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An alternative synthesis of the lipophilic tail portion of abediterol using linear-selective hydroformylation

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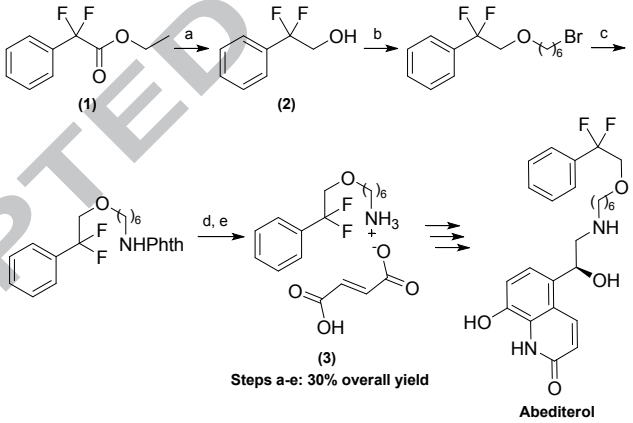
Abstract

Abediterol is a compound currently in development for the treatment of respiratory disease at AstraZeneca. In this work we employ hydroformylation, an under-utilised reaction in the synthesis of pharmaceutical intermediates, as a key step to access the lipophilic amine portion of this molecule. The route described herein addresses some of the issues identified in the original route. Namely, hazardous materials are avoided and increased levels of control - from a process chemistry point of view - are demonstrated, with isolation of intermediates possible at multiple points in the synthesis. This work provides 'proof-of-concept' for an alternative synthetic route and provides high-quality material using a series of robust transformations.

Introduction

Abediterol (AZD0548) is a highly-potent, long-acting β_2-agonist that is currently in development at AstraZeneca for the treatment of respiratory disease.[1] The currently employed synthetic route to the lipophilic amine of abediterol is shown below (Scheme 1) and commences from a commercially available fluorinated ester (**1**).



Scheme 1: Current synthetic route.

Reagents and conditions: (a) $LiAlH_4$, THF, reflux; (b) 1,6-dibromohexane (5.2 eq.), TBAB, $NaOH_{aq}$ (33% w/w); (c) potassium phthalimide, acetone, reflux; (d) hydrazine, EtOH, reflux; (e) fumaric acid, EtOH. (30 % isolated yield over telescoped sequence, Steps a-e)

This synthesis, although relatively concise, uses over five equivalents of 1,6-dibromohexane in step (b), to minimise the formation of the unwanted symmetrical di-ether. Residual 1,6-dibromohexane is then present in the starting material for the phthalimide substitution in step (c), which leads to the formation of further impurities. Finally, the phthalimide group is removed using hydrazine, a highly toxic and potentially explosive compound.[2] Hydrazine use is also of regulatory concern and is on the European Chemicals Agency (ECHA) 'candidate list of substances of very high concern for authorisation' and as a result requires an application for authorisation of use, which involves a 45-day public consultation period.[3] Therefore, an alternative route that avoids the use of hydrazine is desirable.

Route design and selection for the synthesis of an active pharmaceutical intermediate are complex decisions with many factors to be considered.[4] For example, the current synthesis contains only a single isolation i.e. the precipitation and filtration of the fumarate salt. Demonstration of 'control' in a pharmaceutical process is a key regulatory requirement and a telescoped process that uses a large excess of reagents, generating relatively large quantities of impurities, is sub-optimal from this point of view. The ultra-high potency of abediterol means that the projected annual global supply after launch is of the order of kilograms. Therefore, our synthetic efforts focused on the production of material using an increased number of potential isolation points, robust chemistry, and minimal reagent excess where possible. Thus, we envisioned the alternative route *vide infra* that employs a linear-selective hydroformylation as a key step.

Hydroformylation is now a highly developed reaction technology, with millions of tonnes of aldehydes produced every year *via* this olefin homologation process.[5] The linear-selective hydroformylation of unfunctionalized olefins is particularly refined, driven largely by the identification, and subsequent development, of wide bite-angle diphosphine and bulky diphosphite ligands.[6] Despite the obvious potential utility of this reaction, there are relatively few reports of its application to the synthesis of pharmaceutical intermediates.[5a, 7] Some examples of the use of this reaction in the synthesis of active pharmaceutical intermediates are given in Figure 1, with the key 'hydroformylation disconnection' and the carbon atom derived from carbon monoxide highlighted. Our planned application of a hydroformylation approach to the current target and subsequent downstream chemistry is described below.

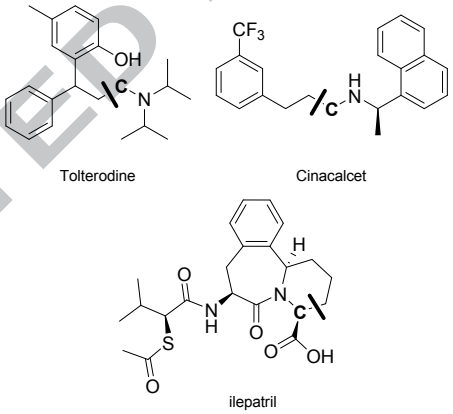
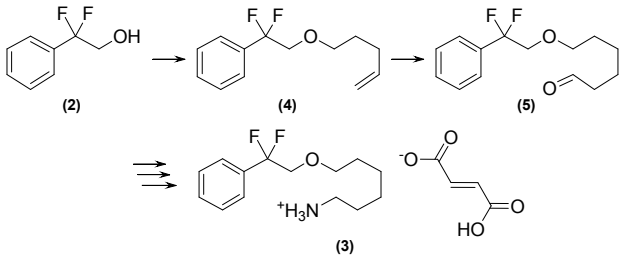


Figure 1: *API's previously accessed through hydroformylation showing the key disconnection. The C-atom in bold is added via hydroformylation*

Results and Discussion

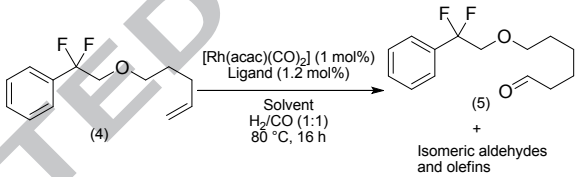
Our alternative synthetic strategy is shown in Scheme 2. Alkylation of intermediate (**2**) - the product of the first step of the currently employed synthetic route, with 5-bromopent-1-ene, would form olefin (**4**). Then, linear selective hydroformylation would convert (**4**) to (**5**). The resulting aldehyde would be reduced to the alcohol and the protected amine subsequently formed *via* a Mitsunobu reaction.[8] Deprotection would generate the free amine, which can then be converted to salt (**3**).



Scheme 2: *Proposed strategy for the synthesis of (**3**)*

Reduction of ethyl 2,2-difluoro-2-phenyl-acetate using lithium aluminium hydride produced the desired product (**2**) in 75% yield and the subsequent phase-transfer-catalysed alkylation gave (**4**) in 80% yield. With the olefin in-hand we next turned our attention to the hydroformylation reaction.

Initially, we carried out the reaction using a rhodium-diphosphite pre-catalyst system (Biphephos as ligand), previously shown to produce the linear aldehyde in high yield.[7f] To our surprise, the reaction generated close to a 1:1 mixture of linear and branched aldehydes. Repeating the initial reaction at a variety of temperatures did not change the selectivity significantly. These results prompted us to look at alternative ligands to increase selectivity. As expected, variation of the catalyst system had a large effect on reactivity/selectivity. However, we also found that significant changes in reaction concentration - for a given catalyst system - produced very different profiles, in terms of both regioselectivity and by-product formation. Table 1 shows a small selection of results obtained using the Rh-Xantphos[6d] and Rh-BISBI[6c] catalyst systems to illustrate this concentration effect.



Ligand	Solvent (rel. vol.)[a]	alkenes +alkane[c] (%)[b]	branched aldehydes (%)[b]	Linear aldehyde (%)[b]
Xantphos[d]	10	5	3	92
Xantphos[d]	100	44	11	45
BISBI[d]	10	6	2	92
BISBI[d]	100	11	13	76

[a] Refers to the number of solvent volumes of toluene relative to the weight of substrate i.e. 10 mL solvent for 1 g of substrate = 10 rel. vol.; [b] Percentage of total peak area in GC; [c] Note: Side-products not isolated and characterised, were designated 'alkenes+alkane', as these products have very similar GC retention times to the olefin, whereas the retention time for the 'oxo-products' are ~ 1 min later on the chromatogram [d] For ligand structures see ESI

Table 1: Effect of concentration on selectivity

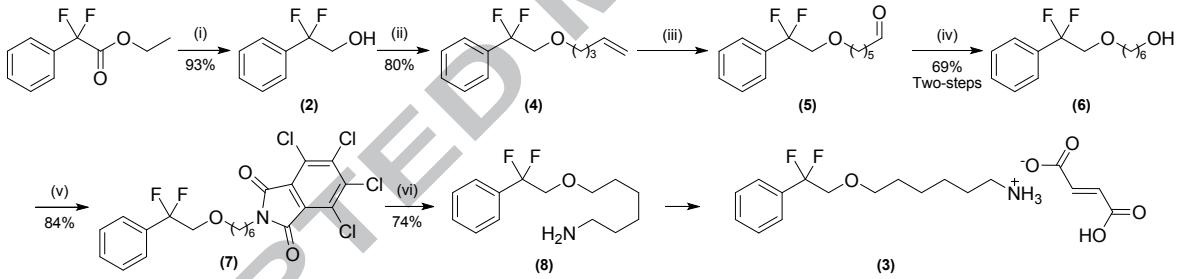
Under otherwise identical conditions, the relative proportion of reaction by-products - which we ascribe to the hydrogenation product and alkene isomerisation products - increases significantly under dilute conditions. The regioselectivity also decreases under dilute reaction conditions. These changes are not particularly surprising, as the reaction mechanism for a hydroformylation reaction is complex, with the reaction outcome very much dependent on the conditions employed.[9]

Having carried out reactions using a variety of monodentate and bidentate ligands, in a number of solvents, we found that the diphosphine ligands Xantphos[6d] and BISBI[6c] gave relatively clean formation of the linear aldehyde, when the reactions were carried out using 10 relative volumes of toluene. The hydroformylation process was carried out successfully on 4 g-scale using the Rh-Xantphos system and

produced the linear aldehyde cleanly in very high selectivity (l:b > 30:1). A minor impurity, which we ascribe to olefin isomerisation was also observed (see ESI). The resulting aldehyde sample was then reduced to the corresponding alcohol using sodium borohydride. This resulted in a 77% yield after purification, over the hydroformylation-reduction sequence (Steps (c)-(d), Scheme 3).

As an aside, the alkyl aldehyde product of the hydroformylation reaction is prone to atmospheric oxidation on standing. The rate of this product degradation can be reduced dramatically by the addition of an appropriate alcohol additive.[10] As well as the high boiling alcohols previously reported e.g. benzyl alcohol, we have found that the more easily removed *n*-butanol can also be employed. If the reduction is carried out soon after the aldehyde is produced, the formation of the acid is not an issue.

Conversion of the alcohol to the corresponding amine was performed by a Mitsunobu reaction (Step (e), Scheme 3) using tetrachlorophthalimide as a 'pre-nucleophile', producing material of very high purity (> 99.5% based on proton NMR assay) in 84% yield.[11] Tetrachlorophthalimide has been shown to be an effective ammonia equivalent for the Mitsunobu reaction,[11] with the benefit of facile deprotection in the presence of aqueous methylamine.[12] Deprotection using methylamine (Step (f), Scheme 3) provided the desired amine in 74% yield. Although not demonstrated here, this amine can be straight-forwardly converted to the corresponding fumarate salt, as per our currently employed route. This new route produces intermediate (**8**) in 29 % overall yield; making it competitive in terms of yield relative to the process shown in Scheme 1 (assuming the fumarate salt formation is high yielding).



Scheme 3: *Hydroformylation route to 'tail amine'*

Reagents and conditions: (a) $LiAlH_4$, THF, reflux; (b) 5-bromopent-1-ene, TBAB, NaOH (aq., 33% w/w), 70 °C; (c) $[Rh(acac)(CO)_2]$ (1 mol %), Xantphos (1.2 mol%), $CO:H_2$ 1:1 (3 barg), toluene, 80 °C; (d) $NaBH_4$, MeOH, 0 °C-rt; (e) triphenylphosphine, 3,4,5,6-tetrachlorophthalimide, DIAD, THF, 0 °C-rt; (f) methylamine (aq., 40% w/w), DMF, 40 °C.

Conclusion

We have developed an alternative synthesis of the lipophilic amine portion of abediterol, which represents a successful proof-of-concept for a hydroformylation approach and provides the amine product in moderate yield and high purity. The primary benefit of this route is the increased *control*, provided by several optional points of isolation, where the intermediates can be purified and may be amenable to long-term storage. Also, each intermediate is formed cleanly, with few reaction by-products; this could lead to shorter processing time, another key consideration when carrying the synthesis of an active pharmaceutical intermediate. Finally, the undesirable use of hydrazine is obviated by the route described herein.

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- Application of hydroformylation to the synthesis of a pharmaceutical intermediate
- Improved synthesis with fewer impurities formed

- Avoids the use of toxic and explosive hydrazine