ORGANIC LETTERS

2011
Vol. 13, No. 24
6480–6483

Iron-Catalyzed Rearrangements and Cycloaddition Reactions of 2*H*-Chromenes

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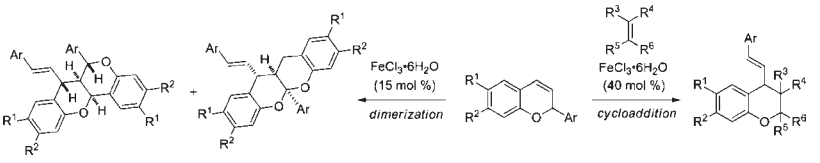
Received October 14, 2011

ABSTRACT



Iron(III) salts catalyze the tandem rearrangement/hetero-Diels–Alder reaction of 2*H*-chromenes to yield tetrahydrochromeno heterocycles. The process can occur as a homodimerization and cycloaddition process using electron-rich dienophiles. Deuterium labeling and mechanistic studies revealed a hydride shift and *ortho*-quinone methide cycloaddition reaction pathway.

The tetrahydrochromeno polycyclic core is a characteristically unique structure among the large number of biologically active phenolic compounds isolated from Nature.[1] Natural product examples include mulberrofuran G,[2] australisine A,[3] and sorocenol E,[4] bearing a quaternary ketal carbon (Figure 1). Mulberrofuran, australisine, and sorocenol natural products possess hypotensive effects and cytotoxicities against human cancer cell lines.[2,3] The dimeric flavonoid dependensin isolated from the antimalarial *uvarza dependens* also contains a benzopyranobenzopyran polycyclic ring structure.[5] We envisaged synthetic access to these natural product core structures via tetrahydrochromeno and benzopyrano starting materials. Herein, we describe an $FeCl_3 \cdot 6H_2O$-catalyzed rearrangement and hetero-Diels–Alder reaction of 2*H*-chromenes with dienophiles to access these unique heterocyclic structures.[6]

We have been interested in the synthesis and utility of 2*H*-chromenes (4′-methoxyflav-3-enes).[7] Homodimerization of small molecules is a highly efficient way to construct complex dimeric structures,[8] and recently, Kumar and co-workers demonstrated the homodimerization of 2*H*-chromenes under Brønsted acidic conditions.[9]

The homodimerization of 2*H*-chromenes provides rapid access to ketal polycyclic or benzopyranobenzopyran core structures but, as reported, did not readily provide discrete access to heterodimeric stuctures, similar to those found in Nature. During the course of our study on dimerization of 4′-methoxyflav-3-ene, we discovered that iron salts,

(1) (a) Nomura, T.; Fukai, T.; Hano, Y. In *Studies in Natural Products Chemistry*; Rahman, A., Eds.; Elsevier: 2003. (b) Bhandari, P.; Crombie, L.; Harper, M. F.; Rossiter, J. T.; Sanders, M. D.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1685–1697. (c) Reisch, J.; Adebajo, A. C.; Kumar, V.; Aladesanmi, A. J. *Phytochemistry* **1994**, *36*, 1073–1076.

(2) (a) Fukai, T.; Hano, Y.; Hirakura, K.; Nornura, T.; Uzawa, J.; Fukushima, K. *Chem. Pharm. Bull.* **1985**, *33*, 3195. (b) Fukai, T.; Hano, Y.; Hirakura, K.; Nornura, T.; Uzawa, J.; Fukushima, K. *Heterocycles* **1984**, *22*, 1007–1011.

(3) Zhang, Q. J.; Tang, Y. B.; Chen, R. Y.; Yu, D. Q. *Chem. Biodiversity* **2007**, *4*, 1533–1540.

(4) Hano, Y.; Yamanaka, J.; Momose, Y.; Nomura, T. *Heterocycles* **1995**, *41*, 2811–2821.

(5) Nkunya, M. H. H.; Waibel, R.; Achenbach, H. *Phytochemistry* **1993**, *34*, 853–856.

(6) (a) Bolm, C.; Legros, J.; Paih, J. L.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217–6254. (b) Rao, W. D.; Chan, P. W. H. *Org. Biomol. Chem.* **2010**, *8*, 4016–4025. (c) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913–3917.

(7) Moquist, P. N.; Kodama, T.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 7096–7100.

(8) (a) Ibrahim, A. A.; Wei, P. H.; Harzmann, G. D.; Kerrigan, N. J. *J. Org. Chem.* **2010**, *75*, 7901–7904. (b) Guidi, V.; Sandoval, S.; McGregor, M. A.; Rosen, W. *Tetrahedron Lett.* **2010**, *51*, 5086–5090. (c) Chapman, O. L.; Engel, M. R.; Springer, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696–6698.

(9) Devakarama, R.; Black, D. StC.; Kumar, N. *Tetrahedron Lett.* **2010**, *51*, 3636–3638.

10.1021/ol202772k
Published on Web 11/18/2011

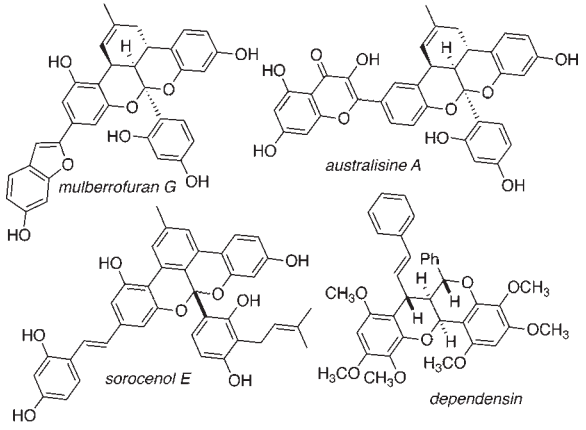


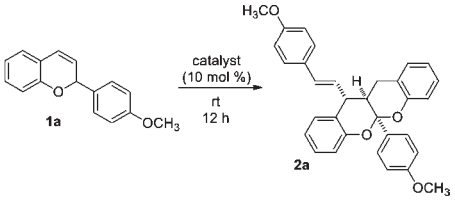
Figure 1. Representative natural products.

especially $FeCl_3 \cdot 6H_2O$, served as an efficient catalyst for the homodimerization of 2*H*-chromene **1a** (Table 1, entries 1−4). Anhydrous $FeCl_3$ performed poorly, suggesting the hydrate as $FeCl_3 \cdot 6H_2O$ is essential for catalytic activity (entry 5). To eliminate the possibility that a trace amount of HCl was acting as the catalytic species, catalytic quantities of aqueous HCl was evaluated in the reaction to afford a low yield of **2a** in 1:1 dr (entriy 6). The yield was slightly improved using anhydrous methanol as the solvent but in no diastereoselectivity (entry 7).[9] Dry HCl failed to provide product from the reaction (entry 8). Similar yields and diastereoselectivities were achieved using alternative iron(III) salts (entries 9−10), while other metal chloride salts gave little or no yield (entries 11−12). We chose $FeCl_3 \cdot 6H_2O$ as the catalyst to further investigate in the reaction.

The optimized reaction conditions proved general for a range of 2*H*-chromenes investigated (Table 2). The reaction proceeded smoothly with 6-methyl chromene **1b**, affording chromeno[2,3-*b*]chromene dimer **2b** in good yields (entry 2). Electron-deficient chromenes **1c**−**1e** underwent dimerization in a similar fashion, providing **2c**−**2e** in moderate to good yields, but ultimately requiring longer reaction times (entries 3−5). The relative stereochemistry of both the major and minor diastereomers was determined by single crystal X-ray analysis of the dimer **2d**.[10] A change in chemoselectivity was observed in the dimerization of 7-methoxy chromene **1f**. Pyran **1f** afforded isomer **3f** as the major product in good yield at rt; only a trace amount (< 5%) of isomer **2f** was identified (entry 6). The chemoselectivity reverted to the hetero-Diels−Alder chromeno-[2,3-*b*]chromene dimer product with the methoxy group in the 6-position (4′,6-dimethoxy-3-flavene **1g**, Table 2, entry 7). Electron-rich chromene **1h** did lead to the formation of isomer **3h** in good yield (entry 8). Alternatively, use of the dimethyl carbamate protecting group attenuated the reactivity of 7-oxygenated arene **1i** to yield the chromeno[2,3-*b*]chromene dimer **2i** (entry 9). The more electron-rich chromene reaction partners appeared to have the appropriate reactivity profile to react with the heterodiene as it was being formed in the reaction mixture.

(10) CCDC 812201 and 812202 contain the supplementary crystallographic data for this paper.

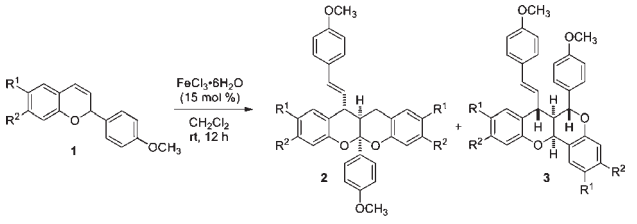
Table 1. Acid-Catalyzed Homodimerization of **1a**[a]



entry	catalyst	solvent	dr[b]	yield[c]
1	$FeCl_3 \cdot 6H_2O$	$PhCH_3$	2:1	40%
2	$FeCl_3 \cdot 6H_2O$	CH_3OH		0%
3	$FeCl_3 \cdot 6H_2O$	CH_2Cl_2	2:1	81%
4[d]	$FeCl_3 \cdot 6H_2O$	CH_2Cl_2	3:1	85%
5[e]	$FeCl_3$	CH_2Cl_2	2:1	22%
6	HCl(aq)	CH_2Cl_2	1:1	5%
7[f]	HCl(aq)	CH_3OH	1:1	34%
8	HCl in ether	CH_2Cl_2		0%
9	$Fe(OTs)_3 \cdot 6H_2O$	CH_2Cl_2	2:1	80%
10	$Fe(OTf)_3$	CH_2Cl_2	2:1	85%
11	$ZnCl_2$	CH_2Cl_2	2:1	14%
12	$AlCl_3$	CH_2Cl_2	2:1	12%

[a] Reaction conditions: 0.25 mmol of **1a**, 10 mol % catalyst, 0.2 M in the solvent for 12 h at room temperature. [b] Ratio was determined by ^1H NMR analysis. [c] Isolated yield. [d] 15 mol % $FeCl_3 \cdot 6H_2O$. [e] Anhydrous conditions. [f] 0.32 mmol of **1a** in 20 mL of methanol, with 10 drops of HCl, then refluxed at 65 °C for 12 h. [9]

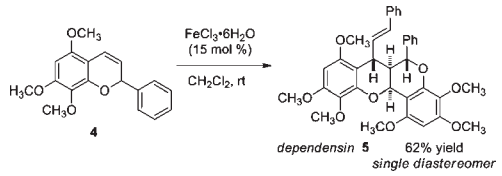
Table 2. $FeCl_3 \cdot 6H_2O$ Catalyzed Dimerization[a]



entry	2*H*-chromene (**1**)	dr[b]	**2**:**3**	yield[c]
1	R^1 = H, R^2 = H (**1a**)	3:1	>99:1	85% (**2a**)
2	R^1 = CH_3, R^2 = H (**1b**)	3:1	>99:1	89% (**2b**)
3	R^1 = H, R^2 = Cl (**1c**)	3:1	>99:1	82% (**2c**)
4[d]	R^1 = Br, R^2 = H (**1d**)	3:1	>99:1	86% (**2d**)
5[e]	R^1 = NO_2, R^2 = H (**1e**)	1.5:1	>99:1	72% (**2e**)
6	R^1 = H, R^2 = OCH_3 (**1f**)	>99:1	5:95	86% (**3f**)
7	R^1 = OCH_3, R^2 = H (**1g**)	2:1	>99:1	87% (**2g**)
8	R^1, R^2 = 6,7-(OCH_2O) (**1h**)	>99:1	3:97	66% (**3h**)
9	R^1 = H, R^2 = $OCON(CH_3)_2$ (**1i**)	3:1	>99:1	70% (**2i**)

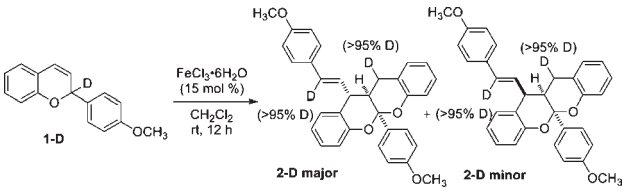
[a] 0.25 mmol of **1**, 15 mol % $FeCl_3 \cdot 6H_2O$, 0.2 M in CH_2Cl_2 for 12 h at rt. [b] ^1H NMR analysis of **2** or **3**. [c] Isolated yield. [d] 24 h. [e] 72 h.

Scheme 1. Synthesis of (±)-Dependensin



The Fe-catalyzed reaction was utilized in the synthesis of dependensin (**5**) via the homodimerization of 5,7,8-trimethoxyflav-3-ene **4**, easily prepared in three steps from commercially available starting materials. Dependensin has been previously synthesized[11] in a similar fashion with our route demonstrating a reduction in reaction sequence steps in high stereocontrol (Scheme 1). Subjecting 5,7,8-trimethoxy-3-flavene **4** to the optimized $FeCl_3$-dimerization conditions afforded (±)-dependensin (**5**) as a single diastereomer in 29% overall yield from 1,2,3,5-tetramethoxybenzene.

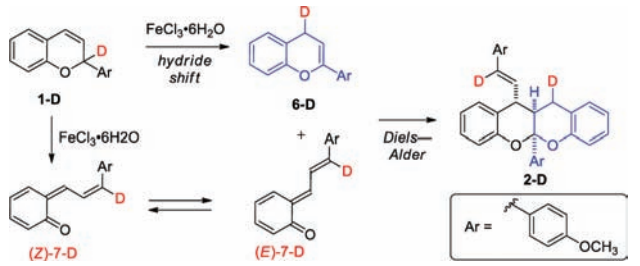
Scheme 2. Deuterium-Labeled **1a** in the Homodimerization



We designed experiments to gain insight into the reaction sequence leading to the dimerization product. We postulated use of 2-deutero-4′-methoxyflav-3-ene **1-D** in the dimerization reaction would illustrate the isomerization of the chromene to the dienophile. The chromene **1-D** was synthesized via boronate addition onto the deuterated 2-ethoxy-2*H*-chromene. Subjecting **1-D** to the dimerization conditions led to the formation of dimer **2-D**, epimeric at the benzylic positions (Scheme 2). Under UV irradiation, *oxa*-6π rearrangement of chromenes[12] results in the formation of the corresponding *ortho*-quinone methide (*o*QM).[13] We propose the similar *oxa*-6π rearrangement of 2*H*-chromene could occur under Fe-catalyzed conditions. Illustrated in Scheme 3, the Fe-catalyst is responsible for promoting the hydride shift to yield the dienophile and the ring-opening reaction.

The ring-opening process can lead to the formation of *Z*-*ortho*-quinone methide that rapidly equilibrates to the

Scheme 3. Proposed Mechanism for Cycloaddition



E-conformer under the reaction conditions (***E*)-7-D**.[14] The second 2*H*-chromene undergoes a hydride shift to yield the 4′-methoxy-2-flavene **6-D** as the reactive dienophile.[15] Cycloaddition of the *E*-configured vinyl *o*QM (***E*)-7-D** and **6-D** in an inverse electron demand [4 + 2] fashion furnishes the dimer **2-D**. The chemoselectivity observed in the 4′,7-dimethoxy-3-flavene **1f** dimerization (Table 2, entry 7) is rationalized by a [4 + 2] cycloaddition of a highly electron-rich olefin with the *o*QM at a faster rate than the hydride shift.

We proposed further experiments based on our mechanistic hypothesis aimed at the heterodimerization process. We first postulated that 4′-methoxy-2-flavene **6** would react with the *o*QM generated *in situ* from 2*H*-chromene **1h** under the Fe-promoted conditions (Scheme 4, reaction 1). The reaction proceeded well yielding the corresponding heterodimer **9h** in high yield and 4:1 diastereoselectivity, with only trace amounts (< 5%) of homodimer **3h** formed. We demonstrated the intermediacy of the *o*QM by making (***E*)-8** and reacting it with dienophile **6** under the same reaction conditions (Scheme 4, reaction 2).[16] The product was isolated in comparable yield and the same diastereoselectivity to provide further evidence for the intermediacy of both reaction partners in the [4 + 2] cycloaddition pathway.

We envisaged a cyloaddition processes to occur with electron-rich dienophiles utilizing 2*H*-chromenes as *o*QM precursors based on our preliminary studies of the reaction.[17] Inspired by natural products such as the mulberrofurans and australisine we first evaluated hetero-Diels–Alder reactions between 2*H*-chromenes **1** and 4′-methoxy-2-flavenes **6** under the Fe-promoted conditions.

The reactions proceeded well with 6-methyl and 1,3-benzodioxol substituted chromenes **1b** and **1j** (Table 3, entries 1 and 9). Electron-deficient 2*H*-chromenes **1c**–**1e** were also able to participate, but at a slower rate (entries 2–4).

(11) Deodhar, M.; Black, D. StC.; Kumar, N. *Tetrahedron* **2007**, *63*, 5227–5235.

(12) (a) Delbaere, S.; Micheau, J. C.; Vermeersch, G. *J. Org. Chem.* **2003**, *68*, 8968–8973. (b) Padwa, A.; Lee, G. A. *J. Chem. Soc., Chem. Commun.* **1972**, 795–796.

(13) Pathak, T. P.; Sigman, M. S. *J. Org. Chem.* **2011**, *76*, 9210–9215.

(14) (a) Bishop, L. M.; Winkler, M.; Houk, K. N.; Bergman, R. G.; Trauner, D. *Chem.—Eur. J.* **2008**, *14*, 5405–5408. (b) Jurd, L. *Tetrahedron* **1977**, *33*, 163–168.

(15) For similar hydride transfer, see: (a) McQuaid, K. M.; Long, J. Z.; Sames, D. *Org. Lett.* **2009**, *11*, 2972–2975. (b) McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402–403.

(16) Jurd, L.; Roitman, J. N.; Wong, R. Y. *Tetrahedron* **1979**, *35*, 1041–1054.

(17) (a) Van de Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367–5405. (b) Wu, K. L.; Mercado, E. V.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2011**, *133*, 6114–6117. (c) Marsini, M. A.; Huang, Y.; Lindsey, C.; Wu, K. L.; Pettus, T. R. R. *Org. Lett.* **2008**, *10*, 1477–1480. (d) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471–17482. (e) Lumb, J. P.; Choong, K. C.; Trauner, D. *J. Am. Chem. Soc.* **2008**, *130*, 9230–9231.

Scheme 4. Cycloaddition Reactions of 4′-Methoxy-2-flavene **6**

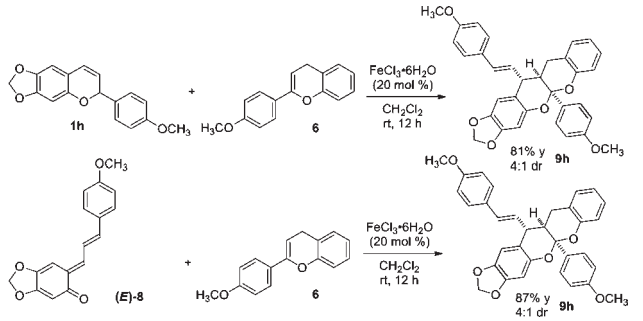
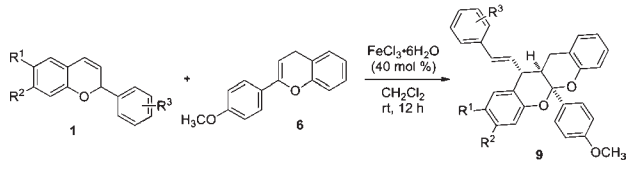


Table 3. Cycloaddition Reactions Using 4′-Methoxyflav-2-ene as the Dienophile



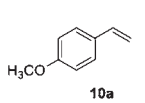
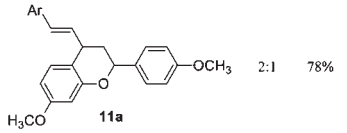
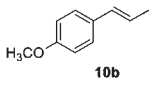
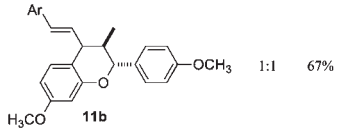
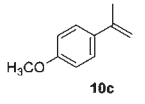
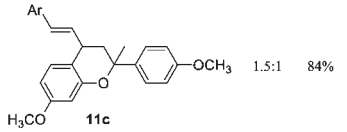
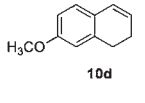
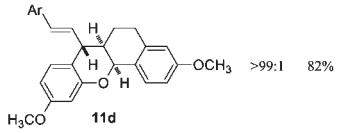
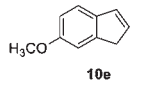
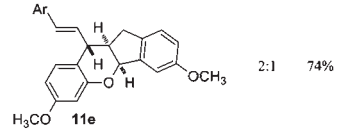
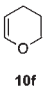
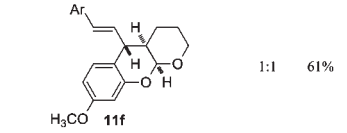
entry	2*H*-chromene (**1**)	dr	yield[a]
1	$R^1 = CH_3$, $R^2 = H$, $R^3 = 4\text{-}OCH_3$ (**1b**)	3:1	87% (**9b**)
2	$R^1 = H$, $R^2 = Cl$, $R^3 = 4\text{-}OCH_3$ (**1c**)	3:1	87% (**9c**)
3	$R^1 = Br$, $R^2 = H$, $R^3 = 4\text{-}OCH_3$ (**1d**)	2:1	72% (**9d**)
4[b]	$R^1 = NO_2$, $R^2 = H$, $R^3 = 4\text{-}OCH_3$ (**1e**)	3:1	65% (**9e**)
5	$R^1 = H$, $R^2 = OCH_3$, $R^3 = 4\text{-}OCH_3$ (**1f**)	3:1	87% (**9f**)
6	$R^1 = OCH_3$, $R^2 = H$, $R^3 = 4\text{-}OCH_3$ (**1g**)	2:1	83% (**9g**)
7	R^1, $R^2 = 6,7\text{-}(OCH_2O)$, $R^3 = 4\text{-}OCH_3$ (**1h**)	4:1	81% (**9h**)
8	$R^1 = H$, $R^2 = OCON(CH_3)_2$, $R^3 = 4\text{-}OCH_3$ (**1i**)	4:1	89% (**9i**)
9	$R^1 = R^2 = H$, $R^3 = 3,4\text{-}(OCH_2O)$ (**1j**)	2:1	90% (**9j**)

[a] Isolated yield. [b] 24 h, another 0.186 mmol of **6** and 40 mol % $FeCl_3 \cdot 6H_2O$ were added after first 12 h.

Electron-rich 2*H*-chromenes **1f**–**1h** underwent a hetero-Diels–Alder reaction in good yields, providing selectively functionalized **9f**–**9h** with similar diastereoselectivities (entries 5–7). Attenuating the electron-donating group with a dimethyl carbamate did not affect the yield or selectivity of the reaction (entry 8).

We further explored the scope of the cycloaddition reaction pathway using the in situ generated *o*QM of chromene **1f** with dienophiles **10** (Table 4). Under the optimized reaction conditions, *p*-methoxystyrene and its derivatives **10a**–**10c** successfully afforded chromans **11a**–**11c** in good yields (Table 4, entries 1–3). Furthermore, dihydronaphthalene **10d** yielded the [4 + 2] adduct **11d** as a single diastereomer (entry 4). Electron-rich indene **10e** was also a suitable dienophile (entry 5), and the reaction proceeded

Table 4. Cycloaddition Reactions Using the *ortho*-Quinone Methide Precursor 4′,7-Dimethoxy-3-flavene **1f**

entry	dienophile	equiv	cycloadduct	dr	yield[a]
1	 **10a**	2	 **11a**	2:1	78%
2	 **10b**	10	 **11b**	1:1	67%
3	 **10c**	2	 **11c**	1.5:1	84%
4	 **10d**	5	 **11d**	>99:1	82%
5	 **10e**	5	 **11e**	2:1	74%
6	 **10f**	20	 **11f**	1:1	61%

[a] Isolated yield. Ar = PMP (*para*-methoxyphenyl).

smoothly with dihydropyran **10f** to produce the corresponding acetal (entry 6).

In conclusion, we have developed an iron-catalyzed tandem rearrangement/hetero-Diels–Alder approach to access tetrahydrochromeno heterocycles. Our studies have revealed an *o*QM involved cycloaddition reaction mechanism. Further mechanistic evidence, including trapping of the *in situ* generated *o*QM and use of the *o*QM (***E*)-8**, supports the proposed multistep process. Ongoing studies include expansion of the scope and synthetic utility of the reaction sequence.

Acknowledgment. This research was supported by the NIH (R01 GM078240, S.E.S. and Y.L.) and BU Undergraduate Research Opportunities Program (H.S.).

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