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Oxidative Rearrangements of Isobenzofurans: Studies toward the Synthesis of the Ajudazols

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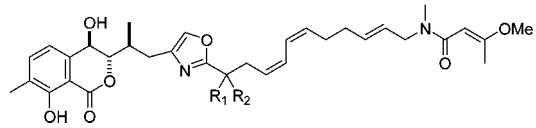
ABSTRACT



We present a new facet of isobenzofuran chemistry which allows for its efficient manipulation to generate biologically relevant entities. This methodology has been successfully applied toward the synthesis of ajudazol A.

As part of our efforts toward the synthesis of biologically active natural products, we have become interested in the development of new approaches toward the efficient synthesis of isochromanones.

Isochromanones are biologically relevant building blocks which are present in a significant number of biologically active compounds such as the ajudazols **1**,[1] (4*R*)-hydroxyochratoxin A **2**,[2] acetoxy-geranyloxymellein **3**,[3] thailandolide B **4**,[4] bergenin **5**,[5] and the *Helminthosporium monoceras* antifungal metabolite monocerin **6**[6] (Figure 1).

Isobenzofurans **7** were conceived originally by Wittig and Pohmer[7] and were later validated by Fieser and Haddadin as highly reactive intermediates through exquisite trapping studies.[8]

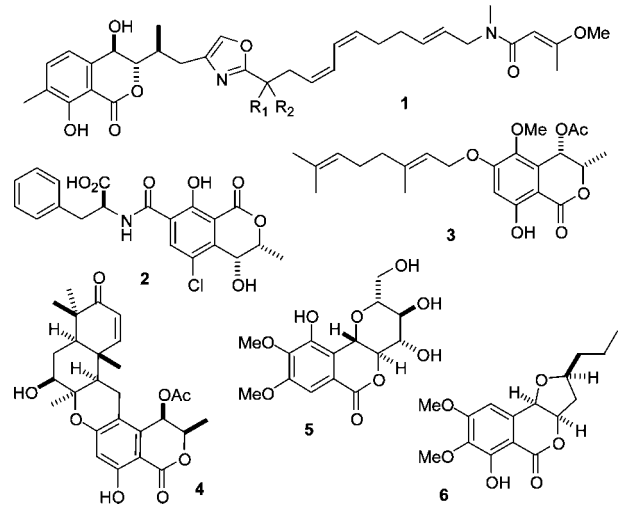


Figure 1. Isochromone-containing natural products.

Although a significant amount of time and effort has been dedicated to the development of excellent methods for the generation of isobenzofuran and its derivatives, their synthetic

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(1) (a) Jansen, R.; Kunze, B.; Reichenbach, H.; Hofle, G. *Eur. J. Org. Chem.* **2002**, 917. (b) Reichenbach, H. *J. Ind. Microbiol. Biotechnol.* **2001**, *27*, 149. (c) Kunze, B.; Rolf, J. A.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **2004**, *57*, 151.

(2) Zepnik, H.; Pahler, A.; Schauer, U.; Dekant, W. *Toxicol. Sci.* **2001**, *59*, 59.

(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) Takahashi, H.; Kosada, M.; Watanabe, Y.; Nakade, K.; Fukuyawa, Y. *Bioorg. Med. Chem.* **2003**, *11*, 1781.

(6) Arai, K.; Ooka, M.; Koizumi, F.; Koda, S.; Iwasaki, Y.; Kanemoto, Y. U.S. Patent Int. 5,530,146, 1996.

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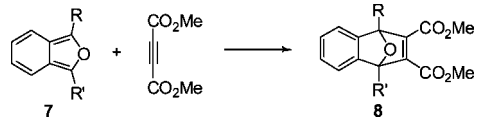
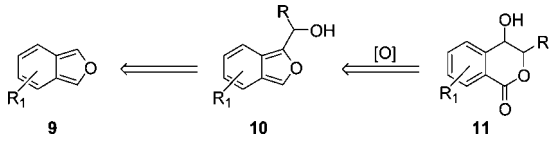
application has been mostly limited to function as dienes in Diels−Alder and singlet oxygen cycloaddition reactions (Scheme 1).[9,10]

Scheme 1. Traditional Use of Isobenzofuran Units



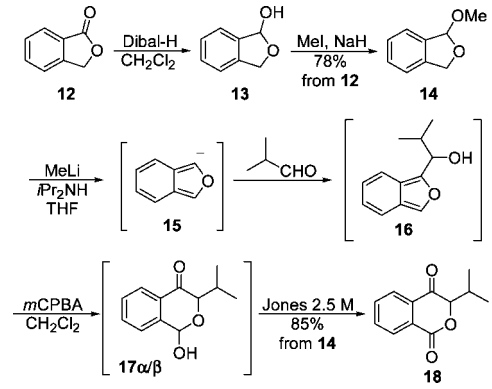
We would now like to report the novel oxidative rearrangement of α-hydroxyisobenzofurans **10**, which radically expands the use and scope of isobenzofurans **9** as synthetic intermediates and permits the fast and efficient generation of isochroman-1-ones **11** (Scheme 2).

Scheme 2. Proposed Approach to Isobenzofurans



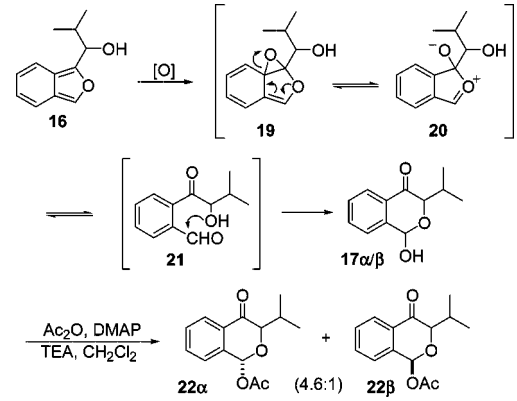
In our approach to the synthesis of isochroman-1-ones, commercially available phthalide **12** was reduced and the resulting lactol **13** was methylated to generate acetal **14**.[11] Reaction of acetal **14** with methyllithium and diisopropylamine then generated the isobenzofuran anion **15**, which was trapped with isobutyraldehyde to produce the highly reactive α-hydroxyisobenzofuran **16**. The key α-hydroxyisobenzofuran **16** was then successfully rearranged under oxidative conditions to generate the labile lactols **17**α/*β*, which upon oxidation then generated the desired keto lactone **18** in excellent yield from methyl acetal **14** and with no need of purification (Scheme 3).

Scheme 3



We believe that the oxidation mechanism is analogous to that postulated by Achmatowicz for the oxidative rearrangement of simple furfuryl alcohols and amines.[12] Hence, it would be reasonable to expect the hydroxyl group to direct the epoxidation to generate epoxide **19** (Scheme 4). Zwitterion formation followed by ring opening generates aldehyde **21**, which can cyclize to generate the unstable lactols **17**α/*β*. However, the lactol intermediates can be isolated as the corresponding acetates **22**α/*β*. As expected, the α-anomer is the dominant species.

Scheme 4



The methodology was applied successfully to a number of substrates to generate the desired keto lactones **18** and **23**−**32** in excellent yield. Surprisingly, a phenyl substituent (entry 9) can be tolerated under the reaction conditions without detrimental effect (Scheme 5).

Having successfully achieved the synthesis of the key keto lactone core unit, conditions for the selective reduction of the ketone unit were investigated. Treatment of the keto lactones **18** and **23**−**32** under Luche conditions proceeded to generate the desired isochroman-1-one units **33**−**43** with complete regioselectivity and in good yield (Scheme 6).

As expected, the stereochemical outcome of the reduction is highly dependent on the nature of the alkyl side chain,

(7) Wittig, G.; Pohmer, L. *Chem. Ber.* **1956**, *89*, 1334.

(8) (a) Fieser, L. F.; Haddadin, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 2081. (b) Fieser, L. F.; Haddadin, M. J. *Can. J. Chem.* **1965**, *43*, 1599. (c) Haddadin, M. J. *Heterocycles* **1978**, *9*, 865. (d) Friedrichsen, W. *Adv. Heterocycl. Chem.* **1980**, *26*, 135. (e) Wiersum, U. E. *Aldrichim. Acta* **1981**, *14*, 53.

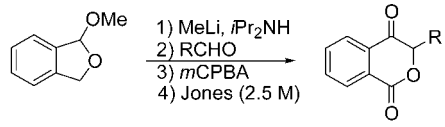
(9) (a) Wiersum, U. E.; Mijs, W. J. *J. Chem. Soc., Chem. Commun.* **1972**, 347. (b) Plaumann, H. P.; Smith, J. G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**, 354. (c) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 3849. (d) Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1976**, 287. (e) Hayakawa, K.; Yamaguchi, Y.; Kanematsu, K. *Tetrahedron Lett.* **1985**, *26*, 2689. (f) Mikami, K.; Ohmura, H. *Org. Lett.* **2002**, *4*, 3355.

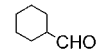
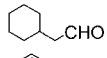
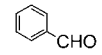
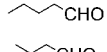
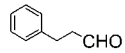
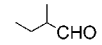
(10) (a) Friedrichsen, W. *Adv. Heterocycl. Chem.* **1999**, *73*, 1. (b) Reck, S.; Friedrichsen, W. *Prog. Heterocycl. Chem.* **1997**, *9*, 117. (c) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093. (d) Wege, D. *Adv. Theor. Interesting Mol.* **1998**, *4*, 1. (e) Rainbolt, J. E.; Miller, G. P. *J. Org. Chem.* **2007**, *72*, 3020. (f) Chan, C. W.; Wong, H. N. C. *J. Am. Chem. Soc.* **1988**, *110*, 462.

(11) Crump, S. L.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 304.

(12) (a) Hobson, S. J.; Marquez, R. *Org. Biomol. Chem.* **2006**, *4*, 3808. (b) Achmatowicz, O.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973. (c) Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, 105. (d) Harris, J. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 2029.

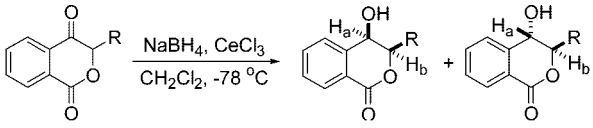
Scheme 5[a,b]

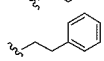


entry	RCHO	keto-lactone[a]	entry	RCHO	keto-lactone[a]
1)		**18** (85%)	7)		**28** (57%)
2)		**23** (94%)	8)		**29** (67%)
3)		**24** (84%)	9)		**30** (64%)
4)		**25** (82%)	10)		**31** (93%)
5)		**26** (72%)	11)		**32** (95%)[b]
6)		**27** (83%)			

[a]Compounds could be taken on without purification. [b]Isolated as a 1.6:1.0 mixture of diastereomers.

Scheme 6



entry	R	(yield)	syn:anti
1)		**33** (96%)	100:0
2)		**34** (90%)	50:50
3)		**35** (71%)	60:40
4)		**36** (56%)	90:10
5)		**37** (80%)	75:25
6)		**38** (77%)	100:0
7)		**39** (82%)	100:0
8)		**40** (58%)	50:50
9)		**41** (48%)	100:0
10)		**42** (90%)	50:50
11)		**43** (76%)	100:0

with the syn diastereomer being the preferred product. The relative stereochemistry was determined through ^{1}H NMR analysis (J_{ab} syn $\leq$ 2.5 Hz; J_{ab} anti $\geq$ 6.0 Hz) and further corroborated through X-ray crystallography in the case of compound **39** (Figure 2).[13]

In a desire to further investigate the synthetic potential of our newly developed α-hydroxyisobenzofuran oxidative rearrangement and to determine the scope of the rearrangement in the presence of more complicated aldehyde systems, the synthesis of the ajudazol A western section model system **44** was undertaken (Figure 3).

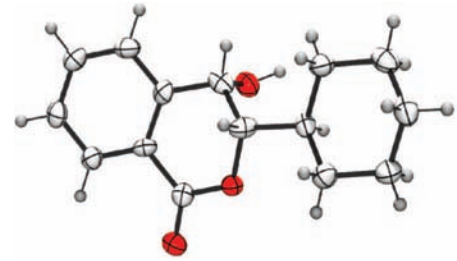


Figure 2. Crystal structure of isochromone **39**.

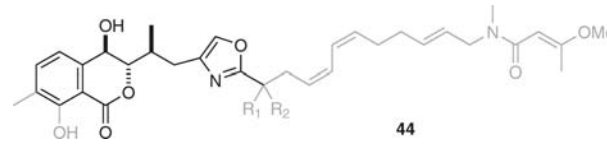


Figure 3. Ajudazol western section model system.

Chondromyces strains have long been recognized as a significant source of biologically active natural products including the crocacins and the chondramines.[1] Ajudazols A and B are two of the latest biologically active metabolites to be 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. Biologically, the ajudazols have been identified as inhibitors of the bacterial mitochondrial electron transport chain at low nanomolar concentrations.[1c]

The combination of novel structural features together with their biological potential makes the ajudazols attractive synthetic targets. Although a total synthesis of either ajudazol has yet to be achieved, Taylor and Rizzacasa have reported their respective approaches to the eastern portion of ajudazol A.[14,15]

Our synthesis began with serine methyl ester **45**, which was rapidly converted to oxazole **46** in acceptable yield. Ester reduction followed by a Swern oxidation then afforded the oxazole aldehyde **47** in reasonable yield (Scheme 7).[16,17] Olefination of aldehyde **47** under stabilized Wittig conditions

(13) The atomic coordinates for **39** (CCDC deposition no. CCDC676871) 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.

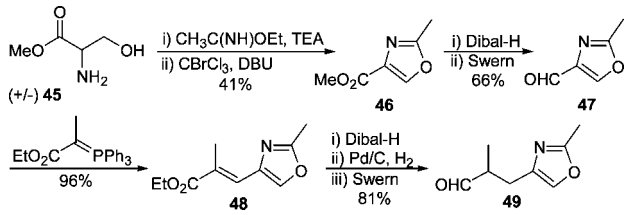
(14) Krebs, O.; Taylor, R. J. K. *Org. Lett.* **2005**, *7*, 1063.

(15) Ganame, D.; Quach, T.; Poole, C.; Rizzacasa, M. A. *Tetrahedron Lett.* **2007**, *48*, 5841.

(16) Benoit, G.-E.; Carey, J. S.; Chapman, A. M.; Chima, R.; Hussain, N.; Popkin, M. E.; Roux, G.; Tavassoli, B.; Vaxelaire, C.; Webb, M. R.; Whatrup, D. *Org. Process Res. Dev.* **2008**, *12*, 88.

(17) We are grateful to Dr. J. Carey for generous amounts of aldehyde **47**.

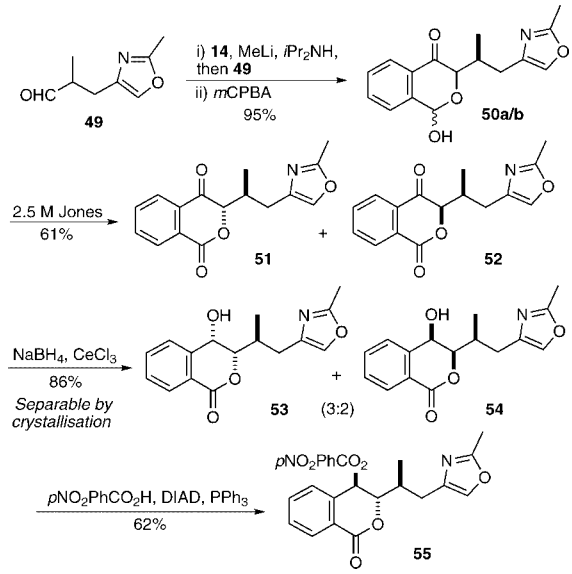
Scheme 7



then produced the required conjugated ester **48** in high yield and complete *E* selectivity. Ester reduction followed by alkene hydrogenation and Swern oxidation produced the pivotal aldehyde **49** in high yield over the three-step sequence.

Coupling of aldehyde **49** with isobenzofuran anion **15** (generated under the same conditions previously described) followed by oxidative rearrangement of the carbinol intermediate and Jones oxidation of the resulting lactols **50**α/β generated the desired keto lactones **51** and **52** in good yield over the entire sequence and as a 3:2 mixture of diastereomers (Scheme 8).

Scheme 8



Luche reduction of the diastereomeric mixture of keto lactones **51** and **52** proceeded in good yield and with complete facial selectivity to afford the isochromones **53** and **54** which could be separated by selective crystallization of the major diastereomer **53** (Figure 4).[18]

(18) The atomic coordinates for **53** (CCDC deposition no. CCDC676872) 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.

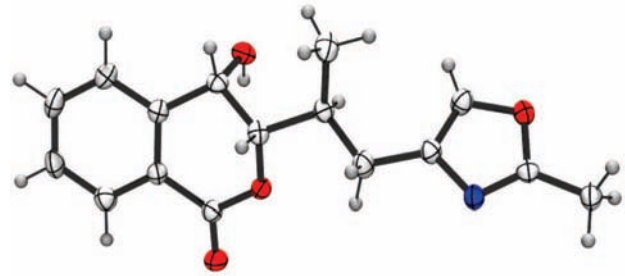


Figure 4. Crystal structure of isochromone **53**.

Treatment of iso-chromone **53** under Mitsunobu conditions successfully produced the benzoate ester **55** matching the stereochemistry present in the western section of the ajudazols.

In conclusion, we have developed a convergent and versatile approach to the synthesis of isochroman-1-ones from simple phthalides through a completely novel application of isobenzofurans **9** as synthetic intermediates. The synthetic methodology is concise, efficient, and amenable to being scaled up and can tolerate diverse range of aldehyde coupling partners as demonstrated by our synthesis of the ajudazol-derived isochromone derivatives **53** and **55**. We are currently in the process of investigating enantioselective versions of this novel rearrangement.[19]

Interestingly, we have recently become aware that König and co-workers have recently reported the isolation of phthalide **56** and 4-hydroxymellein **57** from the algicolous marine fungus *Epicoccum* sp.[20] This finding raises the possibility that phthalide **56** or a derivative of it might be a precursor in the biosynthesis of isochromone **57** (Figure 5).

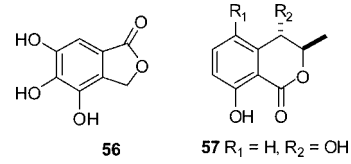


Figure 5. *Epicoccum* sp. metabolites.

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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.

OL8009336

(19) Furstner, A.; Nagano, T. *J. Am. Chem. Soc.* **2007**, *129*, 1906.

(20) Abdel-Lateff, A.; Fisch, K. M.; Wright, A. D.; König, G. M. *Planta Med.* **2003**, *69*, 831.