Prins Cyclization Using Magnesium Halides: Mild Access to 4-Halogenated Polysubstituted Tetrahydropyrans with a Special Feature

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Abstract: Different 4-halo-substituted polyfunctionalized tetrahydropyrans were easily synthesized by segment-coupling Prins cyclization utilizing magnesium halides. The moderate Lewis acidity allows transformation of substrates bearing acid-labile functional groups. A solvent dependency of the stereochemistry at the C4 carbon was observed.

Key words: Prins cyclization, magnesium halides, halogenated tetrahydropyrans, solvent-dependent stereochemistry, polysubstituted tetrahydropyrans

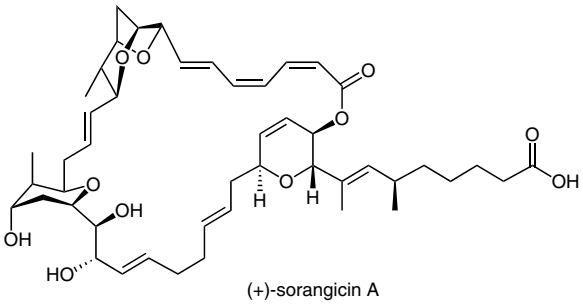
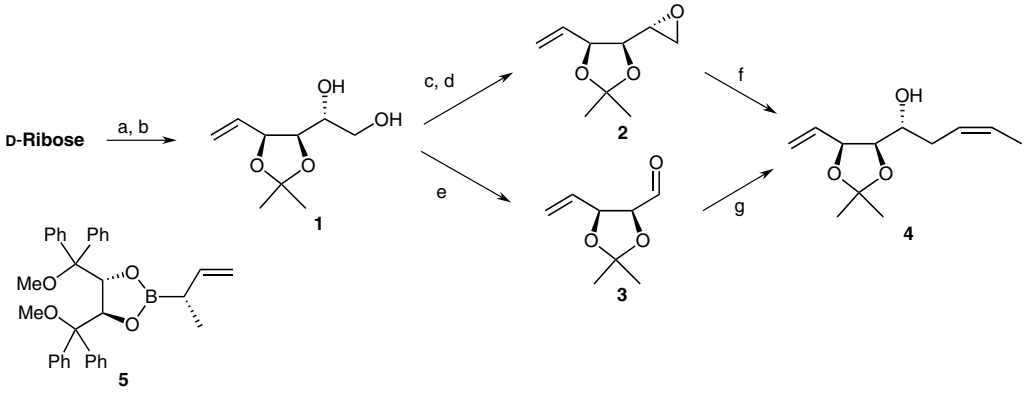


Figure 1

In connection with our studies to synthesize the complex natural product (+)-sorangicin A[1] (Figure 1) we envisioned a new methodology for a general approach to polysubstituted tetrahydropyrans. Sorangicins, secondary metabolites of myxo bacteria,[2] are a new class of powerful antibiotics with several structural challenges, including a 31-membered macrolide, 15 stereogenic centers, and an unusual dioxobicyclo[3.2.1]octane system in conjunction with a rare *Z*,*Z*,*E*-trienate linkage.

Here we wish to report our investigations[3] along these lines using the Prins cyclization as one of the most effective and frequently used methods to synthesize polysubstituted tetrahydropyrans – a common structural motif featured in a large number of natural products and biological active compounds.[4–6] Originally, the Prins cyclization is an intermolecular condensation of homoallylic alcohols and carbonyl compounds utilizing Brønstedt or Lewis acids. In many cases the reactions are saddled with various side reactions often leading to decreased yields and limitations of substrate scope.[7] New mechanistic insights owing to extensive investigations and improved procedures led to a constantly growing scope of application and a range of products.[8] Therefore, this acid-mediated coupling reaction became a commonly used synthetic tool and is utilized for macrocyclizations as well.[5,6]

Halogenated THP are of broad interest due to the opportunity of subsequent functionalization. Numerous Lewis acids have been utilized to introduce halogen substituents.[9] Due to the necessity of a relatively high acidity, the Prins cyclization only shows limited tolerance to acid-labile functional groups in particular. One of the key steps of our synthesis of the 2,3,4,6-tetrasubstituted tetrahydro-



Scheme 1 *Reagents and conditions*: (a) H_2SO_4 (cat.), acetone; (b) Ph_3PMeBr, *t*-BuOK, 68% (2 steps); (c) Et_3N, Bu_2SnO, TsCl; (d) NaH, 97% (2 steps); (e) $NaIO_4$, silica gel, quant.; (f) Mg, Li_2CuCl_4 (cat.), *cis*-1-bromoprop-1-ene, 89%; (g) **5**, 4 Å MS, 80%.

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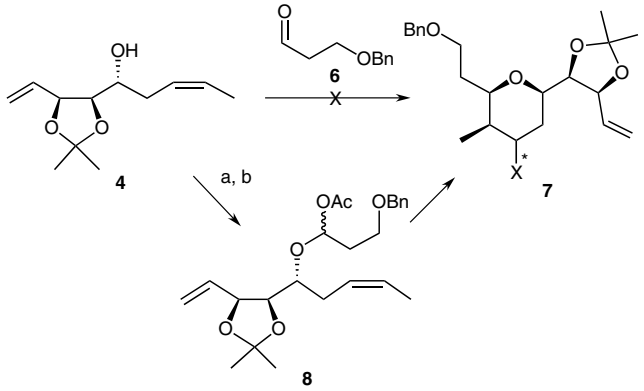
pyran fragment of (+)-sorangicin A was to prepare 4-halogenated tetrahydropyrans **7**. *Z*-Homoallylic alcohol **4** as one of the key intermediates can be synthesized in just a few steps starting from D-ribose (Scheme 1). The natural sugar was converted into diol **1**[10] which can then be transformed into **4** through two different routes. Preparation of epoxide **2**[11] and subsequent Grignard reaction[12] gave **4** in 58% yield over five steps. Stereoselective allylation of aldehyde **3**, obtained by glycol cleavage of **2**,[13] using boron reagent **5**[14] led to **4** in 54% yield over four steps.

The intermolecular coupling of homoallylic alcohol **4** with aldehyde **6** only led to numerous side reactions. Due to the high acidity and a low reaction rate of the intermolecular cyclization in comparison to, for example, cleavage of the acetonide, transketalization, and racemization, in none of the cases a clean product could be observed.



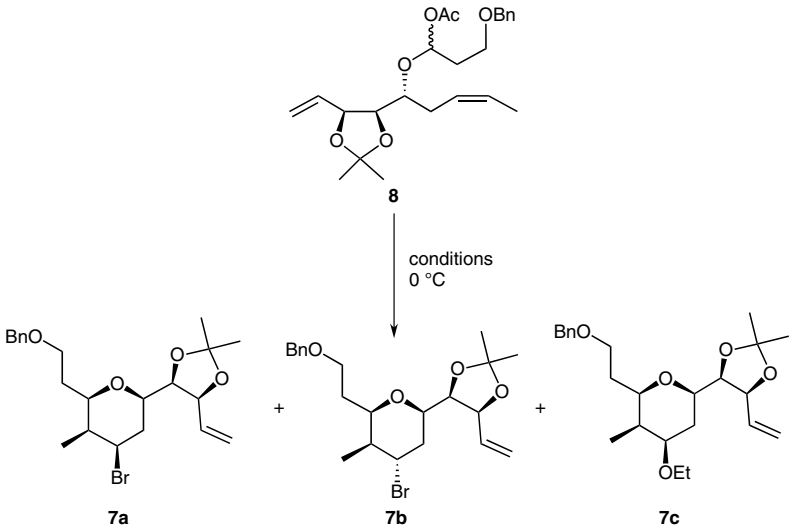
Scheme 2 *Reagents and conditions*: (a) DCC, DMAP, $HOOCCH_2CH_2OBn$; (b) i. DIBAL-H, ii. Ac_2O, pyridine, DMAP, 89% (2 steps).

Improvement could be achieved by intramolecularization of the reaction through transformation of **4** into the mixed acetal **8**[8c,11] and utilization of magnesium halides as Lewis acids (Scheme 2). The only moderate acidity effects a noticeable decrease in hydrolysis and side reactions.

Magnesium bromide in dichloromethane gives two isomers **7a** and **7b** (Table 1). Similar observations were made with other substrates.[8,15] Nucleophilic attack on the intermediate oxocarbenium ion in the chairlike transition state can occur through an axial and equatorial trajectory alike. In the course of optimization we surprisingly observed a solvent dependency of the stereochemical outcome. Addition of coordinating oxygen-containing solvents decreases the Lewis acidity of the metal salt. Using a mixture of dichloromethane and ether results in an enhanced yield and eliminates the axial isomer. Unfortunately, the equatorial 4-ethoxy-substituted tetrahydropyran **7c** emerges as a new side product as a result of solvent attack. Best performance can be achieved by the use of magnesium bromide diethyl etherate in dichloromethane (Table 1). Analogous effects can be observed with magnesium iodide – a Lewis acid so far also unemployed in Prins cyclizations. In this case each of the isomers **7d** and **7e** can be promoted to the main product and be produced in good yields by simple variation of the solvent mixture (Table 2).

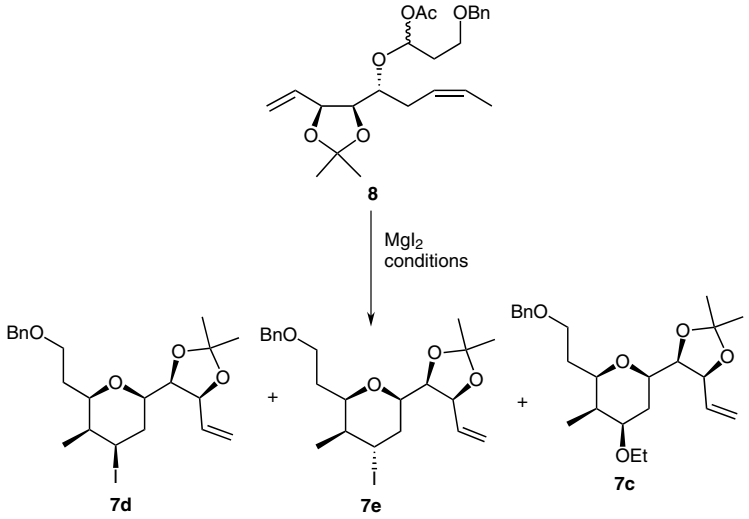
The stereochemistry of the reaction is a result of the chairlike transition state and the two possible pathways for nucleophilic attack.[8] Addition of Lewis acid induces formation of α-halo ether **9** and solvolysis provides the intimate ion pair **10**. Cyclization produces carbenium intermediate **11**, still as an intimate ion pair. At this stage

Table 1 Prins Cyclization of Acetal **4** with Magnesium Bromide



Lewis acid	Solvent	Yield of **7a** (%)	Yield of **7b** (%)	Yield of **7c** (%)
$MgBr_2$	CH_2Cl_2	38	15	–
$MgBr_2$	CH_2Cl_2–Et_2O (3:1)	52	–	31
$MgBr_2 \cdot OEt_2$	CH_2Cl_2	82	–	–

Table 2 Prins Cyclization of Acetal **8** with Magnesium Iodide



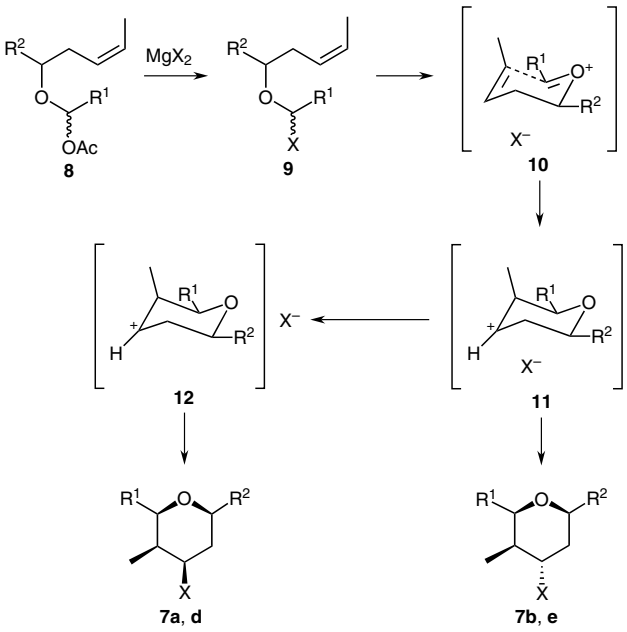
Solvent	Temp	Yield **7d** (%)	Yield **7e** (%)	Yield **7c** (%)
CH_2Cl_2	0 °C	–	49	–
THF	r.t.	–	–	–
CH_2Cl_2–THF (1:2)	r.t.	<20	<10	–
CH_2Cl_2–THF (9:1)	0 °C	15	60	–
Et_2O	r.t.	–	–	–
CH_2Cl_2–Et_2O (1:1)	0 °C	40	–	59
CH_2Cl_2–Et_2O (1:1)	r.t.	55	8	19
CH_2Cl_2–Et_2O (3:1)	r.t.	62	8	10

there are two possible pathways – proximal attack of halogenide leading to axial isomers **7b** or **7e** or dissociation to a solvent-separated ion pair **12** which will then be attacked through an equatorial trajectory to give isomers **7a** or **7d** (Scheme 3).

Decisive for the outcome of the reaction is whether the attack from the intimate ion pair is faster than solvation or not. It seems that ether accelerates solvation, perhaps through promotion of MgX_3^- formation thus decreasing nucleophilicity and enabling solvent attack. Whereas THF apparently in the first instance moderates the reactivity of the Lewis acid.

To the best of our knowledge, there are no reports on such a solvent-dependency of stereochemistry in Prins cyclization. Admittedly, in some cases it has been accomplished to synthesize selectively one epimer or the other, but only by usage of different kinds of Lewis acids and utilization of additives.[8b,15a,c]

In summary, we discovered a mild method for the Prins cyclization by the use of magnesium halides, which enables to convert mixed acetal **8** into different halogen-substituted, highly functionalized tetrahydropyrans.[16] The moderate acidity of these metal salts may expand the scope of the reaction to compounds bearing acid-labile functional groups. The unprecedented solvent dependency of the stereochemical outcome in the case of mag-



Scheme 3

nesium iodide offers opportunities for simple reaction control.

References and Notes

(1) (a) Schinzer, D.; Schulz, C.; Krug, O. *Synlett* **2004**, 2689. (b) Smith, A. B.; Dong, S.; Brenneman, J. B.; Fox, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 12109. (c) Smith, A. B. III.; Dong, S.; Fox, R. J.; Brenneman, J. B.; Vanecko, J. A.; Maegawa, T. *Tetrahedron* **2011**, *67*, 9809. (d) Crimmins, M. T.; Haley, M. W.; O'Bryan, E. A. *Org. Lett.* **2011**, *13*, 4712.

(2) (a) Irschik, H.; Jansen, R.; Gerth, K.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1987**, *40*, 7. (b) Jansen, R.; Höfle, G.; Irschik, H.; Reichenbach, H.; Schomburg, D.; Wray, V. *Liebigs Ann. Chem.* **1989**, *2*, 111. (c) Jansen, R.; Wray, V.; Irschik, H.; Reichenbach, H.; Höfle, G. *Tetrahedron Lett.* **1985**, *26*, 6031. (d) Campbell, E. A.; Pavlova, O.; Zenkin, N.; Leon, F.; Irschik, H.; Jansen, R.; Severinov, K.; Darst, S. A. *EMBO J* **2005**, *24*, 674. (e) Römmele, G.; Wirz, G.; Solf, R.; Vosbeck, K.; Gruner, J.; Wehrli, W. *J. Antibiot.* **1990**, *43*, 88.

(3) Walter, M. *PhD Thesis*; University of Magdeburg: Germany, **2013**.

(4) (a) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683. (b) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045. (c) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

(5) Olier, C.; Kaafarani, M.; Gastaldi, S.; Bertrand, M. P. *Tetrahedron* **2010**, *66*, 413.

(6) Crane, E. A.; Scheidt, K. A. *Angew. Chem.* **2010**, *122*, 8494.

(7) (a) Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, *128*, 13640. (b) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 577. (c) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, 955. (d) Lolkema, L. D. M.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7115.

(8) (a) Kataoka, K.; Ode, Y.; Matsumoto, M.; Nokami, J. *Tetrahedron* **2006**, *62*, 2471. (b) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904. (c) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191. (d) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679.

(9) (a) Kishi, Y.; Inugi, S.; Fuchigami, T. *Eur. J. Org. Chem.* **2009**, 103. (b) Miranda, P. O.; Diáz, D. D.; Padrón, J. I.; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003**, *5*, 1979. (c) Liu, F.; Loh, T.-P. *Org. Lett.* **2007**, *9*, 2063. (d) Patterson, B.; Rychnovsky, S. D. *Synlett* **2004**, 543. (e) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (f) Clarisse, D.; Pelotier, B.; Piva, O.; Fache, F. *Chem. Commun.* **2012**, *48*, 157. (g) Yadav, J. S.; Subba Reddy, B. V.; Narayana Kumar, G. G. K. S.; Swamy, T. *Tetrahedron Lett.* **2007**, *48*, 2205.

(10) Moon, H. R.; Choi, W. J.; Kim, H. O.; Jeong, L. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1189.

(11) Srihari, P.; Kumaraswamy, B.; Yadav, J. S. *Tetrahedron* **2009**, *65*, 6304.

(12) Trost, B. M.; Papillon, J. P. N.; Nussbaumer, T. *J. Am. Chem. Soc.* **2005**, *127*, 17921.

(13) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.

(14) The chiral diol ligand prepared according to: (a) Bischop, M.; Curecki, V.; Ophoren, V.; Pietruszka, J. *Synthesis* **2008**, 2488. (b) The chiral diol ligand prepared[14a] was used to synthesize boron reagent **5** according to: Hoffmann, R. W.; Wolff, J. J. *Chem. Ber.* **1991**, *124*, 563.

(15) (a) Zuwerra, D.; Glaus, F.; Betschart, L.; Schuster, J.; Gertsch, J.; Ganci, W.; Altmann, K.-H. *Chem. Eur. J.* **2012**, *18*, 16868. (b) Borkar, P.; van de Weghe, P.; Reddy, B. V. S.; Yadav, J. S.; Grée, R. *Chem. Commun.* **2012**, *48*, 9316. (c) Miles, R. B.; Davis, C. E.; Coates, R. M. *J. Org. Chem.* **2006**, *71*, 1493. (d) Vitale, J. P.; Wolckenhauer, S. A.; Do, N. M.; Rychnovsky, S. D. *Org. Lett.* **2005**, *7*, 3255.

(16) **General Procedure for Prins Cyclization of 8**
Magnesium halide (2 equiv) was added to a solution of acetoxy ether **8** in the respective solvent (mixture; 5–10 mL/mmol of **8**) at given temperatures. Reaction mixture was stirred for 1–2 h and quenched with sat. $NaHCO_3$ solution and extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (pentane–Et_2O, 7:1).
Spectroscopical Data for (2*R*,3*S*,4*R*,6*R*)-2-(2-Benzyloxyethyl)-4-bromo-6-[(4*R*,5*S*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]-3-methyltetrahydropyran (7a)
Yield 82%; colorless oil; $[a]_D$ +43 (*c* 2.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ = 7.27–7.37 (5 H, m, C_6H_5), 5.83 (1 H, ddd, *J* = 16.8, 10.0, 6.5 Hz, C*H*=CH_2), 5.34 (1 H, dd, *J* = 17.1, 1.5 Hz, CH=CH_2), 5.14 (1 H, d, *J* = 10.5 Hz, CH=CH_2), 4.64 (1 H, dd, *J* = 6.3, 6.3 Hz, C*H*CH=CH_2), 4.44–4.51 (2 H, m, CH_2Ph), 4.42 (1 H, dt, *J* = 12.8, 4.3 Hz, H-4), 3.97 (1 H, dd, *J* = 8.4, 6.3 Hz, 6-CH), 3.39–3.52 (1 H, m, H-2), 3.48–3.52 (2 H, m, CH_2CH_2OBn), 3.36 (1 H, td, *J* = 9.8, 2.4 Hz, H-6), 2.20 (1 H, dt, *J* = 10.2, 2.8 Hz, H-5), 1.92–1.99 (2 H, m, H-5 and H-3), 1.78–1.85 (1 H, m, CH_2CH_2OBn), 1.60–1.66 (1 H, m, CH_2CH_2OBn), 1.45 [3 H, s, C$(CH_3)_2$], 1.36 [3 H, s, C$(CH_3)_2$], 1.07 (3 H, d, *J* = 6.9 Hz, 3-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 ($C_{ar,q}$), 133.6 (*C*H=CH_2), 128.4 (C_{ar}), 127.6 (C_{ar}), 117.4 (CH=*C*H_2), 108.7 [*C*$(CH_3)_2$], 79.2 (6-CH), 78.6 (*C*HCH=CH_2), 76.6 (C-2), 76.3 (C6), 73.0 (CH_2Ph), 66.9 (CH_2CH_2OBn), 54.0 (C-4), 39.7 (C-3), 34.6 (C-5), 33.9 (CH_2CH_2OBn), 27.7 [C(*C*$H_3)_2$], 25.3 [C(*C*$H_3)_2$], 7.6 (3-CH_3). MS: *m/z* (%) = 424 (70), 422 (70), 301 (50), 231 (75), 141 (55), 137 (70), 127 (100). HRMS: *m/z* calcd for $C_{22}H_{31}BrO_4$: 438.1403 $[M]^+$; found: 438.1404.

