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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 PhSiH₃. The stereochemical outcome has been rationalized based on 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 substituents 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, the control of stereochemistry in the formation of natural and synthetic flavanoids is of considerable interest.

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 dihydrocoumarins. 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 lactol (**2**)/ketone (**3**) ratio of the product proved to be highly variable (Table 1). While we do not have a definitive 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 BF₃·Et₂O and Et₃SiH at −78 °C for 1h resulted in complete conversion to the product chroman **4a** as a 1.7:1 *cis:trans* mixture of diastereomers (Scheme 3). In an attempt to improve this ratio, *i*-Pr₃SiH was used as the reductant which indeed provided the *cis*-product in 20:1 dr as determined by ¹H NMR spectroscopy. Interestingly, use of PhSiH₃ 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*-Pr₃SiH, Et₃SiH, or PhSiH₃. While PhSiH₃ always gave more *trans* product than Et₃SiH or *i*-Pr₃SiH 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 optimizations at the B3LYP/6-31G* level of theory, using the Gaussian program,⁹ show that a simple 2,4-phenyl substituted oxocarbenium ion intermediate adopts a half-chair structure where the 4-aryl group can occupy either a pseudo-axial or a pseudo-equatorial position. When R⁵=H, the calculations show that the C4-phenyl group prefers to occupy the equatorial position by 0.4 kcal/mol (Fig. 2). However, if R⁵=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 R⁵=H and 4.8 kcal/mol for R⁵=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).

With large hydride sources such as *i*-Pr₃SiH, 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}>>*k*_{trans}).^{3c,12} In this case, the reaction product is primarily controlled by the rates of hydride delivery (*k*_{cis}/*k*_{trans}>>*K*_{eq}); thus the *cis*-product is favored regardless of the conformational equilibrium.

If the hydride source is small (i.e. PhSiH₃), then hydride can be delivered axially to either conformer (*k*_{cis}~*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 R⁵=H and there is a small preference for the equatorial conformer, PhSiH₃ provides low *cis*-selectivity. However, the

trans-chroman is selectively produced from substrates where $R^5 \neq H$ and the axial conformer is preferred.

In summary, we have developed a convenient, stereoselective procedure for the reduction of 2-chromanols. The reduction is the key step in a convenient 3-step procedure for the formation of diarylchromans from phenols and cinnamic acids (Scheme 5). Furthermore, the stereochemistry of the reduction can be predicted based on 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Figure 2.
Most stable conformations of oxocarbenium ions

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

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	<i>t</i> -Bu	H	H	97	0.69:1
1c	H			H	74	0.64:1
1d	Me	Cl	Me	H	95	6.4:1
1e	Me	H	H	<i>i</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>i</i> -Pr	H	H	Me	62 ^a	15.7:1

^a) the mass balance is recovered starting material

Table 2

Selective reductions of lactol/chalcone mixtures.

prod	R ⁵	R ⁶	R ⁷	R ⁸	X-H	yield (dr) ^a
4a	OMe	H	OMe	H	<i>i</i> -Pr ₃ Si Et ₃ Si	56 (20:1) 65 (1.7:1)
4b	H	<i>t</i> -Bu	H	H	PhH ₂ Si Et ₃ Si	94 (1:11) 90 (>20:1)
4c	H		OCH ₂ O	H	PhH ₂ Si Et ₃ Si	72 (2.7:1) 82 (>20:1)
4d	Me	Cl	Me	H	PhH ₂ Si <i>i</i> -Pr ₃ Si	50 (7.3:1) 76 (11:1)
4e	Me	H	H	<i>i</i> -Pr	PhH ₂ Si <i>i</i> -Pr ₃ Si Et ₃ Si	99 (1:10) 99 (9.1:1) 99 (1.6:1)
4f	H	OMe	H	H	PhH ₂ Si Et ₃ Si	99 (1:17) 89 (14:1)
4g	H	H	OMe	H	PhH ₂ Si Et ₃ Si	49 (2.6:1) 68 (>20:1)
4h	Me	H	Me	H	PhH ₂ Si <i>i</i> -Pr ₃ Si	63 (5:1) 56 (11:1)
4i	OMe	OMe	OMe	H	PhH ₂ Si <i>i</i> -Pr ₃ Si	95 (1:12) 62 (13:1)
4j	Me	H	H	Me	PhH ₂ Si <i>i</i> -Pr ₃ Si	82 (1:4) 55 (4:1)
4k	<i>i</i> -Pr	H	H	Me	PhH ₂ Si <i>i</i> -Pr ₃ Si PhH ₂ Si	96 (1:14) 86 (14:1) 99 (1:11)

^a) yield and *cis:trans* ratio of isolated product