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Preparation of C-3,5-Acyl Furanoses via Highly Selective Intramolecular Acyl Migration

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Received May 25, 2004

Abstract: A practical synthesis of C-3,5-acyl furanose via a base-catalyzed, highly selective intramolecular acyl migration in alcohol solvents is reported.

C-3,5- and C-2,3,5-protected furanoses are useful building blocks in carbohydrate chemistry.[1,2] These synthons, including C-branched or nonbranched, have been widely used in glycosylation[2] to prepare important biologically active compounds such as saccharides, nucleosides, antibiotics, etc. In conjunction with an antiviral nucleoside drug development program, we became interested in developing a general protocol for synthesis of C-3,5-acyl C-2-substituted furanose derivatives. Protected furanoses are often prepared by a series of protection/deprotection operations on a suitable furanose or pyranose in order to achieve selective protection on OH groups. Preparation of C-3,5 acyl-protected furanoses in the literature is limited by choices of protection and deprotection protocols, which are often substrate specific.[3] In particular, few methods have been reported for the preparation of C-2-branched furanoses.[4]

We report here a practical preparation of C-3,5-acyl furanoses via selective intramolecular 1,2 vs 1,3 acyl migration in the presence of base. Intramolecular acyl migration has been reported in carbohydrate chemistry; however, it is often used as an efficient method for selective protection of OH(s) for a specific substrate.[5] It is also well-known the ratio of furanose vs pyranose can be significantly affected by the strerochemistry of the substrates if both the C-4 and C-5 OH's are not capped;[6] however, we reasoned that preparation of furanose could still be achieved[5b] via a selective intramolecular acyl migration on open-chain substrates by achieving reaction conditions in favor of pathway A over B or C. As shown in Scheme 1, only the C-4 or C-5 OH in substrates **II** and **III** is readily available to form furanose or pyranose while the remaining OH's are protected.[7] The 1,2 or 1,3 acyl migration in the pathway A, B, or C could potentially occur via five- and six-membered ring transition intermediates **Va**/**Vb** or even bicyclic ortho ester intermediates **IVa**/**IVb** as shown in Scheme 1.

Starting from the literature known diols **1**,[3d,8] which are easily prepared by several methods from inexpensive commercially available starting materials, the precursors **4** for acyl migration studies can be quickly accessed via a one-pot through process (Scheme 2).

Esterification of **1** with an acyl chloride in the presence of 3 equiv of pyridine and 2.2 equiv of RCOCl in 7 volumes of MeCN at 60 °C gave a homogeneous reaction with 99% selectivity of diester vs monoester and near full conversion (>98% assay yield) within 10 h. Use of MeCN allowed carrying out the three-step preparation in one pot. Thus, direct addition of 3 equiv of aqueous 20%

(1) For recent reviews, see: (a) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, 40, 1624. (b) Vorbrüggen, H. Ruh-Pohlenx, C. *Org. React.* **2000**, *55*, 1.

(2) For recent examples, see: (a) Eldrup, A. B.; Allerson, C. R.; Bennett, C. F.; Bera, S.; Bhat, B.; Bhat, N.; Bosserman, M. R.; Brooks, J.; Burlein, C.; Carroll, S. S.; Cook, P. D.; Getty, K. L.; MacCoss, M.; McMasters, D. R.; Olsen, D. B.; Prakash, T. P.; Prhavc, M.; Song, Q.; Tomassini, J. E.; Xie, J. *J. Med. Chem.* **2004**, *47*, 2283. (b) Li, N., Piccirilli, J. A. *J. Org. Chem.* **2003**, *68*, 6799. (c) Griffon, J.-F.; Mathe, G.; Faraj, A.; Aubertin, A.-M.; De Clercq, E.; Balzarini, J.; Sommadossi, J.-P.; Gosselin, G. *Eur. J. Med. Chem.* **2001**, *36*, 447. (d) Yin, H.; Lowary, T. L. *Tetrahedron Lett.* **2001**, *42*, 5829. (e) D'Souza, F. W.; Ayers, J. D.; McCarren, P. R.; Lowary, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 1251. (f) Wang, Z.; Prudhomme, D. R.; Buck, J. R.; Park, M.; Rizzo, C. J. *J. Org. Chem.* **2000**, *65*, 5969. (g) Girardet J.; Gunic, E.; Esler, C.; Cieslak, D.; Pietrzkowski, Z.; Wang, G. *J. Med. Chem.* **2000**, *43*, 3704. (h) Sabchez, S.; Bamhaoud, T.; Prandi, J. *Tetrahedron Lett.* **2000**, *41*, 7447. (i) Tang, X.; Liao, X.; Piccirilli, J. A. *J. Org. Chem.* **1999**, *64*, 747. (j) Harry-O'kuru, R. E.; Smith, J. M. Wolfe, M. S. *J. Org. Chem.* **1997**, *62*, 1754.

(3) For examples, see: (a) Callam, C. S.; Gadikota, R. R.; Lowery, T. L. *J. Org. Chem.* **2001**, *66*, 4549. (b) McCormick, J.; Li, Y.; McCormick, K.; Duynstee, H. I.; Van Engen, A. K.; Van der Marel, G. A.; Ganem, B.; Van Boom, J. H.; Meinwald, J. *J. Am. Chem. Soc.* **1999**, *121*, 5661. (c) Desire, J.; Prandi, J. C*arbohydr. Res.* **1999**, *317*, 110. (d) Ono, A. M.; Shiina, T.; Ono, A.; Kainosho, M. *Tetrahedron Lett.* **1998**, *3*, 2793. (e) Chen, S.-H.; Lin, S.; King, I.; Spinka, T.; Dutschman, G. E.; Gullen, E. A.; Cheng, Y.-C.; Doyle, T. W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3245. (f) Agrofoglio, L. A.; Jacquinet, J.-C.; Lancelot, G. *Tetrahedron Lett.* **1997**, *38*, 1411. (g) Robles, R.; Rodriguez, C.; Izquierdo, I.; Plaza, M. T.; Mota, A. *Tetrahedron: Asymmetry* **1997**, *8*, 2959. (h) Kraus, G. A.; Maeda, H. *J. Org. Chem.* **1995**, *60*, 2. (i) Genu-Dellac, C.; Gosselin, G.; Imbach, J. L. *Carbohydr. Res.* **1991**, *216*, 249. (j) Jeronic, L. O.; Sznaidman, M. L.; Cirelli, A. F.; De Lederkremer, R. M. *Carbohydr. Res.* **1989**, *191*, 130. (k) Schmidt, R. R.; Gohl, A. *Chem. Ber.* **1979**, *112*, 1689. (l) Ritzmann, G.; Klein, R. S.; Hollenberg, D. H.; Fox, J. J. *Carbohydr. Res.* **1975**, *39*, 227.

(4) (a) Li, N.-S.; Tang, X.-Q.; Piccirilli, J. A. *Org. Lett.* **2001**, *3*, 1025. (b) Schmit, C. *Synlett* **1994**, 2. (c) Beigelman, L. N.; Ermolinskii, B. S.; Gurskaya, G. V.; Tsapkina, E. N.; Karpeiskii, M. Y.; Mikhailov, S. N. *Carbohydr. Res.* **1987**, 166, 219. (d) Novak, J. J. K.; Smejkal, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1971**, *36*, 3670; *Tetrahedron Lett.* **1969**, 1627. (e) Jenkins, S. R.; Arison, B.; Walton, E. *J. Org. Chem.* **1968**, *33*, 2490.

(5) (a) Cipolla, L.; La Ferla, B.; Lay, L.; Peri, F.; Nicotra, F. *Tetrahedron: Asymmetry* **2000**, *11*, 295. (b) Horrobin, T.; Tran, C. H.; Crout, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1069. (c) Shing, T. K. M.; Wan, L. H. *J. Org. Chem.* **1996**, *61*, 8468. (d) Goueth, P. Y.; Gogalis, P.; Bikenga, R.; Gode, P.; Postel, D.; Ronco, G.; Villa, P. *J. Carbohydr. Chem.* **1994**, *13*, 249. (e) Chaplin, D.; Crout, D. H.; Bornemann, S.; Hutchinson, D. W.; Khan, R. *Chem. Soc., Perkin Trans. 1* **1992**, 235.

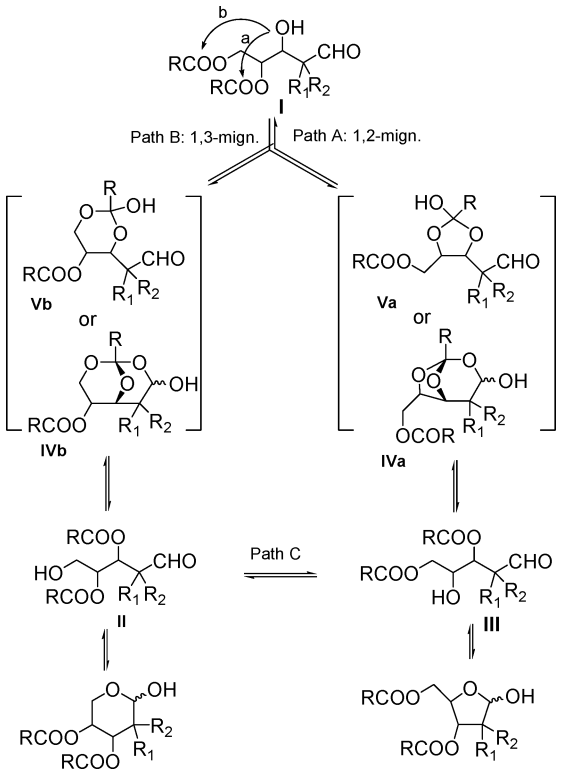
(6) Hough L.; Richardso, A. G. Mono Saccharide Chemistry. In *Comprehensive Organic Chemistry;* Barton, D., Ollis, W. D., Eds.; Pergamon Press: London, 1979; Vol. 5, p 687.

(7) Apparently, multiple equilibria are involved in the process. It is not clear whether the ratio of furanoses vs pyranoses is the kinetic or thermodynamic controlled results. However, it was found later on that exposure of **7a** or **6a** under acyl migration conditions resulted in formation of less than 10% of **6a** or **7a**, respectively. This provided some evidence that (a) formation of furanose through pathways B + C (**I** → **II** → **III**) or C is not the main pathway; (b) formation of furanose/pyranose could be dominated via pathways A and B from **I**.

(8) (a) Shing, T. K. M.; Wong, C.-H.; Yip, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1323−1340. (b) Xie, M.; Berges, D. A.; Robins, M. *J. Org. Chem.* **1996**, *61*, 5178. (c) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1996**, *61*, 2845. (d) Yoshikawa, M.; Okaichi, Y.; Cha, B. C.; Kitagawa, I. *Tetrahedron* **1990**, *47*, 7459. (e) Weber, J. F.; Talhouk, J. W.; Nachman, R. J.; You, T.-P.; Halaska, R. C.; Williams, T. M.; Mosher, H. S. *J. Org. Chem.* **1986**, *51*, 2702−2706. (f) Brimacombe, J. S.; Ching, O. A. *Carbohydr. Res.* **1968**, *8*, 82.

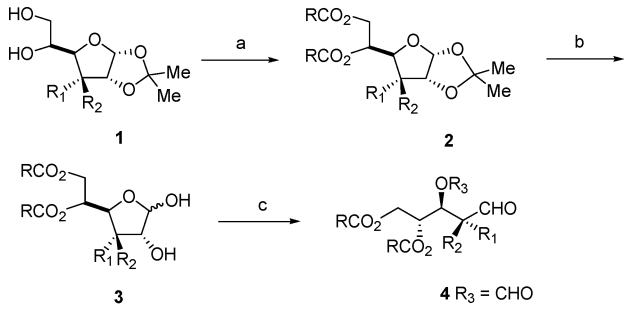
10.1021/jo049121y CCC: $27.50
Published on Web 10/06/2004

SCHEME 1. Expected Acyl Migration Pathways Leading to Furanoses/Pyranoses[a]



[a] Possible five- and six-membered ring or bicyclic ortho ester intermediates for pathway C are not shown here for simplicity.

SCHEME 2. Preparation of C-4,5-Diacyl Aldehydes[a]

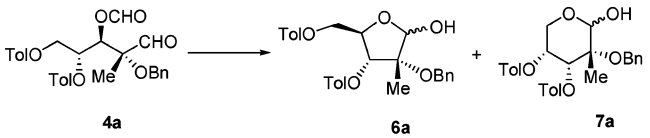


2, **3**, **4**, **5**	R	R_1	R_2
a	*p*-Me-C_6H_4	OBn	Me
b	C_6H_5	OBn	Me
c	*p*-Cl-C_6H_4	OBn	Me
d	*t*-Bu	OBn	Me
e	C_6H_5	OBn	H
f	C_6H_5	H	OBn
g	*p*-Me-C_6H_4	OBn	*n*-Bu
h	*p*-Me-C_6H_4	OBn	CH_2=CH
i	*p*-Me-C_6H_4	OBn	Ph

[a] Reagents and conditions: (a) RCOCl, Py, MeCN, 60 °C, 10 h; (b) $HClO_4$, MeCN−H_2O, 55 °C; (c) H_5IO_6, MeCN−H_2O, 0 °C.

$HClO_4$ to the crude reaction mixture of **2** at 55 °C led to about 95% conversion to **3**. Periodic acid (1.2 equiv) was charged at 0 °C to oxidatively cleave lactol **3** with full conversion within 1 h. Then, the mixture was partitioned between *i*-PrOAc and water. The organic phase was washed with water, $NaHCO_3$, 5% sodium thiosulfate (to remove color), and H_2O. Partial deformylation (R_3 = H) was observed for some substrates.[9]

TABLE 1. Selected Screening Results for Acyl Migration



Tol = *p*-MeC_6H_4CO

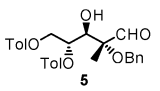
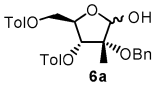
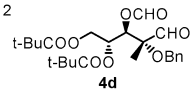
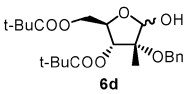
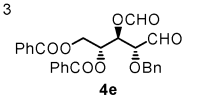
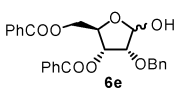
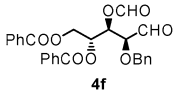
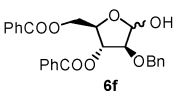
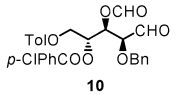
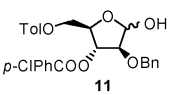
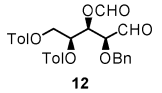
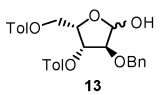
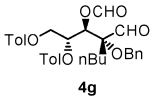
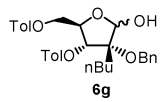
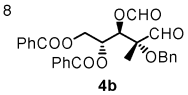
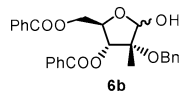
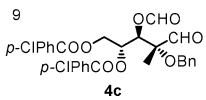
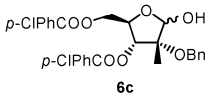
entry	base	solvents	conditions (*T* (°C), time (days))	conv (%)	**6a**/**7a**
1	Et_3N	10%H_2O−MeOH	22, 2	99	92:8
2	Et_3N	10%H_2O−MeOH	60, 5 h	97	90:10
3	Et_3N	MeOH	60, 10 h	98	90:10
4	Et_3N	EtOH	60, 2	97	94:6
5	Et_3N	*i*-PrOH	60, 2	52	94:6
6	Et_3N	*n*-PrOH	60, 2	90	85:15
7	Et_3N	THF−H_2O	60, 2	54	88:12
8	Et_3N	THF	60, 2	4	63:37
9	*i*-Pr_2NH	MeOH	0, 1	99	96:4
10	*i*-Pr_2NH	MeOH−*i*-PrOAc	0, 2	98	96:4
11	*i*-Pr_2NH	MeOH	22, 1	99	88:12
12	DMAP	MeOH	22, 2	80	93:7
13	imidazole	MeOH	45, 3	45	94:6
14	$NaHCO_3$	MeOH	45, 2	97	88:12

Our studies on selective acyl migration were initially focused on substrate **4a**. A variety of solvents and bases were examined to improve/optimize the selectivity. Table 1 illustrates selected results. Under certain conditions, hydrolysis and methanolysis of toluoyl esters become significant. Use of polar protic solvents such as MeOH or water greatly accelerates the reaction rate. The reaction rate decreases as MeOH is replaced with EtOH, *n*-PrOH, and *i*-PrOH (entries 3−6). In the absence of alcohol, solvent acyl migration suffers either low selectivity or low conversion (entries 7 and 8). Bases used to catalyze acyl migration affect the selectivity dramatically. *i*-Pr_2NH is one of the best in terms of selectivity and yield. Lower reaction temperature helps to improve the selectivity (entries 9−11). Use of *i*-Pr_2NH in 20% *i*-PrOAc/MeOH or MeOH at 0 °C improves the selectivity to 96% with >98% conversion (entry 9).[10] Adding other solvents such as *i*-PrOAc slows down the reaction rate (entry 10). Acyl migration in Et_3N/MeOH/H_2O or Et_3N/EtOH was found to work well, too. However, use of *i*-Pr_2NH/*i*-PrOAc/MeOH in the through process[9] avoids the need for a complete solvent switch[11] from *i*-PrOAc to MeOH between the oxidation and acyl migration steps and streamlines the process for large-scale preparation.

(9) For example, about 10% of **5** was formed during the oxidation. Although the aldehyde **4a** can be isolated as a crystalline solid, the deformylated product **5** (oil) would be lost leading to lower overall yields. In practice, the crude oxidation product is used for through process without loss of acyl migration selectivity and yield, because acyl migration goes through the deformylated alcohol (Table 2, entry 1), which can be observed and isolated during acyl migration. Unless otherwise mentioned, the results listed in Tables 1 and 2 were obtained by using purified material to minimize possible peak overlap caused by other byproducts with pyranose or furanose on HPLC.

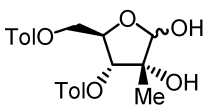
(10) The ratio of furanose vs pyranose was almost unchanged during the entire course of the acyl migration.

TABLE 2. Synthesis of Furanose via Selective Acyl Migration

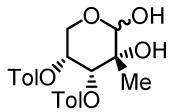
Entry	Starting Material	Products	Conditions[a]	Selectivity[b]	Yield[c]
1	 **5**	 **6a**	A, 20 h	96:4	90%[d]
2	 **4d**	 **6d**	C, 48 h	92:8	83%[d]
3	 **4e**	 **6e**	B, 30 h A, 36 h	94:6 3:1	70%[d, f] 52%[e, f]
4	 **4f**	 **6f**	D, 36 h A, 96 h	84:16 3:1	65%[d] 48%[e]
5	 **10**	 **11**	D, 14 h	>98:2	79%[d, f]
6	 **12**	 **13**	A, 4 h	>99:1	70%[d]
7	 **4g**	 **6g**	A, 36 h	89:11	72%[e]
8	 **4b**	 **6b**	A, 20 h	93:7	85%[e]
9	 **4c**	 **6c**	A, 5 h B, 20 h	94:6 95:5	85%[e] 88%[e]

[a] 1.5 equiv of *i*-Pr_2NH was used for all reactions. Key: (A) MeOH, 0 °C; (B) EtOH, 0 °C; (C) MeOH, 35 °C; (D) EtOH, 30 °C. [b] Selectivity = furanose vs pyranose. The ratio is determined by HPLC analysis (Zorbox RX-C8, 5 μm particle size, 250 × 4.6 mm, mobile phase: 10 mM pH 6.5 $NaKHPO_4-NaH_2PO_4$/MeCN, 35 °C). [c] Yield of furanoses. [d] Isolated yield. [e] Assay yields calculated by HPLC using an external reference standard. [f] Four-step through-process yield.

In a typical experiment, a solution of **4a** or a crude mixture of **4a** and **5** (**5** works equally well as **4** under the same reaction conditions; Table 2, entry 1) in MeOH or MeOH/*i*-PrOAc in the presence of 1.5−0.5 equiv of *i*-Pr_2NH is aged at 0−5 °C. The desired product can be isolated by column chromatography in 82% overall yield (four steps from **1a**). The ratio of α,*β*-lactols (by ^1H NMR) usually changes after column chromatography. Although a mixture of α,*β*-lactols **6a** or **7a** is obtained, both **6a** and **7a** can be unambiguously characterized by NMR techniques. In addition, we further demonstrated that the crude acyl migration products could be directly hydrogenated to give the crystalline diol **8** in five-step through process. Thus, after workup and charcoal treatment, the crude *i*-PrOAc reaction mixture of **6a** and **7a** (typical ratio 96:4) is subjected to hydrogenolysis, which has typically been performed using 20 wt % of 10% Pd/C, 45 psi, 60 °C, 24 h. The product **8**, in 66% isolated overall yield of five-step through process, is directly crystallized from 20% *i*-PrOAc/heptane as white solid with excellent rejection of pyranose **9**.



8



9

Next, the scope of the selective acyl migration with other substrates was explored. Selective migration of aromatic or alkyl esters works well when alcoholysis/hydrolysis of ester is minimized under reaction conditions. For aromatic esters, having electron-withdrawing or electron-donating substituents on aromatic rings does not greatly influence the selectivity of acyl migration. For example, high selectivity of acyl migration can be still obtained by replacing the toluoyl ester group in **4a** with *p*-chlorobenzoyl or benzoyl esters (Table 1, entries 9 and 10; Table 2, entries 8 and 9). However, the acyl migration reaction rate, as expected, does increase when an aromatic ester has an electron-withdrawing group and is more labile under basic reaction conditions. For example, **6c** was obtained in about 45% yield and 4:1 selectivity due to methanolysis of the *p*-chlorbenzoyl group if **4c** was exposed to *i*-Pr_2NH in MeOH for 20 h. However, **6c** can be obtained in 85% yield with 94:6 selectivity if the reaction was quenched within 5 h. This methanolysis issue could be easily overcome by replacing MeOH with EtOH, while the selectivity remains almost unaffected.[12] Exposure of the product in EtOH/*i*-Pr_2NH for days does affect the yield and selectivity. Migration of bulky pivaloyl ester **4d**[8c] can also be achieved highly selectively although the reaction needs to be carried out at 30−35 °C.

While intramolecular acyl migration works well with C-2-branched substrates, our initial selectivity for preparing C-2 nonbranched furanoses in MeOH are as low as ∼3:1 (Table 2, entries 3 and 4). By carefully monitoring the reaction with HPLC and ^1H NMR, it was found that lower selectivity is partially due to significant competition reactions between migration vs hydrolysis/methanolysis of benzoyl esters and cyclized lactols. Thus, treatment of **4e** with *i*-Pr_2NH in EtOH at 0−5 °C for 30 h gave the desired furanose in 94:6 selectivity and 82% yield. Although no epimerization on C-2 was observed under reaction conditions, the stereochemistry of C-2 in this case does influence the reaction rate. Acyl migration of **4e** is significantly faster than that of **4f** at 0 °C. It almost required a week to reach 95% conversion. However, **4f** is converted to furanose **6f** at 30 °C within 1.5 days in 65% yield and 84:16 selectivity (vide infra).[7,10]

(11) MeCN was removed during the concentration of the organic extracts, obtained from the oxidation cleavage step, to give a solution of **4** and **5** in *i*-PrOAc, which can be directly used for acyl migration. For detailed experimental procedures, see the Supporting Information.

(12) As we noticed in Table 1, acyl migration can also be carried out in EtOH to achieve 94% selectivity for **4a**.

By taking advantage of the observed ester migration rate differences on **4a**−**c**, we could achieve higher selectivity by installing different esters at C-5,6 on substrates **1** to expand the scope of our methodology. Actually, when **10**[13] was subjected to typical acyl migration conditions, above 98:2 acyl migration selectivity was achieved. **11** was isolated as a solid in 70% overall yield over four steps.

To further probe the influence of stereochemistry on acyl migration, **12**, which is the C-4 epimer of **10** and **4f**, was prepared.[13] Acyl migration of **12** vs **4e** and **4f** is much faster. Exposure of **12** in *i*-Pr_2NH/MeOH at 0 °C for 4 h afforded the desired furanose **13** in 70% yield and >99:1 selectivity.[14]

The variability of the substituents on C-2 was also studied. High yield and selectivity can be achieved when R_1 = OBn and R_2 = H or alkyl (such as Me and *n*-Bu) on C-2. However, when **4h** and **4i** are subjected to typical reaction conditions, retro-aldol reaction instead of acyl migration via the corresponding deformylated alcohol becomes the main reaction pathway when R_2 = vinyl or phenyl.[15]

In conclusion, a practical method for preparation of C-3,5 acyl furanoses via base catalyzed, highly selective intramolecular acyl migration was demonstrated. In addition, higher acyl migration selectivity could be obtained by having different ester groups, whose migration rates can be differentiated, on substrates. However, the substituents on C-2 do affect the reaction pathway. In the cases of both vinyl and aryl substituents are installed on C-2 position, retro-aldol reaction becomes a major reaction pathway. By applying this methodology, a variety of C-2,3,5 or C-3,5 selectively protected furanoses can be quickly accessed via a practical through process in high selectivity and yield.

Acknowledgment. We gratefully acknowledge Dr. E. J. J. Grabowski for his encouragement.

Supporting Information Available: Experimental procedures and characterization data for compounds **4a**−**c**,**f**−**i**, **6a**−**g**, **8**, and **10**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) **10** and **12** were prepared from its corresponding monoester by following the same procedures used for making **4a**−**h**. For detailed experimental procedures, see the Supporting Information.

(14) Although the toluoyl ester migrates for **12** vs benzoyl ester for **4e** and **4f**, the following migration rate order was observed for other substrates: toluoyl < benzoyl < *p*-chlorbenzoyl. Therefore, the observed acyl migration rate order (**12** > **4e** > **4f**) is conceivable. The detailed migration mechanism is unclear;[7,10] however, the interesting observed rate and selectivity differences between **4e**, **4f,** and **12** (**4e** and **4f** are C-2 epimers; **4f** and **12** are C-4 epimers) seems to indicate that the aldehyde group could possibly participate in formation of a key acyl migration intermediate such as the bicyclic ortho ester intermediates (Scheme 1). The conformational/stereochemical differences in the bicyclic ortho esters intermediates **IVa**/**IVb** resulted from the substituents at C-2 and C-4 of **4e**, **4f** and **12** are significant,[7] which could contribute to the observed rate and selectivity differences. Similarly, the differences of the stereogenic centers at C-2, C-3, and C-4 on the five or six member ring intermediates **Va**/**Vb** (Scheme 1) would not be expected to result in such a dramatic difference in terms of the reaction rate.

(15) For example, **14** and **15** were obtained when **4h** was treated with 1.5 equiv of *i*-Pr_2NH in MeOH at 0 °C for 10 h. Formation of **16**, observed by HPLC, was completed within 2 h. The stereochemistry of **15** was determined by NOE studies.