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NATURAL PRODUCTS SYNTHESES USING ANODIC OXIDATION OF PHENOLS AS A KEY STEP

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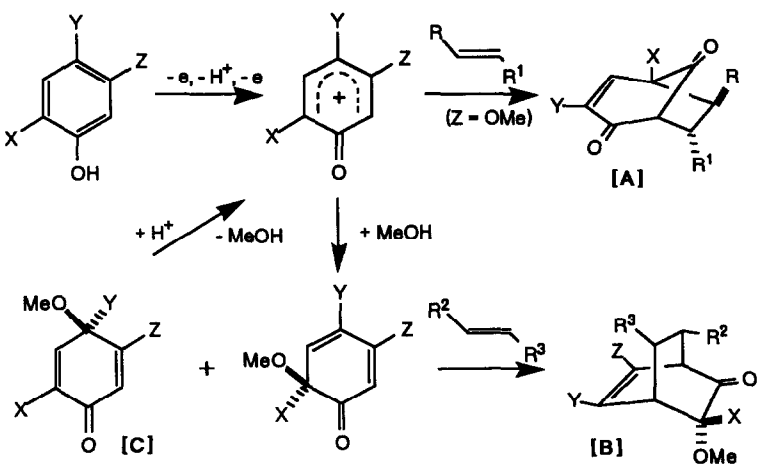
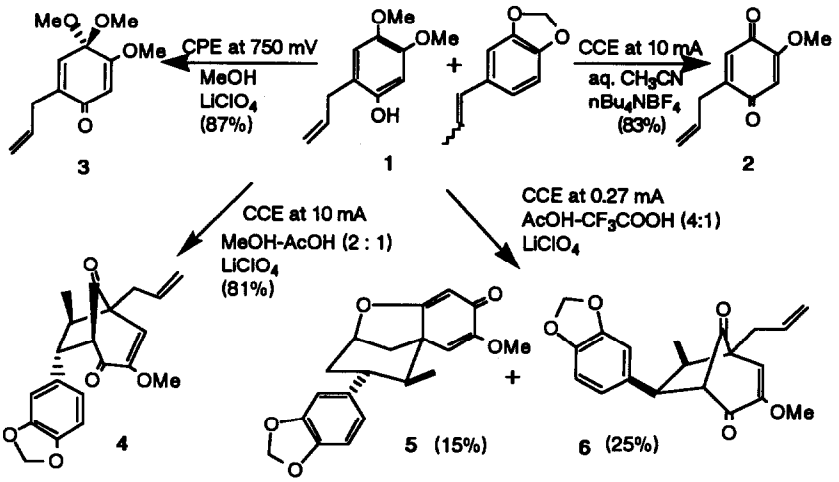
Summary Some bioactive natural products such as terpenoids, neolignans and others have been synthesized by means of an electrochemical method, wherein anodic oxidation of phenols is carried out as a key step.

Electrochemical studies on phenols and their alkyl ethers have been made for a long time.[1] In the case of phenols, however, it is not always easy to obtain a desired compound in a regio- and stereoselective manner, because three unstable species ($ArO^{+\bullet}H$, $ArO^{\bullet}$, ArO^{+}) are electrogenerated and each one exhibits chemical reactivity. Therefore, it is quite important to find the optimum conditions by changing oxidation potential, current density, electrode, supporting electrolyte ($LiClO_4$, R_4NBF_4) and others. Of these three unstable species, the electrogenerated phenoxy cation is further converted into three different types of compounds [A], [B] and [C] depending on the substituents (X, Y, Z), the solvent used for electrolysis and the olefins included in the reaction system, as seen in Scheme 1.



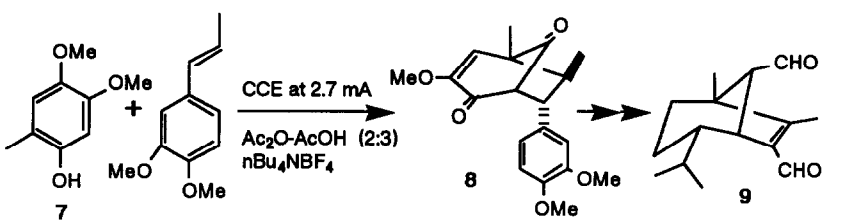
Scheme 1. Reactivity of electrogenerated cation.

In the course of our synthetic studies on bioactive neolignans, as described in the previous paper,[2] 2-allyl-4,5-dimethoxyphenol (1) was electrolyzed at a controlled potential or a constant current using 90% aq. CH_3CN, MeOH, and MeOH - AcOH (2 : 1) including excess (E)-isosafrole and $LiClO_4$ as a supporting electrolyte to



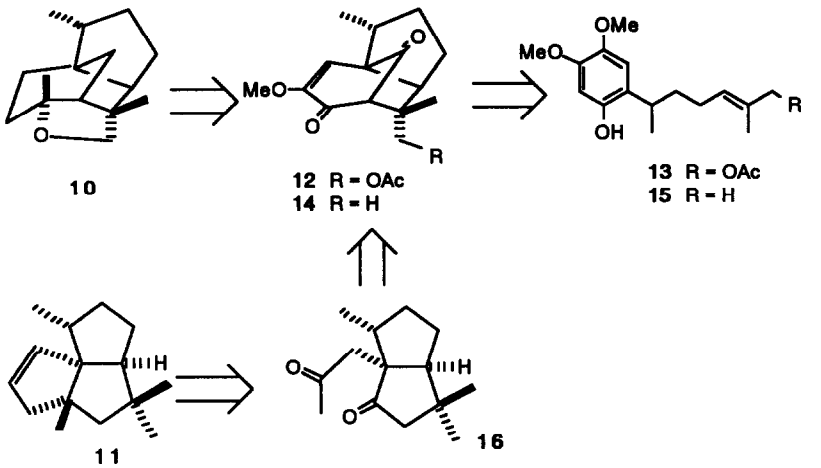
Scheme 2. Product selectivity depending on solvents.

afford 2-allyl-5-methoxy-1,4-benzoquinone (**2**), 2-allyl-4,4,5-trimethoxycyclohexa-2,5-dien-1-one (**3**) and one of aniba neolignans (**4**) with a bicyclo[3.2.1]oct-3-en-2,8-dione system[3] in high yields, respectively. When (Z)-isosafrole was used instead of the E-isomer, futoenone (**5**) and an exo addition product (**6**) were selectively obtained, as shown in Scheme 2. Similarly, 3,4-dimethoxy-6-methylphenol (**7**) was electrolyzed at a constant current in Ac_2O - AcOH (2:3) containing excess (E)-isoeugenol methyl ether and nBu_4NBF_4 as a supporting electrolyte to give rise to a desired bicyclic compound (**8**), in 80% yield, from which helminthosporal (**9**) was successfully synthesized as shown in Scheme 3.[4] In the case of phenols bearing an olefinic double bond at the side



Scheme 3. Total synthesis of helminthosporal.

chain, as expected, the electrogenerated phenoxy cations may react with the double bond in a manner of intramolecular [5 + 2] cycloaddition to afford the corresponding tricyclic compounds. We describe herein total syntheses of both (±)-8,14-cedranoxide (**10**)[5] and (±)-silphinene (**11**),[6] whose retrosyntheses are shown in Scheme 4, wherein the former is derived from 6-acetoxymethyl-2,6-dimethyl-9-methoxytricyclo[5.3.1.$0^{1,5}$]undec-9-en-8,11-dione (**12**) as a key intermediate which is produced by means of anodic oxidation of the corresponding phenol (**13**) derivable from 3,4-dimethoxyphenol. Silphinene (**11**) is also synthesized from 2,6,6-trimethyl-9-

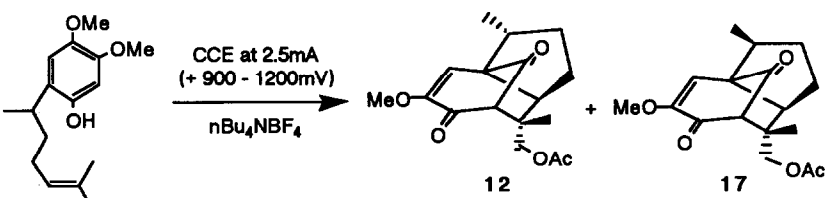


Scheme 4. Retrosyntheses of (±)-8,14-cedranoxide and (±)-silphinene

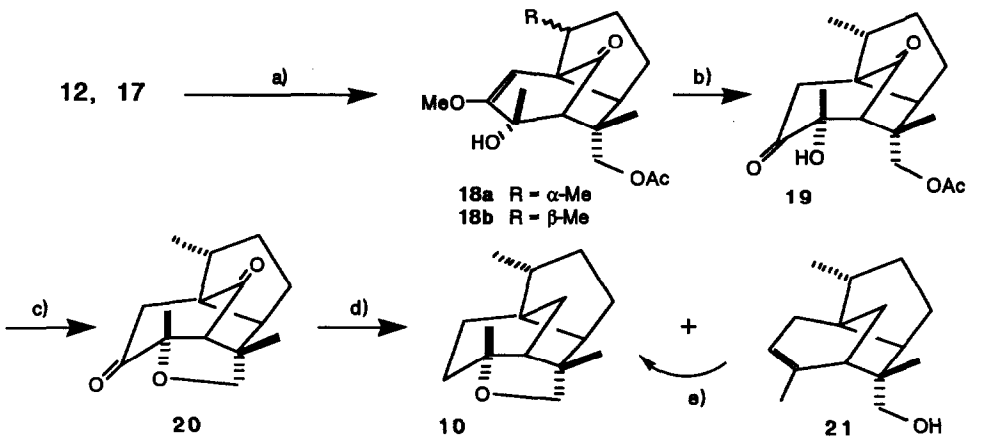
methoxytricyclo[5.3.1.$0^{1,5}$]undec-9-en-8,11-dione (**14**), an oxidation product of the phenol (**15**), through a bicyclic compound (**16**).

When electrolyzed at a constant current [2.5 mA (+900 - 1200 mV *vs* SCE); ca. 2F/mol] using nBu_4NBF_4 as a supporting electrolyte, the phenol (**13**) was converted into an inseparable mixture of two tricyclo[5.3.1.$0^{1,5}$] undec-9-en-8,11-diones (**12** and **17**), whose isolated yields varied with a solvent system, as described below. Their stereostructures are based on ^1H NMR spectral data: particularly, the methyl doublet (δ 1.42) in **17** is observed in lower magnetic field as compared with the corresponding one (δ 1.15) in **12**, because of an anisotropic effect of the carbonyl group at C_{11}-position.

The mixture (**12** and **17**) so obtained was treated with MeMgI (1.4 equiv.) in THF to give an inseparable mixture of two hydroxy compounds (**18a** and **18b**), which was further hydrolyzed with oxalic acid in MeOH to afford the desired diketone (**19**) as colorless needles, in high yield. This pure diketone (**19**) was treated with BF_3-etherate to afford a tetrahydrofuran (**20**) which was subjected to Wolff - Kishner reduction to give rise to 8,14-cedranoxide (**10**) and 8-cedren-14-ol (**21**) in 20 and 50% yields, respectively. When treated with catalytic amount of *p*-TsOH in benzene, the latter was converted into the natural sesquiterpene (**10**) in 88% yield. Therefore, total yield of 8,14-cedranoxide (**10**) from **20** was 65%.



Ac_2O - AcOH (3:2)	44%	trace
Ac_2O - AcOH (5:1)	51%	trace
Ac_2O	64%	16%



Scheme 5. Total synthesis of (±)-8,14-cedranoxide.

a) MeMgI (1.4 equiv.) / THF (51%); b) $(COOH)_2$ / MeOH (93%); c) $BF_3{\cdot}OEt_2$ / benzene under Ar (72%); d) KOH-NH_2NH_2 / ethylene glycol (10; 20%; 21: 50%);e) p-TsOH /toluene under Ar (88%).

Silphinene, a constituent of the roots of *Silphium perfoliatum*,[6] has attracted the considerable attention of synthetic chemists.[7] As demonstrated in Scheme 4, our synthetic strategy may be used for other triquinane sesquiterpenes. The phenol (**15**) was subjected to anodic oxidation [1.8 mA (+ 750 - 1200 mV *vs*SCE); ca. 2 F/mol] in Ac_2O containing nBu_4NBF_4 as a supporting electrolyte to afford the desired tricyclo[5.3.1.$0^{1,5}$] undec-9-en-8,11-dione (**14**) (Scheme 6). The tricyclic compound (**14**) obtained was selectively reduced with DIBAL-H (1.1 equiv.) and then subjected to acetylation followed by hydrolysis with oxalic acid giving an α-acetoxyketone (**22**), in good yield. On Grignard reaction using MeMgBr, the carbonyl group at C_9-position in **22** was selectively attacked by the reagent to afford a diol (**23**), which was further treated with $LiAlH_4$ to give a triol (**24**), in high yield.

The triol (**24**) was further oxidized with $Pb(OAc)_4$ in MeOH and then $NaClO_2$ to give a bicyclic compound (**25**), in quantitative yield, which was subjected to esterification using MOMCl - K_2CO_3 followed by PDC oxidation to give a mixture of two ketones (**26** and **27**). The former was treated with 1N HCl to afford the desired intermediate (**16**) which was directly converted into a tricyclic compound (**28**) in almost quantitative yield. On methylation with $Me_2Cu(CN)Li_2$, finally, **28** was readily converted into the pure ketone (**29**), in 92% yield, from which silphinene (**11**) had been already synthesized.[8] The triketone (**27**) was also converted into a triquinane-type compound (**30**), as seen in Scheme 6.

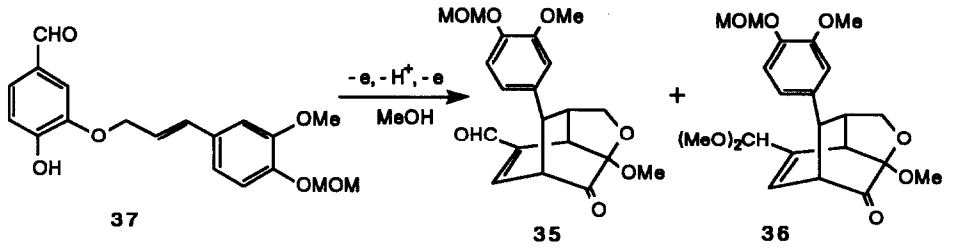
On the basis of Scheme 1 suggesting electrochemical synthesis of a bicyclo[2.2.2]octanone [**B**], asatone (**31**) isolated from the plant *Asarum taitonense* H. was synthesized using anodic oxidation of 4-allyl-2,6-dimethoxyphenol giving the corresponding dienone (**32**), as shown in Scheme 7.[9] In connection with **31** and related neolignans, silydianin (**33**) as an antihepatotoxic agent isolated from the fruits of *Silybum marianum* G.[10] is quite interesting from view points of both molecular structure and physiological activity. Thus, we have also accomplished a facile synthesis of deoxysilydianin methyl ether (**34a**) and its diastereoisomer (**34b**), both of which have the same 9-oxaisotwist-8-en-2-one ring system as that of silydianin (**33**), using an electrochemical method.

Table 3

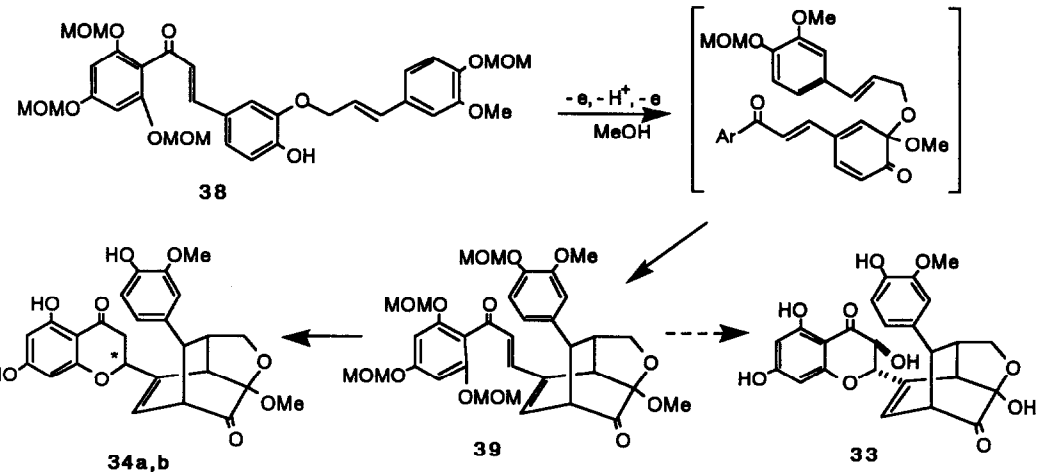
Preparative Results for the anodic Oxidation of DIPE. j = 750 A m^{-2}, T = 35 °C.
Cells: QDCC (300 ml,) Nos 1 – 6, and MPC (1250 ml), Nos 7,8

Group	No	Anode	Cosolv.	Vol %			State	β/% (4 F)	β_{eff} %	Acetone		CH_3COOH		HCN
				1M H_2SO_4	Cosolv.	DIPE				ce(%)	y(%)	ce(%)	y(%)	ce(%)
1	1	Pt	–	67	–	33	het.	53	70	32	20	8	1	–
	2	PbO_2	–	67	–	33	het.	51	42	17	20	7	1	–
2	3	Pt	MeCN	47	30	23	het→hom	50	84	68	66	9	1	0
	4	PbO_2	MeCN	47	30	23	het.	50	66	34	34	5	1	0
	5	Pt	HOAc	47	30	23	het→hom	50	77	46	45	(–)	(–)	–
	6	PbO_2	HOAc	47	30	23	het.	50	72	10	8	(–)	(–)	–
3	7	Pt	–	81	–	19	het.	61	48	10	13	–	–	–
	8	PbO_2	–	79	–	21	het.	39	48	12	11	4	1	–

Group 1,3 : Systems without cosolvent in the QDCC and MPC cell, respectively
Group 2 : Systems with cosolvents.



Thus, the phenol (**38**) obtainable from the same benzaldehyde was subjected to anodic oxidation at a controlled potential (CPE: + 950 mV vs SCE; ca. 2 F/mol) in MeOH - THF (2:1) using $LiClO_4$ as a supporting electrolyte, affording a desired 9-oxaisotwist-8-en-2-one (**39**), in 82% yield, from which both **34a** and **34b** were synthesized in two steps, as shown below.



Experimental

All the melting points were obtained on a Mitamura Riken melting point apparatus and uncorrected. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^1H NMR spectra were taken on a Varian EM-390 (90MHz) or JEOL JNM GX-400 (400MHz) NMR spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Coupling constants are given in Hz (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet). High resolution mass spectra were obtained on a Hitachi M-80 GC-MS spectrometer operating with an ionization energy (70 eV). Preparative and analytical TLC were carried out on silica gel plates (Kieselgel 60 F_{254}, E. Merck A. G. West Germany) using UV light and/or 5% molybdo phosphoric acid in EtOH for detection. Katayama silica gel (K 70) was used for column chromatography. A YANAKO potentiostat V8 was used for anodic oxidation of phenols, and a 200 or 30 ml glassy carbon beaker (Tokai Carbon GC-20) and a platinum wire tip were used as an anode and a cathode, respectively, without dividing two electrodes.

Syntheses of the phenols (13 and 15). The phenol (**13**) was synthesized in 40% overall yield starting from 3,4-dimethoxyphenol, as follows: 1. crotyl chloride (2.0 equiv.) / K_2CO_3 (2.0 equiv.) / acetone (refluxing temp, 2 days) (97%); 2. 200 °C, 2 h under Ar (99%); 3. $tBuMe_2SiCl$ (1.2 equiv.) / imidazole (2.4 equiv.) / DMF (room temp., 18.5 h) (100%); 4. $BH_3 \cdot Me_2S$ (1.0 equiv.) / THF (0°C, 10 min and then room temp., 8 h) and then 3M aq. NaOH / 35% aq. H_2O_2 (room temp., 2h) (87%); 5. DMSO (16 equiv.) / CF_3COOH (0.6 equiv.) / pyridine (1.5 equiv.) / DCC (4 equiv.) / benzene (0 °C, 30 min and then room temp., 3.3 h) (93%); 6. $MeOCH_2PPh_3Cl$ (1.5 equiv.) / tAmOK (1.5 equiv.) / toluene (0 °C, 30 min) under Ar (93%); 7. p-TsOH (catalytic amount) / acetone under Ar (room temp., 1.3 h) (100%); 8. $Ph_3P{=}CMeCOOMe$ (2.0 equiv.) / benzene under Ar (room temp., 18 h) (92%); 9. 1.5M DIBAL-H (4.0 equiv.) / THF under Ar (room temp., ca. 3 h) (99%); 10. excess Ac_2O / pyridine (room temp., 20 min) (100%); 11. nBu_4NF (1.5 equiv.) / THF under Ar (room temp., 15 min) (100%). The phenol (**15**) was also produced in 2 steps [1.

$Ph_3P{=}CMe_2$ (1.2 equiv.) / THF under Ar (room temp., 2 h) (87%); 2. nBu_4NF / THF (room temp., 20 min) (97%)] starting from the synthetic intermediate at 7th step in the above sequence. Each structure of synthetic intermediates was confirmed by IR, ^1H NMR and high resolution mass spectra, and both **13** and **15** have the following spectral data.

13 as a colorless oil: IR (film) 3450, 1730, 1710sh, and 1610 cm^{-1}; δ 1.19 (3H, d, J= 7 Hz), 1.53 (3H, s), 1.5 - 1.8 (2H, complex), 1.9 - 2.1 (2H, complex), 2.03 (3H, s), 2.96 (1H, m), 3.75 (3H, s), 3.78 (3H, s), 4.41 (2H, s), 5.17 (1H, s), 5.42 (1H, brt, J= 7 Hz), 6.40 (1H, s), and 6.63 (1H, s); Calcd for $C_{18}H_{26}O_5$: m/z 322.1778. Found: m/z 322.1754.

15 as a colorless oil: IR (film) 3450 cm^{-1}; δ 1.21 (3H, d, J= 7 Hz), 1.52 (3H, s), 1.67 (3H, s), 1.50 - 2.00 (4H, complex), 2.90 (1H, m), 3.80 (6H, s), 4.57 (1H, brs), 5.11 (1H, t, J= 7 Hz), 6.40 (1H, s), and 6.64 (1H, s); Calcd for $C_{16}H_{24}O_3$: m/z 264.1725. Found: m/z 264.1730.

Anodic oxidation of the phenol (13) in Ac_2O using a 30 ml glassy carbon beaker as an anode. A solution of **13** (15.0 mg) in Ac_2O (10 ml) containing nBu_4NBF_4 (150 mg) was electrolyzed at a constant current (2.5 mA: + 900 - 1200 mV vs SCE) with stirring under Ar, and then the reaction was stopped at ca. 2 F / mol. The reaction solution was concentrated under reduced pressure and directly subjected to preparative TLC using hexane-EtOAc (3 : 2) to give an inseparable mixture of two bicyclic compounds (**12** and **17**, relative ratio: **12**/**17** = 4) (11.4 mg). In addition, the corresponding benzoquinone was obtained in 18.7% yield (2.6 mg).

A mixture of **12** and **17**: IR (film) 1740, 1680, and 1590 cm^{-1}; Calcd for $C_{17}H_{22}O_5$: m/z 306.1465. Found: m/z 306.1442. The NMR signals due to **12**: δ 1.07 (3H, s), 1.15 (3H, d, J= 7 Hz), 1.53 (2H, complex), 1.76 (1H, m), 1.91 (1H, m), 2.03 (3H, s), 2.34 (1H, t, J= 8 Hz), 2.68 (1H, m), 3.43 (1H, s), 3.70 (3H, s), 3.85 (1H, d, J= 11 Hz), 3.96 (1H, d, J= 11 Hz), and 6.38 (1H, s). The NMR signals due to **17**: δ 1.09 (3H, s), 1.42 (3H, d, J= 7 Hz), 1.53 (2H, complex), 1.76 (1H, m), 1.91 (1H, m), 2.02 (3H, s), 2.34 (1H, t, J= 8 Hz), 2.68 (1H, m), 3.31 (1H, s), 3.71 (3H, s), 3.81 (1H, d, J= 11 Hz), 3.95 (1H, d, J= 11 Hz), and 6.25 (1H, s).

Anodic oxidation of the phenol (15) using a 30 ml glassy carbon beaker as an anode. A solution of **15** (9.0 mg) in Ac_2O (10 ml) containing nBu_4NBF_4 (150 mg) was electrolyzed at a constant current (1.84 mA; + 750 - 1200 mV *vs* SCE with stirring and the reaction was stopped at ca. 2.0 F / mol. The reaction solution was concentrated under reduced pressure and then separated by preparative TLC hexane - EtOAc (5:2) to give the bicyclic compound (**14**) in 59% (5.0 mg): IR (film) 1750, 1680, and 1650sh cm^{-1}; δ 1.04 (3H, s), 1.09 (3H, s), 1.16 (3H, d, J= 7 Hz), 1.40 - 1.54 (2H, complex), 1.77 (1H, m), 1.92 (1H, m), 2.16 (1H, t, J= 8 Hz), 2.66 (1H, m), 3.30 (1H, s), 3.70 (3H, s), and 6.43 (1H, s); Calcd for $C_{15}H_{20}O_3$: m/z 248.1411. Found: m/z 248.1414.

Anodic oxidation of the phenol (15) using a 200 ml glassy carbon beaker as an anode. A solution of **15** (616 mg) in Ac_2O (150 ml) containing nBu_4NBF_4 (750 mg) was electrolyzed at a constant current (58 mA; + 920 - 1700 mV *vs* SCE with stirring and the reaction was stopped at ca. 2.0 F / mol. According to the same procedure as described above, **14** (314 mg) was also obtained in 54% yield.

Grignard reaction of a mixture of 12 and 17. To a solution of the mixture (1.09 g) in THF (19 ml) was added a solution of MeMgI [Mg (152 mg) + MeI (0.39 ml)] in Et_2O (30 ml) at -78 °C under Ar. The reaction temperature was gradually elevated to room temperature. After ca. 2 h, the reaction solution was neutralized with 1N HCl and then partitioned between EtOAc and sat.aq. $Na_2S_2O_3$. The EtOAc solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give an oil which was purified by column chromatography using $CHCl_3$ - EtOAc (20:1) giving a mixture of two hydroxy compounds (**18a** and **18b**): IR (film) 3450 and 1740 cm^{-1}; Calcd for $C_{18}H_{26}O_5$: m/z 322.1778. Found: m/z 322.1758. The NMR signals due to **18a**: δ 0.98 (3H, d, J= 7 Hz) and 1.39 (3H, s). The NMR signals due to **18b**: δ 1.29 (3H, d, J= 7Hz) and 1.40 (3H, s).

Hydrolysis of the mixture (18a and 18b). A solution of the mixture (492 mg) and sat. aq. $(COOH)_2$ (5 ml) in MeOH (20 ml) was stirred at room temperature for 14 h, and then partitioned between EtOAc and water. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography using hexane - EtOAc (3:2) to give an oil (443 mg), which was crystallized from hexane - EtOAc to afford the diketone (**19**) as colorless needles: mp 142 - 145 °C; IR (film) 3500, 1740, and 1720 cm^{-1}; δ 0.91 (3H, d, J= 7 Hz) and 1.31 (3H, s); Calcd for $C_{17}H_{24}O_5$: m/z 308.1621. Found: m/z 308.1607.

Formation of a tetrahydrofuran (20). To a solution of **19** (22.3 mg) in toluene (2 ml) was added $BF{\cdot}OEt_2$ (0.07 ml) and the resulting solution was stirred at refluxing temperature for 52 h, and then diluted with EtOAc. The EtOAc solution was washed with sat.aq. $NaHCO_3$, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and then separated by preparative TLC using hexane - EtOAc (2:1) to afford **20** (10.4 mg) and the starting material (4.4 mg). **20** as a colorless oil: δ 2.67 (1H, d, J= 19 Hz) and 2.99 (1H, d, J= 19 Hz); Calcd for $C_{15}H_{20}O_3$: m/z 248.1400. Found: m/z 248.1382.

Wolf - Kishner reduction of 20. A solution of **20** (23 mg) and excess KOH (80 mg) and hydrazine hydrate (0.075 ml) in ethylene glycol (1.5 ml) was stirred at refluxing temperature for 1.5 h, and slightly acidified with 1N HCl and extracted with Et_2O. The ethereal solution was dried over anhydrous Na_2SO_4 and then concentrated to leave an oil, which was separated by preparative TLC using hexane - EtOAc (5:1) to give (±)-8,14-cedranoxide (**10**) (3.71 mg) and an olefin (**21**) (9.9 mg). **21** as an oil: IR (film) 3400 cm^{-1}; δ 1.70 (3H, brs) and 5.27 (1H, brs); Calcd for $C_{15}H_{24}O$: m/z 220.1826. Found: m/z 220.1832. The synthetic sample as racemic form has the following spectral data: IR (film) 1040 cm^{-1}: δ 0.84 (3H, d, J= 7 Hz), 1.00 (3H, s), 1.17 (3H, s), 1.2 - 1.9 (3H, complex), 3.46

(1H, d, J= 8 Hz), and 3.58 (1H, d, J= 8 Hz); Calcd for $C_{15}H_{24}O$: m/z 220.1825. Found: m/z 220.1833. Its ^1H NMR (400MHz) spectrum is compatible with that of natural 8,14-cedranoxide cited in the reference 5.

Conversion of 21 to 10. A solution of **21** (7.05 mg) in toluene (2 ml) containing catalytic amount of p-TsOH was heated under reflux for 1 h and then concentrated. The crude residue was subjected to preparative TLC using hexane - EtOAc (15:1) to give **10** (6.21 mg).

Conversion of 14 to 22. To a solution of **14** (911 mg) in cooled (-78 °C) THF (27 ml) was slowly added a solution of 1.5M DIBAL-H (3.18 ml) in toluene over 5 min. After stirring for 1 h at -78 °C, a portion of 1N HCl was added to the reaction solution, which was extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to yield a crude allylic alcohol, which was directly acetylated with Ac_2O and pyridine in the presence of catalytic DMAP to give the corresponding acetate (900 mg).

To a stirred solution of the acetate in MeOH (10 ml) was added sat.aq. oxalic acid (7 ml), and the solution was heated at 60 °C. After stirring for 4 h, the reaction solution was extracted with EtOAc. The organic layer was then washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by preparative TLC using 20% EtOAc in hexane afforded 80 mg of an α-acetoxy ketone (**22**), as colorless prisms: IR (film) 1750br and 1460 cm^{-1}; δ 0.88 (3H, s), 0.89 (3H, d, J= 7 Hz), 1.35 (3H, s), 1.48 (1H, m), 1.70 (1H, m), 1.85 (1H, m), 2.12 (1H, dd, J= 7, 8 Hz), 2.19 (3H, s), 2.45 (1H, m), 2.52 (1H, d, J= 15 Hz), 2.55 (1H, d, J= 4.4 Hz), 2.58 (1H, d, J= 15 Hz), and 5.45 (1H, dd, J= 1, 4.4 Hz); Calcd for $C_{16}H_{22}O_4$: m/z 278.1517. Found: m/z 278.1524.

Conversion of the acetyl ketone to 23. To a stirred solution of **22** (256 mg) in THF (27 ml) was added 6.2 ml of 1.96M MeMgBr in THF at 0 °C. After stirring for 2 h, a portion of 1N HCl was added to the reaction mixture, which was extracted with EtOAc. The extract was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the resulting oil was purified by preparative TLC using hexane - EtOAc (2:1) to yield 167 mg of a diol (**23**), as colorless needles: mp 140 °C (from EtOAc); IR (film) 3400 and 1720 cm^{-1}; δ 0.83 (3H, s), 0.85 (3H, d, J= 7.6 Hz), 1.30 (3H, s), 1.42 (3H, s), 1.48 - 1.67 (5H, complex), 1.66 (1H, d, J= 14.7 Hz), 2.12 (1H, d, J= 14.7 Hz), 2.31 (1H, d, J= 4.4 Hz), 3.16 (1H, dd, J= 8.8, 14.1 Hz), and 3.83 (1H, d, J= 4.4 Hz); Calcd for $C_{15}H_{24}O_3$: m/z 252.1723. Found: m/z 252.1720.

Reduction of 23 with $LiAlH_4$. To a stirred solution of **23** (55.5 mg) in cooled (-78 °C) THF (5 ml) was added $LiAlH_4$ (84 mg). After stirring for 3 h, a portion of 1N HCl was added to the solution, which was extracted with EtOAc. The extract was washed with sat.aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by preparative TLC using 50% EtOAc in hexane to give 54.7 mg of a triol (**24**) as colorless needles: mp 175 - 180 °C (from EtOAc - hexane); IR (nujol) 3400 cm^{-1}; δ 0.87 (3H, d, J= 7 Hz), 1.22 (3H, s), 1.29 (3H, s), 1.39 (3H, s), 1.40 - 2.10 (6H, complex), 2.20 (1H, d, J= 4 Hz), 2.30 (1H, m), 2.60 (1H, d, J= 9 Hz), 2.70 (1H, d, J= 9 Hz), 3.29 (1H, s), 3.70 (1H, d, J= 4 HZ); Calcd for $C_{15}H_{26}O_3$: m/z 254.1880. Found: m/z 254.1873.

Conversion of the triol (24) to a keto acid (20). To a stirred solution of **24** (4.82 mg) in MeOH (7 ml) was added 84.2 mg of $Pb(OAc)_4$ at room temperature. After stirring for 20 min, sat.aq. $NaHCO_3$ (5 ml) was added to the reaction solution, which was extracted with EtOAc. The extract was washed with H_2O and brine, then dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC using 30% EtOAc in hexane to give 4.97 mg of a diketol which was further used for the next experiment.

To a stirred solution of the diketol (11.3 mg) in 20% aq. acetone (3 ml) was added excess amount of $NaClO_2$ at room temperature. After stirring for 14 h, the reaction mixture was diluted with EtOAc and 10% aq. sodium bisulfite. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by preparative TLC using 10% MeOH in $CHCl_3$ to yield 12.0 mg of an acid (**20**), as colorless crystals: mp 163 - 165 °C (from EtOAc - hexane); IR (nujol) 3500, 1730sh, and 1700 cm^{-1}; δ 0.80 (3H, d, J= 7 Hz), 1.03 (3H, s), 1.08 (3H, s), 1.20 - 1.90 (5H, complex), 2.20 (3H, s), 2.22 (1H, m), 2.38 (1H, d, J= 19.1 Hz), 2.64 (1H, d, J= 11.2 Hz), 3.02 (1H, d, J= 19.1 Hz), and 4.45 (1H, d, J= 11.2 Hz); Calcd for $C_{15}H_{24}O_4$: m/z 268.1673. Found: m/z 268.1685.

Conversion of 20 to α,β-keto ester (26). To a stirred solution of **20** (35.9 mg) in DMF (2 ml) were added 185 mg of K_2CO_3 and 0.5 ml of MOMCl at room temperature. After stirring for 4 h, the reaction mixture was poured into 1N HCl and then extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC using 30% EtOAc in hexane to yield 18.5 mg of a methoxymethyl ester as a colorless oil.

To a stirred solution of the ester (6.02 mg) in CH_2Cl_2 (2 ml) were added 20 mg of 4A MS and 73 mg of PDC at room temperature. After stirring for 2.5 h, the mixture was filtered and washed with Et_2O and the filtrate was concentrated. The residue was separated by preparative TLC using 25% EtOAc in hexane to give a β-keto ester (**26**) (2.09 mg) and 1.6 mg of a triketone (**27**).

26 as an oil: IR (film) 1760, 1720, 1650, and 1610 cm^{-1}; Calcd for $C_{17}H_{20}O_5$: m/z 310.1778. Found: m/z 310.1761.

27 as an yellow oil: IR (film) 1750sh, 1740, and 1710 cm^{-1}; δ 1.05 (3H, s), 1.06 (3H, d, J= 6.5 Hz), 1.27 (3H, s), 1.35 - 2.05 (5H, complex), 2.14 (3H, s), 2.25 (1H, dd, J= 9, 12.5 Hz), 2.85 (1H, d, J= 19 Hz), and 3.29 (1H, d, J= 19 Hz); Calcd for $C_{14}H_{20}O_3$: m/z 236.1412. Found: m/z 236.1427.

Conversion of 26 to a tricyclic compound (28). To a solution of **26** (1.94 mg) in dioxane (1 ml) was added 3 drops of conc HCl at room temperature. The stirred mixture was heated under reflux for 18 h, and then diluted with EtOAc and H_2O. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 1.33 mg of a diketone as an oil.

To a solution of the diketone (1.12 mg) in EtOH (1.5 ml) was added excess amount of NaOEt at room temperature. The reaction mixture was heated under reflux for 3 h and then diluted with EtOAc and water. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by preparative TLC using 20% EtOAc in hexane to afford 1.05 mg of **28**, as an oil: IR (film) 1710 and 1630 cm^{-1}; δ 1.95 (1H, d, J= 17.3 Hz), 2.24 (1H, d, J= 14 Hz), 2.52 (1H, dd, J= 1.5, 14 Hz), 2.64 (1H, d, J= 17.3 Hz), and 5.87 (1H, d, J= 1.5 Hz);Calcd for $C_{14}H_{20}O$: m/z 204.1496. Found: m/z 204.1504.

Conversion of 28 to the known ketone (29). To a stirred solution of **28** (1.02 mg) in Et_2O (1 ml)was added 0.16 ml of $Me_2Cu(CN)Li_2$ in ether at -30 °C. After stirring for 40 min, the reaction mixture was poured into aq. NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by preparative TLC using 20% EtOAc in hexane to yield 1.00 mg of 29 as an oil: IR (film) 1740 cm^{-1}; δ 0.96 (3H, d, J= 6.4 Hz), 0.98 (3H, s), 1.04 (3H, s), 1.11 (3H, s), 1.27 (1H, m), 1.55 - 1.70 (2H, complex), 1.76 (1H, d, J= 15 Hz), 1.80 (1H, d, J= 15 Hz), 1.92 - 2.18 (3H, complex), 2.02 (1H, d, J= 18,1 Hz), 2.15 (1H, d, J= 18.1 Hz), 2.42 (1H, d, J= 18.1 Hz), and 2.44 (1H, d, J= 18.1 Hz); Calcd for $C_{15}H_{24}O$: m/z 220.1826. Found: m/z 220.1830. The ^1H NMR spectral data of the synthetic sample (**29**) are compatible with the data cited in reference 6.

Cyclization of 27 to a triquinane (30). A mixture of **27** (3.13 mg) and 10% aq. KOH (0.6 ml) in benzene (1 ml) was heated under reflux for 2.5 h. After being cooled, the benzene layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by preparative TLC using hexane - EtOAc (3:1) to give 0.92 mg of **30**: IR (film) 1720 and 1690 cm^{-1}; δ 0.79 (3H, d, J= 6 Hz), 1.10 (3H, s), 1.18 (3H, s), 1.40 - 2.40 (6H, complex), 2.14 (1H, d, J= 18 Hz), 2.73 (1H, d, J= 18 Hz), and 6.46 (1H, s); Calcd for $C_{14}H_{18}O_2$: m/z 218.1305. Found: m/z 218.1287.

Preparation of the substrate (37) for anodic oxidation. To a solution of 3,4-dihydroxybenzaldehyde (2.0 g) in CH_2Cl_2 (30 ml) was added iPr_2NH (3.2 ml) and then 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) (2.8 ml) at room temperature under Ar. The reaction solution was stirred at the same temperature for 3.7 h, neutralized with 2N HCl, and diluted with water and EtOAc. The EtOAc layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent gave an oil which was separated by column chromatography using hexane - EtOAc (6:1) to give 1.65 g of a SEM ether and the starting material (0.995 g). The ether has the following spectral data: mp 124 - 125 °C (from hexane - EtOAc); IR (film) 3350, 1730, 1580, and 1500 cm^{-1}; Calcd for $C_{19}H_{20}O_6$: m/z 344.1269. Found: m/z 344.1283.

To a solution of the SEM ether (88.8 mg), an allyl alcohol (118 mg) and Ph_3P (130 mg) in THF (5 ml) was added diethyl azodicarboxylate (0.078 ml) at room temperature under Ar. The solution was allowed to stand at the same temperature for 24 h, concentrated under reduced pressure and directly separated by preparative TLC using $CHCl_3$ - EtOAc (10:1) to give 86.6 mg of an allyl ether, as a colorless oil: IR (film) 1690, 1590, and 1510 cm^{-1}; Calcd for $C_{25}H_{34}O_7Si$: m/z 474.2072. Found: m/z 474.2090.

To a stirred solution of the allyl ether (86.6 mg) in THF (2 ml) was added nBu_4NF (0.728 ml) at room temperature, and the reaction solution was further stirred at 45 °C for 30 h, concentrated under reduced pressure, and separated by preparative TLC using hexane - EtOAc (1:1) to give 51.2 mg of the desired phenol (**37**) as crystals: mp 124 - 125 °C (from hexane - EtOAc); IR (nujol) 3350br, 1660, 1580, and 1500 cm^{-1}; Calcd for $C_{19}H_{20}O$: m/z 344.1290. Found: m/z 344.1283.

Anodic oxidation of the phenol (37). A solution of **37** (29.5 mg) in MeOH (15 ml) - THF (10 ml) containing $LiClO_4$ (200 mg) was electrolyzed at a constant current (3.3 mA: + 860 - 1100 mV *vs* SCE) and the reaction was stopped at ca. 2 F/mol, and then diluted with water and EtOAc. The EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and then separated by preparative TLC using hexane - EtOAc (2:3) to afford two tricyclic compounds [**35** (3.45 mg) and **36** (25.8 mg)] in addition to the starting material (2.93 mg). **35** as colorless crystals: mp 105 - 106 °C (from hexane - EtOAc); IR (film) 1750 and 1680 cm^{-1}; δ 2.81 (1H, m), 3.43 (1H, m), 3.47 (3H, s), 3.49 (3H, s), 3.60 (1H, dd, J= 3, 7 Hz), 3.80 (3H, s), 3.94 (1H, d, J= 8 Hz), 4.16 (1H, dd, J= 2, 5 Hz), 4.28 (1H, dd, J= 4, 8 Hz), 5.14 (2H, s), 6.43 (1H, dd, J= 2, 9 Hz), 6.55 (1H, d, J= 2 Hz), 6.97 (1H, dd, J= 2, 7 HZ), 7.01 (1H, d, J= 9 Hz), and 9.65 (1H, s); Calcd for $C_{20}H_{22}O_7$: m/z 374.1364. Found: m/z 374.1360. **36** as an oil: IR (film): 1745 cm^{-1}; δ 3.30 (3H, s) and 3.43 (3H, s); Calcd for $C_{22}H_{28}O_8$: m/z 420 1782. Found: m/z 420.1778.

Preparation of the substrate (38) for anodic oxidation. To a solution of the above mentioned allyl ether (137 mg) and 2,4,6--trimethoxyacetophenone methoxymethyl ether (150 mg) in benzene (10 ml) was added Triton B (40% methanol solution, 0.5 ml) at room temperature, and the reaction solution was further stirred for 24 h, diluted with water and EtOAc. The EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and then separated by preparative TLC using hexane - EtOAc (3:2) to give 170 mg of a condensation product as an yellow oil.

To a solution of the above condensation product (534 mg) in THF (40 ml) was added 1M nBu_4NF in THF (3 ml) at room temperature. The solution was further stirred at 45 °C for 20 h and concentrated under reduced pressure to give an oil, which was directly purified by column chromatography using $CHCl_3$ - MeOH (50:1) to give 400 mg of the desired phenol (**38**) as an yellow oil: IR (film) 3400, 1630, 1600, 1580, and 1510 cm^{-1}; δ 3.38 (6H, s), 3.51 (6H, s), 3.90 (3H, s), 4.77 (2H, d, J= 6 Hz), 5.07 (4H, s),

5.14 (2H, s), 5.20 (2H, s), 6.01 (1H, s), 6.23 (1H, dt, J= 15.6 Hz), and 6.5 - 7.5 ((10H, complex); Calcd for $C_{33}H_{38}O_{12}$: m/z 626.2361. Found: m/z 626.2361.

Anodic oxidation of the phenol (38). A solution of **38** (200 mg) in MeOH (20 ml) - THF (10 ml) containing $LiClO_4$ (600 mg) was electrolyzed at a controlled potential at 0.95 V vs SCE, and the reaction was stopped at ca. 2 F/mol. The reaction solution was concentrated and diluted with water and EtOAc. The EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and then separated by preparative TLC using hexane - EtOAc (1:2) to give 71 mg of 9-oxaisotwist-8-en-2-one (**39**) and the starting material (117 mg): **39** as an yellow oil: IR (film) 1740, 1645, 1600, and 1590sh cm^{-1}; δ 2.82 (1H, m), 3.40 (6H, s), 3.42 - 3.47 (2H, complex), 3.48 (3H, s), 3.49 (3H, s), 3.55 (3H, s), 3.81 (3H, s), 3.82 - 3.83 (1H, m), 4.00 (1H, d, J= 8.5 Hz), 4.31 (1H, dt, J= 3.5, 8.5 Hz), 5.0 - 5.25 (8H, complex), 6.28 (1H, d, J= 5 Hz), 6.42 (1H, dd, J= 2, 8.5 Hz), 6.53 - 6.55 (3H, complex), 6.68 (1H, d, J= 16 HZ), 6.98 (1H, d, J= 8.5 Hz), and 7.12 (1H, d, J= 16 Hz); Calcd for $C_{34}H_{40}O_{13}$: m/z 656.2466. Found: m/z 656.2446.

Conversion of 39 to both 34a and 34b. A solution of **39** (167 mg) in MeOH (15 ml) containing conc HCl (1 ml) was stirred at refluxing temperature for 5 min, and then concentrated and diluted with EtOAc and water. The EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4 and separated by preparative TLC using hexane - $CHCl_3$ (1:7) to give 89 mg of a tetrol as pale yellow needles: mp 159 - 162 °C (from hexane - EtOAc); IR (film) 3350 and 1740 cm^{-1}; Calcd for $C_{26}H_{24}O_9$: m/z 480.1419. Found: m/z 480.1434.

A solution of the tetrol (88.8 mg) and NaOAc (760 mg) in EtOH (10 ml) was heated at 70 °C for 1.7 h under Ar with stirring, and then neutralized with 1N HCl and diluted with water and EtOAc. The EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated and separated by preparative TLC using $CHCl_3$ - MeOH (12:1) to give 81 mg of **34a** and **34b** (relative ratio 1:1).

34a as colorless prisms: mp 255 - 256 °C (from $CHCl_3$ - MeOH); IR (nujol) 3300, 1730, and 1710 cm^{-1}; δ 2.75 (1H, dd, J= 3, 17 Hz), 2.89 (1H, m), 3.09 (1H, dd, J= 12, 17 Hz), 3.22 (1H, dd, J= 3, 7 Hz), 3.39 (1H, m), 3.57 (3H, s), 3.85 (3H, s), 3.89 (1H, dd, J= 2, 4 Hz), 3.97 (1H, d, J= 8 Hz), 4.30 (1H, dd, J= 3, 8 Hz), 5.31 (1H, dd, J= 3, 12 Hz), 5.97 (1H, d, J= 2 Hz), 6.01 (1H, d, J= 2 Hz), 6.15 (1H, d, J= 7 Hz), 6.68 (1H, dd, J= 2, 8 Hz), 6.75 (1H, d, J= 8 Hz), and 6.85 (1H, d, J= 2 Hz); Calcd for $C_{26}H_{24}O_9$: m/z 480.1419. Found: m/z 480.1450.

34b as colorless prisms: mp 252 - 255 °C (from $CHCl_3$ - MeOH); IR (nujol) 3350, 1730, and 1700 cm^{-1}; δ 2.81 (1H, m), 2.87 (1H, dd, J= 3, 17 Hz), 3.14 (1H, dd, J= 11, 17 Hz), 3.23 (1H, dd, J= 2, 7 Hz), 3.36 (1H, m), 3.54 (3H, s), 3.82 (3H, s), 3.88 (1H, dd, J= 2, 4 Hz), 3.95 (1H, d, J= 8 Hz), 4.28 (1H, dd, J= 3, 8 Hz), 5.29 (1H, dd, J= 3, 11 Hz), 5.98 (1H, d, J= 2 Hz), 6.04 (1H, d, J= 2 Hz), 6.15 (1H, d, J= 7 Hz), 6.46 (1H, dd, J= 2, 8 Hz), 6.71 (1H, d, J= 8 Hz), and 6.84 (1H, d, J= 2 Hz); Calcd for $C_{26}H_{24}O_9$: m/z 480.1419. Found: m/z 480.1446.

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