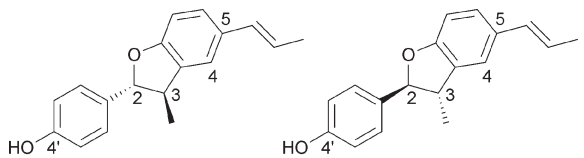
Total synthesis of (−)-conocarpan and assignment of the absolute configuration by chemical methods†

Derrick L. J. Clive* and Elia J. L. Stoffman

Received (in Cambridge, UK) 20th March 2007, Accepted 19th April 2007
First published as an Advance Article on the web 1st May 2007
DOI: 10.1039/b704211f

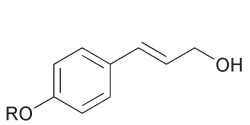
(−)-Conocarpan (1) was synthesized by a method based on radical cyclization, and the absolute configuration was established by chemical degradation; the original 2*R*,3*R*-assignment to (+)-conocarpan should be reversed, as suggested by a later chiroptical study of model 2,3-dihydrobenzofurans.

A neolignan[1,2] called (+)-conocarpan,[3] and assigned the structure and absolute stereochemistry **1**, was first isolated[3] from timber used for underwater construction, the purpose of the investigation being to identify substances that made the wood resistant to attack by a variety of marine organisms. The compound has also been extracted from a number of other plant sources.[2,4–6]

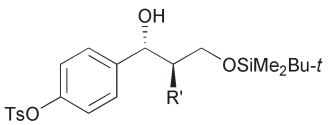


Conocarpan is toxic to mosquito larvae,[4g,4f] although the relevance of this property to malaria control[7] has not been established, and it shows antitrypanosomal, antibacterial, antifungal and photoprotective activity.[8] The 2*R*,3*R* configuration (**1**) was assigned[3] by comparing the CD curve of conocarpan acetate with CD curves of reference compounds having more highly oxygenated aromatic rings; however, a later chiroptical study of 2,3-dihydrobenzofurans fused to the steroid nucleous[9] indicated that this assignment should be reversed (as in **2**).

Racemic conocarpan is readily available by biomimetic oxidation[3] or by manganese(III)-mediated radical cyclization,[10] but preparation of a single enantiomer is a much more complex task because of the fragility of the C(2)–O bond that is part of the *para*-oxygenated benzylic subunit, and the fact that Sharpless asymmetric epoxidation—a potentially ideal method for setting the C(2) absolute stereochemistry—does not work well[11,13] (see below) for compounds of type **3** having an electron-releasing *para*-oxygen substituent.[15] We have also found that benzylic alcohols of type **4**, available by Evans asymmetric aldol condensation, are unsatisfactory substrates for displacement with 4-[(*t*-butyldimethylsilyl) oxy]phenol, after activation of the benzylic hydroxyl in **3** under Mitsunobu conditions, or by triflation or mesylation; the yield was low (*ca.* 40%), or extensive (*ca.* 25%) stereochemical scrambling occured.



3 R = Me, *t*-BuMe$_2$Si



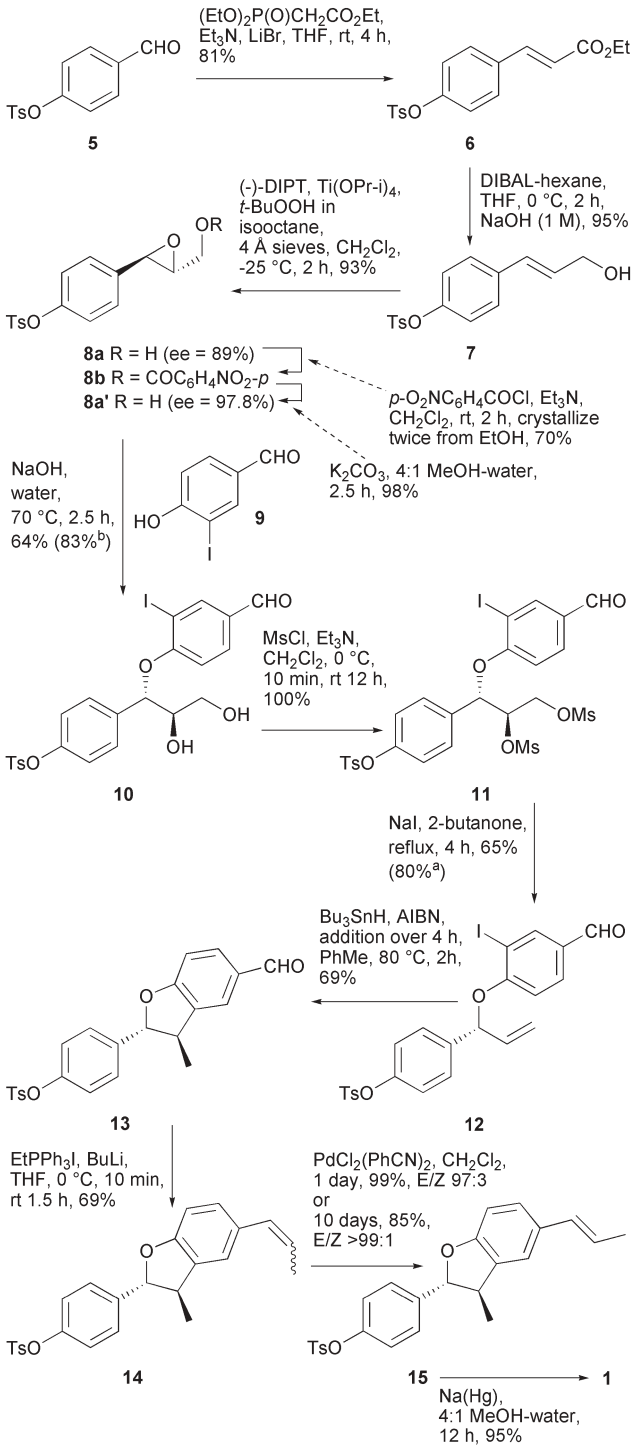
4 R' = Me, CH_2SiPh_2Bu-*t*, vinyl

We report a route that gives optically active (−)-conocarpan (ee 88%)[16] and we prove that the absolute configuration of natural (+)-conocarpan[2,3,4a,6] is 2*S*,3*S* (**2**).

p-Tosyloxybenzaldehyde (**5**)[17] was homologated by Horner–Emmons–Wadsworth olefination (**5** → **6**) and reduced to allylic alcohol **7**, which was then subjected to Sharpless asymmetric epoxidation[12] (**7** → **8a**, 93%, er 94.5 : 5.5[18]). Enantiomeric enrichment *via* crystallization (3 times) of the derived *p*-nitrobenzoate from EtOH gave epoxide **8a′** with an er of 98.9 : 1.1.[18] Epoxide opening under basic conditions with the sodium salt of iodophenol **9**[19] produced diol **10** [64%, or 83% after correction for recovered **8a′** (23%)],[20,21] and the diol segment was then converted into an olefin (**10** → **11** → **12**) by mesylation (100%) and treatment with NaI in refluxing 2-butanone [65%, or 80% corrected for recovered dimesylate (19%)]. At this point, radical cyclization under standard conditions (slow addition of stannane, AIBN, PhMe, 80 °C) gave **13** (69%) with little, if any, of the corresponding *cis* isomer being formed. The Wittig reaction with $Ph_3PEt^+I^-$/*t*-BuLi then afforded a *Z* : *E* mixture of alkenes **14**. Equilibration, mediated by $PdCl_2(MeCN)_2$ (24 h),[22] generated in near quantitative yield material that was largely the *E* isomer (*E* : *Z* = 96.9 : 3.1), but this ratio could be improved by prolonged exposure (10 days) to the catalyst and, under these conditions (85% yield), no *Z* isomer could be detected (^{1}H NMR, 400 MHz). Finally, the tosyl group was removed (95%) by reaction with Na(Hg) to release (−)-conocarpan, mp 120–123 °C [lit.[4a] 133–135 °C; lit.[4g] 124–126 °C], $[\alpha]_D$ −82.2 (*c* 1.4 MeOH) [lit.[4a] 122 (*c* 1.03 MeOH)].[4a,23] Examination of our synthetic material by chiral HPLC[16] showed that it had an ee of 88% (*i.e.* enantiomeric ratio = 94 : 6). We did not establish the stage at which the enantiomeric ratio was eroded from 99 : 1 (for **8a′**) to 94 : 6 (for **1**), but suspect that the allylic-benzylic ether **12** is involved as, in the earlier steps, scrambling at the benzylic position would lead to diastereoisomers—which were not observed.[24]

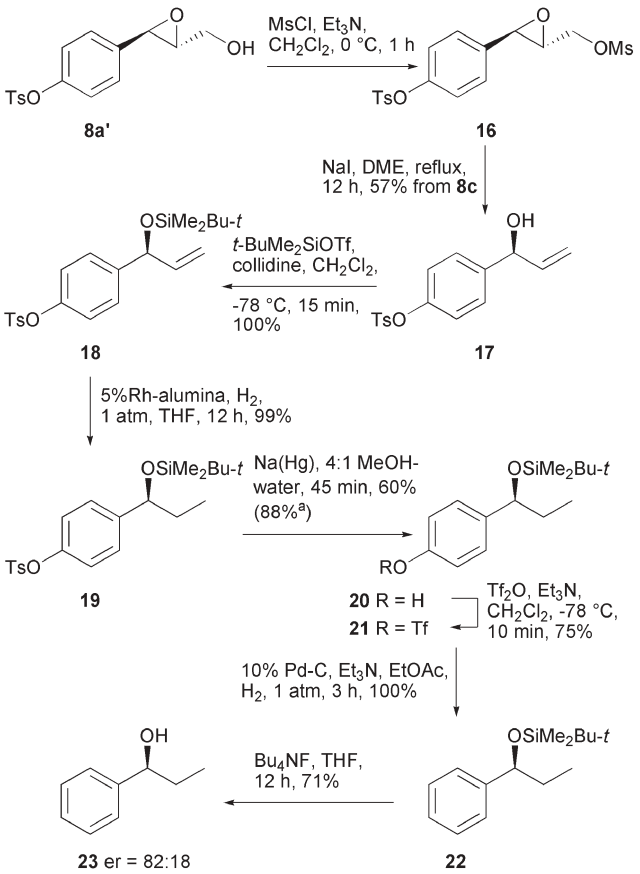
We were unable to obtain satisfactory crystals of a heavy atom derivative of conocarpan or of **8a′**, and so the fact that our synthetic material appeared to be (and, in the event, is) the enantiomer of the *dextrorotatory* natural product caused us to check the absolute stereochemistry of the key epoxide **8a′**. We

Chemistry Department, University of Alberta, Edmonton, Alberta, Canada T6G 2G2. E-mail: derrick.clive@ualberta.ca
† Electronic supplementary information (ESI) available: Experimental and characterization data. See DOI: 10.1039/b704211f



Scheme 1 [a]Corrected for recovered **11** (19%). [b]Corrected for recovered **8a′** (23%).

could find no example in the literature—with proof of the stereochemical outcome—of Sharpless asymmetric epoxidation of a styrene derivative having a *para* oxygen substituent,[15] and so we checked that our substrate **7** behaves in the expected manner during the epoxidation.[14,25] Accordingly, optically active **8a′** was converted into alcohol **17** [$[\alpha]^{22}_{D}$ +4.63 (*c* 0.57, $CHCl_3$)] (Scheme 2) by successive treatment with MsCl/Et_3N and NaI[26] in refluxing DME. The hydroxyl group of **17** was silylated



Scheme 2 [a]Corrected for recovered **19** (23%).

(*t*-$BuMe_2SiOSO_2CF_3$, *S*-collidine, 100%) and the double bond was saturated (H_2, Rh-Al_2O_3, THF, 100%) to afford **19**. Then the tosyl group was removed [**19** → **20**, Na(Hg), MeOH, 60% or 88% after correction for recovered **19** (23%)]. Triflation of the phenolic hydroxyl (**20** → **21**) and hydrogenolysis[27] (H_2, Pd–C, Et_3N, EtOAc, 100%) gave **22**. Finally, desilylation afforded **23** having $[\alpha]_D$ −29.3 (*c* 1.23, $CHCl_3$) [lit.[28] −45.6 (*c* 1.3, $CHCl_3$)], corresponding to an er of 82 : 18. We did not identify the point at which there is erosion of optical purity; our starting epoxide **8a′** had an er of 98.1 : 1.1. The absolute stereochemistry of levorotatory **23** has been established unambiguously,[28,29] and so the experiments summarized in Scheme 2 establish that the stereochemical course of the asymmetric epoxidation (**7** → **8a**) proceeds in the desired sense; consequently, natural (+)-conocarpan must have the absolute stereochemistry shown in **2**, as indicated by the chiroptical study of Antus *et al.*[9] The absolute stereochemistry of (+)-conocarpan has been related to another natural product[30] by chemical interconversion; consequently that assignment should also be reversed, as should the configuration of natural (−)-conocarpan.[5]

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

Notes and references

1 O. R. Gottlieb, *Phytochemistry*, 1972, **11**, 1537–1570 especially p 1546.
2 P. Sartorelli, P. J. C. Benevides, R. M. Ellensohn, M. V. A. F. Rocha, P. R. H. Moreno and M. J. Kato, *Plant Sci.*, 2001, **161**, 1083–1088.
3 T. Hayashi and R. H. Thomson, *Phytochemistry*, 1975, **14**, 1085–1087.

4 *E.g.* (*a*) H. Achenbach, J. Gross, X. A. Dominguez, G. Cano, J. V. Star, L. D. C. Brussolo, G. Muñoz, F. Salgado and L. López, *Phytochemistry*, 1987, **26**, 1159–1166; (*b*) X. A. Dominiguez, C. Rombold, J. V. Star, H. Achenbach and J. Gross, *Phytochemistry*, 1987, **26**, 1821–1823; (*c*) A. Arnone, V. Di Modugno, G. Nasini and I. Venturini, *Gazz. Chim. Ital.*, 1988, **118**, 675–682; (*d*) H. Achenbach, W. Utz and X. A. Dominguez, *Phytochemistry*, 1993, **34**, 835–837; (*e*) A. M. Rimando, J. M. Pezzuto, N. R. Farnsworth, T. Santisuk and V. Reutrakul, *Nat. Prod. Lett.*, 1994, **4**, 267–272; (*f*) C. B. Bernard, H. G. Krishnamurty, D. Chauret, T. Durst, B. J. R. Philogène, P. Sánchez-Vindas, C. Hasbun, L. Poveda, L. San Roman and J. T. Arnason, *J. Chem. Ecol.*, 1995, **21**, 801–814; (*g*) D. C. Chauret, C. B. Bernard, J. T. Arnason and T. Durst, *J. Nat. Prod.*, 1996, **59**, 152–155; (*h*) H. Achenbach, W. Utz, B. Lozano, E. M. G. Touché and S. Moreno, *Phytochemistry*, 1996, **43**, 1093–1095; (*i*) Nguyen Hoang Anh, H. Ripperger, Tran Van Sung and G. Adam, *Phytochemistry*, 1996, **42**, 1167–1169; (*j*) Nguyen Hoang Anh, H. Ripperger, A. Porzel, Tran Van Sung and G. Adam, *Phytochemistry*, 1997, **46**, 569–571; (*k*) P. J. C. Benevides, P. Sartorelli and M. J. Kato, *Phytochemistry*, 1999, **52**, 339–343; (*l*) S. A. S. Silva, J. C. M. De Castro, T. G. Da Silva, E. V. L. Da-Cunha, J. M. Barbosa-Filho and M. S. Da Silva, *Nat. Prod. Lett.*, 2001, **15**, 323–329.

5 Levorotatory conocarpan: (*a*) B. Freixa, R. Vila, E. A. Ferro, T. Adzet and S. Cañigueral, *Planta Med.*, 2001, **67**, 873–875; (*b*) M. R. G. Vega, M. G. de Carvalho, J. R. Velandia and R. Braz-Filho, *Rev. Latinoam. Quim.*, 2001, **29**, 63–72.

6 Conocarpan isolated from the leaves of *Piper regnelli* (ref. 2); the roots of *Krameria cystisoides* (ref. 4*a*), *Krameria tomentosa* (ref. 4*l*) and *Krameria triandra* (ref. 4*c*); and the stems of *Anorgeissus acuminata* (ref. 4*e*) is reported to be dextrorotatory; our own synthetic material, of proven absolute configuration **1**, is levorotatory and the CD curve of its acetate has negative $\Delta\varepsilon$ at 260 nm. The acetate of conocarpan isolated from timber (ref. 3) is reported to have positive $\Delta\varepsilon$ at 260 nm and so the parent conocarpan must be dextrorotatory. Consequently all these plant sources afford material of the same absolute configuration. With the following exception, other references to conocarpan that we have examined do not give the specific rotation. Conocarpan isolated from the leaves of *Piper fulvescens C*. DC (ref. 5) is reported to have $[\alpha]^{21}{}_{D} = -108.26$.

7 R. P. Tripathi, R. C. Mishra, N. Dwivedi, N. Tewari and S. S. Verma, *Curr. Med. Chem.*, 2005, **12**, 2643–2659 and references therein.

8 (*a*) Antitrypanosomal activity: P. S. Luize, T. Ueda-Nakamura, B. P. D. Filho, D. A. G. Cortez and C. V. Nakamura, *Biol. Pharm. Bull.*, 2006, **29**, 2126–2130; (*b*) antibacterial activity: G. L. Pessini, B. P. D. Filho, C. V. Nakamura and D. A. G. Cortez, *Mem. Inst. Oswaldo Cruz*, 2003, **98**, 1115–1120; (*c*) photoprotective activity: M. Carini, G. Aldini, M. Orioli and R. M. Facino, *Planta Med.*, 2002, **68**, 193–197; (*d*) antifungal activity: M. P. De Campos, C. V. Filho, R. Z. Da Silva, R. A. Yunes, S. Zacchino, S. Juarez, R. C. Bella Cruz and A. Bella Cruz, *Biol. Pharm. Bull.*, 2005, **28**, 1527–1530; (*e*) G. L. Pessini, B. P. D. Philo, C. V. Nakamura and D. A. G. Cortez, *J. Braz. Chem. Soc.*, 2005, **16**, 1130–1133.

9 T. Kurtán, E. Baitz-Gács, Z. Majer and S. Antus, *J. Chem. Soc., Perkin Trans. 1*, 2000, 453–461.

10 B. B. Snider, L. Han and C. Xie, *J. Org. Chem.*, 1997, **62**, 6978–6984.

11 When we tried the standard catalytic epoxidation (ref. 12) we observed very little, if any, reaction with **2** (R = Me or *t*-BuMe$_2$Si).

12 (*a*) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune and K. B. Sharpless, *J. Am. Chem. Soc.*, 1987, **109**, 5765–5780; (*b*) We used (−)-diisopropyl tartrate and checked that the material so-labeled was indeed levorotatory.

13 See also: (*a*) ref. 14, page 19; (*b*) M. G. Finn and K. B. Sharpless, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, Orlando, 1985, vol. 5, pp 247–308, especially pp 287–288.

14 T. Katsuki and V. S. Martin, *Org. React.*, 1996, **48**, 1–299.

15 We can find only one example of Sharpless epoxidation of a styrene derivative with a *para*-oxygen substituent (and no additional substituents) on the benzene ring, but it is a kinetic and not a preparative experiment: S. S. Woodard, M. G. Finn and K. B. Sharpless, *J. Am. Chem. Soc.*, 1991, **113**, 106–113.

16 Determined by chiral HPLC: 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.

17 P. C.-M. Mao, J.-F. Mouscadet, H. Leh, C. Auclair and L.-Y. Hsu, *Chem. Pharm. Bull.*, 2002, **50**, 1634–1637.

18 Determined 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.

19 Y. M. Choi-Sledeski, D. G. McGarry, D. M. Green, H. J. Mason, M. R. Becker, R. S. Davis, W. R. Ewing, W. P. Dankulich, V. E. Manetta, R. L. Morris, A. P. Spada, D. L. Cheney, K. D. Brown, D. J. Colussi, V. Chu, C. L. Heran, R. S. Morgan, R. G. Bentley, R. J. Leadley, S. Maignan, J.-P. Guiloteau, C. T. Dunwiddie and H. W. Pauls, *J. Med. Chem.*, 1999, **42**, 3572–3587.

20 Opening of related epoxides with phenols did not work in non-aqueous solvents, and diastereoselection in acidic organic solvents was poor; no epoxide opening occurred in basic organic media.

21 Cf H. Tanaka, I. Kato and K. Ito, *Chem. Pharm. Bull.*, 1987, **35**, 3603–3608.

22 J. Yu, M. J. Gaunt and J. B. Spencer, *J. Org. Chem.*, 2002, **67**, 4627–4629.

23 The ^{1}H and ^{13}C NMR data for our sample matched the values reported in ref. 4*g*, 4*l* and 4*c* extremely closely, but showed some differences from the values reported in ref. 4*a*.

24 For a related, and sensitive, para-alkoxy allylic carbonate, see compound (*R*)-**6** in: P. A. Evans and D. K. Leahy, *J. Am. Chem. Soc.*, 2003, **125**, 8974–8975.

25 T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974–5976.

26 Normally, Zn would be required to react with the intermediate iodo epoxide formed from the mesylate. Direct conversion of an iodo epoxide to an allylic alcohol by iodide ion has been suggested in a mechanistic scheme: J. Barluenga, J. L. Fernandez-Simon, J. M. Concellion and M. Yus, *J. Chem. Soc., Perkin Trans. 1*, 1989, 77–80.

27 A. P. Kozokowski, W. Tückmantel and C. George, *J. Org. Chem.*, 2000, **65**, 5371–5381.

28 Optical rotation: A. Kamal, M. Sandbhor and K. V. Ramana, *Tetrahedron: Asymmetry*, 2002, **13**, 815–820.

29 Levorotatory material corresponds to an *S* configuration: R. MacLeod, F. J. Welch and H. S. Mosher, *J. Am. Chem. Soc.*, 1960, **82**, 876–880.

30 H. Achenbach, W. Utz, A. Usubillaga and H. A. Rodriguez, *Phytochemistry*, 1991, **30**, 3753–3757.