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CHEMISTRY OF *Saururus cernuus* IV: CYCLOOCTADIENE SYSTEMS DERIVED FROM AUSTROBAILIGNAN-5

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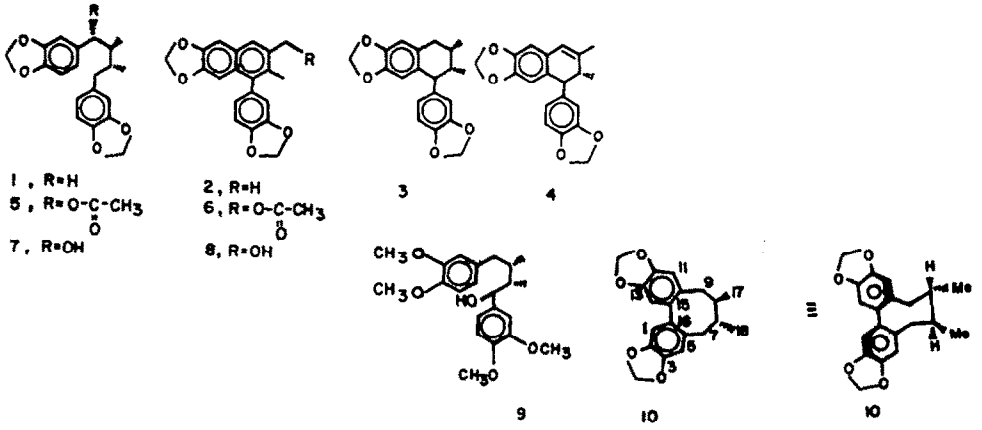
Abstract - Austrobailignan-5, a 1,4-diarylbutane type neolignan from *Saururus cernuus* was converted to a dibenzocyclooctadiene derivative by using two new reagents. The compound was further functionalized by the use of DDQ to mono- and dialcohols. Acid treatment of the monoalcohols led to oxidative demethylenation. The diols were converted to an epoxide and other rearranged products. The stereochemistry of the mono- and dialcohols was established based on nmr and cd spectral data.

In part III was described the conversion of austrobailignan-5, 1, a 1,4-diarylbutane type neolignan and a major constituent of *Saururus cernuus* to the phenylnaphthalene 2 by the action of dichlorodicyanoquinone (DDQ) in dioxane or methanol[1]. Further studies indicated that this reaction could take other courses depending on the solvent and conditions, and this paper describes the products of these reactions.

Austrobailignan-5, 1 was first isolated by Murphy et al., from *Austrobaileye scandens* as an oil[2], synthesized[3] and reisolated from *Saururus cernuus*[4], also as an oil. The compound is now obtained as a crystalline.

In the earlier work[1], reaction of 1 with DDQ was pursued with benzylic substitution as the objective. The main product, however, was 2 with 3 and 4 being the minor products. In an effort to understand the conversion of 1 to 3, the DDQ reaction was carried out in acetic acid which is known to facilitate benzylic acetoxylation[5]. Two products, presumably 5 and 6, were obtained which gave the alcohols 7 and 8 on alkaline hydrolysis. The ^{1}H nmr spectral data of 7, $C_{20}H_{22}O_5$:



δ 0.76 and 0.96, 2d, J = 6Hz, 2x3H; 1.66, broad s, 3H, converted in D_2O to a multiplet, 2H; 2.4, d, J = 6 Hz, 2H; 4.36, d, J = 7.5 Hz, 1H; 6.0, s, 4H; 6.4-6.7 m, 6H were consistent with structure 7 and agreed well with the data given by Gottlieb et al.[6], for 9, isolated from Virola sebifera. Unlike 1 which was levorotatory, 7 showed positive rotation presumably due to the production of the new chiral center at the benzylic position[7].

Treatment of 7 with acid (BF_3/benzene), gave 3, $C_{20}H_{20}O_4$, $[\alpha]_D$-19°, whose ^1H nmr spectrum was identical with that reported for (-) galbulin, excluding the differences due to the methylenedioxy versus methoxyl groups.

The second product of the reaction, 8, $C_{20}H_{16}O_5$ showed uv spectral maxima identical with those of 2. Its ^1H nmr spectrum: δ 1.66, broad s, 1H and D_2O-exchangeable; 2.17, s, 3H; 4.8, s, 2H; 5.97 and 6.06, 2s, 2H each; 6.5-6.7; m, 5H confirmed this assignment.

Thus, reaction of 1 with DDQ in toluene, dioxane or methanol gave mostly 2 with minor amounts of 3 and 4, whereas in acetic acid, the actual benzylic substitution product 5 was obtained in significant yields. Attempts to functionalize the second benzylic position by using longer reaction times or using larger amounts of DDQ were unsuccessful, the product being mostly 6.

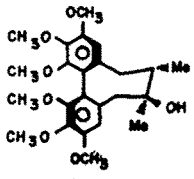
The reaction of 1 with DDQ in trifluoroacetic acid (TFA) took a completely different course, leading to a single crystalline product, $C_{20}H_{20}O_4$ (M^+ 324). The ^1H nmr spectrum (300 MHz) gave evidence for two secondary methyls (δ 1.04, d, J = 6Hz, 6H), two methylene dioxy groups (δ5.95, s, 4H), four benzylic protons and two aliphatic methine protons. The presence of four aromatic protons (in contrast to 6 in 1 and 5 in 3) which appeared as two unsplit singlets (δ6.70 and 6.73) suggested the structure 10 as the most likely and this was found to be correct. The compound in question was prepared by Biftu et al.[8], from 1 by the action of VOF_3/TFA. To our knowledge, the use of DDQ/TFA to generate the dibenzocyclooctadiene system has not been reported in the literature. Furthermore, we found another reagent, manganese^{III} acetate in TFA which was also capable of effecting the conversion of 1 to 10. Thus, these two reagents appear to give a smooth and rapid conversion of 1 to 10 in yields of 75% and they are both more readily accessible, more convenient to handle and lead to higher yields than VOF_3.

In contrast to 1 which was levorotatory and showed negative Cotton effects at 290 and 237 nm in its CD spectrum, 10 was dextroratatory, $[\alpha]_D$ + 187° and showed positive Cotton effects at 298 and 254 nm, thus indicating that the biphenyl groups of the cyclooctadiene system possessed R-configuration[9].

A number of dibenzocyclooctadiene type neolignans have been isolated from the genus Schizandra and Kadsura. Two such neolignans schizandrin 11[10] and kadsurin 12[9,11] possess biological activity and both have been synthesized[12,13]. More recently, related neolignans gomisin A, deoxyschizandrin and wuweizisu[14] have been reported to offer protection against chemically-induced hepatotoxicity[14]. A structurally unique member of this group 13, isolated from Clerodendron inerme possesses an epoxide bridge across the cyclooctadiene ring[15]. All of the naturally occurring neolignans of this class are trisubstituted in both the aromatic rings and 10 is the only disubstituted member. We therefore decided to prepare some analogues of 10 for possible evaluation of their activity.

Functionalization of 10 was successfully achieved by using DDQ in acetic acid. A mixture of two monoacetates was obtained which was hydrolyzed and separated into the corresponding monoalcohols.

The ^1H nmr spectrum of the minor monoalcohol, $C_{20}H_{20}O_5$, showed two distinct doublets for the secondary methyl groups (δ 0.86 and 1.00, J = 6Hz, 2x3H). Such separation of the two doublets



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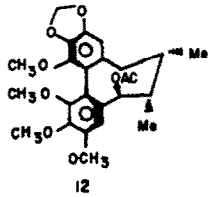

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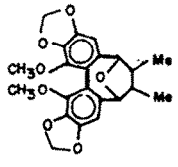
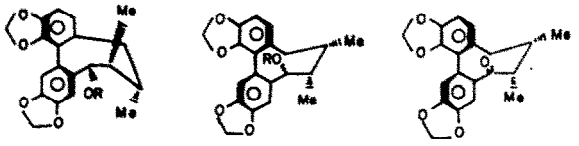


13

is generally considered to support a cis orientation for the two methyl groups[14,16]. In addition to showing the expected functionalities, the spectrum revealed that the minor monoalcohol had the same configurational structure as the naturally occurring epigomisin-O[17] except for the aromatic rings which had a different substitution pattern. Also, in contrast to 10, the minor alcohol was levoratotory $[\alpha]_D$-117° and showed negative Cotton effects at 297 and 248 nm, thus indicating an S-configuration for the aromatic rings[9]. The minor alcohol was assigned the structure 14.



14, R=H
17, R=O-C-CH$_3$ (O)

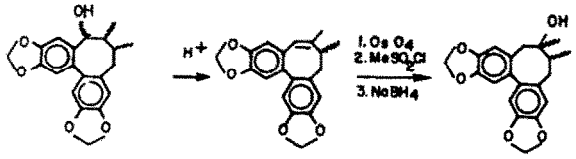
15, R=H
18, R, O-C-CH$_3$ (O)

16

The major alcohol, $C_{20}H_{20}O_5$, $[\alpha]_D$+199 showed positive Cotton effects which indicated R-configuration for the aromatic rings. Its ^{1}H nmr spectrum showed the signal for the benzyloxymethine proton at δ 4.18 which appeared as a doublet (J = 9Hz) and this showed a β-configuration for the C-6 hydroxyl. Structure 15 was assigned for this alcohol. Further support for this structure was obtained through oxidation of 14 with Jones' reagent which gave the ketone 16, $C_{20}H_{18}O_5$, $[\alpha]_D$-84, ν1655 cm^{-1}, followed by reduction with sodium borohydride which gave an equal mixture of 14 and 15. Also, both alcohols gave the same monoketone 16. The ^{1}H nmr spectrum of 16 showed a strong downfield shift (δ7.78) for the aromatic proton (C-4) thus indicating that the carbonyl group was coplanar with the adjacent aromatic ring and that the cyclooctadiene was in boat configuration[13].

The monoacetates 17 and 18 were prepared from 14 and 15 respectively. The optical rotation, spectral characteristics of 17 were identical with those of kadsurin 12 except for the signals of the acetoxy and the aromatic protons. In 12, the position of the acetoxy signal (δ 1.6) reflects the anisotropic ring shielding which results from the trisubstituted aromatic rings. In contrast, both 17 and 18 showed the acetoxyl signal at the normal position (δ 2.06, δ 1.96), thus reflecting lack of pressure of anisotropy. Also, this scheme of making kadsurin analogues is more convenient, straightforward and gives higher yields than the one reported earlier.

Using the two monoalcohols 14 and 15, and using the scheme (Scheme 1) developed by Ghera and Ben-David[12], one can attempt to generate a schizandrin type structure as shown below.

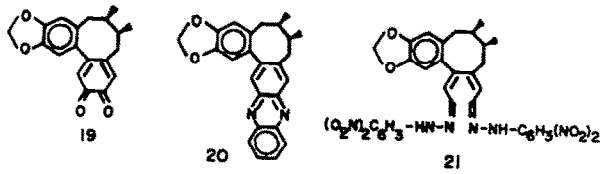


SCHEME 1

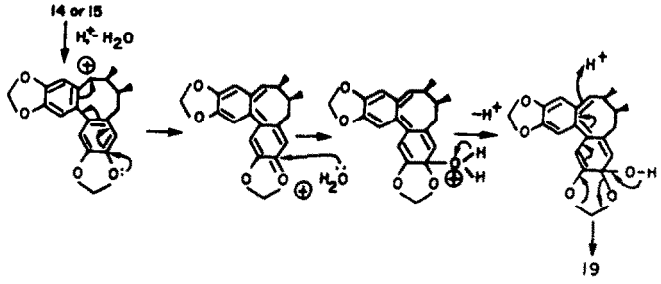
Accordingly, 14 and 15 were treated with acid, but, instead of the expected dehydration product, an unusual oxidative demethylenation took place to yield a yellow crystalline solid 19. 19 contained only one methylenedioxy function and it readily reacted with o-phenylenediamine to give 20. This unusual oxidative demethylenation took place readily under a variety of acidic conditions, eg, alcoholic H_2SO_4; benzene/BF_3;TFA; pyridine-methanesulfonyl chloride, chloroform/$POCl_3$. The proposed mode of formation is indicated in Scheme 2. It is unusual that this reaction has not been observed before, although several of the monoalcohols of the type 14 and 15 have been isolated or synthesized.

When 19 was reduced with $NaBH_4$, instead of the expected catechol derivative, a colorless, crystalline nonphenolic product was formed with four additional protons over 19 instead of two. That the product was a vicinal diol, was shown by oxidation with periodate to a dialdehyde and

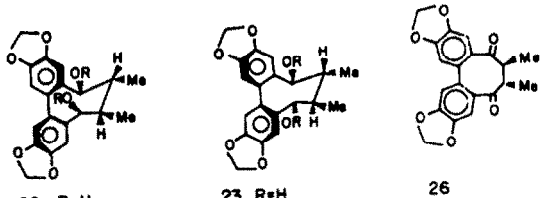
conversion to the bis dinitrophenylhydrazone 21. Such a reaction of an o-quinone to a dihydrobenzenediol is most unusual.



SCHEME 2



Reaction of 10 with four equivalents of DDQ in acetic acid gave a mixture of two diacetoxy derivatives which were separated after basic hydrolysis. The major diol, $C_{20}H_{20}O_6$, M^+ 356, $[\alpha]_D$-109° showed signals for 2-CH-CH_3 (δ 1.0, d, J = 7.5 Hz, 6H), 2-OH (δ 1.53 s) 2 Ar-CH-O (δ 4.4, s, 2H), 2 O-CH_2-O and 4 aromatic H in its ^{1}H nmr spectrum. The spectrum of the minor diol, $C_{20}H_{20}O_6$, M^+ 356, $[\alpha]_D$+144° was very similar except for the pattern of the signals for the Ar-CH-O (δ3.9, d, J = 9 Hz, 2H). The appearance of both methyl groups as one doublet in both diols indicated that the methyl groups were trans to each other.[14,16] Furthermore, the fact that in the major diol, both Ar-CH-O protons gave a single singlet at δ 4.4 suggested that both the hydroxyls had the same configuration with respect to their neighboring methyl groups. By the same reasoning, in the minor diol, appearance of a doublet for the same protons suggested opposite configurations with respect to the neighboring methyl groups. Structures 22 and 23 were assigned to the major and minor diol respectively.



From the preceding comparison of the ^{1}H nmr spectral data of 10, with that of the monoalcohols 14 and 15 and the diols 22 and 23, it is evident that the configurations of the methyl groups C_{17} and C_{18} are not the same in all. The spectra suggest that the methyl groups are trans in 10 but cis in 14 and 15 and again trans in 22 and 23. To gain further support to this finding, ^{13}C nmr spectra of these compounds were studied. Dibenzocyclooctadienes such as 32 with trans methyl groups have symmetrical structures and hence their ^{13}C nmr spectra show only half of the expected carbon signals.[14,18] Accordingly, both the methyl groups appear as one signal. On the other hand cyclooctadienes such as epigomisin O, 33, show two distinct signals for the methyl groups, the upfield signal being assigned to the axial and the downfield signal to the equatorial methyl (see Table 1). This characteristic behavior is also associated with the twist-boat-chair conformation for the cyclooctadiene ring.[14,18]

TABLE 1

^{13}C NMR Data for the Dibenzocyclooctadiene Derivatives

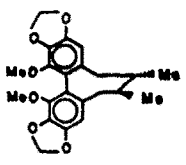
Carbon No.	10	14	15	22	23
1[a]	135.5[a] (x2, C-12a)	131.5	132.3[c]	130.6 (x2, C-12a)	130.3 (x2, C-12a)
1	109.0 (x2, C-12)	108.5	107.1	108.3 (x2, C-12)	106.4 (x2, C-12)
2	145.4 (x2, C-11)	145.2	145.5	145.3 (x2, C-11)	145.3 (x2, C-11)
3	147.0 (x2, C-10)	145.9	147.0	146.0 (x2, C-10)	146.8 (x2, C-10)
4	108.4[a] (x2, C-9)	107.7	106.4	107.5 (x2, C-9)	105.8 (x2, C-9)
4[a]	133.3 (x2, C-8a)	133.0	135.4	135.8 (x2, C-8a)	141.1 (x2, C-8a)
5	42.0 (x2, C-8)	34.6	42.0	66.3 (x2, C-8)	70.7 (x2, C-8)
6	40.7 (x2, C-7)	31.4	-	43.5 (x2, C-7)	47.2 (x2, C-7)
7		43.7	47.0		
8		66.5	70.8		
8[a]		135.6	141.0		
9		111.1	109.0		
10		145.9	147.0		
11		145.2	145.5		
12		109.0	107.1		
12[a]		131.2	131.1[c]		
13	23.5 (x2, C-14)	19.5[b]	24.0	15.7 (x2, C-14)	19.3 (x2, C-14)
14		15.8[b]	18.0		
OCH_2O	100.8 (x2)	100.8 (x2)	101.0 (x2)	100.8 (x2)	100.8 (x2)

1. [a,b,c]: assignments may be reversed.

2. The assignments are based on comparison of the chemical shifts of the aromatic carbons with their counterparts in **35**[19] and those of the cyclooctadiene system with those of other dibenzo cyclooctadienes of this group[14,18].

Thus, **10**, **22** and **23**, which showed a single signal for both the methyl groups must have the trans configuration for the methyl groups as was shown by the ^1H nmr data. On the other hand, **14** and **15** which showed two distinct signals for the methyl groups, clearly have the cis configuration, with the upfield signal being due to the axial methyl group. Finally, although both **14** and **15** showed two distinct signals for the methyl groups, the chemical shifts of **14** differed from those of **15** which showed them in the normal range. This indicated differences in the conformation of the cyclooctadiene ring. The monoalcohol **15** (as well as **10**, **22** and **23**) possess the twist-boat-chair conformation. Comparison of the spectral data of **14** (δ15.8 and 19.5) with that of gomisin O, **34** (δ16.6 and 17.5) indicated that **14**, like **34**, possessed a boat conformation[18].

Thus, conversion of **1** to **10** did not change the stereochemistry of the two methyl groups. However, when **10** was converted to **14** and **15** the trans methyl groups also changed to cis. On the other hand, conversion of **14** and **15** to **22** and **23**, is accompanied by a cis⟶trans conversion. It is considered that the presence of a carbonium ion species at the benzylic position(s) might have facilitated such conversions.



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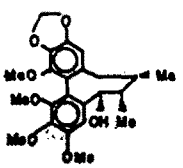

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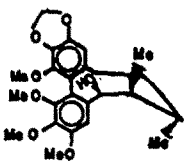

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The cd data of the various compounds listed here are shown in Table 2. Special attention may be paid to the values of the pairs 14 and 15 and 22 and 23. Each member of the pair gave values which are nearly the same but of opposite sign of that of the other member. The data indicate a high degree of stereospecificity of the appropriate reaction.

The diacetates 24 and 25 were prepared from the two diols. In both cases, the signal of the Ar-CH-O protons showed a low field shift: from δ 4.4 to δ5.43 in 22 ⟶ 24 and from δ 3.9 to δ 5.03 in 23 ⟶ 25. In addition, the two diols on oxidation with Jones' reagent gave the same diketone 26 (ν 1700 and 1680 cm^{-1}). The formation of a single diketone from both diols was considered to be due to the presence of twofold symmetry for the two trans oriented methyl groups.[13] This behavior is in contrast to the formation of two different diketones from other members of this group in which both rings are trisubstituted[13].

TABLE 2

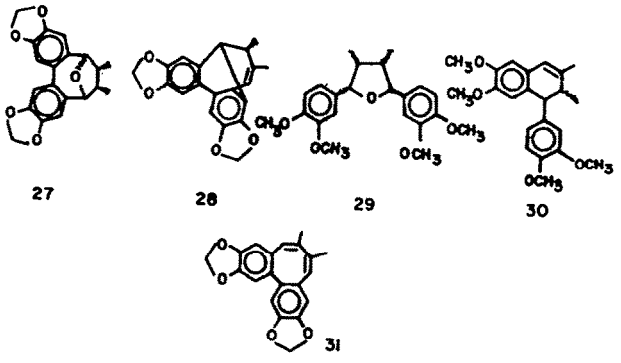
CD-Spectral Data on the Dibenzocyclooctadiene Derivatives

Compound	Wave Length nm	θ
1	290	-1,231
3	291	-19,131
7	290	+1,905
10	297.5, 253.5	+28,080, +164,160
14	297, 248	-20,266, -65,000
15	296, 246	+16,480, +65,600
22	294.5, 241	-12,460, -56,070
23	297, 250	+10,324, +52,213
16	341, 300, 243	-24,336, +28,730, +18.928
29	350, 310, 248	-1,564, -4,693, +33,244

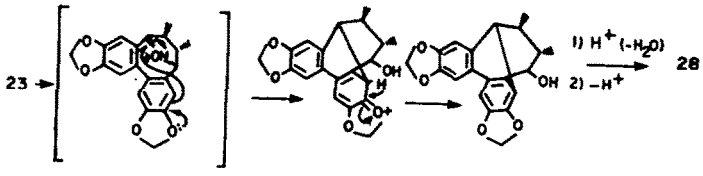
Once the two diols were characterized, an attempt was made to form an epoxide derivative similar to 13. The major diol 22 on treatment with triphenylphosphine dibromide in acetonitrile readily the epoxide 27. The same epoxide was also obtained with BF_3-etherate, but a by-product was formed shown to be the monoketone 16, presumably formed by the breakdown of the epoxide. Reduction of 16, with sodium borohydride gave predominantly the minor monoalcohol 14. Formation of this epoxide first documented synthesis of such in this system. Ghera and Ben-David described a similar compound but no decisive supporting data were given. Also, the route described here is far more practical.

The minor diol 23 was stable to triphenylphosphine dibromide but did react with BF_3-etherate at 25° to produce, instead of the expected epoxide, a pale yellow crystalline compound, $C_{20}H_{16}O_4$ (δ1.15, d, J=6 Hz, 3H; 2.33, s, 3H; 6.88, 7.10, 7.33, 3s, 3 arom. H). In comparison with 23, the product had one less aromatic proton. The spectral data, together with the loss of two oxygen atoms suggested that the compound must have the structure 28. This could arise, as indicated below, by the action of acid on the unstable epoxide intermediate, in an entirely analogous manner to that of the conversion of 2,5-diaryltetrahydrofuran such as 29 to an aryldihydronaphthalene such as 30 as shown in Scheme 3.

When the reaction between 23 and BF_3-etherate was carried out at 70-80°, a yellow crystalline product, isomeric with 28, but different from it, was obtained. Its ^1H nmr spectrum showed aromatic methyl groups (δ2.5, 2.7, 2s) and six aromatic type protons δ 7.2-7.6. This indicated the structure 31 for the product.



SCHEME 3.



EXPERIMENTAL

Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. The following instrumentation was used for the spectra described here: uv, Beckman 35, with alcohol as solvent; ir, Beckman Acculab 3 with KBr as the medium; nmr: Varian 360 (90 MHz) with $CDCl_3$ or $(CD_3)_2SO_4$ as the solvent; 300 MHz spectra, 300 spectrometer, Nicolet Instrument Corporation, with NE 1180 E data system;optical rotations, Perkin-Elmer polarimeter, Model 141 with $CHCl_3$ as solvent; CD spectra, Jasco J5000C spectropolarimeter; MS, Hewlett Packard model 5985B.

Austrobailignan-5 1: The oily sample (4) was purified by HPLC using a silica column with 10% EtOAc in C_6H_{14} as the solvent. The main fraction on trituration with C_6H_{14} gave a crystalline solid which was recrystallized from C_6H_{14}, colorless prisms, m.p. 43-44°. Its analytical and spectral data were identical with 1 described earlier.[4]

Conversion of 1 to 7 and 8: A solution of 1 (1.04 g, 3.2 mM) in HoAc (40 mL) was stirred for 2 h at 25° with DDQ (1.08 g, 4.7 mM). After dilution with H_2O extraction with Et_2O, the solvent layer was washed successively with $NaHSO_3$, H_2O, $NaHCO_3$, H_2O, concentrated and purified by chromatography on silica gel in C_6H_6-C_6H_{14} (1:1) to recover any unreacted 1. Elution with C_6H_6 gave the mixed monoacetates 5 and 6 which were hydrolyzed with MeOH-KOH (1N) for 1 h at 25°. The alcohols were recovered and separated by preparative tlc on silica gel using C_6H_6-C_3H_6O (9:1). The fraction with the higher Rf gave 8 as a crystalline solid, recrystallized from Et_2O-C_6H_{14}, m.p. 138-139°, λ max 237, 275 (sh), 290, 320 and 334 nm; ν 3340, 2900, 1500, 1490, 1460, 1230, 1100, 1035 cm^{-1}; ^1H nmr: δ 1.66, broad s, D_2O exchangeable, 1H; 2.17, s, CH_3; 4.80, s, CH_2OH; 5.97, 6.06, 2s, 2-OCH_2O; 6.70, s, 3 ArH; 6.90-7.65, m, 3 ArH. Anal. calc. for $C_{20}H_{16}O_5$; C, 71.42; H, 4.80. Found: C, 71.31; H, 4.89.

The fraction with the lower Rf gave 7 as a colorless glassy solid, yield, 0.3 g; $[\alpha]_D^{25}$ + 46°; λ max 288, 236 nm; ν 3600-3300, 1610, 1502, 1490, 1445, 1380, 1300, 1190, 1100, 1040 cm^{-1}; δ 0.76 and 0.96 2-d, J=6Hz, 2-CH-CH_3; 1.66, broad s, with D_2O, m, 2 C$\underline{H}$-CH_3; 2.4, d, J=6Hz, $ArCH_2$; 4.36, d, J=7.5 Hz, Ar-CH-O; 5.93, 5.96, 2s, 2-OCH_2O; 6.46-6.70, m, 5 ArH; M^+, m/z 342. Anal. calc. for $C_{20}H_{22}O_5$, 1/2H_2O: 68.41; H, 6.54. Found: 68.11; H, 6.36.

Conversion of 7 to 3: To a solution of 7 (0.1 g) in C_6H_6 (10 mL) was added BF_3-etherate in benzene (0.1 mL of a 1-10 solution). After 15 min it was washed with water, the solvent layer concentrated to dryness and the product purified by preparative tlc; colorless glassy solid, yield 0.07

g; $[\alpha]_D^{25}$-19°; λ max 240 (sh), 293 nm; ν 3020, 2935, 1615, 1505, 1490, 1440, 1380, 1295, 1235, 1190, 1040 cm^{-1}; ^1H nmr: δ 0.86, and 1.03, 2d, J=6Hz, 2-CH-C$\underline{H}_3$; 1.5, m, 2-C$\underline{H}$-CH_3; 2.63, m, $ArCH_2$; 3.40, d, J=9Hz, Ar-CH-Ar; 5.80, 5.90, 2s, 2-OCH_2O; 6.16, s, ArH; 6.53, 6.70, 2s, 4 ArH; M^+, m/z 324 (100%). Anal. calc. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.22. Found: C, 73.85; H, 6.01.

Conversion of 1 to 10: A mixture of 1 (5 g), DDQ (7 g) in TFA (150 mL) was stirred at 25° for 2 h. It was diluted with H_2O and extracted with C_6H_6 (3x500 mL). The solvent layer was washed with $NaHSO_3$, H_2O, NaOH, and H_2O. It was passed through a column of Florisil (a complex magnesium silicate) and the effluent and wash concentrated to dryness. The solid was recrystallized from C_6H_6, yield, 3 g; m.p. 219-220°; $[\alpha]_D^{25}$ + 187°; λ max 212, 235 (sh), 260 (sh), 292 nm; ν 2980, 2940, 1880, 1610, 1500, 1475, 1430, 1410, 1360, 1230, 1150, 1120, 1100, 1035 cm^{-1}; M^+, m/z 324; Anal. Calc. for $C_{20}H_{20}O_4$: C, 74.05, H, 6.22; Found C, 74.21; H, 6.24.

Reaction of 10 with DDQ to form 14 and 15: A mixture of 10 (0.324 g, 1 mM), DDQ (0.5 g, 2 mM) in AcOH (20 mL) was stirred at 80-90°C for 1.5 h. The cooled reaction mixture was diluted with water, treated with $NaHSO_3$ until it was negative to starch/iodide test and extracted with C_6H_6 (3x50 mL). After washing with $NaHCO_3$, H_2O, the C_6H_6 layer was concentrated to an oil and applied to a silica column in C_6H_6: C_6H_{14} (1:1). Elution with C_6H_6 gave a fraction consisting of 17 and 18 which was concentrated and stirred with 0.5 N MeOH-KOH at 25° for 1 h. Extraction with ether, concentration and separation by preparative tlc using C_6H_6-Me_2CO (9:1) gave the products. The higher Rf fraction 15 was a colorless crystalline solid, yield, 0.08 g, m.p. 220-222°C; $[\alpha]_D$+199°; λ max 292, 260 (sh), 237 (sh), 217 nm; ν 3600, 3000, 2900, 1620, 1500, 1480, 1370, 1240, 1045 cm^{-1} ^1H nmr: δ 1.12 and 1.13, 2d, J=5.6 Hz; 2 CHC$\underline{H}_3$ 1.46, m, 2 C$\underline{H}$CH$_3$; 1.58, broad s, D_2O-exchangeable, O$\underline{H}$; 2.02, t, J=14.4 and 15.3 Hz, 1 ArC$\underline{H}$ and 2.3, d, J=16.8 Hz, 1 ArC$\underline{H}$; 4.18, d, J=9 Hz, ArCHO; 5.97 and 5.98, 2s, 2 OCH_2O; 6.66, 6.7, 6.74, 7.12, 4s, 4 ArH; MS: m/z 340 (M^+ 100%), 322 (37), 293 (13) 284 (21), 283 (19), 267 (75), 266 (41), 253 (14), 237 (22), 225 (20), 209 (18), 195 (18), 178 (34), 139 (19). Anal. Calc. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.68; H, 5.94.

The lower Rf fraction afforded a crystalline solid, 14, yield 0.01 g; m.p. 232-233°C; $[\alpha]_D^{25}$-117°, λ max 290, 260 (sh), 235 sh, 217 nm; ν 3600, 3000, 2920, 1505, 1480, 1230, 1040 cm^{-1}; ^1H nmr: δ 0.86 and 1.00, 2 d, J=7.5Hz, 2 CH-C$\underline{H}_3$; 1.54, br. s, D_2O-exchangeable, OH; 1.80, m, 2 C$\underline{H}$·CH_3; 2.38, d, J=4Hz, $ArCH_2$; 4.55, s, ArCHO; 5.96, 6.00, 2 s, 2 OCH_2O; 6.66, s, 3 ArH; 7.13, s, 1 ArH; MS; m/z 340 (M^+ 100), 322 (30), 267 (66), 266 (20), 283 (24), 284 (23), 310 (11), 254 (14), 237 (20), 225 (20), 209 (17), 178 (22), 139 (17). Anal. Calc. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.65; H, 5.95.

Preparation of Acetates 17 and 18: A mixture of 14 or 15 (0.05 g), Ac_2O (3 mL) and pyridine (0.5 mL) was let stand for 20 h at 25°. Addition of water, filtration of the solid and crystallization from MeOH gave the corresponding crystalline acetate, yield 0.05 g.

The acetate, 18 gave m.p. 188-189°; ν 1725 cm^{-1}; ^1H nmr: δ 1.0, d, J=4.5Hz, 2 CHC$\underline{H}_3$; 1.50, m, 2 C$\underline{H}$CH$_3$; 1.96, s, CH_3COO; 2.2, m, $ArCH_2$; 5.20, d, J-9Hz, ArCHO-; 6.0, s, 2 OCH_2O; 6.66, 6.67, 2s, 7 ArH; 6.83, 6.96, 2s, 2 ArH. Calc. for $C_{22}H_{22}O_6$: C, 69.10, H, 5.80. Found: C, 69.04; H, 5.82.

The acetate, 17 was obtained as a colorless glass, ν 1730 cm^{-1}; ^1H nmr: δ 0.90 and 1.02, 2 d, J=7.5Hz, 2 CHC$\underline{H}_3$; 1.8, m, 2 C$\underline{H}$CH$_3$; 2.06, s, CH_3COO; 2.36, d, J=3Hz, $ArCH_2$; 5.5, s, ArCHO; 6.03, s, 2 OCH_2O; 6.70, s, 2 ArCH; 6.73, 6.90, 2 s, 2 ArH. Anal. calc. for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.02; H, 5.83.

Oxidation of 15 to 16: To a solution of 15 (0.07 g) in acetone (10 mL) was added Jones' reagent (1 N CrO_3 in 1 N H_2SO_4), (2 mL). After 2 h it was diluted with water and extracted with ether. The product was a crystalline solid, yield, 0.04 g; m.p. 156-157°C; $[\alpha]_D$-73°, λ max 337, 295 and 242 nm; ν 1660 cm^{-1}; ^1H nmr: δ 0.92, 1.0, 2 d, J-3H, 2 CHC$\underline{H}_3$; 2.04, m, 2 C$\underline{H}$CH$_3$; 2.50, m, $ArCH_2$; 2.93, dd, J=4.5Hz, CO-C$\underline{H}$-CH$_3$; 6.00, s, 2 OCH_2O; 6.63, 6.71, 6.96, 7.78, 4s, 4 ArH. Anal. calc. for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36; Found: C, 70.79; H, 5.41.

Oxidation of 14 under the same conditions gave a ketone identical with 16.

Conversion of 14 to 19: A solution of 14 (0.1 g) in C_6H_6 (10 mL) was treated with BF_3-etherate (0.5 mL of a 1 ⟶ 5 dilution). The bright red reaction mixture was diluted with water after 0.5

h the yellow solid filtered and crystallized, yield, 0.04 g; m.p. 205-206°; λ max; 390, 280 and 250 nm; ν 2940, 2910, 2870, 1725, 1660, 1585, 1490, 1465, 1380, 1345, 1300, 1280, 1265, 1255, 1200, 1165, 1030 cm^{-1}; ^1H nmr: δ 0.95, 1.3, 2d, 2 $CHC\underline{H}_3$; 1.8, m, 2 $C\underline{H}CH_3$; 2.8-3.4, d, 2 $ArCH_2$; 6.1, s, OCH_2O; 6.6, s, 2 ArH; 6.8, 7.0, 2s, 2 ArH; MS: m/z 310 (M^+, 100), 282 (61), 268 (23), 254 (12), 239 (30), 225 (25), 212 (23), 198 (18). Anal. calc. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.31; H, 5.87.

Preparation of 20 from 19: A mixture of 19 (0.11 g), o-phenylenediamine (0.2 g) in AcOH (15 mL) was heated at 60-70°C for 0.5 h. Dilution with water, filtration of the solid and crystallization gave 20, yield, to 0.1 g; m.p. 227-229°; ν 2940, 2860, 1640, 1610, 1555, 1500, 1470, 1420, 1400, 1370, 1320, 1270, 1215, 1130 cm^{-1}; ^1H nmr: δ 0.90, 1.33, 2d, 3 $CHC\underline{H}_3$; 1.8, m, 2 $C\underline{H}CH_3$; 2.95, 3.33, 6 lines $J_{gem.}$ 13 Hz, $J_{vic.}$ 9 and 4.5Hz, $ArCH_2$, 6.03, s, OCH_2O; 6.80, 6.90, 7.05, 7.40, 4s, 4 ArH; 7.65, 8.0, m, 4 ArH. Anal. calc. for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.33. Found: C, 78.60; H, 5.83; N, 7.30.

Preparation of 21 from 19: A solution of 19 (0.1 g) in MeOH (10 mL) was stirred with $NaBH_4$ (0.1 g) for 15 min at 25°. It was diluted with water (10 mL) and treated with 2N H_2SO_4 (2 mL) and, after 10 min with $NaIO_4$ (0.2 g). After 1 h, the mixture was extracted with C_6H_6. The concentrated extract was heated with 2,4-dinitrophenylhydrazine (0.2 g) in THF (5 mL) for 1 h. Concentration of the solvent and purification by a SiO_2 column (2% C_3H_6O in C_6H_6) gave a red crystalline solid, yield, 0.05 g; m.p. 238-240°d. Anal. calc. for $C_{31}H_{28}N_8O_{10}$: C, 55.35; H, 4.16; N, 16.66. Found: C, 55.67; H, 4.42; N, 16.46.

Preparation of 22 and 23 from 10: A mixture of 10 (2 g, 16.2 mM), DDQ (5.64 g, 24.8 mM) in AcOH (50 mL) was stirred at 80-90°C for 2 h and the mixture processed as described under 7 or 8. The mixture of resulting acetates 24 and 25 was hydrolyzed with 0.5 N MeOH-KOH at 25°C for 1 h. The recovered product was separated by low pressure chromatography on a silica gel column using 2% Me_2CO in C_6H_6. The two fractions were concentrated separately and the solids crystallized.

The major diol 22, yield, 0.62 g; gave a m.p. 267-268°C; $[\alpha]_D$-109°, λ max 288, 262 (sh), 215 nm; ν 3600, 3400, 2980, 2950, 1610, 1500, 1475, 1380, 1350, 1230, 1110, 1035, 985, 925 cm^{-1}; ^1H nmr: δ1.0, d, J=7.5Hz, 2 $CHC\underline{H}_3$; 1.53 s, D_2O, exchangeable, 2 H; 1.85, q, J=7.5Hz, 2 $CHC\underline{H}_3$; 4.4, s, 2 ArCHO; 6.01, s, 2 OCH_2O; 6.6, 7.11, 2s, 4 ArH; MS: m/z 356 (M^+ 72), 338 (80), 298 (18), 282 (5), 270 (25), 269 (100), 253 (39). Anal. calc. for $C_{20}H_{20}O_6$: C, 67.60, H, 5.66. Found: C, 67.61, H. 5.70.

The minor diol 23, yield, 0.25 g; gave m.p. 247-248°; $[\alpha]_D^{25}$+144°; λ max 288, 240 (sh), 212 nm; ν3590, 3460, 3000, 2910, 1500, 1475, 1370, 1235, 1035, 1000, 930 cm^{-1}; ^1H nmr:δ 1.13, d, J=6Hz, 2 $CHC\underline{H}_3$; 1.5 broad 4H, with D_2O changed to m, 2 $C\underline{H}CH_3$; 3.9, d, J=9Hz, 2 ArCHO; 6.0, s, 2 OCH_2O; 6.73, 7.11, 2s, 4 ArH; MS: m/z 356 (M^+), 338 (2), 298 (34), 282 (66), 280 (45), 270 (22), 269 (100), 268 (14), 253 (64). Anal. calc. for $C_{20}H_{20}O_6$: C, 67.60, H, 5.66. Found: C, 67.30, H. 5.71.

Preparation of the acetates 24 and 25: The same procedure as described under 17 and 18 was followed.

The acetate 24 was obtained as a colorless solid, ν 1735 cm^{-1}; ^1H nmr: δ 1.02, d, J-6Hz, 2 CH-$C\underline{H}_3$; 1.90, q, J=6H; 2 $C\underline{H}$-CH_3; 2.0, s, 2-$OCOCH_3$; 5.43, s, 2 ArCH-O; 6.00, s, 2 OCH_2O; 6.71, 6.93, 2s, 4 ArH. Anal. calc. for $C_{20}H_{20}O_6$: C, 65.44; H, 5.49. Found: C, 65.22; H, 5.35.

The acetate 25 was obtained as a colorless solid, ν 1735 cm^{-1}; ^1H nmr:δ 1.04, d, J=6Hz, 2 CH-$C\underline{H}_3$; 1.87, m, 2 $C\underline{H}$-CH_3; 1.96, s, 2-$OCOCH_3$; 5.03, d, J-9Hz, 2 ArCHO; 6.00, s, 2 OCH_2O; 6.76, 6.90, 2 s, 4 ArH. Anal. calc. for $C_{24}H_{24}O_8$: C, 65.44; H, 5.49, Found: C, 65.15; H, 5.58.

Oxidation of 22 to 26: To a solution of 22 (10.1 g) in Me_2CO (15 mL) was added Jones' reagent (2.5 mL). After 3 h at 25°C, it was diluted with H_2O, extracted with C_6H_6 and the solvent layer concentrated to dryness. The solid was crystallized from ether, yield 0.05 g; m.p. 227-228°; λ max 291, 232 nm; ν 2970, 2900, 1695, 1675, 1610, 1530, 1500, 1415, 1395, 1370, 1350, 1245, 1195, 1112, 1072, 1035. Anal calc. for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58. Found: C, 68.05; H, 4.74.

Oxidation of 23 by the same method gave a product identical with 26.

Preparation of the epoxide 27: The diol 22 (0.1 g) was dissolved in CH_3CN (15 mL), and was treated dropwise at 25°C with a solution of triphenylphosphine dibromide, prepared from bromine (0.12 g) and triphenylphosphine (0.2 g) in CH_3CN (3 mL). After 10 min at 25°C, water was added, the mixture extracted with C_6H_6 and the C_6H_6 concentrate purified by prep. tlc using 9:1 C_6H_6:C_3H_6O. The major fraction was obtained as a colorless crystalline solid, yield, 0.05 g; m.p. 172-173°; λ max 322, 288. 212 nm; ν 2970, 2900, 1620, 1500, 1480, 1450, 1430, 1410, 1360, 1325, 1295, 1240, 1220, 1120, 1035 cm^{-1}; ^1H nmr; δ 0.71 and 1.13, 2 d, J=6Hz, 2 $CHCH_3$; 1.85 and 7.3, 2m, 2 $CHCH_3$; 4.50 and 5.03, 2d, J=6Hz, 2 ArCHO; 6.01 and 6.03, 2 s, 2 OCH_2O; 6.43 and 6.68, 2s, 2 ArH; 7.30, broad s, 2 ArH. Anal. calc. for $C_{20}H_{18}O_5$: C, 70.99, H, 5.36. Found: C, 70.92; H, 5.38.

Conversion of 22 to 16: A solution of 22 (0.1 g) in C_6H_6-ether (1:1, 20 mL) was let stand at 25° with BF_3-etherate (1 ⟶ 10, 0.5 mL) for 16 h. The product was purified by preparative tlc using C_6H_6:C_3H_6O (9:1). The faster fraction gave a colorless crystalline solid, yield 0.025 g, identical with 16. The slower fraction also gave a colorless crystalline solid which was identical with 27.

Conversion of 23 to 28: To a solution of 23 (0.1 g) in C_6H_6 (10 mL) was added 1 ⟶ 10 BF_3-etherate in C_6H_6 (1 mL) and mixture stirred at 25° for 2 h. After washing with H_2O, the C_6H_6 layer was concentrated and the product purified by prep. tlc using 1:1 C_6H_6-C_6H_{14} with four developments. The major fraction gave a pale yellow crystalline solid which was recrystallized from MeOH, 28, yield 0.03 g; m.p. 141-142°; λ max 345 (3H), 330, 318 (sh), 298 (sh), 250; ν 2900, 1600, 1500, 1465, 1445, 1245, 1185, 1160, 1125, 1014 cm^{-1}; ^1H nmr: δ 1.15, d, J-6Hz, 2.33, s, 3H; 2.5, 3.3, m, 3H; 6.03, 6.06, 2s, 4H; 6.88, 7.1, 7.3, 3s, 3H. Anal. calc. for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 75.07; H, 5.07.

Conversion of 23 to 31: When the preceding reaction was carried out at reflux temperature for 10 min and the mixture worked up as before, the product was a yellow crystalline solid, m.p. 141-143°; λ max 345, 330, 315, 300 (sh) and 250 nm; ν 2920, 1460, 1435, 1270, 1235, 1180, 1150, 1115 and 1030 cm^{-1}; MS., M^+ 320. Anal. calc. for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 75.06; H, 5.04.

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