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Investigation of Synthetic Routes to a Key Benzopyran Intermediate of a $5HT_4$ Agonist

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Abstract:

The supply route to GlaxoSmithKline's $5HT_4$ receptor agonist 1 centred on the construction of key benzopyran fragment 2. Our attempts to define the final manufacturing route for this component are described through a series of disconnections. The systematic approach undertaken towards the construction of the benzopyran skeleton focused on cyclisation strategies from appropriate precursors and evaluation of the performance of the key steps.

1. Introduction

GlaxoSmithKline's 5-HT_4 receptor agonist **1**, 5-amino-6-bromo-chroman-8-carboxylic acid [1-(tetrahydro-pyran-4-ylmethyl)-piperidin-4-ylmethyl]-amide (Figure 1), has been evaluated in several studies. Agonists for the 5-HT_4 receptor have potential utility in the treatment of gastrointestinal disorders such as constipation, irritable bowel syndrome, and functional dyspepsia.[1]

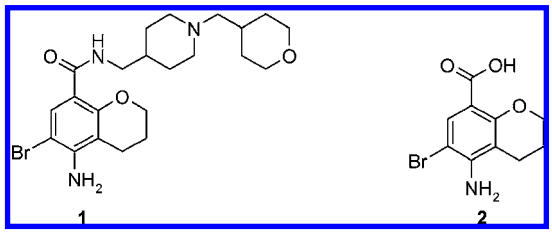


Figure 1. **Target $5HT_4$ agonist and key benzopyran intermediate.**

5-Amino-6-bromo-chroman-8-carboxylic acid, **2** (Figure 1), is the key component of **1**, and our early supply route was based on a high-temperature Claisen rearrangement.[2] In spite of the success of this route in delivering early supplies, there were significant operability and quality issues associated with the Claisen rearrangement that made this route unsuitable for larger-scale manufacturing. Thus, a detailed study on alternative routes was initiated and targeted generic structure **3** as a suitable precursor to **2**. We considered three key disconnections to construct the benzopyran skeleton which warranted experimental investigation (Figure 2).

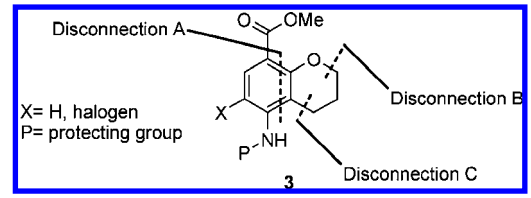


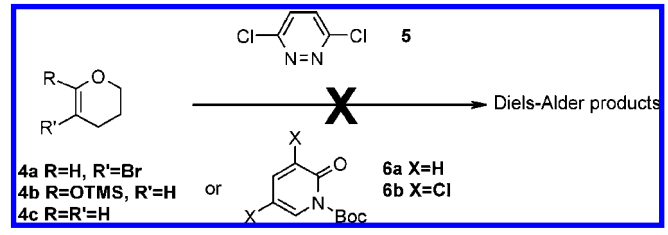
Figure 2. **Disconnections applied to the key benzofuran intermediate.**

Disconnection A requires a 2,3-dihydropyran to participate as a dienophile in a cycloaddition reaction to efficiently form the aromatic ring in **3** (Figure 2). In contrast, disconnections B and C use an appropriately substituted benzene ring on which the pyran ring is constructed. Disconnections B and C differ in their cyclisation strategy, proceeding *via* formation of either a final carbon−carbon or a carbon−oxygen bond to construct the benzopyran. The results from our efforts on disconnections A, B, and C are described below.

2. Results and Discussion

2.1. Disconnection A. The benzopyran skeleton could be constructed by the Diels−Alder reaction between an appropriately substituted dihydropyran (**4a** or **4b**) and 3,6-dichloropyridazine (**5**) or pyrones **6a** and **6b** (Scheme 1).[3,4] The Diels−Alder reaction with 3,6-dichloropyridazine would provide, after extrusion of nitrogen gas and aromatisation (e.g., by loss of HBr or TMSOH), a dichlorobenzopyran intermediate, while the reaction with the pyrone derivatives would allow regiospecific introduction of both the amino and carboxylate groups in **3**. Initial scoping studies using **4a/b** and **5** or **6a/b** suggested that the high-temperature conditions required for Diels−Alder reaction were detrimental for dihydropyran substrates **4a/b** as well as for pyrones **6a/b** (loss of the Boc group).

Scheme 1. **Attempted Diels−Alder reactions**



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(1) De Mayer, J.; Lefebvre, R.; Schuurkes, J. *Neurogastroentero. Motil.* **2008**, *20* (2), 99. For tegaserod see: Seerden, T. C.; De Man, J. G.; Holzer, P.; Van Den Bossche, R. M.; Herman, A. G.; Pelckmans, P. A.; De Winter, B. Y. *Neurogastroentero. Motil.* **2007**, *19* (10), 856.

(2) Walker, A. J.; Adolph, S.; Connell, R. B.; Laue, K.; Roeder, M.; Carsten, J.; Rueggeberg, C. J.; Hahn, D. U.; Voegtli, K.; Watson, J. *Org. Process Res. Dev.* **2009**. DOI: 10.1021/op900193v.

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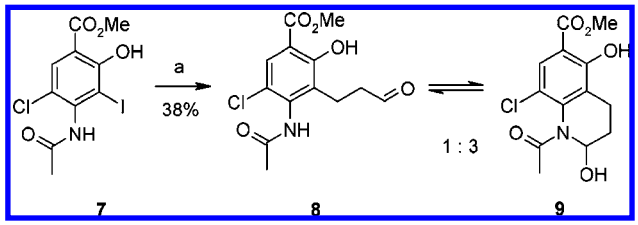
Attempts to promote the cycloaddition at lower temperatures by the use of Lewis acids were also unsuccessful. In contrast, dihydropyran **4c** as stable under all reaction conditions attempted but failed to give the desired Diels−Alder adducts.

2.2. Disconnection B. In disconnection B formation of the benzopyran skeleton involves an etherification reaction as the final step. The Heck reaction of **7**[5] with allyl alcohol occurred selectively at the iodo-position, but the resulting aldehyde **8** did not cyclise with the phenol terminus to form the desired cyclic acetal (or dehydrate to the dihydropyran) (Scheme 2). Instead, a 1:3 equilibrating mixture of **8** and **9** was isolated in 38% yield after chromatography. We reasoned that disconnection approach B (Figure 2) would be undermined by chemoselectivity issues since both the anilide and phenolic groups may compete for the pendant activated intermediate. The option of doubly protecting the aniline was considered, but the length of the synthetic route drove us to prioritise more attractive retrosynthetic options under disconnection C.

Scheme 2. **Chemoselectivity issues in the cyclisation step**[a]

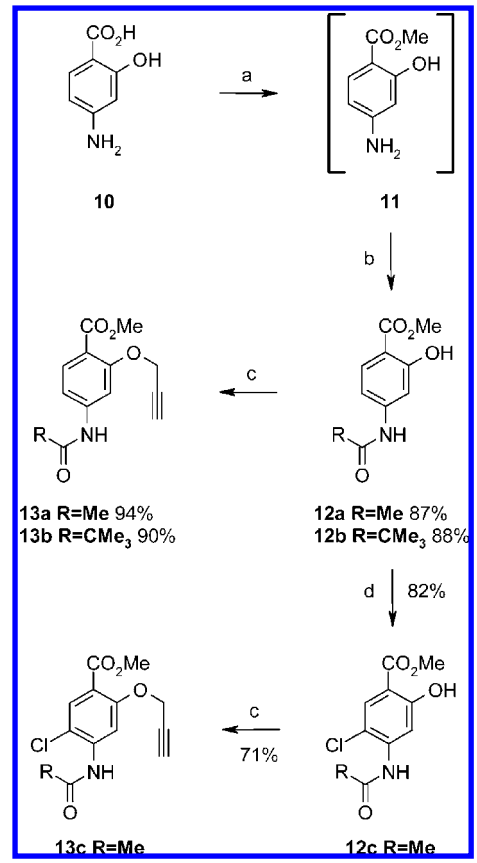


[a] Reagents and conditions: a) $Pd(OAc)_2$, allyl alcohol, *n*-Bu_4NCl, NMP, 55 °C.

2.3. Disconnection C. *2.3.1. Metal-Catalysed Cycloisomerisation of Aryl-Propargyl Ethers.* The strategy in disconnection C focused on accessing appropriately substituted aryl ether intermediates that allowed regiospecific formation of the pyran ring by reaction at the adjacent aromatic carbon atom.[6] In recent years there have been several literature reports regarding the metal-catalysed cycloisomerisation of aryl-propargyl ethers to chromenes as an alternative to the high-temperature Claisen rearrangement.[7] We decided to test this approach and investigate the performance of various substrates and their interaction with potential catalysts. In addition to our chloro-substrate **13c** (utilised in the Claisen route),[2] we prepared the des-chloro phenols **12a** and **12b** on multikilogram scale and converted them to their corresponding propargyl ethers **13a** and **13b** (Scheme 3).

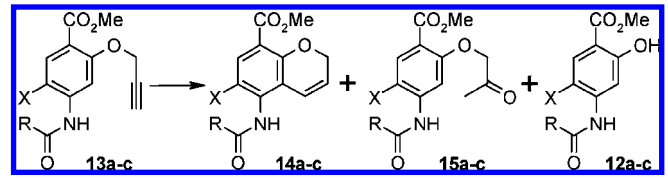
Following the work of the Sames, Echavaren, and Gagosz groups,[7,8] we screened our substrates against platinum(II) and -(IV) chlorides as well as gold(I) complexes (Table 1). Chloro-

Scheme 3. **Preparation of aryl-propargyl ether substrates**[a]



[a] Reagents and conditions: a) Methanol, H_2SO_4, 90 °C, 3 h; b) RCOCl, $NaHCO_3$ (aq), EtOAc, rt; c) propargyl bromide, K_2CO_3, NMP at 90 °C or acetone reflux; d) SO_2Cl_2, EtOAc, rt.

Scheme 4. **Metal-catalysed cycloisomerisation of aryl-propargyl ethers**[a]



[a] Reagents and conditions: see Table 1.

substrate **13c** performed very poorly, presumably due to solubility issues although stereoelectonic factors cannot be discounted. Our best results were obtained in nonpolar solvents such as 1,4-dioxane, 2-MeTHF, or toluene at 80−100 °C with substrates **13a**,**b**. Triphenylphosphine-gold(I) catalysis proved superior to both platinum(II) and -(IV) reactions in terms of yield and selectivity for the desired cycloisomerisation process.[9] The main side reaction, which is more pronounced when the platinum catalysts are employed, is the depropargylation of the ether substrate, furnishing the parent phenol **12a**−**c** as the main impurity (Scheme 4). With substrates **13a**,**b** the depropargylation reaction is significantly suppressed under the gold(I) conditions. Reports exist in the literature where platinum(II) chloride is optimal for this type of process although no rationale has been offered to date.[7,8] We reasoned that coordination of

(3) Barluenga, J.; Vazquez-Villa, H.; Merino, I.; Ballesteros, A.; Gonzalez, J. M. *Chem.−Eur. J.* **2006**, *12* (22), 5790.
(4) (a) Broch, S.; Anizon, F.; Moreau, P. *Synthesis* **2008**, *13*, 2039. (b) Mouaddib, A.; Joseph, B.; Hasnaoui, A.; Merour, J.-Y. *Synthesis* **2000**, *4*, 549.
(5) Intermediate **7** was prepared in one step from the des-iodo analogue which was used in the first supply route of **1**; see reference 2.
(6) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.
(7) (a) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055. (b) Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859. (c) Martin-Mahute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757.
(8) (a) Nevado, C.; Echavarren, A. M. *Chem.−Eur. J.* **2005**, *11*, 3155. (b) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.
(9) Curtis, N. R.; Prodger, J. C.; Rassias, G.; Walker, A. J. *Tetrahedron Lett.* **2008**, *49*, 6279.

Table 1. **Results from substrate and catalyst screening in the metal-catalysed cycloisomerisation of aryl propargyl ethers**

substrate	catalyst (mol %)	conditions	HPLC ratio (% a/a)		
			14	**12**	**15**
13a	$PtCl_4$ (5)	1,4-dioxane, 55 °C, 18 h	27.8	49.1	4.1
13a	$PtCl_2$ (5)	1,4-dioxane, 85 °C, 18 h	50.2	25.9	2.0
13a	$PtCl_2$ (5)	2-MeTHF, 70 °C, 24 h	53.4	23.5	1.8
13a	$PtCl_2$ (5)/AgOTf (5)	toluene, 100 °C, 24 h	50.5	21.8	2.0
13a[a]	AgOTf (5)	2-MeTHF, 75 °C, 18 h	47.0	8.0	2.7
13a	$(Ph_3P)AuNTf_2$ (0.5)	toluene, 85 °C, 1 h	92.1	3.1	1.3
13b	$(Ph_3P)AuNTf_2$ (0.5)	2-MeTHF, 70 °C, 5 h	84.1	7.9	3.7
13b	$(Ph_3P)AuNTf_2$ (0.5)	$CF_3C_6H_5$, 85 °C, 1 h	90.5	2.8	2.2
13b	$(Ph_3P)AuNTf_2$ (0.5)	toluene, 85 °C, 1 h	91.9	2.5	1.5
13b	$(Ph_3P)AuNTf_2$ (0.1)	toluene, 85 °C, 2 h	94.0	2.3	0.9
13b	$(Ph_3P)AuCl/AgOTf$ (1)	2-MeTHF, 70 °C, 3 h	79.1	11.6	6.0
13c[b]	$(Ph_3P)AuCl/AgOTf$ (2)	2-MeTHF, 70 °C, 3 h	10.7	5.5	2.1

[a] Mass balance is **16** and **17**. [b] Mass balance is unreacted starting material.

the phenolic oxygen atom to the catalyst (assisted by the neighbouring ester group) could compete with the desired coordination of the alkyne moiety to the catalyst. This metal complexation of the ethereal oxygen atom could activate the methylene group of the propargyl ether towards nucleophilic attack by the halide anions present in the metal salt. For this reason we decided to include silver(I) triflate in an attempt to sequester the chloride anions. This modification accelerated the rate of the desired reaction, but the extent of depropargylation was not suppressed. On the basis of this result we reasoned that the depropargylation reaction is probably not chloride assisted. Instead we propose that the propargyl ether isomerises to the allenyl enol ether,[10] which in turn hydrolyses into the parent phenol and acrolein under the hplc conditions we use to monitor the reaction.

Interestingly, silver(I) triflate alone catalysed the cycloisomerisation of our substrates, but the product distribution was typical of the high-temperature Claisen process,[2] furnishing significant amounts of the corresponding 3-methyl benzofuran (**16**) and 3-methyl indole (**17**) products (Figure 3). Apparently, when silver(I) and platinum(II) salts are combined, the catalytic process promoted by platinum overrides that offered by silver, and regiospecific insertion of the aryl−hydrogen bond across the triple bond of the propargyl group is observed.

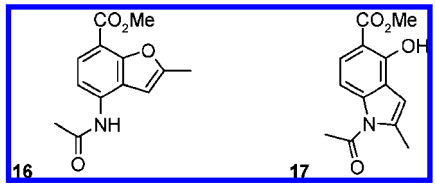


Figure 3. **Impurities from Ag(I) catalysis are also associated with the Claisen route.**

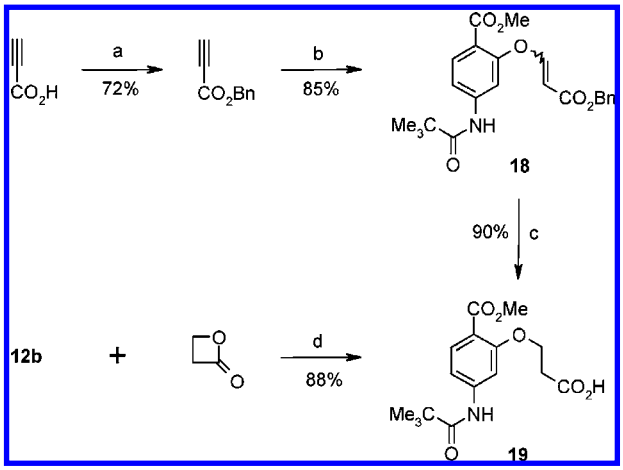
The combination of chloro(triphenylphospine)gold(I) and silver(I) triflate generates the triphenylphospine-gold(I) cation, presumably the active species, but triphenylphospine-gold(I) triflate is not an isolable precursor of the active form. Triphenylphosphine gold(I) bis(trifluoromethanesulfonyl)imidate [$(Ph_3P)AuNTf_2$] (Gagozs' catalyst) is commercially available and does not require additives to generate the active species.[8b] The work using this catalyst was performed on small scale (up to 5 g) due to its limited commercial availability. Under our optimised conditions (0.1 mol % of catalyst, toluene, 85 °C), the desired chromenes **14a** and **14b** were isolated in 80% yield, while depropargylation was limited to less than 3% and the levels of ketones **15a** and **15b** (attributed to hydration of the activated alkyne) did not exceed 2%.[11] The content of residual gold in the isolated chromenes was approximately 200 ppm. This was not regarded as an issue since heavy metal levels are managed effectively over the remaining four steps of the synthesis.[2] The low catalyst loading and the ease of synthesis of substrates **13a** and **13b** offset the cost of triphenylphosphine-gold(I) bis(trifluoromethanesulfonyl)imidate and render this route superior to the Claisen approach on the grounds of both operability and cost.

2.3.2. Intramolecular Friedel−Crafts Approaches. Following our initial brainstorm, one of the most attractive approaches involved the intramolecular Friedel−Crafts approach via activation of appropriately substituted aryl alkyl ether substrates. In order to explore this approach we prepared benzyl 3-aryloxyacrylate **18** in 78% yield (*cis/trans* ∼1:6) via the DABCO-catalysed addition of **12b** to benzyl propiolate (Scheme 5).[12] The subsequent one-pot hydrogenolysis/hydrogenation to give the desired substrate **19** was more problematic than originally anticipated. Most of the commercial Pd/C catalysts were successful in the hydrogenolysis of the benzyl ester, but very few were effective in the hydrogenation of the 3-aryloxyacrylic acid intermediate. At best, hydrogenation of the double bond took no less than one week to reach completion (THF, 50 °C, 50 psi). In addition, benzyl propiolate itself is not commercially available and had to be prepared by treating propiolic acid with benzyl trichloroacetimidate. Interestingly, only 11% of the combined mass of these reagents ends up as part of the structure in **19**, rendering the atom economy of the process extremely poor. In contrast, we succeeded in preparing **19** in one step and 88% yield, by reacting the phenolate anion of **12b** with β-propiolactone (Scheme 5).[13]

With a good supply route to **19** in hand, we explored activation of the carboxylic acid terminus and promotion of the intramolecular Friedel−Crafts reaction. Treatment of a toluene

(10) Shen, R.; Zhu, S.; Huang, X. *J. Org. Chem.* **2009**, *74*, 4118.
(11) The levels of the ketone impurity may be connected to the difficulty in rigorously excluding water on the small scale at which these experiments were conducted.
(12) Fan, M.-J.; Li, G.-Q.; Li, L.-H.; Yang, S.-D.; Liang, Y.-M. *Synthesis* **2006**, *14*, 2286.
(13) Buckle, D. R.; Eggleston, D. S.; Houge-Frydrych, C. S. V.; Pinto, I. L.; Readshaw, S. A.; Smith, D. G.; Webster, R. A. B. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2763.

Scheme 5. **Syntheses of the Friedel−Crafts substrate 19[a]**

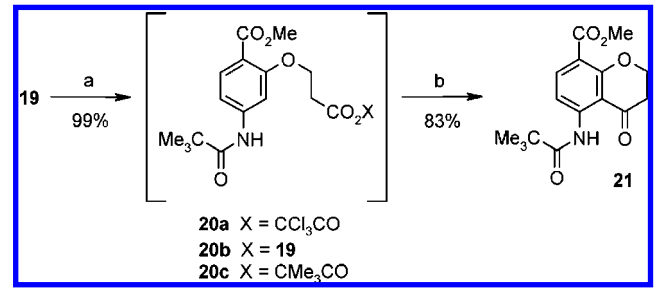


[a] Reagents and conditions: a) Benzyl trichloroacetimidate, DCM, rt; b) **12b**, DABCO (5 mol %), DCM, rt; c) Pd/C, THF, 50 °C, 50 psi; d) ^{t}BuOK, 2-MeTHF, rt.

solution of **19** at 60 °C with trichloroacetic anhydride generated the corresponding mixed anhydride **20a** as a crystalline solid suspended in the solution (Scheme 6). Addition of a catalytic amount of $BF_3 \cdot Et_2O$ to this suspension at 100 °C gave the crude benzopyranone **21** in 52% isolated yield but in moderate purity.[14] By studying the activation and cyclisation events in isolation we established that the performance of the Friedel−Crafts reaction reflected the quality of **20a**. When the mixed anhydride was preisolated by filtration of the original slurry and subjected to the cyclisation conditions, the desired benzofuranone was obtained in excellent quality at 60% yield. Isolation of the mixed anhydride **20a** was problematic due to its hygroscopicity, and this was compounded by contamination with the symmetrical anhydride **20b**, even when large amounts of trichloroacetic anhydride were used. Depending on the solvent and the mode of addition of trichloroacetic acid anhydride to **19**, the ratio between **20a** and **20b** ranged from 5:1 to 1:10 as determined by ^{1}H NMR spectroscopy. Higher levels of symmetrical anhydride **20b** (which did not cyclise under the reaction conditions) impacted adversely on the intramolecular Friedel−Crafts reaction, at least when $BF_3 \cdot Et_2O$ was used as the Lewis acid. We reasoned that the high reactivity of **20a** was responsible for both moisture sensitivity and formation of **20b**. In order to address these issues we decided to explore pivaloyl chloride as the activator of **19** as it would lead to a more stable activated species. Rewardingly, treatment of **19** with pivaloyl chloride afforded **20c** quantitatively and without contamination from **20b**. The pivaloyl-mixed anhydride is a crystalline solid which can be stored for several days under ambient conditions. Exposure of this material to a catalytic amount of $BF_3 \cdot Et_2O$ in toluene for 7 h at 100 °C provided **21** as a yellow crystalline solid in excellent quality and in 83% yield from **19** (Scheme 6).

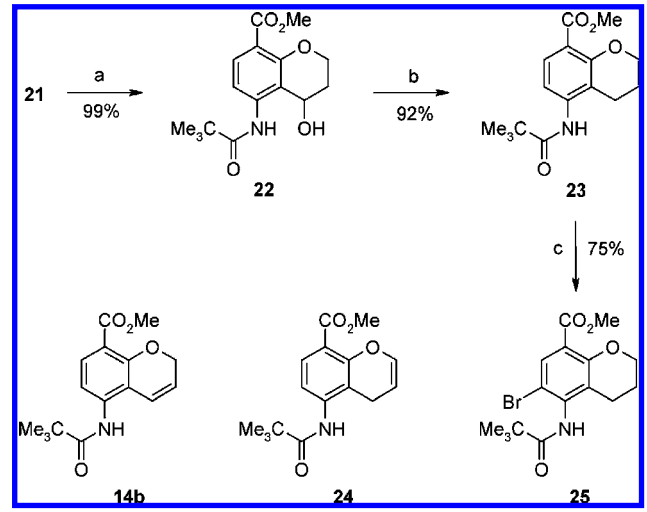
Subsequently, we demonstrated that isolation of **19** and **20c** was not necessary as we prepared the key benzopyranone

Scheme 6. **Benzopyranone synthesis via intramolecular Friedel−Crafts cyclisation[a]**



[a] Reagents and conditions: a) Toluene, $(Cl_3CCO)_2O$ or Me_3CCOCl/ Et_3N, rt; b) $BF_3 \cdot Et_2O$, toluene 99 °C.

Scheme 7. **Synthesis of the bromobenzopyran intermediate 25[a]**



[a] Reagents and conditions: a) $NaBH_4$, MeOH, rt; b) H_2SO_4 (conc.), MeOH, Pd/C, H_2, 50 °C, 50 psi; c) NBS, MeOH, rt.

intermediate **21** from phenol **12b** in 67% yield through a simplified, telescoped process.

The synthesis of the desired benzopyran skeleton could now be completed by reduction of the benzopyranone carbonyl to the methylene group. Unfortunately, ketone **21** was inert to a wide range of hydrogenation conditions that encompassed solvents, pressures, temperatures, additives, and no less than 20 catalysts. Our substrate was also inert to trifluoroacetic acid/triethyl silane, while significant decomposition occurred using a modification of the Clemmensen reduction.[15] Exploring a stepwise approach, addition of half an equivalent of sodium borohydride to a methanolic suspension of **21** at ambient temperature resulted in the rapid and quantitative reduction of the benzopyranone to the corresponding benzopyranol **22** which was isolated in greater than 99% yield and excellent quality (Scheme 7). We subsequently established that reduction of the secondary alcohol **22** to benzopyran **23** by hydrogenation is facilitated by the presence of a strong acid. Upon addition of sulphuric acid, **22** converts into two intermediates (initially ~1:1 by HPLC area) both of which convert to **23** when the catalyst is added and a hydrogen atmosphere is established. These intermediates were identified as chromene **14b** and enol ether

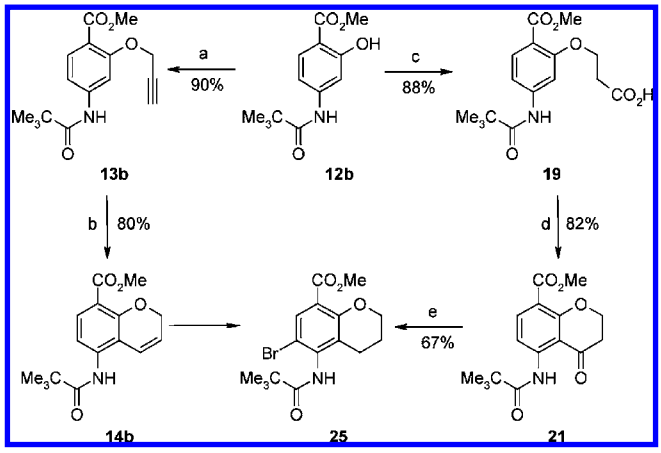
(14) (a) Wilkinson, M. C.; Saez, F.; Hon, W. L. *Synlett* **2006**, *7*, 1063. (b) Bianco, G. G.; Ferraz, H. M. C.; Costa, A. M.; Costa-Lotufo, L. V.; Pessoa, C.; de Moraes, M. O.; Schrems, M. G.; Pfaltz, A.; Silva, L. F., Jr. *J. Org. Chem.* **2009**, *74*, 2561.

(15) Prugh, J. D.; Alberts, A. W.; Deana, A. A.; Gilfillian, J. L.; Huff, J. W.; Smith, R. L.; Wiggins, J. M. *J. Med. Chem.* **1990**, *33*, 758.

24 (major product under nonreductive conditions), presumably arising from dehydration of **22** and isomerisation of **14b**, respectively. Enol ether **24** is hydrogenated at a much slower rate to give **23** although conversion to the desired benzopyran via equilibration to **14b** cannot be dismissed. The rate of their hydrogenation was greatly dependent on the type of catalyst used and best results were obtained with unreduced palladium on wet charcoal. When other types of catalysts were used, **24** persisted for days. Under our optimised conditions **23** was isolated in approximately 90% yield and excellent quality. When ethanol was used as the solvent in the reductive steps, significant trans-esterification of the methyl ester group in **22** and **23** was observed. For this reason, methanol was chosen as the reaction solvent, which also allowed the borohydride reduction to be telescoped into the hydrogenation process.

Methanol was also found to be the optimum solvent in the bromination of **23** to **25** with NBS (equally clean although much slower in EtOAc, THF, or TBME at ambient temperature) (Scheme 7). This aspect rendered the work-up of the combined reduction steps and isolation of **23** unnecessary, as we demonstrated the synthesis of **25** from **21** in a one-pot, telescoped process in 67% yield on a 20 g scale (Scheme 8).

Scheme 8. **Summary of the successful syntheses of the benzopyran intermediate**[a]



[a] Reagents and conditions: a) propargyl bromide, K_2CO_3, acetone, reflux; b) 0.1 mol % $(Ph_3P)AuNTf_2 \cdot 0.5C_7H_8$, toluene, 85 °C; c) ^tBuOK, β-propiolactone, 2-MeTHF, rt; d) Me_3CCOCl, Et_3N, $BF_3 \cdot Et_2O$, toluene 100 °C; e) (i) $NaBH_4$, MeOH, rt, 99%. (ii) H_2SO_4 (conc.), MeOH, Pd/C, H_2, 50 °C, 50 psi, 90%. (iii) NBS, MeOH, rt, 75% unoptimised.

By-passing the isolation of **25** and further telescoping the protected bromobenzopyran intermediate into the hydrolysis of the ester and pivaloyl groups is also being considered.

To conclude, three pivotal disconnections to a key benzopyran intermediate were considered, and a number of synthetic routes were evaluated experimentally. The disconnection across the bond joining the aromatic ring to the benzylic benzopyran carbon atom proved the best approach as it produced two successful syntheses (Scheme 8). The first route involves the use of a transition-metal catalysed cycloisomerisation, whereas the other is based on an intramolecular Friedel−Crafts cyclisation. The two routes are similar in length, cost, and efficiency and constitute attractive alternatives to previously established routes.[16]

3. Experimental Section

Phenol 12b. *Methyl 4-[(2,2-Dimethylpropanoyl)amino]-2-hydroxybenzoate.* 4-Amino salicylic acid (700 g, 4.57 mol, 1 equiv) was dissolved in methanol (5.25 L, 7.5 vol), and the clear brown solution was cooled to 0−5 °C. Sulphuric acid (1.4 L, 2 vol, 2.57 kg, 26.2 mol, 5.73 equiv) was added slowly, maintaining the temperature below 20 °C. The reaction was then heated to 80 °C and kept at that temperature for 3 h before cooling to 20−30 °C. Water (10.5 L, 15 vol) was added, and the pH was adjusted to 7 using 10 M NaOH (3.0 L, 4.29 vol, 9 °C exotherm). The white precipitate was filtered under vacuum, washed with water (1.4 L, 2 vol), and dried for 2 days under vacuum at 80 °C to give dry **11b** (727 g, 1.04 wt, 1.04 mol, 95.1% yield). In another experiment, the wet cake obtained after the water wash was dissolved directly in ethyl acetate (10.5 L, 15 vol) and added to water (3.5 L, 5 vol). Sodium hydrogen carbonate (525 g, 0.75 wt, 6.25 mol, 1.37 equiv) was added followed by pivaloyl chloride (700 g, 1 wt, 5.8 mol, 1.27 equiv), and the reaction mixture was stirred at 25−30 °C for approxomately 2 h. After settling of the biphase, the aqueous phase was removed, and the organic phase was washed with water (2 × 3.5 L, 2 × 5 vol). The organic phase was then concentrated to approximately 2.8 L (4 vol) and cooled to 20 °C; heptane (7 L, 10 vol) was then added. The resulting slurry was filtered, and the cake was washed with heptane (2.1 L, 3 vol) and dried under vacuum at 50 °C to give the titled compound (954 g, 1.31 wt, 3.8 mol, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.83 (s, 3H), 7.77 (d, J = 8.80 Hz, 1H), 7.37 (br s, 1H), 7.18 (d, J = 2.20 Hz, 1H), 7.13 (dd, J = 8.68, 2.08 Hz, 1H), 3.93 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 170.2, 163.0, 144.6, 131.1, 110.5, 107.8, 106.45, 52.1, 40.2, 27.5; HRMS calculated for the protonated molecular ion (MH^+): $C_{13}H_{18}NO_4$ 252.1236, found 252.1226.

Propargyl Ether 13b. *Methyl 4-[(2,2-Dimethylpropanoyl)amino]-2-(2-propyn-1-yloxy)benzoate.* Potassium carbonate (2.00 g, 14.5 mmol, 1.22 equiv) was added to a solution of methyl 4-[(2,2-dimethylpropanoyl)amino]-2-hydroxybenzoate (3.00 g, 11.9 mmol, 1 equiv) in acetone (15 mL, 5 vol) and the resulting slurry heated at reflux for 20 h. The mixture was cooled, diluted with water (75 mL, 25 vol), and extracted with ethyl acetate (30 mL, 10 vol). The organic extract was washed with water (30 mL, 10 vol) and then 10% w/w sodium chloride in water, was dried over sodium carbonate, and concentrated *in vacuo*. The residue was suspended in toluene (9 mL, 3vol) and the mixture heated until the solid had dissolved. The solution was cooled to ambient temperature. The crystalline solid was collected under suction, washed with toluene (3 mL, 1 vol) followed by heptane (6 mL, 2 vol), and dried *in vacuo* at 45 °C to afford **13b** (3.10 g, 1.03 wt, 10.7 mmol, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.31 Hz, 1H), 7.76

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(d, $J = 1.96$ Hz, 1H), 7.43 (br s, 1H), 6.95 (dd, $J = 8.56$, 1.96 Hz, 1H), 4.82 (d, $J = 2.45$ Hz, 2H), 3.87 (s, 3H), 2.55 (t, 2.45 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.17, 165.72, 158.68, 143.13, 132.92, 115.91, 111.57, 105.08, 78.15, 75.94, 56.88, 51.84, 39.81, 27.29; HRMS calculated for the protonated molecular ion (MH^+): $C_{16}H_{20}NO_4$ 290.1392, found 290.1395 (APCI).

Chromene 14b. *Methyl 5-[(2,2-Dimethylpropanoyl)amino]-2H-chromene-8-carboxylate.* A mixture of aryl propargyl ether **13b** (731 mg, 2.53 mmol) and $(Ph_3P)AuNTf_2 \cdot 0.5C_7H_8$ (2.0 mg, 2.5 μmol, 0.1 mol %) in toluene (14.6 mL, 20 vol) was stirred at 85 °C under nitrogen for 2 h. The reaction mixture was allowed to cool to 55 °C and was filtered and washed with toluene (3.6 mL, 5 vol). The filtrate was concentrated *in vacuo* and the residual solid dissolved in hot toluene (2.9 mL, 4 vol). The solution was allowed to cool and stirred at room temperature overnight. The crystalline solid was collected under suction, washed with toluene (1.5 mL, 2 vol), and dried *in vacuo* at 45 °C to afford **14b** (584 mg, 0.8 wt, 2.02 mmol, 80% yield) as an off-white solid; mp 153−155 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, 1H, $J = 8.8$ Hz); 7.42 (d, $J = 8.8$ Hz, 1H), 7.37 (br s, 1H), 6.38 (m, 1H), 5.96 (dt, $J = 9.8$, 3.9 Hz, 1H), 4.83 (m, 2H), 3.87 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.81, 165.83, 155.07, 136.72, 131.49, 122.71, 118.97, 115.96, 115.65, 115.36, 64.97, 51.93, 39.82, 27.68; HRMS calculated for the protonated molecular ion (MH^+): $C_{16}H_{20}NO_4$ 290.1392, found 290.1387 (APCI). The product contained ~220 ppm Au and 6 ppm P by ICP. HPLC analysis of the combined filtrate and wash indicated a ~10% yield of **14b** was present by comparison to a standard solution.

3-Aryloxy Propionic Acid 19. *3-({5-[(2,2-Dimethylpropanoyl)amino]-2-[(methyloxy)carbonyl]phenyl}oxy) Propanoic Acid.* To a solution of **12b** (20 g, 0.08 mol) and β-propiolactone (5 mL, $d = 1.15$, 0.08 mol) in 2-MeTHF (250 mL, 12.5 vol) at 20 °C, was added a 20% w/w solution of KO^{t}Bu in THF (45 mL, 0.08 mol) over 5 min, and the reaction mixture was stirred at the same temperature for at least 4 h (marginal improvement in conversion by HPLC after reacting overnight). The reaction mixture was quenched by the addition of water (120 mL, 6 vol), and the pH of the aqueous phase was adjusted from 14 to 8−9 with 2 M HCl. The aqueous phase was separated, and its pH was adjusted to 1 with 2 M HCl before it was extracted with 2-MeTHF (160 mL, 8 vol). The product in the organic phase is of sufficient purity to be telescoped into the next stage directly (after concentration to 80 mL). Alternatively, the 2-MeTHF solution may be dried over sodium sulphate and evaporated to dryness to isolate **19** directly or solvent-swapped to toluene to give a slurry of **19** which is then filtered to afford the titled compound (22 g, 1.1 wt, 0.68 mol, 88% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.67 (d, $J = 8.56$ Hz, 1H), 7.60 (d, $J = 1.71$ Hz, 1H), 7.42 (dd, $J = 8.56$, 1.71 Hz, 1H), 4.19 (t, $J = 6.24$ Hz, 2H), 3.74 (s, 3H), 2.74 (t, $J = 6.24$ Hz, 2H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.04, 172.01, 165.44, 158.47, 144.54, 131.83, 113.97, 111.29, 104.60, 64.55, 51.37, 39.14, 34.00, 27.02. HRMS calculated for the protonated molecular ion (MH^+): $C_{16}H_{21}NO_5$ calculated 324.1447, found 324.1448.

Benzopyranone 21. *Methyl 5-[(2,2-Dimethylpropanoyl)amino]-4-oxo-3,4-dihydro-2H-chromene-8-carboxylate.* To a solution of **19** (11 g, 0.034 mol, 1 equiv) in 2-MeTHF (80 mL, 7.27 vol)—preisolated or telescoped from the previous step—was added triethylamine (3.77 g, 0.037 mol, 1.09 equiv). The new solution was added dropwise to a solution of pivaloyl chloride (12.5 g, 0.104 mol, 2.94 equiv) in toluene (80 mL, 7.27 vol) at 20 °C. The precipitated triethylammonium chloride was removed by filtration, and the solution was solvent-swapped to pure toluene. Further put and take distillation with toluene was performed to remove the excess of pivaloyl chloride. The toluene suspension (solution at >60 °C) of the mixed anhydride was diluted with toluene (90 mL, 8.18 vol) and heated to 100 °C. A catalytic amount of $BF_3 \cdot Et_2O$ (0.38 g, 8 mol %) was added, and the reaction mixture was kept at the same temperature for at least 7 h before it was cooled to 60 °C. The reaction mixture was quenched with saturated sodium bicarbonate solution (45 mL, 4 vol). The aqueous phase was discarded, and the organic phase was washed with 2 M HCl (45 mL, 4 vol) and finally with water (45 mL, 4 vol) (all washes conducted at >60 °C). The toluene solution was concentrated to approximately 35 mL and cooled to ambient temperature, and heptane (60 mL, 5.45 vol) was added. The resulting slurry was filtered, washed with heptane (30 mL, 2.72 vol, and dried to afford **21** (8.6 g, 0.78 wt, 0.28 mol, 83% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (s, 1H), 8.29 (d, $J = 9.05$ Hz, 1H), 7.96 (d, $J = 9.05$ Hz, 1H), 4.61 (t, $J = 6.60$ Hz, 2H), 3.80 (s, 3H), 2.94 (t, $J = 6.60$ Hz, 2H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.90, 177.68, 164.53, 161.88, 145.09, 138.79, 113.52, 110.25, 108.58, 66.41, 51.87, 39.97, 37.44, 27.04. HRMS calculated for the protonated molecular ion (MH^+): $C_{16}H_{19}NO_4$ calculated 306.1341, found 324.1334.

Benzopyran 23. *Methyl 5-[(2,2-Dimethylpropanoyl)amino]-3,4-dihydro-2H-chromene-8-carboxylate.* Sodium borohydride (0.3 g, 8 mmol, 0.51 equiv) was added to a suspension of benzopyranone **21** (5.0 g, 0.015 mol, 1 equiv) in methanol (50 mL, 10 vol) at 20 °C, and the resulting solution was stirred at the same temperature for at least 15 min (reduction to the alcohol is complete) before it was quenched with glacial acetic acid (5 mL, 1 vol). Concentrated sulphuric acid (2.5 mL, 0.05 mol, 0.5 vol) was added followed by 5% Pd/C (5.0 g, 2.4 mmol, 0.29 equiv unreduced catalyst E196 R/W by Degussa). A hydrogen atmosphere (50 psi) was established, and the solution was heated to 50 °C and stirred for at least 24 h. The reaction mixture was filtered over Celit, and the Celite cake was washed with methanol (10 mL, 2 vol) which was combined with the filtrate (this solution may be processed further to give **25** by treatment with NBS). The methanolic solution was concentrated and solvent-swapped to toluene by distillation (~100 mbar). The resulting toluene solution (~50 mL) was washed successively at 60 °C with water (20 mL) and aqueous 20% $KHCO_3$ solution (2 × 50 mL). The toluene solution was then concentrated to approximately 10 mL, resulting in a slurry of the product which was filtered, washed with toluene (10 mL, 2 vol), and dried overnight under vacuum at 60 °C, to afford the titled compound (4.25 g, 0.85 wt, 14.5 mmol, 89% yield). ^{1}H NMR

(400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 7.48 (d, J = 8.31 Hz, 1H), 6.92 (d, J = 8.31 Hz, 1H), 4.17 (m, 2H), 3.78 (s, 3H), 2.63 (t, J = 6.48 Hz, 2H), 1.92 (m, 2H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.30, 165.95, 154.54, 140.75, 127.98, 119.29, 117.14, 116.23, 65.89, 51.64, 39.82, 27.26, 20.72, 20.58. HRMS calculated for the protonated molecular ion (MH^+): $C_{16}H_{22}NO_3$ 292.1549, found 292.1537.

Bromobenzopyran 25. *Methyl 6-Bromo-5-[(2,2-dimethylpropanoyl)amino]-3,4-dihydro-2H-chromene-8-carboxylate.* To a solution of benzopyran **23** (2.12 g, 7.26 mmol, 1 equiv) in methanol (15 mL, 6.91 vol) (preisolated or telescoped from the previous step after removal of the catalyst) was added *N*-bromosuccinimide (1.3 g, 7.26 mmol, 1 equiv) in a single charge at 20 °C. The reaction mixture was stirred for at least 15 min before it was concentrated and solvent-swapped to toluene by distillation (~100 mbar). The resulting toluene solution (~20 mL) was washed at 60 °C with aqueous 20% $KHCO_3$ solution (2 × 10 mL). The toluene solution was then concentrated to dryness to afford 1.8 g, 59% yield of sufficiently pure (>98% by ^{1}H NMR) bromobenzopyran **25** to be processed further. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (s, 1H), 7.72 (s, 1H), 4.17 (t, J = 4.89 Hz, 2H), 3.80 (s, 3H), 2.58 (m, 2H), 1.92 (m, 2H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.92, 164.77, 153.62, 139.47, 130.68, 124.89, 119.49, 112.63, 66.06, 52.09, 38.75, 27.25, 21.56, 20.49. HRMS calculated for the protonated molecular ion (MH^+): $C_{16}H_{21}BrNO_3$ 370.0654, found 370.0644.

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