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Second-Generation Process Research Towards Eletriptan: A Fischer Indole Approach

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Abstract:

The development of a second-generation process for the synthesis of eletriptan via a Fischer indole cyclisation is described. The finalised process offers several potential advantages over the current route of manufacture including cost, throughput, and safety.

Eletriptan **(R)-7** belongs to the class of drugs known as triptans and was approved in the United States in December 2002. It is a potent and selective 5-HT agonist and is marketed as Relpax for the treatment of migraine. It is currently a low volume product; however, at the time the research was started, the development of novel formulations and drug delivery systems could have significantly increased bulk demand for the drug. The current manufacturing route[1] to eletriptan **7** is well developed and robust, but does suffer some limitations (scheme 1). The key starting material **5** is extremely expensive and contributes approximately 50% of the total cost of manufacture. It uses the costly, unnatural isomer of proline as well as the highly noxious and sensitizing reagent phenyl vinyl sulfone. The synthesis also incorporates a lithium aluminium hydride reduction, generating large waste aqueous streams. Thus an alternative route of manufacture was sought that would be able to deliver this increase in bulk demand.

During the assessment of alternative routes to eletriptan, the Fischer indole synthesis was highlighted as a particularly attractive way to build up the molecule. It had the potential to deliver a convergent, highly efficient synthesis (scheme 2), as well as being a well understood and reliable transformation. The Fischer indole reaction was discovered in 1883 by Hermann Emil Fischer,[2] and despite its age, is still one of the most commonly used methods to synthesise indole containing molecules. Indeed several other members of the Triptan family of drugs are manufactured via this method.[3] If this approach were successful, then many of the issues associated with the current route of manufacture could be avoided.

The Fischer reaction proceeds via condensation of an aryl hydrazine with a carbonyl compound, followed by a 1,3-sigmatropic rearrangement and subsequent elimination of ammonia.[4] In order to prove that the Fischer reaction was viable for the preparation of eletriptan **(R)-7**, the synthesis of either aldehyde **8** or a suitably protected form would be required, together with the hydrazine **10**. Formation of **8** or **9** and indeed **10** however, proved to be quite challenging. The first successful synthesis (scheme 3) of **9** was via lithiation of N-methylpyrolle[5] **11** and subsequent alkylation with 2-(2-bromoethyl)-1,3-dioxolane, followed by hydrogenation of the pyrrole to yield the racemic pyrrolidine **9a.**

This synthesis was not amenable to further scale up, due to the low yields, cryogenic reaction conditions and chromatography. However sufficient material was isolated to validate the use of **9a** in the Fischer indole reaction by condensation with commercially available 4-bromophenyl hydrazine. This delivered **rac-5**, a racemic form of an intermediate in the original synthesis, in good yield.

The need for a more robust and scalable synthesis, led to the development of two further routes. The first starts from 4-methylaminobutyric acid **13** which is protected as the benzyl carbamate and transformed to the Weinreb amide **14**. Addition of the Grignard reagent formed from 2-(2-bromoethyl)-1,3-dioxane **15**, followed by deprotection with concomitant cyclisation and imine reduction gave a high yielding, robust four-step synthesis of compound **9b** (Scheme 4). The acetal of choice was changed from the five-membered 1,3-dioxolane to the six-membered 1,3-dioxane due to the improved stability of the respective Grignard reagent at the required reaction temperature. This route was reproducible, reliable, and very easily scaled, but suffers from the use of expensive reagents (all intermediates being oils) and the need for a protecting group. However a 50-g batch of the fumarate salt of **9b** was easily made using this chemistry.

The third successful synthesis of racemic pyrrolidine acetal **9** starts from *N*-methylpyrrole-2-carboxaldehyde **20** (scheme 5). This undergoes a key Wittig olefination[6] with a phosphorous ylide derived from bromoacetaldeyde, followed by global hydrogenation and isolation as the fumarate salt. The acetal has again been changed to the 5,5-dimethyl-1,3-dioxane as this gives a crystalline intermediate **20** that was less prone to hydrolysis than either the unsubstituted dioxane or dioxolane acetals. Wittig reaction of Aldehyde **19** with the triphenylphosphonium ylide derived from **18a** failed to give any conversion to the olefin **20**. However, switching to the tri^{n}butylphosphonium ylide **18b** afforded complete conversion to olefin **20**. Since the tri^{n}-butylphosphine oxide byproduct is partially water-soluble, it can be removed with multiple water washes of the product solution. Despite the increased stability of the dimethyldioxane acetal, olefin **20** still hydrolyses to the corresponding aldehyde upon

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(2) Fischer, E.; Jourdan, F. *Chem. Ber.* **1883**, *16*, 2241.
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(5) Brittain, J. M.; Jones, R. A.; Arques, J. S.; Saliente, T. A. *Synth. Commun.* **1982**, *12*, 231.
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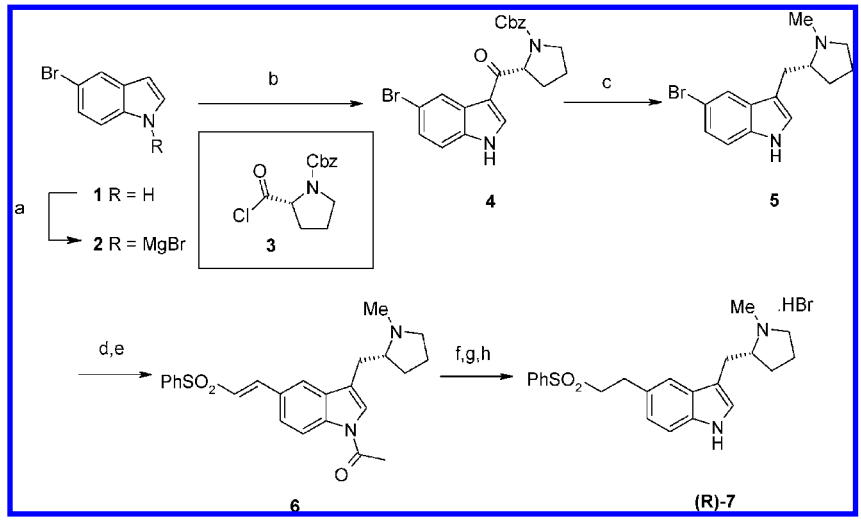
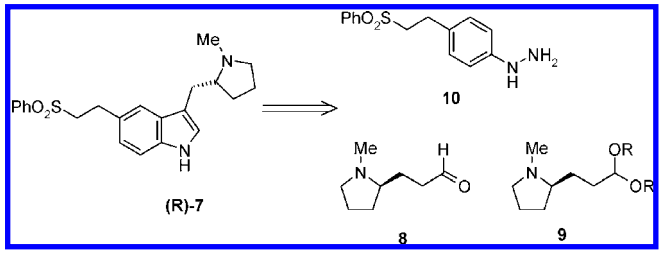
Scheme 1. **Current manufacturing route to eletriptan (R)-7[a]**

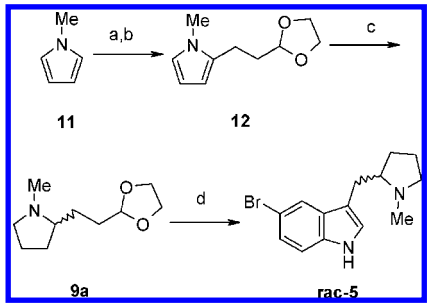


[a] Reagents and conditions: (a) EtMgBr, Et_2O. (b) **3**, DCM, 50% from **1**. (c) $LiAlH_4$, THF, 72%. (d) Ac_2O, TEA, DMF. (e) Phenyl vinyl sulfone (PVS), $Pd(OAc)_2$, $P(°Tol)_3$, TEA, DMF, 80% from **5**. (f) H_2, Pd/C, $MeSO_3H$, acetone, 95%. (g) K_2CO_3, MeOH, 92%. (h) HBr, acetone 73%.

Scheme 2. **Fischer indole approach to eletriptan (R)-7**



Scheme 3. **First synthesis of racemic pyrrolidine acetal 9a[a]**

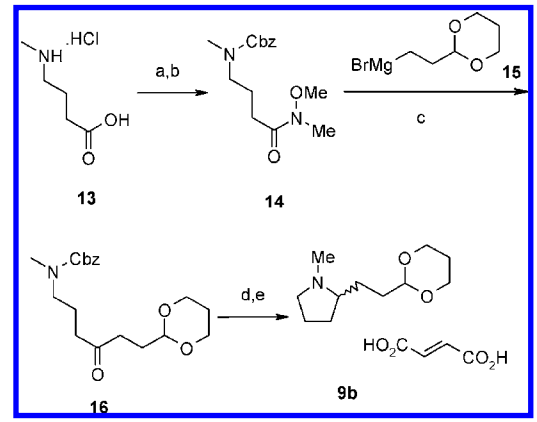


[a] Reagents and conditions: (a) ^nBuLi, TMEDA, hexane, 50 °C. (b) 2-(2-Bromoethyl)-1,3-dioxolane, THF, −60 °C 25% from **11**. (c) H_2, Rh/C, 100 psi, 100 °C, 100%. (d) 4-Bromophenyl hydrazine hydrochloride, H_2SO_4 (4% w/v), 75%.

prolonged exposure to water and as a result, the best isolated yield of **20** from **18b** was only 35%. A significantly improved procedure was developed using the triethylphosphonium ylide derived from **18c**. Again the conversion to olefin **20** is high, but the triethylphosphine oxide byproduct is highly water-soluble and so can be completely removed with a single water wash. This minimizes the contact of the product with water and a significantly improved yield is attained (77%). Triethylphosphine is extremely pyrophoric and difficult to handle, but can be conveniently purchased as a solution in THF which is much easier and safer to handle. The different pyrrolidine acetals **9a,b** and **c** were shown to react identically under Fischer reaction conditions.

With racemic **9** in hand, attention switched to the synthesis of aryl hydrazine **10**. The required aniline **22** was readily

Scheme 4. **Improved synthesis of racemic pyrrolidine acetal 9b[a]**



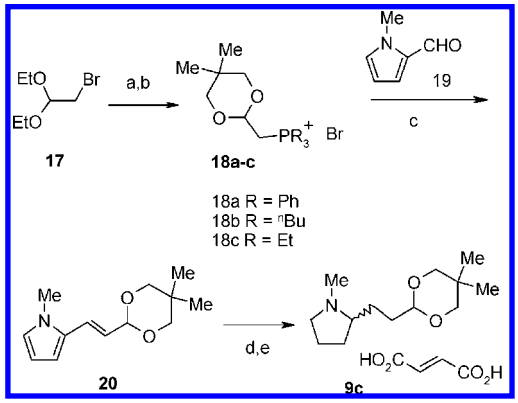
[a] Reagents and conditions: (a) CbzCl, KOH, water, toluene. (b) CDI, TEA, DCM, HN(OMe)Me·HCl, 82% from **13**. (c) THF, 60 °C, 85%. (d) H_2, Pd/C, MeOH, 60 psi, 50 °C. (e) Fumaric acid, MeOH, EtOAc, 78% from **16**.

synthesized in two steps from commercially available 4-nitrophenethyl bromide **21** (Scheme 6). However, conversion to the hydrazine **10** via the diazonium salt **23** was unsuccessful. It was clear from LC/MS analysis that the diazotisation was working efficiently and that the problem lay with the stability of the free hydrazine **10**. Even the hydrochloride salt of the hydrazine **10** degraded rapidly at ambient temperature. The best results were obtained using tin(II) chloride as reductant and isolating **10** as its hydrochloride salt, with storage of the material at −20 °C. This yieded a meagre 13% of **10**.

It was at this point that a recent patent[7] was found, detailing the reduction of diazonium salts with L-ascorbic acid (vitamin C). Of particular interest was the potential to form a stable, isolable oxalyl hydrazide intermediate **24**, which could be cleaved to the free hydrazine on treatment with acid. It was hoped that we could utilize **24** as a hydrazine equivalent in the

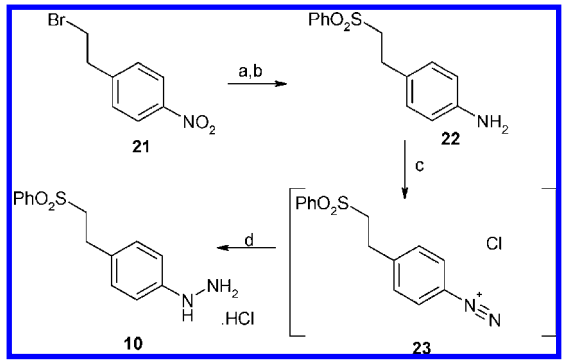
(7) Lambert, J. F.; Norris, T. Preparation of N-(5-cyclopropyl-1-quinolin-5-yl-1H-pyrazole-4-carbonyl)guanidine and other sodium-hydrogen exchanger type-1 (NHE-1) inhibitors, with improved product color, via an improved preparation of arylhydrazines using ascorbic acid reduction; WO/2002/044133, 2002.

Scheme 5. **Alternative synthesis of racemic pyrollidine acetal 9c[a]**



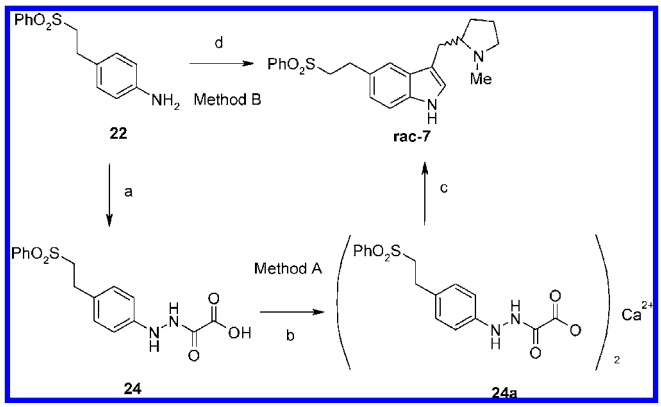
[a] Reagents and conditions: (a) Neopentyl glycol, H_2SO_4, toluene, 90%. (b) PR_3, MeCN, 100%. (c) NaOEt, DMF, EtOH R = Ph = 0%; R = ^{n}Bu = 35%; R = Et = 77%. (d) H_2, Rh/C, EtOH, 100 psi, 70 °C. (e) Fumaric acid, MeOH, EtOAc, 95% from **20**.

Scheme 6. **Synthesis of aryl hydrazine 10[a]**



[a] Reagents and conditions: (a) $PhSO_2Na$, IPA, H_2O. (b) H_2, Pd/C, THF 80% from **21**. (c) $NaNO_2$, HCl, H_2O, MeCN. (d) $SnCl_2$, HCl, H_2O 13% from **22**.

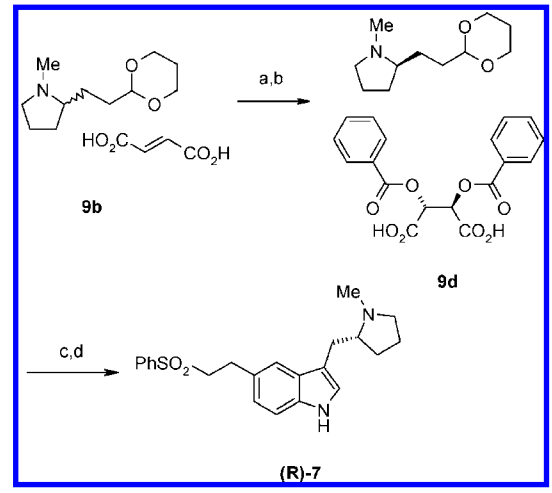
Scheme 7. **Formation of oxalyl hydrazide 24 and subsequent Fischer reaction[a]**



[a] Reagents and conditions: (a) $NaNO_2$, H_2SO_4, H_2O, MeCN, L-ascorbic acid, H_2O, 83%. (b) KOH, H_2O, MeCN, $CaCl_2$ 86%. (c) **9b**, H_2SO_4, H_2O, MeCN, 84%. (d) $NaNO_2$, H_2SO_4, H_2O, MeCN, L-ascorbic acid, H_2O, **9b**, 75%.

Fischer reaction, as the acidic conditions would reveal the free hydrazine **10** in situ. Oxalyl hydrazide **24** is not a solid and is tricky to isolate, but can be obtained as a crystalline calcium salt **24a** prior to running the Fischer reaction. Alternatively, a one-pot procedure was developed to take the aniline **22** directly through to racemic eletriptan (**rac-7**) (Scheme 7). The ascorbic acid reduction of diazonium salts offers some general advantages over the more traditional methods used for this process. Ascorbic acid is extremely cheap, nontoxic, and environmentally benign. It is added directly to the diazonium salt mixture as an aqueous solution in a dose-controlled manner, avoiding the need to transfer the diazonium salt solution between vessels. As such, this process was deemed suitable for further scale up onto plant scale.

Scheme 8. **Resolution approach to give the desired (R)-7[a]**



[a] Reagents and conditions: (a) $NaOH_{(aq)}$, DCM. (b) Dibenzoyl-L-tartaric acid, MEK, IPA, 35%, 94% ee from **9b**. (c) **24a**, $H_2SO_{4\ (aq)}$, MeCN, 59%, 94% ee.

Having successfully demonstrated an efficient synthesis of racemic eletriptan **rac-7**, the final objective for the project was to synthesis the single enaniomer of eletriptan **(R)-7**. This was achieved via classical resolution of rac-**9b**, by formation of a diastereoisomeric salt. Both enantiomers of **9b** were isolated as either the L or D-dibenzoyltartarate salt and reacted with hydrazine oxalate **24a**, under the Fischer reaction conditions, to furnish both enantiomers of eletriptan **(R)-7** and **(S)-7**. Comparison with an authentic marker showed that the enantiomer of **9d** isolated from the L-benzoyl tartaric acid gave the desired enantiomer of eletriptan **(R)-7** (scheme 8).

Conclusions

A scalable, commercially viable alternative route for the synthesis of eletriptan **(R)-7** has been developed.[8] It is believed that this new synthesis would have been better able to support the potentially dramatic increase in bulk demand for this compound, had alternative dosage formulations and drug delivery systems been successful. The route uses benign reagents, avoids the noxious phenyl vinyl sulfone and eliminates the large waste streams derived from lithium aluminium hydride reduction. A safe, scalable diazotisation and reduction protocol was developed, via a stable, acid labile oxalyl hydrazide intermediate. Despite the requirement for a classical resolution of a key intermediate, the cost of the synthesis is predicted to be significantly lower than the current route of manufacture.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. LC/MS analysis was performed using

(8) Ashcroft, P. C. Modified Fischer Indole Synthesis of Eletriptan; WO/2005/103035, 2005.

the following system; Hewlett-Packard 1100 with SB C18 3.0 mm ×50 mm, 1.8 μm particles; mobile phase consisting of solvent A, 0.05% TFA in water, solvent B, 0.05% TFA in acetonitrile. 0 min = 5% solvent B; 3.5 min = 100% solvent B; 4.5 min = 100% solvent B; 4.6 min = 5% solvent B; run time 5 min; column temperature 50 °C; λ = 225 nm; with Waters Micromass ZQ 2000/4000 mass detector.

Benzyl {4-[Methoxy(methyl)amino]-4-oxobutyl}methylcarbamate (14). To a solution of 4-(methylamino)butanoic acid hydrochloride **13** (30.0 g, 195 mmol) in aqueous potassium hydroxide solution (3 M, 260 mL, 780 mmol), was added the benzyl chloroformate (33.3 g, 195 mmol) and stirred for 2 h. The reaction was quenched into aqueous hydrochloric acid (5 M, 200 mL) and extracted twice with *(tert)*-butylmethyl ether (TBME) (2 × 100 mL). The combined extracts were washed with water (100 mL), dried with magnesium sulfate and filtered. Solvent was removed by distillation and the residue redissolved in dichloromethane (200 mL). Carbonyldiimidazole (32 g, 195 mmol) was added and stirred for 1 h. To the reaction was added triethylamine (27 mL, 195 mmol) followed by *N*,*O*-dimethylhydroxylamine hydrochloride, and this was stirred for 16 h. The reaction was quenched into hydrochloric acid (2 M, 200 mL), and the organic layer was washed with water (200 mL). Distillation of solvent gave the title compound (47.0 g, 160 mmol, 82% from **13**, 95.6% purity by LC/MS analysis) as a clear oil. ^{1}H NMR ($CDCl_3$): δ = 1.86−1.89 (m, 2H), 2.37−2.44 (m, 2H), 2.93 (s, 3H), 3.13−3.15 (br s, 3H), 3.33−3.37 (t, 2H), 3.59−3.63 (br s, 3H), 5.11 (s, 2H), 7.26−7.34 (m, 5H); LC/MS: R_t = 2.68 min; *m*/*z* 295 $[MH]^+$.

Benzyl [6-(1,3-Dioxan-2-yl)-4-oxohexyl]methylcarbamate (16). To a slurry of magnesium turnings (4.6 g, 190 mmol) in tetrahydrofuran (THF) (100 mL), was added a crystal of iodine, followed by 2-(2-bromoethyl)-[1,3]-dioxane (7.4 g, 38 mmol) as a solution in THF (10 mL). The reaction was heated to 65 °C with stirring and further 2-(2-bromoethyl)-[1,3]-dioxane (29.6 g, 152 mmol) was added as a solution in THF (40 mL). After heating at 65 °C for a further 1 h, the reaction was cooled to 20 °C. This freshly prepared Grignard solution was added to a solution of **14** (40 g, 136 mmol) in THF (250 mL) at 4 °C. The mixture was heated to 65 °C for 2 h, then quenched into aqueous citric acid solution (10% w/v, 250 mL), and the organic layer was concentrated at reduced pressure and redissolved in TBME (200 mL). This was then washed with the original citric acid solution followed by water (200 mL) and dried with magnesium sulfate. The mixture was filtered and concentrated under reduced pressure to give **16** (47.5 g, 136 mmol, 95%, 90.2% purity by LC/MS analysis) as a clear oil. ^{1}H NMR ($CDCl_3$): δ = 1.31−1.35 (m, 1H), 1.83−1.88 (m, 4H), 2.03−2.08 (m, 1H), 2.38−2.54 (m, 4H), 2.92 (s, 3H), 3.27−3.31 (m, 2H), 3.71−3.77 (m, 2H), 4.05−4.09 (m, 2H), 4.54−4.56 (m, 1H), 5.12 (s, 2H), 7.29−7.36 (m, 5H); LC/MS: R_t = 2.98 min; *m*/*z* 350 $[MH]^+$.

2-[2-(1,3-Dioxan-2-yl)ethyl]-1-methylpyrrolidine Fumarate (9b). To a solution of **16** (35 g, 95.5 mmol) in methanol (200 mL) was added 5% palladium on carbon (50% wet) (3.5 g) and hydrogenated at 50 °C and 60 psi of hydrogen for 16 h with stirring. The catalyst was removed by filtration through a filter aid, and the solvent was distilled at reduced pressure to give the free base as a clear oil. This was redissolved in ethyl acetate (200 mL) and methanol (20 mL), and to this was added a solution of fumaric acid (10.5 g, 95 mmol) in methanol (100 mL). The methanol was removed azeotropically by distillation and replaced with ethyl acetate. The product was granulated for 16 h then collected by filtration and dried under vacuum to constant mass to yield **9b** (20.2 g, 64.1 mmol, 64%) as a white crystalline solid. ^{1}H NMR ($(CD_3)_2SO$): δ = 1.30−1.55 (m, 5H), 1.73−1.89 (m, 4H), 1.98−2.06 (m, 1H), 2.48 (s, 3H), 2.50−2.67 (m, 2H), 3.26−3.31 (m, 1H), 3.65−3.71 (m, 2H), 3.95−3.99 (m, 2H), 4.50−4.52 (t, 1H), 6.49 (s, 2H); Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.31; H, 8.03; N, 4.43.

(5,5-Dimethyl-[1,3]-dioxan-2-ylmethyl)triethylphosponium bromide (18c). To a solution of 2-bromo-1,1-diethoxyethane (11.7 g, 59.2 mmol) in toluene (55 mL) was added neopentyl glycol (9.24 g, 88.8 mmol) followed by sulfuric acid (98%, 3.2 mL, 59.2 mmol). The mixture was heated at 110 °C for 16 h, then cooled to 4 °C and diluted with water (117 mL). The mixture was extracted with TBME (2 × 117 mL), washed with water (55 mL) and dried with magnesium sulfate. The mixture was filtered and concentrated under reduced pressure. The residue was redissolved in THF (55 mL) and triethylphosphine (1 M solution in THF) (88.8 mL, 88.8 mmol) was added and heated at 65 °C for 48 h. Solvent was removed at reduced pressure to give **18c** (17.4 g, 53.3 mmol, 90%) as a brown oil. ^{1}H NMR ($CDCl_3$): δ = 0.77 (s, 3H), 1.18 (s, 3H), 1.29−1.38 (m, 9H), 2.57−2.66 (m, 6H), 2.98−3.03 (dd, 2H), 3.51−3.53 (d, 2H), 3.63−3.65 (d, 2H), 4.97−5.03 (m, 1H).

2-[(E)-2-(5,5-dimethyl-1,3-dioxan-2-yl)vinyl]-1-methyl-1H-pyrrole (20). To a solution of **18c** (7.0 g, 21.4 mmol) in dimethylformamide (DMF) (47 mL) was added 1-methyl-1H-pyrrole-2-carboxaldehyde **19** (4.73 g, 21.4 mmol). Sodium ethoxide solution in ethanol (21%w/w, 8.8 mL, 23.5 mmol) was added and heated at 80 °C for 3 h. The reaction was quenched with water (100 mL) and extracted with TBME (2 × 50 mL). The combined organics were washed with water (50 mL), dried ($MgSO_4$), filtered and concentrated. The residue was recrystallised from ^{n}heptane (10 mL) to give **20** (3.65 g, 16.5 mmol, 77%, 97.9% purity by LC/MS analysis) as a beige solid. ^{1}H NMR ($CDCl_3$): δ = 0.79 (s, 3H), 1.26 (s, 3H), 3.55−3.58 (d, 2H), 3.66 (s, 3H) 3.70−3.73 (d, 2H), 5.01−5.03 (d, 1H), 5.97−6.02 (dd, 1H), 6.10−6.12 (m, 1H), 6.40−6.41 (m, 1H), 6.60−6.61 (m, 1H), 6.66−6.70 (d, 1H); LC/MS: R_t = 2.02 min; *m*/*z* 223 $[MH]^+$.

2-[2-(5,5-Dimethyl-1,3-dioxan-2-yl)ethyl]-1-methylpyrrolidine Fumarate (9c). To a solution of **20** (4.9 g, 22.1 mmol) in ethanol (100 mL) was added 5% rhodium on carbon (50% wet) (1 g), and the mixture was hydrogenated at 70 °C and 100 psi of hydrogen for 16 h with stirring. After this time the catalyst was removed by filtration through a filter aid, and the solvent was distilled at reduced pressure. The residue was redissolved in ethyl acetate (25 mL), and to this was added fumaric acid (2.57 g, 22.1 mmol) as a solution in methanol (25 mL). The methanol was distilled azeotropically and replaced with ethyl acetate, maintaining a volume of 50 mL. The product was granulated for 16 h then collected by filtration and dried under vacuum to constant mass to yield **9c** (7.2 g, 21.0 mmol,

95%) as a white crystalline solid. ^{1}H NMR ($(CD_3)_2SO$): δ = 0.68 (s, 3H), 1.08 (s, 3H), 1.34−1.60 (m, 4H), 1.71−1.82 (m, 3H), 1.96−2.05 (m, 1H), 2.45 (s, 3H), 2.51−2.61 (m, 2H), 3.21−3.26 (m, 1H), 3.36−3.39 (d, 2H), 3.50−3.52 (d, 2H), 4.42−4.44 (t, 1H), 6.50 (s, 2H); Anal. Calcd for $C_{17}H_{29}NO_6$: C, 59.46; H, 8.51; N, 4.08. Found: C, 59.83; H, 8.07; N, 4.38.

4-(2-Benzenesulfonylethyl)phenylamine (22). To a mixture of 4-nitrophenethyl bromide **21** (10 g, 43.5 mmol) in 2-propanol (120 mL) and water (30 mL) was added sodium benzenesulfinate (13.1 g, 65.2 mmol) and heated to 70 °C for 42 h. The reaction mixture was cooled to ambient temperature and filtered. The solid was dissolved in methanol (150 mL), and 5% Pd/C (50% wet) (1 g) was added and the mixture hydrogenated at 60 °C and 60 psi of hydrogen for 18 h. The mixture was filtered through a filter aid and concentrated. The residue was dissolved in ethyl acetate (30 mL) and hexane (250 mL) added. Filtration gave **22** (6.96 g, 34.8 mmol, 80%, 98.8% purity by LC/MS analysis) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 2.87−2.96 (m, 2H), 3.25−3.35 (m, 2H), 3.32−3.69 (b, 2H), 6.57 (d, 2H), 6.87 (d, 2H), 7.52−7.60 (m, 2H), 7.62−7.69 (m, 1H), 7.92 (d, 2H); LC/MS: R_t = 1.66 min; *m*/*z* 262 $[MH]^+$.

Oxo(2-{4-[2-(phenylsulfonyl)ethyl]phenyl}hydrazino)acetic Acid (24) (Method A). To a solution of **22** (20.2 g, 77.3 mmol) in acetonitrile (60 mL) at 4 °C was added sulfuric acid (9.4 M, 60 mL, 563 mmol) followed by sodium nitrite (5.9 g, 85.0 mmol) in aqueous solution (11.8 mL). After stirring for 1 h at 4 °C, ascorbic acid (15.0 g, 85.0 mmol) was added as an aqueous solution (30 mL). After stirring for a further 1 h at 4 °C, the reaction was warmed to ambient temperature and stirred for 16 h. After this time the reaction was diluted with water (40 mL) and extracted twice with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with water (100 mL) and dried ($MgSO_4$). The mixture was filtered and concentrated under reduced pressure to give **24** (22.3 g, 64.2 mmol, 83%, 90.9% purity by LC/MS analysis) as a red oil. ^{1}H NMR ($(CD_3)_2SO$): δ = 2.75−2.78 (m, 2H), 3..50−3.53 (m, 2H), 6.59−6.61(d, 2H), 6.95−6.97 (d, 2H), 7.62−7.66 (m, 2H), 7.71−7.75 (m, 1H), 7.90−7.92 (m, 2H), 10.54 (s, 1H); LC/MS: R_t = 2.13 min; *m*/*z* 347 $[M - H]^-$.

Calcium Bis[oxo(2-{4-[2-(phenylsulfonyl)ethyl]phenyl}-hydrazino)acetate] (24a) (Method A). 22 (22.3 g, 64.0 mmol) was dissolved in acetonitrile (100 mL) and aqueous potassium hydroxide solution (0.64 M, 100 mL, 64.0 mmol) added and stirred for 1 h. Aqueous calcium chloride solution (1 M, 32 mL, 32.0 mmol) was added, and the precipitate was granulated for 16 h. The solid was collected by filtration and dried under vacuum until constant volume to give the title compound (20.2 g, 27.5 mmol, 86%, 98.4% purity by LC/MS analysis) as a white crystalline solid. ^{1}H NMR ($(CD_3)_2SO$): δ = 2.71−2.75 (m, 2H), 3..49−3.53 (m, 2H), 6.56−6.58 (d, 2H), 6.92−6.94 (d, 2H), 7.60 (br s, 1H), 7.63−7.67 (m, 2H), 7.73−7.75 (m, 1H), 7.90−7.92 (d, 2H), 10.13 (br s, 1H); LC/MS: R_t = 2.13 min; *m*/*z* 347 $[M - H]^-$.

3-[(1-Methylpyrrolidin-2-yl)methyl]-5-[2-(phenylsulfonyl)-ethyl]-1*H*-indole (rac-7) (Method A). To a slurry of **24a** (11.7 g, 15.9 mmol) and **9b** (10.0 g, 31.8 mmol) in acetonitrile (84 mL) was added aqueous sulfuric acid (10% v/v, 1.88 M, 84 mL, 158 mmol). The solution was heated at 80 °C with stirring for 16 h, and then quenched into aqueous potassium hydroxide solution (2 M, 82 mL, 164 mmol). The product was extracted twice with ethyl acetate (2 × 200 mL), washed with water (200 mL), and dried with magnesium sulfate. The mixture was filtered and concentrated under reduced pressure. The residue was purified via flash chromatography, eluting with dichloromethane (95) ethanol (5) ammonia solution (1) to give **rac-7** (10.2 g, 13.4 mmol, 84%, 96.8% purity by LC/MS analysis). ^{1}H NMR ($CDCl_3$): δ = 1.51−1.85 (m, 4H), 2.22−2.28 (m, 1H), 2.43−2.49 (m, 4H), 2.56−2.62 (m, 1H), 3.11−3.18 (m, 4H), 3.42−3.46 (m, 2H), 6.91−6.93 (s, 1H), 7.01 (s, 1H), 7.23−7.27 (d, 1H), 7.31 (s, 1H), 7.56−7.60 (m, 2H), 7.65−7.68 (m, 1H), 7.96−7.98 (d, 2H), 8.14 (s, 1H); LC/MS: R_t = 2.30 min; *m*/*z* 383 $[MH]^+$.

3-[(1-Methylpyrrolidin-2-yl)methyl]-5-[2-(phenylsulfonyl)-ethyl]-1*H*-indole (rac-7) (Method B, One-Pot Procedure). To a solution of **22** (1.0 g, 3.83 mmol) in acetonitrile (10 mL) at 4 °C was added sulfuric acid (9.4 M, 7 mL, 65.8 mmol) followed by sodium nitrite (0.29 g, 4.20 mmol) in aqueous solution (1 mL). After stirring for 1 h at 4 °C, ascorbic acid (0.74 g, 4.20 mmol) was added as an aqueous solution (1.5 mL). After stirring for a further 1 h at 4 °C, the reaction was warmed to ambient temperature and stirred for 16 h. The mixture was diluted with water (10 mL) and **9b** (1.2 g, 3.83 mmol) was added. The reaction was heated at +80 °C for 16 h, then neutralised with aqueous potassium hydroxide solution (15 mL, 5 M, 75.0 mmol), and diluted with water (50 mL). The product was extracted twice with ethyl acetate (2 × 20 mL), washed with water (20 mL), and dried with magnesium sulfate. The mixture was filtered and concentrated under reduced pressure. The residue was purified via flash chromatography, eluting with dichloromethane (95 mL), ethanol (5 mL), and ammonia solution (1 mL) to give **rac-7** (1.1 g, 2.87 mmol, 75%, 95.9% by LC/MS analysis). ^{1}H NMR ($CDCl_3$): δ = 1.51−1.85 (m, 4H), 2.22−2.28 (m, 1H), 2.43−2.49 (m, 4H), 2.56−2.62 (m, 1H), 3.11−3.18 (m, 4H), 3.42−3.46 (m, 2H), 6.91−6.93 (s, 1H), 7.01 (s, 1H), 7.23−7.27 (d, 1H), 7.31 (s, 1H), 7.56−7.60 (m, 2H), 7.65−7.68 (m, 1H), 7.96−7.98 (d, 2H), 8.14 (s, 1H); LC/MS: R_t = 2.30 min; *m*/*z* 383 $[MH]^+$.

(2*R*)-2-[2-(1,3-Dioxan-2yl)ethyl]-1-methylpyrrolidine(2*R*,3*R*)-2,3-Bis(benzyloxy)succinic Acid. 9b (2.37 g, 7.52 mmol) was partitioned between DCM (20 mL) and 1 M potassium hydroxide solution (20 mL, 20 mmol), and the aqueous was extracted with further DCM (2 × 20 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated. The residue was redissolved in 2-butanone (7.5 mL) at 75 °C, and dibenzoyl-L-tartaric acid (2.7 g, 7.53 mmol) was added as a solution in 2-butanone (7.5 mL). The solution was cooled to 0 °C, and the product was granulated for 16 h and then collected by filtration and dried under vacuum to constant mass. The solid was recrystallised from 2-propanol (7.5 mL) to give **9d** (1.3 g, 2.63 mmol, 35%, 94% ee) as a white crystalline solid. ^{1}H NMR ($(CD_3)_2SO$): δ = 1.30−1.55 (m, 5H), 1.73−1.89 (m, 4H), 2.02−2.13 (m, 1H), 2.48 (s, 3H), 2.80−2.93 (m, 1H), 2.96−3.08 (m, 1H), 3.37−3.46 (m, 1H), 3.61−3.71 (m, 2H), 3.95−3.99 (m, 2H), 4.51−4.54 (m, 1H), 5.64 (s, 1H), 7.42−7.54 (t, 2H), 7.60−7.64 (t, 1H) 7.92−7.99 (d, 2H); Anal. Calcd for

$C_{29}H_{35}NO_{10}$: C, 62.47; H, 6.33; N, 2.51. Found: C, 62.64; H, 6.39; N, 2.46.

(*R*)-3-[(1-Methylpyrrolidin-2-yl)methyl]-5-[2-(phenylsulfonyl)ethyl]-1*H*-indole ((R)-7). To a slurry of **24a** (1.0 g, 1.35 mmol) and **9d** (1.5 g, 2.7 mmol) in acetonitrile (8 mL) was added aqueous sulfuric acid (10% v/v, 1.88 M, 8 mL, 15 mmol). The solution was heated at 80 °C with stirring for 16 h, and then quenched into aqueous potassium hydroxide solution (50 mL, 2 M, 100 mmol). The product was extracted twice with ethyl acetate (2 × 50 mL), washed with water (50 mL), and dried with magnesium sulfate. The mixture was filtered and concentrated under reduced pressure. The residue was purified via flash chromatography, eluting with dichloromethane (95 mL), ethanol (5 mL), and ammonia solution (1 mL) to give **(R)-7** (0.6 g, 0.797 mmol, 59%, 94% ee, 97.8% achiral purity by LC/MS analysis). ^{1}H NMR ($CDCl_3$): δ = 1.51−1.85 (m, 4H), 2.22−2.28 (m, 1H), 2.43−2.49 (m, 4H), 2.56−2.62 (m, 1H), 3.11−3.18 (m, 4H), 3.42−3.46 (m, 2H), 6.91−6.93 (s, 1H), 7.01 (s, 1H), 7.23−7.27 (d, 1H), 7.31 (s, 1H), 7.56−7.60 (m, 2H), 7.65−7.68 (m, 1H), 7.96−7.98 (d, 2H), 8.14 (s, 1H); LC/MS: R_t = 2.30 min; *m*/*z* 383 $[MH]^+$.

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