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Regiocontrolled Rearrangement of Isobenzofurans

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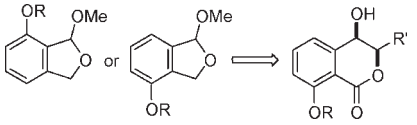
ABSTRACT



The regioselective alkylation and oxidative rearrangement of isobenzofurans has been achieved to generate substituted 4,8-dihydroxyisochromanones in good yields and with complete regiocontrol.

Isochroman-1-ones are pharmacophores present in a number of natural products with therapeutic potential.[1] The 4,8-dihydroxyisochroman-1-one motif is particularly significant, as it is a key structural component in a number of biologically active metabolites such as the ajudazols **1**,[2] acetoxygeranyloxymellein **2**,[3] thailandolide **3**,[4] the *Helminthosporium monoceras* antifungal metabolite **4**,[5] and (4*R*)-hydroxyochratoxin **5** (Figure 1).[6]

However, despite their potential as therapeutic leads, the approaches currently available for the syntheses of substituted 4,8-dihydroxyisochroman-1-ones tend to be either low yielding or not flexible enough for the efficient generation of analogues.

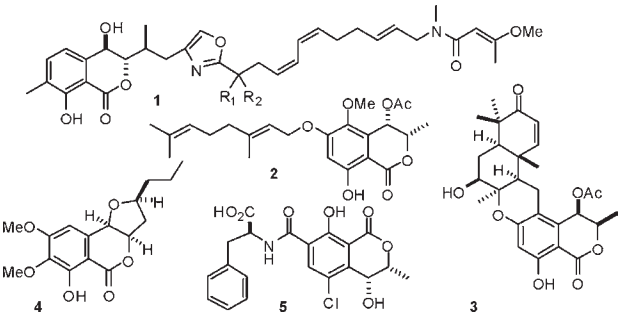


Figure 1. 4,8-Dihydroxyisochroman-1-one containing natural products.

Recently, we reported the fast and efficient synthesis of simple 4-hydroxyisochroman-1-one units **7** through a high-yielding four-step sequence starting from phthalan **6**. The entire process requires minimal purification and does not require the isolation of any of the intermediate species (Scheme 1).[7]

Mechanistically, we believe that the phthalan unit **6** is deprotonated with LDA to generate the unstable

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(1) Wittig, G.; Pohmer, L. *Chem. Ber.* **1956**, *89*, 1334.
(2) (a) Jansen, R.; Kunze, B.; Reichenbach, H.; Hofle, G. *Eur. J. Org. Chem.* **2002**, 917. (b) Kunze, B.; Jansen, R.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **2004**, *57*, 151.
(3) Appendino, G.; Ozen, H. C.; Jakupovic, J. *Phytochemistry* **1994**, *36*, 531.
(4) Dethoup, T.; Manoch, L.; Kijjoa, A.; Pinto, M.; Gales, L.; Damas, A. M.; Silva, A. M. S.; Eaton, G.; Herz, W. *J. Nat. Prod.* **2007**, *70*, 1200.
(5) Arai, K.; Ooka, M.; Koizumi, F.; Koda, S.; Iwasaki, Y.; Kanemoto, Y. U.S. Patent Int. 5,530,146, 1996.
(6) Zepnik, H.; Pahler, A.; Schauer, U.; Dekant, W. *Toxicol. Sci.* **2001**, *59*, 59.
(7) Hobson, S. J.; Parkin, A.; Marquez, R. *Org. Lett.* **2008**, *10*, 2813.

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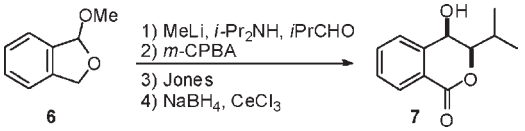
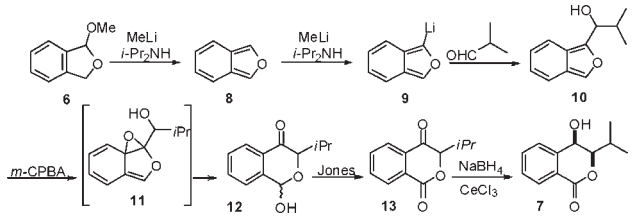
Scheme 1



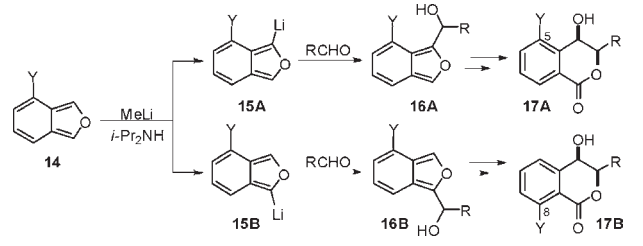
isobenzofuran unit **8** which is deprotonated to afford the lithiated isobenzofuran **9**. The isobenzofuran anion **9** is then trapped with an aldehyde to generate the postulated α-hydroxyisobenzofuran **10**, which upon treatment with *m*-CPBA undergoes a hydroxyl-directed epoxidation to generate epoxide **11** that then rearranges to the desired lactol **12**. Oxidation of the lactol **12** to the lactone **13** followed by regioselective reduction completes the diastereoselective synthesis of the isochromanone **7**. The stereochemical outcome of the reduction is dependent on the nature of the alkyl side chain, with the *syn* diastereomer being the preferred product. The relative stereochemistry can be determined by ^{1}H NMR analysis (J_{ab} *syn* ≤ 2.5 Hz; J_{ab} *anti* ≥ 6.0 Hz) (Scheme 2).

Scheme 2



On the basis of our proposed mechanism, it was postulated that if a C4-substituted isobenzofuran unit **14** could be generated, then it would be possible to use the C4 group to influence the subsequent deprotonation step. A regioselective deprotonation would then allow for the selective formation of either the C5 **17A** or the C8-substituted isochromanone **17B** (Scheme 3). The ability to control the regiochemistry of the deprotonation step is crucial if substituted 4,8-dihydroxyisochromanones are to be accessed using this methodology.

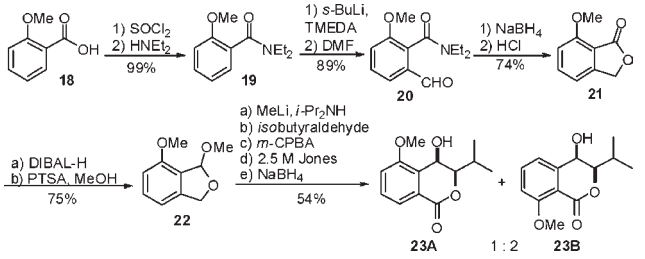
Scheme 3



It was decided to focus initially on the synthesis and rearrangement of 4-methoxyisobenzofuran. The methoxy group was chosen because of its likely stability to withstand the reaction conditions while simultaneously allowing the assessment of the reliability and flexibility of the oxidative rearrangement in the presence of a potentially competing methyl enol ether.

Our synthesis began with 2-methoxybenzoic acid **18**, which was converted to the diethylamide **19** in excellent yield. Ortho-formylation of amide **19** cleanly generated the desired aldehyde **20**, which upon reduction followed by acid treatment afforded lactone **21**.[8] Dibal reduction provided the desired lactol, which was then converted to the key methyl acetal **22** in excellent yield (Scheme 4).

Scheme 4



Treatment of methyl acetal **22** under our rearrangement conditions yielded the isochromanones **23A** and **23B** in excellent yield and, significantly, as a 1:2 ratio of regioisomers. The regiochemistry of the isochromanones was corroborated by X-ray crystallography (Figure 2).[9]

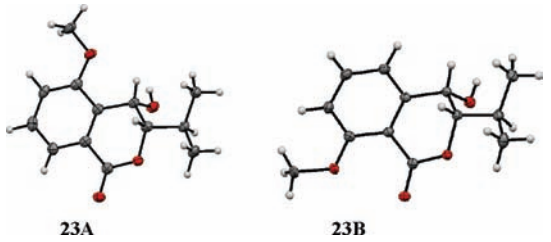


Figure 2. Crystal structure of isochromanones **23A** and **23B**.

This result was consistent with the methoxy group directing the deprotonation of the isobenzofuran unit to the C1 position **B** over the C3 position **A** (Figure 3). This highly encouraging result made us confident that a more

(8) De Silva, S. O.; Reed, J. N.; Billedeau, R. J.; Wang, X.; Norris, D. J.; Snieckus, V. *Tetrahedron* **1992**, *48*, 4863.

(9) The atomic coordinates for **23A**, **23B**, and **48B** (CCDC deposition nos. CCDC809799, CCDC809800, and CCDC813670) are available upon request from the Cambridge Crystallographic Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K. The crystallographic numbering system differs from that used in the text; therefore, any request should be accompanied by the full literature citation of this paper.

sterically demanding group at the C7 position of the phthalan starting material **22** would be able to further influence the product ratio in favor of the desired C1 alkylation product.

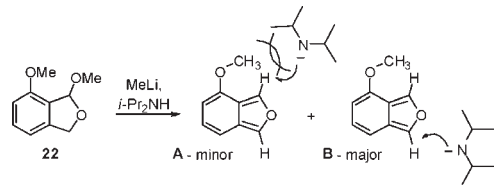
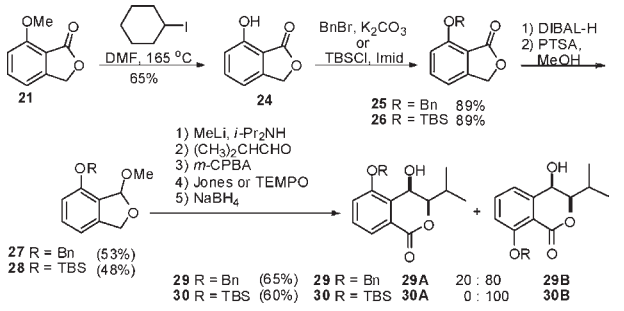


Figure 3. Methoxy-directed isobenzofuran deprotonation.

Deprotection of methoxy phthalide **21** with iodocyclohexane afforded the free hydroxyl **24** in good yield. The hydroxyl group was then capped as the benzyl and *tert*-butyl dimethylsilyl ethers **25** and **26** in excellent yield (Scheme 5). DIBAL reduction followed by treatment of the resulting lactols with methanol under acidic conditions generated the required phthalans **27** and **28**.

Scheme 5



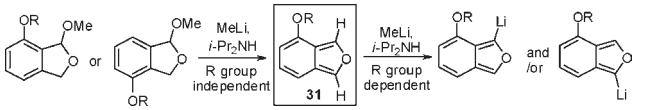
Treatment of phthalans **27** and **28** with LDA followed by trapping with isobutyraldehyde and oxidative rearrangement of the resulting α-hydroxy isobenzofurans generated the desired lactol intermediates. At this point, it was decided to replace the Jones oxidation step of the original sequence with the milder TEMPO oxidation to avoid any undesired loss of the C4 isobenzofuran protecting groups. Regioselective reduction of the ketone unit then afforded the isochromanones **29** and **30** in excellent overall yield.

As expected, introduction of the more sterically demanding benzyl ether at the C7 position of the starting phthalan resulted in an improved ratio of regioisomeric isochromanones **29A**/**29B** (1:4) compared to that obtained with the methoxy substituent.

The C7 OTBS-substituted phthalan **28** on the other hand, afforded the desired isochromanone **30B** as a single product in excellent yield over the reaction sequence.

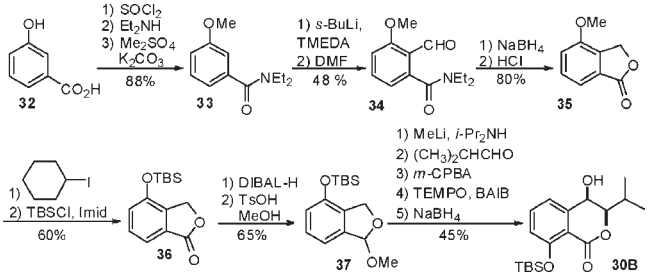
At this point, it was decided to explore the effects of C4 phthalan substituents on the regioselectivity of isochromanone formation. It was hypothesized that if the reaction proceeds through an isobenzofuran intermediate **31**, rearrangement of the C4 silyloxy-substituted phthalan derivative should yield the same isochromanones as the C7-substituted phthalan **28** with the same regioisomeric selectivity (Scheme 6).

Scheme 6



The synthesis of the C4 silyloxy-substituted phthalan **37** began with benzoic acid **32**, which was converted into the diethyl amide and then methylated to afford methyl ether **33**. Regioselective formylation of amide **33** using Snieckus' conditions afforded aldehyde **34**, which upon reduction and acid treatment afforded lactone **35** in good yield (Scheme 7).

Scheme 7



Iodocyclohexane promoted deprotection followed by silylation afforded the TBS ether **36**. Reduction of lactone **36** followed by acidic methanol treatment resulted in the desired TBS phthalan **37**. Gratifyingly, treatment of phthalan **37** under our optimized conditions yielded the desired isochromanone **30B** in 45% yield and as a single regioisomer.

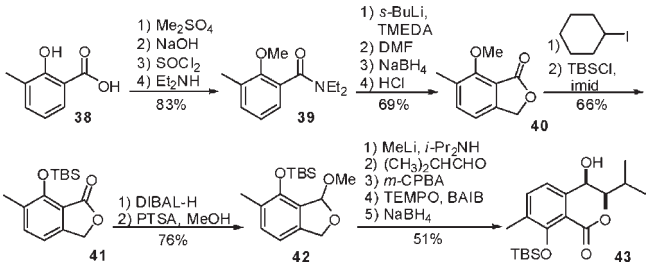
We believe that the drop in yield observed in the case of the C4 isomer is likely to be due to the steric hindrance provided by the silyloxy group during the initial rate-determining isobenzofuran formation. However, once the isobenzofuran unit is generated, the same steric hindrance provided by the TBS group controls the regiochemistry for alkylation.

Having shown the ability of using either a C7 or C4 phthalan substituent to control the regiochemistry of isobenzofuran alkylation and subsequent rearrangement to yield C8-substituted isochromanones exclusively, this approach was applied to the synthesis of the isochromanone unit of the ajudazols

The ajudazols **1** are biologically active metabolites isolated from the myxobacteria *Chondromyces crocatus*. Structurally, the ajudazols showcase a number of highly unusual features such as 4,8-dihydroxy-7-methylisochroman-1-one and 3-methoxybutenoic acid methyl amide.[6]

Our synthesis of the ajudazols' 4,8-dihydroxy-7-methylisochroman-1-one subunit began with 3-methylsalicylic acid **38**, which was converted into diethyl amide **39** (Scheme 8). Directed *ortho*-formylation of amide **39** generated the corresponding aldehyde, which upon reduction and acid treatment yielded the desired lactone **40**.[8] Replacement of the methyl protecting group for the required TBS unit proceeded cleanly to yield lactone **41**. Lactone reduction followed by methanolic acid treatment afforded the required phthalan **42**.

Scheme 8



Treatment of phthalan **42** under our optimized protocol conditions afforded the desired 4,8-dihydroxy-7-methylisochroman-1-one **43** in good yield and as a single regioisomer.

Having observed the ability of phthalan **42** to regioselectively couple with a simple aldehyde, a more relevant model system was envisioned which incorporated the functionality present in the ajudazols.

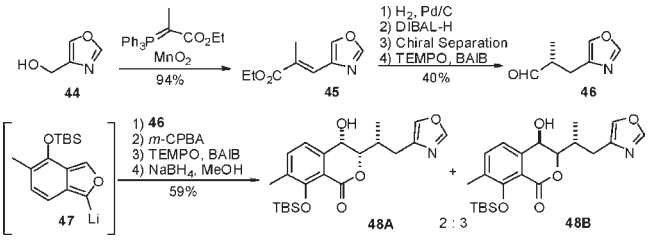
Oxazole **44** was subjected to a Taylor tandem oxidation–olefination to afford ester **45** in excellent yield.[10] Hydrogenation of ester **45** followed by DIBAL reduction afforded the primary alcohol, which was resolved through the use of chiral HPLC.[11] The novel nature of the enantiomeric alcohols obtained meant that one of the enantiomeric components had to be arbitrarily chosen. TEMPO oxidation of the enantiomerically pure alcohol yielded aldehyde **46**. Reaction of aldehyde **46** with the phthalan **42** derived isobenzofuran **47** produced the diastereomeric isochromanones **48A** and **48B** in 59% yield (Scheme 9). The regiochemical outcome of the rearrangement as well as the absolute stereochemistry of the isochromanone (and *via infra* that of aldehyde **46**) were corroborated by X-ray crystallographic analysis of the 4,8-dihydroxyisochroman-1-one **48B** (Figure 4).

In conclusion, we have demonstrated the ability to control the regiochemistry of isobenzofuran alkylation

(10) Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851.

(11) Each enantiomeric alcohol was obtained in 49% yield and 99% ee.

Scheme 9



to generate 4,8-dihydroxyisochroman-1-ones regioselectively and in excellent overall yield. Although the reduction step of the rearrangement sequence yields the *syn* relation exclusively, the analogous *anti* relationship can be obtained by treatment of the isochromanone product under Mitsunobu conditions as demonstrated previously.[7]

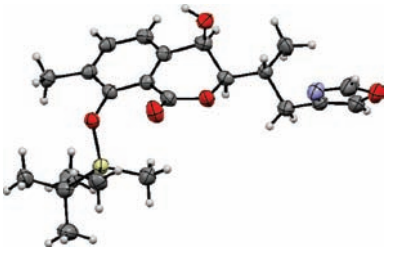


Figure 4. 4,8-Dihydroxyisochroman-1-one **48B**.

Crucially, however, the successful coupling of isobenzofuran **47** with aldehyde **46** demonstrates the ability of the isobenzofuran rearrangement to take place in the presence of potentially conflicting unsubstituted C2-oxazoles. Efforts are currently underway to apply this methodology to the total synthesis of the ajudazols.

Acknowledgment. We thank the EPSRC Pharma Synthesis Network and Pfizer for postgraduate support (B.A. E.). We also thank Dr. Ian Sword, the EPSRC, and Pfizer for funding.

Supporting Information Available. Experimental procedures and characterization data of the described compounds and intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.