Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 411–415
Tetrahedron Letters

Studies on the intramolecular oxa-Pictet–Spengler rearrangement of 5-aryl-1,3-dioxolanes to 4-hydroxy-isochromans

Darío A. Bianchi, Federico Rúa and Teodoro S. Kaufman*

Instituto de Química Orgánica de Síntesis (CONICET-UNR) and Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, S2002LRK Rosario, Argentina

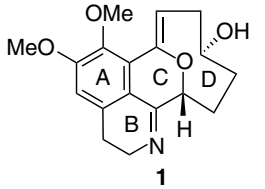
Received 21 September 2003; revised 21 October 2003; accepted 23 October 2003

Dedicated to Professor Edmundo A. Rúveda on the occasion of his 70th Birthday

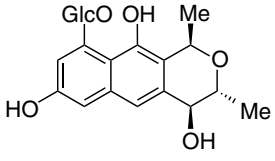
Abstract—The success and stereochemical outcome of the $TiCl_4$-promoted oxa-Pictet–Spengler cyclization of 5-aryl-1,3-dioxolanes to produce 1,3-disubstituted-4-hydroxy-isochromans, is influenced by the length and nature of the side chains bound to C-2 and C-4 of the dioxolane. Methyl groups yield a mixture of 4-hydroxy-isochromans in which the 1,3-*trans* diastereomer predominates, while bulkier substituents give 1,3-*cis* diastereomers. Functional groups in the C-2 side chain of the dioxolane ring may hinder cyclization by complexation with the promoter.

Many interesting natural products are isochroman derivatives, such as stephaoxocanine (**1**),[1] glucoside B (**2**), an aphid insect pigment derivative,[2] the topoisomerase II inhibitor CJ-12,373 (**3**),[3] and the unnamed compound **4**, isolated from softwood lignins.[4] Synthetic isochromans with activities as herbicides,[5a] dopamine receptor ligands,[5b] and fragrances, such as the commercial musk odorant galaxolide® (**5**),[5c] have also been described.

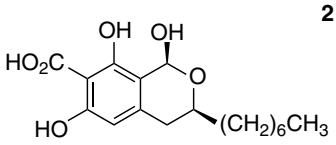
The oxa-Pictet–Spengler[6] isomerization of aryl dioxolanes **6** to 4-hydroxy-isochromans **7** (Scheme 1)[7] has been employed for the synthesis of natural products, but its scope has been only partially studied. The overall yield of the transformation was observed to be influenced by the stereochemistry of the C-2 center of the dioxolane, the reaction temperature, and the nature of the substituent of the aromatic ring *ortho* to the dioxolane; however, the factors, which determine the relative stereochemistry at the newly generated C-1 center were found to be difficult to understand,[8] and ascribed to the 4,5-stereochemistry of the substrate, steric elements, the characteristics of the transition state, the reaction temperature, and the aromatic ring substitution pattern.[9] Interestingly, the effect of the dioxolane substituents R_1 and R_2 on the stereochemistry of C-1 in the product has not been evaluated, since only 4-hydroxy-isochroman derivatives **7** bearing methyl and acetate residues on C-3 (sometimes γ-lactonized with the vicinal carbinol), and solely methyl groups on C-1 have been synthesized to date.[9,10]



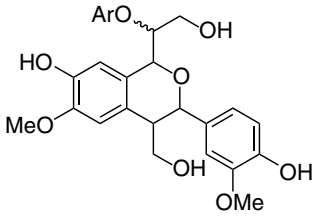
1



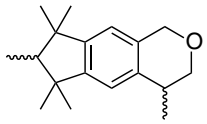
2



3



4

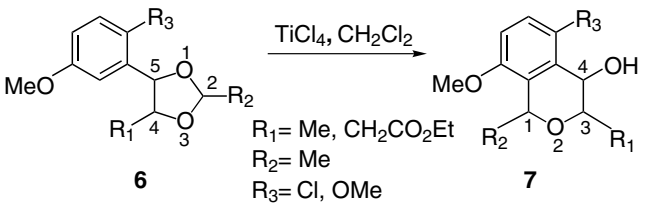


5

Keywords: oxa-Pictet–Spengler; isochromans; rearrangement; dioxolanes; isomerization.

* Corresponding author. Tel./fax: +54-341-4370477; e-mail: tkaufman@fbioyf.unr.edu.ar

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.10.143

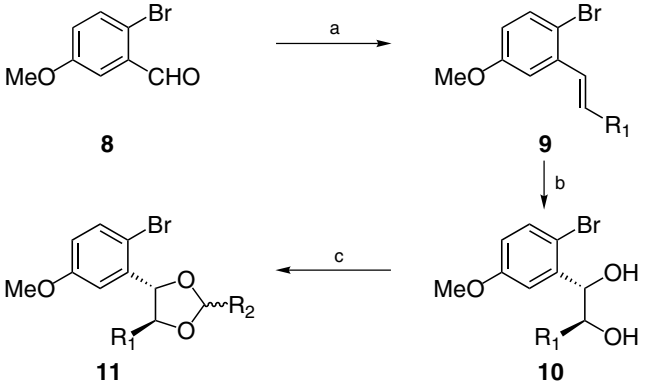


Scheme 1.

As part of our interest in the synthesis of stephaoxocanes,[11] employing this dioxolane isomerization as key transformation for the elaboration of the isochroman AC-ring system embodied in these natural products[12] we investigated the structural requirements of the substituents R_1 and R_2 for the cyclization in precursors **6**, aiming to elaborate *cis*-1,3-disubstituted 4-hydroxy-isochromans, conveniently ω-functionalized in their side chains.

Dioxolanes **11a–k** were prepared from **8**[13] by olefination[10] (Scheme 2), followed by alkene equilibration[14] to ***E-9***, vicinal dihydroxylation, and PPTS assisted[15] acetalization of the resulting diols **10** with aldehydes or acetals. Superior yields were obtained when the acetalizations were carried out in a Soxhlet apparatus containing 4 Å MS in the thimble. Aldehydes and acetals were accessed following literature procedures,[16] while Wittig reagents were prepared in 52–87% yield by reaction of PPh_3 with 4-chlorobutyronitrile, 4-bromo butyric acid, 5-bromovaleric acid, and 4-benzyloxy-bromobutane[17] in refluxing xylene.[18]

The isomerization of the dioxolanes **11a–k** was carried out under the influence of $TiCl_4$. [19] Stereochemical assignments (Table 1) were made by ^1H and ^{13}C NMR spectroscopies. In addition, unequivocal assignments for C-1, C-3, and C-4 of this series of isochromans,[7–10] were obtained by analysis of two-dimensional C–H heteronuclear correlation NMR spectra demonstrating unambiguously that C-4 is the more protected carbon atom among the three, being C-3 the most deprotected one. Nuclear Overhauser effect (NOE) difference spectroscopy and ^1H–^1H decoupling experiments evidenced that the small methyl substituents gave rise to a diastereomeric mixture of 1,3-*cis* and 1,3-*trans* 4-hydroxy-isochromans (entry 1), with the latter prevailing at −78, −65, and −30 °C, in agreement with previous observations made during the isomerization of related substrates.[8]



Scheme 2. Reagents and conditions: (a) 1. $R_1CH_2PPh_3^+X^-$ (1.25 equiv, X = Cl, Br), K_tBuO, PhMe, −30 °C → rt, overnight; 2. PhSH (0.05 equiv), AIBN (cat.), PhMe, 80 °C, 1 h ($20 < E/Z > 36$; 45–85%, overall); (b) NMO, OsO_4 (cat.), Me_2CO–H_2O (9:1), rt, overnight (80–86%); (c) R_2CHO or $R_2CH(OEt)_2$ (2 equiv), PhH, PPTS (0.1 equiv), MS 4 Å, reflux (68–93%). For the structural identities of R_1 and R_2, see Table 1.

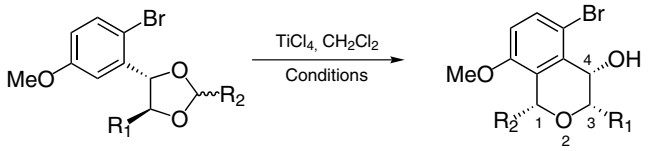
Further analysis revealed that increase in bulkiness of the Wittig (R_1) and acetal (R_2) derived side chains promoted the stereoselective production of the all-*cis* substituted heterocycles in those substrates undergoing the rearrangement. This was clearly evidenced from results of various NOE difference experiments; for example, H-1 of **12d** (entry 4) showed 2% signal enhancement when H-3 was irradiated and vice versa (5%); similarly, **12k** (entry 11) demonstrated 6% signal enhancement of H-1 upon irradiation of H-3 and reciprocal irradiation yielded 7% enhancement of the H-1 resonance. The remaining NOE and decoupling experiments carried out on all of the 4-hydroxy-isochromans gave results fully consistent with the proposed stereochemistry in each case.[20]

In addition, the small vicinal coupling constant between H-3 and H-4 evidenced their respective pseudoaxial and pseudoequatorial orientations and confirmed the exact transfer of the stereochemical features of the dioxolanes to the corresponding 4-hydroxy-isochromans.[6,8] The signals of C-4 were generally observed as broad doublets, due to their coupling with the hydroxylic proton ($J = 8.9$–13.3 Hz), which collapsed into broadened singlets or doublets with J values smaller than 1.8 Hz upon exchange with D_2O. Furthermore, the diagnostic signals of H-3, resonating around δ 3.6, were also supportive of the *cis* relationship between both side chains.[8]

Noteworthy, in the camphorsulfonic acid (CSA)-mediated rearrangement of aryldioxolanyl acetates to isochroman-3-yl acetates, Giles et al. found a strong dependence between the concentration of the promoter and the epimeric ratio of the products.[9a] Changing the CSA concentration from 5.7×10^{-3} mol L^{-1} (0.27 equiv) to 8.6×10^{-2} mol L^{-1} (4 equiv), they were able to modify the *cis*:*trans* products ratio from 6.8:1 to 0.28:1. In our case, CSA was ineffective and, regardless of the final concentration of $TiCl_4$ employed (0.01–0.15 mol L^{-1}), 1,3-*trans* diastereomers were not detected (except for **12a**, where the dioxolane precursor bears two methyl groups). This outcome may be attributed to the presence of bulky side chains, which tend to minimize 1,3-diaxial interactions in the cationic intermediate.[21]

The characteristics of the side chains, in terms of length and nature of their functional groups also effect the isomerization ability of the dioxolanes. The structure of the R_1 chain does not appear to have pronounced influence upon the feasibility of the rearrangement; however, a highly favored acid-catalyzed intramolecular lactonization (entry 2) furnished the corresponding

Table 1. $TiCl_4$-promoted rearrangement of 5-aryl-1,3-dioxolanes carrying different substituents (synthesis of 1,3-disubstituted 4-hydroxy-isochromans)



Entry no	Acetal no	R_1	R_2	Temperature (°C)	Time (h)	Product no	Yield (%)[a]	^{1}H NMR			^{13}C NMR		
								H-1	H-3	H-4	C-1	C-3	C-4
1[b]	**11a**	Me	Me	−78	0.5	**12a**	*trans* 50	5.08, q, $J = 6.0$	4.11, dq $J = 1.7, 6.4$	4.44, dd $J = 1.7, 8.9$	67.01	68.44	66.20
							cis 25[c]	4.93, q, $J = 6.2$	3.69, dq, $J = 1.2, 6.4$	4.49, dd, $J = 1.2, 9.6$	70.83	71.98	68.33
2	**11b**	$(CH_2)_2CO_2Et$	CH_2Br	−30	2		—[d]						
3	**11c**	$(CH_2)_3CO_2Et$	CH_2Br	−30 → rt	2	**12c**	47	5.13, dd, $J = 2.4, 2.6$	3.55, dd, $J = 4.1, 7.7$	4.55, bd, $J = 11.6$	72.53	75.95	67.07
4	**11d**	$(CH_2)_3OBn$	CH_2SPh	−60 → −30	2	**12d**	26	5.21, dd, $J = 2.8, 3.2$	3.54, dd, $J = 2.3, 9.8$	4.56, bd, $J = 13.3$	72.47	75.70	67.14
5	**11e**	CH_2CH_2CN	CH_2SPh	−30	2	**12e**	87	5.30, dd, $J = 2.8, 3.0$	3.70, bdd, $J = 3.2, 11.1$	4.58, bd, $J = 11, 1$	72.67	73.66	67.22
6	**11f**	CH_2CH_2CN	$CH_2CH{=}CH_2$	−78 °C	2		—[e]						
7	**11g**	CH_2CH_2CN	$(CH_2)_2SPh$	−30 → rt	24		—[f]						
8	**11h**	CH_2CH_2CN	$(CH_2)_3SPh$	−78 → rt	16		—[g]						
9	**11i**	CH_2CH_2CN	$(CH_2)_3SO_2Ph$	−78	1.5	**12i**	59	4.84, dd, $J = 1.5, 5.7$	3.56, bdd, $J = 3.5, 9.8$	4.51, bs, $w_{1/2} = 12$	73.82	73.82	67.12
10	**11j**	CH_2CH_2CN		−78 → rt	3		—[g]						
11	**11k**	CH_2CH_2CN	$(CH_2)_3OTBDPS$	−45	4	**12k**	60	4.90, dd, $J = 2.3, 6.6$	3.63, bdd, $J = 3.5, 8.7$	4.54, bd, $J = 10.7$	73.80	74.70	67.46

[a] Isolated yields, after silica gel 60H flash column chromatography (eluent: hexane–EtOAc mixtures).
[b] According to IUPAC naming rules, the starting material is a 4-aryl-1,3-dioxolane.
[c] A 2:1 mixture, being the all-*cis* diastereomer the minor product.
[d] Converted into the five-membered ring lactone (mp 128–129 °C)[22a] in isolated yield of 93%.
[e] The precursor diol **10** ($R_1 = CH_2CH_2CN$) was recovered almost quantitatively.
[f] The thioether side chain cyclized intramolecularly, furnishing 4-hydroxy-thiochroman[22a] (81%).
[g] No cyclization was observed at rt after 24 h of incubation with 2.2–6.3 equiv of $TiCl_4$.

γ-butyrolactone[22a] and the benzyloxy-substituted substrate **11d**, was labile to the Lewis acid used and both, starting material and product partially decomposed during the reaction, diminishing the isolated yield of the expected isochroman **12d** (entry 4).

On the contrary, length and terminal substitution of R_2 seem to be key factors for success of the oxa-Pictet–Spengler transformation. Comparative inspection of acetals bearing a homologous series of phenyl thioethers lead us to suspect that the coordination ability of these substrates' side chain to the metal ion could be determining the success of the isomerization.

In fact, while the thioether **11e** carrying the shortest chain was capable of cyclizing in good yield (entry 5), its next homolog (**11g**, entry 7) reacted through an alternative path (probably involving an intramolecular Friedel Crafts acylation) furnishing 4-hydroxy-thiochroman (81%),[22b] and that bearing a four-carbon side chain (**11h**, entry 8) was completely unreactive under various conditions (2–4 equiv $TiCl_4$). Our suspicion found additional support when dithiane **11j**, a three carbon side chain analog of **11g**, remained unreactive against $TiCl_4$ (2.2–6.3 equiv), being found unchanged after 24 h at 0 °C. In neither of the last three cases production of 4-hydroxy-isocromans could be detected. Furthermore, contrasting with the unreactive thioether **11h**, the related sulfone **11i** provided the corresponding 4-hydroxy-isochroman **12i** in 59% yield (entry 10) and the silyl ether **11k**, a highly hindered oxygen analog of **11h**, furnished 60% of cyclized product **12h** (entry 11). Involvement of the heteroatoms in the side chains leading to insoluble complexes may have hindered the rearrangements of **11g** and **11h**; analogously, the successful rearrangements of **11i** and **11k** may be interpreted as being a consequence of difficulties in titanium coordination to the heteroatoms in the side chain (R_2),[23–25] probably due to unfavorable chain length in the former case or to steric congestion surrounding the oxygen atom of the side chain in the latter.

In conclusion, it has been demonstrated that in the $TiCl_4$-assisted isomerization of 5-aryl-1,3-dioxolanes **11** derived from *threo*-diols **10**, bulky substituents on C-2 and C-4 of the dioxolane ring produced exclusively the 1,3-*cis* 4-hydroxy-isochroman. The functional groups at the end of the side chains of the starting dioxolane, particularly those incorporated during the acetalization step (R_2), proved to have influence on the ability of the substrates to undergo cyclization, probably through complex formation with the catalyst. Application of the above observations to the elaboration of tricyclic intermediates toward the synthesis of natural stephaoxocanes is in progress.

Acknowledgements

The authors acknowledge the financial support provided by SECyT-UNR, ANPCyT, Fundación Antorchas and CONICET. D.A.B. thanks CONICET for a fellowship.

References and Notes

1. Kashiwaba, N.; Morooka, S.; Kimura, M.; Ono, M.; Toda, J.; Suzuki, H.; Sano, T. *J. Nat. Prod.* **1996**, *59*, 803–805.
2. Cameron, D. W.; Cromartie, R. I. T.; Kingston, D. G. I.; Todd, A. R. *J. Chem. Soc.* **1964**, 51–72.
3. Inagaki, T.; Kaneda, K.; Suzuki, Y.; Hirai, H.; Nomura, E.; Sakakibara, T.; Yamauchi, Y.; Huang, L. H.; Norcia, M.; Wondrack, L. M.; Sutcliffe, J. A.; Kojima, N. *J. Antibiot.* **1998**, *51*, 112–116.
4. Ralph, J.; Peng, J.; Lu, F. *Tetrahedron Lett.* **1998**, *39*, 4963–4964.
5. (a) Cutler, H. G.; Majetich, G.; Tian, X.; Spearing, P. U.S. Patent 5,922,889, 1999; *Chem. Abstr.* **1999**, *131*, 73559; (b) TenBrick, R. E.; Bergh, C. L.; Ducan, J. N.; Harris, D. W.; Huff, R. M.; Lathi, R. A.; Lawson, C. F.; Lutzke, B. S.; Martin, I. J.; Rees, S. A.; Schlachter, S. K.; Sih, J. S.; Smith, M. W. *J. Med. Chem.* **1996**, *39*, 2435–2437; (c) Fráter, G.; Kraft, P. *Helv. Chim. Acta* **1999**, *82*, 1656–1665.
6. Giles, R. G. F.; Green, I. R.; Knight, L. S.; Lee Son, V. R.; Rickards, R. W.; Senanayake, B. S. *J. Chem. Soc., Chem. Commun.* **1991**, *1*, 287–288.
7. Some representative examples: (a) Mohler, D. L.; Thompson, D. W. *Tetrahedron. Lett.* **1987**, 2567–2570; (b) Wünsch, B.; Zott, M. *Tetrahedron: Asymmetry* **1993**, *4*, 2307–2310; (c) Xu, Y.-Ch.; Kohlman, D. T.; Liang, S. X.; Erikkson, C. H. *Org. Lett.* **1999**, *1*, 1599–1602; (d) Guiso, M.; Marra, C.; Cavarischia, C. *Tetrahedron Lett.* **2001**, *42*, 6531–6534.
8. Giles, R. G. F.; Rickards, R. W.; Senanayake, B. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3361–3370.
9. (a) Giles, R. G. F.; Rickards, R. W.; Senanayake, B. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3949–3956; (b) Giles, R. G. F.; Rickards, R. W.; Senanayake, B. S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2241–2248.
10. Giles, R. G. F.; Green, I. R.; Knight, L. S.; Lee Son, V. R.; Yorke, S. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 865–874.
11. (a) Kaufman, T. S. *Heterocycles* **2001**, *55*, 323–330; (b) Bianchi, D. A.; Kaufman, T. S. *ARKIVOC* **2003**, *X*, 178–188.
12. Kaufman, T. S.; Bernardi, C. R.; Cipulli, M.; Silveira, C. C. *Molecules* **2000**, *5*, 493–494.
13. Fleming, I.; Woolias, M. *J. Chem. Soc. (C)* **1979**, 829–837.
14. Schwarz, M.; Graminski, G. F.; Waters, R. M. *J. Org. Chem.* **1986**, *51*, 260–263.
15. (a) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248–2256; (b) Fuhry, M. A. M.; Holmes, A. B.; Marshall, D. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2743–2746.
16. (a) Kritchevsky, D. *J. Am. Chem. Soc.* **1943**, *65*, 487; (b) Crimmins, M.; Kirincich, S. J.; Wells, A. J.; Choy, A. L. *Synth. Commun.* **1998**, *2*, 3675–3680; (c) Enders, D.; Schäfer, T.; Piva, O.; Zamponi, A. *Tetrahedron* **1994**, *50*, 3349–3362; (d) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231–237; (e) Priebe, W.; Grynkiewicz, G. *Tetrahedron Lett.* **1991**, *32*, 7353–7356; (f) Freeman, F.; Kim, D. S. H. L.; Rodriguez, E. *J. Org. Chem.* **1992**, *57*, 1722–1727.
17. Mp: 216–218 °C; 244–246 °C (lit.[18b] 241–243 °C); 195–197 °C (lit.[18b] 192–195 °C) and 159–160 °C, respectively.
18. (a) Bestmann, H. J.; Koschatzky, K. H.; Stransky, W.; Vostrowsky, O. *Tetrahedron Lett.* **1976**, 353–356; (b) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217–226.
19. New compounds gave single spots on TLC employing several solvent systems and were fully characterized.

Inseparable mixtures of dioxolanes were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. Assignment of individual ^{13}C resonances was supported by DEPT experiments.

20. The elaboration of **12k** is representative. A freshly prepared solution of $TiCl_4$ (1.2 mmol) in CH_2Cl_2 (1.41 mL) was added dropwise to acetal **11k** (303 mg, 0.5 mmol) in dry CH_2Cl_2 (10 mL), cooled to −45 °C. After stirring the mixture 4 h, the reaction was quenched with saturated NH_4Cl (5 mL), warmed to rt, and extracted with EtOAc (3 × 30 mL). The organic extracts were washed with brine (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the residue afforded **12k** (183 mg, 60%), as an oil; $R_f = 0.47$ (hexanes–EtOAc, 7:3); IR (film): 3460, 2950, 2865, 1580, 1470, 1390, 1260, 1125, 1070, 930, 840, and 720 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (s, 9H), 1.60 (d, $J = 10.7$ Hz, 1H), 1.75–2.10 (m, 4H), 2.15–2.35 (m, 2H), 2.51 (d, $J = 6.5$ Hz, 1H), 2.55 (d, $J = 6.1$ Hz, 1H), 3.63 (bdd, $J = 3.5$ and 8.7 Hz, 1H), 3.68 (dd, $J = 6.0$ and 6.3 Hz, 2H), 3.75 (s, 3H), 4.54 (bd, $J = 10.7$ Hz, 1H), 4.90 (dd, $J = 2.3$ and 6.6 Hz, 1H), 6.72 (d, $J = 8.8$ Hz, 1H), 7.30–7.51 (m, 6H), 7.42 (d, $J = 8.8$ Hz, 1H), and 7.58–7.70 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.45, 19.06, 26.70 (4C), 28.39, 31.01, 55.26, 63.71, 67.46, 73.80, 74.70, 111.78, 115.69, 119.34, 127.41 (4C), 129.19, 129.36 (2C), 131.30, 133.92 (2C), 135.39 (4C), 136.13, and 155.26. HRMS: Found M^+ 607.1750; $C_{32}H_{38}BrNO_4Si$ requires M^+ 607.1753.

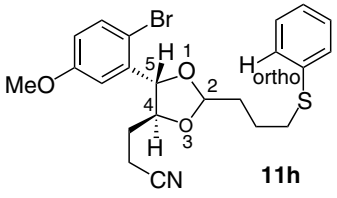
21. (a) Melany, M. L.; Lock, G. A.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 3925–3927; (b) Miles, W. H.; Heinsohn, S. K.; Brennan, M. K.; Swarr, D. T.; Eidam, P. M.; Gelato, K. A. *Synthesis* **2002**, *1*, 1541–1545, and references cited therein.

22. (a) ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10–2.36 (m, 2H), 2.44–2.78 (m, 2H), 2.85 (bs, $w_{1/2} = 14$ Hz, 1H), 3.79 (s, 3H), 4.70 (ddd, $J = 4.2$, 5.0, 6.7 Hz, 1H), 5.11 (bd, $J = 5.0$ Hz, 1H), 6.74 (dd, $J = 3.1$, 8.8 Hz, 1H), 7.10 (d, $J = 3.1$ Hz, 1H), and 7.42 (d, $J = 8.8$ Hz, 1H); (b) ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.77 (bs, 1H), 1.98–2.14 (m, 1H), 2.20–2.43 (m, 1H), 2.82–2.92 (m, 1H), 3.32 (ddd, $J = 3.1$, 12.1, 12.5 Hz, 1H), 4.80 (bt, 1H), and 7.02–7.35 (m, 4 H).

23. A coordinating group *para* to the MeO substituent appears to favor good yields of products. The rearrangement proceeds with similar stereoselectivity when acetals having MeO or Cl groups[8] instead of Br are employed; however, *rel*-(2*R*,4*S*,5*S*)- and *rel*-(2*S*,4*S*,5*S*)-4-(3′-methoxyphenyl)-2,5-dimethyl-1,3-dioxolane gave less than 20% of *rel*-(1*S*,3*S*,4*S*)-1,3-dimethyl-4-hydroxy-6-methoxy-isochroman.

24. Chemical shift changes have been observed in other titanium complexes. See, for example: (a) Singh, D. K.; Springer, J. B.; Goodson, P. A.; Corcoran, R. C. *J. Org. Chem.* **1996**, *61*, 1436–1442; (b) Corcoran, R. C.; Ma, J. *J. Am. Chem. Soc.* **1992**, *114*, 4536–4542.

25. Exposure of **11h** in $CDCl_3$ to 0.9 equiv of $TiCl_4$ at −30 °C resulted in chemical shift changes (in ppm) of H-2 (0.25), *ortho*-ArH (0.14), CH_2SPh (0.09), and CH_2CN (0.08).



11h