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Asymmetric Synthesis of A-240610.0 via a New Atropselective Approach for Axially Chiral Biaryls with Chirality Transfer

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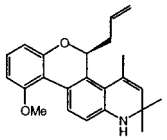
Abstract: A new approach for atropselective preparation of axially chiral biaryl was developed. This process proceeded through a chirality transfer from a stereogenic center of a secondary alcohol to the stereogenic axis via regioselective intramolecular silyl group migration. This methodology allowed for the preparation of a single atropisomer **2** in good yield (85%) with high diastereoselectivity (99:1), which subsequently led to the successful development of an efficient asymmetric synthesis of **A-240610.0**, **1**.

Introduction

Glucocorticoids have been used for the treatment of inflammatory diseases for the last 40 years,[1] but many undesirable side effects[2] are associated with the current therapies. These side effects largely occur because glucocorticoids have poor selectivity toward the glucocorticoid receptor[3] and have cross-reactivity with other steroid receptors.[4] **A-240610.0**[5] has demonstrated equivalent antiinflammatory activity relative to that of the synthetic glucocorticoids, such as prednisolone,[1c] and has shown an improved side effect profile in vivo.



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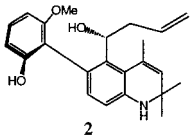
A-240610.0



2

During the process of developing an asymmetric synthesis for **A-240610.0,** we needed to prepare the homoallylic alcohol **2** as a single atropisomer to effect an efficient ether-forming reaction (vide infra). Axial chirality, resulting from the formation of two or more stable (noninterconverting) rotational isomers, has played an important role in asymmetric synthesis.[6] The increasing awareness of the importance of axial chirality in organic chemistry is partially due to the growing number of isolated chiral biaryl natural products.[7] Currently, considerable efforts are directed toward effective generation and control of axial chirality for the synthesis of axially chiral biaryls.[8] Besides the commonly used methodology of resolution of a racemic mixture, several regio- and stereoselective approaches have been recently developed.[9]

We were not able to achieve an efficient synthesis of **A-240610.0** using the existing methodologies. For example,

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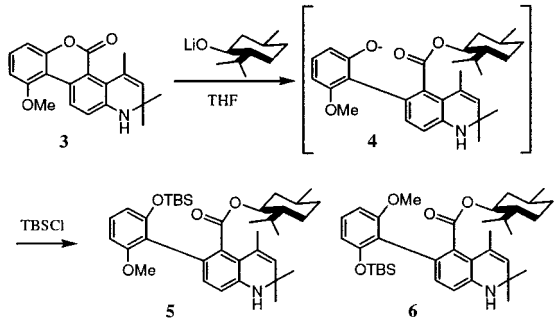
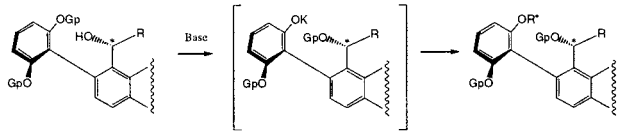
Scheme 1



using the Bringmann's lactone approach[8a] to open the lactone **3** with the chiral *O*-nucleophile (namely, the alkoxy anion generated from (+)-menthol and *n*-BuLi) only resulted in a mixture of atropisomers **5** and **6** with a ratio of 65:35 (Scheme 1). Using CBS reduction of the lactone **3** also gave unsatisfactory results.

We report here the synthesis of **A-240610.0** utilizing a novel concept to achieve atropisomeric control of axial chirality. In this approach, the chirality is transferred efficiently from an easily accessible stereogenic center of a secondary alcohol to the stereogenic axis via stereoselective intramolecular group migration (Scheme 2).

Scheme 2



(Gp = migrating group, e.g. TBS)

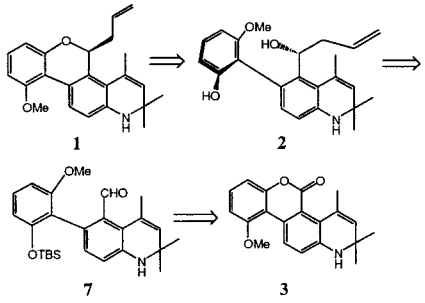
This approach converts a molecule with one easily accessible stereogenic center to a molecule possessing two stereogenic centers, of which one is axial and much more difficult to control. The success of this methodology and subsequent Mitsunobu cyclization of **2** was crucial for the synthesis of multigram quantities of **A-240610.0**.

Results and Discussion

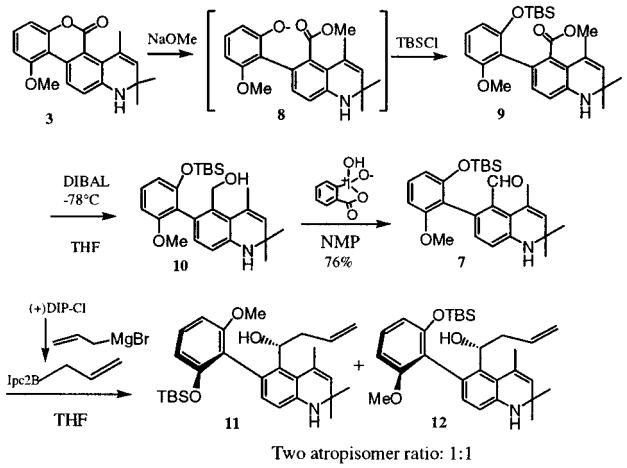
Our initial retrosynthetic analysis for the asymmetric synthesis of **1** is outlined in Scheme 3. The chiral homoallylic alcohol **2** was envisioned to arise from an asymmetric allylation of aldehyde **7** to introduce the chirality to the molecule. It should subsequently undergo cyclization under the Mitsunobu reaction conditions to produce the desired final product **1**. The aldehyde **7** could be derived from the lactone derivative **3**, which has been previously prepared.[5]

Initially, preparation of aldehyde **7** was accomplished as follows (Scheme 4): the lactone **3** was first treated with NaOMe to generate the phenolic anion intermediate **8** in situ, which was trapped with TBSCl to obtain the ester intermediate **9**. Attempted direct reduction of the ester to aldehyde was unsuccessful. The reduction with DIBAL at −78 °C produced the alcohol

Scheme 3



Scheme 4



Two atropisomer ratio: 1:1

intermediate **10** without detectable amounts of aldehyde **7**. Oxidation of the alcohol **10** to the aldehyde **7** was not straightforward. After considerable experimentation using a variety of oxidation conditions (Swern, Jones, Corey−Kim, Dess−Martin, MnO_2, PDC, TPAP, PCC, SO_3·Py), the Dess−Martin-precursor [1-hydroxy-1,2-benziodoxol-3(1 *H*)-one 1-oxide][10] was found to be the only oxidizing reagent to produce the desired aldehyde **7** in 76% yield. Later, a more efficient process for the aldehyde analogue was developed which involved DIBAL-reduction of lactone followed by the ring opening of the lactol to produce the aldehyde derivative directly (Scheme 6). Asymmetric allylation was carried out with H. C. Brown's chiral allylboron reagent,[11] prepared in-situ from commercially available DIP-Cl and allyl Grignard reagents,[11a] to produce the homoallylic alcohols **11** and **12** as a diastereomeric mixture with a ratio of about 50:50. The allylation proceeded in high yield (95%) and with high enantioselectivity[12] (90−95% ee, depending on the % ee of DIP-Cl used).

We speculated that use of this atropisomeric mixture for the cyclization could result in a low yield. Three-dimensional structures of **2** and **13** after energy minimization clearly indicated that only one atropisomer could have the correct stereoconfor-

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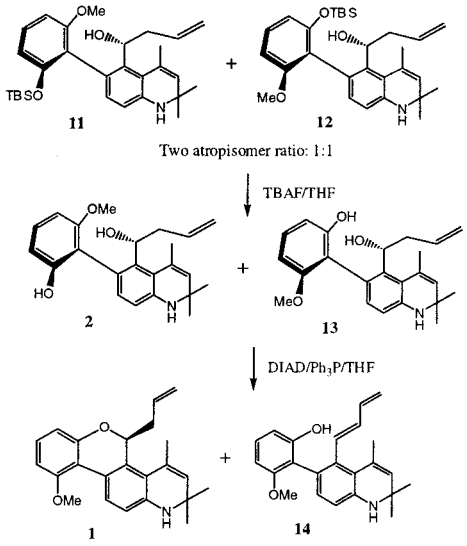
(12) The % ee of the diastereomeric mixture **11** and **12** was determined by chiral HPLC analysis using a Chiralcel OJ 4.6 mm × 250 mm column eluting with Super Critical Fluid CO_2/5% EtOH.

Scheme 5



mation to undergo an S_N2-type cyclization under Mitsunobu reaction conditions. This atropisomer has its leaving group and attacking group opposite to each other. The other atropisomer has both leaving group and attacking group on the same side so that its stereoconformation would be unfavorable for the cyclization. In addition, racemization under the Mitsunobu reaction conditions could be problematic,[13] because the atropisomers, **2** and **13**, are not only benzylic but also homoallylic.

After desilylation of the mixture of atropisomers **11** and **12**, a mixture of atropisomers **2** and **13** was obtained and was subjected to the Mitsunobu reaction conditions.[14] As predicted, low yield (42%) of the desired cyclization product **1** was obtained with the elimination product **14** as the major byproduct (Scheme 5). However, it was encouraging to find that racemization was minimal.

Interestingly, when the Mitsunobu reaction was carried out at low temperature (0 °C), only homoallylic alcohol **13** reacted, producing predominately the elimination product and other byproducts. When the reaction temperature was raised to room temperature, the atropisomer **2** then reacted, producing the desired cyclization product. The atropisomers **2** and **13** were found to be stable at room temperature (the ratio of a mixture of the atropisomers had not changed after 30 days in a THF solution). However, when the mixture was heated to 80 °C for 24 h, the ratio changed from 50:50 to 30:70 with the atropisomer **13** as the major product. As expected, when this new atropisomer mixture with a ratio of 30:70 (**2**:**13**) was subjected to the Mitsunobu reaction conditions, the reaction produced lower yield (26%) of the desired cyclization product. These experiments provided further evidence that only atropisomer **2** produces the desired cyclization product, while atropisomer **13** only leads to the elimination and other byproducts.

To improve the cyclization, other approaches using the sulfonates (tosylate, mesylate) to activate the secondary alcohol for the ring closure were also attempted. These reactions produced complex mixtures composed of several unidentified byproducts in addition to the cyclization and elimination products.

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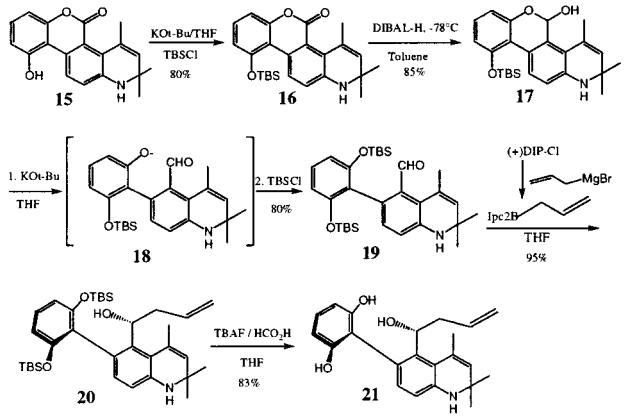
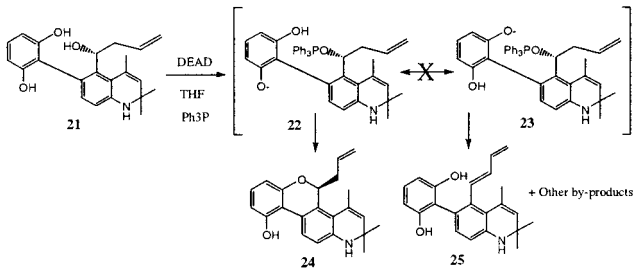
Scheme 6



Scheme 7



To overcome the atropisomer issue, we have attempted to prepare the single enantiomer **21** (Scheme 6) containing a symmetric bis-hydroxylphenol. It was hoped that the cyclization of this homoallylic alcohol would produce a higher yield of the cyclization product.

A more efficient process (Scheme 6) for the preparation of the aldehyde **19** was developed to overcome the drawbacks associated with the earlier route involving an impractical oxidation of the alcohol **10**. The 10-OH lactone derivative **15**, previously synthesized,[5] was silylated to give the lactone derivative **16**. The lactone **16** was then reduced to the lactol **17** with DIBAL. Upon treatment with KO*t*-Bu, the lactol ring of **17** was opened, producing the phenolic anion **18**, in situ. This phenolic anion **18** was then reacted with TBSCl to generate the symmetric biaryl aldehyde **19** in good yield (80%). The allylation of the aldehyde **19** was carried out following the same procedure as described in Scheme 4 using the chiral allylboron reagent to afford the bis-OTBS homoallylic alcohol **20** in high yield (95%) and with high enantioselectivity (90% ee). Desilylation under the conditions of TBAF/HCO_2H afforded the symmetric triol **21** in good yield (83%).

The triol **21** was subjected to the Mitsunobu reaction (Scheme 7); again a low yield (41%) was obtained where the major byproduct was the elimination product. Attempts to improve the reaction yield by changing the reaction parameters, such as temperature, solvent, diazo compounds, phosphine compounds, did not improve the reaction. It was interesting to find out that when the trialkylphosphine compound was used, the reaction gave much higher yield, however, complete racemization occurred. Presumably, when trialkylphosphine compounds were used in the Mitsunobu reaction, the reaction completely underwent undesired S_N1 pathway. These experiments suggested that although the starting material is symmetric, the equilibrium between the phenolic anions generated in situ is slow enough so that the atropisomerism still exists. Subsequently, only one

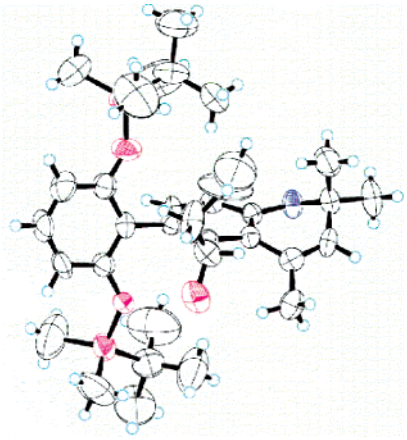
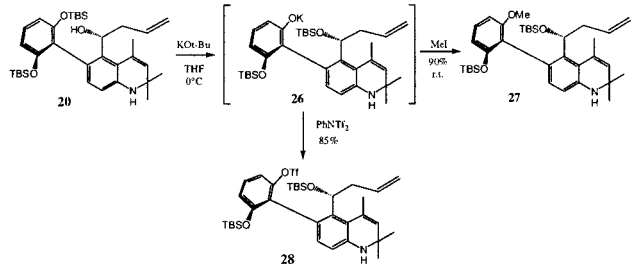
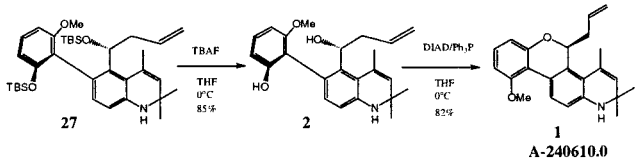


Figure 1. X-ray structure of bis-OTBS homoallylic alcohol **20**.

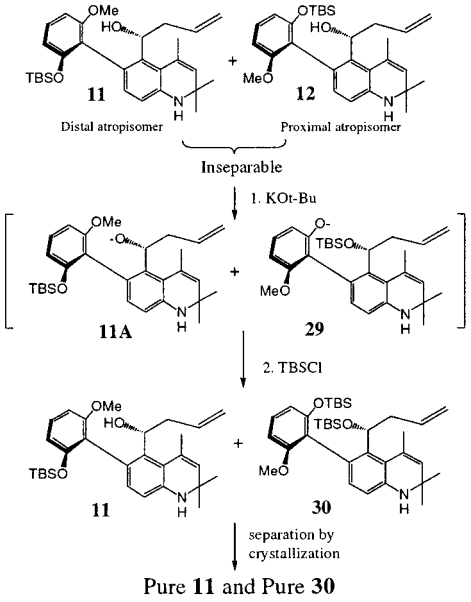
Scheme 8



Scheme 9



Scheme 10



phenolic anion atropisomer **22** has the right stereoconformation leading to the cyclization product **24**. The other atropisomer **23** has the wrong conformation which leads to elimination product **25** and other byproducts. These results are similar to the earlier results obtained in the case when the two atropisomers **2** and **13** were subjected to the Mitsunobu reaction condition (Scheme 5).

The X-ray structure of **20** (Figure 1) clearly shows that the two OTBS groups have very different spatial relationships with respect to the chiral homoallylic alcohol. Considering the fact that the stability difference between a TBS group on a secondary alcohol and on a phenolic alcohol is quite noticeable, the approach to achieve control of axial chirality via intramolecular silyl group migration was proposed. When bis-OTBS homoallylic alcohol **20** was treated with KO*t*-Bu in THF at 0 °C, a clean intramolecular silyl group migration occurred (Scheme 8) to form a more stable phenolic anion **26**. The intermediate **26** was then trapped with methyl iodide to obtain the atropisomer **27** in high yield (85%) with high diastereoselectivity (99:1). The original chirality was unaffected (90% ee). Similarly, the phenolic anion **26** was trapped with *N*-phenylbis(trifloromethanesulfonimide) to generate the triflate **28**.

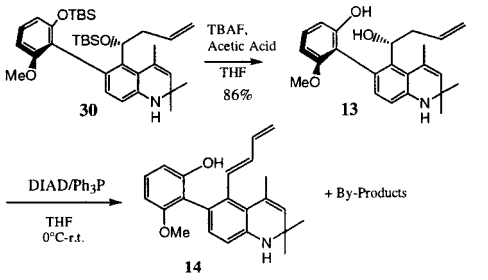
Thus, a single atropisomer was easily prepared by a simple intramolecular silyl group migration process. The easily accessible chirality of molecule **20** was transferred to molecule **27** along with generating a new axial chirality that is normally not easily installed.

With the single atropisomer **27** in hand, desilylation with TBAF provided the pure atropisomer **2** in good yield (85%). Two-dimensional NMR experiments of **2** showed a strong NOE between the hydroxyl group of homoallylic alcohol and the methoxy group, which indicated that the hydroxyl group of homoallylic alcohol was in a proximal relationship to the 10-methoxy group. The Mitsunobu reaction of **2** (Scheme 9) produced the desired cyclization product **1** in good yield (82%) and satisfactory optical purity (85% ee). The % ee of the product can be further improved by crystallization with IPA to greater than 99%.

To further confirm that atropisomer **13** leads to elimination product and other byproducts under the Mitsunobu reaction conditions. The isolation of the opposite atropisomer **13** was attempted (Scheme 10). The initially formed atropisomers **11** and **12** (Scheme 4) from the asymmetric allylation were found to be inseparable by column chromatography, as were the desilylation products **2** and **13**. By using the strategy of proximal silyl group migration, separation of the two atropisomers was achieved. Thus, when a mixture of atropisomers **11** and **12** (ratio: 50:50) was reacted with KO*t*-Bu, the regioselective intramolecular silyl group migration occurred only with the atropisomer **12** containing an OTBS group proximal to the hydroxyl group of the homoallylic alcohol. The phenolic hydroxyl anion **29** generated was trapped with TBSCl to produce a highly nonpolar bis-OTBS compound **30**. No intramolecular silyl group migration was observed with atropisomer **11**, because the OTBS group was distal to the hydroxyl group of homoallylic alcohol. The alkoxyl anion **11A** generated was too bulky to be silylated. Now the bis-OTBS atropisomer **30** obtained had very different physical properties compared to the unreacted mono-OTBS derivative **11**. These two atropisomer derivatives were now easily separated by crystallization.

The bis-OTBS homoallylic alcohol **30** was then desilylated to produce the atropisomer **13** (Scheme 11). Two-dimensional NMR experiments of **13** provide strong evidence of a proximal relationship between the phenolic hydroxyl group and the hydroxyl group of homoallylic alcohol. A strong NOE was observed between the 10-methoxy group and the proton on the

Scheme 11



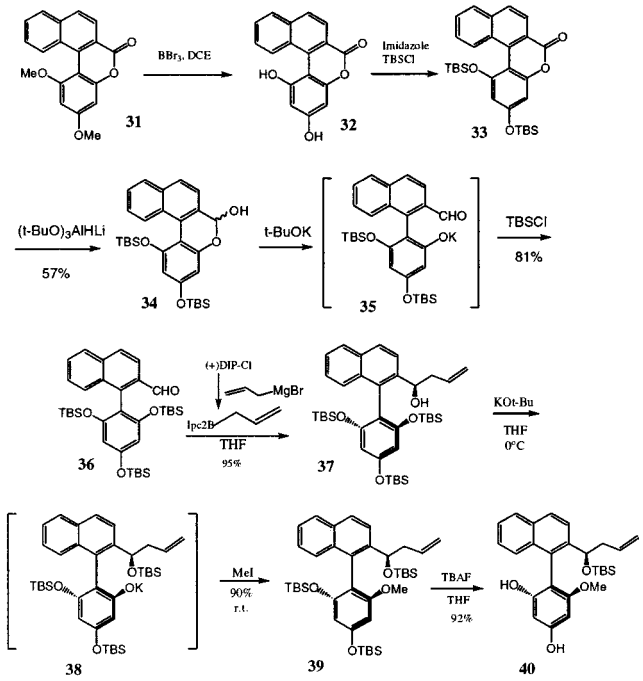
adjacent aryl ring, and a weak NOE was observed between the phenolic hydroxyl group and the allyl methylene group.

When the homoallylic alcohol **13** was subjected to Mitsunobu reaction conditions, the elimination product **14** was confirmed as the major product along with several other unidentified byproducts. A very small amount (<5%) of cyclization product was also produced, presumably through the undesired S_N1 pathway.

The further application of this methodology for atropselective transformation to produce axially chiral biaryls is demonstrated by an additional example (Scheme 12). The aldehyde intermediate **36** was prepared using a protocol similar to that described in Scheme 6. Thus, the lactone intermediate **31**, prepared using the literature procedure,[15] was demethylated using BBr_3 followed by protecting the phenolic hydroxy groups with TBSCl. The TBS protected lactone **33** was then reduced with (*t*-BuO)$_3$AlHLi to give lactol **34** in 57% yield; the ring opening of lactol with KO*t*-Bu followed by trapping the phenolic intermediate **33** with TBSCl gave the aldehyde **36** in 81% yield. The asymmetric allylation was achieved using the procedure similar to that described in Scheme 4 with the chiral allylboron reagent to afford the tris-OTBS homoallylic alcohol **37** in high yield (95%) and with good enantioselectivity (86% ee). The single atropisomer **39** was then prepared in 90% yield with high diastereoselectivly (other diastereomers were not detected by both HPLC and NMR) using the same procedure as described in Scheme 8 involving an intramolecular silyl group migration process. Desilylation of **39** produced the single atropisomer **40** in 92% yield.

In summary, we have developed a new methodology for atropselective preparation of axially chiral biaryls. The chirality

Scheme 12



transfer from an easily accessible stereogenic center of a secondary alcohol to the stereogenic axis can be easily accomplished by a regioselective intramolecular silyl group migration. This methodology has been successfully demonstrated in the synthesis of the single atropisomer intermediate **27**, ultimately leading to an efficient and practical process for the asymmetric synthesis of **A-240610.0 1**

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Supporting Information Available: Complete experimental procedures, spectroscopic data, and X-ray structure data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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