Synthesis of (−)-conocarpan by two routes based on radical cyclization and establishment of its absolute configuration†

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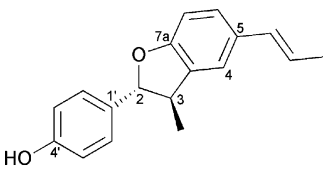
Received 1st February 2008, Accepted 25th February 2008
First published as an Advance Article on the web 1st April 2008
DOI: 10.1039/b801858h

Two independent routes for the total synthesis of the bioactive neolignan (−)-conocarpan are described. The first (98% ee) is based on formal radical cyclization onto a benzene ring, and involves a 5-*exo*-trigonal closure onto a double bond restrained within a 6-membered ring. The second route (88% ee), which is shorter, is based on 5-*exo*-trigonal cyclization of an aryl radical onto a pendant terminal double bond. The two routes differ in their degree of stereoselectivity. The absolute configuration originally assigned to (+)-conocarpan had previously been called into question on the basis of empirical chiroptical rules; the present chemical work confirms the need for revision, and the assigned absolute configurations of several compounds correlated with (+)-conocarpan must also be changed.

Introduction

(+)-Conocarpan, originally assigned the structure and absolute configuration shown in **1**,[1] is a neolignan[2,3] that was first isolated from timber used for marine construction. The purpose of that investigation was to identify substances in the timber that conferred resistance to a variety of marine organisms. A number of other plant sources were later also found to contain conocarpan.[3–6] The compound possesses a wide range of biological activities—some of them potentially important, such as toxicity to mosquito larvae,[4f,g,7] antitrypanosomal,[8a] antibacterial,[8b] antifungal[8c,d] and photoprotective activity.[8e] This broad spectrum activity is characteristic of numerous neolignans,[9] and their biological activity clearly makes them a class worth examining from a synthetic point of view.[9] Although many appear to be structurally simple, those such as conocarpan actually contain a fragile stereocenter at C(2) that imposes some restriction on the type of synthetic approaches that can be used.



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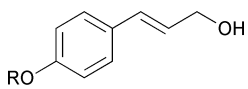
The structure of (+)-conocarpan was established spectroscopically, and the absolute configuration was assigned as 2*R*,3*R* (see **1**) on the basis of a comparison of the CD curve of conocarpan acetate with the CD curves of a number of dihydrobenzofurans that had different substitution patterns in the aromatic rings. Some years later, the configurational assignment was called into question as a result of chiroptical studies by the Antus group[10,11] who had extended to dihydrobenzofurans the helicity rules proposed by Snatzke *et al.*[12] that relate absolute configuration with the sign of the Cotton effect for a number of other compound classes. This is an empirical method which was validated by application to a small number of dihydrobenzofurans.[10]

Several compounds have been chemically[13] or spectroscopically[4h] correlated with (+)-conocarpan and so their absolute configuration is also called into question and the need for revision is confirmed by the present work. Likewise, the absolute configuration of natural (−)-conocarpan must also be reversed.

Results and discussion

We examined (+)-conocarpan as a synthetic target[14–17] that might be accessible by using radical cyclization to construct the dihydrofuran segment. Racemic conocarpan can be made easily by biomimetic oxidation[1] or by manganese(III)-mediated radical cyclization,[18,19] but the presence of a labile C–O bond at an asymmetric center that is part of a *para*-oxygenated benzylic subunit makes the preparation of the optically active material a much more difficult task. In addition, Sharpless asymmetric epoxidation, which is potentially an ideal method for setting up the C(2) stereochemistry, does not work well[20] for compounds of type **2** that have a strongly electron-releasing *para* oxygen substituent.[22,23,25]



2 R = Me, $SiMe_2Bu$-*t*

As indicated above, both enantiomers of conocarpan are known, and we arbitrarily aimed at the originally assigned configuration **1**. Our initial plan was to generate a cross-conjugated enone of type **3** (Scheme 1), in the expectation that radical closure (**3** → **4**) would preferentially give the indicated C(2)–C(3) *trans* stereochemistry. On the basis of prior methodology work in this laboratory,[26] we were confident that **4** could be converted *via* **5** or **6** into **7**, which is a protected version of conocarpan.

We considered two approaches to structures of type **3**[27] by way of the transformations **8** → **10** and **11** → **12** (Scheme 2). Both routes

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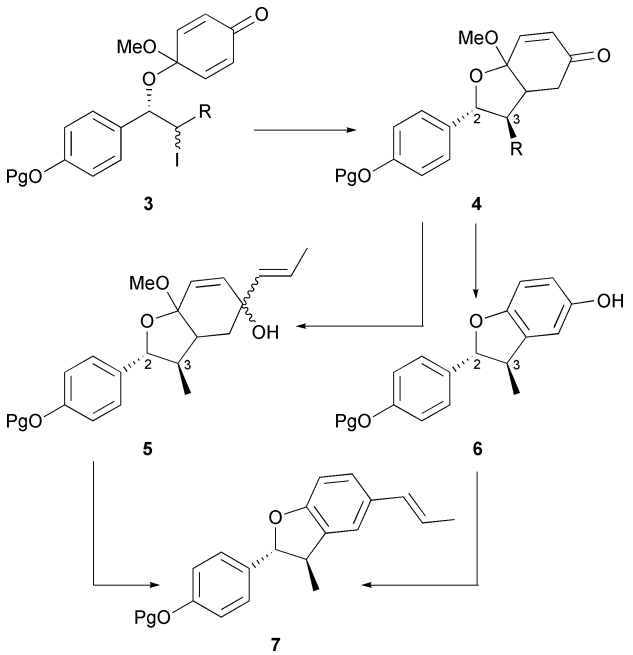
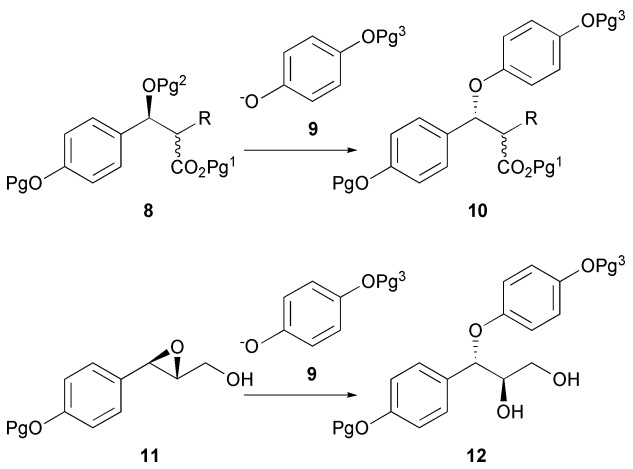
† Electronic supplementary information (ESI) available: Additional experimental procedures. See DOI: 10.1039/b801858h



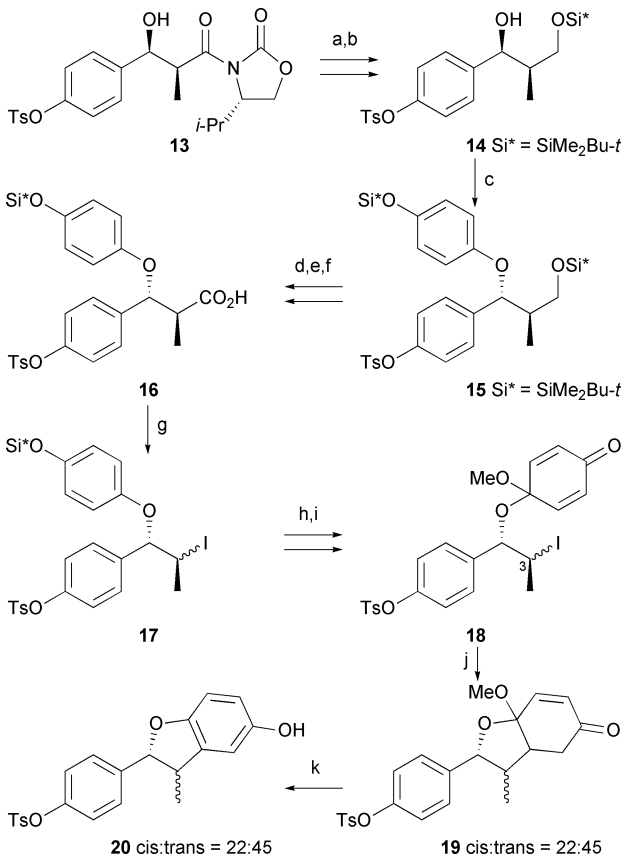
Scheme 1 Pg = protecting group; R = Me or group convertible into Me.



Scheme 2 Pg, Pg^1, Pg^2, Pg^3 = protecting groups; R = Me or group convertible into Me.

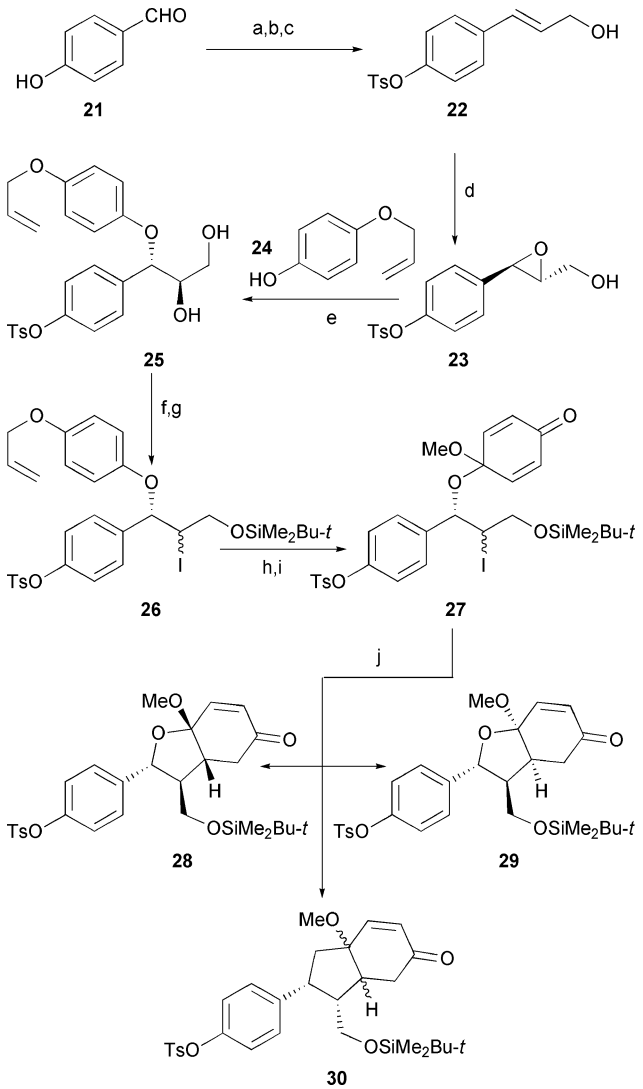
involve displacement at a benzylic carbon[28–30] with a phenolate **9** as the nucleophile.

With Scheme 2 in mind, we first made **14** by an Evans aldol route (Scheme 3) but met problems with the displacement (see **14** → **15**) either under Mitsunobu conditions or after modifying the benzylic hydroxyl to the triflate or mesylate. Nonetheless, with some of the required displacement product **15** in hand, we generated acid **16** and used a Barton–Hunsdiecker process[31] to make the iodides **17**. Desilylation and oxidation in MeOH with $PhI(OAc)_2$ produced the cross-conjugated ketones **18**, but the radical cyclization[32] (**18** → **19**) gave poor diastereoselectivity and, after aromatization (**19** → **20**), the *cis* : *trans* ratio was only *ca.* 33 : 67. In an effort to improve the diastereoselectivity, we planned to prepare substrates of type **18** with other groups in place of the C(3) methyl. However, using **14** with vinyl or CH_2SiPh_2t-Bu in place of this methyl, we again met serious problems in the benzylic displacement with respect to both yield and diastereoselectivity.



Scheme 3 *Reagents and conditions*: (a) $LiBH_4$; (b) *t*-$BuMe_2SiCl$, ImH, 89% over two steps; (c) see text, 68% *via* triflate; (d) $BF_3{\cdot}OEt_2$ (for selective deprotection of the $-CH_2OSiMe_2t$-Bu unit), 66–74%; (e) Dess–Martin periodinane; (f) Pinnick oxidation, 81% over two steps; (g) Barton halogenative decarboxylation, 43–66% over two steps; (h) Bu_4NF, AcOH, 85%; (i) $PhI(OAc)_2$, MeOH, 88%; (j) Bu_3SnH, AIBN, PhMe, 72%; (k) $TsOH{\cdot}H_2O$, 4 Å molecular sieves, CH_2Cl_2, 92%.

At this point we decided to examine an epoxide of type **11** (see Scheme 2) with the intention of subsequently protecting the primary OH with a bulky silyl group so as to enhance stereoselectivity in the planned radical cyclization (see below). To this end allylic alcohol **22** was prepared from *p*-hydroxybenzaldehyde **21** and Sharpless asymmetric epoxidation,[24] using (−)-diisopropyl tartrate, then gave epoxide **23** (Scheme 4). The derived Mosher esters from this epoxide, and from corresponding racemic material, were examined by ^1H NMR to establish the er of **23** as 95 : 5. In retrospect we should have measured the optical purity of the commercial Mosher acid chloride, but failed to do so; nonetheless, at the end of the synthesis the optical purity of conocarpan (ee 98%) was measured by the more reliable method of chiral HPLC (see later). Reaction of the epoxide with the sodium salt of phenol **24**[33,34] in water produced diol **25**, which we could obtain as a single isomer in 76% by chromatography. The stereochemistry shown for **25** is based on the assumption that epoxide opening occurs with inversion; prior literature[35] as well as the presumed mechanism provides a basis for this assumption. Use of a basic aqueous solution for epoxide opening, as opposed to an organic solvent, appeared to represent the optimum conditions. The primary hydroxyl of **25** was protected by silylation and the remaining secondary hydroxyl was replaced by iodine using Ph_3P–I_2–imidazole



Scheme 4 *Reagents and conditions*: (a) TsCl, Et_3N; (b) $(EtO)_2P(O)$-CH_2CO_2Et, Et_3N, LiBr, 81%; (c) DIBAL, 95%; (d) Sharpless asymmetric epoxidation, 93%; (e) NaOH, water, **24**, 76%; (f) *t*-$BuMe_2SiCl$, ImH, 96%; (g) Ph_3P, I_2, ImH, 89%; (h) $Pd(PPh_3)_4$, dimedone, 99%; (i) $PhI(OAc)_2$, MeOH, 91%; (j) Bu_3SnH, AIBN, PhMe, 80°C, 72% yield of **28** and **29**.

(**25** → **26**). Oxidation with $PhI(OAc)_2$ in MeOH generated the key cross-conjugated ketones **27** and these underwent 5-*exo*-trigonal radical cyclization under standard conditions (slow addition of stannane and AIBN to a hot solution of **27** in PhMe) to afford three fractions after chromatography. The fastest eluting compound was **28** (26%) and the slowest eluting was **29** (45%). The middle fraction was the isomer mixture **30** (10.5%). This latter material had the two substituents on the dihydrofuran *cis* and was discarded. We did not characterize the ring fusion stereochemistry of **30**, but expect[36] that it was a mixture of the two possible *cis*-fused compounds. The relative stereochemistry of **28** and **29** was established by the NOE measurements summarized in Fig. 1.

Compounds **28** and **29** were processed individually (Scheme 5). The former was treated with *E*-1-propenyllithium, generated by the action of *t*-BuLi on commercial *E*-1-bromopropene (labeled 99% *E*). This experiment gave alcohol **31** with an *E* : *Z* ratio of 97 : 3, as estimated by ^{1}H NMR. Since we did not obtain exclusively

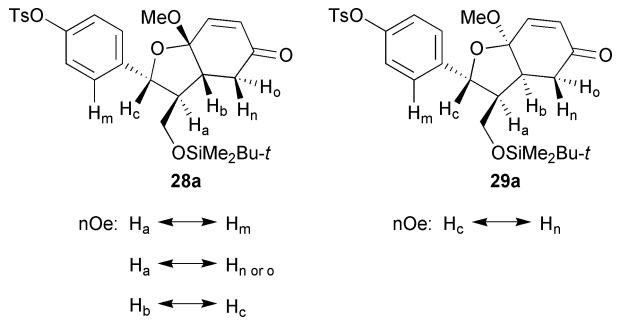
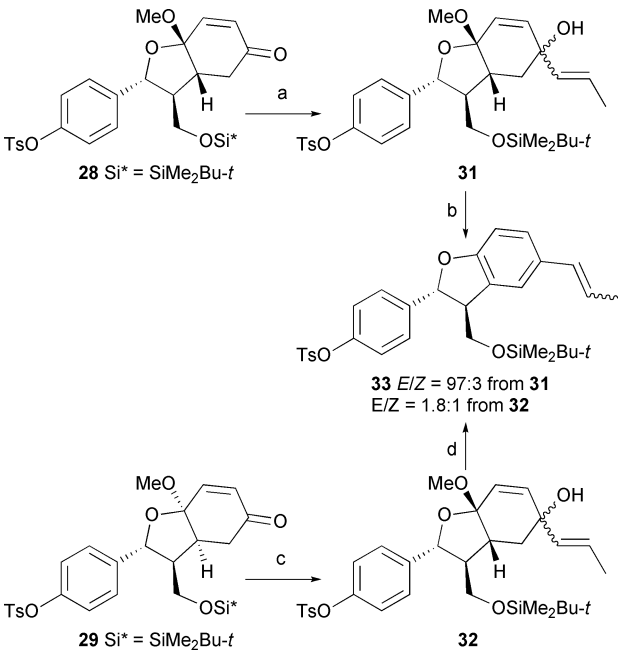


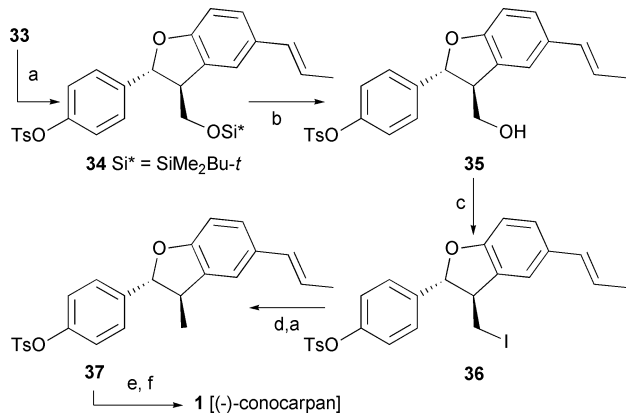
Fig. 1 NOE measurements.



Scheme 5 *Reagents and conditions*: (a) *E*-1-propenyllithium; (b) camphorsulfonic acid, CH_2Cl_2, 30 min, 54% over two steps; (c) 1-propenylmagnesium bromide; (d) camphorsulfonic acid, CH_2Cl_2, 2 h, 71% over two steps.

the *E*-isomer we decided to treat the slower-eluting compound **29** with 1-propenylmagnesium bromide, which is commercially available and also gives an *E* : *Z* mixture (**32**). With both reagents a double bond isomerization (*Z* → *E*) would be required, as we were unable to effect separation of the geometrical isomers, even by argentic chromatography.

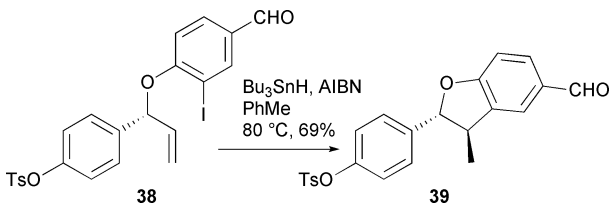
In both cases, treatment with CSA effected aromatization (**31** → **33**; **32** → **33**). We then equilibrated the *E*/*Z* isomers originating from **31**, using $PdCl_2(PhCN)_2$,[37] to obtain **34** with an *E* : *Z* ratio of *ca.* 97 : 3 (Scheme 6). Removal of the silicon protecting group and replacement of the resulting hydroxyl by iodine[38] (**34** → **35** → **36**), followed by hydride displacement of the iodine (Et_3BHLi[39]) gave **37**. At this time, using the second route described below, we had discovered that prolonged exposure to the palladium catalyst during double bond equilibration improved the *E* : *Z* ratio to a level where the *Z*-isomer was not detectable by high field ^{1}H NMR. Accordingly, compound **37** was treated with the isomerization catalyst[37] for 48 h to afford geometrically pure material (74% from the iodide). Desulfonylation [Na(Hg), MeOH,



Scheme 6 *Reagents and conditions*: (a) $PdCl_2(PhCN)_2$, CH_2Cl_2, 3.5 days, 95%; (b) Bu_4NF, 100%; (c) Ph_3P, I_2, ImH (82%) or MsCl, Et_3N (85%) and then NaI, 1,2-dimethoxyethane, reflux, 98%; (d) Et_3BHLi; (e) Na(Hg), MeOH, 95%; (f) $PdCl_2(PhCN)_2$, CH_2Cl_2, 2 days, 74% from **36**.

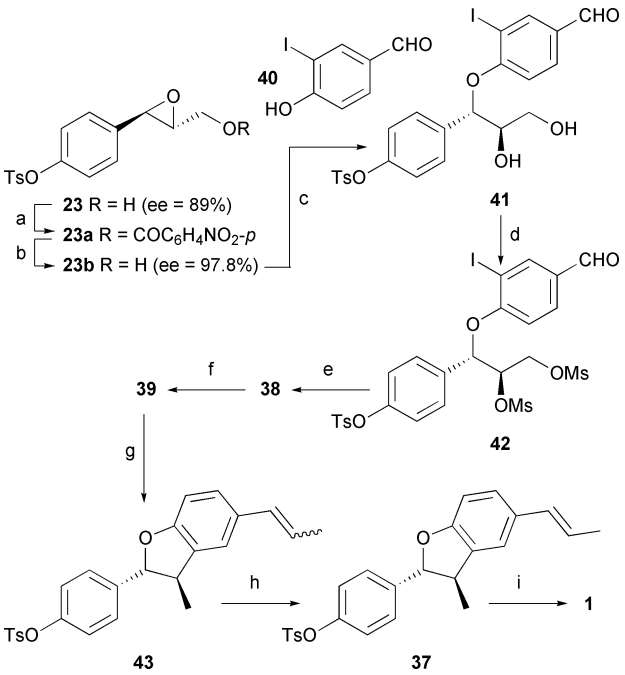
95%] then gave conocarpan.[40] This material was examined by chiral HPLC and found to have an ee of 98%; its $[\alpha]_D^{22}$ was −99.7 (*c* 1.03, MeOH). The sign of the specific rotation is opposite to that reported[1] for (+)-conocarpan indicating that either the original configurational assignment was indeed in error, as suggested by the chiroptical studies,[10] or that the Sharpless epoxidation had taken an abnormal stereochemical course. As described below, these matters were later settled in favor of configurational revision of (+)-conocarpan, so that the compound we had made was actually (−)-conocarpan, with the 2*R*,3*R* absolute configuration shown by structure **1**. However, experimental proof was not obtained until we had completed a second route to the natural product (see below).

While working on the above synthesis we developed another route that is shorter and that also provided an opportunity to compare the *cis* : *trans* ratio for two different modes of 5-*exo*-trigonal radical cyclization. The key step in this second approach is the radical cyclization **38** → **39**.



Our starting point was again epoxide **23**, but with this batch we crystallized the derived *p*-nitrobenzoate (**23** → **23a** → **23b**) to raise the ee (measured by chiral HPLC) from *ca.* 89% to 97.8% (Scheme 7).

Opening of epoxide **23b** under basic conditions (aqueous NaOH) with the sodium salt of phenol **40**[41] (2 equiv.) gave diol **41** in 83% yield (after correction for recovered epoxide). Bis-mesylation (100%) and treatment with NaI[42] in refluxing 2-butanone served to convert the diol into the olefin **38**[43,44] [65% or 80% after correction for recovered bis-mesylate (19%)] needed for the radical cyclization. This was conducted in the usual way by slow addition of a solution of stannane and AIBN in PhMe to a hot (80 °C) solution of the substrate in the same solvent. The desired *trans* disubstituted dihydrobenzofuran **39** was isolated in 69% yield. We did not observe (^{1}H NMR, 300 MHz) the corresponding *cis* isomer



Scheme 7 *Reagents and conditions*: (a) *p*-$NO_2C_6H_4COCl$, Et_3N, then re-crystallize product, 70% after first crystallization; in a separate experiment yield was 62% after three crystallizations; (b) K_2CO_3, 80% MeOH, 97%; (c) NaOH, water, **40**, 64% or 83% after correction for recovered **23b**; (d) MsCl, Et_3N, 100%; (e) NaI, 2-butanone, reflux, 71%; (f) Bu_3SnH, AIBN, PhMe, 80 °C, 69%; (g) ethylidenetriphenylphosphorane, 69%; (h) $PdCl_2(PhCN)_2$, CH_2Cl_2, 10 days, 85%; (i) Na(Hg), MeOH, 95%.

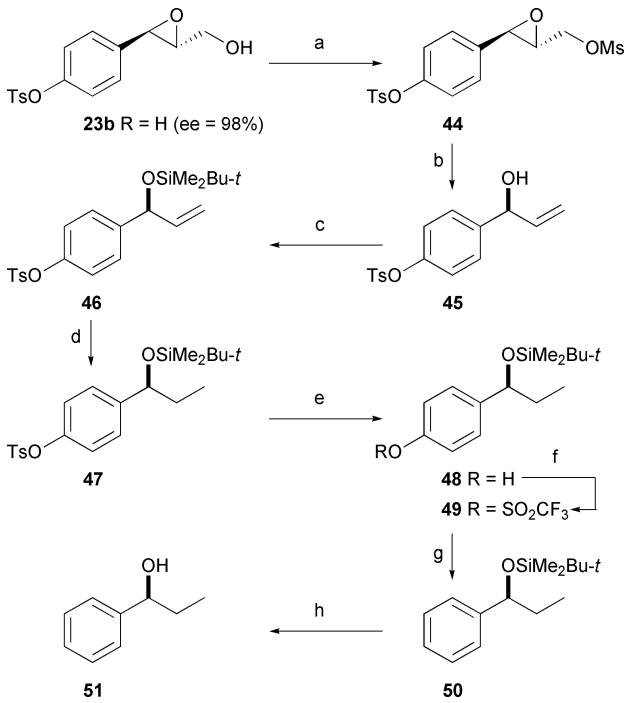
and so the amount formed, if any, must have been very small. The aldehyde group was next converted into a 1-propenyl unit by Wittig reaction with ethylidenetriphenylphosphorane. This reaction afforded a 3 : 1 *Z* : *E* mixture (**43**), and equilibration with $PdCl_2(PhCN)_2$[37] for 24 h gave material (**37**) that was largely the *E*-isomer (*E* : *Z* = 96.9 : 3.1) in near quantitative yield. When the equilibration time was prolonged for 10 days, no *Z*-isomer could be detected (^{1}H NMR, 400 MHz), but this was achieved at the expense of a lower yield (85%). Finally, removal of the tosyl group with Na(Hg) produced (−)-conocarpan (95%); $[\alpha]_D^{22}$ −46.5 (*c* 0.28, MeOH).[40,45] Our synthetic material had an ee of 88% (*i.e.* enantiomeric ratio = 94 : 6) as judged by chiral HPLC. We did not establish the stage at which the enantiomeric ratio was eroded from 99 : 1 (for epoxide **23b**) to 94 : 6 (for synthetic conocarpan **1**), but suspect that the allylic benzylic ether **38** is involved[46] as, in the earlier steps, scrambling at the benzylic position would lead to diastereoisomers—which were not observed by ^{1}H NMR for any of the material used in the synthesis.

Proof of absolute stereochemistry

Since our synthetic conocarpan was levorotatory instead of dextrorotatory, and our target had been the absolute configuration shown by **1**, which is reported for dextrorotatory material, we needed to establish that the Sharpless asymmetric epoxidation had followed the expected course[21,47] so that the absolute configuration of our synthetic compound was indeed that shown in **1**. We were unable to find an example in the literature—with proof of the stereochemical outcome—of Sharpless asymmetric epoxidation

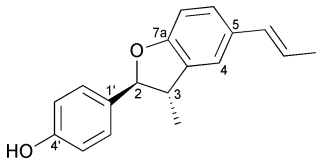
of a styrene derivative with a *para* oxygen substituent.[22] The most straightforward method of obtaining such proof in our case would have been by X-ray analysis, but attempts to obtain suitable crystals of a heavy atom derivative of conocarpan or of epoxide **23b** were unsuccessful. Accordingly, we sought evidence based on chemical degradation of epoxide **23b** to (*S*)-1-phenyl-1-propanol, whose absolute configuration is known from chemical correlation with *S*-(−)-mandelic acid.[48,49]

Our enantiomerically enriched epoxide **23b** was converted into mesylate **44** (Scheme 8), from which olefin **45** was smoothly formed by treatment with NaI in refluxing DME. Normally Zn would be used to convert the presumed intermediate iodo epoxide into an olefin; the present method does not seem to have been reported before, although direct conversion of an iodo epoxide into an allylic alcohol by reaction with iodide ion has been suggested in a mechanistic scheme.[50] Hydroxyl protection by silylation (**45** → **46**) and double bond hydrogenation gave **47**. The tosyl group was then removed by the action of Na(Hg). Triflation of the resulting phenol (**48** → **49**) allowed us to remove the phenolic oxygen by hydrogenolysis[51] (**49** → **50**). Finally, (*S*)-1-phenylpropanol **51** was released by desilylation. The compound had $[\alpha]_D^{22}$ −29.3 (*c* 1.23, $CHCl_3$) [lit.[48] −45.6 (*c* 1.3, $CHCl_3$)], corresponding to an ee of 64%. Our starting epoxide **23b** had an ee of 98% and we did not identify the stage at which there is erosion of optical purity; possibly, it occurs during the hydrogenation *via* migration of the double bond into conjugation with the benzene ring, followed by saturation. Stereochemical scrambling at any other stage is unlikely on mechanistic grounds. The absolute configuration of levorotatory **51** has been established[48,49] and so our degradation



Scheme 8 *Reagents and conditions*: (a) MsCl, Et_3N; (b) NaI, 1,2-dimethoxyethane, reflux, 57% over two steps; (c) *t*-$BuMe_2SiOSO_2CF_3$, *sym*-collidine, 100%; (d) 5% Rh–Al_2O_3, THF, H_2, 99%; (e) Na(Hg), MeOH, 60% and recovered **47** (32%); (f) $(CF_3SO_2)_2O$, Et_3N, 75%; (g) Pd/C, Et_3N, H_2, 100%; (h) Bu_4NF, 71%.

experiments confirm that the asymmetric epoxidation (**22** → **23**) follows the expected course; consequently, natural (+)-conocarpan must have the absolute stereochemistry shown in **52**.



52 [(+)-conocarpan]

Conclusions

The present work shows that stereochemical revision for (+)-conocarpan is required, as discussed above. Our first synthesis, which gives a final product of very high ee, does not proceed *via* an ether that is both benzylic and allylic, and there appears to be no erosion of enantiomeric purity. In the second route, which does involve such a fragile C–O bond, we started with an epoxide of high ee and obtained conocarpan of lower ee. The two modes of 5-*exo*-trigonal radical closure also afford different levels of *cis*/*trans* selectivity, with closure of an aryl radical onto a pendant vinyl group, as in the second route, being more selective.

Experimental

General methods

The *J* values are spacings measured directly from the spectrum. All experiments were done under an inert atmosphere (N_2 or Ar), unless stated to the contrary. Column sizes are quoted as diameter × height. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}.

First route

Toluene-4-sulfonic acid 4-[(2*S*,3*R*)-3-hydroxymethyloxyranyl)]-phenyl ester (23). Crushed 4 Å molecular sieves (0.5 g), activated at >200 °C and 0.3 mmHg for 24 h, were added to a solution of (−)-diisopropyl tartrate (0.050 mL, 0.23 mmol) in CH_2Cl_2 (4 mL), and the flask was lowered into a cold bath (−25 °C, CO_2–CCl_4). $Ti(Oi\text{-}Pr)_4$ (0.10 mL, 0.34 mmol) was then added, followed by *t*-BuOOH (3 M in isooctane, 1.6 mL, 4.8 mmol). The mixture was stirred for 10 min and then **22** (728.4 mg, 2.390 mmol) in CH_2Cl_2 (1.2 mL plus 0.8 mL as a rinse) was added dropwise by syringe. The mixture was stirred for 2 h and then quenched by addition of aqueous NaOH (30% w/v, 0.38 mL) saturated with NaCl. Stirring was continued for 10 min and then $MgSO_4$ (*ca.* 500 mg) and Celite (*ca.* 1 g) were added. The mixture was swirled and the solids were filtered off. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.5 × 35 cm), using first 50–60% EtOAc–hexane (step gradient elution) and then 6 : 3 : 1 EtOAc–hexane–MeOH, gave **23** (712.4 mg, 93%) as a white solid: mp 51–53 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.74 (dd, J = 5.1, 7.7 Hz, 1 H), 2.49 (s, 3 H), 3.18 (ddd, J = 2.3, 2.3, 3.6 Hz, 1 H), 3.83 (ddd, J = 3.6, 7.8, 12.6 Hz, 1 H), 3.93 (d, J = 2.0 Hz, 1 H), 4.06 (ddd, J = 2.5, 4.9, 12.9 Hz, 1 H), 6.99 (apparent d as part of AA′BB′ system, J = 8.7 Hz, 2 H), 7.21 (apparent d as part of AA′BB′ system, J = 8.5 Hz, 2 H), 7.30 (apparent d as part of AA′BB′ system, J = 8.3 Hz, 2 H), 7.71 (apparent d as part of AA′BB′ system, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$,

100 MHz) δ 22.0 (t), 55.1 (d), 61.3 (t), 62.8 (d), 122.8 (d), 127.2 (d), 128.7 (d), 130.1 (d), 132.5 (s), 136.1 (s), 145.7 (s), 149.7 (s); ν_{max} ($CHCl_3$ cast; cm^{-1}) 3419, 3069, 2986, 2926, 2872, 1598, 1505, 1372, 1198, 1176, 1150; exact mass m/z calcd for $C_{16}H_{16}NaOS$ 343.06107, found 343.06134.

Samples of the Mosher esters (from the above optically active epoxy alcohol and the corresponding racemic epoxy alcohol) were prepared by adding (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride to a stirred solution of the epoxy alcohol and Et_3N in CH_2Cl_2. Analysis of the derived crude Mosher esters by ^1H NMR showed the diastereomeric ratio of the above epoxy alcohol to be 94 : 6. Analysis of the epoxy alcohol from another batch (but prepared under the same conditions) by chiral HPLC [Chiralpak AD-RH (150 × 4.6 mm), 1 : 1 MeCN–water, flow 0.5 mL min^{-1}, detection at 232 nm. Baseline separation of a racemic sample; retention times 11.9 min and 14.3 min] showed the enantiomeric ratio to be 94.7 : 5.3.

Toluene-4-sulfonic acid 4-[(1*S*,2*R*)-1-(4-Allyloxyphenoxy)-2,3-dihydroxypropyl]phenyl ester (25). Epoxy alcohol **23** (>88% ee, 10.94 g, 34.15 mmol) was added in one portion to a stirred and heated (70 °C) solution of *O*-allylhydroquinone (12.32 g, 82.04 mmol) and aqueous NaOH (1 M, 34 mL, 34 mmol) in water (66 mL), and stirring was continued for 2.5 h. The mixture was allowed to cool, poured into aqueous NaOH (1 M, 100 mL), and extracted three times with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (5 × 35 cm), using 50–80% EtOAc–hexane containing Et_3N (*ca.* 3 drops per 100 mL) (gradient elution), gave **25** (12.26 g, 76%) as a yellowish oil, and recovered **23** (1.09 g, 10%). Diol **25** had: $[\alpha]_D^{22}$ +46.77 (*c* 1.94, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.16 (br s, 1 H), 2.46 (overlapping s and br s, 4 H), 3.79 (m, 2 H), 3.93 (dd, J = 5.4, 9.8 Hz, 1 H), 4.45 (ddd, J = 1.5, 1.5, 5.3 Hz, 2 H), 5.08 (d, J = 6.1 Hz, 1 H), 5.27 (dddd, J = 1.4, 1.4, 1.4, 10.5 Hz, 1 H), 5.38 (dddd, J = 1.6, 1.6, 1.6, 17.3 Hz, 1 H), 6.02 (dddd, J = 5.3, 5.3, 10.6, 17.3 Hz, 1 H), 6.71–6.77 (m, 4 H), 7.00 (apparent d as part of AA′BB′ system, J = 8.6 Hz, 2 H), 7.30 (apparent d as part of AA′BB′ system, J = 8.1 Hz, 2 H), 7.33 (apparent d as part of AA′BB′ system, J = 8.6 Hz, 2 H), 7.69 (apparent d as part of AA′BB′ system, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7 (q), 62.8 (t), 69.4 (t), 74.5 (d), 81.1 (d), 115.6 (d), 117.1 (d), 117.6 (s), 122.6 (d), 128.3 (d), 128.4 (d), 129.7 (d), 132.4 (s), 133.4 (d), 137.1 (s), 145.4 (s), 149.3 (s), 151.4 (s), 153.4 (s); ν_{max} ($CDCl_3$ cast; cm^{-1}) 3400, 3069, 2924, 1597, 1505, 1373, 1212, 1199; exact mass m/z calcd for $C_{25}H_{26}NaO_7S$ 493.12915, found 493.12900.

Toluene-4-sulfonic acid 4-[(1*S*,2*S*)-3-(*tert*-butyldimethylsilanyloxy)-2-iodo-1-(1-methoxy-4-oxocyclohexa-2,5-dienyloxy)propyl]-phenyl ester (27).

*(a) Toluene-4-sulfonic acid 4-[(1S,2S)-3-(*tert*-butyldimethylsilanyloxy)-1-(4-hydroxyphenoxy)-2-iodopropyl]phenyl ester.* $(Ph_3P)_4Pd$ (269.3 mg, 0.2330 mmol) was added to a stirred solution of **26** (2.5371 g, 3.652 mmol) and dimedone (1.1353 g, 8.099 mmol) in THF (13 mL), and stirring was continued for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 45 cm), using 10–20% EtOAc–hexane (gradient elution), gave toluene-4-sulfonic acid 4-[(1*S*,2*S*)-3-(*tert*-butyldimethylsilanyloxy)-1-(4-hydroxyphenoxy)-2-iodopropyl]phenyl ester (2.3587 g, 99%) as an unstable, brownish oil that was processed promptly: $[\alpha]_D^{22}$ +13.04 (*c* 1.38, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 3 H), 0.04 (s, 3 H), 0.88 (s, 9 H), 2.43 (s, 3 H), 3.79 (dd, J = 4.5, 10.6 Hz, 1 H), 3.99 (dd, J = 8.2, 10.6 Hz, 1 H), 4.21 (ddd, J = 4.3, 4.3, 8.3 Hz, 1 H), 5.05 (d overlapping with br s, J = 4.2 Hz, 2 H), 6.65–6.73 (m, 4 H), 6.96 (apparent d as part of AA′BB′ system, J = 8.6 Hz, 2 H), 7.27 (apparent d as part of AA′BB′ system, J = 8.5 Hz, 2 H), 7.29 (apparent d as part of AA′BB′ system, J = 8.7 Hz, 2 H), 7.65 (apparent d as part of AA′BB′ system, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.5 (q), −5.4 (q), 18.2 (s), 21.7 (q), 25.8 (q), 40.9 (d), 65.7 (t), 77.9 (d), 115.9 (d), 117.5 (d), 122.4 (d), 127.8 (d), 128.5 (d), 129.7 (d), 132.0 (s), 138.8 (s), 145.5 (s), 149.1 (s), 150.2 (s), 151.7 (s); ν_{max} ($CHCl_3$ cast; cm^{-1}) 3489, 2952, 2927, 2856, 1597, 1507, 1373, 1198, 1176, 1092, 837; exact mass m/z calcd for $C_{28}H_{35}INaO_6SSi$ 677.08606, found 677.08627.

*(b) Toluene-4-sulfonic acid 4-[(1S,2S)-3-(*tert*-butyldimethylsilanyloxy)-2-iodo-1-(1-methoxy-4-oxocyclohexa-2,5-dienyloxy)-propyl]phenyl ester (27).* $PhI(OAc)_2$ (45.4 mg, 0.141 mmol) was added in one portion to a stirred and cooled (0 °C) solution of the above toluene-4-sulfonic acid 4-[(1*S*,2*S*)-3-(*tert*-butyldimethylsilanyloxy)-1-(4-hydroxyphenoxy)-2-iodopropyl]-phenyl ester (containing *ca.* 6.5% *anti* isomer) (81.0 mg, 0.124 mmol) in MeOH (1.3 mL). Stirring was continued for 30 min and then EtOAc (10 mL) was added. The mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 30 cm), using 0–20% EtOAc–hexane containing Et_3N (*ca.* 3 drops per 100 mL) (gradient elution), gave **27** (77.3 mg, 91%) as a light orange oil, which appeared to be a single isomer (^1H NMR, ^{13}C NMR): $[\alpha]_D^{22}$ +39.38 (*c* 1.49, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 3 H), 0.04 (s, 3 H), 0.88 (s, 9 H), 2.41 (s, 3 H), 3.33 (s, 3 H), 3.52 (dd, J = 4.2, 11.0 Hz, 1 H), 3.79 (dd, J = 6.9, 11.0 Hz, 1 H), 3.99 (ddd, J = 4.3, 5.1, 6.8 Hz, 1 H), 4.72 (d, J = 5.2 Hz, 1 H), 5.95 (dd, J = 2.1, 10.3 Hz, 1 H), 6.08 (dd, J = 2.1, 10.5 Hz, 1 H), 6.48 (dd, J = 3.2, 10.3 Hz, 1 H), 6.64 (dd, J = 3.2, 10.4 Hz, 1 H), 6.90 (apparent d as part of AA′BB′ system, J = 8.7 Hz, 2 H), 7.18 (apparent d as part of AA′BB′ system, J = 8.6 Hz, 2 H), 7.27 (apparent d as part of AA′BB′ system, J = 8.5 Hz, 2 H), 7.64 (apparent d as part of AA′BB′ system, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.4 (q), −5.2 (q), 18.2 (s), 21.7 (q), 25.8 (q), 41.3 (d), 51.5 (q), 65.5 (t), 73.1 (d), 93.6 (s), 122.3 (d), 128.2 (d), 128.5 (d), 129.0 (d), 129.7 (d), 129.8 (d), 132.2 (s), 139.7 (s), 143.5 (d), 144.2 (d), 145.5 (s), 149.3 (s), 184.8 (s); ν_{max} (CH_2Cl_2 cast; cm^{-1}) 3055, 2953, 2930, 2896, 2857, 1688, 1674, 1639, 1599, 1501, 1471, 1378, 1199, 1177, 1094, 867, 839; exact mass m/z calcd for $C_{29}H_{37}INaO_7SSi$ 707.09663, found 707.09677. Anal. calcd for $C_{29}H_{37}IO_7SSi$: C 50.87; H 5.45; S 4.68. Found: C 50.78; H 5.55; S 4.87%.

Toluene-4-sulfonic acid 4-[(2*R*,3*S*,3a*S*,7a*S*)-3-(*tert*-butyldimethylsilanyloxymethyl)-2,3,3a,4,5,7a-hexahydro-7a-methoxy-5-oxobenzofuran-2-yl]phenyl ester (29) and Toluene-4-sulfonic acid 4-[(2*R*,3*S*,3a*R*,7a*R*)-3-(*tert*-butyldimethylsilanyloxymethyl)-2,3,3a,4,5,7a-hexahydro-7a-methoxy-5-oxobenzofuran-2-yl]phenyl ester (28). A solution of Bu_3SnH (0.04 mL, 0.15 mmol) and AIBN (6.0 mg, 0.037 mmol) in PhMe (3 mL) was added over 4 h to a stirred and heated (80 °C) solution of **27** (65.4 mg, 0.0955 mmol) in PhMe (1 mL) (N_2 atmosphere). After the addition, heating was continued for 1 h, and the mixture was

then allowed to cool to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 30 cm), using 8–20% EtOAc–hexane containing Et_3N (*ca.* 3 drops per 100 mL), gave three fractions, each as a yellowish oil. The fastest eluting fraction was one isomer (**28**) (14.0 mg, 26.3%), the middle eluting fraction was a mixture of unwanted diastereomers [*i.e. cis* disubstitution on the oxygen heterocycle (see below)] (5.6 mg, 10.5%), and the slowest eluting fraction was another diastereoisomer (**29**) (23.6 mg, 45.3%). The total yield of desired product amounted to 72%.

The relative configurations were established by NOE measurements shown in Fig. 1.

The fast eluting isomer **28** had: $[\alpha]_D^{22}$ −56.66 (*c* 2.49, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz) δ 0.00 (s, 6 H), 0.97 (s, 9 H), 1.80 (dddd, J = 4.3, 4.3, 8.8, 8.8 Hz, 1 H), 1.87 (s, 3 H), 2.48 (dd, J = 4.8, 16.6 Hz, 1 H), 2.60 (dd, J = 6.4, 16.6 Hz, 1 H), 2.93 (dddd, J = 1.4, 4.9, 6.2, 9.7 Hz, 1 H), 3.28 (s, 3 H), 3.30 (dd, J = 4.2, 10.9 Hz, 1 H), 3.41 (dd, J = 4.6, 10.8 Hz, 1 H), 5.05 (d, J = 8.9 Hz, 1 H), 5.95 (d, J = 10.4 Hz, 1 H), 6.56 (dd, J = 1.4, 10.4 Hz, 1 H), 6.70 (apparent dd as part of AA′BB′ system, J = 0.6, 8.5 Hz, 2 H), 7.12 (apparent d as part of AA′BB′ system, J = 8.7 Hz, 2 H), 7.22 (apparent d as part of AA′BB′ system, J = 8.8 Hz, 2 H), 7.77 (apparent dd as part of AA′BB′ system, J = 0.3, 8.5 Hz, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) (two signals overlap in the aromatic region) δ −5.6 (q), 18.3 (s), 21.1 (q), 25.9 (overlapping q and d), 37.9 (t), 44.1 (d), 49.4 (q), 55.1 (d), 60.0 (t), 81.8 (d), 103.5 (s), 122.9 (d), 128.8 (d), 129.7 (d), 133.5 (s), 140.1 (s), 143.0 (d), 144.8 (s), 149.9 (s), 196.0 (s); ν_{max} ($CHCl_3$ cast; cm^{-1}) 2953, 2929, 2857, 1689, 1597, 1502, 1376, 1198, 1176, 1155, 866, 837.

The slow eluting isomer **29** had: $[\alpha]_D^{22}$ −20.65 (*c* 5.88, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz) 0.00 (s, 3 H), 0.01 (s, 3 H), 0.95 (s, 9 H), 1.92 (s, 3 H), 2.46 (dd, J = 11.7, 15.9 Hz, 1 H), 2.63 (dd, J = 4.9, 15.9 Hz, 1 H), 2.92–3.00 (m, 2 H, found to be H_a and H_b by 2D experiments), 3.13 (s, 3 H), 3.45 (d, J = 5.9 Hz, 2 H), 4.90 (d, J = 9.0 Hz, 1 H), 6.04 (dd, J = 0.7, 10.5 Hz, 1 H), 6.58 (d, J = 10.3 Hz, 1 H), 6.76 (apparent d as part of AA′BB′ system, J = 8.1 Hz, 2 H), 7.18 (apparent d as part of AA′BB′ system, J = 8.6 Hz, 2 H), 7.33 (apparent d as part of AA′BB′ system, J = 8.6 Hz, 2 H), 7.80 (apparent d as part of AA′BB′ system, J = 8.3 Hz, 2 H); ^{13}C NMR (C_6D_6, 125 MHz) δ −5.7 (q), −5.6 (q), 18.1 (s), 21.1 (q), 25.8 (q), 36.3 (t), 46.6 (d), 49.3 (q), 50.9 (d), 59.8 (t), 83.8 (d), 103.8 (s), 122.8 (d), 128.3 (d), 128.8 (d), 129.65 (d), 129.71 (d), 133.6 (s), 140.7 (d), 140.9 (s), 144.8 (s), 150.0 (s), 196.6 (s); ν_{max} ($CHCl_3$ cast; cm^{-1}) 2953, 2929, 2886, 2857, 1720, 1691, 1502, 1376, 1198, 1178, 1154, 1093, 867, 838; exact mass m/z calcd for $C_{29}H_{38}NaO_7SSi$ 581.19997, found 581.19977.

The fact that some *cis* disubstitution product was formed was established by aromatizing that material (by treatment with $TsOH{\cdot}H_2O$) and showing that the aromatic product was isomeric with the product of aromatization of the desired *trans* disubstitution product.

Toluene-4-sulfonic acid 4-[(2*R*,3*S*)-3-(*tert*-butyldimethylsilanyloxymethyl)-2,3-dihydro-5-(1*E*)-1-propenylbenzofuran-2-yl]phenyl ester (34). $PdCl_2(PhCN)_2$ (84.6 mg, 0.221 mmol) was added in one portion to a stirred solution of **33** (E : Z = 1.8 : 1, 1.4696 g, 2.6680 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred for 3.5 days (N_2 atmosphere), diluted with Et_2O (10 mL) and filtered through a pad of Florisil (3 × 3 cm), using Et_2O. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 × 35 cm), using 8% EtOAc–hexane, gave **34** (1.3980 g, 95%) as a colorless oil (containing *ca.* 3% of the Z isomer) with ^1H NMR data identical to those reported for **33**.

Toluene-4-sulfonic acid 4-[(2*R*,3*S*)-2,3-dihydro-3-iodomethyl-5-(1*E*)-1-propenylbenzofuran-2-yl]phenyl ester (36).

*(a) Toluene-4-sulfonic acid 4-[(2*R*,3*S*)-2,3-dihydro-3-(methanesulfonyloxy)methyl-5-(1*E*)-1-propenylbenzofuran-2-yl]-phenyl ester.* $MeSO_2Cl$ (0.025 mL, 0.32 mmol) was added dropwise by syringe to a stirred and cooled (0 °C) solution of **35** (120.0 mg, 0.2750 mmol) and Et_3N (0.04 mL, 0.29 mmol) in CH_2Cl_2 (3 mL). The cooling bath was removed and stirring was continued for 15 min. The mixture was washed with water and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 30 cm), using 20% EtOAc–hexane, gave toluene-4-sulfonic acid 4-[(2*R*,3*S*)-2,3-dihydro-3-(methanesulfonyloxy)methyl-5-(1*E*)-1-propenylbenzofuran-2-yl]phenyl ester (120.1 mg, 85%) as a white solid, which contained 4% of the Z isomer (^1H NMR): mp 40–42 °C; $[\alpha]_D^{22}$ −49.71 (*c* 6.59, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.86 (dd, J = 1.7, 6.6 Hz, 3 H), 2.45 (s, 3 H), 2.98 (s, 3 H), 3.71 (ddd, J = 5.1, 5.1, 8.9 Hz, 1 H), 4.39 (dd, J = 8.4, 10.3 Hz, 1 H), 4.50 (dd, J = 5.0, 10.3 Hz, 1 H), 5.58 (d, J = 5.2 Hz, 1 H), 6.08 (dq, J = 6.6, 15.6 Hz, 1 H), 6.33 (dd, J = 1.6, 15.7 Hz, 1 H), 6.84 (d, 8.2 Hz, 1 H), 6.97 (apparent d as part of AA′BB′ system, J = 8.7 Hz, 2 H), 7.18 (s, 1 H), 7.20 (dd, J = 1.7, 8.3 Hz, 1 H), 7.29 (apparent d as part of AA′BB′ system, J = 8.8 Hz, 2 H), 7.31 (apparent dd as part of AA′BB′ system, J = 0.5, 8.1 Hz, 2 H), 7.70 (apparent d as part of AA′BB′ system, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3 (q), 21.6 (q), 37.5 (q), 50.7 (d), 70.0 (t), 85.7 (d), 109.8 (d), 121.9 (d), 122.6 (d), 124.0 (d), 124.1 (s), 126.7 (d), 127.8 (d), 128.4 (d), 129.7 (d), 130.0 (d), 131.9 (s), 132.2 (s), 139.7 (s), 145.4 (s), 149.3 (s), 158.5 (s); ν_{max} ($CHCl_3$ cast; cm^{-1}) 3024, 2937, 1503, 1490, 1360, 1198, 1176, 1154, 960, 867, 816; exact mass m/z calcd for $C_{26}H_{26}NaO_7S_2$ 537.10122, found 537.10121.

*(b) Toluene-4-sulfonic acid 4-[(2*R*,3*S*)-2,3-dihydro-3-iodomethyl-5-(1*E*)-1-propenylbenzofuran-2-yl]phenyl ester (**36**).* NaI (177.8 mg, 1.186 mmol) was added to a stirred suspension of Zn powder (0.1681 g, 2.571 mmol) and toluene-4-sulfonic acid 4-[(2*R*,3*S*)-2,3-dihydro-3-(methanesulfonyloxy)methyl-5-(1*E*)-1-propenylbenzofuran-2-yl]phenyl ester (containing 4% of Z isomer) (120.1 mg, 0.2334 mmol) in glyme (0.26 mL). The mixture was refluxed overnight, allowed to cool, and then filtered through a pad of Celite (3 × 1.5 cm). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 30 cm), using 5–8% EtOAc-hexane, gave iodide **36**.

Evidently the iodide is inert to reduction in refluxing glyme when treated with Zn powder. This crude material was therefore reduced using Bu_3SnH (see later).

In another experiment, specifically designed to prepare the iodide, NaI (566.0 mg, 3.776 mmol) was added in one portion to a stirred solution of toluene-4-sulfonic acid 4-[(2*R*,3*S*)-2,3-dihydro-3-(methanesulfonyloxy)methyl-5-(1*E*)-1-propenylbenzofuran-2-yl]phenyl ester (a batch containing 6% of Z isomer) (403.5 mg, 0.7841 mmol) in glyme (3 mL). The mixture was refluxed for 1.5 h, allowed to cool and diluted with EtOAc (10 mL). The mixture was washed with water (1 × 5 mL), saturated aqueous $Na_2S_2O_3$

solution (1 × 5 mL), and brine (1 × 5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 30 cm), using 13% EtOAc–hexane, gave **36** (421.1 mg, 98%) as a colorless oil, which contained 6% of the *Z* isomer (^{1}H NMR): $[\alpha]_D^{22}$ −80.22 (*c* 5.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88 (dd, J = 1.4, 6.6 Hz, 3 H), 2.47 (s, 3 H), 3.34 (dd, J = 9.7, 9.7 Hz, 1 H), 3.53 (dd, J = 4.0, 10.2 Hz, 1 H), 3.54 (ddd, J = 4.0, 4.0, 8.9 Hz, 1 H), 5.49 (d, J = 4.3 Hz, 1 H), 6.10 (dq, J = 6.6, 15.6 Hz, 1 H), 6.36 (dd, J = 1.2, 15.8 Hz, 1 H), 6.85 (d, J = 8.2 Hz, 1 H), 6.98 (apparent d as part of AA′BB′ system, J = 8.7 Hz, 2 H), 7.21 (s, 1 H), 7.24 (d, J = 8.3 Hz, 1 H), 7.32–7.36 (m, 4 H), 7.73 (apparent d as part of AA′BB′ system, J = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.7 (t), 18.6 (q), 22.0 (q), 53.4 (d), 89.3 (d), 110.2 (d), 122.1 (d), 122.8 (d), 124.2 (d), 127.0 (d), 128.0 (d), 128.4 (s), 128.8 (d), 130.1 (d), 130.5 (d), 132.2 (s), 132.7 (s), 140.3 (s), 145.6 (s), 149.6 (s), 158.6 (s); ν_{max} ($CDCl_3$ cast; cm^{-1}) 3021, 2913, 2851, 1597, 1502, 1489, 1374, 1245, 1198, 1177, 1154, 1093, 966, 862, 551; exact mass *m*/*z* calcd for $C_{25}H_{23}INaO_4S$ 569.02540, found 569.02546.

Toluene-4-sulfonic acid 4-[(2*R*,3*S*)-2,3-dihydro-3-methyl-5-(1*E*)-1-propenylbenzofuran-2-yl]phenyl ester (37). AIBN (7.9 mg, 0.048 mmol) was added to a stirred solution of crude iodide **36** [from mesylate (0.1201 g) and assumed to be 0.233 mmol] and Bu_3SnH (0.09 mL, 0.3 mmol) in PhMe (3.6 mL). The reaction vessel was flushed thoroughly with N_2 and then heated in an oil bath set at 80 °C. Heating was continued for 1 h and then the mixture was allowed to cool. Evaporation of the solvent and flash chromatography of the residue over 10% KF–silica gel[52] (1.5 × 30 cm), using 5–8% EtOAc–hexane (gradient elution), gave an inseparable 7 : 3 mixture of starting iodide and **37**. This mixture was re-subjected to the above conditions, using Bu_3SnH (0.08 mL) in PhMe (3.6 mL). Chromatography of the crude material under the same conditions as above gave **37** (67.0 mg, 68% over 2 steps from the mesylate).

In an improved reduction procedure, Et_3BHLi (1 M in THF, 3.4 mL, 3.4 mmol) was added dropwise by syringe to a stirred and cooled (0 °C) solution of **36** obtained *via* the procedure below (923.4 mg, 1.690 mmol) in THF (10 mL). The ice bath was left in place but not recharged and stirring was continued for 3.5 h. Water (0.5 mL) was added, followed by aqueous NaOH (1 M, 4 mL) and finally H_2O_2 (1.5 mL, 30%). The mixture was stirred for an additional 20 min and then partitioned between water (10 mL) and Et_2O (20 mL). The organic phase was washed with water (1 × 10 mL) and brine (1 × 10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 35 cm), using hexane and then 13% EtOAc–hexane, gave **37** (697.9 mg, 98%) as a colorless oil which contained 3% of the *Z* isomer (^{1}H NMR): $[\alpha]_D^{22}$ −59.93 (*c* 2.24, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (d, J = 6.9 Hz, 3 H), 1.86 (dd, J = 1.7, 6.6 Hz, 3 H), 2.45 (s, 3 H), 3.34 (m, 1 H), 5.12 (d, J = 8.4 Hz, 1 H), 6.09 (dq, J = 6.7, 15.7 Hz, 1 H), 6.36 (dd, J = 1.7, 15.7 Hz, 1 H), 6.77 (d, J = 8.8 Hz, 1 H), 6.99 (apparent d as part of AA′BB′ system, J = 8.7 Hz, 2 H), 7.12 (s, 1 H), 7.12–7.13 (m, 1 H), 7.32 (apparent dd as part of AA′BB′ system, J = 0.7, 7.9 Hz, 2 H), 7.33 (apparent d as part of AA′BB′ system, J = 8.4 Hz, 2 H), 7.72 (apparent d as part of AA′BB′ system, J = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3 (q), 18.4 (q), 21.7 (q), 45.6 (d), 91.7 (d), 109.3 (d), 120.8 (d), 122.6 (d), 123.3 (d), 126.4 (d), 127.2 (d), 128.5 (d), 129.8 (d), 130.6 (d), 131.6 (s), 131.8 (s), 132.4 (s), 140.0 (s), 145.4 (s), 149.3 (s), 158.1 (s); ν_{max} (CH_2Cl_2 cast; cm^{-1}) 3021, 2962, 2928, 1598, 1503, 1486, 1375, 1243, 1199, 1177, 1154, 1094, 968, 868; exact mass *m*/*z* calcd for $C_{25}H_{24}NaO_4S$ 443.12875, found 443.12864.

This material was then exposed to the action of $PdCl_2(PhCN)_2$ as follows:

$PdCl_2(PhCN)_2$ (21 mg, 0.55 mmol) was added in one portion to a stirred solution of **37** (0.281 mg, 0.667 mmol) in CH_2Cl_2 (3 mL) and the mixture was stirred for 48 h (N_2 atmosphere), diluted with Et_2O (10 mL) and filtered through a pad of Florisil (3 × 3 cm), using Et_2O. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 × 35 cm), using 8% EtOAc–hexane, gave **37** (0.2072 mg, 74% from the iodide) as a colorless oil free of the *Z* isomer (^{1}H NMR 400 MHz).

Toluene-4-sulfonic acid 4-[(2*R*,3*S*)-2,3-dihydro-3-iodomethyl-5-(1*E*)-1-propenylbenzofuran-2-yl]phenyl ester (36). Imidazole (20.6 mg, 0.303 mmol), followed by Ph_3P (42.6 mg, 0.162 mmol) and then I_2 (46.9 mg, 0.185 mmol), was added to a stirred solution of **35** (74.0 mg, 0.170 mmol) in PhMe (3 mL). The mixture was heated at 100 °C for 1.5 h and then allowed to cool. EtOAc (10 mL) was added and the mixture was washed with saturated aqueous $Na_2S_2O_3$ solution (2 × 5 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 30 cm), using 13% EtOAc–hexane, gave **36** (75.9 mg, 82%) as a colorless oil with spectral data identical to those reported above.

4-[(2*R*,3*R*)-2,3-Dihydro-3-methyl-5-(1*E*)-1-propenylbenzofuran-2-yl]phenol [(+)-conocarpan] (1). Na(Hg) (Aldrich, 10% Na, 868.9 mg, 3.779 mmol Na) was added in one portion to a stirred solution of isomerically pure **37** (197.0 mg, 0.4685 mmol) in 80% MeOH (8 mL), and stirring was continued overnight. The solution was then decanted from the Hg, and diluted with water (10 mL). The mixture was extracted with Et_2O (3 × 10 mL), by which stage the aqueous layer was free of product (TLC control, silica, 30% EtOAc–hexane). The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 25 cm), using 0–15% EtOAc–hexane, gave **1** (119.0 mg, 95%) as a white, crystalline solid: mp 120–123 °C [lit.[4a] 133–135 °C; lit.[4g] 124–126 °C]; $[\alpha]_D^{22}$ −99.7 (*c* 1.03, MeOH), lit.[4a] $[\alpha]_D^{21}$ +122 (for dextrorotary conocarpan) (*c* 1.03, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.40 (d, J = 6.8 Hz, 3 H), 1.86 (dd, J = 1.6, 6.6 Hz, 3 H), 3.37–3.43 (m, 1 H), 5.00 (s, 1 H), 5.08 (d, J = 8.9 Hz, 1 H), 6.09 (dq, J = 6.6, 15.6 Hz, 1 H), 6.37 (d, J = 15.6 Hz, 1 H), 6.76 (d, J = 8.1 Hz, 1 H), 6.83 (apparent d as part of AA′BB′ system, J = 8.5 Hz, 2 H), 7.12–7.14 (m, 2 H), 7.30 (apparent d as part of AA′BB′ system, J = 8.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.9 (q), 18.4 (q), 45.3 (d), 92.7 (d), 109.3 (d), 115.5 (d), 120.8 (d), 123.1 (d), 126.3 (d), 127.9 (d), 130.8 (d), 131.3 (s), 132.4 (s), 132.9 (s), 155.7 (s), 158.3 (s); ν_{max} (CH_2Cl_2 cast, microscope; cm^{-1}) 3395, 3022, 2962, 2928, 2882, 1614, 1517, 1487, 1240, 1202, 1171, 964, 831; exact mass *m*/*z* calcd for $C_{18}H_{18}O_2$ 266.13068, found 266.13042. HPLC analysis [Chiralcel OD column (0.46 × 15.0 cm); 95:5 heptane–isopropanol; flow rate 1 mL min^{-1}; 40 °C; detection at 207 nm.; retention times 7.4 min and 10.9 min] showed that the compound had an ee of 98%.

Second route

Toluene-4-sulfonic acid 4-[(1*S*,2*R*)-1-(4-formyl-2,3-dihydroxy-2-iodophenoxy)propyl]phenyl ester (41). Epoxy alcohol **23b** (er = 98.9 : 1.1) (1.8694 g, 5.8350 mmol) was added in one portion to a stirred and heated (sand bath, 70 °C) solution of 4-hydroxy-3-iodobenzaldehyde[41] (2.6359 g, 10.628 mmol) in a mixture of aqueous NaOH (1 M, 5.8 mL, 5.8 mmol) and water (6 mL). Stirring at 70 °C was continued for 2.5 h. The mixture was allowed to cool and was then poured into aqueous NaOH (1 M, 10 mL). The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 × 35 cm), using 50–80% EtOAc–hexane containing Et_3N (*ca.* 3 drops per 100 mL) (gradient elution), gave **41** [2.1124 g, 64%, or 83% based on recovered **23b** (436.8 mg, 23%)] as a white, crystalline solid: mp 55–58 °C; $[\alpha]_D^{22}$ −39.52 (*c* 5.69, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.33 (br s, 1 H), 2.45 (s, 3 H), 2.75 (br s, 1 H), 3.82 (dd, J = 3.7, 11.5 Hz, 1 H), 3.94 (dd, J = 5.2, 11.5 Hz, 1 H), 4.03–4.06 (m, 1 H), 5.40 (d, J = 5.8 Hz, 1 H), 6.64 (d, J = 8.6 Hz, 1 H), 7.03 (apparent d as part of AA′BB′ system, J = 8.7 Hz, 2 H), 7.30 (apparent dd as part of AA′BB′ system, J = 0.6, 8.6 Hz, 2 H), 7.33 (apparent d as part of AA′BB′ system, J = 8.6 Hz, 2 H), 7.60 (dd, J = 2.0, 8.6 Hz, 1 H), 7.69 (apparent d as part of AA′BB′ system, J = 8.4 Hz, 2 H), 8.27 (d, J = 2.0 Hz, 1 H), 9.76 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7 (q), 62.3 (t), 74.4 (d) 81.4 (d), 87.4 (s), 113.3 (d), 122.9 (d), 128.2 (d), 128.3 (d), 129.8 (d), 131.7 (d), 131.8 (s), 132.3 (s), 135.2 (s), 140.9 (d), 145.6 (s), 149.6 (s), 160.1 (s), 189.2 (d); ν_{max} ($CDCl_3$ cast; cm^{-1}) 3417, 3067, 2927, 2883, 2731, 1694, 1587, 1502, 1480, 1371, 1255, 1198, 1177, 1155, 1093, 1038, 869; exact mass *m*/*z* calcd for $C_{23}H_{21}INaO_7S$ 590.99450, found 590.99454.

Toluene-4-sulfonic acid 4-[(*R*)-1-(4-formyl-2-iodophenoxy)allyl]-phenyl ester (38). NaI (91.7 mg, 0.612 mmol) was added to a stirred solution of **42** (29.5 mg, 0.0408 mmol) in 2-butanone (2 mL), and the mixture was refluxed for 4 h, and then allowed to cool. The solvent was evaporated and the residue was partitioned between EtOAc and saturated aqueous $Na_2S_2O_3$. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 20 cm), using 30% EtOAc–hexane, gave **38** (15.7 mg, 71%) as an amber oil: $[\alpha]_D^{22}$ −8.88 (*c* 13.43, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.48 (s, 3 H), 5.36 (dd, J = 0.8, 10.4 Hz, 1 H), 5.50 (dd, J = 0.8, 17.1 Hz, 1 H), 5.83 (d, J = 5.9 Hz, 1 H), 6.05 (ddd, J = 5.9, 10.4, 17.0 Hz, 1 H), 6.88 (d, J = 8.5 Hz, 1 H), 7.06 (apparent d as part of AA′BB′ system, J = 8.6 Hz, 2 H), 7.33 (apparent d as part of AA′BB′ system, J = 8.5 Hz, 2 H), 7.45 (apparent d as part of AA′BB′ system, J = 8.8 Hz, 2 H), 7.73 (apparent d as part of AA′BB′ system, J = 8.3 Hz, 2 H), 7.76 (dd, J = 2.0, 8.5 Hz, 1 H), 8.34 (d, J = 1.9 Hz, 1 H), 9.83 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7 (q), 81.4 (d), 87.8 (s), 113.6 (d), 117.8 (t), 122.8 (d), 127.8 (d), 128.4 (d), 129.8 (d), 131.5 (d), 131.6 (s), 132.4 (s), 136.2 (d), 137.6 (s), 141.2 (d), 145.5 (s), 149.3 (s), 160.6 (s), 189.2 (d); ν_{max} (CH_2Cl_2 cast; cm^{-1}) 3065, 2922, 2834, 2727, 1695, 1587, 1501, 1479, 1371, 1252, 1197, 1177, 1154, 1093, 866; exact mass *m*/*z* calcd for $C_{23}H_{19}INaO_5S$ 556.98902, found 556.98890. Anal. calcd for $C_{23}H_{19}IO_5S$: C 51.69; H 3.58; S 6.00. Found: C 51.41; H 3.65; S 5.92%.

When the experiment was repeated on a larger scale with the dimesylate (2.1255 g, 2.94 mmol), the yield was 65% [or 80% based on recovered **38** (398.1 mg, 19%)].

Toluene-4-sulfonic acid 4-[(2*S*,3*R*)-2,3-dihydro-5-formyl-3-methylbenzofuran-2-yl]phenyl ester (39). A solution of Bu_3SnH (0.62 mL, 2.3 mmol) and AIBN (48.1 mg, 0.293 mmol) in PhMe (18 mL) was added over 4 h (syringe pump) to a stirred and heated (80 °C) solution of **38** (910.4 mg, 1.704 mmol) in PhMe (18 mL) (N_2 atmosphere). After the addition the mixture was heated for a further 2 h and then allowed to cool. Evaporation of the solvent and flash chromatography of the residue over KF–silica gel (10% w/w, 2.5 × 30 cm), using 25% EtOAc–hexane, gave **39** (482.6 mg, 69%) as a light yellowish oil: $[\alpha]_D^{22}$ −50.54 (*c* 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (d, J = 6.9 Hz, 3 H), 2.38 (s, 3 H), 3.31–3.38 (m, 1 H), 5.19 (d, J = 8.4 Hz, 1 H), 6.88 (d, J = 8.1 Hz, 1 H), 6.96 (apparent d as part of AA′BB′ system, J = 8.7 Hz, 2 H), 7.24–7.27 (m, 4 H), 7.64–7.67 (m, 4 H), 9.80 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (the spectrum shows minor aromatic impurities) δ 18.3 (q), 21.7 (q), 44.8 (d), 92.7 (d), 109.8 (d), 122.8 (d), 124.7 (d), 127.1 (d) 128.5 (d), 129.8 (d), 131.0 (s), 132.4 (s), 133.1 (s), 133.4 (d), 138.9 (s), 145.5 (s), 149.6 (s), 164.3 (s), 190.5 (d); ν_{max} ($CHCl_3$ cast; cm^{-1}) 2964, 2928, 1690, 1605, 1504, 1483, 1373, 1247, 1198, 1177, 1154, 1093, 867; exact mass *m*/*z* calcd for $C_{23}H_{20}NaO_5S$ 431.09237, found 431.09242.

Toluene-4-sulfonic acid 4-[(2*R*,3*S*)-2,3-dihydro-(3-methyl-5-(1*E*)-1-propenylbenzofuran-2-yl)phenyl ester (*E*-43) and toluene-4-sulfonic acid 4-[(2*R*,3*S*)-2,3-dihydro-3-methyl-5-(1*Z*)-1-propenyl-benzofuran-2-yl]phenyl ester (*Z*-43).

(a) Use of t-*BuOK.* *t*-BuOK (33.0 mg, 0.294 mmol) was added to a stirred suspension of $Ph_3PEt^+I^-$ (129.6 mg, 0.3098 mmol) in Et_2O (2 mL), and the mixture was stirred for 0.5 h. A solution of **39** (54.2 mg, 0.133 mmol) in Et_2O (1 mL) was added by syringe. The mixture was stirred for 15 min and then Et_2O (5 mL) was added, and the mixture was washed twice with water and once with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 30 cm), using 5–10% EtOAc–hexane (gradient elution), gave **43** (33.9 mg, 62%) as a yellowish oil. Integration of the allylic methyl peaks in the ^{1}H NMR spectrum showed the *E* : *Z* ratio to be 1 : 3; apart from this ratio difference, all spectral data corresponded to those reported above for **37** (*i.e.* the 97 : 3 mixture of the same compounds).

(b) Use of BuLi. BuLi (1.6 M in hexanes, 0.06 mL, 0.096 mmol) was added to a stirred and cooled (0 °C) suspension of $Ph_3PEt^+I^-$ (39.5 mg, 0.0944 mmol) in THF (2 mL). Stirring was continued for 15 min and **39** (35.7 mg, 0.0796 mmol) in THF (1.3 mL plus 0.3 mL as a rinse) was added dropwise by syringe. Stirring was continued for 2 h and the mixture was then quenched by addition of saturated aqueous $NaHCO_3$ (0.5 mL), and partitioned between water (5 mL) and Et_2O (10 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 30 cm), using 20% EtOAc–hexane containing *ca.* 1% Et_3N, gave **43** (23.2 mg, 69%) as a yellowish oil, which was a mixture of *Z* and *E* isomers.

Toluene-4-sulfonic acid 4-[(2*R*,3*S*)-2,3-dihydro-3-methyl-5-(1*E*)-1-propenylbenzofuran-2-yl]phenyl ester (37). $PdCl_2(PhCN)_2$ (9.4 mg, 0.025 mmol) was added to a stirred solution of **43**

(102.3 mg, 0.2433 mmol) in CH_2Cl_2 (2 mL), and stirring was continued for 23 h. Et_2O (3 mL) was added and the solution was filtered through a pad of Florisil (3 × 2 cm) using Et_2O (25 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 30 cm) using 8% EtOAc–hexane containing Et_3N (*ca.* 3 drops per 100 mL), gave **37** (100.9 mg, 99%) as a colorless oil: $[\alpha]_D^{22}$ −54.15 (*c* 5.94, CH_2Cl_2). The material contained 3.1% of the *Z* isomer (^{1}H NMR).

Isomerization with 10-day reaction time. $PdCl_2(PhCN)_2$ (5.3 mg, 0.0138 mmol) was added to a stirred solution of **43** (36.0 mg, 0.0856 mmol) in CH_2Cl_2 (2 mL), and stirring was continued for 10 days. The solution was filtered through a pad of Florisil (1 × 1 cm), using CH_2Cl_2 as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 × 30 cm), using 13% EtOAc–hexane containing Et_3N (*ca.* 3 drops per 100 mL), gave **37** (30.5 mg, 85%) as a colorless oil with spectral data identical to those reported above for the first route, except that the *Z* isomer could not be detected in the ^{1}H NMR spectrum (400 MHz).

4-[(2*R*,3*R*)-2,3-dihydro-3-methyl-5-(1*E*)-1-propenylbenzofuran-2-yl]phenol [(+)-conocarpan] (1). Desulfonylation was done by the same method as described for the first route: $[\alpha]_D$ −46.5 (*c* 0.28, MeOH). HPLC analysis of the synthetic conocarpan [Chiralcel OD column (0.46 × 15.0 cm); 90 : 10 heptane–isopropanol; flow rate 0.6 mL min^{-1}; 40 °C; detection at 210 nm.; retention times 10.69 min and 12.60 min] showed that the compound had an ee of 88%.

Proof of absolute configuration

Toluene-4-sulfonic acid 4-[(*S*)-1-hydroxyallyl]phenyl ester (45). NaI (2.42 g, 16.1 mmol) was added to a stirred solution of **44** (total product from previous experiment, *ca.* 1.6 mmol) in glyme (8 mL). The vessel was flushed with Ar and the mixture was refluxed for 12 h, and then allowed to cool. The mixture was diluted with EtOAc (10 mL), washed with saturated aqueous $Na_2S_2O_3$ (8 mL), water (8 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 30 cm), using 27% EtOAc–hexanes containing a trace (0.4–1% v/v) of Et_3N, gave **45** (279.8 mg, 57% over 2 steps from the hydroxy epoxide) as a colorless oil: $[\alpha]_D^{22}$ +4.63 (*c* 0.57, $CHCl_3$); ^{1}H NMR (C_6D_6, 300 MHz) δ 1.10 (d, J = 3.7 Hz, 1 H), 1.74 (s, 3 H), 4.62–4.65 (m, 1 H), 4.86 (dt, J = 1.5, 10.3 Hz, 1 H), 5.03 (dt, J = 1.5, 17.1 Hz, 1 H), 5.64 (ddd, J = 5.9, 10.3, 17.1 Hz, 1 H), 6.57 (apparent d as part of AA′BB′ system, J = 8.3 Hz, 2 H), 6.92–6.98 (m, 4 H), 7.63 (apparent d as part of AA′BB′ system, J = 8.3 Hz, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) (two signals coincident) δ 21.2 (q), 74.4 (d), 114.7 (t), 122.6 (d), 128.7 (d), 129.8 (d), 133.4 (s), 140.5 (d), 142.3 (s), 144.9 (s), 149.5 (s); ν_{max} ($CHCl_3$ cast; cm^{-1}) 3533, 3400, 3068, 2981, 2924, 2872, 1597, 1500, 1402, 1371, 1197, 1175, 1154, 1093, 867; exact mass *m*/*z* calcd for $C_{16}H_{16}NaO_4S$ 327.06615, found 327.06657.

Attempts to prepare the Mosher ester by a literature method[53] gave material that had clearly undergone extensive epimerization during the derivatization, as the ratio of diastereoisomers was 2.3 : 0.95 (^{1}H NMR), while the parent epoxide had an er of 98.9 : 1.1. We were unable to separate the corresponding racemic alcohol by chiral HPLC.

Toluene-4-sulfonic acid 4-[(*S*)-1-(*tert*-butyldimethylsilanyloxy)-propyl]phenyl ester (47). Rh–Al_2O_3 (5% w/w, 9.7 mg, 0.0047 mmol) was added to a solution of **46** (30.3 mg, 0.0724 mmol) in THF (1.8 mL). The mixture was stirred and degassed by sequentially evacuating the flask (house vacuum) and then admitting H_2, this sequence being repeated twice more. The mixture was stirred overnight under H_2 (balloon) and then filtered through a short pad (0.5 × 1 cm) of silica gel, using CH_2Cl_2 as a rinse. Evaporation of the filtrate gave **47** (30.3 mg, 99%) as a colorless oil: $[\alpha]_D^{22}$ −26.43 (*c* 3.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 3 H), 0.18 (s, 3 H), 1.00 (t, J = 7.2 Hz, 3 H), 1.03 (s, 9 H), 1.72–1.88 (m, 2 H), 2.61 (s, 3 H), 4.70 (apparent t, J = 5.5 Hz, 1 H), 7.08 (apparent d as part of AA′BB′ system, J = 8.6 Hz, 2 H), 7.36 (apparent d as part of AA′BB′ system, J = 8.7 Hz, 2 H), 7.45 (apparent d as part of AA′BB′ system, J = 8.6 Hz, 2 H), 7.84 (apparent d as part of AA′BB′ system, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.0 (q), −4.7 (q), 9.8 (q), 18.2 (s), 21.7 (q), 25.8 (q), 33.5 (t), 75.5 (d), 121.9 (d), 127.0 (d), 128.5 (d), 129.6 (d), 132.3 (s), 144.7 (s), 145.2 (s), 148.3 (s); ν_{max} ($CHCl_3$ cast; cm^{-1}) 3034, 2957, 2929, 2857, 1598, 1501, 1472, 1463, 1378, 1257, 1198, 1175, 1155, 1094, 1060, 1014; exact mass *m*/*z* calcd for $C_{22}H_{32}NaO_4SSi$ 443.16828, found 443.16826.

4-[(*S*)-1-(*tert*-Butyldimethylsilanyloxy)propyl]phenol (48). Na-(Hg) (815.0 mg, 10% Na, 3.543 mmol) was added to a stirred, cloudy solution of **47** (316.4 mg, 0.7444 mmol) in 80% MeOH (5.4 mL). The flask was flushed with Ar and stirring was continued for 45 min to give a clear, colorless solution. The mixture was then decanted from the remaining amalgam into a separatory funnel containing phosphate buffer solution (KH_2PO_4–NaOH, pH 7, 8 mL) and Et_2O (8 mL). Saturated aqueous oxalic acid (2 mL) was then added and the biphasic mixture was shaken and separated. The aqueous layer was extracted with Et_2O (2 × 6 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 25 cm), using 0–20% EtOAc–hexanes (gradient elution), gave **48** as a colorless oil (119.3 mg, 60%) and recovered **47** (102.3 mg, 32%). Phenol **48** had: $[\alpha]_D^{22}$ −19.32 (*c* 1.41, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) (phenolic OH not observed) δ −0.09 (s, 3 H), 0.05 (s, 3 H), 0.87 (t, J = 6.7 Hz, 3 H), 1.06 (s, 9 H), 1.66–1.88 (m, 2 H), 4.54 (dd, J = 5.5, 7.1 Hz, 1 H), 6.62 (apparent d as part of AA′BB′ system, J = 8.8 Hz, 2 H), 7.19 (apparent dd as part of AA′BB′ system, J = 0.6, 8.6 Hz, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) δ −4.8 (q), −4.4 (q), 10.3 (q), 18.4 (s), 26.1 (q), 34.1 (t), 76.5 (d), 115.1 (d), 127.4 (d), 137.7 (s), 155.4 (s); ν_{max} ($CHCl_3$ cast; cm^{-1}) 3349, 3024, 2958, 2930, 2858, 1614, 1600, 1514, 1472, 1463, 1361, 1252, 1059, 836; exact mass *m*/*z* calcd for $C_{15}H_{26}NaO_2Si$ 289.15943, found 289.15935.

Trifluoromethanesulfonic acid 4-[(*S*)-1-(*tert*-butyldimethylsilanyloxy)propyl]phenyl ester (49). $(CF_3SO_2)_2O$ (0.07 mL, 0.4 mmol) was added dropwise by syringe to a stirred and cooled (−78 °C) solution of **48** (99.9 mg, 0.375 mmol) and Et_3N (0.09 mL, 0.6 mmol) in CH_2Cl_2 (1.8 mL) (Ar atmosphere). Stirring was continued for 10 min and then saturated aqueous $NaHCO_3$ (0.5 mL) was added. The cooling bath was removed and the mixture was poured into a separatory funnel containing water (5 mL) and CH_2Cl_2 (5 mL). The mixture was shaken and the organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using

13% EtOAc–hexanes containing a trace (0.5–1% v/v) of Et_3N, gave **49** (111.6 mg, 75%) as a colorless oil: $[\alpha]_D^{22}$ −21.08 (*c* 0.48, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz) δ 0.00 (s, 3 H), 0.18 (s 3 H), 0.95 (t, J = 7.4 Hz, 3 H), 1.12 (s, 9 H), 1.57–1.77 (m, 2 H), 4.54 (dd, J = 5.1, 6.9 Hz, 1 H), 7.04 (apparent d as part of AA′BB′ system, J = 8.7 Hz, 2 H), 7.18 (apparent dd as part of AA′BB′ system, J = 0.5, 8.9 Hz, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) δ −5.0 (q), −4.7 (q), 9.7 (q), 18.3 (s), 25.9 (q), 33.6 (t), 75.4 (d), 119.3 (s, CF_3 quartet, J = 318.6 Hz), 121.0 (d), 127.7 (d), 146.1 (s), 148.6 (s); ν_{max} ($CHCl_3$ cast; cm^{-1}) 2959, 2932, 2859, 1500, 1427, 1251, 1214, 1143, 890, 861, 837; exact mass m/z calcd for $C_{16}H_{25}F_3NaO_4SSi$ 421.10872, found 421.10906.

(*S*)-*tert*-Butyldimethyl(1-phenylpropoxy)silane (50). Pd/C (10% w/w, 60.8 mg, 0.0571 mmol) was added to a solution of **49** (99.0 mg, 0.248 mmol) and Et_3N (0.11 mL, 0.79 mmol) in EtOAc (5 mL). The stirred mixture was degassed by sequentially evacuating the flask (house vacuum) and then admitting H_2, the procedure being repeated twice more. A hydrogen-filled balloon was then connected to the flask and stirring was continued for 3 h. The heterogeneous mixture was filtered through a short pad (0.5 × 1.0 cm) of silica gel, using EtOAc as a rinse. Evaporation of the solvent gave **50** (62.6 mg, 100%) as a yellowish oil: $[\alpha]_D^{22}$ −32.21 (*c* 0.66, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz) δ −0.10 (s, 3 H), 0.04 (s, 3 H), 0.87 (t, J = 7.3 Hz, 3 H), 0.97 (s, 9 H), 1.58–1.79 (m, 2 H), 4.51 (dd, J = 5.2, 7.0 Hz, 1 H), 7.07 (tt, J = 1.3, 6.7 Hz, 1 H), 7.16–7.19 (m, 2 H), 7.26–7.28 (m, 2 H); ^{13}C NMR (C_6D_6, 100 MHz) δ −4.8 (q), −4.5 (q), 10.2 (q), 18.4 (s), 26.1 (q), 34.0 (t), 76.7 (d), 126.2 (d), 127.2 (d), 128.3 (d), 145.8 (s); ν_{max} ($CHCl_3$ cast; cm^{-1}) 3065, 3028, 2958, 2930, 2858, 1493, 1472, 1463, 1453, 1361, 1257, 1104, 1086, 1058, 1013, 860, 837, 775, 699; exact mass m/z calcd for $C_{15}H_{26}NaOSi$ 273.16451, found 273.16448.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

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