

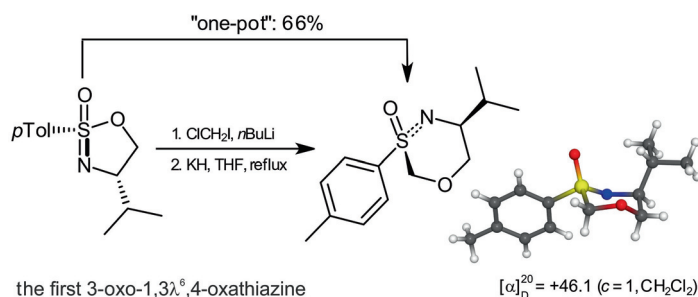
3-Oxo-1,3λ⁶,4-oxathiazines: A Novel Class of Heterocyclic S,O-Acetals

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Dedicated to Prof. D. Enders on the occasion of his 70th birthday



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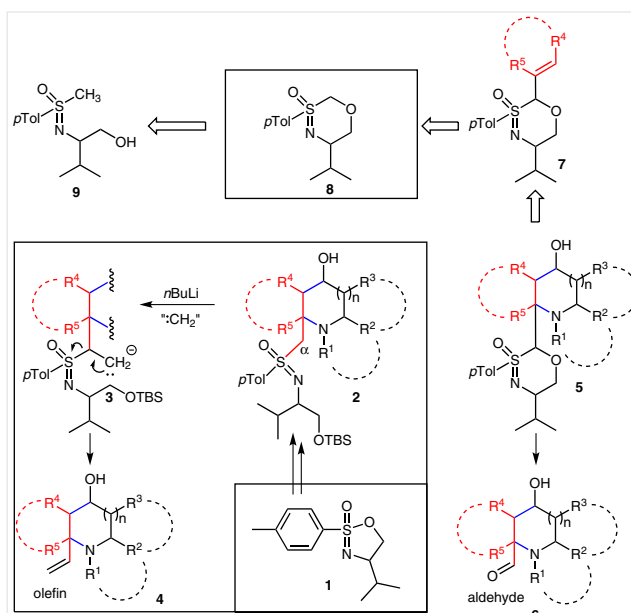
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Abstract In this study, two synthetic methods for the synthesis of a hitherto unknown class of heterocyclic diastereo- and enantiopure S,O-acetals are described. Method A involves a chemoselective monohalogenation of sulfoximines and method B a stereoselective ring opening of sulfonimidates with a carbenoid as the key step, both followed by a base-induced cyclization of the S-(halomethyl)sulfoximine intermediates. The absolute configuration of the resulting 3-oxo-1,3λ⁶,4-oxathiazines has been confirmed by X-ray structural analysis. Furthermore, the first experiments exploring the reactivity of the new compounds are described.

Key words sulfoximines, sulfonimidates, oxathiazines, carbenoids, umpolung

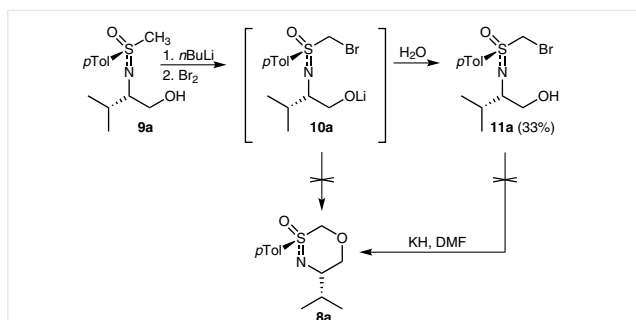
Chiral, non-racemic 2-alkenyl sulfoximines have proven to be valuable and versatile solutions for asymmetric d^3 -synthons.^{1,2} The enantiomerically pure allylic sulfoximines required were prepared either by reacting the corresponding allyllithium or Grignard compounds with cyclic sulfonimidates such as **1** (Scheme 1) or by a procedure employing a cycloalkanone and an S-methylsulfoximine like **9**.^{1b,f,h} The sulfonimidates were prepared from sulfinic acid amides of O-silylated amino alcohols.³ Deprotonation of the 2-alkenyl sulfoximines with *n*-BuLi followed by transmetalation to the corresponding titanium complex furnished a chiral carbon nucleophile that can be γ -hydroxyalkylated in a highly diastereoselective manner.^{1b,f,g} When amino aldehydes were used for this process, then the resulting vinyl sulfoximines can undergo a cyclizing Michael-type addition with the nitrogen as the nucleophile.^{1e} This sequence finally delivers diastereo- and enantiomerically pure highly substituted (poly)heterocyclic compounds as illustrated by structure **2** (Scheme 1).^{1b,e}



As is often the case with auxiliary-based asymmetric syntheses, its removal frequently poses problems. Although we found some solutions delivering either an angular methyl^{1b} or a vinyl group,^{1a} there is still room for improvement. Stimulated by the discovery that the sterically highly congested α -deprotonated sulfoximine **2** is a rather unreactive species that only reacts with small and highly reactive electrophiles like carbenoids, we thought about the possibility to introduce oxygen substitution in such a way that sulfonamide extrusion may become possible furnishing a valuable formyl group in **6** instead of the olefin **4**. After some unsuccessful experimentation with oxene precursors like lithiated

tert-butyl hydroperoxide, the idea was born to use the oxygen atom of the auxiliary itself that would lead to a special kind of an *O,S*-acetal like **5**, which in turn should easily be hydrolyzed to form the desired aldehyde **6**.

The precursor of **5** would be the α -oxygenated 2-alkenyl sulfoximine **7** which may be synthesized starting from hitherto unknown oxathiazine oxides **8**. Interestingly, this heterocyclic ring system has never been described before, for which reason we had to find a method to prepare these compounds in an enantiomerically pure state. One obvious way to reach this goal is to cyclize *S*-(halomethyl)sulfoximines, which should be accessible by halogenation of known *S*-methylsulfoximines like **9a** (Scheme 2).^{3c} In a first attempt we tried a ‘one-pot’ procedure combining the α -halogenation with the cyclization. Double deprotonation of **9a**, followed by bromination was hoped to deliver the alkoxide **10a**, which should cyclize to the desired oxathiazine **8a**.

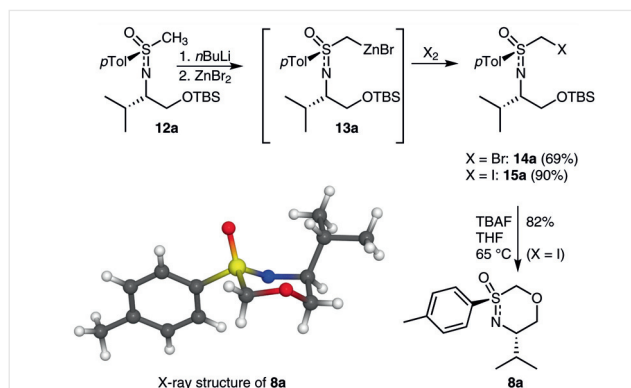


Scheme 2 Unsuccessful attempts to prepare the target heterocycle **8a**

Unfortunately, this does not happen. After aqueous workup only the hydrolysis product of the intermediate, the *S*-(bromomethyl)sulfoximine **11a** was isolated in a low yield. Moreover, unexpectedly, this compound does not cyclize under basic conditions.

A possible explanation for these disappointing results may be the increased acidity of the α -position caused by the bromination, leading to a proton exchange within **10a** yielding a carbanionic species that cannot cyclize. Therefore, we next aimed at the synthesis of *O*-silylated *S*-(halomethyl)sulfoximines that may undergo a fluoride ion induced cyclization (Scheme 3).

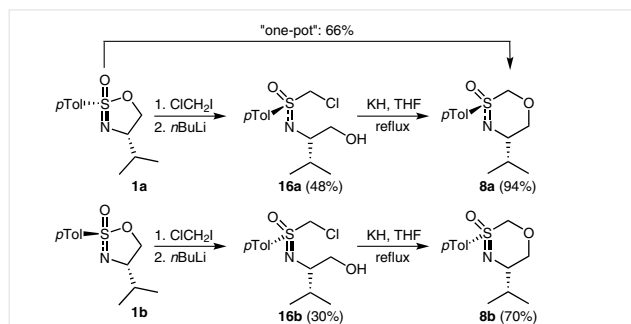
To avoid lengthy procedures involving triethylalanes,⁴ we envisioned the application of less basic zincates to avoid deprotonation of the halogenated product. In the event, we lithiated the TBS-protected *S*-methylsulfoximine **12a**,^{1f} transmetalated to the organozinc species **13a**, which undergoes clean reactions with bromine (69% yield) and especially with iodine to deliver the desired *S*-(iodomethyl)sulfoximine **15a** in 90% yield. To our delight the latter compound indeed cyclizes under the influence of tetrabutylammonium fluoride as the desilylating reagent, delivering the target oxathiazine *S*-oxide **8a** in 82% yield.



Scheme 3 First successful preparation of an oxathiazine *S*-oxide via desilylating cyclization of *S*-(iodomethyl)sulfoximine **15a**

The new compound is a white crystalline solid and we managed to obtain single crystals suited for X-ray structural analysis.⁵ From the crystal structure the expected absolute configuration R_S, S_C was confirmed.⁶ The six-membered ring adopts a chair conformation with the aryl group in an equatorial and the isopropyl group in an axial position. Despite this successful preparation, we began to think about the possibilities to shorten the route to the oxathiazines. In particular, we looked for alternatives avoiding the protection/deprotection steps associated with the described silyl ether chemistry.

As early as 1986 Matteson showed that in situ generated chloromethyl lithium obtained by reaction of *n*-butyllithium or methyl lithium with chloriodomethane can be used to prepare chlorohydrins or epoxides from aldehydes.⁷ Based on these observations we wondered whether it would be possible to use the diastereomeric sulfonimidates **1a** and **1b** as electrophiles in Barbier-type reactions with the dihalomethane and *n*-BuLi (Scheme 4).



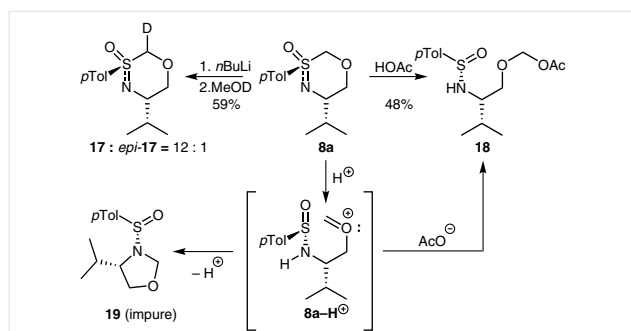
Scheme 4 The carbenoid route to the oxathiazine *S*-oxides

To our delight this turned out to be a feasible route to the *S*-(chloromethyl)sulfoximines **16a** and **16b**. The moderate yields are due to instabilities of the products towards the workup conditions and column chromatography. After protection of the alcohol *ent*-**16a** as its TBS ether, it was

possible to isolate the corresponding *S*-(chloromethyl)sulfoximine in 78% yield (not shown). To be sure that the reaction with the carbenoid occurs with inversion of the sulfur configuration, we conducted an X-ray structural analysis of **16b** derived from the sulfonimidate **1b**.⁵ In accordance with the stereochemical course of reactions of the sulfonimidates with other carbon nucleophiles used so far,^{1g} inversion of the sulfur configuration was observed, thus confirming the configurations given for **16a** and **16b** in Scheme 4. Their conversion into the target oxathiazines **8a** and **8b** proceeded smoothly by refluxing the precursors in the presence of potassium hydride in THF. Their relative and absolute configurations were also verified by crystal structural analyses.⁵ Finally, we found that a one-pot procedure, avoiding the yield losses due to the already mentioned work-up problems with the intermediates **16**, was the superior variant maximizing yield and minimizing the number of steps (Scheme 4).

With the new compounds at hand, we next explored the possibility to deprotonate the α -position and the reactivity of the potential carbon nucleophile towards electrophilic substitution (Scheme 5). Furthermore, the anticipated ring cleavage under acidic conditions was of interest. As hoped, it was possible to lithiate **8a** with *n*-BuLi in THF at low temperatures and to deuterate the resulting carbanionic species with methanol-*d*₁. Interestingly, not only was it possible to isolate the deuterated compound **17** in a reasonable yield of 59%, but it turned out that this deuteration was quite stereoselective. The ratio of the two diastereomers **17** and *epi*-**17** was around 10:1 (judged by ²H NMR spectroscopy of the mixture) in favor of an isomer with unknown configuration at the new stereogenic center. It should be noted that the crude reaction mixture contains a second (non-deuterated) compound of unknown structure, which surprisingly was not the expected hydrolysis product (the sulfinic acid amide of valinol; checked by comparison with an authentic sample) of the oxathiazine. Treatment of **8a** with concentrated acetic acid leads, presumably via the oxonium ion **8a-H** to the transacetalization product **18**, thus proving the expected hydrolyzability of the *S,O*-acetal-like moiety in the oxathiazine *S*-oxide. Finally, it should be noted that the new heterocyclic compounds are not stable at room temperature on the month timescale. Even in the solid state they are prone to decomposition, forming complex mixtures containing *N*-sulfinylated oxazolidines like **19**, probably again via the ring-opened intermediate **8a-H**.

In conclusion, we developed methods for the synthesis of *S*-(bromomethyl)- and *S*-(iodomethyl)sulfoximines like **14a** and **15a**, starting from the corresponding *S*-methylsulfoximine **12a** in good yields without resorting to aluminates. Furthermore, a direct asymmetric synthesis of *S*-(chloromethyl)sulfoximines **16** by reaction of sulfonimidates **1** with chloromethyl lithium has been developed. These reactions, whose stereochemical course was secured by X-ray



Scheme 5 Selective deuteration and transacetalization of **8a**

structural analyses, are the first instances of carbenoid reactions leading to sulfoximines. The resulting *S*-(halomethyl)sulfoximines were cyclized to hitherto unknown 3-oxo-1,3 λ ⁶,4-oxathiazines **8**; the potential of these compounds as solutions for asymmetric *d*¹ and *d*³-synthons will be explored in the future.

All solvents used were dried with appropriate drying agents and distilled under an argon atmosphere prior to use. Moisture sensitive steps were carried out under an argon atmosphere, using flame-dried glassware and syringe/Schlenk techniques. Unless otherwise stated, sat. aq NaHCO₃ and sat. aq Na₂S₂O₃ solutions were used. TLC was performed on SilG/UV254 (Macherey Nagel & Co.). Chromatographic separations were carried out on Merck silica gel 60 (15–40 μ m) at 2–3 bar. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Specific optical rotations were determined on a Perkin-Elmer Polarimeter 241 with Haake D8 thermostat in 1-dm cuvettes. NMR spectra were measured on Bruker AC 300 or DRX 500 spectrometers using TMS as internal reference. Mass spectra were run on a Bruker-Franzen Esquire LC mass spectrometer (MS (ESI)) and on a double-focusing spectrometer MAT 95 (EI-MS). Elemental analyses were performed on a Vario EL by Elementar. The crystallographic data were collected at r.t. on an Enraf-Nonius CAD-4 diffractometer with CuK α radiation (λ = 1.54180 Å). The atom numbering in the experimental used for the assignment of the NMR spectra differs from IUPAC conventions and is shown in Figure 1.

(*R*_S)-*S*-(Bromomethyl)-*N*-{[(1*S*)-1-[(*tert*-butyldimethylsiloxy)methyl]-2-methylpropyl]-*S*-*p*-tolylsulfoximine (**14a**)

To a stirred solution of *S*-methylsulfoximine **12a**^{3a,c} (539 mg, 1.46 mmol, 1 equiv) in THF (2 mL) and Et₂O (10 mL), 2.5 M *n*-BuLi in hexane (0.63 mL, 1.55 mmol, 1.0 equiv) was added dropwise by syringe at –78 °C and the mixture was stirred for 30 min. After warming the mixture to 0 °C anhyd ZnBr₂ (478 mg, 2.12 mmol, 1.5 equiv) was added. The resulting suspension was stirred for 1 h at 0 °C. Then the resulting solution was added dropwise to a well-stirred solution/emulsion of Br₂ (256 mg, 1.60 mmol, 1.1 equiv) in Et₂O (5 mL) over 30 min at 0 °C. The resulting mixture was stirred for a further 15 min at 0 °C and then warmed to r.t. After the addition of Et₂O (20 mL), the mixture was washed with Na₂S₂O₃ solution (30 mL). The layers were separated and the aqueous phase was extracted with Et₂O (3 × 20 mL). The combined organic layers were dried (Na₂SO₄) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (hexane/Et₂O, 10:1) furnishing **14a** (448 mg, 69%) as a colorless oil; *R*_f = 0.41 (hexane/Et₂O, 5:1); [α]_D²⁰ –26.7 (*c* 1.05, CH₂Cl₂).

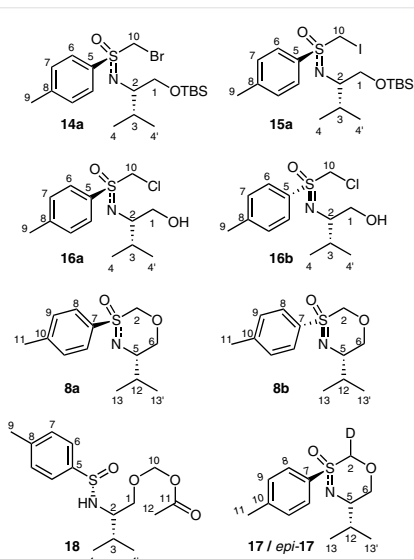


Figure 1

IR (film): 2974.6, 2930.5, 2859.6, 1597.5, 1472.0, 1382.6, 1258.4, 1181.7, 1119.7, 1019.8, 837.3, 815.1, 776.9, 718.2, 666.0 cm^{-1} .

$^1\text{H NMR}$ (500 MHz, CDCl_3 , 300 K): δ = 0.035 [s, br, 6 H, $2 \times \text{Si}(\text{CH}_3)_2$], 0.884 [s, 9 H, $\text{SiC}(\text{CH}_3)_3$], 0.945 (d, 3 H, 4-H), 1.031 (d, 3 H, 4-H'), 2.030 (dq, 1 H, 3-H), 2.443 (s, 3 H, 9-H), 3.255 (ddd, 1 H, 2-H), 3.591 (d, 1 H, 1-H), 3.622 (d, 1 H, 1-H'), 4.525 (d, 1 H, 10-H), 4.550 (d, 1 H, 10-H'), 7.329 (d, 2 H, 7-H), 7.902 (d, 2 H, 6-H); $J_{1,2}$ = 6.8 Hz, $J_{1',2}$ = 6.4 Hz, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 6.8 Hz, $J_{3,4'}$ = 6.9 Hz, $J_{6,7}$ = 8.3 Hz, $J_{10,10'}$ = 11.4 Hz.

$^{13}\text{C NMR}$ (125 MHz, CDCl_3 , 300 K): δ = -5.12, -5.30 [$2 \times \text{Si}(\text{CH}_3)_2$], 16.72 (C-4), 18.52 [$\text{SiC}(\text{CH}_3)_3$], 20.64 (C-4'), 21.71 (C-9), 26.15 [$\text{SiC}(\text{CH}_3)_3$], 30.24 (C-3), 44.66 (C-10), 62.32 (C-2), 66.19 (C-1), 129.65 (C-7), 129.99 (C-6), 134.22 (C-5), 144.33 (C-8).

MS (ESI) (MeOH): m/z (%) = 448.2 (100, $[\text{M} + \text{H}]^+$), 472.2 (95, $[\text{M} + \text{H} + 2]^+$), 470.2 (60, $[\text{M} + \text{Na}]^+$), 472.2 (70, $[\text{M} + \text{Na} + 2]^+$).

Anal. Calcd for $\text{C}_{19}\text{H}_{34}\text{NO}_2\text{Si}$ (448.53): C, 50.88; H, 7.64; N, 3.12. Found: C, 50.84; H, 7.61; N, 3.14.

(*R_S*)-*N*-[(1*S*)-1-[(*tert*-Butyldimethylsiloxy)methyl]-2-methylpropyl]-*S*-p-tolylsulfoximine (**15a**)

To a stirred solution of *S*-methylsulfoximine **12a**^{3a,c} (18.011 g, 48.73 mmol, 1.0 equiv) in THF (30 mL) and Et_2O (150 mL), 2.5 M *n*-BuLi in hexane (19.51 mL, 3.121 g, 48.73 mmol, 1.0 equiv) was added dropwise by syringe at -78°C and the mixture was stirred for 30 min. After the addition of anhyd ZnBr_2 (13.168 g, 58.47 mmol, 1.2 equiv) the mixture was warmed to 0°C within 1.5 h. Then the resulting solution was added dropwise at 0°C to a well-stirred solution of I_2 (13.604 g, 53.60 mmol, 1.1 equiv) in THF (30 mL) and Et_2O (150 mL) within 30 min. The resulting mixture was stirred for a further 15 min at 0°C and then warmed to r.t. After the addition of Et_2O (150 mL), the mixture was washed with $\text{Na}_2\text{S}_2\text{O}_3$ solution (100 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×40 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (hexane/ Et_2O , 20:1, 10:1, 3:1) furnishing **15a** (21.706 g, 90%) as a colorless oil; R_f = 0.25 (hexane/ Et_2O , 5:1); $[\alpha]_{\text{D}}^{20}$ = -11.31 (c 1.2, CH_2Cl_2).

IR (film): 3026.6, 2955.6, 2928.5, 2857.0, 1596.0, 1471.1, 1386.3, 1362.4, 1305.0, 1256.5, 1102.6, 837.0, 813.9, 775.8, 524.3 cm^{-1} .

$^1\text{H NMR}$ (500 MHz, CDCl_3 , 300 K): δ = 0.009 [s, br, 6 H, $2 \times \text{Si}(\text{CH}_3)_2$], 0.867 [s, 9 H, $\text{SiC}(\text{CH}_3)_3$], 0.945 (d, 3 H, 4-H), 1.035 (d, 3 H, 4-H'), 2.034 (dq, 1 H, 3-H), 2.447 (s, 3 H, 9-H), 3.232 (ddd, 1 H, 2-H), 3.572 (d, 2 H, 1-H), 4.460 (d, 1 H, 10-H), 4.678 (d, 1 H, 10-H'), 7.326 (d, 2 H, 7-H), 7.891 (d, 2 H, 6-H); $J_{1,2}$ = 6.6 Hz, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 6.8 Hz, $J_{3,4'}$ = 6.9 Hz, $J_{6,7}$ = 8.3 Hz, $J_{10,10'}$ = 11.2 Hz.

$^{13}\text{C NMR}$ (125 MHz, CDCl_3 , 300 K): δ = -5.29, -5.13 [$2 \times \text{Si}(\text{CH}_3)_2$], 16.78 (C-4), 18.38 (C-10), 18.52 [$\text{SiC}(\text{CH}_3)_3$], 20.59 (C-4'), 21.71 (C-9), 26.14 [$\text{SiC}(\text{CH}_3)_3$], 30.30 (C-3), 62.17 (C-2), 66.00 (C-1), 129.66 (C-7), 129.84 (C-6), 134.60 (C-5), 144.23 (C-8).

MS (ESI) (MeCN): m/z (%) = 188.9 (100), 496.0 (3, $[\text{M} + \text{H}]^+$), 518.0 (26, $[\text{M} + \text{Na}]^+$), 534.0 (5, $[\text{M} + \text{K}]^+$).

Anal. Calcd for $\text{C}_{19}\text{H}_{34}\text{INO}_2\text{Si}$ (495.53): C, 46.05; H, 6.92; N, 2.83. Found: C, 46.22; H, 6.94; N, 2.85.

(*R_S*)-*S*-(Chloromethyl)-*N*-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-*S*-*p*-tolylsulfoximine (**16a**); Typical Procedure

To a stirred solution of sulfonimidate **1a** (4.048 g, 16.91 mmol, 1 equiv) and ClCH_2I (6.1 mL, 83.57 mmol, 5 equiv) in THF (70 mL, 4 mL/mmol), 2.5 M *n*-BuLi in hexane (33.24 mL, 5.353 g, 83.57 mmol, 5 equiv) was added dropwise via syringe over 50 min at -78°C . The resulting mixture was stirred for 1 h at -78°C , and then quenched by the addition of NaHCO_3 solution (6 mL/mmol) under vigorous stirring at -78°C . After warming to r.t. with stirring, the layers were separated and the aqueous phase was extracted with Et_2O (3×100 mL). Then the combined organic extracts were dried (Na_2SO_4) and then the solvents were removed under reduced pressure. The residue was purified by flash chromatography (hexane/ Et_2O , 1:1, 1:2) furnishing *S*-(chloromethyl)sulfoximine **16a** (2.338 g, 48%) as a colorless oil; R_f = 0.09 (hexane/ Et_2O , 1:1); $[\alpha]_{\text{D}}^{20}$ = -34 (c 1, CH_2Cl_2).

IR (film): 3491.9, 2960.0, 2873.9, 1597.4, 1492.4, 1467.0, 1263.5, 1135.3, 1082.8, 1018.7, 861.5, 808.7, 711.4, 628.8, 526.8 cm^{-1} .

$^1\text{H NMR}$ (500 MHz, CDCl_3 , 300 K): δ = 1.022 (d, 3 H, 4-H), 1.041 (d, 3 H, 4-H'), 1.881 (dq, 1 H, 3-H), 2.459 (s, 3 H, 9-H), 3.016 (s, br, 1 H, OH), 3.234 (ddd, 1 H, 2-H), 3.527 (dd, 1 H, 1-H), 3.662 (dd, 1 H, 1-H'), 4.558 (d, 1 H, 10-H), 4.805 (d, 1 H, 10-H'), 7.370 (d, 2 H, 7-H), 7.938 (d, 2 H, 6-H); $J_{1,1'}$ = 11.2 Hz, $J_{1,2}$ = 8.3 Hz, $J_{1',2}$ = 2.1 Hz, $J_{2,3}$ = 5.2 Hz, $J_{3,4}$ = 6.8 Hz, $J_{3,4'}$ = 6.9 Hz, $J_{6,7}$ = 8.4 Hz, $J_{10,10'}$ = 12.3 Hz.

$^{13}\text{C NMR}$ (125 MHz, CDCl_3 , 300 K): δ = 18.72 (C-4), 20.19 (C-4'), 21.72 (C-9), 32.06 (C-3), 64.39 (C-2), 65.52 (C-1), 56.21 (C-10), 129.85 (C-7), 129.95 (C-6), 132.99 (C-5), 144.93 (C-8).

MS (ESI) (CHCl_3 , MeOH): m/z (%) = 312.1 (100, $[\text{M} + \text{Na}]^+$), 313.1 (15, $[\text{M} + \text{Na} + 1]^+$), 314.1 (38, $[\text{M} + \text{Na} + 2]^+$).

HRMS (EI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{21}\text{ClNO}_2\text{S}$: 290.0977; found: 290.0976; ± 0.003 .

(*S_S*)-*S*-(Chloromethyl)-*N*-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-*S*-*p*-tolylsulfoximine (**16b**)

Analogous to the typical procedure for **16a**, the diastereomer **16b** was prepared from sulfonimidate **1b** (10.416 g, 43.52 mmol, 1 equiv), ClCH_2I (8.6 mL, 117.51 mmol, 2.7 equiv), and 2.5 M *n*-BuLi in hexane (43.91 mL, 7.025 g, 109.67 mmol, 2.5 equiv). Flash chromatography (hexane/ Et_2O , 1:2, 1:3) gave *S*-(chloromethyl)sulfoximine **16b** (3.811 g, 30%) as colorless crystals; R_f = 0.30 (hexane/ Et_2O , 1:3); mp 91°C ; $[\alpha]_{\text{D}}^{20}$ = -51.9 (c 1, CH_2Cl_2).

IR (KBr): 3497.4, 3066.7, 3001.4, 2965.3, 2930.0, 2870.7, 1596.4, 1488.6, 1465.3, 1385.3, 1258.9, 1236.4, 1153.0, 1123.4, 1090.1, 1051.8, 981.4, 962.0, 953.1, 864.4, 807.8, 714.2, 629.0, 534.6 cm^{-1} .

^1H NMR (500 MHz, CDCl_3 , 300 K): δ = 0.950 (d, 3 H, 4-H), 0.968 (d, 3 H, 4-H'), 1.797 (dq, 1 H, 3-H), 2.454 (s, 3 H, 9-H), 2.767 (dd, 1 H, OH), 3.033 (ddd, 1 H, 2-H), 3.527 (ddd, 1 H, 1-H), 3.614 (ddd, 1 H, 1-H'), 4.622 (d, 1 H, 10-H), 4.700 (d, 1 H, 10-H'), 7.368 (d, 2 H, 7-H), 7.825 (d, 2 H, 6-H); $J_{1,1'} = 11.4$ Hz, $J_{1,2} = 8.0$ Hz, $J_{1,\text{OH}} = 4.1$ Hz, $J_{1,2'} = 3.0$ Hz, $J_{1,\text{OH}} = 9.0$ Hz, $J_{2,3} = 5.5$ Hz, $J_{3,4} = 6.8$ Hz, $J_{3,4'} = 6.8$ Hz, $J_{6,7} = 8.3$ Hz, $J_{10,10'} = 12.1$ Hz.

^{13}C NMR (125 MHz, CDCl_3 , 300 K): δ = 18.92 (C-4), 19.81 (C-4'), 21.69 (C-9), 31.92 (C-3), 59.61 (C-10), 63.72 (C-2), 65.45 (C-1), 129.91 (C-6), 130.02 (C-7), 132.31 (C-5), 144.77 (C-8).

MS (ESI) (CHCl_3 , MeOH): m/z (%) = 312.1 (100, $[\text{M} + \text{Na}]^+$), 313.1 (18, $[\text{M} + \text{Na} + 1]^+$), 314.1 (41, $[\text{M} + \text{Na} + 2]^+$).

Anal. Calcd for $\text{C}_{13}\text{H}_{20}\text{ClNO}_2\text{S}$ (289.82): C, 53.87; H, 6.96; N, 4.83. Found: C, 53.98; H, 6.97; N, 4.79.

(3R,5S)-5-Isopropyl-3-oxo-3-p-tolyl-5,6-dihydro-2H-1,3 λ^6 ,4-oxathiazine (8a) from S-(Iodomethyl)sulfoximine 15a

To a stirred solution of S-(iodomethyl)sulfoximine **15a** (21.706 g, 43.80 mmol, 1.0 equiv) in THF (260 mL), 1 M TBAF in THF (87.5 mL, 87.61 mmol, 2.0 equiv) was added. The resulting solution was refluxed for 44 h. After cooling to r.t. and extraction with NaHCO_3 solution (100 mL) the layers were separated and the aqueous phase was extracted with Et_2O (3 \times 100 mL). The combined organic layers were dried (Na_2SO_4) and then the solvents were removed under reduced pressure. The residue was taken up in Et_2O (300 mL) and insoluble solids were filtered off. The Et_2O was removed from the filtrate under reduced pressure and the residue was recrystallized (*t*-BuOMe) furnishing **8a** (9.089 g, 82%) as colorless crystals; $R_f = 0.29$ (hexane/ Et_2O , 1:3); mp 98 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} +46.1$ (c 1, CH_2Cl_2).

^1H NMR (500 MHz, CDCl_3 , 300 K): δ = 0.980 (d, 3 H, 13-H), 1.132 (d, 3 H, 13-H'), 2.016 (m, 1 H, 12-H), 2.431 (s, 3 H, 11-H), 3.368 (m, 1 H, 5-H), 3.738 (dd, 1 H, 6-H), 3.984 (dd, 1 H, 6-H'), 4.461 (d, 1 H, 2-H), 4.757 (d, 1 H, 2-H'), 7.338 (d, 2 H, 9-H), 7.862 (d, 2 H, 8-H); $J_{2,2'} = 10.8$ Hz, $J_{5,6} = 7.1$ Hz, $J_{5,6'} = 4.1$ Hz, $J_{6,6'} = 11.8$ Hz, $J_{8,9} = 8.3$ Hz, $J_{12,13} = 6.7$ Hz, $J_{12,13'} = 6.7$ Hz.

^{13}C NMR (125 MHz, CDCl_3 , 300 K): δ = 19.47 (C-13), 19.65 (C-13'), 21.62 (C-11), 32.98 (C-12), 61.53 (C-5), 69.21 (C-6), 85.06 (C-2), 128.57 (C-8), 129.92 (C-9), 136.40 (C-7), 144.93 (C-10).

Anal. Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_2\text{S}$ (253.36): C, 61.63; H, 7.56; N, 5.53. Found: C, 61.60; H, 7.61; N, 5.43.

(3R,5S)-5-Isopropyl-3-oxo-3-p-tolyl-5,6-dihydro-2H-1,3 λ^6 ,4-oxathiazine (8a) from S-(Chloromethyl)sulfoximine 16a; Typical Procedure

To a stirred solution of S-(chloromethyl)sulfoximine **16a** (121 mg, 0.42 mmol, 1 equiv) in THF (3 mL) was added KH (18 mg, 0.45 mmol, 1.1 equiv) at 0 $^\circ\text{C}$. Then the mixture was refluxed until complete consumption of **16a** (TLC monitoring: hexane/ Et_2O , 1:1 + 1% EtNMe₂). After cooling the mixture to r.t., Et_2O (1 mL) and NaHCO_3 solution (3 mL) were added. The layers were separated and the aqueous phase was extracted Et_2O (3 \times 3 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residue was dissolved under reflux in a small quantity of *t*-BuOMe and recrystallized slowly, first at r.t. then at 4 $^\circ\text{C}$, furnishing **8a** (99 mg, 94%) as a crystalline solid.

(3R,5S)-5-Isopropyl-3-oxo-3-p-tolyl-5,6-dihydro-2H-1,3 λ^6 ,4-oxathiazine (8a) by One-Pot Procedure from Sulfonylimidate 1a

To a stirred solution of sulfonylimidate **1a** (6.779 g, 28.32 mmol, 1 equiv) and ClCH_2I (5.2 mL, 70.81 mmol, 2.5 equiv) in THF (90 mL), 2.5 M *n*-BuLi in hexane (28.35 mL, 4.536 g, 70.81 mmol, 2.5 equiv) was added dropwise by syringe over 50 min at -78 $^\circ\text{C}$. The resulting mixture was stirred for 1 h at -78 $^\circ\text{C}$, and then quenched by the addition of NaHCO_3 solution (150 mL) under vigorous stirring at -78 $^\circ\text{C}$. After warming to r.t. with stirring, the layers were separated, the aqueous phase was extracted with Et_2O (3 \times 150 mL) and the combined organic layers were dried (Na_2SO_4). All volatiles were removed under reduced pressure delivering the crude S-(chloromethyl)sulfoximine as a yellow oil.

To a stirred solution of the crude S-(chloromethyl)sulfoximine in THF (200 mL) was added KH (1.200 g, 29.92 mmol, 1.1 equiv) at 0 $^\circ\text{C}$. Then the mixture was refluxed until complete consumption of the S-(chloromethyl)sulfoximine (TLC monitoring: hexane/ Et_2O , 1:1 + 1% EtNMe₂). After cooling to r.t. and addition of Et_2O (60 mL), NaHCO_3 solution (150 mL) was added. The layers were separated and the aqueous phase was extracted with Et_2O (3 \times 100 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residue was recrystallized (*t*-BuOMe) at 4 $^\circ\text{C}$ furnishing **8a** (4.71 g, 66%) as a crystalline solid.

(3S,5S)-5-Isopropyl-3-oxo-3-p-tolyl-5,6-dihydro-2H-1,3 λ^6 ,4-oxathiazine (8b) from S-(Chloromethyl)sulfoximine 16b

Following the typical procedure for **8a** from **16a**, S-(chloromethyl)sulfoximine **16b** (3.696 g, 12.75 mmol, 1 equiv) and KH (588 mg, 14.67 mmol, 1.2 equiv) were reacted in THF. Crystallization (*t*-BuOMe) gave 3-oxo-oxathiazine **8b** (2.251 g, 70%) as colorless crystals; $R_f = 0.23$ (hexane/ Et_2O , 1:1 + 1% EtNMe₂); mp 111 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} -126.5$ (c 1, CH_2Cl_2).

IR (KBr): 2988.2, 2960.7, 2868.7, 2832.2, 1595.7, 1473.8, 1364.4, 1267.6, 1241.4, 1201.6, 1138.4, 1092.0, 1045.5, 1003.2, 915.3, 839.0, 816.0, 687.9, 599.9, 534.9, 504.3 cm^{-1} .

^1H NMR (500 MHz, CDCl_3 , 300 K): δ = 1.003 (d, 3 H, 13-H), 1.039 (d, 3 H, 13-H'), 1.758 (dq, 1 H, 12-H), 2.431 (s, 3 H, 11-H), 3.551 (dd, 1 H, 6-H_{ax}), 3.712 (ddd, 1 H, 5-H_{ax}), 4.028 (dd, 1 H, 6-H_{eq}), 4.377 (d, 1 H, 2-H), 4.655 (d, 1 H, 2-H'), 7.349 (d, 2 H, 9-H), 7.963 (d, 2 H, 8-H); $J_{2,2'} = 10.2$ Hz, $J_{5,6} = 10.7$ Hz, $J_{5,6'} = 3.8$ Hz, $J_{6,6'} = 11.0$ Hz, $J_{5,12} = 5.7$ Hz, $J_{8,9} = 8.3$ Hz, $J_{12,13} = 6.8$ Hz, $J_{12,13'} = 6.8$ Hz.

^{13}C NMR (125 MHz, CDCl_3 , 300 K): δ = 18.51 (C-13), 18.58 (C-13'), 21.68 (C-11), 32.59 (C-12), 55.38 (C-5), 69.60 (C-6), 83.19 (C-2), 129.85 (C-8), 129.92 (C-9), 133.83 (C-7), 144.96 (C-10).

Anal. Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_2\text{S}$ (253.36): C, 61.63; H, 7.56; N, 5.53. Found: C, 61.60; H, 7.59; N, 5.49.

(S₅)-N-[(1S)-1-(Acetoxymethoxymethyl)-2-methylpropyl]-p-toluenesulfonamide (18)

To a stirred solution of 3-oxo-oxathiazine **8a** (519 mg, 2.05 mmol, 1 equiv) in CH_2Cl_2 (5 mL), HOAc (371 mg, 6.15 mmol, 3.0 equiv) was added. After 4 h at r.t., Et_2O (15 mL) was added and the mixture was neutralized by washing it with NaHCO_3 solution. The aqueous layer was extracted with Et_2O (3 \times 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (hexane/ Et_2O , 1:2 + 1% EtNMe₂) furnishing *p*-toluenesulfonamide **18** (306 mg, 48%) as a colorless oil, $R_f = 0.18$ (hexane/ Et_2O , 1:2 + 1% EtNMe₂); $[\alpha]_{\text{D}}^{20} +72.9$ (c 1.01, CH_2Cl_2).

IR (film): 3213.5, 2962.0, 2931.0, 2879.3, 1744.6, 1596.5, 1491.8, 1465.3, 1367.7, 1230.0, 1165.8, 1150.8, 1135.1, 1090.4, 1066.9, 1014.5, 945.1, 812.3 cm^{-1} .

^1H NMR (500 MHz, CDCl_3 , 300 K): δ = 0.989 (d, 3 H, 4-H), 0.994 (d, 3 H, 4-H'), 1.978 (m, 1 H, 3-H), 2.067 (s, 3 H, 12-H), 2.408 (s, 3 H, 9-H), 3.257 (m, 1 H, 2-H), 3.729 (dd, 1 H, 1-H), 3.807 (dd, 1 H, 1-H'), 4.227 (d, 1 H, NH), 5.179 (d, 1 H, 10-H), 5.244 (d, 1 H, 10-H'), 7.295 (d, 2 H, 7-H), 7.607 (d, 2 H, 6-H); $J_{1,1'} = 9.9$ Hz, $J_{1,2} = 4.7$ Hz, $J_{1,2'} = 4.1$ Hz, $J_{3,4} = 6.8$ Hz, $J_{3,4'} = 6.8$ Hz, $J_{6,7} = 8.2$ Hz, $J_{10,10'} = 6.2$ Hz.

^{13}C NMR (125 MHz, CDCl_3 , 300 K): δ = 18.75 (C-4), 19.28 (C-4'), 21.04 (C-12), 21.39 (C-9), 29.93 (C-3), 60.80 (C-2), 71.16 (C-1), 89.07 (C-10), 125.49 (C-6), 129.55 (C-7), 141.37 (C-8), 142.91 (C-5), 170.52 (C-11).

MS (ESI) (MeOH): m/z (%) = 336.2 (100, $[\text{M} + \text{Na}]^+$).

MS (EI): m/z (%) = 313.0 (18, $[\text{M}]^+$), 297.0 (100, $[\text{C}_{14}\text{H}_{19}\text{NO}_4\text{S}]^+$).

HRMS (EI): m/z $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{23}\text{NO}_4\text{S}$: 313.1348; found: 313.1348; ± 0.002 .

Anal. Calcd for $\text{C}_{15}\text{H}_{23}\text{NO}_4\text{S}$ (313.41): C, 57.48; H, 7.40; N, 4.47. Found: C, 57.38; H, 7.44; N, 4.45.

(3R,5S)-5-Isopropyl-3-oxo-3-p-tolyl-5,6-dihydro-[2- ^2H]-2H-1,3,4-oxathiazine (17/epi-17)

To a stirred solution of 3-oxo-oxathiazine **8a** (241 mg, 0.95 mmol, 1 equiv) in THF (10 mL) 2.5 M *n*-BuLi in hexane (0.4 mL, 64 mg, 1.00 mmol, 1.1 equiv) was added dropwise by syringe at -78 °C and the mixture was stirred for 4 min at which point CH_3OD (1.90 mmol, 2.0 equiv) was added to the yellow solution, whereupon the yellow color disappeared immediately. The mixture was allowed to warm to r.t., and then it was washed with NaHCO_3 solution (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 \times 30 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residue was dissolved under reflux in a small quantity of Et_2O and was recrystallized at -27 °C furnishing the [^2H]-3-oxathiazines **17/epi-17** (143 mg, 59%) as a colorless crystalline solid; dr **17/epi-17** 12:1 (^2H NMR spectrum of the crude reaction mixture); $R_f = 0.32$ (hexane/ Et_2O , 1:3).

^1H NMR (500 MHz, CDCl_3 , 300 K; major): δ = 0.980 (d, 3 H, 13-H), 1.132 (d, 3 H, 13-H'), 2.022 (m, 1 H, 12-H), 2.430 (s, 3 H, 11-H), 3.379 (m, 1 H, 5-H), 3.744 (dd, 1 H, 6-H), 3.980 (dd, 1 H, 6-H'), 4.440 (d, *epi* 1 H, 2-H), 4.731 (d, 1 H, 2-H'), 7.337 (d, 2 H, 9-H), 7.863 (d, 2 H, 8-H); $J_{5,6} = 7.0$ Hz, $J_{5,6'} = 4.1$ Hz, $J_{5,12} = 7.8$ Hz, $J_{6,6'} = 11.8$ Hz, $J_{8,9} = 8.3$ Hz, $J_{12,13} = 6.7$ Hz, $J_{12,13'} = 6.7$ Hz.

^2H NMR (76.77 MHz, CDCl_3 , 300 K): δ = 4.45 (major; s, 2- ^2H), 4.74 (minor; s, *epi* 2- ^2H).

^{13}C NMR (125 MHz, CDCl_3 , 300 K; major): δ = 19.46 (C-13), 19.64 (C-13'), 21.59 (C-11), 32.94 (C-12), 61.47 (C-5), 69.11 (C-6), 84.70 (C-2), 128.56 (C-8), 129.87 (C-9), 136.32 (C-7), 144.28 (C-10).

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Supporting Information

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Primary Data

Primary data for this article are available online at <http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000085> and can be cited using the following DOI: 10.4125/pd0085th.

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