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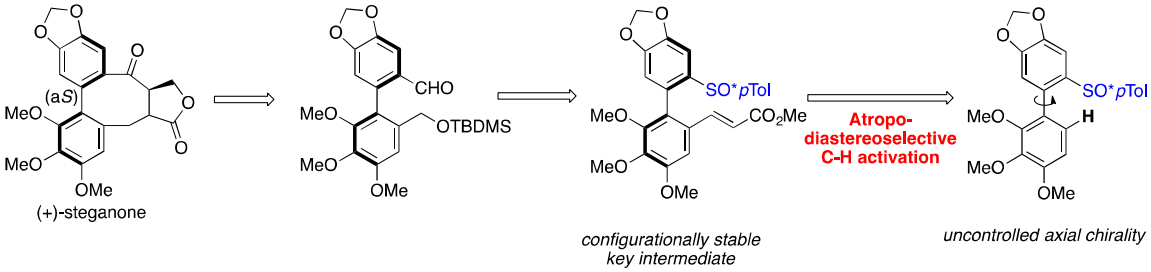

configurationally stable key intermediate

uncontrolled axial chirality

Asymmetric C-H activation as modern strategy towards expedient synthesis of steganone

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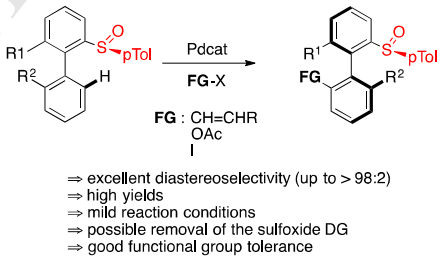
1. Introduction

Over the last decade organic chemistry and more particularly transition metal-based homogenous catalysis has been profoundly impacted by the development of C-H activation field. Such transformations enabling step- and waste economic construction of molecular scaffolds using simple, non-prefunctionalized substrates has progressively become a valuable alternative to classical metal-catalyzed cross-coupling reactions.[1] Moreover, the development of a large panel of the direct functionalization reactions unlocks the door towards expedient synthesis of complex molecular skeletons as new retrosynthetic disconnections can now be designed.[2] Accordingly, the synthetic value of the C-H activation field has been beautifully illustrated by an elegant implementation of this strategy in the total synthesis of numerous biologically active compounds like (-)-Incarviatone,[3] Verruculogen,[4] (+)-Linoxepin,[5] and Dictyodendrin[6] for example. In the majority of cases the C-H functionalization approach is utilized either to functionalize (hetero)aromatic cores or to construct cyclic moieties by means of intramolecular transformations. In contrast, related stereoselective reactions remain highly challenging and their implementation into multi-step synthesis is clearly less documented. Recently, we discovered asymmetric C-H activation reactions enabling very efficient and highly selective formation of highly substituted axially chiral biaryls.[7] Our strategy is based on the use of a chiral sulfoxide moiety as both directing group and chiral auxiliary allowing atropo-diastereoselective functionalization of a biaryl skeleton (Scheme 1). Importantly, as the sulfoxide moiety can be readily removed after the C-H activation step via sulfoxide/lithium exchange followed by an electrophilic trapping,[8] our strategy gives promise to access an almost unlimited panel of the axially chiral molecules. Consequently, this approach seems perfectly suited for the construction of high value-added scaffolds.[9]



Scheme 1 : Sulfoxide-directed atropo-diastereoselective C-H activation

Axial chirality is a key feature of many privileged ligands for both organo- and transition metal catalysis, like phosphoric acids, BINOL and BINAP for example. Besides, the atropisomerism plays also a key role in the biological activities of several natural products amongst which (-)-stegane and its related compounds like (-)-steganacine and (-)-steganone are particularly important (Fig. 1).[10]

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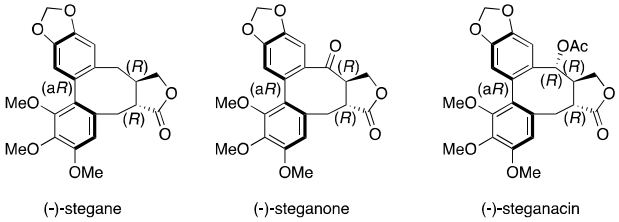
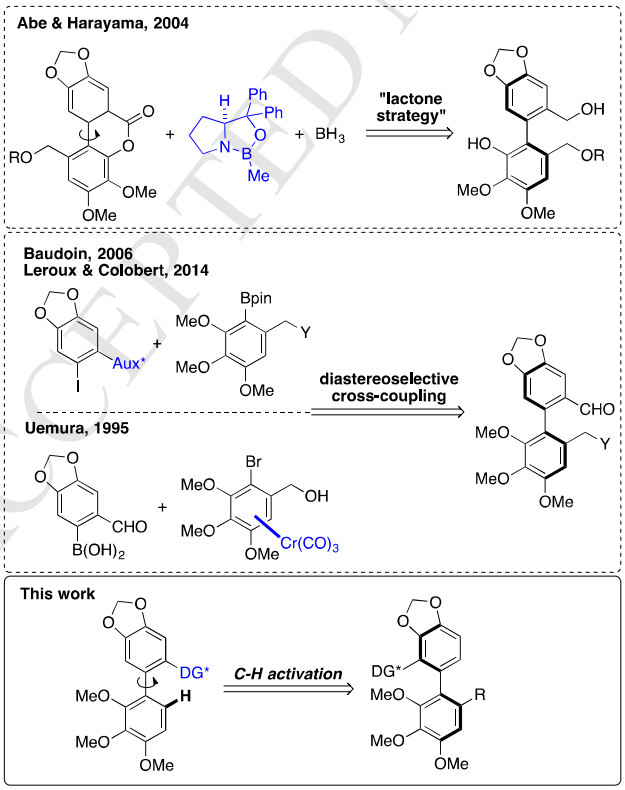


Fig. 1

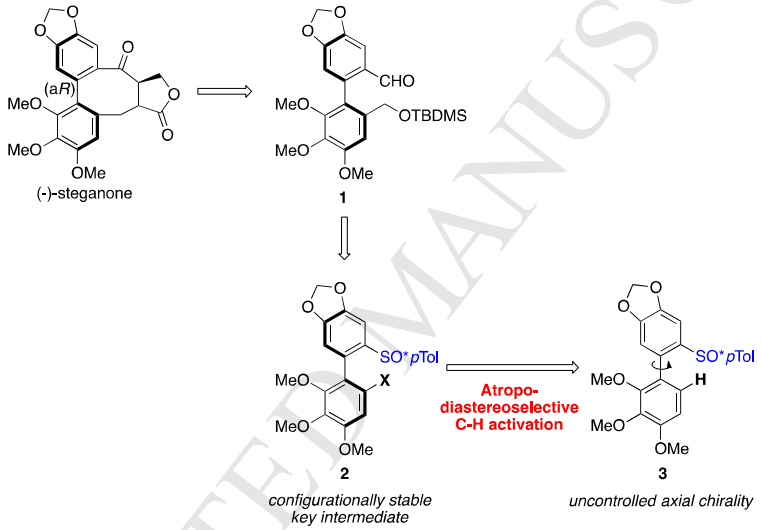
These dibenzocyclooctadiene lignan lactones isolated in 70's from *Steganotaenia araliacea* are inhibitors of tubulin polymerization into microtubules. Besides, their interesting activity against P-388 leukemia has also been evidenced. Accordingly, asymmetric synthesis of the related axially chiral scaffolds has attracted a significant interest of the scientific community (Scheme 2). In 2004 Abe and Harayama used the "lactone strategy" initially devised by Bringmann[11] and implying enantioselective opening of a configurationally instable (possible rotation around the Ar-Ar axis) lactone equivalent of a steganacine precursor, to fix the axial chirality.[12] Besides diastereoselective construction of the biaryl linkage via Suzuki-Miyaura coupling using stereogenic haloarenes bearing either central-chiral auxiliary[13] or planar-chiral (arene)chromium complex[14] proved to be a valuable solution. In particular, when β–hydroxy sulfoxide was used as the chiral auxiliary, the biaryl scaffold could be synthesized with an excellent atropocontrol (97:3 er).[15] However, this approach requires 14 steps to afford a literature reported direct precursor of (-)-steganone in a total yield of 8.3%. Accordingly, a design of more straightforward and highly stereoselective route towards such an important scaffold is challenging. Regarding the excellent atroposelection generated during our asymmetric C-H activation[7] and the traceless character of the sulfoxide directing group, we speculated that this synthetic pathway could now be used to build-up the steganone derivative in an expedient manner.



Scheme 2 : Synthetic routes towards axially chiral steganacine derivatives.

2. Results & discussion

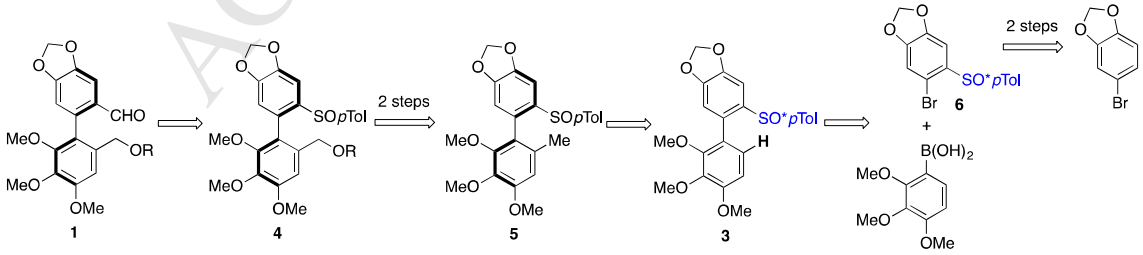
Recently, we discovered that biaryl scaffolds bearing the enantiopur sulfoxide directing group in the *ortho* position to the Ar-Ar axis are prompt to undergo, in presence of palladium catalyst, a direct metallation and subsequent C-C, C-O and C-I couplings to afford highly substituted products with excellent control of the axial chirality.[7] As these reactions are generally high yielding, tolerant to various functional groups and are compatible with very mild reaction conditions, this approach seems perfectly suited to be used in the context of a total synthesis of steganacine derivatives, and in particular, its known precursor **1** previously synthesized in our laboratory. The key step of such retrosynthetic pathway would consist on blocking the axial chirality by introducing, via an atropo-diastereoselective C-H activation, an additional substituent on the optically active biaryl precursor with uncontrolled axial chirality (Scheme 3). Accordingly, the direct asymmetric C-C is requested and the newly introduced alkyl substituent should be straightforwardly converted into a benzylic alcohol via simple functional group manipulations.



Scheme 3 : General retrosynthetic approach to the steganacine derivative 1

2.1. Retrosynthetic disconnection implying atropo-diastereoselective C-H alkylation

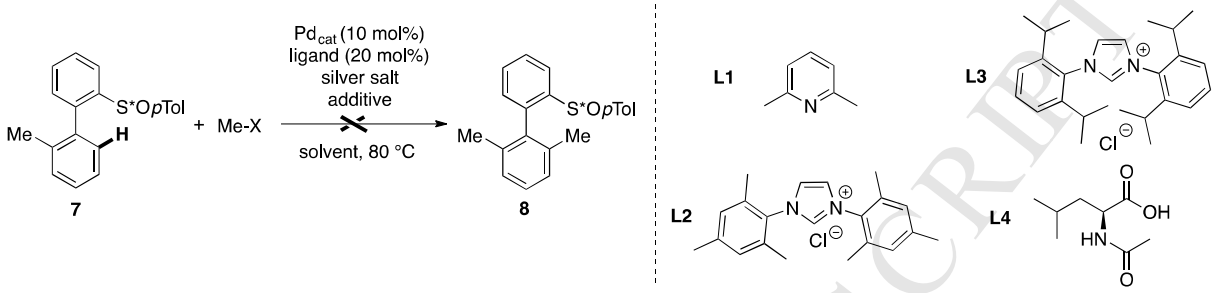
Following such hypothesis, a first retrosynthetic pathway implying an atropodiastereoselective C-H alkylation key step was designed (Scheme 4). A stereoselective introduction of the methyl substituent at the 6' position, followed by its hydroxylation should lead to the formation of a configurationally stable biaryl benzylic alcohol **4** in only 7 steps.



Scheme 4 : Retrosynthetic approach based on atropo-diastereoselective alkylation reaction.

Encouraged by our previous work on the Pd-catalyzed atropodiastereoselective direct olefination, iodination and acetoxylation, we hypothesized that a closely related alkylation, although

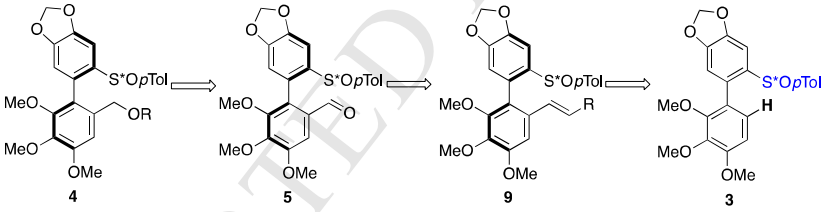
much more challenging,[16] could also be achieved using iodomethane as coupling partner (for details see SI). Disappointingly, the targeted C(sp^2)-C(sp^3) coupling between **7** and iodomethane coupling failed when using reaction conditions previously optimized for the oxidative Heck reaction (Scheme 5). Addition of ancillary ligands, such as pyridine derivative (L1), N-heterocyclic carbenes (L2 and L3) and monoprotected amino acid (L4), in presence or absence of an acidic additive (TFA or PivOH) was also fruitless. Finally, no desired product was detected when methyl boronic acid and potassium methyl trifluoroborate were employed as the coupling partners. With regard to these deceiving results, this synthetic route was abandoned.



Scheme 5 : Atropodiastereoseletive C-H alkylation of 7.

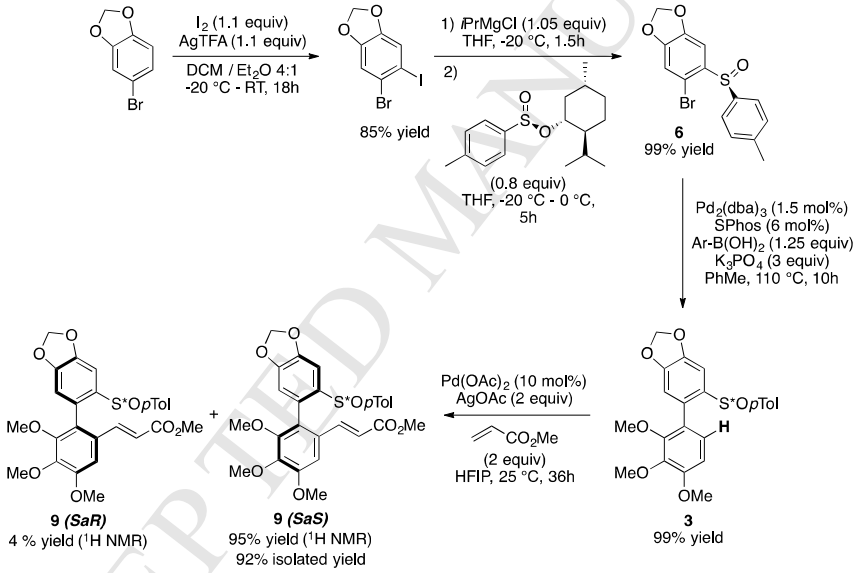
2.2. Synthesis of steganone precursor by means of atropo-diastereoselective oxidative Heck reaction.

An alternative route to prepare an axially chiral precursor of **1** is directly based on the oxidative Heck reaction, previously developed in our laboratory (Scheme 6).[7b] Indeed, an oxidative cleavage of the double bond of the C-H olefination product **9**, followed by a reduction of the corresponding aldehyde would deliver the targeted intermediate **4**.



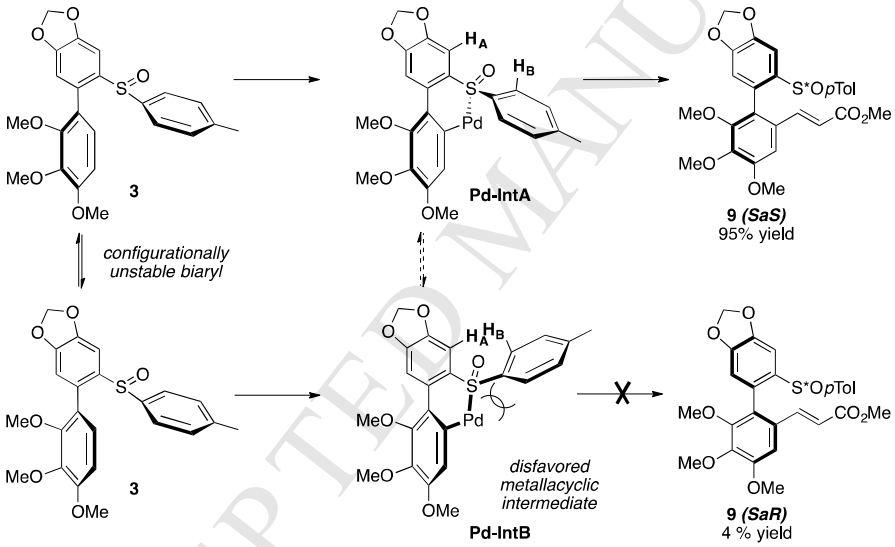
Scheme 6 : Alternative retrosynthetic approach based on atropo-diastereoselective C-H activation

We commenced our synthetic efforts by preparing the biaryl sulfoxide substrate **3** (Scheme 7). This compound may be obtained via Suzuki-Miyaura coupling between the enantiomerically pure (*S*)-bromo-6-(p-tolylsulfinyl)benzo(d)(1,3)dioxole **6** and the commercially available 2,3,4-trimethoxyphenyl boronic acid. To access **6**, iodination of 1-bromo-3,4-(methylenedioxy)benzene was firstly performed using iodine and silver trifluoroacetate.[17] The corresponding bromo-iodo derivative was reacted with *i*PrMgCl and a following trapping with the optically pure and the less expensive (*1R,2S,5R)-(S*) enantiomer of the menthysulfinate [18] afforded the desired aryl-sulfoxide **6** in enantiomerically pure form and quantitative yield. The first attempt to build up the biaryl scaffold via Suzuki coupling using $Pd(OAc)_2$ catalyst, sodium carbonate base and *tert*-butyl ammonium bromide, in water and under microwave heating was rather disappointing as the desired product was isolated in 55% yield. We speculated that the electron-richness of both coupling partners might account for this moderate efficiency. Pd-PEPPSI complex was therefore tested[19] but no improvement of this Ar-Ar coupling was observed. Finally, we were pleased to discover that applying Buchwald's conditions[20] for the Suzuki coupling the desired biaryl **3** was obtained in quantitative yield. Importantly, this reaction worked perfectly well also at 2g scale. As expected, this axially chiral compound was obtained as a mixture of two atropodiastereomers in a relatively rapid equilibrium, as indicated by NMR analysis (broad signals in ^{1}H NMR confirm that the coalescence temperature of **3** is close to



Scheme 7 : Synthesis of 9 with controlled axial chirality.

RT). **3** was subsequently submitted to our oxidative Heck reactions conditions, employing methyl acrylate coupling partner, $Pd(OAc)_2$ catalyst, silver acetate oxidant and HFIP medium. As foreseen based on our previous work, this C-H functionalization could be performed under extremely mild reaction conditions (25 °C), affording **9** quantitatively and the yield of both diastereomers of 95:4 was evaluated by ^{1}H NMR. Importantly, atropopure **9** could be isolated in 92% yield by recrystallization. The stereoselective outcome of this transformation is believed to be controlled by a distinct steric environment of the two atropodiastereomeric palladacyclic intermediates influenced by the stereogenic character of the sulfoxide moiety (Scheme 8). Based on the X-Ray structures of the closely related products previously obtained via such sulfoxide-directed atroposelective C-H activation, it can be assumed that the functionalization occurs from the opposite site of the *p*Tol-substituent of the sulfoxide. Indeed the two atropisomers of **3** are in equilibrium, formation of Pd-IntA is favored because of the reduced steric hindrance between the Pd atom and the stereogenic DG and a simultaneous minimized pseudo-allylic interaction between H_A and H_B in Pd-IntA. Consequently, the configuration of the major **9** diastereomer can be assigned as *aS*. Noteworthy, because two atropisomers of **3** are converted into (*SaS*)-**9**, this asymmetric C-H activation follows a dynamic kinetic resolution scenario. However, epimerization of the two atropisomeric palladacycles cannot be excluded.

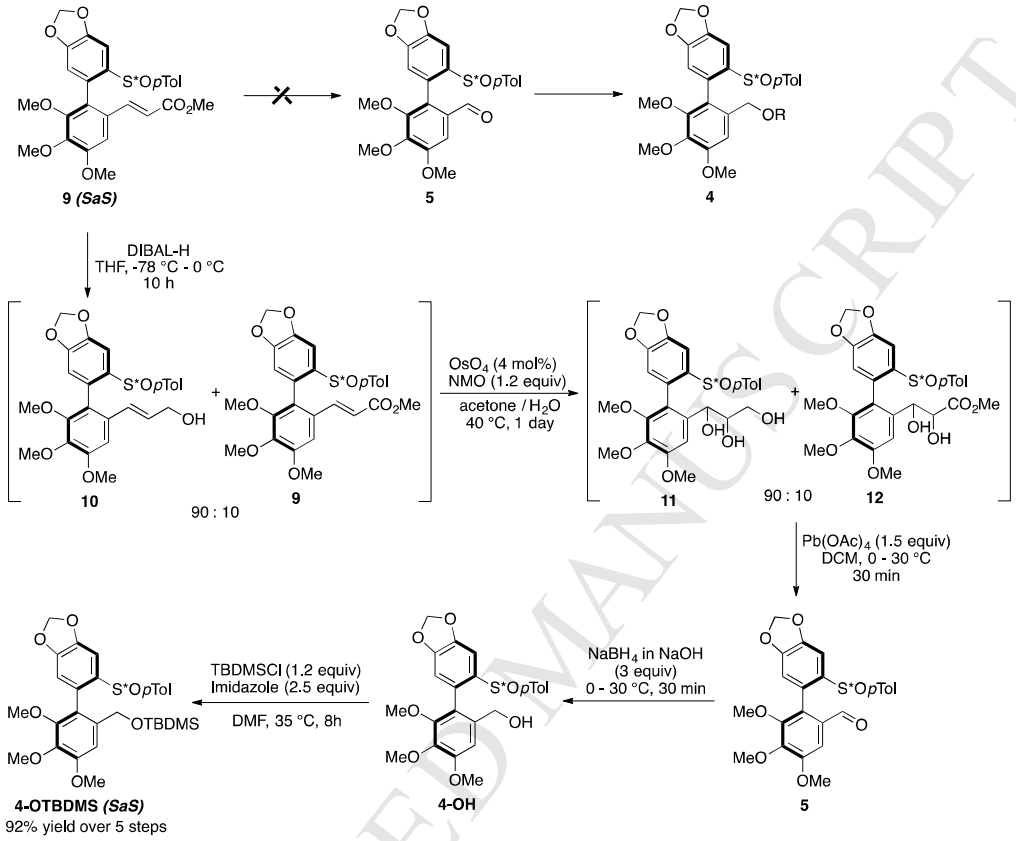


Scheme 8 : Proposed mechanism of the stereoinduction during the C-H activation step.

Once the axial chirality of the biaryl scaffold installed, the functional group interconversion is undertaken to access steganone precursor **4** (Scheme 9). Initially, ozonolysis of the alkene moiety was targeted but a complex crude mixture was obtained when performing the reaction in a mixture of CCl_4 and CH_2Cl_2 at -20 °C. Subsequently, we explored the OsO_4-catalyzed oxidative cleavage. Deceivingly, although several different oxidants (hydrogen peroxide, oxone, NMO, $NaIO_4$) and solvents (DMF, acetonitrile, water/dioxane) were tested, a clean reaction was not achieved. Addition of a weak base, such as 2,6-lutidine,[21] or phenyl boronic acid (to convert the double bond into bulky phenylboronic ester) did not produce the expected results neither.[22]

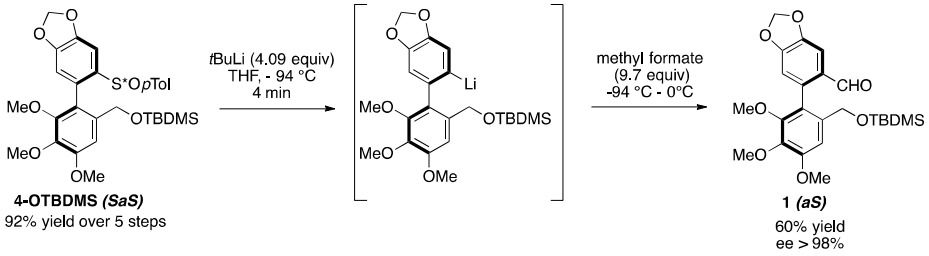
In light of these difficulties, we reasoned that the electron withdrawing character of the ester substituent of the olefin moiety accounts for the moderate reactivity of this oxidative cleavage and hence reduction of the ester group into alcohol should be beneficial. Following this hypothesis, DIBAL-H reduction of **9** was performed and the corresponding benzylic alcohol was isolated together with a small amount of the remaining starting material (9:1 mixture of **10** and **9**). This mixture was

directly engaged in the oxidative cleavage using OsO_4 catalyst and NMO oxidant in acetone/water medium. Rewardingly, the starting material was fully consumed but a complex stereoisomeric mixture of **11** and **12** was observed on TLC and LC-MS. Fortunately, this crude could be successfully converted into the desired aldehyde **5** by means of $Pb(OAc)_4$ mediated oxidative cleavage of the diol motif. Reduction of the crude **5** and subsequent protection of the corresponding alcohol delivered the atropodiastereomerically pure **4** (R = TBDMS) in an exceptional 92% yield over 5 steps.



Scheme 9 : Synthesis of 4-OTBDMS.

Completion of the targeted synthesis consists on removal of the sulfoxide directing group and concomitant installation of the aldehyde motif (Scheme 10). A cleavage of the Ar-SO*p*Tol bond in presence of lithium bases followed by an electrophilic trapping is well described in literature.[8] In the context of the synthesis of atropoenantiopure biaryl scaffolds, a major difficulty may arise from the possible atropo-epimerization when an Ar-Li intermediate is formed.[8] Aware of this sensitive step, we performed the targeted sulfoxide/lithium exchange followed by the electrophilic trapping implying methyle formate as the aldehyde precursor, using 4.09 equiv. of *t*BuLi in THF at -94 °C.[23] We were delighted to see that the targeted molecule **1** could be synthesized in a good yield of 60%. Importantly, the optical purity of **1** was maintained as confirmed by chiral HPLC analysis.



Scheme 10 : Final step – sulfoxide/lithium exchange.

3. Conclusions

In summary, we have successfully executed a formal synthesis of (+)-steganone. The herein described approach is very straightforward as the targeted scaffold is afforded in only 10 steps, amongst which 5 of them are performed without isolation of the crude products. Accordingly, the final product **1** is isolated in remarkable overall yield of 42.3% and with an enantiomeric excess above 98%. Importantly, the key step of this synthesis allowing induction of the chiral information implies the asymmetric C-H activation. Important to note is also the fact that this synthesis does not require any expensive chemicals and catalysts and all catalytic steps may be performed on multigram scale. We note that using (*S*)-sulfoxide directing group, the enantiomer of the precursor of the naturally occurring (-)-steganone is prepared. However, strictly identical synthetic approach would deliver (*aR*)-**1** if (*R*)-sulfoxide is embedded on the biaryl substrate at the beginning of this synthesis.

Accordingly, we illustrate herein that thanks to its excellent stereoselectivity, efficiency, robustness and traceless character of the DG, the sulfoxide-directed asymmetric C-H activation can be astutely employed to construct natural products, allowing design of unprecedented and very efficient synthetic strategies.

4. Experimental section

General information: Unless otherwise noted, all reagents were purchased from commercial suppliers (Sigma-Aldrich, Fluka, Acros, Alfa Aesar) and were used without further purification.

Anhydrous conditions term denotes reactions conducted under argon in dry glassware (flame-dried or oven-dried) using dry solvents: THF was distillated over Na/benzophenone. Anhydrous diethylether, dichloromethane and toluene were purchased from Aldrich (Sure/Seal packaging, kept over 3 Å molecular sieves). Molecular sieves were activated by heating at > 180 °C under vacuum overnight.

Organolithium reagents were titrated using the no-D NMR procedure. [24]

Flash chromatography refers to column chromatography using silica gel (Merck 60, 40-63 µm size), driven by pressurized air and according to the guidelines of Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43* (14), 2923.

Thin layer chromatography (TLC): was carried out using Merck Kieselgel 60 F_{254} silica gel plates.

NMR : recorded on Brücker Avance 400 or 300, the FID was treated with NMR notebook, TopSpin. The chemical shift (δ) is given relative to the residual signal of the solvent ($CHCl_3$: δ (^{1}H) = 7 .26 ppm ; δ (^{13}C) = 77.16 ppm. Broad = Br, singulet = s, doublet = d, triplet = t, quadruplet = q, multiplet = m. Specific description of signals: 7.06 (***AA'***BB'm, 2H) refers to an AA'BB' spin system using Pople notation, where the AA' multiplet part is centered at 7.06 ppm and integrates for 2 protons.

HRMS measurements were performed by Service de Spectrométrie de Masse de L'institut de Chimie at the University of Strasbourg.

Elemental Analysis measurements were performed by the Analytical, Physical Measurements and Optical Spectroscopy Service of the University of Strasbourg.

6-bromo-5-iodobenzo[*d*][1,3]dioxole[17] :

To a vigorously stirred solution of 5-bromobenzo[*d*][1,3]dioxole (1 eq., 8 g, 4.82 mL, 39.8 mmol) and silver trifluoroacetate (1.1 eq., 9.67 g, 43.8 mmol) in DCM (100 mL) at -20 °C was added dropwise

over 1 h a solution of iodine (1.1 eq., 11.1 g, 43.8 mmol) in a mixture of DCM (200 mL) and diethylether (100 mL). The mixture was then allowed back to room temperature and stirred overnight. The reaction mixture was quenched with a 10 % (w/w) solution of sodium thiosulfate, the phases were separated and the aqueous phase was extracted with diethylether. The combined organic phases were washed with a saturated $NaHCO_3$ solution, brine, and dried over sodium sulfate. The solvent was removed under reduced pressure and the crude product was recrystallized from methanol yielding 6-bromo-5-iodobenzo[*d*][1,3]dioxole (11.1 g, 33.9 mmol, 85 %).
^{1}**H-NMR** ($CDCl_3$, 400 MHz): 7.24 (s, 1H), 7.08 (s, 1H), 5.99 (s, 2H) ppm. ^{13}**C-NMR** ($CDCl_3$, 101 MHz): δ = 149.1, 147.9, 120.7, 119.1, 112.7, 102.3, 89.3 ppm

6:(*S*)-5-bromo-6-(p-tolylsulfinyl)benzo[*d*][1,3]dioxole .
To a solution of 6-bromo-5-iodobenzo[*d*][1,3]dioxole (1.25 eq., 8.13 g, 24.87 mmol) in THF (33 mL) at -20 °C was added dropwise a solution of *i-Pr*MgCl (1.306 eq., 2 M in THF, 13 mL, 26 mmol). The resulting mixture was stirred at -20 °C for 1.5 hour. The Grignard solution was cannulated to a solution of (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate[25] (1 eq., 5.86 g, 19.9 mmol) in THF (100 mL) at -20 °C and stirred at this temperature for 3 hours. The reaction mixture was then allowed back to 0 °C over 1 hour and stirred for another hour at this temperature.
The reaction was diluted with diethylether and quenched by a saturated solution of ammonium chloride. The phases were separated and the aqueous phase was extracted with diethylether. The combined organic phases were dried over sodium sulfate and the solvent was removed under reduced pressure; the crude product was then charged in a sublimator and placed under vacuum at 40 °C overnight in order to sublimate the menthol out of the crude product. The resulting solid was purified by crystallization by liquid/liquid diffusion of *n*-pentane into DCM, yielding (*S*)-5-bromo-6-(p-tolylsulfinyl)benzo[*d*][1,3]dioxole (6.7 g, 19.8 mmol, 99 %), with an enantiomeric ratio > 95 : 5.
^{1}**H-NMR** ($CDCl_3$, 400 MHz) : 7.62 (**AA'**BB'm, 2H), 7.43 (s, 1H), 7.25 (AA'**BB'**m, 2H), 6.95 (s, 1H), 6.06 (dd, J = 16.1, 1.2 Hz, 2H), 2.37 (s, 3H) ppm. ^{13}**C-NMR** ($CDCl_3$, 101 MHz): δ = 150.9, 148.8, 142.0, 142.0, 130.1 ($2C_{p\text{Tol}}$ + 1C), 125.8 ($2C_{p\text{Tol}}$), 113.0, 111.8, 106.1, 102.7, 21.6 ppm. $[\alpha]_D^{20}$ = -16.5 ° (c = 2.32, $CHCl_3$). **EA :** *Calcd. for* : (C) 49.57, (H) 3.27 ; *found* : (C) 49.50, (H) 3.32.

3:(*S*)-5-(*p*-tolylsulfinyl)-6-(2,3,4-trimethoxyphenyl)benzo[*d*][1,3]dioxole.
A sealed tube, flushed with argon, was charged with (*S*)-5-bromo-6-(*p*-tolylsulfinyl)benzo[*d*][1,3]dioxole (1 eq., 1 g, 2.95 mmol), dicyclohexyl[2-(2,6-dimethoxyphenyl)phenyl]phosphane (6.03 mol%, 73 mg, 0.178 mmol) and Tris(dibenzylideneacetone) dipalladium (1.52 mol%, 41 mg, 0.0448 mmol), along with K_3PO_4 (3.04 eq., 1.9 g, 8.95 mmol). Anhydrous toluene (20 mL) was added, followed by a solution of 2,3,4-trimethoxyphenylboronic acid (1.25 eq., 780 mg, 3.68 mmol) in anhydrous toluene (10 mL) The reaction mixture was stirred at 110 °C for 10 hours.
The reaction mixture was cooled down to room temperature and filtrated over celite. The filtrate was diluted with diethylether and washed with a 1M NaOH solution to remove unreacted boronic acid, and the aqueous phase was extracted with diethylether. The combined organic phases were concentrated to approx. 20 mL and filtrated over a silica plug. After removal of the solvent under pressure, the crude product is pure enough for most utilization. Nevertheless, flash chromatographiy (c-Hex/EtOAC) yielded analytically pure (*S*)-5-(*p*-tolylsulfinyl)-6-(2,3,4-trimethoxyphenyl)benzo[*d*][1,3]dioxole (1244 mg, 2.92 mmol, 99 %)**.**
Note : because we are near the coalescence temperature for most of the signals in ^{1}H-NMR and ^{13}C-NMR at room temperature, some signals are split (~50 : 50) between the two atropisomers in the ^{1}H spectra, whereas some are not ; however the majority of the signals are very broad. In the ^{13}C spectra

some signal are too broad to be detected. ^{1}**H-NMR** ($CDCl_3$, 400 MHz) : 7.42 (brd, 0.5H), 7.31 (Brd, 0.5H), 7.18 (Brd, 1.5 H), 7.13 (s, 2H), 7.11 (s, 1H), 6.70 (brd, 2H), 6.54 (Brd, 0.5H), 6.01 (d, J = 8.1 Hz, 2H), 3.91 (s, 3H), 3.85 (Brd, 3H), 3.79 (Brd, 1.5H), 3.32 (Brd, 1.5H), 2.30 (s, 3H) ppm. ^{13}**C-NMR** ($CDCl_3$, 101 MHz): δ = 154.2, 151.3, 149.8, 148.2, 142.4, 141.0, 129.6, 126.2, 125.4, 124.4, 110.9, 110.9, 107.0, 105.2, 104.3, 102.0, 61.1, 56.2, 27,0 21.4 ppm. **HRMS (ESI):** *calc. for* $C_{23}H_{23}O_6S^+$ 427.120 ; found 427.121.

9: methyl (*E*)-3-(3,4,5-trimethoxy-2-((a*S*)-6-((*S*)-p-tolylsulfinyl)benzo[*d*][1,3]dioxol-5-yl)phenyl)acrylate.

To a solution of (*S*)-5-(*p*-tolylsulfinyl)-6-(2,3,4-trimethoxyphenyl)benzo[*d*][1,3]dioxole (1 eq., 1244 mg, 2.92 mmol), palladium diacetate (10 mol%, 65.5 mg, 0.292 mmol) and silver acetate (2.03 eq., 990 mg, 0.305 mL, 5.93 mmol) in hfip (10 mL) was added methyl acrylate (1.9 eq., 478 mg, 0.5 mL, 5.55 mmol). The resulting mixture was stirred at 25 °C for 36 hours.
The reaction mixture was diluted with diethylether and filtrated over celite. The organic phase was washed with water, the phases were separated and the aqueous phase extracted with ethylacetate. The combined organic phases were filtrated over a silica plug and the solvent was removed under reduced pressure. Crude proton NMR showed the presence of two atropodiastereomers : methyl (*E*)-3-(3,4,5-trimethoxy-2-((a***S***)-6-((*S*)-p-tolylsulfinyl)benzo[*d*][1,3]dioxol-5-yl)phenyl)acrylate (1420 mg, 2.78 mmol, 95 %), and methyl (*E*)-3-(3,4,5-trimethoxy-2-((a***R***)-6-((*S*)-p-tolylsulfinyl)benzo[*d*][1,3]dioxol-5-yl)phenyl)acrylate (62 mg, 0.121 mmol, 4 %); total yield of methyl (*E*)-3-(3,4,5-trimethoxy-2-(-6-((*S*)-p-tolylsulfinyl)benzo[*d*][1,3]dioxol-5-yl)phenyl)acrylate (1482 mg, 2.901 mmol, 99 %) .
In order to obtain pure methyl (*E*)-3-(3,4,5-trimethoxy-2-((a*S*)-6-((*S*)-p-tolylsulfinyl)benzo[*d*][1,3]dioxol-5-yl)phenyl)acrylate, the crude mixture of both atropisomers was dissolved at room temperature in a 10 : 1 mixture of diethylether/DCM; slow evaporation of this solution yielded methyl (*E*)-3-(3,4,5-trimethoxy-2-((a*S*)-6-((*S*)-p-tolylsulfinyl)benzo[*d*][1,3]dioxol-5-yl)phenyl)acrylate (1370 mg, 2.68 mmol, 92 %) as colorless small prisms.
^{1}**H-NMR** ($CDCl_3$, 400 MHz) : 7.42 (d, J = 15.9 Hz, 1H), 7.32 (s, 1H), 7.26 (***AA'***BB'm, 2H), 7.16 (AA'***BB'***m, 2H), 7.00 (s, 1H), 6.62 (s, 1H), 6.30 (d, J = 15.9 Hz, 1H), 6.08 (dd, J = 12.5, 1.3 Hz, 2H), 3.96 (s, 3H), 3.81 (s, 3H), 3.72 (s, 3H), 3.37 (s, 3H), 2.32 (s, 3H) ppm. ^{13}**C-NMR** ($CDCl_3$, 101 MHz): δ = 167.0, 154.1, 151.6, 150.0, 148.8, 143.6, 142.1, 141.9, 141.3, 138.9, 129.8 (2 $C_{p\text{Tol}}$), 129.7, 129.3, 125.6 (2 $C_{p\text{Tol}}$), 125.6, 119.6, 111.1, 105.7, 104.9, 102.2, 61.0, 60.4, 56.2, 51.8, 21.5 ppm. $[\alpha]_D^{20}$ = -70.4 ° (c = 0.9, $CHCl_3$). **EA :** *Calcd. for* : (C) 63.52, (H) 5.13; *found* : (C) 63.40, 5.15 (H).

4-OTBDMS:*tert*-butyldimethyl((3,4,5-trimethoxy-2-((a*S*)-6-((*S*)-p-tolylsulfinyl)benzo[*d*][1,3]dioxol-5-yl)benzyl)oxy)silane.

-Step 1. To a solution of methyl (*E*)-3-(3,4,5-trimethoxy-2-((a*S*)-6-((*S*)-p-tolylsulfinyl)benzo[*d*][1,3]dioxol-5-yl)phenyl)acrylate (1 eq., 451 mg, 0.8834 mmol) in THF (2.5 mL) at -78 °C was added dropwise DIBAL (3.51 eq., 1 M in THF, 3.10 mL, 3.10 mmol). The reaction mixture was stirred at - 78°C for 4 h (TLC analysis showed low conversion), and was then allowed back to 0°C over 6 hours.
The mixture diluted with ether and was quenched by an ice-cold 1M HCL solution. The phases were separated and the aqueous phase was extracted with diethylether. The combined organic phases were washed with an 1M HCl solution, a saturated $NaHCO_3$ solution, and dried over sodium sulfate. The solvent was removed under reduced pressure, yielding approx.. 90 : 10 mixture of **10:** (*E*)-3-(3,4,5-trimethoxy-2-((a*S*)-6-((*S*)-p-tolylsulfinyl)benzo[*d*][1,3]dioxol-5-yl)phenyl)prop-2-en-1-ol / **9:** methyl (*E*)-3-(3,4,5-trimethoxy-2-((a*S*)-6-((*S*)-p-tolylsulfinyl)benzo[*d*][1,3]dioxol-5-yl)phenyl)acrylate which was directly engaged in the next step.

- ***Step 2***. The approx. 90 : 10 mixture of **10**:**9** was dissolved in acetone (6 mL), and OsO_4 (3.98 mol%, 0.08 M (2.5 % w/w) in *t*-BuOH, 440 µL, 0.0352 mmol) was added. The resulting mixture was stirred 5 min. at 25 °C, when a solution of NMO (1.2 eq., 124 mg, 1.06 mmol) in water (1.5 mL) was added. The reaction was stirred at 40 °C for 1 day, when TLC analysis (cHex/EtOAC/AcOH 3 : 7 : 0.5) and proton NMR showed complete conversion. The reaction was diluted with diethyl ether and quenched by the addition of a saturated sodium sulfite solution (8 mL) and vigorously stirred at 35 °C for 30 min. The phases were separated, and the pH of the aqueous phase was adjusted to ~1/2 with an 1 M sulfuric acid solution. The aqueous phase was then extracted with EtOAc, and the combined organic phases were washed with a saturated $NaHCO_3$ solution, dried over sodium sulfate, and the solvent was removed under reduced pressure. (*The crude product from step 2 was dried by addition of toluene (2 x ~10 mL) and removal of the solvent under reduced pressure at 60 °C.*)

-*Step 3*. Under an inert atmosphere, the crude product was dissolved in anhydrous DCM (30 mL), to which was added portion wise $Pb(OAc)_4$ (1.55 eq., 608 mg, 1.37 mmol) at 0 °C. The ice bath was removed, and the mixture was stirred at 25 °C for 30 min, when TLC analysis (*c*-Hex/EtOAc/AcOH 3 : 7 : 0.2 ; revealed with 2,4-DNPH) showed complete conversion and only one aldehyde/ketone product.
The reaction mixture was filtrated over a silica/celite plug (washed with DCM) and the solvent was removed under reduced pressure. The crude product was directly engaged in the next step.

-*Step 4*. To the crude product was added methanol (8 mL) and the resulting mixture was cooled down to 0 °C. A freshly prepared solution of $NaBH_4$ (2.99 eq., 3 M in 1 M NaOH aqueous solution, 880 µL, 2.64 mmol) was then added drop wise to the methanol solution at 0 °C. The reaction was stirred at 30 °C for 30 min., diluted with diethylether and water, and quenched by careful addition of an 1 M sulfuric acid solution. The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with a saturated $NaHCO_3$ solution, the solvent was removed under reduced pressure and the crude product was directly engaged in the next step.

-*Step 5*. To a solution of the crude product and imidazole (2.5 eq., 150 mg, 2.203 mmol) in DMF (4 mL) was added portion wise at 0 °C TBDMSCl (1.25 eq., 167 mg, 0.19 mL, 1.108 mmol). The mixture was stirred at 35 °C for 8 h, quenched by an 1 M NaOH solution, and diluted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine and dried over sodium sulfate. After removal of the solvent under reduced pressure, flash chromatography (*c*-Hex/EtOAc), yielded, over five steps, **4-OTBDMS**:*tert*-butyldimethyl((3,4,5-trimethoxy-2-((a*S*)-6-((*S*)-*p*-tolylsulfinyl)benzo[*d*][1,3]dioxol-5-yl)benzyl)oxy)silane (462 mg, 0.8094 mmol, 92 %).
^{1}**H-NMR** ($CDCl_3$, 400 MHz) : 7.36 (***AA'***BB'm, 2H), 7.19 (AA'***BB'***m, 2H), 7.19 (s, 1H), 7.04 (s, 1H), 6.63 (s, 1H), 6.04 (dd, J = 10.6, 1.4 Hz, 2H), 4.63, (d, J = 13.8 Hz, 1H), 4.42 (d, J = 13.8 Hz, 1H), 3.94 (s, 3H), 3.81 (s, 3H), 3.52 (s, 3H), 2.34 (s, 3H), 0.93 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H) ppm. ^{13}**C-NMR** ($CDCl_3$, 101 MHz): δ = 153.9, 151.1, 150.1, 148.4, 142.0, 140.9, 140.5, 138.8, 135.8, 130.6, 129.7 (2 $C_{p\text{-}Tol}$), 125.2 (2 $C_{p\text{-}Tol}$), 121.6, 110.4, 105.7, 105.7, 102.0, 62.9, 60.8, 60.6, 56.0, 26.0, 21.4, 18.4 (3 $C_{t\text{-}Bu}$), -5.2, -5.3 ppm. $[\alpha]_D^{20}$ = -102.45 ° (c = 1, $CHCl_3$). **HRMS (ESI):** *calc. for* $C_{30}H_{38}LiO_7SSi^+$ 577.227; found 577.225.

1:(a*S*)-6-(6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,3,4-trimethoxyphenyl)benzo[*d*][1,3]dioxole-5-carbaldehyde.[15]

Anhydrous conditions. To a solution of *tert*-butyldimethyl((3,4,5-trimethoxy-2-((a*S*)-6-((*S*)-*p*-tolylsulfinyl)benzo[*d*][1,3]dioxol-5-yl)benzyl)oxy)silane (1 eq., 95 mg, 0.1664 mmol) in THF (3 mL) was added quickly *tert*-BuLi (4.09 eq., 1.70 M in pentane, 0.40 mL, 0.68 mmol) at -94 °C. The color of the reaction mixture changed from pale yellow to a strong yellow/orange, and, when no more color change was evident (approx. 4 min. at – 94 °C), methylformate (9.7 eq., 96.8 mg, 0.10 mL, 1.612 mmol) was immediately added in one portion. The mixture was then stirred for 15 min at -94 °C then allowed to warm up in air to 0°C.
The reaction was quenched by a saturated ammonium chloride solution, diluted with diethylether and the phases were separated. The aqueous phase was extracted with EtOAc; the combined organic phases were dried over sodium sulfate. Flash chromatography (*c*-Hex/EtOAC from 90 : 10 to 80 : 20) yielded (a*S*)-6-(6-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,3,4-trimethoxyphenyl)benzo[*d*][1,3]dioxole-5-carbaldehyde (46 mg, 0.0995 mmol, 60 %)
^{1}**H-NMR** ($CDCl_3$, 400 MHz) : 9.50 (s, 1H), 7.46 (s, 1H), 6.96 (s, 1H), 6.68 (s, 1H), 6.10 (d, J = 7.43 Hz, 2H), 4.34 (d, J = 13.2 Hz, 1H), 4.25 (d, J = 13.2 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.61 (s, 3H), 0.88 (s, 9H), -0.03 (s, 3H), -0.03 (s, 3H) ppm. ^{13}**C-NMR** ($CDCl_3$, 101 MHz): δ = 190.5, 153.8, 152.4, 151.4, 148.1, 140.9, 137.2, 135.6, 129.7, 121.8, 111.0, 106.4, 106.1, 102.2, 63.0, 61.1, 61.0, 56.1, 26.0, 18.4 (3 $C_{t\text{-}Bu}$), -5.3, -5.3 ppm. $[\alpha]_D^{20}$ = +2.38 ° (c = 0.85, $CHCl_3$). **HRMS (ESI):** *calc. for* $C_{24}H_{32}LiO_7SSi^+$ 467.208; found 467.209. The optical purity of **1** > 98% was determined by chiral HPLC analysis using IB column (hexane/*i*PrOH 98:2, 0.5 mL/min), R_T^{major} = 14,73 min, R_T^{minor} = 15,78 min. For details see SI.
Remarks: The product **1** was manipulated with special caution to avoid its epimerization at higher temperature (evaporation of solvents using bath not exceeding 35 °C).

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Supplementary Material

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