Diacetone-*D*-glucose-mediated Asymmetric Syntheses of *N*-Carboxyalkylated and *O*-Carboxyalkylated Flavones

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A number of *O*-alkylated and *N*-alkylated flavones have recently been prepared to improve the biochemical and pharmacological properties of naturally occurring flavones.[1,2] In particular *O*-carboxyalkylated flavones have attracted high interest not only for their interesting bioactivities, but also as valuable intermediates for further synthetic elaboration of flavone derivatives.[3] In order to allow structure-activity relationship studies and to find carboxyalkylated flavones with improved biological activities, asymmetric syntheses of those compounds should be emphasized. In our continuing investigation on the stereoselective preparation of alkylated flavonoids and their activity studies,[4] we have attempted to synthesize highly enantioenriched *O*-carboxyalkylated and *N*-carboxyalkylated flavones. Herein, we report our efforts to synthesize *N*-carboxyalkylated and *O*-carboxyalkylated flavones by stereoselective nucleophilic substitution of α-haloacetates mediated by diacetone-*D*-glucose (DAG).

Diacetone-*D*-glucose-mediated asymmetric nucleophilic substitution of α-bromoacetates has recently been developed in our laboratory for stereoselective preparation of α-amino-acid derivatives.[5] The chiral information of *D*-glucose is transferred to the substitution at α-halo carbon center *via*

dynamic kinetic resolution (DKR) in the nucleophilic substitution with amine nucleophiles. In the presence of TBAI and DIEA, the α-bromoacetate undergoes rapid epimerization and (α*R*)-epimer reacts with a nucleophile preferentially. The successful results on dynamic resolution of diacetone-*D*-glucose α-bromoacetates prompt us to extend the methodology to asymmetric syntheses of *N*-carboxyalkylated aminoflavones. As shown in Scheme 1, treatment of two diastereomeric mixture (1:1) of α-bromo-α-phenylacetate **1** with 6-aminoflavone (1.2 equiv) in the presence of TBAI (tetrabutylammonium iodide, 1.0 equiv) and DIEA (diisopropylethylamine, 1.0 equiv) for 20 h provided the substitution product **2** in 87% yield with 99:1 diastereomeric ratio (dr, α*S*:α*R*).[6] The observed dr and yield of the product **2** suggest that the α-bromo stereogenic center is configurationally labile with respect to the rate of substitution and two diastereomers of **1** are dynamically resolved under the reaction condition. Subsequent removal of the chiral auxiliary with EtOH and *p*-toluenesulfonic acid gave *L*-phenylglycine-flavone conjugate **3** in 43% yield with 99:1 enantiomeric ratio (er).

In order to assess the effect of leaving group, TBAI and DIEA on yield and stereoselectivity, a series of reactions
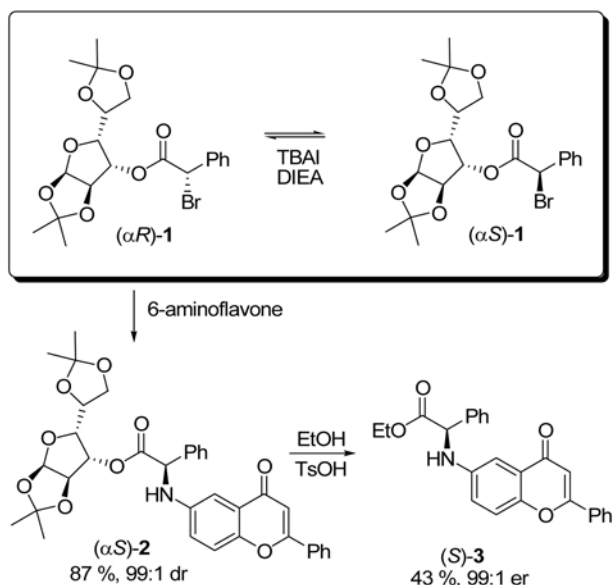
Scheme 1

Table 1.
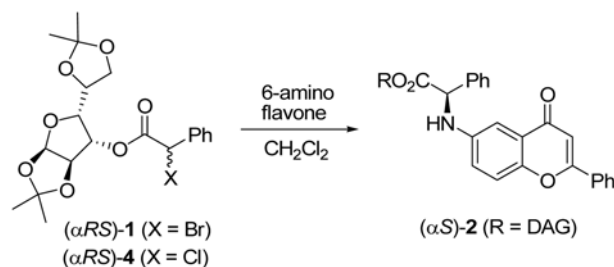
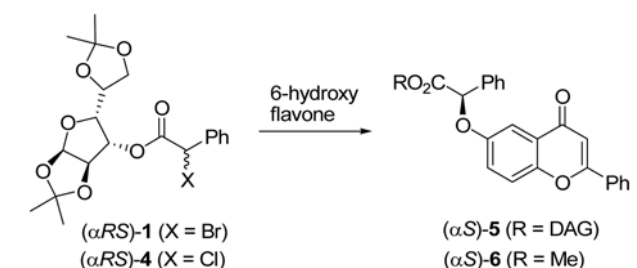| Entry	X	Substitution Condition[a]	Yield[b] (%)	Dr[c] (α*S*:α*R*)
1	Br	TBAI	71	99:1
2	Br	DIEA	56	97:3
3	Br	none	24	96:4
4	Cl	TBAI, DIEA	87	95:5
5	Cl	TBAI	64	95:5
6	Cl	DIEA	29	94:6
7	Cl	none	8	84:16

[a]The substitutions were carried out for 20 h at rt. [b]Isolated yields. [c]Drs were determined by ^{1}H-NMR.

was examined as shown in Table 1. All reactions in Table 1 were carried out in CH_2Cl_2 since none of other solvents explored gave better selectivities than CH_2Cl_2. Compared to the reaction of **1** in Scheme 1, almost same stereoselectivity was observed in the absence of DIEA, while mild drop in stereoselectivity (97:3 dr) with lower yield (56% yield) was observed in the absence of TBAI. (entries 1and 2) We speculate that the lowering of dr and yield in the absence of TBAI probably results from the slower epimerization of α-bromoacetate **1**.[7] In addition, the result in entry 3 suggests that the presence of both TBAI and DIEA is crucial for the rate acceleration of the substitution. When α-chloroacetate **4** was treated with 6-aminoflavone in the presence of both TBAI and DIEA, the substitution provided **2** in 87% yield with lower diastereoselectivity (95:5 dr) compared to the reactions of α-bromoacetate **1**. (entry 4) The reaction of α-chloroacetate **4** in the absence of DIEA gave the substitution product **2** with almost same stereoselectivity. (95:5 dr, entry 5) In the absence of TBAI, however, mild drop of selectivity was observed and the rate of the substitution was substantially decreased to provide **3** in 29% yield after 20 h stirring at room temperature. (entry 6) The substitution of α-chloroacetate **4** was very slow in the absence of both TBAI and DIEA to provide **2** in 8% yield with 84:16 dr and most of unconverted α-chloroacetate **4** was recovered.

The successful results on dynamic resolution of α-halo-α-phenylacetate **1** with aminoflavone led us to examine the methodology for asymmetric syntheses of *O*-carboxyalkylated flavones. Initial studies were carried out with (αRS)-**1** and 6-hydroxyflavone as shown in Table 2. Treatment of (αRS)-**1** (56:44 dr) with 6-hydroxyflavone (1.0 equiv) and potassium carbonate (K_2CO_3, 1.0 equiv) in DMF for 5 h provided **5** in 83% yield with 75:25 dr and following removal of chiral auxiliary gave methyl ester **6** with 75:25 er. (entry 1) The use of Cs_2CO_3 as a base in MeCN gave lower stereoselectivity as shown in entry 2. In an effort to reduce the risk of the epimerization after the substitution by a base, we examined the reaction at lower temperatures. However, the reactions at 0 °C and −15 °C produced *O*-carboxyalkylated flavone **5** with same dr of 60:40. (entry 3) When α-chloroacetate **4** was treated with 6-hydroxyflavone and K_2CO_3 in DMF, the substitution provided **5** in 67% yield with lower diastereoselectivity (67:33 dr) compared to the reaction of α-bromoacetate **1** under the analogous condition. (entry 4) We previously proposed that the origin of the high diastereoselectivity in the reactions of amine nucleophiles is due essentially to the formation of an intermolecular hydrogen bond that facilitates delivery of the nucleophile.[5b] The low selectivities observed in the reactions of the metallated flavonoxide nucleophiles shown in Table 2 might be attributed to their incapability for the hydrogen bonding interaction.

The scope of the observed dynamic kinetic resolution has been examined with various amino- and hydroxyflavone nucleophiles and α-bromo-α-methylacetate **7**. As shown in Table 3, entry 1, treatment of the diastereomeric mixture of **1** with 7-aminoflavone (1.2 equiv), TBAI (1.0 equiv) and DIEA (1.0 equiv) in CH_2Cl_2 for 20 h at room temperature
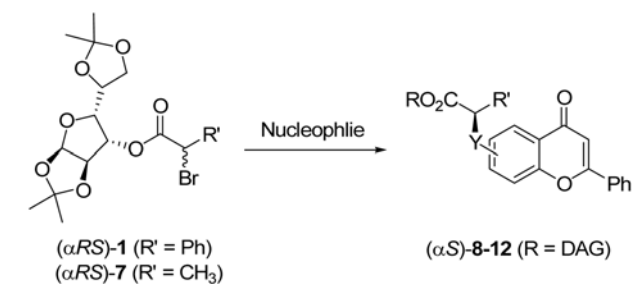
Table 2.

Entry	Y	Substitution Condition[a]	Yield[b] (%) of **5**	Dr[c] ($\alpha S : \alpha R$)
1	Br	K_2CO_3, DMF	83	75:25
2	Br	Cs_2CO_3, MeCN	82	60:40
3	Br	0 °C, Cs_2CO_3, MeCN	68	60:40
4	Cl	K_2CO_3, DMF	67	67:33

[a]The substitutions were carried out for 5 h. [b]Isolated yields. [c]Drs were determined by ^{1}H-NMR.

Table 3.

Entry	R	Nucleophile	Condition	Yield[a] (%)	Dr[b] ($\alpha S : \alpha R$)
1	Ph		DIEA, TBAI in DMF	46 (**8**)	95:5
2	Me		DIEA, TBAI in DMF	40 (**9**)	99:1
3	Ph		K_2CO_3 in DMF	86 (**10**)	61:39
4	Me		K_2CO_3 in DMF	63 (**11**)	67:33
5	Me		K_2CO_3 in DMF	99 (**12**)	61:39
6	Me		NaH in CH_3CN	43 (**12**)	70:30

[a]Isolated yields. [b]Drs were determined by ^{1}H-NMR.

gave **8** in 46% yield with 95:5 dr. Encouraged by the high asymmetric induction in the reactions of α-bromo-α-
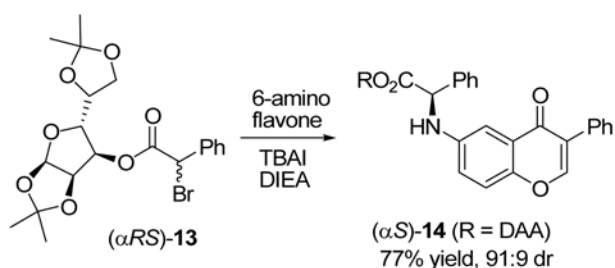
Scheme 2

phenylacetate **1**, we examined the nucleophilic substitution of α-bromo-α-methylacetate **7** as shown in entry 2. When **7** was treated with 6-aminoflavone, TBAI and DIEA in DMF for 48 h, the reaction gave *L*-alanine-flavone conjugate **9** with 99:1 dr as shown in entry 2. As expected, however, substitutions of **1** and **7** with 6- or 7-hydroxyflavone nucleophiles gave much lower selectivities as shown in entries 3-6. When α-bromoacetates **1** and **7** were treated with 7-hydroxyflavone and K_2CO_3 in DMF for 5 h, the substitutions provided **10** and **11** with 61:39 dr and 67:33 dr, respectively. (entries 3 and 4) In the reaction of α-bromo-α-methylacetate **7** with 6-hydroxyflavone, NaH in MeCN gave better selectivity than K_2CO_3 in DMF as shown in entries 5 and 6.

Our next concern was to examine the reactivity and the stereocontrolling ability of diacetone-*D*-allofuranose (DAA) template for the dynamic kinetic resolution of α-bromoacetate in nucleophilic substitution with an aminoflavone. Treatment of α-bromo-α-phenylacetate **13** with 6-aminoflavone in the presence of TBAI and DIEA gave the substitution product **14** in 77% isolated yield with 91:9 dr (α*S*:α*R*) as shown in Scheme 2. Diacetone-*D*-allose-mediated nucleophilic substitution did give lower selectivity compared to the diacetone-*D*-glucose-mediated substitution. The (*S*)-configuration at α-position of **14** was assigned by CSP-HPLC analysis of ethyl ester **3** derived from **14**. Also, the reaction of α-bromoacetate **13** with 6-hydroxyflavone and K_2CO_3 in DMF took place with lower stereoselectivity (61:39 dr).

In summary, we have developed a novel and practical method for the asymmetric syntheses of *N*-carboxyalkylated 6- and 7-aminoflavones *via* dynamic kinetic resolution of α-haloacetates using carbohydrates as a chiral auxiliary. The present results indicate that the stereoselectivity is significantly influenced by epimerizing agents such as TBAI and DIEA and the hydrogen bonding capability of the nucleophile. The finding for highly asymmetric syntheses of *L*-Phg-flavone and *L*-Ala-flavone conjugates **2**, **8**, **9** and **14** suggests that many kinds of aminoacid-flavonoid conjugates could be synthesized in the same way.

Experimental

General procedure for the preparation of *N*-carboxyalkylated flavones 2, 8, 9 and 14: To a solution of α-haloacetate in CH_2Cl_2 (or DMF) (*ca.* 0.1 M) at rt were added DIEA (1.0 equiv), TBAI (1.0 equiv) and an aminoflavone

(1.2 equiv). After the resulting reaction mixture was stirred at rt for 20 h, the solvent was evaporated and the crude material was purified by column chromatography to give the product.

General procedure for the preparation of *O*-carboxyalkylated flavones 5 and 10-12: To a solution of α-haloacetate in DMF (*ca.* 0.1 M) at rt were added a hydroxyflavone (1.0 equiv) and K_2CO_3 (1.0 equiv). After the reaction mixture was stirred at rt for 5 h, the mixture was quenched with saturated aqueous NH_4Cl solution. The resulting mixture was extracted with EtOAc twice and the combined extracts were washed with brine. The solvent was evaporated and the crude material was purified by column chromatography to give the product.

(1,2:5,6-Di-*O*-isopropylidene-α-*D*-glucofuranos-3-*O*-yl) 2-[(4-oxo-2-phenyl-4H-chromem-6-yl)amino]phenylacetate (2) 87% yield; ^1H NMR ($CDCl_3$, 400 MHz, major) 7.87 (m, 2H), 7.52-7.22 (m, 10H), 7.04 (m, 1H), 6.73 (s, 1H), 5.44 (d, *J* = 3.6 Hz, 1H), 5.31 (d, *J* = 2.9 Hz, 1H), 5.26 (d, *J* = 6.2 Hz, 1H), 5.22 (d, *J* = 6.2 Hz, 1H), 4.25 (m, 1H), 4.17 (m, 2H), 4.06 (m, 1H), 3.97 (d, *J* = 3.6 Hz, 1H), 1.47 (s, 3H), 1.41 (d, 3H), 1.32 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major) 178.6, 170.7, 163.2, 150.3, 143.6, 136.9, 132.5, 131.7, 129.5, 129.4, 129.2, 127.5, 126.6, 125.2, 121.7, 119.6, 112.9, 110.0, 107.1, 105.8, 105.3, 83.1, 80.0, 77.7, 72.8, 67.8, 61.0, 27.3, 27.1, 26.5, 25.6. The mixture of **2** and *p*-toluenesulfonic acid (0.1 equiv) in ethanol was refluxed for 24 h to give **3** in 43% yield. ^1H NMR ($CDCl_3$, 400 MHz) 7.86 (m, 2H), 7.53-7.22 (m, 10H), 7.00 (m, 1H), 6.72 (s, 1H), 5.23 (d, *J* = 6.6 Hz, 1H), 5.19 (d, *J* = 6.6 Hz, 1H), 4.20 (m, 2H), 1.24 (t, *J* = 9.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 178.7, 172.0, 163.1, 150.2, 143.9, 137.6, 132.5, 131.7, 129.4, 128.9, 127.7, 126.6, 125.2, 121.9, 119.5, 107.1, 105.6, 62.4, 60.8, 14.5; Chiral HPLC: 99:1 er (*S*)-major, 85.3 min; (*R*)-minor, 98.7 min; (Chiralcel OD; 5% *i*-PrOH in hexane; 0.5 mL/min).

(1,2:5,6-Di-*O*-isopropylidene-α-*D*-glucofuranos-3-*O*-yl) 2-[(4-oxo-2-phenyl-4H-chromem-6-yl)oxy]phenylacetate (5) 83% yield; ^1H NMR ($CDCl_3$, 400 MHz, major) 7.90 (m, 2H), 7.63-7.40 (m, 11H), 6.79 (s, 1H), 6.15 (d, *J* = 3.7 Hz, 1H), 5.81 (s, 1H), 5.35 (d, *J* = 2.9 Hz, 1H), 4.61 (d, *J* = 3.6 Hz, 1H), 4.14-3.90 (m, 4H), 1.50 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, major) 178.1, 168.4, 163.8, 154.9, 152.0, 134.6, 132.2, 129.8, 129.5, 129.3, 127.8, 127.6, 125.2, 120.5, 112.7, 109.6, 107.2, 106.7, 105.8, 83.5, 80.4, 79.0, 77.6, 72.3, 67.8, 27.2, 27.1, 26.5, 25.3. For removal of chiral auxiliary, the mixture of **5** and Et_3N (15 equiv) in methanol (0.03 M) was stirred for 2 days at rt. (46% yield) ^1H NMR ($CDCl_3$, 400 MHz) 7.92 (m, 2H), 7.61-7.40 (m, 11H), 6.79 (s, 1H), 5.82 (s, 1H), 3.76 (s, 3H); Chiral HPLC: 75:25 er, (*S*)-major, 6.9 min; (*R*)-minor, 5.6 min; (Chiralpak AD-H; 10% *i*-PrOH in hexane; 0.5 mL/min).

(1,2:5,6-Di-*O*-isopropylidene-α-*D*-glucofuranos-3-*O*-yl) 2-[(4-oxo-2-phenyl-4H-chromem-7-yl)amino]phenylacetate (8) 46% yield; ^1H NMR ($CDCl_3$, 400 MHz, major) 7.98 (d, *J* = 8.8 Hz, 1H), 7.81 (m, 2H), 7.53-7.40 (m, 8H), 6.70 (m,

1H), 6.66 (s, 1H), 6.44 (d, J = 2.1 Hz, 1H), 5.72 (d, J = 5.6 Hz, 1H), 5.44 (d, J = 3.6 Hz, 1H), 5.33 (d, J = 2.8 Hz, 1H), 5.23 (d, J = 5.7 Hz, 1H), 4.25 (m, 1H), 4.17-4.01 (m, 3H), 3.94 (d, J = 3.6 Hz, 1H), 1.47 (s, 3H), 1.42 (d, 3H), 1.32 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz, major) 178.0, 170.2, 162.8, 158.7, 150.7, 136.4, 132.4, 131.6, 129.7, 129.5, 129.3, 127.4, 127.3, 126.5, 116.1, 113.6, 113.0, 110.0, 107.9, 105.3, 98.7, 83.1, 80.0, 77.7, 72.8, 67.8, 61.0, 27.3, 27.1, 26.5, 25.6.

(1,2:5,6-Di-*O*-isopropylidene-*α*-D-glucofuranos-3-*O*-yl) 2-[(4-oxo-2-phenyl-4H-chromem-6-yl)amino]ethanoate (9) 40% yield; ^{1}H NMR (CDCl$_3$, 400 MHz, major) 7.90 (m, 2H), 7.52 (m, 3H), 7.43 (d, J = 9.0 Hz, 1H), 7.27 (m, 1H), 7.04 (m, 1H), 6.78 (s, 1H), 5.76 (d, J = 3.6 Hz, 1H), 5.33 (d, J = 2.6 Hz, 1H), 4.42-4.01 (m, 7H), 1.54 (d, J = 6.8 Hz, 3H), 1.50 (s, 3H), 1.38 (d, 3H), 1.26 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz, major) 178.6, 173.0, 163.3, 150.3, 144.3, 132.5, 131.8, 129.4, 126.6, 125.2, 121.9, 119.7, 112.8, 109.9, 107.2, 105.5, 105.4, 83.6, 80.2, 72.8, 67.8, 53.8, 52.5, 27.3, 27.1, 26.5, 25.6, 19.1.

(1,2:5,6-Di-*O*-isopropylidene-*α*-D-glucofuranos-3-*O*-yl) 2-[(4-oxo-2-phenyl-4H-chromem-7-yl)oxy]phenylacetate (10) 86% yield; ^{1}H NMR (CDCl$_3$, 400 MHz, major) 8.17 (m, 1H), 7.86 (m, 2H), 7.62-7.02 (m, 10H), 6.74 (s, 1H), 5.90 (d, J = 3.6 Hz, 1H), 5.83 (s, 1H), 5.35 (d, J = 2.8 Hz, 1H), 4.42 (d, J = 3.7 Hz, 1H), 4.12-3.36 (m, 4H), 1.50 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz, major) 177.9, 168.1, 163.7, 161.8, 158.0, 134.4, 132.1, 130.0, 129.5, 127.9, 127.5, 126.6, 119.2, 115.2, 112.9, 109.7, 107.2, 105.5, 103.4, 83.4, 80.3, 79.2, 77.6, 72.2, 67.6, 27.1, 26.6, 25.6, 25.2.

(1,2:5,6-Di-*O*-isopropylidene-*α*-D-glucofuranos-3-*O*-yl) 2-[(4-oxo-2-phenyl-4H-chromem-7-yl)oxy]ethanoate (11) 63% yield; ^{1}H NMR (CDCl$_3$, 400 MHz, major) 8.16 (d, J = 8.6 Hz, 1H), 7.89 (m, 2H), 7.63-7.01 (m, 5H), 6.77 (s, 1H), 5.94 (d, J = 3.5 Hz, 1H), 5.35 (d, J = 2.8 Hz, 1H), 4.95 (q, 1H), 4.50 (d, J = 3.6 Hz, 1H), 4.14-3.80 (m, 4H), 1.71 (d, J = 6.7 Hz, 3H), 1.51 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz, major) 178.0, 170.4, 163.7, 162.3, 158.1, 132.1, 129.5, 127.9, 126.6, 119.0, 114.9, 113.0, 109.8, 108.0, 105.5, 102.5, 83.7, 80.4, 77.3, 73.2, 72.5, 67.9, 53.8, 27.3, 26.6, 25.7, 25.3, 18.8.

(1,2:5,6-Di-*O*-isopropylidene-*α*-D-glucofuranos-3-*O*-yl) 2-[(4-oxo-2-phenyl-4H-chromem-6-yl)oxy]ethanoate (12) 99% yield; ^{1}H NMR (CDCl$_3$, 400 MHz, major) 7.91 (m, 2H), 7.55-7.44 (m, 6H), 6.78 (s, 1H), 6.14 (d, J = 3.7 Hz, 1H), 5.37 (d, J = 2.9 Hz, 1H), 4.93 (q, J = 6.8 Hz, 1H), 4.62 (d, J = 3.7 Hz, 1H), 4.22-3.98 (m, 4H), 1.69 (d, J = 6.7 Hz, 3H), 1.50 (s, 3H), 1.39 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz, major) 178.1, 170.1, 163.8, 155.1, 152.0, 132.0, 129.5, 126.7, 125.2, 120.5, 112.7, 109.6, 107.2, 106.3, 105.8, 105.4, 83.5, 80.4, 77.6, 73.1, 72.8, 68.1, 60.8, 27.2, 27.0, 26.5, 25.6, 18.6. For removal of chiral

auxiliary, the mixture of **12** and Et$_3$N (15 equiv) in methanol (0.03M) was stirred for 2 days at rt. (43% yield) Chiral HPLC: 70:30 er, (*S*)-major, 24.3 min; (*R*)-minor, 29.5 min; (Chiralpak AD-H; 20% *i*-PrOH in hexane; 0.5 mL/min).

(1,2:5,6-Di-*O*-isopropylidene-*α*-D-allofuranos-3-*O*-yl) 2-[(4-oxo-2-phenyl-4H-chromem-6-yl)amino]phenylacetate (14) 77% yield; ^{1}H NMR (CDCl$_3$, 400 MHz, major) 7.86 (m, 2H), 7.55-7.23 (m, 10H), 7.04 (m, 1H), 6.71 (s, 1H), 5.83 (d, J = 3.8 Hz, 1H), 5.26 (m, 2H), 4.90 (m, 1H), 4.83 (m, 1H), 4.12 (m, 2H), 3.75 (dd, J = 8.7, 6.9 Hz, 1H), 3.20 (dd, J = 8.5, 6.9 Hz, 1H), 1.63 (s, 3H), 1.34 (d, 3H), 1.23 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz, major) 178.6, 171.1, 163.1, 150.2, 143.8, 136.9, 132.5, 131.7, 129.5, 129.3, 129.2, 127.9, 126.5, 125.1, 121.8, 119.5, 113.7, 110.2, 107.1, 105.7, 104.6, 77.8, 74.9, 73.7, 27.2, 27.1, 26.3, 25.7.

References and Notes

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6. In references 5a-c, we have established that (*αS*)-products were provided in the substitution of diacetone-*D*-glucofuranosyl *α*-haloacetates with various nucleophiles. The absolute configurations of carboxyalkylated flavone derivatives are provisionally assigned by analogy.

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