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Stereoselective synthesis of deoxy analogues of the 3C-protease inhibitor thysanone

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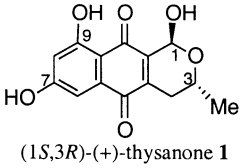
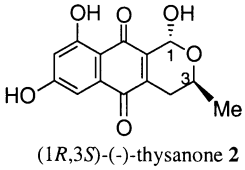
Abstract—The synthesis of racemic 7,9-dideoxythysanone **9** was achieved starting from allylnaphthalene **5** via epoxidation and reduction to bromoalcohol **7**. Subsequent lithiation of the bromide and quenching with DMF afforded lactol **8** which underwent clean oxidative demethylation to racemic 6,8-dideoxythysanone **9**. The synthesis of (1*R*,3*S*)-(+)-7,9-dideoxythysanone **9** was then achieved albeit in low ee, starting from (*R*)-epoxide **6** which in turn was obtained via Sharpless asymmetric dihydroxylation of allylnaphthalene **5**. An improved asymmetric synthesis of (1*S*,3*R*)-(+)-7,9-dideoxythysanone **9** in 72% ee was then accomplished starting from (*R*)-bromoalcohol **7** which was obtained via asymmetric reduction of ketone **12** using a modified chiral oxazaborolidine. The key ketone **12** in turn was prepared by Wacker oxidation of allylnaphthalene **5**.

The replication of many animal and plant viruses relies on proteolytic processing and is dependent upon two virally encoded proteases 3C-protease and 2A-protease. Human rhinoviruses are responsible for causing common colds in humans,[1] therefore, 3C-protease and 2A-protease are attractive targets for the development of antiviral chemotherapeutic agents for eventual control of the common cold. (+)-Thysanone **1** was isolated from *Thysanophora penicilloides*[2] and is one of a few effective inhibitors of human rhinovirus 3C-protease and therefore provides a lead compound for understanding the mechanism of 3C-protease inhibition. (+)-Thysanone **1** is closely related to the pyranonaphthoquinone family of antibiotics[3] and the one reported synthesis of its enantiomer, (−)-thysanone **2**,[4] established the stereochemistry of the natural product **1** to be (1*S*,3*R*).



(1*S*,3*R*)-(+)-thysanone **1**



(1*R*,3*S*)-(-)-thysanone **2**

In the synthesis of (1*S*,3*R*)-(−)-thysanone **1** by Gill et al.[4] the (*S*)-stereochemistry at C-3 was derived in nine steps from (*S*)-mellein which in turn was prepared in several steps from (*S*)-propylene oxide. We herein report our approach to deoxy analogues of thysanone in which the stereochemistry at C-3 is controlled by incorporating an asymmetric dihydroxylation or an asymmetric reduction step into the synthetic strategy. Our initial attention focussed on the synthesis of racemic 7,9-dideoxythysanone **9** (Scheme 1) and allylbromonaphthalene **5** served as a suitable starting material for this purpose. It was envisaged that the bromine substituent in **5** can be readily transformed into an aldehyde and the allyl substituent converted to a secondary alcohol as required for formation of the lactol ring. The synthesis could also be carried out in an asymmetric fashion by effecting formation of bromoalcohol **7** enantioselectively.

Allylbromonaphthalene **5** has been used by De Kimpe et al.[5] in the synthesis of the pyranonaphthoqinone antibiotics psychorubin and pentalongin and was prepared by the reductive methylation of 3-bromo-2-allyl-1,4-naphthoquinone **4** which was available via allylation of 2-bromo-1,4-naphthoquinone **3**. The most facile route for the allylation of 2-bromo-1,4-naphthoquinone **3** involved treating this compound **3** with allyltrimethylsilane using methylaluminum dichloride at −78°C for 2 h. This procedure afforded the desired product **4** and minimized formation of the undesired 1,2-addition product. 3-Bromo-2-allyl-1,4-naphthoquinone **4** was immediately subjected to reductive methylation using aqueous sodium dithionite, potassium hydroxide and dimethyl sulfate affording dimethyl ether **5** in 93% yield.

With allylnaphthalene **5** in hand, it next remained to prepare bromoalcohol **7** from epoxide **6**. Treatment of **5** with freshly distilled dimethyldioxirane in acetone for

Keywords: asymmetric reduction; 3C-protease inhibitors; pyranonaphthoquinones.

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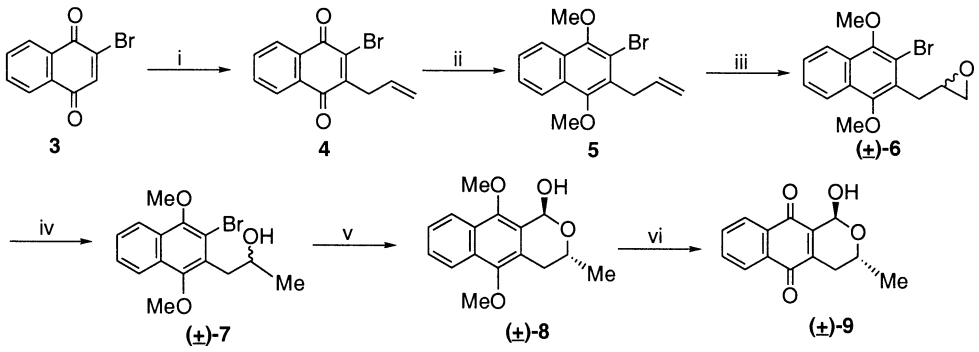


Scheme 1. *Reagents and conditions*: (i) allyltrimethylsilane, $MeAlCl_2$, CH_2Cl_2, −78°C, 61%; (ii) $Na_2S_2O_4$, Me_2SO_4, Bu_4NI, THF, aq. KOH, 93%; (iii) dimethyldioxirane, acetone, 74%; (iv) $LiAlH_4$, Et_2O, 0°C, 81%; (v) BuLi, THF, −78°C, 10 min, DMF, 3 h, 72%; (vi) 10% $(NH_4)_4Ce(NO_3)_6$, MeCN, 0°C, 61%.

12 h afforded epoxide **6** in 74% yield after purification by flash chromatography.[6] Addition of an ethereal solution of lithium aluminum hydride to epoxide **6** in ether at 0°C then afforded alcohol **7** in 81% yield. Significant quantities of debrominated material resulted if the reduction was carried out at higher temperatures.

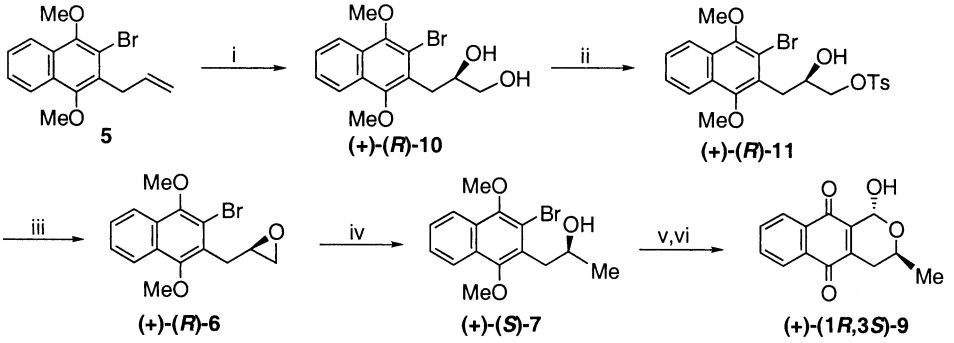
It next remained to condense the dianion generated from bromoalcohol **7** with DMF affording lactol **8**. This was achieved by effecting halogen–metal exchange of bromoalcohol **7** with 3 equiv. of butyllithium at −78°C, adding DMF, then warming the reaction to room temperature to afford the desired lactol in 72% yield. The final oxidative demethylation step required for the synthesis of racemic 7,9-dideoxythysanone **9** then proceeded in 61% yield using ceric ammonium nitrate. The ^1H NMR data for 7,9-dideoxythysanone **9** compared well to that reported for natural[2] and synthetic thysanone[4] and the *trans* relationship between the methyl group at C-3 and the hydroxyl group at C-1 was established by the observation of an NOE between 1H and the methyl group at C-3.

Our initial strategy to introduce an asymmetric step into the synthesis of 7,9-dideoxythysanone **9** focused on the asymmetric epoxidation or dihydroxylation of alkene **5** to form epoxide **6** in enantiomeric excess (Scheme 2). After much experimentation epoxide **6** was prepared indirectly from diol **10** albeit in moderate ee. Treatment of alkene **5** with freshly prepared AD-mix β, potassium osmate and potassium ferricyanide in *tert*-butanol at 0°C for 14 days afforded (*R*)-diol **10** in 80% yield with a disappointing 35% ee. The ee was established by HPLC using a Pirkle type 1A chiral column. Use of AD-mix α afforded equally disappointing ee values.

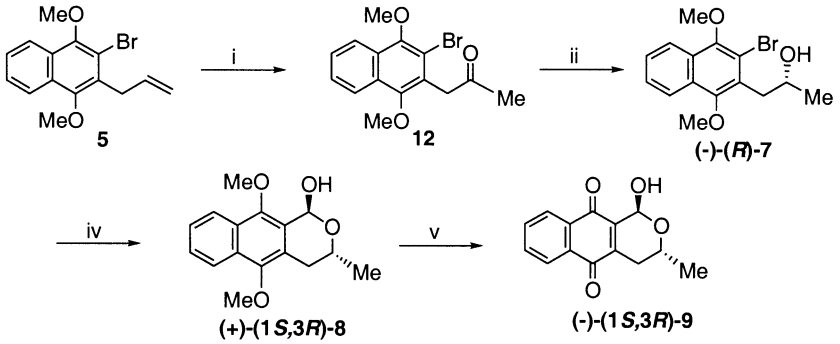
Selective tosylation of the primary alcohol of diol **10** afforded tosylate **11** which then underwent smooth displacement to (+)-epoxide **6** in 91% yield upon treatment with sodium hydride. Conversion of (+)-epoxide **6** to (+)-bromoalcohol **7** and thence to (+)-(1*R*,3*S*)-7,9-dideoxythysanone **9** then proceeded as described earlier for racemic material. Subsequent comparison of the optical rotation observed for (+)-(1*R*,3*S*)-7,9-dideoxythysanone **9** with that of its (−)-enantiomer obtained by an alternative synthesis (vide infra), established the ee of this material to be 35%.

The poor ee values obtained from the Sharpless asymmetric dihydroxylation route described above led us to consider an alternative enantioselective synthesis of bromoalcohol **7** (Scheme 3). It was reasoned that enantioenriched alcohol **7** could be obtained by asymmetric reduction of ketone **12** which in turn could be obtained by Wacker oxidation of allylnaphthalene **5**. Oxidation of alkene **5** in the presence of copper(I) chloride (1.2 equiv.) and palladium(II) chloride (0.2 equiv.) in DMF for 24 h afforded ketone **12** in 74% yield.

The optimum procedure for the asymmetric reduction of ketone **12** involved 'in situ' generation[7] of the chiral oxazaborolidine[8] from triisopropyl borate and (*S*)-(−)-2,2-diphenylhydroxymethylpyrrolidine in THF for 16 h in the



Scheme 2. *Reagents and conditions*: (i) AD-mix-β, ^tBuOH, H_2O, 0°C, 14 days, 80%; (ii) *p*-toluenesulfonyl chloride, py, CH_2Cl_2, 0°C, 120 h, 63%; (iii) NaH, THF, room temperature, 24 h, 91%; (iv) $LiAlH_4$, Et_2O, 0°C, 81%; (v) BuLi, THF, −78°C, 10 min, DMF, 3 h, then 10% $(NH_4)_4Ce(NO_3)_6$, MeCN, 0°C, 59% over two steps.



Scheme 3. *Reagents and conditions*: (i) CuCl, $PdCl_2$, DMF, H_2O, room temperature, O_2, 24 h, 0°C, 74%; (ii) $B(O^iPr)_3$, (*S*)-(−)-2,2-diphenylhydroxymethylpyrrolidine, THF, room temperature, 16 h then BH_3–DMS, **12**, CH_2Cl_2, 0°C, 120 h, 78, 72% ee; (iv) BuLi, THF, −78°C, 10 min, DMF, 3 h, 59, 72% ee; (v) 10% $(NH_4)_4Ce(NO_3)_6$, MeCN, 0°C, 61, 72% ee.

presence of 4 Å molecular sieves followed by the addition of a fresh solution of borane–dimethylsulfide complex (2.0 equiv.) and ketone **12**. Work up and purification by flash chromatography afforded the desired alcohol **7** in 78% yield and 72% ee The enantiomeric excess of alcohol **7** was measured by ^{1}H NMR spectroscopy upon addition of 1.5 equiv. of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III). Two distinct doublets due to the methyl group protons were observed at δ_H 1.25 (*S*-enantiomer) and δ_H 1.31 (*R*-enantiomer). The absolute configuration of alcohol **7** was assigned as (*R*) by separate conversion of (+)-alcohol **7** to its (*R*)- and (*S*)-methoxy(trifluoromethyl)phenylacetate derivative and comparison of the ^{1}H NMR data and the diastereomeric esters. The (*R*)-configuration was also in agreement with that predicted using the transition state model described in the literature for asymmetric reductions of prochiral ketones using this chiral oxazaborolidine.

(+)-(1*S*,3*R*)-7,9-Dideoxythysanone **9** in 72% ee was then obtained from (−)-bromoalcohol **7** via the intermediacy of (+)-(1*S*,3*R*)-lactol **8** in a fashion similar to that described earlier for the conversion of racemic bromoalcohol **7** to racemic 7,9-dideoxythysanone **9**.

In conclusion, we have developed a practical synthesis of (+)-(1*S*,3*R*)-7,9-dideoxythysanone **9** from achiral allylnaphthalene **5**. The synthesis of (+)-(1*S*,3*R*)-7,9-dideoxythysanone **9** involved seven steps from 1-naphthol and incorporated an asymmetric reduction step using a modified chiral oxazaborolidine. The methodology reported herein is also applicable to the synthesis of related pyranonaphthoquinone antibiotics.

1. Experimental

1.1. General details

All reactions were conducted in flame-dried or oven-dried glassware under a dry nitrogen atmosphere unless otherwise noted. Tetrahydrofuran and diethyl ether were dried over sodium/benzophenone and distilled prior to use. Flash chromatography was performed by using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Thin layer chromatography (TLC) was carried out on precoated silica plates (Merck Kieselgel $60F_{254}$) and compounds were visualized by UV fluorescence or by staining with alkaline potassium permanganate solution or vanillin in methanolic sulfuric acid and heating. Infrared spectra were recorded with a Perkin–Elmer 1600 series Fourier-transform infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}) with the following abbreviations—s: strong, m: medium, w: weak and br: broad. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AC 200B or a Bruker AM 400 spectrometer. All chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane as internal standard (^{1}H) or relative to $CDCl_3$ (^{13}C) and *J* values are given in Hz. ^{1}H NMR data are tabulated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. High resolution mass spectra were recorded using a VG70-SE spectrometer operating at nominal accelerating voltage of 70 eV. Chemical ionization (CI) mass spectra were obtained with ammonia as the reagent gas. Fast atom bombardment (FAB) mass spectra were obtained with 3-nitrobenzyl alcohol as the matrix.

1.1.1. 2-Bromo-1,4-naphthoquinone 3. To a mixture of *N*-bromosuccinimide (7.4 g, 40 mmol) in glacial acetic acid (200 mL) and water (400 mL) at 65°C was added 1-naphthol (3.0 g, 20 mmol) in glacial acetic acid (200 mL) dropwise with stirring. After the addition, the mixture was stirred at 65°C for 1 h, then cooled and water (400 mL) added. The product was extracted with chloroform (3×80 mL) and the organic layer washed with aqueous sodium hydrogen carbonate (5%, 2×200 mL), water (2×200 mL) and brine (200 mL). The organic layer was then dried over anhydrous magnesium sulfate and the solvent removed at reduced pressure. The crude product was then purified by flash chromatography using hexane/ethyl acetate (9:1) as eluent to yield 2-bromo-1,4-naphthoquinone (3.77 g, 77%) as a bright yellow solid, mp 132–133°C (lit.[9] 131–132°C).

1.1.2. 2-Allyl-3-bromo-1,4-naphthoquinone 4. To 2-bromo-1,4-naphthoquinone **3** (0.442 g, 1.86 mmol) in dichloromethane (30 mL) at −78°C was added methylaluminum dichloride (3.0 mL, 1.0 M solution in dichloromethane) dropwise with stirring under nitrogen. After 5 min, allyltrimethylsilane (0.3 mL, 1.88 mmol) was added dropwise and the mixture stirred for 2 h at −78°C before being

quenched with water (30 mL) with vigorous stirring. The mixture was warmed to room temperature, the organic layer separated and washed with water (3×20 mL) and brine (2×20 mL). After drying over anhydrous magnesium sulfate, the solvent was removed at reduced pressure. The crude product was then purified by flash chromatography using hexane/ethyl acetate (99:1) as eluent to yield 2-allyl-3-bromo-1,4-naphthoquinone **4** (0.315 g, 61%) as orange/yellow crystals, mp 76–78°C (lit.[5] mp 79°C).

1.1.3. 2-Allyl-3-bromo-1,4-dimethoxynaphthalene 5. To 2-allyl-3-bromo-1,4-naphthoquinone **4** (0.389 g, 1.4 mmol) and tetrabutylammonium iodide (4 mg, 0.01 mmol) in tetrahydrofuran (50 mL) under nitrogen was added saturated sodium dithionite solution (25 mL) with vigorous stirring. After 20 min, dimethyl sulfate (2.7 mL, 28 mmol) was added followed by aqueous potassium hydroxide (4×7 mL portions, 1 M). The mixture was stirred vigorously for 4 h then quenched with aqueous ammonia (20 mL, 1.5 M) and poured onto water (250 mL). The mixture was extracted with ethyl acetate (3×50 mL) and the organic extract washed with hydrochloric acid (50 mL), water (3×50 mL) and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure and the crude product purified by flash chromatography using hexane/ethyl acetate (9:1) as eluent to yield 2-allyl-3-bromo-1,4-dimethoxynaphthalene (0.398 g, 93%) as an off-white solid, mp 58–60°C (lit.[5] mp 57°C).

1.1.4. 3-Bromo-2-(2′,3′-epoxypropyl)-1,4-dimethoxynaphthalene 6. Oxone™ (48 g) was added in four portions over 15 min to a stirred slurry of sodium hydrogen carbonate (22 g), water (96 mL) and acetone (72 mL) at 5–10°C. After 20 min the ice bath was removed and the mixture distilled at reduced pressure (17–19 mmHg) with the receiver flask attached to a dry ice/acetone condenser, and containing 2-allyl-3-bromo-1,4-dimethoxynaphthalene (0.132 g, 0.4 mmol), anhydrous potassium carbonate (2 g) and acetone (10 mL). After approx. 50 mL of dimethyldioxirane had been collected, the mixture was refrigerated under nitrogen for 12 h. The solution was dried over anhydrous potassium carbonate and the solvent removed at reduced pressure. The crude product was purified by flash chromatography using hexane/ethyl acetate (9:1) as eluent to give *epoxide* **6** (0.102 g, 74%) as colourless crystals, mp 119–120°C; (Found: C, 55.93; H, 4.49. $C_{15}H_{15}O_3Br$ requires C, 55.90; H, 4.69%. Found: M^+, 324.0137; 322.0215. $C_{15}H_{15}O_3{}^{81}Br$ and $C_{15}H_{15}O_3{}^{79}Br$ require 324.0184; 322.0205); ν_{max} (NaCl plates) (cm^{-1}) 1729 and 1692 (C–O); δ_H (400 MHz, $CDCl_3$) 2.69–2.71 (1H, m, 3′-H), 2.77–2.80 (1H, m, 3′-H), 3.21 (1H, dd, J_{gem}=16 Hz and $J_{1',2'}$=5.6 Hz, 1′-H_A), 3.32–3.35 (1H, m, 2′-H), 3.43 (1H, dd, J_{gem}=16 Hz and $J_{1',2'}$=4 Hz, 1′-H_B), 3.95 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 7.52–7.58 (2H, m, 6-H and 7-H), 8.03–8.12 (2H, m, 5-H and 8-H); δ_C (100 MHz, $CDCl_3$) 33.6 (CH_2, C-1′), 48.2 (CH_2, C-3′), 51.9 (CH, C-2′), 62.0 (OCH_3), 63.3 (OCH_3), 117.1 (quat., C-3), 123.3 (CH, C-5 or C-8), 123.5 (CH, C-8 or C-5), 126.9 (quat., C-2), 127.4 (CH, C-6 or C-7), 127.8 (CH, C-7 or C-6), 128.5 (quat., C-4a or C-8a), 129.1 (quat., C-8a or C-4a), 150.9 (quat., C-1 or C-4), 152.4 (quat., C-4 or C-1); *m/z* (%) 324 (M^+ ^{81}Br, 38), 322 (M^+ ^{79}Br, 38), 308 (M^+ $^{81}Br-CH_4$,41), 306 (M^+ $^{79}Br-CH_4$,41).

1.1.5. 3-Bromo-2-(2′-hydroxypropyl)-1,4-dimethoxynaphthalene 7. To a solution of epoxide **6** (0.117 g, 0.4 mmol) in diethyl ether (20 mL) at 0°C was added a pre-cooled solution of lithium aluminum hydride (4×1 mL, 0.43 M solution in diethyl ether) dropwise with stirring under nitrogen. After 15 min the reaction was quenched with pre-cooled ethyl acetate (10 mL) and the organic layer washed with hydrochloric acid (30 mL, 1 M), water (2×30 mL) and brine (40 mL). After drying over anhydrous magnesium sulfate the solvent was removed at reduced pressure and the crude product purified by flash chromatography using hexane/ethyl acetate (9:1 then 4:1) as eluent to yield *bromoalcohol* **7** (96 mg, 81%) as colourless crystals, mp 118–120°C; (Found: C, 55.65; H, 5.34. $C_{15}H_{17}O_3Br$ requires C, 55.55; H, 5.29%. Found: M^+, 326.0324; 324.0356. $C_{15}H_{17}O_3{}^{81}Br$ and $C_{15}H_{17}O_3{}^{79}Br$ require 326.0341; 324.0361); ν_{max} (NaCl plates) (cm^{-1}) 3660–3200 (OH); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, $J_{3',2'}$=6.2 Hz, 3′-Me), 1.90–2.20 (1H, bs, OH), 3.18 (2H, d, $J_{1',2'}$=5.2 Hz, 1′-CH_2), 3.95 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.15–4.23 (1H, m, 2′-H), 7.52–7.57 (2H, m, 6-H and 7-H), 8.05 (1H, d, J_{ortho}=7.6 Hz, 5-H or 8-H), 8.13 (1H, d, J_{ortho}=7.5 Hz, 8-H or 5-H); δ_C (100 MHz, $CDCl_3$) 24.2 (CH_3, C-3′), 40.5 (CH_2, C-1′), 62.0 (OCH_3), 62.7 (OCH_3), 68.9 (CH, C-2′), 117.3 (quat., C-3), 123.3 (CH, C-5 or C-8), 123.4 (CH, C-8 or C-5), 127.4 (CH, C-6 or C-7), 127.5 (CH, C-7 or C-6), 128.3 (quat., C-2), 128.5 (quat., C-4a or C-8a), 128.9 (quat., C-8a or C-4a), 151.1 (quat., C-1 or C-4), 151.9 (quat., C-4 or 1); *m/z* (%) 326 (M^+ ^{81}Br, 52), 324 (M^+ ^{79}Br, 60), 282 (M^+ $^{81}Br-CH_3CHO$, 34), 280 (M^+ $^{79}Br-CH_3CHO$, 48), 267 (M^+ $^{81}Br-[CH_3CHO+CH_3]$, 75), 265 (M^+ $^{79}Br-[CH_3CHO+CH_3]$, 76), 201 (M^+ $^{81}Br-[CH_3CHO+{}^{81}Br]$, 43), 200 ($M^+$ $^{79}Br-[CH_3CHO+{}^{79}Br]$, 21), 185 ($M^+$ $^{79}Br-C_3H_7OBr$, 58).

1.1.6. (1*R,3*S**)-9,10-Dimethoxy-1-hydroxy-3-methyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran 8.** To bromoalcohol **7** (71 mg, 0.22 mmol) in tetrahydrofuran (10 mL) at −78°C under nitrogen was added *n*-butyllithium (0.5 mL, 1.3 M solution in hexanes, 0.66 mmol). After 10 min, dry dimethylformamide (0.10 mL, 1.3 mmol) was added and the mixture stirred at −78°C for 3 h, followed by warming to room temperature and quenching with phosphate buffer (0.1 M, pH 7). The mixture was extracted with dichloromethane (3×40 mL) and the organic layer washed with water (30 mL) and brine (2×50 mL). After drying over anhydrous magnesium sulfate the solvent was removed at reduced pressure and the crude product purified by flash chromatography using hexane/ethyl acetate (4:1 then 1:1) as eluent to yield *lactol* **8** (43 mg, 72%) as colourless crystals, mp 146–147°C; (Found: C, 69.9; H, 6.85. $C_{16}H_{18}O_4$ requires C, 70.0; H, 6.62%. Found: M^+, 274.1208. $C_{16}H_{18}O_4$ requires 274.1205); ν_{max} (NaCl plates) (cm^{-1}) 3650–3140 (OH); δ_H (400 MHz, $CDCl_3$) 1.44 (3H, d, $J_{Me,3}$=6.0 Hz, CH_3), 2.60 (1H, dd, J_{gem}=17 Hz and $J_{4,3}$=11.6 Hz, 4-H_A), 3.12 (1H, dd, J_{gem}=17.0 Hz and $J_{4,3}$=3.2 Hz, 4-H_B), 3.34 (1H, bs, OH), 3.89 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 4.45–4.60 (1H, m, 3-H), 6.41 (1H, s, 1-H), 7.47–7.52 (2H, m, 6-H and 7-H), 8.06–8.08 (2H, m, 5-H and 8-H); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_3), 31.0 (CH_2, C-4), 61.6 (CH, C-3), 63.3 (OCH_3), 63.7 (OCH_3), 89.9 (CH, C-1), 122.9 (CH, C-5 or C-8), 123.3 (CH, C8 or C-5), 124.3 (quat., C-4a or C-8b), 124.9,

(quat., C-8b or C-4a), 126.3 (CH, C-6 or C-7), 127.1 (CH, C-7 or C-6), 128.0 (quat., C-4b or C-8a), 129.5 (quat., C-8a or C-4b), 150.1 (quat., C-9 or C-10), 151.5 (quat., C-10 or C-9); *m/z* (%) 274 (M^+, 39).

1.1.7. (1*R,3*S**)-1-Hydroxy-3-methyl-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 9. [(±)-7,9-Dideoxythysanone].** To lactol **8** (52 mg, 0.19 mmol) in acetonitrile (10 mL) at 0°C was added 10% aqueous ceric ammonium nitrate (0.218 g, 0.40 mmol) with stirring. After 5 min the mixture was poured into water (10 mL) containing pH 7 phosphate buffer (1 mL, 0.1 M) and the aqueous phase extracted with dichloromethane (3×10 mL). The organic layer was washed with brine (2×10 mL), dried over anhydrous magnesium sulfate and the solvent removed at reduced pressure. The crude product was purified by flash chromatography using hexane/ethyl acetate (2:1) as eluent to yield *(±)-7,9-dideoxythysanone* **9** (28 mg, 61%) as yellow crystals, mp 161–162°C (dec); (Found: C, 68.4; H, 5.14. $C_{14}H_{12}O_4$ requires C, 68.7; H, 5.00%. Found: M^+, 244.0713. $C_{14}H_{12}O_4$ requires 244.0736); ν_{max} (NaCl plates) (cm^{-1}) 1665 (C=O, quinone), 2890–3040 (OH); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, $J_{Me,3}$=6.3 Hz, CH_3), 2.27 (1H, dd, J_{gem}=19.6 Hz and $J_{4A,3}$=10.8 Hz, 4-H_A), 2.78 (1H, dd, J_{gem}=19.6 Hz and $J_{4B,3}$=3.3 Hz, 4-H_B), 3.59 (1H, bs, OH), 4.32–4.40 (1H, m, 3-H), 6.07 (1H, bs, 1-H), 7.72–7.76 (2H, m, 7-H and 8-H), 8.07–8.10 (2H, m, 6-H and 9-H); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 30.1 (CH_2, C-4), 63.3 (CH, C-3), 87.5 (CH, C-1), 127.1 (2×CH, C-7 and C-8), 132.5 (2×quat., C-5a and C-9a), 141.0 (quat., C-4a or C-10a), 144.2 (quat., C-10a or C-4a), 184.0 (quat., C-5 or C-10), 185.0 (quat., C-10 or C-5); *m/z* (%) 244 (M^+, 28), 243 (M−H, 42), 226 (M−H_2O, 70), 200 (M−CH_3CHO, 100).

1.1.8. (+)-(*R*)-3-Bromo-2-(2′,3′-dihydroxypropyl)-1,4-dimethoxynaphthalene 10. To a mixture of AD-mix b (Aldrich™, 0.7 g) was added *tert*-butyl alcohol (3 mL) and water (5 mL) and the mixture stirred vigorously for 20 min before being cooled to 0°C. 2-Allyl-3-bromo-1,4-dimethoxynaphthalene (0.151 g, 0.5 mmol) in *tert*-butyl alcohol (2 mL) was added and the mixture stirred for 14 days. Sodium sulfite (0.62 g, 5 mmol) and water (20 mL) were added and crude product extracted with dichloromethane (3×20 mL). The solvent was removed at reduced pressure and the residue redissolved in ethyl acetate (200 mL). The organic layer was washed with sulfuric acid (30 mL, 1 M), 10% aqueous sodium hydrogen carbonate (30 mL), brine (3×50 mL) and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure and the crude product purified by flash chromatography using hexane/ethyl acetate (9:1, 1:1, then 1:2) as eluent to yield *(R)-diol* **10** (0.133 g, 80, 35% ee) as colourless crystals, mp 162–163°C, $[\alpha]_D$=+14.9° (*c* 2.68, CH_3CN). The enantiomeric excess (ee) was determined by high pressure liquid chromatography (HPLC) using a chiral Pirkle Type 1A column with 10% isopropyl alcohol/hexane as eluent, at a flow rate of 1.5 mL min^{-1}. The retention times were 36–38 min. (Found: C, 52.79; H, 4.97. $C_{15}H_{17}O_4Br$ requires C, 52.78; H, 5.02%. Found: M^+, 340.0309. $C_{15}H_{17}O_4{}^{79}Br$ requires 340.0310); ν_{max} (NaCl plates) (cm^{-1}) 3670–3020 (OH); δ_H (400 MHz, $CDCl_3$) 2.41–2.68 (1H, bs, OH), 2.62–2.79 (1H, bs, OH), 3.19 (1H, dd, J_{gem}=13.5 Hz and $J_{1',2'}$=6.2 Hz, 1′-H), 3.28 (1H, dd, J_{gem}=13.5 Hz and $J_{1',2'}$=7.2 Hz, 1′-H), 3.53 (1H, dd, J_{gem}=11.6 Hz and $J_{3',2'}$=4.9 Hz, 3′-H), 3.68 (1H, dd, J_{gem}=11.6 Hz and $J_{3',2'}$=2.9 Hz, 3′-H), 3.96 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.06–4.08 (1H, m, 2′-H), 7.52–7.59 (2H, m, 6-H and 7-H), 8.00–8.04 (1H, m, 5-H or 8-H), 8.09–8.13 (1H, m, 5-H or 8-H); δ_C (100 MHz, $CDCl_3$) 34.9 (CH_2, C-1′), 62.1 (OCH_3), 63.0 (OCH_3), 66.4 (CH_2, C-3′), 72.3 (CH, C-2′), 117.1 (quat., C-3), 123.3 (CH, C-5 or C-8), 123.4 (CH, C-8 or C-5), 127.5 (CH, C-6 or C-7), 127.6 (CH, C-7 or C-6), 127.7 (quat., C-2), 128.2 (quat., C-4a or C-8a), 129.0 (quat., C-8a or C-4a), 151.3 (quat., C-1 or C-4), 151.7 (quat., C-4 or C-1); *m/z* (%) 342 (M^+ ^{81}Br, 11), 340 (M^+ ^{79}Br, 12), 262 (M^+−Br, 33), 170 (M^+−$C_4H_{12}O_2Br$, 100).

1.1.9. (+)-(*R*)-3-Bromo-2-(2′-hydroxy-3′-*p*-toluenesulfonyl)propyl-1,4-dimethoxynaphthalene 11. To a mixture of the above (*R*)-diol **10** (0.202 g, 0.59 mmol) and *p*-toluenesulfonyl chloride (0.123 g, 0.65 mmol) in dichloromethane (10 mL) cooled to 0°C, was added pyridine (0.2 mL, 2.5 mmol) with stirring under nitrogen. The mixture was allowed to warm to room temperature, stirred for 120 h, then poured into hydrochloric acid (30 mL, 2 M). The aqueous layer was extracted with dichloromethane (3×20 mL) and the combined organic extracts washed with hydrochloric acid (2×20 mL, 2 M), water (2×30 mL) and brine (30 mL). After drying over anhydrous magnesium sulfate the solvent was removed at reduced pressure and the crude product purified by flash chromatography using hexane/ethyl acetate (9:1, 4:1, 1:1 then 1:2) as eluent to yield *(R)-monotosylate* **11** (0.184 g, 63, 35% ee) as a colourless oil, $[\alpha]_D$=+1.4° (*c* 3.68, EtOH), and starting material **10** (59 mg, 29%); (Found: C, 53.8; H, 4.70. $C_{22}H_{23}O_6SBr$ requires C, 53.4; H, 4.69%. Found: M^+, 496.0379; 494.0396. $C_{22}H_{23}O_6S^{81}Br$ and $C_{22}H_{23}O_6S^{79}Br$ require 496.0378; 494.0399); ν_{max} (NaCl plates) (cm^{-1}) 3555–3099 (OH), 1359 and 1176 (RSO_2OR); δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, 4″-CH_3), 2.67 (1H, bs, OH), 3.16 (1H, dd, J_{gem}=13.7 Hz and $J_{1',2'}$=4.9 Hz, 1′-H), 3.24 (1H, dd, J_{gem}=13.7 Hz and $J_{1',2'}$=7.7 Hz, 1′-H), 3.91 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.12 (2H, d, 3′-CH_2), 4.12–4.20 (1H, m, 2′-H), 7.30 (2H, d, $J_{3'',2''}$=8.2 Hz, 3″-H), 7.53–7.57 (2H, m, 6-H and 7-H), 7.78 (2H, d, $J_{2'',3''}$=8.2 Hz, 2″-H), 7.99–8.02 (1H, m, 5-H and 8-H); δ_C (100 MHz, $CDCl_3$) 21.7 (CH_3, 4″-CH_3), 34.2 (CH_2, C-1′), 61.4 (OCH_3), 62.2 (OCH_3), 69.5 (CH_2, C-3′), 73.5 (CH, C-2′), 116.1 (quat., C-3), 122.6 (CH, C-5 or C-8), 122.7 (CH, C-8 or C-5), 126.1 (quat., C-2), 126.9 (CH, C-6 or C-7), 127.0 (CH, C-7 or C-6), 127.6 (quat., C-4a or C-8a), 128.0 (CH, C-2″ or C-3″), 128.5 (quat., C-8a or C-4a), 129.9 (CH, C-3″ or C-2″), 132.8 (quat., C-4″), 144.9 (quat., C-1″), 150.5 (quat., C-1 or C-4), 151.4 (quat., C-4 or C-1); *m/z* (%) 496 (M^+ ^{81}Br, 14), 494 (M^+ ^{79}Br, 12), 324 (M^+ ^{81}Br−$C_7H_8SO_3$, 54), 322 (M^+ ^{79}Br−$C_7H_8SO_3$, 53).

1.1.10. (+)-(*R*)-3-Bromo-2-(2′,3′-epoxypropyl)-1,4-dimethoxynaphthalene 6. To a solution of (*R*)-monotosylate **11** (53 mg, 0.11 mmol) in tetrahydrofuran (20 mL) at room temperature was added sodium hydride (20 mg of a 60% dispersion in mineral oil, 0.4 mmol) and the mixture stirred under nitrogen for 24 h. Water (50 mL) was added slowly and the mixture extracted with dichloromethane (3×30 mL).

The combined extracts were washed with water (2×20 mL), brine (2×30 mL), and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure and the crude product purified by flash chromatography using hexane/ethyl acetate (9:1 then 4:1) as eluent to yield *(R)-epoxide* **6** (31 mg, 91, 35% ee) as colourless crystals, mp 119–120°C, $[\alpha]_D=+4.2°$ (*c* 2.38, CH_2Cl_2). The melting point and ^1H NMR spectrum were consistent with racemic epoxide **6** reported earlier.

1.1.11. (+)-(*S*)-3-Bromo-2-(2′-hydroxypropyl)-1,4-dimethoxynaphthalene 7. In an analogous procedure to that described earlier for the preparation of (±)-bromoalcohol **7**, (*R*)-epoxide **6** (27 mg, 0.08 mmol) was reduced with lithium aluminum hydride (0.9 mL, 0.38 M, 0.34 mmol) at 0°C, to give *(S)-bromoalcohol* **7** (22 mg, 81, 35% ee) as colourless crystals, mp 118–120°C, $[\alpha]_D=+8.1°$ (*c* 2.05, $CHCl_3$). Comparison of optical rotation with (*R*)-bromoalcohol **7** (vide infra) indicated the enantiomeric excess to be 35%. The melting point and ^1H NMR spectrum were consistent with (±)-bromoalcohol **7** as reported earlier. The absolute stereochemistry was determined via conversion to Mosher ester derivatives using (*R*)- and (*S*)-methoxy(trifluoromethyl)phenylacetic acid.

1.1.12. (+)-(1*R*,3*S*)-1-Hydroxy-3-methyl-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 9. [(+)-7,9-Dideoxythysanone]. To a solution of (*S*)-bromoalcohol **7** (40 mg, 0.12 mmol) in tetrahydrofuran (5 mL) at −78°C under nitrogen was added *n*-butyllithium (0.3 mL, 1.3 M solution in hexanes, 0.37 mmol). After 10 min, dry dimethylformamide (0.05 mL, 0.6 mmol) was added and the mixture stirred at −78°C for 3 h, followed by warming to room temperature and quenching with phosphate buffer (0.1 M, pH 7). The mixture was extracted with dichloromethane (3×10 mL) and the organic layer washed with water (20 mL) and brine (2×10 mL). After drying over anhydrous magnesium sulfate the solvent was removed at reduced pressure and the residue dissolved in acetonitrile (5 mL). 10% Aqueous ceric ammonium nitrate (110 mg, 0.2 mmol) was added, and after the usual work up *(+)-(1R,3S)-7,9-dideoxythysanone* **9** (10 mg, 59%) was afforded as a yellow solid, mp 161–162°C (dec), $[\alpha]_D=+29.5°$ (*c* 0.80, CH_2Cl_2). The melting point and ^1H NMR spectrum were consistent with racemic 7,9-dideoxythysanone **9** reported earlier. Comparison of the optical rotation obtained for (1*S*,3*R*)-7,9-dideoxythysanone **9** (vide infra) indicated an enantiomeric excess of 35% for (1*R*,3*S*)-7,9-dideoxythysanone **9**.

1.1.13. 3-Bromo-2-(2′-oxopropyl)-1,4-dimethoxynaphthalene 12. Copper(I) chloride (19 mg, 0.19 mmol) and palladium(II) chloride (6 mg, 0.03 mmol) were added to *N*,*N*-dimethylformamide (3 mL) and water (0.5 mL) and the resultant mixture stirred under oxygen for 2 h. 2-Allyl-3-bromo-1,4-dimethoxynaphthalene **5** (49 mg, 0.16 mmol) in *N*,*N*-dimethylformamide (2 mL) was added and the mixture stirred under oxygen for 24 h. Water (20 mL) was added followed by the addition of hydrochloric acid (2 M) until the cloudy solution became clear. The mixture was extracted with ethyl acetate (3×30 mL) and the organic extracts washed with water (5×50 mL), dried over anhydrous magnesium sulfate and the solvent removed at reduced pressure. The crude product was purified by flash chromatography using hexane/ethyl acetate (9:1 then 4:1) as eluent to yield *title compound* **12** (39 mg, 74%) as white crystals, mp 114–115°C; (Found: C, 55.8; H, 4.75. $C_{15}H_{15}O_3Br$ requires C, 55.9; H, 4.69%. Found: M^+, 324.0197; 322.0205. $C_{15}H_{15}O_3{}^{81}Br$ and $C_{15}H_{15}O_3{}^{79}Br$ require 324.0184; 322.0205); ν_{max} (NaCl plates) (cm^{-1}) 1717 (C=O); δ_H (400 MHz, $CDCl_3$) 2.31 (3H, s, 3′-CH_3), 3.83 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.15 (2H, s, 1′-CH_2), 7.53–7.56 (2H, m, 6-H and 7-H), 8.04–8.07 (1H, m, 5-H or 8-H), 8.10–8.12 (1H, m, 8-H or 5-H); δ_C (100 MHz, $CDCl_3$) 29.7 (CH_3, C-3′), 45.4 (CH_2, C-1′), 61.4 (OCH_3), 62.5 (OCH_3), 116.2 (quat., C-2), 122.4 (CH, C-5 or C-8), 122.6 (CH, C-8 or C-5), 125.0 (quat., C-3), 126.7 (CH, C-6 or C-7), 126.9 (CH, C-7 or C-6), 127.7 (quat., C-4a or C-8a), 128.6 (quat., C-8a or C-4a), 150.2 (quat., C-1 or C-4), 151.6 (quat., C-4 or C-1), 205.4 (quat., C-2′); *m/z* (%) 324 (M^+ ^{81}Br, 24), 322 (M^+ ^{79}Br, 22), 243 (M^+ $^{81}Br-{}^{81}Br$ and M^+ $^{79}Br-{}^{79}Br$, 61), 185 (M^+ $^{81}Br-C_3H_6O^{81}Br$ and M^+ $^{79}Br-C_3H_6O^{79}Br$, 100).

1.1.14. (−)-(*R*)-3-Bromo-2-(2′-hydroxypropyl)-1,4-dimethoxynaphthalene 7. Triisopropyl borate (0.21 mL, 0.91 mmol) was added to (*S*)-2-[diphenylhydroxymethyl]-pyrrolidine (Aldrich™, 0.194 g, 0.77 mmol) in tetrahydrofuran (1 mL) at room temperature and under a nitrogen atmosphere. The mixture was stirred for 16 h and borane dimethylsulfide (0.6 mL, 2.0 M, 1.2 mmol) was added dropwise. After 20 min, ketone **12** (0.183 g, 0.57 mmol) in tetrahydrofuran (2 mL) was added dropwise and the mixture stirred for 5 h. The reaction mixture was exposed to air and water (2 mL) added dropwise, followed by hydrochloric acid (20 mL, 2 M) and stirring was continued for 16 h. The mixture was extracted with dichloromethane (3×30 mL), the organic layer washed with brine (2×100 mL) and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure and the crude product purified by flash chromatography using hexane/ethyl acetate (9:1 then 4:1) as eluent to yield *(R)-alcohol* **7** (0.142 g, 78, 72% ee) as white crystals, mp 118–120°C, $[\alpha]_D=-16.3°$ (*c* 1.25, $CHCl_3$). The melting point and ^1H NMR spectrum were consistent with (±)-bromoalcohol **7** reported earlier.

The absolute stereochemistry of (−)-(*R*)-bromoalcohol **7** was determined via conversion to a Mosher ester derivative using (*R*)- and (*S*)-methoxy(trifluoromethyl)phenylacetic acid. The enantiomeric excess was measured by ^1H NMR spectroscopy (400 MHz) with 1.5 equiv. of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III). The doublet assigned to the methyl group for the individual enantiomers resonated at δ_H 1.25 ppm (*S*-enantiomer) and δ_H 1.31 ppm (*R*-enantiomer) the enantiomeric excess was calculated by integration of these two doublets.

1.1.15. (1*S*,3*R*)-(+)-9,10-Dimethoxy-3-methyl-1-hydroxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran 8. In an analogous procedure to the preparation of (±)-lactol **8**, (*R*)-bromoalcohol **7** (0.117 g, 0.36 mmol) was converted to (1*S*,3*R*)-lactol **8** (58 mg, 59, 72% ee), mp 146–147°C, $[\alpha]_D=+14.5°$ (*c* 1.05, $CHCl_3$). The melting point and ^1H NMR spectrum were consistent with (±)-lactol **8** reported earlier.

1.1.16. (1*S*,3*R*)-(−)-1-Hydroxy-3-methyl-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 9. [(−)-7,9-Dideoxythysanone]. In an analogous procedure to the preparation of (±)-7,9-dideoxythysanone **9**, (1*S*,2*R*)-lactol **8** (20 mg, 0.07 mmol) underwent oxidative demethylation using ceric ammonium nitrate (80 mg, 0.14 mmol) to afford *(−)-(1S,3R)-7,9-dideoxythysanone* (11 mg, 61, 72% ee) as a yellow solid, mp 161–162°C (dec), $[\alpha]_D = -60.7°$ (*c* 1.10, $CHCl_3$). The melting point and proton NMR spectrum were consistent with (±)-7,9-dideoxythysanone **9** reported earlier.

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