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Total synthesis of the amaryllidaceae alkaloid (+)-plicamine using solid-supported reagents

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Abstract—In this report we describe in full the total synthesis of the amaryllidaceae alkaloid (+)-plicamine **1** including a model compound study. In both cases the compounds were prepared using solid-supported reagents and scavengers in multi-step sequences of reactions to give materials which required no conventional purification but could be carried on to the next synthetic step.

1. Introduction

Recently a study of the Turkish Amayllidaceae *Glanthus plicatus* subspecies *byzantinus* has lead to the isolation of a new optically active compound, (+)-plicamine **1** (Fig. 1).[1]

This compound is amongst the first representatives of a new subgroup of amaryllidaceae alkaloids possessing a distinct dinitrogenous skeletal arrangement. (+)-Plicamine has an unusual tetracyclic structure containing an interesting 6,6-spirocyclic core defining three of the four stereogenic centers. At present this compound has no reported biological activity. Although the directly related members of the 2-benzopyrano-(3,4-*c*)hydroindole derived family of compounds as exemplified by tazettine, pretazettine, criwelline, percriwelline and 6a-epipretazettine have shown an interesting spectrum of medicinal properties.[2] These include anticholinergic, antitumour, immunosuppressive and analgesic activity. They have also been shown to inhibit various cell cycle mechanisms (including HIV-1 activity), and have found recent application in the therapeutic treatment of Alzheimer's diseases.

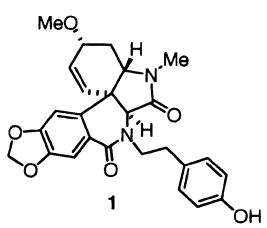

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Figure 1. The structure of the natural product (+)-plicamine **1**.

In our work on the use of solid-supported reagents and scavengers[3] we continue to discover new ways in which these systems can be effectively applied to the multi-step synthesis of small compound libraries,[4] more advanced natural products[5] and target synthesis in general.[6] In particular we have been investigating the intramolecular oxidative coupling reactions of electron rich aromatic rings with phenolic partners mediated by polymer-supported hypervalent iodine reagents.[7] This specific interest lead us to devise a suitable strategy to construct the core architecture of the natural product (+)-plicamine. We have previously demonstrated the effectiveness of this process in the synthesis of (±)-oxomaritidine.[5e,8] Here we report in full on the application of these concepts to the entantioselective synthesis of (+)-plicamine.[9]

2. Retrosynthesis

Retrosynthetic analysis of plicamine **1** suggests a simple amino acid, L-4-hydrohyphenylglycine **5** as a suitable starting material (Scheme 1). The desired core structure **2** would be formed via an intramolecular oxidative coupling reaction of **4** followed by a stereofacial conjugate addition controlled by the existing chiral centre in **3**. Compound **4** could in turn be prepared by standard peptide coupling chemistry of a suitably activated derivative of **5** and the fragments **6** and **7**. We were confident the selective reduction of the C-4 carbonyl could be achieved with a high degree of stereoselectivity as demonstrated by a number of related transformations in the literature.[10] The final synthetic steps would involve only simple alkylations of the alcohol and amide heteroatoms. This approach would also have the added advantage of permitting the parallel synthesis of both enantiomeric forms of the product starting

Keywords: amaryllidaceae; quinone; alkylation; solid-supported reagents.
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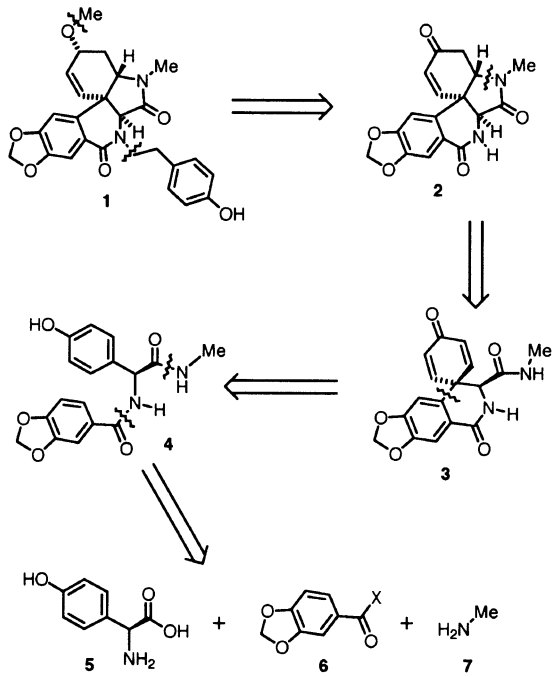
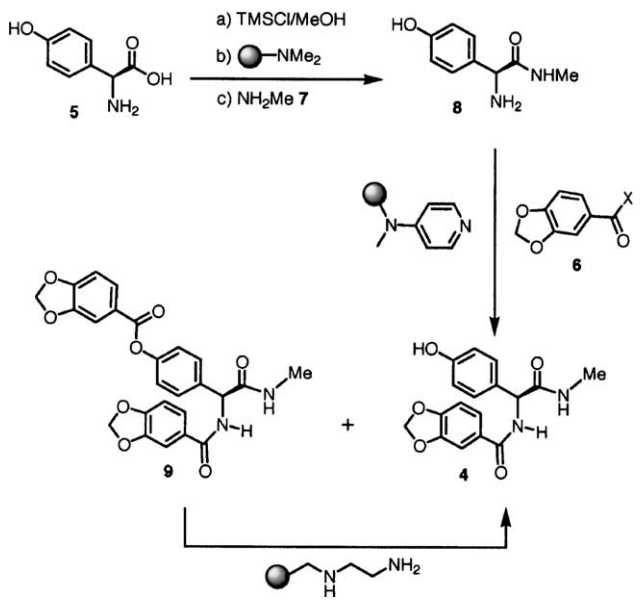


Scheme 1. Retrosynthetic approach to (+)-plicamine **1**.

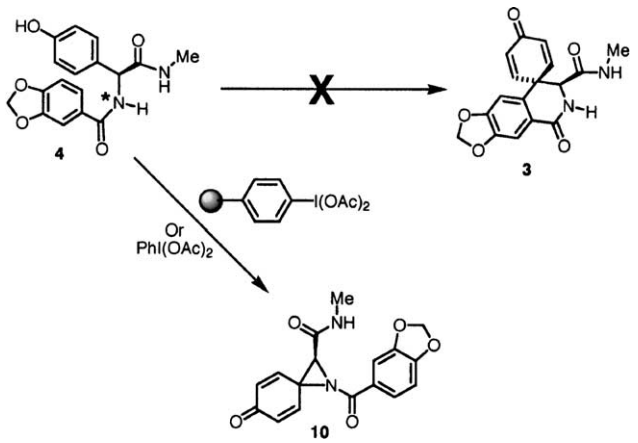
from the correspondingly configured amino acid (both of which are commercially available in quantity).

3. Synthesis

The synthesis of compound **4** was accomplished in a straightforward manner starting from L-4-hydroxyphenylglycine **5** (Scheme 2). The initial reaction with trimethylsilylchloride (TMSCl) in methanol resulted in the formation of an intermediate methyl ester. Subsequent treatment with Amberlyst 21 resin, to act as a scavenger for hydrochloric acid, produced the free base, which was directly converted to the corresponding amide **8** in essentially quantitative



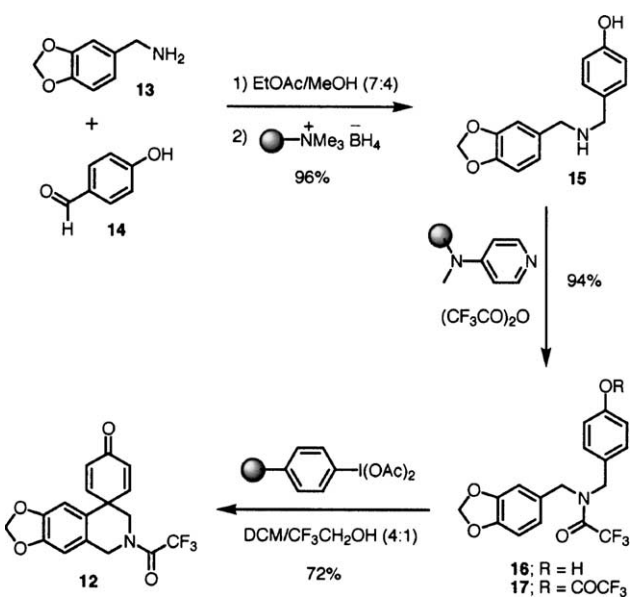
Scheme 2. Initial synthetic pathway. Preparation of fragment **4**.



Scheme 3. Attempted cyclisiation and resulting formation of aziridine **10**.

yield by the addition of excess methlyamine. This material was then coupled with piperanyl chloride (X=Cl) using an excess of polymer-supported dimethylaminopyridine (PS-DMAP) to give the desired product **4** along with an impurity of the doubly acylated material **9** (7–12%). This second material could be easily degraded to the target compound by treatment with a polymer-supported amine resin, namely *N*-(2-aminoethyl)aminomethyl polystyrene to give the final yield of **4** as 93% over five steps. Attempted cyclisation of this material using both polymer-supported and solution phase equivalents of diacetoxyiodobenzene under various conditions failed to generate the spirodienone structure **3**. Instead it was discovered that the linking amide nitrogen (*) acted as a nucleophile resulting in the formation of the corresponding acyl aziridine **10** (Scheme 3). All additional attempts at reacting *N*-protected derivatives such as Boc, sulfonamide, benzyl or methyl gave complete recovery of the starting material. The adoption of more vigorous conditions, such as heating lead to substantial decomposition, again with no sign of and spiro compound **3** being formed.

To gain a greater understanding of this process a number of molecular modelling studies were carried out. These



Scheme 4. Model compound preparation using solid-supported reagents.

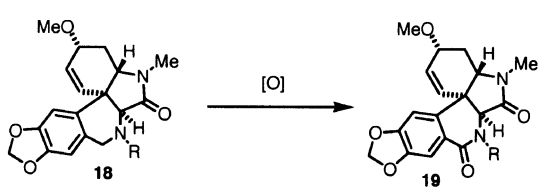
indicated that the problem might be due to the sp^2-hybridised carbon of the linking amide that was preventing the molecule adopting the required orientation for the successful coupling. In agreement with this hypothesis we were able to locate literature examples of spiro-cyclisations that had been used to prepare 6,6-fused systems, in all these examples the linking tether was a fully sp^3 hybridised unit.[11]

Therefore we prepared a model compound **12** where a methylene unit replaced the sp^2 carbonyl and the second pendant amide function was absent (cf. compound **4**) (Scheme 4). This compound was rapidly prepared from the condensation of 3,4-(methylendioxy)benzylamine **13** and 4-hydroxybenzaldehyde **14** followed by reduction to the secondary amine **15** using polymer-supported borohydride. Protection of the amine function as the trifluoroacetate **16** was carried out using PS-DMAP and trifluoroacetic anhydride. It should be noted that during the early stages of this reaction quantities of the doubly protected material **17** were detected although these were slowly consumed during the latter stages of the reaction. With the desired cyclisation precursor **16** in hand we studied the oxidative coupling reaction. This reaction was performed using solid-supported iodonium diacetate {PS-I$(OAc)_2$} in a mixture of DCM/2,2,2-trifluoroethanol (4:1) at ambient temperature and gave a modest 72% yield of the product. The solvent combination was crucial for achieving the dual requirements of polymer swelling and solvation of the radical cationic intermediate.[8] Other combinations gave much lower yields, at this stage no further optimisation was carried out on this reaction.

This model study gave us encouragement to progress a modified synthetic plan to incorporate the new structural requirements by introducing a later oxidation step of a species such as **18** to the amide **19** (Scheme 5). Amine to amide transformations are well documented in the literature and with the additional advantage of the centre being benzylic in our system it would certainly favour the proposed oxidation reaction.[12]

It was also decided to use the model compound to investigate a number of the proposed reactions and to also explore the synthetic potential for the generation of combinatorial libraries. Accordingly a short synthetic program was devised as shown in Scheme 6.

Facile reduction of the quinone **12** was achieved via hydrogenation using 10% Pd/C to furnish the key intermediate **20** in 94% isolated yield (Scheme 6). Treatment of ketone **20** with PS-borohydride (IRA-400 support) in DCM/MeOH lead to the simultaneous reduction and deprotection of the amide to yield **34** (also prepared from **23a**). This problem could be readily avoided by the judicious use of PS-cyanoborohydride as the reductant. This gave a mixture of the diastereoisomers **23a** and **23b** in a ratio of 98:2; the major isomer was identified as **23a** by nOe experiments. Thus indicating a high selectivity for the alcohol with the desired orientation as required in the plicamine synthesis.



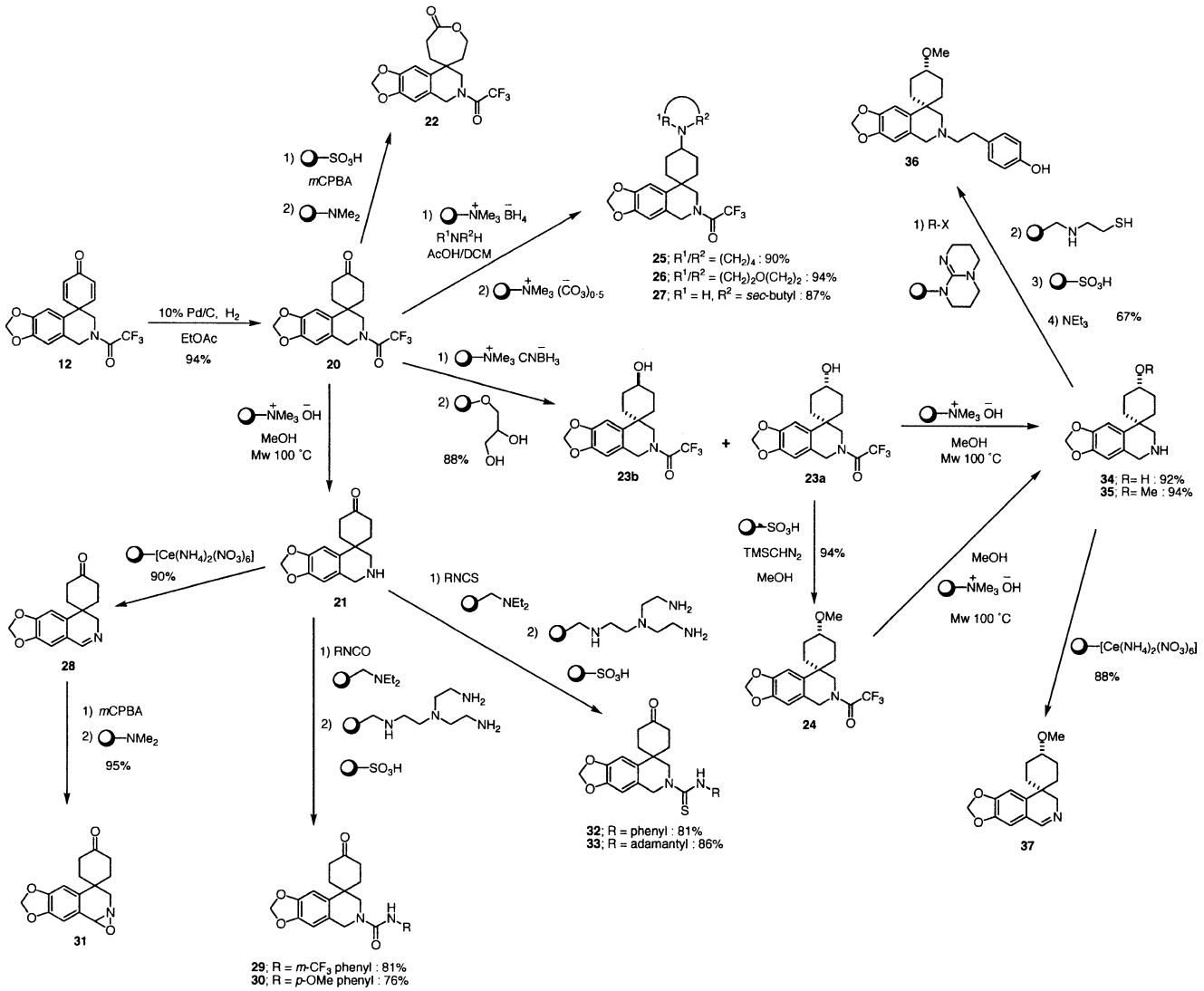
Scheme 5. Oxidation to the corresponding amide functionality.

Additionally with gram quantities of compound **20** we were able to further explore a number of other interesting reactions. These included a Baeyer–Villiger oxidation **23**, reductive aminations **25**–**27** and following deprotection of the TFA (trifluoroacetate) group the formation of the urea **29**, **30** and thiourea **32**, **33** derivatives. From the same material **21** we were also able to prepare the corresponding imine **28** and from this material the oxaziridine **31**.

Having shown the high level of selectivity in the reduction step of **20** to **23a** (98%) we next looked at methods for the preparation of the methylated compound **24**. The use of trimethylsilyl diazomethane for the methylation of acids and alcohols using various conditions has been well documented.[13] Most of the examples reported for the formation of methyl ethers have been promoted by the presence of a strong non-nucleophilic acid normally tetrafluoroboric acid or *p*-toluenesulfonic acid. We reasoned that we could modify these reaction conditions using a solid-supported sulfonic acid. The preparation of the ether **24** was therefore carried out using PS-SO_3H[14] and 4 equivalents of trimethyl diazomethane in a mixture of dichloromethane and methanol. We found this reaction to be extremely effective for the small-scale transformation but we experienced difficulties achieving complete conversion when attempting larger reactions on more than 2 g of substrate. Nevertheless this is a new procedure that may find application in other systems.

Another valuable method for the preparation of ethers is the direct alkylation of alcohols via activated alkyl halides. The methylation of both primary and secondary alcohols with MeI and silver triflate in the presence of a hindered base has been reported.[15] We attempted to convert these conditions for our own use by replacement of the 2,6-ditertbutylpyridine base with the polymer-supported equivalent to aid work-up. We envisaged that the removal of the silver salts could be achieved by simple filtration through a plug of silica. Initial reactions gave ~85% conversion to the product **24** after 6 h at reflux (MeCN solvent). We found the use of excess reagents (based on 3 equiv. of MeI) allowed the reaction to be pushed to completion although this made the work of the reaction difficult due to the formation of silver precipitates resulting in only moderate isolated yields (55–62%). No additional optimisation was carried out at this stage.

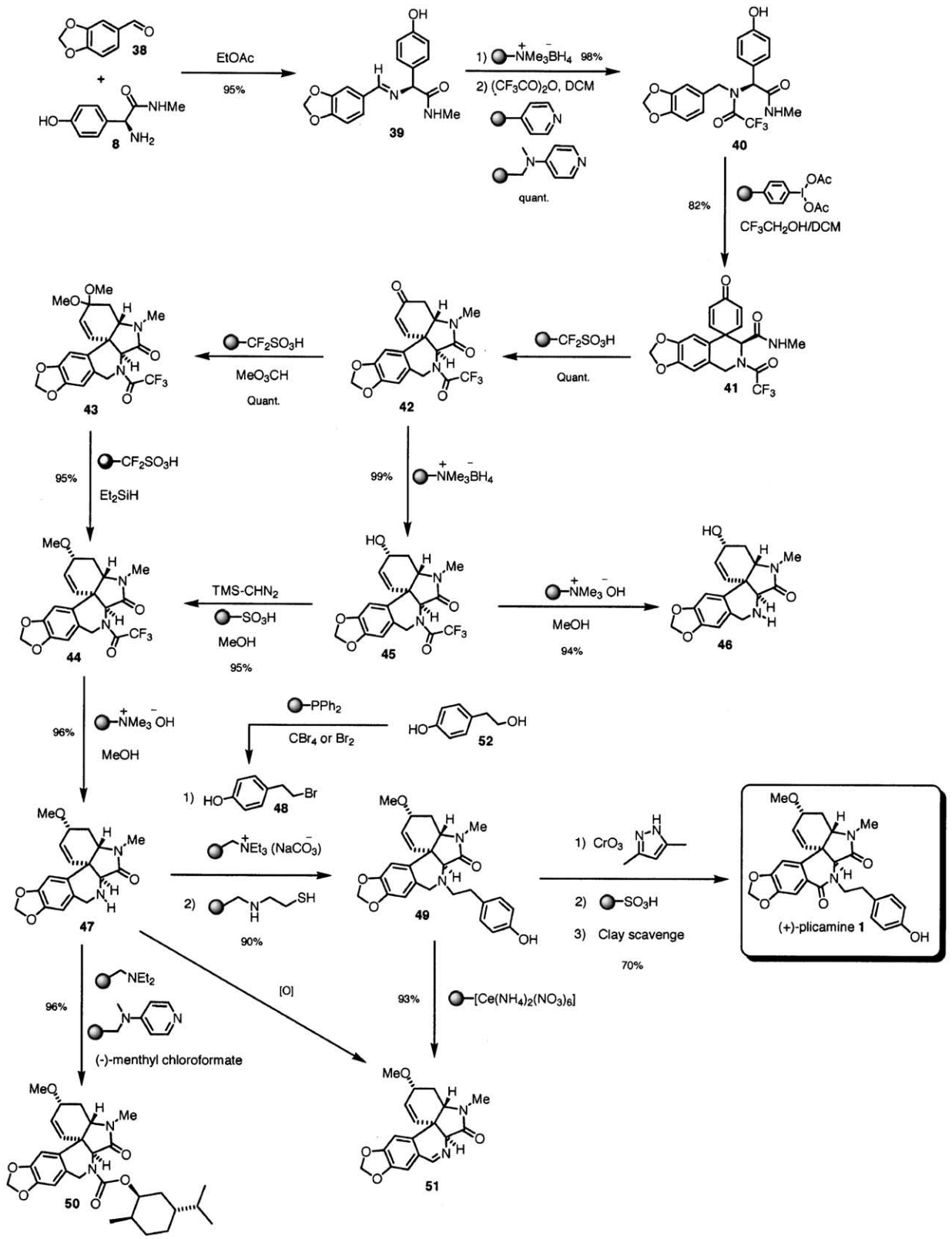
From compound **24** the synthesis of the requisite amine **35** was accomplished by basic hydrolysis (Ambersep 900, MeOH, microwave heating). Again the amine was easily converted to the imine material **37** as a potentially interesting core structure for biological screening. Formation of the amine **35** also permitted the chance to attach the pendant side chain as present in the natural product plicamine **1**. This was carried out in a two step process, firstly the alkylation using PS-TBU as the base then a



Scheme 6. Model compound studies and sampling the feasability and scope for compound decoration of the template **12**.

immobilised aminothiol as a scavenger for excess alkyl halide (1.5 equiv. were used). This gave **36** but in only approximately 85% purity (HPLC). Following a catch and release protocol with Amberlyst 15 and the triethylamine the product was obtained in a final 67% isolated yield and >95% purity.

Encouraged by the successful cyclisation and subsequent template modifications shown by the model study, the synthesis of (+)-plicamine **1** was initiated with the assembly of the key fragment **41** (Scheme 7). Thus, transformation of the previously described amide **8** into the imine **39** by reaction with piperanal **38** proceeded smoothly. Spontaneous precipitation of the imine product from the reaction mixture resulted in the easy isolation of imine **39** as a pure white solid in 95% yield by simple filtration. In an analogous manner to the preparation of the model compound **12**, the imine **39** was reduced with PS-borohydride and protected as the trifluoroacetate, to furnish **40**. For the large scale protection of this material it was found to be more economical to use the PS-DMAP as a catalyst and excess poly(4-vinylpyridine) (PVP) as the base.[16] Again this gave excellent yields of the product although the reaction times were slightly longer than when a stoicheometric excess of the PS-DMAP was used. Having proved the cyclisation was feasible on the model compound it was pleasing to find the reaction proceeded equally well on the real system. Cyclisation of **41** induced by PS-I(OAc)$_2$ gave a good yield of the spiro compound **42** as the only isolated compound from the reaction (82% yield). It is worth noting that we were unable to optimise the yield further nor were we able to detect any by-products or starting material in solution at the end of the reaction. Another interesting issue was that increasing the amount of resin used in the reaction past the optimal 1.5 equiv. lead to a proportional decline in the isolated yields. Extensive washing sequences with various solvents (DCM, MeOH, $CHCl_3$ and EtOAc) failed to liberate any additional material from the resin. We therefore speculate that this loss of material may arise through the reaction of the substrate with the polymer. This can be envisaged to occur as a consequence of the proposed radical pathway of the reaction.[17] Therefore it is possible for the substrate to become covalently attached to the polymer by reaction with for example uncapped vinylbenzene groups present from incomplete divinylbenzene (DVB) cross-linking in the polymer manufacturing process. Despite



Scheme 7. Synthesis of (+)-plicamine **1** using solid-supported reagents and scavengers.

this, the yield and purity were such that it was possible to continue with the synthesis.

Efficient and quantitative cyclisation of **41** to the tetracyclic lactame **42** was achieved using Nafion-H or Nafion SAC-13 (10–20% flourosulfonic acid wt.) resins in dichloromethane, this process could also be carried out using an ether solution of HCl as the catalyst. The following conversion to the methoxy-substituted intermediate **44** could be achieved by one of two options. Initially, we

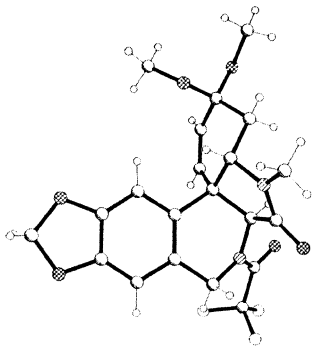


Figure 2. The X-ray crystal structure of the dimethoxy material **43**.

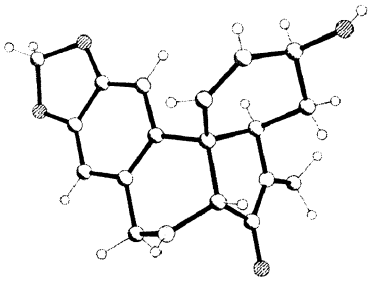
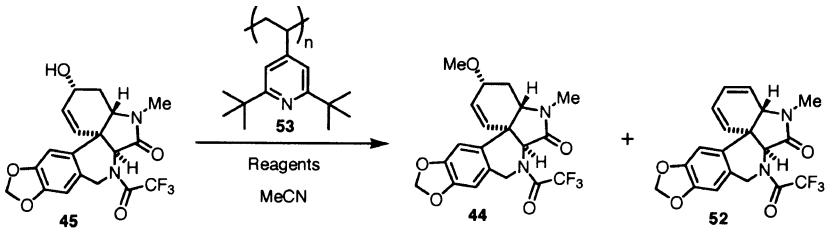


Figure 3. X-Ray crystal structure of the D-form amino alcohol **46**.

pursued the preparation of **44** via the reduction of the corresponding dimethyl acetal **43**. This compound was readily synthesised by heating a mixture of the ketone **42**, trimethyl orthoformate (or dimethoxy acetone) and Nafion SAC-13 in methanol at 100°C for 45 min under microwave irradiation. The transformation proved to be extremely efficient giving quantitatively the acetal compound **43** as a crystalline material (the structure was confirmed by X-ray crystallography, Fig. 2) upon filtration and solvent evaporation. Unfortunately, the subsequent reduction reaction was not as successful. Although the starting material was rapidly consumed upon exposure to Nafion-H and PS-borohydride, chiefly the hydrolysis products were obtained (28:59:13; **44/45/42**). Vigorous drying of the polymers over phosphorous pentoxide drastically improved the ratio of methoxy derived product (69:23:8; **44/45/42**) but never entirely eliminated the hydrolysed by-products. Believing the problem to be associated with moisture retained in the borohydride resin we turned our attention to conditions pioneered by Olah and co-workers for reductively cleaving acetals using triethylsilane.[18] Following a modification of this literature procedure triethylsilane was used to reduce the acetal **43** to the corresponding methyl ether **44** in 95% conversion under microwave heating conditions (120°C for 30 min). Although this reaction was successful we found the reaction, at least with this substrate, to be extremely inconsistent with conversions fluctuating from 65 to 95%. Even following the specified literature procedure we were only able to obtain modest conversions of 43–56%. In all cases only the single isomer of the reduced material (**44** or **45**) could be detected which was determined as the desired stereochemical configuration (see below for details).

Alternatively, treatment of the ketone **42** with 2 equiv. of PS-borohydride (A-26) in dichloromethane afforded the C-4 alcohol **45** in quantitative conversion and 93% isolated yield. Unlike the model compound, in this case only a single isomer of the alcohol could be detected. The facial selectivity of the reduction was determined by extensive nOe experiments, NMR coupling studies and later confirmed by single X-ray crystal analysis of the deprotected amino alcohol **46**. X-Ray crystallographic data was obtained on both enantiomers of this highly crystalline material confirming both the relative and absolute stereochemistry of the compounds at this point in the synthesis (Fig. 3).

Table 1. Conditions for the preparation of methyl ether **44**



Entry	**53**[a] (equiv.)	Conditions[a,b]	Temperature (°C)	Reaction time	Product composition (**45/44/52**)[c]
1	1.0	AgOTf (1 equiv.), MeI (1 equiv.)	60	24 h	38:12:50
2	1.5	AgOTf (1 equiv.), MeI (1 equiv.)	85	24 h	32:20:48
3	2.0	AgOTf (1 equiv.), MeI (1.2 equiv.)	85	12 h	34:29:37
4	3.0	AgOTf (1.75 equiv.), MeI (2 equiv.)	85	12 h	22:44:34
5	3.0	AgOTf (1.75 equiv.), MeI (2 equiv.)	85	8 h	26:47:27
6	3.0	AgOTf (1.75 equiv.), MeI (2 equiv.)	85	2 h[d]	76:24:0
7	2.5	AgOTf (1.75 equiv.), MeI (2 equiv.), iPr$_2$NEt (0.1 equiv.)[e]	85	8 h	20:49:31
8	2.0	MeOTf (1 equiv.)	85	8 h	5:59:36
9	2.0	MeOTf (1 equiv.), Mw	85	2.5 h	6:80:14
10	2.5	MeOTf (1.0 equiv.), Mw	100	1 h	5:85:10
11	2.5	MeOTf (1.2 equiv.), Mw	100	1 h	0:91:9
12	2.5	MeOTf (1.2 equiv.), Mw	120	35 min	0:97:3

[a] Mw=heating under microwave irradiation.
[b] Based on equivalents of substrate **44**.
[c] As determined by HPLC and LC-MS.
[d] Reaction stopped after allotted time.
[e] Used as a phase transfer catalyst.

The compound **46** was easily accessed from the simultaneous reduction and deprotection of the ketone **42** with the more active PS-borohydride (IRA-400) or treatment of alcohol **45** with Ambersep 900 (OH-form) in methanol at 100°C for 1 h under microwave irradiation.

On the basis of the above results and those obtained from the model compound study, it would seem that the origin of the diastereoselectivity in the reduction of each substrate is as a result of the axial conformational preference of the hydride nucleophile.

Having successfully obtained the alcohol **45** we next looked at methods of stereoselectively forming the methyl ether **44**. We had previously demonstrated in the model study that a combination of trimethylsilyl diazomethane and a sulfonic acid resin could be used to effect this type of transformation. In an analogous manner this procedure was used for the preparation of **44**, giving a high yield and clean product when employed for the small scale conversion (see discussion above).

We were also able to prepare the same methylated material **44** albeit as a mixture using the conditions worked out in the model compound study {poly(4-vinyl-2,6-*tert*-butylpyridine), iodomethane and silver trifluorosulfonate at reflux} (Table 1). The rather disappointing yield was due to the formation of the diene elimination product **52** (under the standard contions; entry 1; **52** was the main product). Following a rapid sequence of evaluation and optimisation reactions (Table 1) we were able to determine a modified set of conditions. In the new version of this reaction we substituted the iodomethane and silver trifluorosulfonate for methyl trifluorosulfonate (entry 8), we also found the reaction to be dramatically accelerated and the resulting product obtained cleaner when heated under microwave irradiation. In this case the reaction time was reduced from 8 h to 35 min and the corresponding product was not heavily contaminated with the diene **52** which was detected (LC-MS) after prolonged thermal heating (>4 h). We were unable to isolate the diene **52** as this material proved to be highly unstable and rapidly decomposed to give multiple unidentified products.

Next the synthesis of the amine **47** was accomplished by basic hydrolysis of the TFA protected amide **44** using an ion exchange hydroxide resin, namely, Ambersep 900 in methanol at 100°C. Again it was found expedient to heat this reaction under microwave irradiation rather than conventional thermal conditions reducing reaction times from 6 to 1 h whilst maintaining an almost quantitative yield (96% isolated). The ^{1}H NMR spectrum of **47** showed only a single diastereoisomer indicating epimerisation of the allylic methoxy group had not occurred under these basic reaction conditions. We were also able to confirm the configuration of the methoxy group by nOe experiments. In order to confirm the absolute stereochemistry we derivatised the L-form[19] of **47** to the menthyl carbamate **50** using a combination of polymer-supported triethylamine, catalytic PS-DMAP and (−)-menthyl chloroformate. From this reaction we were able to isolate material that proved suitable for X-ray crystallographic studies (Fig. 4). Thus we were able to conclusively demonstrate that the stereochemistry had been maintained through the sequence from the original amino acid **5**.

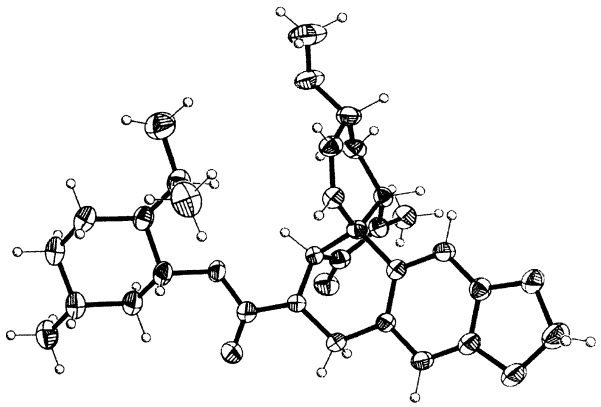


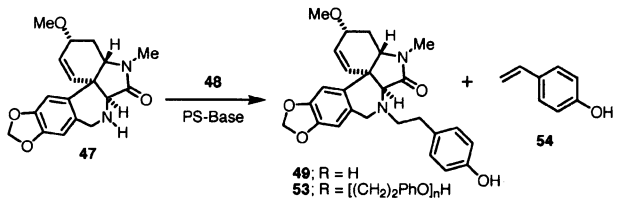
Figure 4. The X-ray crystal structure of the derivative **50**.

In the penultimate step of the synthesis the secondary amine **47** was alkylated with the halide **48** to eventually give an excellent yield of the advanced intermediate **49**. The alkyl halide **48** was itself prepared from 4-(2-hydroxyethyl)-phenol **52** using polymer-supported triphenylphosphine and carbon tetrabromide (or Br_2) in quantitative yield. The best conditions for the transformation of **47** to **49** were determined after screening a number of solid-phase bases and conditions (Table 2). This screening process was easily carried out in parallel using a Radleys carousel.[20]

The use of the stronger supported bases such as PS-BEMP or PS-TBU promoted substantial amounts of O-alkylation leading to chain extended compounds **53** in addition to many short chain polymeric impurities (Table 2). These same bases also tended to promote the elimination of the alkylating agent giving rise to the fully conjugated 4-vinylphenol **54**[21] as another impurity. By comparison, the use of weaker bases such as Amberlyst 21 and poly(4-vinylpyridine) (PVP) along with other supported tertiary amines resulted in only very slow and partial conversion to the product **49** (<49% after 24 h). Although these mixtures contained reduced quantities of the elimination by-product **54** they were still contaminated with unacceptable amounts of the sequential alkylated products **53**. Interestingly, changing the solvent or concentration of the reactions seemed to have little effect on the product distribution as shown by entries 3–8 Table 2. However, heating the reactions dramatically improved not only the conversion but also the product profile especially when using microwave heating (Table 1; entries 12–16). From the table it can also be clearly seen that the supported carbonate reagent was by far the superior base for use in this reaction. Hence this base was employed for the conversion of **47** to **49** in MeCN under microwave irradiation using 2×15 min pulses heating at 140°C.

Finally, the alkylated material **49** was then oxidised to plicamine **1** using chromium trioxide and 3,5-dimethylpyrazole. This reaction proved to be the most difficult transformation in the sequence. The reaction mixture required extensive scavenging with Amberlyst 15 resin to remove contaminating unoxidised amine and the pyrazole. Subsequent filtration through a mixed bed column of Varian

Table 2. Conditions for the preparation of compound **49**



Entry	Supported base	**48**[a] (equiv.)	Solvent	Temperature (°C)	Conversion (purity, %)[b]
1	PS-BEMP	1.5	MeCN	rt	79 (66)
2	PS-TBU	1.5	MeCN	rt	72 (74)
3	PS-NEt_2	1.5[c]	MeCN	rt	48 (78)
4	PS-NEt_2	1.5[d]	MeCN	rt	45 (76)
5	PS-NEt_2	1.5	MeCN	rt	46 (74)
6	PS-NEt_2	1.2	DCM	rt	41 (76)
7	PS-NEt_2	1.2	MeCN	rt	38 (ND)
8	PS-NEt_2	1.2	DMF	rt	39 (79)
8	A-21	1.2	MeCN	rt	34 (ND)
9	PVP	1.2	MeCN	rt	28 (ND)
10	PS-N*i*Pr_2	1.2	MeCN	rt	49 (80)
11	PS-CO_3	1.2	MeCN	rt	16 (ND)
12	A-21	1.2	MeCN	80	49 (ND)
13	PVP	1.2	MeCN	80	65 (92)
14	PS-N*i*Pr_2	1.2	MeCN	80	80 (92)
15	PS-CO_3	1.2	MeCN	80	88 (96)
16	PS-CO_3	1.2	MeCN	140[e]	99 (95)

ND, not determined.
[a] Based on equivalents of substrate **47**.
[b] Conversion to **49** as determined by HPLC and LC-MS. Purity excluding starting materials.
[c] Half concentration.
[d] Double concentration.
[e] Heating under microwave irradiation.

Chem Elut CE1005 packing material and montmorillonite K 10 (1:1 wt), which had been preconditioned by eluting with a 10:1 mixture of acetonitrile/water proved effective in removing the chromium salts. After this scavenging process, (+)-plicamine **1** was obtained in a reasonable 70% yield but in greater than 90% purity as determined by HPLC. To obtain analytically pure material a rapid pass through a short plug of silica gel was sufficient. A number of alternative oxidising systems were tried for this final step but all lead to the formation of the imine **51** by elimination of the side chain. The formation of this product was confirmed by the direct oxidation of **47** to the same material **51** by the use of ceric ammonium nitrate on silica.[26] A mechanism involving initial oxidation of the benzylic position followed by spontaneous dehydration to the iminium ion and elimination of 4-vinylphenol **54** would account for this product. We are currently investigating new methods for this oxidation that should avoid this problem.

4. Experimental

4.1. General

Unless otherwise specified, all reactions involving polymers were carried out on a laboratory shaker IKA 125 at 250 rpm. All moisture sensitive reactions were carried out under an argon atmosphere using oven-dried glassware. Amberlyst resins were of technical grade and washed with methanol and dichloromethane (DCM) before use, dried in vacuum at 60°C. Poly-DMAP was pre-washed with DCM, MeOH, Et_2O then dried at 60°C for 20 h. Tetrahydrofuran (THF) was distilled over sodium benzophenone and dichloromethane over calcium hydride. All others solvents and reagents were used as supplied unless otherwise specified. Analytical TLC was performed using precoated glass-backed plates (Merck Kieselgel 60 F254) and visualized by ultra-violet radiation, acidic ammonium molybdate (IV) or potassium permanganate. Infra-red spectra were obtained on Perkin–Elmer Spectrum One FT-IR spectrometer. Optical rotations were measured at 25°C on a Perkin–Elmer Polarimeter Model 343. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker Advance DPX-400 spectrometer at 400 MHz with residual chloroform as the internal reference (δ_H=7.26 ppm). ^{13}C NMR spectra were recorded in $CDCl_3$ on the same spectrometer at 100 MHz with the central peak of chloroform as the internal reference (δ_C=77.0 ppm). DEPT 135 and two-dimensional (COSY, HMQC and HMBC) NMR spectroscopy were used, where appropriate, to aid in the assignment of signal in the ^{1}H and ^{13}C NMR spectra. Mass spectra and accurate mass data were obtained on Hewlett-Packard LC/MSD, Kratos MS890MS or Bruker BIOAPEX 4.7 T FTICR spectrometers at the Department of Chemistry, University of Cambridge. LC-MS analysis was performed on a Hewlett-Packard HPLC 1050 chromatograph (Supelcosil ABZ+PLUS; 3 μm, 33 mm×4.6 mm) attached to a Micromass Platform LC Electrospray mass spectrometer. Elution was carried out using the gradient given in Table 3—Method B. Alternatively, LC-MS was performed on a Hewlett-Packard HPLC 1100 chromatograph (Mercury hexylphenyl column) attached to a HP LC/MSD Platform LC APCI mass

Table 3. Elution gradient for LC-MS Method B

Time (min)	A (%)[a]	B (%)[b]	Flow rate (mL/min)
0.00	100	0	0
0.70	100	0	1
4.20	0	100	1
7.70	0	100	1
8.00	100	0	1

[a] 10 mmol solution of ammonium acetate in water+0.1% formic acid.
[b] 95% Acetonitrile+5% water+0.05% formic acid.

Table 4. Elution gradient for LC-MS Method A

Time (min)	A (%)[a]	B (%)[b]	Flow rate (mL/min)
0.00	95	5	0
3.00	5	95	0.6
5.00	5	95	0.6
5.50	95	5	0.6
8.00	95	5	0.6

[a] Water+0.1% trifluoroacetic acid.
[b] Acetonitrile+0.1% trifluoroacetic acid.

spectrometer. Elution was carried out using the gradient given in Table 4—Method A. For details on compound numbering please consult supplementary data.

4.1.1. Preparation of (+)-plicamine 1. An oxidising solution was prepared from a suspension of CrO_3 (250 mg, 2.5 mmol, 5 equiv.) and 3,5-dimethylpyrazole (240 mg, 2.5 mmol, 5 equiv.) in DCM (10 mL) at 0°C then cooled to −45°C.[22] To the reaction mixture was added compound **49** (221 mg, 0.5 mmol, 1 equiv.) in DCM (5 mL), the resulting dark red solution was stirred at −45°C for 8 h, then allowed to warm to ambient temperature. The reaction was worked-up by the addition of Amberlyst 15 (6.0 g; Fluka Cat. No. 06423) and the reaction shaken for 1 h. The mixture was then filtered through a mixed bed column (1:1 wt, 10 g) of Varian Chem Elut CE1005 packing material (Chem Elut Column; Varian Cat. No. 1219-8007) and montmorillonite K 10 (Aldrich Cat No. 28,152-2), which had been preconditioned by eluting with a 10:1 mixture of MeCN/water (30 mL). The column was flushed with DCM (25 mL) and the filtrate evaporated under reduced pressure to yield plicamine **1** as a brown solid (162 mg, 70%).[1] $[\alpha]_D$=+77.5 (c=0.867 in MeOH), IR (neat) 3293, 2976, 2984, 1706, 1669, 1613, 1514.5, 1482.7, 1442.7, 1400.7, 1386.1, 1348.3, 1233.6, 1158, 1103, 1036, 932, 930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=7.59 (s, 1H, H-9), 7.08 (d, 2H, J=8.3 Hz, H-2′ and H-6′), 6.73 (d, 2H, J=8.3 Hz, H-3′ and H-5′), 6.49 (s, 1H, H-12), 6.01 (s, 2H, OCH_2O), 5.81 (d, 1H, J=10.1 Hz, H-2), 5.36 (d, 1H, J=10.1 Hz, H-1), 4.51 (ddd, 1H, J=13.8, 8.3, 4.3 Hz, H-8′a), 4.06 (m, 1H, H-4a), 3.93 (s, 1H, H-6a), 3.87 (dd, 1H, J=12.3, 4.3 Hz, H-4a), 3.51 (m, 1H, H-8′b), 3.44 (s, 3H, OMe), 2.93 (m, 2H, H-7′), 2.78 (s, 3H, NMe), 2.58 (m, 1H, H-3β), 1.39 (m, 1H, H-3α); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.7 (C-6), 161.9 (C-8), 154.6 (C-12′), 151.2/148.3 (C-10/11), 136.0 (C-12a), 133.7 (C-1), 131.8 (C-9′), 131.1 (C10′), 125.6 (C-2), 124.1 (C-8a), 116.0 (C-11′), 108.8 (C-9), 106.6 (C-12), 101.8 (C-15), 71.6 (C-3), 64.6 (C-4a), 60.5 (C-6a), 57.0 (C-13), 50.5 (C-8′), 44.7 (C-12b), 34.2 (C-7′), 31.1 (C-4), 28.0 (C-14); HR-MS (ESI, Q-tof) calcd for $C_{26}H_{26}N_2O_6Na$: 485.1689; found 485.1694. (−)-Plicamine $[\alpha]_D$=−76.5 (c=0.678 in MeOH); HR-MS (ESI, Q-tof) calcd for $C_{26}H_{26}N_2O_6Na$: 485.1689; found 485.1678.

4.1.2. Preparation of benzo[1,3]dioxole-5-carboxylic acid [(4-hydroxyphenyl)methylcarbonylmethyl]amide 4. To a suspension of poly-DMAP (1.25 g, 3.75 mmol, 1.5 equiv., dimethylaminopyridine, polymer bound 3 mmol/g; Aldrich Cat. No. 35,988-2) in THF (25 mL) was added piperanyl chloride **6** (512 mg, 3 mmol, 1.2 equiv.) and the solution shaken for 20 min. To the reaction mixture was then added L-form **8** (450 mg, 2.5 mmol, 1 equiv.) in THF (15 mL) and the reaction monitored for completion by LC-MS. The resin was removed by filtration washed with THF (3×10 mL). If required *N*-(2-aminoethyl)aminomethyl polystyrene (0.89 g, 2.5 mmol, 2.8 mmol/g; NovaBiochem Cat No. 01-64-0178) was added to degrade any residual compound **9** and remove traces of chloride **6**. The resin was filtered and washed THF (3×10 mL) and the combined filtrate evaporated under reduced pressure to give the title compound **4** as a cream powder (0.82 g, quantitative): $[\alpha]_D$=+108.8 (c=1.20 in MeOH), IR (neat) 3297, 2892, 1682, 1634, 1598, 1556, 1518, 1502, 1481, 1441, 1410, 1353, 1327, 1299, 1257, 1225, 1115, 1040, 930 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=9.35 (br. s, 1H, OH), 8.46 (d, 1H, J=7.7 Hz, H-3), 8.02 (q, 1H, J=4.75 Hz, H-11), 7.51 (dd, 1H, J=8.1, 1.4 Hz, H-6), 7.46 (d, 1H, J=1.4 Hz, H-10), 7.23 (d, 2H, J=8.5 Hz, H-2′), 6.94 (d, 1H, J=8.1 Hz, H-7), 6.72 (d, 2H, J=8.5 Hz, H-3′), 6.07 (s, 2H, OCH_2O), 5.47 (d, 1H, J=7.7 Hz, H-2), 2.58 (d, 3H, J=4.75 Hz, NMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.2 (C-1), 165.4 (C-4), 157.3 (C-4′), 150.2/147.7 (C-8/9), 129.4/128.4 (C-1′/5), 129.3 (C-2′), 123.2 (C-6), 115.4 (C-3′), 108.2/108.2 (C-7/10), 102.1 (C-13), 57.1 (C-2), 26.1 (C-12); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{16}N_2O_5Na$: 351.0987; found 351.0958.

4.1.3. Preparation of 2-amino-2-(4′-hydroxyphenyl)-*N*-methyl acetamide 8. To a suspension of 4-hydroxyphenyl glycine (50.0 g, 0.3 mol, 1 equiv.) in MeOH (500 mL) at 0°C was added dropwise over 30 min trimethylsilyl chloride (64.6 mL, 0.75 mol, 2.5 equiv.), the resulting clear solution was then stirred at 35°C for 48 h. Evaporation of an aliquot (1 mL) gave the hydrochloride salt **8a** as a white solid. The reaction mixture was diluted with a further volume of MeOH (250 mL) and Amberlyst 21 (500 g, 1.5 mol, 5 equiv., 3 mmol/g; Fluka Cat. No. 06424) was added and the mixture shaken at ambient temperature for 2 h (caution this process was mildly exothermic). The resin was removed by filtration and washed with MeOH (3×150 mL). Removal and evaporation of a second aliquot (1 mL) of the pale yellow filtrate gave an off-white solid which was characterised as the free base **8b**. The bulk solution was then reduced in volume to one half and methylamine (31.06 g, 0.9 mol, 3 equiv.) was added and the mixture stirred at 45°C for 48 h. When the reaction had reached completion as indicated by ^1H NMR the solvent was removed by evaporation to yield **8** as a pale brown oil (quantitative).

*2-Amino-2-(4′-hydroxyphenyl)-methyl ester hydrochloride salt **8a**.* $[\alpha]_D$=+145.4 (c=0.987 in 1N HCl); D-form $[\alpha]_D$=−149.8 (c=1.38 in 1N HCl); ^1H NMR (400 MHz, d_6-DMSO): δ=8.97 (br s, 1H, OH), 7.26 (d, 2H, J=8.6 Hz, 2×*o*-H), 6.82 (d, 2H, J=8.6 Hz, 2×*m*-H), 5.06 (q, 1H,

J=4.5 Hz, CH), 3.67 (s, 3H, OMe); ^{13}C NMR (100 MHz, d_6-DMSO): δ=169.7 (C), 159.0 (C), 130.1 (C), 123.0 (CH), 116.1 (CH), 55.3 (CH), 53.4 (CH_3).[23]

2-Amino-2-(4′-hydroxyphenyl)-methyl ester **8b**. L-form $[\alpha]_D$=+128.7 (c=0.55 in MeOH); IR: 3259, 2971, 2343, 1737, 1727, 1647, 1612, 1593, 1546, 1511, 1447, 1411, 1373, 1220, 1174 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO): δ=9.40 (br s, 1H, OH), 7.13 (d, 2H, J=8.44 Hz, 2×o-H), 6.68 (d, 2H, J=8.44 Hz, 2×m-H), 4.40 (s, 1H, CH), 3.56 (s, 3H, OMe), 2.65 (br. s, 2H, NH_2); ^{13}C NMR (100 MHz, d_6-DMSO): δ=175.1 (C), 157.2 (C), 131.5 (C), 128.4 (CH), 115.5 (CH), 58.0 (CH), 52.1 (CH_3); HR-MS (ESI, Q-TOF) calcd for $C_9H_{11}NO_3$: 181.0739; found 181.0740. D-form $[\alpha]_D$=−122.9 (c=0.35 in MeOH); HR-MS (ESI, Q-TOF) calcd for $C_9H_{11}NO_3$: 181.0739; found 181.0748.[24]

2-Amino-2-(4′-hydroxyphenyl)-N-methyl acetamide **8**. L-form $[\alpha]_D$=+127.4 (c=1.2 in MeOH); ^{1}H NMR (600 MHz, d_6-DMSO): δ=8.09 (q, 1H, J=4.6 Hz, CONH), 7.17 (d, 2H, J=8.5 Hz, H-2′), 6.70 (d, 2H, J=8.5 Hz, H-3′), 4.33 (s, 1H, H-2), 2.55 (d, 3H, J=4.6 Hz, NMe); ^{13}C NMR (150 MHz, d_6-DMSO): δ=173.3 (CO), 157.3 (C-4′), 131.7 (C-1′), 128.4 (C-2′), 115.4 (C-3′), 58.2 (C-2), 25.9 (C-CH_3); HR-MS (ESI, Q-tof) calcd for $C_9H_{12}N_2O_2Na$: 203.0796; found 203.0789. D-form $[\alpha]_D$=−126.4 (c=1.1 in MeOH); HR-MS (ESI, Q-tof) calcd for $C_9H_{12}N_2O_2$: 180.0896; found 180.0907.[25]

4.1.4. Preparation of 1-(benzo[1,3]dioxole-5-carbonyl)-6-oxo-1-aza-spiro[2.5]octa-4,7-diene-2carboxylic acid methylamide 10. R_f 4.26 (Method B); IR (solid): 3300, 2937, 1669, 1646, 1606, 1535, 1504, 1488, 1450, 1366, 1306, 1258, 1190, 1103, 1076, 1032, 928 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.54 (dd, 1H, J=8.15, 1.7 Hz, H-3′), 7.43 (d, 1H, J=1.7 Hz, H-7′), 6.91 (dd, 1H, J=10.0, 3.1 Hz, H-2), 6.86 (d, 1H, J=8.15 Hz, H-4′), 6.73 (br. q, 1H, J=~5 Hz, NH), 6.64 (dd, 1H, J=10.1, 3.1 Hz, H-6), 6.37 (dd, 1H, J=10.0, 1.9 Hz, H-3), 6.31 (dd, 1H, J=10.1, 1.9 Hz, H-5), 4.83 (s, 1H, H-7), 2.85 (d, 3H, J=5.0 Hz, NMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ=184.9 (C-4), 168.4 (C), 165.2 (C), 151.9 (C), 148.4 (C), 145.3 (CH), 141.8 (CH), 130.7 (CH), 130.2 (CH), 124.6 (CH), 120.2 (C), 109.0 (CH), 108.7 (CH), 102.3 (C-8′), 82.0 (C), 77.2 (CH), 26.4 (C-9); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{14}N_2O_5Na$: 349.0800; found 349.0807.

4.1.5. Preparation of PS-iodobenzene. To a mixture of sulfuric acid (conc. 16.5 mL), water (16 mL) and nitrobenzene (120 mL) was added iodine (20 g, HIO_3 (6.6 g) and carbon tetrachloride (50 mL). Polystrene (20 g, 2% cross-linked, 200–400 mesh; Acros Cat. No. 41810-2500) was added and the reaction mixture heated at reflux (~105°C) for 7 days. The reaction was cooled to ambient temperature, the resin removed by filtration and thoroughly washed with portions of DCM and ether (until no further colour was present in the washings). The polymer was washed with DCM in a soxhlet extraction apparatus, over 2 days. The resulting brown polymer was dried in vacuo.

4.1.6. Preparation of PS-diacetoxyiodobenzene. Acetic anhydride (18 mL) was cooled to 0°C and hydrogen peroxide (5.6 mL, 30% solution) was added dropwise. The reaction was allowed to warm slowly to ambient temperature over night. Iodopolystyrene (1 g) was added and the reaction heated at 40°C for 12 h. The resin was removed by filtration and washed with DCM (5×50 mL) and dried in vacuo away from light to yield a yellow resin.

4.1.7. Preparation of 2′,3′-dihydro-6′,7′-methylendioxy-2′-trifluoroacetyl-spiro[cyclohexa-2,5-diene-1,4′-(1*H*)isoquinolin]-4-one 12. To a slurry of PS-diacetoxyiodobenzene (470 mg, 0.56 mmol, 2 equiv.) swollen in DCM/2,2,2-trifluoroethanol (4:1; 5 mL) was added a solution of protected amine **16** (100 mg, 0.28 mmol, 1 equiv.) in DCM/2,2,2-trifluoroethanol (4:1; 15 mL) and the mixture shaken at ambient temperature for 1 h. The reaction was filtered and the spent resin washed with DCM (3×10 mL), the filtrates were combined and the solvent was removed under reduced pressure to yield **12** as a pale yellow solid (72 mg, 73%): R_f 3.03 (Method A), R_f 4.80 (Method B); IR (solid): 1690, 1671, 1504, 1481, 1435, 1392, 1237, 1196, 1178, 11645, 1083, 989 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO): δ=7.04 (d, 2H, J=10.0 Hz, H-2/6-rotomer 1), 7.00 (s, 1H, H-5′-rotomer 1), 6.97 (s, 1H, H-5′-rotomer 2), 6.89 (d, 2H, J=10.0 Hz, H-2/6-rotomer 2), 6.42 (s, 1H, H-8′-rotomer 1), 6.40 (s, 1H, H-8′-rotomer 2), 6.30 (d, 4H, J=10.0 Hz, H-3/5-rotomers 1 and 2), 5.97 (s, 4H, CH_2O_2-rotomers 1 and 2), 4.83 (s, 2H, H-1′-rotomer 1), 4.78 (s, 2H, H-1′-rotomer 2), 3.93 (s, 2H, H-3′-rotomer 1), 3.85 (s, 2H, H-3′-rotomer 2); ^{13}C NMR (100 MHz, d_6-DMSO): δ=185.0/186.0 (C-4), 151.4/151.0 (C-2/6-rotomer 1), 147.9/147.4/147.2 (C-6′/7′), 128.9/125.2 (C-2/6-rotomer 2), 128.85/128.8 (C-3/5), 125.2/125.2/125.1/125.1 (C-4a′/8a′), 107.3/107.4/107.3/106.9 (C-5′/8′), 101.9/101.85 (C-10′), 48.2/47.4/45.8 (C-1′/3′). ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.81 (d, 2H, J=10.04 Hz, H-2/6-rotomer 1), 6.74 (d, 2H, J=10.0 Hz, H-2/6-rotomer 2), 6.65 (s, 1H, H-5′-rotomer 1), 6.61 (s, 1H, H-5′-rotomer 2), 6.45 (s, 2H, H-8′-rotomers 1 and 2), 6.39 (d, 2H, J=10.04 Hz, H-3/5-rotomer 1), 6.36 (d, 2H, J=10.07 Hz, H-3/5-rotomers 2), 5.95 (s, 4H, CH_2O_2-rotomers 1 and 2), 4.81 (s, 2H, H-1′-rotomer 1), 4.79 (s, 2H, H-1′-rotomer 2), 3.93 (s, 2H, H-3′-rotomer 1), 3.83 (s, 2H, H-3′-rotomer 2); ^{13}C NMR (100 MHz, $CDCl_3$): δ=185.1/185.0 (C-4; rotomers 1 and 2), 149.8/149.3 (C-2/6; rotomers 1 and 2), 148.31/148.30/147.88/147.9 (C-6′/7′; rotomers 1 and 2), 129.4/129.3 (C-3/5; rotomers 1 and 2), 125.0/124.3/123.9/123.7 (C-4a′/8a′; rotomers 1 and 2), 107.6/107.0/106.7/106.3 (C-5′/8′; rotomers 1 and 2),101.7/101.6 (C-10′; rotomers 1 and 2), 50.4/48.5 (C-1′/3′; rotomer 1), 47.4/45.7 (C-1′/3′; rotomer 2), 44.8/44.6 (C-1; rotomers 1 and 2); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{12}NO_4F_3Na$: 374.0616; found 374.0634.

4.1.8. Preparation of 4-{(benzo[1,3]dioxol-5-ylmethyl ene)methyl}phenol 15. A solution of 3,4-(methylendioxy) benzylamine **13** (27.50 g, 182 mmol, 1 equiv.) and 4-hydroxybenzaldehyde **14** (22.23 g, 182 mmol) in EtOAc/MeOH (7:4; 500 mL) was stirred at ambient temperature for 45 min during this time an off-white precipitate formed. A small sample of the precipitate was removed by filtration, washed with cold EtOAc (3×10 mL, 0°C), dried and characterised as the imine **15a**. To the stirred suspension was added PS-borohydride (87.4 g, 2.5 mmol/g, 1.2 equiv., borohydride on Amberlite IRA 400, ~2.5 mmol/g; Aldrich Cat. No. 32,864-2) and the mixture stirred for 3.5 h, during

which time the precipitate dissolved. The spent resin was removed by filtration, washed with EtOAc (2×75 mL) and the combined solutions evaporated under reduced pressure to yield amine **15** as a white solid (44.90 g, 96%).

4-{[(Benzo[1,3]dioxol-5-ylmethyl)amino]methyl}phenol ***15a***. R_f 2.472; (256.1, MH+) (Method A); IR (solid): 2912, 2560, 1633, 1601, 1517, 1505, 1489, 1442, 1369, 1288, 1244, 1223, 1211, 1038, 1025, 990, 840 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO): δ=9.83 (s, 1H, OH), 8.28 (s, 1H, H-5), 7.57 (d, 2H, J=8.4 Hz, H-3), 6.83 (d, 1H, J=8.0 Hz, H-6), 6.81 (s, 1H, H-10), 6.79 (d, 2H, J=8.4 Hz, H-2), 6.75 (d, 1H, J=8.0 Hz, H-7), 5.95 (s, 2H, CH_2O_2), 4.57 (s, 2H, H-4); ^{13}C NMR (100 MHz, d_6-DMSO): δ=161.3 (C-5), 160.3 (C-1), 147.7 (C-8), 146.4 (C-9), 139.3 (C-5a), 130.1 (C-3), 127.9 (C-3a), 121.3 (C-7), 115.9 (C-2), 108.8/108.5 (C-6/10), 101.2 (C-11), 64.0 (C-4). HR-MS (ESI, Q-tof) calcd for $C_{15}H_{14}NO_3$: 256.0973; found 256.0971.

4-{(Benzo[1,3]dioxol-5-ylmethylene)methyl}phenol ***15***. R_f 2.28 (Method A); IR (solid): 3242, 2369, 1608, 1491, 1462, 1437, 1374, 1338, 1254, 1234, 1195, 1038 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO): δ=9.15 (br. s, 1H, OH), 7.08 (d, 2H, J=8.4 Hz, H-3), 6.83 (s, 1H, H-10), 6.80/6.73 (d, 1H, J=8.0 Hz, H-6 and H-7), 6.67 (d, 1H, J=8.4 Hz, H-2), 5.94 (s, 2H, CH_2O_2), 3.53 (s, 2H, CH_2), 3.49 (s, 2H, CH_2), 3.35 (br. s, 1H, NH); ^{13}C NMR (100 MHz, d_6-DMSO): δ=158.5 (C-1), 148.1 (C-9), 147.8 (C-8), 132.0 (C-3), 125.7/124.5 (C-3a/5a), 122.2 (C-7), 115.8 (C-2), 110.6 (C-6), 108.1 (C-10), 101.8 (C-11), 50.0/49.9 (C-4/5). HR-MS (ESI, Q-tof) calcd for $C_{15}H_{14}NO_3$: 258.1130; found 258.1131.

4.1.9. Preparation of *N*-benzo[1,3]dioxol-5-ylmethyl-2,2,2-trifloro-*N*-(4-hydroxybenzyl)acetamide 16. To a cooled (ice bath) mixture of poly-DMAP (3.89 g, 11.67 mmol, 3 equiv., dimethylaminopyridine, polymer bound 3 mmol/g; Aldrich Cat. No. 35,988-2) and amine **15** (1.00 g, 3.89 mmol, 1 equiv.) in DCM (25 mL) was added dropwise trifluoroacetic anhydride (0.66 mL, 4.67 mmol, 1.2 equiv.). The mixture was then allowed to warm to ambient temperature with mixing for 6 h. (A by-product **17** was detected by TLC (8:2; toluene/EtOAc) during the early stages of the reaction that was slowly consumed during the course of the reaction. If any of the material remained at the end of the reaction *N*-(2-aminoethyl)aminomethyl polystyrene (2.8 mmol/g; Nova-Biochem Cat. No. 01-64-0178) could be added to degrade it to the product.). The reaction was filtered, the resin washed with MeOH (3×20 mL) and the combined filtrate evaporated under reduced pressure to yield **16** as a pale yellow oil (94%): R_f 5.12 (Method B); IR (solid): 3382, 3024, 2919, 1671, 1616, 1598, 1519, 1499, 1485, 1443, 1435, 1359, 1242, 1203, 1169, 1129, 1039, 1000, 929, 839 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO): δ=9.47 (br. s, 1H, OH-rotomer 1), 9.42 (br. s, 1H, OH-rotomer 2), 7.03 (d, 2H, J=8.4 Hz, H-3-rotomer 1), 6.98 (d, 2H, J=8.4 Hz, H-3-rotomer 2), 6.90 (d, 1H, J=8.0 Hz, rotomer 1), 6.84 (d, 1H, J=8.0 Hz, rotomer 2), 6.78 (s, 1H, H-10-rotomer 1), 6.76 (d, 2H, J=8.4 Hz, H-2-rotomer 1), 6.71 (d, 2H, J=8.4 Hz, H-2-rotomer 2), 6.70 (s, 1H, H-10-rotomer 2), 6.69 (dd, 1H, J=8.0, 1.2 Hz, rotomer 1), 6.64 (dd, 1H, J=8.0, 1.2 Hz, rotomer 2), 6.00 (s, 2H, CH_2O_2-rotomer 1), 5.98 (s, 2H, CH_2O_2-rotomer 2), 3.53 (s, 2H, CH_2), 4.45 (s, 2H, CH_2), 4.33 (s, 2H, CH_2); ^{13}C NMR (100 MHz, d_6-DMSO): δ=157.6/157.5 (C-1), 156.7 (CF_3), 148.2/148.0/ 147.4/147.3 (C-7/8), 129.9, 129.5, 129.1, 1291, 125.9, 125.2, 121.9, 121.0, 116.1, 115.9, 108.7, 106.9, 101.6/101.5 (C-11), 49.6/49.5/ 48.7/48.6 (C-4/5). HR-MS (ESI, Q-tof) calcd for $C_{17}H_{14}NO_4F_3Na$: 376.0773; found 376.0763.

4.1.10. Preparation of 2′,3′-dihydro-6′,7′-methylendioxy-2′-trifluoroacetyl-spiro[cyclohexane-1,4′-(1*H*)isoquinolin]-4-one 20. A slurry of carbonyl **12** (6.0 g, 16.8 mmol) in EtOAc (250 mL) was sonicated for 2.5 h until a clear solution was formed. To the solution was added 10% Pd/C (3.0 g) and the solution then vigorously stirred under an atmosphere of hydrogen (balloon) (TLC 7:3; hexane/EtOAc) for 3 h. The mixture was filtered through a pad of celite (3 g) and the filtrate evaporated under reduced pressure to yield the title compound **20** as a white solid (5.6 g, 94%): R_f 3.10 (Method A), R_f 4.80 (Method B); IR (solid): 1708, 1679, 1504, 1490, 1466, 1446, 1248, 1207, 1183, 1167, 1138, 1040, 1005, 932 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO): δ=7.12 (s, 1H, H-5′), 6.84 (s, 1H, H-8′), 5.95 (s, 2H, CH_2O_2), 4.75 (s, 1.4H, H-1′-rotomer 1), 4.64 (s, 0.6H, H-1′-rotomer 2), 4.08 (s, 1.4H, H-3′-rotomer 1), 3.87 (s, 0.6H, H-3′-rotomer 2), 2.69 (m, 2H, CH_2), 2.19 (m, 2H, CH_2), 1.68 (m, 2H, CH_2); ^{13}C NMR (100 MHz, d_6-DMSO): δ=209.9 (C-4), 155.2/154.9 (CF_3) 147.3/146.9 (C-6′/7′), 135.1 (C-8a′), 124.1 (C-4a′), 118.3 (C-CF_3), 106.4 (C-5′), 106.2 (C-8′), 101.5 (C-10′), 48.2 (C-1′), 47.0 (C-3′), 37.9 (C-2/6), 34.9 (C-1), 33.7 (C-3/5); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{16}NO_4F_3Na$: 378.0929; found 378.0980.

4.1.11. Preparation of 2′,3′-dihydro-6′,7′-methylendioxy-2′-trifluoroacetyl-spiro[cyclohexane-1,4′-(1*H*)isoquinolin]-4-one 21. Following the same procedure as for **45**; amide **20** (355 mg, 1 mmol) was deprotected with Amber-sep 900 (950 mg, OH-form; Fluka Cat. No. 06476) in MeOH (4.5 mL) at 100°C under microwave irradiation for 30 min to yield amine **21** (249 mg, 96%): R_f 2.238 (260.1; MH+) (Method A); IR (solid): 3242, 3226, 1708, 1677, 1501, 1490, 1460, 1367, 1285, 1243, 1225, 1185, 1169, 1159, 1141, 1065, 927 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO): δ=7.01 (s, 1H, H-5′), 6.50 (s, 1H, H-8′), 5.86 (s, 2H, CH_2O_2), 4.76 (s, 2H, H-1′), 3.30 (m, 1H, NH), 3.05 (s, 2H, H-3′), 2.50 (m, 2H, H-3_A/5_A), 2.21–2.00 (m, 4H, H-2_A/3_B/5_B/6_A), 1.90 (m, 2H, H-3_B/5_B); ^{13}C NMR (100 MHz, d_6-DMSO): δ=211.1 (C-4), 146.1/145.4/ 136.4/129.9 (C-4a′/8a′/6′/7′), 106.6/106.0 (C-5′/8′), 100.8 (C-10′), 50.6/49.6 (C-1′/3′), 37.8/35.6 (C-2/3/5/6), 36.2 (C-1); HR-MS (ESI, Q-tof) calcd for $C_{15}H_{17}NO_3Na$: 282.1107; found 282.1111.

4.1.12. Preparation of 6′,7′-methylendioxy-4-oxa-spiro-[cyclohexane-1,4′-(3′*H*)isoquinolin]-5-one 22. To a mixture of ketone **20** (50 mg, 0.14 mmol, 1 equiv.) and Amberlyst 15 (125 mg; Fluka Cat. No. 06423) in DCM (5 mL) at ambient temperature was added *m*CPBA (48.6 mg, 0.14 mmol). The reaction was shaken for 3 h then Amberlyst 21 (1.0 g, 3 mmol, 3 mmol/g; Fluka Cat. No. 06424) was added and the mixture shaken over night. The reaction mixture was filtered, the resin washed with DCM (3×5 mL), and the filtrate evaporated under reduced pressure to give the title compound **22** as a pale yellow oil (85% pure by LC-MS): ^1H NMR (400 MHz, d_6-DMSO): δ

7.17 (s, 1H, Ar), 6.83 (s, 1H, Ar), 5.98 (s, 2H, CH_2O_2), 4.70 (s, 2H, H-1′), 4.52 (m, 1H, H-3_A), 4.08 (m, 1H, H-3_B), 4.03 (d, 1H, J=13.0 Hz, H-$3'_A$), 3.14 (m, 1H, H-5_A), 2.36 (m, 1H, H-5_B), 2.25–1.98 (m, 2H, H-2_A/6_A), 1.1.73–1.48 (m, 2H, H-2_B/6_B); ^{13}C NMR (100 MHz, d_6-DMSO): δ=175.4 (CO), 154.7 (CF_3), 147.3/146.4 (C-6′/7′), 135.3 (C-8a′), 124.5 (C-4a′), 106.9/106.0 (C-5′/8′), 101.4 (C-10′), 63.7 (C-3), 48.2 (CH_2), 47.2 (CH_2), 38.2 (CH_2), 32.0 (CH_2), 30.1 (CH_2); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{16}F_3NO_5$: 371.0981; found 371.0972.

4.1.13. Preparation of 2′,3′-dihydro-6′,7′-methylendioxy-2′-trifluoroacetyl-spiro[cyclohexane-1,4′-(1*H*)isoquinolin]-4-ol 23a and 23b. A mixture of PS-cyanoborohydride (6.00 g, 24 mmol, 3.87 equiv., 4 mmol/g, polystylmethyltrimethylammonium cyanoborohydride; Novabiochem Cat. No. 01-64-0337) and carbonyl **20** (2.20 g, 6.2 mmol, 1 equiv.) in DCM/AcOH (9:1; 50 mL) was shaken at ambient temperature for 14 h. The mixture was filtered and the resin washed with DCM (3×50 mL), the filtrates were combined and the solvent was removed under reduced pressure. The crude material was redissolved in DCM/MeOH (9:2; 50 mL) and treated with a mixture of glycerol resin (5.00 g, 2.8 mmol/g, Advanced ChemTech Cat. No. SA 5760) and Amberlyst 15 (5.0 g; Fluka Cat. No. 06423) for 1 h, then filtered and the resin washed with DCM (3×50 mL). After solvent evaporation the resulting cream solid (1.94 g, 88%) consisted of a 98:2 mixture of alcohol stereoisomers **23a** and **23b** as determined by ^{1}H NMR. The isomers could be easily separated by column chromatography (7:3; hexane/EtOAc).

*2′,3′-Dihydro-6′,7′-methylendioxy-2′-trifluoroacetyl-spiro-[cyclohexane-1,4′-(1H)isoquinolin]-4-ol **23a** (major isomer).* R_f 3.03 (Method A); IR (solid): 3224, 2875, 1694, 1487, 1361, 1332, 1272, 1218, 1187, 1139, 1080, 1037, 1001, 935 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO): δ=7.04 (s, 1H, H-5′), 6.78 (s, 1H, H-8′), 5.94 (s, 2H, CH_2O_2), 4.65 (s, 1.4H, H-1′-rotomer 1), 4.60 (d, 1H, J=4.7 Hz, OH), 4.58 (s, 0.6H, H-1′-rotomer 2), 3.82 (s, 1.4H, H-3′-rotomer 1), 3.71 (s, 0.6H, H-3′-rotomer 2), 3.50 (m, 1H, H-4), 1.83–1.65 (m, 4H, H-2_A/3_A/5_A/6_A), 1.55–1.30 (m, 4H, H-2_B/3_B/5_B/6_B); ^{13}C NMR (100 MHz, d_6-DMSO, major rotomer): δ=154.7 (CF_3), 147.2/146.2 (C-6′/7′), 136.4/124.4 (C-4a′/8a′), 106.3/106.0 (C-5′/8′), 101.4 (C-10′), 68.8 (C-4), 48.0 (C-1′), 47.0 (C-3′), 34.3 (C-1), 33.6 (C-2/6), 31.8 (C-3/5); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{18}NO_4F_3Na$: 380.1086; found 380.1078.

*2′,3′-Dihydro-6′,7′-methylendioxy-2′-trifluoroacetyl-spiro-[cyclohexane-1,4′-(1H)isoquinolin]-4-ol **23b** (minor isomer).* R_f 3.11 (Method A); IR (solid): 3235, 2872, 1691, 1532, 1481, 1361, 1332, 1272, 1220, 1187, 1139, 1083, 1040, 1026, 1004 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO): δ=6.95 (s, 1H, H-5′), 6.80 (s, 1H, H-8′), 5.95 (s, 2H, CH_2O_2), 4.67 (s, 1.6H, H-1′-rotomer 1), 4.58 (s, 0.4H, H-1′-rotomer 2), 3.97 (m, 1H, H-4), 3.85 (s, 1.6H, H-3′-rotomer 1), 3.63 (s, 0.4H, H-3′-rotomer 2), 2.09–2.01 (m, 2H, CH_2), 1.77–168 (m, 2H, CH_2), 1.57–1.54 (m, 2H, CH_2), 1.30–1.11 (m, 2H, CH_2); ^{13}C NMR (100 MHz, d_6-DMSO, major rotomer): δ=155.0 (CF_3), 147.1/146.2 (C-6′/7′), 137.2/124.2 (C-4a′/8a′), 105.9/106.0 (C-5′/8′), 101.4 (C-10′), 63.3 (C-4), 48.0 (C-1′), 46.8 (C-3′), 38.3 (C-1), 29.5/29.0 (C-2/3/5/6); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{18}NO_4F_3Na$: 380.1086; found 380.1084.

4.1.14. Preparation of 2′,3′-dihydro-6′,7′-methylendioxy-2′-trifluoroacetyl-spiro[cyclohexane-1,4′-(1*H*)isoquinolin]-4-methylether 24. To a vigorously stirred mixture of alcohol **23a** (780 mg, 2.18 mmol, 1 equiv.), sulfonic acid resin (3.0 g, 4.2 mmol, MP-TsOH 1.40 mmol/g; Argonaut Technologies Inc. Cat. No. 800286) and MeOH (2.5 mL) in DCM (45 mL) was added dropwise over 30 min trimethylsilyl diazomethane (1.09 mL, 2 M in Hexane's, 2.18 mmol, 1 equiv.). The reaction was stirred for a further 20 min then a second portion of trimethylsilyl diazomethane (1.09 mL, 2 M in Hexanes, 2.18 mmol, 1 equiv.) was added directly and the reaction stirred for 2.5 h. The reaction was filtered, the resin washed with MeOH (3×25 mL) and the combined filtrates evaporated under reduced pressure to yield the title compound **24** as a pale yellow solid (743 mg, 94%): R_f 3.38 (Method A); R_f 5.10 (Method B); IR (solid): 2928, 2901, 2875, 2824, 1689, 1509, 1489, 1474, 1464, 1368, 1270, 1231, 1200, 1182, 1167, 1120, 1100, 1032, 921 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO): δ=7.05 (s, 1H, H-5′), 6.80 (s, 1H, H-8′), 5.94 (s, 2H, CH_2O_2), 4.66 (s, 1.67H, H-1′-rotomer 1), 4.58 (s, 0.33H, H-1′-rotomer 2), 3.81 (s, 1.67H, H-3′-rotomer 1), 3.70 (s, 0.33H, H-3′-rotomer 2), 3.24 (m, 4H, OMe and H-4), 1.93–1.71 (m, 4H, H-2_A, H-3_A, H-5_A and H-6_A), 1.58–1.10 (m, 4H, H-2_B, H-3_B, H-5_B and H-6_B); ^{13}C NMR (100 MHz, d_6-DMSO, major rotomer): δ=155.0 (CO, CF_3), 147.2/147.1 (C-6′/7′), 136.1/124.5 (C-4a′/8a′), 106.5/106.1 (C-5′/8′), 101.3 (C-10′), 78.2 (C-4), 55.4 (C-Me), 48.0 (C-1′), 46.8 (C-3′), 38.2 (C-1), 33.9 (C-2/6), 28.0 (C-3/5); HR-MS (ESI, Q-tof) calcd for $C_{18}H_{20}NO_4F_3Na$: 394.1242; found 394.1231.

4.1.15. Preparation of 2′,3′-dihydro-6′,7′-methylendioxy-2′-trifluoroacetyl-spiro[cyclohexane-1,4′-(1*H*)isoquinolin]-4-methylether 24. A mixture of 2,6-di*t*butylpyridine polymer bound (0.85 g, 1.53 mmol, 2.5 equiv., poly(2,6-di-*tert*-butyl 4-vinylpyridine), 1% cross-linked, 1.8 mmol/g, poly(2,6-*tert*-butyl 4-vinylpyridine); Aldrich Cat. No. 37,782-1), iodomethane (0.15 mL, 341 mg, 2.4 mmol, 1.2 equiv.), silver trifluoromethanesulfonate (257 mg, 2 mmol, 1 equiv.) and alcohol **23a** (410 mg, 2 mmol, 1 equiv.) in MeCN (10 mL) were heated at reflux for 6 h. The reaction was filtered and the resin washed with MeCN (3×15 mL). The combined solutions were then passed through a frit of silica (1.5 g) and the filtrate evaporated under reduced pressure to yield the title compound **24** as a mixture with **23a** (85% conversion.). The compound **24** was identical to that prepared by the previous method.

4.2. General procedure for the reductive amination of ketone 21

A mixture of the amine (1 mmol), PS-cyanoborohydride (2 mmol, 4 mmol/g, polystyl methyltrimethylammonium cyanoborohydride Novabiochem Cat. No. 01-64-0337) and ketone **21** (1 mmol) in DCM/AcOH (9:1; 10 mL) was stirred at ambient temperature for 3–7 h. The solution was filtered, the resin washed with DCM (3×10 mL) and the filtrate evaporated under reduced pressure. The residue was dissolved in MeOH (20 mL) and polymer-supported carbonate (4 mmol, MP-carbonate, 2.85 mmol/g; Argonaut

Cat. No. 800267) was added and the mixture shaken for 1 h. The resin was removed by filtration and washed with MeOH (3×10 mL). The filtrate was concentrated under reduced pressure to give the product.

4.2.1. Preparation of 6′,7′-methylendioxy-spiro[cyclohexane-1,4′-(3′*H*)isoquinolin]-4-pyrrolidine 25. (370 mg, 90%); IR (solid): 2957, 1671, 1570, 1505, 1486, 1408, 1235, 1196, 1172, 1109, 1035 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO): δ=7.06 (s, 1H, Ar), 6.80 (s, 1H, Ar), 5.96 (s, 2H, CH_2O_2), 4.68 (s, 1.67H, H-1′-rotomer 1), 4.58 (s, 0.33H, H-1′-rotomer 2), 3.80 (s, 1.67H, H-3′-rotomer 1), 3.68 (s, 0.33H, H-3′-rotomer 2), 2.58 (m, 4H, 2×CH_2N), 2.20 (m, 1H, H-4), 1.87–1.59 (m, 8H), 1.55–1.25 (m, 4H); ^{13}C NMR (100 MHz, d_6-DMSO): δ=172.7 (CO), 154.7 (CF_3), 147.2/146.2 (C-6′/7′), 136.3 (C-8a′), 124.4 (C-4a′), 106.1/106.0 (C-5′/8′), 101.3 (C-10′), 62.2 (C-4), 60.1 (CH_2N), 51.2 (C-1′), 46.7 (C-3′), 38.0 (C-1), 34.3 (CH_2), 27.4 (CH_2), 23.3 (CH_2); HR-MS (ESI, Q-tof) calcd for $C_{21}H_{26}N_2O_3F_3$: 411.1895; found 411.1887.

4.2.2. Preparation of 6′,7′-methylendioxy-spiro[cyclohexane-1,4′-(3′*H*)isoquinolin]-4-morpholine 26. (400 mg, 94%); IR (solid): 2958.1, 16744, 1563, 1486, 1435, 1400, 1246, 1221, 1184, 1104, 1055 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO): δ=7.06 (s, 1H, Ar), 6.08 (s, 1H, Ar), 5.96 (s, 2H, CH_2O_2), 4.70 (s, 1.6H, H-1′-rotomer 1), 4.61 (s, 0.4H, H-1′-rotomer 2), 3.78 (s, 1.6H, H-3′-rotomer 1), 3.67 (s, 0.4H, H-3′-rotomer 2), 3.55 (m, 4H, 2×CH_2O), 2.33 (m, 1H, H-4), 1.85–0.95 (m, 12H); ^{13}C NMR (100 MHz, d_6-DMSO): δ=173.8 (CO), 154.4 ($CF_)$), 147.4/146.1 (C-6′/7′), 136.3 (C-8a′), 124.4 (C-4a′), 106.1/106.0 (C-5′/8′), 101.4 (C-10′), 67.0 (CH_2O), 62.3 (C-4), 49.9 (CH_2), 38.7 (C-1), 36.7 (CH_2), 34.8 (CH_2), 24.4 (CH_2); HR-MS (ESI, Q-tof) calcd for $C_{21}H_{25}N_2O_4F_3$: 426.1766; found 426.1754.

4.2.3. Preparation of 6′,7′-methylendioxy-spiro[cyclohexane-1,4′-(3′*H*)isoquinolin]-4-*sec*-butylamine 27. (359 mg, 87%); IR (solid): 2955, 1690, 1624, 1553, 1487, 1466, 1395, 1267, 1231, 1193, 1154, 1006 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO): δ=7.04 (s, 1H, Ar), 6.79 (s, 1H, Ar), 5.94 (s, 2H, CH_2O_2), 4.65 (s, 2H, H-1′), 8.16 (s, 2H, H-3′), 2.98 (s, 2H, H-3′), 2.73 (m, 1H, H-4), 1.89–1.61 (m, 14H), 1.50 (m, 3H); ^{13}C NMR (100 MHz, d_6-DMSO): δ=172.9 (CO), 154.7 (CF_3), 147.2/146.2 (C-6′/7′), 136.4 (C-8a′), 124.5 (C-4a′), 106.3/106.0 (C-5′/8′), 101.4 (C-10′), 56.2 (C-4), 56.2 (CH), 54.1 (CH_2N), 48.1/47.0 (C-1′/3′), 38.2 (C-1), 28.1 (CH_2), 22.3 (CH_3), 21.1 (CH_3); HR-MS (ESI, Q-tof) calcd for $C_{21}H_{27}N_2O_3F_3$: 413.2052; found 413.2052.

4.2.4. Preparation of 6′,7′-methylendioxy-spiro[cyclohexane-1,4′-(3′*H*)isoquinolin]-4-one 28. Following the procedure for the formation of **37**, amine **21** (259 mg, 1 mmol) was converted to the title compound **28** (231 mg, 90%): R_f 2.289 (Method A); ^1H NMR (400 MHz, d_6-DMSO): δ=6.98 (s, 1H, H-5′), 6.52 (s, 1H, H-8′), 5.88 (s, 2H, CH_2O_2), 3.76 (s, 2H, H-1′), 3.32 (m, 1H, NH), 3.05 (m, 1H, H-3′), 2.48 (m, 2H, H-3_A and H-5_A), 2.21–2.00 (m, 4H, H-3_B, H-5_B, H-2_A and H-6_A), 1.87 (m, 2H, H-2_B and H-6_B); ^{13}C NMR (100 MHz, d_6-DMSO): δ=211.1 (CO, CF_3), 146.1/145.4 (C-6′/7′), 136.4/129.9 (C-4a′/8a′), 106.6 (C-5′), 105.9 (C-8′), 100.8 (C-10′), 50.6 (C-3′), 49.6 (C-1′), 36.4 (C-1), 37.8 (C-3/5), 35.6 (C-2/6); HR-MS (ESI, Q-tof) calcd for $C_{15}H_{15}NO_3$: 257.1052; found 257.1063.

4.3. General procedure for the preparation of urea and thiourea compounds from amine 21

A mixture of the amine **21** (1 mmol), polymer-suppsorted diethylamine (3 mmol, 3.2 mmol/g, diethylaminomethyl polystrene; Fluka Cat. No. 31866) and isocyanate or isothiocyanate (3 mmol) in DCM (20 mL) was stirred under argon at ambient temperature for 12 h. To the reaction mixture was added polymer-supported trisamine (3 mmol, 3.3 mmol/g, tris(2-aminoethyl)amine polystyrene; Novabiochem Cat. No. 01-64-0170) and Amberlyst 15 (1.5 mmol; Fluka Cat. No. 06423) the mixture was then stirred for a further 15 min. The resin was removed by filtration and washed with DCM (3×10 mL). The filtrate was concentrated under reduced pressure to give the product.

4.3.1. Preparation of 6′,7′-methylendioxy-2-carboxylic acid (3-trifluoromethylphenyl)amido-spiro[cyclohexane-1,4′-(3′*H*)isoquinolin]-4-one 29. A pale yellow foam (362 mg, 81%); R_f 3.498 (447.1; MH+) (Method A); IR (solid): 2902, 2309, 1709, 1641, 1542, 1486, 1444, 1399, 1331, 1232, 1162, 1119, 1070, 1037, 932 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO): δ=8.89 (s, 1H, H-12′), 7.90 (s, 1H, H-18′), 7.75 (d, 1H, J=8.3 Hz, H-14′), 7.46 (dd, 1H, J=8.3, 7.7 Hz, H-15′), 7.26 (d, 1H, J=7.7 Hz, H-16′), 7.08 (s, 1H, H-5′ or H-8′), 6.68 (s, 1H, H-5′ or H-8′), 5.95 (s, 2H, CH_2O_2), 4.68 (s, 2H, H-1′), 3.91 (s, 2H, H-3′), 2.65 (m, 2H, H-3_A/5_A), 2.20 (m, 4H, H-2_A/3_B/5_B/6_A), 1.76 (m, 2H, H-2_B/6_B); ^{13}C NMR (100 MHz, d_6-DMSO): δ=210.3 (C-4), 154.9 (C), 146.8/146.2 (C-6′/7′), 141.8 (C), 135.8 (C), 129.9 (C-15′), 126.5 (C-Ar), 123.6 (C-14′), 118.5 (C-16′), 116.3 (C-18′), 106.2/106.1 (C-5′/8′), 101.3 (C-10′), 47.0 (C-1′), 46.7 (C-3′), 38.0 (C-1), 37.7 (C-3/5), 34.4 (C-2/6); HR-MS (ESI, Q-tof) calcd for $C_{23}H_{22}N_2O_4F_3$: 447.1531; found 447.1524.

4.3.2. Preparation of 6′,7′-methylendioxy-2-carboxylic acid (4-methoxyphenyl)amido-spiro[cyclohexane-1,4′-(3′*H*)isoquinolin]-4-one 30. (269 mg, 66%); ^1H NMR (400 MHz, d_6-DMSO): δ=8.39 (s, 1H, H-12′), 7.22 (d, 2H, J=8.3 Hz, H-14′), 6.86 (d, 2H, J=8.3 Hz, H-15′), 7.04 (s, 1H, H-5′ or H-8′), 6.72 (s, 1H, H-5′ or H-8′), 5.98 (s, 2H, CH_2O_2), 4.74 (s, 2H, H-1′), 4.21 (s, 2H, H-3′), 3.92 (s, 3H, OMe), 2.60 (m, 2H, H-3_A/5_A), 2.15–1.87 (m, 4H, H-2_A/3_B/5_B/6_A), 1.60 (m, 2H, H-2_B/6_B); HR-MS (ESI, Q-tof) calcd for $C_{23}H_{24}N_2O_5$: 408.1685; found 408.1672.

4.3.3. Preparation of 2′,3′-dihydro-6′,7′-methylendioxy-1′-oxo-spiro[cyclohexane-1,4′-(1*H*)isoquinolin]-4-methylether 31. To a solution of imine **28** (70 mg, 0.25 mmol, 1 equiv.) in DCM (5 mL) was added *m*CPBA (73.7 mg, 0.25 mmol, 60% mixture). The reaction was stirred at ambient temperature for 12 h. To the solution was added Amberlyst 21 (2.0 g, 6 mmol, 3 mmol/g; Fluka Cat. No. 06424) and the mixture shaken over night. The reaction mixture was filtered, the resin washed with DCM (3×5 mL) and the filtrate evaporated under reduced pressure to give the title compound **31** as a pale yellow oil (65 mg, 95%): ^1H NMR (400 MHz, d_6-DMSO): δ=7.70 (s, 1H, H-1′), 7.06 (s,

1H, H-5′), 6.86 (s, 1H, H-8′), 6.01 (s, 2H, CH_2O_2), 3.88 (s, 2H, H-3′), 3.24 (s, 3H, OMe), 3.16 (m, 1H, H-4), 3.16 (m, 2H, H-3_A and H-5_A), 1.64 (m, 4H, H-2/6), 1.30 (m, 2H, H-3_B and H-5_B); ^{13}C NMR (100 MHz, d_6-DMSO): δ=148.7/146.6 (C-6′/7′), 134.9/122.6 (C-4a′/8a′), 131.4 (C-1′), 106.1/105.0 (C-5′/8′), 102.0 (C-10′), 78.3 (C-4), 63.6 (C-3′), 38.0 (C-1), 31.4 (C-2/6), 27.2 (C-3/5); HR-MS (ESI, Q-tof) calcd for $C_{15}H_{15}NO_4$ (MH+): 273.1001; found 273.1034. R_f 2.670 (Method A).

4.3.4. Preparation of 6′,7′-methylendioxy-2-carbothioic acid phenylamido-spiro[cyclohexane-1,4′-(3′*H*)isoquinolin]-4-one 32. White solid (338 mg, 81%); IR (solid): 3326, 2881, 1698, 1592, 1525, 1500, 1485, 1442, 1403, 1336, 1308, 1233, 1168, 1037, 1121, 1081 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO): δ=6.48 (br. s, 1H, NH), 7.49–7.23 (m, 5H, NPh), 7.09 (s, 1H, Ar), 6.68 (s, 1H, Ar), 5.97 (s, 2H, CH_2O_2), 5.03 (s, 2H, H-1′), 4.42 (s, 2H, H-3′), 2.75 (m, 2H, H-3_A and H-5_A), 2.20 (m, 4H, H-3_B, H-5_B, H-2_A and H-6_A), 1.87 (m, 2H, H-2_B and H-6_B); ^{13}C NMR (100 MHz, d_6-DMSO): δ=210.3 (C-4), 181.8 (CS), 147.0/146.4 (C-6′/7′), 141.3 (C-11′), 135.7 (C-8a′), 130.4 (C-Ph), 128.5 (C-Ph), 126.4 (C-Ph), 126.0 (C-4′), 125.2 (C-4a′), 107.2/107.0 (C-5′/8′), 101.4 (C-10′), 51.3/50.6 (C-1′/3′), 38.6 (C-1), 38.3/34.2 (C-2/6 and C-3/5); HR-MS (ESI, Q-tof) calcd for $C_{22}H_{22}N_2SO_3$: 417.1249; found 417.1245.

4.3.5. Preparation of 6′,7′-methylendioxy-2-carbothioic acid tricyclo[3.3.1.1]dec-2-ylamido-spiro[cyclohexane-1,4′-(3′*H*)isoquinolin]-4-one 33. White solid (388 mg, 86%); R_f 3.956 (453.2; MH+) (Method A); IR (solid): 2909, 2853, 2120, 2089, 2060, 1740, 1713, 1533, 1505, 1488, 1553, 1368, 1353, 1305, 1233, 1217, 1164, 1090, 1032 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.07 (s, 1H, Ar), 6.68 (s, 1H, Ar), 6.45 (br. s, 1H, NH), 5.96 (s, 2H, CH_2O_2), 4.78 (s, 2H, H-1′), 4.36 (s, 2H, H-3′), 2.80 (m, 2H), 2.25 (br. s, 6H), 2.21–2.08 (m, 4H), 2.05 (br. s, 3H), 1.75 (m, 2H), 1.62 (br. s, 6H); ^{13}C NMR (100 MHz, d_6-DMSO): δ=210.4 (CO), 179.9 (CS), 146.7/146.1 (C-6′/7′), 135.8 (C-8a′), 126.2 (C-4a′), 106.2/105.8 (C-5′/8′), 101.2 (C-10′), 54.5 (CH), 50.5 (CH_2), 49.6 (CH), 43.4 (CH_2), 41.4 (CH_2), 38.1 (CH_2), 36.7 (CH_2), 34.8 (CH_2), 29.5 (CH); HR-MS (ESI, Q-tof) calcd for $C_{26}H_{32}N_2SO_3Na$: 475.2031; found 475.2028.

4.3.6. Preparation of 2′,3′-dihydro-6′,7′-methylendioxy-spiro[cyclohexane-1,4′-(1*H*)isoquinolin]-4-ol 34. A mixture of PS-borohydride (1.69 g, 16.9 mmol, 4 equiv., borohydride on Amberlite IRA 400, ~2.5 mmol/g; Aldrich Cat. No. 32,864-2) and carbonyl **20** (1.50 g, 4.23 mmol, 1 equiv.) in DCM/MeOH (7:3; 50 mL) was stirred at ambient temperature for 24 h. The resin was removed by filtration, washed with a mixture of DCM/MeOH (7:3; 3×30 mL) and the filtrates combined and evaporated under reduced pressure to yield the title compound **34** as a off-white solid (1.02 g, 92%): R_f 2.242 (262.1 MH+) (Method A), R_f 3.52 (Method B); ^{1}H NMR (600 MHz, d_6-DMSO): δ=6.87 (s, 1H, H-5′), 6.53 (s, 1H, H-8′), 5.88 (s, 2H, CH_2O_2), 3.73 (s, 2H, H-1′), 3.55 (m, 1H, H-4), 3.17 (s, 1H, NH), 2.82 (s, 2H, H-3′), 1.63 (m, 6H, H-2_{AB}/3_A/5_A/6_{AB}), 1.32 (m, 2H, H-3_B/5_B); ^{13}C NMR (150 MHz, d_6-DMSO): δ=146.1/145.2 (C-6′/7′), 137.6/136.3 (C-4a′/8a′), 106.6/105.9 (C-5′/8′), 100.7 (C-10′), 69.2 (C-4), 50.6 (C-3′), 49.0 (C-1′), 35.9 (C-1), 35.1 (C-2/6), 31.7 (C-3/5); HR-MS (ESI, Q-tof) calcd for $C_{16}H_{19}NO_3Na$: 284.1263; found 284.1269.

4.3.7. Preparation of 2′,3′-dihydro-6′,7′-methylendioxy-spiro[cyclohexane-1,4′-(1*H*)isoquinolin]-4-ol 34. Following the same procedure as for **45**; alcohol **23a** (257 mg, 1 mmol) was deprotected with Ambersep 900 (1.0 g, OH-form; Fluka Cat. No. 06476) in MeOH (5 mL) at 100°C under microwave irradiation for 45 min to yield amine **34** (150 mg, 93%). The compound was identical to the material prepared previously.

4.3.8. Preparation of 2′,3′-dihydro-6′,7′-methylendioxy-spiro[cyclohexane-1,4′-(1*H*)isoquinolin]-4-methylether 35. Following the same procedure as for **45**; amide **24** (339 mg, 1 mmol) was deprotected with Ambersep 900 (1.25 g, OH-form; Fluka Cat. No. 06476) in MeOH (5 mL) at 110°C under microwave irradiation for 1 h to yield amine **35** (228 mg, 94%): R_f 2.47 (Method A); IR (solid): 2935, 2824, 1503, 1482, 1378, 1230, 1199, 1262, 1230, 1094, 1028, 1011, 929 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO): δ=6.92 (s, 1H, H-5′), 6.48 (s, 1H, H-8′), 5.89 (s, 2H, CH_2O_2), 3.68 (s, 2H, H-1′), 3.23 (m, 4H, H-4 and OMe), 2.81 (s, 2H, H-3′), 1.81 (m, 2H, H-3_A and H-5_A), 1.66 (m, 4H, H-2 and H-6), 1.23 (m, 2H, H-3_B and H-5_B); ^{13}C NMR (100 MHz, d_6-DMSO): δ=146.0 (C-6′), 145.2 (C-7′), 137.5 (4a′), 130.0 (8a′), 106.6 (C-5′), 105.9 (C-8′), 100.7 (C-10′), 79.0 (C-4), 55.3 (C-Me), 51.0 (C-3′), 49.7 (C-1′), 36.2 (C-1), 34.8 (C-2/6), 27.9 (C-3/5); HR-MS (ESI, Q-tof) calcd for $C_{16}H_{22}NO_3$ (MH+): 276.1599; found 276.1587.

4.3.9. Preparation of 2′,3′-dihydro-6′,7′-methylendioxy-[2′-(4″-hydroxyphenyl)-ethyl]-spiro[cyclohexane-1,4′-(1*H*)isoquinolin]-4-methylether 36. A mixture of 4-(2-bromoethyl)phenol **52** (109 mg, 0.54 mmol, 1.5 equiv.), PS-TBD (415 mg, 1.08 mmol, 5 equiv., 1,5,7-triazobicyclo-[4.4.0]dec-5-ene bound to polystyrene 2% crosslinked, 2.6 mmol/g; Fluka Cat. No. 90603) and amine **35** (100 mg, 0.36 mmol, 1 equiv.) in DCM (3 mL) was heated at reflux for 6 h. The reaction mixture was filtered and the resin washed with DCM (3×3 mL), to the combined filtrate was added Amberlyst 15 (1.5 g; Fluka Cat. No. 06423) and the mixture shaken for 3 h. The resin was then filtered washed (3×5 mL) and transferred to a mixture of NEt_3/-DCM (1:5; 15 mL) and stirred for 1.5 h. The resin was removed by filtration and washed with DCM (3×5 mL), the combined washings were evaporated under reduced pressure to yield the title compound **36** (95 mg, 67%, >95% purity by LC-MS): R_f 2.68 (Method A), R_f 4.00 (Method B); IR (solid): 3285.5, 2934, 2818, 1735, 1614, 1595, 1515, 1485, 1448, 1328, 1249, 1174, 1100, 1040, 935 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO): δ=9.16 (br. s, 1H, OH), 7.02 (d, 2H, J=8.36 Hz, H-5″), 6.90 (s, 1H, 5′), 6.64 (d, 2H, J=8.36 Hz, H-6″), 6.52 (s, 1H, H-8′), 5.88 (s, 2H, CH_2O_2), 3.44 (s, 2H, H-1′), 3.32 (m, 4H, OMe and H-4), 2.67 (m, 2H, CH_2), 2.58 (m, 2H, CH_2), 2.55 (m, 2H, H-3′), 1.82 (m, 2H, H-3_A and H-5_A), 1.64 (m, 4H, H-2 and H-6), 1.28 (m, 2H, H-3_B and H-5_B); ^{13}C NMR (100 MHz, d_6-DMSO): δ=170.8 (C-7″), 155.9 (C), 146.3/145.4 (6′/7′), 137.1 (C), 130.9 (C), 129.9 (C-5″), 128.5 (C), 115.4 (C-6″), 106.2/106.1 (C-5′/8′), 100.9 (C-10′), 78.9 (C-4),

60.2/57.8/57.6 (C-2″ or C-3″ and C-1′/3′), 55.3 (C-Me), 38.1 (C-1), 35.0 (C-2/6), 32.6 (C-2″ or C-3″), 27.9 (C-3/5); HR-MS (ESI, Q-tof) calcd for $C_{24}H_{30}NO_4$ (MH+): 396.2175; found 396.2213.

4.3.10. Preparation of 6′,7′-methylendioxy-spiro[cyclohexane-1,4′-(3′*H*)isoquinolin]-4-methylether 37. To a cooled (0°C) suspension of ceric ammonium nitrate on silica (12 g, 3 mmol, Ammonium cerium(IV) nitrate on silica gel ~0.25 mmol/g; Fluka Cat. No. 22254) in acetone (35 mL) was added a solution of amine **35** (243 mg, 1 mmol) in acetone (5 mL). The solution was stirred for 2 h then filtered through a pad of celite (5 g) and the solvent removed under reduced pressure to yield the title compound **37** (212 mg, 88%): R_f 2.50 (Method A); ^{1}H NMR (400 MHz, d_6-DMSO): δ=8.17 (s, 1H, H-1′), 7.03 (s, 1H, H-5′), 6.97 (s, 1H, H-8′), 6.02 (s, 2H, CH_2O_2), 3.58 (s, 2H, H-3′), 3.20 (s, 3H, OMe), 3.13 (m, 1H, H-4), 1.80 (m, 2H, H-3_A and H-5_A), 1.54 (m, 4H, H-2/6), 1.35 (m, 2H, H-3_B and H-5_B); ^{13}C NMR (100 MHz, d_6-DMSO): δ=159.8 (C-1′), 150.2/146.1 (C-6′/7′), 140.9/122.3 (C-4a′/8a′), 108.1 (C-5′), 104.3 (C-8′), 101.8 (C-10′), 78.8 (C-4), 55.4 (C-Me), 53.1 (C-3′), 33.6 (C-1), 31.8 (C-2/6), 27.6 (C-3/5); HR-MS (ESI, Q-tof) calcd for $C_{16}H_{19}NO_3$: 273.1365; found 273.1372.

4.3.11. Preparation of 2-[(benzo[1,3]dioxol-5-ylmethylene)-amino]-2-(4′-hydroxyphenyl)-*N*-methyl acetamide 39. To a solution of **8** (54.0 g; 0.3 mol) in a mixture of EtOAc/MeOH (5:1; 300 mL) at ambient temperature was added piperonal **38** (48.0 g, 0.32 mol). The solution was mixed by rotation of the reaction vessel for 1 h on a rotary evaporator during which time a white precipitate formed. The solid was collected by filtration, washed with cold EtOAc (3×100 mL) and dried under vacuum to give **39** (93.6 g, 95%) as a white solid: R_f 4.44 (Method B). L-form $[\alpha]_D$=−59.2 (c=0.56 in MeOH); IR: 3211, 1739, 1639, 1608, 1548, 1502, 1446, 1366, 1254, 1242, 1219, 1107, 1033, 933, 836 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO): δ=9.34 (s, 1H, OH), 8.27 (s, 1H, H-4), 7.89 (q, 1H, J=4.7 Hz, NH), 7.64 (s, 1H, H-10), 7.26 (dd, 1H, J=7.8, 1.5 Hz, H-6), 7.17 (d, 2H, J=8.6 Hz, H-2′), 6.99 (d, 1H, J=7.8 Hz, H-7), 6.71 (d, 2H, J=8.6 Hz, H-3′), 6.10 (d, 2H, J=1.9 Hz, CH_2O_2), 4.84 (s, 1H, H-2), 2.69 (d, 3H, J=4.7 Hz, NMe); ^{13}C NMR (100 MHz, d_6-DMSO): δ=171.6 (CO), 161.3 (C-4), 156.8 (C-4′), 150.0 (C-5), 148.1 (C-8), 131.2 (C-1′), 130.8 (C-9), 128.5 (2×C-3′), 125.4 (C-6), 115.2 (2×C-2′), 108.2 (C-7), 106.6 (C-10), 101.7 (C-13), 75.9 (C-2), 25.9 (C-12); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{16}N_2O_4Na$: 335.1023; found 335.1018. D-form $[\alpha]_D$=+60.2 (c=0.59 in MeOH); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{16}N_2O_4Na$: 335.1023; found 335.1028.

4.3.12. Preparation of 2-[(benzo[1,3]dioxol-5-ylmethyl)-amino]-2-(4′-hydroxyphenyl)-*N*-methyl acetamide 40a. To a suspension of **39** (50.0 g, 0.16 mol, 1 equiv.) in a mixture of DCM/MeOH (3:1; 300 mL) was added in five equal portions polymer-supported borohydride (64.1 g, 3 mmol/g, 1.2 equiv., borohydride on Amberlite IRA 400, ~2.5 mmol/g; Aldrich Cat. No. 32,864-2). The reaction was shaken and monitored by TLC (9:1; EtOAc/MeOH) until the reaction was complete (~4 h). The spent resin was filtered from the resulting clear solution and the solvent removed to give the title compound **40a** as an off-white solid (49.2 g, 98%): R_f 1.23 (Method A); R_f 3.90 (Method B). L-form $[\alpha]_D$=+81.4 (c=2.167 in MeOH); IR: 3333, 3168, 1627, 1608, 1540, 1517, 1503, 1489, 1442, 1408, 1361, 1306, 1281, 1249, 1205, 1032, 925, 834 cm^{-1}, ^{1}H NMR (400 MHz, d_6-DMSO): δ=9.30 (s, 1H, OH), 7.89 (q, 1H, J=4.5 Hz, CONH), 7.16 (d, 2H, J=8.3 Hz, H-2′), 6.93 (s, 1H, H-10), 6.85 (d, 1H, J=7.9 Hz, H-6), 6.72 (d, 1H, J=7.9 Hz, H-7), 6.68 (d, 2H, J=8.3 Hz, H-3′), 5.99 (s, 2H, CH_2O_2), 3.97 (s, 1H, H-2), 3.51 (s, 2H, H-4), 2.73 (br. s, 2H, NH_2), 2.61 (d, 3H, J=4.5 Hz, NMe); ^{13}C NMR (100 MHz, d_6-DMSO): δ=172.8 (CO), 156.7 (C-4′), 147.3 (C-9), 146.6 (C-8), 134.4 (C-5), 130.5 (C-1′), 128.5 (C-3′), 121.2 (C-6), 115.0 (C-2′), 108.6 (C-10), 108.0 (C-7), 100.8 (C-13), 64.5 (C-2), 50.5 (C-4), 25.7 (C-12); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{18}N_2O_4Na$: 337.1164; found 337.1158. D-form $[\alpha]_D$=−80.8 (c=2.453 in MeOH); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{18}N_2O_4Na$: 337.1164; found 337.11760.

4.3.13. Preparation of *N*-benzo[1,3]dioxol-5-ylmethyl-2,2,2-trifluoro-*N*-[(4-hydroxyphenyl)-methylcarbamoyl-methyl]-acetamide 40. To a cooled suspension of poly-DMAP (25.0 g, 75 mmol, dimethylaminopyridine, polymer bound, 3 mmol/g; Aldrich Cat. No. 35,988-2) and poly(4-vinylpyridine) (78.75 g, 0.75 mol, poly(4-vinylpyridine) 2% cross-linked; Aldrich Cat. No. 22,696-3) in DCM (400 mL) at 0°C was added dropwise trifluoroacetic anhydride (53 mL, 78.75 g, 0.375 mol). The suspension was shaken for 5 min then a solution of amine **40a** (94.2 g, 0.3 mol) in DCM (400 mL) was added and the reaction monitored by TLC (6:4; EtOAc/PE). During the early stages of the reaction a second product was detected which was subsequently identified as the phenol protected material, this by-product was slowly consumed during the course of the reaction. The reaction was worked-up by filtration, the resin was washed with DCM/MeOH (3:1; 3×150 mL), the organic fractions were combined and evaporated to yield the title compound **40** (quantitative) as a pale yellow oil: R_f 2.974 (Method A), R_f 4.62 (Method B). L-form $[\alpha]_D$=+51.7 (c=1.805 in MeOH); IR: 1682, 1615, 1541, 1517, 1485, 1441, 1257, 1230, 1218, 1136, 1034, 1007, 923, 803, 704 cm^{-1}, High temperature ^{1}H NMR (400 MHz, d_6-DMSO at 80°C): δ=9.36 (s, 1H, OH), 7.67 (br. s, 1H, NH), 7.03 (d, 2H, J=8.1 Hz, H-2′), 6.65 (d, 2H, J=8.1 Hz, H-3′), 6.60 (d, 1H, J=7.9 Hz, H-6), 6.37 (s, 1H, H-10), 6.35 (d, 1H, J=7.9 Hz, H-7), 5.87 (d, 2H, J=5.4 Hz, CH_2O_2), 5.62 (s, 1H, H-2), 4.72 (d, 1H, J=16.4 Hz, H-4_A), 3.38 (d, 1H, J=16.4 Hz, H-4_B), 2.62 (d, 3H, J=4.3 Hz, NMe); HR-MS (ESI, Q-tof) calcd for $C_{19}H_{17}N_2O_5F_3Na$: 433.0958; found 433.0987. D-form $[\alpha]_D$=−48.5 (c=1.03 in MeOH); HR-MS (ESI, Q-tof) calcd for $C_{19}H_{17}N_2O_5F_3Na$: 433.0958; found 433.09980.

4.3.14. Preparation of 2′,3′-dihydro-6′,7′-methylene-dioxy-2′-trifluoroacetyl-spiro[cyclohexa-2,5-dien-4-one-1,4′-(1*H*)isoquinolin]-3′-carboxylic acid methylamide 41. To a solution of **40** (2.05 g, 5 mmol, 1 equiv.) in 2,2,2-trifluoroethanol (15 mL) and DCM (60 mL) at −10°C was added portionwise over 10 min polymer-supported diacetoxyiodobenzene (6.82 g, 7.5 mmol, 1.1 mmol/g, 1.5 equiv.). The resulting mixture was allowed to warm to ambient temperature and was stirred for 6 h. The resin was filtered and washed with DCM (3×25 mL) and the filtrate

evaporated to afforded the spirodiene **41** as a golden yellow solid (1.68 g, 82%): R_f 2.974 (Method A); R_f 4.56 (Method B). L-form $[\alpha]_D$=+102.9 (c=1.15 in $CHCl_3$); IR: 3328, 2902, 1685, 1663, 1626, 1505, 1485, 1450, 1244, 1201, 1140, 1036, 985, 933, 861 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ=7.07 (dd, 1H, J=10.25, 2.7 Hz, H-6), 6.70 (dd, 1H, J=10.25, 2.7 Hz, H-2), 6.63 (s, 1H, H-5′), 6.57 (dd, 1H, J=10.25, 1.83 Hz, H-5), 6.47 (s, 1H, H-8′), 6.32 (br. s, 1H, NH), 6.16 (dd, 1H, J=10.25, 1.83 Hz, H-2), 5.94 (s, 2H, CH_2O_2), 5.05 (s, 1H, H-3′), 4.97 (s, 2H, H-1′), 2.79 (d, 3H, J=4.8 Hz, NMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ=184.8 (C-4), 166.2 (CON), 157.2 (CF_3), 150.7 (C-2), 147.7 (C-6), 147.4 (C), 132.1 (C-5′), 126.6 (C-3), 123.0 (C), 122.9 (C), 106.6 (C-8′), 106.2 (C-5), 101.6 (C-10′), 60.3 (C-3′), 45.3 (C-1), 45.1 (C-1′), 26.2 (C-9′); HR-MS (ESI, Q-tof) calcd for $C_{19}H_{15}N_2O_5F_3Na$: 431.0831; found 431.0816. D-form $[\alpha]_D$=−105.4 (c=1.50 in $CHCl_3$); D-form $[\alpha]_D$=−88.3 (c=1.25 in MeOH [decreasing over time]); HR-MS (ESI, Q-tof) calcd for $C_{19}H_{15}N_2O_5F_3Na$: 431.0831; found 431.0839.

4.3.15. Preparation of 5-methyl-4a,5-dihydro-4*H*,8*H*-7-trifluoroacetyl-[1,3]dioxolo[4′,5′:6,7]isoquinolin[3,4-*c*]indol-3,6-dione 42. Direct treatment of the filtrate from the preparation of **41** with Nafion SAC-13 (3.0 g, 10–20% flourosulfonic acid wt.; Aldrich Cat. No. 47,454-1) for 24 h followed by filtration and evaporation resulted in the complete conversion to the tetracyclic compound **42** as a pale yellow solid. Alternatively, a solution of HCl (2 M in ether, 5 mL) could be substituted to give the same product following evaporation of the solvent. R_f 3.036 (Method A). L-form $[\alpha]_D$=+248.3 (c=1.25 in $CHsCl_3$); IR: 1710, 1687, 1505, 1487, 1460, 1405, 1235, 1199, 1144, 1035, 930 cm^{-1}, High temperature ^1H NMR (400 MHz, d_6-DMSO at 120°C): δ=6.71 (s, 1H, Ar), 6.65 (s, 1H, Ar), 6.58 (d, 1H, J=10.18 Hz, H-1), 6.10 (d, 1H, J=10.18 Hz, H-2), 5.98 (s, 2H, CH_2O_2), 5.19 (s, 1H, H-6a), 4.86 (d, 1H, J=14.5 Hz, H-8_A), 4.36 (d, 1H, J=14.5 Hz, H-8_B), 4.16 (dd, 1H, J=11.2, 6.2 Hz, H-4a), 2.99 (ddd, 1H, J=15.8, 6.2, 0.75 Hz, H-4_A), 2.73 (d, 3H, J=0.62 Hz, NMe), 2.71 (dd, 1H, J=15.8, 11.2 Hz, H-4_B); HR-MS (ESI, Q-tof) calcd for $C_{19}H_{15}N_2O_5F_3Na$: 431.0831; found 431.0815. D-form $[\alpha]_D$=−255.1 (c=1.35 in $CHCl_3$); HR-MS (ESI, Q-tof) calcd for $C_{19}H_{15}N_2O_5F_3Na$: 431.0831; found 431.0844.

4.3.16. Preparation of 3,3-dimethoxy-5-methyl-3,4,4a,5-tetrahydro-8*H*-7-trifluoroacetyl-[1,3]dioxolo[4′,5′:6,7]isoquinolin[3,4-*c*]indol-6-one 43. A mixture of the ketone **42** (410 mg, 1 mmol, 1 equiv.), trimethyl orthoformate (318 mg, 3 mmol, 3 equiv.) or dimethoxy acetone (312 mg, 3 mmol, 3 equiv.) and Nafion SAC-13 (300 mg, 10–20% flourosulfonic acid wt.; Aldrich Cat. No. 47,454-1) in dry MeOH (5 mL) was heated in a sealed tube under microwave irradiation at 100°C for 45 min. The resin was removed by filtration and the solvent evaporated to yield the title compound **43** as a white solid in quantitative yield: R_f 2.997 (Method A). L-form $[\alpha]_D$=+270.8 (c=1.5 in $CHCl_3$); IR: 2970, 1715, 1694, 1488, 1461, 1235, 1203, 1151, 1039, 933 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ at 130°C): δ=6.70 (s, 1H, Ar), 6.68 (s, 1H, Ar), 6.19 (dd, 1H, J=9.8, 5.5 Hz, H-1), 5.96 (s, 2H, CH_2O_2), 5.70 (d, 1H, J=9.8 Hz, H-2), 4.86 (br. m, 1H, H-6a), 4.24 (br. m, 1H, H-8_A), 3.94 (m, 1H, H-8_B), 3.85 (dd, 1H, J=11.8, 4.95 Hz, H-4a), 3.46 (s, 3H, OMe), 3.44 (s, 3H, OMe), 2.71 (s, 3H, NMe), 2.43 (m, 1H, H-4_A), 1.46 (m, 1H, H-4_B); HR-MS (ESI, Q-tof) calcd for $C_{21}H_{21}N_2O_6F_3Na$: 477.1249; found 477.12480. Crystal structure determination of the L-form of compound **43**. Crystals of **43** were obtained by recystallisation from methanol/EtOAc 1:1. Crystal data: $C_{21}H_{21}F_3N_2O_6$, M=454.40, Monoclinic, a=13.947, b=11.440, c=12.654 Å, α=90°, β=96.77°, γ=90°, U=2004.9 $Å^3$, T=180(2) K, space group $P2_1/c$, Z=4, μ=0.128 mm^{-1}, 10,617 reflections collected, 4575 independent reflections (R_{int}=0.0776), The final $wR(F^2)$ was 0.0544.

4.3.17. Preparation of 3-methoxy-5-methyl-3,4,4a,5-tetrahydro-8*H*-7-trifluoroacetyl-[1,3]dioxolo[4′,5′:6,7]iso-6,7]isoquinolin[3,4-*c*]indol-6-one 44. To a suspension of alcohol **45** (2.05 g, 5 mmol, 1 equiv.) and sulfonic acid resin (35.7 g, 50 mmol, 10 equiv., MP-TsOH 1.40 mmol/g; Argonaut Technologies Inc. Cat. No. 800286) in a mixture of DCM/MeOH (3:2; 50 mL) at 0°C was added dropwise trimethylsilyl diazomethane (5 mL, 2 M in hexane, 10 mmol, 2 equiv.). The initial pale yellow solution showed signs of effervescence and slowly over 10 min turned clear. After 25 min periods a second, and subsequently third portion of trimethylsilyl diazomethane (2.5 mL, 2 M in hexane, 5 mmol, 1 equiv.) was added. Reaction progress was monitored by LC-MS (additional amounts of trimethylsilyl diazomethane were added if required. The reaction was worked-up by filtration and the filtrate evaporated to yield **44** as a white solid (2.02 g, 95%): R_f 3.201 (Method A), R_f 4.41 (Method B). L-form $[\alpha]_D$=+238.7 (c=1.25 in $CHCl_3$); IR: 2938, 1708, 1681, 1505, 1486, 1460, 1249, 1236, 1200, 1171, 1147, 1089, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ at 100°C): δ=6.74 (s, 1H, Ar), 6.71 (s, 1H, Ar), 6.03 (d, 1H, J=9.95 Hz, H-1), 5.96 (d, 2H, J=1.4 Hz, CH_2O_2), 5.53 (d, 1H, J=9.95 Hz, H-2), 4.73 (br. s, 1H, H-6a), 4.66 (br. s, 1H, H-8_A), 4.36 (ddt, 1H, J=10.25, 4.7, 1.96 Hz, H-3), 4.33 (br. s, 1H, H-8_B), 3.85 (dd, 1H, J=12.05, 4.70 Hz, H-4a), 3.38 (s, 3H, OMe), 2.73 (s, 3H, NMe), 2.60 (ddt, 1H, J=12.0, 4.7, 1.4 Hz, H-4_A), 1.46 (dt, 1H, J=12.0, 10.25 Hz, H-4_B); HR-MS (ESI, Q-tof) calcd for $C_{20}H_{19}N_2O_5F_3Na$: 447.1144; found 447.1143. D-form $[\alpha]_D$=−285.7 (c=1.4 in MeOH); HR-MS (ESI, Q-tof) calcd for $C_{20}H_{19}N_2O_5F_3Na$: 447.1144; found 447.1143.

4.3.18. Preparation of 3-methoxy-5-methyl-3,4,4a,5-tetrahydro-8*H*-7-trifluoroacetyl-[1,3]dioxolo[4′,5′:6,7]iso-6,7]isoquinolin[3,4-*c*]indol-6-one 44. A mixture of 2,6-di^{t}butylpyridine polymer bound (0.85 g, 1.53 mmol, 2.5 equiv., poly(2,6-di-*tert*-butyl 4-vinylpyridine), 1% cross-linked, 1.8 mmol/g, poly(2,6-*tert*-butyl 4-vinylpyridine); Aldrich Cat. No. 37,782-1), methyl trifluoromethanesulfonate (120 mg, 0.73 mmol, 1.2 equiv.) and alcohol **45** (250 mg, 0.61 mmol, 1 equiv.) in MeCN (5 mL) were heated in a sealed tube using microwave radiation at 120°C for 35 min. The reaction was filtered and the resin washed with MeCN (3×15 mL), the combined filtrate was evaporated under reduced pressure to yield the title compound **44** as a cream solid (quant.). The compound was identical to that prepared by the previous method.

4.3.19. Preparation of 3-methoxy-5-methyl-3,4,4a,5-tetrahydro-8*H*-7-trifluoroacetyl-[1,3]dioxolo[4′,5′:6,7]iso-6,7]isoquinolin[3,4-*c*]indol-6-one 44. A mixture of the dimethyl acetal **43** (250 mg, 0.61 mmol, 1 equiv.),

triethylsilane (85 mg, 0.73 mmol, 1.2 equiv.) and Nafion SAC-13 (250 mg, 10–20% flourosulfonic acid wt.; Aldrich Cat. No. 47,454-1) in DCM (5 mL) was heated in a sealed tube under microwave irradiation at 120°C for 30 min. The resin was removed by filtration washed with DCM (3×5 mL) and the solvent evaporated to yield the title compound **44** (95% conversion). The compound was identical to that prepared by the previous method.

4.3.20. Preparation of 3-hydroxy-5-methyl-3,4,4a,5-tetrahydro-8*H*-7-trifluoroacetyl-[1,3]dioxolo[4′,5′:6,7]isoquinolin[3,4-*c*]indol-6-one 45. Polymer-supported borohydride (7.9 g, 19.8 mmol, 1.2 equiv., borohydride on Amberlite IRA400, ~2.5 mmol/g; Aldrich Cat. No. 32,864-2) was added to a solution of **42** (6.75 g, 16.5 mmol) in a mixture of DCM/MeOH (3:1; 50 mL) at 10°C (higher temperature resulted in partial removal of the trifluoro protecting group). The reaction mixture was shaken and monitored by LC-MS until the reaction had reached completion (1.5–2 h). The spent resin was filtered, washed with DCM/MeOH (3:1; 3×25 mL) and the filtrate evaporated under reduced pressure to give the title compound **45** as a pale yellow oil (6.72 g, 99%): R_f 2.869 (Method A), R_f 3.42 (Method B). L-form $[\alpha]_D$=+347.3 (c=1.64 in MeOH); IR: 3366, 2359, 1705, 1486, 1456, 1403, 1247, 1171, 1154, 1039, 934 cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO at 130°C): δ=6.73 (s, 1H, H-Ar), 6.69 (s, 1H, H-Ar), 5.96 (s, 2H, CH_2O_2), 5.92 (d, 1H, J=10.05 Hz, H-1), 5.46 (dd, 1H, J=10.05, 2.05 Hz, H-2), 4.84 (br. s, 1H, H-6a), 4.67 (d, 1H, J=16.8 Hz, H-8$_A$), 4.52 (m, 1H, H-3), 4.35 (d, 1H, J=16.8 Hz, H-8$_B$), 3.83 (dd, 1H, J=12.3, 4.65 Hz, H-4a), 2.72 (s, 3H, NMe), 2.48 (m, 1H, H-4$_A$), 1.42 (m, 1H, H-4$_B$); HR-MS (ESI, Q-tof) calcd for $C_{19}H_{17}N_2O_5F_3Na$: 433.0987; found 433.0980. D-form $[\alpha]_D$=−341.8 (c=0.55 in MeOH); HR-MS (ESI, Q-tof) calcd for $C_{19}H_{17}N_2O_5F_3Na$: 433.0987; found 433.0999.

4.3.21. Preparation of 3-hydroxy-5-methyl-3,4,4a,5-tetrahydro-8*H*-[1,3]dioxolo[4′,5′:6,7]isoquinolin[3,4-*c*]indol-6-one 46. A sealed tube containing compound **45** (250 mg, 0.59 mmol) and Ambersep 900 (1 g, OH-form; Fluka Cat. No. 06476) in MeOH (4 mL) was heated at 100°C under microwave irradiation for 1 h. The resin was removed by filtration and washed with MeOH (3×10 mL), the combined organic fractions were evaporated under reduced pressure to yield **46** as a yellow solid (174 mg, 94%). L-form $[\alpha]_D$=+425.7 (c=1.2 in MeOH); IR: 3333, 2925, 1678, 1503, 1485, 1242, 1038, 932, 864, 768 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.50 (s, 1H, 12), 6.43 (s, 1H, 9), 5.92 (dt, 1H, J=10.05, 1.3 Hz, H-1), 5.87 (ap. q, 2H, J=1.4 Hz, CH_2O_2), 5.77 (dd, 1H, J=10.05, 2.0 Hz, H-2), 4.49 (ddt, 1H, J=9.9, 4.6, 2.0 Hz, H-3), 3.91 (d, 1H, J=15.25 Hz, H-8$_A$), 3.69 (br. s, 1H, H-6a), 3.66 (d, 1H, J=15.25 Hz, H-8$_B$), 3.58 (dd, 1H, J=11.9, 4.6 Hz, H-4a), 2.78 (s, 3H, NMe), 2.46 (ddt, 1H, J=11.9, 4.7, 1.1 Hz, H-4β), 1.43 (dt, 1H, J=11.9, 9.9 Hz, H-4α); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.9 (CO), 147.0 (C-Ar), 146.8 (C-Ar), 132.5/131.5 (C-1/2), 130.7 (C-Ar), 129.7 (C-Ar), 108.3 (C-9), 106.3 (C-12), 101.3 (C-15), 65.6 (C-3), 64.7 (C-4a), 62.6 (C-6a), 44.4 (C-8), 43.2 (C-12b), 35.5 (C-4), 28.4 (C-14); ^{1}H NMR (400 MHz, d_6-DMSO): δ=6.62 (s, 1H, 12), 6.50 (s, 1H, 9), 5.90 (dd, 2H, J=6.96, 0.76 Hz, CH_2O_2), 5.75 (d, 1H, J=10.0 Hz, H-1), 5.59 (dd, 1H, J=10.0, 2.1 Hz, H-2), 5.01 (m, 1H, NH), 4.44 (m, 1H, H-3), 3.66 (d, 1H, J=15.6 Hz, H-8$_A$), 3.61 (dd, 1H, J=12.0, 4.48 Hz, H-4a), 3.51 (d, 1H, J=15.6 Hz, H-8$_B$), 3.54 (br. s, 1H, H-6a), 3.04 (br. s, 1H, OH), 2.62 (s, 3H, NMe), 2.35 (ddt, 1H, J=11.8, 4.9, 0.85 Hz, H-4β), 1.43 (dt, 1H, J=11.8, 10.4 Hz, H-4α); ^{13}C NMR (100 MHz, d_6-DMSO): δ=170.9 (CO), 146.3/146.0 (C-10/11), 132.5 (C-1), 131.9 (C-Ar), 131.5 (C-2), 130.4 (C-Ar), 108.6 (C-9), 105.8 (C-12), 101.0 (C-15), 64.5 (C-3), 63.4 (C-4a), 62.1 (C-6a), 44.2 (C-12b), 43.7 (C-8), 35.5 (C-4), 27.7 (C-14); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{19}N_2O_4$: 315.1345; found 315.1342. D-form HR-MS (ESI, Q-tof) calcd for $C_{17}H_{19}N_2O_4$: 315.1345; found 315.1337. D-form $[\alpha]_D$=+421.3 (c=1.3 in MeOH); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{19}N_2O_4$: 315.1345; found 315.1337. R_f 2.156 (Method A), R_f 3.40 (Method B). Crystal structure determination of compound **46** D-form. Crystals of **46** were obtained by recystallisation from methanol. Crystal data: $C_{17}H_{18}N_2O_4$, M=314.33, orthorhombic, a=8.4037(3), b=11.0952(4), c=15.9005(5) Å, α=90°, β=90°, γ=90°, U=1482.57(9) Å^3, T=180(2) K, space group $P2_12_12_1$, Z=4, μ=0.101 mm^{-1}, 9418 reflections collected, 3245 independent reflections (R_{int}=0.0379). The final $wR(F^2)$ was 0.0415. L-Form crystal was confirmed as the direct reflection.

4.3.22. Preparation of 3-hydroxy-5-methyl-3,4,4a,5-tetrahydro-8*H*-[1,3]dioxolo[4′,5′:6,7]isoquinolin[3,4-*c*]indol-6-one 46. Polymer-supported borohydride (1.22 g, 3.05 mmol, 4 equiv., borohydride on Amberlite IRA 400, ~2.5 mmol/g; Aldrich Cat. No. 32,864-2) was added to a solution of ketone **42** (1.25 g, 3.05 mmol) in a mixture of DCM/MeOH (1:1; 30 mL) at 50°C. The reaction mixture was shaken and monitored by LC-MS until the reaction had reached completion (4 h). The spent resin was filtered, washed with DCM/MeOH (1:1; 3×25 mL) and the filtrate evaporated under reduced pressure to give the title compound **46** as a glassy solid (0.87 g, 91%). The compound was identical to that prepared by the previous method (Table 5).

4.3.23. Preparation of 3-methoxy-5-methyl-3,4,4a,5-tetrahydro-8*H*-[1,3]dioxolo[4′,5′:6,7]isoquinolin[3,4-*c*]indol-6-one 47. A sealed tube containing compound **44** (250 mg, 0.58 mmol) and Ambersep 900 (1.0 g, OH-form; Fluka Cat. No. 06476) in MeOH (4 mL) was heated at 100°C under microwave irradiation for 20 min. The resin was removed by filtration and washed with MeOH (3×10 mL) the combined organic fractions were evaporated under reduced pressure to yield **47** as a yellow solid (186 mg, 96%): R_f 2.380 (Method A); R_f 3.61 (Method B). L-form $[\alpha]_D$=+231.5 (c=0.75 in $CHCl_3$); IR: 2903, 2823, 1733, 1684, 1503, 1483, 1386, 1373, 1238, 1100, 1037, 931, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=6.49 (s, 1H, Ar), 6.42 (s, 1H, Ar), 5.95 (dt, 1H, J=10.1, 1.5 Hz, H-1), 5.88 (s, 2H, H-CH_2O_2), 5.82 (dd, 1H, J=10.1, 2.1 Hz, H-2), 4.09 (ddt, 1H, J=10.25, 4.7, 1.9 Hz, H-3), 3.95 (d, 1H, J=15.3 Hz, H-8$_A$), 3.71 (s, 1H, H-6a), 3.65 (d, 1H, J=15.3 Hz, H-8$_B$), 3.57 (dd, 1H J=12.0, 4.7 Hz, H-4a), 3.43 (s, 3H, OMe), 2.77 (s, 3H, NMe), 2.52 (ddt, 1H, J=12.0, 4.7, 1.35 Hz, H-4$_A$), 1.38 (dt, 1H, J=12.0, 10.25 Hz, H-4$_B$); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.7 (CO), 147.0/146.8 (C-10/11), 133.2 (C-1), 130.9 (C-Ar), 129.9 (C-Ar), 128.5 (C-2), 108.3 (C-9), 106.4 (C-12), 101.3

Table 5. nOe couplings from compound **46**

Proton	NOESY
1	6a, 12
2	1, 3
3	2, 4β, 4a
4α	4β, 6a
4β	3, 4α, 4a
4a	3, 4β, 12, NMe
6a	1
8_A	8_B, 9
8_B	8_A, 9
9	8_A, 8_B
12	1, 3, 4a
NMe	4β, 4a

(C-15), 74.7 (C-3), 64.7 (C-4a), 62.6 (C-6a), 56.5 (C-13), 44.4 (C-8), 43.6 (C-12b), 32.3 (C-4), 28.3 (C-14); HR-MS (ESI, Q-tof) calcd for $C_{19}H_{15}N_2O_5F_3Na$: 431.0815; found 431.0831. D-form $[\alpha]_D=-258.4$ (c=1.8 in $CHCl_3$); HR-MS (ESI, Q-tof) calcd for $C_{19}H_{15}N_2O_5F_3Na$: 431.0815; found 431.0833.

4.3.24. Preparation of 4-(2-bromoethyl)phenol 48. A solution of 4-(2-hydroxyethyl)phenol **52** (25.0 g, 0.181 mol, 1 equiv.), carbon tetrabromide (90.14 g, 0.272 mol, 1.5 equiv.) and diphenylphosphino-polystrene (151 g, 0.453 mol, 2.5 equiv., triphenylphosphine polymer bound ~3 mmol/g; Fluka Cat. No. 93093) in DCM (mL) was stirred at 40°C for 3.5 h. The solution was filtered and the resin washed with DCM (3×175 mL), the filtrate was evaporated under reduced pressure to yield the title compound **48** as a white solid (quantitative): R_f 3.006 (Method A); R_f 4.84 (Method B). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.14 (d, 2H, J=8.4 Hz), 6.75 (d, 2H, J=8.4 Hz), 5.15 (s, 1H, OH), 3.50 (t, 2H, J=7.6 Hz), 3.05 (t, 2H, J=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.70 (C), 154.71 (C), 130.77 (C), 130.05 (2×CH), 115.43 (2×CH), 38.53 (CH_2), 33.42 (CH_2); HR-MS (ESI, Q-tof) calcd for $C_{17}H_{18}N_2O_4$: 315.13370; found 315.1345.[27]

4.3.25. Preparation of 4-(2-bromoethyl)phenol 48. To a suspension of diphenylphosphino-polystrene (15.12 g, 45.3 mmol, 2.5 equiv., triphenylphosphine polymer bound ~3 mmol/g; Fluka Cat. No. 93093) in DCM (250 mL) under argon at 0°C was added dropwise bromine (4.35 g, 1.40 mL, 27.2 mmol, 1.5 equiv.) and the reaction stirred for 20 min. To the reaction mixture was added 4-(2-hydroxyethyl)phenol **52** (2.5 g, 18.1 mmol, 1 equiv.) and the reaction stirred for a further 2 h. The solution was then filtered, the resin washed with DCM (3×50 mL) and the filtrate evaporated under reduced pressure to yield the title compound **48** as a white solid (quantitative). Spectroscopic data was consistent with the material prepared by the previous method.

4.3.26. Preparation of 3-methoxy-5-methyl-3,4,4a,5-tetrahydro-8*H*-7[2′-(4-hydroxyphenyl)-ethyl]-[1,3]dioxolo[4′,5′:6,7]isoquinolin[3,4-*c*]indol-6-one 49. A mixture of amine **47** (250 mg, 0.75 mmol, 1 equiv.), 4-(2-bromoethyl)phenol **48** (276 mg, 0.875 mmol, 1.15 equiv.) and polymer-supported carbonate (0.76 g, 2.66 mmol, 3.5 equiv., carbonate on polymer support on IRA 900, ~3.5 mmol/g ($NaCO_3$); Fluka Cat. No. 21850) in MeCN (5 mL) was heated in a sealed reaction vial at 140°C under microwave radiation for 2×15 min pulses. To the reaction mixtures was added *N*-(2-mercaptoethyl)aminomethyl polystyrene (2.5 g, 3.0 mmol, 2 equiv., 1.2 mmol/g; NovaBiochem. Cat. No. 01-64-0180) and THF (5 mL). After 2 h of shaking at ambient temperature the reaction was filtrated and the resin washed with MeCN (2×15 mL). Removal of the solvent under reduced pressure gave the title compound **49** (354 mg, 90%) in 95% purity as determined by LC-MS, this material was carried through to the next stage. R_f 2.721 (Method A). L-form $[\alpha]_D=+143.6$ (c=0.25 in MeOH); IR: 3293, 2927, 1669, 1613, 1515, 1483, 1454, 1386, 1234, 1102, 1036, 932, 830 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.00 (d, 2H, J=8.3 Hz, H-11′), 6.75 (d, 2H, J=8.3 Hz, H-10′), 6.50 (d, 1H, H-Ar), 6.46 (d, 1H, H-Ar), 5.93 (d, 1H, J=10.15 Hz, H-1), 5.89 (s, 2H, CH_2O_2), 5.79 (d, 1H, J=10.15 Hz, H-2), 4.13 (m, 1H, H-3), 3.94 (d, 1H, J=15.25 Hz, H-8_A), 3.78 (s, 1H, H-6a), 3.67 (d, 1H, J=15.25 Hz, H-8_B), 3.56 (dd, 1H, J=12.35, 4.35 Hz, H-4a), 3.45 (s, 3H, OMe), 3.35 (m, 1H, H-$7'_A$), 3.25 (m, 1H, H-$7'_B$), 2.76 (m, 5H, H-8′ and NMe), 2.53 (m, 1H, H-4_A), 1.39 (m, 1H, H-4_B); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.8 (C-6), 154.7 (C-12′), 146.8/146.6 (C-10/11), 133.1/128.3 (C-1/2), 132.5/131.8/129.6 (C-8a/9′/12a), 129.8 (C-10′), 115.4 (C-11′), 107.7 (C-9), 106.3 (C-12), 101.1 (C-15), 74.6 (C-3), 66.4 (C-4a), 64.6 (C-6a), 56.9 (C-7′), 56.2 (C-13), 50.5 (C-8′), 44.8 (C-12b), 34.0/32.0 (C-4/8), 27.9 (C-14); HR-MS (ESI, Q-tof) calcd for $C_{26}H_{28}N_2O_5Na$: 467.1896; found 467.1901. D-form $[\alpha]_D=-178.7$ (c=0.15 in $CHCl_3$); HR-MS (ESI, Q-tof) calcd for $C_{26}H_{28}N_2O_5Na$: 467.1896; found 467.1890.

4.3.27. Preparation of 3-methoxy-5-methyl-3,4,4a,5-tetrahydro-8*H*-7-[carboxylic acid 2′-isopropyl-5-methyl-cyclohexyl ester]-[1,3]dioxolo[4′,5′:6,7]isoquinolin[3,4-*c*]indol-6-one 50. To a suspension of amine **47** (1.02 g, 2.5 mmol, 1 equiv.), PS-DMAP (400 mg, 1.25 mmol, 0.5 equiv., dimethylaminopyridine, polymer bound, 3 mmol/g; Aldrich Cat. No. 35,988-2) and supported triethylamine (1.67 g, 5 mmol, 2 equiv., 3.2 mmol/g, diethylaminomethyl polystrene; Fluka Cat. No. 31866) in DCM (50 mL) was added (−)-menthyl chloroformate (600 mg, 2.75 mmol, 1.05 equiv.). The mixture was stirred for 6 h then filtered and the resin washed with DCM (3×25 mL) and the combined filtrates evaporated to dryness (1.22 g, 96%). The solid was recrystallised from MeOH to give the title compound **50** as colourless crystals (1.07 g, 84%). L-form $[\alpha]_D=+258.6$ (c=1.10 in MeOH); Crystal structure determination of the L-form of compound **50**. Crystals of **50** were obtained by recystallisation from methanol. Crystal data: $C_{29}H_{38}N_2O_6$, M=510.61, monoclinic, a=10.9958(3), b=11.7140(3), c=11.2943(3) Å, α=90°, β=111.0580(10)°, γ=90°, U=1357.61 Å^3, T=180(2) K, space group $P2(1)$, Z=2, μ=0.087 mm^{-1}, 12,204 reflections collected, 5760 independent reflections (R_{int}=0.0412), The final $wR(F^2)$ was 0.0500.

4.3.28. 3-Methoxy-5-methyl-3,4,4a,5-tetrahydro-[1,3]dioxolo[4′,5′:6,7]isoquinolin[3,4-*c*]indol-6-one 51. Following the procedure for **47**; compound **47** (197 mg, 0.60 mmol) was oxidised to the imine **50** (182 mg, 93%). R_f 2.426 (Method A) MS 327.1 (MH+).

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