Pergamon

Tetrahedron 56 (2000) 9181–9193

TETRAHEDRON

Stereoselective Synthesis of 8,9-Licarinediols

Isabele R. Nascimento,[a] Lucia M. X. Lopes,[a] Laurence B. Davin[b] and Norman G. Lewis[b,*]

[a]*Instituto de Química, Universidade Estadual Paulista, Unesp, C.P.355, 14800-900, Araraquara, São Paulo, Brazil*
[b]*Institute of Biological Chemistry, Washington State University, 467 Clark Hall, Pullman, WA 99164-6340, USA*

Received 7 June 2000; revised 20 September 2000; accepted 21 September 2000

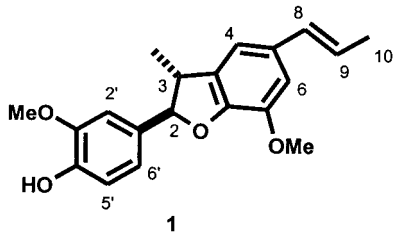
Abstract—The total synthesis of 8,9-licarinediols was selectively carried out from licarin A, previously obtained by oxidative coupling of (*E*)-isoeugenol. The corresponding enantiomerically pure (+)- and (−)-licarin A ester derivatives were subjected to Sharpless oxidation to yield the asymmetric C-8, C-9 dihydroxylation products, whose absolute configurations were established by means of the CD and NMR spectroscopic analyses of their Mosher ester derivatives.

Introduction

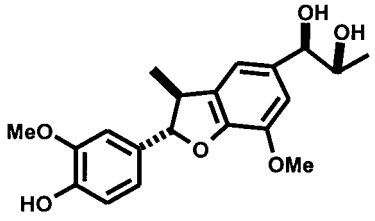
Recently we reported the isolation from *Aristolochia pubescens* of (+)-licarin A (**1**) and the two diols (**2**) and (**3**), the latter two being possible biosynthetic derivatives from (−)-licarin A (**4**), together with several other lignans and nor-lignans.[1] We had suggested by using both NMR spectroscopic techniques and MTPA derivatization that diols **2** and **3a** had opposite absolute configurations at C-8. In this study, in order to unambiguously establish their structures, each was synthesized from (±)-licarin A (**1**+**4**), using the method described by Chioccara et al.,[2] followed by Sharpless oxidation.[3] Note, however, that the absolute configurations of the naturally occurring diols (**2**) and (**3a**) at their C-2 and C-3 centers were established previously as being 2*S*, 3*S* by chemical transformation into well-known compounds, such as (−)-kadsurenin.[1]

Results and Discussion

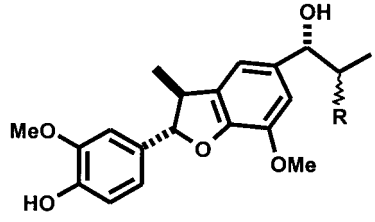
(+)-Licarin A (**1**) and (−)-licarin A (**4**) were regio- and diastereo-selectively synthesised (Scheme 1) by oxidative coupling of (*E*)-isoeugenol (**9**),[2] which in turn was obtained by the stepwise reduction of coniferyl aldehyde (**5**). The reduction of the intermediate mesyl alcohol derivative **7** was more selective than the corresponding tosylate **11**, since the latter mainly gave the C-7, C-8 reduced product **12**. Additionally, by dissolving (*E*)-isoeugenol (**9**) in MeOH, rather than in MeOH-buffer solution as described by Chioccara et al.,[2] the yield of (±)-licarin A (**1**+**4**) was significantly improved (>99%). (±)-Licarin A (**1**+**4**) was further transformed into the (*S*)-MTPA derivatives



1

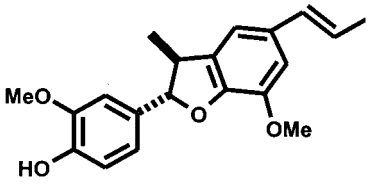


2



3a, R = ▬ OH

b, R = ▪▪▪ OH

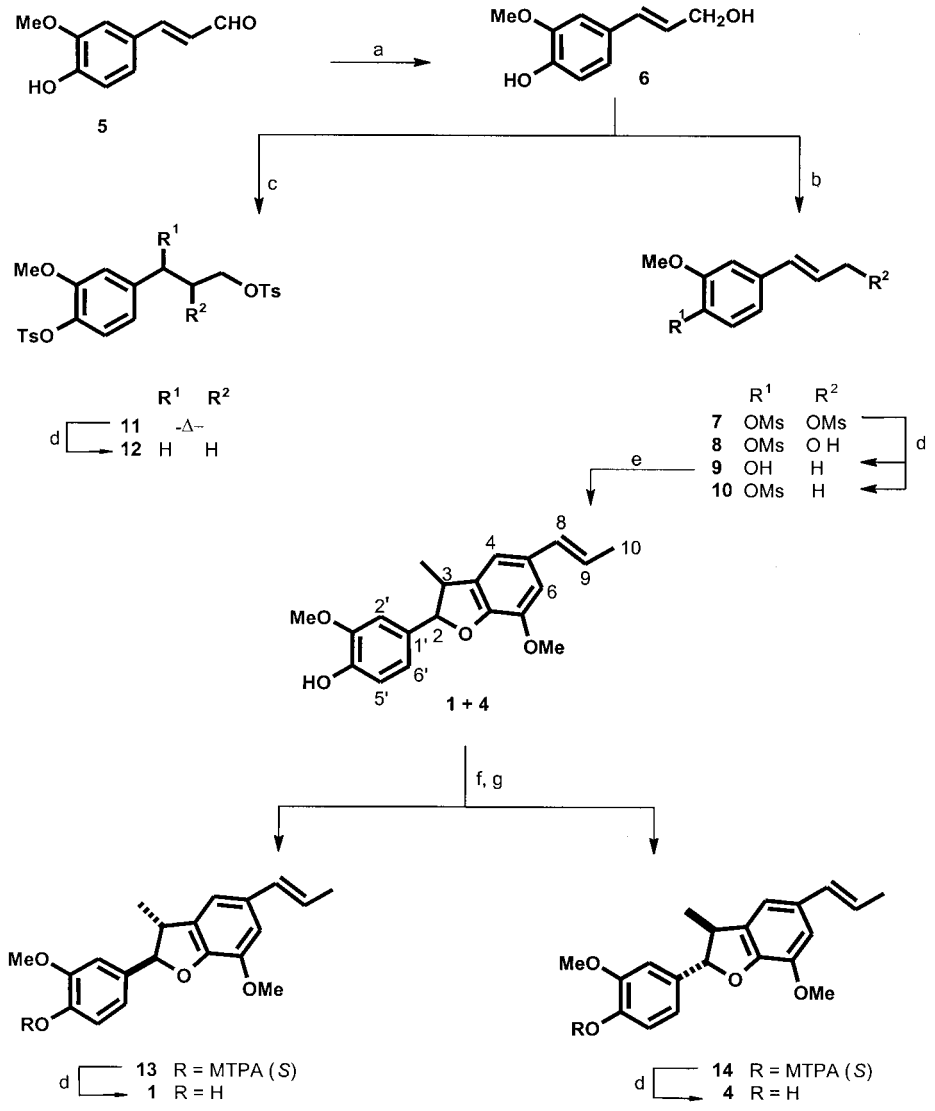


4

Keywords: licarinediols; 2,3-dihydrobenzofuran lignans ligans; licarin A; synthesis; chiral separations; Mosher esters.

* Corresponding author. Tel.: +509-335-8382; fax: +509-335-8206; e-mail: lewisn@wsu.edu

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00873-5

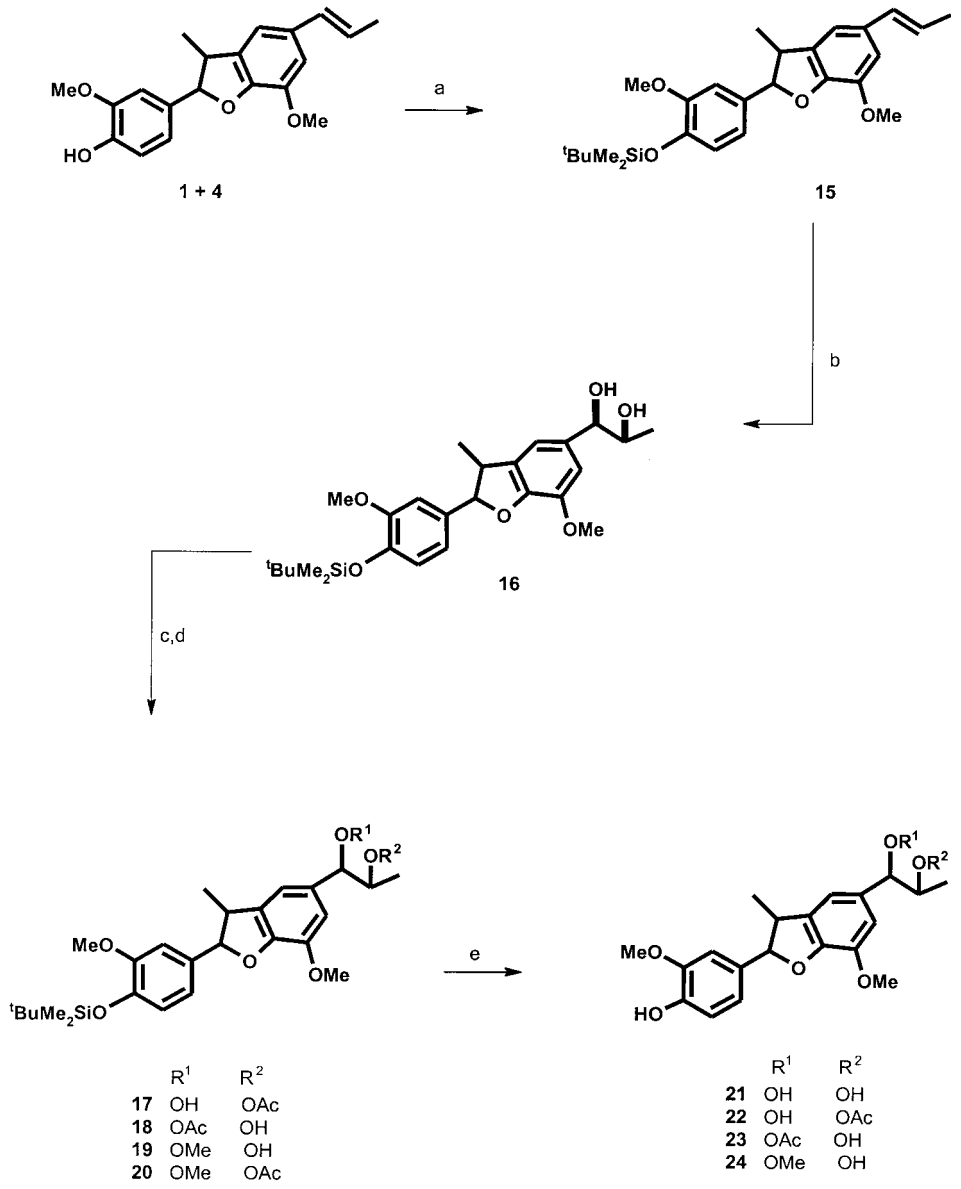


Scheme 1. Synthesis of (+)- and (−)-licarin A (**1**) and (**4**). *Reagents and conditions*: (a) $NaBH_4$, EtOH; (b) MsCl, NEt_3; (c) TsCl, pyridine (or NEt_3), CH_2Cl_2; (d) $LiBHEt_3$, THF; (e) HRP, H_2O_2, MeOH, citrate-phosphate buffer, pH=3; (f) (*R*)-MTPACl, pyridine, CH_2Cl_2; (g) chiral HPLC.

(**13**+**14**). The diastereomers were separated by use of a chiral HPLC protocol (Chiracel® OD column, 99:1 hexanes:2-propanol; 1.0 mL/min) and then reduced to yield (+)-licarin A (**1**) and (−)-licarin A (**4**) (ee>99.8%), respectively. Accordingly, this methodology permits introduction of either radio (^3H) or stable (^2H) isotopes at the terminal C-9 position, this being necessary for future labelling and enzymatic studies involving isoeugenol (**9**) metabolism in *A. pubescens*.

Two independent methods were carried out to determine the chirality at positions C-8 and C-9 of the diol derivatives from (±)-licarin A (**1**+**4**), and to obtain the analogous diastereomers of the natural products **2** and **3**, previously isolated from *A. pubescens*. Both methods involved the synthesis of 8,9-diols by using the Sharpless oxidation procedure[3] to afford the asymmetric C-8, C-9 dihydroxylation products of licarin A (**1**+**4**) (Schemes 2–4). One of the possible strategies involved preparation of epoxides, which in turn could be selectively opened to afford the required other diastereomeric 8,9-diols. Thus, the protected (±)-licarin A (**15**) was oxidised using AD-mix β (Scheme 2), and the crude product **16** was subjected to an attempted stereospecific transformation of the 8,9 diol into the corresponding epoxide. However, no epoxide was obtained under the conditions employed, and only a mixture of other reaction products was isolated, whose constituents **17**–**24** were separated by TLC (Scheme 2). Since an enantiomeric mixture of licarin A (**1**+**4**) was utilised, two sets of NMR spectroscopic signals for each compound were observed relative to the hydrogens and carbons of the aliphatic side chain, and the carbons in the aromatic rings.

Compounds **14** and **13** were next individually subjected to Sharpless oxidation to afford the asymmetric dihydroxylation products from licarin A **1** and **4** (Schemes 3 and 4). Despite being diastereomers, the ^1H and ^{13}C NMR spectra of diols **25/28** and **36/39** were very similar and thus the compounds could not readily be distinguished. Next, the diols were transformed into their corresponding (*R*)- and (*S*)-MTPA derivatives, and two series of enantiomers were obtained for each. Series I compounds were derived from

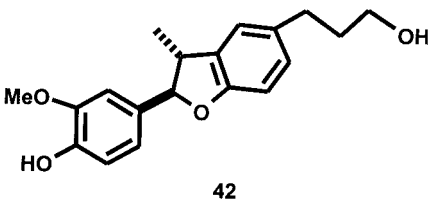


Scheme 2. Asymmetric dihydroxylation of (+)- and (−)-licarin A (**1**) and (**4**). *Reagents and conditions*: (a) $^{t}BuMe_2SiCl$, imidazole, DMF; (b) AD-mix β, $^{t}BuOH$, H_2O, $MeSO_2NH_2$; (c) $MeC(OMe)_3$, Me_3SiCl, CH_2Cl_2; (d) K_2CO_3, MeOH; (e) $^{n}Bu_4NF$, THF.

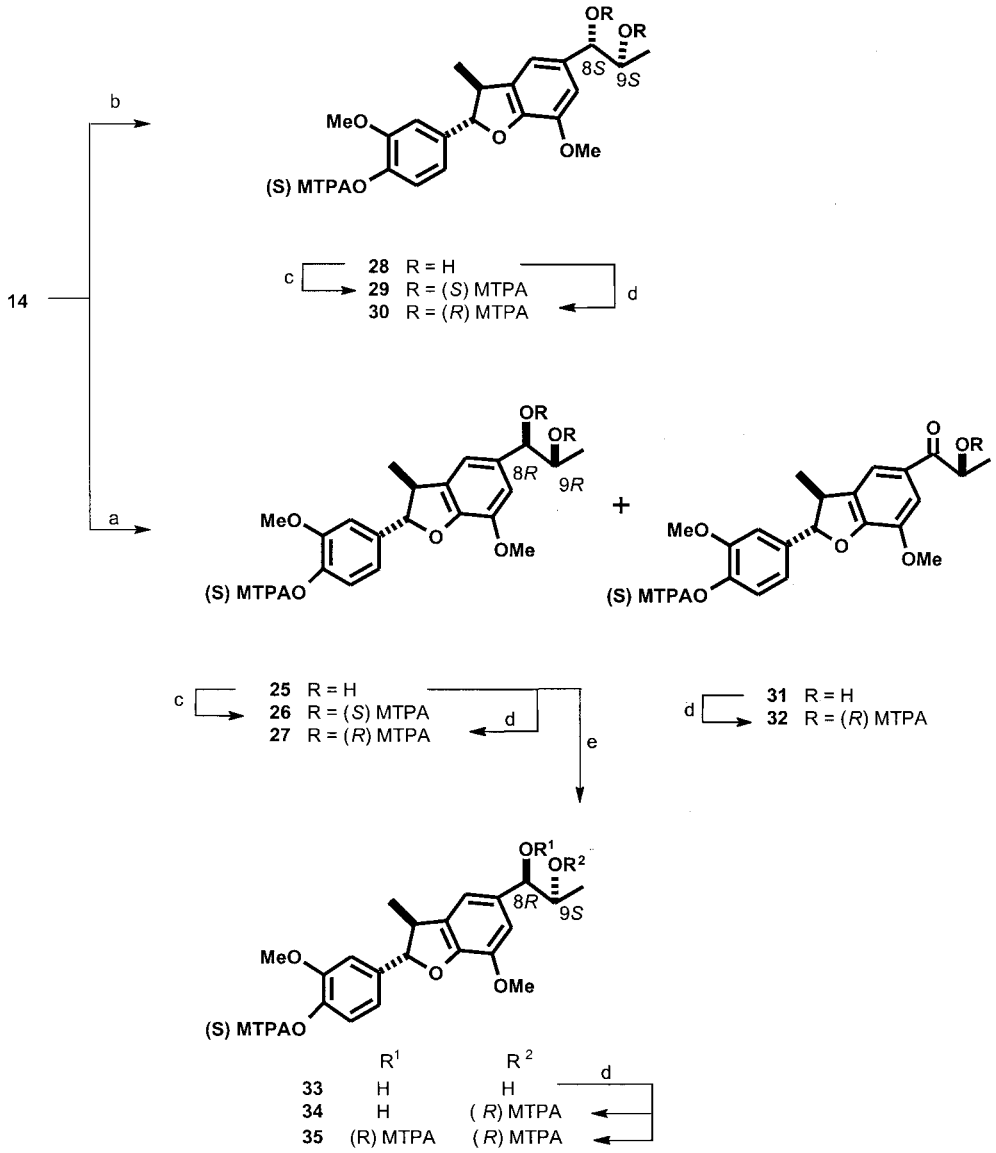
(+)-licarin A (**1**) (Scheme 4, **36**–**41**), whereas Series II compounds originated from (−)-licarin A (**4**) (Scheme 3, **25**–**30**). For each series, two pairs of compounds **26/30**, **27/29**, **37/41** and **38/40** displayed quite similar ^{1}H and ^{13}C NMR spectral data, except for one of the aromatic proton (H-4 or H-6) resonances. Taking into account all of the NOE effects observed by GOESY experiments for each derivative (Table 1), and that the most stable conformation of MTPA groups is that proposed by Dale and Mosher[4] and Ohtani et al.,[5] their conformations can be proposed as shown in Fig. 1.

As previously observed,[1] the CD curve of (+)-licarin A (**1**) displays a positive Cotton effect at 270 nm, whereas (−)-licarin A (**4**) has a negative effect at the same λ value. Accordingly, the (*S*)-MTPA derivative **13** belonging to Series I gave a positive effect at 288 nm, which was opposite to that of derivative **14** of Series II. Comparing the CD curves of (2*R*, 3*R*)-2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-3-methylbenzofuran (**42**),[6] the 8*S*, 9*S* (**28**) and the 8*R*, 9*R* (**25**, **36**) diols and their MTPA ester derivatives (**26**, **27**, **29**, **30**, **37** and **38**), it was possible to confirm to which series each derivative belonged by analysing the sign of the Cotton effect at 240 and 275 nm. However, no effect was observed that enabled differentiation of the configuration at stereocenters C-8, C-9, nor of the configuration of the MTPA moiety linked to these centers (Table 2).

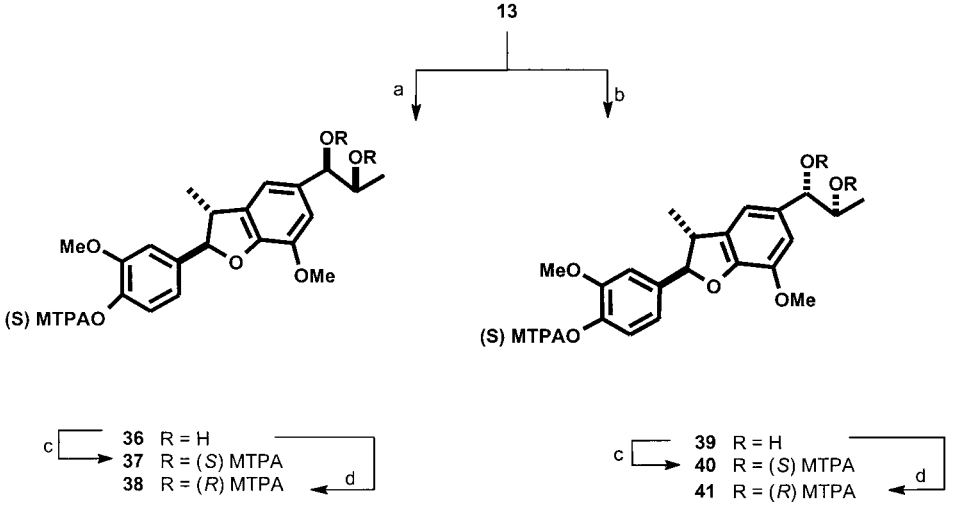
The four diastereomers **26**, **27**, **29**, and **30** belonging to the same series could, however, be separated by reversed phase



42



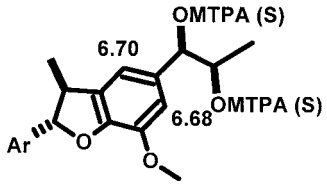
Scheme 3. Synthesis of licarinediols from (−)-licarin A (**4**). *Reagents and conditions*: (a) AD-mix β, ^{t}BuOH, H_2O, $MeSO_2NH_2$; (b) AD-mix α, ^{t}BuOH, H_2O, $MeSO_2NH_2$; (c) (*R*)-MTPACl, pyridine, CH_2Cl_2; (d) (*S*)-MTPACl, pyridine, CH_2Cl_2; (e) H_3O^+, MeOH.



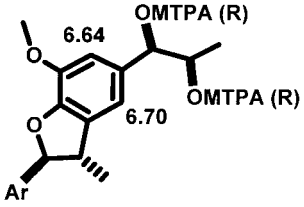
Scheme 4. Synthesis of licarinediols from (+)-licarin A (**1**). *Reagents and conditions*: (a) AD-mix β, ^{t}BuOH, H_2O, $MeSO_2NH_2$; (b) AD-mix α, ^{t}BuOH, H_2O, $MeSO_2NH_2$; (c) (*R*)-MTPACl, pyridine, CH_2Cl_2; (d) (*S*)-MTPACl, pyridine, CH_2Cl_2.

Table 1. Selected correlations observed by GOESY experiments for **26**, **27**, **29**, **30**, **34** and **35** (500 MHz, $CDCl_3$)

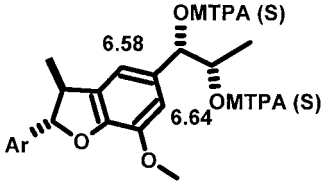
H irradiated	H affected					
	26	**27**	**29**	**30**	**34**	**35**
9	4, 6, 8, 10	4, 6, 8, 10	4, 6, 8, 10, OCH_3-MTPA, Ph-MTPA	4, 6, 8, 10	8, 10	8, 10
8	4, 6, 9, 10	4, 6, 9, 10, Ph-MTPA	4, 6, 9, 10, OCH_3-7, OCH_3-MTPA, Ph-MTPA	4, 6, 9, 10	9	4, 6, OCH_3-MTPA
6	8, OCH_3-7, Ph-MTPA	8, OCH_3-7, Ph-MTPA	OCH_3-7, 8, 9	8, OCH_3-7		8, OCH_3-7, Ph-MTPA
4	8, 9, CH_3-3	8, 9, CH_3-3, OCH_3-MTPA	8, CH_3-3, Ph-MTPA	8, CH_3-3, Ph-MTPA		8, CH_3-3
CH_3-3	2′, 6′, 2, 3, 4	2′, 6′, 2, 3, 4	2′, 6′, 2, 3, 4	2′, 6′, 2, 3, 4	2′, 6′, 2, 3, 4, Ph-MTPA	2′, 6′, 2, 3, 4, Ph-MTPA



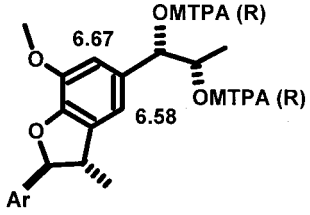
26



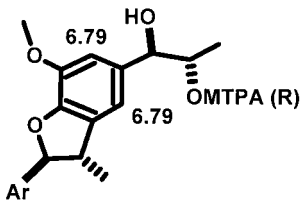
27



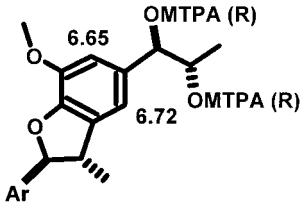
29



30



34



35

Figure 1. Simplified representation of proposed conformations for compounds **26**, **27**, **29**, **30**, **34** and **35** (δ_H, 500 MHz, $CDCl_3$).

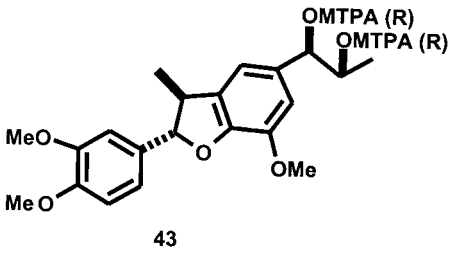
Table 2. Cotton effect observed for **1**, **4**, **13**, **14**, **25**–**30**, **36**–**38**, and **42**.[6]

Compound	$[\theta]_{230-240}$	$[\theta]_{270-275}$	$[\theta]_{285-290}$
1	−1200	+520	
13	− (shoulder)		+2370
25	−6590	−1647	
26	−19042	−2988	
27	−8086	−2210	
28	−3345	−903	
29	−15643	−2657	
30	−10928	−2991	
4	+1735	−1900	
14	+ (shoulder)		−5265
36	+ (shoulder)	−1415	
37	+185	−484	
38	+3120	−703	
42	+16962		−2313

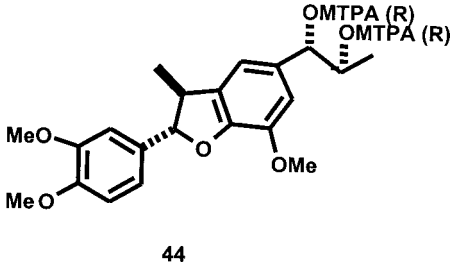
HPLC. Fig. 2 shows the separations obtained for all four diastereomers.

Applying the modified Mosher method for acyclic glycols,[7] in which the parameter values $\Delta(\delta_{SS}-\delta_{RR})$ could lead to the establishment of the absolute configuration of *syn*-glycols, it was observed that the results obtained were in accordance with those from NOE observations, since in the proposed modified Mosher method the group R^2 has a higher priority than R^1 (Fig. 3).

In order to obtain the other diastereomers at C-8 and C-9 and analyse what effect their changes in configuration would have on coupling constants between H-8 and H-9, the diol **25** was subjected to isomerization under acid conditions to yield diol **33**, which in turn was converted into its (*R*)-MTPA derivatives (**34** and **35**) (Scheme 3). The structures of these products were established by comparison of their ^{1}H and ^{13}C NMR spectral data with those previously mentioned, as well as by analyses of the NOEs as evidenced by GOESY experiments (Table 1, Fig. 1). The expected isomerization at C-8 was not observed since products **34** and **35** showed NOEs between the methyl and MTPA groups. Taking into account that isomerization of **25** was obtained only at C-9, it is suggested that under acid conditions an epoxide intermediate was formed. However, both steric interactions and difficulties of this intermediate to assume a planar arrangement necessary for maximum



43



44

stabilization in the transition state may be responsible for the low selectivity toward the C-8.[8,9] Thus, nucleophilic attack at C-9 leading to inversion of stereochemistry of this center could take place. As expected, the 8*R*, 9*S* derivative **35** had a $J_{8,9}$ (8.7 Hz) value larger than that of 8*S*, 9*S* (**29**, **30**) or 8*R*, 9*R* (**26**, **27**) derivatives ($J_{8,9}$=4.8–6.0 Hz). The naturally occurring diol derivatives **43** and **44** displayed coupling constants $J_{8,9}$=5.2 and 5.9 Hz, respectively.[1] Hence, it was inferred that both had either 8*S*, 9*S* or 8*R*, 9*R* configurations at C-8, C-9. Accordingly, the MTPA derivative **43**, except for the substituent at C-4′, showed near identical spectroscopic data to that of **27**, corroborating the structure previously proposed for the natural diol **2**.[1] Thus, the data for **44** are in accordance with those of compound **30**, but not in agreement with those presented for **35**, as expected.[1] This therefore calls for a revision of the configuration of the C-9 stereocenter previously suggested for licarinediol **3a** to that of **3b**, i.e. from 9*R* to 9*S*. These data thus indicate that both natural diols **2** and **3b** isolated, from *A. pubescens*, have 8*R*, 9*R* and 8*S*, 9*S* configurations, respectively.

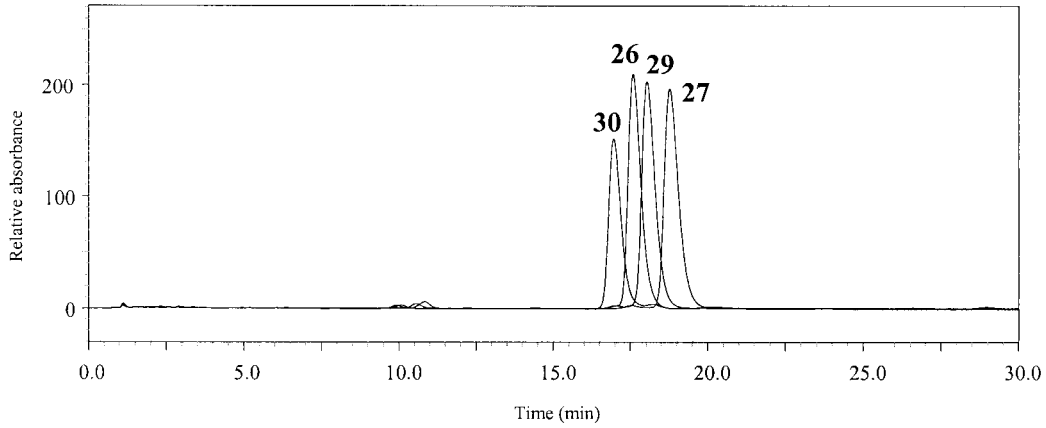


Figure 2. Superposition of chromatograms obtained for **26**, **27**, **29**, and **30** (R_t 17.6, 18.8, 18.1 and 17.0 min, respectively). Conditions: Waters RP-18 column (150×3.9 mm); H_2O:CH_3CN 80:20; flow rate: 0.8 mL min^{-1}; injection volume: 10.0 μL; detection: 240 nm.

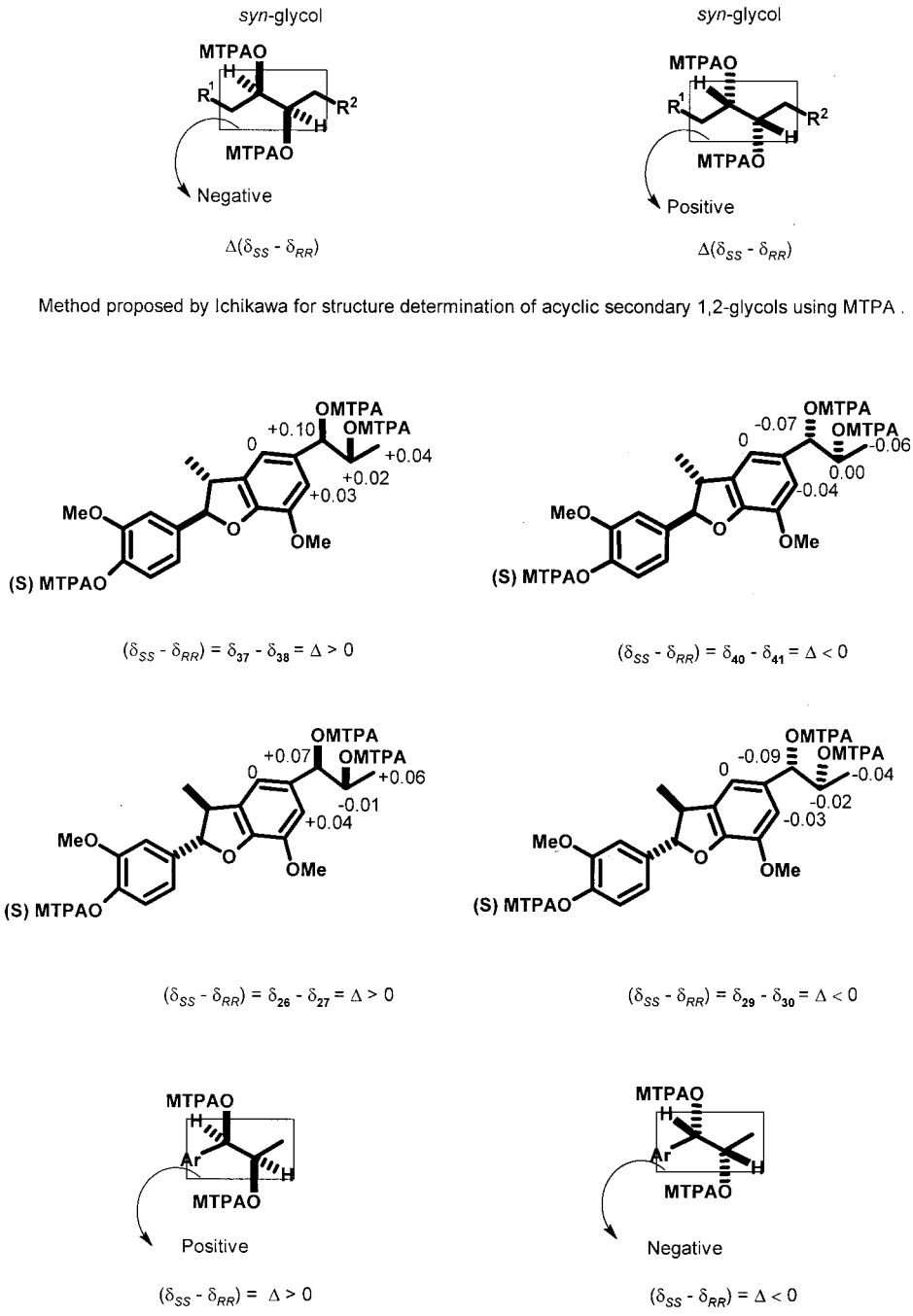


Figure 3. Structure determination of *syn*-diols applying the Ichikawa method[7] for compounds **26**, **27**, **29**, **30**, **37**, **38**, **40**, and **41**.

Experimental

General

All reactions were monitored by thin-layer chromatographic analyses using 0.25 mm E. Merck silica gel plates (60 PF_{254}) with UV and 10% H_2SO_4—heat as developing agent. All reactions were carried out under an argon atmosphere with dry freshly distilled solvents under anhydrous conditions unless otherwise noted. All reagents were purchased from Aldrich Chemical Co., Sigma Chemical Co. or Baker Analysed, and used without purification, except where noted. Solvents employed were of HPLC grade from Mallinckrodt. All yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogenous material unless otherwise stated.

^1H NMR 1D and 2D spectra were obtained at 300 and 500 MHz; ^{13}C NMR and DEPT spectra were taken at 75 MHz; ^1H-^{13}C COSY were optimized for J=7 and 145 Hz. The mass spectra were obtained on an HP 5985 spectrometer (EIMS) and on a Fisons Platform II by flow injection into the electrospray source (ESI/MS). HPLC analyses were carried out using either a Shimadzu liquid chromatograph 10 Avp equipped with a UV–vis detector, automatic fraction collector and/or using a Waters 600 controller, photodiode array detector, auto-sampler injector, and automatic fraction collector. The HPLC columns

employed were Waters 4 μm Novapak C_{18} (150×3.9 mm), eluted with H_2O:CH_3CN (80:20) at a flow rate of 0.8 mL min^{-1}, and (Chiral Technologies, Inc.) Chiralcel OD (250×4.6 mm), eluted with hexanes:2-propanol (99:1) at a flow rate of 1.0 mL min^{-1}, respectively. The injection volumes were 10 μL for analytical and 50 μL for preparative analyses. UV–vis spectra were recorded in the range of 210–350 nm, and the HPLC chromatograms were acquired at 254 and 280 nm. Optical rotations were measured on a Polamat A Carl Zeiss Jena. Circular dichroism spectra were recorded on a JASCO J-720 spectrometer, whereas UV spectra were obtained using a Perkin Elmer Lambda 14P UV/VIS spectrometer. Melting points were recorded on a Fisher–John Melting Point apparatus and were uncorrected. IR spectra were measured on a Nicolet-730 FT-IR spectrophotometer.

Coniferyl alcohol (6)

To coniferyl aldehyde (**5**, 2.5 g, 14 mmol) dissolved in EtOH (125 mL), was added $NaBH_4$ (2.4 g, 63.4 mmol). The solution was then stirred for 10 min, after which EtOH (50 mL) and water (100 mL) were added. A saturated solution of NH_4Cl (30 mL) was added and the solution extracted with EtOAc (3×50 mL). The combined organic phase was washed with water (50 mL), dried (anhydrous Na_2SO_4), and concentrated to yield coniferyl alcohol **6** (2.52 g, 99.7%), which was not purified further.

Coniferyl alcohol mesylates 7 and 8

To each of three stirred solutions of coniferyl alcohol (**6**, 474 mg, 2.63 mmol) in dry CH_2Cl_2 (4 mL) was added MsCl (1.2 mL, 15.5 mmol) and Et_3N (2.2 mL). Each solution was stirred for 30 min, 2 h, and 48 h, respectively, then poured into ice water, and extracted with CH_2Cl_2 (3×5 mL). The combined CH_2Cl_2 soluble extracts from each experiment were washed twice with 10% HCl, saturated $NaHCO_3$ solution and brine, then dried (Na_2SO_4), and evaporated. The resulting oils were individually subjected to flash chromatography (CH_2Cl_2). The best yields for mesylates **7** (538.1 mg, 60.9%) and **8** (203.6 mg, 30.0%) were obtained when the reaction time was 30 min.

7. Yellow oil. ^{1}H NMR ($CDCl_3$): δ 3.05 (3H, s, $MeSO_3$), 3.08 (3H, s, $MeSO_3$), 3.81 (3H, s, OMe), 4.15 (2H, dd, *J*=0.9, 6.9 Hz, H-9), 6.25 (1H, dt, *J*=15.6, 6.9 Hz, H-8), 6.54 (1H, dd, *J*=15.6, 0.9 Hz, H-7), 6.89 (1H, dd, *J*=8.1, 2.1 Hz, H-6), 6.95 (1H, d, *J*=2.1 Hz, H-2), 7.14 (1H, d, *J*=8.1 Hz, H-5). ^{13}C NMR ($CDCl_3$): δ C-1 to C-9: 137.7, 110.6, 137.7, 151.3, 124.1, 119.3, 132.6, 126.1, 45.1, OMe: 55.9, $MeSO_3$: 38.2.

8. Yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.95 (1H, br s, OH), 3.12 (3H, s, $MeSO_3$), 3.85 (3H, s, OMe-3), 4.19 (2H, dd, *J*=0.9, 6.9 Hz, H-9), 6.26 (1H, dt, *J*=15.6, 6.9 Hz, H-8), 6.50 (1H, dd, *J*=15.6, 0.9 Hz, H-7), 6.93 (1H, dd, *J*=8.4, 2.1 Hz, H-6), 6.98 (1H, d, *J*=2.1 Hz, H-2), 7.19 (1H, d, *J*=8.4 Hz, H-5). ^{13}C NMR ($CDCl_3$): δ C-1 to C-9: 136.1, 110.6, 146.0, 151.3, 124.2, 119.3, 132.6, 126.2, 52.5, OMe: 55.9, $MeSO_3$: 38.1. EIMS 70 eV *m/z* (rel. int.): 258 (M^+, 3%), 242 (10), 197 (47), 163 (40), 120 (93), 118 (100), 107 (33).

Compounds 9 and 10[10]

To a stirred solution of the mesylate **7** (1 mmol) in THF was added, in one portion by means of syringe injection, a 1 M $LiEt_3BH$ solution in THF (2.1 mL). The resulting reaction mixture was stirred and heated until reflux began, this being maintained for 4 h. Following reduction, the excess hydride was quenched by dropwise addition of water. The organoboranes were oxidised by adding 3N NaOH (0.7 mL), followed by a slow, dropwise, addition of 30% H_2O_2 (0.7 mL). The reaction mixture was next poured into water (10 mL), extracted with CH_2Cl_2 (30 mL), then washed with H_2O to remove dissolved THF, dried ($MgSO_4$), and concentrated.[†]

Isoeugenol (9). Yellow oil. Yield=84.9%. IR, UV, ^{1}H and ^{13}C NMR spectral data for **9** were identical to those of an authentic sample (Aldrich 1999, I-1,720-6).

10. Yellow oil. Yield=60%. ^{1}H NMR ($CDCl_3$): δ 1.87 (3H, dd, *J*=6.3, 1.3 Hz, H-9), 3.16 (3H, s, $MeSO_3$), 3.89 (3H, s, OMe), 6.23 (1H, dq, *J*=15.6, 6.3 Hz, H-8), 6.37 (1H, dd, *J*=15.6, 1.3 Hz, H-7), 6.94 (1H, d, *J*=2.0 Hz, H-2), 6.91 (1H, dd, *J*=8.1, 2.0 Hz, H-6), 7.21 (1H, d, *J*=8.1 Hz, H-5). ^{13}C NMR ($CDCl_3$): δ C-1 to C-9: 137.1, 110.1, 138.5, 151.3, 124.5, 118.7, 130.1, 127.4, 18.7, OMe: 56.1, $MeSO_3$: 38.4; IR ν_{max}^{KBr} cm^{-1}: 3022, 2932, 2857, 1597, 1507, 1461, 1269, 1160, 1114, 1029, 861.

Compounds 11 and 12

Compound **11** was obtained by the same procedure described as for the mesylates **7** and **8** but using tosyl chloride (**6**, TsCl, Et_3N in CH_2Cl_2, yield=62.5%), as well as by Binkley's procedure (**6**, TsCl, pyridine, in THF, yield=45.1%).[11] Hydrogenolysis did not occur, and only the reduction product **12** (40%) was obtained.

12. Yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.93 (2H, m, H-8), 2.38, 2.40 (6H, 2s, 2Me-OTs), 2.64 (2H, m, H-7), 3.48 (3H, s, OMe), 3.70 (2H, m, H-9), 6.70 (1H, dd, *J*=8.1, 1.0 Hz, H-6), 6.72 (1H, d, *J*=1.0 Hz, H-2), 6.98 (1H, d, *J*=8.1 Hz, H-5), 7.26 (2H, d, *J*=8.4 Hz, H-3′, H-5′), 7.28 (2H, d, *J*=8.1 Hz, H-3′, H-5′), 7.61 (2H, d, *J*=8.4 Hz, H-2′, H-6′), 7.64 (2H, d, *J*=8.1 Hz, H-2′, 6′) ^{13}C NMR ($CDCl_3$): δ C-1 to C-9: 132.5, 112.9, 139.6, 151.5, 123.7, 120.2, 30.2, 23.3, 53.1, OMe: 55.6, OTs C-1′, C1″ to C6′, C6″: 145.3, 142.9; 129.5, 129.3; 128.2, 126.7; 136.8, 136.6; 128.2, 126.7, 129.5, 129.3; 11.6 (2Me). IR ν_{max}^{KBr} cm^{-1}: 2967, 2927, 2861, 1597, 1507, 1457, 1367, 1275, 1182, 1091, 1029, 855.

(±)-Licarin A (1 and 4)[2]

To a solution of isoeugenol (**9**, 1.52 mL, 10 mmol) in MeOH (50 mL) was added citrate-phosphate buffer (450 mL, 20 mM, pH 3, 18°) and horseradish peroxidase (HRP, 20 mL, 2500 U, Boehringer–Mannheim Grade II). The mixture was stirred while H_2O_2 (0.57 mL, 5 mmol) was added dropwise over 10 min. The reaction mixture

[†] When the reaction was carried out with **7**, but without refluxing, the main product obtained was **10** (60%).

was stirred for an additional 1 h and then filtered using a Büchner funnel. The resulting residue was separated and the funnel was washed with EtOAc. The organic solubles and the residue were combined and washed with a saturated solution of NH_4Cl and water, successively, and then dried (Na_2SO_4). The crude product obtained after evaporation of the solvent in vacuo was crystallised from MeOH to afford (±)-licarin A (**1**+**4**, 1.62 g, 99.1%).

Enzyme activity measurements[2]

A solution of HRP (Boehringer, 20 mg Lys/4220.3 U) in 25 mL buffer phosphate (pH 6.0, 18°) and 25 mL of MeOH, was stirred overnight at 18°, cooled and centrifuged (1200 g, 30 min) at 4°. The resulting enzyme solution was diluted 1000 times in 20 mM phosphate buffer. In a cuvette (2 mL) were added phosphate buffer (20 mM, 1.5 mL), guaiacol (20.1 mM, 50 μL) and the previously prepared enzyme solution (50 μL). After mixing, H_2O_2 (12.3 mM, 30 μL) was added and the change in absorbance at 436 nm was monitored over 2 min. The reference blank was prepared as described above except that no H_2O_2 was added. Enzyme activity was calculated using the molar absorption coefficient ($6.39\ M^{-1}\,cm^{-1}$) provided by Pütter.[12]

(*S*)-MTPA derivatives (13+14)[4,5]

To solution of **1**+**4** (0.014 mmol) in dry CH_2Cl_2 (1 mL), was added dry pyridine (130 μL) and (*R*)-2-methoxy-2-trifluoromethyl-2-phenylacetyl chloride [(*R*)-MTPACl, 13 μL, 0.07 mmol]. The mixture was stirred for 30 min and allowed to stand until the reaction was complete (16 h). The residue obtained after solvent evaporation in vacuo was subjected to preparative TLC (hexanes:EtOAc, 2:1) to give the corresponding MTPA esters, in yields of ~99.0% (ee>99.9%). Chiral phase HPLC separation of the diastereomers **13**+**14** (see General) was next achieved as described earlier to give **13** (R_t=20 min) and **14** (R_t=30 min). These were then individually subjected to reduction ($LiBEt_3H$, THF) according to the procedure previously described for preparation of **9**, **10** and **12** to yield, respectively, (+)-licarin A (**1**, R_t=44 min, ee>99.9%, 40%) and (−)-licarin A (**4**, R_t=48 min, ee>99.9%, 30%).

Compounds 13 and 14. ^1H, ^{13}C NMR, IR, UV and EIMS spectral data were identical. Colorless oil. Anal. Calcd for $C_{30}H_{29}F_3O_6$: C, 66.41; H, 5.39. Found: C, 66.48; H, 5.52. ^1H NMR ($CDCl_3$): δ 1.39 (3H, d, *J*=6.8 Hz, Me-3), 1.85 (3H, dd, *J*=6.6, 1.5 Hz, H-10), 3.41 (1H, m, H-3), 3.72 (3H, s, OMe-MTPA), 3.78 (3H, s, OMe-3′), 3.88 (3H, s, OMe-7), 5.16 (1H, d, *J*=9.3 Hz, H-2), 6.13 (1H, dq, *J*=15.6, 6.6 Hz, H-9), 6.36 (1H, dq, *J*=15.6, 1.5 Hz, H-8), 6.77, 6.80 (2H, 2 br s, H-4, H-6), 6.99 (2H, br s, H-5′, H-6′), 7.10 (1H, br s, H-2′), 7.7–7.4 (5H, m, Ph). ^{13}C NMR ($CDCl_3$): δ 18.0 (Me-3), 18.6 (C-10), 46.2 (C-3), 2×56.0, 56.1 (OMe-3′, OMe-7, OMe-MTPA), 93.1 (C-2), 109.3 (C-6), 110.5 (C-2′), 113.4 (C-4), 118.8 (C-6′), 122.2 (C-9), 127.6, 128.5, 129.8 (Ph-MTPA), 130.9 (C-8), 132.1 (C-MTPA), 132.6, 133.0 (C-5, C-3a), 138.8 (C-1′), 140.3 (C-3′), 144.2, 146.4 (C-7a, C-7), 151.1 (C-4′), 164.6 (CO-MTPA). EIMS 70 eV *m/z* (rel. int.): 542 (M^+, 20%), 325 (22), 189 (100), 119 (16), 105 (35). IR ν_{max}^{KBr} cm^{-1}: 2963, 2854, 1772, 1696, 1603, 1504, 768, 715. UV $\lambda_{max}^{CH_3OH}$ nm (log ε): 210 (4.56), 274 (4.10). **13**: α_D^{25}=−17.5° ($CHCl_3$, *c* 1.94). CD (CH_3OH, *c* 0.08) $[\theta]_{256}$=0, $[\theta]_{288}$=+2370. **14**: α_D^{25}=−56.0° ($CHCl_3$; *c* 1.68). CD (CH_3OH, *c* 0.04) $[\theta]_{287}$=−5265.

(+)-Licarin A (1) and (−)-licarin A (4). IR, EIMS, ^1H and ^{13}C NMR spectral data for **1** and **4** were identical to those previously reported for licarin A.[1] (+)-Licarin A (**1**): colorless crystals, mp 106–108° (CH_3OH). α_D^{25}=+43.5°($CHCl_3$; *c* 1.39). CD (CH_3OH, *c* 0.19) $[\theta]_{231}$=−1200, $[\theta]_{252}$=0, $[\theta]_{268}$=+520. (−)-Licarin A (**4**): colorless crystals, mp 106–108° (CH_3OH). α_D^{25}=−44.0° ($CHCl_3$; *c* 1.82), CD (CH_3OH, *c* 0.10) $[\theta]_{231}$=+1735, $[\theta]_{242}$=0, $[\theta]_{270}$=−1900.

Compound 15

^{t}BuMe$_2$SiCl (185.5 mg, 1.23 mmol) was added to a solution of (±)-licarin A (**1**+**4**) (358 mg, 1.1 mmol) and imidazole (205 mg, 3.0 mmol) in dry DMF (1.8 mL). The mixture was stirred at 0° for 10 min,[13] then stirred at room temp for 1 h, after which CH_2Cl_2 (5 mL) was added to the solution. The resulting organic reaction mixture was washed with H_2O (2×5 mL), brine (5 mL), then dried ($MgSO_4$), and concentrated. The crude product was subjected to flash chromatography (silica gel, 8 g, eluted with hexanes:EtOAc, 9:1) to afford **15** (426.7 mg, 87%).

15. Colorless crystals, mp 117–118° (CH_3OH). Anal. Calcd for $C_{26}H_{36}O_4Si$: C, 70.87; H, 8.23. Found: C, 69.66; H, 8.52. ^1H NMR ($CDCl_3$): δ 0.16 (6H, s, 2Me-TBS), 1.01 (9H, s, 3Me-TBS), 1.39 (3H, d, *J*=6.9 Hz, Me-3), 1.88 (3H, dd, *J*=6.6, 1.2 Hz, H-10), 3.48 (1H, m, H-3), 3.80 (3H, s, OMe-3′), 3.90 (3H, s, OMe-7), 5.11 (1H, d, *J*=9.9 Hz, H-2), 6.12 (1H, dq, *J*=15.6, 6.6 Hz, H-9), 6.38 (1H, dd, *J*=15.6, 1.2 Hz, H-8), 6.78 (1H, br s, H-4), 6.80 (1H, br s, H-6), 6.83 (1H, d, *J*=8.1 Hz, H-5′), 6.87 (1H, dd, *J*=8.1, 1.8 Hz, H-6′), 6.97 (1H, d, *J*=1.8 Hz, H-2′). IR ν_{max}^{KBr} cm^{-1}: 2940, 2855, 1603, 1512, 1473, 1285, 1132, 944, 830.

Asymmetric dihydroxylation of 13–15[3]

To a stirred solution of either **13**, **14** or **15** (0.53 mmol) in ^{t}BuOH–H_2O (5 mL, 1:1) was individually added AD-mix α or β (758 mg) at 0°. Each mixture was stirred for 5 min at 0° (two clear phases), to which was then added methanesulfonamide (51.1 mg, 0.53 mmol). The resulting heterogeneous slurries were stirred at 18° for 18 h.[‡] To each solution was then added Na_2SO_3 (1.6 mmol) and EtOAc (10 mL), with stirring continued for a further 30 min. Additional EtOAc (10 mL) was next added to each solution with the organic solubles separated. Each aqueous phase was then extracted with EtOAc (3×10 mL), with the combined organic extracts washed successively with 0.5 M HCl and water, then dried (Na_2SO_4), and concentrated in vacuo. Purification of the products from **13** and **14** by TLC (hexanes:EtOAc, 1:1) yielded the diols (**36**,

[‡] The stereoselectivity of the reaction varied with the rate of stirring. It was observed with **14** that as the stirring rate decreased the yield of **31** increased to give a mixture of **25** and **31** (1:1). The structure of **31** was further confirmed by its conversion to the MTPA ester derivative **32**.

39) and (**25**, **28**) (~94.6% yield), whereas compound **15** gave **16** (87%).

16. Amorphous solid: Anal. Calcd for $C_{26}H_{38}O_6Si$: C, 65.79; H, 8.07. Found: C, 65.37; H, 7.67. $\alpha_D^{25}=-17.7°$ ($CHCl_3$; *c* 2.49). ^1H NMR ($CDCl_3$): δ 0.14 (6H, s, 2Me-TBS), 0.99 (9H, s, 3Me-TBS), 1.10 (3H, d, *J*=6.3 Hz, H-10), 1.38 (3H, d, *J*=6.6 Hz, Me-3), 3.48 (1H, m, H-3), 3.80 (3H, s, OMe-3′), 3.90 (3H, s, OMe-7), 4.0–3.7 (1H, m, H-9), 4.34 (1H, d, *J*=7.5 Hz, H-8), 5.11 (1H, d, *J*=9.6 Hz, H-2), 6.75 (2H, 2 br s, H-4, H-6), 6.81 (1H, d, *J*=8.1 Hz, H-5′), 6.86 (1H, dd, *J*=8.1, 1.8 Hz, H-6′), 6.94 (1H, d, *J*=1.8 Hz, H-2′). ^{13}C NMR: δ −5.4 (2Me-TBS), 17.7 (Me-3), 18.5 (C-TBS), 19.0 (C-10), 25.8 (3Me-TBS), 45.5 (C-3), 55.5, 56.0 (OMe-3′, OMe-7), 2×72.4 (C-9), 2×79.6 (C-8), 93.9 (C-2), 2×110.0, 2×114.1 (C-4, C-6), 110.3 (C-2′), 119.2 (C-6′), 120.6 (C-5′), 133.2, 133.3, 134.7 (C-3a, C-5, C-1′), 144.0, 145.0, (C-7a, C-3′), 146.7 (C-7), 150.9 (C-4′). EIMS 70 eV *m/z* (rel. int.): 474 (M^+, 4%), 456 (3), 430 (29), 399 (35), 219 (74), 87 (65), 85 (100), 83 (96). IR ν_{max}^{KBr} cm^{-1}: 3500, 2950, 2863, 1618, 1510, 1462, 1283, 1128, 837.

25, **28**, **36** and **39.** No significant differences were observed between their ^1H and ^{13}C NMR, EIMS, IR, and UV spectral data. ^1H NMR ($CDCl_3$): δ 1.10 (3H, d, *J*=6.3 Hz, H-10), 1.42 (3H, d, *J*=6.9 Hz, Me-3), 3.46 (1H, dq, *J*=9.0, 6.9 Hz, H-3), 3.74 (3H, s, OMe-MTPA), 3.83 (3H, s, OMe-3′), 3.91 (3H, s, OMe-7), 3.87 (1H, m, H-9), 4.35 (1H, d, *J*=7.5 Hz, H-8), 3.01, 4.85 (2 br s, 2OH), 5.19 (1H, d, *J*=9.0 Hz, H-2), 6.81, 6.77 (2H, 2br s, H-6, 4), 7.01 (2H, 2 br s, H-5′, 6′), 7.09 (1H, s, H-2′), 7.7–7.4 (5H, m, Ph-MTPA). ^{13}C NMR ($CDCl_3$): δ 18.1 (Me-3), 19.3 (C-10), 46.2 (C-3), 56.1, 56.3 (OMe-3′, OMe-7), 55.9 (OMe-MTPA), 72.5 (C-9), 79.9 (C-8), 93.2 (C-2), 110.3 (C-2′), 110.6, 114.5 (C-6, C-4), 118.8 (C-6′), 122.4 (C-5′), 127.7, 128.5, 129.9, 131.7 (Ph-MTPA), 132.1 (C-MTPA), 133.0, 135.1 (C-3a, C-5), 138.9 (C-1′), 140.2 (C-3′), 144.4, 147.2 (C-7a, C-7), 151.2 (C-4′), 164.7 (CO-MTPA). IR ν_{max}^{KBr} cm^{-1}: 3395, 2967, 2928, 2861, 1769, 1618, 1512, 1458, 1277, 1182, 1120, 716. UV $\lambda_{max}^{CH_3OH}$ nm (log ϵ): 210 (4.44), 235 sh (3.70), 280 (3.46). **25**: Colorless oil. Anal. Calcd for $C_{30}H_{31}F_3O_8$: C, 62.50; H, 5.42. Found: C, 62.32; H, 5.52. $\alpha_D^{25}=-30.1°$ ($CHCl_3$; *c* 1.73). CD (CH_3OH, *c* 0.06) $[\theta]_{226}=0$, $[\theta]_{239}=-6590$, $[\theta]_{260}=0$, $[\theta]_{272}=-1647$. **28**: Colorless oil. Anal. Calcd for $C_{30}H_{31}F_3O_8$: C, 62.50; H, 5.42. Found: C, 61.98; H, 5.02. $\alpha_D^{25}=-14.1°$ ($CHCl_3$; *c* 1.28). CD (CH_3OH, *c* 0.04) $[\theta]_{239}=-3345$, $[\theta]_{260}=0$, $[\theta]_{273}=-903$. **36**: Colorless oil. Anal. Calcd for $C_{30}H_{31}F_3O_8$: C, 62.50; H, 5.42. Found: C, 62.74; H, 5.61. $\alpha_D^{25}=-41.4°$ ($CHCl_3$; *c* 2.37).

31. Colorless oil. $\alpha_D^{25}=-39.1°$ ($CHCl_3$; *c* 0.67). ^1H NMR ($CDCl_3$): δ 1.47 (3H, d, *J*=7.2 Hz, H-10), 1.47 (3H, d, *J*=6.6 Hz, Me-3), 3.54 (1H, m, H-3), 3.74 (3H, s, OMe-MTPA), 3.83 (3H, s, OMe-3′), 3.97 (3H, s, OMe-7), 5.13 (1H, q, *J*=7.2 Hz, H-9), 5.32 (1H, d, *J*=8.7 Hz, H-2), 6.99 (1H, dd, *J*=8.1, 1.8 Hz, H-6′), 7.03 (1H, d, *J*=8.1 Hz, H-5′), 7.06 (1H, d, *J*=1.8 Hz, H-2′), 7.37 (1H, br s, H-6), 7.50 (1H, br s, H-4), 7.7–7.4 (5H, m, Ph-MTPA). ^{13}C NMR ($CDCl_3$): δ 18.5 (Me-3), 23.3 (C-10), 45.7 (C-3), 55.9 (OMe-MTPA), 56.2, 56.5 (OMe-3′, OMe-7), 69.1 (C-9), 94.1 (C-2), 110.5 (C-2′), 112.6 (C-6), 117.9 (C-4), 118.7 (C-6′), 122.6 (C-5′), 132.1, 133.2 (C-3a, C-5), 127.8, 128.5, 129.9 (Ph-MTPA), 139.2 (C-1′), 139.4 (C-3′), 144.8 (C-7), 151.3 (C-4′), 152.7 (C-7a), 166.7 (CO-MTPA), 200.6 (C-8).

Compounds 17–20

To a stirred solution of diol **16** (210 mg, 0.44 mmol) in CH_2Cl_2 (1 mL), was added trimethyl orthoacetate (75 μL, 0.62 mmol) and trimethylsilyl chloride (80 μL, 0.74 mmol). After stirring the mixture for 80 min, the solvents were evaporated in vacuo and the residue was dissolved in MeOH (2 mL). K_2CO_3 (74 mg, 0.54 mmol) was added and the mixture was stirred for 2 h, then poured into saturated aqueous NH_4Cl (3 mL), and extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated.[3] Purification of the crude product by TLC (hexanes:EtOAc, 1:1) yielded, besides recovered **16** (81 mg, 27% of original amount), products **17** (14.0 mg, 3.9%), **18** (14.4 mg, 4.1%), **19** (79.6 mg, 25.8%), and **20** (26.8 mg, 8%).

17. Amorphous solid: Anal. Calcd for $C_{28}H_{40}O_7Si$: C, 65.09; H, 7.08. Found: C, 65.39; H, 7.30. ^1H NMR ($CDCl_3$): δ 0.14 (6H, s, 2Me-TBS), 0.99 (9H, s, 3Me-TBS), 1.12 (3H, d, *J*=6.3 Hz, H-10), 1.37 (3H, d, *J*=6.9 Hz, Me-3), 2.12 (3H, s, OAc), 3.45 (1H, m, H-3), 3.80 (3H, s, OMe-3′), 3.90 (3H, s, OMe-7), 4.56 (1H, br d, *J*=6.9 Hz, H-8), 5.05 (1H, dq, *J*=6.3, 6.9 Hz, H-9), 5.11 (1H, d, *J*=9.3 Hz, H-2), 6.77, 6.83 (2H, 2 br s, H-4, H-6), 6.81 (1H, d, *J*=8.1 Hz, H-5′), 6.85 (1H, br d, *J*=8.1 Hz, H-6′), 6.94 (1H, br s, H-2). ^{13}C NMR: δ −5.4 (2Me-TBS), 2×16.8 (C-10), 17.7 (Me-3), 18.5 (C-TBS), 21.4 (OAc), 25.8 (3Me-TBS), 45.5 (C-3), 55.5, 56.0 (OMe-3′, OMe-7), 74.9, 75.0 (C-8, C-9), 93.9 (C-2), 110.1, 114.4 (C-4, C-6), 110.3 (C-2′), 119.3 (C-6′), 120.6 (C-5′), 130.9, 133.2, 133.3 (C-3a, C-5, C-1′), 144.0, 145.0, 147.4 (C-7a, C-3′, C-7), 150.9 (C-4′), 170.3 (OAc). EIMS 70 eV *m/z* (rel. int.): 516 (M^+, 9%), 444 (5), 430 (20), 399 (12), 385 (40), 219 (45), 87 (87), 85 (90), 83 (100). IR ν_{max}^{KBr} cm^{-1}: 3539, 2938, 2861, 1732, 1605, 1508, 1466, 1240, 1130, 836, 778.

18. Amorphous solid: Anal. Calcd for $C_{28}H_{40}O_7Si$: C, 65.09; H, 7.08. Found: C, 65.42; H, 7.25. ^1H NMR ($CDCl_3$): δ 0.14 (6H, s, 2Me-TBS), 0.99 (9H, s, 3Me-TBS), 1.12 (3H, d, *J*=6.3 Hz, H-10), 1.37 (3H, d, *J*=6.9 Hz, Me-3), 2.14 (s, OAc), 3.45 (1H, m, H-3), 3.80 (3H, s, OMe-3′), 3.90 (3H, s, OMe-7), 4.07 (1H, m, H-9), 5.11 (1H, d, *J*=9.3 Hz, H-2), 5.48 (1H, 2d, *J*=5.1, 7.2 Hz, H-8), 6.77, 6.83 (2H, 2 br s, H-4, H-6), 6.81 (1H, d, *J*=8.1 Hz, H-5′), 6.85 (1H, br d, *J*=8.1 Hz, H-6′), 6.94 (1H, br s, H-2). ^{13}C NMR: δ −5.4 (2Me-TBS), 2×17.5 (C-10), 17.7 (Me-3), 19.0 (C-TBS), 21.4 (OAc), 25.8 (3Me-TBS), 45.5 (C-3), 55.5, 56.0 (OMe-3′, OMe-7), 2×70.3 (C-9), 2×80.9 (C-8), 93.9 (C-2), 110.5, 110.4 (C-4, C-6), 110.3 (C-2′), 119.3 (C-6′), 120.6 (C-5′), 130.9, 133.2, 133.4 (C-3a, C-5, C-1′), 144.0, 145.1, 147.4 (C-7a, C-3′, C-7), 150.9 (C-4′), 170.8 (OAc). EIMS 70 eV *m/z* (rel. int.): 516 (M^+ <1%), 471 (<1), 399 (3), 219 (5), 189 (7), 118 (12), 85 (93), 83 (100). IR ν_{max}^{KBr} cm^{-1}: 3486, 2942, 2865, 1732, 1606, 1509, 1463, 1280, 1132, 842, 760.

19. Amorphous solid: Anal. Calcd for $C_{27}H_{40}O_6Si$: C, 66.36; H, 8.25. Found: C, 66.03; H, 8.17. ^1H NMR ($CDCl_3$): δ 0.15

(6H, 2s, 2Me-TBS), 0.99 (9H, s, 3Me-TBS), 1.00 (3H, d, J=6.6 Hz, H-10), 1.38 (3H, d, J=6.9 Hz, Me-3), 3.27 (OMe-8), 3.48 (1H, m, H-3), 3.80 (3H, s, OMe-3′), 3.90 (3H, s, OMe-7), 4.1–3.7 (2H, m, H-8, H-9), 5.12 (1H, d, J=9.6 Hz, H-2), 6.68, 6.71 (2H, 2 br s, H-4, H-6), 6.82 (1H, d, J=8.1 Hz, H-5′), 6.87 (1H, dd, J=8.1, 1.8 Hz, H-6′), 6.97 (1H, d, J=1.8 Hz, H-2′). ^{13}C NMR: δ −5.4 (2Me-TBS), 17.4 (Me-3), 18.2 (C-10), 18.5 (C-TBS), 25.8 (3Me-TBS), 45.5 (C-3), 55.5, 56.0 (OMe-3′, OMe-7), 56.7 (OMe-8), 71.5 (C-9), 2×89.5 (C-8), 93.9 (C-2), 109.5, 114.0 (C-4, C-6), 110.4 (C-2′), 119.3 (C-6′), 120.6 (C-5′), 131.1, 131.7, 133.2, (C-3a, C-5, C-1′), 144.1, 145.0, 147.5 (C-7a, C-3′, C-7), 150.9 (C-4′). EIMS 70 eV m/z (rel. int.): 488 (M^+ <1%), 443 (65), 399 (25), 329 (50), 186 (45), 85 (93), 83 (100). IR ν_{max}^{KBr} cm^{-1}: 3500, 2950, 2860, 1618, 1510, 1460, 1282, 1130.

20. Amorphous solid: Anal. Calcd for $C_{29}H_{42}O_7Si$: C, 65.63; H, 7.98. Found: C, 65.93; H, 8.32. ^{1}H NMR ($CDCl_3$): δ 0.14, 0.15 (6H, 2s, 2Me-TBS), 0.99 (9H, s, 3Me-TBS), 1.09, 1.11 (3H, 2d, J=6.6 Hz, H-10), 1.38 (3H, d, J=6.6 Hz, Me-3), 2.08 (3H, s, OAc-9) 3.27, 3.28 (OMe-8), 3.49 (1H, m, H-3), 3.80 (3H, s, OMe-3′), 2×3.90 (6H, 2s, OMe-7), 4.07 (1H, br d, J=6.0 Hz, H-8), 5.10 (1H, m, H-9), 5.11 (1H, d, J=9.6 Hz, H-2), 2×6.69, 6.74, 6.75 (2H, 4br s, H-4, H-6), 6.82 (1H, d, J=8.1 Hz, H-5′), 6.87 (1H, br d, J=8.1 Hz, H-6′), 6.97 (1H, br s, H-2′). ^{13}C NMR: δ −5.4 (2Me-TBS), 16.9, 16.7 (C-10), 17.5 (Me-3), 18.5 (C-TBS), 21.4 (OAc-9), 25.8 (3Me-TBS), 45.5 (C-3), 55.5, 56.0 (OMe-3′, OMe-7), 57.3 (OMe-8), 2×73.0 (C-9), 2×86.0 (C-8), 93.9 (C-2), 110.4 (C-2′), 115.0, 115.2 (C-4, C-6), 119.3 (C-6′), 120.6 (C-5′), 131.6, 133.2, 133.4 (C-3a, C-5, C-1′), 144.0, 145.1, 147.5 (C-7a, C-3′, C-7), 150.9 (C-4′), 170.6 (OAc-9). EIMS 70 eV m/z (rel. int.): 530 (M^+ <1%), 443 (3), 429 (2), 399 (5), 385 (6), 219 (9), 87 (78), 85 (96), 83 (100). IR ν_{max}^{KBr} cm^{-1}: 2937, 2868, 1734, 1604, 1508, 1460, 1244, 1130, 846, 782.

Compounds 21–24

Compounds **16** (0.17 mmol), **17** (0.025 mmol), **18** (0.025 mmol), and **19** (0.16 mmol) were individually dissolved in dry THF (20 mL) at 0° to which was added a solution of 1.0 M ^{n}Bu$_4$NF in THF (2.2 mL). The resulting solutions were stirred for 60 min, and then partitioned between saturated aqueous NH_4Cl (25 mL) and CH_2Cl_2 (20 mL). The organic phases from each treatment were combined with the aqueous phases then extracted with CH_2Cl_2 (3×25 mL).[15] The respective combined organic extracts were washed with saturated aqueous NaCl (30 mL), dried (Na_2SO_4) and concentrated. Individual purification of the products by TLC (hexanes:EtOAc, 1:1) gave **21** (35.7 mg, 58.3%), **22** (8.1 mg, 80.0%), **23** (8.3 mg, 81.1%) and **24** (7.5 mg, 12.5%).

21. Amorphous solid. Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.63; H, 6.60. ^{1}H NMR ($CDCl_3$): δ 1.10 (3H, d, J=6.3 Hz, H-10), 1.38 (3H, d, J=6.9 Hz, Me-3), 3.49 (1H, m, H-3), 3.89 (3H, s, OMe-3′), 3.90 (3H, s, OMe-7), 4.0–3.8 (1H, m, H-9), 4.34 (1H, d, J=7.2 Hz, H-8), 5.12 (1H, d, J=9.6 Hz, H-2), 5.67 (1H, s, OH-4′), 6.75, 6.80 (2H, 2 br s, H-4, H-6), 6.90 (2H, br s, H-5′, H-6′), 6.97 (1H, br s, H-2′). ^{13}C NMR: δ 17.6 (Me-3), 19.0 (C-10), 45.6 (C-3), 2×56.0 (OMe-3′, OMe-7), 72.3 (C-9), 2×79.7 (C-8), 93.8 (C-2), 108.9 (C-2′), 2×110.1, 114.8 (C-4, C-6), 114.0 (C-5′), 119.9 (C-6′), 131.8 (C-1′), 133.2, 134.5 (C-3a, C-5), 144.1, 145.7, 146.5, 147.1 (C-7a, C-4′, C-7, C-3′). EIMS 70 eV m/z (rel. int.): 360 (M^+, 10%), 342 (20), 315 (45), 163 (20), 137 (21), 87 (62), 85 (97), 83 (100). IR ν_{max}^{KBr} cm^{-1}: 3467, 2967, 2927, 1608, 1509, 1457, 1282, 1130, 754.

22. Amorphous solid. Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.13; H, 6.02. ^{1}H NMR ($CDCl_3$): δ 1.11 (3H, d, J=6.3 Hz, H-10), 1.37 (3H, d, J=6.9 Hz, Me-3), 1.59 (1H, br s, OH-8), 2.13 (3H, s, OAc-9), 3.45 (1H, m, H-3), 3.89, 3.90 (6H, s, OMe-3′, OMe-7), 4.56 (1H, br d, J=7.5 Hz, H-8), 4.95 (1H, dq, J=7.5, 6.3 Hz, H-9), 5.12 (1H, d, J=9.6 Hz, H-2), 6.77, 6.81 (2H, 2 br s, H-4, H-6), 6.90 (2H, br s, H-5′, H-6′), 6.97 (1H, br s, H-2′). ^{13}C NMR: δ 17.0 (C-10), 17.8 (Me-3), 21.7 (OAc-9), 45.8 (C-3), 2×56.2 (OMe-3′, OMe-7), 75.1, 75.2 (C-8, C-9), 94.1 (C-2), 109.0 (C-2′), 110.4, 114.6 (C-4, C-6), 114.2 (C-5′), 120.1 (C-6′), 131.7, 133.4, 133.6 (C-3a, C-5, C-1′), 144.3, 145.9, 146.6, 146.7 (C-7a, C-4′, C-7, C-3′), 171.0 (OAc-9). EIMS 70 eV m/z (rel. int.): 402 (M^+ <1%), 315 (2), 87 (30), 85 (95), 83 (100). IR ν_{max}^{KBr} cm^{-1}: 3533, 2936, 2868, 1728, 1606, 1508, 1458, 1252, 1134, 755.

23. Amorphous solid: Anal. Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.87; H, 6.78. ^{1}H NMR ($CDCl_3$): δ 1.11 (3H, d, J=6.8 Hz, H-10), 1.37 (3H, d, J=6.9 Hz, Me-3), 1.59 (1H, br s, OH-8), 2.14 (3H, s, OAc-8) 3.45 (1H, m, H-3), 3.89, 3.90 (6H, s, OMe-3′, OMe-7), 4.07 (1H, m, H-9), 5.48 (1H, 2d, J=5.1, 7.2 Hz, H-8), 5.12 (1H, d, J=9.6 Hz, H-2), 6.77, 6.81 (2H, 2 br s, H-4, H-6), 6.90 (2H, br s, H-5′, H-6′), 6.97 (1H, br s, H-2′). ^{13}C NMR: δ 17.0 (C-10), 17.6 (Me-3), 21.6 (OAc-9), 45.9 (C-3), 2×56.2 (OMe-3′, OMe-7), 2×81.1 (C-8), 70.5 (C-9), 94.1 (C-2), 109.0 (C-2′), 2×110.5, 115.0 (C-4, C-6), 114.2 (C-5′), 120.1 (C-6′), 131.4, 132.5, 133.6 (C-3a, C-5, C-1′), 144.3, 145.9, 146.6, 146.7 (C-7a, C-4′, C-7, C-3′), 170.0 (OAc-9). EIMS 70 eV m/z (rel. int.): 402 (M^+<1%), 315 (2), 87 (31), 85 (96), 83 (100). IR ν_{max}^{KBr} cm^{-1}: 3500, 2940, 2870, 1730, 1605, 1508, 1458, 1255, 1134, 755.

24. Amorphous solid. EIMS, ^{1}H and ^{13}C NMR spectral data for **24** were similar to those previously reported for fragransol A.[14] Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.34; H, 6.52. ^{1}H NMR ($CDCl_3$): δ 1.00 (3H, d, J=7.2 Hz, H-10), 1.39 (3H, d, J=6.9 Hz, Me-3), 3.27 (3H, s, OMe-8), 3.48 (1H, m, H-3), 2×3.90 (6H, s, OMe-7, OMe-3′), 4.1–3.7 (2H, m, H-8, H-9), 5.13 (1H, d, J=9.9 Hz, H-2), 5.68 (1H, s, OH), 6.68, 6.71 (2H, 2 br s, H-4, H-6), 6.91 (2H, br s, H-5′, H-6′), 7.00 (1H, br s, H-2′). ^{13}C NMR: δ 17.4 (Me-3), 18.2 (C-10), 45.6 (C-3), 2×56.0 (OMe-3′, OMe-7), 56.7 (OMe-8), 71.6 (C-9), 2×89.5 (C-8), 93.9 (C-2), 108.9 (C-2′), 110.4, 115.0 (C-4, C-6), 114.0 (C-5′), 119.9 (C-6′), 131.7, 131.8, 133.1, (C-3a, C-5, C-1′), 144.1, 2×145.7, 146.5, (C-7a, C-3′, C-4′, C-7). EIMS 70 eV m/z (rel. int.): 374 (M^+, 4%), 343 (5), 329 (36), 186 (45), 87 (50), 85 (100), 83 (95). IR ν_{max}^{KBr} cm^{-1}: 3460, 2968, 2934, 1605, 1519, 1460, 1277, 1133, 756.

(*R*)- and (*S*)-MTPA derivatives 26, 27, 29, 30, 32, 37, 38, 40 and 41

These were prepared from compounds **25**, **28**, **31**, **36** and **39** in yields ~99%, as earlier described for formation of compounds **13** and **14**.

26 and 41. IR, EIMS, ^{1}H and ^{13}C NMR spectral data were identical. ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, d, J=6.6 Hz, H-10), 1.34 (3H, d, J=6.3 Hz, Me-3), 3.38 (1H, m, H-3), 3.41, 3.45 (6H, 2s, OMe-MTPA), 3.71 (3H, s, OMe-7), 3.74 (3H, s, OMe-MTPA), 3.84 (3H, s, OMe-3′), 5.19 (1H, d, J=9.3 Hz, H-2), 5.46 (1H, dq, J=6.6, 5.1 Hz, H-9), 6.01 (1H, d, J=5.1 Hz, H-8), 6.68 (1H, br s, H-6), 6.70 (1H, br s, H-4), 6.99 (1H, dd, J=8.4, 1.8 Hz, H-6′), 7.03 (1H, d, J=8.4 Hz, H-5′), 7.08 (1H, d, J=1.8 Hz, H-2′), 7.7–7.4 (15H, m, Ph-MTPA). ^{13}C NMR ($CDCl_3$): δ 16.7 (C-10), 18.1 (Me-3), 46.0 (C-3), 2×55.5 (2×OMe-MTPA), 2×56.0 (OMe-MTPA, OMe-7), 56.2 (OMe-3′), 74.4 (C-9), 78.9 (C-8), 93.3 (C-2), 2×110.6 (C-6, C-2′), 114.9 (C-4), 118.8 (C-6′), 122.4 (C-5′), 127.3, 127.7, 128.6, 128.8, 129.9 (Ph-MTPA), 131.9, 133.1 (C-3a, C-5), 139.0 (C-1′), 139.8 (C-3′), 144.2, 147.6 (C-7a, C-7), 151.2 (C-4′), 164.4, 165.8 (CO-MTPA). IR ν_{max}^{KBr} cm^{-1}: 2956, 2850, 1762, 1611, 1512, 1466, 1295, 1183, 1118, 769, 716. **26**: Colorless oil. Anal. Calcd for $C_{50}H_{45}F_9O_{12}$: C, 59.53; H, 4.50. Found: C, 60.19; H, 5.10. α_D^{25}=−47.1° ($CHCl_3$; c 1.00). CD (CH_3OH, c 0.08) $[\theta]_{241}$=−19042, $[\theta]_{278}$=−2988.

27 and 40. IR, UV, EIMS, ^{1}H and ^{13}C NMR spectral data were identical. ^{1}H NMR ($CDCl_3$): δ 1.24 (3H, d, J=6.0 Hz, H-10), 1.32 (3H, d, J=6.6 Hz, Me-3), 3.38 (1H, m, H-3), 3.43, 3.45 (6H, 2s, OMe-MTPA), 3.68 (3H, s, OMe-7), 3.75 (3H, s, OMe-MTPA), 3.84 (3H, s, OMe-3′), 5.19 (1H, d, J=9.6 Hz, H-2), 5.47 (1H, m, H-9), 5.94 (1H, d, J=5.7 Hz, H-8), 6.64 (1H, br s, H-6), 6.70 (1H, br s, H-4), 7.0–7.2 (2H, m, H-5′, H-6′), 7.09 (1H, br s, H-2′), 7.7–7.4 (15H, m, Ph-MTPA). IR ν_{max}^{KBr} cm^{-1}: 2956, 2850, 1762, 1611, 1512, 1466, 1295, 1183, 1118, 769, 716. UV $\lambda_{max}^{CH_3OH}$ nm (log ϵ): 210 (4.78), 240 sh (4.00), 278 (3.70). **27**: Colorless oil. Anal. Calcd for $C_{50}H_{45}F_9O_{12}$: C, 59.53; H, 4.50. Found: C, 59.98; H, 5.14. α_D^{25}=0° ($CHCl_3$; c 1.01). CD (CH_3OH, c 0.05) $[\theta]_{241}$=−8086, $[\theta]_{271}$=−2210.

29 and 38. IR, EIMS, ^{1}H and ^{13}C NMR spectral data were identical. ^{1}H NMR ($CDCl_3$): δ 1.25 (3H, d, J=6.0 Hz, H-10), 1.32 (3H, d, J=6.9 Hz, Me-3), 3.37 (1H, m, H-3), 3.44, 3.47 (6H, 2s, OMe-MTPA), 3.68 (3H, s, OMe-7), 3.74 (3H, s, OMe-MTPA), 3.83 (3H, s, OMe-3′), 5.18 (1H, d, J=9.0 Hz, H-2), 5.46 (1H, m, H-9), 5.95 (1H, d, J=6.0 Hz, H-8), 6.58 (1H, s, H-4), 6.64 (1H, s, H-6), 6.98 (1H, dd, J=8.1, 1.7 Hz, H-6′), 7.02 (1H, d, J=8.1 Hz, H-5′), 7.09 (1H, d, J=1.7 Hz, H-2′), 7.7–7.4 (15H, m, Ph-MTPA). ^{13}C NMR ($CDCl_3$): δ 16.8 (C-10), 17.8 (Me-3), 46.2 (C-3), 2×55.5, (OMe-MTPA), 55.8 (OMe-7), 55.9 (OMe-MTPA), 56.1 (OMe-3′), 74.7 (C-9), 79.5 (C-8), 2×110.4 (C-2′, C-6), 114.8 (C-4), 118.8 (C-6′), 122.4 (C-5′), 132.2, 133.0 (C-3a, C-5), 131.7, 131.5, 127.7, 128.5, 129.9 (Ph-MTPA), 139.0 (C-1′), 140.0, 144.3, 147.6 (C-3′, C-7a, C-7), 151.0 (C-4′). IR ν_{max}^{KBr} cm^{-1}: 2956, 2850, 1762, 1611, 1512, 1466, 1295, 1183, 1118, 769, 716. **29**: Colorless oil. Anal. Calcd for $C_{50}H_{45}F_9O_{12}$: C, 59.53; H, 4.50. Found: C, 60.09; H, 5.08. α_D^{25}=−10.1° ($CHCl_3$; c 0.99). CD (CH_3OH, c 0.07) $[\theta]_{239}$=−15643, $[\theta]_{275}$=−2657. **38**: Colorless oil. Anal. Calcd for $C_{50}H_{45}F_9O_{12}$: C, 59.53; H, 4.50. Found: C, 59.47; H, 4.97. α_D^{25}=0° ($CHCl_3$; c 1.00).

30 and 37. IR, EIMS, ^{1}H and ^{13}C NMR spectral data were identical. EIMS 70 eV m/z(rel. int.): 809, 808, 807, 793, 792, 791, 777, 776, 775, (<1%), 542 (2), 325 (5), 323 (2), 189 (64), 86 (73), 85 (90), 83 (100). ^{1}H NMR ($CDCl_3$): δ 1.29 (3H, d, J=6.0 Hz, H-10), 1.33 (3H, d, J=6.6 Hz, Me-3), 3.38 (1H, m, H-3), 3.41, 3.44 (6H, 2 s, OMe-MTPA), 3.70 (3H, s, OMe-7), 3.74 (3H, s, OMe-MTPA), 3.84 (3H, s, OMe-3′), 5.18 (1H, d, J=9.3 Hz, H-2), 5.48 (1H, m, H-9), 6.04 (1H, d, J=4.8 Hz, H-8), 6.58 (1H, br s, H-4), 6.67 (1H, br s, H-6), 6.98 (1H, dd, J=8.1, 1.5 Hz, H-6′), 7.02 (1H, d, J=8.1 Hz, H-5′), 7.09 (1H, d, J=1.5 Hz, H-2′), 7.7–7.4 (15H, m, Ph-MTPA). ^{13}C NMR ($CDCl_3$): δ 16.6 (C-10), 17.9 (Me-3), 46.1 (C-3), 2×55.4, (OMe-MTPA), 2×56.0 (OMe-MTPA, OMe-7), 56.1 (OMe-3′), 74.4 (C-9), 78.9 (C-8), 93.3 (C-2), 110.4 (C-6), 110.5 (C-2′), 114.7 (C-4), 118.7 (C-6′), 122.5 (C-5′), 127.5, 127.7, 127.8, 128.5, 128.6, 129.8, 129.9, 131.8 (Ph-MTPA), 131.9, 133.9 (C-3a, C-5), 139.0 (C-1′), 140.0 (C-3′), 144.3, 147.6 (C-7a, C-7), 151.2 (C-4′), 164.7, 165.8, 165.9 (CO-MTPA). IR ν_{max}^{KBr} cm^{-1}: 2956, 2850, 1762, 1611, 1512, 1466, 1295, 1183, 1118, 769, 716. **30**: Colorless oil. Anal. Calcd for $C_{50}H_{45}F_9O_{12}$: C, 59.53; H, 4.50. Found: C, 60.19; H, 5.10. α_D^{25}=+17.0° ($CHCl_3$; c 0.88). CD (CH_3OH, c 0.05) $[\theta]_{241}$=−10928, $[\theta]_{275}$=−2990. **37**: Colorless oil. Anal. Calcd for $C_{50}H_{45}F_9O_{12}$: C, 59.53; H, 4.50. Found: C, 59.84; H, 4.58. α_D^{25}=−44.4° ($CHCl_3$; c 1.06).

32. Colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.47 (3H, d, J=6.6 Hz, Me-3), 1.58 (3H, d, J=6.9 Hz, H-10), 3.51 (1H, m, H-3), 3.68 (3H, s, OMe-MTPA), 3.74 (3H, s, OMe-MTPA), 3.83 (3H, s, OMe-3′), 3.95 (3H, s, OMe-7), 5.31 (1H, d, J=9.0 Hz, H-2), 6.13 (1H, q, J=6.9 Hz, H-9), 6.99 (1H, dd, J=8.1, 1.8 Hz, H-6′), 7.04 (1H, d, J=8.1 Hz, H-5′), 7.05 (1H, d, J=1.8 Hz, H-2′), 7.26 (1H, s, H-6), 7.52 (1H, s, H-4), 7.7–7.4 (10H, m, Ph-MTPA). ^{13}C NMR ($CDCl_3$): δ 17.8 (C-10), 18.4 (Me-3), 45.7 (C-3), 56.4, 2×56.0 (OMe-3′, OMe-MTPA, OMe-7), 55.5, (OMe-MTPA), 73.5 (C-9), 94.1 (C-2), 110.5 (C-2′), 112.5 (C-6), 117.7 (C-4), 118.7 (C-6′), 122.6 (C-5′), 127.7, 128.6, 129.9 (Ph-MTPA), 132.1, 133.1 (C-3a, C-5), 139.2 (C-1′), 139.4 (C-3′), 144.9 (C-7), 151.3 (C-4′), 152.7 (C-7a), 166.4 (CO-MTPA), 194.0 (C-8). IR ν_{max}^{KBr} cm^{-1}: 2960, 2861, 1761, 1697, 1611, 1506, 1466, 1170, 1118, 769.

Compounds 34 and 35

To a stirred solution of diol **25** (19.2 mg, 0.033 mmol) in MeOH (200 μL) was added 2 mL of acetic acid in H_2O (10% v/v). The mixture was heated until reflux began, this being maintained for 20 min. Following cooling to room temperature, the reaction mixture was extracted with CH_2Cl_2 (3×10 mL). The organic solubles were combined, then washed successively with 1N NaOH until pH 7 and water (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product (**25**+**33**) was subjected to esterification with (*S*)-MTPACl. After prep. TLC (hexanes: EtOAc, 2:1), the crude product afforded **27** (5.52 mg, yield 16.6%), **34** (6.82 mg, yield 26.1%), and **35** (3.40 mg, yield 10.3%).

34. Colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.15 (3H, d, J=6.3 Hz, H-10), 1.40 (3H, d, J=6.9 Hz, Me-3), 3.44 (1H, m, H-3), 3.53 (3H, s, OMe-MTPA), 3.74 (3H, s, OMe-MTPA), 3.83 (3H, s, OMe-3′), 3.88 (3H, s, OMe-7), 5.18 (1H, d, J=9.6 Hz, H-2), 5.50 (1H, dq, J=6.3, 8.4 Hz, H-9), 5.73 (1H, d, J=8.4 Hz, H-8), 6.79 (2H, s, H-4, H-6), 7.02 (2H, m, H-5′, H-6′), 7.08 (1H, br s, H-2′), 7.7–7.3 (10H, m, Ph-MTPA). IR ν_{max}^{KBr} cm^{-1}: 3540, 2955, 2850, 1760, 1610, 1510, 1464, 1294, 1182, 1120.

35. Colorless oil. Anal. Calcd for $C_{50}H_{45}F_9O_{12}$: C, 59.53; H, 4.50. Found: C, 58.99; H, 5.02. ^{1}H NMR ($CDCl_3$): δ 1.09 (3H, d, J=6.6 Hz, H-10), 1.35 (3H, d, J=6.6 Hz, Me-3), 3.44 (1H, m, H-3), 3.51 (3H, s, OMe-MTPA), 3.56 (3H, s, OMe-MTPA), 3.78 (3H, s, OMe-7), 3.74 (3H, s, OMe-MTPA), 3.84 (3H, s, OMe-3′), 5.18 (1H, d, J=9.6 Hz, H-2), 5.26 (1H, dq, J=6.6, 8.7 Hz, H-9), 5.80 (1H, d, J=8.7 Hz, H-8), 6.65 (1H, s, H-6), 6.72 (1H, s, H-4), 7.02 (2H, m, H-5′, H-6′), 7.08 (1H, br s, H-2′), 7.7–7.3 (15H, m, Ph-MTPA). IR ν_{max}^{KBr} cm^{-1}: 2956, 2850, 1762, 1611, 1512, 1466, 1295, 1183, 1118, 769, 716.

Acknowledgements

The authors thank the Fundação de Amparo à Pesquisa do Estado de São Paulo for financial support, including a fellowship to I. R. Nascimento. The authors are also grateful to the Arthur M. and Katie E. Eisig-Tode Foundation for generous support, and to the U.S. Dept. of Energy. Thanks are also extended to Dr Leila Beltramini (USP, São Carlos) for measurements of CD spectra.

References

1. (a) Nascimento, I. R.; Lopes, L. M. X. *Phytochemistry* **1999**, *52*, 345–350. (b) Nascimento, I. R.; Lopes, L. M. X. *Phytochemistry* **2000**, *53*, 621.
2. Chioccara, F.; Poli, S.; Rindone, B.; Pilati, T.; Brunow, G.; Pietikainen, P.; Setälä, H. *Acta Chem. Scand.* **1993**, *47*, 610–616.
3. Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515–10530.
4. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
5. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
6. Achenbach, H.; Groß, J.; Dominguez, X. A.; Cano, G.; Star, J. V.; Brussolo, L. del C.; Muñoz, G.; Salgado, F.; López, L. *Phytochemistry* **1987**, *26*, 1159–1166.
7. Ichikawa, A. *Enantiomer* **1997**, *2*, 327–331.
8. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335–5340.
9. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334.
10. Holder, R. W.; Matturro, M. G. *J. Org. Chem.* **1977**, *42*, 2166–2168.
11. Binkley, R. W. *J. Org. Chem.* **1985**, *50*, 5646–5649.
12. Pütter, J. *Methods of Enzymatic Analysis*; Verlag Chemie, Academic: New York, 1974; pp 685–690.
13. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5321–5330.
14. Hada, S.; Hattori, M.; Tezuka, Y.; Kikuchi, T.; Namba, T. *Phytochemistry* **1988**, *27*, 563–568.
15. Carreira, E. M.; du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106–8125.