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Stereochemical Control in the Reduction of 2-Chromanols

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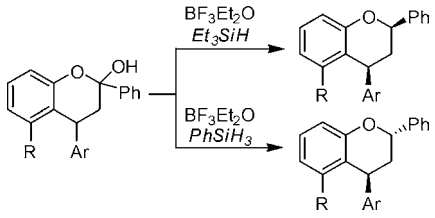
ABSTRACT



Reduction of C5-substituted 2-hydroxychromans selectively provides 2,4-*cis*-chromans using large silane reductants and 2,4-*trans*-chromans using the smaller silane $PhSiH_3$. The stereochemical outcome has been rationalized on the basis of a Curtin–Hammett kinetic situation arising from hydride delivery to two different conformations of an intermediate oxocarbenium ion. This method provides a powerful way to control the relative stereochemistry of these substructures which are prevalent in bioactive natural products.

Substituted chromans are a class of compounds that are found widely in bioactive natural products. The broad range of bioactivities exhibited by molecules containing this core element has led to their description as "privileged structures".[1] Given that the key scaffold in these compounds remains constant, one can attribute their biological selectivity to the nature, pattern, and stereochemistry of substitutents that adorn the chroman core.

For example, the stereochemistry of the myristinin flavanoids has been shown to affect their bioactivities, with myristinin A being a more potent polymerase β-inhibitor and the atropisomeric myristinins B/C being more potent COX-2 inhibitors (Figure 1).[2] Thus, control of stereochemistry in the formation of natural and synthetic flavanoids is of considerable interest.

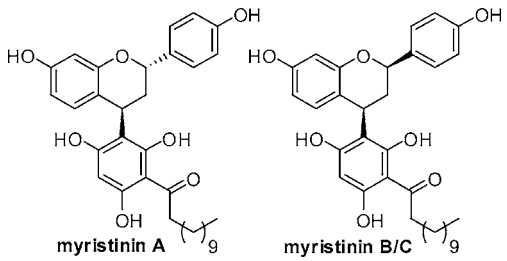


Figure 1.

Herein we report a stereoselective reduction of 2-chromanols to provide molecules that contain the core structure of the myristinins.[3] In some cases, the choice of reductant allows selective synthesis of either the *cis*-2,4 or *trans*-2,4 diastereomers.

To begin, we were interested in examining the stereochemistry of reduction of oxocarbenium ions derived from 2-chromanols using silane reductants (Scheme 1).[3] It was expected that the desired 2-chromanols would be accessible via the addition of organometallic reagents to dihydrocou-

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(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.
(2) (a) Deng, J.-Z.; Starck, S. R.; Li, S.; Hecht, S. M. *J. Nat. Prod.* **2005**, *68*, 1625−1628. (b) Maloney, D. J.; Deng, J.-Z.; Starck, S. R.; Gao, Z.; Hecht, S. M. *J. Am. Chem. Soc.* **2005**, *127*, 4140−4141. (c) Sawadjoon, S.; Kittakoop, P.; Kirtikara, K.; Vichai, V.; Tanticharoen, M.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67*, 5470−5475.

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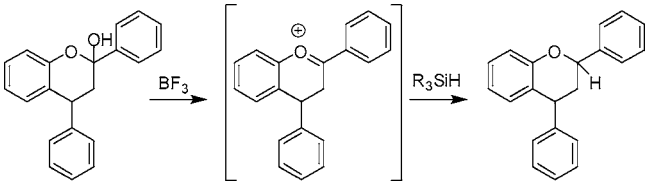
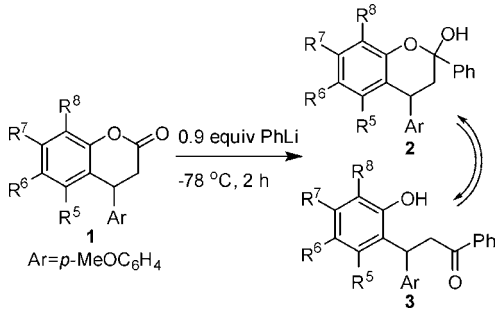
Scheme 1



marins. We have recently reported a simple, atom-economical procedure for the synthesis of dihydrocoumarins based on acid-catalyzed hydroarylation of cinnamic acids.[4] While treatment of dihydrocoumarins with PhMgBr did not lead to any addition product,[5] their reaction with 0.9 equiv of PhLi selectively provided mixtures of the two possible monoaddition products in good yields (Scheme 2).[6,7] The

Scheme 2



lactol (**2**)/ketone (**3**) ratio of the product proved to be highly variable (Table 1). While we do not have a definitive

Table 1. PhLi Additions to Dihydrocoumarins (Scheme 3)

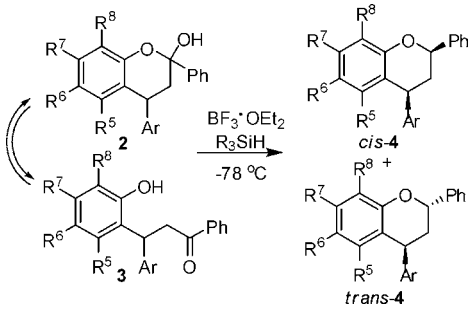
reactant	R^5	R^6	R^7	R^8	yield (%)	lactol/ketone
1a	OMe	H	OMe	H	75[a]	0.54:1
1b	H	*t*-Bu	H	H	97	0.69:1
1c	H	OCH_2O		H	74	0.64:1
1d	Me	Cl	Me	H	95	6.4:1
1e	Me	H	H	*i*-Pr	60[a]	18.5:1
1f	H	OMe	H	H	81	0.48:1
1g	H	H	OMe	H	95	0.47:1
1h	Me	H	Me	H	73[a]	2.4:1
1i	OMe	OMe	OMe	H	61[a]	0.52:1
1j	Me	H	H	Me	82[a]	13.5:1
1k	*i*-Pr	H	H	Me	62[a]	15.7:1

[a] The mass balance is recovered starting material.

explanation for the variability, it appears that R5-alkyl substitution favors lactol (**2**) formation and R5 + R8 alkyl substitution provides the highest ratios of lactol.

Treatment of the lactol/ketone mixture **2a**/**3a** with $BF_3{\cdot}Et_2O$ and Et_3SiH at −78 °C for 1 h resulted in complete conversion to the product chroman **4a** as a 1.7:1 cis/trans mixture of

Scheme 3



diastereomers (Scheme 3). In an attempt to improve this ratio, *i*-Pr_3SiH was used as the reductant which indeed provided the cis product in 20:1 dr as determined by ^1H NMR spectroscopy. Interestingly, use of $PhSiH_3$ as the reductant afforded the trans product selectively (1:11 cis/trans). It is important to note that the *cis*- and *trans*-chromans are both configurationally stable under the reaction conditions.

The observed products could possibly arise from one of two mechanisms. First, hydrosilylation of the ketone followed by intramolecular substitution could produce the chroman.[5] Alternatively, formation of an oxocarbenium ion from the lactol followed by addition of hydride is a possibility (Scheme 1).[8] Since the observed stereochemical dependence on the nature of the silane is inconsistent with an intramolecular S_N1 reaction, we favor the latter mechanism.

Given the silane-dependent reversal of stereochemical outcome, experiments aimed at determining the origin of stereoselectivity were conducted. To begin, a variety of lactol/chalcone mixtures that differ only in the substitution of the arene ring of the chroman were prepared. These substrates were subjected to reductions with *i*-Pr_3SiH, Et_3SiH, or $PhSiH_3$. While $PhSiH_3$ always gave more trans product than Et_3SiH or *i*-Pr_3SiH did, it is clear from the data in Table 2 that a substituent in the 5-position is required for high trans selectivity.

The stereochemical outcome of the reduction can be explained if one considers the delivery of hydride to the hypothetical oxocarbenium ion intermediate. Geometry

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(4) Li, K.; Foresee, L. N.; Tunge, J. A. *J. Org. Chem.* **2005**, *70*, 2881−2883.

(5) Over-addition occurs at higher temperatures: Geissman, T. A. *J. Am. Chem. Soc.* **1940**, *62*, 1363−1367. Overreduction was also observed with PhLi in THF.

(6) Czernecki, S.; Perlat, M. C. *J. Org. Chem.* **1991**, *56*, 6289−6292.

(7) Heating the product mixtures did not change the ratio of products, so we assume that thermodynamic product ratios are obtained.

(8) (a) Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5322−5323. (b) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168−169.

(9) Frisch, M. J. et al. *Gaussian 98, revision A.6*; Gaussian, Inc.: Pittsburgh, PA, 1998.

(10) This is consistent with the known steric interaction between these two aryl groups in the atropisomeric myristinins B and C.

Table 2. Selective Reductions of Lactol/Chalcone Mixtures

product	R^5	R^6	R^7	R^8	X-H	yield (%) (dr)[a]
4a	OMe	H	OMe	H	*i*-Pr_3Si	56 (20:1)
					Et_3Si	65 (1.7:1)
					PhH_2Si	94 (1:11)
4b	H	*t*-Bu	H	H	Et_3Si	90 (>20:1)
					PhH_2Si	72 (2.7:1)
4c	H	OCH_2O		H	Et_3Si	82 (>20:1)
					PhH_2Si	50 (7.3:1)
4d	Me	Cl	Me	H	*i*-Pr_3Si	76 (11:1)
					PhH_2Si	99 (1:10)
4e	Me	H	H	*i*-Pr	*i*-Pr_3Si	99 (9.1:1)
					Et_3Si	99 (1.6:1)
					PhH_2Si	99 (1:17)
4f	H	OMe	H	H	Et_3Si	89 (14:1)
					PhH_2Si	49 (2.6:1)
4g	H	H	OMe	H	Et_3Si	68 (>20:1)
					PhH_2Si	63 (5:1)
4h	Me	H	Me	H	*i*-Pr_3Si	56 (11:1)
					PhH_2Si	95 (1:12)
4i	OMe	OMe	OMe	H	*i*-Pr_3Si	62 (13:1)
					PhH_2Si	82 (1:4)
4j	Me	H	H	Me	*i*-Pr_3Si	55 (4:1)
					PhH_2Si	96 (1:14)
4k	*i*-Pr	H	H	Me	*i*-Pr_3Si	86 (14:1)
					PhH_2Si	99 (1:11)

[a] Yield and cis/trans ratio of isolated product.

optimizations at the B3LYP/6-31G* level of theory, using the Gaussian program,[9] show that a simple 2,4-diphenyl-substituted oxocarbenium ion intermediate adopts a half-chair structure where the 4-aryl group can occupy either a pseudoaxial or a pseudoequatorial position. When R^5 = H, the calculations show that the C4-phenyl group prefers to occupy the equatorial position by 0.4 kcal/mol (Figure 2).

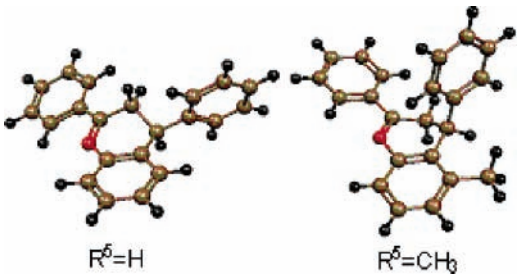
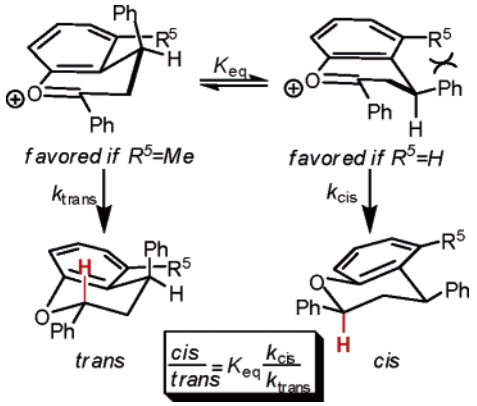


Figure 2. Most stable conformations of oxocarbenium ions.

However, if R^5= Me, then the C4-phenyl group prefers the axial position by 3.2 kcal/mol.[10]

Further calculations show that the barrier for interconversion of the axial and equatorial conformers is 3.8 kcal/mol for R^5 = H and 4.8 kcal/mol for R^5 = Me. Therefore, the conformational equilibrium is rapidly maintained at −78 °C, and reduction of the oxocarbenium is expected to follow Curtin−Hammett kinetics.[11] In the case of a Curtin−Hammett kinetic situation, the cis/trans ratio equals the product of K_{eq} and the ratio of rate constants for hydride delivery (Scheme 4).

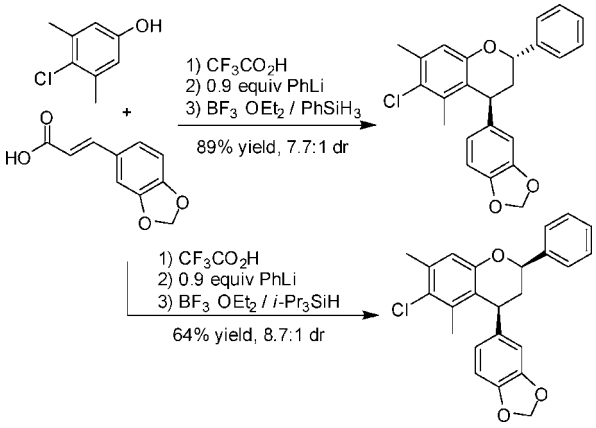
Scheme 4



With large hydride sources such as *i*-Pr_3SiH, axial delivery of the hydride is expected to occur preferentially on the equatorial conformer so as to minimize the incipient 1,3-diaxial interaction ($k_{cis} \gg k_{trans}$).[3c,12] In this case, the reaction product is primarily controlled by the rates of hydride delivery ($k_{cis}/k_{trans} \gg K_{eq}$); thus, the cis product is favored regardless of the conformational equilibrium.

If the hydride source is small (i.e., $PhSiH_3$), then hydride can be delivered axially to either conformer ($k_{cis} \sim k_{trans}$). In this case, the product ratio will have a large dependence on population of conformers as given by K_{eq}.[13] Thus, when R^5 = H and there is a small preference for the equatorial conformer, $PhSiH_3$ provides low cis selectivity. However, the *trans*-chroman is selectively produced from substrates where $R^5 \neq$ H and the axial conformer is preferred.

Scheme 5



In summary, we have developed a convenient, stereoselective procedure for the reduction of 2-chromanols. The reduction is the key step in a convenient three-step procedure

for the formation of diarylchromans from phenols and cinnamic acids (Scheme 5). Furthermore, the stereochemistry of the reduction can be predicted on the basis of a simple Curtin−Hammett kinetic model for hydride delivery to an intermediate oxocarbenium ion. Finally, the ability to selectively access either *cis*- or *trans*-chromans is expected to facilitate production of stereochemically diverse chemical libraries.

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Supporting Information Available: Experimental procedures and spectroscopic data of all compounds. Cartesian coordinates of the DFT-optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) At 20 °C, the rate of conformational interconversion is calculated to be ca. 10^9 s^{-1}, while those for hydride delivery to an oxocarbenium ion are estimated to be 10^2 s^{-1} for $PhSiH_3$ and 10^4 for Et_3SiH. (a) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500−9512. (b) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.