Diastereo- and Enantioselective Synthesis of α,β-Disubstituted γ-Bisalkoxycarbonyl Sulfonates

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Abstract: The asymmetric synthesis of α,β-disubstituted γ-bisalkoxycarbonyl sulfonates is reported. The synthesis is based on the Michael addition of a lithiated enantiopure sulfonate bearing a cheap chiral sugar auxiliary to Knoevenagel acceptors. The reaction proceeds with high asymmetric inductions (ds = 69–96%) and good yields (62–79%). The absolute configuration was determined by X-ray crystal-structure analysis.

Key words: sulfonate, asymmetric synthesis, Michael addition, sugar auxiliary, Knoevenagel acceptor

Sulfonic acid derivatives constitute an important class of organic compounds, which exist in a large number of natural products. They are also present in synthetic compounds with important biological or pharmacological activities, such as antiulcer, antibacterial, antipseudomonal, and squalene synthase inhibition activities.[1] On the other hand, sulfonates are of interest as bioactive isosteres of carboxylates, phosphates, and sulfates such as phospholipids, sulfated steroid conjugates, and oligonucleotides.[2]

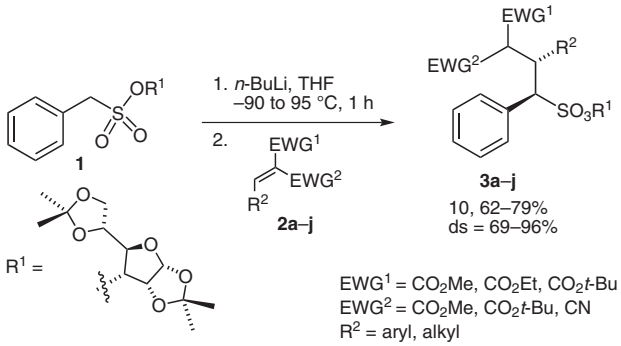
However, only a few asymmetric syntheses of this important class of compounds are described in the literature.[3] In continuation of our research on the asymmetric synthesis of sulfonic acid derivatives,[4] we now wish to report a convenient diastereo- and enantioselective approach for the synthesis of α,β-disubstituted γ-bisalkoxycarbonyl sulfonates.

The asymmetric synthesis of the title compounds is based on a stoichiometric approach employing 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose as a cheap chiral sugar auxiliary. As shown in Scheme 1, the enantiopure sulfonate **1** was deprotonated with *n*-butyllithium in THF and allowed to react with the Knoevenagel acceptor **2a** to give the Michael adduct **3a** in good yield (79%) and high diastereoselectivity (77%).

We explored the generality of this reaction with a wide range of Michael acceptors bearing different substituents. The desired products **3a–j** were obtained with one exception in good yields (10, 62–79%) and high diastereoselectivities (ds = 69–96%). The results are summarized in Table 1.

The variation of the substituents of the Michael acceptors indicated a strong influence on the diastereoselectivity of the reaction. Michael acceptors containing heterocycles (**2e**,**f**) afforded the Michael products in good yields (62% and 69%, respectively) and excellent diastereoselectivities (82% and 96%, respectively). The more sterically hindered alkene **2g** reacted with sulfonate **1** in high diastereoselectivity (87%), whereas the aliphatic Michael acceptor **2h** gave only a moderate diastereoselectivity (69%). The effect of the electron-withdrawing groups of the Michael acceptor was also investigated. The replacement of an ester group with a cyanide function did not lead to any significant changes in yield and diastereoselectivity (entry 9). A significant difference was observed, however, when two *tert*-butyl ester groups instead of the two methyl ester were used (entry 10). This result may be explained by the steric hindrance caused by the two *tert*-butyl groups.

In all of these cases, only three out of four possible diastereomers could be detected. The major diastereomers could be isolated by preparative HPLC as was demonstrated with **3b** (de ≥ 98%).



Scheme 1

Encouraged by these results, we turned our attention to coumarins as Michael acceptors. Coumarins and their derivatives are important structural features of many natural compounds, which show pharmacological activities and of optical brighteners and laser dyes.[5]

We found that the reaction of sulfonate **1** with coumarin **4** proceeded well to give the corresponding Michael adduct **5** in good diastereoselectivity (ds = 63%) and moderate yield (52%, Scheme 2). The relative configuration of the

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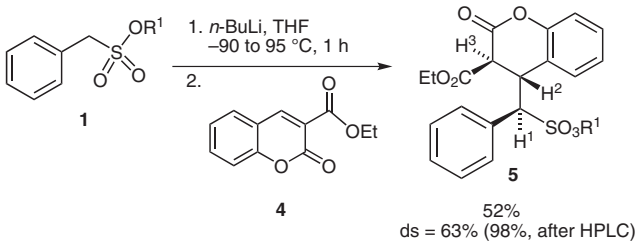


Scheme 2

Michael adduct **5** was determined by NOE experiments, coupling constants ($J_{1,2}$ = 10.7 Hz; $J_{2,3(eq)}$ = 1.9 Hz), and results obtained from related reactions of **1**.[4]

The absolute configuration of the newly formed stereogenic centers was determined to be *R*,*R*,*R* by X-ray crystal-structure analysis in the case of product **3i** bearing a cyano group as EWG[2] and therefore a third stereocenter. Thus, the hydrogen atoms at the α- and β-position of the major diastereomer are *anti* to each other (Figure 1).[6] This stereochemical outcome is in agreement with the relative topicity observed in previous electrophilic substitutions of **1**.[4]

The racemization-free cleavage of the chiral auxiliary to form the corresponding sulfonic acid proceeded by refluxing the stereoisomerically pure Michael adduct **3b**, obtained after preparative HPLC in a MeOH–H_2O mixture containing 2% TFA. To isolate the final product in a more accessible form, the sulfonic acid was converted with triisopropyl orthoformate to the corresponding sulfonate **6** (Scheme 3). The desired isopropyl sulfonate was obtained in good overall yield (48%) and virtually complete diastereomeric and enantiomeric purity (de, ee ≥ 98%).

In summary, we have developed an efficient asymmetric synthesis of α,β-disubstituted γ-bisalkoxycarbonyl sulfonates via Michael addition of a lithiated sulfonate bearing 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose as a chiral auxiliary to Knoevenagel acceptors with one exception in good yields (62–79%) and excellent diastereoselectivities (ds = 69–96%). The cleavage of the chiral sugar auxiliary demonstrated in a typical case proceeded without any epimerization or racemization to form the corresponding isopropyl sulfonate in good overall yield (48%) and excellent diastereomeric and enantiomeric excess (de, ee ≥ 98%).[7]

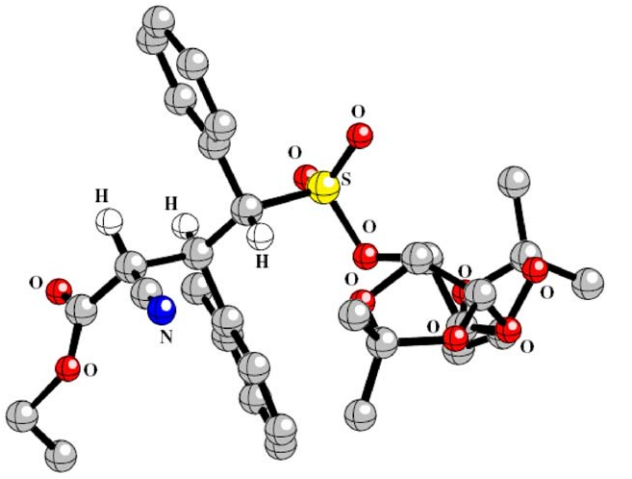
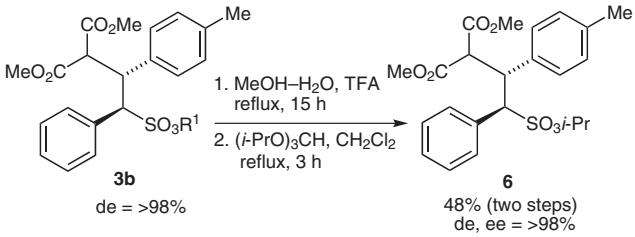


Figure 1 X-ray crystal structure of **3i**[6]



Scheme 3

Table 1 Diastereoselective Synthesis of Sulfonates **3**

Entry	**3**	R^2	EWG^1	EWG^2	Yield (%)	ds (%)[a]
1	**3a**	Ph	CO_2Me	CO_2Me	79	77
2	**3b**	*p*-Tol	CO_2Me	CO_2Me	70	73 (98)[b]
3	**3c**	4-$MeOC_6H_4$	CO_2Me	CO_2Me	76	76
4	**3d**	3-ClC_6H_4	CO_2Me	CO_2Me	71	72
5	**3e**	3-pyridyl	CO_2Me	CO_2Me	62	82
6	**3f**	2-furyl	CO_2Me	CO_2Me	69	96
7	**3g**	1-naphthyl	CO_2Me	CO_2Me	66	87
8	**3h**	*n*-Pr	CO_2Me	CO_2Me	62	69
9	**3i**	*o*-Tol	CO_2Et	CN	73	79
10	**3j**	*p*-Tol	CO_2t-Bu	CO_2t-Bu	10	92

[a] Determined by ^1H NMR spectroscopy.
[b] After preparative HPLC.

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(6) CCDC-739752 (**3i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(7) **General Procedure for the Synthesis of α,β-Disubstituted γ-Alkoxycarbonyl Sulfonates 3a–j**

To a solution of enantiopure sulfonate **1** (1.0 mmol) in dry THF (10 mL), *n*-BuLi (1.6 M solution in hexane, 0.63 mL) was added dropwise at –90 °C to – 95 °C under argon. The solution was stirred for 1 h, after which the Michael acceptor **2** (1.0 mmol in 1 mL dry THF) was added dropwise. The mixture was stirred for 4–6 h at –90 °C to – 95 °C. The progress of the reaction was monitored by TLC. The mixture was quenched with sat. NH_4Cl (3 mL). After separation of the organic layer, the aqueous phase was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over $MgSO_4$, evaporated, and the crude product was purified by flash column chromatography (silica gel, Et_2O–pentane, 1:2) to afford **3a–j**.

Dimethyl 2-(2-{5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yloxysulfonyl}-2-phenyl-1-*p*-tolylethyl)malonate (3b)

Yield 454 mg (70%); colorless solid; ds = 73%; the major diastereomer was separated by preparative HPLC; de 98%; mp 66–68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32, 1.36, 1.37, 1.70 [4 × s, 12 H, $(O)_2C(CH_3)_2$], 2.32 (s, 3 H, CH_3), 3.33 (dd, *J* = 7.4, 8.5 Hz, 1 H, C*H*HOC), 3.44, 3.52 (2 × s, 6 H, OCH_3), 3.72 (dd, *J* = 7.0, 8.5 Hz, 1 H, CH*H*OC), 3.76 [dd, *J* = 2.5, 8.8 Hz, 1 H, C*H*(OC)CH(OC)CH_2O], 3.81 [d, *J* = 7.1 Hz, 1 H, $CH(CO_2)_2$], 4.13 [dt, *J* = 2.5, 7.0 Hz, 1 H, C*H*(OC)CH_2O], 4.20–4.26 [m, 2 H, C*H*(OC)CH$(OC)_2$, C*H*$CH(CO_2)_2$], 4.47 (dd, *J* = 4.7, 8.8 Hz, 1 H, $CHOSO_2$), 5.60 (d, *J* = 9.6 Hz, 1 H, $PhCHSO_3$), 5.64 [d, *J* = 3.6 Hz, 1 H, $CH(OC)_2$], 7.11 (d, *J* = 8.0 Hz, 2 H, ArH), 7.38–7.46 (m, 7 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1 (CH_3), 25.3, 25.9, 26.4, 26.6 [$O_2C(CH_3)_2$], 47.5 [*C*HCH$(CO_2)_2$], 52.1, 52.3 (OCH_3), 54.7 [*C*H$(CO_2)_2$], 64.1 (CH_2), 70.7 ($PhCHSO_3$), 73.7 [*C*H(OC)CH_2O], 76.0 [*C*H(OC)CH(OC)CH_2O], 76.6 [*C*H(OC)CH$(OC)_2$], 76.9 ($CHOSO_2$), 103.2 [*C*H$(OC)_2$], 109.7, 113.2 [$(O)_2C(CH_3)_2$], 128.2, 128.7, 129.2, 129.9, 130.2 (ArCH), 131.4, 132.7, 137.3 (ArC), 167.5, 167.9 (CO_2). IR (KBr): 2954, 2986, 1736, 1602, 1516, 1436, 1370, 1163, 1017, 931, 833, 701 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 633.6 (10) [$M^+ - CH_3$], 261.3 (37), 235.3 (66), 205.3 (40), 169.2 (89), 135.3 (100), 127.3 (66). Anal. Calcd for $C_{32}H_{40}O_{12}S$ (648.6): C, 59.25; H, 6.21. Found: C, 59.13; H, 6.12.

General Procedure for the Removal of the Chiral Auxiliary

The sulfonate **3b** (0.5 mmol) was dissolved in a solution of 2% TFA in MeOH–H_2O (10:1 mL). The solution was refluxed for 15 h and then evaporated to dryness. The resulting oil was dissolved in CH_2Cl_2, $(i\text{-PrO})_3CH$ (5 mmol) was added dropwise, and the mixture was refluxed for 3 h. The solvent was removed in vacuo, and the crude product was purified by flash column chromatography (SiO_2, Et_2O–pentane, 1:3) to yield the final product **6**.

Dimethyl 2-[2-(Isopropoxysulfonyl)-2-phenyl-1-*p*-tolylethyl]malonate (6)

Yield 107 mg (48%); colorless solid; mp 72–74 °C; de and ee 98% (HPLC); $[\alpha]_D^{22}$ +52.24 (*c* 0.67, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89, 1.03 [2 × d, *J* = 6.0 Hz, 6 H, $(CH_3)_2$CH], 2.32 (s, 3 H, CH_3), 3.42, 3.54 (2 × s, 6 H, OCH_3), 3.95 [d, *J* = 8.0 Hz, 1 H, $CH(CO_2)_2$], 4.19 [dd, *J* = 8.0, 9.1 Hz, 1 H, C*H*$CH(CO_2)_2$], 4.47 (sept, *J* = 6.0 Hz, 1 H, $CHOSO_2$), 5.13 (d, *J* = 9.1 Hz, 1 H, $PhCHSO_3$), 7.10 (d, *J* = 8.0 Hz, 2 H, ArH), 7.30–7.42 (m, 7 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (CH_3), 22.3, 23.1 [$(CH_3)_2$CH], 47.4 [*C*H$CH(CO_2)_2$], 52.3, 52.6 (OCH_3), 55.1 [*C*H$(CO_2)_2$], 70.0 ($CHSO_3$), 77.9 ($CHOSO_2$), 128.6, 128.6, 129.0, 130.0, 130.1 (ArCH), 132.3, 132.7, 137.5 (ArC), 167.8, 168.2 (CO_2). IR (KBr): 2987, 2954, 1738, 1596, 1436, 1370, 1213, 1165, 1017, 871, 840, 698 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 448.2 (5.7) [M^+], 235.2 (43), 205.2 (21), 135.1 (100). Anal. Calcd for $C_{23}H_{28}O_7S$ (448.2): C, 61.59; H, 6.29. Found: C, 61.31; H, 6.78. HRMS: *m/z* calcd for $C_{23}H_{28}O_7S$: 448.1550; found: 448.1552.

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