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Efficient diastereo- and enantioselective synthesis of α,β-disubstituted γ-phosphono sulfonates

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ABSTRACT

The first asymmetric synthesis of α,β-disubstituted γ-phosphono sulfonates is reported. The key step is the Michael addition of a lithiated enantiopure sulfonate bearing an inexpensive chiral sugar auxiliary to α,β-unsaturated phosphonates in good diastereoselectivities. After chromatographic purification, the cleavage of the chiral sugar auxiliary proceeds without any epimerization or racemization to form the corresponding isopropyl sulfonate in very good overall yield (75%) and excellent diastereomeric and enantiomeric excess (de, ee ⩾ 95%).

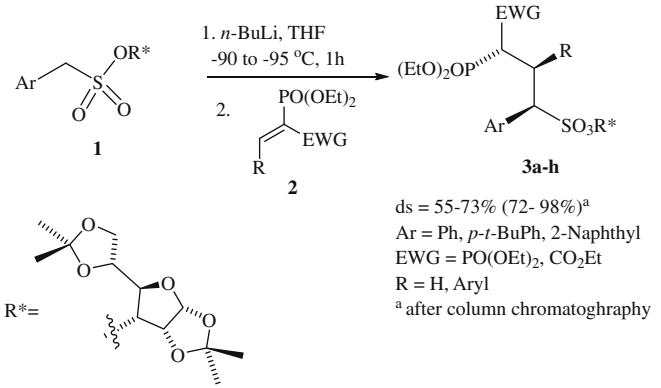
1. Introduction

There is a constant need for the asymmetric synthesis of organophosphorus compounds, since they constitute an important class of pharmacologically active molecules.[1] They are useful for the treatment of bone disorders, such as myeloma, Paget's disease, bone metastases, and rheumatoid arthritis.[2] They are also used extensively as ligands in asymmetric synthesis.[3] In addition, natural products containing a P–C bond mostly exhibit important biological activities.[4] On the other hand, sulfonic acid derivatives are a class of organic compounds, which show important biological and pharmacological activities, such as antiulcer, antibacterial, and antipseudomonal activities.[5] Phosphonosulfonic acids are selective inhibitors of squalene synthase and effective cholesterol-lowering agents.[6] α,β-Unsaturated phosphonates bearing an additional electron-withdrawing group (EWG) at the α-position are highly reactive acceptors for asymmetric Michael additions.[7] Although a few reports on enantioselective Michael additions to α,β-unsaturated phosphonates exist,[8] no asymmetric 1,4-additions of sulfonates bearing a chiral auxiliary have been described so far.

In continuation of our efforts in developing an asymmetric synthesis of sulfonic acid derivatives based on 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose as an inexpensive chiral sugar auxiliary,[9] we herein report an efficient asymmetric synthesis of α,β-disubstituted γ-phosphono sulfonates.

2. Results and discussion

As shown in Scheme 1, the enantiopure sulfonate **1** was deprotonated with *n*-butyllithium in tetrahydrofuran at −90 to −95 °C and reacted with the α,β-unsaturated phosphonate **2a** at this temperature for 4 h to give the desired Michael adduct **3a** with an excellent conversion of 96% and good diastereoselectivity (ds = 73%).



Scheme 1.

Table 1 shows the generality of this reaction with a range of α,β-unsaturated phosphonates bearing different substituents and with various sulfonates. The α,β-disubstituted γ-phosphono sulfonates **3a**–**h** were obtained with good to excellent conversion (73–98%) and good diastereoselectivities (55–73%). The diastereomeric purity of the major stereoisomer was further improved by column

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chromatography and moderate yields (42–55%), and ds-values (72–98%) were reached.

Table 1
Diastereoselective synthesis of sulfonates **3**

3	Ar	R	EWG	ds[a] (%)	Conv. (yield)[b] (%)
3a	Ph	Ph	CO_2Et	73 (96)	96 (55)
3b	Ph	2-ClC_6H_4	CO_2Et	73 (81)	96
3c	Ph	4-$MeOC_6H_4$	CO_2Et	60 (98)	95 (48)
3d	Ph	Ph	$PO(OEt)_2$	64 (72)	80
3e	*p*-*t*-BuC_6H_4	Ph	CO_2Et	73 (95)	98 (51)
3f	*p*-*t*-BuC_6H_4	4-$MeOC_6H_4$	CO_2Et	62 (95)	93 (53)
3g	*p*-*t*-BuC_6H_4	4-ClC_6H_4	$PO(OEt)_2$	63 (98)	73 (30)
3h	2-Naphthyl	4-$MeOC_6H_4$	CO_2Et	55 (94)	90 (42)

[a] Determined by ^{31}P NMR spectroscopy of the crude reaction mixture; in brackets, after column chromatography.
[b] Determined by ^{31}P NMR of the crude reaction mixture; in brackets, yield of the isolated major diastereomer.

The configuration of the three newly created stereogenic centers was determined by NOE experiments on the major diastereoisomer **3c** and was found to be (2*S*,3*R*,4*R*) (Fig. 1). The observed values of the coupling constants clearly proved the trans arrangement of the phosphoryl and aryl groups ($^3J_{ipso}$ = 11.4–15.3 Hz) as well as H_A and H_B ($^3J_{H_A-H_B} = 10.5—11.5$ Hz). This stereochemical outcome with respect to the α-sulfonate stereocenter is in agreement with the relative topicity observed in the previous electrophilic substitutions of **1**.[9]

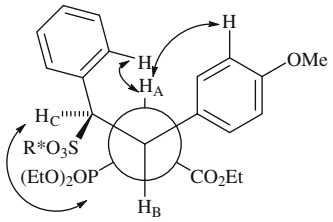

Figure 1. Selected NOE enhancements on the major diastereomer **3c**.

In order to remove the sugar auxiliary without racemization the stereoisomerically pure Michael adduct **3c** was refluxed in an EtOH–H_2O mixture containing 2% TFA. The resulting sulfonic acid was directly converted with triisopropyl orthoformate into the corresponding sulfonate **4**, which was obtained in very good yield of 75% for the two steps and with excellent diastereomeric and enantiomeric excess (de, ee ⩾ 95%) (Scheme 2).

3. Conclusion

In conclusion, the diastereo- and enantioselective Michael addition of lithiated sulfonates bearing an inexpensive chiral sugar auxiliary to activated α,β-unsaturated phosphonates offers an efficient entry to a variety of α,β-disubstituted γ-phosphono sulfonates in good diastereoselectivities (ds = 55–73%). The diastereomers of high purity were isolated after separation by column chromatography (ds = 72–98%). In addition, the cleavage of the chiral sugar auxiliary was demonstrated in a typical case, and proceeded without any epimerization or racemization to afford the corresponding isopropyl sulfonate in 75% yield over two steps and excellent diastereomeric and enantiomeric excess (de, ee ⩾ 95%).[10]

Acknowledgments

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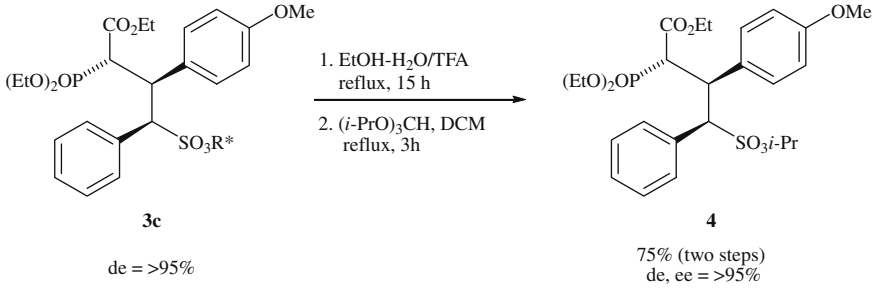

3c

de = >95%

4

75% (two steps)
de, ee = >95%

Scheme 2.

Harnying, W.; Vignola, N. *Eur. J. Org. Chem.* **2003**, 3939–3947; (f) Enders, D.; Harnying, W. *Synthesis* **2004**, 2910–2918; (g) Enders, D.; Harnying, W. *Arkivoc* **2004**, *2*, 181–188; (h) Enders, D.; Harnying, W.; Raabe, G. *Synthesis* **2004**, 590–594; (i) Enders, D.; Adelbrecht, J.-C.; Harnying, W. *Synthesis* **2005**, 2962–2968; (j) Enders, D.; Vignola, N.; Berner, O. M.; Harnying, W. *Tetrahedron* **2005**, *61*, 3231–3243; (k) Harnying, W.; Kitisriworaphan, W.; Pohmakotr, M.; Enders, D. *Synlett* **2007**, 2529–2532; (l) Enders, D.; Iffland, D. *Synthesis* **2007**, 1837–1840; (m) Enders, D.; Iffland, D.; Raabe, G. *Synthesis* **2009**, 1683–1688; (n) Enders, D.; Saeidian, H.; Mirjafary, Z.; Iffland, D.; Raabe, G.; Runsink, J. *Synlett* **2009**, 2872–2874; For a general review on chiral auxiliaries, see: (o) Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899–1930.

10. *Synthesis of α,β-disubstituted γ-phosphono sulfonates* **3a–h**; *general procedure*: 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 to −95 °C under argon. The solution was stirred for 1 h, after which the Michael acceptor **2** (1.0 mmol) dissolved in dry THF (1 mL) was added dropwise. The mixture was stirred for 4 h at −90 to −95 °C and was then quenched with satd NH_4Cl (5 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 column chromatography (silica gel, Et_2O–DCM, 10:1) to afford **3a–h**.

Ethyl 2-(diethoxyphosphoryl)-4-(5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3] dioxol-6-yloxysulfonyl)-3-(4-methoxyphenyl)-4-phenyl-butanoate **3c**; ds: 60%; the major diastereomer was separated by column chromatography; yield: 364 mg (48%); de = 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.1 Hz, 3H, CH_3CH$_2$OCO), 1.12, 1.33 [2 × s, 6H, (O)$_2$C(CH_3)$_2$], 1.36 (t, J = 7.1 Hz, 3H, CH_3CH$_2$OP), 1.41, 1.43 [2 × s, 6H, (O)$_2$C(CH_3)$_2$], 1.44 (t, J = 7.1 Hz, 3H, CH_3CH$_2$OP), 3.27 [dd, J = 4.4, 3.8 Hz, 1H, C*H*(OC)CH(OC)$_2$], 3.40 (dd, J = 20.3, 11.5 Hz, 1H, H$_A$), 3.76 (s, 3H, OCH$_3$), 3.79–3.85 [m, 3H, CH$_2$OCO, C*H*HOC(CH$_3$)$_2$], 3.98 [dd, J = 8.5, 6.6 Hz, 1H, C*H*HOC(CH$_3$)$_2$], 4.02 (dd, J = 8.5, 3.8 Hz, 1H, C*H*(OC)CH(OC)CH$_2$O), 4.15–4.33 (m, 5H, C*H*(OC)CH$_2$O, 2 × CH$_2$OP), 4.36 [dd, J = 8.5, 4.7 Hz, 1H, C*H*(OC)CH(OC)$_2$], 4.65 (ddd, J = 11.7, 11.5, 3.0 Hz, 1H, H$_B$), 5.45 [d, J = 3.6 Hz, 1H, CH(OC)$_2$], 5.61 (d, J = 2.8 Hz, 1H, H$_C$), 6.65–7.38 (m, 9H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (*C*H$_3$CH$_2$OCO), 16.3 (d, $^3J_{CP}$ = 6.1 Hz, *C*H$_3$CH$_2$OP), 16.5 (d, $^3J_{CP}$ = 6.1 Hz, *C*H$_3$CH$_2$OP), 25.3, 26.3, 26.4, 26.6 [O$_2$C(*C*H$_3$)$_2$], 43.5 (d, $^2J_{CP}$ = 2.2 Hz, C$_B$), 49.1 (d, $^1J_{CP}$ = 126.6 Hz, C$_A$), 55.1 (OCH$_3$), 61.3 (CH$_2$OCO), 63.3 (d, $^2J_{CP}$ = 6.1 Hz, CH$_2$OP), 63.6 (d, $^2J_{CP}$ = 6.8 Hz, CH$_2$OP), 64.9 [*C*H$_2$OC(CH$_3$)$_2$], 68.2 (d, $^3J_{CP}$ = 1.5 Hz, C$_C$), 74.7 (CH(OC)CH$_2$O), 76.5 (CH(OC)-CH(OC)CH$_2$O), 77.2 [CH(OC)CH(OC)$_2$], 77.7 (CHOSO$_2$), 103.2 [CH(OC)$_2$], 109.9 [(O)$_2$*C*(CH$_3$)$_2$], 112.5 (ArCH), 113.3 [(O)$_2$*C*(CH$_3$)$_2$], 127.0 (d, $^3J_{CP}$ = 14.5 Hz, C$_{ipso}$), 127.6 (ArCH), 128.9 (ArC), 129.0, 131.6, 132.4 (ArCH), 160.0 (ArC), 166.8 (d, $^2J_{CP}$ = 6.8 Hz, CO$_2$); ^{31}P NMR (162 MHz, $CDCl_3$): 20.4; IR (KBr): 3471, 2986, 2936, 2250, 1736, 1612, 1513, 1457, 1373, 1297, 1250, 1171, 1027, 974, 916, 844, 733, 598, 513 cm^{-1}; MS (EI, 70 eV): m/z (%) = 741 (13), 433 (85), 343 (100), 299 (19), 224 (24), 210 (67), 169 (28), 165 (54), 161 (71), 127 (23); HRMS: m/z calcd for $C_{35}H_{49}O_{14}PS$: 741.2340 [M$^+$−CH$_3$]; found: 741.2345.

Removal of the chiral auxiliary; general procedure: Sulfonate **3c** (0.5 mmol) was dissolved in a solution of 2% TFA in EtOH/H_2O (10/1 mL). The solution was refluxed for 15 h and then was evaporated to dryness. The resulting oil was dissolved in CH_2Cl_2, then (*i*-PrO)$_3$CH (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 column chromatography (SiO_2, Et_2O–DCM, 10:1) to yield the final product **4**.

Ethyl 2-(diethoxyphosphoryl)-4-(isopropoxysulfonyl)-3-(4-methoxyphenyl)-4-phenyl-butanoate **4**; yield: 208 mg (75%); de, ee: ⩾95% (HPLC); $[\alpha]_D^{24} = +79.3$ (c 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.1 Hz, 3H, CH_3CH$_2$OCO), 0.93, 1.22 (2 × d, J = 6.0 Hz, 6H, (CH_3)$_2$CH), 1.36, 1.44 (2 × t, J = 7.1 Hz, 6H, 2 × CH_3CH$_2$OP), 3.40 (dd, J = 20.3, 11.5 Hz, 1H, H$_A$), 3.76 (s, 3H, OCH$_3$), 3.85 (q, J = 7.1 Hz, 2H, CH$_2$OCO), 4.21, 4.32 (2 × qd, J = 7.2, 7.1 Hz, 4H, 2 × CH$_2$OP), 4.53 (sept, J = 6.0 Hz, 1H, CHOSO$_2$), 4.60 (ddd, J = 11.5, 11.3, 3.0 Hz, 1H, H$_B$), 5.52 (dd, J = 3.0, 0.6 Hz, 1H, PhCHSO$_3$), 6.69 (d, J = 8.5 Hz, 1H, ArH), 6.65–7.38 (m, 8H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH$_3$CH$_2$OCO), 16.3, 16.5 (d, $^3J_{CP}$ = 6.1 Hz, *C*H$_3$CH$_2$OP), 22.3, 23.4 [(*C*H$_3$)$_2$CH], 43.4 (d, $^2J_{CP}$ = 2.2 Hz, C$_B$), 49.2 (d, $^1J_{CP}$ = 127.4 Hz, C$_A$), 55.1 (OCH$_3$), 61.3 (CH$_2$OCO), 63.2 (d, $^2J_{CP}$ = 7.1 Hz, CH$_2$OP), 63.7 (d, $^2J_{CP}$ = 6.9 Hz, CH$_2$OP), 67.4 (d, $^3J_{CP}$ = 1.5 Hz, C$_C$), 78.7 (CHOSO$_2$), 112.4 (ArCH), 127.3 (d, $^3J_{CP}$ = 14.5 Hz, C$_{ipso}$), 127.7, 128.8 (ArCH), 129.6 (ArC), 131.8, 132.4 (ArCH), 158.9 (ArC), 166.9 (d, $^2J_{CP}$ = 6.9 Hz, CO$_2$); ^{31}P NMR (162 MHz, $CDCl_3$): 20.6. IR (KBr): 3471, 2984, 2936, 1735, 1611, 1514, 1456, 1357, 1296, 1253, 1169, 1032, 968, 912, 881, 733, 703, 589, 536 cm^{-1}; MS (EI, 70 eV): m/z (%) = 556 (12), 432 (18), 343 (100), 299 (11), 224 (61), 210 (16), 169 (28), 161 (58); HRMS: m/z calcd for $C_{26}H_{37}O_9PS$: 556.1890; found: 556.1893.