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Total Synthesis of (+)-Varitriol

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Dedicated to Professor Hans-Ulrich Reissig on the occasion of his 60th birthday

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The total synthesis of natural (+)-varitriol (**1**) was accomplished by starting from dimethyl L-tartrate. The key features were a substrate selective and diastereoselective Pd^{II}-catalysed bicyclisation of unsaturated protected triol **9** followed by regioselective ring-opening of bicyclic skeleton **10**. The absolute configuration of the target was confirmed by single-crystal X-ray analysis for the first time.

Introduction

In the last decade, increased interest in the chemistry of fungi isolated from the marine environment has been indicated.[1] Marine fungi are interesting organisms from an ecological point of view, because they are significant pathogens in the marine environment.[2] Furthermore, because many can be cultured, they represent an important biomedical resource. Recently, a new natural tetrahydrofuran derivative, (+)-varitriol (**1**), was isolated from a marine-derived strain of fungus *Emericella variecolor* and has been revealed to have significant activity against a variety of tumours. In particular, (+)-**1** showed notably increased potency towards selected renal, CNS and breast cancer cell lines, although its mode of action has not yet been established.[3,4] The structure and relative stereochemistry of **1** was assigned on the basis of NMR spectroscopy and the absolute configuration was determined in the course of the synthesis of its unnatural enantiomer (–)-**1**.[5]

Recently, two synthetic approaches to unnatural (–)-**1** varitriol were published. Jennings et al.[5] achieved the total synthesis of (–)-**1** by utilising alkene metathesis to link together the carbohydrate and aromatic moieties of the molecule. The group of Taylor[6] reported a short and flexible route to (–)-**1** by applying their methodology featuring the Horner–Wadsworth–Emmons/conjugate addition/Ramberg–Bäcklund rearrangement sequence. Both syntheses utilised D-ribose to construct the furanoside portion of (–)-**1**. Very recently, the paper describing the first total synthesis of natural varitriol [(+)-**1**] appeared in the literature.[7] The approach is based on a cross metathesis reaction of the corresponding styrene and tetrahydrofuran subunits, for which the latter was obtained from methyl α-D-mannopyranoside. In addition, impressive biological activity of (+)-varitriol initiated the synthesis of its analogues and their testing for pharmacological properties.[8]

In the course of our long-term programme directed towards the application of Pd^{II}-catalysed bicyclisation of unsaturated polyols[9] to natural products synthesis, we developed the total syntheses of goniofufurone,[10] goniothalesdiol[11] and erythroskyrine.[12] Herein, we report on the total synthesis of natural varitriol.

Results and Discussion

Our analysis of the synthetic problem suggested the coupling of fragments **2** and **3** as the key step; namely, suitably protected furan derivative **2** bearing a sulfonyl group and substituted benzaldehyde through Kocieński–Julia olefination[13] (Scheme 1). Intermediate **3**[14] in turn was clearly available from 2,3-dimethylanisole, whereas subunit **2** could be prepared from dimethyl tartrate by employing our bicyclisation strategy developed for the construction of 2,3-*trans*-substituted tetrahydrofurans.[9b,9c] Thus, sulfone **2** with the correct configuration of the target molecule could be accessible from key intermediate L-*xylo*-**9** by $PdCl_2$/$CuCl_2$-catalysed bicyclisation followed by regioselective ring opening of **10** and inversion of configuration at C3.

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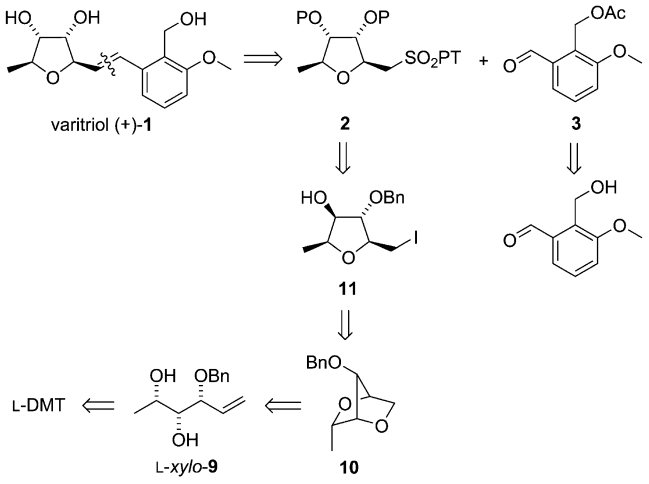
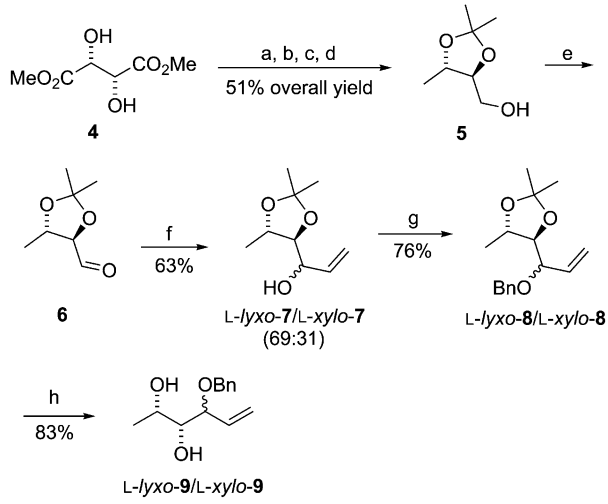


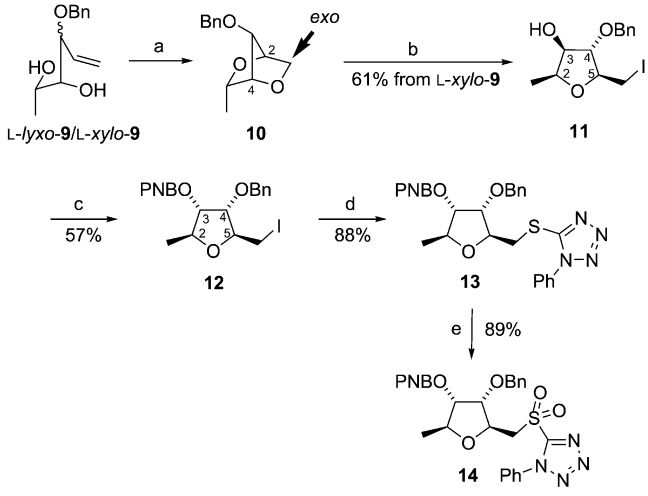
Scheme 1. Retrosynthetic analysis of (+)-**1**.

The key intermediate for bicyclisation, protected triol **9**, was obtained by using standard carbohydrate chemistry (Scheme 2). Known protected triol **5** was easily prepared from dimethyl L-tartrate (**4**) by using a published procedure involving acetonide formation,[15] ester reduction,[16] selective monotosylation[17] and hydride displacement (51% overall yield). Swern oxidation of **5** afforded aldehyde **6**, which was subjected without further purification to Grignard addition with vinylmagnesium bromide in THF. A diastereomeric mixture of partially protected triols L-*xylo*-**7**/L-*lyxo*-**7** in a 69:31 ratio and 63% yield was obtained. Finally, benzylation of the free hydroxy function of **7** and acidic hydrolysis of the acetonide protecting group furnished the required intermediate for bicyclisation, α-benzyl-protected **9**, with the L-*xylo* configuration along with its diastereomer L-*lyxo*-**9**.



Scheme 2. Synthesis of L-*lyxo*-**9**/L-*xylo*-**9**. Reagents and conditions: (a) ref.[15] DMP, PTSA, benzene, 98%; (b) ref.[16] $NaBH_4$, MeOH, 80%; (c) ref.[17] TsCl, Bu_4NHSO_4, 15% NaOH, CH_2Cl_2, 86%; (d) ref.[17] LAH, Et_2O, 76%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to room temp., 2 h; (f) vinylmagnesium bromide, THF, 0 °C to room temp., 12 h, 63% from **5** (*anti*/*syn*, 69:31); (g) BnBr, NaH, DMF, 0 °C to room temp., 12 h, 76%; (h) 60% AcOH, room temp., 10 h, 83%. DMP = 2,2-dimethoxypropane, PTSA = *p*-toluenesulfonic acid.

The mixture of diastereomers L-*lyxo*-**9**/L-*xylo*-**9** (69:31) was subjected to the crucial transformation of the synthesis: a two-step sequence to convert protected triol L-*xylo*-**9** into tetrahydrofuran **11** with the *trans* relationship of C4–C5 substituents (Scheme 3). The present approach takes advantage of recent work[9b,9c] showing that unsaturated polyols undergo Pd^{II}–Cu^{II}-catalysed bicyclisation to yield 1,4:2,5-dianhydroalditols with high *xylo*-substrate preference and excellent *threo* diastereoselectivity (concerning the newly formed stereocentre at C2 relative to the hydroxy group at C4).



Scheme 3. Synthesis of sulfone **14**. Reagents and conditions: (a) $PdCl_2$ (0.1 equiv.), $CuCl_2$ (3 equiv.), AcONa (3 equiv.), AcOH, room temp., 12 h; (b) TMSCl, TBAI, HCl, CH_2CI_2, room temp., 2 d, 61% from L-*xylo*-**9**; (c) DIAD (5 equiv.), Ph_3P (5 equiv.), *p*-NBA (5 equiv.), reflux, 2 h, 57%; (d) KSPT, DMF, room temp., 8 h, 76%; (e) Mo^{VI}/H_2O_2, EtOH, THF, 0 °C to room temp., 10 h, 89%. TMSCl = trimethylsilyl chloride, TBAI = tetrabutylammonium iodide, DIAD = diisopropyl azodicarboxylate, *p*-NBA = *p*-nitrobenzoic acid, KSPT = potassium 1-phenyl-1*H*-tetrazol-5-thiolate, PNB = *p*-nitrobenzoyl.

The reaction was carried out under standard conditions with $PdCl_2$ as catalyst (0.1 equiv.), $CuCl_2$ as oxidant (3 equiv.) and NaOAc (3 equiv.) in acetic acid as buffer at room temperature. Only L-*xylo*-**9** diastereomer was transformed into required bicycle **10**, with high substrate and *threo* selectivity as expected.[9b,9c] The products of the transformation of the other diastereomer were not identified. Treatment of the crude material with TBAI/TMSCl/HCl in CH_2Cl_2 at room temperature furnished iodide **11** (61% yield from L-*xylo*-**9**), as a product of the *exo*-regioselective ring-opening reaction of bicyclic skeleton **10**.

Next, the configuration at C3 was inverted by Mitsunobu reaction with DIAD/PPh_3/*p*-nitrobenzoic acid in THF to afford iodide **12** (57%). Nucleophilic displacement of iodine with potassium thiolate efficiently installed the phenyltetrazole sulfide moiety (88% yield) and subsequent oxidation with hydrogen peroxide/ammonium molybdate completed the construction of sulfone **14** in 89% yield. Single-crystal X-ray analysis[18] secured the structure of **14** with correct absolute configuration of all stereogenic centres (Figure 1).

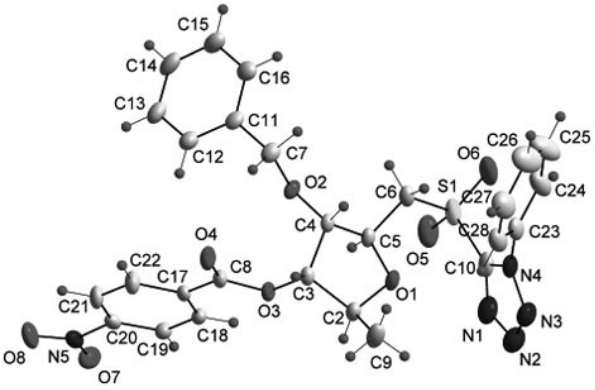
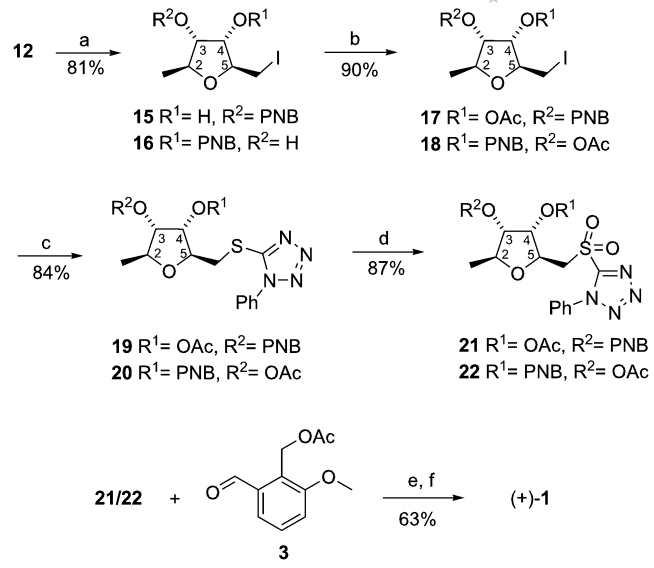


Figure 1. An ORTEP view of the crystal and molecular structure of sulfone **14**.

In the next steps of the synthesis, the set up of the free hydroxy groups was required. Because many attempts using various protocols for debenzylation of the hydroxy function at C4 had failed, this seemed to be a dead end to this approach. Fortunately, removal of the benzyl protecting group of iodide **12** was successfully achieved by smooth reaction with BCl_3 in CH_2Cl_2 at –50 °C,[19] even though concomitant partial migration of the *p*-nitrobenzoyl moiety (Scheme 4) took place; a mixture of isomers **15** and **16** in a 71:29 ratio and 81% yield was obtained. As the protecting groups for the OH functionalities were to be removed in the final step, the synthesis continued with the acetylation of the **15/16** mixture by using acetic anhydride and pyridine in the presence of DMAP to afford corresponding acetates **17/18** (90%, 1:1 ratio). Finally, the suitably protected sulfone fragment **2** for the Kocieński–Julia olefination was prepared as described above. A two-step substitution/oxidation sequence completed the synthesis of **21/22** as an equimolar mixture.

Fragment **3**, 2-formyl-6-methoxybenzyl acetate, was prepared in 88%[20] yield from 2,3-dimethylanisole by adopting a known three-step procedure.[14]

With both key fragments in hand we then looked at the key Kocieński–Julia olefination[13] of aldehyde **3** with the mixture of sulfones **21/22**. The coupling was performed under various reaction conditions by using different bases and solvents. The best result, in terms of both *E* selectivity (only the *E* isomer was observed) and yield was achieved with KHMDS (1.4 equiv.) in dimethoxyethane by adopting the so-called Barbier protocol.[13c] The base was added to the mixture of sulfones **21/22** and an excess amount of aldehyde **3** (5 equiv.) at –55 °C, and the mixture was stirred at room temperature for 10 h. The final global removal of the acetyl and benzoyl protecting groups with NaOMe in MeOH applied on the crude mixture of isomers furnished the desired natural varitriol. Purification by flash chromatography provided analytically pure (+)-**1** as a white solid in 63% yield, which was crystallised from EtOAc/hexanes (1:1) to furnish colourless needles. The spectroscopic data of (+)-**1** were in good agreement with those obtained from a natural source,[3] as well as with the synthetic probes.[5–7] Our measured value of specific rotation for (+)-**1** {$[\alpha]_D^{20}$ = +43.4 (*c* = 0.53, MeOH)} closely matched the value reported by Taylor et al.[6] for unnatural (–)-**1** {$[\alpha]_D^{20}$ = –40.6 (*c* = 1.6, MeOH)}. However, it was substantially distinct from all other values reported in the literature {ref.[3] $[\alpha]_D^{25}$ = +18.5 (*c* = 2.3, MeOH), ref.[7] $[\alpha]_D^{28}$ = +19.4 (*c* = 0.16, MeOH), ref.[5] $[\alpha]_D^{25}$ = –18.2 (*c* = 0.0033, MeOH). Therefore, we decided to definitively clear the situation regarding the absolute configuration and corresponding specific rotation of natural varitriol. Thus, we performed a single-crystal X-ray analysis[18] of the obtained compound (Figure 2) and measured its optical activity. On the basis of the results, the absolute configuration was determined as to be the same as published by Malmstrøm.[3] Hence we believe we have finally set straight the correct specific rotation for varitriol.



Scheme 4. Synthesis of varitriol [(+)-**1**]. Reagents and conditions: (a) BCl_3, CH_2Cl_2, –50 °C, 50 min, 81% (71:29); (b) Ac_2O, DMAP, pyridine, room temp., 3 h, 90% (50:50); (c) KSPT, DMF, room temp., 8 h, 84% (50:50); (d) Mo^{VI}/H_2O_2, EtOH, THF, 0 °C to room temp., 10 h, 87% (50:50); (e) KHMDS (1.4 equiv.), DME, –55 °C to room temp., 10 h; (f) NaOMe, MeOH, room temp., 4 h, 63% over 2 steps. DMAP = 4-(dimethylamino)pyridine, KHMDS = potassium hexamethyldisilazane.

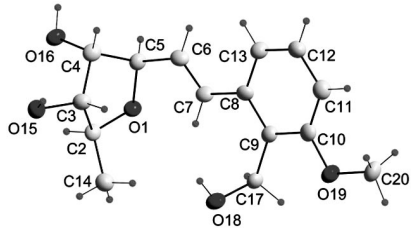


Figure 2. An ORTEP view of the crystal and molecular structure of natural (+)-varitriol [(+)-**1**].

Conclusions

In summary, natural varitriol was synthesised in 17 steps from commercially available dimethyl L-tartrate and dimethylanisole. Tetrahydrofuran derivative **11** with a *trans*

arrangement of the substituents at C4–C5 was constructed by using a bicyclisation strategy in two steps, namely, substrate and diastereoselective Pd^{II}–Cu^{II}-catalysed bicyclisation of L-*lyxo*-**9**/L-*xylo*-**9** unsaturated polyols followed by *exo*-regioselective ring opening of bicyclic dianhydroalditol **10**. The furanoside subunit of **1** with correct stereochemistry at all stereogenic centres was achieved by inversion of configuration at C3 by using the Mitsunobu reaction. For the first time the absolute configuration of natural (+)-varitriol was confirmed by X-ray analysis.

Experimental Section

General Procedure: ^1H (^{13}C) NMR spectra were recorded with either a 300 (75) MHz or 600 (150) MHz Varian spectrometer. Chemical shifts (δ) are quoted in ppm and are referenced to tetramethylsilane (TMS) as internal standard. High-resolution mass spectra (HRMS) were recorded with a Kratos Concept-IS mass spectrometer and are accurate to ±0.001. Optical rotations were measured with a POLAR ^{L}-μP polarimeter (IBZ Messtechnik) with a water-jacketed 10.000 cm cell at the wavelength of the sodium D line (λ = 589 nm). Elemental analyses were run with a FISONS EA1108 instrument. Infrared spectra were recorded with either a Philips Analytical PU9800 FTIR spectrometer or a Perkin–Elmer 1750 FTIR spectrophotometer as KBr discs or as thin films on KBr plates (film). Melting points were obtained by using a Boecius apparatus and are uncorrected. Commercial reagents were used without further purification. All solvents were distilled before use. Hexanes refer to the fraction boiling at 60–65 °C. Flash-column liquid chromatography (FLC) was performed on silica gel Kieselgel 60 (40–63 μm, 230–400 mesh), and analytical thin-layer chromatography (TLC) was performed on aluminum plates precoated with either 0.2 mm (DC-Alufolien, Merck) or 0.25 mm silica gel 60 F_{254} (ALUGRAM® SIL G/UV_{254}, Macherey–Nagel). The compounds were visualised by UV fluorescence and by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate followed by charring with a heat gun.

6: A solution of DMSO (14.81 g, 189.6 mmol, 2.25 equiv.) in CH_2Cl_2 (130 mL) was slowly added to a solution of oxalyl chloride (15.939 g, 126.6 mmol, 1.5 equiv.) in CH_2Cl_2 (130 mL) at –78 °C and stirred for 30 min under an atmosphere of argon. A solution of **5** (12.335 g, 84.3 mmol) in CH_2Cl_2 (130 mL) was added dropwise at –78 °C. After 30 min stirring at –78 °C, Et_3N (47.1 mL, 337.2 mmol, 4 equiv.) was added. After 1 h at –78 °C, the mixture was warmed to room temperature over 1 h. The mixture was concentrated in vacuo, diluted with diethyl ether and filtered through a silica gel pad. The filtrate and washings were combined and concentrated under reduced pressure. The crude product (17.9 g) was used without further purification in the next step. R_f = 0.57 (EtOAc/hexanes, 1:1)

L-*lyxo*-7 and L-*xylo*-7: A dry flask was charged with Mg turnings (3.15 g, 134.6 mmol, 1.59 equiv.) and a few crystals of iodine and then heated under an atmosphere of argon until the iodine started to sublime. A solution of vinyl bromide (10 mL, 15.17 g, 141.2 mmol, 1.67 equiv.) in dry THF (80 mL) was added dropwise to start a vigorous exothermic reaction. The reaction mixture was left at reflux for 1 h, until no magnesium remained in the flask and subsequently cooled to 0 °C. Crude aldehyde **6** (17.5 g) in THF (120 mL) was added, and the solution was left to stand overnight (12 h) and then quenched with saturated solution of NH_4Cl (20 mL). Ether (100 mL) was added, and the separated aqueous phase was extracted with Et_2O (5 × 250 mL). The combined organic phase was dried with Na_2SO_4 and concentrated. The residue was distilled with a Kugelrohr (bath temp. 120–130 °C/0.1–0.15 Torr) to afford **7** (9.14 g, 63% after two steps) as a mixture of diastereomers L-*lyxo*-**7**/L-*xylo*-**7** (69:31, GC–MS). R_f = 0.64 (EtOAc/hexanes, 1:1). Data for the mixture of isomers: ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.28 (d, $J_{1,2}$ = 6.04 Hz, 3 H, 1-H, minor), 1.30 (d, $J_{1,2}$ = 6.04 Hz, 3 H, 1-H, major), 1.41, 1.43 (all s, 4 × 3 H, all CH_3), 2.48 (br. s, 2 × 1 H, 2 × OH), 3.55 (dd, J = 4.7, 8.1 Hz, 1 H, 3-H, minor), 3.62 (dd, J = 4.1, 8.1 Hz, 1 H, 3-H, major), 3.96–4.14 (m, 3 H), 4.32–4.37 (m, 1 H), 5.20–5.45 (m, 4 H, 2 × 6A-H, 6B-H), 5.80–5.95 (m, 2 H, 2 × 5-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.2 (q, 1-C, minor), 19.19 (q, 1-C, major), 26.8, 27.4 (2 × q, 2 × CH_3, major), 26.9, 27.4 (2 × q, 2 × CH_3, minor), 71.6, 72.5 (2 × d, 2-C, 4-C, major), 72.5, 73.3 (all d, 2-C, 4-C, minor), 84.3 (d, 3-C, major), 84.8 (d, 3-C, minor), 109.4 [s, $C(CH_3)_2$, major], 110.2 [s, $C(CH_3)_2$, minor], 116.8 (t, 6-C, major), 117.1 (t, 6-C, minor), 135.6 (d, 5-C, major), 136.9 (d, 5-C, minor) ppm.

L-*lyxo*-8 and L-*xylo*-8: A suspension of hexanes-washed NaH (60% in paraffin, 6.1 g, 151 mmol, 1.3 equiv.) in dry DMF (100 mL) was cooled to 0 °C and a solution of L-*lyxo*-7/L-*xylo*-7 (69:31, 19.981 g, 116 mmol) in DMF (120 mL) was added dropwise over 45 min. The resulting mixture was stirred for 15 min and benzyl bromide (25.83 g, 151 mmol, 1.3 equiv.) was added in one portion by syringe. The reaction mixture was left to stir at room temperature overnight and it was then quenched with MeOH (10 mL). The volatiles were removed in vacuo, and the residue was dissolved in water (80 mL) and extracted with EtOAc (5 × 130 mL). The combined organic phase was dried (Na_2SO_4). After concentration at 30–40 °C/15 Torr, the remaining residue was purified by flash chromatography (EtOAc/hexanes, 1:10) to afford **8** (23.1 g, 76%) as a colourless oil and as a mixture of isomers L-*lyxo*-**8**/L-*xylo*-**8** (69:31). R_f = 0.72 (EtOAc/hexanes, 1:8). Data for the mixture of isomers: ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.24 (d, $J_{5,6}$ = 6.0 Hz, 3 H, 1-H, minor), 1.32 (d, $J_{5,6}$ = 6.1 Hz, 3 H, 1-H, major), 1.36, 1.41 (all s, 4 × 3 H, all CH_3), 3.62–3.69 (m, 2 H), 3.78–4.05 (m, 4 H), 4.41 (d, J = 12.2 Hz, 1 H, CH_2Ph, major), 4.45 (d, J = 12.2 Hz, 1 H, CH_2Ph, minor), 4.65 (d, J = 12.2 Hz, 1 H, CH_2Ph, major), 4.69 (d, J = 12.2 Hz, 1 H, CH_2Ph, minor), 5.28–5.41 (m, 4 H, 2 × 6A-H, 6B-H), 5.72–5.92 (m, 2 H, 2 × 5-H), 7.25–7.37 (m, 2 × 5 H, 2 × Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.6 (q, 1-C, minor), 19.0 (q, 1-C, major), 26.7, 27.38 (all q, 2 × CH_3, major), 26.8, 27.4 (all q, 2 × CH_3, minor), 70.1 (t, CH_2Ph, minor), 71.5 (t, CH_2Ph, major), 73.2, 80.0, 83.8 (all d, 2-C, 3-C, 4-C, minor), 74.9, 80.8, 83.8 (all d, 2-C, 3-C, 4-C, major), 108.40 [s, $C(CH_3)_2$, minor], 108.5 [s, $C(CH_3)_2$, major], 119.5 (t, 6-C, major), 119.6 (t, 6-C, minor), 127.4, 127.5, 127.6, 127.8, 128.2, 128.3 (all d, Ph), 134.5 (d, 5-C, minor), 135.1 (d, 5-C, major), 138.1 (s, *i*-Ph, major), 138.3 (s, *i*-Ph, minor) ppm.

L-*lyxo*-9 and L-*xylo*-9: A solution of diastereomers L-*lyxo*-**8**/L-*xylo*-**8** (69:31) (22 g, 83.86 mmol) dissolved in 60% AcOH (10 mL) was left to stir at room temperature for 10 h. The solvents were removed in vacuo, and the crude product was purified by FLC (EtOAc/hexanes, 1:8). Yield: 15.49 g (83%); colourless viscous oil. Data for the mixture of isomers: ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.18 (d, $J_{1,2}$ = 6.4 Hz, 3 H, 1-H, major), 1.19 (d, $J_{1,2}$ = 6.4 Hz, 3 H, 1-H, minor), 2.30–2.71 (br. s, 4 H, 4 × OH), 3.30–3.35 (m, 1 H, minor), 3.38–3.43 (m, 1 H, major), 3.80–4.07 (m, 4 H), 4.34 (d, J = 11.7 Hz, 1 H, CH_2Ph, minor), 4.39 (d, J = 11.6 Hz, 1 H, CH_2Ph, major), 4.65 (d, J = 11.6 Hz, 1 H, CH_2Ph, major), 4.66 (d, J = 11.6 Hz, 1 H, CH_2Ph, minor), 5.33–5.44 (m, 4 H, 2 × 6A-H, 6B-H), 5.78–5.92 (m, 2 H, 2 × 5-H), 7.26–7.38 (m, 10 H, 2 × Ph) ppm.

^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 19.2 (q, 1-C, major), 19.9 (q, 1-C, minor), 66.4, 75.8, 81.8 (all d, 2-C, 3-C, 4-C, major), 67.4, 75.9, 81.9 (all d, 2-C, 3-C, 4-C, minor), 70.3 (t, *C*H_2Ph, minor), 71.0 (t, *C*H_2Ph, major), 119.9 (t, 6-C, major), 120.3 (t, 6-C, minor), 127.8, 127.9, 127.9, 128.0, 128.6, 128.5 (all d, Ph), 134.6 (d, 5-C, major), 137.9 (d, 5-C, minor), 137.6 (s, *i*-Ph, minor), 137.6 (s, *i*-Ph, major) ppm.

10: A mixture of L-*lyxo*-**9**/L-*xylo*-**9** (2.656 g, 11.95 mmol, 69:31), $PdCl_2$ (212 mg, 1.19 mmol, 0.1 equiv.), anhydrous $CuCl_2$ (4.822 g, 35.84 mmol, 3 equiv.) and anhydrous AcONa (2.94 g, 35.84 mmol, 3 equiv.) in glacial AcOH (75 mL) was stirred at 25–30 °C under an atmosphere of argon for 12 h. The solvent was evaporated in vacuo, and the residue was distributed between an aqueous solution of ammonia (10%, 250 mL) and AcOEt (100 mL). The water phase was extracted with AcOEt (4 × 200 mL). The combined organic extract was dried with sodium sulfate, filtered and concentrated under reduced pressure. Purification of the resultant residue by FLC (160 g of silica gel; AcOEt/hexanes, 3:7) yielded bicycle **10** along with two other compounds (1.05 g) as a slightly yellow oil, which was used in the next step as such.

11: A mixture of derivative **10** (1.05 g), trimethylsilyl chloride (0.6 mL, 442 mg, 4.1 mmol, 1.1 equiv.), tetrabutylammonium iodide (2.715 g, 8.1 mmol, 2.2 equiv.) and aqueous concentrated HCl (1.5 mL) was stirred in CH_2Cl_2 (14 mL) at room temperature for 2 d. The mixture was diluted with CH_2Cl_2 (40 mL) and washed with an aqueous solution of $Na_2S_2O_3$ (10%, 25 mL). The organic phase was dried with $MgSO_4$ and concentrated. The crude oil was purified by flash chromatography (300 g of silica gel; toluene/EtOAc, 3:1). Pure iodide **11** was isolated as a colourless oil (787 mg, 61% after two steps corrected to the amount of pure L-*xylo*-**9**). R_f = 0.48 (toluene/EtOAc, 4:1), $[\alpha]_D^{20}$ = +14.2 (*c* = 0.6, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3443 (s), 3030 (m), 2975 (m), 2931 (s), 2871 (m), 1714 (w), 1454 (s), 1119 (s), 1071 (s), 1012 (s), 984 (s), 739 (s), 698 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.29 (d, $J_{Me,2}$ = 6.5 Hz, 3 H, Me), 1.89 (d, 1 H, OH), 3.28 (dd, B of ABX, $J_{5,HB}$ = 4.9 Hz, $J_{HA,HB}$ = 10.3 Hz, 1 H, CH_2I), 3.36 (dd, A of ABX, $J_{5,HA}$ = 6.8 Hz, $J_{HA,HB}$ = 10.3 Hz, 1 H, CH_2I), 3.80 (dd, $J_{3,4}$ = 0.7 Hz, $J_{4,5}$ = 3.0 Hz, 1 H, 4-H), 3.89 (ddd, X of ABX, $J_{4,5}$ = 3.0 Hz, $J_{5,HB}$ = 4.9 Hz, $J_{5,HA}$ = 6.8 Hz, 1 H, 5-H), 4.02–4.07 (m, 1 H, 3-H), 4.15 (dq, $J_{2,3}$ = 3.2 Hz, $J_{Me,2}$ = 6.5 Hz, 1 H, 2-H), 4.63 (s, 2 H, C*H*$_2$Ph), 7.35 (br. s, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 7.8 (t, *C*H_2I), 13.5 (q, Me), 71.9 (t, *C*H_2Ph), 77.0, 78.1, 82.8, 89.5 (all d, 2-C, 3-C, 4-C, 5-C), 127.9 (d, *p*-Ph), 127.8, 128.5 (all d, Ph), 137.5 (s, *i*-Ph) ppm. $C_{13}H_{17}IO_3$ (348.18): calcd. C 44.84, H 4.92; found C 44.74, H 4.95.

12: Diisopropyl azodicarboxylate (232 mg, 1.171 mmol, 1.2 equiv.) was added to a solution of Ph_3P (301 mg, 1.171 mmol, 2 equiv.) in dry THF (3 mL) under an atmosphere of argon. After 1 h stirring at room temperature, a solution of alcohol **11** (204 mg, 0.585 mmol) in THF (3 mL) and *p*-nitrobenzoic acid (192 mg, 1.171 mmol, 2 equiv.) was added. After 2 h at reflux, the solvent was evaporated in vacuo (20–30 °C/10 Torr), and the crude residue was purified by flash chromatography (50 g of silica gel, toluene) to afford **12** (167 mg, 57%) as a yellow solid. R_f = 0.6 (EtOAc/toluene, 1:3). M.p. 49–52 °C. $[\alpha]_D^{20}$ = +57.9 (*c* = 0.58, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3435 (s), 3113 (w), 2970 (m), 2926 (m), 2851 (w), 1719 (s), 1608 (m), 1524 (s), 1350 (s), 1279 (s), 1269 (s), 1133 (s), 1123 (s), 1106 (s), 1015 (s), 870 (m), 754 (m), 719 (s), 702 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ 25 °C): δ = 1.42 (d, $J_{Me,2}$ = 6.5 Hz, 3 H, Me), 3.23 (dd, A of ABX, $J_{5,HA}$ = 4.6 Hz, $J_{HA,HB}$ = 10.9 Hz, 1 H, CH_2I), 3.39 (dd, B of ABX, $J_{5,HB}$ = 4.2 Hz, $J_{HA,HB}$ = 10.9 Hz, 1 H, CH_2I), 3.80 (dddd, X of ABX, $J_{5,HB}$ = 4.3 Hz, $J_{5,HA}$ = 4.5 Hz, $J_{4,5}$ = 6.7 Hz, 1 H, 5-H), 3.98 (dd, $J_{3,4}$ = 5.6 Hz, $J_{4,5}$ = 6.6 Hz, 1 H, 4-H), 4.34 (dq, $J_{2,3}$ = 4.2 Hz, $J_{Me,2}$ = 6.5 Hz, 1 H, 2-H), 4.52 (d, *J* = 11.4 Hz, 1 H, C*H*$_2$Ph), 4.59 (d, *J* = 11.4 Hz, 1 H, C*H*$_2$Ph), 5.12 (dd, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 5.5 Hz, 1 H, 3-H), 7.23–7.26 (m, 5 H, Ph), 8.21 (d, $J_{o,m}$ = 9.0 Hz, 2 H, *o*-$NO_2C_6H_4$), 8.29 (d, $J_{o,m}$ = 9.0 Hz, 2 H, *m*-$NO_2C_6H_4$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 7.6 (t, *C*H_2I), 19.5 (q, Me), 73.3 (t, *C*H_2Ph), 77.6, 78.2, 80.0, 80.9 (all d, 2-C, 3-C, 4-C, 5-C), 123.6, 128.0, 128.2, 128.5, 130.9 (all d, $C_6H_4NO_2$), 135.1, 137.1, 150.7 (all s, *i*-$C_6H_4NO_2$), 164.1 (s, CO) ppm. $C_{20}H_{20}INO_6$ (497.28): calcd. C 48.31, H 4.05, N 2.82; found C 49.12, H 4.12, N 2.81.

13: Potassium 1-phenyl-1*H*-tetrazol-5-thiolate (48 mg, 0.221 mmol, 1.1 equiv.) was added to a solution of iodide **12** (100 mg, 0.2 mmol) in DMF (5 mL) at room temperature. After stirring for 8 h, the reaction mixture was concentrated in vacuo (20–30 °C/5 Torr), and the crude residue was purified by flash chromatography (20 g of silica gel; AcOEt/hexanes, 3:7) to afford sulfide **13** (96 mg, 88%) as a yellow oil. R_f = 0.6 (EtOAc/toluene, 1:3). $[\alpha]_D^{20}$ = +44.2 (*c* = 1.52, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3056 (s), 3015 (s), 2976 (m), 2952 (s), 2873 (m), 1728 (s), 1606 (m), 1597 (s), 1528 (s), 1500 (s), 1417 (s), 1386 (s), 1276 (s), 1130 (s), 1102 (s), 1014 (s), 984 (m), 912 (m), 873 (m), 760 (s), 721 (s), 695 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.35 (d, $J_{Me,2}$ = 6.6 Hz, 3 H, Me), 3.59 (dd, A of ABX, $J_{5,HA}$ = 6.3 Hz, $J_{HA,HB}$ = 13.5 Hz, 1 H, CH_2S), 3.86 (dd, B of ABX, $J_{5,HB}$ = 4.2 Hz, $J_{HA,HB}$ = 13.5 Hz, 1 H, CH_2S), 4.10 (dd, $J_{3,4}$ = 6.0 Hz, $J_{4,5}$ = 7.2 Hz, 1 H, 4-H), 4.27 (dq, $J_{2,3}$ = 3.9 Hz, $J_{Me,2}$ = 6.3 Hz, 1 H, 2-H), 4.35 (ddd, X of ABX, $J_{5,HB}$ = 4.2 Hz, $J_{5,HA}$ = 6.6 Hz, $J_{4,5}$ = 7.5 Hz, 1 H, 5-H), 4.50 (d, *J* = 11.4 Hz, 1 H, C*H*$_2$Ph), 4.57 (d, *J* = 11.4 Hz, 1 H, C*H*$_2$Ph), 5.12 (dd, $J_{2,3}$ = 3.9 Hz, $J_{3,4}$ = 5.7 Hz, 1 H, 3-H), 7.19 (s, 5 H, Ph), 7.55 (s, 5 H, Ph), 8.20 (d, $J_{o,m}$ = 9.0 Hz, 2 H, *o*-$C_6H_4NO_2$), 8.27 (d, $J_{o,m}$ = 9.0 Hz, 2 H, *m*-$C_6H_4NO_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.5 (q, Me), 35.9 (t, *C*H_2S), 73.2 (t, *C*H_2Ph), 77.3, 78.5, 79.2, 79.3 (all d, 2-C, 3-C, 4-C, 5-C), 123.5, 123.7, 128.3, 128.4, 129.8, 130.2, 130.9 (all d, $NO_2C_6H_4$, Ph), 133.4, 134.9, 136.9, 150.6, 153.9 (all s, *i*-$C_6H_4NO_2$, *i*-Ph, *i*-Tetr), 164.0 (s, CO) ppm. $C_{27}H_{25}N_5O_6S$ (547.58): calcd. C 59.22, H 4.60, N 12.79, S 5.86; found C 59.42, H 4.65, N 12.67, S 5.77.

14: To a solution of sulfide **13** (96 mg, 0.18 mmol) in a mixture of EtOH (3 mL) and THF (3 mL) was added a mixture of 35% aqueous H_2O_2 (0.4 mL, 5.28 mmol, 29.3 equiv.) and ammonium molybdate (40 mg, 0.032 mmol, 0.18 equiv.) at 0 °C. After stirring overnight at room temperature, the reaction was diluted by the addition of water (4 mL) and CH_2Cl_2 (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo. Purification on silica gel (30 g; EtOAc/hexanes, 3:7) provided **14** (93 mg, 89%) as a white solid. R_f = 0.6 (EtOAc/toluene, 1:3). M.p. 107–108 °C, colourless needles were obtained by recrystallisation from EtOAc/hexanes (1:3). $[\alpha]_D^{20}$ = +32.6 (*c* = 1.3, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3064 (w), 3030 (w), 2975 (m), 2931 (m), 1728 (s), 1672 (m), 1607 (m), 1529 (s), 1497 (w), 1448 (s), 1349 (s), 1308 (s), 1275 (s), 1103 (s), 1015 (m), 873 (m), 753 (s), 719 (s), 700 (s) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.20 (d, $J_{Me,2}$ = 6.5 Hz, 3 H, Me), 3.71–3.73 (m, *J* = 2.7 Hz, *J* = 4.2 Hz, 2 H, CH_2SO_2), 3.99 (dd, $J_{3,4}$ = 5.7 Hz, $J_{4,5}$ = 7.8 Hz, 1 H, 4-H), 4.16 (dq, $J_{2,3}$ = 3.3 Hz, $J_{Me,2}$ = 6.5 Hz, 1 H, 2-H), 4.35 (ddd, X of ABX, $J_{5,HB}$ = $J_{5,HA}$ = 4.8 Hz, $J_{4,5}$ = 7.8 Hz, 1 H, 5-H), 4.39 (d, *J* = 11.7 Hz, 1 H, C*H*$_2$Ph), 4.58 (d, *J* = 11.6 Hz, 1 H, C*H*$_2$Ph), 5.06 (dd, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 5.4 Hz, 1 H, 3-H), 7.20–7.25 (m, 5 H, Ph), 7.58 (s, 5 H, Ph), 8.17 (d, $J_{o,m}$ = 8.9 Hz, 2 H, *o*-$C_6H_4NO_2$), 8.27 (d, $J_{o,m}$ = 8.9 Hz, 2 H, *m*-$C_6H_4NO_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.4 (q, Me), 58.7 (t, *C*H_2SO_2), 73.4 (t, *C*H_2Ph), 75.0, 76.0, 79.4, 79.5 (all d, 2-C, 3-C, 4-C, 5-C), 123.6, 125.6, 128.0,

128.4, 128.6, 129.5, 130.9, 131.5 (all d, $C_6H_4NO_2$, Ph), 133.0, 134.7, 136.7, 150.6, 153.9 (all s, *i*-$C_6H_4NO_2$, *i*-Ph, *i*-Tetr), 163.9 (s, CO) ppm. $C_{27}H_{25}N_5O_8S$ (579.58): calcd. C 55.95, H 4.35, N 12.08, S 5.53; found C 55.75, H 4.41, N 11.96, S 5.48.

15 and 16: To a solution of **12** (1.474 g, 2.96 mmol) in CH_2Cl_2 (30 mL) at –50 °C was added BCl_3 (0.236 M in CH_2Cl_2, 50 mL, 11.84 mmol, 4 equiv.) dropwise by syringe. After 50 min at –50 °C, the reaction was quenched by the addition of MeOH (10 mL) and then concentrated in vacuo. The residual oil was purified by flash column chromatography (40 g of silica gel; EtOAc/hexanes, 3:7) to afford a mixture of **15** and **16** as a colourless oil (780 mg, 81%, mixture of isomers in a 71:29 ratio by ^{1}H NMR spectroscopy). R_f = 0.3 (EtOAc/hexanes, 3:7). IR (film): $\tilde{\nu}$ = 3504 (m), 3111 (w), 2974 (m), 1727 (s), 1607 (m), 1527 (s), 1349 (s), 1275 (s), 1126 (s), 1105 (s), 1104 (m), 873 (m), 783 (w), 718 (s) cm^{-1}. Data for the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, mixture of **15/16**): δ = 1.43 (d, $J_{Me,2}$ = 6.4 Hz, 3 H, Me), 2.07 (br. s, 1 H, OH), 3.38 (dd, A of ABX, $J_{5,HA}$ = 4.9 Hz, $J_{HA,HB}$ = 10.8 Hz, 1 H, CH_2I), 3.49 (dd, B of ABX, $J_{5,HB}$ = 4.6 Hz, $J_{HA,HB}$ = 10.8 Hz, 1 H, CH_2I), 3.76 (ddd, X of ABX, $J_{5,HB}$ = 4.7 Hz, $J_{5,HA}$ = 4.9 Hz, $J_{4,5}$ = 6.7 Hz, 1 H, 5-H), 4.27 (dd, $J_{3,4}$ = 6.2 Hz, $J_{4,5}$ = 6.7 Hz, 1 H, 4-H), 4.32 (dq, $J_{2,3}$ = 4.6 Hz, $J_{Me,2}$ = 6.4 Hz, 1 H, 2-H), 5.01 (dd, $J_{2,3}$ = 4.6 Hz, $J_{3,4}$ = 6.0 Hz, 1 H, 3-H), 8.23 (d, $J_{o,m}$ = 9.0 Hz, 2 H, *o*-$NO_2C_6H_4$), 8.31 (d, $J_{o,m}$ = 9.0 Hz, 2 H, *m*-$NO_2C_6H_4$) ppm. Data for the minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, mixture of **15/16**): δ = 1.42 (d, $J_{Me,2}$ = 6 Hz, 3 H, Me), 2.07 (br. s, 1 H, OH), 3.39 (dd, A of ABX, $J_{5,HA}$ = 5.4 Hz, $J_{HA,HB}$ = 10.7 Hz, 1 H, CH_2I), 3.45 (dd, B of ABX, $J_{5,HB}$ = 4.6 Hz, $J_{HA,HB}$ = 10.8 Hz, 1 H, CH_2I), 4.06–4.14 (m, 3 H, 2-H, 3-H, 5-H), 5.17 (dd, $J_{4,5}$ = 3.9 Hz, $J_{3,4}$ = 6.0 Hz, 1 H, 4-H), 8.23 (d, $J_{o,m}$ = 9.0 Hz, 2 H, *o*-$NO_2C_6H_4$), 8.31 (d, $J_{o,m}$ = 9.0 Hz, 2 H, *m*-$NO_2C_6H_4$) ppm. Data for the major isomer: ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, mixture of **15/16**): δ = 7.0 (t, *C*H_2I), 19.3 (q, Me), 74.6, 77.7, 79.6, 81.5 (all d, 2-C, 3-C, 4-C, 5-C), 123.7, 130.8, (all d, $C_6H_4NO_2$), 134.7, 150.8 (all s, *i*-$C_6H_4NO_2$), 164.4 (s, CO) ppm. Data for the minor isomer: ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, mixture of **15/16**): δ = 6.7 (t, *C*H_2I), 18.1 (q, Me), 75.8, 78.8, 79.0, 80.5 (all d, 2-C, 3-C, 4-C, 5-C), 123.7, 130.9, (all d, $C_6H_4NO_2$), 134.6, 150.2 (all s, *i*-$C_6H_4NO_2$), 164.4 (s, CO) ppm.

17 and 18: To a stirred solution of **15/16** (71:29, 948 mg, 2.32 mmol) in CH_2Cl_2 (50 mL) was added acetanhydride (0.44 mL, 4.65 mmol, 2 equiv.), pyridine (0.18 mL, 2.32 mmol, 1 equiv.) and DMAP (3 mg, 0.02 mmol, 0.008 equiv.) at room temperature under an atmosphere of argon. The mixture was allowed to stir for 3 h, by which time TLC (EtOAc/hexanes, 3:7) showed complete conversion of the starting material. The solvent was then evaporated in vacuo. Flash chromatography (35 g silica gel; EtOAc/hexanes, 3:7) afforded **17** and **18** as a colourless oil (941 mg, 90%, mixture of isomers in a 50:50 ratio by ^{1}H NMR spectroscopy). R_f = 0.6 (EtOAc/hexanes, 3:7). IR (film): $\tilde{\nu}$ = 2977 (m), 1734 (s), 1608 (m), 1528 (s), 1350 (s), 1227 (s), 1121 (s), 1105 (s), 1104 (m), 873 (m), 783 (w), 718 (s) cm^{-1}. Data for a 1:1 mixture of **17/18**: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.42 (d, $J_{Me,2}$ = 6.2 Hz, 3 H, Me), 1.46 (d, $J_{Me,2}$ = 6.3 Hz, 3 H, Me), 2.00 (s, 3 H, CO*C*H_3), 2.01 (s, 3 H, CO*C*H_3), 3.37–3.48 (m, $J_{5,HA}$ = 4.3 Hz, $J_{5,HA}$ = 4.9 Hz, $J_{5,HB}$ = 5.0 Hz, $J_{HA,HB}$ = 9.8 Hz, $J_{HA,HB}$ = 10.9 Hz, 4 H, CH_2I), 3.98 (ddd, $J_{5,HA}$ = 4.9 Hz, $J_{5,HB}$ = $J_{4,5}$ = 5.0 Hz, 1 H, 5-H), 4.09 (ddd, $J_{5,HB}$ = $J_{5,HA}$ = $J_{4,5}$ = 4.9 Hz, 1 H, 5-H), 4.20 (dq, $J_{Me,2}$ = $J_{2,3}$ = 6.3 Hz, 1 H, 2-H), 4.29 (dq, $J_{2,3}$ = 5.3 Hz, $J_{Me,2}$ = 6.4 Hz, 1 H, 2-H), 4.99 (dd, $J_{2,3}$ = $J_{3,4}$ = 6.4 Hz, 1 H, 3-H), 5.12–5.21 (m, *J* = 5.9 Hz, *J* = 5.3 Hz, 2 H, 3-H, 4-H), 5.33 (dd, $J_{3,4}$ = 4.7 Hz, $J_{2,3}$ = 6.1 Hz, 1 H, 4-H), 8.20 (d, $J_{o,m}$ = 9.1 Hz, 4 H, *o*-$NO_2C_6H_4$), 8.33 (d, $J_{o,m}$ = 8.9 Hz, 4 H, *m*-$NO_2C_6H_4$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 6.0, 6.2 (2×t, *C*H_2I), 18.4, 18.8 (2×q, Me), 20.5, 20.6 (2×q, CO*C*H_3), 74.8, 75.6, 76.2, 77.7, 80.2, 80.3, 80.6, 80.7 (all d, 2×2-C, 3-C, 4-C, 5-C), 123.7, 123.7, 130.7, 130.8 (all d, $C_6H_4NO_2$), 134.6, 134.7, 151.5, 151.9 (2×s, *i*-$C_6H_4NO_2$), 163.5, 163.6 (2×s, *C*$OC_6H_4NO_2$), 169.6, 169.7 (2×s, *C*OCH_3) ppm.

19 and 20: To a stirred solution of isomeric iodides **17/18** (1:1, 935 mg, 2.08 mmol) in DMF (40 mL) was added potassium 1-phenyl-1*H*-tetrazolyl-5-thiolate (495 mg, 2.28 mmol, 1.1 equiv.) at room temperature. After stirring overnight, the mixture was concentrated in vacuo and purified by flash chromatography (30 g silica gel; EtOAc/hexanes, 3:7) to afford a mixture of sulfides **19** and **20** as a colourless oil (874 mg, 84%, mixture of isomers in a 50:50 ratio by ^{1}H NMR spectroscopy). R_f = 0.2 (EtOAc/hexanes, 2:8). IR (film): $\tilde{\nu}$ = 2975 (m), 1747 (s), 1733 (s), 1606 (m), 1526 (s), 1499 (s), 1349 (s), 1272 (s), 1120 (s), 1105 (s), 1015 (s), 873 (m), 763 (m), 719 (s) cm^{-1}. HRMS (ESI+): calcd. for $C_{22}H_{22}N_5O_7S$ $[M + H]^+$ 500.1234; found 500.1236. Data for the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, mixture of **19/20** in a 58:42 ratio): δ = 1.38 (d, $J_{Me,2}$ = 6.4 Hz, 3 H, Me), 2.01 (s, 3 H, CO*C*H_3), 3.66 (dd, A of ABX, $J_{5,HA}$ = 6.5 Hz, $J_{HA,HB}$ = 13.9 Hz, 1 H, CH_2S), 3.93 (dd, B of ABX, $J_{HA,HB}$ = 14.0 Hz, 1 H, CH_2S), 4.24 (dq, $J_{2,3}$ = 4.2 Hz, $J_{Me,2}$ = 6.4 Hz, 1 H, 2-H), 4.45 (dddd, X of ABX, $J_{2,5}$ = 1.9 Hz, $J_{4,5}$ = 4.2 Hz, $J_{5,HA}$ = 6.4 Hz, 1 H, 5-H), 5.17 (m, 2 H, 3-H, 4-H), 7.58–7.61 (m, 5 H, Ph), 8.20 (d, $J_{o,m}$ = 9.1 Hz, 2 H, *o*-$NO_2C_6H_4$), 8.31 (d, $J_{o,m}$ = 9.0 Hz, 2 H, *m*-$NO_2C_6H_4$) ppm. Data for the minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, mixture of **19/20** in a 58:42 ratio): δ = 1.35 (d, $J_{Me,2}$ = 6.4 Hz, 3 H, Me), 2.00 (s, 3 H, CO*C*H_3), 3.69 (dd, A of ABX, $J_{5,HA}$ = 6.4 Hz, $J_{HA,HB}$ = 14.0 Hz, 1 H, CH_2S), 3.91 (d, B of ABX, $J_{HA,HB}$ = 14.0 Hz, 1 H, CH_2S), 4.14 (dq, $J_{2,Me}$ = 6.4 Hz, $J_{2,3}$ = 6.0 Hz, 1 H, 2-H), 4.54 (ddd, $J_{2,5}$ = 4.1 Hz, $J_{4,5}$ = 6.0 Hz, $J_{5,HA}$ = 6.4 Hz, 1 H, 5-H), 5.00 (dd, $J_{3,4}$ = 5.8 Hz, $J_{4,5}$ = 5.9 Hz, 1 H, 4-H), 5.37 (dd, $J_{3,4}$ = 5.9 Hz, $J_{2,3}$ = 6.0 Hz, 1 H, 3-H), 7.56–7.57 (m, 5 H, Ph), 8.20 (d, $J_{o,m}$ = 9.1 Hz, 2 H, *o*-$NO_2C_6H_4$), 8.31 (d, $J_{o,m}$ = 9.0 Hz, 2 H, *m*-$NO_2C_6H_4$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, mixture of **19/20** in a 58:42 ratio): δ = 18.7, 19.0 (2×q, Me), 20.4, 20.5 (2×q, CO*C*H_3), 35.6, 35.7 (2×t, *C*H_2S), 72.9, 74.4, 75.5, 76.9, 78.2, 78.4, 78.6, 78.9 (all d, 2×2-C, 3-C, 4-C, 5-C), 123.7, 123.8, 123.9, 124.2, 129.7, 129.8, 129.9, 130.2, 130.7, 130.8 (all d, $C_6H_4NO_2$, Ph), 133.4, 133.5, 134.4, 134.6, 150.8, 150.9, 153.7, 153.8 (all s, 2×*i*-$C_6H_4NO_2$, *i*-Ph, *i*-Tetr), 163.5, 163.6 (2×s, *C*$OC_6H_4NO_2$), 169.6, 169.6 (2×s, *C*OCH_3) ppm.

21 and 22: Ammonium molybdate (355 mg, 0.287 mmol, 0.17 equiv.) and hydrogen peroxide (35% solution in H_2O, 2.9 mL, 33.8 mmol, 25 equiv.) were combined at 0 °C and stirred for 15 min. This bright yellow solution was added dropwise to a cooled (0 °C) solution of starting sulfides **19/20** (1:1, 844 mg, 1.69 mmol) in the mixture of EtOH (15 mL) and THF (15 mL). The mixture was allowed to stir overnight at room temperature and then concentrated in vacuo. The residue was partitioned between dichloromethane (25 mL) and water (15 mL). The water layer was washed with dichloromethane (4×20 mL). The combined organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (30 g silica gel; EtOAc/hexanes, 3:7) afforded **21/22** as a colourless viscous oil (779 mg, 87%, mixture of isomers in a 50:50 ratio by ^{1}H NMR spectroscopy). R_f = 0.5 (EtOAc/hexanes, 4:6). IR (film): $\tilde{\nu}$ = 2975 (m), 2931 (m), 1728 (s), 1672 (s), 1607 (m), 1529 (s), 1448 (s), 1349 (s), 1319 (s), 1308 (s), 1275 (s), 1148 (s), 1132 (s), 1015 (m), 873 (w), 753 (s), 719 (s) cm^{-1}. HRMS (ESI+): calcd. for $C_{22}H_{25}N_6O_9S$ $[M + NH_4]^+$ 549.1398; found 549.1406. Data for the major isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, mixture of **21/22** in a 56:44ratio): δ = 1.26 (d, $J_{Me,2}$ = 6.4 Hz, 3 H, Me), 1.99 (s, 3 H, CO*C*H_3), 3.97–4.18 (m, 3 H, CH_2SO_2, 2-H), 4.46 (ddd, $J_{5,HA}$ = 3.2 Hz, $J_{5,HB}$ = 5.1 Hz, $J_{4,5}$ = 6.3 Hz, 1 H, 5-H), 5.06

(dd, $J_{2,3}$ = 5.9 Hz, $J_{3,4}$ = 6.1 Hz, 1 H, 3-H or 4-H), 5.18 (dd, $J_{3,4}$ = 5.9 Hz, $J_{4,5}$ = 6.1 Hz, 1 H, 4-H or 3-H), 7.59–7.66 (m, 5 H, Ph), 8.19 (d, $J_{o,m}$ = 9.0 Hz, 2 H, *o*-$NO_2C_6H_4$), 8.32 (d, $J_{o,m}$ = 8.9 Hz, 2 H, *m*-$NO_2C_6H_4$) ppm. Data for the minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, mixture of **21/22** in a 56:44ratio): δ = 1.23 (d, $J_{Me,2}$ = 6.3 Hz, 3 H, Me), 2.03 (s, 3 H, CO*C*H$_3$), 3.97–4.18 (m, 3 H, CH_2SO_2, 2-H), 4.56 (ddd, $J_{5,HA}$ = 3.9 Hz, $J_{5,HB}$ = 4.7 Hz, $J_{4,5}$ = 5.8 Hz, 1 H, 5-H), 4.88 (dd, $J_{2,3}$ = 6.1 Hz, $J_{3,4}$ = 6.4 Hz, 1 H, 3-H or 4-H), 5.35 (dd, $J_{4,5}$ = 5.9 Hz, $J_{3,4}$ = 6.0 Hz, 1 H, 4-H or 3-H), 7.59–7.66 (m, 5 H, Ph), 8.16 (d, $J_{o,m}$ = 8.9 Hz, 2 H, *o*-$NO_2C_6H_4$), 8.32 (d, $J_{o,m}$ = 8.9 Hz, 2 H, *m*-$NO_2C_6H_4$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, mixture of **21/22** in a 1:1 ratio): δ = 18.3, 18.6 (2 × q, Me), 20.4, 20.5 (2 × q, CO*C*H$_3$), 58.7, 58.8 (2 × t, *C*H_2SO_2), 73.2, 74.5, 74.8, 75.7, 75.8, 75.9, 78.3, 78.6 (all d, 2 × 2-C, 3-C, 4-C, 5-C), 123.7, 123.8, 125.4, 125.5, 129.6, 130.7, 130.8, 131.5 (all d, $C_6H_4NO_2$, Ph), 133.0, 133.1, 134.0, 134.3, 143.2, 143.8, 153.8, 153.9 (all s, *i*-Ph, *i*-$C_6H_4NO_2$, *i*-Tetr), 163.6, 163.7 (2 × s, *C*O$C_6H_4NO_2$), 169.6, 170.8 (2 × s, *C*OCH$_3$) ppm.

(+)-Varitriol {(+)-1}: To a stirred solution of **21/22** (65 mg, 0.122 mmol) and aldehyde **3** (127 mg, 0.608 mmol, 5 equiv.) in dimethoxyethane (5 mL) was added KHMDS (15% in toluene, 0.260 mL, 0.170 mmol, 1.4 equiv.) at –55 °C. The reaction mixture was warmed slowly to room temperature and stirred for 10 h. The reaction was then quenched by the addition of water (0.2 mL) and concentrated in vacuo. The crude product was dissolved in MeOH (3 mL) and freshly prepared sodium methoxide (0.6 M in MeOH, 1 mL) was added. The mixture was allowed to stir for 4 h, by which time TLC (EtOAc/hexanes, 3:7) showed complete conversion of the starting material. Strong acidic DOWEX (2 g) was added, and the mixture was stirred for 30 min until the pH of the mixture was neutral. The resin was filtered off, and the mixture was concentrated in vacuo. Purification (10 g silica gel; CH_2Cl_2/acetone, 3:2) provided [(+)-**1**] (21.5 mg, 63%) as a white solid. R_f = 0.3 (CH_2Cl_2/acetone, 3:2). M.p. 109–112 °C, colourless needles by recrystallisation from EtOAc/hexanes, 1:1. $[\alpha]_D^{20}$ = +43.4 (*c* = 0.53, MeOH) {ref.[3] $[\alpha]_D^{25}$ = +18.5 (*c* = 2.3, MeOH), ref.[7] $[\alpha]_D^{28}$ = +19.4 (*c* = 0.16, MeOH), ref.[5] $[\alpha]_D^{25}$ = –18.2 (*c* = 0.0033, MeOH), ref.[6] $[\alpha]_D^{20}$ = –40.6 (*c* = 1.6, MeOH) for (–)-**1**}. IR (nujol): $\tilde{\nu}$ = 3385 (s), 2968 (m), 2929 (m), 1597 (w), 1578 (s), 1472 (s), 1456 (m), 1439 (m), 1255 (s), 1091 (s), 1004 (s), 974 (m), 799 (w), 748 (w) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]acetone, 25 °C): δ = 1.27 (d, $J_{Me,2}$ = 6.2 Hz, 3 H, Me), 3.69 (dd, $J_{2,3}$ = $J_{3,4}$ = 5.7 Hz, 1 H, 3-H), 3.82 (s, 3 H, OCH_3), 3.83 (dq, $J_{2,3}$ = 5.9 Hz, $J_{2,Me}$ = 6.2 Hz, 1 H, 2-H), 3.90 (dd, $J_{3,4}$ = $J_{4,5}$ = 5.6 Hz, 4-H), 4.28 (ddd, $J_{5,2'}$ = 1.2 Hz, $J_{4,5}$ = 5.4 Hz, $J_{5,1'}$ = 6.5 Hz, 1 H, 5-H), 4.71 (s, 2 H, OCH_2), 6.20 (dd, $J_{1',5}$ = 6.5 Hz, $J_{1',2'}$ = 15.8 Hz, 1 H, 1′-H), 6.89 (dd, $J_{6',8'}$ = 1.1 Hz, $J_{6',7'}$ = 8.0 Hz, 1 H, 6′-H), 7.13 (dd, $J_{6',8'}$ = 1.1 Hz, $J_{7',8'}$ = 8.0 Hz, 1 H, 8′-H), 7.13 (dd, $J_{5,2'}$ = 1.2 Hz, $J_{1',2'}$ = 15.8 Hz, 1 H, 2′-H), 7.19 (dd, $J_{6',7'}$ = $J_{7',8'}$ = 8.0 Hz, 1 H, 7′-H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone, 25 °C): δ = 19.5 (q, Me), 55.2 (t, CH_2OH), 56.1 (q, OCH_3), 76.5 (d, 4-C), 77.2 (d, 3-C), 80.1 (d, 2-C), 85.4 (d, 5-C), 110.7 (d, 6′-C), 119.4 (d, 8′-C), 128.1 (s, 4′-C), 129.3 (d, 7′-C), 129.4 (d, 2′-C), 132.6 (d, 1′-C), 139.1 (s, 3′-C), 159.0 (s, 5′-C) ppm. $C_{15}H_{20}O_5$ (280.32): calcd. C 64.27, H 7.19; found C 63.86, H 7.26.

Supporting Information (see footnote on the first page of this article): Additional experimental procedures and physical and spectroscopic data; structure refinement details of **14** and (+)-**1**; ^{1}H and ^{13}C NMR spectra for all new compounds.

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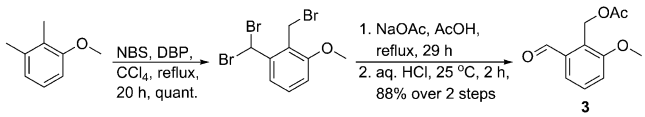

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