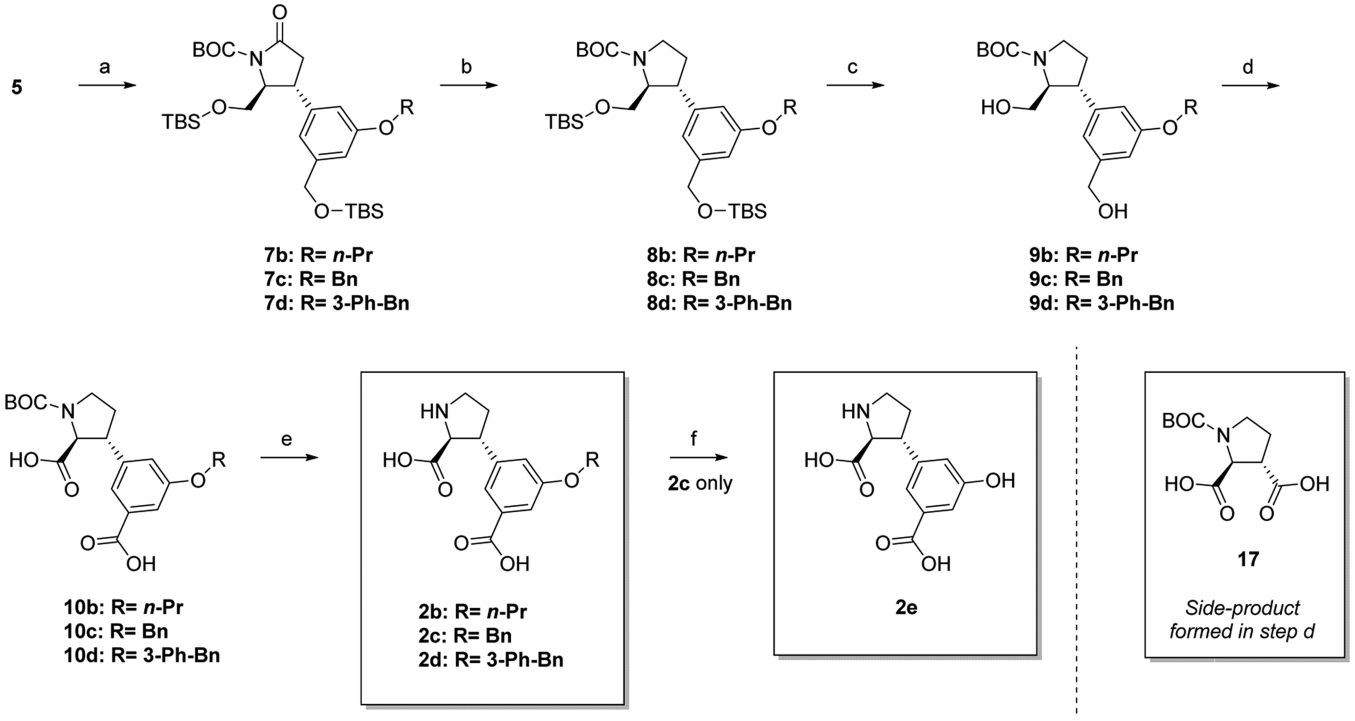


[a]Reagents and conditions: (a) BH_3·THF, THF, 0 °C to rt, aq workup, then TBSCl, imidazole, DMF, 0 °C to rt (71%); (b) for **6b**, *n*-PrBr, K_2CO_3, rt in DMF (90%); for **6c,d**, RBr, K_2CO_3, reflux in acetone (92–95%).

out at 0 °C to prevent overoxidation of the electron-rich phenyl ring, resulting in the side product *N*-BOC-L-*trans*-2,3-dicarboxy-pyrrolidine **17** (Scheme 4). Finally, removal of the BOC-group under dry, acidic conditions gave target compounds **2b–d**, as the HCl salts in purities of 97–99% (HPLC). The 5′-phenolic analogue **2e** was obtained by hydrogenation of benzyloxy **2c** over Pd/C to give the desired product **2e** in 44% after purification by preparative HPLC.

The synthesis of the two *cis*-2,4-substituted analogues **2f,g** commenced with a stereoselective alkylation of lactam **18**[30] with allyl bromide and benzyl bromide to give **19a** and **19b**, respectively (Scheme 6). In both cases, the expected 3,4-*trans* relationship, being energetically favored over the 3,4-*cis* relationship, was determined by COSY and HMQC NMR experiments. The subsequent sequence of reactions followed the strategy described for proline analogues **2a–e**: reduction of the lactam functionality to give **20a,b**, hereafter removal of the TBS-groups

Scheme 4. Synthesis of 2b–e and Chemical Structure of Side Product 17[a]



[a]Reagents and conditions: (a) **6b–d**, *tert*-BuLi, CuCN, lithium thiophene, Et_2O, −78 to −42 °C (42–62%); (b) BH_3·THF, THF, reflux, 20 h, then H_2O, NaOH, H_2O_2, rt, 1 h (51–60%); (c) TBAF, THF, rt, (92–94%); (d) $NaIO_4$, $RuCl_3$, 0 °C, 2 h (66–83%); (e) 2 M HCl in Et_2O, AcOH, rt, 18 h (87–99%); (f) **2c** only, H_2(g), Pd/C (10%), AcOH, rt, 6 days (44%).

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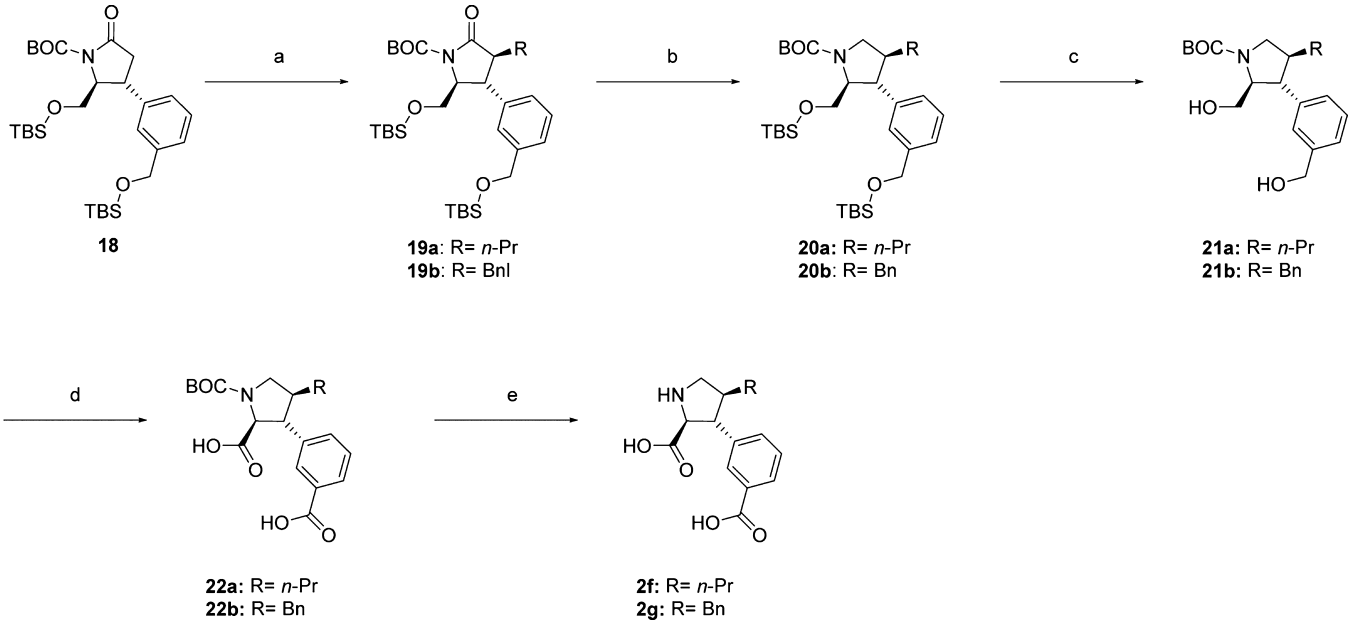
Scheme 6. Synthesis of *cis*-2,4-Substituted Target Compounds 2f and 2g from Intermediate 18[a]

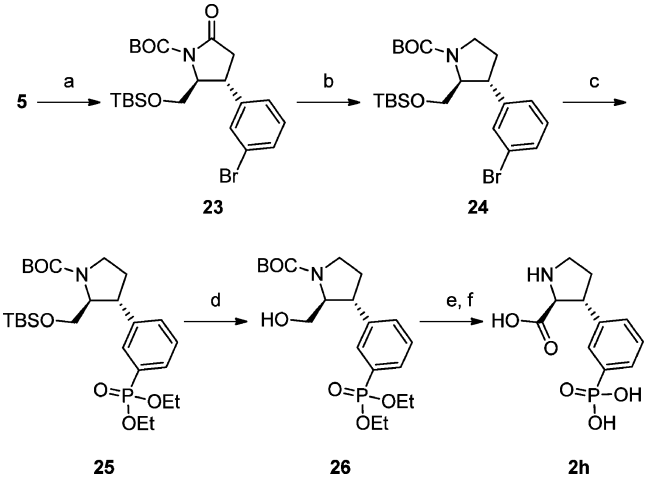


[a]Reagents and conditions: (a) LHMDS, RBr, THF −42/−52 °C (49% and 72%); (b) for **19a**, first H_2, Pd/C, rt, then for both **19a,b**, BH_3·THF, THF, reflux, 20 h, then H_2O, NaOH, H_2O_2, rt, 1 h (59% and 30%); (c) TBAF, THF, rt, (89% and 79%); (d) $NaIO_4$, $RuCl_3$, 0 °C, 2 h (93% and 45%); (e) HCl in AcOH, rt, 18 h (82% and 69%).

to give diols **21a,b**, followed by oxidation to diacids **22a,b**, and finally removal of the BOC group to give the target compounds **2f** and **2g**.

As for **2a−g**, the synthesis of **2h** also commenced with a 1,4-addition of a cuprate to enone **5** to give adduct **23** as a single diastereomer, determined by ^{1}H NMR (Scheme 7).[36]

Scheme 7. Strategy for the Synthesis of 2h[a]



[a]Reagents and conditions: (a) 1,3-dibromobenzene, *n*-BuLi, CuCN, TMSCl, THF, −50 °C (63%); (b) BH_3·THF then NaOH, H_2O_2 (73%); (c) *n*-BuLi, $ClPO_3Et_2$, THF, −78 °C (66%); (d) TBAF, THF rt, (65%); (e) $RuCl_3$, $NaIO_4$, H_2O, CH_3CN, EtOAc, rt (82%); (f) 2 N HCl, H_2O, 80 °C (40%).

Chemoselective reduction of the lactam with a solution of BH_3·THF under reflux conditions afforded pyrrolidine **24**. At this stage, the phosphonate was introduced by metal−halogen exchange of the 3′-bromine with *n*-BuLi followed by addition of $ClPO_3Et_2$ to give **25**.[37,38] Removal of the TBS protection group by treatment with TBAF led to alcohol **26**, which was oxidized according to the modified Sharpless procedure using a catalytic amount of Ru(III) and periodate as the co-oxidant to give acid **27**.[39] Purification of **27** on silica gel was accompanied by hydrolysis of the phosphonate ester, even with prior washing with NEt_3. For this reason, crude **27** underwent global deprotection in 2 M HCl to give desired product **2h**, which was then purified by HPLC.

Pharmacological Characterization. All analogues **2a−h** were characterized pharmacologically in radioligand binding assays at native iGluRs (rat synaptosomes) and cloned rat homomeric subtypes, GluK1−3 (Table 3). 4′-Hydroxy analogue **2a** displayed a generally higher binding affinity for the iGluRs in native tissue and reduced iGluR class selectivity compared to lead structure **1**. In detail, a 25- and 15-fold higher affinity for AMPA and KA receptors was observed, while a 6-fold higher affinity at NMDA receptors could be demonstrated. However, most interestingly, **2a** displayed a 10-fold increase in binding affinity for homomeric GluK3 (K_i = 0.87 μM), while affinity for homomeric GluK1 and GluK2 was essentially unchanged. This 5-fold preference for GluK3 over GluK1 (K_i = 4.8 μM) is indeed a unique binding affinity profile for a KA receptor antagonist and encourages future structure−activity relationship (SAR) investigations of the 4′-position. Furthermore, as the binding affinity profile of the 5′-hydroxy analogue **2e** is essentially unchanged compared to lead structure **1**, this strengthens the interest in the 4′-position as a point of modification to obtain receptor selectivity.

Lipophilic 5′-ethers **2b−d** displayed increased affinity for native AMPA receptors (up to 10-fold) with increasing steric bulk of the 5′-substituent, while binding affinities at KA and NMDA receptors were largely unaffected. At cloned homomeric GluK1−3 the three analogues **2b−d** displayed only modest changes in affinity as compared to **1** (Table 3); a general 4-fold increase was observed for **2b**, whereas **2c** only displayed a 4-fold

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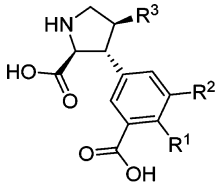
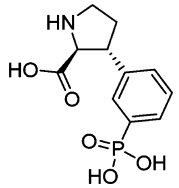
Table 3. Chemical Structures and Binding Affinities of Analogues 2a−g at Native iGluRs (Rat Synaptosomes) and Homomeric Recombinant iGluRs (All Values in μM)[a]



1, 2a-g



2h

				native iGluRs (synaptosomes)[b]			cloned homomeric iGluRs[c]				
	R^1	R^2	R^3	AMPA IC_{50}	KA IC_{50}	NMDA K_i	GluA2 K_i	GluK1 K_i	GluK2 K_i	GluK3 K_i	$K1/K3$
1[d]	-	-	-	51	22	6.0	67	4.3	>100	8.1	0.5
2a	HO−	-	-	2.0 [5.71 ± 0.03]	1.4 [5.87 ± 0.07]	1.0 [6.02 ± 0.11]	--	4.8 ± 1.5	10−100[e]	0.87 ± 0.09	5.5
2b	-	PrO−	-	25 [20;30]	7.2 [6.4;8.0]	5.0 [3.9;6.4]	35 ± 0.29	1.7 ± 0.05	56 ± 1.4	2.7 ± 0.30	0.6
2c	-	BnO−	-	6.3 [5.20 ± 0.04]	6.7 [5.18 ± 0.06]	4.1 [5.41 ± 0.10]	6.45 ± 0.29	3.7 ± 0.80	32 ± 2.5	2.1 ± 0.40	1.8
2d	-	mPh-BnO−	-	4.9 [5.34 ± 0.09]	12 [4.92 ± 0.03]	4.0 [5.41 ± 0.08]	6.10 ± 0.32	8.7 ± 1.2	68 ± 7.6	8.6 ± 0.60	1.0
2e	-	HO−	-	54 [4.28 ± 0.05]	34 [4.52 ± 0.11]	5.4 [5.27 ± 0.04]	--	8.3 ± 0.20	>100	8.5 ± 1.2	1.0
2f	-	-	Pr−	48[4.32 ± 0.03]	22[4.72 ± 0.11]	25[4.61 ± 0.03]	--	0.62 ± 0.10	81 ± 8.3	2.2 ± 0.37	0.28
2g	-	-	Bn−	>100	>100	>100	>100	8.8 ± 1.5	>100	34 ± 1.0	0.26
2h	-	-	-	>100	>100	>100	>100	130 ± 26	>1000	78 ± 0.80	1.6

[a]-, H. --, value not determined. [b]Data are mean values of three to six individual experiments performed in triplicate. For AMPA and KA: pIC_{50} values with SEM in brackets. For NMDA: pK_i values with SEM in brackets. [c]IC_{50} values of two experiments. pIC_{50} is given in parentheses [mean ± SEM]. [d]Values obtained from ref 30. [e]Mean ± SEM has not been included for **2a** due to limited amount of compound available.

higher affinity for GluK2 and −3. Analogue **2d** displayed slightly lower affinity for GluK1, midmicromolar affinity for GluK2, and comparable affinity for GluK3 with lead structure **1**. Together, these data suggest that a lipophilic side chain in the 5′-position is directed into the spacious compartment in the receptors located between the D1 and D2 domains, in agreement with preliminary structural data (see Supporting Information Figure S1). By further exploring and targeting differences in amino acid residues in this area of the receptors, it may be possible to achieve class or subtype selectivity.

The influence of placing a substituent in the 2,4-*cis*-position was explored by the design and synthesis of analogues **2f** and **2g**. An *n*-propyl group, analogue **2f**, induced an 8-fold increase in affinity for GluK1 (K_i = 0.62 μM) and a 4-fold increase in affinity for GluK3. At the same time, native AMPA and KA receptors were unaffected, whereas a 4-fold decrease in affinity for native NMDA receptors was observed. Introduction of a benzyl group in the very same position, analogue **2g**, led to a noticeable reduction in binding affinity at all iGluRs, except for subtype GluK1 at which it displayed affinity in the low micromolar range (K_i = 8.8 μM).

Phosphonic acid **2h** displayed negligible affinity (12−30% displacement at 100 μM) at native AMPA, KA, and NMDA receptors. At cloned homomeric GluA2 receptors binding affinity was also low (3 ± 3% displacement at 100 μM). **2h** also displayed low affinity at cloned homomeric GluK1 and GluK3 receptors (K_i = 130 and 78 μM, respectively) and no affinity for GluK2 subtype (K_i >1 mM). In comparison with **1** and ATPO, the low-affinity pharmacological profile of **2h** is unexpected and the underlying origin remains to be understood.

X-ray Crystal Structure of 2e in GluA2-LBD and 2f in GluK1-LBD. To unequivocally determine the binding mode of the core scaffold and obtain structural insight into how substituents in the 5′-position (R^2 groups) and 4-position (R^3 groups) are accommodated by iGluR proteins, we attempted to crystallize analogues **2c**, **2d**, **2e**, and **2f** in GluA2-LBD and GluK1-LBD. Crystals suitable for data collection were obtained of **2c**, **2d**, and **2e** in GluA2-LBD and of **2f** in GluK1-LBD.

The structure of GluA2-LBD with **2e** was determined at 1.9 Å resolution (Table 4) and comprises two molecules in the asymmetric unit of the crystal, forming a dimer (Figure 2A). The compound **2e** induces a D1−D2 domain opening in GluA2-LBD of 18.8° (molA) and 17.3° (molB) relative to the structure of GluA2-LBD with glutamate (PDB ID: 1FTJ, molB). This domain opening is similar to that observed with the antagonist DNQX (PDB ID: 1FTL) (17.4° (molA) and 15.9° (molB)). On the basis of the close structural relationship to the parent antagonist **1**, combined with a domain opening typical of antagonists, it suggests that compound **2e** also acts as an antagonist.

The pyrrolidine-carboxylate group of **2e** forms a salt bridge to the D1 residue Arg506 (side chain guanidinium group) and a charge-assisted hydrogen bond to Thr501 (backbone NH) as well as to one water molecule (Figure 2B). The pyrrolidine-nitrogen atom forms a charge-assisted hydrogen bond to the D1 residue Pro499 (backbone carbonyl oxygen) and a salt bridge to the D2 residue Glu726 (side chain carboxylate). Thus, the pyrrolidine-2-carboxylate moiety of **2e** has similar binding mode as that of kainate (Figure 2C).[34] However, the orientation of the side chain of Thr501 is different in the two structures. In the structure of GluA2-LBD with kainate, the side chain hydroxyl group forms a hydrogen bond to the carboxylate of Glu726, whereas in the structure with **2e**, the two side chains are too far apart. Instead, the hydroxyl group makes a hydrogen bond to the side chain of Arg506 (Figure 2C).

The 3-phenyl moiety of **2e** holds a 3′-carboxylate and a 5′-hydroxyl group both capable of forming polar contacts (Figure 2B). The 3′-carboxylate of **2e** forms charge-assisted hydrogen bonds to the D2 residue Thr676 (backbone NH as well as side chain hydroxyl group) and water molecules. These contacts are comparable to those of the distal carboxylate in kainate, but the larger 3-carboxyphenyl moiety of **2e** leads to a larger domain opening (Figure 2C) compared to that in the

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Table 4. Crystal Data, Data Collection, and Refinement Statistics of GluA2-LBD in Complex with 2e and GluK1-LBD in Complex with 2f

	GluA2-LBD with **2e**	GluK1-LBD with **2f**
Crystal Data		
beamline	I911-3	I911-3
space group	$P2_1$	$P4_12_12$
cell dimensions		
a (Å)	48.88	71.81
b (Å)	65.25	71.81
c (Å)	91.55	230.13
β (deg)	92.36	90.00
molecules in a.u.[a]	2	2
Data Collection		
resolution (Å)	36.39−1.89 (2.00−1.89)[b]	44.90−1.93 (2.03−1.93)
unique reflections	45862	46519
average multiplicity	4.2 (4.1)	7.5 (6.8)
completeness (%)	100 (100)	100 (100)
Wilson *B*-factor (Å^2)	20.9	18.3
R_{merge} (%)[c]	8.3 (37.2)	7.1 (33.8)
$I/\sigma I$	6.3 (2.0)	6.1 (2.0)
Refinement		
amino acid residues	518	507
ligand molecules	2	2
water	698	488
glycerol/ethylene glycol/PEG	2/2/0	0/1/1
sulfate/acetate/chloride	6/1/0	0/4/4
R_{work} (%)[d]/R_{free} (%)[e]	17.1/22.9	17.9/22.0
average *B* values (Å^2) for:		
residues/ligands	27.0/18.9	29.4/17.7
water	32.8	29.6
glycerol/ethylene glycol/PEG	47.8/49.8/−	−/63.9/57.3
sulfate/acetate/chloride	90.6/45.0/−	−/40.6/40.3
rmsd bond length (Å)/angles (deg)	0.006/1.0	0.009/1.1
Ramachandran favored/outliers (%)[f]	99.2/0.0	98.5/0.0

[a]a.u.: asymmetric unit. [b]Numbers in parentheses are for the outermost bin. [c]A measure on agreement among multiple measurements of the same reflections. R_{merge} is calculated as follows: $I_i(hkl)$ is the intensity of an individual measurement of the reflection with Miller indices *hkl*, and $I(hkl)$ is the intensity from multiple observations. $R_{merge} = \sum_{hkl}\sum_i|I_i(hkl) - I(hkl)| / \sum_{hkl}\sum_i|I_i(hkl)|$. [d]$R_{work} = \sum_{hkl}(||F_{o,hkl}| - |F_{c,hkl}||)/|F_{o,hkl}|$, where $|F_{o,hkl}|$ and $|F_{c,hkl}|$ are the observed and calculated structure factor amplitudes. [e]R_{free} is equivalent to R_{work} but calculated with 5% reflections omitted from the refinement process. [f]The Ramachandran plots were calculated using PHENIX.

structure of GluA2-LBD with kainate (PDB ID: 1FW0, 10.7°). The 5′-hydroxyl group of **2e** makes only indirect contacts to GluA2-LBD, through a water molecule to Ser673 (backbone carbonyl oxygen) and a putative sulfate ion to Tyr471 (backbone NH) (Figure 2B). The lack of direct contacts from the 5′-hydroxyl group of **2e** might explain why **2e** has a similar binding affinity as the parent compound **1** (Table 1) and a lower binding affinity at AMPA receptors compared to compounds containing larger substituents at this position (**2b−d**; Table 3). When comparing **2e** with compound **2a**, the only difference is that the hydroxyl group is positioned in the 4′-position and this leads to an approximately 25-fold better binding affinity at AMPA receptors (Table 3). Assuming a similar binding mode of **2a** and **2e** in GluA2-LBD, the 4′-hydroxyl group in **2a** will form a direct hydrogen bond to Ser673, which most likely explains the observed difference in binding affinities. Compound **2e** was found to possess similar binding affinities at AMPA and kainate receptors (Table 3), in agreement with the fact that the four binding site residues making direct polar contacts to **2e** are conserved in most AMPA and kainate receptor subunits: the essential Arg506 (GluA2 numbering), Pro499 (except in GluK4 and GluK5 where it is Gly and Ala, respectively), Thr501 (except in GluK2 where it is Ala), and Glu726 (Table 2). However, **2e** forms polar contacts to backbone atoms only in Pro499 and Thr501.

GluK1-LBD was successfully crystallized with the most active compound **2f** (Table 3), allowing exploration of how substituents on the pyrrolidine-2-carboxylic acid moiety of **1** affect the binding mode. The complex crystallized with two molecules in the asymmetric unit of the crystal (Figure 3A) and the structure was determined at 1.9 Å resolution (Table 4). The pyrrolidine carboxylate and nitrogen of analogue **2f** form similar contacts to GluK1 as kainate[40] and analogue **2e** in GluA2, i.e., residues Pro531, Thr533, Arg538, and Glu753 (Figure 3B). However, the *n*-propyl substituent in analogue **2f** leads to a different pyrrolidine ring conformation compared to that in kainate (Figure 3C), as the *n*-propyl group would otherwise clash with Glu456. Instead, the *n*-propyl group is squeezed in between the residues Glu456 and Ser756. A domain opening in the GluK1-LBD structure with analogue **2f** is calculated to 17.0° (molA) and 17.5° (molB). The carboxylate group in the 3-carboxyphenyl moiety of analogue **2f** forms charge-assisted hydrogen bonds to the D2 residues Thr705 (side chain hydroxyl group) and Glu753 (backbone NH) as well as water molecules.

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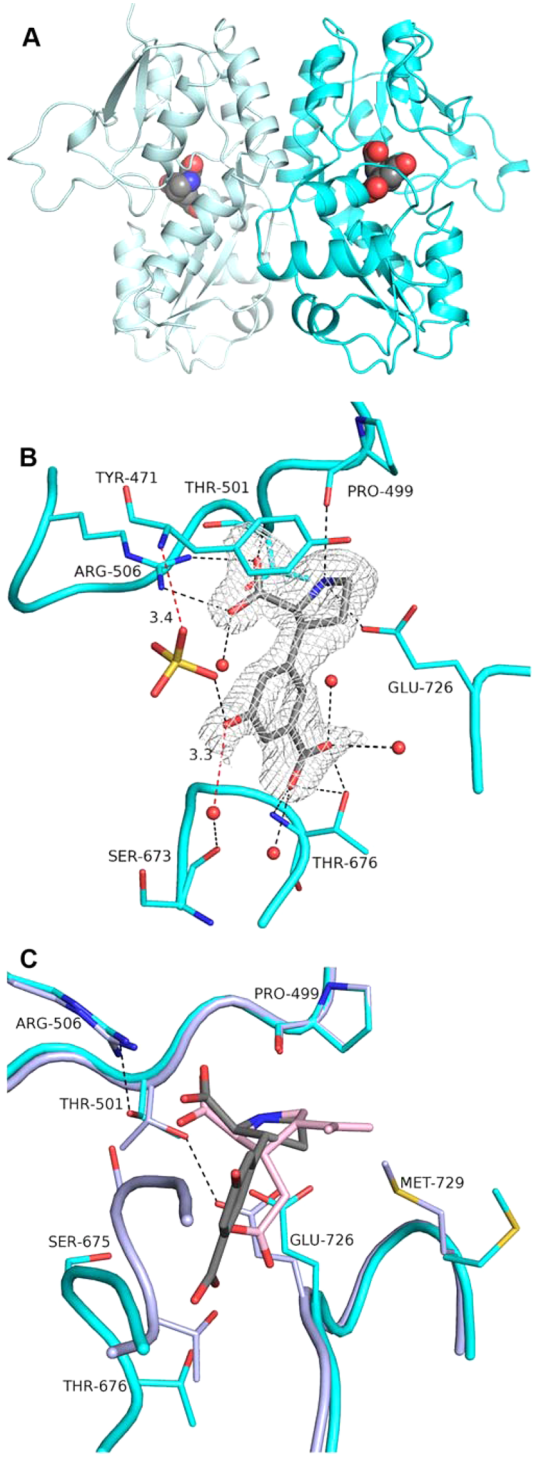

Figure 2. Ligand binding domain of GluA2 in complex with **2e**. (A) Cartoon representation of the GluA2-LBD dimer (molA cyan and molB light cyan) with **2e** (gray space fill representation) bound at the binding site. (B) Zoom on the binding site (molA). Possible hydrogen bonds (up to 3.2 Å) between **2e** and GluA2, as well as to water molecules and a putative sulfate ion, are displayed as black dashes. Indirect interactions through water and sulfate are shown as red dashes. The electron density map (omit $2mF_o - F_c$) is shown at 1.0 σ and carved around the ligand at 1.6 Å radius. (C) Comparison of the structures of GluA2-LBD with **2e** (gray) and kainate (light pink; PDB ID 1FW0). The structures were superimposed on domain D1 residues. GluA2 residues for complex with kainate are shown in light blue.

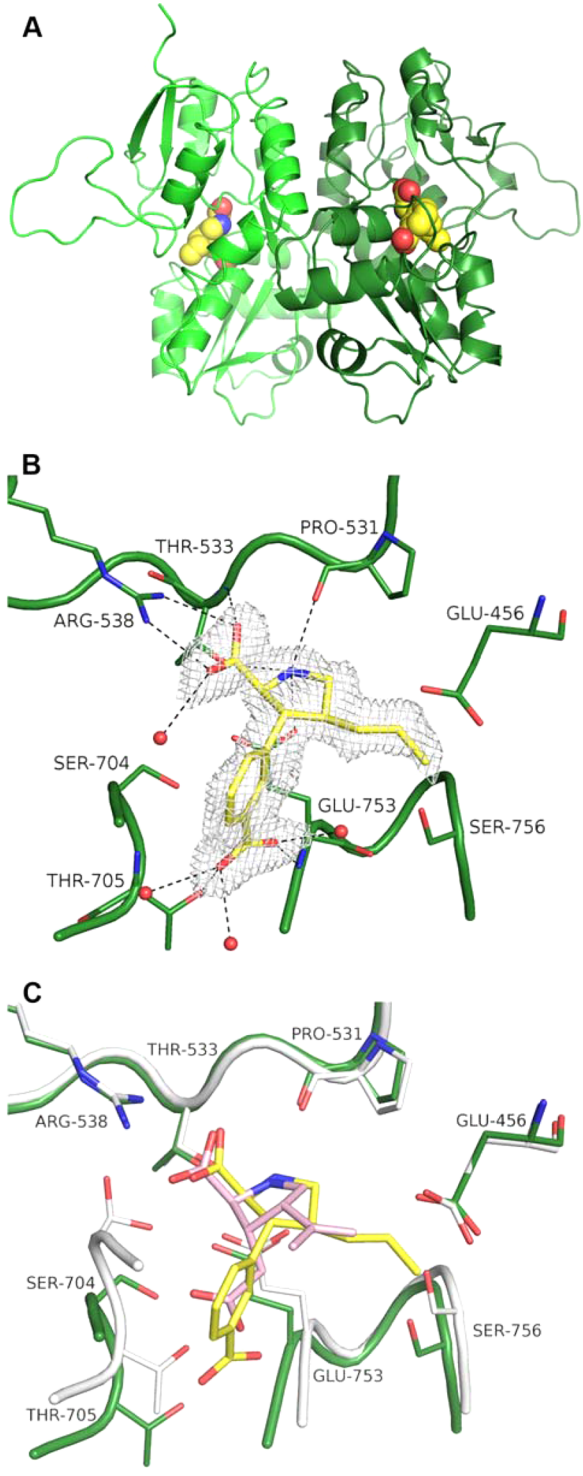

Figure 3. Ligand binding domain of GluK1 in complex with **2f**. (A) Cartoon representation of the GluK1-LBD dimer (mol A forest green; mol B green) with **2f** (yellow space fill representation) bound at the binding site. (B) Zoom on the binding site (molA). Possible hydrogen bonds (up to 3.2 Å) between **2f** and GluK1 as well as to water molecules are displayed as black dashes. The electron density map (omit $2mF_o - F_c$) is shown at 1.0 σ and carved around the ligand at 1.6 Å radius. (C) Comparison of the structures of GluK1-LBD with **2f** and kainate (light pink; PDB ID 4E0X). The structures were superimposed on domain D1 residues. GluK1 residues are shown in white for complex with kainate.

It is evident that only limited space is available for a substituent in the 4-position as the more bulky benzyl substituent, analogue **2g**,

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results in a significant decrease in affinity for all iGluRs compared to **2f** (Table 3).

The structure of GluA2-LBD with **2c** did unfortunately not allow unambiguous assignment of the ligand despite a resolution of 1.8 Å. The structure of GluA2-LBD in complex with **2d** was solved at 3.0 Å resolution. The data were processed in space group $P1$ with 16 molecules in the asymmetric unit of the crystal (Supporting Information Table S1). After refinement, R/R_{free} values were high, and therefore space group $P2_1$ was investigated but resulted in even higher R_{merge} for low angle reflections and higher R/R_{free} values. However, the partly refined structure of GluA2-LBD with **2d** clearly showed the same domain opening (17.1−17.6°) and binding mode of the pyrrolidine-2-carboxylic acid moiety of **2d** as compound **2e**. The biphenyl moiety of **2d** reaches into a new area of the ligand binding cleft, with the biphenyl moiety positioned out of the cleft (Supporting Information Figure S1).

CONCLUSION

In conclusion, we have designed and synthesized seven analogues **2a−g** of the broad-range iGluR antagonist **1** and characterized them in binding affinity studies as ligands for the iGluRs. Most interestingly, the introduction of a 4′-hydroxyl group (compound **2a**) induced a 10-fold increase in affinity for GluK3, resulting in a 5-fold preference over the GluK1 subtype. This shift in GluK1/3 affinity ratio is an important step toward the discovery of fully selective GluK3 antagonists. In contrast, the 5′-hydroxyl regioisomer **2e** did not display an altered affinity profile as compared to lead structure **1**, underlining that subtle chemical differences induce major changes in the pharmacological profile. Lipophilic substituents in the 5′ position (compounds **2b−d**) did not induce a remarkable change in the pharmacological profile, whereas a lipophilic substituent in the *cis*-2,4-position led to an 8-fold higher affinity for GluK1, a 4-fold increase in affinity for GluK3 and a 4-fold reduced affinity for native NMDA receptors (compound **2f**). A benzyl group in the very same *cis*-2,4-position (compound **2g**) reduced the affinity for all iGluRs except for GluK1.

X-ray crystal structures of analogue **2e** in GluA2-LBD and analogue **2f** in GluK1-LBD were obtained. The pyrrolidine-2-carboxylic acid moiety of analogues **2e** and **2f** shows a similar binding mode as in kainate, while the 3-(3-carboxy)-phenyl group in analogues **2e** and **2f** induces the change in receptor domain opening (antagonist states). This is in accordance with modeling data during the design phase of lead structure **1**.

All together, the findings in this study add to the growing pool of insight into the SAR of the iGluRs to facilitate the discovery of new truly subunit selective iGluR antagonists.

EXPERIMENTAL SECTION

Synthesis. *General.* All reagents were obtained from commercial suppliers and used without further purification. THF was distilled over sodium/benzophenone. Et_2O was dried over neatly cut sodium. All solvents were analyzed for water content using a Karl Fisher apparatus. Water or air sensitive reactions were conducted in flame-dried glassware under an atmosphere of nitrogen with the syringe−septum cap technique. Purification by DCVC (dry column vacuum chromatography) was performed with silica gel size 25−40 μm (Merck, Silica gel 60). For TLC, Merck TLC Silica gel F_{254} with appropriate spray reagents was used: $KMnO_4$ or molybdenum blue. ^1H NMR and ^{13}C NMR spectra were obtained on a Varian Mercury Plus (300 MHz) and a Varian Gemini 2000 instrument (75 MHz), respectively. Preparative HPLC was done using an Agilent Prep HPLC system with consisting of an Agilent 1100 series pump, Agilent 1200 series diode array, multiple wavelength detector (G1365B), connected to an Agilent PrepHT high performance preparative cartridge column (Zorbax, 300 SB-C18 Prep HT, 21.2 mm × 250 mm, 7 μm) with a flow-rate of 20 mL/min. Alternatively, preparative HPLC was performed using Spectraseries UV100 detector with a JASCO 880-PU HPLC pump and a Merck Hitachi D-2000 Chromato Integrator connected to XTerraPrep MS C18 (10 μm, 10 mm × 300 mm) column with a flow-rate of 10 mL/min. LC-MS was performed using an Agilent 1200 series solvent delivery system equipped with an autoinjector coupled to an Agilent 6400 series triple quadrupole mass spectrometer equipped with an electrospray ionization source gradient of the binary solvent system of H_2O/CH_3CN/formic acid (A:90/10/0.05, and B: 10/90/0.046) were employed. Optical rotation was measured using a PerkinElmer 241 spectrometer, with Na lamp at 589 nm. Melting points were measured using an automated melting point apparatus, MPA100 OptiMelt (SRS), and are uncorrected. Compounds were dried either under high vacuum or freeze-dried using a Holm & Halby, Heto LyoPro 6000 freeze dryer.

*(2S,3R)-3-(3-Carboxy-4-hydroxyphenyl)pyrrolidine-2-carboxylic Acid Trifluoroacidic Acid (**2a**).* The carboxylic acid (44 mg, 0.11 mmol, 1.00 equiv) was dissolved in TFA:H_2O (1:1) (4 mL) and stirred 18 h at rt. The clear, colorless reaction mixture was concentrated in vacuo and afterward azeotropically concentrated using CH_3CN (5 × 10 mL) and then lyophilized overnight to remove the remaining water. The brownish viscous oil (34 mg, 83%) was trituated with ice-cold Et_2O (2 × 1 mL) by which the product precipitated. The final product was dried using high vacuum to yield **2a** (24 mg, 59%) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 7.77 (1H, s), 7.36 (1H, d, J = 8.1 Hz), 6.81 (1H, d, J = 8.6 Hz), 4.10−4.04 (2H, m), 3.42 (2H, t, J = 8.4 Hz), 3.26−3.18 (1H, m), 3.15−3.06 (2H, m), 2.36−2.27 (1H, m), 2.13−2.05 (1H, m), 2.00−1.91 (1H, m). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6, 171.5, 170.0, 169.7, 160.9, 133.3, 129.4, 129.0, 116.7, 64.6, 60.0, 46.8, 45.5, 45.3, 43.1, 33.5, 26.8. MS (m/z) calcd for $C_{12}H_{14}NO_5$ $[M + H]^+$ 252.1, found 252.1. HPLC (254 nm) >99%; $[\alpha]^{25}_D$ −65.7° (c = 0.067, 10% DMSO in H_2O); mp 172−178 °C (decomp).

*(2S,3R)-3-(3-Carboxy-5-propoxyphenyl)pyrrolidine-2-carboxylic Acid Hydrochloride (**2b**).* Protected amine **10b** (180 mg, 0.46 mmol, 1.00 equiv) was dissolved in AcOH (2.5 mL) and 2 M HCl in Et_2O was added (2.5 mL, 5.0 mmol, 11 equiv). The mixture was left to stir under an atmosphere of nitrogen at rt for 18 h. The mixture was suspended in H_2O (10 mL), solidified by cooling on a dry ice/acetone bath, and lyophilized to yield **2b** (149 mg, 99%) as a slightly off-white, crisp solid. ^1H NMR (300 MHz, DMSO-d_6): δ 7.51 (1H, m), 7.30 (1H, m), 7.28 (1H, m), 4.17 (1H, m), 3.96 (2H, m), 3.54 (1H, m), 3.41 (1H, m), 3.23 (1H, m), 2.36 (1H, m), 2.01 (1H, m), 1.73 (2H, m), 0.98 (3H, t, J = 7 Hz). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.6, 166.8, 158.7, 142.5, 132.2, 120.8, 118.6, 112.9, 69.2, 64.3, 47.3, 45.2, 33.6, 22.1, 10.5. MS: (m/z) calcd for $C_{15}H_{20}NO_5$ $[M + H]^+$ 294.1, found: 294.2. HPLC (254 nm) 99.4%; $[\alpha]^{35}_D$ +42.1° (c = 0.43, abs EtOH:H_2O (3:1)).

*(2S,3R)-3-(3-(Benzyloxy)-5-carboxyphenyl)pyrrolidine-2-carboxylic Acid Hydrochloride (**2c**).* To protected amine **10c** (302 mg, 0.68 mmol, 1.00 equiv) dissolved in AcOH (4 mL) was added 2 M HCl in Et_2O (4 mL, 8 mmol, 11.8 equiv). The mixture was left to stir under an atmosphere of nitrogen at rt for 18 h. The mixture was suspended in H_2O (20 mL), solidified by cooling on a dry ice/acetone bath, and freeze-dried to yield **2c** (228 mg, 88%) as a slightly off-white, crisp solid. ^1H NMR (300 MHz, DMSO-d_6): δ 9.53 (1H, bs), 7.56 (1H, m), 7.49−7.28 (7H, m), 5.15 (2H, s), 4.19 (0.9H, d, J = 8 Hz), 4.04 (0.1H, d, J = 11 Hz), 3.56 (1H, q, J = 9 Hz), 3.48−3.05 (2H, m), 2.37 (1H, m), 2.01 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.5, 166.8, 158.4, 142.5, 136.6, 132.2, 128.3, 127.8, 127.7, 121.2, 119.1, 113.3, 69.5, 64.2, 47.2, 45.3, 33.6. MS (m/z) calcd for $C_{19}H_{20}NO_5$ $[M + H]^+$ 342.1, found: 342.2. HPLC (254 nm) 97%; $[\alpha]^{35}_D$ −11.5° (c = 0.41, abs EtOH:DMSO (3:1)).

*(2S,3R)-3-(3-([1,1′-Biphenyl]-3-ylmethoxy)-5-carboxyphenyl)-pyrrolidine-2-carboxylic Acid Hydrochloride (**2d**).* Protected amine **10d** (247 mg, 0.48 mmol, 1.0 equiv) was dissolved in AcOH (4 mL) and 2 M HCl in Et_2O was added (4 mL, 8 mmol, 16.7 equiv). The mixture was left to stir under an atmosphere of nitrogen at rt for 18 h. The mixture was suspended in H_2O (20 mL), solidified by cooling on a dry ice/acetone bath, and lyophilized to yield **2d** (188 mg, 87%) as a slightly

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off-white, crisp solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.74 (1H, s), 7.70−7.30 (11H, m), 5.20 (2H, s), 4.15 (1H, d, J = 9 Hz), 3.54 (1H, q, J = 8 Hz), 3.38 (1H, m), 3.22 (1H, m), 2.35 (1H, m), 1.98 (1H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ 201.9, 169.5, 166.8, 158.3, 142.8, 140.2, 139.7, 137.3, 132.3, 129.0, 128.9, 127.5, 126.8, 126.6, 126.2, 126.1, 121.2, 119.3, 113.0, 69.4, 64.7, 47.1, 45.2, 33.5. MS: (m/z) calcd for $C_{25}H_{24}NO_5$ [M + H]$^+$ 418.2, found: 418.2. HPLC (254 nm) 99.9%; $[\alpha]^{35}_D$ +37.5° (c = 0.40, abs EtOH:DMSO (3:1)).

*(2S,3R)-3-(3-Carboxy-5-hydroxyphenyl)pyrrolidine-2-carboxylic Acid Trifluoroacidic Acid (**2e**).* The *O*-benzyl analogue **2c** (91 mg, 0.24 mmol, 1.00 equiv) was dissolved in AcOH (7 mL), and an atmosphere of nitrogen was applied. 10% Pd/C (10 mg) was added, followed by purging with hydrogen gas. The reaction was stirred for 6 days, after which HPLC did not show further change in reaction outcome. The mixture was diluted with CH_3CN (50 mL), filtered through a syringe filter, and concentrated in vacuo. The residue was coevaporated with CH_3CN (3 × 50 mL), and the crude product was dried in high vacuum overnight, affording a pale-brown glass (57 mg, 83%). The product was purified by preparative HPLC to yield **2e** (30 mg, 44%) as a clear, colorless oil. ^{1}H NMR (300 MHz, NaOD): δ 7.47 (1H, t, J = 1 Hz), 7.29 (1H, dd, J = 2, 1 Hz), 7.04 (1H, t, J = 2 Hz), 4.25 (1H, d, J = 9 Hz), 3.64−3.53 (2H, m), 3.51−3.40 (1H, m), 2.53−2.41 (1H, m), 2.24−2.10 (1H, m). ^{13}C NMR (75 MHz, NaOD): δ 172.1, 170.2, 156.6, 141.5, 132.2, 121.0, 120.4, 116.1, 66.0, 48.5, 46.4, 33.6. MS: (m/z) calcd for $C_{12}H_{14}NO_5$ [M + H]$^+$ 252.1, found: 252.1. HPLC (254 nm) >99.9%; $[\alpha]^{35}_D$ +52.6° (c = 0.35, 2 M NaOH).

*(2S,3R,4S)-3-(3-Carboxyphenyl)-4-propylpyrrolidine-2-carboxylic Acid Hydrochloride (**2f**).* The diacid **22a** (264 mg, 0.699 mmol, 1.00 equiv) was dissolved in DCM (3 mL), followed by the addition of TFA (3 mL). The reaction mixture was stirred at rt for 2 h. The solvents were removed by evaporation in vacuo and coevaporation with DCM (3 × 25 mL), which afforded an off-white solid (285 mg, quant.). The crude product (143 mg) was dissolved in 1 M HCl (5 mL) and evaporated in vacuo, which was repeated twice. The off-white solid was dried in high vacuum (90 mg, 82%). ^{1}H NMR (DMSO-d_6) δ 13.07 (1H, bs), 10.51 (1H, bs), 8.99 (1H, bs), 7.95 (1H, s), 7.87 (1H, d, J = 7.8 Hz), 7.69 (1H, d, J = 7.8 Hz), 7.51 (1H, t, J = 7.7 Hz), 4.33 (1H, d, J = 9.8 Hz), 3.58 (1H, dd, J = 11.0, 7.3 Hz), 3.17 (1H, t, J = 10.3 Hz), 2.97 (1H, t, J = 10.9 Hz), 2.47−2.35 (1H, m), 1.37−1.03 (4H, m), 0.72 (3H, t, J = 7.3 Hz). ^{13}C NMR (DMSO-d_6) δ 169.6, 167.1, 139.5, 132.6, 131.2, 129.0, 128.9, 128.4, 64.4, 53.4, 49.9, 46.0, 32.2, 20.4, 12.9. MS (m/z) calcd for $C_{15}H_{20}NO_4$ [M + H]$^+$ 278.1, found 278.2. $[\alpha]^{25}_D$ +13.3° (c = 0.33 1 M HCl); mp 240−245 °C.

*(2S,3R,4S)-4-Benzyl-3-(3-carboxyphenyl)pyrrolidine-2-carboxylic Acid Hydrochloride (**2g**).* Diacid **22b** (45 mg, 0.11 mmol, 1.00 equiv) in glacial acetic acid (1 mL) was added 2 M HCl/Et_2O (1.0 mL, 2.0 mmol, 18 equiv). The reaction mixture was stirred at rt under nitrogen overnight. The mixture was concentrated in vacuo. The crude product was purified by preparative HPLC (CH_3CN:H_2O (1:1) containing 0.1% TFA) to yield a greenish oil. The crude product was dissolved in 1 M HCl (2 × 40 mL) and concentrated in vacuo. The product was dissolved in H_2O (40 mL) and then lyophilized, affording **2g** (26.5 mg, 69%) as a greenish solid. ^{1}H NMR (300 MHz, (DMSO-d_6): δ 10.55 (1H, bs), 8.00−7.75 (2H, m), 7.48 (1H, m), 7.30−6.80 (5H, m), 4.34 (1H, m), 3.54−2.85 (4H, m), 7.68 (1H, m), 8.96 (1H, bs), 2.57−2.50 (2H, m). ^{13}C NMR (75 MHz, DMSO-d_6): δ 178.3, 169.3, 166.8, 138.8, 138.4, 132.4, 130.9, 128.94, 128.89, 128.3, 128.2, 126.1, 64.4, 52.7, 49.5, 47.5, 35.5. MS (m/z) calcd for $C_{19}H_{20}NO_4$ [M + H]$^+$ 326.1, found: 326.2. $[\alpha]^{27}_D$ +3.1° (c = 0.26, MeOH).

*(2S,3R)-3-(3-Phosphonophenyl)pyrrolidine-2-carboxylic Acid Hydrochloride (**2h**).* To a solution of $NaIO_4$ (601 mg, 4.1 equiv) in H_2O (2.05 mL) and CH_3CN (1.37 mL) was added $RuCl_3$·H_2O (0.015 mmol; 0.022 equiv), followed by a solution of **26** (283 mg, 0.685 mmol, 1.00 equiv) previously dissolved in EtOAc (1.37 mL). The reaction mixture was stirred for 2 h at rt and then filtered and washed by EtOAc. The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed with brine, dried over Na_2SO_4, and evaporated in vacuo to give the crude product (240 mg, 82%), which was used directly in the next step to avoid undesired hydrolysis of the diethyl phosphonate group on purification with silica gel.

A solution of the crude product (83 mg, 0.28 mmol, 1.00 equiv) in 2 M HCl (5 mL, 10 mmol, 36 equiv) was stirred at reflux for 3 days. The aqueous solution was then concentrated in vacuo to give a brown solid (75 mg; quant). The crude product (60 mg) was dissolved in aqueous 0.1% TFA (2 mL) and purified by preparative HPLC. Evaporation to dryness followed by lyophilization from a 1 M HCl solution provided **2h** (32 mg, 47%), as a light-brown crispy solid (hygroscopic). ^{1}H NMR (300 MHz, D_2O, rotamers) δ 7.70−7.59 (2H, m), 7.55−7.40 (2H, m), 4.35 (1H, d, J = 10 Hz), 3.72−3.55 (2H, m), 3.52−3.39 (1H, m), 2.55−2.43 (1H, m), 2.30−2.10 (1H, m). ^{13}C NMR (75 MHz, D_2O, rotamer and carbon−phosphor coupling) δ 178.7, 171.1, 139.3, 139.1, 133.9, 131.72, 131.70, 131.5, 130.5, 130.4, 130.1, 130.0, 129.8, 78.5, 67.2, 65.4, 48.4, 46.6, 44.0, 33.7, 30.5, 21.5. HPLC (210 nm): >99%. MS (m/z) calcd for $C_{11}H_{14}NO_5P$ [M + H]$^+$ 272.0, found 272.0. $[\alpha]^{28}_D$ = +26.8° (c = 0.164, H_2O).

*(S)-tert-Butyl 2-(((tert-Butyldimethylsilyl)oxy)methyl)-5-oxopyrrolidine-1-carboxylate (**4**).* To a solution of commercially available (*S*)-pyroglutaminol (**3**) (1.00 g, 8.69 mmol, 1.0 equiv) in DCM (10 mL) was added imidazole (1.48 g, 21.7 mmol, 2.5 equiv) and TBSCl (1.56 g, 10.4 mmol, 1.2 equiv). The mixture was stirred at rt for 24 h. The solution was diluted with Et_2O (100 mL), and the organic phase was washed with H_2O (2 × 100 mL) and brine (2 × 100 mL), respectively. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo to yield a yellow oil (1.90 g). The oil (1.90 g, 8.2 mmol, 10.0 equiv) was dissolved in CH_3CN (70 mL), cooled to 0 °C, and DMAP (0.11 g, 0.83 mmol, 1.0 equiv) and BOC_2O (3.60 g, 16.5 mmol, 2.0 equiv) added. The reaction mixture was left to stir at rt overnight. The organic phase was washed with brine (3 × 100 mL) and dried over $MgSO_4$. The solution was filtered and concentrated in vacuo to yield a dark, red oil, which was purified using flash chromatography (EtOAc:heptane (1:9)), affording **4** (2.61 g, 91%) as a thick, yellow oil. ^{1}H NMR (300 mHz, $CDCl_3$): δ 4.16 (1H, m), 3.91 (1H, dd, J = 11, 4 Hz), 3.68 (1H, dd, J = 10, 2 Hz), 2.71 (1H, dt, J = 18, 11 Hz), 2.37 (1H, ddd, J = 18, 9, 2 Hz), 2.20−1.95 (2H, m), 1.54 (9H, s), 0.88 (9H, s), 0.05 (3H, s), 0.04 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 150.0, 82.7, 64.4, 59.0, 32.5, 28.2, 26.0, 21.3, 18.3, −5.3, −5.4. $[\alpha]^{22}_D$ −71.6° (c = 0.55, EtOAc); R_f 0.13 (EtOAc:heptane (1:9)).[30]

*(S)-tert-Butyl 2-(((tert-Butyldimethylsilyl)oxy)methyl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (**5**).* Pyrrolidone **4** (7.00 g, 21.2 mmol, 1.00 equiv) was dissolved in dry THF (12.5 mL), cooled to −78 °C, and 1 M LHMDS (48.0 mL, 48.0 mmol, 2.26 equiv) added dropwise over the course of 1 h. The mixture was left to stir at −78 °C for 1 h, after which a solution of PhSeCl (5.50 g, 28.7 mmol, 1.35 equiv) in dry THF (8 mL) was added dropwise over the course of 30 min. The mixture was left to stir at −78 °C for 45 min before being quenched with satd NH_4Cl (10 mL) and stirred for 10 min. The mixture was transferred to a separation funnel containing satd $NaHCO_3$ (100 mL) and the flask flushed with Et_2O (2 × 50 mL), which was also transferred to the separation funnel. The organic phase was isolated and filtered through a plug of Celite to remove insoluble material. The aqueous phase was re-extracted with Et_2O (2 × 75 mL), and the combined organic phases were washed with brine (75 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified using DCVC (7 cm, 75 mL fractions, 0−20% EtOAc in heptane) to yield an orange solid (7.52 g).

The selenyl diastereomers were dissolved in EtOAc (60 mL), cooled to 0 °C, and 30% H_2O_2 (15 mL) added over the course of 10 min. The mixture was left at 0 °C for 15 min before stirred at rt for 1 h. The mixture was poured into a separation funnel containing satd $NaHCO_3$ (100 mL). The phases were separated and the aqueous phase extracted with EtOAc (2 × 75 mL). The combined organic phases was washed with brine (75 mL), dried over $MgSO_4$, concentrated in vacuo, and purified using DCVC (diameter 7 cm, 75 mL fractions, 0−30% EtOAc in heptane) to yield enone **5** (4.42 g, 64%) as a white solid. ^{1}H NMR (300 mHz, $CDCl_3$): δ 7.26 (1H, dd, J = 6, 2 Hz), 6.13 (1H, dd, J = 6, 2 Hz), 4.60 (1H, m), 4.16 (1H, dd, J = 10, 4 Hz), 3.72 (1H, dd, J = 10, 7 Hz), 1.57 (9H, s), 0.88 (9H, s), 0.06 (1.5H, s), 0.05 (1.5H, s), 0.01 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 149.7, 149.4, 127.0, 82.9, 63.6, 62.4, 28.2, 25.7, 18.1, −5.4, −5.5. MS (m/z) calcd for $C_{11}H_{22}NO_2Si$ [M + H]$^+$ 228.1, found: 228.0. $[\alpha]^{31}_D$ −173.4° (c = 0.77, abs EtOH); R_f 0.25 (EtOAc:heptane (1:4)).

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*6-Bromo-2,2-dimethyl-4H-benzo[d][1,3]dioxane (**6a**).* A round-bottomed flask was charged with 4-bromo-2-(hydroxymethyl)phenol (5.46 g, 26.9 mmol, 1.00 equiv) and anhydrous $ZnCl_2$ (9.89 g, 72.6 mmol, 2.70 equiv) under an atmosphere of nitrogen. Dry acetone (40 mL) was added via a syringe, followed by 2,2-dimethoxypropane (16.5 mL, 14.0 g, 135 mmol, 5.00 equiv). The reaction mixture was heated to 40 °C and stirred for 1.5 h and then cooled to ambient temperature. Saturated aqueous Na_2CO_3 (50 mL) was added to quench the reaction and filtered by suction to remove $ZnCO_3$. The solid was washed with EtOAc (40 mL). The biphasic filtrate was transferred to a separating funnel, and the yellow organic layer was separated. The colorless aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were quickly dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to dryness. The crude product was purified by DCVC using an isocratic eluent (10% EtOAc in heptane). The purified product was coevaporated with DCM (3 × 25 mL), followed by drying in high vacuum overnight (5.73 g, 88%). The product **6a** crystallized upon storage in the refrigerator. ^{1}H NMR ($CDCl_3$): δ 7.23 (1H, dd, J = 7.4, 1.5 Hz), 7.08 (1H, d, J = 1.5 Hz), 6.68 (1H, d, J = 8.5 Hz), 4.79 (2H, s), 1.52 (6H, s). R_f 0.57 (15% EtOAc in heptane).[41]

*((3-Bromo-5-propoxybenzyl)oxy)(tert-butyl)dimethylsilane (**6b**).* Phenol **16** (4.00 g, 12.6 mmol, 1.00 equiv) was dissolved in DMF (25 mL) and added K_2CO_3 (3.48 g, 25.2 mmol, 2.00 equiv) and propyl bromide (2.30 mL, 3.11 g, 25.3 mmol, 2.01 equiv). The mixture was left to stir at rt for 18 h. The mixture was added Et_2O (200 mL) and washed with water (3 × 100 mL) and brine (75 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The mixture was purified by DCVC (diameter = 6 cm, 75 mL fractions, 0−10% EtOAc in heptane) to yield **6b** (4.09 g, 90%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (1H, s), 6.92 (1H, s), 6.81 (1H, s), 4.67 (2H, s), 3.90 (2H, t, J = 7 Hz), 1.81 (2H, sextet, J = 7 Hz), 1.04 (3H, t, J = 8 Hz), 0.96 (9H, s), 0.12 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 144.7, 122.6, 121.1, 116.2, 111.1, 69.9, 64.4, 26.2, 22.7, 18.7, 10.7, −5.0. R_f 0.77 (EtOAc:heptane (1:10)).

*((3-(Benzyloxy)-5-bromobenzyl)oxy)(tert-butyl)dimethylsilane (**6c**).* Phenol **16** (3.50 g, 11.0 mmol, 1.00 equiv) was dissolved in acetone (50 mL) and added K_2CO_3 (3.10 g, 22.4 mmol, 2.04 equiv) and benzyl bromide (2.10 mL, 3.02 g, 17.7 mmol, 1.61 equiv). The mixture was left to stir at reflux for 24 h. Piperazine (4.75 g, 55.1 mmol, 5.01 equiv) was added and the mixture refluxed for another 2.5 h. The mixture was cooled to rt and concentrated in vacuo. To the mixture was added water (50 mL) and EtOAc (50 mL) and transferred to a separation funnel containing EtOAc (100 mL) and satd NH_4Cl (100 mL). After separation, the aqueous phase was extracted with EtOAc (50 mL). The combined organic phases were washed with brine (80 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The mixture was purified by DCVC (diameter = 7 cm, 75 mL fractions, 0−8% EtOAc in heptane) to yield 7 (4.25 g, 95%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45−7.30 (5H, m), 7.06 (1H, s), 7.02 (1H, s), 6.90 (1H, s), 5.05 (2H, s), 4.68 (2H, s), 0.96 (9H, s), 0.12 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 144.8, 136.5, 128.6, 128.1, 127.5, 122.6, 121.5, 116.6, 111.3, 70.3, 64.3, 26.2, 18.6, −5.0. R_f 0.65 (EtOAc:heptane (1:10)).

*((3-([1,1′-Biphenyl]-3-ylmethoxy)-5-bromobenzyl)oxy)(tert-butyl)dimethylsilane (**6d**).* Phenol **16** (3.00 g, 9.46 mmol, 1.00 equiv) was dissolved in acetone (50 mL) and added K_2CO_3 (2.61 g, 18.9 mmol, 2.00 equiv) and 3-phenylbenzyl bromide (3.52 g, 14.2 mmol, 1.50 equiv). The mixture was left to stir at reflux for 24 h. Piperazine (4.10 g, 47.6 mmol, 5.0 equiv) was added and the mixture refluxed for another 2.5 h. The mixture was cooled to rt and concentrated in vacuo. To the mixture was added water (50 mL) and EtOAc (50 mL) and transferred to a separation funnel containing EtOAc (100 mL) and satd NH_4Cl (100 mL). After separation, the aqueous phase was extracted with EtOAc (50 mL). The combined organic phases was washed with brine (80 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The mixture was purified using DCVC (diameter = 7 cm, 75 mL fractions, 0−8% EtOAc in heptane) to yield **6d** (4.21 g, 92%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67−7.53 (4H, m), 7.51−7.32 (5H, m), 7.09−7.02 (2H, m), 6.92 (1H, s), 5.11 (2H, s), 4.68 (2H, s), 0.96 (9H, s), 0.11 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.0, 129.1, 128.8, 127.5, 127.2, 127.0, 126.4, 126.3, 122.6, 121.6, 116.6, 111.3, 70.3, 64.3, 26.2, 18.6, −5.0. R_f 0.58 (EtOAc:heptane (1:10)).

*tert-butyl (2S,3R)-2-(((tert-butyldimethylsilyl)oxy)methyl)-3-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)-5-oxopyrrolidine-1-carboxylate (**7a**).* A dry round-bottomed flask was charged with the bromide (1.86 g, 7.63 mmol, 2.50 equiv), and a nitrogen atmosphere was applied thoroughly. Dry Et_2O (25 mL) was added via a syringe, and the clear, pale-yellow solution was cooled to −78 °C. *tert*-BuLi in pentane (10.2 mL, 978 mg, 15.3 mmol, 5.00 equiv, 1.50 M) was added dropwise over the course of 25 min. The reaction mixture became milky due to precipitation. After 10 min of stirring at −78 °C, a suspension of CuCN (342 mg, 3.82 mmol, 1.25 equiv) in dry Et_2O (2.4 mL) was added portionwise. The resulting suspension was stirred at −78 °C for 5 min and then at −42 °C for 10 min, after which it was recooled to −78 °C. Enone **5** (1.00 g, 3.05 mmol, 1.00 equiv) was dissolved in dry Et_2O (3.0 mL) and added dropwise to the cuprate mixture at −78 °C, which resulted in a slight color change to orange. The temperature was raised to −42 °C, and the reaction mixture was stirred at this temperature for 1 h. The dark-brown solution with barely any precipitation was quenched by addition of satd aqueous NH_4Cl (5 mL), allowed to warm up to ambient temperature, and then transferred to a separating funnel with brine (30 mL) and EtOAc (30 mL). The organic layer was separated, and the blue aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to dryness. Purification by DCVC (0−20% EtOAc in heptane) afforded the desired product **7a** (1.05 g, 70%) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 6.98 (1H, dd, J = 8.5, 2.2 Hz), 6.78 (2H, dd, J = 5.1, 3.2 Hz), 4.82 (2H, s), 4.05−3.97 (2H, m), 3.80 (1H, dd, J = 9.9, 1.7 Hz), 3.38 (1H, dt, J = 9.4, 2.5), 3.15 (1H, dd, J = 17.7, 9.5 Hz), 2.50 (1H, dd, J = 17.6, 2.5 Hz), 1.56 (6H, s), 1.55 (9H, s), 0.93 (9H, s), 0.10 (3H, s), 0.09 (3H, s). ^{13}C NMR ($CDCl_3$): δ 174.1, 150.1, 149.8, 136.1, 126.2, 122.2, 119.7, 117.5, 99.9, 99.5, 83.1, 67.0, 63.6, 60.9, 40.1, 38.2, 28.2, 25.9, 24.9, 24.8, 18.3, −5.4. MS (m/z) calcd for $C_{21}H_{34}NO_4Si$ $[M-Boc+H]^+$ 392.2, found 392.2. $[\alpha]^{25}_D$ −20.7° (c = 0.28, EtOH); R_f 0.40 (25% EtOAc in heptane).

*(2S,3R)-tert-Butyl 2-(((tert-Butyldimethylsilyl)oxy)methyl)-3-(3-(((tert-butyldimethylsilyl)oxy)-methyl)-5-propoxyphenyl)-5-oxopyrrolidine-1-carboxylate (**7b**).* Solution A: Thiophene (482 mg, 5.74 mmol, 1.57 equiv) was dissolved in dry Et_2O (6 mL) in a dry vial under an atmostphere of nitrogen and cooled to 0 °C. *n*-BuLi (2.34 mL, 5.85 mmol, 1.60 equiv, 2.50 M) was added dropwise over 15 min and the mixture left to stir at 0 °C for 15 min, then at rt for 2 h (a white, colloid precipitate was formed). Bromide **6b** (1.65 g, 4.59 mmol, 1.25 equiv) was dissolved in dry Et_2O (50 mL) in a dry flask under an atmosphere of nitrogen and cooled to −78 °C. *tert*-BuLi (5.76 mL, 9.22 mmol, 2.52 equiv, 1.60 M) was added dropwise over the course of 20 min. The mixture was left to stir at −78 °C for 45 min (the solution became slightly colored and unclear) before a suspension of CuCN (410 mg, 4.58 mmol, 1.25 equiv) in dry Et_2O (4 mL) was added dropwise over the course of 6 min. The mixture was left to stir at −78 °C for 10 min, then 10 min at −42 °C before being recooled to −78 °C. The mixture was added dropwise to solution A (7.1 mL, 4.6 mmol, 1.25 equiv) over the course of 20 min and left to stir at −78 °C for 10 min, then at −42 °C for 10 min before being recooled to −78 °C. A solution of enone **5** (1.20 g, 3.66 mmol, 1.00 equiv) dissolved in Et_2O (10 mL) was dropwise added over the course of 25 min. The mixture instantly turned highly yellow and was left to stir at −78 °C for 10 min, then at −42 °C for 45 min before being quenched using satd NH_4Cl (8 mL). The mixture was transferred to a separation funnel containing satd $NaHCO_3$ (50 mL) and EtOAc (50 mL). The phases were separated and the aqueous phase extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by DCVC (0−12% EtOAc in heptane and 0−5% EtOAc in PhMe) yielded **7b** (1.38 mg, 62%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.80 (1H, m), 6.68 (1H, s), 6.60 (1H, m), 4.68 (2H, s), 4.07 (1H, m), 4.00 (1H, dd, J = 10, 4 Hz), 3.91 (2H, t, J = 7 Hz), 3.79 (1H, dd, J = 11, 2 Hz), 3.40 (1H, dt, J = 10, 2 Hz), 3.12 (1H, dd, J = 18, 10 Hz), 2.54 (1H, dd, J = 18, 3 Hz), 1.81 (2H, d, J = 7 Hz), 1.54 (9H, s), 1.04 (3H, t, J = 8 Hz), 0.96 (9H, s),

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0.92 (9H, s), 0.12 (6H, s), 0.10 (3H, s), 0.08 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 159.7, 149.8, 145.6, 143.9, 116.0, 111.6, 110.5, 83.0, 69.6, 66.8, 64.9, 63.8, 40.0, 38.9, 28.3, 26.2, 26.1, 22.8, 18.6, 18.4, 10.7, −5.0, −5.2. MS (m/z) calcd for $C_{27}H_{50}NO_4Si_2$ $[M + H - Boc]^+$ 508.3, found 508.1. R_f 0.49 (EtOAc:toluene (1:10)); $[\alpha]^{23}_D$ −22.3° (c = 0.30, abs EtOH).

*(2S,3R)-tert-Butyl 3-(3-(Benzyloxy)-5-(((tert-butyldimethylsilyl)-oxy)methyl)phenyl)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-oxo-pyrrolidine-1-carboxylate (**7c**).* Bromide **6c** (2.01 g, 4.93 mmol, 1.25 equiv) was dissolved in dry Et_2O (60 mL) in a dry flask under an atmosphere of nitrogen and cooled to −78 °C. *tert*-BuLi (6.18 mL, 9.89 mmol, 2.51 equiv, 1.60 M) was added dropwise over the course of 15 min, and the mixture was left to stir at −78 °C for 30 min. The solution became slightly yellow colored and unclear before a suspension of CuCN (440 mg, 4.91 mmol, 1.25 equiv) in dry Et_2O (4 mL) was added dropwise over the course of 5 min. The mixture was left to stir at −78 °C for 10 min, then 10 min at −42 °C before being recooled to −78 °C. To the mixture was added dropwise solution A (9.0 mL, 4.9 mmol, 1.34 equiv) over the course of 15 min and left to stir at −78 °C for 10 min, then at −42 °C for 10 min before being recooled to −78 °C. A solution of enone **5** (1.29 g, 3.94 mmol, 1.00 equiv) dissolved in Et_2O (4 mL) was dropwise added over the course of 15 min, and the mixture instantly turned bright yellow. The mixture was left to stir at −78 °C for 15 min, then at −42 °C for 40 min before quenched using satd NH_4Cl (10 mL). The mixture was transferred to a separation funnel containing satd $NaHCO_3$ (75 mL) and EtOAc (75 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine (75 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by DCVC (diameter = 7, 75 mL fractions, 0−10% EtOAc in heptane) to yield **7c** (1.11 g, 43%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45−7.28 (5H, m), 6.89 (1H, s), 6.73−6.67 (2H, m), 5.05 (2H, s), 4.69 (2H, s), 4.07 (1H, m), 4.00 (1H, dd, J = 11, 4 Hz), 3.79 (1H, dd, J = 11, 2 Hz), 3.31 (1H, d, J = 9 Hz), 3.13 (1H, dd, J = 18, 10 Hz), 2.53 (1H, dd, J = 18, 2 Hz), 1.54 (9H, s), 0.95 (9H, s), 0.93 (9H, s), 0.11 (6H, s), 0.10 (3H, s), 0.09 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 159.5, 150.0, 145.8, 144.2, 137.0, 128.8, 128.2, 127.7, 116.6, 112.2, 111.0, 83.2, 70.2, 67.0, 65.1, 64.0, 40.2, 39.1, 28.5, 26.4, 26.3, 18.8, 18.6, −4.8, −5.0. MS (m/z) calcd for $C_{31}H_{50}NO_4Si_2$ $[M + H - Boc]^+$ 556.3, found: 556.3. R_f 0.44 (EtOAc:heptane (1:4)); $[\alpha]^{35}_D$ −22.2° (c = 0.89, abs EtOH).

*(2S,3R)-tert-Butyl 3-(3-([1,1′-Biphenyl]-3-ylmethoxy)-5-(((tert-butyldimethylsilyl)oxy)-methyl)phenyl)-2-(((tert-butyldimethylsilyl)-oxy)methyl)-5-oxopyrrolidine-1-carboxylate (**7d**).* Bromide **6d** (3.17 g, 6.56 mmol, 1.24 equiv) was dissolved in dry Et_2O (80 mL) in a dry flask under an atmosphere of nitrogen and cooled to −78 °C. *tert*-BuLi (8.28 mL, 13.25 mmol, 2.51 equiv, 1.60 M) was then added dropwise over the course of 30 min. The mixture was left to stir at −78 °C for 45 min (the solution became yellow colored) before a suspension of CuCN (590 mg, 6.59 mmol, 1.25 equiv) in dry Et_2O (4 mL) was added dropwise over the course of 15 min. The mixture was left to stir at −78 °C for 10 min (mixture turned wine red), then 15 min at −42 °C before recooled to −78 °C over the course of 10 min. The mixture was dropwise added to solution A (9.9 mL, 6.6 mmol, 1.25 equiv) over the course of 30 min and left to stir at −78 °C for 10 min, then at −42 °C for 10 min before being recooled to −78 °C. A solution of enone **5** (1.73 g, 5.28 mmol, 1.00 equiv) dissolved in Et_2O (4 mL) was dropwise added over the course of 15 min (the mixture turned slightly yellow). The mixture was left to stir at −78 °C for 15 min, then at −42 °C for 90 min before being quenched using satd NH_4Cl (12 mL). The mixture was transferred to a separation funnel containing satd $NaHCO_3$ (75 mL) and EtOAc (75 mL). The phases were separated and the aqueous phase extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine (75 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by DCVC (0−10% EtOAc in heptane and 0−4% EtOAc in toluene) yielded **7d** (1.62 g, 42%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70−7.53 (4H, m), 7.52−7.33 (5H, m), 6.94 (1H, m), 6.74 (2H, m), 5.13 (2H, s), 4.71 (2H, s), 4.10 (1H, m), 4.02 (1H, dd, J = 10, 4 Hz), 3.81 (1H, dd, J = 10, 2 Hz), 3.44 (1H, dm, J = 10 Hz), 3.16 (1H, dd, J = 18, 9 Hz), 2.57 (1H, dd, J = 18, 3 Hz), 1.55 (9H, s), 0.96 (9H, s), 0.94 (9H, s), 0.12 (6H, s), 0.11 (3H, s), 0.10 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.3, 149.8, 145.7, 144.0, 141.6, 140.8, 137.3, 129.1, 128.8, 127.4, 127.2, 126.9, 126.4, 126.3, 116.4, 112.1, 110.6, 83.1, 70.1, 66.8, 64.9, 63.8, 40.1, 38.9, 28.3, 26.2, 26.1, 18.6, 18.4, −5.0, −5.2. MS (m/z) calcd for $C_{37}H_{54}NO_4Si_2$ $[M + H - Boc]^+$ 632.4, found: 632.4. R_f 0.38 (EtOAc:heptane (1:4)); $[\alpha]^{31}_D$ −22.7° (c = 0.71, abs EtOH).

*(2S,3R)-tert-Butyl 2-(((tert-Butyldimethylsilyl)oxy)methyl)-3-(2,2-dimethyl-4H-benzo[d][1,3]-dioxin-6-yl)pyrrolidine-1-carboxylate (**8a**).* A round-bottomed flask was charged with lactam **7a** (558 mg, 1.14 mmol, 1.00 equiv) and equipped with a condenser, and an atmosphere of nitrogen was applied. Through the septum, dry THF (15 mL) and 1 M BH_3·THF (7.5 mL, 648 mg, 7.54 mmol, 6.00 equiv) were added via syringes, and the colorless reaction mixture was heated to reflux (80 °C) for 3.5 h, then cooled to 0 °C and THF (10 mL), H_2O (1 mL), 2 M NaOH (13 mL), and 30% H_2O_2 (4 mL) were added sequentially. The mixture was stirred for 3.5 h at rt and then quenched by addition of satd aqueous $NaHCO_3$ (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to dryness. Purification by DCVC (0−15% EtOAc in heptane) afforded the desired product **8a** (248 mg, 46%) as a colorless, viscous oil. R_f 0.47 (25% EtOAc in heptane). ^{1}H NMR ($CDCl_3$): δ 7.05−6.96 (1H, m), 6.81−6.75 (2H, m), 4.83 (2H, s), 4.01 (1H, dd, J = 10.3, 3.7 Hz), 3.79−3.60 (4H, m), 3.45 (1H, td, J = 7.2, 5.4 Hz), 3.37−3.26 (1H, m), 2.30−2.16 (1H, m), 1.94−1.79 (1H, m), 1.56 (6H, s), 1.50 (9H, s), 0.91 (9H, s), 0.06 (6H, s). ^{13}C NMR ($CDCl_3$): δ (rotamers) 154.2, 149.6, 135.7, 135.1, 127.0, 126.8, 123.2, 123.1, 119.2, 117.0, 99.4, 79.4, 65.7, 65.5, 62.8, 61.4, 61.0, 47.0, 46.4, 46.0, 44.9, 33.0, 31.8, 28.7, 26.0, 24.9, 18.3, −5.2. MS (m/z) calcd for $C_{21}H_{36}NO_3Si$ $[M - Boc + H]^+$ 378.3, found 378.2. $[\alpha]^{25}_D$ +9.7° (c = 0.68, abs. EtOH).

*(2S,3R)-tert-Butyl 2-(((tert-Butyldimethylsilyl)oxy)methyl)-3-(3-(((tert-butyldimethylsilyl)oxy)-methyl)-5-propoxyphenyl)-pyrrolidine-1-carboxylate (**8b**).* Lactam **7c** (1.43 g, 2.35 mmol, 1.0 equiv) was dissolved in dry THF (25 mL) and 1 M BH_3·THF complex (25 mL, 25 mmol, 10.6 equiv) added over the course of 5 min. The mixture was refluxed under an atmosphere of nitrogen for 20 h. The mixture was cooled to 0 °C and H_2O (5 mL) added dropwise over the course of 10 min, NaOH (2 M, 25 mL) dropwise over the course of 20 min, and H_2O_2 (30%, 5 mL) over the course of 5 min (organic/aqueous ratio important). After 5 min, the mixture was remove from the ice bath and left to stir at rt for 1 h. The mixture was poured into satd $NaHCO_3$ (100 mL) and EtOAc (75 mL). After separation, the aqueous phase was extracted with EtOAc (2 × 75 mL), and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and purified using DCVC (dia = 4 cm, 30 mL fractions, 0−5% EtOAc in toluene) to yield **8b** (820 mg, 59%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (1H, m), 6.73 (1H, s), 6.66 (1H, m), 4.07−3.98 (0.5H, m), 3.91 (2H, t, J = 6 Hz), 3.80−3.55 (3H, m), 3.87−3.80 (0.5H, m), 3.49 (1H, m), 3.42−3.25 (1H, m), 2.32−2.17 (1H, m), 1.95−1.82 (1H, m), 1.81 (2H, h, J = 7 Hz), 1.49 (9H, s), 1.04 (3H, t, J = 7 Hz), 0.96 (9H, s), 0.91 (9H, s), 0.12 (6H, s), 0.06 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 154.3, 154.2, 145.4, 144.9, 143.2, 143.1, 117.4, 117.1, 112.3, 110.2, 109.9, 79.5, 79.1, 69.5, 65.7, 65.5, 65.1, 62.9, 61.5, 47.2, 46.7, 45.7, 32.8, 31.8, 28.8, 26.2, 26.1, 22.8, 18.7, 18.4, 10.8, −4.9, −5.1. MS (m/z) calcd for $C_{27}H_{52}NO_3Si_2$ $[M - Boc + H]^+$ 494.4, found 494.4. R_f 0.44 (EtOAc:toluene (1:20)); $[\alpha]^{23}_D$ +11.5° (c = 0.30, abs EtOH).

*(2S,3R)-tert-Butyl 3-(3-(Benzyloxy)-5-(((tert-butyldimethylsilyl)-oxy)methyl)phenyl)-2-(((tert-butyldimethylsilyl)oxy)methyl)-pyrrolidine-1-carboxylate (**8c**).* Lactam **7c** (1.66 g, 2.53 mmol, 1.00 equiv) was dissolved in dry THF (20 mL) and 1 M BH_3·THF complex (25 mL, 25 mmol, 9.88 equiv) added over the course of 5 min. The mixture was refluxed under an atmosphere of nitrogen for 20 h. The mixture was cooled to 0 °C, THF (40 mL) added, and H_2O (6 mL) added dropwise over the course of 15 min. NaOH (2 M, 30 mL) was added dropwise over the course of 15 min and H_2O_2 (30%, 10 mL) over the course of 15 min (organic/aqueous ratio important). After 5 min, the mixture was removed from the ice bath and left to stir at rt for 1 h. The mixture was poured into satd $NaHCO_3$ (100 mL) and EtOAc

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(75 mL). After separation, the aqueous phase was extracted with EtOAc (2 × 75 mL) and the combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified using DCVC (dia = 4 cm, 30 mL fractions, 0−2% EtOAc in toluene) to yield **8c** (976 mg, 60%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47−7.30 (5H, m), 6.86 (1H, m), 6.80−6.71 (2H, m), 5.06 (2H, s), 4.71 (2H, s), 4.05 (0.5H, dd, J = 10, 4 Hz), 3.86 (0.5H, m), 3.80−3.58 (3H, m), 3.55−3.46 (1H, m), 3.43−3.27 (1H, m), 2.35−2.18 (1H, m), 2.00−1.85 (1H, m), 1.51 (9H, s), 0.97 (9H, s), 0.93 (9H, s), 0.12 (6H, s), 0.08 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 154.2, 154.1, 145.4, 145.0, 143.3, 143.2, 137.03, 136.99, 128.6, 127.9, 127.5, 117.7, 117.5, 112.7, 110.4, 110.2, 79.5, 79.2, 77.6, 77.2, 76.7, 70.0, 65.6, 65.5, 65.0, 62.8, 61.5, 47.2, 46.7, 45.7, 32.8, 31.8, 28.8, 26.2, 26.1, 18.7, 18.4, −4.9, −5.1. MS (m/z) calcd for $C_{31}H_{52}NO_3Si_2$ $[M - Boc + H]^+$ 542.4, found 542.4 (−Boc). R_f 0.20 (EtOAc:toluene (1:40)); $[\alpha]^{35}_D$ +3.2° (c = 0.50, abs EtOH).

*(2S,3R)-tert-Butyl 3-(3-([1,1′-Biphenyl]-3-ylmethoxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-phenyl)-2-(((tert-butyldimethylsilyl)-oxy)methyl)pyrrolidine-1-carboxylate (**8d**).* Lactam **7d** (1.77 g, 2.42 mmol, 1.00 equiv) was dissolved in dry THF (20 mL) and 1 M BH_3·THF complex (25 mL, 25 mmol, 10.3 equiv) added over the course of 5 min. The mixture was refluxed under an atmosphere of nitrogen for 20 h. The mixture was cooled to 0 °C, THF (40 mL) added, and H_2O (6 mL) added dropwise over the course of 15 min. NaOH (2 M, 30 mL) was added dropwise over the course of 15 min and H_2O_2 (30%, 10 mL) over the course of 15 min (organic/aqueous ratio important). After 5 min, the mixture was removed from the ice bath and left to stir at rt for 1 h. The mixture was poured into satd $NaHCO_3$ (100 mL) and EtOAc (75 mL). After separation, the aqueous phase was extracted with EtOAc (2 × 75 mL) and the combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified using DCVC (dia = 4 cm, 30 mL fractions, 0−2% EtOAc in PhMe) to yield **8d** (887 mg, 51%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72−7.55 (4H, m), 7.52−7.33 (5H, m), 6.91 (1H, m), 6.84−6.78 (2H, m), 5.14 (2H, s), 4.74 (2H, s), 4.08 (0.5H, dd, J = 10, 4 Hz), 3.90 (0.5H, m), 3.86−3.62 (3H, m), 3.55 (1H, m), 3.38 (1H, m), 2.28 (1H, m), 1.94 (1H, m), 1.53 (9H, s), 0.99 (9H, s), 0.95 (9H, s), 0.14 (6H, s), 0.10 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 154.23, 154.15, 145.4, 145.0, 143.34, 143.26, 141.6, 140.9, 137.54, 137.49, 129.0, 128.8, 127.4, 127.2, 126.8, 126.44, 126.35, 117.8, 117.6, 112.8, 110.3, 110.1, 79.5, 79.2, 70.0, 65.6, 65.5, 65.0, 62.8, 61.5, 47.2, 46.7, 45.7, 32.8, 31.8, 28.8, 26.2, 26.1, 18.6, 18.4, −4.9, −5.1. MS (m/z) calcd for $C_{37}H_{56}NO_3Si_2$ $[M - Boc + H]^+$ 618.4, found 618.4. R_f 0.21 (EtOAc:toluene (1:40)); $[\alpha]^{35}_D$ +1.9° (c = 0.67, abs EtOH).

*(2S,3R)-tert-Butyl 3-(2,2-Dimethyl-4H-benzo[d][1,3]dioxin-6-yl)-2-(hydroxymethyl)-pyrrolidine-1-carboxylate (**9a**).* The protected alcohol (448 mg, 0.94 mmol, 1.0 equiv) was dissolved in dry THF (9 mL) under an atmosphere of nitrogen and 1 M TBAF in THF (2.8 mL, 736 mg, 2.81 mmol, 3.0 equiv) was added at rt. The reaction mixture was stirred for 2 h, whereafter H_2O (20 mL) and satd $NaHCO_3$ (20 mL) were added, and following extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated in vacuo to dryness. Purified by DCVC (15−35% EtOAc in heptane), followed by drying in high vacuum overnight, afforded the desired alcohol as a colorless, viscous oil, which crystallized to a white solid (295 mg, 87%). ^{1}H NMR ($CDCl_3$): δ 7.02 (1H, dd, J = 8.4, 2.3 Hz), 6.84 (1H, bs), 6.76 (1H, d, J = 8.3 Hz), 5.13 (1H, bd, J = 8.0 Hz), 4.82 (2H, s), 3.86 (1H, t, J = 7.8 Hz), 3.73 (2H, t, J = 9.4 Hz), 3.64−3.57 (1H, m), 3.33 (1H, dt, J = 10.6, 6.3 Hz), 2.84−2.76 (1H, m), 2.15−2.08 (1H, m), 1.99−1.85 (1H, m), 1.55 (6H, s), 1.51 (9H, s). ^{13}C NMR ($CDCl_3$): δ 156.7, 150.1, 132.2, 127.2, 123.5, 119.4, 117.2, 99.5, 80.5, 67.2, 66.0, 60.9, 47.3, 47.1, 33.1, 28.5, 24.8, 24.7. MS (m/z) calcd for $C_{16}H_{22}NO_5$ $[M - {}^tBu + H]^+$ 308.2, found 308.1. $[\alpha]^{25}_D$ +14.2° (c = 0.86, EtOH); mp 110−112 °C.

*(2S,3R)-tert-Butyl 2-(Hydroxymethyl)-3-(3-(hydroxymethyl)-5-propoxyphenyl)pyrrolidine-1-carboxylate (**9b**).* Pyrrolidine **8b** (1.30 g, 2.19 mmol, 1.00 equiv) was dissolved in dry THF (12 mL) in a dry vial and 1 M TBAF (8.80 mL, 8.80 mmol, 4.02 equiv) added. The mixture was left to stir at rt for 18 h. The mixture was quenched using 50% satd $NaHCO_3$ (50 mL) and transferred to a separation funnel containing EtOAc (25 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL), and the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified using DCVC (dia = 3 cm, 25 mL fractions, 0−90% EtOAc in heptane) to yield diol **9b** (736 mg, 92%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84−6.78 (2H, m), 6.70 (1H, m), 5.07 (1H, m), 4.65 (2H, s), 3.92 (2H, t, J = 7 Hz), 3.90−3.68 (3H, m), 3.62 (1H, dd, J = 11, 7 Hz), 3.35 (1H, m), 2.86 (1H, m), 2.15 (1H, m), 2.07−1.90 (2H, m), 1.81 (2H, h, J = 7 Hz), 1.51 (9H, s), 1.05 (3H, t, J = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 156.8, 142.9, 142.5, 118.2, 113.6, 111.3, 80.7, 69.7, 67.2, 66.2, 65.4, 48.1, 47.4, 33.1, 28.7, 22.8, 10.8. MS (m/z) calcd for $C_{16}H_{24}NO_5$ $[M - {}^tBu + H]^+$ 310.2, found 310.2. R_f 0.37 (EtOAc:heptane (3:1)); $[\alpha]^{23}_D$ +23.9° (c = 0.31, abs EtOH).

*(2S,3R)-tert-Butyl 3-(3-(Benzyloxy)-5-(hydroxymethyl)phenyl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**9c**).* Pyrrolidine **8c** (967 g, 1.51 mmol, 1.00 equiv) was dissolved in dry THF (15 mL) in a dry vial and 1 M TBAF (6 mL, 6 mmol, 3.97 equiv) added. The mixture was left to stir at rt for 18 h. The mixture was quenched using 50% satd $NaHCO_3$ (50 mL) and transferred to a separation funnel containing EtOAc (50 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL), and the combined organic phases were washed with brine (75 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified using DCVC (dia = 4 cm, 30 mL fractions, 0−100% EtOAc in heptane) to yield diol **9c** (572 mg, 92%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45−7.28 (5H, m), 6.88 (1H, m), 6.85 (1H, m), 6.79 (1H, m), 5.09 (1H, m), 5.06 (2H, s), 4.65 (2H, s), 3.95 (1H, m), 3.90−3.67 (3H, m), 3.61 (1H, dd, J = 11, 7 Hz), 3.34 (1H, m), 2.87 (1H, m), 2.14 (1H, m), 2.08−1.89 (2H, m), 1.51 (9H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.3, 153.6, 153.2, 145.0, 144.8, 144.2, 137.0, 128.3, 127.7, 127.5, 117.4, 111.8, 110.4, 78.5, 78.4, 69.0, 65.5, 62.8, 60.8, 60.7, 46.0, 45.8, 45.3, 44.5, 31.2, 30.5, 28.2. MS (m/z) calcd for $C_{20}H_{24}NO_5$ $[M - {}^tBu + H]^+$ 358.2, found: 358.2. R_f 0.42 (EtOAc:heptane (3:1)); $[\alpha]^{35}_D$ +12.3° (c = 0.44, abs EtOH).

*(2S,3R)-tert-Butyl 3-(3-([1,1′-Biphenyl]-3-ylmethoxy)-5-(hydroxymethyl)phenyl)-2-(hydroxymethyl)-pyrrolidine-1-carboxylate (**9d**).* **8d** (800 g, 1.11 mmol, 1.00 equiv) was dissolved in dry THF (15 mL) in a dry vial and 1 M TBAF (5.00 mL, 5.00 mmol, 4.50 equiv) added. The mixture was left to stir at rt for 18 h. The mixture was quenched using phosphate buffer (50 mL, pH 7) and transferred to a separation funnel containing EtOAc (50 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL), and the combined organic phases was washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified using DCVC (dia = 4 cm, 30 mL fractions, 0−90% EtOAc in heptane) to yield diol **9d** (512 mg, 94%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60−7.53 (4H, m), 7.50−7.32 (5H, m), 6.91 (1H, m), 6.86 (1H, s), 6.81 (1H, m), 5.24 (1H, m), 5.10 (2H, s), 4.63 (2H, s), 3.96 (1H, m), 3.65 (2H, m), 3.63 (1H, dd, J = 11, 7 Hz), 3.34 (1H, m), 3.00−2.60 (2H, m), 2.14 (1H, m), 1.97 (1H, m), 1.51 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 156.7, 143.2, 142.5, 141.5, 140.8, 137.3, 129.0, 128.8, 127.4, 127.2, 126.8, 126.5, 126.4, 118.5, 113.7, 111.3, 80.7, 70.1, 67.0, 65.9, 64.9, 47.9, 47.2, 32.9, 28.6. MS (m/z) calcd for $C_{26}H_{28}NO_5$ $[M - {}^tBu + H]^+$ 434.2, found 434.2. R_f 0.39 (EtOAc:heptane (3:1)); $[\alpha]^{35}_D$ +10.2° (c = 0.53, abs EtOH).

*(2S,3R)-1-(tert-Butoxycarbonyl)-3-(2,2-dimethyl-4-oxo-4H-benzo-[d][1,3]dioxin-6-yl)pyrrolidine-2-carboxylic Acid (**10a**) and (2S,3R)-1-(tert-Butoxycarbonyl)-3-(2,2-dimethyl-4H-benzo[d][1,3]dioxin-6-yl)-pyrrolidine-2-carboxylic Acid (**11**).* To an ice-cooled mixture of the protected alcohol **9a** (150 mg, 0.413 mmol, 1.0 equiv) dissolved in CH_3CN (2.5 mL) and EtOAc (2.5 mL) was added dropwise $NaIO_4$ (883 mg, 4.13 mmol, 10.0 equiv) and $RuCl_3$·H_2O (4 mg, 0.02 mmol, 0.04 equiv) dissolved in H_2O (4 mL). The reaction was stirred at 0 °C for 1.5 h. The brownish reaction mixture was filtered through a plug of Celite and washed with EtOAc (15 mL). The filtrates were transferred to a separating funnel, and the organic layer was isolated. The aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic phases were washed with brine (25 mL) and dried over anhydrous Na_2SO_4. The crude product was isolated as a dark-brown oil by evaporation in vacuo (179 mg). Purification by DCVC (5−25% EtOAc in heptane containing 1% AcOH) afforded compound **10a** and **11**, respectively. For **10a**: White foam (36 mg, 22%). ^{1}H NMR ($CDCl_3$): δ 7.88−7.84 (1H, m),

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7.49 (1H, t, J = 7.7 Hz), 6.98−6.94 (1H, m), 4.36 (0.5H, d, J = 5.9 Hz), 4.25 (0.5H, d, J = 7.0 Hz), 3.86−3.73 (2H, m), 3.64−3.45 (1H, m), 2.40−2.30 (1H, m), 2.13−2.02 (1H, m), 1.76 (6H, s), 1.54 (5H, s), 1.45 (4H, s). ^{13}C NMR ($CDCl_3$): δ 196.3, 183.3, 174.9, 174.4, 173.7, 172.8, 161.1, 155.6, 154.9, 153.6, 135.5, 135.2, 134.9, 127.8, 127.5, 117.6, 113.3, 106.5, 81.1, 80.8, 65.6, 65.3, 61.4, 61.2, 49.8, 49.0, 48.1, 47.3, 46.3, 45.9, 45.4, 32.6, 32.4, 29.7, 28.4, 28.2, 25.8 (rotamers). MS (m/z) calcd for $C_{15}H_{18}NO_5$ $[M - Boc + H]^+$ 292.1, found 292.1. R_f 0.25 (50% EtOAc in heptane +1% AcOH); $[\alpha]^{25}_D$ +21.8° (c 0.21 abs. EtOH); mp 200 °C (decomp.). For **11**: White solid (62 mg, 40%). ^{1}H NMR ($CDCl_3$): δ 10.77 (1H, bs), 7.04 (1H, d, J = 8.0 Hz), 6.85 (1H, s), 6.78 (1H, d, J = 8.3 Hz), 4.84 (2H, s), 4.36 (0.5H, bs), 4.21 (0.5H, d, J = 6.1 Hz), 3.81−3.41 (3H, m), 2.38−2.22 (1H, m), 2.04−1.94 (1H, m), 1.55 (6H, s), 1.51 (4H, s), 1.44 (5H, s). ^{13}C NMR ($CDCl_3$): δ 178.1, 155.3, 153.6, 150.2, 132.5, 132.0, 126.6, 126.5, 123.1, 123.0, 119.4, 117.2, 99.5, 81.1, 80.7, 65.8, 60.8, 49.3, 47.3, 46.3, 46.0, 33.0, 32.6, 28.5, 28.3, 24.8 (rotamers present). MS (m/z) calcd for $C_{15}H_{20}NO_4$ $[M - Boc + H]^+$ 278.1, found 278.0. R_f 0.35 (50% EtOAc in heptane + 1% AcOH, $KMnO_4$ staining); $[\alpha]^{25}_D$ +49.4° (c = 0.23, abs EtOH); mp 128−130 °C.

*(2S,3R)-1-(tert-Butoxycarbonyl)-3-(3-carboxy-5-propoxyphenyl)-pyrrolidine-2-carboxylic Acid (**10b**).* Suspension A: $NaIO_4$ (1.92 g, 8.98 mmol, 9.98 equiv) was suspended in H_2O (6 mL), and after stirring at rt for 5 min, $RuCl_3{\cdot}H_2O$ (8 mg, 0.035 mmol, 0.04 equiv) was added. The black suspension was stirred for 1 min at rt prior to use. Diol **9b** (276 mg, 0.90 mmol, 1.00 equiv) was dissolved in CH_3CN (5 mL) and EtOAc (5 mL), cooled to 0 °C, and suspension A added dropwise. The flask containing suspension A was washed with H_2O (2 mL), which was added the mixture. The mixture was left to stir at 0 °C for 1.5 h. The mixture was filtered through a plug of Celite, and the plug was afterward washed with EtOAc (2 × 5 mL). The organic phases were pooled in a separation funnel and H_2O (20 mL) added. After separation of the two phases, the aqueous phase was extracted with EtOAc (2 × 20 mL). The pooled organic phases was washed with brine (20 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified using DCVC (dia = 3 cm, 30 mL fractions, 0−50% EtOAc in heptane containing 2% AcOH) to yield diacid **10b** (196 mg, 66%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.0 (2H, bs), 7.59 (1H, m), 7.49 (1H, m), 7.06 (1H, m), 4.46 (0.4H, d, J = 6 Hz), 4.30 (0.6H, d, J = 7 Hz), 3.97 (2H, t, J = 7 Hz), 3.86−3.50 (3H, m), 2.35 (1H, m), 2.09 (1H, m), 1.83 (2H, h, J = 7 Hz), 1.52 (4H, s), 1.44 (5H, s), 1.06 (3H, t, J = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 176.7, 171.5, 171.4, 159.4, 155.0, 153.8, 142.6, 142.1, 131.0, 130.9, 121.1, 121.0, 119.9, 119.7, 113.8, 113.7, 81.3, 81.2, 69.9, 65.7, 65.2, 49.8, 48.1, 46.4, 46.2, 33.1, 32.7, 28.6, 28.4. MS (m/z) calcd for $C_{15}H_{20}NO_5$ $[M - Boc + H]^+$ 294.1, found 294.1. R_f 0.36 (EtOAc:heptane:AcOH (40:20:1)).

*(2S,3R)-3-(3-(Benzyloxy)-5-carboxyphenyl)-1-(tert-butoxycarbonyl)-pyrrolidine-2-carboxylic Acid (**10c**).* Suspension A: $NaIO_4$ (2.40 g, 11.22 mmol, 10.0 equiv) and $RuCl_3{\cdot}H_2O$ (10 mg, 0.044 mmol, 0.04 equiv) were suspended in H_2O (7.5 mL) and stirred at rt for 1 min prior to use. Diol **9c** (462 mg, 1.12 mmol, 1.00 equiv) was dissolved in CH_3CN (10 mL) and EtOAc (10 mL), cooled to 0 °C, and suspension A added dropwise over the course of 15 min. The flask containing suspension A was washed with H_2O (7.5 mL), to which was added the mixture over the course of 5 min. The mixture was left to stir at 0 °C for 2 h. The mixture was filtered through a plug of Celite, and the plug was afterward washed with EtOAc (2 × 20 mL). The organic phases were pooled in a separation funnel and H_2O (40 mL) added. After separation of the two phases, the aqueous phase was extracted with EtOAc (2 × 50 mL). The pooled organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified using DCVC (dia = 3 cm, 30 mL fractions, 0−50% EtOAc in heptane containing 2% AcOH) to yield diacid **10c** (410 mg, 83%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.40−7.75 (2H, bs), 7.64−7.57 (2H, m), 7.47−7.30 (5H, m), 7.14 (1H, t, J = 7 Hz), 5.10 (2H, s), 4.44 (0.5H, d, J = 6 Hz), 4.28 (0.5H, d, J = 7 Hz), 3.85−3.45 (3H, m), 2.34 (1H, m), 2.06 (1H, m), 1.52 (4.5H, s), 1.44 (4.5H, s). ^{13}C NMR (75 MHz, DMSO): δ 173.3, 172.8, 166.8, 158.4, 153.2, 152.7, 143.1, 142.7, 136.6, 132.2, 128.3, 127.8, 127.7, 120.7, 120.6, 118.7, 118.5, 113.3, 79.1, 69.4, 65.4, 65.1, 49.1, 48.0, 46.0, 32.6, 32.1, 28.2, 28.0. MS (m/z) calcd for $C_{19}H_{20}NO_5$ $[M - Boc + H]^+$ 342.1, found 342.2. R_f 0.36 (EtOAc:heptane:AcOH (10:5:0.1)); $[\alpha]^{35}_D$ +49.7° (c = 0.39, abs EtOH).

*(2S,3R)-3-(3-([1,1′-Biphenyl]-3-ylmethoxy)-5-carboxyphenyl)-1-(tert-butoxycarbonyl)-pyrrolidine-2-carboxylic Acid (**10d**).* Suspension A: $NaIO_4$ (1.71 g, 11.46 mmol, 16.4 equiv) and $RuCl_3{\cdot}H_2O$ (8 mg, 0.035 mmol, 0.05 equiv) were suspended in H_2O (6 mL) and stirred at rt for 1 min prior to use. Diol **9d** (342 mg, 0.699 mmol, 1.00 equiv) was dissolved in CH_3CN (8 mL) and EtOAc (8 mL), cooled to 0 °C, and suspension A added dropwise over the course of 15 min. The flask containing suspension A was washed with H_2O (6 mL), to which was added the mixture over the course of 5 min. The mixture was left to stir at 0 °C for 2 h. The mixture was filtered through a plug of Celite, and the plug was afterward washed with EtOAc (2 × 15 mL). The organic phases were pooled in a separation funnel and H_2O (40 mL) added. After separation of the two phases, the aqueous phase was extracted with EtOAc (2 × 50 mL). The pooled organic phases was washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified using DCVC (dia = 3 cm, 30 mL fractions, 0−45% EtOAc in heptane containing 2% AcOH) to yield diacid **10d** (250 mg, 69%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69−7.54 (6H, m), 7.50−7.31 (5H, m), 7.17 (1H, t, J = 2 Hz), 5.16 (2H, s), 4.45 (0.5H, d, J = 6 Hz), 4.29 (0.5H, d, J = 8 Hz), 3.86−3.45 (3H, m), 2.35 (1H, m), 2.07 (1H, m), 1.52 (4.5H, s), 1.44 (4.5H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 177.4, 175.5, 171.3, 159.2, 155.6, 153.7, 142.9, 142.3, 141.8, 140.8, 136.8, 131.1, 129.2, 128.9, 127.6, 127.3, 127.2, 126.7, 126.6, 122.0, 121.7, 120.3, 114.1, 81.8, 81.3, 70.5, 65.7, 65.4, 50.0, 47.8, 46.6, 46.3, 33.1, 32.8, 28.7, 28.5. MS (m/z) calcd for $C_{25}H_{24}NO_5$ $[M - Boc + H]^+$ 418.2, found: 418.2. R_f 0.40 (EtOAc:heptane:AcOH (10:5:0.1)); $[\alpha]^{35}_D$ +42.7° (c = 0.33, abs EtOH).

*3-Bromo-5-(((tert-butyldimethylsilyl)oxy)methyl)phenol (**16**).* Commercially available acid **15** (10.0 g, 46.8 mmol, 1.00 equiv) was dissolved in dry THF (60 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this solution was added $BH_3{\cdot}$THF complex (70 mL, 70 mmol, 1.50 equiv) over the course of 30 min (gas formation). After stirring at 0 °C for 15 min, the reaction mixture was left to stir at rt overnight. The mixture was transferred to a separation funnel containing phosphate buffer (100 mL, pH 7) and added Et_2O (100 mL). The phases were separated and the aqueous phase extracted with EtOAc (2 × 75 mL). The combined organic phases was washed with brine (80 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to yield a white solid.

The solid was dissolved in DMF (20 mL) and cooled 0 °C under an atmosphere of nitrogen. Imidazole (4.13 g, 60.7 mmol, 1.30 equiv) was added followed by portionwise addition of TBSCl (7.95 g, 52.7 mmol, 1.13 equiv) over the course of 1 min. The mixture was left to stir at 0 °C for 15 min and then 10 min at rt before DMF (10 mL) was added due to extensive formation of solid material. The mixture was left to stir at rt overnight. The mixture was transferred to a separation funnel containing Et_2O (100 mL), EtOAc (100 mL), and satd $NaHCO_3$ (100 mL). The organic phase was washed with water (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The mixture was purified by DCVC (diameter = 6 cm, 50 mL fractions, 0−30% EtOAc in heptane) to yield **16** (10.4 g, 71%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01 (1H, s), 6.86 (1H, s), 6.74 (1H, s), 6.66 (2H, s), 5.64 (1H, s), 0.96 (9H, s), 0.13 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 144.8, 122.6, 121.5, 117.4, 112.0, 64.3, 26.2, 18.7, −5.0. R_f 0.20 (EtOAc:heptane (1:10)).

*(3S,4R,5S)-tert-Butyl 3-Allyl-5-(((tert-butyldimethylsilyl)oxy)-methyl)-4-(3-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)-2-oxo-pyrrolidine-1-carboxylate (**19a**).* Compound **18**[30] (2.76 g, 5.02 mmol, 1.00 equiv) was dissolved in dry THF (20 mL) and cooled to −78 °C. A solution of LHMDS in THF (6.02 mL, 6.02 mmol, 1.20 equiv) was added dropwise over the course of 20 min. The solution was stirred at −78 °C for 1 h before adding allyl bromide (1.70 mL, 2.43 g, 20.1 mmol, 4.0 equiv) dropwise over the course of 15 min. After stirring at −78 °C for 15 min, the solution was transferred to an acetone bath cooled to −52 °C (the temperature was maintained at this temperature by use of a cryostat) and stirred at this temperature for 20 h. The reaction mixture was quenched with satd NH_4Cl (5 mL) over the course of 5 min and transferred to a separation funnel with EtOAc (75 mL) and satd

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$NaHCO_3$ (75 mL). The aqueous phase was extracted with EtOAc (75 mL), and the combined organic phases were washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The mixture was purified by DCVC (diameter 7 cm, 75 mL fractions, 0−2.5% EtOAc in toluene) to yield **19a** (1.44 g, 49%) as a viscous, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (1H, t, J = 8 Hz), 7.23−7.16 (2H, m), 7.09 (1H, dm, J = 8 Hz), 5.68 (1H, m), 5.10−4.98 (2H, m), 4.13 (1H, dd, J = 10, 3 Hz), 3.98 (1H, ddd, J = 7, 3, 2 Hz), 3.54 (1H, dd, J = 11, 2 Hz), 3.34 (1H, dd, J = 10, 7 Hz), 2.74 (1H, m), 2.58−2.37 (2H, m), 1.56 (9H, s), 0.95 (9H, s), 0.91 (9H, s), 0.11 (6H, s), 0.06 (3H, s), 0.05 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.6, 150.1, 142.2, 141.8, 134.8, 128.8, 126.4, 125.6, 124.9, 117.7, 83.1, 65.0, 64.9, 60.6, 50.4, 42.9, 34.0, 28.3, 26.1, 26.0, 18.6, 18.4, −5.0, −5.2. MS (m/z) calcd for $C_{27}H_{48}NO_3Si$ $[M - Boc + H]^+$ 490.3, found 490.3. R_f 0.41 (EtOAc:toluene (1:20)); $[\alpha]^{22}_D$ −2.7° (c = 0.49, EtOAc).

*(3S,4R,5R)-tert-Butyl 3-Benzyl-5-((tert-butyldimethylsilyloxy)-methyl)-4-(3-((tert-butyldimethylsilyloxy)methyl)phenyl)-2-oxocyclopentanecarboxylate (**19b**).* Compound **18** (1.20 g, 2.18 mmol, 1.00 equiv) was dissolved in dry THF (4.7 mL) and cooled to −78 °C. A 1 M solution of LHMDS in THF (2.60 mmol, 2.60 mL, 1.19 equiv) was added dropwise over the course of 20 min. The solution was stirred at −78 °C for 1 h before adding benzyl bromide (1.3 mL, 1.9 g, 11 mmol, 5.0 equiv) dropwise over the course of 15 min. After stirring at −78 °C for 15 min, the solution was transferred to an CH_3CN/dry ice bath (−42 °C) and stirred at this temperature for 5 h. The reaction mixture was quenched with satd NH_4Cl (5 mL) and transferred to a separation funnel with EtOAc (30 mL) and satd $NaHCO_3$ (15 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL), and the combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The mixture was purified by flash chromatography (2.5% EtOAc in toluene) to afford **19b** (1.00 g, 72%) as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45−7.06 (7H, m), 6.92 (1H, s), 6.84 (1H, dm, J = 7 Hz), 4.65 (2H, s), 4.02 (1H, dd, J = 10, 4 Hz), 3.95 (1H, m), 3.52 (1H, dd, J = 11, 2 Hz), 3.22 (1H, m), 3.15−2.95 (3H, m), 1.57 (9H, s), 0.96 (9H, s), 0.87 (9H, s), 0.11 (6H, s), 0.02 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 150.1, 142.02, 141.97, 138.2, 137.9, 129.6, 129.1, 128.7, 128.32, 128.25, 126.4, 126.1, 125.3, 125.2, 124.7, 83.1, 65.2, 64.9, 60.9, 52.6, 43.0, 35.6, 28.3, 26.2, 26.1, 21.7, 18.7, 18.5, −4.9, −5.12, −5.15. MS (m/z) calcd for $C_{31}H_{50}NO_3Si_2$ $[M - Boc + H]^+$ 540.3, found 540.4. R_f 0.34 (EtOAc:toluene (1:19)); $[\alpha]^{20}_D$ +4.6° (c = 0.56, CH_2Cl_2).

*(2S,3R,4S)-tert-Butyl 2-(((tert-Butyldimethylsilyl)oxy)methyl)-4-propyl-3-(m-tolyl)pyrrolidine-1-carboxylate (**20a**).* Compound **19a** (1.24 g, 2.10 mmol, 1.00 equiv) was dissolved in dry THF (6 mL) and dry EtOH (32 mL) added. The mixture was thoroughly purged with nitrogen, followed by thoroughly purging with hydrogen gas. The mixture was stirred under an atmosphere of hydrogen (1 atm) for 18 h. The mixture was filtered through a plug of Celite, which was afterward washed with EtOAc (5 × 5 mL). The mixture was concentrated in vacuo to yield a colorless but slightly milky oil. (b) The colorless oil was dissolved in dry THF (15 mL) and 1 M BH_3·THF complex (20 mL, 20 mmol, 9.52 equiv) added and stirred at reflux for 1.5 h and afterward 18 h at rt. The mixture was cooled to 0 °C, and THF (32 mL) was added. Afterward, H_2O (6 mL) was added dropwise over the course of 2 h, 2 M NaOH (25 mL) over the course of 30 min, and 30% H_2O_2 (10 mL) over the course of 15 min. After being stirred for 5 min at 0 °C, the mixture was removed from the ice bath and left to stir at rt for 1 h. The reaction mixture was quenched with satd $NaHCO_3$ (75 mL) and transferred to a separation funnel with EtOAc (50 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL), and the combined organic phases were washed with brine (75 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified using DCVC (diameter 4 cm, 30 mL fractions, 0−6% EtOAc in heptanes) to yield **20a** (551 mg, 59%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24−7.16 (1H, m), 7.08−6.99 (3H, m), 4.19 (0.5H, dd, J = 11, 3 Hz), 4.08 (0.5H, dd, J = 11, 7 Hz), 3.98−3.84 (1H, m), 3.77 (0.5H, dm, J = 9 Hz), 3.66 (0.5H, dm, J = 9 Hz), 3.52 (0.5H, d, J = 10 Hz), 3.41 (0.5H, d, J = 10 Hz), 3.15−3.02 (1H, m), 2.89 (1H, t, J = 11 Hz), 2.36 (3H, m), 2.30−2.05 (1H, m), 1.51 (4.5H, s), 1.49 (4.5H, s), 1.45−1.08 (4H, m), 0.91 (4.5H, s), 0.90 (4.5H, s), 0.83 (3H, t, J = 7 Hz), 0.04 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.1, 154.0, 141.7, 141.4, 138.1, 129.1, 128.44, 128.35, 127.5, 125.7, 125.3, 79.4, 79.1, 66.8, 61.6, 59.9, 53.72, 53.65, 53.0, 52.2, 45.6, 45.2, 34.1, 28.8, 26.1, 21.7, 21.6, 18.4, 14.6, −5.1, −5.2. MS (m/z) calcd for $C_{21}H_{38}NOSi$ $[M - Boc - TBS\text{-}O + H]^+$ 348.3, found 348.3. R_f 0.37 (EtOAc:heptane (1:10)); $[\alpha]^{22}_D$ −29.8° (c = 0.43, EtOAc).

*(2S,3R,4S)-tert-Butyl 4-Benzyl-2-(((tert-butyldimethylsilyl)oxy)-methyl)-3-(3-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)-pyrrolidine-1-carboxylate (**20b**).* Compound **19b** (370 mg, 0.58 mmol, 1.00 equiv) was dissolved in dry THF (2.5 mL) and a solution of 1 M BH_3·THF (3.5 mL, 3.5 mmol, 6.0 equiv) added and stirred at reflux for 21 h. The mixture was cooled to 0 °C, and THF (7.4 mL) was added dropwise. Afterward, H_2O (0.3 mL), 2 M NaOH (4.7 mL), and H_2O_2 (30%, 1.7 mL) were added dropwise in that particular order. After being stirred for 5 min at 0 °C, the mixture was removed from the ice bath and left to stir at rt for 1.5 h. The reaction mixture was quenched with satd $NaHCO_3$ (5 mL) and transferred to a separation funnel with EtOAc (20 mL). The aqueous phase was extracted with EtOAc (2 × 30 mL), and the combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified using flash chromatography (5% EtOAc in heptane) to afford **20b** (108 mg, 30%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.10 (7H, m), 7.08−7.00 (2H, m), 4.78 (2H, s), 4.22 (0.44H, dm, J = 11 Hz), 4.00−3.85 (1H, m), 3.84−3.67 (1.55H, m), 3.53 (0.55H, d, J = 10 Hz), 3.43 (0.45H, d, J = 11 Hz), 3.27 (1H, t, J = 10 Hz), 3.01 (1H, t, J = 11 Hz), 2.76 (1H, dm, J = 12 Hz), 2.57−2.33 (2H, m), 1.46 (9H, s), 0.98 (9H, s), 0.92 (9H, s), 0.15 (6H, s), 0.05 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.0, 153.9, 141.9, 141.8, 141.0, 140.8, 140.1, 139.9, 128.7, 128.6, 128.3, 127.1, 126.4, 126.1, 126.0, 124.7, 79.5, 79.2, 66.8, 65.1, 61.5, 59.8, 53.04, 52.98, 52.7, 51.5, 47.3, 37.6, 28.8, 26.2, 26.1, 18.7, 18.4, −4.9, −5.1. MS (m/z) calcd for $C_{31}H_{52}NO_2Si_2$ $[M - Boc + H]^+$ 526.4, found 526.4. R_f 0.48 (EtOAc:heptane (1:4)); $[\alpha]^{20}_D$ −15.3° (c = 0.51, CH_2Cl_2).

*(2S,3R,4S)-tert-Butyl 2-(Hydroxymethyl)-4-propyl-3-(m-tolyl)-pyrrolidine-1-carboxylate (**21a**).* Compound **20a** (515 mg, 1.11 mmol, 1.00 equiv) was dissolved in dry THF (10 mL) in a dry flask and 1 M TBAF (4.8 mL, 4.8 mmol, 4.32 equiv) added. The mixture was left to stir at rt for 18 h. The mixture was quenched using satd $NaHCO_3$ (40 mL) and transferred to a separation funnel containing EtOAc (40 mL). The aqueous phase was extracted with EtOAc (2 × 40 mL), and the combined organic phases were washed with brine (75 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and purified using DCVC (dia = 3 cm, 25 mL fractions, 0−18% EtOAc in toluene) to yield **21a** (340 mg, 89%) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (1H, t, J = 8 Hz), 7.08−6.95 (3H, m), 5.31 (0.7H, dm, J = 8 Hz), 4.00−3.70 (2H, m), 3.70−3.45 (2H, m), 2.96 (1H, t, J = 11 Hz), 2.35 (3H, s), 2.35−2.10 (2H, m), 1.51 (9H, s), 1.40−1.20 (2H, m), 1.20−1.05 (2H, m), 0.81 (3H, t, J = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 139.2, 138.3, 128.9, 128.6, 128.1, 125.5, 80.6, 68.5, 66.0, 54.8, 53.2, 44.8, 33.8, 28.7, 21.7, 21.4, 14.5. MS (m/z) calcd for $C_{16}H_{24}NO_3$ $[M - O^tBu + H]^+$ 278.2, found 278.2. R_f 0.22 (EtOAc:toluene (2:15)); $[\alpha]^{22}_D$ −48.2° (c = 0.53, EtOAc).

*(2S,3R,4S)-tert-Butyl 4-Benzyl-2-(hydroxymethyl)-3-(3-(hydroxymethyl)phenyl)pyrrolidine-1-carboxylate (**21b**).* Compound **20b** (453 mg, 0.73 mmol, 1.00 equiv) was dissolved in dry THF (4 mL) and 1 M TBAF in THF (2.2 mL, 2.2 mmol, 3.0 equiv) added. The solution was stirred at rt for 21 h under an atmosphere of nitrogen. The mixture was quenched with satd $NaHCO_3$ (1 mL) and H_2O (1 mL). The mixture was transferred to a separation funnel containing EtOAc (10 mL) and brine (10 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL), and the combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The mixture was purified by flash chromatography (33% heptane in EtOAc) to afford **21b** as a white foam (252 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.13 (7H, m), 7.04−6.99 (2H, m), 5.31 (1H, dm, J = 8 Hz), 4.67 (2H, m), 4.00−3.45 (4H, m), 3.07 (1H, m), 2.75−2.65 (1H, m), 2.60−2.30 (4H, m), 1.47 (9H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.5, 141.8, 139.4, 139.0, 128.9, 128.5, 128.3, 127.4, 126.7, 126.1, 126.0, 80.8, 68.3, 65.5, 64.9, 54.1, 52.6, 46.3, 37.4,

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28.6. MS (m/z) calcd for $C_{20}H_{24}NO_4$ $[M - {}^tBu + H]^+$ 342.2, found 342.1. R_f 0.38 (EtOAc:heptane (2:1)); $[\alpha]^{20}_D$ −28.3 (c = 0.57, CH_2Cl_2).

*(2S,3R,4S)-1-(tert-Butoxycarbonyl)-3-(3-carboxyphenyl)-4-propylpyrrolidine-2-carboxylic Acid (**22a**).* The diol **21a** (303 mg, 0.87 mmol, 1.00 equiv) was dissolved in CH_3CN (5 mL) and EtOAc (5 mL), cooled to 0 °C, and a suspension of $NaIO_4$ (1.86 g, 8.70 mmol, 10.00 equiv) and $RuCl_3 \cdot H_2O$ (8.0 mg, 0.035 mmol, 0.04 equiv) in H_2O (4 mL) added dropwise. Additional H_2O (4 mL) was used to rinse the flask for efficient transfer of reagents. The reaction mixture was stirred at 0 °C for approximately 1.5 h, followed by filtration through a plug of Celite, which was washed with EtOAc (3 × 10 mL). To the filtrate was added H_2O (40 mL) and brine (5 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic phases were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to dryness. The crude product was purified by DCVC, which afforded the diacid **22a** as a white solid (304 mg, 93%). ^{1}H NMR ($CDCl_3$): δ 8.04−7.97 (2H, m), 7.54−7.43 (2H, m), 4.39 (0.5H, d, J = 9.0 Hz), 4.26 (0.5H, d, J = 9.5 Hz), 4.04 (0.5H, dd, J = 10.5, 7.3 Hz), 3.96 (0.5H, dd, J = 10.7, 7.4 Hz), 3.22−3.03 (2H, m), 2.41−2.30 (1H, m), 1.52 (4H, s), 1.43 (5H, s), 1.30−1.18 (4H, m), 0.83−0.79 (3H, m). ^{13}C NMR ($CDCl_3$): δ 178.3, 177.0, 175.4, 171.5, 155.4, 153.4, 139.6, 139.1, 133.7, 133.1, 130.0, 129.7, 129.6, 129.5 (2 peaks), 129.2, 129.1, 81.6, 81.0, 66.9, 66.6, 56.7, 55.0, 52.5, 51.9, 46.1, 45.6, 33.3, 33.2, 28.4, 28.3, 21.2, 20.7, 14.1 (rotamers). MS (m/z) calcd for $C_{15}H_{20}NO_4$ $[M - Boc + 2H]^+$ 278.1, found 278.2. mp. 130−135 °C; $[\alpha]^{25}_D$ +3.0° (c = 0.33, EtOH).

*(2S,3R,4S)-4-Benzyl-1-(tert-butoxycarbonyl)-3-(3-carboxyphenyl)-pyrrolidine-2-carboxylic Acid (**22b**).* Suspension A: $NaIO_4$ (451 mg, 2.11 mmol, 8.22 equiv) and $RuCl_3 \cdot H_2O$ (1.1 mg, 0.005 mmol, 0.02 equiv) were suspended in H_2O (3 mL) and stirred at rt for 1 min prior to use. Diol **21b** (102 mg, 0.26 mmol, 1.00 equiv) was dissolved in CH_3CN (2 mL) and EtOAc (2 mL). Suspension A was dropwise added to the reaction mixture over the course of 5 min and stirred at rt for 30 min. The mixture was filtered through a plug of Celite, and the plug was afterward washed with EtOAc (2 × 5 mL). The aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The mixture was purified by DCVC (0−25% EtOAc in heptane containing 2% AcOH) to afford **22b** (50 mg, 45%) as white foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.31 (2H, bs), 8.06−7.97 (2H, m), 7.56−7.41 (2H, m), 7.27−7.08 (3H, m), 7.06−6.96 (2H, m), 4.42 (0.39H, d, J = 9 Hz), 4.28 (0.61H, d, J = 9 Hz), 3.99−3.71 (1H, m), 3.37−3.13 (2H, m), 2.78−2.57 (2H, m), 2.57−2.42 (1H, m), 1.47 (3.3H, s), 1.42 (5.7H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.9, 176.3, 171.3, 154.8, 153.3, 139.2, 139.0, 138.9, 138.7, 133.5, 133.2, 130.2, 129.65, 129.58, 129.2, 128.5, 126.4, 81.4, 81.1, 66.7, 67.0, 56.2, 54.9, 52.2, 51.8, 48.1, 47.5, 37.4, 37.2, 28.6, 28.4. MS (m/z) calcd for $C_{19}H_{20}NO_4$ $[M - Boc + H]^+$ 326.1, found 326.2. R_f 0.47 (EtOAc:heptane:AcOH (32:16:1)); $[\alpha]^{20}_D$ +28.0° (c = 0.10, CH_2Cl_2).

*(4R,5S)-N-(tert-Butoxycarbonyl)-5-[[(tert-butyl)dimethylsilyloxy]-methyl]-4-(3-bromophenyl)pyrrolidin-2-one (**23**).* To a solution of 1,3-dibromobenzene (5.4 g, 22.9 mmol) in dry THF (37 mL) at −78 °C was added n-BuLi (22.9 mmol; 3 equiv). After stirring for 20 min, a slurry of CuCN (1.025 g, 11.45 mmol) in THF (5 mL) was added. The reaction mixture was allowed to warm to −50 °C for 20 min. The flask was recooled to −78 °C for 25 min, and a solution of enone **5** (2.5 g; 7.63 mmol) in THF (8.25 mL) was added followed by addition of TMSCl (2.07 g; 2.42 mL; 19.05 mmol). The flask was allowed to warm to −50 °C and then stirred at this temperature 80 min. The reaction was quenched by satd NH_4Cl (20 mL), and the organic layer was extracted by EtOAc (2 × 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (EtOAc/heptane 1:9) gave **23** (2.13 g, 58%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76−6.82 (4H, m), 4.06 (1H, m), 4.00 (1H, dd, J = 10.5, 3.8 Hz), 3.81 (1H, dd, J = 10.5, 2.1 Hz), 3.43 (1H, d, J = 9.4 Hz), 3.16 (1H, dd, J = 17.8, 9.6 Hz), 2.51 (1H, dd, J = 17.8, 2.5 Hz), 1.55 (9H, s), 0.92 (9H, s), 0.09 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 149.7, 146.4, 130.6, 130.2, 129.7, 124.8, 123.0, 83.2, 66.4, 63.6, 39.8, 38.5, 28.0, 25.8, 18.2, −5.5. mp. 87.3 °C; $[\alpha]_D^{25}$ −26.6° (c = 0.51, CH_2Cl_2).

*(2S,3R)-N-(tert-Butoxycarbonyl)-2-[[(tert-butyl)dimethylsilyloxy]-methyl]-3-(3-bromophenyl)pyrrolidine (**24**).* To a solution of **23** (180 mg; 0.37 mmol) in THF (1.6 mL) was added a solution of $BH_3 \cdot$THF (2.47 mmol; 1N solution), and the reaction mixture was stirring under reflux for 20 h. The flask was cooled to 0 °C for 20 min and the solution diluted with THF (4.5 mL). H_2O (0.2 mL) was added, followed by NaOH (3.04 mL; 6.08 mmol; 2 N solution) and H_2O_2 (0.95 mL; 10.97 mmol; 35% in water). The reaction mixture was allowed to warm up to rt for 80 min and quenched by saturated $NaHCO_3$ (3 mL). The aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic layers were washed with brine (3 × 30 mL), dried over Na_2SO_4, and evaporated in vacuo. Purification by flash column chromatography (EtOAc:heptane (1:9)) gave **24** (127 mg, 73%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, two rotamers): δ 7.30 (2H, m), 7.23−7.05 (2H, m), 4.04−3.57 (4H, m), 3.54−3.44 (1H, m), 3.34 (1H, dd, J = 14.4, 8.7 Hz), 2.27 (1H, dd, J = 12.4, 6.5 Hz), 1.96−1.80 (1H, m), 1.48 (9H, s), 0.90 (9H, s), 0.06 (6H, d, J = 10.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers): δ 154.1, 146.3, 145.9, 130.4, 130.3, 130.1, 129.5, 128.5, 127.3, 127.1, 126.4, 125.9, 125.8, 122.6, 79.6, 79.2, 65.3, 65.2, 62.9, 61.5, 46.8, 46.4, 46.2, 45.3, 32.6, 31.5, 28.5, 25.8, 18.1, −5.4. $[\alpha]^{24}_D$ +1.9° (c = 0.62, CH_2Cl_2).

*(2S,3R)-N-(tert-Butoxycarbonyl)-2-[[(tert-butyl)dimethylsilyloxy]-methyl]-3-(3-diethylphosphonate)pyrrolidine (**25**).* To a solution of **24** (0.217 mmol; 102 mg) in dry THF (5 mL) at −78 °C was added n-BuLi (0.16 mL, 1.4 M solution, 1.00 equiv) over 10 min. After stirring for 15 min at −78 °C, $ClPO_3Et_2$ (37 μL, 1.2 equiv) was added, and the reaction mixture was stirred at −78 °C for 1 h and then quenched by addition of satd $NaHCO_3$ (1.5 mL). The aqueous phase was extracted by EtOAc (3 × 30 mL), and the combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and evaporated in vacuo. Purification by flash column chromatography (EtOAc:heptane 2:8, then EtOAc:heptane (1:1)) gave **25** (75.4 mg, 66%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, two rotamers): δ 7.75−7.58 (2H, m), 7.45−7.32 (2H, m), 4.22−3.95 (4H, m), 3.90−3.50 (5H, m), 3.45−3.29 (1H, m), 2.38−2.21 (1H, m), 2.00−1.81 (1H, m), 1.47 (9H, s) 1.35 (6H, t, J = 7.1 Hz), 0.90 (9H, s) 0.04 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers and carbon−phosphor coupling): δ 154.0, 131.3, 131.2, 130.7, 130.5, 130.4, 129.9, 129.7, 128.9, 128.6, 127.4, 79.6, 79.2, 65.3, 62.8, 62.1, 62.0, 61.4, 46.9, 46.6, 46.3, 45.5, 32.6, 31.7, 28.5, 25.8, 18.1, 16.4, 16.3, −5.4. R_f 0.18 (EtOAc:heptane (1:1)); $[\alpha]^{24}_D$ +0.8° (c = 0.58, CH_2Cl_2).

*(2S,3R)-tert-Butyl 3-(3-(Diethoxyphosphoryl)phenyl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (**26**).* To a solution of **25** (468 mg, 0.849 mmol, 1.00 equiv) in dry THF (8 mL) was added TBAF (2.66 mL, 1 M solution in THF, 3.00 equiv). The reaction mixture was stirred for 1 h at rt and then quenched by addition of satd $NaHCO_3$:H_2O (1:1) (8 mL). The aqueous phase was extracted with EtOAc (3 × 100 mL), and the combined organic phases were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. Purification by flash column chromatography (EtOAc) gave **26** (253 mg, 65%) as a colorless oil. R_f 0.21 (EtOAc 100%). ^{1}H NMR (300 MHz, $CDCl_3$, two rotamers): δ 7.74−7.61 (2H, m), 7.46−7.37 (2H, m), 5.05 (1H, br s), 4.24−4.00 (1H, m), 3.99−3.88 (1H, m), 3.86−3.56 (4H, m), 3.43−3.28 (1H, m), 3.01−2.88 (1H, m), 2.25−2.08 (1H, m), 2.08−1.91 (1H, m), 1.50 (9H, s), 1.33 (6H, t, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, two rotamers and carbon−phosphor coupling): δ 156.9, 142.0, 141.8, 132.0, 131.6, 131.4, 130.8, 130.5, 129.4, 129.2, 128.0, 80.9, 67.4, 65.9, 65.8, 62.6, 47.9, 47.4, 33.2, 28.8, 16.8, 16.7. $[\alpha]^{24}_D$ −2.8° (c = 0.61, CH_2Cl_2).

Pharmacology. *Binding Affinity at Native iGluRs.* Affinities for AMPA, KA, and NMDA receptors in rat cortical synaptosomes were determined using 5 nM [^{3}H]AMPA, 5 nM [^{3}H]KA, and 2 nM [^{3}H]CGP39653, respectively, with minor modifications as previously described.[42] Competition radioligand binding to native and cloned rat iGluR was carried out as previously detailed.[30]

X-ray Structures. Rat GluA2-LBD,[34] comprising segment S1 residues 413−527, a GT linker, and segment S2 residues 653−797 (numbering including signal peptide), was expressed and purified in the presence of L-Asp as previously reported.[43] Rat GluK1 LBD (GRIK1_RAT, UNP P22756, segment S1 residues 445−559, a GT

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linker, and segment S2 residues 682−820) was expressed and purified in the presence of Glu as previously described.[44]

*Crystallization of GluA2-LBD with **2e**.* GluA2-LBD in complex with **2e** was crystallized using the hanging drop vapor diffusion method at 7 °C. The crystals containing **2e** were obtained by coincidence when attempting to crystallize GluA2-LBD with **2d**. This implies that **2d** to some extent has been degraded into **2e** or that compound **2d** contains minor amounts of **2e**. The protein solution consisted of 5.0 mg/mL GluA2-LBD in 10 mM HEPES, pH 7.0, 20 mM NaCl, and 1 mM EDTA. Solid **2d** was added to the diluted protein solution and left to equilibrate overnight. Precipitation was removed before setting up the drops. The drop contained 1 μL of the complex solution and 1 μL of reservoir solution (20% PEG4000, 0.1 M lithium sulfate, and 0.1 M phosphate citrate buffer, pH 4.5). Reservoir volume was 0.5 mL. The crystals were flash cooled in liquid nitrogen after soaking in cryobuffer consisting of the reservoir solution with 20% glycerol added. Flash-cooled crystals were stored in liquid nitrogen until data collection.

*Crystallization of GluK1-LBD with **2f**.* GluK1-LBD in complex with **2f** was crystallized using the hanging drop vapor diffusion method at 7 °C. The drop contained 1 μL of the complex solution (5.5 mg/mL GluK1-LBD and 12.5 mM **2f** in 10 mM HEPES, pH 7.0, 20 mM NaCl, and 1 mM EDTA) and 1 μL of reservoir solution (20% PEG8000, 0.3 M lithium sulfate, and 0.1 M Tris pH 8.0). Reservoir volume was 0.5 mL. The crystals were flash cooled in liquid nitrogen after soaking in cryobuffer consisting of the reservoir solution with 20% glycerol added.

Data Collection and Structure Determination. X-ray data of the GluA2-LBD in complex with **2e** and GluK1-LBD in complex with **2f** were collected at the I911-3 (MX) beamline (MaxLab, Lund, Sweden).[45] Data processing was performed using MOSFLM[46] within the CCP4i suite of programs[47] (**2e** complex) or XDS[48] (**2f** complex). The data were scaled and merged using SCALA[49] within the CCP4i suite of programs.

Structure determinations were carried out using molecular replacement and the program PHASER[50] implemented in CCP4i. The GluA2-LBD with an antagonist (PDB ID: 3TZA, molA[51]) was used as a search model for solving the structure of GluA2-LBD with **2e**, including protein atoms only. The search model was divided into two domains: D1 (411−514, 749−791) and D2 (515−527+GT+653−748). A solution was found, showing electron density for two molecules in the asymmetric unit of the crystal for the complex with **2e**. Missing residues, **2e**, and other ions and molecules from the crystallization buffer were gradually built into the structure using the program COOT.[52] Ligand coordinates were created in Maestro (Maestro version 9.5, Schrödinger, LLC, New York, NY, 2013), whereas topology and parameter files for the ligand **2e** were obtained using eLBOW.[53] The structures were refined in PHENIX[54] using individual isotropic *B*-factors and TLS. Between refinement steps, the structure was inspected and corrected in COOT. For statistics on data collection and refinements, see Table 4.

The structure of GluK1-LBD with **2f** was solved by molecular replacement using PHASER within CCP4i, and the structure of GluK1-LBD with an antagonist (PDB ID: 4DLD, molA; protein atoms only)[55] was used as a search model. The search model was defined as two domains: D1 (446−552, 780−820) and D2 (553−559+GT+682−779). Two molecules were found in the asymmetric unit of the crystal. Subsequently, the amino acid residues of the GluK1 LBD complex were automatically built using AutoBuild within Phenix except for a few residues, which were manually built using COOT. Visual inspection of the structure in COOT revealed clear density corresponding to the ligand **2f**. The ligand coordinates were created in Maestro (Maestro version 9.8, Schrödinger, LLC, New York, NY, 2014) and fitted into the electron density. Topology and parameter files for **2f** were obtained using eLBOW. The structure was refined in PHENIX with isotropic *B* factors, TLS, and riding H atoms. Between refinement steps, the structure was inspected and corrected in COOT. Gradually, acetate and chloride ions, as well as water, ethylene glycol, and PEG molecules, were manually modeled into the electron densities. For statistics on data collection and refinements, see Table 4.

Structure Validation and Analysis. The structures were validated using tools in PHENIX and COOT. Domain openings of GluA2-LBD were calculated relative to the structure of GluA2-LBD with glutamate (PDB ID: 1FTJ, molB),[34] using the DynDom Server.[56] Domain openings of GluK1-LBD in complex with **2f** were determined relative to the structure of GluK1-LBD with glutamate (PDB ID: 2F36, molA).[57] Figures were prepared in PyMOL (The PyMOL Molecular Graphics System, version 1.3, and version 1.5.0.5, Schrödinger, LLC).

In Silico Study. The modeling study was performed using the software package MOE 2013.08 (Molecular Operating Environment, Chemical Computing Group) using the built-in mmff94x force field and the GB/SA continuum solvation model. Docking: The receptor proteins were prepared for docking by running the algorithm Protonate 3D. Docking studies were performed using the *Induced Fit* algorithm under standard setup with the mmff94x force field, solvation set to distance, and *ligand atoms* selected as docking site. Explicit water molecules in the binding site were excluded during the docking process.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystal data and data collection statistics of GluA2-LBD in complex with **2d** and the ligand binding domain of GluA2 in complex with **2d**(PDF). SMILES data (CSV). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.5b00750.

Accession Codes

The coordinates and structure factors have been deposited in the Protein Data Bank: GluA2-LBD with **2e** (PDB entry 4YMA) and GluK1-LBD with **2f** (PDB entry 4YMB).

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

ALS, amyotrophic lateral sclerosis; CNS, central nervous system; COSY, homonuclear correlation spectroscopy; D1, domain 1 of the LBD; D2, domain 2 of the LBD; DCM, dichloromethane; DCVC, dry column vacuum chromatography; KA, kainic acid (kainate at pH = 7); Glu, (*S*)-glutamate; GluA2-LBD, ligand binding domain of GluA2; HMQC, heteronuclear multiple-bond correlation; iGluR, ionotropic Glu receptor; LBD, ligand binding domain; LHMDS, lithium hexamethyldisilazide; mGluR, metabotropic Glu receptor; rt, room temperature; SAR, structure−activity relationship; TBAF, tetrabutylammonium fluoride; TBS, *tert*-butyldimethylsilyl; TBSCl, *tert*-butyldimethylsilyl chloride; TFA, trifluoroacetic acid; TMSCl, trimethylsilyl chloride

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