Highly Diastereoselective 1,4-Addition of an Organocuprate to Methyl α-D-Gluco-, α-D-Manno-, or α-D-Galactopyranosides Tethering an α,β-Unsaturated Ester. Novel Asymmetric Access to β-C-Substituted Butanoic Acids

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The 1,4-addition of magnesium divinylcuprate prepared from vinylmagnesium bromide and cuprous bromide to some 4-*O*-crotonyl derivatives of methyl α-D-glucopyranoside proceeds with a high level of diastereochemical induction, providing the adduct in good-to-excellent yields. Other organocuprates also serve as effective carbon nucleophiles for the 1,4-addition. Removal of the carbohydrate moiety from each adduct afforded a variety of β-C-substituted butanoic esters in remarkable enantiomeric excess. The 1,4-addition of the same cuprate to some methyl α-D-manno- or α-D-galactopyranosidic substrates in which a crotonyl group was incorporated, each at 3-OH, was also investigated. The reverse π-facial attack of the cuprate was observed when some D-manno-type substrates were subjected to 1,4-addition conditions similar to those used for the D-gluco-type substrates. Furthermore, some D-galacto-type substrates provided 1,4-adducts with higher diastereoselectivities.

Introduction

The introduction of effective stereocontrolling factors in the molecule is one of the prominent subjects in stereoselective organic synthesis. In this context, the development of novel chiral auxiliaries prepared from readily available natural products is an ongoing subject in the field of asymmetric synthesis; the effort is similar to the continuous effort devoted to the search for asymmetric catalysts. Although many existing chiral auxiliaries can achieve a useful level of diastereoselection, making possible the preparation of chiral compounds with high optical purity,[1] it is still desirable to find effective chiral auxiliaries for achieving practical asymmetric carbon−carbon bond-forming reactions. It has been widely recognized that a number of carbohydrate-based templates, which in many cases exist in acyclic, pentofuranose, or hexopyranose forms, can serve as effective auxiliaries as a consequence of forming a stereochemically biased spatial environment. In one of the earliest studies on the use of carbohydrate-derived chiral auxiliaries, Vasella reported in 1977 the stereoselectivity and reactivity in the 1,3-dipolar cycloaddition of *N*-(alkoxyalkyl)nitrones derived from D-ribose.[2] Heathcock et al. reported in 1981 the use of enolates attached to carbohydrate templates for stereoselective carbon−carbon bond-forming reactions.[3] Another early example of the carbohydrate-based auxiliary concept was the introduction of a carbohydrate titanium complex prepared from diacetoneglucose and cyclopentadienyltitanium trichloride, originated by Duthaler et al.[4] For asymmetric synthesis of α-amino acids and β-amino acids, Kunz et al. investigated the use of glycosylamines as chiral auxiliaries for Strecker- and Mannich-type reactions.[5] For asymmetric cycloadditions such as cyclopropanations,[6] Diels−Alder reactions,[7] and 1,3-dipolar additions,[8] the use of carbohydrates as chiral auxiliaries has been explored during the past two decades. A number of carbohydrate-derived templates have been used as chiral auxiliaries for a variety of stereoselective organic

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reactions, such as polar, radical-mediated, and pericyclic carbon−carbon bond-forming reactions.[9] In the field of current organic synthesis, one of the significant developments is the use of stereoselective 1,4-additions[10] in the preparation of optically active chiral compounds, which are achieved by using a variety of chiral auxiliaries. In the early 1980s, Oppolzer et al. reported the 1,4-addition of an organocopper reagent to chiral enoates prepared from (−)-8-phenylmenthol and later to chiral enoates prepared from their camphor-derived sultam.[11] Tomioka and Koga demonstrated the 1,4-addition of organocopper reagents to an unsaturated amide attaching a chiral auxiliary prepared from L-glutamic acid.[12] In the early 1990s, Evans et al. reported the effectiveness of their chiral acyloxazolidinone-derived enolates as Michael donors. The donors reacted with representative electrophilic olefins.[13] Kunz et al. reported the 1,4-addition of organoaluminum reagents to Evans oxazolidinone-type auxiliary-bonded unsaturated carboxylates.[14] The Lewis acid-promoted 1,4-addition of allyltrimethylsilane to analogous unsaturated *N*-acylamides was also investigated.[15] Enders et al. demonstrated the utility of their chiral auxiliaries SAMP/RAMP for asymmetric 1,4-addition reactions.[16] The development of highly stereoselective 1,4-additions using chiral auxiliaries is still being extensively explored.[17] Asymmetric 1,4-additions based on the carbohydrate-derived auxiliaries have also been investigated in this decade.[18] In this paper, we describe the results of the diastereoselective 1,4-addition of a variety of organocuprates to 3-*O*-, 4-*O*-, or 6-*O*-crotonyl derivatives of three methyl α-D-hexopyranosides.[19−22]

Results and Discussion

Diastereoselective 1,4-Addition of a Vinylcuprate to α,β-Unsaturated Esters Incorporated into Methyl α-D-Glucopyranoside. To explore feasibility and diastereoselectivity in the 1,4-addition of a vinyl group to hexopyranosidic templates, we designed a variety of 4-*O*-crotonyl derivatives of methyl α-D-glucopyranoside as the substrates.[23] First, we prepared three 6-iodo-4-*O*-crotonyl esters **9**−**11** from known methyl 2,3-di-*O*-protected α-D-glucopyranosides **1**,[24] **2**,[25] and **3**,[26] as shown in Scheme 1. Thus, preferential tosylation of 6-OH in **1**−**3** provided the respective primary tosylates **4**−**6**. The introduction of a crotonyl ester at C-4 was carried out for **4** or **5** by acylation with crotonic anhydride. The resulting 4-*O*-

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(22) For our report on the stereoselective Diels−Alder reaction achieved on some hexopyranosidic templates, see: Nagatsuka, T.; Yamaguchi, S.; Totani, K.; Takao, K.; Tadano, K. *Synlett* **2001**, 481−484.

(23) We also explored the reactivity and stereoselectivity in the 1,4-addition of two 3-*O*-crotonyl derivatives: methyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-crotonyl-α-D-glucopyranoside and methyl 2,4,6-tri-*O*-benzyl-3-*O*-crotonyl-α-D-glucopyranoside. Under reaction conditions similar to those used for the 4-*O*-crotonyl derivatives, the former 3-*O*-crotonyl derivative gave the 1,4-vinyl adduct as a 62:38 diastereomeric mixture (^{1}H NMR analysis) in 75% yield. The latter gave the 1,4-adduct as an approximately 1:1 diastereomeric mixture (88%). In both cases, a useful level of stereoselectivity could not be obtained. Therefore, we focused our interest on the substrates in which the reaction site was installed on 4-OH or 6-OH. To date, we have not conducted 1,4-additions using any 2-*O*-crotonyl derivatives.

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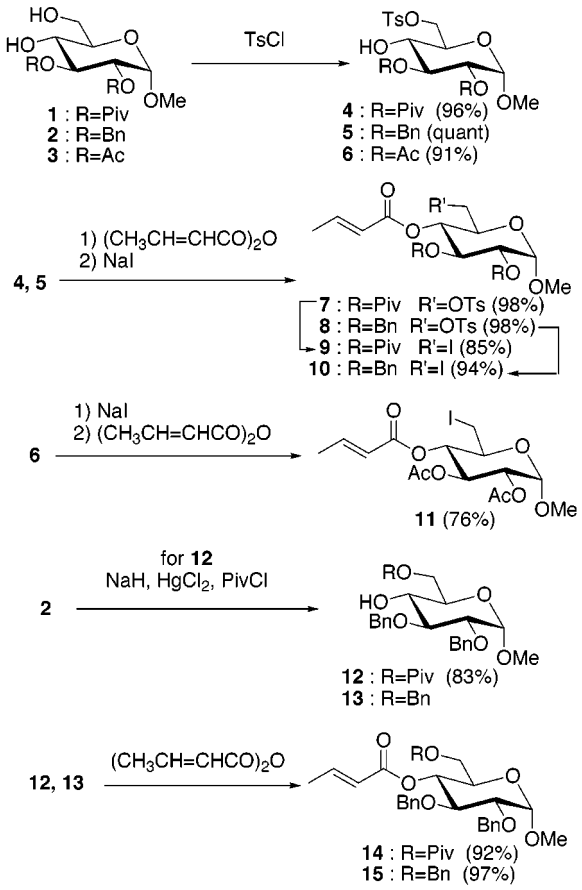
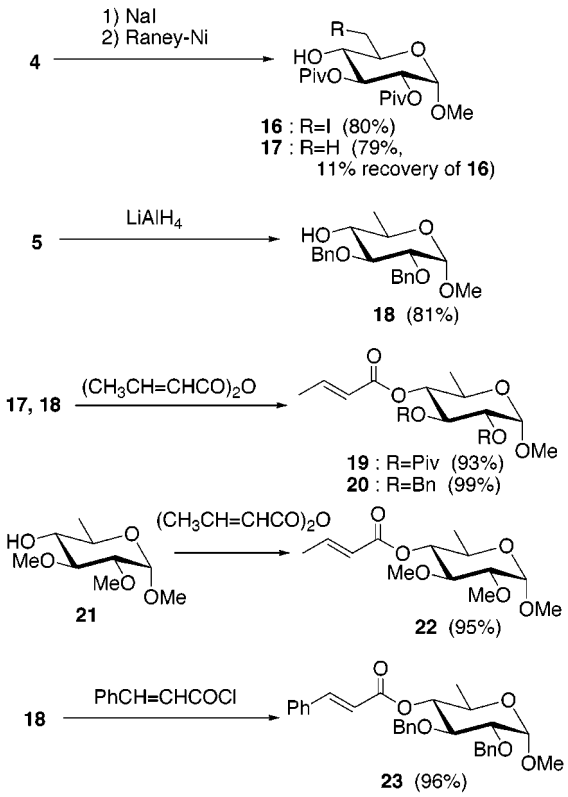
Scheme 1



Scheme 2



crotonyl derivatives **7** and **8** were treated with sodium iodide for conversion into the respective iodides **9** and **10**. On the other hand, replacement of the tosyloxy group in **6** by an iodo group followed by acylation provided **11**. We also prepared two 6-*O*-protected 4-*O*-crotonyl derivatives **14** and **15.** Regioselective pivaloylation of **2** according to a reported procedure[27] provided 6-*O*-pivaloyl derivative **12**, which was acylated to afford the 4-*O*-crotonyl derivative **14**. Acylation of known 2,3,6-tri-*O*-benzyl derivative **13**[28] gave the 4-*O*-crotonyl derivative **15**. Moreover, we prepared 6-deoxy derivatives **19**, **20**, and **22** (Scheme 2). Replacement of the tosyloxy group in **4** by an iodo atom, followed by hydrogenolysis of the resulting iodide **16**, gave **17**, which was acylated to **19**. Reductive removal of the sulfonyloxy group in the 6-*O*-tosyl derivative **5** gave **18**, which was acylated, affording 4-*O*-crotonyl derivative **20**. Known 6-deoxy-2,3-di-*O*-methyl derivative **21**[29] was acylated to give 4-*O*-crotonyl ester **22**. We also prepared a 4-*O*-cinnamoyl ester **23** as another substrate for 1,4-addition by acylation of **18** with cinnamoyl chloride.

We investigated the 1,4-addition of a vinylcuprate to **9**−**11**, **14**, **15**, **19**, **20**, and **22.** The results are summarized in Table 1. All reactions were conducted at −78 °C in a mixed solution of THF and dimethyl sulfide (2:1, v/v). In many cases, the 1,4-addition took place smoothly at that temperature, providing each 1,4-adduct **9a**−**22a**[30] as a diastereomeric mixture in good-to-high yields. In some cases, the diastereomeric ratio of the mixture could be determined on the basis of ^{1}H NMR analysis of each reaction mixture after chromatographic purification on silica gel. The 6-iodo derivative **9** gave the 1,4-adduct **9aRe** with high diastereoselectivity (entry 1). Recrystallization of the crude adduct **9aRe** gave crystals suitable for single-crystal analysis.[31] Consequently, the *R*-configuration for the newly introduced stereogenic carbon in **9aRe** was assigned unambiguously. To evaluate the diastereoselectivity accurately, we performed a chiral HPLC analysis to determine the enantiomeric ratio of 3-methyl-4-pentenoic acid benzyl esters (***R*)-a** and (***S*)-a**, which were prepared from a **9aRe/Si** mixture by saponification followed by benzyl ester formation. The *R*-configuration in the predominant diastereomer **9aRe** was further supported by the fact that the levorotatory property of enantioenriched 3-methyl-4-pentenoic acid prepared from **9aRe/Si** was in accord with that reported for the known (*R*)-(−) enantiopure sample.[32] It was established that substrate **9** afforded **9aRe** with a

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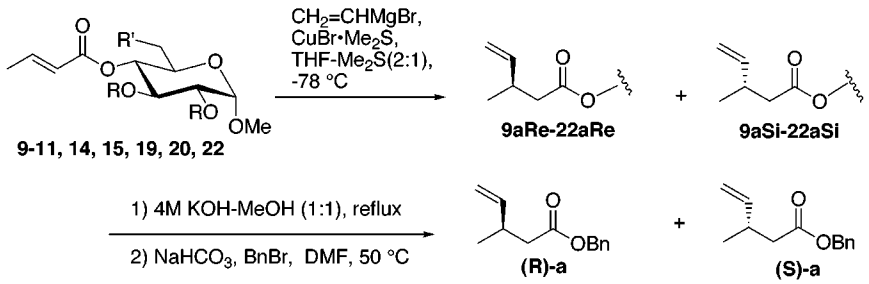
(31) X-ray crystallographic data on **9aRe** are described in ref 20 and have been deposited at the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U.K.

(32) Enantioenriched (*R*)-3-methyl-4-pentenoic acid prepared from the mixture of **9aRe/Si**: $[\alpha]^{26}_D$ −17.2 (*c* 0.58, $CHCl_3$). Enantiopure (*R*)-3-methylpentenoic acid: $[\alpha]^{24}_D$ −17.42 (*c* 2.06, $CHCl_3$). Uematsu, T.; Umemura, T.; Mori, K. *Agric. Biol. Chem.* **1983**, *47*, 597−601.

Table 1. 1,4-Additions of a Vinylcuprate to 9−11, 14, 15, 19, 20, and 22

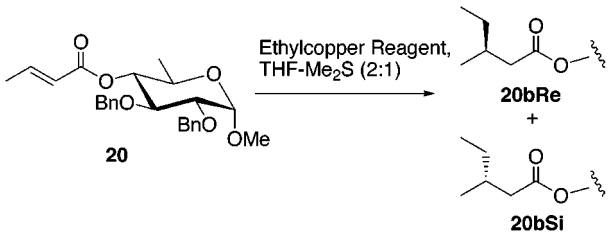


entry	substrate	R	R^1	CH_2=CHMgBr (equiv)	CuBr•Me_2S (equiv)	major adduct	yield (%)	d.r. of adducts[d]	e.r., (*R*)-a:(*S*)-a[f]
1	**9**	Piv	I	10.0	5.0	**9aRe**[a]	56 (84)[c]	*e*	94:6
2	**10**	Bn	I	10.0	5.0	**10aRe**	75	*e*	87:13
3	**11**	Ac	I	10.0	5.0	**11a**	51	55:45	*g*
4	**14**	Bn	OPiv	10.0	5.0	**14aRe**	81	82:18	79:21
5	**15**	Bn	OBn	10.0	5.0	**15aRe**	84	86:14	83:17
6	**19**	Piv	H	10.0	5.0	**19aRe**	61 (95)[c]	*e*	97:3
7	**19**	Piv	H	5.0	0	**19**[b]	79		
8	**20**	Bn	H	10.0	5.0	**20aRe**	90	*e*	87:13
9	**20**	Bn	H	4.0	0.1	**20aRe**	72 (89)[c]	*e*	83:17
10	**20**	Bn	H	5.0	0	**20**[b]	84		
11	**22**	Me	H	10.0	5.0	**22a**	72 (86)[c]	56:44	*g*

[a] Determined by single-crystal X-ray analysis. [b] Complete recovery of the substrate. [c] Yield based on the recovered starting material. [d] Determined by ^{1}H NMR. [e] Could not be determined by ^{1}H NMR analysis. [f] Determined by HPLC (DAICEL Chiralcel OD + OD-H, *i*-PrOH/hexane = 1:400); $t_{(R)-\mathbf{a}}$ = 27.5 min and $t_{(S)-\mathbf{a}}$ = 28.5 min. [g] Not determined.

remarkably high diastereomeric ratio of 94:6. In the case of substrate **10**, the diastereoselectivity of the 1,4-addition decreased to an enantiomeric ratio of 87:13 with a preference for the formation of **10aRe** (entry 2).[33] No stereoselection was observed in the case of 3-*O*-acetyl derivative **11** (entry 3). The effect of the C-6 substituent on the diastereoselectivity of the 1,4-addition was examined using substrates **14** and **15**. In the cases of bulkier 6-*O*-pivaloyl **14** and 6-*O*-benzyl derivative **15**, adducts **14aRe** and **15Re**, both formed by the re-face attack of the cuprate, were predominantly obtained, although their diastereoselectivities were reduced (entries 4 and 5). The highest diastereoselectivity was observed in the case of 6-deoxy derivative **19**, which produced **19aRe** almost as a single product.[34] The enantiomeric excess of **(*R*)-a** was determined to be 94%, using HPLC analysis (entry 6). As indicated in entries 7 and 10, the 1,4-addition did not occur in the absence of the copper(I) salt. Moreover, the amount of cuprous salt could be reduced to 10 mol % (entry 8 versus 9).[35] On the other hand, the amount of the Grignard reagent was critical for maintaining the effective progress of the reaction. The use of 1.0−2.0 mol equiv of the Grignard reagent resulted in a dramatic reduction in the yield of the adduct. It is apparent that the combination of a larger 3-*O*-substituent and a smaller 6-*O*-substituent results in higher diastereoselectivity. Thus, it is possible that the proximal steric environment around the reaction site, formed by both the substituents at C-3 and C-6, predominantly affects the approaching direction of the cuprate to the crotonyl ester. The steric bulkiness of the 3-*O*-substituent seems to be the more important stereocontrolling factor. This is supported by the result of the 1,4-addition to 3-*O*-methyl derivative **22**, resulting in the formation of **22aRe/Si** with a complete lack of diastereoselectivity (entry 11).

Table 2. 1,4-Additions of Three Organocopper Reagents to 20



entry	reagent	temp (°C)	major adduct	yield (%)	d.r.[b]
1	$Et_2CuMgBr$	−78 to −18	**20bRe**	88	84:16
2	$EtCuBF_3$	−78 to 0	**20bRe**	72 (81)[a]	73:27
3	Et_2CuLi	−78	**20bSi**	76 (84)[a]	66:34

[a] Yield based on the recovered starting material. [b] Determined by ^{1}H NMR.

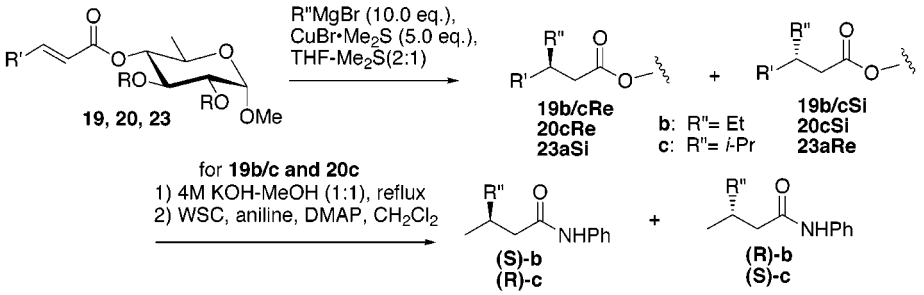
Next, we investigated the inevitability of the use of cuprates prepared from the Grignard reagents to realize the observed diastereoselectivity. Three types of ethylcopper reagents were prepared for the 1,4-addition to **20**. The results are summarized in Table 2. In the case of magnesium diethylcuprate prepared from ethylmagnesium bromide, the 1,4-adduct **20bRe**[36] was obtained with a similar diastereomeric ratio to that observed in the case of the 1,4-addition to **20**, using magnesium divinylcuprate. An ethylcopper boron trifluoride complex, prepared by mixing ethyllithium (1.1 mol equiv) and cuprous bromide−dimethyl sulfide (1.3 mol equiv), followed by the addition of boron trifluoride diethyl ether complex (1.3

(33) In our preliminary report (ref 20), we inadvertently described the diastereomeric ratios of the 1,4-adducts **9aRe/Si**, **10aRe/Si**, **19aRe/Si**, and **20aRe/Si** as >99:1. Later, we established a precise HPLC analysis procedure for evaluating the stereoisomeric ratios more accurately after converting the diastereomeric mixture of the 1,4-adducts into the corresponding *β*-chiral butanoic acid ester or anilide.

(34) The *R*-configuration for the introduced stereogenic carbon in **19aRe** was confirmed by coincidence with an authentic specimen, which was prepared from the stereochemically defined **9aRe** by deiodination.

(35) Although we did not examine all the substrates, it seems that the amount of cuprous salt does not significantly influence the diastereoselectivity of the 1,4-addition. However, the use of a catalytic amount of cuprous salt in general caused a decrease in the yield.

Table 3. 1,4-Additions of Other Organocuprates to 19, 20, and 23



entry	substrate	R	R′	R″	temp (°C)	major adduct	yield (%)	d.r. of adduct[b]	e.r., **(S)-b:(R)-b** or **(R)-c:(S)-c**
1	**19**	Piv	Me	Et	−78 to −18	**19bRe**	71 (80)[a]	*c*	98:2[d]
2	**19**	Piv	Me	*i*-Pr	−78 to −18	**19cRe**	77 (86)[a]	*c*	96:4[e]
3	**20**	Bn	Me	*i*-Pr	−78	**20cRe**	51 (94)[a]	88:12	88:12[e]
4	**23**	Bn	Ph	vinyl	−78	**23aSi**	60 (90)[a]	89:11	*f*

[a] Yield based on the recovered starting material. [b] Determined by ^{1}H NMR. [c] Could not be determined by ^{1}H NMR analysis. [d] Determined by HPLC (DAICEL Chiralcel OD-H, EtOH/hexane = 1:30); t_R = 24.5 min and t_S = 26.7 min. [e] Determined by HPLC (DAICEL Chiralcel OD, *i*-PrOH/hexane = 1:10); t_R = 23.3 min and t_S = 29.0 min. [f] Not determined.

mol equiv), gave **20bRe** as the major product, but with decreased diastereoselectivity (entry 2). Interestingly, the reverse π-facial selection was observed in the case of lithium diethylcuprate, which provided **20bSi** in a remarkably reduced diastereomeric ratio (entry 3). Although we have no reasonable explanation for this stereochemical reversal, we concluded that significant stereoselectivity could be achieved when an organocuprate prepared from the Grignard reagent was used.

To examine the generality of the diastereoselective 1,4-addition achieved using magnesium divinylcuprate, we conducted the 1,4-additions using other organocuprates. As shown in Table 3, the 1,4-additions of two magnesium dialkylcuprates (R″ = ethyl or isopropyl) to **19** provided the 1,4-adduct **19bRe** or **19cRe**, respectively, with high diastereoselectivity (entries 1 and 2). The diastereoselectivity in the attack of the isopropylcuprate to **20** was slightly diminished (entry 3). The diastereomeric ratios of **19bRe/Si**, **19cRe/Si**, and **20cRe/Si** were confirmed by HPLC analysis of the enantiomeric anilide pairs **(*S*)-b**/**(*R*)-b** or **(*R*)-c**/**(*S*)-c**, prepared from each diastereomeric mixture by hydrolysis and followed by the anilide formation of the resulting enantioenriched (*S*)-3-methylpentanoic acid[37] or (*R*)-3,4-dimethylpentanoic acid.[38] The 4-*O*-cinnamoyl derivative **23** provided the 1,4-vinyl adduct **23aSi**[39] with a diastereoselectivity of 89:11 (^{1}H NMR analysis) (entry 4).

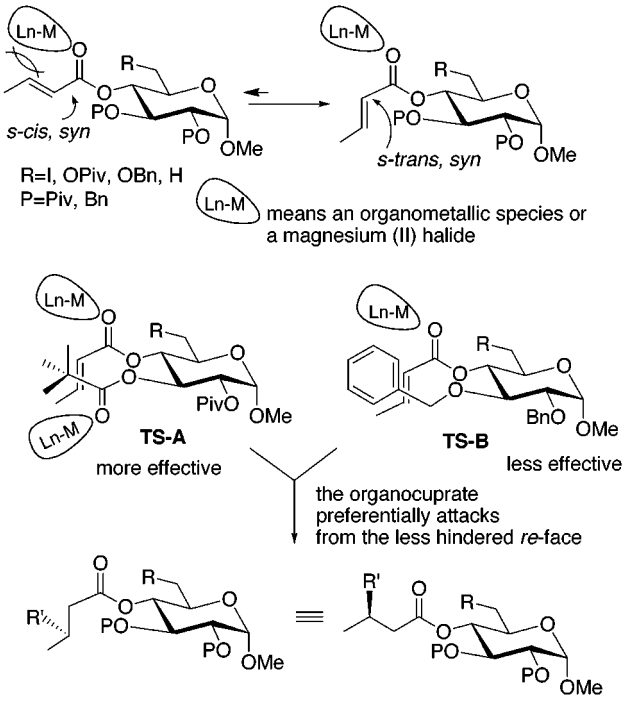


Figure 1. Plausible transition state (TS) models for π-facial selectivity in the attack of an organocuprate to the 4-*O*-crotonyl derivatives prepared from methyl α-D-glucopyranoside.

A plausible mechanistic rationale for the stereochemical outcome observed using the aforementioned 4-*O*-α,*β*-unsaturated esters is speculated (Figure 1). It is most likely that the used magnesium organocuprate or the formed magnesium halide, each of which exists in excess in the reaction solution, coordinates with the crotonyl carbonyl and other ester functionalities. This causes a severely disfavorable interaction between the metal-coordinating carbonyl and the carbon−carbon double bond existing in the s-cis, syn conformation. Conse-

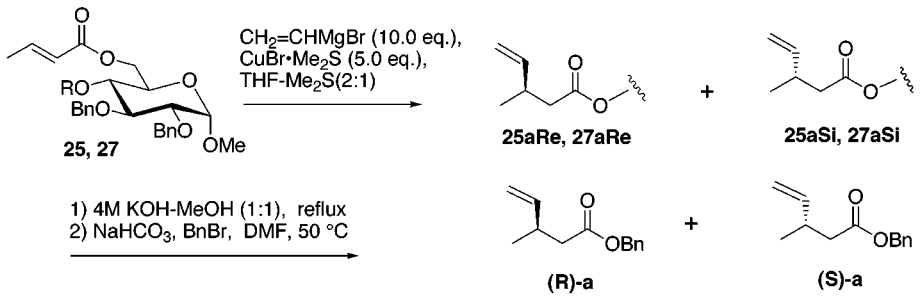
(36) The structure of **20bRe** was unequivocally determined by chemical correlation with an authentic specimen. Namely, the stereochemically defined adduct **9aRe** (d.r. = 94:6) was hydrogenated (Raney Ni), giving methyl 6-deoxy-4-[(*S*)-3-methylpentanoyl]-2,3-di-*O*-pivaloyl-α-D-glucopyranoside (**i**). On the other hand, simultaneous hydrogenation and hydrogenolysis of the adduct **10aRe** (d.r. = 87:13) provided methyl 6-deoxy-4-[(*S*)-3-methylpentanoyl]-α-D-glucopyranoside (**ii**), from which compound **i** was obtained by per-*O*-pivaloylation. In addition, hydrogenolysis of **20bRe** in the presence of $Pd(OH)_2$ on charcoal gave **ii**. This experimental correlation led to the conclusion that the newly introduced stereogenic carbon in **20bRe** is *S*.

(37) For enantiopure (*S*)-(+)-3-methylpentanoic acid, see: Mori, K.; Kato, M.; Kuwahara, S. *Liebigs Ann. Chem.* **1985**, 861−865. For enantiopure (*R*)-(−)-3-methylpentanoic acid, see: Mori, K.; Kuwahara, S.; Ueda, H. *Tetrahedron* **1983**, *39*, 2439−2444.

(38) Enantioenriched (*R*)-3,4-dimethylpentanoic acid prepared from **20cRe/Si** (d.r. = 88:12, ^{1}H NMR analysis): $[\alpha]^{14}_D$ +12.0 (*c* 0.54, $CHCl_3$). Enantiopure (*R*)-(+)-3,4-dimethylpentanoic acid in the literature, $[\alpha]^{20.5}_D$ +13.7 (*c* 1.54, $CHCl_3$): Mori, K.; Ueda, H. *Tetrahedron* **1982**, *38*, 1227−1233.

(39) The *R*-configuration for the newly introduced stereogenic carbon in **23aSi** was determined as follows. After hydrolytic removal of the carbohydrate template from the mixture of **23aSi/Re**, enantioenriched (*R*)-3-phenyl-4-pentenoic acid thus obtained was hydrogenated to (*S*)-3-phenylpentanoic acid with $[\alpha]^{27.5}_D$ +39.0 (*c* 0.58, benzene). For (*R*)-3-phenylpentanoic acid, $[\alpha]^{25}_D$ −47.3 (*c* 5.3, benzene), see ref 18c.

Table 4. 1,4-Additions of a Vinylcuprate to 25 and 27

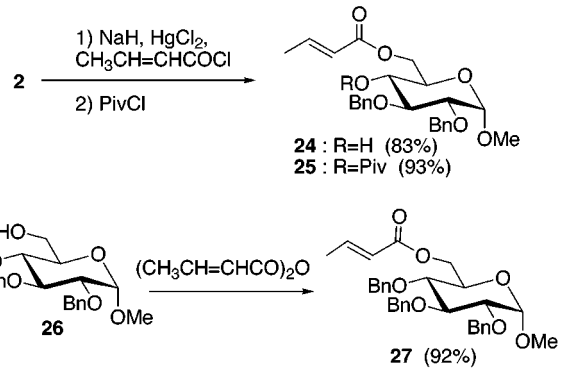


entry	substrate	R	temp (°C)	major adduct	yield (%)	d.r. of adducts[b]	e.r.,[c] **(S)-a:(R)-a**
1	**25**	Piv	−78	**25aSi**	58 (73)[a]	86:14	85:15
2	**27**	Bn	−78	**27aRe**	62 (73)[a]	60:40	40:60

[a] Yield based on the recovered starting material. [b] Determined by ^{1}H NMR. [c] Determined by HPLC.

quently, it is probable that the conformation of the α,β-unsaturated ester changes favorably to the s-trans, syn conformation.[40,41] When the α,β-unsaturated ester is stabilized in the s-trans, syn conformation, a C-3 substituent such as the pivaloyloxy group effectively shields the front side, that is, the si-face on the β-carbon of the unsaturated ester, as depicted in **TS-A** or **TS-B.** Consequently, the cuprate attacks from the less-hindered re-face (from the rear), providing the adduct possessing the *R*-configuration (R′ = vinyl). Regarding the shielding effect of the C-3 substituent, the pivaloyloxy group is superior to the benzyloxy group, as verified in the 1,4-additions to **9**, **10**, **19**, and **20** (entry 1 versus 2 or 6 versus 8, Table 1).[42] In the cases of an acetoxy and a methoxy group at C-3, the shielding effect is rather unpromising (entries 3 and 11, Table 1). The steric effect of the C-6 substituent seems not to be critical for the formation of the stereochemically biased chiral environment compared to the stereochemical outcome affected by the C-3 substituent. Although the influence of pivaloyloxy or benzyloxy at C-6 on diastereoselectivity is less effective, as revealed in entries 4 or 5 (Table 1), both 6-deoxy substrates **19** and **20** revealed a comparably high diastereoselectivity observed in the cases of 6-iodo counterparts **9** and **10** (entry 1 versus 6 and 2 versus 8, Table 1).

Scheme 3



To obtain further insight into the chiral environment formed by the D-glucopyranosidic template, we executed the 1,4-addition of 6-*O*-crotonoyl derivatives **25** and **27**. The preparation of these substrates is summarized in Scheme 3. Regioselective acylation of **2** gave 6-*O*-crotonyl derivative **24**, which was acylated to give 4-*O*-acylated substrate **25**. On the other hand, crotonoylation of known methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**26**)[43] afforded the 4-*O*-benzylated substrate **27**. As summarized in Table 4, a comparably high diastereoselectivity (diastereomeric ratio (d.r.) = 86:14) was observed in the case of the 1,4-addition of the vinylcuprate to **25** with the preferential formation of **25aSi**. Regarding the introduced stereogenic carbon, the major diastereomer **25aSi** possesses the reverse configuration of that in the major adducts obtained using most 4-*O*-crotonyl esters. It is apparent that the pivaloyloxy group at C-4 is important for realizing this diastereoselective outcome. The 4-*O*-benzyl derivative **27** provided the 1,4-adduct with decreased diastereoselectivity (at most, 1.5 to 1). The ^{1}H NMR analysis of **25** did not provide any decisive information regarding the conformation of **25** in the absence or presence of the vinylcuprate.

Diastereoselective 1,4-Addition Achieved Using the Substrates Prepared from Methyl α-D-Mannopyranoside. Our next concern was to examine the reactivity and the stereocontrolling ability of D-mannopyranosidic templates for the 1,4-addition of a magnesium organocuprate. The preparation of the substrates

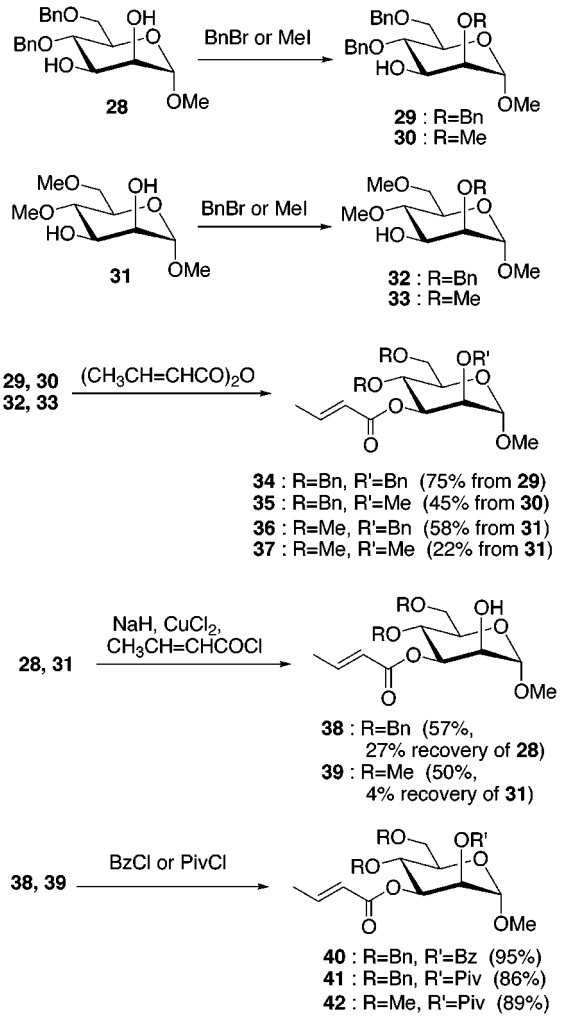
(40) We could not identify the exact coordinating metallic species. We consider that the coordinating metal is magnesium in the organocuprate or the formed magnesium halide. However, the contribution of copper as the coordinating metal cannot be ruled out. We tried to confirm the conformational change of the unsaturated ester by the ^{1}H NMR technique before and after the addition of the cuprate. Unfortunately, we could not obtain any useful information from the ^{1}H NMR spectra in the presence of magnesium divinylcuprate or magnesium(II) bromide, which showed a set of broad signals below 0 °C.

(41) It is reported that the s-trans, syn conformation of the α,β-unsaturated esters attached to chiral auxiliaries is preferable to the s-cis, syn conformation, especially in the presence of a coordinating metallic species or in the presence of a Lewis acid. For previous descriptions of the analogous conformational change of the reaction site, see: (a) Oppolzer, W.; Löher, H. *Helv. Chim. Acta* **1981**, *64*, 2808−2811. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876−889. (c) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14−23. (d) Mezrhab, B.; Dumas, F.; d'Angelo, J.; Riche, C. *J. Org. Chem.* **1994**, *59*, 500−503.

(42) It cannot be ruled out that the carbonyl group of the C-3 pivaloyloxy substituent in **9** or **19** participates in the transition state (**TS-A)** and thus explains the superior diastereoselectivity compared to that of the C-3 benzyloxy group (**TS-B**). We consider that the bulkiness of the pivaloyloxy group works as an effective shielding factor to govern the diastereoselection. We also observed a similar high diastereoselectivity in the 1,4-addition of an alkyl radical species to the substrate possessing a *tert*-butyldimethylsilyloxy group at C-3 (not shown). The silyl ether at C-3 works as a bulky substituent to control the approach of the radical species. In this particular case, the silyl ether cannot participate as a coordinating group with a metallic species. For this previous observation, see ref 21.

(43) Liptak, A.; Jodal, I.; Nanasi, P. *Carbohydr. Res.* **1975**, *44*, 1−11.

Scheme 4



we designed[44] is summarized in Scheme 4. Starting from known methyl 4,6-di-*O*-benzyl- (**28**),[45] 2,3,6-tri-*O*-benzyl- (**29**),[45] or 4,6-di-*O*-methyl-α-D-mannopyronoside (**31**),[46] seven 3-*O*-crotonyl derivatives, **34**−**37** and **40**−**42**, were prepared using standard procedures. 1,4-Addition of these substrates using magnesium divinylcuprate was conducted under reaction conditions similar to those used for the D-glucopyranosidic substrates. The results are summarized in Table 5. The ratio of the diastereomeric mixture obtained from each 1,4-addition was determined by ^{1}H NMR analysis. The stereoselectivity in the 1,4-addition was finally confirmed by chiral HPLC analysis of enantioenriched 3-methyl-4-pentenoic acid benzyl esters **(*R*)-a** or **(*S*)-a**. The substrates carrying an axial alkyloxy group (OBn or OMe), such as **34**−**37**, afforded 1,4-adducts **34aRe**−**37aRe** with the best diastereomeric ratio of 88:12 (entries 1−5). The amount of cuprous salt can be reduced to a catalytic amount without a significant loss of yield or diastereoselectivity (entry 3). On the other hand, the 1,4-addition using substrates **40**−**42**, possessing an axial acyloxy group (OBz or OPiv), proceeded with higher levels of diastereoselectivity (entries 6−13), regardless of the bulkiness of the substituent at C-4 (OMe or OBn). In the case of **40**, the major diastereomer **40aSi** was obtained in crystalline form. By a single-crystal X-ray analysis of **40aSi**,[47] the *S*-configuration was assigned unambiguously for the newly introduced stereogenic carbon. As indicated in entries 7, 11, and 12, the 1,4-addition proceeded efficiently in the presence of a catalytic amount of cuprous salt. The amount of the Grignard reagent can be reduced to 4 mol equiv without a loss of the diastereoselectivity (entry 12). A significant reduction in yield occurred in the case of 2 mol equiv of the Grignard reagent (entry 13), and the 1,4-addition did not proceed without the cuprous salt (entry 14). We also examined the 1,4-addition of other organocuprates to substrates **34** and **41**. The results are summarized in Table 6. The diastereoselectivity observed using 2-*O*-pivaloyl ester **41** was superior to that obtained using 2-*O*-benzyl ether **34**. Each introduced stereogenic carbon in the 1,4-adduct **34bRe** or **41bSi** was established through stereochemical correlation to an authentic specimen derived from the stereochemically defined **40aSi**.[48] Two alkyl cuprates attack preferentially from the re-face on the β-carbon for the 2-*O*-benzyl derivative **34** or from the si-face for the 2-*O*-pivaloyl derivative **41**.

A mechanistic account for the diastereoselectivity obtained from the 3-*O*-crotonyl esters of methyl α-D-mannopyranoside can be provided by assuming the similar transition state models used for the D-gluco-type substrates. As discussed in the case of the D-glucopyranosidic substrates, the crotonyl ester in **34**−**37** and **40**−**42** is most likely to exist in the s-trans, syn conformation to minimize the expected steric repulsion. In the cases of the D-manno-type substrates, the C-2 substituent significantly governs the π-facial selection in the cuprate attack regardless of the bulkiness of the C-4 substituent (Figure 2). In the cases of **34**−**37** (**TS-C**), the steric effect of the benzyloxy or methoxy group is modest. On the other hand, the C-2 acyloxy group effectively shields the re-face of the β-carbon on the double bond, resulting in the preferential attack of the cuprate from the si-face (**TS-D**).

Diastereoselective 1,4-Addition Achieved Using the Substrates Prepared from Methyl α-D-Galactopyranoside. Finally, we explored 1,4-addition using five 3-*O*-crotonyl esters of methyl α-D-galactopyranoside, substrates **44** and **49**−**52**. As shown in Scheme 5, the preparation of these substrates was started from known methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside **43**[49] (for **44**), known 4,6-di-*O*-benzyl **45**[50] (for **49** and **50**), or 4,6-

(44) We also conducted the 1,4-addition of magnesium divinylcuprate to methyl 3,4,6-tri-*O*-benzyl-2-*O*-crotonyl-α-D-mannopyranoside (−78 °C, 1 h), in which the reaction site was installed at an axial OH on C-2. As a result, the 1,4-adducts were obtained as a nearly 1:1 diastereomeric mixture in a yield of 49% (40% recovery of the substrate). In addition, methyl 2-*O*-crotonyl-4,6-di-*O*-methyl-3-*O*-pivaloyl-α-D-mannopyranoside gave the 1,4-vinyl adducts as a nearly 1:1 diastereomeric mixture (86%). Both 1,4-additions proceeded completely devoid of diastereoselectivity.

(45) Kong, F.; Schuerch, C. *Carbohydr. Res.* **1983**, *112*, 141−147.

(46) Khan, S. H.; Matta, K. L. *Carbohydr. Res.* **1993**, *243*, 29−42.

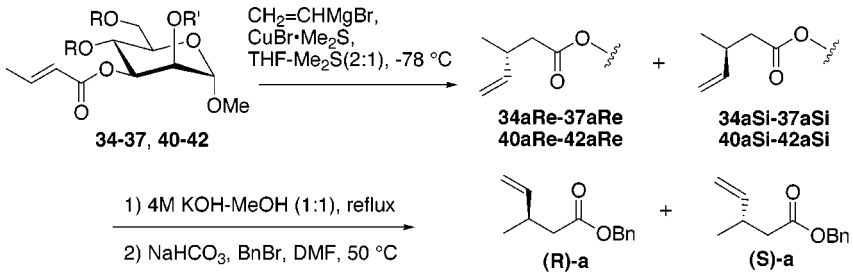
(47) X-ray crystallographic data for **40aSi** (colorless, platelike crystals were grown from a methanol solution): molecular formula = $C_{34}H_{38}O_8$, MW = 574.67, triclinic; a = 11.298(2), b = 15.254(2), and c = 9.830(1) Å; α = 99.77(1), β = 90.34(1), and γ = 109.41(1)°; and V = 1571.1 Å^3. A space group $P1$ (No. 1), Z = 2, D_c = 1.22 g/cm^3. Data collection was done on a Rigaku AFC7R diffractometer (50 kV, 200 mA) using Cu Kα radiation (μ = 7.04 cm^{-1}) with a rotating anode generator. In total, 5407 reflections were collected, of which 755 reflections with $I > 2.00\sigma(I)$ were variable parameters. The final R factor was 0.073 (R_w = 0.102). The final difference peaks were ρ_{max} = 0.50 and ρ_{min} = −0.40 e/Å^3.

(48) The stereochemical assignment for the isopropyl adducts **34cRe** and **41cSi** was also carried out by chemical transformation and hydrolytic removal of the carbohydrate template.

(49) Rashid, A.; Mackie, W. *Carbohydr. Res.* **1992**, *223*, 147−155.

(50) Schneider, J.; Lee, Y. C.; Flowers, H. M. *Carbohydr. Res.* **1974**, *36*, 159−166.

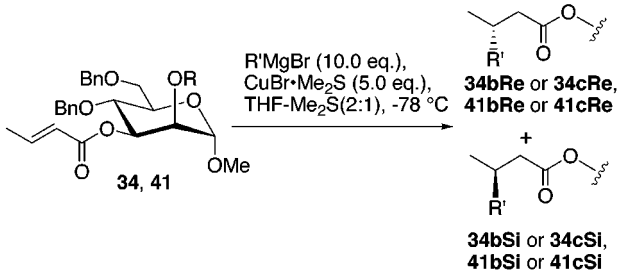
Table 5. 1,4-Additions of a Vinylcuprate to 34−37 and 40−42



entry	substrate	R	R′	CH_2=CHMgBr (equiv)	CuBr•Me_2S (equiv)	major adduct	yield (%)	d.r. of adducts[c]	e.r.,[e] **(S)-a:(R)-a**
1	**34**	Bn	Bn	10.0	5.0	**34aRe**	84	88:12	88:12
2	**35**	Bn	Me	10.0	5.0	**35aRe**	85	87:13	84:16
3	**35**	Bn	Me	5.0	0.1	**35aRe**	77	87:13	*d*
4	**36**	Me	Bn	10.0	5.0	**36aRe**	75	*d*	64:36
5	**37**	Me	Me	10.0	5.0	**37aRe**	74	80:20	83:17
6	**40**	Bn	Bz	10.0	5.0	**40aSi**[a]	84	91:9	9:91
7	**40**	Bn	Bz	5.0	0.1	**40aSi**	83	90:10	*d*
8	**41**	Bn	Piv	10.0	5.0	**41aSi**	78	89:11	9:91
10	**42**	Me	Piv	10.0	5.0	**42aSi**	92	91:9	9:91
11	**42**	Me	Piv	8.0	0.1	**42aSi**	91	91:9	*d*
12	**42**	Me	Piv	4.0	0.1	**42aSi**	91	91:9	*d*
13	**42**	Me	Piv	2.0	0.1	**42aSi**	18	91:9	*d*
14	**42**	Me	Piv	5.0	0	**42**[b]	77		

[a] Determined by single-crystal X-ray analysis. [b] Recovery of the substrate. [c] Determined by ^{1}H NMR analysis. [d] Not determined. [e] Determined by HPLC.

Table 6. 1,4-Additions of Other Organocuprates to 34 and 41



entry	substrate	R	R′	major adduct	yield (%)	d.r.[c]
1	**34**	Bn	Et	**34bRe**	51 (63)[b]	68:32
2	**34**	Bn	*i*-Pr	**34cRe**	74	81:19
3	**41**	Piv	Et	**41bSi**	83	90:10
4[a]	**41**	Piv	*i*-Pr	**41cSi**	83	73:27

[a] The reaction was carried out at −18 °C. [b] Yield based on the recovered starting material. [c] Determined by ^{1}H NMR analysis.

di-*O*-methyl derivative **47**[51] (for **51** and **52**). The results of the 1,4-addition using these substrates are summarized in Table 7. The 4-*O*-benzyl derivative **44** gave the 1,4-adduct with preferential formation of **44aSi**. The 4-*O*-acyl derivatives **49**−**52** provided the respective 1,4-adduct in good yield with the best diastereomeric ratio of 98:2. As shown in Table 8, magnesium diethyl or diisopropylcuprate provided the respective adduct **50bRe** or **50cRe** with excellent diastereoselectivity (>94% enantiomeric excess for the anilides **(*S*)-b** or **(*R*)-c**).[52]

The high-to-excellent diastereoselectivity obtained using the 3-*O*-crotonyl esters of D-galactopyranoside can also be explained by the same transition states argument

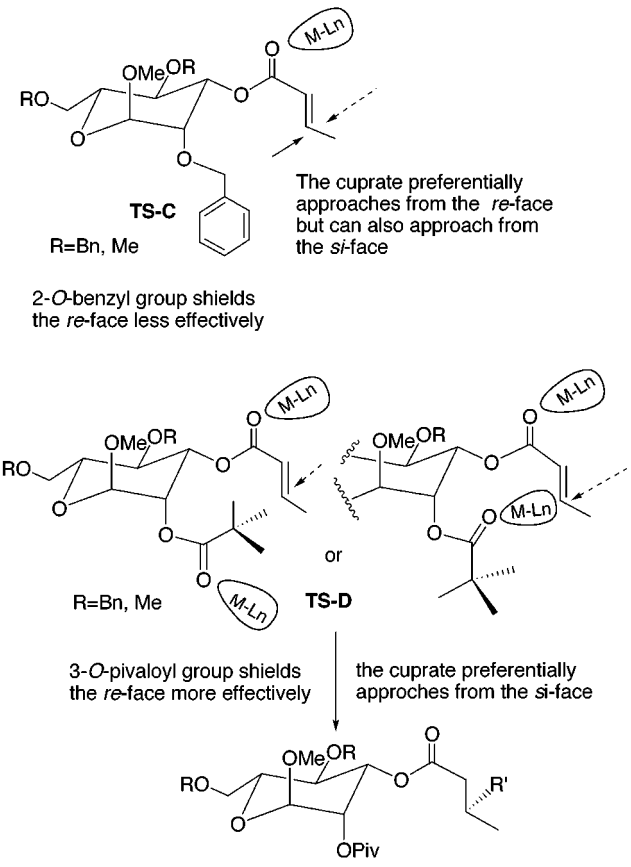


Figure 2. Plausible transition state models for π-facial selective attack of the organocuprates to the 3-*O*-crotonyl derivatives of D-mannopyranoside.

employed for the D-glucosidic and D-mannosidic substrates (Figure 3). The crotonyl ester favorably exists in an s-trans, syn conformation. As anticipated, the diastereoselectivity was not sufficiently high in the case of

(51) Rao, A. S.; Roy, N. *Carbohydr. Res.* **1977**, *59*, 393−401.

(52) The absolute configuration of the major adduct was established from the optical sign of the enantioenriched 3-methylpentanoic acid or 3,4-dimethylpentanoic acid, obtained by the removal of the carbohydrate template.

Scheme 5

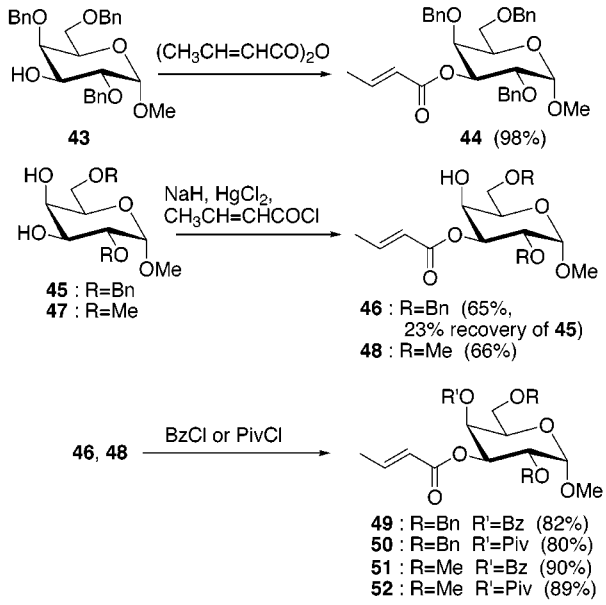
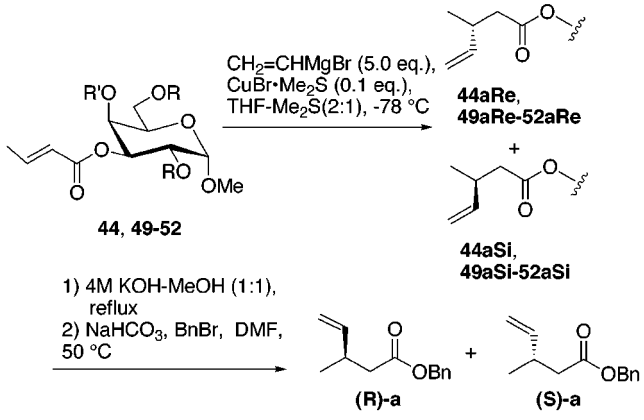


Table 7. 1,4-Additions of the Vinylcuprate to 44 and 49−52



entry	substrate	R	R′	major adduct	yield (%)	d.r. of adduct[a]	e.r., **(R)-a**:**(S)-a**[c]
1	**44**	Bn	Bn	**44aSi**	82	84:16	14:86
2	**49**	Bn	Bz	**49aRe**	82	*b*	97:3
3	**50**	Bn	Piv	**50aRe**	94	*b*	98:2
4	**51**	Me	Bz	**51aRe**	80	95:5	94:6
5	**52**	Me	Piv	**52aRe**	80	*b*	98:2

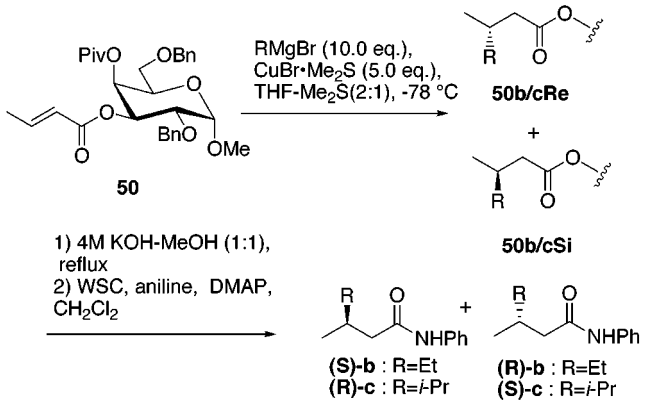
[a] Determined by ^{1}H NMR analysis. [b] Could not be determined. [c] Determined by HPLC.

the C-4 alkylated substrate **44**. In contrast, the effect of the C-4 acyloxy groups was remarkable, resulting in high diastereoselection. As indicated by **TS-E**, a preferential attack of the organocuprate from the less-hindered re-face on the β-carbon of the double bond occurred.

Conclusions

We have developed a novel and highly diastereoselective 1,4-addition using a variety of hexopyranosidic substrates as chiral templates. Consequently, a variety of β-alkylated butanoic acids are available in a high-to-excellent enantioenriched form. A number of *O*-crotonyl derivatives of D-gluco-, D-manno-, and D-galactopyranosides are approved as good stereocontrollers for realizing the practical asymmetric 1,4-additions. Furthermore, these substrates complementarily provide a variety of

Table 8. 1,4-Additions of Other Organocuprates to 50



entry	R	major adduct	yield (%)	e.r., **(S)-b**:**(R)-b** or **(R)-c**:**(S)-c**[b]
1	Et	**50bRe**	70 (84)[a]	98:2
2	*i*-Pr	**50cRe**	44 (98)[a]	97:3

[a] Yield based on the recovered starting material. [b] Determined by HPLC.

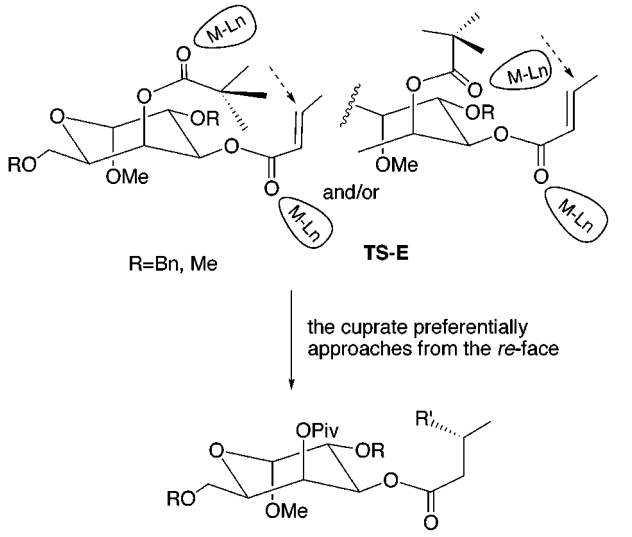


Figure 3. Plausible transition models for π-facial selective attack of the organocuprates to the 3-*O*-crotonyl derivatives of D-galactopyranoside.

β-carbon substituted butanoic acids in both enantiomeric forms. Although the precise mechanism of the transition state in the 1,4-addition is still unclear, it should be emphasized that the present results show one of the effective uses of carbohydrate scaffolds for achieving a highly stereoselective organic reaction. We are currently investigating the applicability of the present concept to other types of carbon−carbon bond-forming reactions.

Experimental Section

Melting points are uncorrected. Specific rotations were measured in a 10 mm cell. ^{1}H NMR spectra were recorded at 270 or 300 MHz in $CDCl_3$ solution with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ solution. Thin-layer chromatography (TLC) was performed with a glass plate coated with Kieselgel 60 GF254 (Merck). The crude reaction mixtures and extractive materials were purified by chromatography on silica gel 60 K070 (Katayama Chemicals). Combined organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed by concentra-

tion under reduced pressure using an evaporator with a water bath at 35−45 °C. Solvents were dried (drying reagent) and distilled prior to use: tetrahydrofuran (THF) (KANTO CHEMICALS; water, 0.005% max) and CH_2Cl_2 (CaH_2).

General Procedure for the 1,4-Additions. Methyl 6-Deoxy-6-iodo-4-*O*-[(*R*)-3-methyl-4-pentenoyl]-2,3-di-*O*-pivaloyl-α-D-glucopyranoside (9aRe) (Entry 1 in Table 1). The reaction was carried out under argon. To a cold (−78 °C) solution of CuBr·Me_2S (204 mg, 0.993 mmol) in THF−Me_2S (2:1) (3 mL) was added vinylmagnesium bromide (1.04 M solution in THF, 1.91 mL, 1.99 mmol). The solution was stirred at −78 °C for 1 h, and then a solution of **9** (107 mg, 0.200 mmol) in THF (1 mL) was added. The solution was stirred at −78 °C for 25 min and then quenched with saturated aq NH_4Cl (1 mL). After being stirred for 10 min, the solution was diluted with EtOAc (20 mL) and washed with saturated aq NH_4Cl (10 mL × 5). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:30) to give 66.7 mg (56%) of **9aRe** as colorless crystals (enantiomeric ratio (e.r.) of the corresponding benzyl ester = 94:6, HPLC analysis), and 35.6 mg (33%) of **9** was recovered. **9aRe**: mp 88−90 °C; TLC, R_f 0.61 (EtOAc/hexane, 1:5); IR (neat) 1740 cm^{-1}; ^1H NMR (300 MHz) δ 1.05 (d, J = 6.8 Hz, 3H), 1.11, 1.16 (2 s, 9 H × 2), 2.29 (d, J = 7.1 Hz, 2H), 2.61−2.70 (m, 1H), 3.10 (dd, J = 8.5, 11.0 Hz, 1H), 3.29 (dd, J = 2.3, 11.0 Hz, 1H), 3.46 (s, 3H), 3.77−3.83 (m, 1H), 4.80 (dd, J = 3.8, 9.9 Hz, 1H), 4.91 (t, J = 9.9 Hz, 1H), 4.96 (d, J = 3.8 Hz, 1H), 4.98−5.07 (m, 2H), 5.52 (t, J = 9.9 Hz, 1H), 5.74 (ddd, J = 7.1, 10.3, 17.3 Hz, 1H); ^{13}C NMR (75 MHz) δ 3.86, 20.02, 26.91 × 6, 27.01, 34.05, 38.69 × 2, 40.89, 55.86, 68.96, 71.06, 71.97, 96.59, 113.95, 142.08, 170.85, 177.03, 177.61. Anal. Calcd for $C_{23}H_{37}O_8I$: C, 48.60; H, 6.56. Found: C, 48.48; H, 6.81.

Methyl 2,3-Di-*O*-benzyl-6-deoxy-4-*O*-[(*R*)-3-methyl-4-pentenoyl]-α-D-glucopyranoside (20aRe). Use of a Catalytic Amount of CuBr·Me_2S (Entry 9 in Table 1). 47.1 mg (0.110 mmol) of **20** in THF (1 mL) was treated with CuBr·Me_2S (2.3 mg, 11.2 μmol) in THF−Me_2S (2:1) (4.5 mL) and vinylmagnesium bromide (0.95 M solution in THF, 0.46 mL, 0.44 mmol) at −78 °C for 50 min. Extractive workup and purification by column chromatography on silica gel (EtOAc/hexane, 1:16) gave 35.9 mg (72%) of the mixture of **20aRe/Si** (e.r. of the corresponding benzyl ester = 83:17, HPLC analysis), and 8.9 mg (19%) of **20** was recovered. **20aRe/Si** as a colorless oil: TLC, R_f 0.69 (EtOAc/hexane, 1:2); IR (neat) 1740 cm^{-1}; ^1H NMR for the major **20aRe** (300 MHz) δ 1.01 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 6.3 Hz, 3H), 2.13 (dd, J = 7.3, 15.4 Hz, 1H), 2.25 (dd, J = 7.0, 15.4 Hz, 1H), 2.56−2.68 (m, 1H), 3.38 (s, 3H), 3.57 (dd, J = 3.7, 9.5 Hz, 1H), 3.69−3.79 (m, 1H), 3.87 (t, J = 9.5 Hz, 1H), 4.53 (d, J = 3.7 Hz, 1H), 4.63, 4.64 (2 d, J = 11.9 Hz, 1H × 2), 4.77 (t, J = 9.5 Hz, 1H), 4.77 (d, J = 12.2 Hz, 1H), 4.86−5.02 (m, 3H), 5.73 (ddd, J = 6.7, 10.4, 17.3 Hz, 1H), 7.23−7.31 (m, 10H); ^{13}C NMR for the major **20aRe** (75 MHz) δ 17.45, 19.64, 33.87, 47.11, 55.25, 65.32, 73.40, 74.98, 75.14, 78.97, 79.90, 98.06, 113.44, 127.45, 127.63 × 2, 127.93, 128.13 × 2, 128.26 × 2, 128.44 × 2, 137.98, 138.65, 142.27, 171.34. Anal. Calcd for $C_{27}H_{34}O_6$: C, 71.34; H, 7.54. Found: C, 71.32; H, 7.55.

General Procedure for Removal of the Carbohydrate Template Followed by Benzyl Ester Formation. Formation of (*R*)-a/(*S*)-a from a Diastereomeric Mixture (87:13) of 20aRe/Si. To a solution of the mixture (47.4 mg, 0.104 mmol) in MeOH (1 mL) was added 4 M KOH solution (1 mL). This solution was refluxed for 16 h, diluted with H_2O (5 mL), and extracted with $CHCl_3$. The organic layer was dried and concentrated in vacuo to give 36.0 mg (97%) of **18**. The aqueous layer was acidified with 1 M HCl (to pH 2) and extracted with $CHCl_3$. The combined extracts were dried and concentrated in vacuo to give 3-methyl-4-pentenoic acid, which was benzylated without purification. The residue was dissolved in DMF (1 mL), and $NaHCO_3$ (18 mg, 0.22 mmol) and benzyl bromide (24.5 μL, 0.20 mmol) were added. After being stirred at 50 °C for 19 h, the solution was diluted with EtOAc (10 mL) and washed with H_2O (5 mL) and saturated aq $NaHCO_3$ (5 mL × 2). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:100) to give 20.0 mg (94%) of a mixture of **(*R*)-a** and **(*S*)-a** as a colorless oil: TLC, R_f 0.76 (EtOAc/hexane, 1:2); IR (neat) 3060−2880, 1740, 1560 cm^{-1}; ^1H NMR (300 MHz) δ 1.05 (d, J = 6.6 Hz, 3H), 2.32 (dd, J = 7.3, 14.8 Hz, 1H), 2.42 (dd, J = 7.3, 14.9 Hz, 1H), 2.66−2.73 (m, 1H), 4.93−5.04 (m, 2H), 5.11 (s, 2H), 5.77 (ddd, J = 7.0, 10.4, 17.2 Hz, 1H), 7.30−7.38 (m, 5H); ^{13}C NMR (75 Hz) δ 19.71, 34.43, 41.27, 66.14, 113.42, 128.18 × 2, 128.22, 128.50 × 2, 135.97, 142.34, 172.33; HRMS calcd for $C_{13}H_{16}O_2$ (M^+), 204.1150; found, 204.1155. The enantiomeric ratio of the mixture was determined by HPLC analysis (DAICEL Chiralcel OD + ODH, *i*-PrOH/hexane = 1:400).

General Procedure for Removal of the Carbohydrate Template Followed by Anilide Formation. Formation of (*R*)-c/(*S*)-c from a Diastereomeric Mixture (88:12) of 20cRe and 20cSi. To a solution of a mixture of **20cRe/Si** (48.3 mg, 0.103 mmol) in MeOH (1 mL) was added 4 M KOH solution (1 mL). This solution was refluxed for 23 h, diluted with H_2O (5 mL), and extracted with $CHCl_3$. The organic layer was dried and concentrated in vacuo to give 35.1 mg (95%) of **18**. The aqueous layer was acidified with 1 M HCl (to pH 2) and extracted with $CHCl_3$. The combined extracts were dried and concentrated in vacuo to give 3,4-dimethylpentanoic acid, which was subjected to the next step without purification. The residue was dissolved in CH_2Cl_2 (1 mL) and 1-ethyl-(3-dimethylaminopropyl)carbodiimide (58 mg, 0.30 mmol), and aniline (28 μL, 0.31 mmol) and DMAP (3.8 mg, 0.31 mmol) were added. After being stirred for 20 h, the solution was diluted with EtOAc (10 mL) and washed with H_2O (5 mL × 3). The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:10) to give 20.7 mg (98%) of a mixture of **(*R*)-c** and **(*S*)-c** as colorless crystals: TLC, R_f 0.58 (EtOAc/hexane, 1:2); IR (neat) 2960, 1660, 1600, 1550 cm^{-1}; ^1H NMR (270 MHz) δ 0.88 (d, J = 7.0 Hz, 3H), 0.92, 0.93 (2 d, J = 6.6 Hz, 3H × 2), 1.67 (m, 1H), 1.96−2.10 (m, 2H), 2.43 (dd, J = 2.9, 8.8 Hz, 1H), 7.53 (m, 5H); ^{13}C NMR (75 Hz) δ 16.00, 18.60, 20.35, 32.47, 36.70, 43.10, 120.25 × 2, 124.56, 129.34 × 2, 138.37, 171.83; HRMS calcd for $C_{13}H_{19}NO$ (M^+), 205.1467; found, 205.1450. The enantiomeric ratio of the mixture was determined by HPLC analysis (DAICEL Chiralcel OD, *i*-PrOH/hexane = 1:10).

Methyl 2-*O*-Benzoyl-4,6-di-*O*-benzyl-3-*O*-[(*S*)-3-methyl-4-pentenoyl]-α-D-mannopyranoside (40aSi) (Entry 6 in Table 5). As described for the preparation of **9aRe**, 1.05 g (2.00 mmol) of **40** in THF (3.25 mL) was treated with CuBr·Me_2S (2.06 g, 10.0 mmol) in THF−Me_2S (2:1) (21 mL) and vinylmagnesium bromide (1.10 M solution in THF, 18.0 mL, 20.0 mmol) at −78 °C for 1 h. Extractive workup and purification by column chromatography on silica gel (EtOAc/hexane, 1:5) gave 0.93 g (84%) of a mixture of **40aSi/Re** (e.r. of the corresponding benzyl ester = 91:9, HPLC analysis) as colorless crystals, which was recrystallized from isopropyl ether to give pure **40aSi**: mp 80.5−81.5 °C; TLC, R_f 0.71 (EtOAc/hexane, 1:2); IR (neat) 1730, 1600, 1500 cm^{-1}; ^1H NMR (270 MHz) δ 0.95 (d, J = 7.0 Hz, 3H), 2.11 (dd, J = 7.9, 15.0 Hz, 1H), 2.28 (dd, J = 6.6, 15.0 Hz, 1H), 2.53−2.63 (m, 1H), 3.42 (s, 3H), 3.75−3.94 (m, 3H), 4.20 (t, J = 9.2 Hz, 1H), 4.55, 4.68 (2 d, J = 11.1 Hz, 1H × 2), 4.55, 4.76 (2 d, J = 11.5 Hz, 1H × 2), 4.80−4.94 (m, 2H), 4.84 (d, J = 2.9 Hz, 1H), 5.44−5.50 (m, 2H), 5.67 (ddd, J = 6.8, 10.4, 17.2 Hz, 1H), 7.17−8.08 (m, 15H); ^{13}C NMR (75 MHz) δ 19.51, 33.95, 40.96, 55.15, 68.78, 70.50, 71.42, 72.00, 72.90, 73.50, 74.75, 98.52, 113.26, 127.55 × 3, 127.62 × 2, 127.70, 128.32 × 2, 128.36 × 2, 128.45 × 2, 129.67, 129.84 × 2, 133.26, 138.00, 138.32, 142.17, 165.42, 171.44; HRMS calcd for $C_{34}H_{38}O_8$ (M^+), 574.2566; found, 574.2564.

Methyl 2,6-Di-*O*-benzyl-3-*O*-[(*R*)-3-methyl-4-pentenoyl]-4-*O*-pivaloyl-α-D-galactopyranoside (50aRe) (Entry 3 in Table 7). As described for the preparation of **9aRe**, 44.5 mg (84.5 mmol) of **50** in THF (1 mL) was treated with CuBr·Me_2S (3.2 mg, 16 μmol) in THF−Me_2S (2:1) (1.2 mL) and vinylmagnesium bromide (0.95 M solution in THF, 0.44 mL, 0.42 mmol) at −78 °C for 1 h. Extractive workup and purification by

column chromatography on silica gel (EtOAc/hexane, 1:5) gave 44.1 mg (94%) of **50aRe** (e.r. of the corresponding benzyl ester = 98:2, HPLC analysis) as a colorless oil: TLC, R_f 0.63 (EtOAc/hexane, 1:2); IR (neat) 1740 cm^{-1}; ^1H NMR (300 MHz) δ 1.04 (d, J = 6.8 Hz, 3H), 1.15 (s, 9H), 2.10 (dd, J = 8.3, 15.1 Hz, 1H), 2.29 (dd, J = 6.1, 15.1 Hz, 1H), 2.58−2.72 (m, 1H), 3.37−3.49 (m, 5H), 3.81 (dd, J = 3.7, 10.4 Hz, 1H), 4.14−4.18 (m, 1H), 4.42, 4.52 (2 d, J = 11.9 Hz, 1H × 2), 4.60, 4.68 (2 d, J = 12.4 Hz, 1H × 2), 4.75 (d, J = 3.7 Hz, 1H), 4.95 (dt, J = 1.5, 10.5 Hz, 1H), 5.01 (dt, J = 1.5, 17.3 Hz, 1H), 5.36 (dd, J = 3.4, 10.4 Hz, 1H), 5.44−5.45 (m, 1H), 5.78 (ddd, J = 6.6, 10.5, 17.3 Hz, 1H), 7.24−7.35 (m, 10H); ^{13}C NMR (75 MHz) δ 19.28, 27.09 × 3, 33.65, 38.95, 40.94, 55.45, 67.59, 68.41, 68.71, 69.75, 73.02, 73.22, 73.43, 98.37, 113.19, 127.62 × 2, 127.68, 127.94, 128.06 × 2, 128.37 × 4, 137.68, 137.77, 142.39, 171.14, 177.06; HRMS calcd for $C_{32}H_{42}O_8$ (M^+), 554.2880; found, 554.2887.

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Supporting Information Available: Experimental details for the preparation and characterization of **4**−**12**, **14**−**20**, **22**−**25**, **27**, **32**, **34**−**42**, **44**, **46**, **48**−**52**, **10aRe**, **19aRe**, **19bRe**, **19cRe**, **20aRe**, **20bRe**, **25aSi**, **34aRe**, **41bSi**, **42aSi**, and **50bRe**; copies of ^1H and ^{13}C NMR spectra of **4**−**12**, **14**−**20**, **22**−**25**, **27**, **32**, **34**−**42**, **44**, **46**, **48**−**52**, **10aRe**, **19aRe**, **19bRe**, **19cRe**, **20aRe**, **20bRe**, **25aSi**, **34aRe**, **41bSi**, **42aSi**, and **50bRe**; and the ORTEP plot for **40aSi**. This material is available free of charge via the Internet at http://pubs.acs.org.

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