The First Synthesis of Spirocyclic Sulfates from Tertiary Cyclopropanols and Their Reaction with Normant Homocuprates

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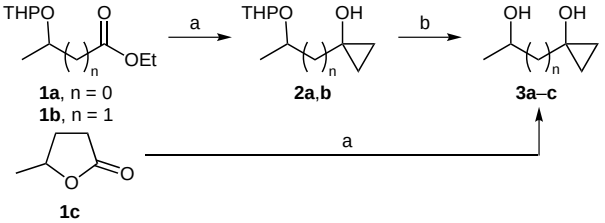
Abstract: Spirocyclic sulfates of 2- and 3-(hydroxyalkyl)cyclopropanols, obtainable through the Kulinkovich reaction from β-and γ-hydroxy carboxylic acid esters, respectively, were synthesized for the first time. The possibility of regio- and stereoselective alkylating the spirocyclic sulfates by using Normant homocuprates has been demonstrated.

Key words: cyclopropanols, spiro compounds, sulfates, cuprates, alkylation

Cyclic sulfuric acid ester derivatives of glycols have been known for a long time,[1] but the absence of effective methods for preparing these compounds limited their use in organic synthesis. In 1988, Gao and Sharpless proposed a smooth procedure for obtaining sulfates of vicinal diols through oxidation of the corresponding sulfates with sodium metaperiodate in the presence of a catalytic amount of ruthenium(III) chloride in a biphasic carbon tetrachloride–water system at room temperature.[2] Sulfates of chiral diols can be used as oxirane-like substrates for nucleophilic substitution and elimination reactions, as well as in rearrangements and other transformations.[3]

Substituted cyclopropanols can be easily prepared by the reaction of esters with titanacyclopropane reagents (the Kulinkovich reaction).[4] Because the hydroxycyclopropane moiety can remain intact[5] or can undergo cleavage to form a new functional group[6] during reactions involving hydroxycyclopropane group-containing substrates, cyclopropanols are now widely used in direct organic syntheses of many natural compounds or their building blocks.[7]

We investigated the possibility of applying the Sharpless approach in the synthesis of novel cyclic sulfates from hydroxyalkyl-substituted tertiary cyclopropanols **3** (Scheme 1). These diols can be easily prepared in enantiomerically pure form by the Kulinkovich reaction[8] from the corresponding protected lactate **1a** or β-hydroxybutyrate **1b** (which are commercially available), or from lactone **1c**.[9] First, we attempted to use the standard Sharpless procedure[10] for the synthesis of spirocyclic sulfites from hydroxyalkyl cyclopropanols **3a**–**c**. In these cases, the reaction mixture turned dark with the formation of copious amounts of tar-like material, and low yields of the target sulfites **4a**–**c** were obtained. This problem was solved by replacing triethylamine with pyridine, a less basic reagent. Compound **4b** was obtained as a single stereoisomer, whereas sulfites **4a** and **4c** were obtained as nonequimolar mixtures of diastereomers with a chiral sulfur atom (as determined by ^{1}H NMR spectroscopy).[11,12]



Scheme 1 *Reagents and conditions*: (a) EtMgBr, Ti(O*i*-Pr)$_4$, THF–Et$_2$O, 15 °C, 3 h (87% for **2a**, 90% for **2b**, 97% for **3c**); (b) MeOH, PPTS, r.t., 0.5 h (76% for **3a**, 83% for **3b**).

Because these compounds are known to be thermally unstable,[3a,b] they were used in subsequent oxidation reactions without further purification.

Oxidation of the six-membered sulfite **4b** by sodium metaperiodate in the presence of a catalytic amount of ruthenium(III) chloride[10] gave the target sulfate **5b** as a pale-yellow oil that slowly crystallized in a refrigerator.[13] Compound **5b** was quite stable: no changes were noticed during purification by column chromatography on silica gel, boiling in tetrahydrofuran with an excess of lithium aluminum hydride for eight hours, or on treatment with an ethereal solution of isopropylamine overnight at room temperature.

The attempt to oxidize sulfite **4a** to the corresponding sulfate gave 2-methylcyclobutanone (**5a**)[14] (Scheme 2). The structure of this compound was confirmed by comparing the ^{1}H NMR spectrum of the reaction mixture, in which ketone **5a** was the predominant product, with literature data.[15] Ketone **5a** was probably formed by a pinacol rearrangement with ring expansion, as previously observed for 1-(1-hydroxyalkyl)cyclopropanols in the presence of thionyl chloride,[16] sulfuryl chloride,[17] organosulfonyl chlorides,[18] Brønsted acids,[19] or Lewis acids.[19b]

Sulfates **5b** and **5c** underwent nucleophilic substitution reactions[20] with Normant homocuprates ($R_2CuMgBr$) **6**.[21] These homocuprates were generated in situ from the corresponding Grignard reagents and copper(I) iodide in anhydrous tetrahydrofuran at − 25 °C (Table 1). As can be seen from the table, sulfates **5b** and **5c** smoothly underwent alkylation with Normant reagents[22] prepared from

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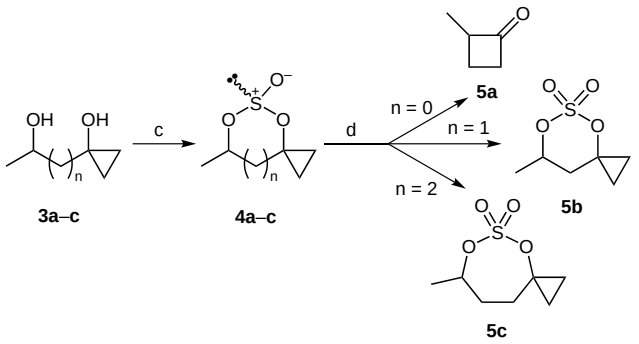
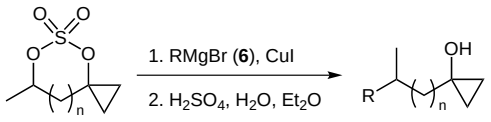


Scheme 2 *Reagents and conditions*: (c) $SOCl_2$, py, CH_2Cl_2, 0 °C, 0.5 h; (d) $NaIO_4$, $RuCl_3 \cdot xH_2O$ (cat.), MeCN, CCl_4/H_2O, r.t., 2–3 h (87% for **5b**, 82% for **5c**; two steps).

primary alkyl magnesium compounds to give products of substitution at a secondary carbon atom (Table 1, Entries 1–4 and 8). A Grignard reagent carrying a secondary alkyl group reacted in the same manner, but gave a lower yield of the corresponding product (entry 5). Attempts to vinylate or arylate sulfate **5b** under similar conditions did not give the expected products (entries 6 and 7), possibly because of the low reactivity of cuprates containing bonds between copper and sp^2-hybridized carbon atoms, as noted in previous studies.[23]

Table 1 Reactions of Cyclic Sulfates **5b** and **5c** with Normant Cuprates

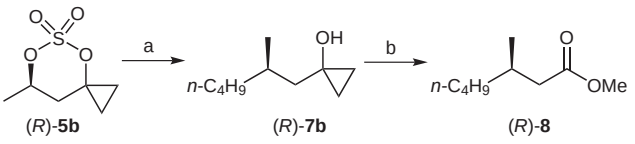


Entry	Sulfate	R	Product	Yield[a] (%)
1	**5b**	Et	**7a**	80
2	**5b**	Bu	**7b**	89
3	**5b**	$(CH_2)_2CH{=}CH_2$	**7c**	90
4	**5b**	$(CH_2)_5Me$	**7d**	85
5	**5b**	*i*-Pr	**7e**	66
6	**5b**	$CH{=}CH_2$	**7f**	0[b]
7	**5b**	Ph	**7g**	0[b]
8	**5c**	Bu	**7h**	72

[a] Isolated yield after column chromatography, based on the starting sulfate.
[b] Starting material was isolated.

Substitution reactions involving cuprates are generally described in terms of an S_N2 mechanism.[24] In some cases, however, the reaction occurs by an SET mechanism accompanied by racemization of chiral substrates.[25]

To determine whether inversion of the configuration at the secondary carbon atom in the sulfate (*R*)-**5b**[26] was complete after nucleophilic attack by the cuprate reagent, we subjected the substituted cyclopropanol (*R*)-**7b** to oxidative cleavage by reaction with phenyliodine(III) diacetate[27] in methanol to give methyl (3*R*)-3-methylheptanoate (**8**; Scheme 3). Comparison of the specific rotation of ester **8**[28] with the reference value in the literature[29] showed conclusively that the inversion was complete and that the reaction of sulfate (*R*)-**5b** with Normant homocuprates proceeds stereospecifically.



Scheme 3 *Reagents and conditions*: (a) BuMgBr, CuI, THF, –25 °C, overnight, then H_2SO_4 (25 wt% in H_2O), r.t., 5 h (89%); (b) $PhI(OAc)_2$, MeOH, r.t., 0.5 h (91%).

We have therefore shown that 1-(2-hydroxyalkyl)- and 1-(3-hydroxyalkyl)cyclopropanols can be converted into spirocyclic sulfates in good yields through the formation of an intermediate sulfite. Replacement of the sulfate group by reaction with a Normant homocuprate proceeds with complete inversion of configuration of the asymmetric carbon atom. Note that this reaction occurs with conservation of the unprotected cyclopropanol moiety, which can be subjected to further transformations to create new functional groups, opening up pathways to various areas of synthetic application.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(11) The ratio of diastereomers with a chiral sulfur atom equilibrated by boiling a solution of sulfite **4a** in diethyl ether for four hours, as determined by ^{1}H-NMR spectroscopy (see Supporting Information).

(12) Sulfites **4a–c** were obtained by a slightly modified Sharpless procedure using freshly distilled $SOCl_2$ with anhyd pyridine instead of Et_3N as the base. The mixture was stirred at 0 °C for 0.5 h (TLC). The crude products were obtained as clear pale-yellow liquids and were used in the next step without further purification. Samples for spectroscopic analysis were purified by chromatography on a short column of silica gel.

(13) **7-Methyl-4,6-dioxa-5-thiaspiro[2.4]heptane 5-Oxide (4a)**
Colorless liquid (7:3 mixture of two inseparable diastereomers); R_f = 0.61 (hexane–EtOAc, 4:1); IR (neat): 1199, 3099 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.62–0.70 (m, 0.3 H), 0.79–0.93 (m, 1.3 H), 1.00–1.13 (m, 1 H), 1.19–1.32 (m, 0.7 H), 1.28 (d, *J* = 6.1 Hz, 2.1 H), 1.38–1.45 (m, 0.7 H), 1.41 (d, *J* = 6.1 Hz, 0.9 H), 4.68 (q, *J* = 6.1 Hz, 0.3 H), 5.04 (q, *J* = 6.1 Hz, 0.7 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 5.32, 5.94, 8.49, 8.94, 16.10, 17.41, 67.78, 69.16, 78.28, 81.13; MS (EI): *m/z* (%) = 149 (0.03) $[M + 1]^+$, 92 (80.2), 56 (100), 43 (64.4).
7-Methyl-4,6-dioxa-5-thiaspiro[2.5]octane 5-Oxide (4b)
Pale-yellow liquid (single diastereomer); R_f = 0.38 (hexane–EtOAc, 4:1); IR (neat): 3092, 1230, 1180 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68–0.81 (m, 2 H), 1.08–1.18 (m, 3 H), 1.44 (d, *J* = 6.1 Hz, 3 H), 2.40 (dd, *J* = 12.6, 12.6 Hz, 1 H), 4.72–4.80 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.26, 13.02, 21.09, 38.03, 59.09, 74.05; MS (EI): *m/z* (%) = 163 (0.22) $[M + 1]^+$, 120 (6.69), 56 (100), 42 (36.3).
7-Methyl-4,6-dioxa-5-thiaspiro[2.6]nonane 5-Oxide (4c)
Colorless liquid (7:3 mixture of two inseparable diastereomers); R_f = 0.69 (hexane–EtOAc, 4:1); IR (neat): 1207, 3090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.41–0.48 (m, 0.3 H), 0.53–0.60 (m, 0.7 H), 0.67–0.79 (m, 1 H), 0.88–0.95 (m, 0.3 H), 1.00–1.06 (m, 0.7 H), 1.14–1.26 (m, 1.7 H), 1.38 (d, *J* = 6.1 Hz, 2.1 H), 1.42 (d, *J* = 7.1 Hz, 0.9 H), 1.69–2.07 (m, 2.3 H), 2.25–2.34 (m, 0.3 H), 2.45–2.54 (m, 0.7 H), 4.42–4.49 (m, 0.3 H), 5.19–5.27 (m, 0.7 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.80, 11.18, 11.29, 13.59, 22.21, 22.49, 33.65, 34.21, 35.13 (×2), 60.53, 61.71, 70.96, 73.47; MS (EI): *m/z* (%) = 177 (0.09) $[M + 1]^+$, 104 (10.18), 97 (20.70), 83 (28.66), 56 (100), 41 (32.5).
7-Methyl-4,6-dioxa-5-thiaspiro[2.5]octane 5,5-Dioxide (5b)
Pale-yellow liquid (crystallized in refrigerator); yield: 6.8 g; (87%); R_f = 0.34 (hexane–EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$):
IR (neat): ν = 832, 1174, 1205, 1398, 3103 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72–0.88 (m, 2 H), 1.08–1.15 (m, 1 H), 1.38 (dd, *J* = 14.6, 2.2 Hz, 1 H), 1.37–1.43 (m, 1 H), 1.47 (d, *J* = 6.1 Hz, 3 H), 2.55 (dd, *J* = 14.6, 12.6 Hz, 1 H), 5.13 (dqd, *J* = 12.6, 6.1, 2.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.32, 12.65, 20.22, 36.73, 66.95, 82.04; MS (EI): *m/z* (%) = 178 (0.19) $[M^+]$, 98 (4.37), 70 (11.0), 56 (100), 42 (20.6). HRMS (HESI): *m/z* $[M + H]^+$ calcd for $C_6H_{11}O_4S$: 179.0373; found: 179.0371.
7-Methyl-4,6-dioxa-5-thiaspiro[2.6]nonane 5,5-Dioxide (5c)
Colorless crystals; yield: 2.5 g; (82%); mp 38–39 °C (after column chromatography); R_f = 0.45 (hexane–EtOAc, 4:1); IR (neat): 835, 1180, 1231, 1386, 3090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.64–0.77 (m, 2 H), 1.13–1.20 (m, 1 H), 1.40 (dt, *J* = 15.2, 4.0 Hz, 1 H), 1.48 (d, *J* = 6.1 Hz, 3 H), 1.75–1.83 (m, 1 H), 1.90–1.96 (m, 1 H), 2.01–2.11 (m, 1 H), 2.58–2.67 (m, 1 H), 4.86–4.94 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.73, 13.18, 21.42, 33.67, 33.87, 66.96, 82.03; MS (EI): *m/z* (%) = 193 (0.09) $[M + 1]^+$, 112 (20.48), 97 (23.32), 83 (28.79), 56 (100), 41 (22.06); HRMS (HESI): *m/z* $[M + H]^+$ calcd for $C_7H_{13}O_4S$: 193.0535; found: 193.0534.

(14) **2-Methylcyclobutanone (5a)**
The reaction mixture was analyzed by NMR (1D TOCSY). Spectroscopic data for the residue after Vigreux column distillation of a CCl_4 extract are given.
Colorless liquid; IR (CCl_4): 1785 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 7.2 Hz, 3 H), 1.52–1.62 (m, 1 H), 2.18–2.28 (m, 1 H), 2.88–2.98 (m, 1 H), 3.01–3.12 (m, 1 H), 3.27–3.37 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.03, 18.64, 44.67, 54.91, 212.48.

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(20) **Alkylation of Tertiary Cyclopropanol Sulfates 5 with Normant Homocuprates; General Procedure**
A solution of the Grignard reagent prepared from Mg (0.283 g, 11.8 mmol) and RBr (11.2 mmol) in anhyd THF (12 mL) was added dropwise to a solution of sulfate **5** (2.8 mmol) and CuI (0.64 g, 3.4 mmol) in dry THF (7 mL) at –25 °C (sat. aq $CaCl_2$/liq. N_2 bath) under argon. The mixture was stirred overnight in a freezer at –25 °C, warmed to r.t., and concentrated under reduced pressure. The residue was diluted with Et_2O (25 mL) and cooled to 0 °C (ice–water bath). The solution was treated with portions of 25 wt% H_2SO_4 (total volume 9 mL) and stirred at r.t. for 5–6 h until no cyclic sulfate was detected (TLC) and a dark-green or black precipitate formed (low-valent copper compounds). The solids were collected by filtration and washed with Et_2O (2 × 5 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), and the organic extracts were combined, washed with H_2O (2 × 20 mL), sat. aq $NaHCO_3$ (1 × 20 mL), and brine (1 × 20 mL) then dried (Na_2SO_4). The solvents were evaporated under reduced pressure and the residue was purified by column chromatography [silica gel, PE–EtOAc (20:1)].

1-(2-Methylbutyl)cyclopropanol (7a)
Colorless liquid; yield: 287 mg; (80%); R_f = 0.54 (hexane–EtOAc, 10:1); IR (neat): 3085, 3350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.37–0.42 (m, 1 H), 0.44–0.50 (m, 1 H), 0.69–0.81 (m, 2 H), 0.89 (t, *J* = 7.6 Hz, 3 H), 0.98 (d, *J* = 7.1 Hz, 3 H), 1.13–1.28 (m, 2 H), 1.41–1.52 (m, 1 H), 1.68–1.80 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.28, 13.33, 14.35, 19.56, 29.85, 32.14, 44.92, 54.44; MS (EI): *m/z* (%) = 128 (1.10) [M^+], 99 (42.2), 72 (92.9), 57 (93.9), 43 (100), 41 (52.4).

1-(2,3-dimethylbutyl)cyclopropanol (7e)
Colorless liquid; yield: 263 mg; (66%); R_f = 0.47 (hexane–EtOAc, 10:1); IR (neat): 3085, 3338, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.36–0.41 (m, 1 H), 0.46–0.51 (m, 1 H), 0.68–0.73 (m, 1 H), 0.75–0.79 (m, 1 H), 0.80 (d, *J* = 7.1 Hz, 3 H), 0.87 (d, *J* = 7.1 Hz, 3 H), 0.92 (d, *J* = 7.1 Hz, 3 H), 1.12 (dd, *J* = 14.1, 9.1 Hz, 1 H), 1.59–1.70 (m, 1 H), 1.71–1.84 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.98, 14.77, 15.65, 17.83, 20.01, 32.27, 35.89, 42.13, 54.53; MS (EI): *m/z* (%) = 142 (0.17) [M^+], 113 (3.75), 99 (21.8), 70 (71.0), 57 (26.6), 43 (100), 41 (18.0).

1-(2-Methylheptyl)cyclopropanol (7h)
Colorless liquid; yield: 319 mg; (72%); R_f = 0.40 (hexane–EtOAc, 10:1); IR (neat): 3085, 3309, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.41–0.45 (m, 2 H), 0.71–0.74 (m, 2 H), 0.86 (d, *J* = 6.1 Hz, 3 H), 0.88 (t, *J* = 7.1 Hz, 3 H), 1.08–1.16 (m, 1 H), 1.20–1.63 (m, 10 H), 1.83 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.46, 13.56, 14.11, 19.68, 23.01, 29.26, 32.72, 32.95, 35.75, 36.68, 56.09; MS (EI): *m/z* (%) = 170 (0.09) [M^+], 123 (6.58), 98 (16.2), 85 (53.7), 72 (65.1), 57 (100), 43 (90.9);

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(22) For recent examples of homocuprates for alkylation of sulfates, see: (a) Tello-Aburto, R.; Johnson, E. M.; Valdez, C. K.; Maio, W. A. *Org. Lett.* **2012**, *14*, 2150. (b) Tello-Aburto, R.; Newar, T. D.; Maio, W. A. *J. Org. Chem.* **2012**, *77*, 6271.
(23) For the reaction of Ph_2CuLi and $(CH_2{=}CH)_2CuLi$ with sulfonates of primary and secondary alcohols, see: (a) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777. (b) Kant, J.; Sapino, C. Jr.; Baker, S. R. *Tetrahedron Lett.* **1990**, *31*, 3389.
(24) (a) Mori, S.; Nakamura, E. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, **2002**, 315. (b) Nakamura, E.; Yoshikai, N. *Theory of Organocopper-mediated Reactions*, In *The Chemistry of Organocopper Compounds*; Rappoport, Z.; Marek, I., Eds.; Wiley: Chichester, **2009**, Chap. 1. (c) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339.
(25) Ashby, E. C.; Coleman, D. *J. Org. Chem.* **1987**, *52*, 4554.
(26) Spirosulfate (*R*)-**5b** was prepared by means of Sharpless procedures starting from commercially available ethyl (*R*)-3-hydroxybutanoate.
(27) Kirihara, M.; Yokoyama, S.; Kakuda, H.; Momose, T. *Tetrahedron* **1998**, *54*, 13943.
(28) **Methyl (3*R*)-3-Methylheptanoate**
Colorless liquid; yield: 461 mg; (91%); R_f = 0.81 (hexane–EtOAc, 10:1); $[\alpha]_D$ +3.08 (*c* 6.49, $CHCl_3$); IR (neat): 1742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.1 Hz, 3 H), 0.91 (d, *J* = 8.0 Hz, 3 H), 1.14–1.36 (m, 6 H), 1.89–1.98 (m, 1 H), 2.10 (dd, *J* = 13.1, 8.1 Hz, 1 H), 2.30 (dd, *J* = 13.1, 6.1 Hz, 1 H), 3.66 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.00, 19.73, 22.76, 29.10, 30.14, 36.40, 41.67, 51.27, 173.77.
(29) Taguri, T.; Yamakawa, R.; Fujii, T.; Muraki, Y.; Ando, T. *Tetrahedron: Asymmetry* **2012**, *23*, 852.

