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Approaches to *p*-Hydroxyphenoxymethylquinolines Which Avoid Intermediate Chloromethylquinolines for the Synthesis of the LTD_4 Antagonist, RG 12525

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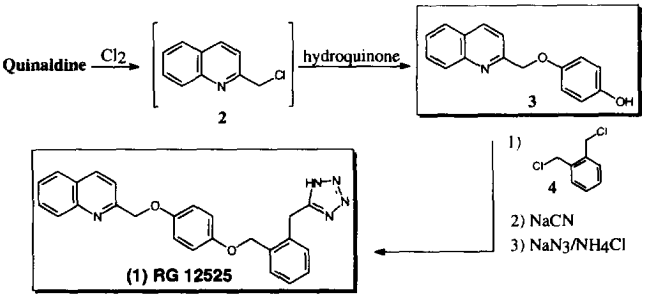
Abstract: As part of an effort to develop an industrial synthesis of the LTD_4 antagonist RG 12525 (**1**), several approaches to the intermediate (2-quinolinylmethoxy)phenol **3** were investigated that avoided the generation of the lachrymatory sensitizer α-chloro-2-methylquinoline **2**. Utilization of a cyclic sulfate in place of α,α′-dichloro-*o*-xylene **4** showed promise as a selective dialkylating agent in the conversion of **3** to RG 12525 (**1**). © 1997, Elsevier Science Ltd. All rights reserved.

In the course of the development of an orally active leukotriene antagonist for the acute treatment of asthma,[1a-c] large quantities of the promising drug candidate, RG 12525 (**1**), were needed. An early synthetic route[2] to this compound utilized the key intermediate, (2-quinolinylmethoxy)phenol **3**, which was prepared in <50% yield *via* an *in situ* chlorination of quinaldine and subsequent treatment of the nonisolated 2-chloromethylquinoline **2** with excess hydroquinone. Conversion of **3** to RG 12525 (**1**) was then effected in a straightforward manner: Monoalkylation with a large excess of α,α′-dichloro-*o*-xylene, **4**, followed by cyanide displacement of the intermediate chloromethylbenzyl ether afforded the penultimate phenylacetonitrile in moderate yield. This was converted to the tetrazole **1** (NaN_3/NH_4Cl) in an overall yield, from quinaldine, of *ca.* 27%. Although this synthesis was expedient,

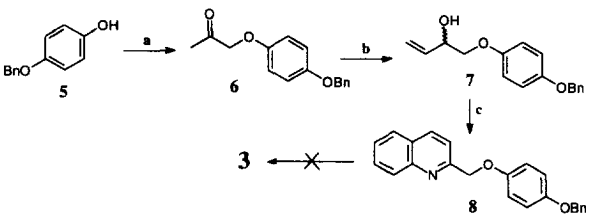


Scheme 1

alternative methodologies were needed to address the following selectivity and industrial hygiene/safety issues: *i*) The synthesis of **3** required the use of gaseous chlorine and the intermediate chloromethylquinoline **2** was a serious lachrymatory and hypersensitizing agent; *ii*) Significant amounts of the dimeric ether **13** were generated in the *p*-hydroquinone treatment of **2**. This was difficult to completely remove; *iii*) To minimize dimer formation in the alkylation of **3**, an excess of the lachrymatory α,α′-dichloro-*o*-xylene **4** was required. There also were health concerns associated with the manipulation of this material; *iv*) Hazardous waste streams containing either **2** or **4** had to be handled with great care.

To address the issues endemic to the earlier synthesis of **3**, three alternative routes were investigated, two of which postpone assembly of the quinoline framework until the end of the sequence and one which utilizes a nucleophilic substitution of an electrophilic (yet non-halogenated) methylquinoline.[3] Likewise, avoiding the use of **4** in the second half of the process prompted us to investigate a selective alkylation of a dichloroxylene synthon (cyclic sulfate of benzenedimethanol) to complete the RG 12525 synthesis.

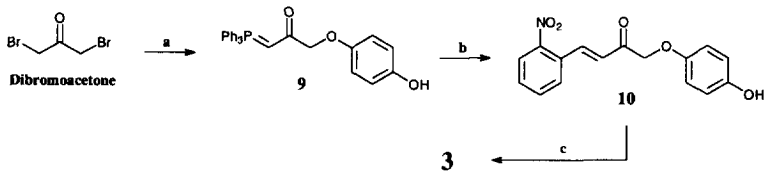
Since it had been reported[4] that 2-hydroxybut-3-ene reacts with *o*-iodoaniline in the presence of catalytic Pd(II) to give quinaldine in 62% yield, we had hoped to employ a 1-aryloxysubstituted hydroxybut-3-ene in a similar manner (Scheme 2). Alkylation of the diethylacetal of bromoacetaldehyde with monoprotected hydroquinone **5**, followed by



Scheme 2: *Reagents and Conditions:* (a) (i) NaH, THF, bromoacetaldehyde diethyl acetal, 10d; (ii) dilute HCl; (b) 1.2 eq. vinylMgBr, THF, reflux 1h, 61% from **5**; (c) 0.7 eq. *o*-iodoaniline, 0.03 eq. $PdCl_2$, 0.03 eq. PPh_3, 1.5 eq. $NaHCO_3$, 140°C, HMPA, 18h, 50% after chromatography.

hydrolysis and condensation of the aryloxyacetone intermediate **6** with vinyl magnesium bromide, afforded the desired allylic alcohol **7** in 61% overall yield. The Heck arylation of **7** with *o*-iodoaniline, cat. $PdCl_2/PPh_3$ and HMPA at 140°C proceeded sluggishly to give **8** in a 50% yield after silica gel chromatography. Unfortunately, removal of the benzyl protecting group *via* catalytic hydrogenation was nonselective, yielding toluene, hydroquinone and quinaldine rather than the intended product **3**. Although the feasibility of this general approach which constructs the quinoline ring late in the sequence had been demonstrated,[5] other strategies being concurrently examined held greater promise for a more practical solution to the overall problem.

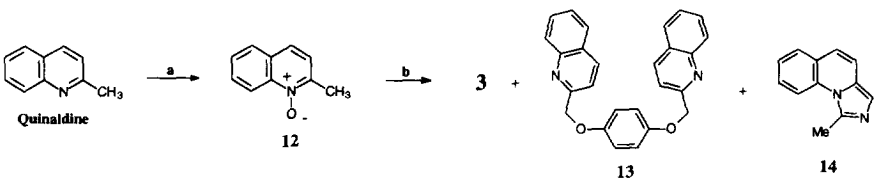
The synthesis of quinolines *via* the reduction of *o*-nitrocinnamyl derivatives is well documented.[6] Furthermore, the reductive cyclization of the condensate of *o*-nitrobenzaldehyde and the enolate of acetophenone to give 2-phenylquinolines had been previously reported,[7] albeit in low yield (17%). Nonetheless, the general approach (Friedlander type) was attractive. Since it is difficult to achieve regiospecificity in enolate formation of substituted acetones,[8] the regioisomerically pure triphenylphosphorane of 4-hydroxyphenyloxyacetone[9] was utilized instead to



Scheme 3: *Reagents and Conditions:* (a) (i) 1 eq. PPh_3, toluene (ii) NaOEt (2.5eq), hydroquinone (2.5 eq), EtOH, reflux 2h, 55% after CH_2Cl_2/EtOAc Rx; (b) *o*-nitrobenzaldehyde, EtOH, reflux 5h, 90.5% after chromatography; (c) 10 eq. Fe, AcOH, EtOH, H_2O, cat. HCl, reflux 5h, 82% after IPA Rx (41% overall from dibromoacetone).

generate the key *o*-nitrophenyl enone precursor (Scheme 3). It was found that dibromoacetone could be regiospecifically converted, in the presence of a base and hydroquinone (HQ), to the aryloxy ylide **9** in a single, concatenated step. Thus, treatment of commercially available dibromoacetone with triphenylphosphine in toluene, followed by the addition of NaOEt and excess hydroquinone, afforded the 4-hydroxyaryloxy ylide **9** in 55% yield as an off white solid after recrystallization. When carried out in two discreet operations (isolation of bromoacetonetriphenylphosphorane followed by HQ displacement), the yield of **9** increased to 65%. In either strategy, dimer formation to the bisaryloxyacetone was found to be <2%. Wittig condensation of **9** with 1 eq. of *o*-nitrobenzaldehyde afforded the desired enone **10** in 90% yield after silica gel chromatography. Reduction with Fe^0 afforded **3** in an 82% yield after recrystallization.[10] The yield of **3** from dibromoacetone ranged between 41 and 48% depending on whether the concatenated or sequential approach was used. Although unoptimized, this range was similar to that found in the earlier processes. However, dimer formation was reduced significantly and the need to generate hazardous chloromethylquinoline was completely eliminated.

In an approach related to the early process, which incorporated the quinoline fragment as starting material, the N-oxide of quinaldine[11] **12** was converted to an electrophilic methylquinoline which could be treated with oxygen nucleophiles to access the desired intermediate **3** in a single operation. Thus, **12**, in the presence of *p*-toluenesulfonic anhydride (or TsCl), underwent an intramolecular rearrangement, which upon treatment with 3 eq. of hydroquinone, afforded a 65% yield of a 9:1 mixture of **3** and the dimeric byproduct **13**. When acetonitrile was employed as the

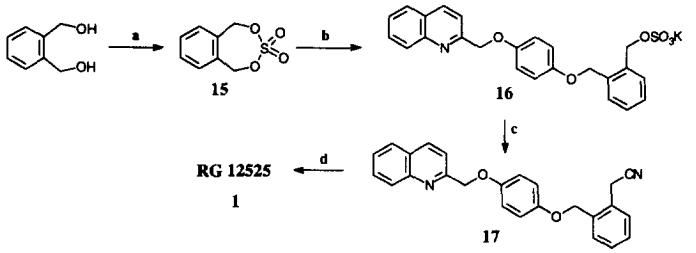


Scheme 4: *Reagents and Conditions:* (a) $H_2NCONH_2{\cdot}H_2O_2$ (UHP), phthalic anhydride, CH_2Cl_2, rt to 40°C, 82%; b) Ts_2O , K_2CO_3, MeCN, Hydroquinone (3eq), NaOH (3eq), MeOH, 65°C, 2h, 65%.

solvent, it was found to also react with the *in situ* generated quinaldine tosylate (or chloride) to generate *ca.* 3% of the imidazoquinoline byproduct **14**.[12] Both the dimer and the imidazoquinoline could be readily removed by recrystallization. The use of TsCl in place of the anhydride worked equally well from a chemical standpoint, however 3 - 10% of the lachrymatory chloromethylquinoline **2** was present in the reaction mixture (whereas the use of tosic anhydride avoided this undesirable byproduct). The unoptimized yield of **3** from quinaldine was 53%, however, as in the two previously discussed routes, dimer formation was reduced and the chloromethylquinoline intermediate was eliminated. Furthermore, this latter process required only two steps from commercially available quinaldine, which was most desirable from an industrialization point of view.

With several syntheses of **3** in hand, an approach to RG 12525 which avoids the selectivity and industrial hygiene problems associated with the use of excess α,α′-dichloro-*o*-xylene was investigated (Scheme 5). To this end, the symmetrical cyclic sulfate of 1,2-benzenedimethanol **15** was prepared in two steps[13] and 81% yield *via* the protocol of Sharpless.[14,15] Treatment with the potassium salt of **3** afforded **16** in quantitative yield after filtration. The cyanide displacement of the potassium sulfonate group generated the penultimate **17** in moderate yield (50%) after chromatography. The only other products were starting material (35%) and the benzyl alcohol (15%) which resulted

from hydrolysis of the sulfonate group. Conversion of **17** to RG 12525 (**1**) was effected in moderately high yield using established methodology (see previously discussed early synthetic method). Although unoptimized, utilization of **15** in place of **4** completely eliminated the formation of dimeric byproducts, removed the necessity of working with the strong lachrymator **4**, and required the same number of steps as the earlier process.



Scheme 5: *Reagents and Conditions:* (a) (i) 1.3 eq. $SOCl_2$, CH_2Cl_2, 0°C, 2h, 90% yield (ii) 1.5 eq. $NaIO_4$, 0.004 eq. $RuCl_3$, CCl_4:MeCN:H_2O (1:1:1.5), 91%; (b) **3**, KH, THF, 1h rt, reflux 10 min., 100%; (c) 10 eq. KCN, H_2O, reflux 8h, 50%; (d) 10 eq. NaN_3, 10 eq. NH_4Cl, DMF, 110°C, 82%.

In conclusion, several alternative processes to (2-quinolinylmethoxy)phenol **3** which avoided the selectivity and industrial hygiene issues endemic to earlier routes were identified as development candidates. Furthermore, a promising 3-step sequence for its conversion to RG 12525 (**1**) was found which utilized a ring opening of the symmetrical cyclic sulfate of benzenedimethanol as the key step. This latter approach eliminated the need for the lachrymatory, nonselective *bis*-electrophile α,α′-dichloro-*o*-xylene.

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