Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 3004–3015
Tetrahedron

Atom transfer radical cyclization reactions (ATRC): synthetic applications

Chris D. Edlin,[a] James Faulkner,[b] Madeleine Helliwell,[b] Christopher K. Knight,[b] Jeremy Parker,[c] Peter Quayle[b,*] and James Raftery[b]

[a]*Medicinal Chemistry 1, GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts. SG1 2NY, UK*
[b]*School of Chemistry, The University of Manchester, Manchester M13 9PL, UK*
[c]*AstraZeneca Process R&D, Avlon Works, Severn Road, Hallen Bristol BS10 7ZE, UK*

Received 7 November 2005; revised 21 December 2005; accepted 12 January 2006

Available online 13 February 2006

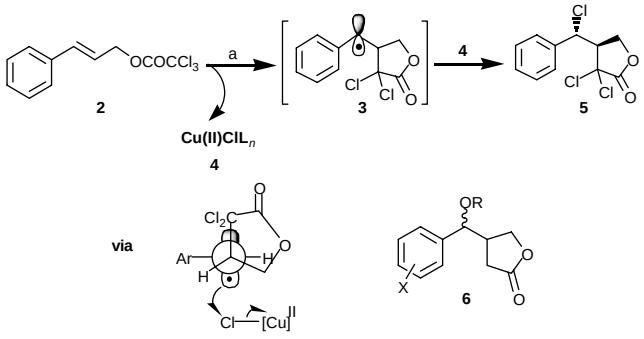
Abstract—Atom transfer cyclization reactions (ATRC) provide rapid access to functionalized γ-butyrolactones.

1. Introduction

Transition metal catalyzed atom transfer radical cyclization reactions[1] (ATRC) provide a useful alternative to the more widely adopted[2] 'tin hydride' variants of this process. ATRC reactions are of interest in that they generate intermediates, which possess a potentially useful carbon–halogen bond for manipulation after cyclization has taken place. Although a number of groups[1] have reported on the ATRC of polyhaloacetates and amides, leading to γ-butyrolactones and γ-butyrolactams, there are scant reports concerning their use in target-oriented synthesis.[3] In this paper, we detail our preliminary results in this area.

2. Results and discussion

In previous reports,[4] we demonstrated that a range of catalysts including the 1st generation Grubbs catalyst promotes cyclization of the ester **2** affording the lactone **5** in high yield. Of note was the observation that the reaction proceeds with very high levels of diastereoselectivity affording the *threo*-isomer **5** as the sole product. Subsequent studies established that the stereochemical outcome of this radical reaction is essentially independent of the catalyst used, the same result being obtained with, for example, copper catalysts. This stereochemical result may be rationalized[5] in terms of an 'allylic strain model' depicted below (Scheme 1). Cyclization of **2** initially generates **3** in which the (planar) benzylic radical adopts a conformation in which the bulky aromatic residue takes up an 'outside-' orientation with respect to the lactone ring, thereby minimizing unfavorable steric interactions. Halogen abstraction from the copper (II) complex **4**, generated in the first step of the reaction, proceeds in a direction *anti*- to the bulky geminal dichloromethylene residue[6] (steric approach control). Given that structurally related γ-butyrolactones, for example, **6** have found application[7] in the synthesis of a variety of lignans we wondered whether an ATRC approach[8] could be employed in the preparation of these synthetically useful intermediates.

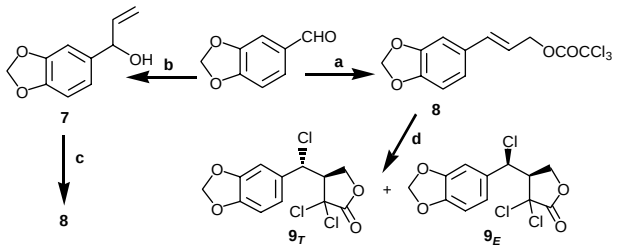


Scheme 1. Reagents and conditions: (a) CuCl (5 mol%), dHbipy (5 mol%), DCE, 80 °C, 89% (dr > 95:5).

Initial studies were concerned with the synthesis of the trichloroacetate **8**, which was readily accomplished[9] in three steps from piperonal (Scheme 2). Purely fortuitously we also observed that attempted trichloroacetylation of 1′-hydroxysafrole **7** also resulted in the isolation of

Keywords: Atom; Transfer; Cyclization; Radical; ATRC; Copper.
* Corresponding author. Tel.: +44 161 275 4619; fax: +44 161 275 4598; e-mail: peter.quayle@manchester.ac.uk

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.038



Scheme 2. Reagents and conditions: (a) i. $Ph_3P{=}CHCO_2Et$ (1 equiv), THF, 20 °C, 89%, ii. Dibal-H (2.2 equiv), THF, −78 °C, 88% (cf. Ref. 9), iii. $ClCOCCl_3$ (1 equiv), Et_3N (1 equiv), Et_2O, 0 °C, 85%; (b) $H_2CCHMgBr$, THF, −78 °C, (c) $ClCOCCl_3$ (1 equiv), Et_3N (1 equiv), Et_2O, 0 °C, 91% (over two steps); (d) CuCl (5 mol%); dHbipy (5 mol%); DCE, 80 °C; 90%.

the rearranged ester **8**. This facile high-yielding reaction (>90% over two steps) sequence could be conducted very simply on a preparative scale and became the route of choice to this particular substrate. Surprisingly exposure of the ester **8** (3 mmol) to a preformed solution of a Cu(I)–dHbipy catalyst[10] (5 mol%) in degassed 1,2-dichloroethane for 3.5 h at reflux was almost stereo-random and afforded the diastereoisomeric chlorolactones $\mathbf{9}_T$ and $\mathbf{9}_E$ ($\mathbf{9}_T$:$\mathbf{9}_E$=3:2) in 90% isolated yield. Stereochemical assignments in this series were secured on the basis of a single crystal X-ray structure[11] carried out on the major diastereisomer $\mathbf{9}_T$ (Fig. 1). On scaling-up this reaction (46 mmol) we observed that the initial product of the reaction was indeed the *threo*-isomer $\mathbf{9}_T$, as predicted ($\mathbf{9}_T$:$\mathbf{9}_E$=19:1), suggesting that equilibration had taken place after cyclization in our initial experiments. That this was the case was confirmed when it was found that subjecting either of the isomers $\mathbf{9}_T$ or $\mathbf{9}_E$ separately to mild thermolysis in DCE again afforded $\mathbf{9}_T$ and $\mathbf{9}_E$ as a 3:2 mixture at equilibrium. This isomerisation is apparently thermally driven and does not necessitate the addition of a copper catalyst, Scheme 2.

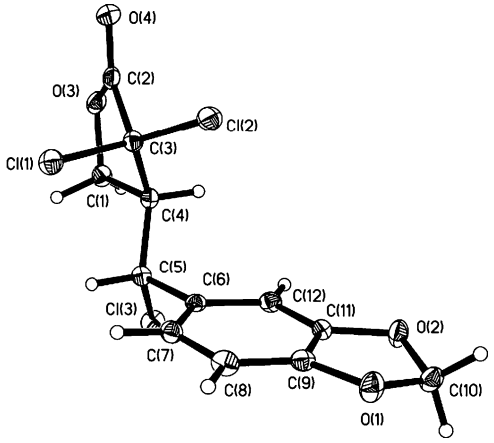


Figure 1. X-ray structure of $\mathbf{9}_T$ (crystallographic numbering).

With the chlorolactones $\mathbf{9}_T$ and $\mathbf{9}_E$ in hand their solvolysis[12] was next attempted. After some experimentation it was discovered that dissolution of a diastereoisomeric mixture of lactones $\mathbf{9}_T$,$\mathbf{9}_E$ ($\mathbf{9}_T$:$\mathbf{9}_E$=3:2) in CH_2Cl_2 containing benzyl alcohol (2 equiv of a 1.7 M soln) at 50 °C resulted in a clean conversion into a single crystalline *threo*-ether **11a** in 85% yield. Again stereochemical assignments were based upon single crystal X-ray analysis (Fig. 2). We presume that these reactions proceed via heterolysis of the C–Cl bond,

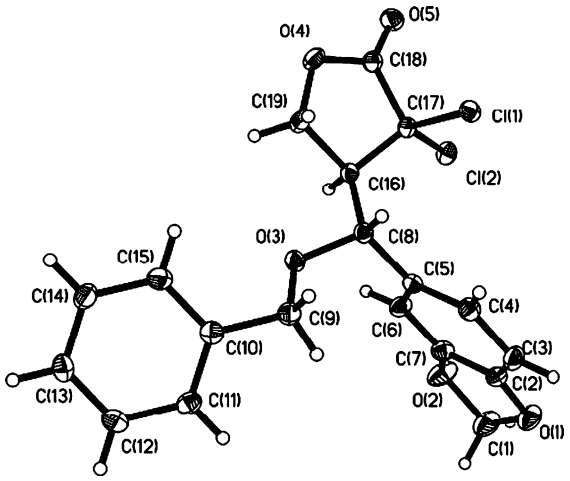
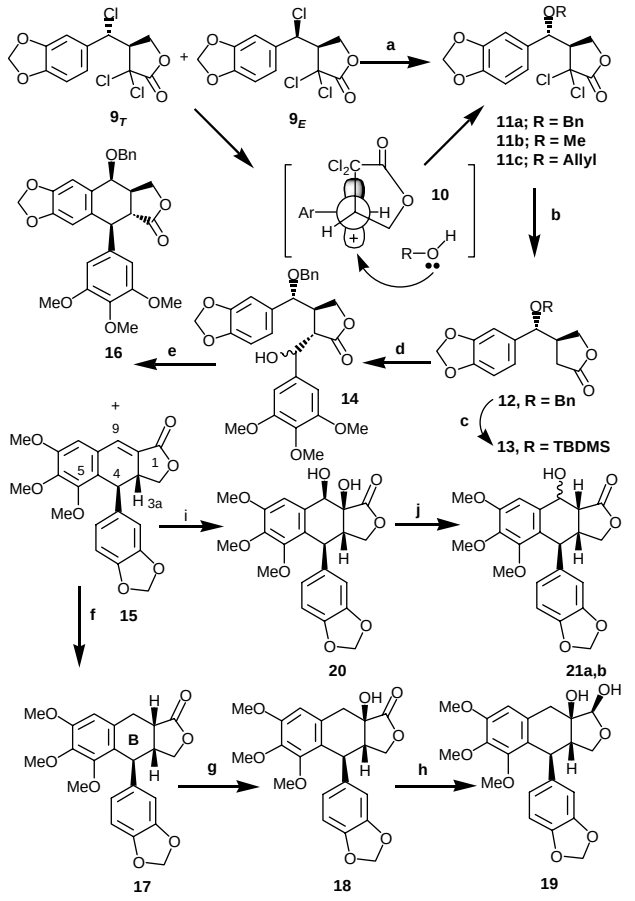


Figure 2. X-ray structure of **11a** (crystallographic numbering).

generating a planar benzylic cation **10** whose interception by benzyl alcohol would, as in the case of the radical chemistry, affords the *threo*-product $\mathbf{11a}_T$ (dr>95:5). Replacing benzyl alcohol with allyl alcohol or methanol in this reaction also resulted in the isolation of the ethers **11b** (91%) and **11c** (75%), both with reasonable levels of diastereoselectivity (dr ca. 9:1; stereochemistry by analogy, vide supra). Dechlorination of **11a** (Bu_3SnH, AIBN, PhH, 80 °C) proved uneventful and afford the known[13] lactone **12** in 83% isolated yield. Regioselective catalytic hydrogenolysis (10% Pd–C, H_2, EtOAc, of **12** followed by in situ protection (TBDMSCl, imidazole, DMAP, TBAB, CH_2Cl_2) led directly to the known[14] TBS ether **13** in 72% overall yield from **12**. The spectral data for **13** were identical to that reported by Coelho[14] thereby providing additional support for our stereochemical assignments (Scheme 3).

With a practical synthesis of the intermediate **12** to hand we have briefly investigated its chemistry. In keeping with Brown's[13] earlier work, enolate generation (LDA, 1.2 equiv, THF; −78 °C; 1 h) followed by reaction with 3,4,5-trimethoxybenzaldehyde afforded the aldol products **14** as a 1:1 mixture of diastereoisomers at the newly created benzylic centre (76% yield). Exposure of the diastereoisomeric mixture **14** to a Lewis acid ($BF_3{\cdot}OEt_2$, 1.0 equiv; CH_2Cl_2; −78 °C, 30 min) resulted in the isolation[15a] of the retro-lignan **15** (71%) together with the bis-epipodophyllotoxin[15b] derivative **16** as a minor component (12%). Molecular models indicate that the cyclohexene ring of **15** adopts a half-boat conformation in which the aromatic substituent at C-4 is pseudo-equatorially disposed ($^3J_{H3a–H4}$ 15 Hz), Figure 3.

This conformational bias places the aromatic ring of the C-1 substituent over the C-5 methoxy group, a situation which results in a large upfield shift[16] of this substituent in its ^1H NMR spectrum compared to **14** ($\Delta\delta\approx0.5$ ppm). Catalytic hydrogenation of **15** (10% Pd–C; EtOAc; H_2) proved to be highly stereoselective[17] (dr>95:5), as depicted in Figure 3, and afforded the tetrahydronaphthalene **17** possessing a cis-fused lactone in high yield (86%). Reduction of the $\Delta^{9,9a}$-double bond of **15** results in a conformational change in ring **B** of **17**. Detailed NOE experiments led us to conclude that whilst the cyclohexane ring of **17** still



Scheme 3. Reagents and conditions: (a) ROH (2.0 equiv), CH_2Cl_2, 50 °C, 85% (R=Bn) or ROH (excess), 20 °C, 82% (R=Allyl); 78% (R=Me); (b) TBTH (2.0 equiv), AIBN (20 mol%), PhH, 80 °C, 83%; (c) i. 10% Pd–C, H_2, EtOAc, ii. TBDMSCl (1.0 equiv), imidazole (1 equiv), DMAP (cat.), CH_2Cl_2, RT, 72% overall; (d) i. LDA (1.2 equiv), THF, −78 °C, ii. ArCHO (1.2 equiv), THF, −78 °C, 76% (1:1 mixture of isomers), (e) $BF_3.Et_2O$ (1.0 equiv), CH_2Cl_2, RT, **15** (71%) and **16** (12%), (f) 10% Pd–C; H_2, EtOAc, 86%; (g) i. KHMDS (1.0 equiv), THF, −78 °C, ii. (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (2.2 equiv), −78 °C; 67%; (h) $LiAlH_4$ (2.4 equiv), THF, 0 °C; 87%; (i) i. OsO_4 (1.2 equiv), pyridine, 20 °C, 12 h, ii. Na_2SO_3, 65%; (j) SmI_2: 3 equiv, THF:H_2O (98:2), 20 °C, 15 min, 86%.

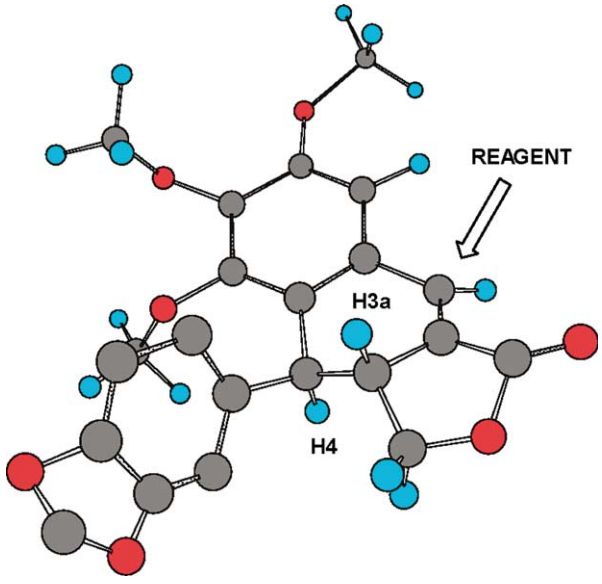


Figure 3. Chem 3D representation of **15**.

adopts a half-boat conformation[18a] the aryl residue at the C-1 substituent is now pseudo axially disposed ($^3J_{H3a–H4} \approx 1$ Hz). Presumably this conformational change occurs in order to minimize a potentially destabilizing *peri*-interaction between the bulky substituent at C-4 and the C-5 methoxy group (Fig. 4). Reaction of the enolate derived from **17** was highly stereoselective[19a] resulting in attack from the *exo*-face of the cup-shaped enolate. Hence, enolate generation (KHMDS, 1 equiv; THF, −78 °C) followed by reaction with (1*R*)-camphorsulfonyloxaziridine (2.2 equiv; THF; −78 °C) afforded the diastereoisomerically pure hydroxylated lactone **18**[19b] in good yield (67%).

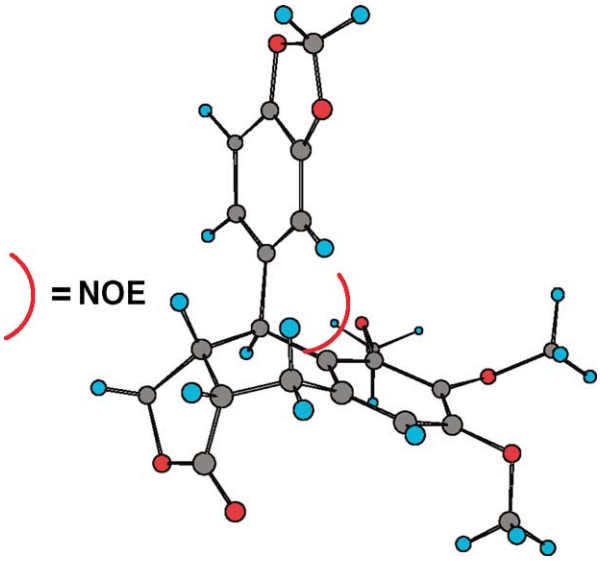


Figure 4. Chem 3D representation of **17**.

Again, NOE studies infer that ring **B** of **18** exists in a half-boat conformation in which the aryl substituent at C-4 is pseudo-axially disposed ($^3J_{H3a–H4}$ 1.5 Hz). Reduction[20] of the lactone **18** ($LiAlH_4$, 2.4 equiv; THF; 0 °C; 5 min) afforded the lactol **19** as a single diastereoisomer in 87% yield, which we have tentatively assigned as the β-epimer on the basis of NOE measurements. The lactol **19** is related to other oxygenated lignans such as the africanal[21] and the triol cycloovitol[22] which, notwithstanding their interesting biological activity, have received scant attention from synthetic chemists.[22] In addition, dihydroxylation of the electron deficient $\Delta^{9,9a}$-bond of **15** proved sluggish but proceeded cleanly following the procedure adopted by Criegee,[23a] which is stoichiometric in osmium tetroxide.

This reaction also proved to be highly stereoselective, affording the diol **20** in 65% yield, again as a result of the reagent approaching from the *β*-face of **15** as depicted in Figure 3. In passing it is also noteworthy that the intermediate osmate ester, **20′** (Fig. 5), formed during this reaction, proved to be quite stable towards hydrolysis and survived chromatography although its demetallation could be readily achieved using Sarrett's procedure.[23b] Analysis of the coupling constant data derived from the ^{1}H NMR spectrum of **20′** suggests that this molecule rapidly interchanges[18b] between two boat conformations on the NMR time scale and that the resulting coupling pattern differs from that which would be expected for the conformationally constrained isomer **20″**,

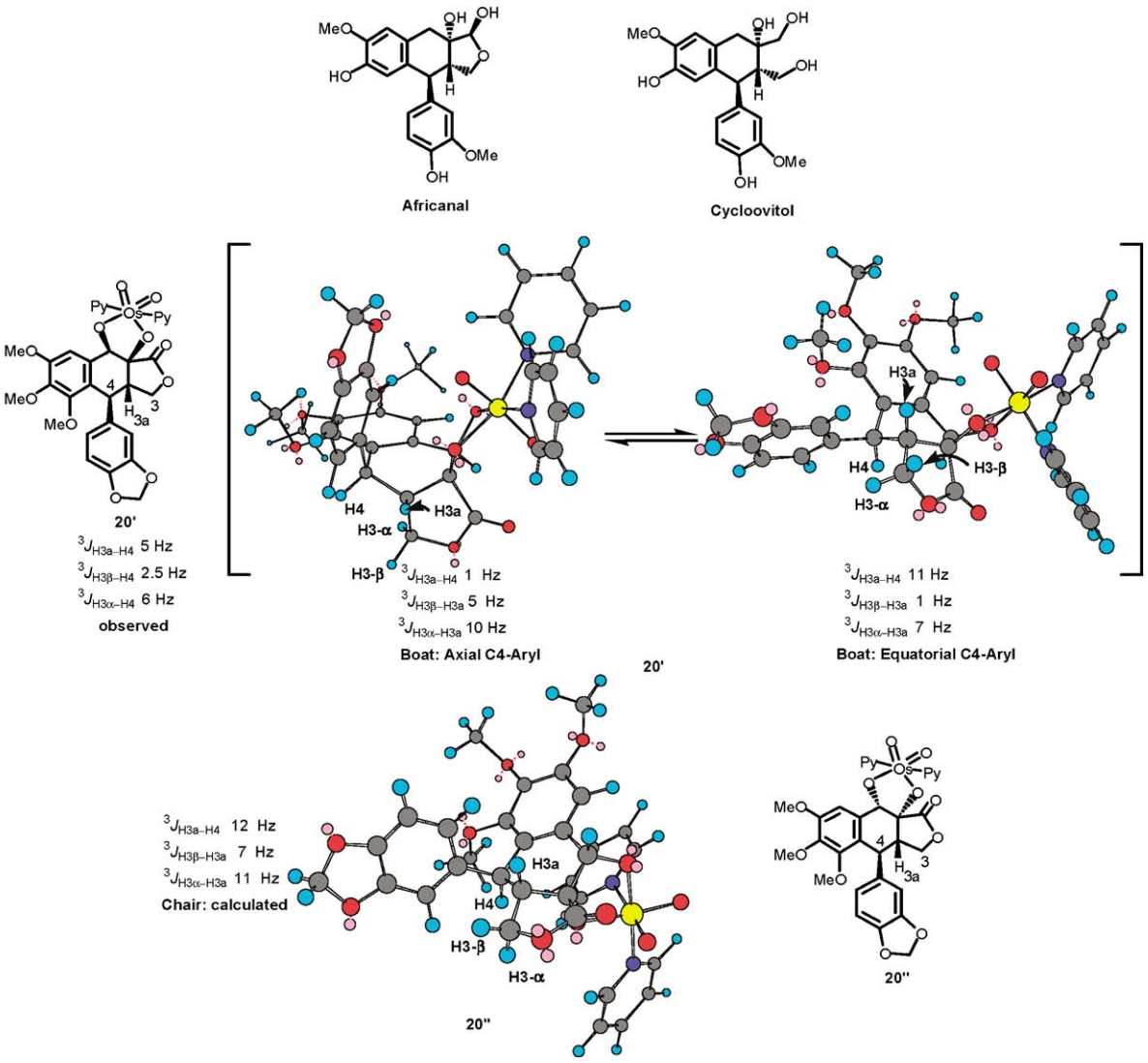
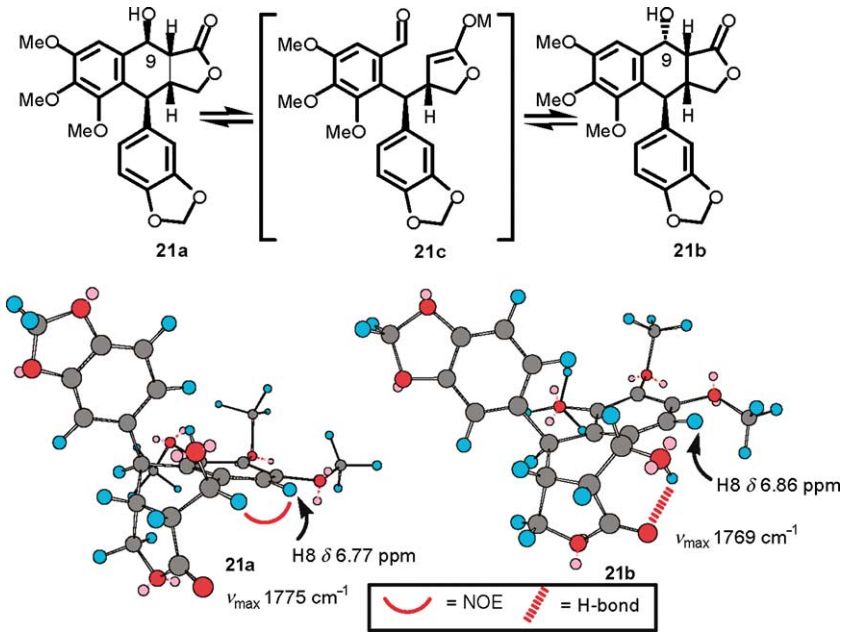


Figure 5. Conformational analysis of **20**′ and **20**″.



Scheme 4. Interconversion of **21a**,**b**.

the product of α-attack by the oxidizing agent on lactone **15**, Figure 5.

Whilst the deoxygenation of the diastereoisomerically pure diol **20** was readily achieved, in high isolated yield, using the conditions reported by Hanessian[24] (SmI_2 in wet THF; 86%) we were surprised to find that this reaction afforded an inseparable mixture of isomeric alcohols, tentatively assigned as **21a**,**b**[25] (dr=3:1). Specifically, NOE measurements support the assertion that both isomers possess a cis-lactone moiety, with the β-isomer, **21a**, exhibiting an additional mutual enhancement between C8–H and C9–Hα. Molecular models suggest these substituents in **21a** are almost co-planar, whilst in **21b**, the C9–OH group is coplanar with the C8–H resulting in a down-field shift of C8–H ($\Delta\delta \approx 0.1$ ppm) in this isomer. We presume that the formation of **21b** during this reaction proceeds via an aldol–retroaldol reaction[26] involving the intermediacy of an enolate anion **21c** or its equivalent, Scheme 4.

The synthesis of steganone and related lignans has been a popular target[27] in recent years and we mused whether a direct approach to the steganacin system could be accomplished via a bi-aryl coupling reaction[28] of the lactone **22**. In order to investigate this strategy we therefore embarked upon the synthesis of the model substrate **23**. Unfortunately, attempts to alkylate the enolate derived from **12** were fraught with problems and resulted in the preferential formation of the di-alkylated lactone **24**. Nevertheless enough of **24** could be prepared in order to investigate the pivotal oxidative coupling reaction. Waldvogel[29] has recently advocated the use of $MoCl_5$ for the promotion of such reactions, demonstrating it to be superior to other oxidizing agents more commonly employed in intramolecular oxidative coupling of aromatics. However, exposure of the lactone **24** to $MoCl_5$ (2 equiv; CH_2Cl_2; 0 °C) resulted not in oxidative coupling of the aromatic rings but rather in the isolation of the cyclolignan **25**, as a single diatereosisomer, in 50% yield. Again stereochemical assignments were established on the basis of NOE experiments, Figure 6. It would appear that the intended bi-aryl coupling reaction is again dogged by the proclivity of the benzylic substituents to undergo ionization and subsequent intramolecular Friedel–Crafts alkylation, a process presumably aided by the Lewis acidity of the oxidizing agent.[30]

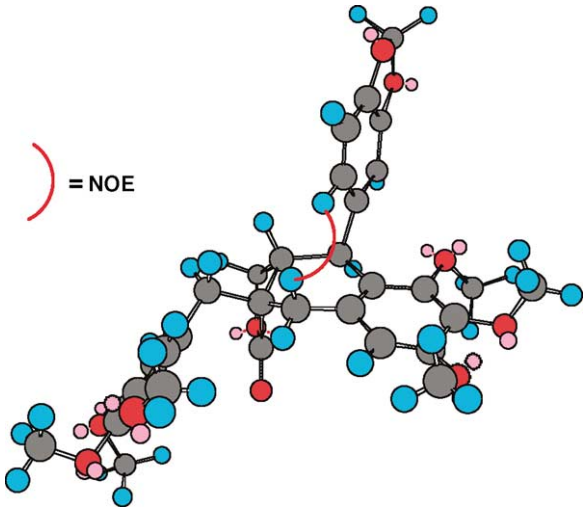
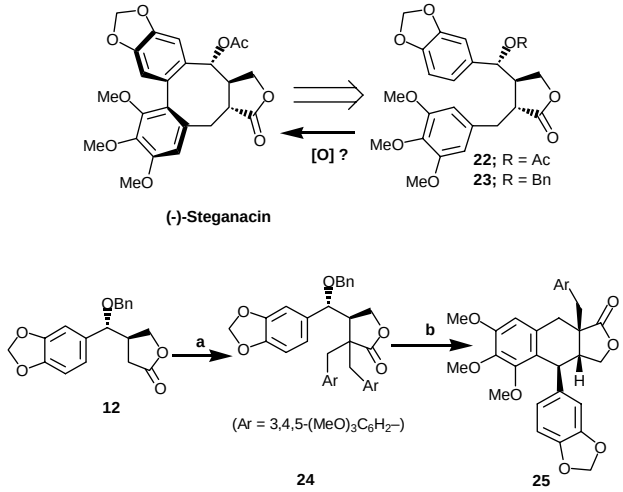


Figure 6. Chem 3D representation of **25**.

3. Conclusion

This work demonstrates that ATRC reactions can be utilized in the rapid, stereoselective synthesis of functionalized γ-butyrolactones (Scheme 5).



Scheme 5. Reagents and conditions: (a) i. KHMDS (2 equiv); THF; 2 h; −78 °C, ii. $ArCH_2Br$ (2.0 equiv); THF; −78 °C; 55%; (b) $MoCl_5$ (2.0 equiv); CH_2Cl_2; 0 °C; 50%.

4. Experimental

4.1. General

All non-aqueous reactions were performed under an atmosphere of dry nitrogen at temperatures, which were those of the external bath. Proton nuclear magnetic resonance (^1H) spectra were recorded on Varian INOVA 400 (400 MHz) or Varian INOVA Unity 300 (300 MHz) spectrometers, with residual non-deuterated solvent as internal standard. All chemical shifts are quoted in parts per million downfield from tetramethylsilane. *J* values are given in Hz. Splitting patterns were abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Carbon NMR spectra (^{13}C NMR) were recorded on a Varian INOVA unity 300 spectrometer at 75 MHz. Infrared spectra were recorded on a Perkin-Elmer 1710 FT spectrometer as evaporated films unless otherwise stated. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Mass spectra were recorded on a Micromass Trio 200 spectrometer (low resolution). High-resolution mass spectra were recorded on a Kratos Concept IS spectrometer using electron impact (EI), chemical ionization (CI; ammonia) or electrospray in positive mode (ES^+) modes of ionization. Microanalysis was performed at the University of Manchester. Melting points were recorded on a Kofler heated stage microscope, and are uncorrected. Hexanes refers to that fraction of light petroleum ether, which distills between 40 and 60 °C, and was redistilled

prior to use. Tetrahydrofuran (THF) was dried over sodium-benzophenone ketyl and distilled under an atmosphere of dry nitrogen. Dichloromethane was dried over phosphorus pentoxide and distilled. Triethylamine and pyridine were dried over potassium hydroxide pellets and redistilled under nitrogen. Where ether is mentioned it refers to diethyl ether. *n*-Butyllithium was supplied as solution in hexanes. Trichloroacetyl chloride and tri-*n*-butyltin hydride were distilled prior to use. Chromatography refers to flash column chromatography and was carried out using Merck silica gel 60H (40–63 μm, 230–400 mesh) as stationary phase. Thin-layer chromatography was carried out on plates pre-coated with Kieselgel 60 F_{254} silica. Visualization was achieved by ultraviolet absorption or treatment with an ethanolic solution of dodecamolybdophosphoric acid followed by heating. 4,4′-Di-*n*-heptyl-2,2′-bipyridine (dHbipy) was prepared according to the literature[31] procedure.

4.1.1. (2*E*)-3-(1′,3′-Benzodioxol-5-yl)prop-2-enyl trichloroacetate, 8. a. To a solution of (2*E*)-3-(1′,3′-benzodioxol-5-yl)prop-2-en-1-ol[9] 4.63 g, 26 mmol) and triethylamine (3.61 mL, 26 mmol) in dry ether (90 mL) was slowly added, at 0 °C, freshly redistilled trichloroacetyl chloride (2.89 mL, 26 mmol) and the mixture was allowed to stir at 0 °C for 3 h. After stirring for 3 h, the reaction was quenched with water (100 mL) and the organic phase was extracted with ether (2×100 mL). The combined organic phases were washed with saturated sodium hydrogencarbonate solution (10%, 50 mL), brine (200 mL), dried ($MgSO_4$) and the solvent removed in vacuo to afford the title compound as a pale yellow, chromatographically unstable oil which solidified on standing, which was used without further purification. Yield 7.15 g, (85%). δ_H (300 MHz, $CDCl_3$) 6.95 (1H, s), 6.70–6.90 (2H, m, ArH), 6.66 (1H, br d, $J=16$ Hz, alkene), 6.20 (1H, dt, $J=16$, 7 Hz, alkene), 6.0 (2H, s, O–CH_2–O), 5.00 (2H, dd, $J=7$, 1 Hz, CH_2–$OCOCCl_3$) ppm; δ_C (75 MHz, $CDCl_3$) 162.1, 148.4, 148.3, 136.8, 130.3, 122.3, 118.8, 108.6, 106.2, 101.7, 90.2, 70.2 ppm; ν_{max} (evaporated film) 2896, 1763 (s), 1607, 1503, 1491, 1447, 1250 cm^{-1}; *m/z* (ES) 323, 325, 329.

b. To a solution of piperonal (2.0 g, 1.3 mmol) in anhydrous THF (50 mL) at −78 °C was added, under an atmosphere of nitrogen, vinylmagnesium bromide (14.6 mL of a 1 M solution in THF *ex* Aldrich; 14.7 mmol) and the reaction mixture allowed to warm up to room temperature. On re-cooling to 0 °C the reaction was quenched by the addition of saturated aqueous ammonium chloride (20 mL), the organic phase was extracted with ether (3×30 mL), the combined extracts dried ($MgSO_4$) and concentrated in vacuo to afford 1′-hydroxysafrole **7** [δ_H (300 MHz, $CDCl_3$) 3.00 (1H, br s, OH), 5.07 (1H, br d, $J=6$ Hz, CH_2O), 5.18 (1H, dt, $J=10$, 1.5 Hz, alkene), 5.32 (1H, dt, $J=16$, 1.5 Hz, alkene), 5.94 (2H, s, OCH_2O), 5.96–6.06 (1H, m, alkene), 6.76–6.88 (3H, m, ArH) ppm] in an essentially pure state (yield 2.27 g, 95%), which was used in the next step without further purification. The crude product, **7**, was redissolved in dry ether (100 mL), to which was added, at 0 °C, triethylamine (1.8 mL, 12.8 mmol) followed by trichloroacetyl chloride (1.4 mL, 12.8 mmol). The reaction mixture was left to stir at 0 °C for 1 h after which time it was quenched by the addition of water (30 mL). The aqueous layer was extracted (ether, 3×20 mL), the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo to afford the title compound **8** as a low-melting solid, which was used in subsequent ATRC reactions without further purification. Crude overall yield 4.04 g (91%).

4.1.2. (4*R)-4-[(*R**)-1,3-Benzodioxol-5-yl(chloro)-methyl]-3,3-dichlorodihydrofuran-2(3*H*)-one and 9_T and (4*R**)-4-[(*S**)-1,3-benzodioxol-5-yl(chloro)methyl]-3,3-dichlorodihydrofuran-2(3*H*)-one, 9_E.** A dry Schlenck tube was charged with CuCl (0.014 g, 5 mol%), dHbipy (0.046 g; 5 mol%) and anhydrous 1,2-DCE (3 mL) and the resulting brown solution was allowed to stir for 10 min at room temperature. The contents of the flask were then degassed (three times using freeze–thaw cycle). To this solution was added, by syringe, a solution of trichloroacetate **8** (0.91 g, 2.8 mmol) in 1,2-DCE (1 mL). After degassing (three times freeze–thaw cycle), the Schlenck tube was placed in a pre-heated oil bath (90 °C) and was allowed to stir for 3.5 h under an atmosphere of argon. Upon cooling, the solvent was removed in vacuo and the residue chromatographed (silica; 1:19 EtOAc/hexanes) to give the diastereoisomeric lactones 9_T and 9_E. The major product 9_T (R_f 0.2; silica; 1:19 EtOAc/hexanes) was isolated as a white solid. Yield 0.30 g (31%), mp 165–166 °C (from DCE–hexanes). δ_H (300 MHz, $CDCl_3$) 3.59 (1H, td, $J=10$, 8 Hz, C4–H), 3.75 (1H, apparent t, $J=10$ Hz, C5–H), 3.90 (1H, dd, $J=9$, 8 Hz, C5–H), 5.12 (1H, d, $J=10$ Hz, CHCl), 5.95 (2H, s, OCH_2O), 6.82 (1H, d, $J=8$ Hz, ArH), 6.88 (1H, dd, $J=8$, 1.5 Hz, ArH), 6.93 (1H, d, $J=1.5$ Hz, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 167.9, 149.1, 149.0, 130.6, 121.4, 108.8, 107.4, 102.0, 79.3, 67.5, 58.4, 57.8 ppm; ν_{max} (Nujol) 2906, 1803 (s), 1609, 1503, 1447, 1374, 1250 cm^{-1}; *m/z* (EI) 323 (M^+10%), 287 (20%), 169 (100%), 135 (40%), 122 (40%); *m/z* (CI) 341 ($[M+NH_4]^+$10%), 287 (50%), 236 (70%), 168 (100%). HRMS (EI) $C_{12}H_9^{35}Cl_3O$ (M^+) requires: 321.9561; found: 321.9569. The minor isomer 9_E (R_f 0.35; silica; 1:19 EtOAc/hexanes), was isolated as a white solid. Yield 0.192 g (21%), mp 159–160 °C (from DCE–hexanes). δ_H (300 MHz, $CDCl_3$) 3.50–3.64 (1H, m, C4–H), 4.20 (1H, apparent t, $J=7$ Hz, C5–H), 4.75–4.85 (1H, m, C5–H), 5.20 (1H, d, $J=10$ Hz, CHCl), 5.95 (2H, s, OCH_2O), 6.72 (1H, dd, $J=8$, 2 Hz, ArH), 6.95–7.05 (2H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 167.8, 149.1, 148.4, 130.6, 122.5, 108.4, 108.2, 101.8, 78.8, 69.1, 60.5, 57.7 ppm; ν_{max} (Nujol) 2925, 1810 (s), 1613, 1528 cm^{-1}; *m/z* (EI) 323 (M^+10%), 287 (20%), 169 (100%), 135 (40%), 122 (40%); *m/z* (CI) 341 ($[M+NH_4]^+$10%), 287 (50%), 236 (70%), 168 (100%). HRMS (EI) $C_{12}H_9^{35}Cl_3O_4$ (M^+) requires: 321.9561; found: 321.9563.

4.1.3. (4*R)-4-[(*R**)-1,3-Benzodioxol-5-yl(benzyloxy)-methyl]-3,3-dichlorodihydrofuran-2(3*H*)-one, 11a.** The trichlorolactone $9_{E,T}$ (0.56 g, 1.73 mmol) and benzyl alcohol (0.374 g, 3.46 mmol, 2.0 equiv) were dissolved in a minimum volume of anhydrous dichloromethane (2 mL). The resulting solution was placed in a preheated oil-bath (50 °C), which was maintained at this temperature until TLC analysis indicated that all of the starting material had been consumed. The solvent was removed in vacuo and the residue was purified by chromatography (silica, 1:17 EtOAc/hexanes) affording the title compound as a white solid. Yield 0.622 g (91%), 152–154 °C (from DCM–hexanes). δ_H (300 MHz, $CDCl_3$) 3.20 (1H, q, $J=7$ Hz,

C4–H), 4.28 (1H, d, $J=11$ Hz, CH_2Ph), 4.34 (1H, dd, $J=9$, 7 Hz, C5–H), 4.48 (1H, d, $J=11$ Hz, CH_2Ph), 4.62 (1H, dd, $J=9$, 7 Hz, C5–H), 4.80 (1H, d, $J=7$ Hz, $CHOCH_2Ph$), 6.05 (2H, s, OCH_2O), 6.85–6.95 (3H, m, ArH), 7.22–7.40 (5H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 168.3, 148.6, 148.4, 142.2, 137.2, 131.0, 128.8, 128.2, 128.0, 121.6, 108.7, 107.5, 101.6, 79.3, 79.1, 70.5, 68.1, 60.6, 57.1 ppm; ν_{max} (evaporated film) 2900, 1803, 1502, 1489, 1241, 1182, 1038 cm^{-1}; *m/z* (EI); 394 (M^+, 5%), 324 (5%), 287 (10%), 241 (10%), 169 (20%), 149 (30%), 91 (100%); *m/z* (CI); 412 ($[M+NH_4]^+$, 25%), 340 (20%), 246 (30%), 230 (60%), 126 (100%). HRMS (EI) $C_{19}H_{16}^{35}Cl_2O_5$ (M^+) requires: 394.0369; found: 394.0360.

4.1.4. (4*R)-4-[(*R**)-1,3-Benzodioxol-5-yl(benzyloxy)-methyl]-dihydrofuran-2(3*H*)-one, 12.**[13] To a stirred solution of the lactone **11a** (1.04 g, 2.65 mmol) and AIBN (88 mg, 0.53 mmol, 20 mol%) in benzene (35 mL) was added tri-*n*-butyltin hydride (1.42 mL, 5.30 mmol). The resulting mixture was placed in an oil bath at 80 °C and heated for 6 h. The solvent was removed in vacuo and the residue was chromatographed (silica, 1:9 EtOAc/hexanes) to afford the title compound as a white solid. Yield 0.717 g (83%), mp 126–128 °C (from DCM–hexanes; lit.[13] mp 120–123). δ_H (300 MHz, $CDCl_3$) 2.28 (1H, dd, $J=18$, 8 Hz, C3–H), 2.32 (1H, dd, $J=18$, 8 Hz, C3–H), 2.85–2.95 (1H, m, C4–H), 4.15 (1H, d, $J=8$ Hz, ArCHO), 4.20 (1H, d, $J=11$ Hz, CH_2Ph), 4.34 (1H, dd, $J=10$, 6 Hz, C5–H), 4.42 (1H, dd, $J=10$, 6 Hz, C5–H), 4.48 (1H, d, $J=11$ Hz, CH_2Ph), 6.0 (2H, s, OCH_2O), 6.75–6.85 (3H, m, ArH), 7.22–7.40 (5H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 176.4, 148.4, 147.8, 137.4, 132.8, 128.5, 127.9, 120.9, 108.3, 106.7, 101.2, 81.7, 70.9, 70.3, 42.3, 31.3 ppm; ν_{max} (evaporated film) 1778, 1505, 1487, 1253 cm^{-1}; *m/z* (EI); 326 (M^+, 20%), 219 (40%); *m/z* (CI) 344 ($[M+NH_4]^+$, 25%) 246 (30%), 230 (60%), 126 (100%). HRMS (CI) $C_{19}H_{18}O_5$ (M^+) requires: 326.1145; found: 326.1149.

Treatment of $\mathbf{9}_{E,T}$ with methanol or allyl alcohol similarly afforded the ethers **11b** and **11c**, respectively.

4.1.5. (4*R)-4-[(*R**)-1,3-Benzodioxol-5-yl(methoxy)-methyl]-3,3-dichlorodihydrofuran-2(3*H*)-one, 11b.** Dissolution of $\mathbf{9}_{E,T}$ (50 mg) in methanol (2 mL) for 12 h at ambient temperature, followed by removal of the solvent in vacuo and column chromatography afforded the title compound as a colourless oil. Yield 38 mg (78%). δ_H (300 MHz, $CDCl_3$) 3.09–3.13 (1H, m, C4–H), 3.25 (3H, s, OMe), 4.40 (1H, dd, $J=9$, 6 Hz, C5–H), 4.56 (1H, dd, $J=10$, 7 Hz, C5–H), 4.63 (1H, d, $J=6$ Hz, ArCH), 6.05 (2H, s, OCH_2O), 6.88–6.90 (3H, m, ArH); δ_C (75 MHz, $CDCl_3$) 168.4, 148.6, 148.3, 131.0, 121.3, 108.7, 107.3, 101.6, 81.4, 79.5, 67.8, 57.0, 56.8 ppm; ν_{max} (evaporated film) 2904, 1802 (s), 1505, 1489, 1242 cm^{-1}; *m/z* (ES) 341, 343, 345 ($[M+Na]^+$). HRMS (ES) $C_{13}H_{12}^{35}Cl_2NaO_5$ ($[M+Na]^+$) requires: 340.9954; found: 340.9956. The presence of a minor amount of an isomeric compound, presumably (4*R**)-4-[(*S**)-1,3-benzodioxol-5-yl(methoxy)methyl]-3,3-dichlorodihydrofuran-2-(3*H*)-one, was also apparent from the ^1H NMR spectrum of **11b**: δ_H (300 MHz, $CDCl_3$) 3.30 (3H, s, OMe), 3.75–3.85 (2H, m, C5–H), 4.49 (1H, d, $J=9$ Hz, ArCH).

4.1.6. (4*R)-4-[(*R**)-1,3-Benzodioxol-5-yl(allyloxy)-methyl]-3,3-dichlorodihydrofuran-2(3*H*)-one, 11c.** Dissolution of $\mathbf{9}_{E,T}$ (100 mg) in allyl alcohol (2 mL) for 12 h at ambient temperature followed by removal of the solvent in vacuo and column chromatography afforded the title compound as a colourless oil. Yield 88 mg (82%). δ_H (300 MHz, $CDCl_3$) 3.75 (1H, ddt, $J=13$, 6, 1.5 Hz, CH_2O), 3.15 (1H, q, $J=7$ Hz, C4–H), 3.95 (1H, ddt, $J=13$, 6, 1.5 Hz, CH_2O), 4.38 (1H, dd, $J=9$, 7 Hz, C5–H), 4.58 (1H, dd, $J=9$, 7 Hz, C5–H), 4.77 (1H, d, $J=7$ Hz, ArCH), 5.16–5.25 (2H, m, alkene), 5.76–5.84 (1H, m, alkene), 6.00 (2H, s), 6.78–6.90 (3H, m, ArH); δ_C (75 MHz, $CDCl_3$) 168.4, 148.6, 148.3, 133.8, 131.1, 131.0, 121.4, 117.8, 107.0, 101.7, 79.5, 78.7, 69.5, 68.0, 57.0 ppm; ν_{max} (evaporated film) 2901, 1803 (s), 1504, 1489, 1445, 1242, 1182, 1039 cm^{-1}; *m/z* (ES) 367 ($[M+Na]^+$, 100%). HRMS (ES) $C_{15}H_{14}^{35}Cl_2NaO_5$ ($[M+Na]^+$) requires: 367.0111; found: 367.0109.

4.1.7. (4*R)-4-{(*R**)-Benzo[1,3]dioxol-5-yl(*tert*-butyldimethy-lsilyloxy)methyl}-dihydrofuran-2(3*H*)-one, 13.** A solution of **12** (0.102 g, 0.312 mmol) in ethyl acetate (5 mL) was hydrogenolysed over 5% Pd–C (0.051 g, 50 wt%) at 20 °C under atmospheric pressure for 5 h. The reaction mixture was filtered through a pad of Celite®, the cake was washed (EtOAc, 2×20 mL), and the combined filtrates concentrated in vacuo to afford the crude product, (4*R**)-4-[(*R**)-benzo-1,3-dioxol-5yl)hydroxymethyl]dihyd-rofuran-2-one,[32] as a viscous oil, which was used in the next step without further purification. Yield 0.065 g (82%). δ_H (300 MHz, $CDCl_3$) 2.25 (1H, dd, $J=18$, 7 Hz, C3–H), 2.38 (1H, dd, $J=18$, 9 Hz, C3–H), 2.42–2.52 (1H, br s, OH), 2.78–2.90 (1H, m, C4–H), 4.38 (2H, apparent d, $J=7$ Hz, C5–H), 4.55 (1H, d, $J=8$ Hz, CHO), 5.98 (2H, s, OCH_2O), 6.75–6.85 (3H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 177.2, 148.4, 147.9, 136.0, 119.9, 108.6, 106.5, 101.5, 75.4, 70.8, 42.8, 31.6 ppm; ν_{max} (evaporated film) 3600–3200, 1771 (s), 1457, 144, 1243 cm^{-1}; *m/z* (ES) 235 (100%). HRMS (ES) $C_{12}H_{12}NaO_5$ ($[M+Na]^+$) requires: 259.0577; found: 259.0575.

To a suspension of imidazole (0.018 g, 0.26 mmol) in DCM (3 mL) was added *tert*-butyldimethylsilylchloride (0.038 g, 0.26 mmol) before cooling to 0 °C. A solution of crude (4*R**)-4-[(*R**)-benzo-1,3-dioxol-5-yl)hydroxyme-thyl]dihydrofuran-2-one (0.051 g, 0.22 mmol) in DCM (2 mL) was added by syringe and the resulting mixture was allowed to warm to room temperature. DMAP (cat.) and TBAI (cat.) were added before stirring for 14 h, dilution with DCM (20 mL), and filtration. The filtrate was partitioned with water (10 mL), the organic layer separated and the aqueous layer re-extracted (DCM; 3×10 mL). The combined organic extracts were washed (brine; 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (1:9 EtOAc/hexanes) affording the title compound **13**, as a colourless oil. Yield 0.079 g (88%). δ_H (300 MHz, $CDCl_3$) −0.21 (3H, s, $SiMe_2$), 0.04 (3H, s, $SiMe_2$), 0.92 (9H, s, SiC $(CH_3)_3$), 2.28 (1H, dd, $J=18$, 8 Hz, C3–H), 2.36 (1H, dd, $J=18$, 8 Hz, C3–H), 2.71–2.84 (1H, m, C4–H), 4.24–4.36 (2H, m, OCH_2), 4.49 (1H, d, $J=7$ Hz, CHOSi), 5.96–5.98 (2H, m, OCH_2O), 6.70 (1H, dd, $J=8$, 1.5 Hz, ArH), 6.76 (1H, d, $J=8$ Hz, ArH), 6.77 (1H, br s, ArH) ppm; δ_C (75 MHz, $CDCl_3$)

176.9, 148.1, 147.4, 136.3, 119.7, 108.2, 106.4, 101.3, 75.8, 70.2, 44.3, 31.5, 25.9, 18.2, −4.2, −5.0 ppm; ν_{max} (evaporated film) 1769, 1515, 1468 cm^{-1}; *m/z* (CI) 368 ($[M+NH_4]^+$, 100%) 351 ($[M+H]^+$, 20%), 219 (60%), 91 (20%). HRMS $C_{18}H_{26}O_5Si$ (M^+) requires: 350.1544; found: 350.1539

4.1.8. (3*S,4*R**)-4-[(*R**)-1,3-Benzodioxol-5-yl(benzyloxy)-methyl]-3-[(*R***S**)-hydroxy(3,4,5-trimethoxyphenyl)-methyl]dihydrofuran-2(3*H*)-one, 14a,b.** To a solution of di-isopropylamine (0.31 mL, 2.21 mmol, 1.20 equiv) in anhydrous tetrahydrofuran (2 mL) was added, at −78 °C, *n*-butyllithium (1.26 mL, 2.02 mmol, 1.1 equiv, 1.6 M in hexanes) and the resulting mixture was stirred at −78 °C for 5 . After this time the solution was allowed to warm to 0 °C and was stirred for 30 min then re-cooled to −78 °C. The resulting solution of lithium di-isoproplyamide was then added by cannula to a solution of the benzylether **12** (0.60 g, 1.84 mmol, 1.0 equiv) in anhydrous tetrahydrofuran (5 mL). The resulting solution was stirred for 1 h, at −78 °C, and a solution of 3,4,5-trimethoxybenzaldehyde (0.433 g, 2.21 mmol, 1.20 equiv) in anhydrous tetrahydrofuran (1 mL) was added dropwise over 10 min by syringe. The solution was stirred for 2 h at −78 °C and allowed to warm to 20 °C over 2 h after which time the reaction was quenched by addition of saturated aqueous ammonium chloride solution (2 mL). The aqueous layer was extracted (DCM, 3×10 mL) and the combined organic extracts were washed (brine, 2×10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica, 7:13 EtOAc/hexanes) affording the diastereomeric products **14a**,**b**. The less polar isomer, R_f 0.43 (silica, 7:13 EtOAc/hexanes) was isolated as a white foam, yield 0.394 g (41%): δ_H (300 MHz, $CDCl_3$) 2.50 (1H, br s, OH), 2.62 (1H, dd, *J*=8, 3 Hz, C3–H), 2.77–2.87 (1H, m, C4–H), 3.80 (6H, 2×overlapping s, 2×OCH_3), 3.85 (3H, s, OCH_3), 3.90 (1H, dd, *J*=9, 4 Hz, OCH_2), 4.0 (1H, d, *J*=12 Hz, OCH_2Ph), 4.30 (1H, d, *J*=12 Hz, OCH_2Ph), 4.39 (1H, apparent triplet, *J*=9 Hz, $CHOCH_2Ph$), 4.52 (1H, dd, *J*=9, 4 Hz, OCH_2), 5.20 (1H, d, *J*=2 Hz, C*H*OH), 5.98 (1H, d, *J*=1 Hz, OCH_2O), 6.08 (1H, d, *J*=1 Hz, OCH_2O), 6.32–6.36 (3H, m, ArH), 6.44 (1H, dd, *J*=8, 2 Hz, ArH), 6.63 (1H, d, *J*=8 Hz, ArH), 7.20–7.40 (5H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 178.7, 153.5, 148.6, 147.9, 137.7, 137.3, 136.6, 132.2, 128.8, 128.2, 121.2, 107.5, 106.1, 101.9, 81.4, 72.7, 70.9, 70.6, 61.1, 56.2, 50.7, 42.0, 28.1, 27.1 ppm; *m/z* (EI); 522 (M^+, 5%), 405 (10%) 209 (20%); *m/z* (CI) 540 ($M+NH_4^+$, 20%). HRMS $C_{29}H_{34}O_9N$ ($[M+NH_4]^+$) requires: 540.2228; found: 540.2215. The more polar isomer, R_f 0.38 (silica, 7:13 EtOAc/hexanes) was isolated as a white foam, yield 0.336 g (35%): δ_H (300 MHz, $CDCl_3$) 2.58 (1H, ddd, *J*=13, 8, 5 Hz, C4–H), 2.92 (1H, t, *J*=8 Hz, C3–H), 3.58 (1H, d, *J*=5 Hz, OCHAr), 3.82 (6H, 2×overlapping s, 2×OCH_3), 3.84 (3H, s, OCH_3), 3.88 (1H, d, *J*=12 Hz, OCH_2Ph), 4.00–4.18 (1H, m, C5–H), 4.32 (1H, d, *J*=12 Hz, OCH_2Ph), 4.45 (1H, dd, *J*=9, 8 Hz, C5–H), 4.76 (1H, d, *J*=9 Hz, C*H*OH), 6.0 (2H, dd, *J*=8, 1 Hz, OCH_2O), 6.44–6.50 (2H, m, ArH), 6.56 (2H, s, ArH), 6.75 (1H, d, *J*=8 Hz, ArH), 7.20–7.40 (5H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 178.9, 153.7, 148.6, 147.9, 137.6, 136.0, 132.4, 128.8, 128.2, 127.7, 120.2, 108.4, 106.2, 103.7, 101.6, 79.0, 74.6, 71.2, 68.0, 61.1, 60.6, 56.3, 48.6, 45.2, 21.3 ppm; *m/z* (EI); 522 (M^+, 10%), 405 (15%) 209 (15%); *m/z* (CI) 540 ($[M+NH_4]^+$, 10%). HRMS (CI) $C_{29}H_{34}NO_9$ ($[M+NH_4]^+$) requires: 540.2228; found: 540.2221.

4.1.9. (3a*R,4*S**)-4-{(1,3-Benzodioxol-5-yl)-5,6,7-trimethoxy-3a,4-dihydronaphtho[2,3-*c*]}furan-1(3*H*)-one, 15 and *O*-benzyl-isoepipodophyllotoxin, 16.**[15a] To a solution of the aldol adducts **14a**,**b** (0.10 g, 0.19 mmol) in anhydrous dichloromethane (5 mL) was added, at 20 °C, boron trifluoride diethyl ether complex (0.023 mL, 0.19 mmol, 1.0 equiv) and the resulting solution was stirred for 30 . The reaction was quenched by the addition of saturated sodium hydrogencarbonate solution (1 mL) and the aqueous phase was extracted with dichloromethane (3× 5 mL). The combined organic extracts were washed (brine; 2×10 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (silica, 1:4 EtOAc/hexanes) afforded two products, the less polar of which was identified as the olefin **15**, a white crystalline solid. Yield 0.051 g (71%), mp 171–173 °C (from DCM–hexanes), (lit. mp[15a] 170–172 °C), R_f 0.19 (silica, 1:4 EtOAc–hexanes). δ_H (300 MHz, $CDCl_3$) 3.25 (3H, s, OCH_3), 3.30–3.41 (1H, m, C3a–H), 3.94 (1H, d, *J*= 15 Hz, C4–H), 3.82 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.98 (1H, t, *J*=9 Hz, C3–H), 4.36 (1H, t, *J*=7 Hz, C3–H), 5.98 (2H, m, OCH_2O), 6.73 (1H, dd, *J*=7, 2 Hz, ArH), 6.73 (1H, s, ArH), 6.76 (1H, s, ArH), 6.78 (1H, d, *J*=8 Hz, ArH), 7.32 (1H, d, *J*=3.5 Hz, alkene) ppm; δ_C (75 MHz, $CDCl_3$) 169.9, 153.1, 153.0, 148.1, 146.3, 138.8, 132.5, 129.4, 125.6, 124.2, 120.1, 109.6, 108.5, 107.7, 101.2, 72.6, 61.0, 60.2, 60.7, 56.3, 48.1, 44.0 ppm; ν_{max} (evaporated film) 1771, 1510, 1472, 1287 cm^{-1}; *m/z* (EI); 396 (M^+, 100%); *m/z* (CI) 414 ($[M+NH_4]^+$, 100%). HRMS $C_{22}H_{20}O_7$ (M^+) requires: 396.1209; found: 396.1204. The more polar product was identified as the aryltetralin, **16**, an amorphous, white solid. Yield 0.011 g (12%), R_f 0.31 (silica, 1:4 EtOAc–hexanes). δ_H (300 MHz, $CDCl_3$) 2.66–2.80 (1H, m, C8a–H), 3.48 (1H, dd, *J*=14, 11 Hz, C5a–H), 3.75 (6H, 2× overlapping s, OCH_3), 3.92 (3H, s, OCH_3), 4.05 (1H, d, *J*= 11 Hz, C5–H), 4.34–4.44 (2H, m, 2×C8–H), 4.55 (1H, d, *J*=2 Hz, C9–H), 4.62 (1H, d, *J*=12 Hz, OCH_2Ph) 4.75 (1H, d, *J*=12 Hz, OCH_2Ph), 5.98–6.00 (2H, m, OCH_2O), 6.46 (2H, s, ArH), 6.51 (1H, s, ArH), 6.74–6.80 (2H, m, ArH), 7.34–7.40 (5H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 176.3, 153.3, 148.6, 146.1, 139.6, 138.1, 136.9, 134.4, 132.5, 129.4, 128.7, 128.3, 128.1, 127.5, 111.0, 109.9, 106.3, 101.6, 101.2, 73.2, 70.3, 67.4, 61.0, 60.2, 56.2, 48.1, 46.5, 45.1, 42.4 ppm; *m/z* (EI) 504 (M^+, 5%), 230 (50%); *m/z* (CI) 522 ($[M+NH_4]^+$, 100%), 414 (40%). HRMS (CI) $C_{29}H_{32}NO_8$ ($[M+NH_4]^+$) requires: 522.2122; found: 522.2116

4.1.10. (3a*R,4*S**,9a*S**)-4-(1,3-Benzodioxol-5-yl)-5,6,7-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one, 17.** A solution of the unsaturated lactone **15** (0.050 g, 0.132 mmol) in ethyl acetate (2 mL) was hydrogenated over 5% Pd–C (0.025 g, 50 wt%) at room temperature and atmospheric pressure for 2 h. The reaction mixture was filtered through a pad of Celite®, and the filtrate concentrated in vacuo. Chromatography of the crude product (silica, 17:3 EtOAc/hexanes) afforded the title compound as a colourless oil. Yield 0.043 g (86%). δ_H (500 MHz, $CDCl_3$) 2.83 (1H, dd, *J*=15, 8 Hz, C9–H), 2.95

(1H, J=15, 2 Hz, C9–H), 3.03 (1H, ddd, J=11, 7, 2 Hz, C9a–H), 3.55–3.64 (1H, ddt, J=11, 7, 2 Hz, C3a–H), 3.64 (1H, dd, J=7, 3 Hz, C3–H), 3.78 (3H, s, OCH_3), 3.88 (6H, 2×overlapping s, 2×OCH_3), 4.48 (1H, br s, C4–H), 4.60 (1H, t, J=7 Hz, C3–H), 5.95 (2H, s, OCH_2O), 6.45 (1H, ddd, J=8, 1.5, 1 Hz, ArH), 6.47 (1H, br s, ArH), 6.53 (1H, d, J=1.5 Hz, ArH), 6.63 (1H, d, J=8 Hz, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 178.5, 153.0, 152.2, 148.2, 146.3, 141.3, 135.9, 131.3, 122.4, 120.3 108.4, 108.2, 101.3, 72.9, 61.4, 61.1, 59.2, 40.1, 39.5, 38.8, 29.9, 29.6 ppm; ν_{max} (evaporated film); 1765, 1501, 1379 cm^{-1}; *m/z* (EI); 398 (M^+, 100%), 277 (20%), 135 (50%); *m/z* (CI); 416 ($[M+NH_4]^+$, 100%), 399 ($[M+H]^+$, 20%). HRMS $C_{22}H_{22}O_7$ (M^+) requires: 398.1365; found: 398.1360.

4.1.11. (4*R)-4-[(*R**)-1,3-Benzodioxol-5-yl(benzyloxy)-methyl]-3,3-bis[3,4,5-trimethoxyphenyl)methyl]dihydrofuran-2(3*H*)-one, 24.** To potassium hexamethyldisilazide (3.92 mL, 1.96 mmol, 0.5 M solution in toluene) was added slowly by syringe, at −78 °C, a solution of the lactone **12** (0.32 g, 0.98 mmol) in anhydrous tetrahydrofuran (3 mL) and the resulting mixture was stirred for 2 h whilst warming up to 20 °C. To this solution was added, slowly by syringe at 0 °C, 3,4,5-trimethoxybenzyl bromide[33] (0.512 g, 1.96 mmol) in anhydrous tetrahydrofuran (3 mL) and the resulting mixture was stirred for 2 h at 20 °C. The reaction was quenched by the addition of saturated ammonium chloride solution (5 mL) and the aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with brine, dried $MgSO_4$ and concentrated in vacuo and the residue was purified by column chromatography (silica, 40% EtOAc/hexanes) affording the bisalkylated lactone, **24** as a glass (0.370 g, 55%). δ_H (300 MHz, $CDCl_3$) 2.19 (1H, d, J=12 Hz, CH_2Ar), 2.90–2.98 (1H, m, C4–H), 2.95 (1H, d, J=12 Hz, CH_2Ar), 3.16 (2H, dd, J=14, 7 Hz, CH_2Ar), 3.78–3.85 (1H, m, C5–H), 3.85 (6H, s, OCH_3), 3.86 (6H, s, OCH_3), 3.88 (6H, s, OCH_3), 4.18 (1H, d, J=12 Hz, OCH_2Ph), 4.31 (1H, t, J=7 Hz, C5–H), 4.40 (1H, d, J=12 Hz, OCH_2Ph), 4.72 (1H, d, J=7 Hz, C*H*OCH_2Ph), 6.08 (2H, s, O–CH_2–O), 6.38 (2H, s, ArH), 6.46 (2H, s, ArH), 6.95–7.00 (3H, m, ArH), 7.18–7.24 (2H, m, ArH), 7.32–7.38 (3H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 179.8, 171.4, 153.2, 153.1, 148.8, 148.3, 137.5, 137.4, 137.1, 133.6, 132.2, 131.7, 129.1, 129.0, 128.8, 128.3, 128.1, 121.6, 108.6, 107.9, 107.8, 107.7, 101.8, 78.5, 70.2, 67.9, 61.2, 61.1, 60.6, 56.4, 56.4, 56.1, 51.5, 46.6, 41.1, 40.5, 34.1, 28.7, 24.1 ppm; ν_{max} (evaporated film) 3067, 2937, 2838, 1766, 1590, 1505, 1459 cm^{-1}; *m/z* (EI); 686 (M^+, 5%), 578 (5%), 455 (5%), 399 (25%), 314 (20%), 181 (100%). HRMS (CI) $C_{39}H_{46}NO_{11}$ ($[M+NH_4]^+$) requires: 704.3065; found: 704.3079.

4.1.12. (3a*R,4*S**,9a*R**)-4-[(1,3-Benzodioxol-5-yl)-((3,4,5-trimethoxyphenyl)methyl)]-5,6,7-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one, 25.** To a solution of the bis-alkylated lactone **24** (0.071 g, 0.1035 mmol) in anhydrous dichloromethane (2 mL) was added, at 0 °C, a solution of molybdenum pentachloride (0.056 g, 0.207 mmol) in anhydrous dichloromethane (1 mL). The resulting solution was stirred for 2 h and was then quenched by the addition of saturated sodium hydrogencarbonate solution (2 mL). The aqueous layer was extracted with dichloromethane (3×5 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (silica, 3:7 EtOAc/hexanes) affording compound **25** as an oil. Yield (0.030 g, 50%). δ_H (300 MHz, $CDCl_3$) 2.22 (1H, d, J=15 Hz, ArCH), 2.75 (1H, d, J=15 Hz, ArCH), 3.08 (1H, d, J=15 Hz, ArCH), 3.25 (1H, d, J=15 Hz, ArCH), 3.30–3.40 (1H, m, C3a–H), 3.45–3.55 (1H, m, C3–H), 3.76 (3H, s, OCH_3), 3.86–3.95 (15H, m, OCH_3), 4.08 (1H, t, J=9 Hz, C3–H), 4.50 (1H, br s, C4–H), 6.0 (2H, s, O–CH_2–O), 6.35 (2H, s, ArH), 6.46 (1H, d, J=9 Hz, ArH), 6.65 (2H, d, J=4 Hz, ArH), 6.75 (1H, d, J=9 Hz, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 182.7, 153.3, 153.1, 152.4, 148.3, 146.4, 141.4, 137.1, 135.0, 132.3, 131.4, 122.2, 120.6, 108.3, 108.1, 107.0, 101.4, 71.7, 61.6, 61.2, 61.1, 56.3, 56.2, 51.2, 45.4, 42.3, 41.1, 39.0, 24.0, 21.3 ppm; ν_{max} 2938, 1763, 1590, 1488, 1462 cm^{-1}; *m/z* (CI); 596 ($[M+NH_4]^+$, 50%), 578 (M^+, 40%). APCI 579 (30%), 491 (30%), 458 (100%), 411 (65%). HRMS (APCI) $C_{32}H_{34}O_{10}$ ($[M+H]^+$) requires: 579.2225; found: 579.2225.

4.1.13. (3a*S,4*S**,9a*R**)-4-(Benzo-1,3-dioxol-5-yl)-5,6,7-trimethoxy-9a-hydroxy-3a,4,9,9a-tetrahydro-naphtho-[2,3-*c*]furan-1(3*H*)-one, 18.** To a stirred solution of **17** (0.067 g, 0.17 mmol) in THF (5 mL) was added potassium hexamethyldisilazide (0.034 mL, 0.17 mmol of a 2.0 M soln in THF), at −78 °C. After 1 h at 78 °C a solution of (1*R*)-(−)-(10-camphorsulfonyl)oxaziridine (0.085 g, 0.37 mmol) in THF (1 mL) was added dropwise by syringe before stirring for a further 3 h. The reaction was quenched by the addition of saturated ammonium chloride solution (5 mL), the phases separated, and the aqueous phase extracted repeatedly with ethyl acetate (3×20 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), the solvent removed under reduced pressure and the crude residue residue chromatographed (3:7 ethyl acetate/hexanes) affording the title compound as a colourless viscous oil. Yield 0.046 g (67%). R_f 0.25 (3:7 EtOAc/hexanes). δ_H (300 MHz, $CDCl_3$) 2.88 (1H, d, J=2 Hz, OH), 2.95 (1H, dd, J=13, 1 Hz, C9–H), 3.12 (1H, d, J=13 Hz, C9–H), 3.48–3.55 (1H, m, C3a–H), 3.62 (1H, dd, J=9, 7 Hz, C3–H), 3.84 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.58 (1H, d, J=2 Hz, C4–H), 4.68 (1H, t, J=9 Hz, C3–H), 5.95 (2H, apparent t, J=2 Hz, OCH_2O), 6.54 (1H, s, ArH), 6.75–80 (3H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 180.4, 153.2, 152.1, 148.1, 146.3, 141.5, 135.1, 128.8, 122.6, 120.7, 108.5, 108.3, 108.2, 101.2, 71.4, 61.4, 61.1, 56.2, 49.6, 46.5, 43.0, 41.0, 38.8 ppm; ν_{max} (evaporated film) 3458 (br), 2960, 1772 (s), 1646, 1600, 1489 cm^{-1}; *m/z* (EI); 414 (M^+, 5%), 398 (5%), 108 (60%); *m/z* (CI); 432 ($[M+NH_4]^+$, 50%), 231 (100%). HRMS (CI) $C_{22}H_{26}NO_8$ ($[M+NH_4]^+$) requires: 432.1662; found: 432.1653.

4.1.14. (1*S,3a*S**,4*S**,9a*R**)-4-(Benzo-1,3-dioxol-5-yl-5,6,7-trimethoxy)-3,3a,4,9-tetrahydronaphtho[2,3-*c*]-furan-1,9a-diol, 19.** To a solution of **18** (0.030 g, 0.072 mmol) in anhydrous THF (1 mL) was added lithium aluminium hydride (0.072 ml, 0.072 mmol, 1.0 M in THF) at 0 °C. After 15 min the reaction was quenched by the addition of saturated aqueous sodium potassium tartrate solution (1 mL) and diluted with ethyl acetate (10 mL).

The organic layer was separated and the aqueous phase extracted repeatedly with ethyl acetate (3×5 mL). The combined organic extracts were washed (brine; 10 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed (silica; 2:3 ethyl acetate/hexanes) affording the title compound as a colourless, viscous oil. Yield 0.026 g (87%). δ_H (300 MHz, $CDCl_3$) 2.80 (1H, d, J=13 Hz, C9–H), 2.93 (1H, dd, J=13, 1 Hz, C9–H), 3.02 (1H, td, J=8.5, 2 Hz, C3a–H), 3.17 (1H, apparent triplet, J=9 Hz, C3–H), 3.76 (3H, s, OCH_3), 3.89 (6H, 2×overlapping s, OCH_3), 4.35 (1H, apparent t, J=9 Hz, C3–H), 4.40 (1H, br s, C4–H), 4.62 (1H, s, C1–H), 5.95 (2H, s, OCH_2O), 6.54 (1H, s, ArH), 6.67 (1H, ddd, J=8, 2, 1 Hz ArH), 6.74 (1H, d, J=8 Hz, ArH), 6.74–6.76 (1H, m, ArH) ppm; δ_C (75 MHz, $CDCl_3$) 153.3, 151.8, 149.4, 145.9, 141.3, 135.2, 127.4, 123.5, 120.7, 108.6, 108.3, 108.1, 101.2, 101.1, 69.5, 61.2, 61.1, 56.2, 51.0, 46.5, 40.0, 37.8 ppm; ν_{max} (evaporated film) 3449 (br), 2945, 1659, 1639, 1475, 1372 cm^{-1}; *m/z* (CI); 434 ($M+NH_4^+$, 30%), 416 (M^+, 30%), 221 (40%), 161 (100%). HRMS (CI) $C_{22}H_{28}NO_8$ ($[M+NH_4]^+$) requires: 434.1809; found: 434.1796.

4.1.15. (3a*S,4*S**,9*R**,9a*S**)-4-(1,3-Benzodioxol-5-yl)-9,9a-dihydroxy-5,6,7-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one, 20.** To a solution of **15** (0.050 g, 0.126 mmol) in anhydrous pyridine (2 mL) was added OsO_4 (0.038 g, 0.15 mmol, 1.2 equiv) (CARE) at room temperature. The solution was allowed to stir overnight and was then quenched by the addition saturated aqueous sodium sulfite (10 mL) and left to stir at ambient temperature for 3 h. Ether (20 mL) was then added and the organic phase was separated, washed [satd sodium sulfite (5 mL), copper (II) sulfate (5 mL) then and brine (5 mL)], dried ($MgSO_4$) and the solvent removed under reduced pressure. Chromatography of the residue (silica; 4:5 ethyl acetate/hexanes) afforded the title compound as an off-white crystalline compound. Yield 0.035 g (65%), mp 152–154 °C (from DCM–hexanes). δ_H (300 MHz, $CDCl_3$) 2.81 (1H, br s, OH), 3.25 (1H, td, J=9, 2 Hz, C3a–H), 3.54 (3H, s, C5–OMe), 3.86 (3H, s, C6–OMe), 3.92 (3H, s, C7–OMe), 3.93 (1H, t J=8 Hz, C3–H), 4.28 (1H, d, J=2 Hz, C4–H), 4.70 (1H, t, J=9 Hz, C3–H), 4.80 (1H, s, C9–H), 5.95, (2 H, s, OCH_2O), 6.62 (1H, dd, J=8, 1.5 Hz, ArH), 6.73 (1H, d, J=8 Hz, ArH), 6.75 (1H, d, J=2 Hz, ArH), 6.88 (1H, s, ArH); δ_C (75 MHz, $CDCl_3$) 40.5, 46.9, 56.3, 60.8, 60.9, 69.8, 71.5, 75.2, 101.4, 108.1, 108.4, 108.5, 120.7, 122.7, 129.9, 139.0, 143.1, 146.5, 148.2, 152.1, 153.6, 177.8 ppm; ν_{max} (evaporated film) 3368, 1709 (s), 1504, 1491, 1449, 1251 cm^{-1}; *m/z* (EI) 430 (M^+, 98%), 412 (20%), 395 (30%), 313 45%); *m/z* (CI) 448 ($[M+NH_4]^+$). HRMS (CI) $C_{22}H_{26}NO_9$ ($[M+NH_4]^+$) requires: 448.1602; found: 448.1605.

4.1.16. Isolation of osmate ester 20′. To a stirred solution of **15** (0.050 g, 0.13 mmol) in anhydrous pyridine (2 mL) was added OsO_4 (0.038 g, 0.15 mmol, 1.2 equiv) (CARE) at room temperature. This solution was allowed to stir overnight at 20 °C and then the reaction was quenched by the addition of a saturated aqueous solution of sodium sulfite (10 mL) and ethyl acetate (10 mL). The organic phase was separated then washed with sodium sulfite (5 mL), brine (5 mL) and dried (MgSO4). Removal of the solvent in vacuo afforded the crude osmate ester **20′** as a brown amorphous solid. Attempted purification of **20′** by column chromatography led to its partial decomposition. Crude yield 0.072 g (87%). δ_H (300 MHz, $CDCl_3$) 8.89 (4H, apparent t, J=5 Hz, py), 7.92 (2H, apparent q, J=7 Hz, py), 7.53 (4H, apparent q, J=8 Hz, py), 6.98 (1H, d, J=2 Hz, ArH), 6.85 (1H, dd, J=8, 2 Hz, ArH), 6.72 (1H, d, J=8 Hz, ArH), 5.94 (1H, d, J=1.5 Hz, OCH_2O), 5.90 (1H, d, J=1.5 Hz, OCH_2O), 5.65 (1H, s, ArCHO), 4.78 (1H, dd, J=10, 6 Hz, C3–H), 4.28 (1H, dd, J=9, 2.5 Hz, C3–H), 4.25 (1H, d, J=5 Hz, C4–H), 3.91 (3H, s, OMe), 3.82 (3H, s, OMe), 3.38 (3H, s, OMe), 3.25–3.30 (1H, m, C3a–H) ppm; δ_C (75 MHz, $CDCl_3$) 175.5, 153.1, 151.7, 150.0, 149.9, 147.7, 145.7, 143.2, 141.8, 141.1, 141.0, 129.9, 125.7, 125.6, 124.7, 121.7, 109.3, 109.1, 107.8 100.9, 91.3, 90.5, 74.7, 60.8, 60.4, 56.1, 46.6, 46.1 ppm; ν_{max} (evaporated film) 2937, 1774, 1608, 1486, 1413, 1245, 1035, 838 cm^{-1}.

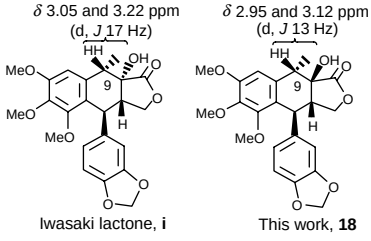
4.1.17. (3a*R,4*S**,9*S***R**,9a*R**)-4-(1,3-Benzodioxol-5-yl)-9-hydroxy-5,6,7-trimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-*c*]furan-1(3*H*)-one, 21a,b.** A dry Schlenck tube was charged with **15** (0.030 g, 0.070 mmol and 'wet' THF (1 mL) and the resulting solution degassed (three times using freeze–thaw cycle) to which was added, by syringe, a 0.1 M solution SmI_2 in THF (1.5 ml, 0.15 mmol, 3 equiv). The deep blue solution of Sm(II) was immediately discharged, turning first to a red and then a pale-yellow coloured solution within 5 min. This solution was allowed to stir for a further 30 min at 20 °C and then quenched by the addition of water (20 mL). The organic layer was separated, the aqueous layer extracted (EtOAc, 2×20 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated in vacuo. Chromatography of the residue (silica; 100% ethyl acetate) afforded the title compound (3:1 mixture of diastereoisomers) as an off-white crystalline solid. Yield 0.025 g (86%), mp 138–140 °C (from DCM–hexanes). Major isomer, **21a**: δ_H (300 MHz, $CDCl_3$) 3.31 (1H, dd, J=9, 2.5 Hz, C9a–H), 3.40–3.50 (1H, m, C3a–H), 3.62 (3H, s, OMe), 3.88 (3H, s, OMe), 3.91 (3H, s, OMe), 4.15 (1H, dd, J=9, 5 Hz, C3–H), 4.35 (1H, d. J=2.5 Hz), 4.59 (1H, dd, J=9, 7.5 Hz, C3–H), 5.01 (1H, d, J=2.5 Hz, C9–H), 5.95 (2 H, s, OCH_2O), 6.62 (1H, br d, J=7 Hz, ArH), 6.74 (1H, d, J=7 Hz, ArH), 6.77 (2H, 2×overlapping s, ArH); δ_C (75 MHz, $CDCl_3$) 177.0, 153.4, 152.3, 152.2, 148.4, 146.6, 139.4, 143.1, 131.5, 122.7, 120.4, 108.5, 108.4, 101.4, 73.8, 69.2, 61.0, 60.9, 56.3, 46.8, 40.8, 39.6 ppm; ν_{max} (evaporated film) 3418, 2915, 1775, 1501, 1487, 1243, 1122, 1036 cm^{-1}; *m/z* (ES^+) 437 (100%). HRMS (ES^+) $C_{22}H_{22}NaO_8$ ($[M+Na]^+$) requires 437.1207; found: 437.1200. Minor isomer **21b** exhibits resonances at δ_H (300 MHz, $CDCl_3$) 6.86 (1H, s, ArH), 4.76 (1H, br s, C9–H), 4.70 (1H, t, J=9 Hz, C3–H), 4.30 (1H, d, J=2 Hz, C4–H), 3.86–3.96 (1H, m, C3–H), 3.57 (3H, s, OMe); ν_{max} (evaporated film) 1769 cm^{-1}.

Acknowledgements

We thank the EPSRC (C.K.K.; J.F.), AstraZeneca and GSK for the provision of a research studentship through the Industrial CASE Scheme.

References and notes

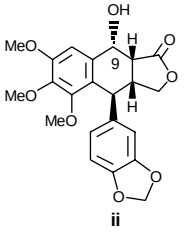
1. Wetter, C.; Studer, A. *Chem. Commun.* **2004**, 174–175. Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1–11. Kobrakov, K. I.; Ivanov, A. V. *Chem. Heterocycl. Compd.* **2001**, *37*, 529–539.
2. Majumdar, K. C.; Mukhopadhyay, P. P.; Basu, P. K. *Heterocycles* **2004**, *63*, 1903–1958. Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2004**, *60*, 6239–6278. Rheault, T. R.; Sibi, M. P. *Synthesis* **2003**, 803–819.
3. For recent examples see: De Buyck, L.; Danieli, C.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Pattarozzi, M.; Roncaglia, F. *Tetrahedron* **2005**, *61*, 2871–2877. Robertson, J.; Menard, M.; Ford, R. *Synlett* **2004**, 2788–2790. Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 2417–2422. Yoshimitsu, T.; Nakajima, H.; Nagaoka, H. *Tetrahedron Lett.* **2002**, *43*, 8587–8590. Iwamatsu, S.-I.; Matsubara, K.; Nagashima, H. *J. Org. Chem.* **1999**, *64*, 9625–9631.
4. Quayle, P.; Fengas, D.; Richards, S. *Synlett* **2003**, 1797–1800. For mechanistic discussions see: Faulkner, J.; Edlin, C. D.; Fengas, D.; Preece, I.; Quayle, P.; Richards, S. N. *Tetrahedron Lett.* **2005**, *46*, 2381–2385. Edlin, C. D.; Faulkner, J.; Fengas, D.; Knight, C. K.; Parker, J.; Preece, I.; Quayle, P.; Richards, S. N. *Synlett* **2005**, 572–576.
5. Bar, G.; Parsons, A. F. *Chem. Soc. Rev.* **2003**, *32*, 251–263. Giese, B.; Damm, W.; Batra, R. *Chemtracts: Org. Chem.* **1994**, *7*, 355–370. Smadja, W. *Synlett* **1994**, 1–26.
6. For a similar stereochemical outcome observed in ATRC reactions leading to γ-lactams see: Cagnoli, R.; Ghelfi, F.; Pagnoni, U. M.; Parsons, A. F.; Schnetti, L. *Tetrahedron* **2003**, *59*, 9951–9960. Parvez, M.; Lander, S. W.; DeShong, P. *Acta Crystallogr., Sect. C* **1992**, *48*, 568–570.
7. Yoda, H.; Suzuki, Y.; Matsuura, D.; Takabe, K. *Heterocycles* **2005**, *65*, 519–522. Eklund, P.; Sillanpää, R.; Sjöholm, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1906–1910. Eklund, P.; Lindholm, A.; Mikkola, J.-P.; Smeds, A.; Lehtilä, R.; Sjöholm, R. *Org. Lett.* **2003**, *5*, 491–493. Fischer, J.; Reynolds, A. J.; Sharp, L. A.; Sherburn, M. S. *Org. Lett.* **2004**, *6*, 1345–1348. Yoshida, S.-I.; Yamanaka, T.; Miyake, T.; Moritani, Y.; Van Speybroeck, R.; Guo, H.; Van der Eycken, J.; Vandewalle, M. *Tetrahedron* **1991**, *47*, 4675–4682. Ohmizu, H.; Iwasaki, T. *Tetrahedron* **1997**, *53*, 9585–9598. Yamauchi, S.; Yamaguchi, M. *Biosci., Biotechnol., Biochem.* **2003**, *67*, 838–846. For pertinent reviews of lignan chemistry see: Brown, R. C. D.; Swain, N. A. *Synthesis* **2004**, 811–827. Ward, R. S. *Stud. Nat. Prod. Chem.* **2000**, *24E*, 739–798. Ward, R. S. *Synthesis* **1992**, 719–730. Lee, K.-H.; Xiao, Z. *Phytochem. Rev.* **2003**, *2*, 341–362. Sefkow, M. *Top. Curr. Chem.* **2005**, *243*, 185–224.
8. For approaches utilising TBTH-mediated radical cyclisations see: Belletire, J. L.; Mahmoodi, N. O. *J. Nat. Prod.* **1992**, *55*, 194–206. Belletire, J. L.; Mahmoodi, N. O. *Tetrahedron Lett.* **1989**, *30*, 4363–4366.
9. Galland, J.-C.; Dias, S.; Savignac, M.; Genêt, J.-P. *Tetrahedron* **2001**, *57*, 5137–5148.
10. This and related catalyst systems have found use in the relarted ATRP polymerization reactions, see: Patten, T. E.; Xia, J.; Abernathy, T.; Matyjaszewski, K. *Science* **1996**, *272*, 866–868.
11. Crystal data: $\mathbf{9}_T$ $C_{12}H_9Cl_3O_4$, $M_r=323.54$, monoclinic, $a=6.9064(6)$, $b=20.7797(18)$, $c=9.2375(8)$, $V=1306.6(2)$ Å^3, $T=100(2)$ K, space group $P2(1)/n$, $Z=4$, Mo Kα radiation, 0.71073 Å, 3056 independent reflections. Final $R1=0.0352$ and $wR2=0.0806$ (all data); Crystal data for **12**: $C_{19}H_{16}Cl_2O_5$, $M_r=395.22$, orthorhombic, $a=11.446(3)$, $b=10.168(2)$, $c=29.897(7)$, $V=3479.5(14)$ Å^3, $T=100(2)$ K, space group $Pbca$, $Z=8$, Mo Kα radiation, 0.71073 Å, 3580 independent reflections. Final $R1=0.0380$ and $wR2=0.0982$ (all data).
12. For related benzylic substitution reactions see Ref. 13 and Boissin, P.; Dhal, R.; Brown, E. *Tetrahedron Lett.* **1989**, *30*, 4371–4374. Ishiguro, T.; Mizuguchi, H.; Tomioka, K.; Koga, K. *Chem. Pharm. Bull.* **1985**, *33*, 609–617. Vogel, K.; Sterling, J.; Herzig, Y.; Nudelman, A. *Tetrahedron* **1996**, *52*, 3049–3056.
13. Boissin, P.; Dhal, R.; Brown, E. *J. Chem. Res. (S)* **1991**, 332–333.
14. Masunari, A.; Ishida, E.; Trazzi, G.; Almeida, W. P.; Coelho, F. *Synth. Commun.* **2001**, *31*, 2127–2136. We thank Prof. Coelho for a copy of his ^{1}H NMR spectrum for **13**.
15. (a) Pelter, A.; Ward, R. S.; Pritchard, M. C.; Kay, I. T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1603–1613. (b) We presume that epimerization at the benzylic centre takes place post-cyclization.
16. See: Ara, Y.; Takeya, T.; Tobinaga, S. *Chem. Pharm. Bull.* **1995**, *43*, 1977–1984.
17. For a related example see: Chackalamannil, S.; Doller, D.; Clasby, M.; Xia, Y.; Eagen, K.; Lin, Y.; Tsai, H.-A.; McPhail, A. T. *Tetrahedron Lett.* **2000**, *41*, 4043–4047. Kuo, Y.-H.; Yu, M.-T. *Heterocycles* **1993**, *36*, 529–535.
18. (a) For discussions see: Maddaford, S. P.; Charlton, J. L. *J. Org. Chem.* **1993**, *68*, 4132–4138. Forsey, S. P.; Rajapaksa, D.; Taylor, N. J.; Rodrigo, R. J. *J. Org. Chem.* **1989**, *54*, 4280–4290. (b) See: Zhao, C.; Nagatsu, A.; Hatano, K.; Shirai, N.; Kato, S.; Ogihara, Y. *Chem. Pharm. Bull.* **2003**, *51*, 255–261 and references therein for related examples.
19. (a) Paquette, L. A.; Hong, F.-T. *J. Org. Chem.* **2003**, *68*, 6905–6918. Clive, D. L. J.; Manning, H. W.; Boivin, T. L. B. *J. Chem. Soc., Chem. Commun.* **1990**, 972–974. Mostler, U.; Urban, E. *Monatshefte für Chemie* **1989**, *120*, 349–355. For exceptions see: Glinski, M. B.; Freed, J. C.; Durst, T. *J. Org. Chem.* **1987**, *52*, 2749–2753. Berkowitz, D. B.; Choi, S.; Maeng, J.-H. *J. Org. Chem.* **2000**, *65*, 847–860. Gensler, W. J.; Gatsoni, C. D. *J. Org. Chem.* **1966**, *31*, 4004–4008. (b) Iwasaki et al.[22] have prepared the isomeric lactone **i**



whose spectral data exhibits minor, yet significant, differences compared to that for lactone **18**.

20. cf. Nishibe, S.; Tsukamoto, H.; Hisada, S.; Yamanouchi, S.; Takido, M. *Chem. Pharm. Bull.* **1981**, *29*, 2082–2085.
21. Viviers, P. M.; Ferreira, D.; Roux, D. G. *Tetrahedron Lett.* **1979**, *20*, 3773.
22. Moritani, Y.; Ukita, T.; Hiramatsu, H.; Okamura, K.; Ohmizu, H.; Iwasaki, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2747–2753.
23. (a) Criegee, R.; Marchand, B.; Wannowius, H. *Ann.* **1942**, *550*, 99–133. See also: Hashimoto, S.-I.; Sakata, S.; Sonegawa, M.; Ikegami, S. *J. Am. Chem. Soc.* **1988**, *110*, 3670–3672. (b) Sarett, L. H. *J. Am. Chem. Soc.* **1948**, *70*, 1454–1458.

24. Hanessian, S.; Girard, C. *Synlett* **1994**, 861–862.
25. Tobinaga et al.[16] previously reported the isolation of a compound assigned as **ii**, which has identical spectroscopic data to **21a**. We tentatively suggest, on the basis of NOE and other data, that its structure be more correctly represented as the 9β-alcohol, **21a** and not the 9α-epimer, **21b**.



ii

26. For a related aldol reaction see: Suryawanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902–921.
27. See: Abe, H.; Takeda, S.; Fujita, T.; Nishioka, K.; Takeuchi, Y.; Harayama, T. *Tetrahedron Lett.* **2004**, *45*, 2327–2329 and references therein.
28. Lessene, G.; Feldman, K. S. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002; pp 479–538. Quideau, S.; Pouysegu, L.; Deffieux, D. *Curr. Org. Chem.* **2004**, *8*, 113–148.
29. Kramer, B.; Averhoff, A.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2981–2982. Mirk, D.; Wibbeling, B.; Fröhlich, R.; Waldvogel, S. R. *Synlett* **2005**, 1970–1974.
30. cf. Tanaka, M.; Mitsuhashi, H.; Wakamatsu, T. *Tetrahedron Lett.* **1992**, *33*, 4161–4164. Eklund, P. C.; Rainer, E. S. *Tetrahedron* **2003**, *59*, 4515–4523.
31. Matyjaszewski, K.; Patten, T. E.; Xia, J. *J. Am. Chem. Soc.* **1997**, *119*, 674–680.
32. The ^{1}H NMR spectrum of our sample is in agreement with that previously reported (although stereochemical assignments were not made by these groups): Ishiguro, T.; Mizuguchi, H.; Tomioka, K.; Koga, K. *Chem. Pharm. Bull.* **1985**, *33*, 609–617. Lewis, S. N.; Popper, T. L. *Tetrahedron* **1967**, *23*, 4197–4208. Curiously Coelho's[14] data for this compound does not match that in the literature or that from our study whilst his data for the silylether derivative **13** is identical to that reported here.
33. Ohta, A.; Tonomura, Y.; Sawaki, J.; Sato, N.; Akiike, H.; Ikuta, M.; Shimazaki, M. *Heterocycles* **1991**, *32*, 965–973.