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Efficient enantioselective synthesis of (*R*)-2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene, the key intermediate in the synthesis of anthracycline antibiotics†

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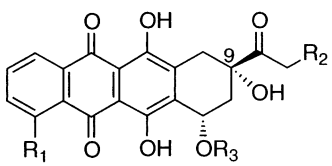
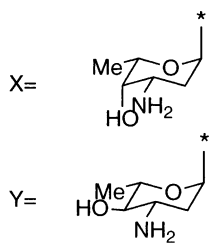
Abstract—A simple, efficient, enantioselective synthesis of (*R*)-2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene, the key intermediate in the synthesis of anthracycline antibiotics, is described. The synthetic procedure starts with the Sharpless asymmetric dihydroxylation of 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene: the diol obtained is regioselectively transformed into the corresponding chloroacetate which is dehalogenated and saponified to give the desired title compound in four steps with satisfactory yield (52%). No separation step is necessary at any point of the synthetic process. An efficient procedure for the synthesis of the starting enone and the stereoselectivity of the methanolysis of the intermediate chloroacetate are also reported.

1. Introduction

Compounds which belong to the class of anthracycline antibiotics, such as daunomycin **1**, doxorubicin **2**, hydarubicin **3**, and epirubicin **4** have widespread therapeutic use as antineoplastic agents. The configuration at C(9) of the corresponding anthracyclinones **1**–**4** (R_3 = H) is very important as only compounds with (*S*)-configuration at this position show the desired pharmacological activity.[1]





1, R_1= OMe; R_2= H; R_3= X
2, R_1= OMe; R_2= OH; R_3= X
3, R_1= H; R_2= H; R_3= X
4, R_1= OMe; R_2= OH; R_3= Y

1,2,3,4-Tetrahydronaphthalene-derived hydroxy ketone (*R*)-**5** (Scheme 1), which possesses the requisite configuration at C(2), corresponding to the C(9) carbon of anthracyclines **1**–**4**, is a key intermediate in the industrial synthesis of these important pharmacologically active compounds.[2,3] As a consequence, an efficient and straightforward method for the synthesis of (*R*)-**5** constitutes a point of sure interest.

Since the pioneering work of Wong[2] and Arcamone,[3] several stereoselective procedures have been described for the synthesis of hydroxy ketone (*R*)-**5** with good e.e. Some of these procedures utilize:

(a) Sharpless asymmetric epoxidation (SAE) of racemic allylic alcohols (±)-**6**[4] and (±)-**7**[5] with concomitant kinetic resolution or SAE or TBHP/$VO(acac)_2$ oxidation of non-racemic allylic alcohols (*S*)-**6**[6] and (*R*)-**7**[7] followed by a typical LAH-reduction/reoxidation protocol;

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† Dedicated to the memory of Dr. Raffaello Giorgi.

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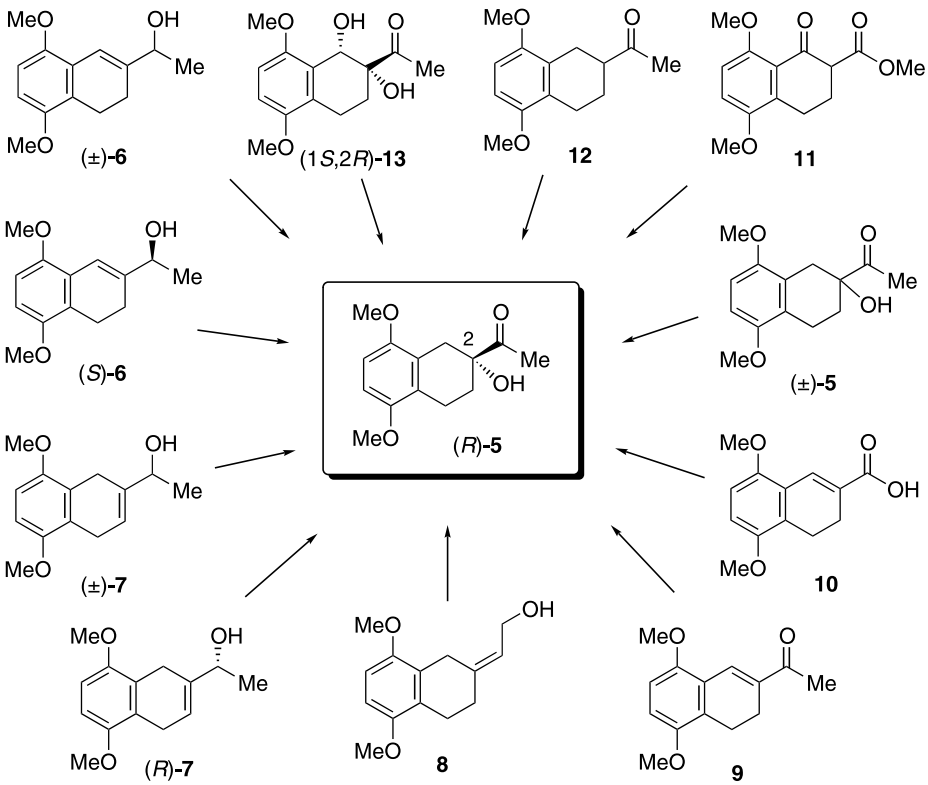


Scheme 1.

(b) SAE of allylic alcohol **8** followed by a Payne rearrangement (PhSNa) and a final desulfurization and oxidation;[8]

(c) bromolactonization of chiral acetals and amides derived from unsaturated ketone **9**[9] and acid **10**[10] respectively, followed by appropriate debromination and other necessary transformations;

(d) microbial reduction of (±)-**5** with fermenting baker's yeast followed by separation of diastereoisomeric diols and a necessary final reoxidation;[11]

(e) hydroxylation of the potassium enolate of β-keto ester **11** using a chiral *N*-sulfonyl oxaziridine, followed by reduction of the carbonyl group and transformation of the methoxycarbonyl group into an acetyl group (Scheme 1).[12,13]

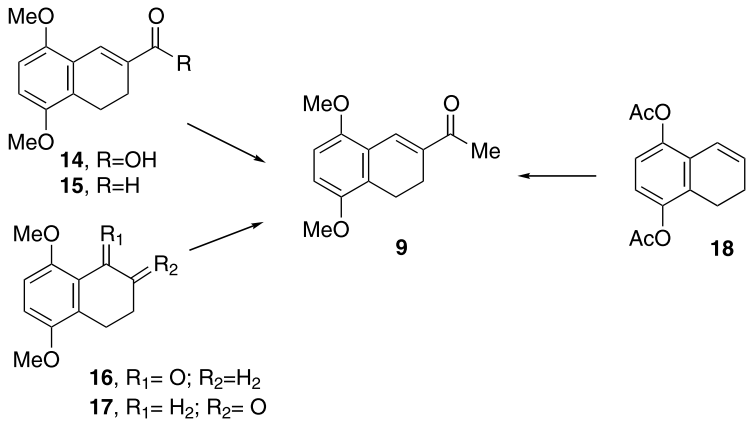
However, these procedures are often complex and generally difficult to transfer to large scale to the point that hydroxy ketone (*R*)-**5** has been commonly prepared on an industrial scale by resolution of the corresponding racemic mixture obtained by α-hydroxylation (*t*-BuOK/O_2) of ketone **12** (Scheme 1).[2,3a]

2. Results and discussion

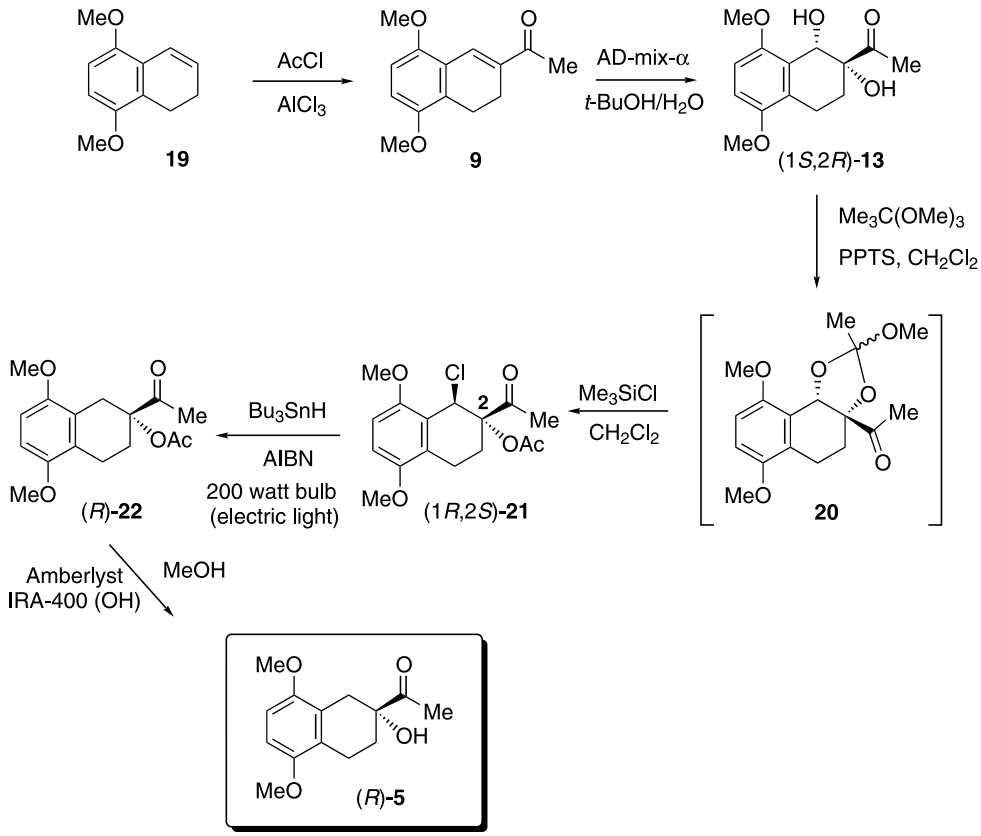
We describe herein a new and simple protocol for the enantioselective synthesis of (*R*)-**5** starting from 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene **9**, which in turn has been prepared in a straightforward way also. Several procedures are known for the synthesis of enone **9**, starting from the corresponding unsaturated carboxylic acid **14**,[6a] aldehyde **15**,[14] 1-tetralone **16**[15] and 2-tetralone **17**[16] or based on acylation ($AcCl/AlCl_3$) of 5,8-diacetoxy-3,4-dihydronaphthalene **18**.[9,17] However, in some cases the yields are poor or the protocol decidedly complex (Scheme 2).

We have found that direct acylation of 5,8-dimethoxy-3,4-dihydronaphthalene **19**[4] with AcCl in the presence of an excess of $AlCl_3$ (8 equiv./mol) allows the direct preparation of enone **9** by a very simple protocol with a satisfactory yield (70% after recrystallization) (Scheme 3).

We made use of the Sharpless asymmetric dihydroxylation (SAD) for the introduction of the required configuration of the target compound into the skeleton of enone **9**, by means of an enriched [1% $K_2OsO_2(OH)_4$] AD-mix-α in the presence of methanesulfonamide (Scheme 3).[18] Diol (1*S*,2*R*)-**13** was obtained in satisfactory yield (71%, after recrystallization) and excellent e.e. (98%). This first part of our synthetic approach to compound (*R*)-**5** had also been previously utilized by Tomioka, even if in less effective and more drastic operating conditions.[19] However, in that case, diol (1*S*,2*R*)-**13** was reductively dehydroxylated (Et_3SiH/CF_3COOH) at the benzylic position with concomitant reduction of the carbonyl group to the corresponding secondary alcohol, which then had to be reoxidized in order to form the target compound (*R*)-**5**.



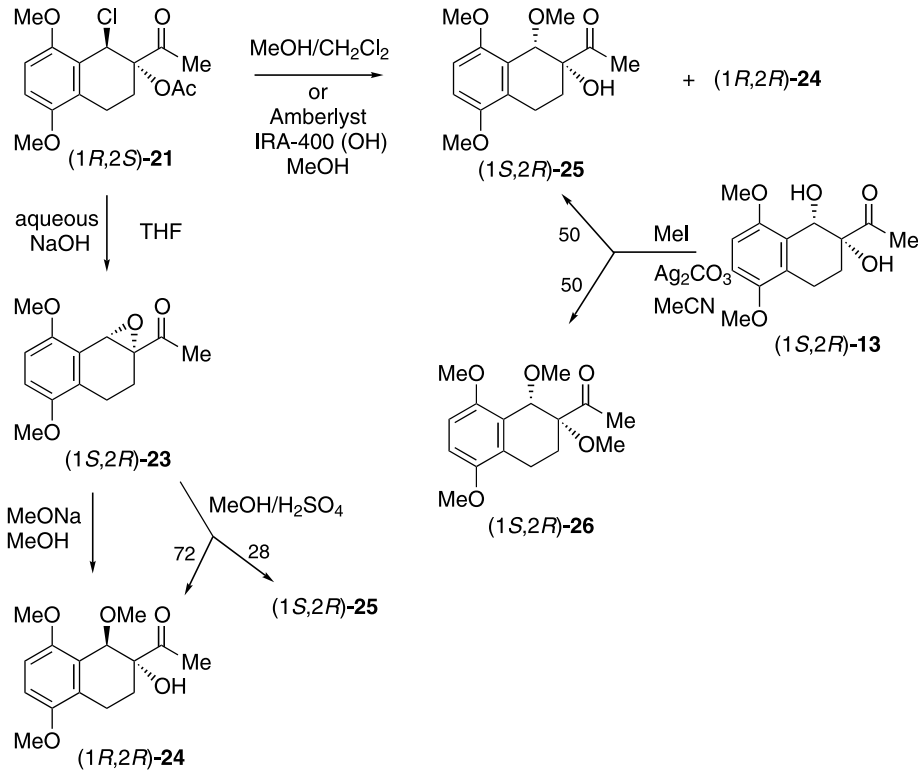
Scheme 2.



Scheme 3.

In our present approach, we took advantage of the Sharpless procedure for transforming a diol into the corresponding epoxide.[18,20] Treatment of the diol (1*S*,2*R*)-**13** with $MeC(OMe)_3$ in CH_2Cl_2 in the presence of PPTS for 24 h led to the sufficiently stable cyclic orthoester intermediate **20** (^{1}H NMR), which was exposed to Me_3SiCl for 1 h to give the chloroacetate (1*R*,2*S*)-**21** as the only reaction product. Chloroacetate (1*R*,2*S*)-**21** has the desired substitution and stereochemistry at C(2) for the target compound (*R*)-**5**. Treatment of (1*R*,2*S*)-**21** with Bu_3SnH in the presence of AIBN under irradiation from a common 200 Watt electric light bulb yielded the acetate (*R*)-**22**. Saponification of (*R*)-**22** with Amberlyst IRA-400 (OH) afforded (*R*)-**5** in workable yield (52% from enone **9**) and excellent e.e. (99%) (Scheme 3).

In our preliminary, more tedious synthetic approach to (*R*)-**5**, subsequently abandoned, it was decided to transform chloroacetate (1*R*,2*S*)-**21** into the corresponding epoxide (1*S*,2*R*)-**23**. However, when chloroacetate (1*R*,2*S*)-**21** was treated with Amberlyst IRA-400 (OH) in MeOH, instead of the expected epoxide (1*S*,2*R*)-**23**, the *cis*-methoxy alcohol (1*S*,2*R*)-**25** was obtained as the main product (87%), accompanied by a small amount (13%) of the *trans*-diastereoisomer (1*R*,2*R*)-**24** (Scheme 4).[21]



Scheme 4.

This result indicated that rapid methanolysis had occurred at the benzylic chloro-substituted position, largely with inversion of configuration, impeding cyclization.[22] The exact structure and configuration of the *cis*-methoxy alcohol (1*S*,2*R*)-**25** was unequivocally demonstrated by its stability under acetylation conditions (Ac_2O/Py) and by the fact that (1*S*,2*R*)-**25** is also obtained, together with the dimethoxy derivative (1*S*,2*R*)-**26**, in the methylation (MeI/Ag_2CO_3) of diol (1*S*,2*R*)-**13**, whose configuration is certain.[18,19] As for the *trans*-methoxy alcohol (1*R*,2*R*)-**24**, its structure and configuration were demonstrated by preparing it, for comparison, in a rigidly stereocontrolled way by ring-opening reaction of epoxide (1*S*,2*R*)-**23** under alkaline conditions. For this purpose, chloroacetate (1*R*,2*S*)-**21** was cyclized to the corresponding epoxide (1*S*,2*R*)-**23** by treatment with 10% aqueous NaOH in THF. Subsequent treatment of epoxide (1*S*,2*R*)-**23** with catalytic MeONa in anhydrous methanol afforded the methoxy alcohol (1*R*,2*R*)-**24** as the only reaction product, by a well-known S_N2 opening process with nucleophilic attack on the benzylic less substituted oxirane carbon (Scheme 4). The formation of both (1*R*,2*R*)-**24** and (1*S*,2*R*)-**25** in the acid methanolysis of epoxide (1*S*,2*R*)-**23** (**24**/**25** ratio = 72:28) further confirmed the *trans*-/*cis*-diastereoisomeric relationship between these products.[23]

3. Conclusion

In conclusion, our procedure makes it possible to obtain the tetraline-derived hydroxy ketone (*R*)-**5**, the key intermediate for the synthesis of anthracycline antibiotics, in a decidedly efficient and straightforward way. The process requires four simple steps starting from enone **9**, without the necessity of any chromatographic separation, and the target compound (*R*)-**5** is obtained in good overall yield (52%) and excellent enantioselectivity (99% e.e.). The method appears to be decidedly competitive with, and even superior to, other previously described procedures and is thus a candidate for application on a large scale.[24] Moreover, a simple and efficient procedure for the synthesis of the starting material, enone **9**, is described.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were determined with a Bruker AC-200 spectrometer on $CDCl_3$ solutions using Me_4Si as the internal standard. Optical rotations were measured with a Perkin–Elmer 241 digital polarimeter with a 1 dm cell. E.e. Values for diol (1*S*,2*R*)-**13** and hydroxy ketone (*R*)-**5** were determined by HPLC on a Chiracel OD-H chiral column [(25 cm×0.46 cm (i.d.)]. All reactions were followed by TLC on Alugram SIL G/UV254 silica gel sheets (Macherey–Nagel) with detection by UV and/or spraying with 20% phosphomolybdic acid in EtOH. Toluene and CH_2Cl_2 were distilled under nitrogen from sodium/benzophenone ketyl and CaH_2, respectively. Commercially available Amberlyst IRA-400 (Aldrich) was activated by treatment with 30% aqueous NaOH, followed by washings with water and MeOH.

4.2. 2-Acetyl-5,8-dimethoxy-3,4-dihydronaphthalene 9

AcCl (41.9 g, 0.53 mol) was dropwise added at 0°C under nitrogen to a suspension of $AlCl_3$ (44.9 g, 0.33 mol) in anhydrous CH_2Cl_2 (200 mL). After stirring for 30 min at the same temperature, a solution of 5,8-dimethoxy-3,4-dihydronaphthalene **19**[4] (8.0 g, 0.042 mol) in anhydrous CH_2Cl_2 (250 mL) was slowly added and the resulting reaction mixture was further stirred for 30 min at 0°C. Ice was cautiously added and the organic phase was separated. Evaporation of the washed (5% aqueous HCl, water and brine) afforded a crude solid product (9.80 g) which was recrystallized from AcOEt to give pure **9** as a solid (6.83 g, 70% yield), mp 105–106°C (lit.[6a] mp 106–107°C): IR 1650 cm^{-1} (C=O); ^1H NMR δ 7.81 (t, 1H, $J=1.4$ Hz), 6.84 (d, 1H, $J=8.9$ Hz), 6.69 (d, 1H, $J=8.9$ Hz), 3.84 (s, 3H), 3.80 (s, 3H), 2.75–2.83 (m, 2H), 2.47–2.56 (m, 2H), 2.45 (s, 3H). ^{13}C NMR δ 198.8, 151.0, 150.4, 137.2, 131.5, 127.2, 122.6, 113.2, 108.5, 56.1, 55.9, 25.3, 20.5, 19.9. Anal. calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.64; H, 7.02%.

4.3. (1*S*,2*R*)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1,2-diol 13

A solution of commercial AD-mix-α (60.0 g) (Aldrich), previously enriched with $K_2OsO_2(OH)_4$ (0.10 g), in a 1:1 H_2O/*t*-BuOH mixture (400 mL) was treated with $NaHCO_3$ (10.9 g) and $MeSO_2NH_2$ (4.07 g, 0.043 mol) and the resulting reaction mixture was stirred at rt until complete solubilization was obtained. After cooling at 0°C, ketone **9** (10.0 g, 0.043 mol) was added and the reaction mixture was vigorously stirred at the same temperature for 96 h. After this period, TLC analysis showed that all starting material was reacted. Solid $Na_2S_2O_5$ (63.0 g) was added in portions and, after stirring the mixture for 1 h at rt, AcOEt (400 mL) was added. Evaporation of the washed (10% aqueous NaOH, and water) organic solution afforded a crude solid product which was taken up with CH_2Cl_2 (80 mL). Evaporation of the washed (3% aqueous H_2SO_4, saturated aqueous $NaHCO_3$ and water) organic solution afforded a crude solid product consisting of diol (1*S*,2*R*)-**13**, which was recrystallized from 1:1 AcOEt/hexane to give pure diol (1*S*,2*R*)-**13** as a clear crystalline product (8.07 g, 71% yield), mp 141–143°C, $[\alpha]_D^{25}=-21.9$ (*c* 1.0, $CHCl_3$), 98% e.e. [lit.[19b] $[\alpha]_D^{25}=-17.6$ (*c* 1.10, $CHCl_3$), 82% e.e.]: IR 3531 and 3450 (OH) and 1714 cm^{-1} (C=O); ^1H NMR δ 6.71 (s, 2H), 5.30 (s, 1H), 4.48 (d, 1H, $J=1.3$ Hz), 3.84 (s, 3H), 3.82 (d, 1H, $J=1.8$ Hz), 3.78 (s, 3H), 2.75–2.82 (m, 2H), 2.39 (s, 3H), 2.01 (dt, 1H, $J=13.5$, 4.0 Hz), 1.79 (ddd, 1H, $J=13.6$, 9.5, 8.0 Hz). ^{13}C NMR δ 215.1, 152.9, 151.8, 127.7, 126.4, 109.4, 108.6, 79.4, 69.2, 56.4, 56.3, 29.4, 26.6, 19.8. Anal. calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.44; H, 6.72%.

4.4. (1*R*,2*S*)-2-Acetoxy-2-acetyl-1-chloro-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene 21

A stirred solution of the diol (1*S*,2*R*)-**13** (7.72 g, 0.029 mol) in CH_2Cl_2 (60 mL) was treated at rt under nitrogen with $MeC(OMe)_3$ (5.60 g, 0.046 mol) and PPTS (0.20 g, 0.079 mmol) and the resulting reaction mixture was maintained at the same temperature for 24 h. Evaporation of the organic solvent afforded a crude solid product consisting of intermediate **20** (9.35 g) [^1H NMR δ 6.70 (t, 2H, $J=6.5$ Hz), 5.77 (s, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.27 (s, 3H), 2.85–3.05 (m, 2H), 2.34 (s, 3H), 1.95–2.19 (m, 2H), 1.54 (s, 3H)], which was taken up in anhydrous CH_2Cl_2 (60 mL) and treated with Me_3SiCl (5.56 g, 0.051 mol). The reaction mixture was stirred at rt for 1 h, then the solvent was evaporated to give a solid residue. Hexane (100 mL) was added and the resulting suspension was vigorously stirred for 3 h, then filtered to give pure chloroacetate (1*R*,2*S*)-**21** as a solid (9.41 g, 99% yield), mp 125–127°C: $[\alpha]_D^{25}=-16.2$ (*c* 1.0, CH_2Cl_2): IR 1737 and 1714 cm^{-1} (C=O); ^1H NMR δ 6.72 (d, 1H, $J=8.9$ Hz), 6.65 (d, 1H, $J=8.9$ Hz) 5.27 (d, 1H, $J=1.7$ Hz), 3.79 (s, 3H), 3.73 (s, 3H), 2.98 (ddd, 1H, $J=17.5$, 5.5, 1.6 Hz), 2.30 (s, 3H), 2.13–2.73 (m, 3H), 1.89 (s, 3H). ^{13}C NMR δ 204.2, 169.6, 151.6, 150.7, 125.4, 123.2, 110.1, 108.3, 82.9, 56.0, 55.6, 52.9, 26.3, 20.5, 20.2, 19.6. Anal. calcd for $C_{16}H_{19}O_5Cl$: C, 58.81; H, 5.86. Found: C, 58.98; H, 5.57%.

4.5. (*R*)-2-Acetoxy-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene 22

A solution of chloroacetate (1*R*,2*S*)-**21** (9.80 g, 0.030 mol) in toluene (200 mL) was treated under nitrogen with AIBN (0.15 g) and Bu_3SnH (24.3 g, 0.083 mol) and the reaction mixture was stirred for 24 h at rt under the irradiation of a 200 Watt electric light bulb. Evaporation of the washed (water) organic solvent afforded a solid residue, which was repeatedly washed with hexane, then filtered to give pure acetate (*R*)-**22** as a white solid (7.04 g, 80% yield), mp 116–118°C, $[\alpha]_D^{25}=-46.3$ (*c* 1.0, $CHCl_3$): IR 1733 and 1720 cm^{-1} (C=O); ^1H NMR δ 6.65 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.02 (ABdd, 2H, $J=18.3$ Hz), 2.80–2.90 (m, 1H), 2.37–2.62 (m, 2H), 2.21 (s, 3H), 2.04 (s, 3H), 1.85–2.02 (m, 1H). ^{13}C NMR δ 206.5, 170.5, 151.4, 150.9, 125.1, 122.7, 107.2, 107.0, 83.6, 55.5, 55.6, 30.2, 26.7, 24.0, 21.0, 19.5. Anal. calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.56; H, 6.69%.

4.6. (*R*)-2-Acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene 5

A solution of acetate (*R*)-**22** (6.72 g, 0.023 mol) in MeOH (400 mL) was treated under stirring at rt with Amberlyst IRA-400 (OH) (13.40 g) and the suspension was stirred for 18 h at the same temperature. Evaporation of the filtered organic solution afforded a solid residue, which was recrystallized from hexane/AcOEt to give pure (*R*)-**5** as a solid (5.30 g, 92% yield), mp 128–129°C, $[\alpha]_D^{25}=-46.2$ (*c* 1.0, $CHCl_3$), 99% e.e. [lit.[9] mp 129.5–130.5°C, $[\alpha]_D^{20}=-48.7$ (*c* 0.368, $CHCl_3$), 100% e.e.]: IR 1701 cm^{-1} (C=O); ^1H NMR δ 6.66 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.63 (s, 1H), 2.95 (ABdd, 2H, $J=17.3$ Hz), 2.68–3.00 (m, 2H), 2.32 (s, 3H), 1.78–2.04 (m, 2H). ^{13}C NMR δ 212.3, 151.6, 151.1, 125.5, 122.7, 107.4, 107.0, 76.4, 55.6, 55.5, 32.4, 29.7, 23.9, 19.2.

Anal. calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.01; H, 7.10%.

4.7. Treatment of chloroacetate (1*R*,2*S*)-21 with MeOH

A solution of chloroacetate (1*R*,2*S*)-**21** (0.326 g, 1.0 mmol) in MeOH (30 mL) containing CH_2Cl_2 (2 mL) was stirred at rt for 18 h. Dilution with ether and evaporation of the washed (saturated aqueous $NaHCO_3$ and water) organic solution afforded a liquid product (0.25 g) consisting of a 90:10 mixture of methoxy alcohols (1*S*,2*R*)-**25** and (1*R*,2*R*)-**24** (^{1}H NMR), which was subjected to preparative TLC (a 98:2 mixture of CH_2Cl_2 and Et_2O was used as the eluant). Extraction of the most intense band afforded pure (1*S*,2*R*)-2-acetyl-2-hydroxy-1,5,8-trimethoxy-1,2,3,4-tetrahydronaphthalene **25** as a liquid (0.20 g, 71% yield), $[\alpha]_D^{25}=+44.7$ (*c* 1.3, $CHCl_3$): IR 3475 (OH) and 1712 cm^{-1} (C=O); ^{1}H NMR δ 6.63 (s, 2H), 4.83 (s, 1H), 3.75 (s, 3H), 3.68 (s, 1H), 3.57 (s, 3H), 3.42 (s, 3H), 2.74 (ddd, 1H, $J=17.7$, 7.5, 5.9 Hz), 2.55 (dt, 1H, $J=17.7$, 6.1 Hz), 2.26 (s, 3H), 1.97 (dt, 1H, $J=13.2$, 6.2 Hz), 1.74 (ddd, 1H, $J=13.2$, 7.5, 6.0 Hz). ^{13}C NMR δ 212.5, 153.3, 151.3, 127.9, 125.3, 110.1, 108.7, 78.9, 75.0, 59.8, 56.4, 56.2, 29.8, 25.7, 20.3. Anal. calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.61; H, 7.44%.

Methoxy alcohol (1*S*,2*R*)-**25** was recovered completely unreacted when subjected to acetylation conditions (Ac_2O/Py) for 24 h at rt.

In an attempt to prepare epoxide (1*S*,2*R*)-**23**, a solution of chloroacetate (1*R*,2*S*)-**21** (0.10 g, 0.30 mmol) in MeOH (6 mL) containing a few drops of CH_2Cl_2 was treated with Amberlyst IRA-400 (OH) (0.050 g) and the resulting suspension was stirred at rt for 20 h. Evaporation of the filtered organic solution afforded a crude liquid product consisting of a 13:87 mixture of methoxy alcohols (1*R*,2*R*)-**24** and (1*S*,2*R*)-**25** (^{1}H NMR).

4.8. Methylation reaction of diol (1*S*,2*R*)-13

A solution of diol (1*S*,2*R*)-**13** (0.134 g, 0.50 mmol) in anhydrous MeCN (1.5 mL) was treated with Ag_2CO_3 (0.276 g, 1.0 mmol) and MeI (0.290 g, 2.0 mmol) and the resulting reaction mixture was stirred at 80°C for 18 h. After cooling, evaporation of the filtered organic solvent afforded a crude product (0.13 g) consisting of an almost 1:1 mixture of methoxy derivatives (1*S*,2*R*)-**25** and (1*S*,2*R*)-**26** (^{1}H NMR), which was subjected to preparative TLC (an 8:2 mixture of hexane and AcOEt was used as the eluant). Extraction of the two most intense bands (the faster moving band contained **26**) afforded methoxy alcohol (1*S*,2*R*)-**25** (0.046 g, 33% yield) and (1*S*,2*R*)-2-acetyl-1,2,5,8-tetramethoxy-1,2,3,4-tetrahydronaphthalene **26** as a solid (0.056 g, 38% yield), mp 74–75°C, $[\alpha]_D^{25}=+114.7$ (*c* 2.2, $CHCl_3$): IR 1712 cm^{-1} (C=O); ^{1}H NMR δ 6.61 (s, 2H), 4.99 (s, 1H), 3.75 (s, 3H), 3.66 (s, 3H), 3.37 (s, 3H), 3.23 (s, 3H), 2.84 (ddd, 1H, $J=18.5$, 5.9, 3.9 Hz), 2.51 (ddd, 1H, $J=18.5$, 10.2, 8.1 Hz), 2.11–2.19 (m, 2H), 2.03 (s, 3H). ^{13}C NMR δ 207.6, 152.0, 151.9, 127.0, 125.0, 110.2, 108.4, 85.0, 70.7, 58.2, 56.5, 55.9, 52.5, 25.2, 22.3, 21.8. Anal. calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 64.98; H, 7.26%.

4.9. (1*S*,2*R*)-2-Acetyl-1,2-epoxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene 23

A solution of chloroacetate (1*R*,2*S*)-**21** (0.22 g, 0.67 mmol) in THF (16 mL) was treated with 10% aqueous NaOH (2 mL) and the reaction mixture was stirred at 50°C for 5 h, then at rt for 20 h. Dilution with ether and evaporation of the washed (water) organic solvent afforded a solid (0.16 g) of practically pure epoxide (1*S*,2*R*)-**23**, which was recrystallized from hexane to give pure (1*S*,2*R*)-**23** as a solid (0.12 g, 72% yield), mp 109–111°C, $[\alpha]_D^{25}=-209.3$ (*c* 2.3, $CHCl_3$): IR 1706 cm^{-1} (C=O); ^{1}H NMR δ 6.70 (d, 1H, $J=9.0$ Hz), 6.62 (d, 1H, $J=9.0$ Hz), 4.50 (s, 1H), 3.73 (s, 3H), 3.67 (s, 3H), 2.92–3.08 (m, 2H), 2.03–2.30 (m, 2H), 2.12 (s, 3H). ^{13}C NMR δ 208.2, 153.8, 151.0, 127.8, 120.7, 112.0, 109.1, 66.8, 56.6, 51.9, 24.4, 20.9, 18.0. Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.84; H, 6.19%.

4.10. (1*R*,2*R*)-2-Acetyl-2-hydroxy-1,5,8-trimethoxy-1,2,3,4-tetrahydronaphthalene 24

A solution of epoxide (1*S*,2*R*)-**23** (0.070 g, 0.28 mmol) in MeOH (3.5 mL) was treated with a catalytic amount of MeONa (7 mg) and the reaction mixture was stirred at 80°C for 72 h. After cooling, evaporation of the solvent afforded a crude reaction mixture (0.065 g) mostly consisting of methoxy alcohols (1*R*,2*R*)-**24** (94%) [unreacted epoxide (6%) was also present], which was subjected to preparative TLC (a 98:2 mixture of CH_2Cl_2 and Et_2O was used as the eluant). Extraction of the most intense band afforded pure (1*R*,2*R*)-**24** (0.048 g, 60% yield) as a liquid, $[\alpha]_D^{25}=-113.1$ (*c* 1.2, $CHCl_3$): IR 3465 (OH) and 1708 cm^{-1} (C=O); ^{1}H NMR δ 6.68 (d, 1H, $J=9.0$ Hz), 6.63 (d, 1H, $J=9.0$ Hz), 4.31 (d, 1H, $J=1.4$ Hz), 3.71 (s, 6H), 3.53 (s, 1H), 3.28 (s, 3H), 2.82–2.94 (m, 1H), 2.41–2.70 (m, 2H), 2.38 (s, 3H), 1.74–1.84 (m, 1H). ^{13}C NMR δ 214.4, 153.1, 151.8, 127.1, 124.5, 110.1, 108.2, 77.7, 76.1, 58.6, 56.2, 27.4, 24.9, 20.6, 20.1 Anal. calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.41; H, 6.95%.

4.11. Acid methanolysis of epoxide (1*S*,2*R*)-23

A solution of epoxide (1*S*,2*R*)-**23** (0.050 g, 0.20 mmol) in 0.2N H_2SO_4 in anhydrous MeOH (5 mL) was stirred at rt for 3 h. Dilution with Et_2O and evaporation of the washed (saturated aqueous $NaHCO_3$) organic solution afforded a crude product consisting of a 72:28 mixture of methoxy alcohols (1*R*,2*R*)-**24** and (1*S*,2*R*)-**25** (^{1}H NMR).

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19. In Tomioka's procedure, the asymmetric dihydroxylation of enone **9** is carried out with OsO_4 at −110°C for 6 h in the presence of a pyrrolidine-derived chiral diamine. Diol (1*S*,2*R*)-**13** is obtained with 96% yield and 82% e.e.: (a) Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1993**, *49*, 10807–10816; (b) Tomioka, K.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1921–1922.
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21. The methanolysis of chloroacetate (1*R*,2*S*)-**21** occurs also in the absence of the resin (see Section 4).
22. If (1*S*,2*R*)-**25**, the inversion product, reasonably derives from an S_N2 process by nucleophilic attack of MeOH on the reactive secondary benzylic position of (1*R*,2*S*)-**21**, a participation of the vicinal OCOMe group could reasonably be invoked for the formation of (1*R*,2*R*)-**24**, the retention product.
23. As previously observed in other related 2-aryloxirane systems, in epoxide (1*S*,2*R*)-**23** nucleophilic attack occurs exclusively, under acid ring-opening conditions, at the electronically more favored benzylic oxirane carbon. See for example: (a) Chini, M.; Crotti, P.; Minutolo, F.; Martinelli, A.; Micali, E. *Gazz. Chim. Ital.* **1994**, *124*, 27–33; (b) Chini, M.; Crotti, P.; Minutolo, F.; Dezi, E.; Lombardozzi, A.; Pizzabiocca, A.; Renzi, G. *Tetrahedron* **1993**, *49*, 5845–5858; (c) Crotti, P.; Dell'Omodarme, G.; Ferretti, M.; Macchia, F. *J. Am. Chem. Soc.* **1987**, *109*, 1463–1469.
24. When the same synthetic procedure was repeated on a ten-fold scale starting from enone **9**, the hydroxy ketone (*R*)-**5** was obtained in similar yield and enantioselectivity.