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A new stereocontrolled entry into the anthracyclinone families. Part 1: Synthesis of bicyclic precursors of 4-demethoxy-7-deoxy-derivatives

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Abstract

A new and versatile strategy to obtain enantiomerically pure bicyclic precursors of compounds belonging to different anthracyclinone families is reported. Completely stereoselective hydrocyanation of (*R*)-4-(2,5-dimethoxyphenyl)-1-*p*-tolylsulfinyl-2-butanone and further intramolecular capture of the Pummerer intermediate generated from the resulting sulfinylcyanohydrin are the key steps to obtain the bicyclic nitrile **2** with the proper configuration and functionality at C-9.

1. Introduction

Anthracyclinone antibiotics, the powerful antitumor substances assembled by fermentation,[1] have received great attention because of their clinical usefulness in the treatment of a large variety of human cancers.[2] Thus, the naturally occurring daunomycin and adriamycin (**1a** and **1b**, Scheme 1) are increasingly used for the treatment of breast and lung cancers as well as lymphocytic and myelocytic leukemias. However, cardiotoxicity of these natural products, as well as development of resistance (acquired resistance) after initially effective systemic chemotherapy,[3] often limit the scope of their effectiveness. As a result, there has been a considerable interest in the search for new analogues, with lower undesired side effects. This is the case of the demethoxy derivatives **1c** and **1d** which exhibit lower toxicity, and 9-alkylanthracyclines,[4] **1e**, which show a clear trend for decreasing resistance factors as the 9-alkyl side-chain increases. It is therefore desirable to have a general method for the synthesis of these families of compounds, but it is more significant to be able to extend the same strategy to a large variety of analogues in all their possible configurations. Although many approaches to this end have been

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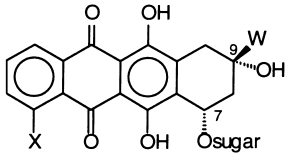
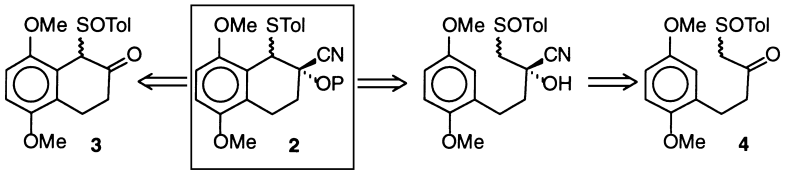
screened,[5] most of them showed the drawback of the low flexibility and the moderate stereoselectivity, as well as of lengthy sequences.



Compound	X	W
Daunomycin **1a**	OMe	COMe
Adriamycin **1b**	OMe	$COCH_2OH$
Demethoxydaunomycin **1c**	H	COMe
Demethoxyadriamycin **1d**	H	$COCH_2OH$
9-Alkylanthracyclines **1e**	H	Alkyl

Scheme 1.

As a part of our research program directed to the use of chiral sulfoxide groups for the construction of important chiral building blocks, potentially useful in the total synthesis of a broad range of natural and non-natural products,[6] we have undertaken the synthesis of the anthracyclinone family. We have envisioned that starting from the intermediate **2** (Scheme 2) with the correct configuration at the hydroxylated carbon (which will become C-9 in anthracyclinones), we would be able to obtain many such compounds, taking advantage of the fact that the problems of the creation of the hydroxylic stereogenic center at C-7,[7] the introduction of the sugar moiety[8] and the formation of the tetracyclic skeletons from the bicyclic ones[9] have been successfully solved in racemic series. In this paper we describe the synthesis of enantiomerically pure compound **2**, as well as the transformation of its CN group into the moieties usually present at C-9 in the bicyclic precursor of the different anthracyclinones.

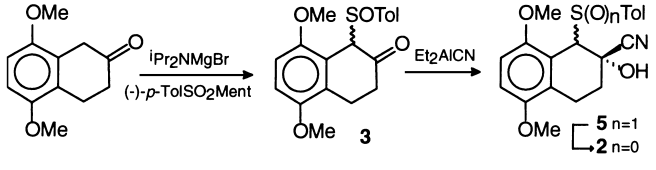


Scheme 2.

2. Results and discussion

Two different strategies were designed to prepare compound **2** (Scheme 2), starting from monocyclic and bicyclic compounds (**3** and **4**, Scheme 2) making use of the highly diastereoselective hydrocyanation of β-ketosulfoxides[10] as the key step for the preparation of the stereogenic center.

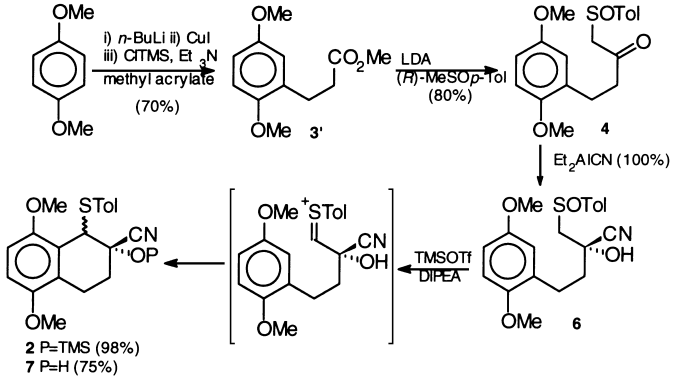
Taking into account the successful results obtained in the hydrocyanation reactions of 2-*p*-tolylsulfinyl cyclohexanone,[10b] the most direct strategy is that involving the reactions of compound **3** (prepared by sulfinylation of 5,8-dimethoxy-2-tetralone) with Et_2AlCN, yielding the sulfinyl cyanohydrin **5**, eventually easily transformed into **2** (Scheme 3). The instability of compounds **3** and **5** (prone to pyrolysis of the sulfinyl group and further aromatization) and their low enantiomeric excess (<20%) led us to abandon this strategy.



Scheme 3.

Therefore the synthesis of the key intermediate **2** was carried out starting from monocyclic β-ketosulfoxide **4** (Scheme 4), which was prepared by orthometallation of 1,4-dimethoxybenzene, sub-

sequent copper–lithium exchange prior to the 1,4-addition of the aryl copper to methyl acrylate, and final reaction of the ester with the α-lithio derivative of (*R*)-methyl *p*-tolyl sulfoxide. Reaction of **4** with Et_2AlCN in the previously reported[10a] mild conditions affords sulfinylcyanohydrin **6** in 97% yield as the sole diastereomer. The configuration of **6** was assigned as (*S*)- according to the stereochemical behavior of other acyclic β-ketosulfoxides previously studied.[10]

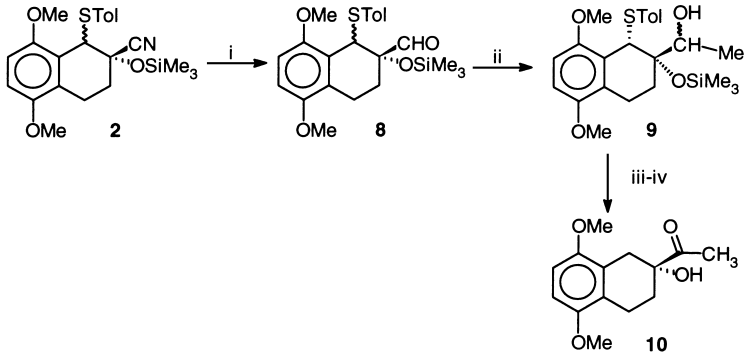


Scheme 4.

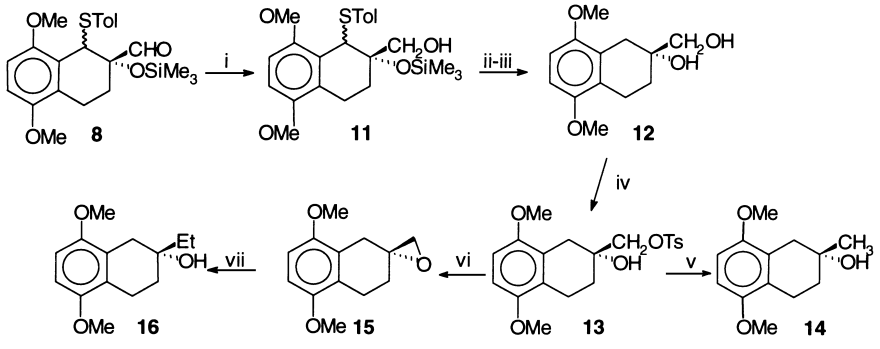
The intramolecular capture of the thionium cations, generated from sulfoxides under Pummerer conditions, has been used to form tetrahydronaphthalene derivatives in the case of activated aromatic rings.[11] On the basis of this precedent, we treated compound **6** with TMSOTf and *i*Pr_2NEt, according to the procedure reported by Craig but slightly modified.[12] The nature of the product isolated in the process of the ring closure was dependent on the method of performing the hydrolysis (Scheme 4). When the resulting reaction mixture was quenched by addition of a solution of sodium hydrogencarbonate, the alcohol **7** was isolated in 75% yield, but injecting the reaction mixture to the same basic solution afforded the silyl derivative **2**[11] in almost quantitative yield as a 9:1 mixture of two diastereoisomers, the epimers at C-1. The higher stability of the silylated cyanohydrins to dehydrocyanation made it advisable to follow the sequence with the protected alcohol.

With compound **2** in hand, we focused on some possible conversions of CN group in order to synthesize a series of bicyclic derivatives, direct precursors of 4-demethoxyanthracyclinones. The results obtained from such transformations are depicted in Scheme 5. The DIBAL reduction of the cyano group at **2** yielded the aldehyde **8**,[11] which could be used to prepare the corresponding tetracyclic aldehyde, a key intermediate in the synthesis of 14,14-difluoridarubicin.[13] The reaction of **8** with MeMgBr yielded a mixture of epimeric alcohols, which was treated with Raney-Ni to eliminate the Stol[14] group, and further oxidized to acetyl derivative **10**[15] using the conditions reported by Tomioka et al.[5c] Specific rotation of the obtained compound **10** {$[\alpha]_D^{20}$=−46.2 (*c* 1 $CHCl_3$); lit.[16a] $[\alpha]_D^{20}$=−46.3 ($CHCl_3$), and lit.[16b] $[\alpha]_D^{20}$=−47.1 (*c* 1.11 $CHCl_3$)} indicates that it was essentially optically pure and had the right configuration.

Obtention of chiral precursors of 9-alkyl anthracyclines **1e** (R=Me, Et) (Scheme 1) was carried out from **12** (Scheme 6), obtained by reduction of compound **8** with $NaBH_4$ followed by desulfenylation with Raney-Ni and further desylilation. Tosylation of the CH_2OH group of **12** and treatment with $LiAlH_4$ gave methyl derivative **14** {$[\alpha]_D^{20}$=−26.2 (*c* 1.09 $CHCl_3$), 86% ee}. Reaction of **13** with NaOH in *i*PrOH afforded the epoxide **15**, which can be used as precursor of any 9-alkyl derivative. Thus, its reaction with $Me_2Cu(CN)Li$ yielded ethyl carbinol **16** {$[\alpha]_D^{20}$=−22.8 (*c* 1.4 $CHCl_3$) 90% ee; lit.[17] $[\alpha]_D^{20}$=−24.5 (*c* 1.31 $CHCl_3$)}. The loss of optical purity observed for compounds **14** and **16** could have occurred during the desulfenylation step.[18]



Scheme 5. (i) (a) DIBAL-H (70%); (ii) MeMgBr (70%); (iii) Raney-Ni (90%); (iv) $SO_3 \cdot Py$, DMSO, Et_3N (61%)



Scheme 6. (i) $NaBH_4$ (80%); (ii) Raney-Ni (72%); (iii) *n*Bu_4NF (98%); (iv) TsCl, Py (97%); (v) $LiAlH_4$ (90%) (vi) NaOH, *i*PrOH (92%); (vii) $Me_2Cu(CN)Li$ (83%)

In summary we have presented herein a convergent synthetic approach to a series of chiral bicyclic precursors of 4-demethoxyanthracyclinones. The successful approach expanded and took advantage of our earlier studies on the stereoselective hydrocyanation mediated by a chiral sulfoxide group. This step has been efficiently coupled to the intramolecular trapping of the Pummerer intermediate generated from the sulfinylcyanohydrin to assemble the bicyclic compound **2** with the desired configuration at C-9. Modifications of these bicyclic structures in the sense the proper way for them to evolve into tetracyclic structures with X≠H (Scheme 1) in a highly regioselective manner, as well as the introduction of functionalities such as OH and CO_2R at C-10 (present in rhodomycins and aclavinomycins respectively) will be published in due course.

3. Experimental

3.1. General

All reagents were purchased from commercial suppliers and were used without further purification, unless stated otherwise. THF and ether were dried by refluxing and distilling from sodium-benzophenone ketyl immediately prior to use. Diisopropylamine and diisopropylethylamine were distilled from sodium hydroxide, methylene chloride and pyridine were distilled from calcium hydride. Chlorotrimethylsilane was distilled from calcium hydride immediately prior to use. All experiments were conducted in a dry argon atmosphere. All melting points are given uncorrected. IR spectra were taken on a Perkin–Elmer 257 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded at 200 MHz and 300 MHz with $CDCl_3$

as solvent, and tetramethylsilane as an internal standard. Mass spectra were determined at an ionization voltage of 70 eV. Microanalyses were performed by CONSEJO Laboratories, Madrid, Spain.

3.2. *Methyl-3-(2,5-dimethoxyphenyl)propionate* ***3′***

A solution of 1,4-dimethoxybenzene (10 g, 72 mmol) in 55 mL of dry THF was added to a solution of *n*BuLi (29 mL, 72.5 mmol, 2.5 M in hexane) in THF at 23°C under an argon atmosphere. After stirring for 1 h, the reaction mixture was transferred via cannula to a stirred suspension of CuI (13.78 g, 72.5 mmol) in 30 mL of dry THF at 0°C. The reaction mixture was stirred at 0°C for 1 h and the resulting green solution was cooled to −78°C before adding successively, TMSCl (50 mL, 0.36 mol), methyl acrylate (6.5 mL, 68 mmol) and Et_3N (10 mL, 72 mmol). The mixture was stirred for 48 h from −78°C to rt, hydrolyzed with 10% NH_3 in saturated aqueous NH_4Cl solution and extracted with 2×200 mL of ether. The combined extracts were washed with the ammoniacal solution until no blue color remained and finally washed with brine. The resulting colorless solution was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexane/AcOEt, 95/5) to give **3′** (16 g, 70% yield) as colorless oil. IR (film, cm^{-1}) 1720, 1430. ^1H NMR ($CDCl_3$) δ 6.73 (m, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H), 2.91 (t, J=8.3 Hz, 2H), 2.6 (t, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 172.9, 153.02, 151.20, 129.43, 115.81, 110.89, 110.51, 55.06, 54.89, 50.82, 33.45, 25.73. MS, *m/z* 224 (M^+, 100), 193 (95.9), 167 (25.4), 151 (61.28), 135 (9.47), 121 (34.63). Anal. calcd for $C_{12}H_{16}O_4$: C: 64.27, H: 7.19. Found: C: 64.20, H: 6.84%.

3.3. *(*R_S*)-4-(2,5-Dimethoxyphenyl)-1-*p*-tolylsulfinyl-2-butanone* ***4***

To a solution of LDA (20 mmol) in 20 mL of THF was added a solution of (*R*)-methyl-*p*-tolyl sulfoxide[19] (3.16 g, 20 mmol) in 20 mL of THF at −78°C. After 90 min a solution of **3** (2.2 g, 9.8 mmol) in 10 mL of THF was added dropwise. After 2 h sat. NH_4Cl (20 mL) was added and the cool bath was removed. The mixture was stirred for 10 min and then acidified with 7% HCl. Ether (30 mL) was added and the phases were separated. The aqueous phases were combined and extracted twice with ether (20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Solvent was removed in vacuo and the residue was purified by flash chromatography (50% AcOEt/hexane) yielding **4** (2.7 g, 80% yield) as a white solid. Mp=78–80°C, $[\alpha]_D^{20}$=+149 (*c* 1.01 $CHCl_3$). IR (film, cm^{-1}): 1700, 1040. ^1H NMR ($CDCl_3$) δ 7.41 (AA′BB′, J=8.1 Hz, 4H), 6.71 (m, 3H), 3.8 (AB, J_{AB}=13.5 Hz, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 2.77 (m, 4H, 2×CH_2), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 201, 151.48, 142.04, 139.62, 129.98, 129.53, 123.94, 116.36, 111.45, 110.95, 68.11, 55.56, 44.74, 24.51, 21.32. MS, *m/z* 346 (M^+, 17.5), 330 (9.3), 222 (8.9), 207 (19.5), 165 (14.8), 151 (100), 121 (35.8), 105 (6.1), 91 (34.9) 77 (22.9). Anal. calcd for $C_{19}H_{22}O_4S$: C, 65.88; H, 6.40. Found: C, 66.01; H, 6.37%.

3.4. *(2*S,R_S*)-2-Cyano-4-(2,5-dimethoxyphenyl)-1-(*p*-tolylsulfinyl)-2-butanol* ***6***

A solution of **4** (3.5 g, 10 mmol) in 30 mL of dry THF was added dropwise to Et_2AlCN (20 mL, 20 mmol, 1 M in toluene) under argon at −35°C. The mixture was stirred for 5 min and then transferred via cannula into 60 mL of MeOH/$HCl_{conc.}$ 1/1 at −78°C. The resulting mixture was stirred for 15 min and poured carefully into 200 g of ice with 30 mL of $HCl_{conc.}$. CH_2Cl_2 (50 mL) was added and the phases were separated. The aqueous phase was extracted with 2×50 mL of CH_2Cl_2. The organic phases were combined, dried over Na_2SO_4 and evaporated in vacuo yielding pure **5** (3.6 g, 97% yield) as a white solid. Mp=119–120°C, $[\alpha]_D^{20}$=+144 (*c* 1 $CHCl_3$). IR. (film, cm^{-1}): 3500–3300, 1500, 1200, 1050. ^1H NMR

($CDCl_3$) δ 7.48 (AA′BB′, J=8.2 Hz, 4H), 6.73 (m, 3H), 5.99 (s, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.0 (AB, J_{AB}=13.2 Hz, 2H), 2.86 (m, 2H), 2.45 (s, 3H), 2.07 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 153.41, 151.47, 142.99, 138.91, 130.42, 123.96, 119.33, 116.13, 11.73, 11.12, 70.81, 62.50, 55.62 (2C), 41.05, 24.88, 21.43. Anal. calcd for $C_{20}H_{18}SO_4N$: C, 64.33%; H, 6.20%; S, 8.58%; N, 3.75%. Found: C, 64.52%; H, 6.50%; S, 8.28%; N, 3.55%.

*3.5. (*1S,2S*)-2-Cyano-1,2,3,4-tetrahydro-5,8-dimethoxy-*O*-trimethylsilyl-1-(*p*-tolylthio)-2-naphthol **2***

To a solution of **6** (3.6 g, 9.6 mmol) in 30 mL of dry CH_2Cl_2 under argon at 0°C was added TMSOTf (8.4 mL, 43.2 mmol, 4.5 equiv.) and *i*Pr_2NEt (7.5 mL, 43.2 mmol, 4.5 equiv.). The cold bath was removed and the mixture was stirred for 30 min. The mixture was transferred via a cannula into a saturated aqueous solution of $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with 2×10 mL of CH_2Cl_2. The organic phases were combined and washed with brine, dried over Na_2SO_4 and evaporated in vacuo. Purification by flash chromatography (hexane/AcOE, 14/1) yielded **2** (4 g, 97% yield) as a mixture of epimers at C-1 (9/1). Mp=142–144°C, major isomer $[\alpha]_D^{20}$=+288.6 (*c* 0.5 $CHCl_3$). IR (film, cm^{-1}): 2950, 1480, 1260, 1140, 1090. ^{1}H NMR ($CDCl_3$) δ 7.27 (AA′BB′, J=8.0 Hz, 4H), 6.69 (s, 2H), 4.96 (d, J_W=2.3 Hz, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 2.74 (m, 2H, CH_2), 2.33 (s, 3H, Me), 2.16 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ 150.72, 150.56, 136.76, 133.69, 132.73, 132.0, 129.40 (2C), 129.12, 108.92, 108.29, 72.26, 55.67, 55.34, 53.57, 29.72, 22.10, 21.15, 1.07. MS, *m/z* 427 (M^+, 34.6), 304 (100), 263 (8.8), 205 (94.4), 177 (87.9), 123 (15.6), 91 (17.9), 73 (64.2). Anal. calcd for $C_{23}H_{19}SO_3NSi$: C, 64.61%; H, 6.83%; S, 7.49%; N, 3.27%. Found: C, 64.39%; H, 7.02%; S, 7.23%; N, 3.09%.

*3.6. (*1S,2S*)-2-Cyano-1,2,3,4-tetrahydro-5,8-dimethoxy-1-(*p*-tolylthio)-2-naphthol **7***

When the reaction mixture was hydrolyzed by addition of a solution of $NaHCO_3$ the unprotected product was obtained. After chromatography purification (hexane/AcOEt, 7/3) **6** was obtained as a solid in 75% yield. Mp=134–136°C. IR (film, cm^{-1}) 2940, 1480, 1260, 1110, 1070. ^{1}H NMR ($CDCl_3$) δ 7.3 (AA′BB′, J=8.0 Hz, 4H), 6.72 (s, 2H), 4.96 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.16–2.7 (m, 3H), 2.35 (s, 3H), 2.33 (m, 2H).

*3.7. (*1S,2R*)-2-Formyl-1,2,3,4-tetrahydro-5,8-dimethoxy-*O*-trimethylsilyl-1-(*p*-tolylthio)-2-naphthol **8***

To a solution of **2** (4.2 g, 9.8 mmol) in 40 mL of dry THF at room temperature was added DIBAL-H (14.7 mL, 1.5 equiv., 1 M in toluene). The mixture was stirred 1 h and then poured carefully into 100 mL of 5% H_2SO_4. CH_2Cl_2 (50 mL) was added and the phases were separated. The aqueous phase was extracted with 2×25 mL of CH_2Cl_2. The organic phases were combined, washed with brine, dried over Na_2SO_4 and evaporated in vacuo. The residue was crystallized from ether/hexane. Compound **8** was obtained as a white solid (3.2 g, 76% yield, mixture of epimers at C-1 (9/1)). Major isomer: mp=134.4–135.7°C, $[\alpha]_D^{20}$=+280.6 (*c* 0.24 $CHCl_3$). IR (film, cm^{-1}): 2950, 1730, 1480, 1260, 1080. ^{1}H NMR ($CDCl_3$) δ 9.35 (d, J=1.4 Hz, 1H), 7.27 (AA′BB′, J_{AB}=8.1 Hz, 4H), 6.63 (s, 2H), 4.81 (d, J=2.3 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3–2.4 (m, 4H), 2.3 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 198.62, 150.73, 150.33, 136.11, 134.08, 132.67, 132.05, 131.77, 128.84, 125.00, 124.16, 108.42, 107.63, 80.38, 55.45, 55.17, 49.30, 25.27, 21.66, 20.87, 2.03, 0.73. MS, *m/z* 430 (M^+ 3.17), 307 (27.3), 279 (71.3), 189.1 (21.4), 91 (10.0), 73 (100). Anal. calcd for $C_{23}H_{30}SO_4Si$: C, 64.15%; H, 7.02%; S, 7.44%. Found: C, 63.88%; H, 7.03%; S, 7.45%.

3.8. (1S,2R,1′R), (1S,2R,1′S)-1,2,3,4-Tetrahydro-2-(1-hydroxyethyl)-5,8-dimethoxy-O-trimethylsilyl-1-(p-tolyl thio)-2-naphthol **9**

To a solution of **8** (3.2 g, 7.4 mmol) in 30 mL of dry THF under argon at 0°C was added MeMgBr (5 mL, 2 equiv., 3 M in ether). The ice bath was removed and the mixture was stirred for 4 h. The mixture was cooled at 0°C and 10 mL of sat. NH_4Cl was added. CH_2Cl_2 (15 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2×15 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4 and evaporated in vacuo. Purification by flash chromatography (hexane/AcOEt, 9/1) afforded diol **9** (2.2 g, 68% yield) as a mixture 1/1 of epimers at the secondary hydroxylic center. Mp=130–132°C, $[\alpha]_D^{20}$=+200.2 (*c* 0.55 $CHCl_3$). IR (film, cm^{-1}): 3500, 2920, 1250, 1080. ^1H NMR ($CDCl_3$) δ 7.15 (m, 8H, 2×AA′BB′), 6.59 (m, 4H), 5.20 (d, J=2.4 Hz, 1H), 4.67 (d, J=2.0 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.59 (s, 3H), 3.56 (s, 3H), 3.1–2.85 (m, 2H), 2.8–2.2 (m, 12H), 1.9 (m, 2H), 1.47 (d, J=9.5 Hz, 1H), 1.17 (d, J=6.4 Hz, 3H), 1.11 (d, J=6.2 Hz, 3H), 0.14 (m, 18H). ^{13}C NMR ($CDCl_3$) δ 151.29, 151.01, 150.61, 135.66, 135.32, 135.10, 134.59, 129.80, 128.95, 128.84, 128.44, 127.09, 126.69, 124.94, 123.99, 108.08, 107.96, 107.80, 80.38, 80.21, 68.76, 68.25, 55.62, 55.50, 50.09, 48.73, 27.47, 26.85, 22.39, 21.99, 20.98, 17.26, 3.10, 2.93. MS, *m/z* 446 (M^+, 6.3), 279 (100), 264 (16.6), 189 (16.8), 124 (7.1), 91 (11.3), 73 (49.1). Anal. calcd for $C_{24}H_{34}SO_4Si$: C, 64.55%; H, 7.68%; S, 7.17%. Found C, 64.75%; H, 7.37%; S, 7.17%.

3.9. (R)-(−)-2-Acetyl-1,2,3,4-tetrahydro-5,8-dimethoxy-2-naphthol **10**

To a solution of **8** (98 mg, 0.22 mmol) in 5 mL of EtOH at room temperature was added Raney-Ni under argon atmosphere. The mixture was stirred for 90 min. The mixture was filtered through a pad of Celite and the solvent was evaporated under reduced pressure. The resulting oil was dissolved in ether and 5 mL of 7% HCl was added. It was stirred for 5 min and the phases were separated. The aqueous phase was washed with 2×10 mL of ether. The organic phases were combined, dried over Na_2SO_4 and evaporated in vacuo. Purification by flash chromatography (hexane/AcOEt, 1/1) afforded **9** (50 mg, 90% yield) as a white solid. Diol **9** was oxidized as described[5c] (SO_3·Py (318 mg, 10.25 equiv.), Et_3N (0.7 mL), DMSO (0.7 mL)). Purification by flash chromatography (AcOEt/hexane, 3/7) yielded **10** as a solid (21.6 mg, 56% yield) $[\alpha]_D^{20}$=−46.2 (*c* 1 $CHCl_3$) (lit.[16a] $[\alpha]_D^{20}$=−46.3 ($CHCl_3$), lit.[16b] $[\alpha]_D^{20}$=−47.1 (*c* 1.11 $CHCl_3$). IR (film, cm^{-1}): 3500, 1700, 1480, 1260, 1090. ^1H NMR ($CDCl_3$) δ 6.66 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.65 (br s, 1H, OH), 3.1–2.7 (m, 4H), 2.32 (s, 3H), 1.95 (m, 2H).

3.10. (1S,2R)-(+)-1,2,3,4-Tetrahydro-2-hydroxymethyl-5,8-dimethoxy-O-trimethylsilyl-1-p-tolylthio-2-naphthol **11**

To a solution of **8** (640 mg, 1.48 mmol) in 5 mL of absolute EtOH at 0°C was added $NaBH_4$ (1.5 equiv.). The mixture was stirred for 30 min and two drops of AcOH were added. EtOH was removed in vacuo and the residue was dissolved in 10 mL of CH_2Cl_2 and washed with brine. The phases were separated and the aqueous phase was extracted with 10 mL of CH_2Cl_2. The organic phases were combined and dried over Na_2SO_4. The solvent was evaporated in vacuo yielding **11** (570 mg, 90% yield) as a white solid. Mp=122.8–123.4°C, $[\alpha]_D^{20}$=+120 (*c* 0.7 $CHCl_3$). IR (film, cm^{-1}): 2940, 1480, 1150. ^1H NMR ($CDCl_3$) δ 7.19 (AA′BB′, J=8.1 Hz, 4H), 6.62 (s, 2H), 4.9 (d, J=2.1 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.46 (m, 3H), 2.96 (m, 1H), 2.53 (m, 2H), 2.30 (s, 3H), 1.9 (m, 1H), 0.11 (s, 9H, TMS). ^{13}C NMR ($CDCl_3$) δ 150.66, 150.45, 135.22, 134.82, 129.81, 128.56, 126.09, 123.55, 107.74, 107.63, 77.95, 66.22, 55.22, 54.99, 48.87, 27.46, 21.70, 20.64, 2.19. MS, *m/z* 432 (M^+, 16.34), 309 (31), 278 (56.5),

219 (100), 177 (90.8), 124 (21.4), 91 (30.7), 73 (92.1). Anal. calcd for $C_{23}H_{30}SO_4SiC$: C, 63.87%; H, 7.45%; S, 7.39%. Found: C, 63.98%; H, 7.41%; S, 7.63%.

*3.11. (R)-(−)-1,2,3,4-Tetrahydro-2-(hydroxymethyl)-5,8-dimethoxy-2-naphthol **12***

To a solution of **11** (460 mg, 1.06 mmol) in 20 mL of EtOH was added Raney-Ni in excess under argon. The mixture was stirred overnight, filtered through a pad of Celite and the solvent was removed in vacuo. The solid was dissolved in 5 mL of THF under argon. At 0°C, 1.1 equiv. of *n*Bu_4NF (1 M in THF) was added dropwise. After 3 min water (5 mL) and 5 mL of ether were added and the organic phases were separated. The aqueous phase was extracted with 2×10 mL of ether. The organic phases were combined and dried over Na_2SO_4. The solvent was evaporated in vacuo yielding diol **12** (182 mg, 72% yield) as a white solid. Mp=145.5–146.5°C, $[\alpha]_D^{20}$=−27.4 (*c* 0.55 acetone). IR (film, cm^{-1}): 3600–3400, 1480, 1240, 1100. ^{1}H NMR ($CDCl_3$) δ 6.64 (s, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.53 (m, 3H), 2.76 (m, 5H), 1.7 (m, 2H). ^{13}C NMR (CD_3OD) δ 153.98, 153.43, 126.58 (2C), 108.83 (2C), 72.33, 71.18, 56.84, 34.24, 31.32, 22.00. MS, *m/z* 238 (M^+ 89.3), 220 (25.9), 207 (84.7), 189 (100), 177 (23.5), 164 (39.1), 149 (35.4), 131 (12.5), 91 (24.8), 77 (21.1). Anal. calcd for $C_{13}H_{18}O_4$: C, 65.53%; H, 7.61%. Found: C, 65.40%; H, 7.59%.

*3.12. (R)-(−)-1,2,3,4-Tetrahydro-5,8-dimethoxy-2-methyl-2-naphthol **14***

To a solution of **12** (217 mg, 0.9 mmol) in 7 mL of pyridine at rt was added TsCl (1.5 equiv.). After 15 h, pyridine was evaporated in vacuo. The oil obtained was dissolved in 10 mL of CH_2Cl_2 and washed with 7% HCl and $NaHCO_3$ several times and finally with sat. NaCl. The organic phase was then dried over Na_2SO_4. The solvent was evaporated in vacuo yielding pure **13** (346 mg, 97% yield). ^{1}H NMR ($CDCl_3$) δ 7.57 (4H, AB, J_{AB}=8.3 Hz), 6.6 (s, 2H, AB), 4.0 (2H, AB), 3.76 (s, 3H), 3.74 (s, 3H), 2.72 (m, 4H), 2.44 (s, 3H), 1.79 (m, 2H). A solution of **13** (85 mg) in 4 mL of ether was added to a stirring suspension of $LiAlH_4$ (30 mg in 2 mL of dry ether) under argon at rt. After 16 h, 5 mL of water and 5 mL of 1 M NaOH were added. The mixture was stirred for 10 min and the phases were separated. The aqueous phase was extracted with 2×10 mL of benzene. The organic phases were combined and dried over Na_2SO_4. The solvent was evaporated in vacuo to yield **14** (43.5 mg, 90% yield) as an oil that crystallized in the cold. $[\alpha]_D^{20}$=−26.2 (*c* 1.09 $CHCl_3$) (86% ee determined by chiral HPLC, Chiracel OD, hexane/*i*PrOH, 9/1, (*S*)-**13** t=7.22 min, (*R*)-**13** *t*=10.86 min. IR (film, cm^{-1}): 3500–3430, 1470, 1240. ^{1}H NMR ($CDCl_3$) δ 6.63 (s, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 2.77 (m, 4H), 1.80 (m, 2H), 1.66 (br s, 1H, OH), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 151.46, 151.18, 125.46, 125.0, 106.73, 68.19, 55.42, 37.57, 34.52, 28.71, 20.87. MS, *m/z* 222 (M^+, 100), 204 (49.7), 189 (62.6), 164 (68.9), 149 (56.6), 121 (20.2), 91 (28.2), 77 (18.3). Anal. calcd for $C_{13}H_{18}O_3$: C, 70.23%; H, 8.17%. Found: C, 69.90%; H, 8.10%.

*3.13. (R)-(+)-Epoxide **15***

To a solution of tosyl derivative of **13** (260 mg, 1 mmol) in 5 mL of *i*PrOH was added NaOH (60 mg). After 1 h, water (5 mL) was added and the phases were separated. The aqueous phase was extracted with 2×10 mL CH_2Cl_2. The organic phases were combined and dried over Na_2SO_4. The solvent was evaporated in vacuo yielding epoxide **15** (134 mg, 92% yield) as an oil. $[\alpha]_D^{20}$=+4 (*c* 1 $CHCl_3$). IR (film, cm^{-1}): 2940, 1480, 1250, 980. ^{1}H NMR ($CDCl_3$) δ 6.65 (2H, AB), 3.79, 3.76 (6H), 2.8 (m, 6H), 1.84 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 151.12 (2C), 126.24, 125.06, 107.23, 106.89, 57.08, 55.62, 55.45, 54.15, 31.13, 29.05, 22.11. MS, *m/z* 220 (M^+, 100), 205 (41.4), 190 (38.3), 189 (39.1), 175 (51.6), 159 (35.1),

147 (27.4), 131 (29.7), 115 (70.2), 103 (33.5), 91 (43.2), 77 (45). Anal. calcd for $C_{13}H_{16}O_3$: C, 70.87%; H, 7.33%. Found: C, 71.14%; H, 7.11%.

*3.14. (R)-(−)-2-Ethyl-1,2,3,4-tetrahydro-5,8-dimethoxy-2-naphthol **16***

To a solution of $Me_2Cu(CN)Li$ (prepared from 0.21 mmol CuCN in 1 mL dry ether and 0.44 mmol MeLi (1.6 M in ether) from −78°C to −50°C) at −78°C was added dropwise a solution of epoxide **15** (31 mg, 0.14 mmol) in 1 mL dry ether. The temperature was allow to rise to −20°C. After 2.5 h, 10 mL of a solution of 10% NH_4OH/sat. NH_4Cl was added. The phases were separated and the organic phase was washed with 2×10 mL of 10% NH_4OH/sat. NH_4Cl until total elimination of the blue color. The organic phases were combined and dried over Na_2SO_4. Evaporation of the solvent in vacuo yielded 27.6 mg (83% yield) of pure **16** as a liquid. $[\alpha]_D^{20}$=−22.8, (*c* 1.4 $CHCl_3$). (90% ee determined by chiral HPLC, Chiracel OD, hexane/*i*PrOH, 9/1, (*S*)-**15** *t*=7.07 min, (*R*)-**15** *t*=13.18 min) (lit.[17] $[\alpha]_D^{20}$=−24.5, (*c* 1.31 $CHCl_3$)). IR (film, cm^{-1}) 3620–3400, 2920, 1480, 1240. ^{1}H NMR δ 6.63 (s, 2H, AB), 3.79, 3.77 (2s, 6H, 2×MeO), 2.8–2.6 (m, 4H, 2×CH_2-Ar), 1.8–1.6 (m, 5H, 2×CH_2, OH), 1.05 (t, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 151.75, 151.23, 125.95, 124.83, 106.95, 106.84, 70.11, 55.56, 35.65, 34.12, 32.04, 20.47, 7.50.

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