
Christopher P. Ashcroft,*† Paul Hellier,‡ Alan Pettman,† and Simon Watkinson†

Chemical Research and Development, Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, United Kingdom, and Process Development Centre, Pfizer Global Manufacturing, Loughbeg API Site, Loughbeg, Cork, Ireland

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 route1 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 amine 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-methylpyrrolidine5 11 and subsequent alkylation with 2-(2-bromomethyl)-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-bromomethyl)-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 olefination6 with a phosphorous ylide derived from bromoacetaldyde, followed by global deprotection 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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* christopher.ashcroft@pfizer.com.
† Pfizer Global Research and Development, U.K.
‡ Pfizer Global Manufacturing, Ireland.

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,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 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 yielded a meagre 13% of 10. It was at this point that a recent patent7 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

Fischer reaction, as the acidic conditions would reveal the free hydrazine \( \text{10} \) in situ. Oxalyl hydrazide \( \text{24} \) is not a solid and is tricky to isolate, but can be obtained as a crystalline calcium salt \( \text{24a} \) prior to running the Fischer reaction. Alternatively, a one-pot procedure was developed to take the aniline \( \text{22} \) directly through to racemic eletriptan (rac-\( \text{7} \)) (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.

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

**Conclusions**

A scalable, commercially viable alternative route for the synthesis of eletriptan (R)-\( \text{7} \) has been developed. 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
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.

Benzy1 [4-[(6-methoxymethyl)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). Carboxyldimidazole (32 g, 195 mmol) was added and stirred for 1 h. To the reaction was added triethylamine (27 mL, 195 mmol) followed by N,N-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 concentrated at reduced pressure and redissolved in THF (10 mL). The reaction was heated to 65 °C with stirring and further 2-(2-bromoethyl)-[1,3]-dioxane (40 g, 136 mmol) in THF (250 mL) at 4 °C. This freshly prepared Grignard solution was added to a solution of 18c (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 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. 1H NMR (CDCl3): 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).

Benzyl [6-(1,3-Dioxan-2-yl)-4-o xoethyl]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. 1H NMR (CDCl3): 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: Rf = 2.98 min; m/z: 350 [MH]+.

2-[2-(1,3-Dioxan-2-yl)ethyl]-1-methylpyrro lidine Fumarate (9c). 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 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 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 9c (7.2 g, 21.0 mmol,
95%) as a white crystalline solid. 1H NMR (CDCl3): 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 C17H29NO6: C, 59.46; H, 8.51; N, 4.08. Found: C, 59.83; H, 8.07; N, 4.38.

4-[2-Benzensulfonyl]ethylphenylamine (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.

Oxo(2-{4-[2-(phenylsulfonyl)ethyl]phenyl}hydrazino)acetate (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, 56.8 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 (0.74 g, 4.20 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 (MgSO4). The mixture was filtered and concentrated under reduced pressure. The residue was dissolved in acetonitrile (100 mL) and aqueous potassium hydroxide solution (15 mL, 5 M, 75.0 mmol) was added, and the precipitate was granulated for 16 h and then collected by filtration and dried under reduced pressure. The residue was purified via flash chromatography, eluting with dichloromethane (95%) ethanol (5%) and ammonia solution (1 mL). 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 (15 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%), ethanol (5%), and ammonia solution (1 mL) to give rac-7 (1.1 g, 2.87 mmol, 75%, 95.9% by LC/MS analysis). 1H NMR (CDCl3): 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: Rf = 2.30 min; m/z 383 [M+H]+.

3-{(1-Methylpyrrolidin-2-yl)methyl}-5-[2-(phenylsulfonyl)ethyl]-1H-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 (15 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%), ethanol (5%), and ammonia solution (1 mL) to give rac-7 (1.1 g, 2.87 mmol, 75%, 95.9% by LC/MS analysis). 1H NMR (CDCl3): 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: Rf = 2.30 min; m/z 383 [M+H]+.

2-(1,3-Dioxan-2-yl)-1-methylpyrrolidine (2R,3R)-2,3-Bis(benzoxyl)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 (MgSO4), filtered, and concentrated. The residue was redissolved in 2-butanol (7.5 mL) at 75 °C, and dibenzoyl-t-tartaric acid (2.7 g, 7.53 mmol) was added as a solution in 2-butanol (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. 1H NMR (CDCl3): 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 (m, 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]-1H-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\(_3\)): \(\delta = 1.51–1.85\) (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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