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Versatile synthesis of ibotenic acid analogues with potential for activity at glutamate receptors by use of a homochiral β-lactam template in our 'ring switching' strategy

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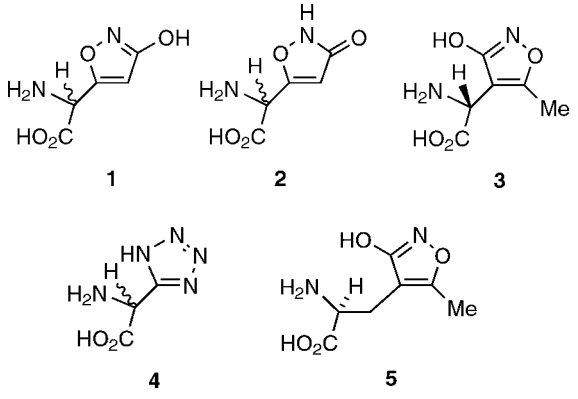
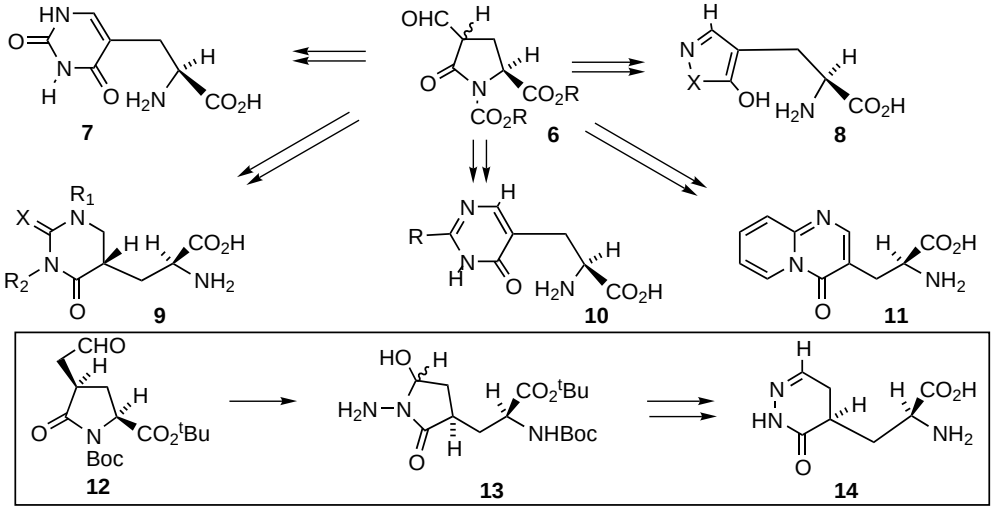
Abstract—The activated β-lactam aldehydes **31** and **55** were synthesised and found to be excellent substrates for our 'ring switching' strategy for preparation of libraries of homochiral compounds with potential for activity at specific glutamate receptor sub-types. The product heteroaromatic glycine derivatives were ibotenate analogues and the β-lactam templates proved to be more versatile than the previously used pyroglutamic templates. © 2002 Published by Elsevier Science Ltd.

The natural product ibotenic acid **1**, an active constituent of the psychotropic fly agaric mushroom *Amanita muscaria*, acts at both ionotropic and metabotropic (G-protein linked) glutamate receptor sub-types.[1] It is racemic, presumably because of the acidity of the α-hydrogen in the amide tautomer **2**.[2] Its analogues (*R*)-AMAA **3** and DL-tetrazolylglycine **4** act specifically at the NMDA receptor sub-type.[1] These compounds consist of a heterocyclic ring system fused to a glycine moiety. The homologue AMPA **5** and many of its analogues with a heterocyclic ring fused to the β-carbon of L-alanine are active at a different ionotropic glutamate receptor sub-type, the AMPA





Scheme 1.

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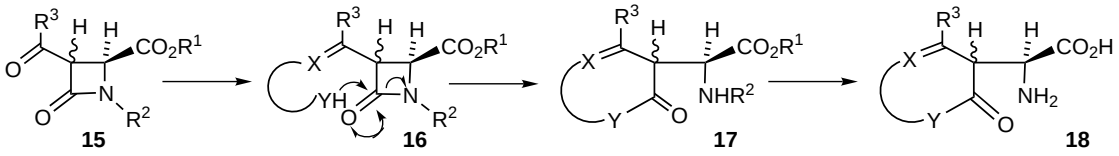


Scheme 2.

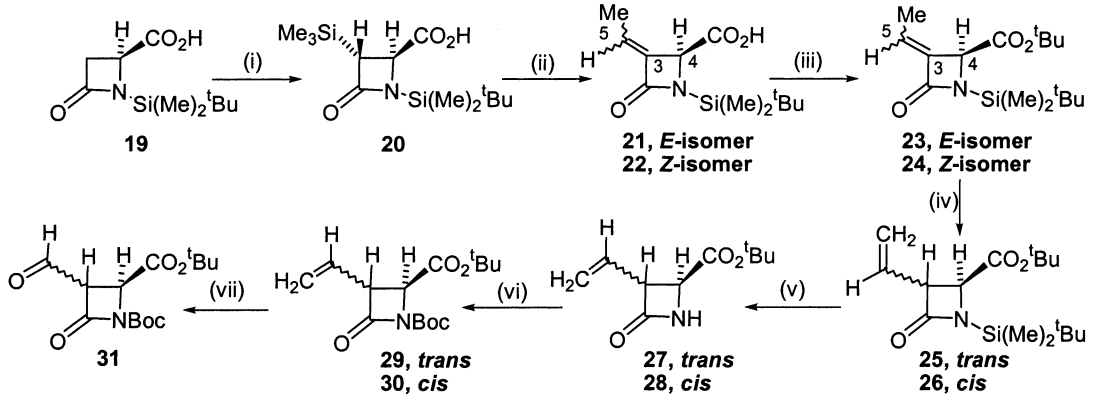
site.[1] The glutamate receptors are involved in memory and learning processes and antagonists have been identified as potential drugs for a variety of illnesses, including Alzheimer's disease,[3] epilepsy[4] and ischaemia.[5]

We have discovered a versatile and economical synthesis for a large variety of homochiral compounds in which a heterocyclic ring system is fused to the β-carbon atom of L-alanine. These compounds have potential for activity at the AMPA receptor[6–9] and some were tested for biological activity at metabotropic receptors and were found to be active. The synthesis, shown in Scheme 1, involved reaction of the protected pyroglutamic acid aldehyde **6** or its homologue **12** with bisnucleophiles and involved a minimum of steps. We have referred to this powerful synthetic tool as a 'ring switching' reaction.[6]

The possibility of preparing a large variety of ibotenic acid **1** analogues by applying our 'ring switching' reaction to a β-lactam template such as **15** using bisnucleophiles, as in Scheme 2, was appealing in spite of the fact that an attempt to prepare an analogue of the natural product TAN-950 by reacting an unactivated 3-acyl-β-lactam with hydroxylamine had been unsuccessful.[10]

Our first synthetic target was the aldehyde **31** and we were able to prepare this compound by the route outlined in Scheme 3. The 3-trimethylsilyl-β-lactam **20** (mp 85–87°C, $[\alpha]_D^{22}$ −98.5 (*c* 1.07, $CHCl_3$))† was first prepared in 95% yield from the acid **19** by using 2.2 equiv. of LDA followed by TMSCl.[11] This was subjected to a Peterson reaction using LDA and acetaldehyde. The separate isomeric products, **21** (mp 83–85°C, $[\alpha]_D^{20}$ −2.7 (*c* 1.08, $CHCl_3$))† and **22** (oil, $[\alpha]_D^{26}$ −10.5 (*c* 1 $CHCl_3$)),† were isolated in 46% (*E*-isomer) and 22% (*Z*-isomer) overall yields, respectively, from the acid **19**. The geometry of the *E* isomer **21** was shown by irradiating the methyl signal at δ 1.84 when an NOE at the signal at δ 4.62 for H-4 was observed. In the *Z*-isomer **22**, when the signal at δ 4.48 for H-4 was irradiated, a NOE was induced in the olefinic signal at δ 5.84 for H-5.

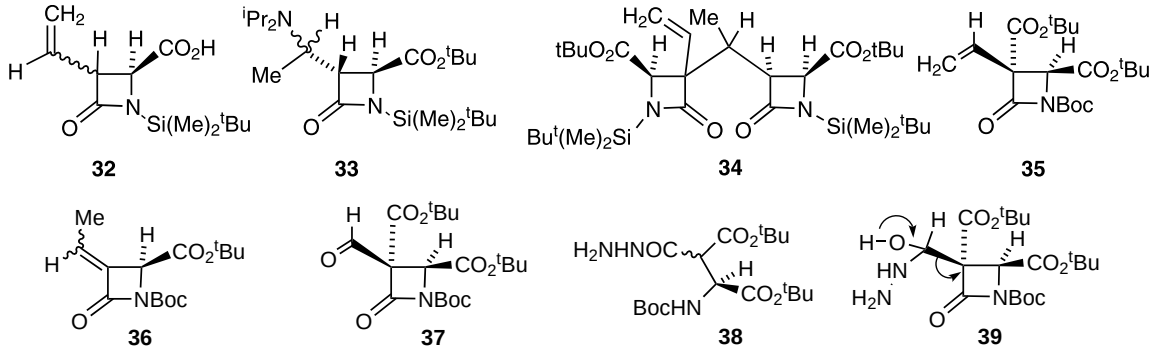
Our plan was to rearrange the exocyclic double bond in the isomers **21**+**22** to obtain the less strained isomer **32** by reaction with 2.2 equivalents of LDA, but very little reaction ensued. We therefore converted the mixture of **21**+**22** into the *tert*-butyl esters **23** (oil, $[\alpha]_D^{25}$ +1.1 (*c* 1, $CHCl_3$))† (51%) and **24** (oil, $[\alpha]_D^{28}$ −46.7 (*c* 1, $CHCl_3$))† (32%) using (*O*-*tert*-butyl)trichloroacetimidate and $BF_3{\cdot}Et_2O$ in dichloromethane/cyclohexane. The geometry of the double bond in the esters was inferred from chemical shift similarities to the acids **21** and **22**. An initial attempt at deconjugation using LDA gave the expected products **25** (oil, $[\alpha]_D^{27}$ +11.2 (*c* 1, $CHCl_3$))† and **26** in 5% yield together with the di-isopropylamine adducts **33**† (11%) and the dimeric product **34**† (15%). We were eventually able to minimise the Michael adducts **33** and **34** by adding a dilute solution of the conjugated β-lactams to a solution of LDA at −100°C when a mixture of the vinyl-β-lactams **25**+**26**† was obtained in 65% yield. These were deprotected by reaction with 1N aqueous HCl in MeOH to give the unstable products **27**‡ and **28**‡ in quantitative yield. The relative stereochemistries of these compounds were



Scheme 3. *Reagents and conditions*: (i) (a) 2.2 LDA/THF/0°C, (b) TMSCl (95%); (ii) (a) 1.1 LDA/THF/0°C, (b) CH_3CHO (22% **21**, 46% **22**); (iii) $Cl_3C(NH)O^tBu/BF_3{\cdot}Et_2O/CH_2Cl_2/C_6H_{12}$ (51% **23**, 32% **24**); (iv) LDA/THF/−100°C (65%); (v) 1N aq. HCl/MeOH (quant.); (vi) Boc_2O/DMAP/^{t}BuOH/CH_3CN (45% **29**, 22% **30**); (vii) (a) $O_3/CH_2Cl_2/-78$°C, (b) Me_2S.

† This compound had the expected analytical and spectroscopic properties.

‡ This relatively unstable compound was characterised by NMR spectroscopic methods only.



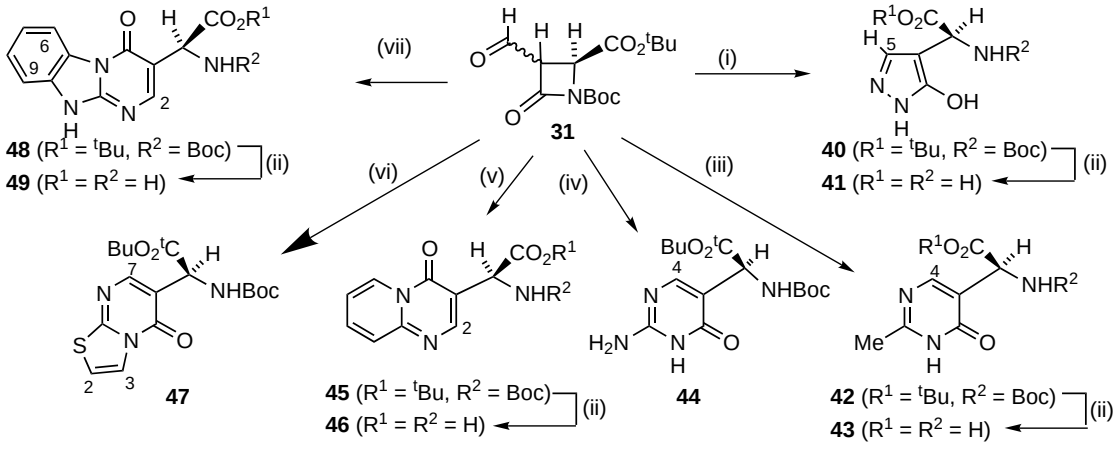
assigned from the coupling constants between H-3 and H-4 of the β-lactam rings (**27**, *trans* $J_{3,4}$ 2.6; **28**, *cis* $J_{3,4}$ 5.9).

Activation of the β-lactam ring towards 'ring switching' now required preparation of an *N*-urethane and in our first attempt we reacted the mixed β-lactams **27**+**28** with 2.2 equiv. of Boc_2O in acetonitrile in the presence of a catalytic amount of DMAP. The product was the bisacylated compound **35** (oil, $[\alpha]_D^{21}$ +37.6 (*c* 1, $CHCl_3$)),[†] obtained as a single diastereoisomer in 45% yield. The stereochemistry was indicated by NOE experiments since irradiation of the two *tert*-butyl singlets at δ 1.47 and 1.43 caused NOE of both olefinic protons whereas irradiation of the third at δ 1.50 did not. Use of an equimolecular amount of Boc_2O in the urethanation reaction was accompanied by conjugation to yield the urethanes **36**[†] in 30% yield. The desired vinyl-β-lactam urethanes **29** (oil, $[\alpha]_D^{26}$ +8.8 (*c* 1, $CHCl_3$))[†] (45%, *trans* $J_{3,4}$ 3.2) and **30** (mp 97–98°C, $[\alpha]_D^{28}$ −35.8 (*c* 1, $CHCl_3$))[†] (22%, *cis* $J_{3,4}$ 6.9) were obtained by reacting the β-lactams **27**+**28** with 2.5 equivalents of Boc_2O in CH_3CN in the presence of the proton source ^{t}BuOH and a catalytic amount of DMAP. Ozonolysis of the mixed diastereoisomers gave the aldehydes **31**[‡] in a *cis*:*trans* ratio of 1:9, irrespective of the *cis*:*trans* ratio of the olefinic starting material. Ozonolysis of the vinylic compound **35** gave the aldehyde **37**.[‡] Both aldehydes were used directly in the next step without further purification.

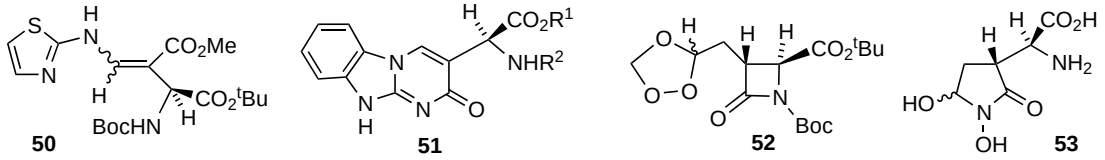
We now had two aldehydes **31** and **37** to use in 'ring switching' reactions. Reaction of the aldehyde **37** with hydrazine hydrate gave the diastereoisomeric acylhydrazides **38**[†] in 49% overall yield from the vinylurethane **35**. These might be formed by reaction of the aldehyde **37** with hydrazine to give the adduct **39**, followed by a reverse aldol type reaction as shown, and hydrazinolysis of the resultant β-lactam.

When the aldehyde **31** was treated with hydrazine in MeOH at room temperature, as in Scheme 4, the product was obtained as a white solid in 75% yield. The characteristic β-lactam urethane absorption was no longer present in the infra red and a broad exchangeable doublet at δ 5.80 (NHBoc) and singlets at δ 9.20 (pyrazole NH) and δ 7.23 (H-5) in the ^{1}H NMR spectrum were consistent with the product **40** (mp 181°C, $[\alpha]_D^{28}$ +44.2 (*c* 1, MeOH))[†] having been formed by a 'ring switching' reaction. Hydrolysis to the hydrochloride of the amino acid **41** (mp>250°C, $[\alpha]_D^{26}$ +56.3 (*c* 0.71, H_2O)) was achieved using 6N aq. HCl at room temperature. Although ibotenic acid had been shown to be racemic,[2] the specific rotation of this compound showed no change after leaving as a solution in ^2H_2O for 1 month. This compound cannot convert to a tautomer such as **2** with potential for additional enolisation to the asymmetric centre.

The yield in the 'ring switching' reaction was considerably better than had been obtained in the correspond-



Scheme 4. *Reagents and conditions*: (i) H_2NNH_2/MeOH (75%); (ii) 6N HCl (>94%); (iii) $CH_3C(=NH)NH_2\cdot HCl/K_2CO_3$/MeOH (61%); (iv) $H_2NC(=NH)NH_3\cdot HCO_3$/dioxan (39%); (v) 2-aminopyridine/dioxan (38%); (vi) 2-aminothiazole/dioxan (32%); (vii) 2-aminobenzimidazole/dioxan (70%). (All yields are quoted for the two steps from the olefins **29**/**30**.)

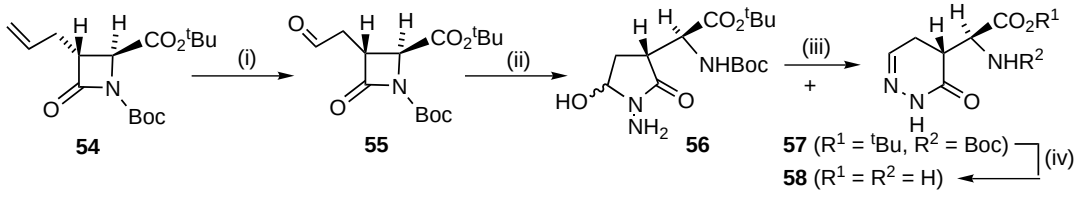


ing reaction in the pyroglutamic acid series.[6,8] Reaction of the aldehyde **31** with hydroxylamine gave no recognisable products. When the aldehyde **31** was reacted at room temperature with acetamidine hydrochloride in MeOH containing potassium carbonate, the pyrimidinone **42** (mp 178°C, $[\alpha]_D^{23}$ +138.7 (*c* 0.6, $CHCl_3$))† was obtained in 61% yield. A broad exchangeable doublet at δ 5.82 (NHBoc) and a singlet at δ 8.01 (H-4) in the ^1H NMR spectrum and absorption in the UV spectrum at λ_{max} 223 and 276 nm were consistent with the structure **42**. Hydrolysis in 6N aq. HCl at room temperature gave the hydrochloride of the amino acid **43** (mp >250°C, $[\alpha]_D^{32}$ +42.2 (*c* 0.45, H_2O))† in 97% yield and the specific rotation of this compound showed no change after leaving as a solution in ^2H_2O for 1 month. Reaction with guanidine carbonate in dioxan similarly gave the pyrimidinone **44** (mp>250°C, $[\alpha]_D^{25}$ +46.3 (*c* 1, $CHCl_3$)).

In work in the pyroglutamate series, we had been able to achieve 'ring switching' using a very limited number of 2-aminoheteroaromatic compounds as bisnucleophiles and a two-step process had been required to achieve this. When we reacted the aldehyde **31** with 2-aminopyridine in dioxan at room temperature, 'ring switching' was achieved in one step, yielding the pyrido[1,2-*a*]pyrimidinone **45** (mp 185–187°C, $[\alpha]_D^{28}$ +140.7 (*c* 1, $CHCl_3$))† in 38% yield and this could be deprotected to the amino acid **46** (mp >250°C, $[\alpha]_D^{29}$ +16.3 (*c* 1 H_2O)).† The ^1H NMR spectrum had the characteristic NHBoc exchangeable doublet at δ 6.04 and a singlet at δ 8.39 for H-2. Initially when we reacted the aldehyde **31** with 2-aminothiazole in methanol the desired product **47** (mp 194°C, $[\alpha]_D^{26}$ +92.4 (*c* 1, $CHCl_3$))† was obtained in 16% yield together with 30% of a mixture of the *E*- and *Z*-alkylidene aspartates **50**.† Changing the solvent to dioxan eliminated the by-products and gave the product **47** in 32% yield. The ^1H NMR spectrum of this compound had an exchangeable doublet at δ 5.96 for NHBoc, a singlet at δ 8.11 for H-7, and doublets at δ 7.96 and 7.03 for H-2 and H-3. The UV spectrum had absorption maxima at λ_{max} 226, 255, 263, 324 and 336 nm. Reaction of the aldehyde **31** with 2-aminobenzimidazole in dioxan at room temperature gave the benzimidazo[1,2-*a*]pyrimidinone **48** (mp > 250°C, $[\alpha]_D^{29}$ +155.3 (*c* 1, $CHCl_3$))† in 70% yield. The ^1H NMR spectrum had an exchangeable doublet at δ 6.39 (NHBoc), and a singlet at δ 8.48 for H-2. The doublet for H-6 was at δ 8.09, deshielded by the carbonyl group, whereas H-9 was at δ 7.2. This is in keeping with the structure **48** rather than the alternative structure **51**. Hydrolysis in 6N aq. HCl at room temperature gave the hydrochloride of the amino acid **49** (mp >250°C, $[\alpha]_D^{28}$ +79.2 (*c* 1, H_2O)).†

The homologous aldehyde **55** was synthesised as in Scheme 5, by preparing the ester–urethane **54** by modification of a literature route,[12] followed by ozonolysis using Me_2S as reducing agent. When insufficient Me_2S was used, the stable diastereoisomeric ozonides **52**† were isolated, but use of 35 equivalents of Me_2S gave the crude aldehyde **55**,‡ which was reacted directly with hydrazine hydrate in MeOH at room temperature to give the epimeric hydroxypyrrolidinones **56**† in 62% yield and the pyridazine **57** (mp 93–94 and 126–128°C, $[\alpha]_D^{25}$ −96.6 (*c* 0.61, $CHCl_3$))† in 17% yield. When the aldehyde **55** was heated to reflux in benzene with four equivalents of hydrazine hydrate, then the sole product was the pyridazine **57** in 65% yield from the olefin **54**. Hydrolysis of the protected pyridazine **57** with trifluoroacetic acid in dichloromethane gave the trifluoroacetate of the amino acid **58** (mp >250°C, $[\alpha]_D^{29}$ −60.0 (*c* 0.57, H_2O))† in nearly quantitative yield.

It is of interest to note that compound **57** is structurally similar to the natural product dealanylalahopcin **53**[13] which might be accessed directly by a ring switching reaction of the aldehyde **55** with hydroxylamine. Unfortunately we could isolate no discernible products when we attempted this reaction.



Scheme 5. *Reagents and conditions*: (i) (a) O_3/CH_2Cl_2, (b) Me_2S; (ii) H_2NNH_2/MeOH; (iii) Δ; (iv) F_3CCO_2H/CH_2Cl_2.

Acknowledgements

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