Development of a Novel Pathway To Access 6-Deoxy-6,6,6-trifluorosugars via 1,2-Migration of a *tert*-Butyldimethylsilyl Group

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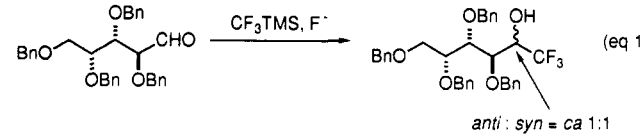
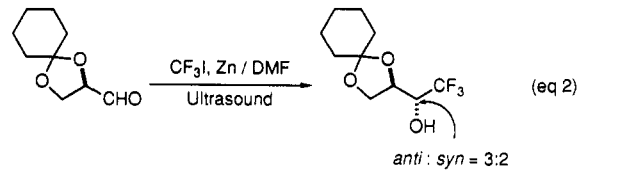
Trifluoromethylated furanols **2** were enzymatically resolved into the corresponding optically active forms in a highly efficient manner and were further converted to the synthetically useful 2-butenolides **6**. Introduction of substituents into these butenolides **6** or their saturated lactone forms **8** was realized by boron trifluoride-mediated Michael addition of cuprates or by capture of the enolates with various kinds of electrophiles, respectively, both of which proceeded with a high degree of diastereoselectivity. Moreover, novel synthetic routes to access 6-deoxy-6,6,6-trifluorosugars were developed by the utilization of 1,2-silyl migration as a key step, which was qualitatively supported by PM3 molecular orbital calculation.

Incorporation of fluorine(s) into organic molecules may bring about drastic changes in the nature of the parent materials. This observation has been broadly applied in the development of novel pharmaceutically active compounds[1] or optical devices.[2] The established fluorination methodologies,[3] usually proceeding with inversion of the stereochemistry, are the methods of choice for the construction of optically active mono- or difluorinated molecules. On the other hand, the corresponding CF_3-containing counterparts are much more difficult to synthesize by direct fluorination since the most familiar fluorinating reagent, SF_4,[4] may require special reaction conditions and may lead to a loss of chemoselectivity or epimerization at the original asymmetric center(s).[5] The direct introduction of the CF_3 group with such species as "CF_3^-"[6a-c] or "CF_3^+"[6d] has been reported recently, but none of these approaches appears to be suitable for preparing compounds in a highly stereocontrolled manner.[7]

6-Deoxysugars[8] are an interesting class of compounds broadly found in nature as the constituent sugars of various antibiotics. Very recently, their 6,6,6-trifluoro analogs have been independently reported by two groups: Toyokuni and co-workers[9] utilized (trimethylsilyl)trifluoromethane ($TMSCF_3$)[6a] for obtaining a trifluorinated analog of L-fucose and 6-deoxy-D-altrose derivatives (eq 1), while Taguchi's group[10] succeeded in the preparation



(eq 1)



(eq 2)

of the corresponding L-daunosamine derivative using CF_3I–Zn under sonication (eq 2).[6c] However, in spite of their pioneering syntheses, control of stereoselectivity is an unsolved problem.

Our basic strategy is based on the concept that such CF_3-containing molecules with multiple stereocenters might more easily be constructed by employing chiral building blocks with appropriate functionalities.[11] Recently, we developed an approach for preparing optically active 2-butenolides starting from silylated furans using

(1) (a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197. (c) Filler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Kodansha & Elsevier Biomedical: Tokyo, 1982.

(2) (a) Johno, M.; Itoh, K.; Lee, J.; Ouchi, Y.; Takezoe, H.; Fukuda, A.; Kitazume, T. *Jpn. J. Appl. Phys.* **1990**, *29*, L107–L110. (b) Koden, M.; Shiomi, M.; Nakagawa, K.; Funada, F.; Awane, K.; Yamazaki, T.; Kitazume, T. *Jpn. J. Appl. Phys.* **1991**, *30*, L1300–L1302. (c) Walba, D. M.; Razavi, H. A.; Clark, N. A.; Parmar, D. S. *J. Am. Chem. Soc.* **1988**, *110*, 8686–8691.

(3) For reviews, see the following: (a) Hudlicky, M. *Org. React.* **1988**, *35*, 513–637. (b) Boswell, G. A., Jr.; Ripka, W. C.; Scribner, R. M.; Tullock, C. W. *Org. React.* **1974**, *21*, 1–124. (c) Sharts, C. M.; Sheppard, W. A. *Org. React.* **1974**, *21*, 125–406.

(4) Wang, C.-L. J. *Org. React.* **1985**, *34*, 319–400.

(5) To the best of our knowledge, there have been reported very few examples for the conversion of carboxylic acids into the corresponding CF_3 derivatives with almost complete retention of configuration as well as high chemoselectivity. (a) Peters, H. M.; Feigl, D. M.; Mosher, H. S. *J. Org. Chem.* **1968**, *33*, 4245–4250. (b) Shustov, G. V.; Denisenko, S. N.; Chervin, I. I.; Kostyanovskii, R. G. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1988**, *37*, 1422–1427.

(6) (a) Krishnamurti, R.; Bellew, D. R.; Prakash, G. S. K. *J. Org. Chem.* **1991**, *56*, 984–989. (b) Ramaiah, P.; Prakash, G. S. K. *Synlett* **1992**, 643–644. (c) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *109*, 5186–5191. (d) Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31*, 3579–3582.

(7) In our laboratory, reaction of $TMSCF_3$ with α-amino or α-hydroxy aldehydes as their *N*- or *O*-protected forms was carried out to prove the disappointingly low diastereoselectivity (usually 1:1 except for phenylpropionaldehyde (86:14 at 0 °C, 93:7 at −78 °C)) of the obtained products (Konno, T.; Yamazaki, T.; Kitazume, T. Unpublished results), while three types of ketones were reported to furnish products as a single stereoisomer.[6a]

(8) *Bioactive Carbohydrates in Chemistry, Biochemistry, and Biology*; Kennedy, J. F., White, C. A., Eds.; Ellis Horwood: Chichester, 1983; Chapter 12.

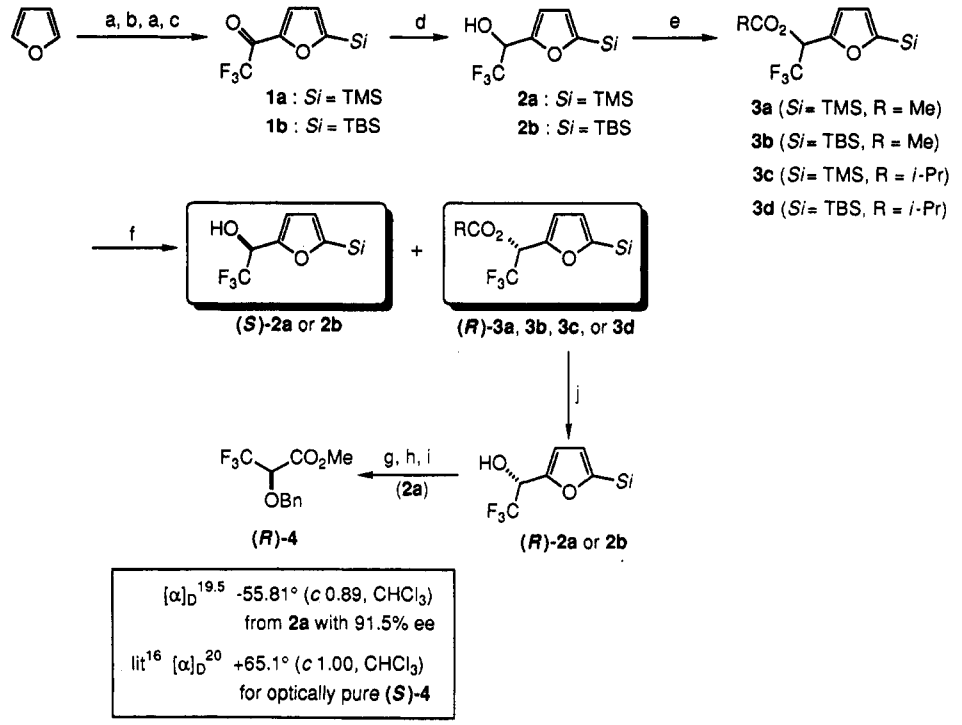
(9) Bansal, R. C.; Dean, B.; Hakomori, S.; Toyokuni, T. *J. Chem. Soc., Chem. Commun.* **1991**, 796–798.

(10) Hanzawa, Y.; Uda, J.; Kobayashi, Y.; Ishido, Y.; Taguchi, T.; Shiro, M. *Chem. Pharm. Bull.* **1991**, *39*, 2459–2461.

(11) (a) Kitazume, T.; Yamazaki, T. In *Selective Fluorination in Organic and Bioorganic Chemistry*; ACS symposium Series No. 456; Welch, J. T., Ed.; ACS: Washington, D.C., 1991; Chapter 12. (b) Yamazaki, T.; Haga, J.; Kitazume, T. *Chem. Lett.* **1991**, 2175–2178. (c) Yamazaki, T.; Okamura, N.; Kitazume, T. *Tetrahedron: Asymmetry* **1990**, *1*, 521–524.

0022-3263/93/1958-4346$04.00/0

Scheme I[a]



[a] Key: (a) *n*-BuLi; (b) *Si*-Cl; (c) CF_3CO_2Et; (d) $NaBH_4$; (e) RC(O)Cl, pyr; (f) lipase PS; (g) NaH, BnBr; (h) O_3; (i) CH_2N_2; (j) K_2CO_3/MeOH.

an enzymatic optical resolution as a key step.[12] We would like to describe the full details of their preparations as well as the extension of these materials as building blocks for the preparation of 6-deoxy-6,6,6-trifluorosugars[13,14] by way of the 1,2-silyl migration.

Results and Discussion

Preparation of Optically Active 2-Butenolides. The starting materials for the enzymatic resolution were conveniently prepared by standard methods as shown in Scheme I. Thus, repetitive anion generation and trapping with electrophiles in a one-pot manner afforded silylated furyl ketones **1a** or **1b**. These compounds were further reduced and acylated to yield the lipase-catalyzed hydrolysis substrates **3**. Of the enzymatic systems investigated,[12,13] the highest efficiency was demonstrated by the combination of lipase PS (*Pseudomonas cepacia*, Amano Pharmaceutical Co., Japan, 30 000 unit/g) and acetate **3a** or **3b**, *E* values[15] of 189 and 645, respectively. Absolute stereochemistry of the recovered acetate was unambiguously determined as *R* by comparison of its optical rotation after derivatization into the known methyl *O*-benzyl-3,3,3-trifluorolactate[16] (Scheme I). On the other hand, lipase MY (*Candida rugosa*, Meito Sangyo Co., Ltd., Japan, 30 000 unit/g) revealed much lower selectivity (*E* values only up to 11).[17] As was noted in the preliminary report,[13] furanols **2**, as opposed to the hydroxy-protected derivatives as **3** or **5**, were relatively unstable even after chromatographic purification and distillation. As a result, it was concluded that compounds **2** were not the appropriate forms for storage longer than 1 week. The stability of these substrates was eventually found to be highly dependent on the bulkiness of the *Si* moiety attached to the furan ring. Decreasing the size of this substituent corresponds to the decrease of the stability; thus, *tert*-butyldimethylsilyl (TBS; **2b**) is more stable than trimethylsilyl (TMS; **2a**) and is much more stable than the furan derivative without a trialkylsilyl group.

At the next stage, transformation of the optically active furyl alcohols **2a** and **2b** into 2-butenolides **6** using the method developed by Kuwajima and Urabe[18] was investigated in detail (Table I and Scheme II). As was in their report, neither **2a** nor **3a** gave satisfactory conversion into the desired 2-butenolides with peracetic acid, hydrogen peroxide, or MMPP (magnesium monoperoxyphthalate, Aldrich), while the protection of a hydroxy group by a trialkylsilyl moiety led predominantly to the formation of 3-butenolides **7a** or **7b** when chloroform was employed as a solvent. On the other hand, changing the solvent to acetic acid was effective for the direct formation of 2-butenolides **6a**, **6b**, or **6c**[19] as a 1:1 diastereomer mixture.

(12) To the best of our knowledge, there have appeared very few reports about enzymatic resolution with silylated materials. See the following as representative examples: (a) De Jeso, B.; Belair, N.; Deleuze, H.; Rascle, M.-C.; Maillard, B. *Tetrahedron Lett.* **1990**, *31*, 653–654. (b) Kawamoto, T.; Sonomoto, K.; Tanaka, A. *J. Biotechnol.* **1991**, *18*, 85–92.

(13) Yamazaki, T.; Mizutani, K.; Takeda, M.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* **1992**, 55–57. Some figures in this communication were incorrectly drawn. For their correction, see: *J. Chem. Soc., Chem. Commun.* **1992**, 796.

(14) 6,6,6-Trifluorooleandrose derivative was prepared by building block methodology. See: Differding, E.; Frick, W.; Lang, R. W.; Martin, P.; Schmit, C.; Veenstra, S.; Greuter, H. *Bull. Soc. Chim. Belg.* **1990**, *99*, 647–671.

(15) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.

(16) Bravo, P.; Frigerio, M.; Resnati, G. *J. Org. Chem.* **1990**, *55*, 4216–4218.

(17) This example is in accord with our empirical rule on *the lipase MY-catalyzed asymmetric hydrolysis of acetates derived from alcohols possessing such a 1-substituted 2,2,2-trifluoroethanol structure as compounds 3, showing (R)-preference for its hydrolysis without any exception out of more than 30 examples.* Recently, the acetate from the same type of tertiary alcohol (hydrogen at the chiral center was replaced by an ethynyl moiety) was reported to be hydrolyzed in a same (*R*)-preferential manner. See: O'Hagan, D.; Zaidi, N. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 947–949.

(18) Kuwajima, I.; Urabe, H. *Tetrahedron Lett.* **1981**, *22*, 5191–5194.

(19) This type of direct formation of 2-butenolides under peracetic acid (4 equiv)/sodium acetate (4 equiv) in methylene chloride conditions was also previously reported. See: Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. *Tetrahedron Lett.* **1983**, *24*, 5835–5838.

Table I. Transformation of Furyl Alcohols into Butenolides by Peracid Oxidation[a]

substrate	peracid	T (°C)	time (h)	yield of butenolide[b] (%) β,γ	α,β	recovery
2a	MMPP	85	8	0	33	27
	H_2O_2	rt	48	32	trace	56
	H_2O_2	85	3	5	36	7
3a	MMPP	85	20	0	0	24[c]
5b	MMPP	85	12	0	61[d,e]	27[e]
	H_2O_2	85	3	0	44[d,e]	19[e]
5a	MMPP	85	4	0	70[d,f]	0
	MMPP[g]	reflux	30	60	0	32
	MMPP[g]	reflux	45	32	0	0
5c	MMPP	85	12	0	63[d]	20
	H_2O_2	rt	96	0	38	9
	H_2O_2	85	3	0	43	0
	MMPP	50	12	39	trace	9

[a] The reaction was performed with 3 equiv of peracid in acetic acid (0.25 M solution) unless otherwise noted. [b] Determined by ^{19}F NMR with $PhCF_3$ as an internal standard unless otherwise noted. [c] 16% of unidentified product was observed. [d] Isolated yield. [e] Desilylated alcohols were obtained or recovered. [f] An almost equal diastereomeric mixture of α,β-unsaturated molecules with and also without a TBS group at the α-position of the carbonyl group. [g] Chloroform was used instead of acetic acid.

Then, for the purpose of obtaining either stereoisomer selectively, when **7a**, **7b**, or **6b** was treated with LDA followed by quenching the reaction with 1 N HCl or AcOH, it was transformed into **6a**, **6c**, or **6b**[20] in a ratio of 87:13, 75:25, or 84:16, respectively, favoring the *anti* isomer in all cases.

The relative stereochemistry of 2-butenolides was determined as follows. After chromatographic separation, each diastereomer of **6c** was independently converted into triethers **9a** and **9b**. The comparison of their spectral data with the reference material **9c** derived from our previously reported compound **10**[11c] has led to the assignment that **9b** possessed the same stereostructure as **9c**. The relative stereochemistry of other 2-butenolides **6a** and **6b**, was also readily clarified after their conversion to **8b**,[21] followed by the comparison with the same material from **6c** via **8c** (Scheme II).

Michael Addition and Alkylation of Chiral 2-Butenolides and the Corresponding γ-Butyrolactones. 2-Butenolides and γ-butyrolactones have been frequently used for the Michael addition reaction[22] and for alkylation at the 2-position of their carbonyl moiety.[23] A bulky substituent at the 4-position of the five-membered ring may play a significant role for the effective diastereofacial control of the reactions. In our hands, a sterically demanding 1-(*tert*-butyldimethylsiloxy)-2,2,2-trifluoroethyl group could effectively shield one olefinic face. The finding that hydrogenation of **6a** gave a single isomer prompted us to examine the above two types of reactions.

In the case of the Michael addition reaction to *anti*-**6c**, $Me_2CuLi{\cdot}2BF_3$[24] was the most effective among the reagents examined (Scheme III and Table II) but a complex mixture was obtained in the absence of boron trifluoride. When MeCu and Me_3Cu_2Li were employed, BF_3 was again essential to obtain the product *anti*-**11a** or **11b** cleanly. Many byproducts were detected by ^{19}F NMR from the reaction mixture when magnesium cuprate was used. On the other hand, the conjugate addition of ketone, ester, or amide enolates did not proceed, but instead, epimerization at the 4-position was observed, suggesting that these species acted only as bases. Every instance in Table II showed good to excellent chemical yields as well as very high diastereoselectivity as expected, and minor isomer could not be detected by any analytical means employed.

Alkylation of γ-butyrolactone *anti*-**8c**[25] by the action of LDA followed by the addition of methyl iodide resulted in the recovery of the starting material. The desired reaction was eventually realized by utilization of LHMDS[22a] as a base with active electrophiles as methyl iodide, allyl bromide, or benzyl bromide (Scheme III and Table III). These products were formed in up to 92% de, but epimerization at the reaction site was also observed with extended reaction times.[23d] Alkylation is limited only to reactive compounds, and alkyl bromide or tosylate did not react in the present procedure. Hydroxylation at this position was possible by trapping the enolate with Davis' oxaziridine **15**.[26] Employment of lithium enolate furnished the desired 2-hydroxylated lactone *syn*-**14** in 48% yield along with the concomitant formation of aldol-type compounds[26b] (49% yield). The less stable sodium and potassium enolates[27] afforded *syn*-**14** in only 18 and 37% yields, respectively.

In an effort to introduce diol function to **6c**, permanganate oxidation in the presence of a catalytic amount of 18-crown-6[28] allowed us to isolate the functionalized diols in a highly stereoselective manner with the moderate conversion (from *anti*-**6c**, 42% yield of *anti*-**12** with 33% recovery of *anti*-**6c**; from *syn*-**6c**, 30% yield of *syn*-**12** with 48% recovery of *syn*-**6c**).

Preparation of 6-Deoxy-6,6,6-trifluorosugars. As was already discussed, stereoselective alkylation or hydroxylation was successively effected in the γ-butyrolactone framework at the 2- or 3-positions. The resultant lactones are intermediates to CF_3-modified 6-deoxyfuranoses, requiring only the reduction of a carbonyl group. Hence, desilylation and treatment with acid gave a 1:1 mixture of *syn*-**17** and *syn*-**16** (eq 3).

Interestingly, hydrogenation and LAH reduction of *anti*-**6c** afforded a *mixture of monoprotected triols*, which were eventually converted to **9a** in good yield (eq 4, Scheme

(20) As is apparent from Table I, MMPP oxidation of **5a** afforded 3-butenolide **7a** along with the recovery of **5a**. Because of their inseparable nature and instability of **7a** toward silica gel, transformation into the corresponding 2-butenolide was carried out using this reaction mixture without further purification. After oxidation, a diastereomeric mixture of **6a** and **5a** was readily separated by column chromatography to be confirmed complete retention of stereochemistry of the latter after its derivatization into MTPA ester.

(21) Since desilylation of **6a** by several reaction conditions (TBAF, CsF, KHF_2, or HF) was found to afford a complex mixture, we chose **8b** as the reference material due to the experimental results that deprotection with TBAF proceeded smoothly when γ-butyrolactones **8a** and **8c** were employed.

(22) (a) Hanessian, S.; Murray, P. J. *J. Org. Chem.* **1987**, *52*, 1170–1172. (b) Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5627–5630. (c) Benezra, C. *Pure Appl. Chem.* **1990**, *62*, 1251–1258.

(23) (a) Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1979**, 3315–3318. (b) Robin, J. P.; Gringore, O.; Brown, E. *Tetrahedron Lett.* **1980**, *21*, 2709–2713. (c) Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5623–5626. (d) Davidson, A. H.; Moloney, B. A. *J. Chem. Soc., Chem. Commun.* **1989**, 445–446.

(24) Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 1351–1358.

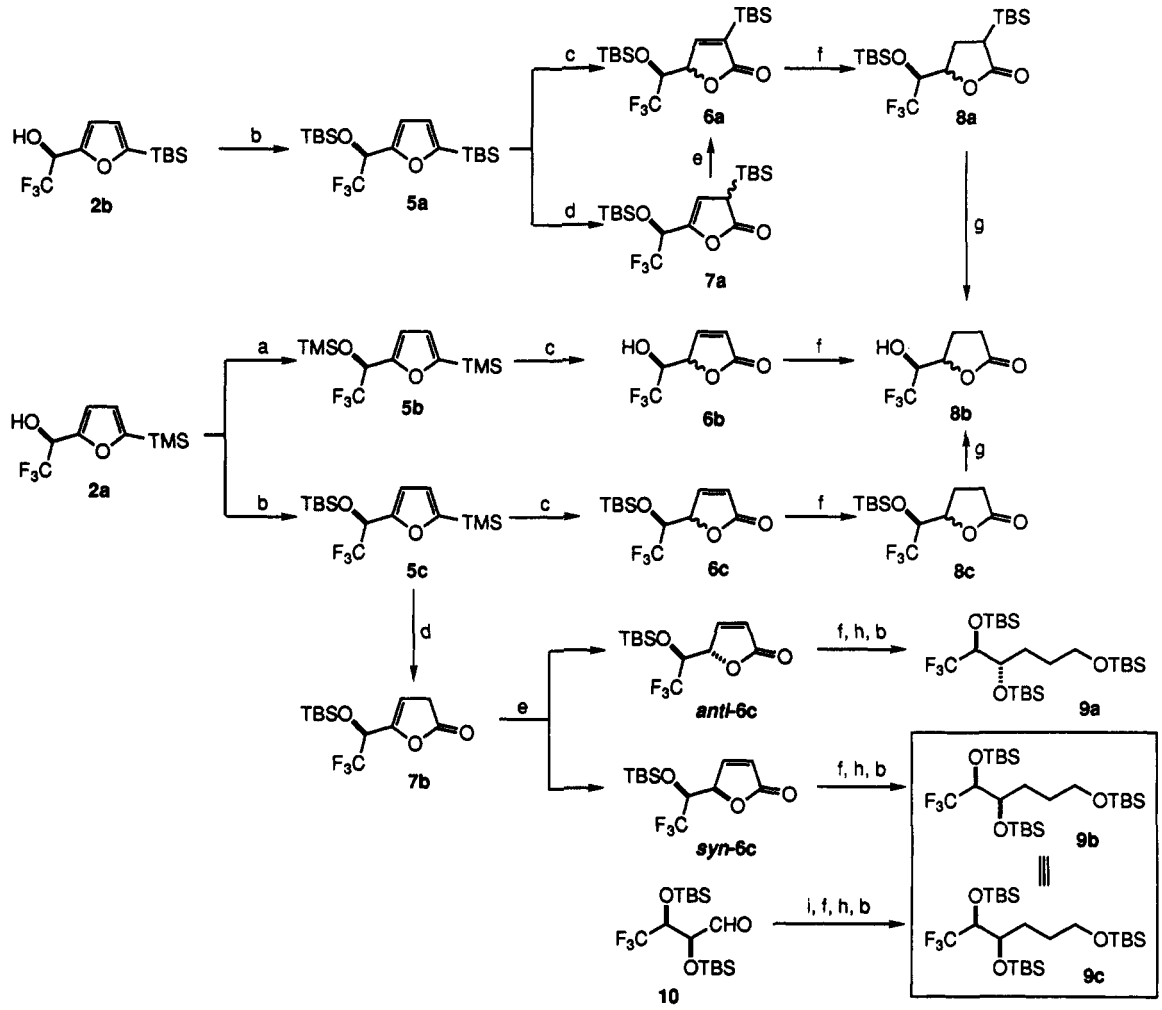
(25) In the text, *syn* and *anti* nomenclatures are used for the expression of the inherent stereochemical relationship in the basic materials, such as **6c** and **8c**, *not for the stereochemical description of the newly formed asymmetric carbon.*

(26) (a) Davis, F. A.; Lamendola, J., Jr.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R., Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000–2005. (b) Evans, D. A.; Morrissey, M. M.; Dorow, R. A. *J. Am. Chem. Soc.* **1985**, *107*, 4346–4348.

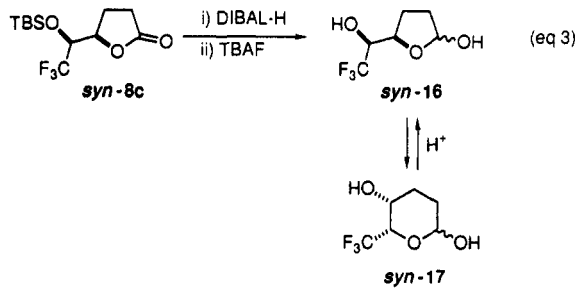
(27) TLC analysis of enolates clearly showed such differences: thus, lithium enolate was the only example giving a single spot due to the starting material by TLC while some additional spots (not characterized yet) were observed from the others.

(28) Mukaiyama, T.; Tabusa, F.; Suzuki, K. *Chem. Lett.* **1983**, 173–174.

Scheme II[a]



[a] Key: (a) TMSCl, imidazole; (b) TBSCl, imidazole; (c) MMPP/AcOH; (d) MMPP/$CHCl_3$; (e) LDA, H^+; (f) Pd/C, H_2; (g) TBAF; (h) LAH; (i) $(EtO)_2P(O)CH_2CO_2Et$, NaH.



IV). This phenomenon can be understood as a result of the TBS migration because of the different nucleophilic ability of the resultant alkoxide ions.[29] The anionic species at the 5-position is more stable than either the 1- or 4-positions due to the strong electron-withdrawing nature of a CF_3 group. In other words, alkoxides at the 1- or 4-position are more nucleophilic than the alkoxide at the 5-position, eventually affording the thermodynamically favored 1- or 4-siloxy derivatives. This observation suggested the investigation of the base catalyzed transformation of furanoses into pyranoses on the basis of the following mechanism.[30] *anti*-**6c** (eq 5, Scheme IV) may furnish the anionic species Int-A, which is in equilibrium with its open chain form, Int-B. The smooth shift of a TBS group, presumably via a 5-membered transition state with a pentavalent silicon atom,[29] would produce the more stable intermediate Int-C, which may be finally recyclized to yield the desired pyranose via Int-D.

Of the reaction conditions examined, treatment of lactol *anti*-**18** with potassium *tert*-butoxide at −78 °C in THF readily completed the conversion into pyranose *anti*-**19** in 3 h (Scheme V).[31] The usual acetylation of the product resulted in the formation of acetyl glycoside *anti*-**20** as a 78:22 anomer mixture. This material could also be synthesized via an alternative one-pot route from *anti*-**18** in an 89:11 anomeric ratio. The first synthesis of the 6,6,6-trifluoro analog of naturally occurring L-amicetose *anti*-**21** was realized by the deprotection of the TBS group by tetra-*n*-butylammonium fluoride (TBAF). The corresponding *syn* isomer, *syn*-**8c**, was also isomerized in the same manner, and trifluorinated L-rhodinose was formed. In this case, even though *syn*-**19** was subjected to the usual isomerization conditions, no trace of furanose *syn*-**18** could be detected. *This result unambiguously demonstrates*

(29) Intramolecular migration of a silyl group has already been reported. (a) Mulzer, J.; Schöllhorn, B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 431–432 (with *tert*-butyldiphenylsilyl group). (b) Jones, S. S.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2762–2764 (with *tert*-butyldimethylsilyl group). See also: Watanabe, Y.; Fujimoto, T.; Ozaki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 681–683.

(30) For the clarity, free alkoxide was drawn instead of its metal alkoxide.

(31) When NaH was also employed as a base under the same conditions, a complex mixture was obtained.

Scheme III

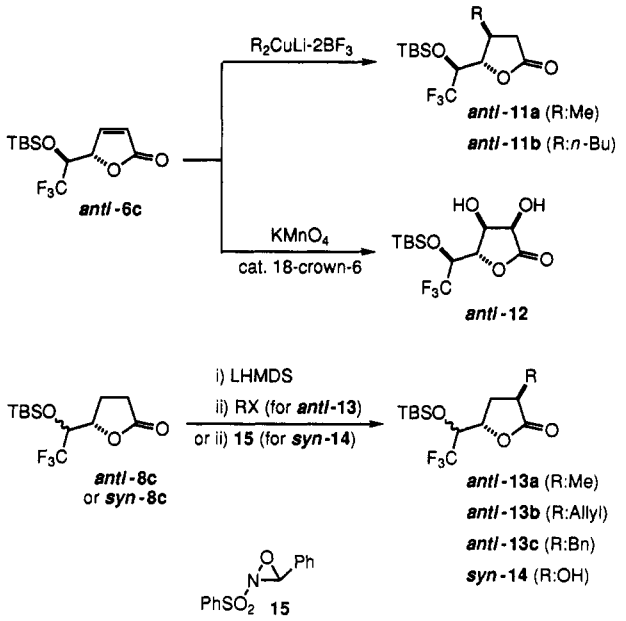


Table II. Michael Addition Reaction of Cuprates in the presence of BF_3 to 2-Butenolides 6c

6c	Nu	time (h)	yield[a] (%)	selectivity[b]
anti	$Me_2CuLi{\cdot}2BF_3$	2	97	>99:1
anti	$MeCu{\cdot}BF_3$	4	64	>99:1
anti	$Me_3Cu_2Li{\cdot}2BF_3$	2	87	>99:1
syn	$Me_2CuLi{\cdot}2BF_3$	2	91	>99:1
anti	$n\text{-}Bu_2CuLi{\cdot}2BF_3$	2	95	>99:1
syn	$n\text{-}Bu_2CuLi{\cdot}2BF_3$	2	88	>99:1

[a] Isolated yields. [b] Determined by capillary GC (GE XE-60) and/or ^1H, ^{13}C, or ^{19}F NMR spectroscopy.

Table III. Diastereoselective Alkylation of γ-Butyrolactones 8c

8c	RX	time (h)	yield[a] (%)	selectivity[b]
anti	MeI	0.5	90	89:11
anti	MeI	2	86	73:27
anti	allyl-Br	2	quant	87:13
anti	BnBr	0.75	71	96:4
syn	MeI	1	82	96:4
syn	allyl-Br	1	82	93:7
syn	BnBr	1	95	80:20
syn	*n*-BuBr	3	0	
syn	*n*-BuOTs	3	0	

[a] Isolated yields. [b] Determined by capillary GC (GE XE-60) and/or ^1H, ^{13}C, or ^{19}F NMR spectroscopy.

that no equilibration between Int-B and Int-C in (eq 5) occurs, at least in this case.

These methods may also be applied to lactols from 2-butenolides as well as hydroxylated γ-butyrolactones (Scheme VI and VII).[32] For example, when *anti*-**22** was transformed into its pyranose form *anti*-**23** in 63% yield, starting material was recovered in 33% yield. After their chromatographic separation and conversion into methyl glycoside, the former was subjected to $KMnO_4$ oxidation to give *anti*-**25** in 55% yield with complete diastereofacial selection. Acetylation of the two hydroxyl groups and removal of a TBS moiety yielded a mixture of CF_3-containing alcohols from which *anti*-**27** was isolated in 62%. This material *anti*-**27** as well as its byproducts were independently acetylated to afford the 6,6,6-trifluorinated D-rhamnose derivative *anti*-**28** from both of the synthetic routes (92% total yield from *anti*-**26**; see Scheme VI). This fact suggests that the unknown byproducts most likely consisted of isomeric acetyl-migrated products. On the other hand, application of the present isomerization process to *syn*-**22** yielded the requisite pyranose *syn*-**29** only in 23% yield along with *syn*-**30**, the major product as determined by ^{19}F NMR.[33,34]

The highly diastereoselective dihydroxylation (*anti*-**24** to *anti*-**25**) might be elucidated from our PM3 semiempirical calculation,[35] fully optimized for the both α- and β-anomers of *anti*-**24** (Figure 1). Thus, it was noticed for the most stable conformer of the former isomer that the trimethylsilyl group[36] was disposed to cover the bottom olefinic face effectively, while the other seemed to possess the steric hindrance at the opposite diastereoface by the methoxy group. Although there is no information on the stereochemistry of *anti*-**24** at the anomeric position (a 96:4 anomer mixture), consideration of this result leads us to speculate that the major diastereomer is the α-anomer.

Conversion of the bis-hydroxylated γ-butyrolactone *anti*-**12** after acetonide formation followed by reduction to lactol *anti*-**33** and then base treatment furnished 6-deoxy-6,6,6-trifluoro-D-tallose derivative *anti*-**34** in 35% yield along with 17% of *anti*-**35** and 46% of recovery of *anti*-**33**. The formation of *anti*-**35** was unexpected and might be a result of *intermolecular* nucleophilic attack. It is interesting to note that the diastereomeric *anti*-**28** and *anti*-**34** could be easily prepared from the same parent 2-butenolide *anti*-**6c** only by changing the order of oxidation and silyl-migration process. On the other hand, *syn*-**33** was highly resistant to the present isomerization conditions and did not form *syn*-**34**.[37] The monohydroxylated γ-butyrolactone *syn*-**14** was also employed as a substrate, but the reaction proceeded very slowly at −78 °C affording trifluorinated 3,6-dideoxy-L-talose *syn*-**38** in only 20%. Increasing the temperature to −50 °C resulted in ready loss of the pivaloyl moiety.

In an attempt to get information about the present isomerization, the PM3 calculation[35] was carried out for *syn* and *anti*-**22**[36] (Figure 2). A similar tendency was noticed in both diastereomeric series: (i) cyclic conformers were energetically disfavored over the corresponding open isomers irrespective of their ring sizes (compare **A1** and **B** or **D** and **E1** in the both series), and (ii) the most stable intermediates were **C** in both cases, possessing a pentavalent silicon atom bound to two adjacent oxygens at the same time. Considering the knowledge of the nonfluorinated sugars, the present processes may be considered to be thermodynamically controlled. In our hands, comparison of the energies of the most stable conformers of **A** and **E** in both series predicts the ease of the furanose–pyranose transformation. In the case of the *anti* isomer, the difference was found to be 4.61 kcal/mol in favor of

(32) Yamazaki, T.; Mizutani, K.; Kitazume, T. *Tetrahedron: Asymmetry*, in press.

(33) Compound *syn*-**30** could not be isolated because of its unstable nature toward silica gel chromatography being transformed into the corresponding furan by a loss of acetic acid.

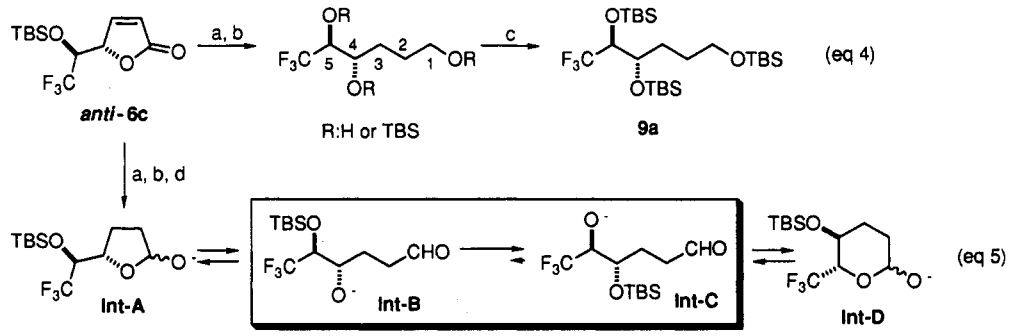
(34) It was because of the unstability of the desired rearranged product *syn*-**23a** under the conditions employed (<10% yield of *syn*-**23a** was isolated) that the intermediate *syn*-**23b** was trapped in situ by acetic anhydride.

(35) Calculations were performed by MOPAC v 6.10 (PM 3) implemented in CAChe Worksystem (SONY/Tektronix Corporation) for the conformers obtained from the rigid search method followed by the optimization by the eigenvector following minimization (EF) method with the extra keyword "PRECISE", final gradient norm being less than 0.01 kcal/Å.

(36) A TBS group in these materials was replaced with a TMS moiety for the reduction of the calculation time.

(37) In this case, not like its diastereomer *anti*-**33**, formation of *syn*-**35** was not observed at all.

Scheme IV[a]



[a] Key: (a) Pd/C, H_2; (b) DIBAL-H; (c) TBS-Cl, imidazole; (d) base.

anti-**E1**, suggesting the ready conversion via the 1,2-silyl migration. On the other hand, for the isomer with *syn* configuration, the furanose was preferred by 1.54 kcal/mol. Consideration of these trends has led to a semiquantitative explanation of the present experimental results: thus, furanoses with *anti* stereochemistry may be transformed more smoothly into the corresponding pyranoses than their *syn* isomers (for example, *anti*-**23** was prepared in 63% yield while *syn*-**29** was obtained only in 23%). This relatively large energy difference independent of the stereostructure suggests the significant role for the strongly electron-withdrawing CF_3 group in the neighboring anion stabilization.

Conclusions

In this paper, an approach to the versatile CF_3-containing 2-butenolide intermediates, utilizing an enzymatic optical resolution as the key step, was described. Moreover, a novel method was developed for the stereoselective preparation of 6-deoxy-6,6,6-trifluorosugars via 1,2-silyl migration, realizing the first synthesis of 6,6,6-trifluoro analogs of L-amicetose, L-rhodinose, D-rhamnose, 6-deoxy-D-talose, and 3,6-dideoxy-L-talose from these 2-butenolides. These new 6-deoxy-6,6,6-trifluorosugars may replace the corresponding nonfluorinated natural counterparts for the modification of the biological activity of the parent compounds.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. All procedures were performed under nitrogen or argon. Ether and THF were distilled from sodium/benzophenone under a nitrogen atmosphere immediately prior to use. CH_2Cl_2 was similarly distilled from calcium hydride.

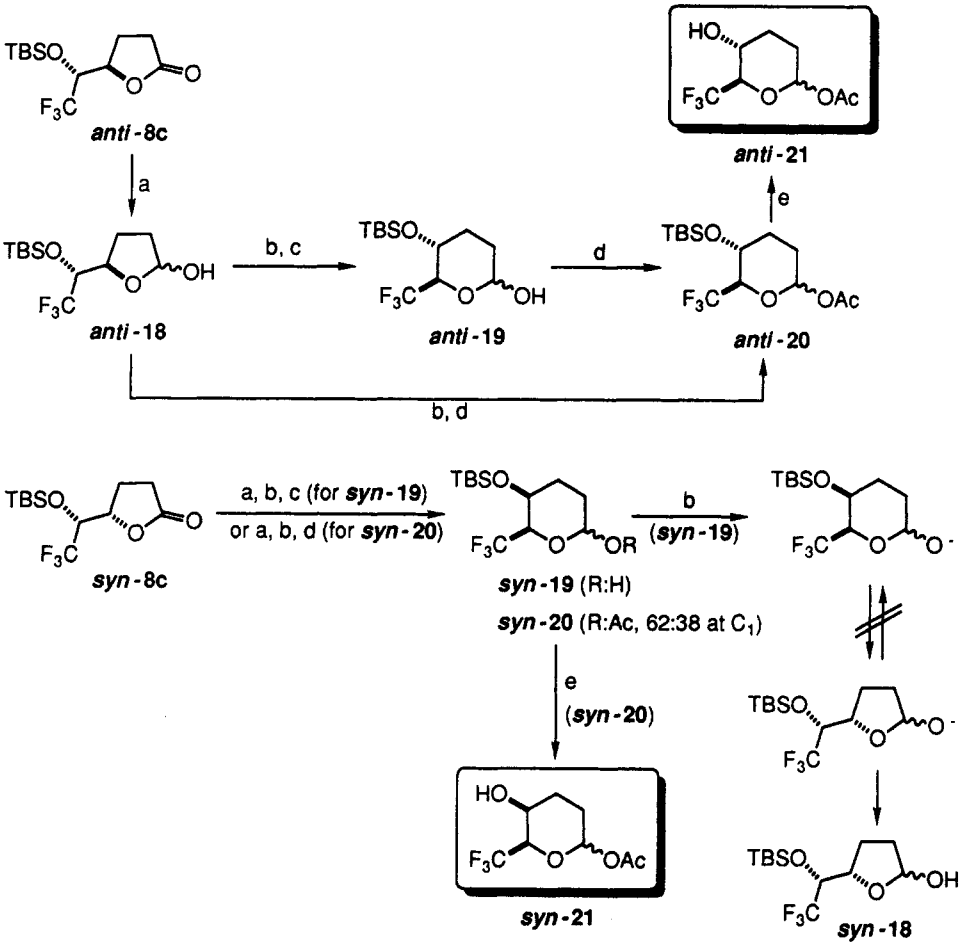
Chemical shifts of ^1H and ^{13}C NMR spectra were recorded in ppm (δ) downfield from the following internal standard (Me_4Si, δ 0.00, or $CHCl_3$, δ 7.24). Chemical shifts of ^{19}F NMR spectra, obtained in $CDCl_3$ unless otherwise noted, were reported in ppm downfield from the external trifluoroacetic acid (TFA). All IR spectra were reported in wavenumbers (cm^{-1}) with the reference at the 1601.4 cm^{-1} absorption of a polystyrene film. In the case of lactols, the optical rotations were measured after they reached their equilibrations, and then the anomeric ratios were determined by ^1H or ^{19}F NMR with the same samples. Mp was listed without correction.

Preparation of 2-(Trifluoroacetyl)-5-silylfurans. To a solution of furan (14.5 mL, 199 mmol) in 150 mL of anhydrous THF at −20 °C was added dropwise *n*-BuLi (2.5 M in hexane, 84 mL, 210 mmol) under N_2. After the solution was stirred for 30 min, an appropriate silyl chloride (200 mmol) was added, and the whole was stirred for 1 h at room temperature. After the solution was recooled to −20 °C, *n*-BuLi (2.5 M, 84 mL, 210 mmol) was added and the whole was stirred for 30 min. The reaction mixture was then treated with ethyl trifluoroacetate (26.2 mL, 220 mmol) in THF (50 mL) at −78 °C, followed by further stirring for 3 h at room temperature. The mixture was quenched with 3 N HCl (aq) (80 mL), and the volatiles were removed under reduced pressure. After extraction with ethyl acetate three times, the combined organic layers were washed with saturated $NaHCO_3$ (aq) and brine, dried ($MgSO_4$), and concentrated in vacuo. Analytical sample was obtained by distillation. Usually, the crude product was used in the next step without further purification. **2-(Trifluoroacetyl)-5-(trimethylsilyl)furan (1a)**: bp 80–85 °C/15 mmHg; ^1H NMR δ 0.32 (9 H, s), 6.79 (1 H, d, J = 3.68 Hz), 7.46 (1 H, dq, J = 3.69, 1.38 Hz); ^{13}C NMR δ −2.33, 116.51 (q, J = 290.5 Hz), 121.95, 124.17 (q, J = 2.9 Hz), 153.41, 172.30, *C*=O was not observed; ^{19}F NMR δ 4.5 (s); IR (neat) ν 2950, 1690; HRMS calcd for $C_9H_{11}F_3O_2Si$ 236.0480, found *m/e* 236.0464. **2-(*tert*-Butyldimethylsilyl)-5-(trifluoroacetyl)furan (1b)**: bp 89–93 °C/4.0 mmHg; ^1H NMR δ 0.32 (6 H, s), 0.96 (9 H, s), 6.85 (1 H, d, J = 3.68 Hz), 7.51 (1 H, dq, J = 3.70, 1.23 Hz); ^{13}C NMR δ −6.54, 16.87, 26.28, 116.86 (q, J = 290.5 Hz), 123.38, 124.04 (q, J = 2.7 Hz), 147.10, 151.07, *C*=O was not observed; ^{19}F NMR δ 3.6 (s); IR (neat) ν 2950, 2900, 2875, 1700; HRMS calcd for $C_{12}H_{17}F_3O_2Si$ 278.0950, found *m/e* 278.0946.

Reduction of 2-(Trifluoroacetyl)-5-silylfurans. To a solution of the crude furyl ketone (starting from 200 mmol of furan) in ethanol (200 mL) was added slowly sodium borohydride (2.27 g, 60.0 mmol) at 0 °C, and the mixture was stirred overnight at room temperature. After the solvent was removed under reduced pressure and the addition of both ethyl acetate (200 mL) and 3 N HCl (aq) (200 mL), the organic materials were extracted, and the separated aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The desired furyl alcohols were obtained after purification by distillation. **2-[1′-(2′,2′,2′-Trifluoro-1′-hydroxyethyl)]-5-(trimethylsilyl)furan (2a)**: 82% total yield from furan; bp 64–67 °C/2.7 mmHg; R_f 0.29 (AcOEt:Hex = 1:7); ^1H NMR δ 0.25 (9 H, s), 2.72 (1 H, dd, J = 1.71, 7.41 Hz), 5.06 (1 H, dq, J = 6.75, 6.75 Hz), 6.47 (1 H, d, J = 3.30 Hz), 6.59 (1 H, d, J = 3.30 Hz); ^{13}C NMR δ −2.02, 67.36 (q, J = 34.2 Hz), 109.80 (q, J = 1.5 Hz), 120.50, 123.62 (q, J = 282.9 Hz), 151.19 (q, J = 1.6 Hz), 162.49; ^{19}F NMR δ 0.5 (d, J = 6.2 Hz); IR (neat) ν 3400, 2975; HRMS calcd for $C_9H_{13}F_3O_2Si$ 238.0637, found *m/e* 238.0634. **2-(*tert*-Butyldimethylsilyl)-5-[1′-(2′,2′,2′-trifluoro-1′-hydroxyethyl)]furan (2b)**: 78% yield; bp 75–77 °C/0.8 mmHg; R_f 0.33 (AcOEt:Hex = 1:7); ^1H NMR δ 0.20 (3 H, s), 0.21 (3 H, s), 0.89 (9 H, s), 2.60 (1 H, br), 5.06 (1 H, q, J = 6.50 Hz), 6.48 (1 H, d, J = 3.29 Hz), 6.61 (1 H, d, J = 3.29 Hz); ^{13}C NMR δ −6.72, −6.70, 16.54, 26.04, 67.39 (q, J = 34.1 Hz), 109.76, 121.71, 123.65 (q, J = 282.9 Hz), 151.40, 161.02; ^{19}F NMR δ 0.0 (d, J = 5.7 Hz); IR (neat) ν 3375, 2950, 2925, 2875, 2850; HRMS calcd for $C_{12}H_{19}F_3O_2Si$ 280.1106, found *m/e* 280.1124.

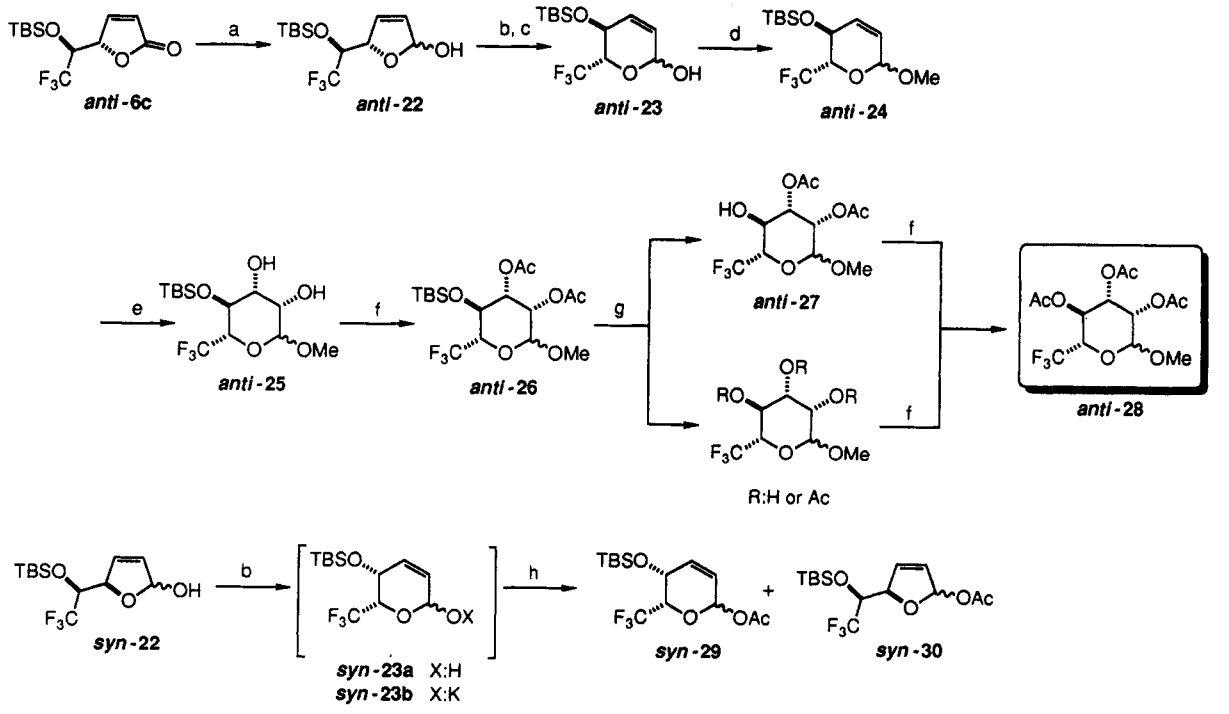
Esterification of Furyl Alcohols. To a 0.5 M solution of furyl alcohol in CH_2Cl_2 under N_2 were added pyridine and acyl chloride (both 1.2 equiv) at 0 °C, and the reaction mixture was stirred overnight. The usual workup procedure followed by purification by silica gel column chromatography and/or distillation afforded the desired esters. **2-[1′-(1′-Acetoxy-2′,2′,2′-trifluoroethyl)]-5-(trimethylsilyl)furan (3a)**: yield 95%; bp 66–68 °C/2.3 mmHg; R_f 0.53 (AcOEt:Hex = 1:7); ^1H NMR δ 0.24 (9 H, s), 2.15 (3 H, s), 6.33 (1 H, q, J = 6.72 Hz), 6.48 (1 H, d,

Scheme V[a]



[a] Key: (a) DIBAL-H; (b) KOBu^t; (c) H$^+$; (d) Ac_2O; (e) TBAF.

Scheme VI[a]



[a] Key: (a) DIBAL-H; (b) KOBu^t; (c) H$^+$; (d) MeOH, H$^+$; (e) $KMnO_4$, cat. 18-crown-6; (f) Ac_2O, pyr; (g) TBAF; (h) Ac_2O.

J = 3.29 Hz), 6.53 (1 H, d, J = 3.32 Hz); ^{13}C NMR δ −2.05, 20.31, 65.62 (q, J = 35.2 Hz), 111.65 (q, J = 1.3 Hz), 120.35, 121.60 (q, J = 281.4 Hz), 148.47, 163.14, 168.97; ^{19}F NMR δ 3.2 (d, J = 6.6 Hz); IR (neat) ν 2975, 1770; HRMS calcd for $C_{11}H_{15}F_3O_3Si$ 280.0743, found m/e 280.0764. **2-(*tert*-Butyldimethylsilyl)-5-[1′-(1′-acetoxy-2′,2′,2′-trifluoroethyl)]furan (3b)**: yield 94%; bp 75–78 °C/0.7 mmHg; R_f 0.63 (AcOEt:Hex = 1:7); ^{1}H NMR δ 0.23 (6 H, s), 0.91 (9 H, s), 2.17 (3 H, s), 6.34 (1 H, q, J = 6.69

s), 0.16 (3 H, s), 0.89 (9 H, s), 0.93 (9 H, s), 1.9–2.5 (3 H, m), 3.94 (1 H, dq, J = 6.56, 6.56 Hz), 4.3–4.6 (1 H, m); ^{13}C NMR (some peaks could not be found because of low intensity) δ −7.74, −7.19, −5.57, −4.49, 16.86, 17.95, 25.33, 26.64, 78.19, 177.81; ^{19}F NMR δ 3.8 (d, J = 6.9 Hz). **(1′*R*,5*R*)-5-[1′-(2′,2′,2′-Trifluoro-1′-hydroxyethyl)]dihydro-2(3*H*)-furanone (*anti*-8b)**: quantitatively yield; bp 190–200 °C/0.6 mmHg; $[\alpha]^{21}_D$ −7.69° (*c* 1.50, $CHCl_3$), 88.2% ee; R_f 0.41 (AcOEt:Hex = 1:1); ^{1}H NMR δ 2.1–2.8 (4 H, m), 4.42 (1 H, dq, J = 2.20, 7.51 Hz), 4.75 (1 H, br), 4.80 (1 H, ddd, J = 2.23, 5.49, 7.71 Hz); ^{13}C NMR δ 20.72 (q, J = 1.7 Hz), 28.23, 69.85 (q, J = 30.3 Hz), 78.27 (q, J = 1.8 Hz), 123.80 (q, J = 283.3 Hz), 179.12; ^{19}F NMR δ 1.5 (d, J = 6.9 Hz); IR (neat) ν 3300, 2950, 1775; HRMS calcd for $C_6H_8F_3O_3$ (M + H) 185.0426, found *m/e* 185.0403. **(1′*S*,5*R*)-5-[1′-(2′,2′,2′-Trifluoro-1′-hydroxyethyl)]dihydro-2(3*H*)-furanone (*syn*-8b)**: yield 97%; mp 85.5–86.0 °C; $[\alpha]^{18}_D$ −55.24° (*c* 0.84, $CHCl_3$), 98.4% ee; R_f 0.18 (AcOEt:Hex = 1:1); ^{1}H NMR δ 2.2–2.8 (4 H, m), 3.99 (1 H, dq, J = 2.58, 7.29 Hz), 4.00 (1 H, br), 4.79 (1 H, ddd, J = 2.61, 7.14, 7.14 Hz); ^{13}C NMR δ 23.65, 27.63, 70.91 (q, J = 30.3 Hz), 76.62 (q, J = 2.2 Hz), 124.07 (q, J = 284.5 Hz), 177.69; ^{19}F NMR δ 1.7 (d, J = 6.9 Hz); IR (neat) ν 3300, 3000, 2950, 1750; HRMS calcd for $C_6H_8F_3O_3$ (M + H) 185.0426, found *m/e* 185.0412.

Desilylation of Butyrolactones. To a 0.5 M solution of butyrolactone in MeOH/THF (1:2, v/v) with molecular sieves 4A under N_2 was added a 1.0 M solution of *tetra-n*-butylammonium fluoride in THF (0.1 equiv) at 0 °C, and the whole was stirred overnight at room temperature. The usual workup and purification by silica gel column chromatography afforded the desired hydroxy butyrolactone. From *anti*-8c, 85% yield; *syn*-8c, 79% yield; 8a (87:13 diastereomeric mixture), 75% yield (82:18 separable diastereomer mixture).

Determination of Stereochemistry, (2*R*)-Methyl 2-(benzyloxy)-3,3,3-trifluoropropionate ((*R*)-4; Absolute Configuration). To a THF (2.5 mL) solution of NaH (0.08 g, 3.33 mmol) was added the furyl alcohol **2a** (0.61 g, 2.56 mmol) at 0 °C, and the whole was stirred for 0.5 h. After addition of benzyl bromide (0.36 mL, 3.03 mmol), the reaction mixture was stirred overnight. The reaction was quenched with water and diluted with ethyl acetate, and the usual workup gave the crude benzyl ether, which was dissolved in MeOH (5 mL) and treated with O_3 for 3 h at −78 °C. After the addition of methyl sulfide (0.5 mL, 6.81 mmol), the reaction mixture was concentrated in vacuo. The residue was diluted with saturated $NaHCO_3$ (aq) and extracted with CH_2Cl_2 twice. The aqueous phase was acidified to pH = 1–2 with 3 N HCl (aq) and extracted with EtOAc three times. The latter extracts were combined, dried ($MgSO_4$), and evaporated to yield the desired propionic acid. A solution of this compound, without further purification, in ether was treated with a solution of diazomethane at 0 °C until the light yellow color was persisted. Addition of acetic acid and removal of the solvent under reduced pressure afforded crude materials, which were purified by silica gel column chromatography to give methyl propionate (*R*)-4 (0.23 g, 0.99 mmol) in 39% total yield: bp 90–100 °C/0.8 mmHg; $[\alpha]^{24}_D$ −55.81° (*c* 0.89, $CHCl_3$), 91.5% ee; R_f 0.29 (ether:Hex = 1:4); ^{1}H NMR δ 3.82 (3 H, s), 4.31 (1 H, q, J = 6.68 Hz), 4.68 (1 H, d, J = 11.81 Hz), 4.82 (1 H, d, J = 11.82 Hz), 7.37 (5 H, s); ^{13}C NMR δ 53.57, 73.79, 75.71 (q, J = 30.9 Hz), 122.11 (q, J = 283.2 Hz), 128.40, 128.71, 130.31, 135.34, 165.96; ^{19}F NMR δ 3.3 (d, J = 7.2 Hz); IR (neat) ν 2975, 2950, 2900, 2850, 1800.

(2*S*,3*S*)-2,3,6-Tris(*tert*-butyldimethylsiloxy)-1,1,1-trifluorohexane (9a; Relative Configuration). To a THF solution (1 mL) of lithium aluminum hydride (0.04 g, 1.05 mmol) was added the butyrolactone *syn*-**6c** (0.533 g, 1.79 mmol) in THF (1 mL) at 0 °C, and the whole was stirred for 2 h at room temperature. The reaction was quenched with 1 N HCl (aq) (2 mL), and the usual workup gave the crude diols. The mixture was, after simple purification by short path chromatography, silylated by the aforementioned conditions. The desired silyl ether **9a** (0.71 g, 1.34 mmol) was obtained after purification in 75% total yield: $[\alpha]^{25}_D$ 0.3° (*c* 1.07, MeOH), 98.1% ee; R_f 0.37 (Hex); ^{1}H NMR δ 0.02 (6 H, s), 0.05 (3 H, s), 0.05 (3 H, s), 0.08 (3 H, s), 0.11 (3 H, s), 0.87 (9 H, s), 0.88 (9 H, s), 0.89 (9 H, s), 1.44–1.67 (4 H, m), 3.58 (2 H, dt, J = 1.43, 5.97 Hz), 3.87 (1 H, ddd, J = 2.59, 3.46, 7.23 Hz), 3.93 (1 H, dq, J = 2.34, 7.55 Hz); ^{13}C NMR δ −5.34, −5.27, −4.66, −4.57, −4.39, 18.06, 18.28, 18.36, 25.68, 25.92, 25.97, 28.39 (q, J = 1.5 Hz), 28.86, 63.22, 71.79 (q, J = 1.4 Hz), 75.94 (q, J = 31.4 Hz), 123.73 (q, J = 284.6 Hz); ^{19}F NMR δ 4.1 (d, J = 6.9 Hz); IR (neat) ν 2975, 2950, 2900, 2875; HRMS calcd for $C_{24}H_{54}F_3O_3Si_3$ (M + H) 531.3332, found *m/e* 531.3293. **(2*S*,3*R*)-2,3,6-Tris(*tert*-butyldimethylsiloxy)-1,1,1-trifluorohexane (9b)** was also prepared in the same manner from *anti*-**6c**: yield 84%; $[\alpha]^{25}_D$ −14.5° (*c* 1.07, MeOH), 98.1% ee; R_f 0.30 (hexane); ^{1}H NMR δ 0.02 (6 H, s), 0.04 (3 H, s), 0.04 (3 H, s), 0.08 (3 H, s), 0.09 (3 H, s), 0.86 (9 H, s), 0.87 (9 H, s), 0.88 (9 H, s), 1.35–1.85 (4 H, m), 3.58 (1 H, dt, J = 10.01, 6.30 Hz), 3.62 (1 H, dt, J = 10.09, 6.22 Hz), 3.70 (1 H, m), 3.88 (1 H, dq, J = 3.29, 7.17 Hz); ^{13}C NMR δ −5.24, −5.07, −5.06, −4.91, −4.48, −4.45, 17.97, 18.10, 18.38, 25.58, 25.70, 25.99, 28.47, 28.86, 63.10, 73.08, 72.93 (q, J = 23.38 Hz), 124.83 (q, J = 284.4 Hz); ^{19}F NMR δ 6.7 (d, J = 6.9 Hz); IR (neat) ν 2975, 2925, 2875, 2850; HRMS calcd for $C_{24}H_{54}F_3O_3Si_3$ (M + H) 531.3332, found *m/e* 531.3331. The known aldehyde **10** was subjected by the usual Höner–Wittig reaction condition followed by hydrogenation, and after brief purification by short path column chromatography, the obtained ester was transformed into the desired silyl ether by LAH reduction and silylation as described above to furnish the compound **9c** in 77% total yield. Its physical property was totally identical to the silyl ether **9b**.

Michael Addition of Cuprates to 2-Butenolides. A solution of copper(I) iodide (1.14 g, 5.99 mmol) in THF (12 mL) was cooled to −78 °C, where methyllithium (1.4 M in ether, 8.6 mL, 12.0 mmol) was added dropwise. The mixture was allowed to warm until it was homogeneous and a colorless solution was obtained, and then boron trifluoride etherate (1.5 mL, 12.2 mmol) was added at −78 °C. 2-Butenolide **6c** (3.00 mmol) was then added, and the mixture was stirred for 2 h at that temperature. The reaction was quenched with 10 mL of saturated NH_4Cl (aq), and the whole was diluted with ethyl acetate and 25% NH_4OH (aq). The separated aqueous phase was extracted twice with ethyl acetate, and the combined organic layers were washed with 25% NH_4OH (aq) and brine, dried over $MgSO_4$, and concentrated. The 3-alkylated butyrolactone was obtained after purification by silica gel column chromatography, whose diastereomeric ratio was determined as >99:1 by capillary GC (GE XE-60) and ^{1}H, ^{13}C, and ^{19}F NMR spectroscopies before purification. **(1′*R*,4*R*,5*R*)-5-[1′-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]-4-methyldihydro-2(3*H*)-furanone (*anti*-11a)**: yield 97%; $[\alpha]^{24}_D$ −4.2° (*c* 1.41, MeOH), 94.3% ee; R_f 0.39 (AcOEt:Hex = 1:4); ^{1}H NMR δ 0.11 (3 H, s), 0.14 (3 H, s), 0.91 (9 H, s), 1.19 (3 H, d, J = 6.93 Hz), 2.17 (1 H, dd, J = 5.44, 17.85 Hz), 2.78 (1 H, dd, J = 9.78, 17.85 Hz), 2.85 (1 H, m), 4.31 (1 H, dq, J = 1.86, 7.24 Hz), 4.34 (1 H, dd, J = 1.82, 4.43 Hz); ^{13}C NMR δ −5.82 (q, J = 1.7 Hz), −5.15, 17.78, 19.68, 25.29, 27.74 (q, J = 1.4 Hz), 36.57, 71.71 (q, J = 30.0 Hz), 84.61 (q, J = 1.9 Hz), 123.73 (q, J = 284.6 Hz), 176.31; ^{19}F NMR δ 3.3 (d, J = 7.2 Hz); IR (neat) ν 2975, 2950, 2900, 2850, 1800; HRMS calcd for $C_{13}H_{24}F_3O_3Si$ (M + H) 313.1447, found *m/e* 313.1432.

(1′*S*,4*R*,5*R*)-5-[1′-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]-4-methyldihydro-2(3*H*)-furanone (*syn*-11a): $[\alpha]^{17}_D$ −15.32° (*c* 1.03, $CHCl_3$), 89.2% ee; yield 91%; R_f 0.33 (AcOEt:Hex = 1:5); ^{1}H NMR δ 0.11 (6 H, s), 0.88 (9 H, s), 1.18 (3 H, d, J = 6.72 Hz), 2.16 (1 H, dd, J = 6.74, 17.09 Hz), 2.55 (1 H, m), 2.74 (1 H, dd, J = 8.88, 17.08 Hz), 4.01 (1 H, dq, J = 3.02, 6.64 Hz), 4.20 (1 H, ddq, J = 3.01, 5.81, 0.59 Hz); ^{13}C NMR δ −5.38 (q, J = 1.9 Hz), −5.23, 17.93, 18.67, 25.33, 30.96, 35.95, 71.30 (q, J = 30.7 Hz), 83.82 (q, J = 1.6 Hz), 123.87 (q, J = 285.3 Hz), 175.70; ^{19}F NMR δ 3.9 (d, J = 6.3 Hz); IR (neat) ν 2975, 2950, 2900, 2875, 1790; HRMS calcd for $C_{13}H_{24}F_3O_3Si$ (M + H) 313.1447, found *m/e* 313.1476. **(1′*R*,4*R*,5*R*)-4-*n*-Butyl-5-[1′-[1′-(*tert*-butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]-dihydro-2(3*H*)-furanone (*anti*-11b)**: $[\alpha]^{27}_D$ −14.21° (*c* 1.11, MeOH), 94.3% ee; R_f 0.52 (AcOEt:Hex = 1:5); ^{1}H NMR δ 0.07 (3 H, s), 0.10 (3 H, s), 0.86 (12 H, m), 1.2–1.9 (6 H, m), 2.17 (1 H, dd, J = 8.43, 12.16 Hz), 2.71 (1 H, dd, J = 9.70, 12.61 Hz), 2.75 (1 H, m), 4.26 (1 H, dq, J = 1.84, 7.19 Hz), 4.38 (1 H, dd, J = 1.99, 3.09 Hz); ^{13}C NMR δ −5.84 (q, J = 1.8 Hz), −5.14, 13.63, 22.20, 28.76, 34.19, 34.68, 17.78, 25.30, 33.05 (q, J = 1.5 Hz), 72.10 (q, J = 30.1 Hz), 83.11 (q, J = 2.0 Hz), 123.71 (q, J = 284.8 Hz), 176.61; ^{19}F NMR δ 3.4 (d, J = 6.3 Hz); IR (neat) ν 2975, 2950, 2925, 2875, 1800; HRMS calcd for $C_{16}H_{30}F_3O_3Si$ (M + H) 355.1916, found *m/e* 355.1931. **(1′*S*,4*R*,5*R*)-4-*n*-Butyl-5-[1′-[1′-(*tert*-butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]dihydro-2(3*H*)-furanone (*syn*-11b)**: $[\alpha]^{15}_D$ −16.47° (*c* 1.38, $CHCl_3$), 89.2% ee;

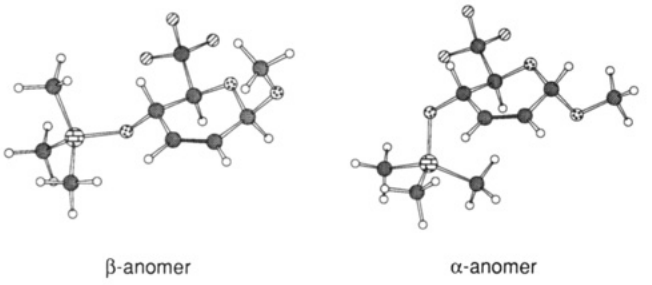


Figure 1. Most stable calculated conformations of anomeric *anti*-**24**.

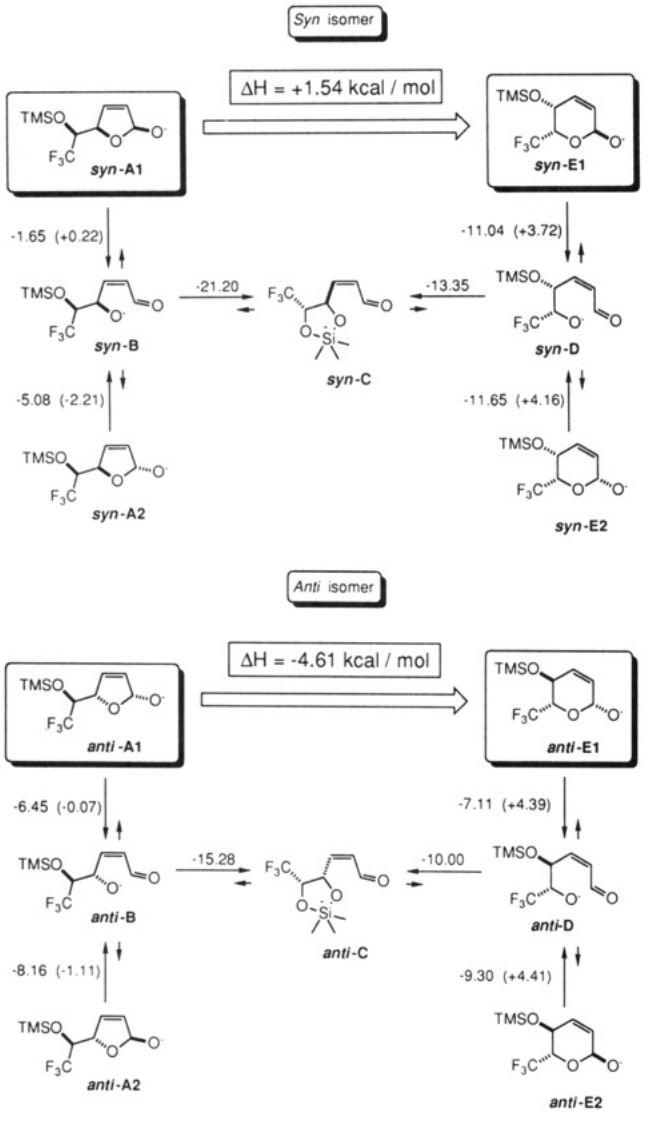


Figure 2. Energy profiles for the present isomerization process. Energy differences between two conformers are described in kcal/mol, and in parentheses are shown the energy differences between the corresponding protonated materials.

2′,2′,2′-trifluoroethyl]]-3-buten-4-olide (7b): bp 100–105 °C/0.6 mmHg; R_f 0.36 (AcOEt:Hex = 1:7); ^{1}H NMR δ 0.13 (3 H, s), 0.16 (3 H, s), 0.92 (9 H, s), 3.29 (2 H, m), 4.65 (1 H, dq, J = 1.59, 6.07 Hz), 5.68 (1 H, dt, J = 1.14, 2.48 Hz); ^{13}C NMR δ −5.73, −5.46, 17.91, 25.22, 33.47, 67.83 (q, J = 34.1 Hz), 104,10, 123.00 (q, J = 286.1 Hz), 150.79, 176.41; ^{19}F NMR δ 0.7 (d, J = 5.8 Hz); IR (neat) ν 2975, 2950, 2900, 2875, 1820. **(1′*S*,4*S*)-4-[1′-(2′,2′,2′-Trifluoro-1′-hydroxyethyl)]-2-buten-4-olide (*anti*-6b)**: bp 170–180 °C/0.15 mmHg; $[\alpha]^{26}_D$ −67.74° (*c* 1.44, $CHCl_3$), 97.6% ee; R_f 0.41 (AcOEt:Hex = 1:1); ^{1}H NMR δ 4.38 (1 H, d, J = 6.22 Hz), 4.45 (1 H, m), 5.31 (1 H, ddd, J = 1.67, 1.67, 3.32 Hz), 6.29 (1 H, ddd, J = 0.53, 1.99, 5.86 Hz), 7.57 (1 H, ddd, J = 1.36, 1.36, 5.84 Hz); ^{13}C NMR δ 69.83 (q, J = 31.5 Hz), 81.16 (q, J = 2.2 Hz), 123.90 (q, J = 283.2 Hz), 124.24, 152.69, 173.78; ^{19}F NMR δ 2.0 (d, J = 6.2 Hz); IR (neat) ν 3000, 1760; HRMS calcd for $C_6H_6F_3O_3$ (M + H) 183.0269, found *m*/*e* 183.0248. Anal. Calcd for $C_6H_5F_3O_3$: C, 39.58; H, 2.77. Found: C, 39.45; H, 2.94. **(1′*S*,4*R*)-4-[1′-(2′,2′,2′-Trifluoro-1′-hydroxyethyl)]-2-buten-4-olide (*syn*-6b)**: mp 103.0–103.5 °C; $[\alpha]^{27}_D$ +87.86° (*c* 0.66, MeOH), 97.6% ee; R_f 0.27 (AcOEt:Hex = 1:1); ^{1}H NMR (acetone-d_6) δ 4.60 (1 H, ddq, J = 2.54, 8.23, 7.45 Hz), 5.45 (1 H, ddd, J = 1.69, 2.23, 2.45 Hz), 5.77 (1 H, d, J = 8.24 Hz), 6.29 (1 H, dd, J = 2.16, 5.78 Hz), 7.67 (1 H, dd, J = 1.77, 5.80 Hz); ^{13}C NMR (acetone-d_6) δ 69.62 (q, J = 30.6 Hz), 81.36 (q, J = 2.1 Hz), 123.86, 125.83 (q, J = 283.2 Hz), 154.75, 173.67; ^{19}F NMR (acetone-d_6) δ 1.3 (d, J = 8.0 Hz); IR (neat) ν 3400, 2950, 2900, 1750; HRMS calcd for $C_6H_6F_3O_3$ (M + H) 183.0269, found *m*/*e* 183.0241. Anal. Calcd for $C_6H_5F_3O_3$: C, 39.58; H, 2.77. Found: C, 39.66; H, 2.87. **4-[1′-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]-2-(*tert*-butyldimethylsilyl)-2-buten-4-olide (*syn*- and *anti*-6a)**: inseparable diastereomer mixture; R_f 0.60 (AcOEt:Hex = 1:5); IR (neat) ν 2975, 2950, 2900, 2875, 1775, 1600. ***anti*-6a** ^{1}H NMR δ 0.04–0.21 (12 H, m), 0.80 (9 H, s), 0.90 (9 H, s), 4.38 (1 H, dq, J = 2.54, 7.20 Hz), 5.12 (1 H, dd, J = 1.55, 2.52 Hz), 7.49 (1 H, m); ^{13}C NMR δ −6.70, −6.57, −5.95, −5.13, 16.35, 17.78, 25.25, 26.24, 71.15 (q, J = 31.1 Hz), 80.92, 125.41 (q, J = 284.6 Hz), 136.21, 160.65, 175.02; ^{19}F NMR δ 2.8 (d, J = 7.0 Hz). ***syn*-6a**: ^{1}H NMR δ 0.04–0.21 (12 H, m), 0.88 (9 H, s), 0.89 (9 H, s), 4.08 (1 H, dq, J = 4.98, 6.53 Hz), 4.98 (1 H, dd, J = 1.57, 4.99 Hz), 7.49 (1 H, m); ^{13}C NMR δ −6.70, −6.57, −5.56, −5.26, 16.41, 17.86, 25.29, 26.16, 71.91 (q, J = 31.2 Hz), 81.82, 126.87 (q, J = 297.3 Hz), 135.69, 160.21, 174.80; ^{19}F NMR δ 3.6 (d, J = 6.0 Hz).

Isomerization of 3-Butenolides to 2-Butenolides. A THF solution (10 mL) of LDA, prepared from diisopropylamine (1.7 mL, 12 mmol) and *n*-BuLi (2.5 M in hexane, 4.4 mL, 11 mmol), was added to a mixture of 3-butenolide **7b** and unchanged silylfuran **5c** at −78 °C (the crude reaction mixture from the above peracid oxidation process on a 10 mmol scale), and the whole was stirred for 30 min. The reaction mixture was then quenched with anhydrous acetic acid (3 mL) at the same temperature. The usual workup and purification by silica gel column chromatography furnished 2-butenolide *syn*- and *anti*-**6c** in a ratio of 13:87 (1.849 g, 4.50 mmol, 45.0%) and silylfuran **5c** (1.185 g, 3.00 mmol, 30%). Their physical properties were identical to that of the already described compounds.

Hydrogenation of 2-Butenolides. To a suspension of 10% palladium on carbon (0.04 g) in anhydrous ethanol (20 mL) under H_2 was added 2-butenolide (3.982 mmol), and the whole was stirred overnight. After removal of the catalyst and concentration of the filtrate, the crude product was chromatographed to yield the desired butyrolactone. **(1′*S*,5*S*)-5-[1′-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]dihydro-2(3*H*)-furanone (*anti*-8c)**: yield 96%; bp 90–100 °C/0.6 mmHg; $[\alpha]^{28}_D$ −0.15° (*c* 1.09, MeOH), 96.1% ee; R_f 0.31 (AcOEt:Hex = 1:5); ^{1}H NMR δ 0.09 (3 H, s), 0.11 (3 H, s), 0.87 (9 H, s), 2.1–2.6 (4 H, m), 4.35 (1 H, dq, J = 1.83, 7.14 Hz), 4.72 (1 H, dt, J = 1.76, 7.29 Hz); ^{13}C NMR δ −5.84, −5.25, 17.75, 20.13, 25.21, 28.01, 71.95 (q, J = 30.1 Hz), 77.64, 123.65 (q, J = 284.6 Hz), 176.41; ^{19}F NMR δ 3.2 (d, J = 8.1 Hz); IR (neat) ν 2950, 2875, 1790; HRMS calcd for $C_{12}H_{22}F_3O_3Si$ (M + H) 299.1290, found *m*/*e* 299.1283. **(1′*R*,5*S*)-5-[1′-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]-dihydro-2(3*H*)-furanone (*syn*-8c)**: yield 97%; $[\alpha]^{27}_D$ +24.32° (*c* 1.13, MeOH), 94.3% ee; R_f 0.50 (AcOEt:Hex = 1:5); ^{1}H NMR δ 0.11 (3 H, s), 0.13 (3 H, s), 0.89 (9 H, s), 2.0–2.7 (4 H, m), 3.97 (1 H, dq, J = 5.02, 6.52 Hz), 4.62 (1 H, dt, J = 4.91, 7.29 Hz); ^{13}C NMR δ −5.46 (q, J = 1.5 Hz), −5.13, 17.94, 23.66 (q, J = 1.9 Hz), 25.32, 27.84, 73.19 (q, J = 30.4 Hz), 77.95 (q, J = 1.8 Hz), 123.78 (q, J = 284.5 Hz), 176.17; ^{19}F NMR δ 2.3 (d, J = 6.5 Hz); IR (neat) ν 2950, 2875, 1780; HRMS calcd for $C_{12}H_{22}F_3O_3Si$ (M + H) 299.1290, found *m*/*e* 299.1311. **5-[1′-[1′-(*tert*-Butyldimethylsiloxy)-2′,2′,2′-trifluoroethyl]]-3-(*tert*-butyldimethylsilyl)-dihydro-2(3*H*)-furanone (8a)**: inseparable diastereomer mixture between C_1 and C_5 (87:13); yield 99%; R_f 0.43 (AcOEt:Hex = 1:7). **Major isomer**: ^{1}H NMR δ 0.03 (3 H, s), 0.09 (3 H, s), 0.11 (3 H, s), 0.16 (3 H, s), 0.88 (9 H, s), 0.92 (9 H, s), 1.9–2.5 (3 H, m), 4.39 (1 H, dq, J = 2.39, 7.11 Hz), 4.54 (1 H, dt, J = 2.41, 5.68 Hz); ^{13}C NMR δ −7.69, −7.10, −5.98, −4.57, 16.77, 17.92, 25.08, 27.17, 25.35, 26.59, 70.04 (q, J = 30.2 Hz), 77.23 (q, J = 1.6 Hz), 123.89 (q, J = 284.2 Hz), 178.03; ^{19}F NMR δ 2.7 (d, J = 6.8 Hz). **Minor isomer**: ^{1}H NMR δ 0.03 (3 H, s), 0.10 (3 H, s), 0.14 (3 H,

= 3.42, 6.42 Hz), 4.4–4.8 (2 H, m), 6.38 (1 H, d, J = 4.76 Hz, N*H*), 6.9–7.7 (10 H, m); ^{13}C NMR δ –5.01 (q, J = 1.8 Hz), –4.97, 18.01, 25.41, 27.26 (q, J = 1.3 Hz), 44.50, 58.60, 72.73 (q, J = 30.1 Hz), 75.58 (q, J = 1.8 Hz), 123.35 (q, J = 284.3 Hz), 127.15, 127.28, 127.35, 128.58, 128.74, 132.52, 136.69, 139.49, 175.74; ^{19}F NMR δ 4.2 (d, J = 6.2 Hz).

Preparation of L-Amicetose Derivative. 5-*O*-(*tert*-Butyldimethylsilyl)-2,3,6-trideoxy-6,6,6-trifluoro-L-*gluco*-hexofuranose (*anti*-18). To a solution of *anti*-**8c** (1.018 g, 3.41 mmol) in ether (7 mL) under N_2 was added DIBAL-H (1.0 M in hexane, 4.0 mL, 4.0 mmol) at –78 °C. After the solution was stirred for 4 h at that temperature, saturated Na_2SO_4 (aq) (4 mL) was added, and the whole was stirred for a further 0.5 h at room temperature. Removal of the resulting solid by filtration and concentration of the solution in vacuo gave crude materials, which were purified by silica gel column chromatography: yield 97%; $[\alpha]^{28}_D$ –8.8° (*c* 1.39, $CHCl_3$, 72:28), 91.5% ee; R_f 0.42 (AcOEt:Hex = 1:4); IR (neat) ν 3450, 3000, 2950, 2925, 2900; HRMS calcd for $C_{12}H_{22}F_3O_3Si$ (M – H) 299.1290, found *m/e* 299.1317. **Major isomer**: ^{1}H NMR δ 0.04 (3 H, s), 0.08 (3 H, s), 0.87 (9 H, s), 1.75–2.10 (4 H, m), 2.0–3.0 (1 H, br), 4.14 (1 H, dq, J = 1.93, 7.36 Hz), 4.43 (1 H, m), 5.53 (1 H, m); ^{13}C NMR δ –5.55 (q, J = 1.2 Hz), –4.75, 18.05, 22.45 (q, J = 1.6 Hz), 25.49, 33.30, 71.89 (q, J = 29.1 Hz), 76.65 (q, J = 1.6 Hz), 98.51, 124.11 (q, J = 283.6 Hz); ^{19}F NMR δ 2.8 (d, J = 6.8 Hz). **Minor isomer**: ^{1}H NMR δ 0.12 (6 H, s), 0.89 (9 H, s), 1.75–2.10 (4 H, m), 2.50 (1 H, br), 4.00–4.21 (2 H, m), 5.44 (1 H, dd, J = 1.67, 3.73 Hz); ^{13}C NMR δ –5.09 (q, J = 2.1 Hz), –4.44, 18.13, 24.48, 25.61, 33.45, 72.80 (q, J = 29.2 Hz), 78.36 (q, J = 1.6 Hz), 98.61, 124.40 (q, J = 283.7 Hz); ^{19}F NMR δ 3.6 (d, J = 6.1 Hz).

4-*O*-(*tert*-Butyldimethylsilyl)-2,3,6-trideoxy-6,6,6-trifluoro-L-*gluco*-hexopyranose (*anti*-19). To a solution of *anti*-18 (0.935 g, 3.11 mmol) in THF (60 mL) was added *t*-BuOK (0.352 g, 3.14 mmol) at –78 °C, and the whole was stirred for 3 h at that temperature. The reaction was quenched with 1 N HCl (3.3 mL), and the volatiles were removed under reduced pressure. After usual workup and purification by silica gel column chromatography the pure pyranose was furnished in a quantitative yield: mp 87.0–88.0 °C; $[\alpha]^{23}_D$ –55.2° (*c* 1.00, $CHCl_3$, 82:18), 91.5% ee; R_f 0.46 (AcOEt:Hex = 1:4); IR (KBr) ν 3475, 2975, 2950, 2925, 2875; HRMS calcd for $C_{12}H_{24}F_3O_3Si$ (M + H) 301.1447, found *m/e* 301.1425. **Major isomer**: ^{1}H NMR δ 0.03 (6 H, s), 0.85 (9 H, s), 1.4–2.1 (4 H, m), 3.00 (1 H, br), 3.78 (1 H, dt, J = 5.59, 8.93 Hz), 4.11 (1 H, dq, J = 9.19, 6.90 Hz), 5.30 (1 H, m); ^{13}C NMR δ –5.25, –4.30, 17.77, 25.56, 28.41, 33.30, 65.93 (q, J = 1.4 Hz), 71.44 (q, J = 29.4 Hz), 90.90, 124.42 (q, J = 280.9 Hz); ^{19}F NMR δ 4.9 (d, J = 6.1 Hz). **Minor isomer**: ^{1}H NMR δ 0.05 (6 H, s), 0.85 (9 H, s), 1.4–2.1 (4 H, m), 3.30 (1 H, br), 3.67 (1 H, dq, J = 8.81, 6.20 Hz), 3.80 (1 H, m), 4.90 (1 H, m); ^{13}C NMR δ –5.32, –4.23, 17.77, 25.56, 27.03, 31.16, 65.42 (q, J = 1.3 Hz), 77.13 (q, J = 29.4 Hz), 96.27, CF_3 was not observed; ^{19}F NMR δ 4.8 (d, J = 7.6 Hz).

Acetyl 4-*O*-(*tert*-Butyldimethylsilyl)-2,3,6-trideoxy-6,6,6-trifluoro-L-*gluco*-hexopyranoside (*anti*-20). This compound was prepared by the above esterification method except for the use of acetic anhydride instead of HCl: yield 95% (68:32 anomeric mixture); $[\alpha]^{28}_D$ –26.5° (*c* 1.08, $CHCl_3$), 91.5% ee; R_f 0.36 (AcOEt:Hex = 1:8); IR (neat) δ 2975, 2950, 2925, 1760; HRMS calcd for $C_{14}H_{28}F_3O_4Si$ (M + H) 343.1552, found *m/e* 343.1552. **Major isomer**: ^{1}H NMR δ 0.05 (6 H, s), 0.85 (9 H, s), 1.5–2.2 (4 H, m), 2.07 (3 H, s), 3.70–4.05 (2 H, m), 5.76 (1 H, dd, J = 2.69, 8.15 Hz); ^{13}C NMR δ –5.30, –4.50, 17.78, 20.97, 25.54, 27.30, 29.51, 69.67 (q, J = 1.3 Hz), 77.39 (q, J = 29.6 Hz), 92.80, 123.22, (q, J = 282.0 Hz), 169.10; ^{19}F NMR δ 4.6 (d, J = 6.2 Hz). **Minor isomer**: ^{1}H NMR δ 0.04 (6 H, s), 0.86 (9 H, s), 1.5–2.2 (4 H, m), 2.10 (3 H, s), 3.70–4.05 (2 H, m), 6.15 (1 H, m); ^{13}C NMR δ –5.30, –4.36, 17.78, 21.04, 25.54, 27.16, 29.51, 65.41 (q, J = 1.3 Hz), 73.26 (q, J = 28.4 Hz), 90.28, 169.05, CF_3 was not observed; ^{19}F NMR δ 4.6 (d, J = 6.2 Hz). This compound was also prepared from furanose *anti*-18 directly in 88% yield (89:11 anomer mixture) by the treatment of the resultant anion with acetic anhydride (2 equiv) at –78 °C.

Acetyl 2,3,6-Trideoxy-6,6,6-trifluoro-L-*gluco*-hexopyranoside (*anti*-21). *anti*-20 was desilylated by the already shown method at 0 °C to yield the glycoside *anti*-21 (90%, 84:16 anomer mixture); $[\alpha]^{23}_D$ +8.79° (*c* 0.90, $CHCl_3$), 91.5% ee; R_f 0.25 (AcOEt:Hex = 1:2); ^{19}F NMR δ 4.3 (d, J = 6.2 Hz, only one peak was observed); IR (neat) ν 3450, 2950, 2875, 1760; HRMS calcd for $C_8H_{12}F_3O_4$ (M + H) 229.0688, found *m/e* 229.0658. **Major isomer**: ^{1}H NMR δ 1.6–2.3 (4 H, m), 2.11 (3 H, s), 2.29 (1 H, d, J = 3.85 Hz), 3.85 (1 H, dq, J = 8.25, 6.34 Hz), 3.92 (1 H, m), 5.78 (1 H, dd, J = 2.40, 8.55 Hz); ^{13}C NMR δ 20.96, 27.45, 28.71, 63.98 (q, J = 1.3 Hz), 77.20 (q, J = 29.5 Hz), 92.90, 123.51 (q, J = 281.5 Hz), 169.22. **Minor isomer**: ^{1}H NMR δ 1.6–2.3 (4 H, m), 2.13 (3 H, s), 2.33 (1 H, d, J = 3.42 Hz), 3.99 (1 H, dq, J = 9.40, 6.12 Hz), 3.92 (1 H, m), 6.18 (1 H, m); ^{13}C NMR δ 21.00, 25.72, 27.28, 64.41 (q, J = 1.5 Hz), 73.22 (q, J = 29.0 Hz), 90.16, 124.15 (q, J = 280.8 Hz), 169.13.

Preparation of L-Rhodinose Derivative. Since, unless otherwise noted, all procedures are identical to that described above, physical properties of products were shown. **5-*O*-(*tert*-Butyldimethylsilyl)-2,3,6-trideoxy-6,6,6-trifluoro-L-*galacto*-hexofuranose (*syn*-18)**: yield 92% from *syn*-**8c**; $[\alpha]^{24}_D$ +8.77° (*c* 1.39, $CHCl_3$, 74:26), 91.5% ee; R_f 0.41 (AcOEt:Hex = 1:4); IR (neat) ν 3400, 2975, 2950, 2900, 2875; HRMS calcd for $C_{12}H_{22}F_3O_3Si$ (M – H) 299.1290, found *m/e* 299.1291. **Major isomer**: ^{1}H NMR δ 0.09 (3 H, s), 0.14 (3 H, s), 0.90 (9 H, s), 1.7–2.3 (4 H, m), 2.90 (1 H, m), 3.84 (1 H, dq, J = 4.89, 6.40 Hz), 4.36 (1 H, m), 5.45 (1 H, dd, J = 3.75, 5.39 Hz); ^{13}C NMR δ –4.74, –4.35, 18.85, 25.30, 26.21, 33.26, 73.79 (q, J = 29.2 Hz), 79.41 (q, J = 1.7 Hz), 99.09, 125.23 (q, J = 284.8 Hz); ^{19}F NMR δ 4.0 (d, J = 6.8 Hz). **Minor isomer**: ^{1}H NMR δ 0.09 (3 H, s), 0.12 (3 H, s), 0.87 (9 H, s), 1.7–2.3 (4 H, m), 2.90 (1 H, m), 3.88 (1 H, dq, J = 4.79, 6.67 Hz), 4.23 (1 H, m), 5.55 (1 H, m); ^{13}C NMR δ –4.71, –4.02, 18.77, 25.33, 26.17, 34.62, 74.65 (q, J = 29.1 Hz), 77.30 (q, J = 1.8 Hz), 99.55, 125.07 (q, J = 284.6 Hz); ^{19}F NMR δ 3.9 (d, J = 6.8 Hz).

4-*O*-(*tert*-Butyldimethylsilyl)-2,3,6-trideoxy-6,6,6-trifluoro-L-*galacto*-hexopyranose (*syn*-19). The above isomerization procedure afforded an inseparable mixture of *syn*-19 (72:28 anomer ratio) and furanose *syn*-18 (72:28 anomer ratio) in a ratio of 70:30: $[\alpha]^{17}_D$ –25.47° (*c* 0.97, $CHCl_3$), 89.2% ee; R_f 0.41 (AcOEt:Hex = 1:4); mp 60.5–61.0 °C; IR (KBr) ν 3500, 2975, 2950, 2900, 2875; HRMS calcd for $C_{12}H_{23}F_3O_3Si$ 300.1369, found *m/e* 300.1369. **Major isomer**: ^{1}H NMR δ 0.04 (3 H, s), 0.05 (3 H, s), 0.87 (9 H, s), 1.6–2.3 (4 H, m), 2.90 (1 H, br), 4.04 (1 H, m), 4.29 (1 H, ddq, J = 0.58, 1.50, 6.96 Hz), 5.40 (1 H, m); ^{13}C NMR δ –5.32, –4.78, 17.90, 23.22, 24.91 (q, J = 0.86 Hz), 25.61, 62.90 (q, J = 1.9 Hz), 69.79 (q, J = 30.2 Hz), 91.86, 123.80 (q, J = 280.2 Hz); ^{19}F NMR δ 4.1 (d, J = 6.9 Hz). **Minor isomer**: ^{1}H NMR δ 0.04 (3 H, s), 0.05 (3 H, s), 0.87 (9 H, s), 1.6–2.3 (4 H, m), 3.21 (1 H, d, J = 10.25 Hz), 3.80 (1 H, dq, J = 1.45, 6.52 Hz), 3.97 (1 H, m), 4.81 (1 H, ddd, J = 2.24, 7.00, 9.09 Hz); ^{19}F NMR δ 4.1 (d, J = 6.9 Hz).

Acetyl 4-*O*-(*tert*-Butyldimethylsilyl)-2,3,6-trideoxy-6,6,6-trifluoro-L-*galacto*-hexopyranoside (*syn*-20). A separable anomer mixture directly from *syn*-**8c**. **Major isomer**: yield 54%; $[\alpha]^{28}_D$ +19.63° (*c* 1.21, $CHCl_3$), 91.5% ee; R_f 0.28 (AcOEt:Hex = 1:8); ^{1}H NMR δ 0.04 (3 H, s), 0.06 (3 H, s), 0.88 (9 H, s), 1.55–2.40 (4 H, m), 2.10 (3 H, s), 3.90 (1 H, dq, J = 1.78, 6.54 Hz), 4.01 (1 H, dt, J = 3.79, 1.97 Hz), 5.73 (1 H, dd, J = 2.44, 9.31 Hz); ^{13}C NMR δ –5.23, –4.80, 17.90, 21.06, 23.96, 29.26, 25.61, 62.17 (q, J = 1.8 Hz), 76.81 (q, J = 30.8 Hz), 93.82, 122.71 (q, J = 280.8 Hz), 169.17; ^{19}F NMR δ 5.0 (d, J = 6.2 Hz); IR (neat) ν 2975, 2950, 2925, 2875, 1760; HRMS calcd for $C_{14}H_{26}F_3O_4Si$ (M + H) 343.1552, found *m/e* 343.1537. **Minor isomer**: yield 33%; $[\alpha]^{24}_D$ –37.65° (*c* 1.17, $CHCl_3$), 91.5% ee; R_f 0.33 (AcOEt:Hex = 1:8); ^{1}H NMR δ 0.04 (3 H, s), 0.06 (3 H, s), 0.88 (9 H, s), 1.56 (1 H, ddddd, J = 0.56, 1.47, 2.44, 4.09, 13.65 Hz), 1.73 (1 H, m), 1.94 (1 H, ddt, J = 2.32, 3.94, 13.64 Hz), 2.28 (1 H, ddt, J = 3.38, 4.59, 13.71 Hz), 2.08 (3 H, s), 4.12 (1 H, ddq, J = 0.56, 1.47, 6.61 Hz), 4.10 (1 H, m), 6.25 (1 H, m); ^{13}C NMR δ –5.37, –4.75, 17.88, 21.06, 22.12, 25.28, 25.58, 62.42 (q, J = 1.8 Hz), 71.80 (q, J = 30.8 Hz), 91.48, 123.19 (q, J = 280.2 Hz), 169.05; ^{19}F NMR δ 4.3 (d, J = 6.9 Hz); IR (neat) ν 2975, 2950, 2900, 2875, 1760.

Acetyl 2,3,6-Trideoxy-6,6,6-trifluoro-L-*galacto*-hexopyranoside (*syn*-21): 72% yield from *syn*-20; mp 74.5–76.0 °C; $[\alpha]^{23}_D$ +13.55° (*c* 1.11, $CHCl_3$), 91.5% ee; R_f 0.31 (AcOEt:Hex = 1:1); ^{1}H NMR δ 1.8–2.2 (4 H, m), 2.14 (3 H, s), 2.13 (1 H, br), 4.00 (1 H, dq, J = 1.38, 6.48 Hz), 4.09 (1 H, m), 5.78 (1 H, dd, J = 2.38, 9.57 Hz); ^{13}C NMR δ 20.99, 23.62, 28.69 (q, J = 1.5 Hz), 61.58 (q, J = 1.6 Hz), 76.30 (q, J = 30.9 Hz), 93.97, 122.67 (q, J = 280.5 Hz), 169.03; ^{19}F NMR δ 5.0 (d, J = 6.1 Hz); IR (KBr) ν 3500, 2975, 2950, 1745; HRMS calcd for $C_8H_{12}F_3O_4$ (M + H) 229.0688, found *m/e* 229.0717.

Preparation of D-Rhamnose Derivative. 5-*O*-(*tert*-Butyldimethylsilyl)-2,3,6-trideoxy-6,6,6-trifluoro-D-*gluco*-hex-2-enofuranose (*anti*-22): 93% yield from *anti*-6c; $[\alpha]^{21}_D$ −79.44° (*c* 1.03, $CHCl_3$, 72:28), 98.1% ee; R_f 0.33 (AcOEt:Hex = 1:4); IR (neat) ν 3450, 2975, 2950, 2925, 2875. **Major isomer**: ^{1}H NMR δ 0.06 (3 H, s), 0.10 (3 H, s), 0.83 (9 H, s), 3.00 (1 H, br), 4.11 (1 H, dq, *J* = 2.68, 7.40 Hz*H*), 5.14 (1 H, ddt, *J* = 1.37, 3.98, 2.62 Hz), 5.90–6.20 (3 H, m); ^{13}C NMR δ −5.38, −5.05, 17.99, 25.41, 72.48 (q, *J* = 29.1 Hz), 83.75 (q, *J* = 1.7 Hz), 103.02, 124.11 (q, *J* = 273.6 Hz), 130.17, 130.83; ^{19}F NMR δ 2.7 (d, *J* = 7.4 Hz). **Minor isomer**: ^{1}H NMR δ 0.04 (6 H, s), 0.87 (9 H, s), 3.00 (1 H, br), 4.02 (1 H, dq, *J* = 4.96, 6.93 Hz), 4.83 (1 H, ddt, *J* = 3.48, 5.26, 1.72 Hz), 6.05 (3 H, m); ^{13}C NMR δ −5.05, −4.40, 18.11, 25.60, 72.30 (q, *J* = 29.59 Hz), 83.13 (q, *J* = 1.8 Hz), 103.31, 128.68, 130.96, *C*F_3 could not be assigned because this type of materials was found to be slowly decomposed during the NMR observation; ^{19}F NMR δ 3.3 (d, *J* = 7.0 Hz).

4-*O*-(*tert*-Butyldimethylsilyl)-2,3,6-trideoxy-6,6,6-trifluoro-D-*gluco*-hex-2-enopyranose (*anti*-23). The aforementioned isomerization procedure afforded an inseparable mixture of *anti*-23 (63% yield, 95:5 anomer ratio) and furanose *anti*-22 (33% yield, 72:28 anomer ratio); mp 65.0–65.5 °C; $[\alpha]^{20}_D$ +77.86° (*c* 1.25, $CHCl_3$, 95:5), 98.1% ee; R_f 0.41 (AcOEt:Hex = 1:6); HRMS calcd for $C_{12}H_{21}F_3O_3Si$ (M + H) 299.1290, found *m/e* 299.1302; ^{1}H NMR δ 0.06 (3 H, s), 0.09 (3 H, s), 0.87 (9 H, s), 3.06 (1 H, d, *J* = 4.95 Hz), 4.16 (1 H, ddq, *J* = 0.64, 8.74, 6.42 Hz), 4.40 (1 H, dddd, *J* = 1.19, 1.32, 1.52, 8.87 Hz), 5.45 (1 H, m), 5.76 (1 H, ddd, *J* = 1.41, 2.12, 10.30 Hz), 5.84 (1 H, m); ^{13}C NMR δ −5.35, −4.48, 17.81, 25.55, 63.09 (q, *J* = 1.6 Hz), 69.56 (q, *J* = 29.3 Hz), 88.79, 124.01 (q, *J* = 280.9 Hz), 125.64, 133.32; ^{19}F NMR δ 3.8 (d, *J* = 6.1 Hz); IR (KBr) ν 3450, 2950, 2935, 2900, 2875.

Methyl 4-*O*-(*tert*-Butyldimethylsilyl)-2,3,6-trideoxy-6,6,6-trifluoro-D-*gluco*-hex-2-enopyranoside (*anti*-24). To a solution of *anti*-23 (0.593 g, 1.987 mmol) in MeOH (10 mL) was added a catalytic amount of *p*-TsOH, and the mixture was stirred for 2 h at room temperature. The residue, after concentration in vacuo, was purified by silica gel column chromatography to afford the methyl pyranoside (0.575 g, 1.841 mmol, 93% yield, a 96:4 inseparable anomer mixture): $[\alpha]^{21}_D$ +117.61° (*c* 1.13, $CHCl_3$), 98.1% ee; R_f 0.64 (AcOEt:Hex = 1:4); ^{1}H NMR δ 0.05 (3 H, s), 0.08 (3 H, s), 0.86 (9 H, s), 3.43 (3 H, s), 4.04 (1 H, dq, *J* = 8.99, 6.52 Hz), 4.41 (1 H, ddd, *J* = 1.52, 2.98, 8.99 Hz), 4.90 (1 H, m), 5.70 (1 H, ddd, *J* = 1.67, 2.35, 10.32 Hz), 5.80 (1 H, m); ^{13}C NMR δ −5.38, −4.49, 17.79, 25.52, 56.02, 63.23 (q, *J* = 1.6 Hz), 69.41 (q, *J* = 29.8 Hz), 95.36, 125.30, 133.30, 124.13 (q, *J* = 280.03 Hz); ^{19}F NMR δ 3.9 (d, *J* = 6.8 Hz); IR (neat) ν 2975, 2950, 2900, 2875; HRMS calcd for $C_{13}H_{24}F_3O_3Si$ (M + H) 313.1447, found *m/e* 313.1443.

Methyl 4-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6,6,6-trifluoro-D-*manno*-hexopyranoside (*anti*-25). $KMnO_4$ oxidation gave the desired methyl glycoside (55% yield, 93:7 anomer mixture) along with the recovery of the starting material *anti*-24 (14%). NMR data were shown only for the major isomer: mp 71.0–72.0 °C; $[\alpha]^{20}_D$ +67.80° (*c* 0.92, $CHCl_3$), 98.1% ee; R_f 0.37 (AcOEt:Hex = 1:2); ^{1}H NMR δ 0.06 (3 H, s), 0.12 (3 H, s), 0.86 (9 H, s), 2.50 (1 H, br), 2.75 (1 H, br), 3.39 (3 H, s), 3.65–4.00 (4 H, m), 4.77 (1 H, d, *J* = 1.57 Hz); ^{13}C NMR δ −5.09 (q, *J* = 1.4 Hz), −3.86, 18.11, 25.74, 55.41, 68.36, 70.45, 71.93, 70.03 (q, *J* = 29.4 Hz), 100.71, 123.95 (q, *J* = 280.1 Hz); ^{19}F NMR δ 5.6 (d, *J* = 5.5 Hz); IR (neat) ν 3350, 3475, 2950, 2925, 2900, 2850; HRMS calcd for $C_{13}H_{26}F_3O_5Si$ (M + H) 347.1502, found *m/e* 347.1482.

Methyl 2,3-*O*-Diacetyl-4-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-6,6,6-trifluoro-D-*manno*-hexopyranoside (*anti*-26): 86% yield from *anti*-25 as a single isomer; mp 63.5–64.0 °C; $[\alpha]^{23}_D$ +31.32° (*c* 1.30, $CHCl_3$), 98.1% ee; R_f 0.32 (AcOEt:Hex = 1:6); ^{1}H NMR δ 0.05 (6 H, s), 0.81 (9 H, s), 2.01 (3 H, s), 2.10 (3 H, s), 3.14 (3 H, s), 3.97 (1 H, dq, *J* = 9.20, 6.48 Hz), 4.14 (1 H, t, *J* = 9.11 Hz), 4.70 (1 H, d, *J* = 1.65 Hz), 5.07 (1 H, dd, *J* = 3.30, 8.98 Hz), 5.22 (1 H, dd, *J* = 1.83, 3.34 Hz); ^{13}C NMR δ −4.96 (q, *J* = 1.6 Hz), −4.07, 17.94, 20.75, 21.06, 25.54, 55.61, 65.45 (q, *J* = 1.4 Hz), 69.07, 71.86, 70.71 (q, *J* = 29.7 Hz), 98.69, 123.74 (q, *J* = 280.7 Hz), 169.74, 169.95; ^{19}F NMR δ 4.5 (d, *J* = 5.4 Hz); IR (KBr) ν2975, 2950, 2900, 2875, 1760; HRMS calcd for $C_{17}H_{30}F_3O_7Si$ (M + H) 431.1713, found *m/e* 431.1718.

Methyl 2,3-*O*-Diacetyl-6-deoxy-6,6,6-trifluoro-D-*manno*-hexopyranoside (*anti*-27). Deprotection of the above methyl glycoside (0.303 g, 0.704 mmol) furnished the desired glycoside (0.137 g, 0.433 mmol, 62% yield as a single isomer) and a mixture of acetyl-migrated products. The latter was transformed into the triacetate *anti*-28 (32% yield, whose physical properties were identical to the product obtained in the next procedure): mp 126.5–127.0 °C; $[\alpha]^{20}_D$ +20.33° (*c* 0.85, $CHCl_3$), 98.1% ee; R_f 0.50 (AcOEt:Hex = 1:1); ^{1}H NMR δ 2.08 (3 H, s), 2.14 (3 H, s), 2.55 (1 H, br), 3.46 (3 H, s), 4.03 (1 H, ddq, *J* = 0.64, 9.65, 6.04 Hz), 4.17 (1 H, dt, *J* = 1.51, 10.12 Hz), 4.75 (1 H, m), 5.18–5.26 (2 H, m); ^{13}C NMR δ 20.78, 55.73, 64.93 (q, *J* = 1.4 Hz), 69.04, 70.76, 70.32 (q, *J* = 29.9 Hz), 98.65, 123.87 (q, *J* = 280.4 Hz), 170.02, 170.68; ^{19}F NMR δ 4.4 (d, *J* = 5.0 Hz); IR (KBr) ν 3515, 3025, 2975, 2850, 1750, 1725; HRMS calcd for $C_{11}H_{16}F_3O_7$ (M + H) 317.0848, found *m/e* 317.0876.

Methyl 2,3,4-*O*-triacetyl-6-deoxy-6,6,6-trifluoro-D-*manno*-hexopyranoside (*anti*-28): 95% yield from *anti*-27 and its acetyl-migrated compounds; $[\alpha]^{20}_D$ +52.69° (*c* 0.82, $CHCl_3$), 98.1% ee; R_f 0.49 (AcOEt:Hex = 1:2); ^{1}H NMR δ 2.01 (3 H, s), 2.05 (3 H, s), 2.17 (3 H, s), 3.47 (3 H, s), 4.15 (1 H, ddq, *J* = 0.59, 9.83, 6.00 Hz), 4.81 (1 H, d, *J* = 1.84 Hz), 5.24 (1 H, dd, *J* = 1.79, 3.36 Hz), 5.35 (1 H, dd, *J* = 3.40, 9.93 Hz), 5.54 (1 H, t, *J* = 9.84 Hz); ^{13}C NMR δ 20.51, 20.63, 20.83, 55.89, 64.04, 68.33, 68.84, 68.33 (q, *J* = 31.3 Hz), 98.68, 123.32 (q, *J* = 280.3 Hz), 169.16, 169.82, 170.04; ^{19}F NMR δ 5.4 (d, *J* = 6.9 Hz); IR (neat) ν 2950, 2850, 1765, 1750; HRMS calcd for $C_{13}H_{18}F_3O_8$ (M + H) 359.0953, found *m/e* 359.0977.

Preparation of 6-Deoxy-D-allose. 5-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6,6,6-trifluoro-2,3-*O*-isopropylidene-D-*allo*-hexofuranone (*anti*-32). To a solution of *anti*-12 (0.197 g, 0.596 mmol) in acetone (1.5 mL) were added 2,2-dimethoxypropane (0.15 mL, 1.2 mmol) and a catalytic amount of concd H_2SO_4, and the reaction mixture was stirred for 2 h at room temperature. The usual workup and purification by silica gel column chromatography gave the acetonide (0.208 g, 0.561 mmol) in 94% yield: mp 122.5–123.5 °C; $[\alpha]^{19}_D$ −29.70° (*c* 1.46, $CHCl_3$), 98.1% ee; R_f 0.56 (AcOEt:Hex = 1:4); ^{1}H NMR δ 0.06 (3 H, s), 0.12 (3 H, s), 0.87 (9 H, s), 1.37 (3 H, s), 1.44 (3 H, s), 4.28 (1 H, dq, *J* = 1.58, 7.08 Hz), 4.66 (1 H, d, *J* = 6.04 Hz), 4.75 (1 H, d, *J* = 6.00 Hz), 4.75 (1 H, d, *J* = 1.55 Hz); ^{13}C NMR δ −5.67 (q, *J* = 1.8 Hz), −4.81, 17.93, 25.44, 26.61, 71.43 (q, *J* = 30.7 Hz), 75.09, 81.15, 75.24 (q, *J* = 2.4 Hz), 113.57, 123.22 (q, *J* = 283.8 Hz), 172.99; ^{19}F NMR δ 4.5 (d, *J* = 6.8 Hz); IR (KBr) ν 3025, 3000, 2975, 2925, 2900, 1815; HRMS calcd for $C_{15}H_{28}F_3O_5Si$ (M + H) 371.1502, found *m/e* 371.1481.

5-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6,6,6-trifluoro-2,3-*O*-isopropylidene-L-*allo*-hexofuranose (*anti*-33). Quantitative yield from *anti*-32 as an inseparable anomer mixture: $[\alpha]^{19}_D$ −13.38° (*c* 0.79, $CHCl_3$, 77:23), 98.1% ee; R_f 0.42 (AcOEt:Hex = 1:4); IR (KBr) ν 3450, 3025, 2975, 2950, 2900, 2875; HRMS calcd for $C_{15}H_{28}F_3O_5Si$ 372.1580, found *m/e* 372.1603. **Major isomer**: ^{1}H NMR δ 0.11 (3 H, s), 0.12 (3 H, s), 0.90 (9 H, s), 1.29 (3 H, s), 1.46 (3 H, s), 2.92 (1 H, d, *J* = 3.29 Hz), 4.05 (1 H, dq, *J* = 8.21, 6.36 Hz), 4.25 (1 H, dd, *J* = 1.53, 8.29 Hz), 4.54 (1 H, d, *J* = 6.05 Hz), 4.82 (1 H, d, *J* = 6.07 Hz), 5.43 (1 H, d, *J* = 3.30 Hz); ^{13}C NMR δ −4.76, 18.15, 24.90, 26.45, 25.62, 71.46 (q, *J* = 29.1 Hz), 79.90, 81.52, 85.06, 102.90, 112.87, 124.39 (q, *J* = 283.7 Hz); ^{19}F NMR δ 4.6 (d, *J* = 5.5 Hz). **Minor isomer**: ^{1}H NMR δ 0.07 (3 H, s), 0.12 (3 H, s), 0.87 (9 H, s), 1.38 (3 H, s), 1.57 (3 H, s), 2.98 (1 H, br), 4.15 (1 H, dq, *J* = 1.69, 4.99 Hz), 4.32 (1 H, m), 4.58 (1 H, dd, *J* = 4.37, 7.08 Hz), 4.95 (1 H, m), 5.34 (1 H, dd, *J* = 4.36, 8.31 Hz); ^{13}C NMR δ −5.35, −4.76, 18.04, 24.76, 26.25, 25.53, 71.57 (q, *J* = 29.89 Hz), 78.82, 80.55, 84.96 (q, *J* = 1.4 Hz), 96.11, 115.23, *C*F_3 was not observed; ^{19}F NMR δ 3.4 (d, *J* = 7.6 Hz).

4-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6,6,6-trifluoro-2,3-*O*-isopropylidene-D-*allo*-hexopyranose (*anti*-34). Isomerization at −5 °C gave the desired pyranose *anti*-34 (35% yield), *anti*-33 (46% yield), and TBS-migrated furanoside *anti*-35 (17% yield), which were separated by silica gel column chromatography. ***anti*-34**: mp 87.5–88.0 °C; $[\alpha]^{17}_D$ +13.50° (*c* 0.83, $CHCl_3$, >99:1), 98.1% ee; R_f 0.34 (AcOEt:Hex = 1:4); ^{1}H NMR δ 0.08 (3 H, s), 0.11 (3 H, s), 0.88 (9 H, s), 1.33 (3 H, s), 1.50 (3 H, s), 3.26 (1 H, d, *J* = 3.85 Hz), 4.12 (1 H, dd, *J* = 3.12, 6.80 Hz), 4:43 (1 H, m), 4.16 (1 H, dq, *J* = 8.60, 7.21 Hz), 4.47 (1 H, dd, *J* = 2.75, 8.51 Hz), 5.02 (1 H, t, *J* = 3.45 Hz); ^{13}C NMR δ −4.99, −4.70, 18.02, 24.84, 26.78, 25.61, 64.47, 74.17, 76.08, 71.12 (q, *J* = 29.6 Hz), 93.98, 112.50, 123.53 (q, *J* = 281.8 Hz); ^{19}F NMR δ 4.2 (d, *J* = 6.2 Hz); IR (KBr) ν 3400, 3000, 2950, 2900, 2875; HRMS calcd for $C_{15}H_{28}F_3O_5Si$ (M + H) 373.1658, found *m/e* 373.1660. ***tert***-

Butyldimethylsilyl-6-deoxy-6,6,6-trifluoro-2,3-*O*-isopropylidene-D-*allo*-hexofuranoside (*anti*-35): R_f 0.56 (AcOEt:Hex = 1:4); ^{1}H NMR δ 0.15 (3 H, s), 0.17 (3 H, s), 0.89 (9 H, s), 1.30 (3 H, s), 1.46 (3 H, s), 4.09 (1 H, tq, J = 1.29, 7.65 Hz), 4.51 (1 H, d, J = 6.00 Hz), 5.06 (1 H, d, J = 6.09 Hz), 4.53 (1 H, m), 4.6–4.7 (1 H, br), 5.39 (1 H, s); ^{13}C NMR δ –5.38, –4.78, 17.69, 24.70, 26.26, 25.48, 71.53 (q, J = 29.8 Hz), 79.89 (q, J = 1.6 Hz), 86.86 (q, J = 2.0 Hz), 87.47, 103.31, 112.51, 123.94 (q, J = 281.1 Hz); ^{19}F NMR δ 2.7 (d, J = 7.5 Hz).

Preparation of 3,6-Dideoxy-L-talose. 5-*O*-(*tert*-Butyldimethylsilyl)-3,6-dideoxy-6,6,6-trifluoro-2-*O*-pivaloyl-L-*talo*-hexofuranone (*syn*-36): 84% yield from *syn*-14; $[\alpha]^{18}_D$ +18.85° (*c* 0.99, $CHCl_3$), 91.1% ee; R_f 0.45 (AcOEt:Hex = 1:4); ^{1}H NMR δ 0.13 (3 H, s), 0.19 (3 H, s), 0.89 (9 H, s), 1.20 (9 H, s), 2.30 (1 H, dt, J = 13.72, 8.38 Hz), 2.55 (1 H, ddd, J = 3.29, 9.19, 13.91 Hz), 4.01 (1 H, dq, J = 2.76, 6.36 Hz), 4.85 (1 H, dt, J = 8.93, 2.95 Hz), 5.38 (1 H, dd, J = 7.93, 9.19 Hz); ^{13}C NMR δ –5.32 (q, J = 2.0 Hz), –4.72, 18.01, 25.41, 26.88, 31.04 (q, J = 1.3 Hz), 38.65, 66.90, 72.72 (q, J = 30.6 Hz), 74.82 (q, J = 2.0 Hz), 123.38 (q, J = 284.5 Hz), 171.95, 177.38; ^{19}F NMR δ 4.9 (d, J = 5.5 Hz); IR (KBr) ν 2975, 2950, 2900, 2875, 1785, 1750; HRMS calcd for $C_{17}H_{30}F_3O_5Si$ (M + H) 399.1815, found *m/e* 399.1810.

5-*O*-(*tert*-Butyldimethylsilyl)-3,6-dideoxy-6,6,6-trifluoro-2-*O*-pivaloyl-L-*talo*-hexofuranose (*syn*-37): 85% yield from *syn*-36 as a 93:7 anomer mixture. Physical properties were shown only for the major isomer: $[\alpha]^{15}_D$ –6.76° (*c* 1.20, $CHCl_3$, 93:7), 91.1% ee; R_f 0.47 (AcOEt:Hex = 1:4); ^{1}H NMR δ 0.13 (3 H, s), 0.14 (3 H, s), 0.90 (9 H, s), 1.16 (9 H, s), 1.99 (1 H, dd, J = 6.82, 14.06 Hz), 2.25 (1 H, dddq, J = 5.01, 9.07, 14.14, 0.81 Hz), 3.07 (1 H, d, J = 5.49 Hz), 3.88 (1 H, dq, J = 4.40, 6.59 Hz), 4.48 (1 H, ddd, J = 4.55, 6.92, 9.02 Hz), 5.02 (1 H, d, J = 4.62 Hz), 5.26 (1 H, d, J = 5.58 Hz); ^{13}C NMR δ –5.21 (q, J = 1.1 Hz), –4.50, 18.26, 25.60, 26.96, 30.81 (q, J = 1.9 Hz), 38.68, 73.23 (q, J = 29.5 Hz), 77.91 (q, J = 1.8 Hz), 78.14, 100.41, 123.96 (q, J = 284.3 Hz), 177.76; ^{19}F NMR δ 4.8 (d, J = 6.2 Hz); IR (neat) ν 3500, 2975, 2950, 2925, 2875, 1740; HRMS calcd for $C_{17}H_{30}F_3O_5Si$ (M – H) 399.1815, found *m/e* 399.1796.

4-*O*-(*tert*-Butyldimethylsilyl)-3,6-dideoxy-6,6,6-trifluoro-2-*O*-pivaloyl-L-*talo*-hexopyranose (*syn*-38). Isomerization procedure for 27 h gave the desired pyranose *syn*-38 (20% yield) and the starting material *syn*-37 (69% yield), which were separated by silica gel column chromatography: $[\alpha]^{20}_D$ –6.97° (*c* 0.76, $CHCl_3$, 93:7), 91.1% ee; R_f 0.40 (AcOEt:Hex = 1:4); ^{1}H NMR δ 0.13 (3 H, s), 0.14 (3 H, s), 0.88 (9 H, s), 1.19 (9 H, s), 1.97 (1 H, dt, J = 14.91, 4.62 Hz), 2.19 (1 H, dt, J = 14.69, 4.62 Hz), 3.85 (1 H, br), 4.12 (1 H, dt, J = 2.93, 4.58 Hz), 4.31 (1 H, dq, J = 3.02, 7.51 Hz), 4.69 (1 H, dt, J = 3.04, 4.74 Hz), 5.13 (1 H, dd, J = 3.62, 4.44 Hz); ^{13}C NMR δ –5.39, –4.12, 18.09, 25.84, 27.04, 30.84, 38.75, 62.62 (q, J = 1.1 Hz), 67.62, 69.95 (q, J = 30.0 Hz), 92.59, 123.84 (q, J = 281.5 Hz), 178.82; ^{19}F NMR δ 7.7 (d, J = 4.8 Hz); IR (neat) ν 3525, 2975, 2950, 2900, 2875, 1710; HRMS calcd for $C_{17}H_{32}F_3O_5Si$ (M + H) 401.1971, found *m/e* 401.1988.

5-*O*-(*tert*-Butyldimethylsilyl)-2,3,6-trideoxy-6,6,6-trifluoro-*galacto*-hex-2-enofuranose (*syn*-22). *syn*-6c was reduced to the crude furanose *syn*-22 (83% yield as a 84:16 anomeric mixture calculated from ^{19}F NMR integration values by using benzotrifluoride as an internal standard). Because of its instability, after purification by short-path silica gel column chromatography, the crude *syn*-22 was used in the next isomerization step: ^{19}F NMR δ 3.8 (d, J = 6.9 Hz, minor), 4.4 (d, J = 6.9 Hz, major).

Acetyl 4-*O*-(*tert*-Butyldimethylsilyl)-2,3,6-trideoxy-6,6,6-trifluoro-D-*galacto*-hex-2-enopyranoside (*syn*-29). The isomerization procedure and direct acetylation gave an inseparable anomer mixture of acetyl glycoside (23% yield) in a ratio of 86:14: $[\alpha]^{21}_D$ –96.78° (*c* 0.81, $CHCl_3$), 89.2% ee; R_f 0.47 (AcOEt:Hex = 1:6); ^{1}H NMR δ 0.06 (6 H, s), 0.84 (9 H, s), 2.05 (3 H, s), 4.18 (1 H, dd, J = 2.48, 5.49 Hz), 4.28 (1 H, dq, J = 2.52, 6.59 Hz), 5.88 (1 H, dd, J = 3.13, 10.11 Hz), 6.11 (1 H, dd, J = 5.46, 10.16 Hz), 6.42 (1 H, d, J = 3.12 Hz); ^{13}C NMR δ –5.09, –4.23, 17.86, 20.92, 25.47, 59.82 (q, J = 1.83 Hz), 71.68 (q, J = 31.4 Hz), 87.88, 122.94 (q, J = 276.7 Hz), 125.68, 129.32, 169.31; ^{19}F NMR δ 5.5 (d, J = 6.2 Hz, major), 8.4 (d, J = 6.9 Hz, minor); IR (neat) ν 3000, 2950, 2925, 2875, 1750; HRMS calcd for $C_{14}H_{23}F_3O_4Si$ 340.1318, found *m/e* 340.1322.

5-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6,6,6-trifluoro-2,3-*O*-isopropylidene-D-*talo*-hexofuranone (*syn*-32): yield 94% from *syn*-12; mp 102.5–103.5 °C; $[\alpha]^{19}_D$ +32.63° (*c* 0.85, $CHCl_3$), 98.1% ee; R_f 0.38 (AcOEt:Hex = 1:4); ^{1}H NMR δ 0.14 (6 H, s), 0.88 (9 H, s), 1.36 (3 H, s), 1.45 (3 H, s), 4.21 (1 H, dq, J = 2.05, 6.36 Hz), 4.65 (1 H, d, J = 5.86 Hz), 4.71 (1 H, d, J = 5.86 Hz), 4.75 (1 H, d, J = 2.01 Hz); ^{13}C NMR δ –5.27 (q, J = 2.2 Hz), –4.77, 18.04, 25.39, 25.44, 26.52, 70.88 (q, J = 31.2 Hz), 74.63, 77.63, 80.07 (q, J = 2.1 Hz), 113.76, 123.19 (q, J = 284.7 Hz), 172.82; ^{19}F NMR δ 5.4 (d, J = 6.2 Hz); IR (KBr) ν 3000, 2975, 2950, 2900, 2875, 1790; HRMS calcd for $C_{15}H_{26}F_3O_5Si$ (M + H) 371.1502, found *m/e* 371.1523.

5-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6,6,6-trifluoro-2,3-*O*-isopropylidene-D-*talo*-hexofuranose (*syn*-33): yield 88% (inseparable mixture); $[\alpha]^{20}_D$ –7.39° (*c* 1.32, $CHCl_3$, 74:26), 98.1% ee; R_f 0.40 (AcOEt:Hex = 1:4); IR (neat) ν 3475, 2975, 2950, 2900, 2850; HRMS calcd for $C_{15}H_{28}F_3O_5Si$ (M + H) 373.1658, found *m/e* 373.1643. **Major isomer**: ^{1}H NMR δ 0.20 (6 H, s), 0.92 (9 H, s), 1.29 (3 H, s), 1.46 (3 H, s), 3.96 (1 H, d, J = 11.09 Hz), 4.11 (1 H, dq, J = 2.54, 6.27 Hz), 4.51 (1 H, d, J = 6.05 Hz), 4.66 (1 H, dd, J = 1.22, 5.92 Hz), 4.56 (1 H, m), 5.34 (1 H, d, J = 11.13 Hz); ^{13}C NMR δ –5.32 (q, J = 1.1 Hz), –4.60, 18.32, 24.90, 26.36, 25.57, 72.00 (q, J = 30.1 Hz), 104.03, 112.71, 123.31 (q, J = 284.00 Hz); ^{19}F NMR δ 5.5 (d, J = 6.2 Hz). **Minor isomer**: ^{1}H NMR δ 0.12 (6 H, s), 0.88 (9 H, s), 1.35 (3 H, s), 1.52 (3 H, s), 3.91 (1 H, d, J = 11.66 Hz), 4.05 (1 H, dq, J = 2.60, 6.50 Hz), 4.34 (1 H, m), 4.56 (1 H, m), 4.67 (1 H, dd, J = 1.16, 6.22 Hz), 5.48 (1 H, dd, J = 3.86, 11.59 Hz); ^{13}C NMR δ –4.76, 18.02, 24.67, 26.42, 25.51, 72.73 (q, J = 30.1 Hz), 98.31, 113.48, CF_3 was not observed; ^{19}F NMR δ 4.9 (d, J = 6.2 Hz). The following were not identified in the ^{13}C NMR spectrum: δ 78.96, 79.53 (q, J = 2.0 Hz), 79.53, 81.68 (q, J = 1.5 Hz), 85.22 (q, J = 1.7 Hz), 86.88.

Supplementary Material Available: A copy of the ^{1}H NMR spectrum of each new compound (65 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Cope Rearrangements in the Benzo[b]thiophene Series†

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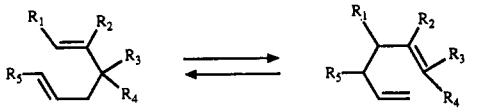
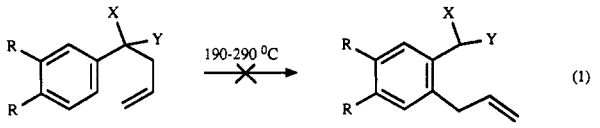
The inability to observe Cope rearrangement products at elevated temperatures for diethyl α-allyl-2-naphthalenemalonate (1) and diethyl α-allyl-9-phenanthrenemalonate (2) does not extend to the analogous systems resulting from replacement of the aromatic units by 2- and 3-benzo[b]thiophene nuclei. Thermal rearrangement of diethyl α-allyl-3-benzo[b]thiophenemalonate (5) at 215–255 °C for 11 h produces the expected Cope rearrangement product diethyl 2-allyl-3-benzo[b]thiophenemalonate (10) (8%) accompanied by *trans*- and *cis*-ethyl 2,3-dihydro-1-(ethoxycarbonyl)-1*H*-benzo[b]cyclopenta[d]thiophene-2-acetate (9a) (10%) and (9b) (5%), respectively. The structure elucidation of 10, 9a, and 9b was done by spectroscopy. The attempted structure verification of 10 by an independent route gave diethyl 2-(1-propenyl)-3-benzo[b]thiophenemalonate (12) which when heated at 230–240 °C for 18 h gave 1-carbethoxy-2-hydroxy-3-methyldibenzothiophene (16) as a major product. Similar results were observed with 2-substituted analogues of 5, both diethyl 3-allyl-2-benzo[b]thiophenemalonate (24) and ethyl 1,2-dihydro-3-(ethoxycarbonyl)-3*H*-benzo[b]cyclopenta[d]thiophene-2-acetate (25) being formed. In this case the structure of 24 was verified by synthesis. An extension of this involved a study of thermal rearrangement of analogous compound ethyl α-allyl-α-cyano-3-benzo[b]thiopheneacetate (30). Thermal rearrangement of 30 at 235–245 °C for 8 h gave the expected Cope rearrangement product ethyl α-cyano-2-allyl-3-benzo[b]thiopheneacetate (32) (6%) along with an unexpected diastereomeric mixture of 1-cyano-1-(ethoxycarbonyl)-2-methyl-2,3-dihydro-1*H*-benzo[b]cyclopenta[d]thiophenes (33) (18%). Speculative mechanistic considerations are offered regarding the mode of transformation of 12 to 16 and 32 to 33.

The thermal intramolecular rearrangement of 1,5-hexadiene systems, commonly known as the Cope rearrangement and now classified as [3.3] sigmatropic rearrangements[1] has been well documented and may be represented as follows.



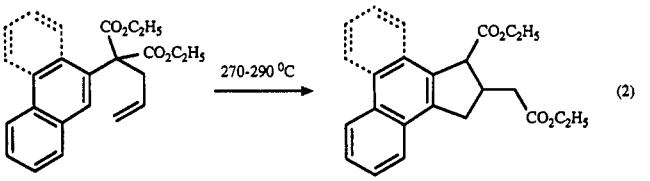
Papers published[2,3] in 1956 reported situations when the R_1R_2 portions of the hexadiene systems was part of an aromatic ring. Failure to observe any rearrangement was reported in the case of RR shown in eq 1.



R = H or -OCH_3 and X, Y = CN, $CO_2C_2H_5$, C_6H_5 (1)

However when the aromatic portions of hexadiene system was naphthalene (1) or phenanthrene (2) as shown in eq 2, rearrangement was observed, but products of rearrangement were not as anticipated but were 3 and 4, respectively.

In 1986, when MacDowell and Pupura[4] replaced the benzene portion in eq 1 by 2- and 3-thienyl moieties, not only the normal Cope rearrangement was observed, but it was also followed by cyclization to produce the abnormal products, in parallel to the phenanthrene or naphthalene series as shown in Scheme I.



1, 2 3, 4 (2)

A mechanistic explanation[4] was given for the cyclization of the normal Cope rearrangement product to the cyclized product. Attempted thermal rearrangement of diethyl α-allyl-2,5-dimethyl-thiophenemalonate gave no indication of the occurrence of any rearrangement.

The present work extends the previous work by blocking one side of the thiophene ring with a benzene ring to produce the benzo[b]thiophene analogues of the naphthalene series formerly studied by Cope. The initial objective was to study the effect of heat on both the 2- and 3-substituted diethyl α-allylbenzo[b]thiophenemalonates in order to see which course the reaction would follow, the normal Cope rearrangement or not. An extension of this involved a study of thermal rearrangement of the analogous cyanoacetates.

Synthesis of Diethyl α-Allyl-3-benzo[b]thiophenemalonate (5). Diethyl α-allyl-3-benzo[b]thiophenemalonate (5)[5] was synthesized from ethyl 3-benzo[b]-thiopheneacetate (6) in a three-step, one-pot reaction carried out without isolation of the intermediate 7 by the

† Dedicated to Professor Gabor B. Fodor on the occasion of his 77th birthday.

(1) Rhoads, S. J.; Raulins, N. R. *Organic Reactions*, John Wiley and Sons, Inc.: New York, 1975; Vol. 22, p 1.

(2) Cope, A. C.; Field, L.; MacDowell, D. W. H.; Wright, M. E. *J. Am. Chem. Soc.* **1956**, *78*, 2547.

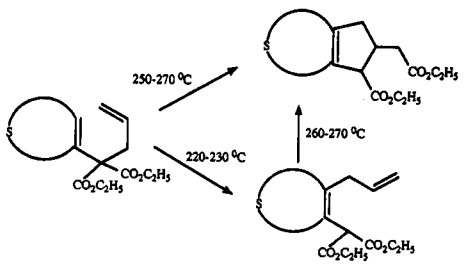
(3) Cope, A. C.; Meili, J. E.; MacDowell, D. W. H. *J. Am. Chem. Soc.* **1956**, *78*, 2551.

(4) MacDowell, D. W. H.; Purpura, J. M. *J. Org. Chem.* **1986**, *51*, 183.

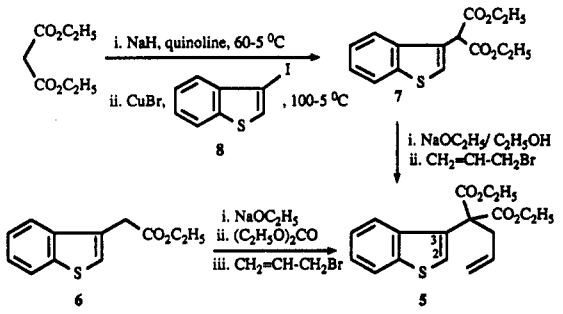
(5) Purpura, J. M. M. S. Thesis, West Virginia University, Morgantown, 1981.

0022-3263/93/1958-4360$04.00/0

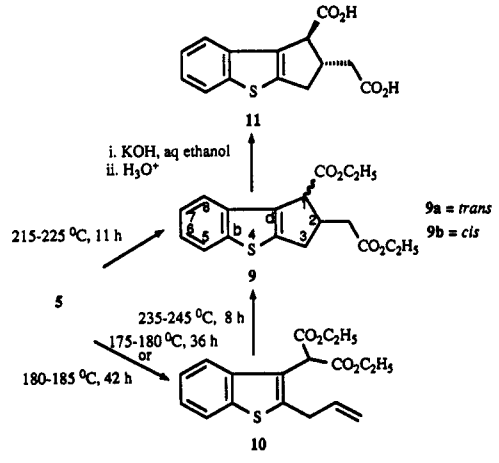
Scheme I



Scheme II



Scheme III



treatment of **6** with sodium ethoxide and diethyl carbonate followed by addition of allyl bromide.

An alternative approach (Scheme II) permitted the isolation of **7**. The reaction of Houbiers and Muris[6] as used by MacDowell and Purpura[4] permitted the direct alkylation of 3-iodobenzo[*b*]thiophene (**8**)[7] to afford the malonate in 48% yield. Alkylation of **7** with allyl bromide gave the desired **5** in 47% yield along with some **6** presumably formed by a retro-Claisen condensation reaction.[8]

Thermal Rearrangement of Diethyl α-Allyl-3-benzo[*b*]thiophenemalonate (5). Preliminary investigation[5] of the thermal rearrangement of **5** gave only (Scheme III) ethyl 2,3-dihydro-1-(ethoxycarbonyl)-1*H*-benzo[*b*]cyclopenta[*d*]thiophene-2-acetate (**9**), the "abnormal" Cope product, at 230–40 °C.

In order to see if the normal Cope rearrangement product **10** was initially produced in the thermal rearrangement, **5** was heated at 175–80 °C for 36 h (Scheme III). Isolation of crude material by column chromatography gave 31% of a product **10** along with 67% unreacted starting material. An ^{1}H NMR spectrum of the polar compound **10** showed not only the presence of vinyl hydrogens but also a singlet at δ 5.03; however, a doublet for the allylic hydrogen which was at δ 3.21 in **5** occurred at δ 3.68 in **10** (Table I). In a ^{13}C NMR spectrum of this compound **10**, allylic and benzylic carbons of **5** shifted upfield from δ 39.97 to 33.01 and δ 60.15 to 50.62, respectively. A mass spectrum showed the molecular ion peak at 332. On the basis of the above evidence, the more polar compound was assigned the structure diethyl 2-allyl-3-benzo[*b*]thiophenemalonate (**10**) which is the regular Cope rearrangement product and is the benzo[*b*]thiophene analogue of the product which Cope expected but did not obtain in the study of the phenanthrene and naphthalene analogues.[2,3] When **5** was heated at 180–85 °C for a longer time period, 42 h, the ^{1}H NMR spectrum of the crude product indicated the product to starting material ratio of 55:48 based on the integration of the methylene protons of the allylic group. The chromatographic separation gave **10** in 44% yield, an improvement in the yield of the regular Cope product **10**.

Diethyl α-allyl-3-benzo[*b*]thiophenemalonate (**5**) was heated (Scheme III) at a higher temperature (215–25 °C) for 11 h to obtain cyclized products as before.

Column chromatography of the crude material **9** by the gradient elution method gave 8% of the normal Cope-rearranged product **10**. Further careful elution of the column gave 10% (major, **9a**) and 5% (minor, **9b**) *trans*- and *cis*-ethyl 2,3-dihydro-1-(ethoxycarbonyl)-1*H*-benzo[*b*]cyclopenta[*d*]thiophene-2-acetate, respectively. With the full physical and spectroscopic characterization of the adducts by ^{1}H NMR and ^{1}H–^{1}H COSY, experimental data allowed proton assignments as depicted in the Table II.

The HETCOR experiment allowed the assignment of the carbon of cyclopentane ring (Table IV). The doublet for a proton at the C-1 position of the *cis* isomer **9b** (δ 3.87) was shifted downfield in the *trans* isomer **9a** and was hidden under the methylene protons of the ester groups (δ 4.03–4.23). Irradiation of the proton, having a chemical shift of δ 3.35–3.61 at the 2-position in **9a**, enhanced the peak at δ 4.20 in the ester groups region and affected the multiplet signals between δ 2.64 and δ 3.24 each of which collapsed into a doublet. Furthermore, saponification of a mixture **9** with ethanolic KOH gave a diacid **11** (50%) as the only product which was assigned *trans* geometry (J = 5.1 Hz) (Table II) based on the analogy with the results obtained by Cope and co-workers[3] for the rearrangement of the naphthalene analogue and its structure elucidation. The separation of diastereomers was achieved and the diesters were assigned unambiguously the geometry *trans* and *cis* based on the coupling constant (J = 7.8 Hz) for the vicinal *trans* protons on carbons C-1 and C-2 and their comparison with the diacid **11** (Table II).

When the normal Cope product **10** was heated for 8 h at 235–45 °C, a mixture of cyclized products (33%) *trans*-**9a** and *cis*-**9b** was obtained.

Attempted Synthesis of Diethyl 2-Allyl-3-benzo[*b*]thiophenemalonate (10). Synthesis of Diethyl 2-(1-Propenyl)-3-benzo[*b*]thiophenemalonate (12). At this point the synthesis of **10** was attempted. The first halogen–metal exchange of 2,3-dibromobenzo[*b*]thiophene (**13**)[9] with 1 equiv of butyllithium at −10 to −15 °C selectively gave 3-bromo-2-benzo[*b*]thienyllithium[10] followed by allylation to give 2-allyl-3-bromobenzo[*b*]thiophene (**14**) in

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