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1-Hydroxymethyl-4-phenylsulfonybutadiene, a Versatile Building Block for the Synthesis of 2,3,4-Trisusbtituted Tetrahydrothiophenes

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Abstract: A method to synthesize chiral 2,3,4-trisusbtituted tetrahydrothiophenes in both enantiomerically pure forms starting from 1-hydroxymethyl-4-phenylsulfonylbutadiene is described.

Keywords: Sulfonylbutadienes, heterocycles, tetrahydrothiophenes, vinylsulfones, chiral.

Introduction

Five-membered oxa-, aza- and thia- ring systems are widely distributed in nature and have attracted the interest of the scientific community, particularly in conjunction with the total synthesis of polyether natural products [1], pyrrolidines with glycosidase inhibitor activity [2], and 5-thiosugars as therapeutic agents. This interest is also due to the use of such molecules for understanding the recognition processes of sugar-binding proteins [3]. Our group is involved in a program seeking to exploit the reactivity of 1-hydroxymethyl-4-sulfonylbutadiene for the synthesis of highly functionalized oxygen, nitrogen and sulfur five-membered heterocycles [4]. Chemo- and

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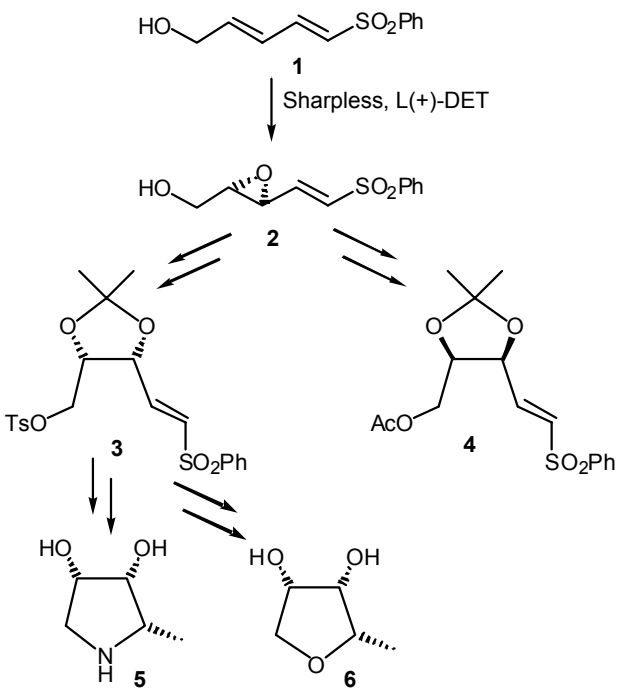
enantioselective epoxidation of 1-hydroxymethyl-4-sulfonylbutadiene (**1)**, under Sharpless conditions [5] gives rise to epoxide **2**. In a recent paper we reported the ability of several protecting groups to provide excellent control of the opening of **2** [6]. In this way, tosylate **3** and acetate **4** could easily be obtained, starting from the same chiral epoxide **2**. Tosylate **3** has been further transformed into pyrrolidine **5,** which possesses glycosidase inhibitory activity, and its oxygen analogue **6** (Scheme 1).

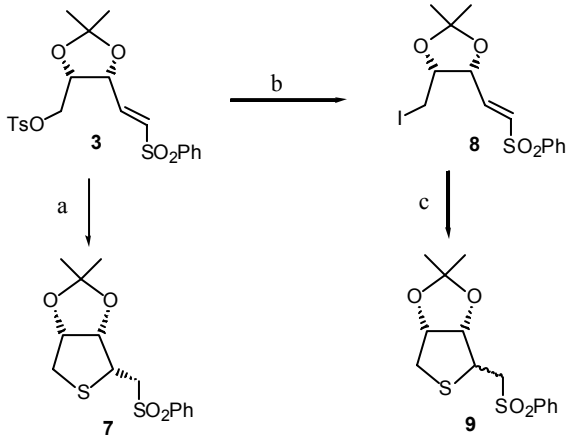
Scheme 1



Results and Discussion

The easy synthesis on a multigram scale of compounds **3** and **4** prompted us to use them for the synthesis of the sulfur analogs, which interested us due to their biological activities. The most common procedure for the synthesis of thiosugars, is based on the introduction of a thiol group by a double nucleophilic replacement of sulfonyloxy groups in the required positions. Other polyhydroxylated chiral thiolanes have been obtained by introduction the thiol group by conjugate addition, followed by internal displacement of a sulfonyloxy group [7]. This tandem reaction has been used by us in the synthesis of pyrrolidines such as **5** [4]. In order to apply the same methodology for the synthesis of tetrahydrothiophenes, we decided to react **3** with sodium sulfide under the usual conditions, thus obtaining the tetrahydrothiophene **7** in low yield (8%). The stereochemistry of **7** was established by NMR studies. In light of this result we decided to transform the tosylate into iodide **8** under the usual conditions [8] (75% yield) and then allow this compound to react with thiourea [9]. Hydrolysis of the resulting thiouronium salt gave a 6:4 epimeric mixture of *cis:trans* tetrahydrothiophenes **9** in good yield (81%) (Scheme 2).

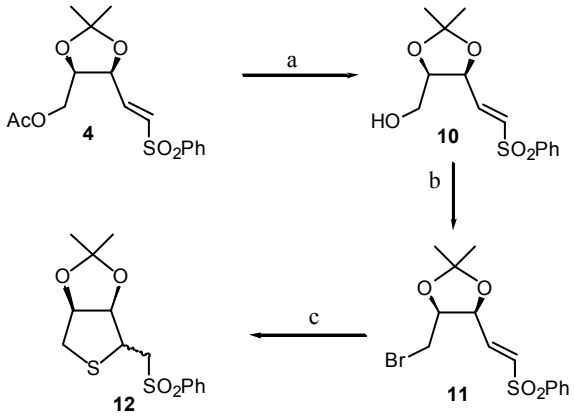
Scheme 2



a) Na_2S, MeOH, 65ºC; b) NaI, acetone, 80ºC;
c) $(H_2N)_2CS$, MeOH, 65ºC, then KOH

In order to obtain the enantiomer, starting from the same epoxide **2**, and to simultaneously test the use of bromide as a leaving group, the acetoxy derivative **4** (obtained from **2** as described previously [6]) was reduced with DIBAL to the alcohol **10** in 89% yield and then transformed into the bromo derivative **11** (70%). This compound was submitted to the same conditions as before, providing the enantiomeric epimeric mixture **12**, in this case in a 79% yield (Scheme 3).

Scheme 3



a) DIBAL, DCM, -78ºC; b) CBr_4, Ph_3P, DCM, 50ºC;
c) $(H_2N)_2CS$, MeOH, 65ºC, then KOH.

Conclusions

This methodology opens a new way for obtaining chiral 2,3,4-trisubstituted-tetrahydrothiophenes that could easily be transformed into sugar analogues or biotin derivatives.

Acknowledgments

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Experimental

General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. Melting points were determined with a Kofler hot stage melting point apparatus and are uncorrected. IR spectra were recorded on a BOMEM 100 FT IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded in deuterochloroform and are referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, respectively, for ^{1}H- and ^{13}C-, on a Bruker WP-200 SY or a BRUKER DRX 400 MHz spectrometer. Chemical shifts are reported in ppm on the δ scale and coupling constants (*J*) are given in Hz. Mass spectra were performed in a VG-TS 250 spectrometer at a 70 eV ionizing voltage. Results are presented as m/z (% rel. int.). HRMS were recorded in a VG Platform spectrometer using Electronic Impact (EI) or Fast Atom Bombardment (FAB) techniques. Optical rotations were determined in a Perkin-Elmer 241 polarimeter in 1 dm cells. Diethyl ether, THF and benzene were distilled from sodium, and pyridine and dichloromethane (DCM) were distilled under argon from CaH_2.

(2*R*,3*S*,4*S*)-*2-Benzenesulfonylmethyl-3,4-isopropylidendioxytetrahydrotiophene* (**7**).

To a solution of **3** (38 mg, 0.08 mmol) in MeOH (1 mL) was added dry Na_2S (13 mg, 0.16 mmol). The mixture was refluxed for 8 h under an argon atmosphere and then the solvent was evaporated. The crude product was dissolved in water (2 mL) and extracted with AcOEt. The combined organic extracts were washed with water and brine. After drying and concentration the residue was purified by chromatography (8:2 *n*-hexane-EtOAc) to give **7** (3 mg, 8%); $[\alpha]_D^{20}$ = +16.5 (c= 0.30, $CHCl_3$); ^{1}H-NMR (200 MHz): 7.97-7.42 (5H, m, Ar), 4.83 (1H, dt, J= 2.4 and 5.2 Hz, H-4), 4.69 (1H, dd, J= 4.0 and 5.2 Hz, H-3), 3.77 (1H, dd, J= 6.2 and 14.0 Hz, H_A-1'), 3.55 (1H, dt, J= 4.0, and 6.2 Hz, H-2), 3.30 (1H, dd, J= 6.2 and 14.0 Hz, H_B-1'), 2.86 (2H, d, J= 2.4 Hz, 2H-5), 1.44 (Me-acetonide), 1.25 (Me-acetonide); ^{13}C-NMR (50.3 MHz): 139.4 (C-*ipso*), 134.2 (CH-*para*), 129.5 (2CH-*meta*), 128.4

(2CH-*ortho*), 111.3 (C-acetonide), 83.1 (CH-3), 83.0 (CH-4), 55.5 (CH_2-1'), 46.1 (CH-2), 38.8 (CH_2-5), 25.9 (Me-acetonide), 24.7 (Me-acetonide); IR ν_{max} (film) ν (cm^{-1}): 2986, 1447, 1373, 1308, 1209, 1148, 1049; EIMS, m/z (%): 314 (M^+, 5), 299 (20), 172 (80), 115 (83), 77 (100); HRMS (EI) calcd. for $C_{14}H_{18}O_4S_2$: 314.0646, found: 314.0671.

(2*R*, 3*R*,4*E*)-*5-Benzenesulfonyl-1-iodo-2,3-isopropylidenedioxypent-4-ene* (**8**).

To a solution of **3** (80 mg, 0.18 mmol) in dry acetone (2.0 mL) was added NaI (81 mg, 0.54 mmol). The reaction mixture was refluxed overnight. The solvent was evaporated and the residue was dissolved in water (2mL) and extracted with EtOAc. The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$, 5% $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4. Concentration followed by flash chromatography on silica gel (85:15 *n*-hexane-EtOAc) gave compound **8** (55 mg, 75 %); $[\alpha]_D^{20}$ = +14.2 (c = 1.2, $CHCl_3$); ^{1}H-NMR (400 MHz) 7.94-7.52 (5H, m, -Ar), 6.99 (1H, dd, J = 4.4 and 15.0 Hz, H-4), 6.66 (1H, dd, J = 1.4 and 15.0 Hz, H-5), 4.85 (1H, m, H-3), 4.57 (1H, ddd, J = 6.6, 6.6, and 7.8 Hz, H-2), 3.10 (1H, dd, J = 6.6 and 10.2 Hz, H_A-1), 2.90 (1H, dd, J = 7.8 and 10.2 Hz, H_B-1), 1.47 (3H, s, Me-acetonide), 1.35 (3H, s, Me-acetonide); ^{13}C-NMR (50.3 MHz) 140.1 (C-*ipso*), 139.6 (CH-4), 133.9 (CH-5), 133.4 (CH-*para*), 129.6 (2CH-*meta*), 128.1 (2CH-*ortho*), 110.2 (C-acetonide), 77.9 (CH-3), 76.1 (CH-2), 76.1 (CH_2-1), 28.1 (Me-acetonide), 25.5 (Me-acetonide); IR (film) ν (cm^{-1}) 1383, 1148, 1086, 1038, 880, 760; EIMS m/z (%) 408 (M^+, 5), 238 (91), 125 (60), 97 (100), 77 (80); HRMS (EI) calcd. for $C_{14}H_{17}O_4SI$: 407.9892, found 407.9921.

(2RS,3S,4R)-2-Benzenesulfonyl-3,4-isopropylidenedioxytetrahydrothiophene (**9**).

To a solution of **8** (55 mg, 0.13 mmol) in EtOH (1.3 mL) was added thiourea (15 mg, 0.19 mmol). After stirring at reflux temperature for 5 days the solvent was evaporated and the residue was dissolved in 0.5 mL of water and added to an aqueous solution of 1 M KOH (0.7 mL). The resulting mixture was refluxed for 14 h, then the mixture was cooled, neutralized with 3M H_2SO_4 and extracted with EtOAc. The combined organic extracts were washed with water and brine. After drying and concentration the residue was purified by chromatography (85:15 *n*-hexane-EtOAc) to give a mixture of cis/trans diastereoisomers **9** (33 mg, 81%) in a ratio of 6:4.

(2*R*,3*S*,4*E*)-*5-Benzenesulfonyl-2,3-isopropylidenedioxypent-4-en-1-ol* (**10**).

To a solution of **4** (48 mg, 0.14 mmol) in DCM (1.5 mL) was added 1.5 M DIBAL-H in toluene (0.2 mL, 0.28 mmol) at -78ºC under an argon atmosphere. The mixture was stirred for 20 minutes, quenched carefully with water and warmed to room temperature. The reaction mixture was then diluted with 100 mL of Et_2O and 2 M HCl (1.5 mL). After stirring for 1h the mixture was dried over Na_2SO_4. Filtration followed by concentration afforded **10** (37 mg, 89%); $[\alpha]_D^{20}$ = -2.6 (c = 0.87, $CHCl_3$); ^{1}H-NMR (200 MHz): 7.94-7.52 (5H, m, -Ar), 7.02 (1H, dd, J= 4.0 and 14.8 Hz, H-4), 6.68

(1H, dd, J= 1.8 and 14.8 Hz, H-5), 4.84 (1H, ddd, J= 1.8, 4.0 and 6.0 Hz, H-3), 4.40 (1H, dt, J= 5.8 and 6.0 Hz, H-2), 3.57 (2H, d, J= 5.8 Hz, 2H-1), 1.46 (3H, s, Me-acetonide), 1.36 (3H, s, Me-acetonide); ^{13}C-NMR (50.3 MHz): 141.3 (CH-4), 140.2 (C-*ipso*), 133.8 (CH-5), 132.0 (CH-*para*), 129.6 (2CH-*meta*), 128.1 (2CH-*ortho*), 110.0 (C-acetonide), 78.1 (CH-3), 75.3 (CH-2), 61.6 (CH_2-1), 27.7 (Me-acetonide), 25.2 (Me-acetonide); IR ν_{max} (film) ν (cm^{-1}): 3500 (wide), 2930, 1447, 1148, 1086.

(2*R*,3*S*,4*E*)- *5-Benzenesulfonyl-1-bromo-2,3-isopropylidenedioxypent-4-ene* (**11**).

To a solution of **10** (37 mg, 0.12 mmol) in DCM (1.5 mL) was added PPh_3 (31 mg, 0.12 mmol) and CBr_4 (40 mg, 0.12 mmol). The mixture was heated at 50ºC for 12 h under an argon atmosphere. The reaction mixture was then quenched with water and extracted with EtOAc. The combined organic extracts were washed with water and brine. After drying and concentration the residue was purified by chromatography (9:1 *n*-hexane-EtOAc) to give **11** (30 mg, 70%); $[\alpha]_D^{20}$ = -4.6 (c= 0.82, $CHCl_3$); ^{1}H-NMR (200 MHz): 7.94-7.52 (5H, m, -Ar), 7.06 (1H, dd, J= 4.4 and 15.0 Hz, H-4), 6.67 (1H, dd, J= 1.8 and 15.0 Hz, H-5), 4.88 (1H, ddd, J= 1.8, 4.4 and 6.2 Hz, H-3), 4.54 (1H, ddd, J= 5.4, 6.2 and 8.0 Hz, H-2), 3.30 (1H, dd, J= 5.4 and 10.2 Hz, H_A-1), 3.10 (1H, dd, J= 8.0 and 10.2 Hz, H_B-1), 1.47 (3H, s, Me-acetonide), 1.35 (3H, s, Me-acetonide); ^{13}C-NMR (50.3 MHz): 140.1 (C-*ipso*), 139.4 (CH-4), 133.9 (CH-5), 133.1 (CH-*para*), 129.6 (2CH-*meta*), 128.1 (2CH-*ortho*), 110.3 (C-acetonide), 77.9 (CH-3), 75.9 (CH-2), 29.5 (CH_2-1), 27.9 (Me-acetonide), 25.4 (Me-acetonide); IR ν_{max} (film) ν (cm^{-1}): 1750, 1319, 1148, 1086, 1047.

(2*RS*,3*R*,4*S*)-*2-Benzenesulfonyl-3,4-isopropylidenedioxy-tetrahydrothiophene* (**12**).

To a solution of **11** (30 mg, 0.08 mmol) in EtOH (1 mL) was added thiourea (9 mg, 0.12 mmol). Following an identical procedure to that described for the preparation of **9** a 6:4 (*cis*/*trans*) mixture of diastereoisomers **12** was obtained (19 mg, 79%).

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Sample availability: Available from the authors.