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Use of a Titanium Thienyl Anion and a Simple Procedure for Introducing a Thiol Group into Thiophene in the Development of a Manufacturing Route to the 5-Lipoxygenase Inhibitor ZD4407

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Abstract:

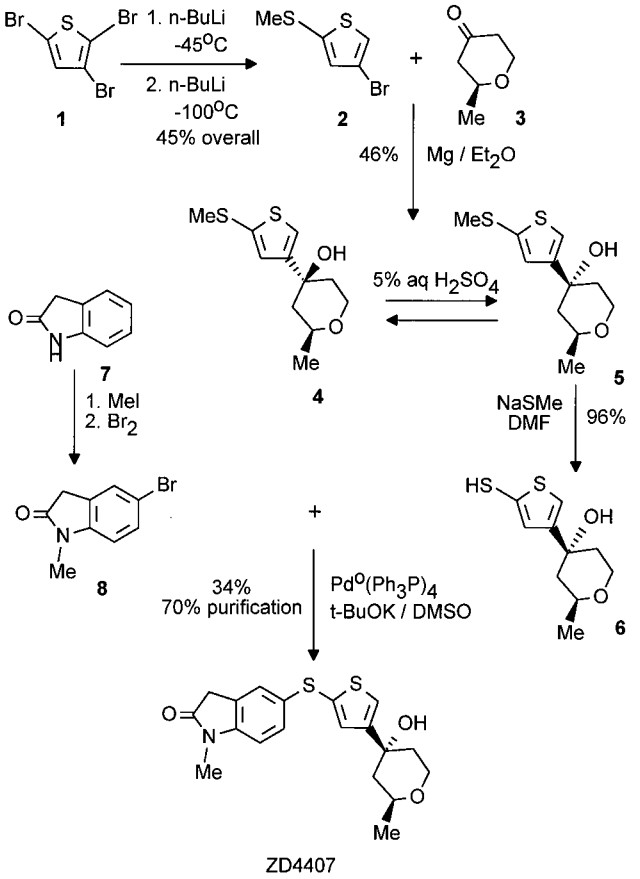
Process development has been conducted to identify a synthetic route to the 5-lipoxygenase inhibitor ZD4407 that could be used for pilot plant manufacture. Efficient and environmentally acceptable carbon-functionalisation of the 3-position of thiophene using readily available 3-bromothiophene has been achieved using a titanium carbanionic intermediate. An efficient functionalisation of the 5-position with a thiol group has also been realised using dimethyl disulphide, where the side product of the functionalisation reaction is used *in situ* as the reagent for the subsequent deprotections, thereby considerably reducing the impact on the environment.

Introduction

In view of the powerful spasmogenic actions of leukotrienes in vascular and bronchial tissue, drugs which block their biosynthesis by inhibiting 5-lipoxygenase may have therapeutic potential in a variety of inflammatory conditions including inflammatory arthropothies, asthma, psoriasis, and inflammatory bowel disease. One such compound is ZD4407 which was initially synthesised on a 100 L pilot plant scale by a research-based route from 2,3,5-tribromothiophene (**1**) using the route outlined in Scheme 1.[1]

Monolithiation of **1** by *n*-butyllithium at −100 °C followed by quenching of the resulting anion with 2-propanol gave 2,4-dibromothiophene. Without isolation, this was further lithiated with a second equivalent of *n*-butyllithium at −100 °C to yield a second anion, which was quenched with dimethyl disulphide to yield 4-bromo-2-(methylsulphanyl)thiophene **2**. The Grignard reagent prepared from **2** by an entrainment method[2] using 8 equiv of dibromoethane in diethyl ether, reacted with (*S*)-pyranone **3**[3] to give a mixture of diastereomers **4** and **5**, which could be equilibrated to a 1:9 mixture using dilute aqueous sulphuric acid. Purification by chromatography yielded the desired isomer, *R*,*S* alcohol **5**, which was demethylated using sodium methanethiolate in DMF to yield the free thiol **6**. The synthesis was completed using a palladium-catalysed coupling of thiol **6** with 1-methyl-5-bromo-2-oxindole (**8**)[4] to give ZD4407.

Scheme 1. **Research route to ZD4407**



Whilst this approach was acceptable for producing modest amounts of ZD4407 to enable the biological activity of the compound to be explored, it would give rise to serious difficulties on a manufacturing scale. For example:

(a) Very low temperatures (−100 °C) are essential to minimise the rearrangement of thienyl anions since they are readily transformed into mixtures of other isomers (the so-called "halogen dance").[5] The initial assessment of scale-up was performed on a pilot plant scale (100 L) with a batch size (4 kg of **1**) chosen so that, having cooled the solution of **1** in THF to −100 °C by the direct injection of liquid nitrogen, the exotherms (up to −75 °C for the first debromination and −80 °C for the second) caused by the

(1) Bird, T. G. C.; Crawley, G. C.; Large, M. S.; Plé, P. European Patent Application No. 0623614 A1.

(2) For general entrainment procedures, see: Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1969; Vol. 1, p 417. Pearson, D. E.; Cowan, D.; Beckler, J. D. *J. Org. Chem.* **1959**, *24*, 504. For procedures specific to 3-bromothiophenes: see Gronowitz, S.; Pettersson, K. *J. Heterocycl. Chem.* **1976,** *13*, 1099.

(3) Holt, R. A.; Rigby, S. R.; Waterson, D. Pending British Patent Application No. 23924.0/95.

(4) Kisteneva, M. S. *Zh. Obshch. Khim.* **1956**, *26*, 2019; *Chem. Abstr.* **1957**, 5044a.

(5) Fröhlich, H.; Kalt, W. J. Org. Chem. **1990**, *55*, 2993 and references cited therein. Van der Plas, H. C.; de Bie, D. A.; Geurtsen, G.; Reinecke, M. G.; Wayne Adickes, H. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 33.

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rapid addition of *n*-butyllithium solution (to minimise rearrangement) did not raise the temperature of the batch sufficiently to allow the rearrangement reaction to occur at a significant rate.

(b) When bromine occupies the 3-position in thiophene, it is very unreactive towards magnesium and consequently this reaction requires the use of an entrainment procedure with 8 equiv of 1,2-dibromoethane in diethyl ether.[2] Although diethyl ether is an undesirable solvent for plant use, it was essential to use it here, rather than THF, to avoid the formation of unstirrable slurries that result from the low solubility of magnesium bromide in "practical" volumes of THF.

(c) The 1:9 mixture of alcohol diastereomers **4** and **5** required separation by chromatography.

(d) The mixture of sodium hydride and DMF, used to generate sodium methanethiolate for the high-temperature demethylation reaction, is thermally unstable,[6] and the mole of dimethyl sulphide liberated requires very efficient containment, since it has an extremely low odour threshold of 10^{-3} ppm.

(e) The coupling of thiol **6** with **8**,[4] using the catalyst tetrakis(triphenylphosphine)palladium, is low yielding, and the product always requires chromatographic purification.

Scale-up of the synthesis for the next stage of development required a revised strategy for assembling the molecule.

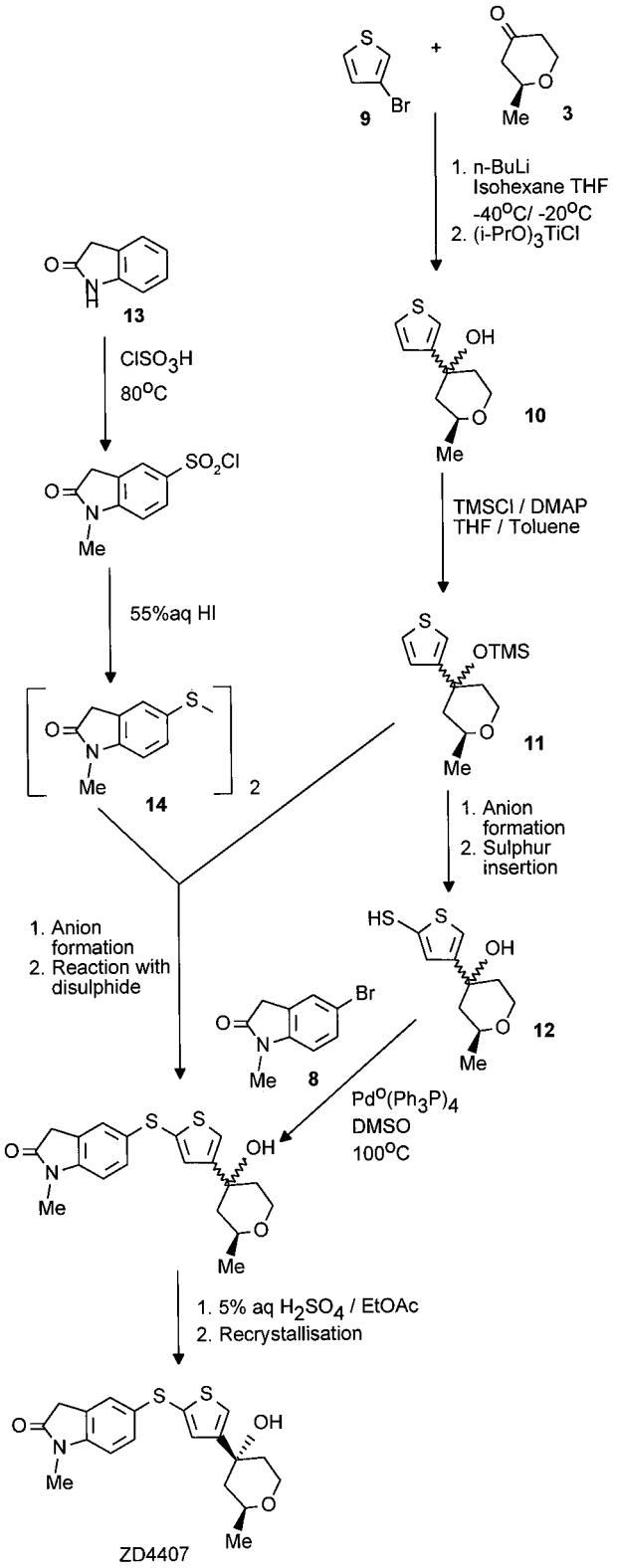
Results and Discussion

General Considerations in Choosing the Route. Of prime importance in the development of any route in a fast-track development are the cost and availability of the key raw materials. Following exploratory discussions with Shell Synthetic Chemicals Ltd it was clear that 3-bromothiophene (**9**) would be a particularly attractive starting material since it possessed bifunctionality, *i.e.*, bromine at the 3-position and an opportunity to produce an anion at the 5-position, and it was already being manufactured at a commercially realistic price by a recently developed environmentally friendly process.

Since most oxindole derivatives are highly crystalline, it seemed likely that the best way to introduce crystallinity into a synthetic route, (the original route contained few crystalline intermediates) was to introduce the oxindole fragment as early as possible. The flaw in this strategy lay in the fact that the carbanion chemistry being used to attach the pyranol fragment was not expected to be compatible with the presence of a lactam group.

Another factor considered was that although the central sulphur atom of the target molecule could in principle be attached to either the thiophene or the oxindole fragments, it was anticipated that an attachment to the latter would be less likely to yield an odorous intermediate, particularly if it was used in the form of a crystalline disulphide such as **14**. Therefore, if the pyranol fragment could be attached to thiophene at the 3-position, the corresponding anion at the 5-position would serve either as a precursor to the synthetically useful thiol **12** or as a substrate to react with the oxindole disulphide **14**.

Scheme 2. **Routes to ZD4407 from 3-bromothiophene**



The above reasoning therefore led us to begin assessment of the route outlined in Scheme 2.

Reaction of 3-Bromothiophene (9) with (*S*)-Pyranone 3.[3] One apparently straightforward way to create the 3-thienyl anion would be to react **9** with *n*-butyllithium via a lithium−halogen exchange reaction.[7] However, 3-thienyllithium species readily rearrange above −70 °C to the more

(6) *Bretherick's Handbook of Reactive Chemical Hazards*; Butterworth-Heinemann Ltd: Oxford, 1992; p 1181 and references cited therein.

(7) Wu, X.; Chen, T.; Zhu, L.; Rieke, R. D. *Tetrahedron Lett.* **1994**, *35*, 3673.

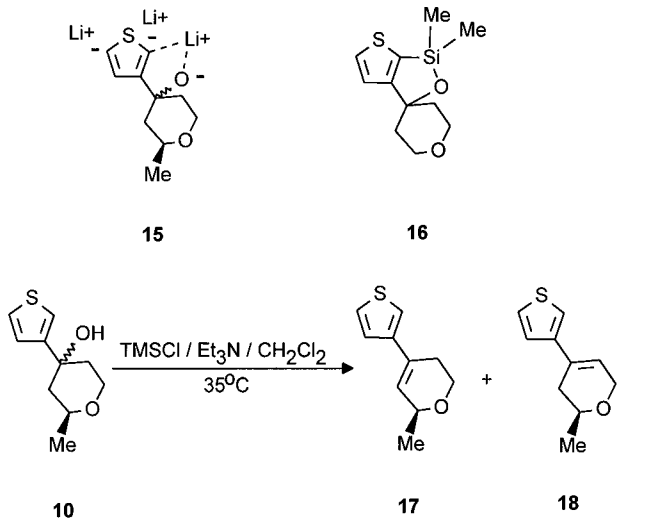
stable 2-thienyllithium species, and it is generally difficult to prevent formation of the corresponding 2-thienyl derivatives[5] (see our observations below). Although Grignard reagents can be prepared from 3-bromothiophenes without substantial rearrangement, by entrainment methods which use 1,2-dibromoethane in diethyl ether,[2] and indeed 3-bromothiophene gave a Grignard reagent that reacted with (*S*)-pyranone **3**[3] to give a mixture of the *S*,*S* and *R*,*S* diastereomeric products, **4** and **5**, this approach possessed all of the disadvantages mentioned above. The problem could not be overcome by initiation of the Grignard reaction in anisole or dimethoxyethane. Consequently an alternative procedure was required, and this was achieved using titanium chemistry.

Using a minor adaptation of a recently published procedure[7] for the preparation of 3-lithiothiophene from 3-bromothiophene and *n*-butyllithium (isohexane was substituted for hexane since it is less toxic[8]), the anion was prepared and reacted with (*R*)-pyranone[9] to give a 3.5:1.0 mixture of the 3- and 2-regioisomers, respectively. The majority of the 2-isomer was probably formed from thiophene generated via enolisation of the (*R*)-pyranone.[9] Equilibration of thiophene and 3-lithiothiophene then gave the 2-lithio species. Rieke,[7] however, claimed the absence of 2-isomeric impurities, but did not include any carbonyl compounds among the electrophiles studied. Consequently it was thought desirable to reduce the basicity of 3-lithiothiophene, by transmetalation with chlorotitanium triisopropoxide,[10] to minimise enolisation of the pyranone and then react the resulting titanium derivative with (*R*)-pyranone.[9] Rather surprisingly, although the benefits resulting from the reduced basicity of the anion were realised, an expected decrease in reaction rate was not observed. There was less than 1% of the 2-regioisomer present. Further optimisation of both the stoichiometry and the temperatures used combined with scale-up, as described in the Experimental Section, gave an isolated but crude yield of 86.2% with no significant formation of the 2-thienyl analogues.

Although the ratio of desired *R*,*S* to undesired *S*,*S* isomer at the end of the reaction was 6.7:1, equilibration occurred during the drown-out into 2 N aqueous hydrochloric acid and the associated separations to give a 1.8:1 mixture. This was not considered detrimental since it had already been decided to continue the synthesis with a mixture of diastereomers and to use a known equilibration of the benzylic diastereomers of the target molecule ZD4407 (see later section) to isolate the desired diastereomer ZD4407.

Concentration of the reaction mixture 3-fold, which was desirable for scale-up, gave no adverse effect on the yield, but this advantage could not be extended into the workup because titanium salts precipitated.

Scheme 3



As far as we are aware, titanation of the thiophene ring has not been reported previously, and it is thus an excellent example of the moderation of the activity of a highly basic anion to a level where its reaction with a ketone is not complicated by α-deprotonation/enolisation of the ketone or elimination of the product. The absence of a reduction in the reaction rate of a titanium species with a ketone, brought about by reducing basicity while retaining nucleophilicity, was unexpected.

Protection of Alcohol 10 as Its Silyl Ether. Early lithiation studies carried out on alcohol **10** revealed that, in order to avoid complete lithiation at the undesired 2-position of the thiophene ring, it was necessary to protect the tertiary alcohol as a methyl or TMS ether. Attempts to prepare and use the trianion **15** and the cyclic siloxane **16** (from dichlorodimethylsilane) were unsuccessful (Scheme 3).

Although TMS was synthetically the more attractive protecting group, early work had revealed that the reaction could not be satisfactorily achieved with TMSCl/NaH or TMSCl/*n*-BuLi, and consequently, the expensive and commercially inaccessible sodium hexamethyldisilazide was required as the base. This reagent also presented an additional problem since the side product, hexamethyldisilazane, could not be removed easily.

Development of the procedure initially provided a satisfactory small-scale process using TMSCl/Et_3N which on scale-up by a factor of 10 gave almost exclusively the elimination products **17** and **18**, which were identified by GC/MS $m/z = 180$.

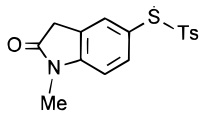
However, TMSCl/DMAP in THF gave a clean reaction which scaled up satisfactorily to give an 86.8% yield of the desired TMS ether in solution.

Introduction of a Sulphur-Bearing Oxindole Fragment. Oxindole disulphide **14** prepared by the route in Scheme 2 was initially chosen for the introduction of the oxindole fragment because it was not expected to possess odour problems and it represented previously successful chemistry within Zeneca.[1] It was appreciated at the outset that this approach used the oxindole fragment inefficiently; however, recovery of the thiol side product and the use of an unsymmetrical derivative such as the tosyl ester **19** were possible ways of improving efficiency.

(8) Occupational Exposure Limits (OEL) for *n*-hexane and isohexane over 8 h are 20 and 1000 ppm, respectively.

(9) Although the *S* configuration was required in the target molecule development work was carried out on the *R*, isomer which was available at the time. Since the procedure used to prepare (*S*)-pyranone **3** also gave ready access to equivalent amounts of (*R*)-pyranone, it was strategically highly efficient to carry out the development work on the (*R*)-pyranone and carry out the production of bulk drug on (*S*)-pyranone **3**.

(10) For an excellent review, see: Ferreri, C.; Palumbo, G.; Caputo, R. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 1, Organotitanium and Organozirconium Reagents, p 145 and references cited therein.



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In practice, attempts to react the oxindole disulphide **14** with the 5-anion of silyl ether **11** (or in a model reaction with 2-thienyllithium) gave very poor yields. The evidence available (see the later section on the coupling reaction) suggested that this lack of success could be attributed to the acidity of the oxindole benzylic protons; all attempts to use protection of this position, for example with the ethoxyformyl group, were disappointing. Consequently the alternative approach of attaching sulphur to the thiophene fragment was explored.

Introduction of Sulphur at the 5-Position of the Silyl Ether (11). There were two major problems: (a) the regiospecific generation of the 5-anion **20** (Scheme 4) and (b) the identification of a readily available, inexpensive reagent to convert this anion to the 5-thiol.

A comprehensive study of procedures to generate the 5-anion **20** was conducted by quenching reaction mixtures with excess dimethyl disulphide and monitoring the immediate reaction by NMR and/or GLC. Parameters explored included bases such as LDA and *n*-, *sec*-, and *tert*-butyllithium in combination with a variety of additives such as TMEDA, THF, and Et_3N, with a range of stoichiometries in a variety of solvents at various temperatures.

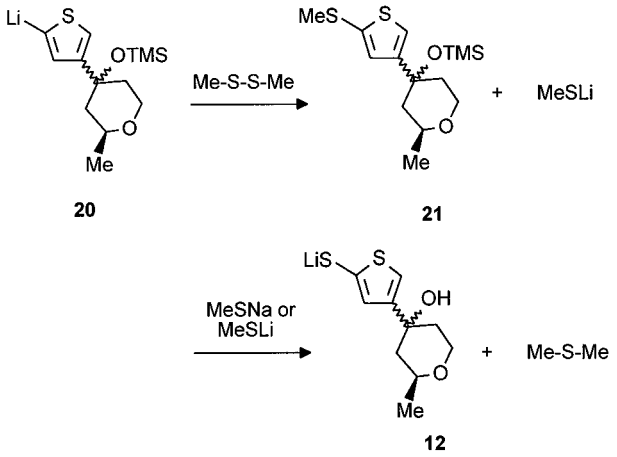
Although much of the early work was disappointing, a step improvement was observed when substantial quantities of THF (*e.g.*, 50% v/v) were introduced into the reaction mixture. The best reactions initially used *tert*-butyllithium, an expensive and hazardous reagent, but subsequently conditions were found using *n*-butyllithium, which gave equally high yielding, clean and regiospecific reactions.

Having generated the anion **20** efficiently, attention was then transferred to its reaction with the oxindole disulphide **14** (see previous section) and also a variety of reagents previously used to introduce the thiol group, *e.g.*, 4-nitro- and 2,4-dinitrobenzenesulphenyl chloride and tetraisopropylthiuram disulphide. Results were disappointing.

Since the only reagent that introduced sulphur efficiently to afford **21** was the analytical tracer dimethyl disulphide, attention was redirected towards developing a manufacturing process using this reaction. Accordingly a high-yielding procedure using solid sodium methanethiolate in *N*-methylpyrrolidinone (NMP) was developed to simultaneously demethylate and remove the TMS group from the thioether **21** to provide thiol **12**, which was known to react acceptably with **8**.[4]

Although the choice of route now appeared clear, solid sodium methanethiolate could not be purchased inexpensively in large quantities and the commercially available aqueous and methanolic solutions gave inferior reactions. The disposal of hydrogen saturated with methanethiol, from an *in situ* generation using the reaction of sodium hydride and commercially available methanethiol, would require capital expenditure for efficient scrubbing equipment etc. and was environmentally unattractive (odour threshold 10^{-3} ppm). There was also an issue reported by our hazards group

Scheme 4



20 **21** **12**

of the potential thermal instability of sodium hydride and NMP mixtures, analogous to the DMF situation mentioned earlier.[6]

A significant advance occurred when it became apparent that the side product from the reaction of dimethyl sulphide with the lithiated thiophene species, *i.e.*, lithium methanethiolate, might serve as a substitute for sodium methanethiolate and thus remove both the environmental problem of its disposal and the commercial problem of the supply of the latter. The crude reaction mixture was therefore distilled in the presence of NMP to remove the more volatile solvents, THF, toluene, and hexane, and on further heating to 130 °C, the desired demethylation and removal of the TMS group proceeded cleanly (Scheme 4). The desired thiol was separated efficiently from neutral impurities by extraction into base.

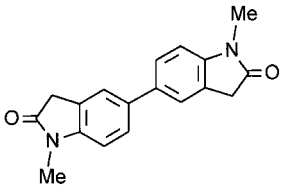
The earlier work on demethylation with solid sodium methanethiolate had revealed that optimum results were achieved using 1.5 equiv of the reagent. Consequently further optimisation was introduced by using 1.5 equiv of *n*-butyllithium (optimum conditions for the formation of the 5-anion), 2.17 equiv of dimethyl disulphide in one addition, and a further 0.5 equiv of *n*-butyllithium to generate the remaining lithium methanethiolate required for the demethylation and removal of the TMS group. Under these conditions, the desired deprotection of the TMS group occurred simultaneously with the demethylation reaction, thereby saving a synthetic step. The overall yield from silyl ether **11** to crude thiol **12** was 77%.

Similar conditions for the generation of the 5-anion were subsequently linked with its reaction with elemental sulphur, and after reduction of higher sulphides with sodium borohydride a good yield of thiol **12** was also observed; nevertheless, this procedure was not optimised since development of the product had meanwhile been put on hold.

Coupling Reaction of Oxindole 8 and Thiol 6. (Note that the work described here was carried out on the single diastereomer **6** (Scheme 1) and not on the mixture of diastereomers **12** (Scheme 2)). Reaction of *R,S* thiol **6** with 1.2 equiv of **8**[4] in DMSO in the presence of 0.1 equiv of tetrakis(triphenylphosphine)palladium and 1.054 equiv of potassium *tert*-butoxide at 100 °C gave a complex mixture of products containing about 55% of the desired product ZD4407 (41% yield after chromatography). Both of the

starting materials were consumed completely in this reaction, and it was not possible to increase the reaction yield further by changing parameters such as time, temperature, and molar ratio. A major dimeric byproduct **22** of the coupling reaction which was characterised by MS $m/z = 292$ and H^1 and C^{13} NMR had chromatographic properties very similar to those of ZD4407 and was consequently difficult to remove. Since isolation of pure product was only possible by column chromatography, this procedure, although suitable for operation on a small scale to support the initial development work, was unsuitable for manufacture on a larger scale.

A model reaction of 1-methyl-3,3-dimethyl-5-bromo-2-oxindole with *R,S* thiol **6** gave the dimethyl analogue of ZD4407 smoothly, suggesting that the acidic protons in the 3-position were responsible for the low yield. Two other bromooxindoles protected at the 3-position were prepared (the ethoxyformyl and enamine derivatives), and both of these coupled smoothly with *R,S* thiol **6** to give the corresponding derivatives of ZD4407 in *ca.* 70% yield. Unfortunately, it was not possible to remove these protecting groups, and so there was no synthetic advantage.



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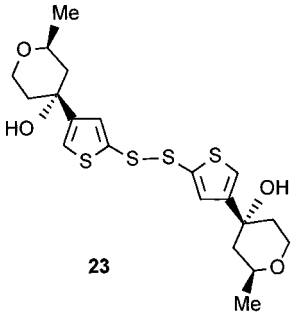

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Replacement of the palladium catalyst by [1,2-bis-(diphenylphosphino)benzene]nickel(II) bromide, which was prepared by refluxing anhydrous nickel(II) bromide with *o*-phenylenebis(diphenylphosphine),[11] gave a clean reaction in NMP at 150 °C using 0.03 equiv of the catalyst to afford ZD4407 in a 42% yield after chromatography. A major byproduct was the disulphide **23** of *R,S* thiol **6**. Although control of this oxidation would be expected to provide a marked improvement in the yield, active development of the compound ceased before this was pursued (Table 1).

Since the reaction of trialkyl stannyl sulphides with aryl bromides under Heck conditions has been shown to be an effective procedure for the formation of Ar−S−Ar bonds,[12] *R,S* thiol **6** was treated with sodium hydride in dimethoxyethane at 5−10 °C and the resulting thiolate quenched with tributyl tin chloride. Reaction of the tin thiolate with **8**[4] at reflux gave ZD4407 in a yield of 75% after chromatography. Although the improved yield and relatively simple chromatography (compared to that with the palladium-catalysed reaction) represented a significant improvement to the coupling reaction, tin levels in both the final product and effluent would nevertheless be obvious concerns.

Combining the trialkyltin reagent with the nickel catalyst gave a disappointing 31% yield of ZD4407.

(11) Cristau, H. J.; Chabaud, B.; Chàne, A.; Christol, H. *Synth. Commun.* **1981**, 892.

(12) Kosugi, M.; Ogata, T.; Terada, M.; Sano, H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3657. Carpita, A.; Rossi, R.; Scamuzzi, B. *Tetrahedron Lett.* **1989**, *30*, No. 20, 2699.

Equilibration of the Diastereomers of ZD4407. The conversion of a mixture of the diastereomers of thiol **12** to ZD4407 unavoidably gives a mixture of diastereomeric products which would require equilibration/purification. A sample of the equilibrium mixture of ZD4407 diastereomers was prepared by equilibrating diastereomerically pure ZD4407 to a 92:8 mixture in ethyl acetate and dilute aqueous sulphuric acid at 25 °C for 24 h. The resulting product was crystallised four times from ethyl acetate to give a 43% recovery of ZD4407 containing less than 0.5% of the unwanted benzylic diastereomer.

Table 1. **Equilibration of ZD4407 diastereomers**

recryst	stage recovery, %	accumulative recovery, %	level of *S,S* diastereomer, %
			8.0[a]
1	71	71	4.9
2	86	60	1.5
3	86	51	0.7
4	85	43	0.3

[a] Starting material.

The various mother liquors were combined and equilibrated to a 9:1 mixture of diastereomers which crystallised with difficulty. In principle, it is possible to use the mixture of diastereomers, and to recover and reuse material from the filtrates, but the process would be tedious on a production scale. A far more attractive strategy would be to allow the desired diastereomer to crystallise under equilibration conditions; active development of the compound ceased before this was pursued.

Conclusions

1. Titanium chemistry is an inexpensive and environmentally friendly means of stabilising and moderating the reactivity of 3-thiophene anions so that they can be used effectively in addition reactions with ketones.

2. The two-stage reaction of dimethyl disulphide with 2-thiophene anions is an inexpensive and environmentally efficient procedure for the introduction of the thiol group into the 2-position of thiophenes. It may have a wider application with other aromatic carbanions.

3. It is worth emphasising that the undesired enantiomer from a resolution can frequently be used for development work thereby conserving the desired enantiomer for manufacture of the target molecule.

4. Further development of the palladium-catalyzed coupling reaction and the crystallisation of ZD4407 under equilibrating conditions would be required to permit further scale-up of this route to ZD4407.

Experimental Section

Structure assignments of intermediates and isomeric mixtures thereof were confirmed by ^{1}H NMR, ^{13}C NMR, and GC/MS or LC/MS where appropriate . Relative amounts and strengths (w/w unless specifically referred to as w/v) were estimated by GC and/or HPLC using reference samples previously assessed by ^{1}H NMR. The structure of the target molecule ZD4407 has been confirmed unambiguously by a

wide variety of physical measurements (400 MHz NMR in particular), the more important ones of which are described below. Unless specified otherwise in the text, all reactions were carried out under an inert atmosphere of argon or nitrogen. GC analysis for the preparations of **10** and **11** using a C19 internal reference standard at 0.52% w/v: column, DB1 30M, 0.25 mm i.d.; injector temperature, 230 °C; programme, 50 °C for 5 min, 50−130 °C at 25 °C/min, 130 °C for 5 min, 130−200 °C at 10 °C/min, 200 °C for 3 min; solvent, dichloromethane; flow rate, 1 mL/min. HPLC analysis for the preparation of **21**: column, Hichrome Spherisorb S5ODS-2 25 cm, 4.6 mm i.d.; eluent, acetonitrile/water, 70:30 v/v; flow rate, 2.0 mL/min; UV detection, 235 nm. HPLC analysis for the preparation of **12**: column, Hichrome Spherisorb S5ODS-2 25 cm, 4.6 mm i.d.; eluent, acetonitrile/water, 50:50 v/v; flow rate, 1.3 mL/min; UV detection, 235 nm. HPLC analysis for the coupling of **8** and **12**: column, Hichrome Spherisorb S5ODS-2 25 cm, 4.6 mm i.d.; eluent, acetonitrile/water/TFA/triethylamine, 100:100:0.2:0.2 v/v; flow rate, 1.3 mL/min; UV detection, 235 nm. Moisture analysis of solvents: Mitsubishi Moisture Meter CA-05. Commercial 3-bromothiophene was purchased from Shell Synthetic Chemicals or Aldrich and was used as received. Other reagents and solvents were laboratory grades and used as received. THF was an anhydrous stabiliser free grade[13] (typically 0.013% w/w water). Toluene was typically 0.022% w/w water.

***R* Analogue of Alcohol 10[9] (Mixture of Diastereomers).** A solution of **9** (0.46 L, 0.802 kg, 6.93 mol) dissolved in isohexane (2.8 L) was added with stirring over 70 min to a solution of *n*-butyllithium in hexanes (2.76 L of a 2.5 M solution, 6.90 mol) at −40 to −45 °C to give a clear pale yellow solution. Dry THF (0.8 L) was added over 70 min at less than −40 °C; halfway through this addition a white solid precipitated. The slurry was stirred for 75 min at −40 °C. After a subsequent addition of a solution of chlorotitanium isopropoxide (1.796 kg, 6.89 mol) in isohexane (1.034 L) over 55 min at −40 to −45 °C, some solid material adhering to the vessel wall was washed down with an additional portion of isohexane (0.1 L) and the orange heterogeneous mixture was warmed to 21 °C and held at 21 °C for 30 min, by which time it had become clear and brown. The reaction mixture was cooled to −20 °C, (*R*)-pyranone[9] (epimer of (*S*)-pyranone **3**) (0.376 kg, 3.30 mol) was added over 15 min at −17 to −22 °C, and the reaction mixture was stirred for 75 min at −20 °C. GC analysis after 60 min confirmed that the reaction was complete, and 10 min later the reaction mixture was added over 10 min at −20 °C to a rapidly stirred mixture of dichloromethane (4.0 L) and 2 N aqueous hydrochloric acid (0.6 L) at 12 °C. The temperature rose from 12 to 19 °C during the addition. The organic phase obtained on separation was washed with water (4.0 L) and evaporated at 30−40 °C under reduced pressure to one-quarter volume. Toluene (0.8 L) was then added and evaporation continued in a water bath at 40 °C under reduced pressure, until there was a significant drop in distillation rate. The yield of alcohol **10** at 100% strength (0.564 kg) in the toluene concentrate (1.80 kg) was 86.2% based on (*R*)-pyranone[9] (epimer of (*S*)-pyranone **3**). GC method as above: retention times, (*R*)-pyranone, 2.45 min; **9**, 3.06 min; diastereomers of **10,** 11.80 and 12.16 min; nonadecane (C19 standard), 19.2 min.

***R* Analogue of Silyl Ether 11[9] (Mixture of Diastereomers).** The oil obtained by evaporation of a toluene solution of the *R* analogue of alcohol **10** (40 mL, 500 mg/mL, 0.10 mol) at 70 °C under vacuum and redissolved in dry unstabilised[13] THF (50 mL) and toluene (20 mL) was added to a stirred mixture of DMAP (18.5 g, 0.15 mol) and dry unstabilised[13] THF (100 mL). Additional THF[13] (50 mL) was added, and trimethylsilyl chloride (16.4 g, 0.15 mol) was added slowly, giving a white precipitate. The mixture was heated and stirred at reflux for 3 h 40 min before being cooled and added to a stirred mixture of toluene (150 mL) and water (20 mL). After stirring for 10 min the upper organic phase was separated, washed with water (50 mL), filtered through Celite, and distilled at 70 °C under vacuum to a concentrate of about 50%, which was assayed by HPLC. The yield of silyl ether **11** at 100% strength (23.2 g) was 86.8%. GC method as above: retention times, (*R*)-pyranone, 2.45 min; **9**, 3.06 min; DMAP, 8.3 min; diastereomers of **11**, 13.96 and 14.12 min; nonadecane (C19 standard), 19.2 min.

***R* Analogue of Thiol 12[9] (Mixture of Diastereomers).** A solution of the *R* analogue of silyl ether **11** diastereomers in toluene (83 mL, 122 mg/mL, 0.0374 mol) was evaporated below 45 °C to 20 mL under vacuum. A solution of the resulting oil in dry toluene (21.5 mL) and dry unstabilised[13] THF (41.5 mL) was lithiated at −40 ± 2 °C under an argon atmosphere by the addition of *n*-butyllithium (21.9 mL of a 2.56 M solution in hexanes, 0.056 mol) over 20 min, and the mixture was stirred for an additional 1.5 h at 40 ± 2 °C. Monitoring of the anion formation was carried out by the HPLC method described above after quenching samples into dimethyl disulphide: retention times, toluene, 3.09 min; diastereomer 1 and 2 of **11**, 6.18 and 8.03 min, respectively; diastereomers 1 and 2 of **21**, 8.9 and 11.76 min, respectively. Dry dimethyl disulphide (7.3 mL, 0.0811 mol) was then added at −40 ± 2 °C and, after a 30 min hold at −40 ± 2 °C, *n*-butyllithium (7.3 mL of a 2.56 M solution in hexanes, 0.0187 mol) was added over 5 min at 40 ± 2 °C and the mixture allowed to warm to 20 °C. *N*-Methyl-2-pyrrolidinone (NMP) (20 mL) was added, and THF and toluene (total volume 50 mL) were removed by distillation *in vacuo*. Additional NMP (50 mL) was added and the mixture heated to 130° C for 3 h under a slow stream of nitrogen, at which point the demethylation reaction and removal of the TMS group were complete. After cooling to 20 °C the reaction was quenched with water (200 mL) and dichloromethane (60 mL), and after separation of the layers, the aqueous phase was acidified to pH 2 at 10−20 °C with 2 M aqueous hydrochloric acid (34.2 mL) and then extracted immediately with methyl *tert*-butyl ether (MTBE) (2 × 150 mL). The MTBE extracts were washed with water (50 mL), saturated aqueous brine (50 mL), and water (50 mL) and filtered through a Celite pad (10 g), which was washed with additional MTBE (10 mL). The combined MTBE extracts were diluted with toluene (20 mL) and evaporated under vacuum at 40 °C to an oil. The yield of crude thiol **12** at

(13) Unstabilised THF was used to avoid unexpected complications in early development and would normally have been developed out later.

100% (6.64 g) was 77.1%. HPLC method as above: retention times, des-TMS diastereomers 1 and 2 of **11**, 3.73 and 4.56 min, respectively; diasteromers 1 and 2 of **12**, 3.15 and 3.81 min, respectively.

Coupling of Thiol 6 to 1-Methyl-5-bromo-2-oxindole (8).[4] (Note that the work described here was carried out on the single diastereomer **6** (Scheme 1) and not on the mixture of diastereomers **12** (Scheme 2)). Potassium *tert*-butoxide (9.24 g, 0.0823 mol) was added to a solution of thiol **6** (18.0 g, 0.0781 mol) in dry DMSO (400 mL) under a nitrogen atmosphere and the solution stirred at 20 °C for 15 min. **8**[4] (21.2 g, 0.0938 mol) was then added, immediately followed by tetrakis(triphenylphosphine)palladium (8.99 g, 0.0078 mol). The mixture was stirred and heated at 100 °C for 1.5 h, when the cooled solution was added to water (700 mL) and the product extracted into dichloromethane (4 × 200 mL). The organic extracts were washed with water (4 × 200 mL) followed by saturated aqueous sodium chloride (200 mL), and the solvent was evaporated to yield a dark brown solid, which was purified by chromatography on silica gel (300 g of Merck 9385), eluting with dichloromethane followed by 5% acetone in dichloromethane and then 10% acetone in dichloromethane. The chromatography was monitored by TLC, and the appropriate fractions were combined and evaporated to give ZD4407 crude as a yellow solid. The yield at 100% (12.0 g) was 41% (97.8% by area-normalised HPLC). HPLC method as above: retention times, thiol **6**, 4.4 min; ZD4407, 4.8 min.

The solid was dissolved in refluxing ethyl acetate (60 mL), the hot solution was filtered, and the product, which crystallised on cooling, was isolated by filtration, washed with cold ethyl acetate (12 mL), and dried *in vacuo* at 40 °C. The yield was 9.0 g (31% based on thiol **6**): mp 129.5−130.3 °C; IR (KBr) 3475, 3100, 1700, 1610, 1498, 1150−1050, 875, 815 cm^{-1}; ^1H NMR (DMSO-d_6) (400 MHz) δ 7.45 (d, J = 1.6 Hz, 1H), 7.36 (d, J = 1.6 Hz, 1H), 7.33 (m, J = 1.4, 8.4 Hz, 1H), 7.27 (d, J = 1.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 5.12 (s, 1H), 3.70−3.83 (m, J = 2.4, 10.8 Hz, 3H), 3.56 (s, 2H), 3.11 (s, 3H), 1.84 (m, J = 5.6, 13.1, 13.1 Hz, 1H), 1.71 (m, J = 2.2, 13.3 Hz, 1H), 1.61 (m, J = 1.8, 13.0 Hz, 1H), 1.50 (m, J = 11.1, 13.2 Hz, 1H), 1.09 (d, J = 6.25 Hz, 3H); ^{13}C NMR (DMSO-d_6) (400 MHz) δ 174.06, 152.94, 144.75, 133.19, 132.51, 129.42, 128.76, 126.17, 125.75, 123.34, 108.96, 68.58, 68.16, 62.63, 45.59, 37.62, 35.04, 25.93, 21.61; MS m/z 375.1. Anal. Calcd for $C_{19}H_{21}NO_3S_2$: C, 60.77; H, 5.64; N, 3.73; S, 17.08. Found: C, 60.95, 61.14, 60.90; H, 5.91, 5.92, 5.91; N, 3.74, 3.73, 3.71; S, 16.79, 16.77, 16.81.

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