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A Convergent Synthesis of an LTD4 Antagonist, RG12525

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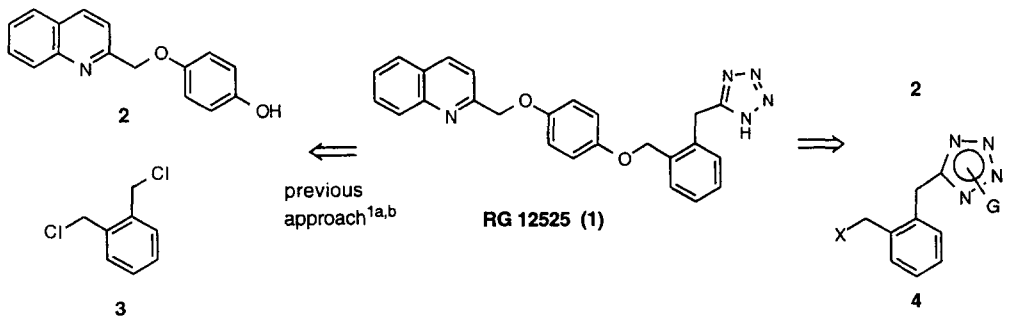
Abstract: An efficient, convergent synthesis of an LTD_4 antagonist, RG12525 (**1**) has been achieved through the alkylation of the (2-quinolinylmethoxy)phenol (**2**) with either a triphenylmethyl protected tetrazole synthon (**4a**) or with a tetrahydropyranyl derivative (**4b**). Preparation of synthons **4a** and **4b**, as well as novel preparation of **2** is described.

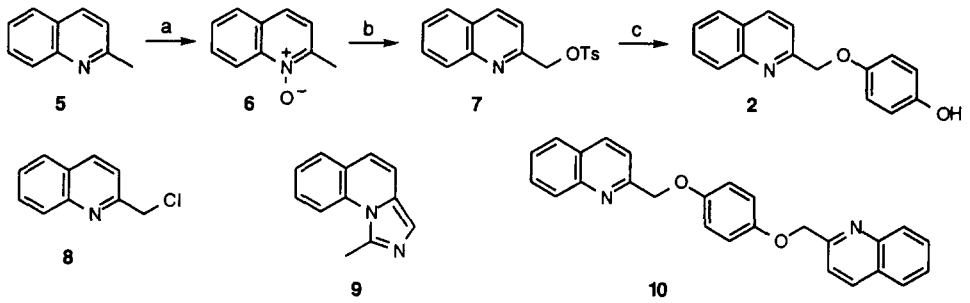
RG12525 (**1**) is an orally active, specific and competitive leukotriene D4 antagonist.[1b-e] The linear synthesis of **1**, described previously,[1a,b] although improved and developed to a multikilogram scale still suffered from a number of drawbacks. The starting material for the assembly of (2-quinolinylmethoxy)phenol (**2**), the 2-(chloromethyl)quinoline, prepared by chlorination of quinaldine in a halogenated solvent, exhibited hypersensitizing properties. Later in the synthesis, considerable dialkylation was associated with the use of the bidentate alkylating agent, α,α'-dichloro-*o*-xylene (**3**). In addition, the potentially hazardous tetrazole formation step, necessitating at a large scale the use of a specialized facility, occurred as the last synthetic operation. For logistic reasons, including better control over the final product, we preferred an approach in which the tetrazole unit would be incorporated at an earlier stage in the form of a building block, such as **4**.



Herein, we report a convergent synthetic route to **1** involving a novel preparation of the phenol **2** and its coupling to protected tetrazole synthons of type **4**.

The preparation of the left hand fragment, (2-quinolinylmethoxy)phenol (**2**)[1a,2] started from the conversion of quinaldine (**5**) to its *N*-oxide (**6**)[3] using a recent protocol.[4] Reacting the *N*-oxide with *p*-toluenesulfonyl chloride in the presence of potassium carbonate in acetonitrile efficiently provided the hitherto

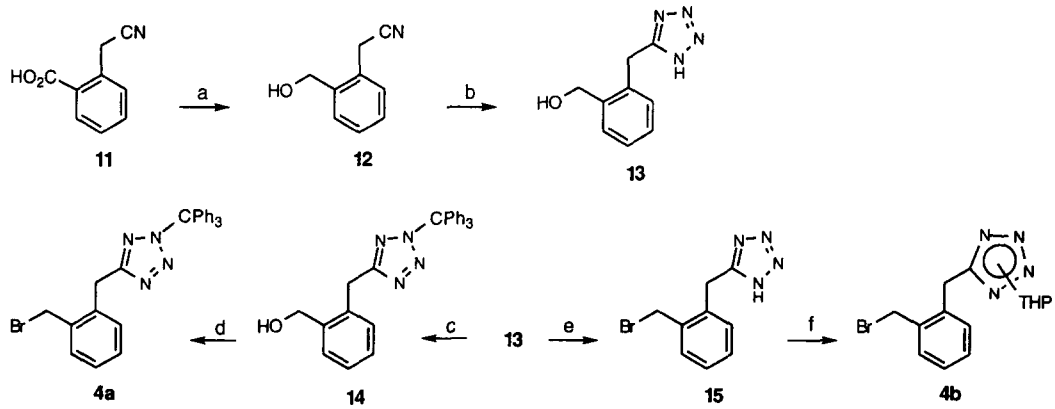
difficult to obtain tosylate **7**[5] in 69% yield after flash chromatography. The corresponding chloride (**8**)[6] and the highly fluorescent imidazoquinoline **9**[7] byproducts were also isolated (ca. 3% of each). Condensation with hydroquinone (3 equiv) afforded **2** in 80% yield. Approximately 8% of the dialkylated compound **10** was formed under these conditions, and was eliminated after recrystallization. Alternatively, a concatenated procedure involving the *in situ* formation of the tosylate **7** could be used to produce **2** in ca. 65% overall yield from the N-oxide **6**.



Scheme 1: (a) $H_2NCONH_2{\cdot}H_2O_2$, phthalic anh., CH_2Cl_2, rt to 40°C, 2h, 82%; (b) TsCl, K_2CO_3, CH_3CN, 0°C to rt, 1h, 69%; (c) hydroquinone (3equiv.), NaOH, MeOH/CH_3CN 1:1, 72%.

To avoid selectivity and hygiene problems associated with the use of **3**, we first examined the use of 2-bromomethylphenylacetonitrile and its chloro analog as alkylating agent for the phenol **2**. Unfortunately, using these reagents under a variety of conditions, we were not able to bring about the desired C-O bond formation in a satisfactory yield most likely due to plaguing ortho-quinodimethane chemistry and / or self condensation.[8] We then decided to explore the possibility of introducing the tetrazole moiety with the alkylating agent. This approach would have the advantage of avoiding the hazardous azide chemistry as the last step of the synthesis.

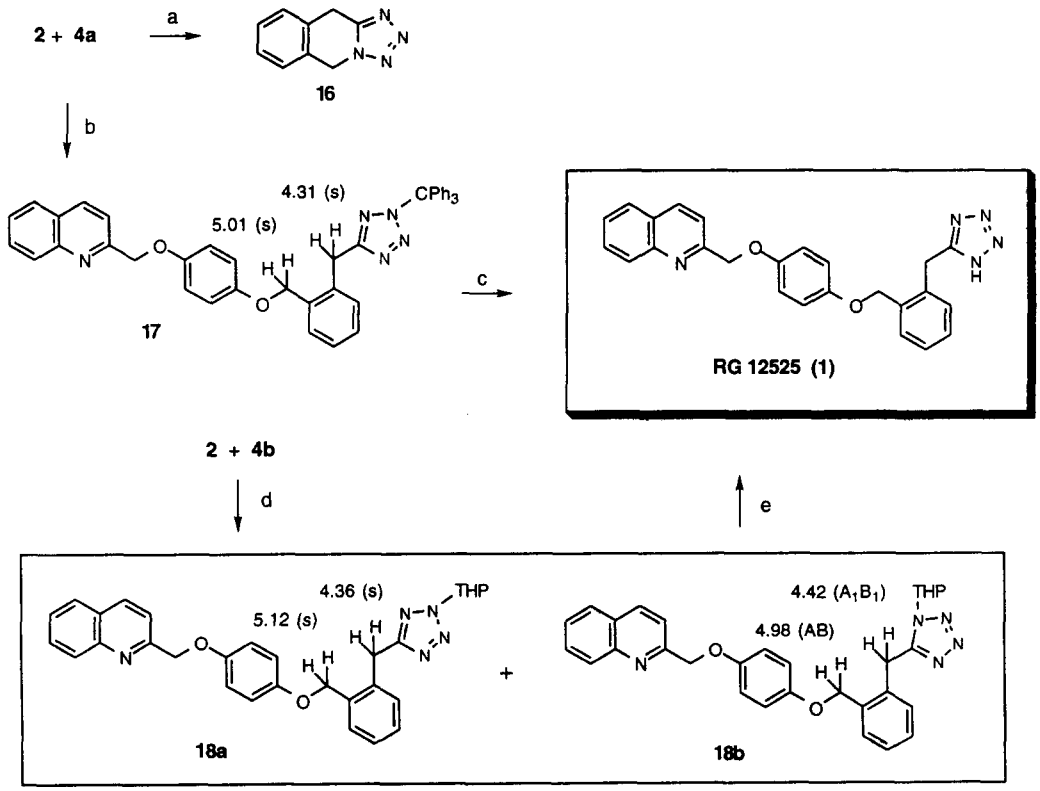
The readily available 2-cyanomethyl benzoic acid **11**[9] was used as a starting point in assembling the



Scheme 2: (a) $NaBH_4$, I_2, THF, 62%; (b) NaN_3, $Et_3N{\cdot}HCl$, NMP, 120°C, 20h, 77%; (c) $ClCPh_3$, pyridine, CH_2Cl_2, rt, 12h, 95%; (d) NBS, Me_2S, CH_2Cl_2, 0°C, 3h, 85%; (e) NBS, PPh3, THF, 0°C to rt, 14h, 66%; (f) DHP, PPTS, CH2Cl2, rt, 1h, 92%.

required tetrazole synthons. Chemoselective reduction of the carboxylic acid functionality using $NaBH_4$-I_2 system[10] provided after Kugelrohr distillation 2-hydroxymethyl benzyl cyanide **12**.[9] The tetrazole **13**[11] obtained after [2+3] azide cycloaddition was isolated as a crystalline solid upon adding water to the crude reaction mixture. Selective protection of the tetrazole moiety as a triphenylmethyl derivative afforded the alcohol **14**[12] as a single (N2) regioisomer (vide infra). The latter was cleanly converted to the required benzylic bromide **4a**[13] upon exposure to the NBS / Me_2S[14] system. The tetrahydropyranyl derivative **4b** was prepared[15] from **13** using an inverted sequence, i.e. formation of the bromide **15**[16] followed by tetrazole ring protection affording in this case **4a** as a 5:1 mixture of N2/N1 regioisomers (vide infra).

The crucial coupling of **2** and **4a** was first attempted in the presence of potassium carbonate in refluxing ethanol. Disappointingly, these conditions resulted in the formation of the fused tetrazole **16** as the main product, along with unreacted **2**. Lowering the temperature of the reaction mixture from reflux to 50 °C did promote the desired pathway to take place in approximately 55% yield. Further improvement was accomplished by using potassium fluoride on alumina[17] in acetonitrile at 50 °C. Removal of the insoluble material followed by addition of water to the filtrate allowed isolation of the crystalline penultimate compound **17** in 83%



Scheme 3: (a) K_2CO_3, EtOH, reflux ; (b) KF•alumina (5 equiv.), CH_3CN, 50°C, 5h, 83%; (c) HCl, MeOH/THF 1:1, rt, 7h, 93%., then aq. NaOH/EtOAc (quant.); (d) KF•alumina (5 equiv.), CH_3CN, 50°C, 5h, 70%; (e) HCl (cat.), MeOH , 95%, then aq. NaOH/EtOAc (quant.)

yield. RG12525 (**1**) was then nearly quantitatively liberated using concentrated HCl in 1:1 mixture of methanol and THF. The same reaction sequence applied to the synthon **4b** afforded **1** in 66% overall yield. In this case the crude **18** was isolated as an oil of which the regioisomeric components could be separated by flash chromatography. ^{1}H-NMR analysis showed that the major (higher eluting) regioisomer in the THP series (**18a**) and the triphenylmethyl derivative **17** displayed single frequencies for both methylenic units, whereas the minor THP regioisomer gave two AB systems. Based on this observation we assigned **17** and **18a** as the N-2 regioisomers, and **18b** as the more hindered N-1 regioisomer.

In summary, a convergent synthesis of the leukotriene D4 antagonist RG12525 (**1**) has been demonstrated. The hyper sensitizing agent used in the previous approach, 2-(chloromethyl)quinoline (**8**), has been replaced by the conveniently *in-situ* generated tosylate **7**. The synthons of the general formula **4** allow the introduction of the tetrazole moiety earlier in the synthesis and avoid the dialkylation and hygiene issues associated with the use of α,α'-dichloro-*o*-xylene (**3**).

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   7 ^{1}H NMR (300 MHz, CDCl3) δ 8.14 (d, 1H), 7.94 (d,1H), 7.79 (m, 3H), 7.67 9m, 1H), 7.52 (m, 2H), 7.28 (d, 2H), 5.27 (s, 2H), 2.37 (s, 3H).
6. Ratio of tosylate **7** to chloride **8** in the final reaction mixture is highly dependent on the reaction conditions. For a selective preparation of 2-(chloromethyl)quinoline (**8**) via a similar process see: White, J.D.; Yager, K.M.; Stappenbeck *J. Org. Chem.* **1993**, *58*, 3466 and cited references.
7. **9** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, 1H), 7.64 (dd, 1H), 7.51 (ddd, 1H), 7.39 (dd, 1H), 7.33 (s, 1H), 7.25 (d, 1H), 6.93 (d, 1h), 3.09 (s, 3H); HRMS calcd. for C12H11N2 (m+1) 183.0922, found 183.0917 (FAB, glycerol). Parent system has been described in: Langry, K.C. *J. Org. Chem.* **1991**, *56*, 2400.
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11. **13** mp 136-138°C, ^{1}H NMR (300 MHz, acetone-d6) δ 7.43 (m, 1H), 7.24 (m, 3H), 4.76 (s, 2H), 4.44 (s, 2H).
12. **14** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.04 (m, 19H), 4.76 (d, J=6.4Hz, 2H), 4.36 (s, 2H), 3.31 (t, J=6.4Hz, 1H, (O-H)).
13. **4a** mp 112-114°C ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.06 (m, 19H), 4.64 (s, 2H), 4.42 (s, 2H).
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16. **15** ^{1}H NMR (300 MHz, acetone-d6) δ 7.46 (m, 1H), 7.29 (m, 3H), 4.80 (s, 2H), 4.54 (s, 2H).
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