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Boron Trifluoride-Acetic Anhydride Catalysed Rearrangement of Dihydroarteannuin B

Asish K. Bhattacharya, Dharam C. Jain and Ram P. Sharma*

Central Institute of Medicinal and Aromatic Plants
P.O. CIMAP, Lucknow-226015, India

Raja Roy

Central Drug Research Institute, Lucknow-226001, India

Andrew T. McPhail

P.M. Gross Chemical Laboratory, Duke University
Durham, NC-27708, USA

Abstract : The reaction of dihydroarteannuin B **2** with boron trifluoride-acetic anhydride furnished compound **3** as the major product whose structure has been established by chemical transformations, spectral data and finally confirmed by x-ray analysis. © 1997 Elsevier Science Ltd.

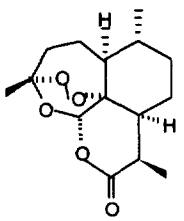
Arteannuin B **1** is one of the three major secondary metabolites of the plant Artemisia annua, the other two being artemisinic acid and artemisinin, the latter is known to be the potent antimalarial drug[1]. The availability of artemisinin from A. annua in low yields prompted the scientists all over the world to devise means for increasing its production by other strategies. There are several total synthesis reported for artemisinin but each of these resulting in low yields thus making them commercially unviable[2]. Therefore, the attention was focused on the chemical conversion of the other two secondary metabolites present in A annua to artemisinin[1].

Arteannuin B **1** has been converted into artemisinin by Lansbury et al[3] through deepoxidation. Since the common direct deepoxidation procedures are reported to yield rearranged lactone[3,4], we decided to use an indirect approach for achieving this objective.

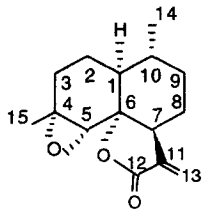
Reduction of arteannuin B **1** with nickel boride generated *in situ* from $NaBH_4$ and $NiCl_2.6H_2O$ in DMF furnished the dihydroarteannuin B **2** in 90% yield. The stereochemistry of the C_{11}-methyl group was assigned as α on the basis of J value between H-7 and H-11 which is 14 Hz and also the chemical shift difference of the C_{11}-methyl in the ^1H NMR spectrum recorded in $CDCl_3$ and C_6D_6 (see experimental)[5]. Compound **2** was treated with boron trifluoride-acetic anhydride at 0-5° and the reaction mixture was stirred at rt for 2 hr. Usual work up procedure furnished one major product (TLC) which was purified by preparative TLC (EtOAc-hexane, 1:4). Although this product appeared to be homogenous in the ^1H NMR spectrum but ^{13}C NMR spectrum indicated it to be a mixture of two compounds in the ratio of $\approx$ 85:15. The ^1H NMR spectrum revealed that the product in hand has an acetoxy function in it by displaying a singlet of three protons at 2.08 ppm. Therefore, it was hydrolysed with 10% KOH-MeOH and the two spots visible on the TLC plate were separated by preparative TLC (EtOAc-hexane, 1:4, double run).

The less polar spot was the major product, m.p. 164-66°. The presence of absorption bands at 1752 and 3472 in the IR spectrum suggested that the major product is a γ-lactone and has an hydroxyl function in it. The ^1H NMR spectrum revealed the presence of an olefinic proton at 5.60 ppm as multiplet and a doublet (J=5 Hz) of one proton at 4.05 ppm was assigned to the proton under the hydroxyl group. A three proton singlet at 1.70 ppm was suggestive of the presence of methyl group on the double bond. Besides, the two doublets with J=7 Hz each at 1.15 ppm and 1.10 ppm were also present. Acetylation of this less polar major product gave the acetate whose ^1H NMR spectrum was superimposible with the BF_3-Ac_2O product of **2**. Reaction of the major alcohol with m-CPBA furnished a compound (M^+ at m/z 266) as a gum whose ^1H NMR spectrum indicated that it is a mixture of two isomeric epoxides which could not be separated on silica gel TLC. Hydrogentation of the alcohol over 10% Pd-C furnished the dihydro compd. (M^+ 252) in whose ^1H NMR the olefinic proton was missing and the methyl on double bond was replaced by a three proton doublet (J=7 Hz) at 0.88 ppm. Oxidation of the alcohol with DMSO-Ac_2O furnished a ketone as an oil whose IR spectrum (peaks at 1793 and 1720 cm^{-1}) revealed that the carbonyl function in it is not conjugated with the double bond. Facile epoxidation of this ketone with m-CPBA further indicated that the double bond is not conjugated with the carbonyl function.

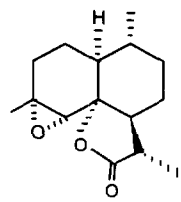
The reaction of dihydroarteannuin B **2** with boron trifluoride-acetic anhydride was expected to yield the corresponding allylic acetate or the C-5 ketone[6] or its enol acetate. However, the above data indicated that a rearrangement has taken place leading to the formation of a product in which the acetoxy function is not at the allylic position. Since the ^1H and ^{13}C NMR spectra of the major product suggested the presence of a methyl group on the double bond, it was envisaged that



Artemisinin



1



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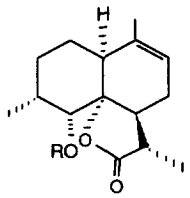
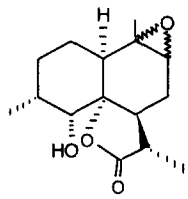


3 R = OAc
4 R = H
9 R = Ts



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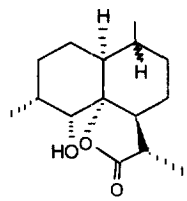

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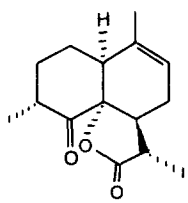
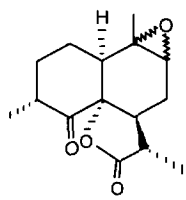
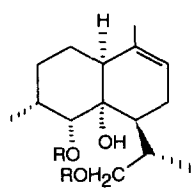


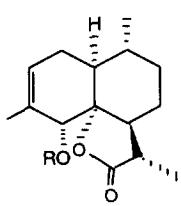
7



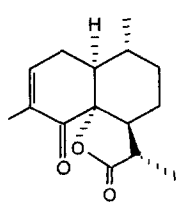
8 a
8 b



10 R = H
11 R = Ac



12 R = H
13 R = Ac
15 R = CH_2-S-CH_3



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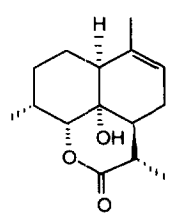

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the rearrangement has led to the formation of compound 3 which was finally proved by the application of COSY, TOCSY, HMQC and HMBC experiments carried out on compound 4 obtained by the alkaline hydrolysis of 3. Thus the structures to products of acetylation, epoxidation, hydrogenation and oxidation of the major alcohol 4 were assigned as 3, 5, 6 and 7 respectively. Accordingly the epoxides obtained from the ketone 7 were assigned structures as **8a** and **8b**.

The multiplicity of each carbon atoms in compound 4 was ascertained by ^{13}C-DEPT NMR. The DEPT edited spectrum showed 3 x C, 6 x CH, 3 x CH_2 and 3 x CH_3 signals. Thus, protonated carbon atoms were readily assigned by HMQC experiment. Analysis of the multiple bond HMBC spectrum established the carbon-carbon connectivity and thus enabling the assignment of all the quaternary carbon atoms. These results were found to be consistent with the results obtained from analysis of the ^1H-^1H COSY and TOCSY spectra.

In the COSY 90° spectrum of 4, H-1 exhibited weak allylic coupling with the H-9 methine at 5.60 ppm. Further correlations of H-1 were observed with signals at 2.25,1.92 and 1.70 ppm (br s) leading to the assignment of these signals to H-2β, H-8β and H-14 respectively. The H-5 (d, J=5 Hz, 4.05 ppm) showed a cross peak with signal at 2.08 ppm which was readily assigned to the H-4 methine signal. Further H-4 showed correlations with signals at 1.46 and 1.10 ppm (d, J=7 Hz) which were assigned to H-3 and H-15 respectively. The H-9 (m, 5.60 ppm) showed strong cross peaks with signals at 2.29 and 1.70 ppm, the former signal being assigned to the H-2α while the latter confirmed the H-14 signal. The H-11 (m, 3.15 ppm) exhibited strong cross peaks with the signals at 1.98, 1.92 and 1.15 ppm (d, J=7 Hz) leading to the assignment of these signals to H-7, H-8β and H-13 respectively. By careful analysis of the cross peaks, further connectivities among the various ^1H resonances could be traced which led to the complete ^1H NMR signal assignment of 4 (see Table 1).

Stereochemistry of 4 :

Oxidation of the alcohol 4 with DMSO-Ac_2O to compound 7 coupled with the fact that compound 7 is converted back to 4 with $NaBH_4$/MeOH indicated that the hydroxyl group at C-5 is hindered and therefore α-oriented. This observation was further corroborated when the reaction of the alcohol 4 with tosyl chloride and pyridine at 110° for 8 hr furnished the tosylate 9 in 10% yield. It has been reported that DMSO-Ac_2O oxidizes the hindered alcohol to the corresponding ketone whereas unhindered alcohols lead to the formation of methylthiomethyl ethers[7]. In agreement with this observation, the absolute configuration of C-5 in compound 4 was established as R by Horeau's method[8]. Reaction of compound 4 with (±) - α - phenylbutyric anhydride in pyridine furnished (+)- α - phenylbutyric acid in 22.6% optical yield. It is pertinent to mention here that H-11 appears at 2.60 ppm in the ^1H NMR spectrum of 3 and at 3.15 ppm in that of 4, this paramagnetic shift could

be explained by hydrogen bonding as suggested by the stereomodel. The stereochemistry of the methyl at C-4 was assigned as α on the basis of coupling constant between H-4 and H-5 which is 5 Hz.

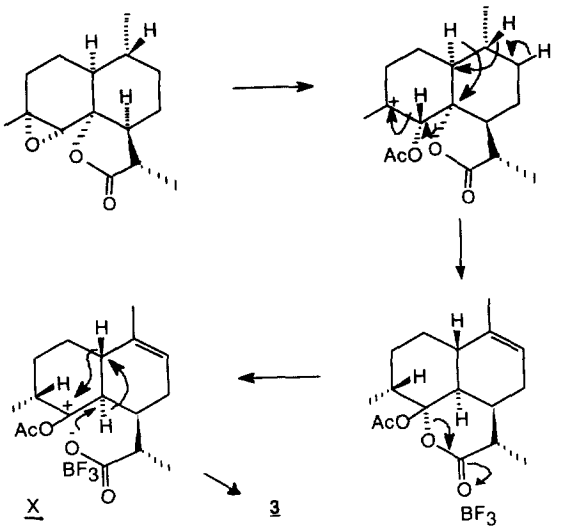
Reaction of compound **4** with LAH furnished the triol **10** which was acetylated with Ac_2O-Py as such to obtain the diacetate **11** as a gum. In the ^1H NMR spectrum of **11**, H-5 appeared as a doublet (J=5 Hz) at 5.05 ppm, H-9 as a multiplet at 5.45 ppm and H-12a, H-12b appeared as multiplets at 4.08 and 3.85 ppm. The methyl on the double bond appeared as a broad singlet at 1.62 ppm. In the ^1H NMR spectrum of **11** addition of trichloroacetyl isocyanate (TAI) produces paramagnetic shift in the signal of H-1 (now appearing at 3.86 ppm) indicating that H-1 and C-6 hydroxyl are *cis* to each other. Considering the observation made by Lansbury et al[3] that the lactone ring junction in **2** is liable to change its configuration under acidic conditions, it was difficult to assign the absolute configuration of C-1 and C-6 though the TAI experiment indicated both to be α assuming that no change in configuration has taken place during treatment with BF_3-Ac_2O.

In the NOESY spectrum of **4**, H-1(m, 2.55 ppm) showed intense interactions with H-7(m, 1.98 ppm) and H-14(br s, 1.70 ppm) suggesting that H-1 is α-oriented. Further H-7 showed noe cross peak with H-13(d, J=7 Hz, 1.15 ppm) and H-11(m, 3.15 ppm) showed interaction with one of the methylene protons of H-8(m, 1.92 ppm). The above observations suggested that the C_{11}-methyl group is α -oriented and H-8 proton at 1.92 ppm and H-11 are β -oriented. In the NOESY spectrum, H-5(d, J=5 Hz, 4.05 ppm) showed noe interactions with one of the methylene protons of H-2(m, 2.25 ppm) and also with H-4(m, 2.08 ppm). The coupling constant between H-4 and H-5 which is 5 Hz suggested that C_4-methyl is α -oriented and hence H-2 proton at 2.25 ppm, H-4 and H-5 are β -oriented (see Table 1).

The structure and absolute stereochemistry of **4** was finally placed on firm footing by its x-ray analysis as given in Figure 1.

The most plausible mechanism for the formation of **3** has been given in Scheme 1. 1,3-Hydride shift may be taking place either as indicated in intermediate X or through a protonated cyclopropane intermediate[9]. At present, the possibility of 1,5-hydride shift can not be ruled out.

The more polar spot obtained in the alkaline hydrolysis of the BF_3-Ac_2O reaction product of **2** was found to be mixture of two compounds ($\approx$ 2:1) in the ^{13}C NMR spectrum. Acetylation of this mixture with Ac_2O-Py led to the isolation of two compounds by preparative TLC (EtOAc-hexane, 2:8). The less polar product was identified as the acetate **13** on the basis of 2D NMR data given in Table 1 and therefore structure **12** was assigned to the alcohol present in the above mentioned polar spot. In the ^1H NMR spectrum of **13**, H-3 appeared as a multiplet at 5.54 ppm, H-5 as a broad singlet at 5.98 ppm, C-15 methyl appeared as a broad singlet at 1.55 ppm, the two secondary methyls appeared at 1.18 ppm and 0.94 ppm as



Scheme 1

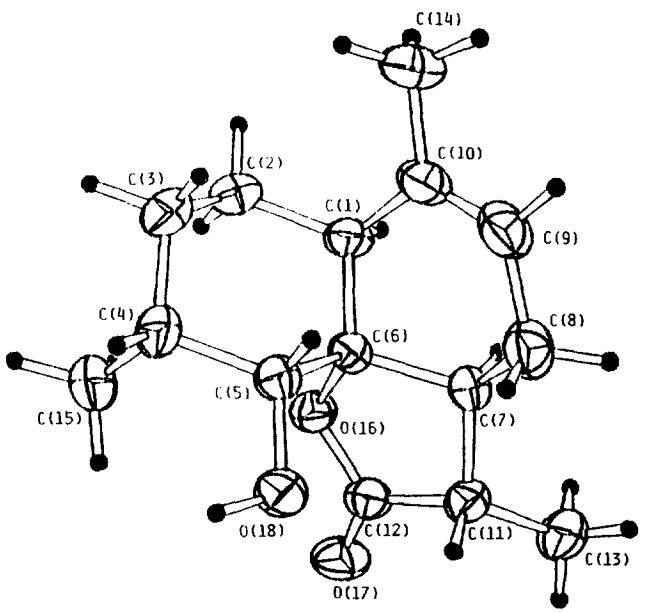


Figure 1. ORTEP diagram (50% probability ellipsoids) showing the crystallographic atom numbering scheme and solid-state conformation; small filled circles represent hydrogen atoms.

Table 1. 2D NMR data of **4** and **13**

	4						**13**		
H#	Type[a]	COSY[b]	TOCSY[b]	HMBC(H→C)	ROESY[c]	NOESY	Type	COSY[b]	NOESY
1	CH	2β,8β,9,14	2α2β,3,7,8α,8β,9,13,14,15	2,3	3,9	7,14	CH	2α,14	2α,7,14
2α	CH_2	2β,7,9,14	1,7,8β,9,11,13,14	6,7,9,10	9	2β,9	CH_2	1,2β,5,15	1,2β
2β		1,2α,7,14	1,7,8β,9,11,13,14		9	2α,5		2α,3,5,15	2α,3
3	CH_2	4,14	1,4,5,8β,14,15	1,4,5,14,15	1,5	4,5,15	CH	2β,5,15	2β,15
4	CH	3,5,15	3,5,15		15	3,5,15	C		
5	CH	4	3,4,15	4,15	3,15	2β,3,4	CH	2α,2β,3,15	15
6	C						C		
7	CH	2α,2β,8α	1,2α,2β,9,11,13,14	1,2,5,6,9,10,11,13	13	1,13	CH	8α,8β,11,13	1,8α,13
8α	CH_2	8β		1,2,5,6,9,10,11,13,14		8β	CH_2	7,8β,9,10,13	7,8β,9,14
8β		1,8α,11,14	1,2α,2β,3,9,11,13,14			8α,11		8α	8α
9	CH	1,2α,14	1,2α,2β,7,8β,11,13,14	1,7,14	1,2α,2β,14	2α,14	CH_2	8α,14	
10	C						CH	8α,14	
11	CH	7,8β,13	2α,2β,7,8β,9,13,14	2,7,12,13	13	8β,13	CH	7,13	13
12	C						C		
13	CH_3	11	1,2α,2β,7,8β,9,11	7,11,12	7,11	7,11	CH_3	7,8α,11	7,11
14	CH_3	1,2α,2β,3,8β,9	1,2α,2β,3,4,7,8β,9,11	1,9,10	9	1,9	CH_3	1,9,10	1,8α
15	CH_3	4	1,3,4,5	2,3,4,5	4,5	3,4	CH_3	2α,2β,3,5	3,5

[a] Determined by DEPT and HMQC NMR experiments.

[b] Stereochemistries indicated were determined by NOESY spectrum.

[c] In ROESY spectrum, TOCSY information was predominant

doublets with J=7 Hz, H-1 appeared as a multiplet at 1.64 ppm and H-11 appeared as a multiplet at 2.25 ppm. Oxidation of the more polar spot (mixture of two compounds) with pyridinium dichromate in DMF furnished the ketone **14** and with DMSO-Ac_2O furnished the methylthiomethyl ether **15** which were characterised on the basis of spectral data. The more polar product which remained unreactive to Ac_2O-Py was identified as **16** on the basis of spectral data. In the ^1H NMR spectrum of compound **16**, H-5 appeared as a doublet (J= 5 Hz) at 4.41 ppm, H-9 appeared as multiplet at 5.43 ppm, H-14 appeared as a broad singlet at 1.70 ppm and the two secondary methyl groups appeared as doublets (J= 7 Hz) at 1.22 ppm and 1.20 ppm. In the ^1H NMR spectrum of **16**, the addition of trichloroacetyl isocyanate (TAI) produced the paramagnetic shift of H-1 which now appeared at 2.90 ppm proving that H-1 and OH at H-6 are cis to each other. The product **16** was obviously formed by rearrangement of γ-lactone **4** to δ-lactone **16** under alkaline conditions.

Interestingly Zn-AcOH reduction of the ketone **7** furnished the alcohol **4** in 20% yield. Also when the ketone **7** was photolysed with 500 W tungsten arc lamp in MeOH, alcohol **4** was obtained in 14% yield as the major product.

X-RAY CRYSTALLOGRAPHY OF 4

X-Ray diffraction data were collected on an Enraf-Nonius CAD-4 diffractometer (Cu-Kα radiation, graphite monochromator) from crystals of dimensions 0.14x0.36x0.50 mm, $C_{15}H_{22}O_3$, MW 250.34, orthorhombic, space group = $P2_12_12_1(D_2^4)$ - No.19 with a = 10.713(1), b=13.300(2), c=9.562(1) Å, V=1362.4(5) $Å^3$, $D_{calcd.}$ = 1.220 g cm^{-3} for Z=4, Cu-Kα , λ= 1.5418 Å, μ =6.3 cm^{-1}, scan type = ω-2θ, scan width (°) = 0.80+0.14 tan θ, θ_{max} (°)=75. 1619 reflections were measured of which 1524 had I $> 3.0\sigma$ (I) and were considered observed.

Intensity data were corrected for the usual Lorentz and polarization effects; an empirical absorption correction, based on the ϕ -dependency of the intensities of several reflections with χ ca. 90°, was also applied. The space group was determined uniquely from the systematic absences (h00 when h≠2n, 0k0 when k≠2n, 00l when l≠2n). Refined unit-cell parameters were calculated from the diffractometer setting angles for 25 reflections ($36° < \theta < 40°$) widely separated in reciprocal space.

The crystal structure was solved by direct methods (MULTAN 11/82). An E-map yielded approximate coordinates for all non-hydrogen atoms. Positional and thermal parameters (first isotropic and then anisotropic) were adjusted by means of several rounds of full matrix least-squares calcultations. Hydrogen atoms were located in a difference Fourier synthesis and their positional and isotropic thermal parameters were also refined in the subsequent least-squares cycles. An extinction correction was included as a variable during the later iterations. A final difference Fourier synthesis contained no unusual features.

Crystallographic calculations were performed on PDP 11/44 and Micro VAX computers by use of the Enraf-Nonius Structure Determination Package (SDP). For all structure-factor calculations, neutral atom scattering factors and their anomalous dispersion corrections were taken from International tables for X-ray crystallography[10,11].

EXPERIMENTAL

General : All melting points were determined in open capillaries and are uncorrected. IR spectra were recorded as thin films unless otherwise stated on Perkin Elmer 1710 FT-IR spectrophotometer. The NMR spectra were recorded on a varian FT-80 (80 MHz) or a Bruker WM-400 (400 MHz) or a Bruker DRX-300 (300 MHz) in $CDCl_3$ unless otherwise stated with TMS as internal standard. Chemical shifts are expressed as δ in ppm. Mass spectra were recorded under electron impact at 70 ev on JEOL JMS D-100 Spectrometer. Fast Atom Bombardment Mass Spectroscopy (FABMS) were carried out with JEOL SX 102/DA-6000 mass spectrometer using m-nitrobenzyl alcohol as matrix at an accelerating voltage of 10 kV. Optical rotations were recorded on JASCO DIP-180 digital polarimeter. Elemental analysis were carried out on HERAEUS CHN-O-RAPID elemental analyser. For preparative TLC silica gel G (E. Merck, India) was used. MCPBA used was obtained from E. Merck (Germany). Hexane refers to the fraction b.p. 65-70°C. Work up reaction mixtures were dried over anhydrous Na_2SO_4.

The two-dimensional NMR experiments were carried out on a Bruker DRX-300 spectrometer operating at 300 MHz in $CDCl_3$. Assignments of ^{13}C signals have been made on the basis of comparison with other compounds in this series except where it has been mentioned by HMQC and HMBC NMR experiments. The 2D ^1H-^1H COSY 90° experiments on **4**, **13** and **15** were carried out with 1024 K data sizes and 2100.91 Hz as the spectral width in both the dimensions with 256 t_1 increments. The raw data were zero filled in W1 dimension from 256 W to 512 W and sine bell window function was used prior to double fourier transformation.

The phase sensitive TOCSY, 2D ROESY experiments on **4** and 2D NOESY experiments on **4** and **13** were carried out with 2100.91 Hz as the spectral width in both the dimensions with 256 t_1 increments. A spin lock time of 82.4 ms was used in all the experiments. Mixing time of 550 ms and 200 ms were used for NOESY and ROESY experiments respectively. The raw data were zero filled in W1 dimension from 256 W to 512 W and 90° shifted squared sine bell window function was used prior to double fourier transformation.

The HMQC and HMBC experiments were carried out using BIRDY pulse sequence with 550 ms for nulling proton coupled to ^{12}C nucleus. Spectral widths of 2100.91 Hz for ^1H and 13525.2 Hz for ^{13}C were used in HMQC experiment on **4**. In HMBC experiment on **4**, spectral widths of 2100.91 Hz for ^1H and 15779.4 Hz for ^{13}C were

used.

Reduction of 1 with nickel boride :

A solution of 100 mg of 1 in 4 ml dimethyl formamide (DMF) was stirred at rt for 5 min and 400 mg of $NiCl_2.6H_2O$ was added to it. To the stirring solution, 100 mg of $NaBH_4$ was added slowly over a period of 30 min and monitored the reaction on TLC. After 3 hr when the reaction was complete, it was diluted with 300 ml of H_2O and extracted with $CHCl_3$ (3x150 ml). The dried $CHCl_3$ extract was evaporated and the traces of DMF were removed by co-distillation with toluene under reduced pressure to give 90 mg of 2 m.p., 179-181°C (EtOAc-hexane), $[\alpha]_D^{25}$-58.5° (c.0.4, $CHCl_3$). Spectral data of 2 : IR (cm^{-1}, KBr) : 1768, 1472, 1442, 1381, 1317, 1257, 1168, 1132, 998, 964; ^1H NMR (400 MHz, $CDCl_3$): 2.85 (s, H-5), 2.68 (m, H-11), 1.38(br s, H-15), 1.24 (d, J=7 Hz, H-13), 0.97 (d, J=7 Hz, H-14). Irradiation of signal at 1.24 ppm (d, J=7 Hz, H-13) collapsed the multiplet at 2.68 ppm (H-11) into a doublet (J= 14 Hz). ^1H NMR (400 MHz, C_6D_6) : 2.45 (s, H-5), 2.14 (m, H-11), 1.09 (br s, H-15), 1.02 (d, J=7 Hz, H-13), 0.63 (d, J=7 Hz, H-14); ^{13}C NMR (Assignment by DEPT NMR experiment) : 178.31(C-12), 80.81(C-6), 57.93(C-5), 57.79(C-4), 54.69(C-7), 44.42(C-1), 37.61(C-11), 34.51(C-9), 30.50(C-10), 24.35(C-3), 22.76(C-15), 22.65(C-8), 18.36(C-13), 16.14(C-2), 12.75(C-14); MS :m/z at 250(M^+), 222, 208, 179, 164, 151, 135, 121, 107, 93, 81, 67, 55, 43. Found : C, 71.84; H, 8.71. $C_{15}H_{22}O_3$ requires C, 71.96; H, 8.85%.

Reaction of 2 with $BF_3.Et_2O$-Ac_2O :

A solution of 100 mg of 2 in 2 ml Ac_2O was cooled to 0-5°C and 0.25 ml of $BF_3.Et_2O$ was added to it with stirring. The reaction was monitored on TLC and after 2 hr when the reaction was complete, reaction mixture was gradually warmed to rt, diluted with 200 ml of H_2O and extracted with CH_2Cl_2 (3 x 100 ml). The CH_2Cl_2 extract was washed with dil. solu. of $NaHCO_3$, water, dried and evaporated. The traces of Ac_2O were removed by co-distillation with toluene to yield a gummy residue showing single spot on TLC which was purified by preparative TLC (EtOAC-hexane, 2:8) to furnish a solid (95 mg). ^{13}C NMR indicated it to be a mixture of two compounds in the ratio of ≈85:15. **Alkaline hydrolysis:** A solution of 100 mg of the product isolated above in 10 ml of MeOH was treated with 0.6 ml of 10% KOH-MeOH with stirring at rt and the reaction was monitored on TLC. After 3 hr when the reaction was complete, the reaction mixture was diluted with 100 ml of H_2O and acidified with 2N HCl solution. The aqueous solution was extracted with CH_2Cl_2(3 x 100 ml), washed with water, dried and evaporated to give a yellow coloured semi-solid which on TLC (EtOAc-hexane, 2:8, double run) showed two spots and these were isolated by prearative TLC (EtOAc-hexane, 2:8) to give 68 mg of the less polar (major product) 4 (m.p. 164-66°C, $CHCl_3$-hexane), $[\alpha]_D^{25}$-75.18°(c.0.415,$CHCl_3$). The more polar (minor product) showed two spots on TLC moving very close to each other and ^{13}C NMR also indicated it to be a mixture of two compounds. Compound

13 was isolated from the crude mixture by acetylation with acetic anhydride and pyridine followed by preparative TLC (EtOAc-hexane, 2:8) after usual work up as a semi-solid, yield (8 mg). Compound **16** was obtained as unreacted as a gum (4 mg). Spectral data of **4** : IR (cm^{-1}, KBr) : 3472, 1752, 1475, 1441, 1384, 1296, 1149, 1076, 970; ^1H NMR (Assignment by ^1H-^1H COSY and TOCSY): 5.60(m, H-9), 4.05(d, J=5 Hz, H-5), 3.15(m, H-11), 2.55(m, H-1), 2.29(m, H-2α), 2.25(m, H-2β), 2.08(m, H-4), 1.98(m, H-7), 1.92(m, H-8β), 1.70(br s, H-14), 1.64(m, H-8α), 1.46(m, H-3), 1.15(d, J=7 Hz, H-13), 1.10(d, J=7 Hz, H-15). The irradiation of signal at 1.15 ppm (d, J= 7 Hz, H-13) transformed the multiplet at 3.15 ppm (H-11) into a doublet (J=14 Hz). ^1H NMR (400 MHz, C_6D_6) : 5.19(m, H-9), 3.69(d, J=5 Hz, H-5), 3.16(m, H-11), 1.40(br s, H-14), 1.09(d, J=7 Hz, H-13), 1.05(d, J=7 Hz, H-15); ^{13}C NMR (Assignment by DEPT, HMQC and HMBC NMR experiments) : 180.86 (C-12), 135.81(C-10), 124.17(C-9), 85.08(C-6), 68.99(C-5), 53.64(C-7), 47.15(C-1), 38.90(C-11), 34.08(C-4), 26.58, 26.49(C-2 & C-3 or reverse), 20.63(C-14), 18.06(C-8), 14.83(C-13), 12.16(C-15) : MS:m/z at 252(M^++2), 233, 218, 190, 177, 160, 149, 122, 92, 56; FAB-MS; m/z at 251 $[MH]^+$ $[C_{15}H_{22}O_3+H]^+$, 273$[M+Na]^+$ $[C_{15}H_{22}O_3+Na]^+$, 233 $[MH-H_2O]^+$. Found : C, 71.88; H, 8.76. $C_{15}H_{22}O_3$ requires C, 71.96; H, 8.85%. Acetylation of **4** with Ac_2O-Py furnished the acetate **3** (m.p. 135-37°C, EtOAc-hexane).

Spectral data of **3** : IR (cm^{-1}, KBr) : 1770, 1740, 1456, 1234, 996; ^1H NMR (400 MHz) : 5.65 (m, H-9), 5.25 (d, J=5.5 Hz, H-5), 2.60(m, H-11), 2.08(s,Acetate), 1.70(s, H-14), 1.20(d, J=7 Hz, H-13), 1.10(d, J=7 Hz, H-15); ^{13}C NMR(Assignment by DEPT NMR experiment); 179.45(C-12), 169.30(OAc), 135.42(C-10), 124.21(C-9), 84.07(C-6), 71.20(C-5), 53.13(C-7), 47.71(C-1), 38.70(C-11), 30.90(C-4), 26.10, 25.92(C-2 & C-3 or reverse), 21.37(OAc), 20.52(C-14), 17.90(C-8), 15.23(C-13), 12.90(C-15),; MS; m/z at 292 (M^+), 250, 232, 204, 189, 177, 167, 159, 126, 84.

Spectral data of **13** : IR (cm^{-1}); 1769, 1737, 1458, 1373, 1239, 1133, 1031, 1010, 933; ^1H NMR (Assignment by ^1H-^1H COSY) : 5.98(br s, H-5), 5.54(m, H-3), 2.47(m, H-2α), 2.25(m, H-11), 2.15(m, H-2β), 2.10(s, Acetate), 1.98(m,H-8α), 1.80(m, H-7), 1.72(m, H-10), 1.64(m,H-1), 1.60(m, H-9), 1.55(br s, H-15), 1.22(m,H-8β), 1.18(d,J-7 Hz, H-13), 0.94(d,J=7 Hz, H-14); MS : m/z at 292 (M^+), 232, 181, 167, 151, 126, 45; FABMS : m/z at 293 $[MH]^+$ $[C_{17}H_{24}O_4+H]^+$, 315$[M+Na]^+$$[C_{17}H_{24}O_4+Na]^+$, 233. HRMS : Found : 292.1670, calcd. for $C_{17}H_{24}O_4$: 292.1674.

Spectral data of **16** : IR(cm^{-1}) : 3439, 2929, 2854, 1713, 1455, 1379, 1211, 1145, 1120, 1088, 1060, 1036, 999, 966, 853, 757; ^1H NMR(400 MHz) : 5.43(m, H-9), 4.41(d, J=5 Hz, H-5), 3.31(m, H-11), 2.39(m, H-1), 1.70(br s H-14), 1.22(d, J=7 Hz, H-13), 1.20(d, J=7 Hz, H-15); MS : m/z at 250(M^+), 234, 231(M^+-1-18), 216, 203, 188, 175, 166, 150, 120, 108, 94,84, 69, 55, 41. HRMS : Found : 250.1560, calcd. for $C_{15}H_{22}O_3$: 250.1568.

^1H NMR of (**16**+TAI) : 5.46(m, H-9), 4.59(d, J=5 Hz, H-5), 3.18(m, H-11), 2.90(m,

H-1), 1.71(br s, H-14), 1.24(d, J=7 Hz, H-13), 1.13(d, J=7 Hz, H-15).

Oxidation of 12 with DMSO/Ac_2O :

To a solution of 25 mg of crude mixture containing 12 and 16 in 1 ml DMSO, 1 ml Ac_2O was added with shaking and the reaction mixture was left overnight at rt. The reaction mixture was diluted with 100 ml of water and extracted with CH_2Cl_2 (3x50 ml), washed with water, dried and evaporated to dryness to give a viscous oily residue which on preparative TLC (EtOAc-hexane, 2:8) yielded (16mg) of 15 as a solid (m.p. 86-87°, EtOAc-hexane) and 4 mg of 16 was recovered unreacted as a gum. Spectral data of 15 : IR (cm^{-1}, KBr) : 2925, 1733, 1455, 1377, 1206, 1175, 1053, 1078, 844, 766, 734 ; ^1H NMR (Assignment by ^1H-^1H COSY) : 5.42(m, H-3), 4.73(br s, H-5), 4.50(s, S-CH_2O), 2.05(s, S-CH_3), 1.90(m, H-11), 1.72(br s, H-15), 1.20(d, J=7 hz, H-13), 0.87(d, J=7 Hz, H-14); MS : m/z at 232 (M^+-C_2H_6SO), 215, 205, 189, 175, 159(100), 147, 123, 119, 81, 77, 61: FABMS : m/z at 233[M-C_2H_5SO]$^+$. Found : C, 65.52; H, 8.22. $C_{17}H_{26}O_3S$ requires C, 65.77; H, 8.44%.

Oxidation of 4 with DMSO/Ac_2O :

To a solution of 15 mg of 4 in 0.4 ml of dimethyl sulfoxide (DMSO) and 0.40 ml of Ac_2O was added, and the reaction mixture was left overnight at rt. The reaction mixture was diluted with 100 ml of H_2O and extracted with $CHCl_3$ (3 x 50 ml), washed with water, dried and evaporated to dryness to give an oily residue which on preparative TLC (EtOAc - hexane, 2 : 8) yielded 7 as an oil (9 mg), $[\alpha]_D$-166.90°(c.0.435,$CHCl_3$). Spectral data of 7 : IR(cm^{-1}) : 1793, 1720, 1458, 1381, 1200, 1130, 1001; ^1H NMR (400 MHz) : 5.65(br s, H-9), 3.06(m, H-11), 2.77(m, H-1), 1.77(br s, H-14), 1.22(d, J=7 Hz, H-13), 1.15(d, J=7Hz, H-15); ^{13}C NMR (Assignment by DEPT NMR experiment): 209.82(C-5), 179.11(C-12), 134.42(C-10), 125.56(C-9), 84.44(C-6), 50.65(C-7), 46.31(C-1), 42.85(C-11), 38.28(C-4), 26.79, 26.07(C-2 and C-3 or reverse), 20.53(C-14), 19.04(C-8), 17.42(C-13), 13.93(C-15); MS : m/z at 248 (M^+, Base peak), 220, 205, 190, 177, 163, 149, 135, 121. Found : C, 72.41; H, 8.07. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%.

Tosylation of 4 :

To a solution of 25 mg of 4 in 1 ml of pyridine, 200 mg of p-TsCl was added and heated in an oil bath at 120°C under anhydrous conditions. After 15 hr, 100 ml of H_2O was poured in the reaction mixture and extracted with CH_2Cl_2 (3 x 50 ml), dried and evaporated. The traces of pyridine were removed by co-distillation with toluene under reduced pressure to yield a semi-solid residue which on preparative TLC (EtOAc-hexane, 1:9) yielded 4 mg of 9 as a gum. Spectral data of 9; IR(cm^{-1}); 1776, 1457, 1365, 1217, 1192, 1176, 1005, 871; ^1H NMR (80 MHz): 7.75(d, J=8 Hz, Aromatic), 7.30(d, J=8 Hz, Aromatic), 5.70(m, H-9), 5.20(d, J=5.5 Hz, H-5), 2.45(br s, 3H), 1.70 (br s, H-14), 1.20(d, J=7 Hz, H-13), 0.95(d, J=7 Hz, H-15); MS: m/z at 249(M^+-$C_7H_7SO_2$), 232(M^+-$C_7H_7SO_3H$), 221, 203, 189, 177, 159, 133, 121, 105, 91. Found : C, 65.18; H, 6.90. $C_{22}H_{28}O_5S$ requires C, 65.32; H, 6.98%.

Reduction of 7 with $NaBH_4$:

A solution of 20 mg of 7 in 2 ml MeOH was treated with 50 mg of $NaBH_4$ with stirring at rt. After 2hr of stirring, when reaction was complete (by monitoring on TLC), 100 ml of H_2O was added and extracted with CH_2Cl_2 (3x50 ml), dried and evaporated to dryness to yield a solid residue which on preprative TLC (EtOAc-hexane, 2:8) yielded 16 mg of a solid (m.p. 164-66°C, $CHCl_3$-hexane), which was found to be identical (m.p., mix m.p. TLC, co-TLC, IR, ^1H NMR) with 4. The $NaBH_4$ reduced product on treatment with Ac_2O-Py gave an acetate (m.p. 135-37°C, EtOAc-hexane) which was found to be identical (TLC, co-TLC, IR, ^1H NMR) with 3.

Hydrogenation of 4 :

A solution of 40 mg of 4 in 22 ml of dry EtOH was hydrogenated in the presence of 100 mg of 10% Pd-C catalyst in a Parr Shaker type hydrogenarator with H_2 pressure set at 50 psi for 2 hr. Catalyst was filtered, and the product purified by preparative TLC (EtOAc-hexane, 2:8) to yield 6 (26 mg) as a gum. Spectral data of 6 : IR (cm^{-1}); 3404, 2922, 2851, 1735, 1464, 1378, 1304, 1216, 1176, 1128, 1081, 1036, 762, 669; ^1H NMR(300 MHz): 3.91(d, J=5 Hz, H-5), 3.12(m, H-11), 1.10(d, J=7 Hz, H-13, H-15, 6H), 0.88(d, J=7 Hz, H-14); MS : m/z at 252(M^+), 185, 171, 157, 143, 129, 111, 97, 85, 73, 57, 43. Found : C, 71.25; H, 9.45. $C_{15}H_{24}O_3$ requires C, 71.39; H, 9.59%.

Epoxidation of 4 :

To a solution of 25 mg of 4 in 2 ml dry dichloromethane was added 50 mg of metachloroperbenzoic acid (MCPBA) and the reaction mixture was stirred at rt monitoring by TLC. After 2 hr when the reaction was complete, it was diluted with 100 ml of dichloromethane, washed successively with dilute solutions of potassium iodide, sodium thiosulphate and sodium bicarbonate and finally with water. The washed and dried extract was then evaporated and the residue showed a single spot on TLC which was isolated by preparative TLC (EtOAc-hexane, 3 :7) to furnish 20 mg of 5 as a gum. Spectral data of 5 : IR (cm^{-1}) : 3503, 2933, 1752, 1456, 1383, 1303, 1262, 1213, 1197, 1144, 1107, 1084, 998, 876, 856, 763. The presence of overlapping signals in the ^1H NMR spectrum indicated that 5 is a mixture of two isomeric epoxides which could not be separated on the silica gel TLC. MS : m/z at 266(M^+), 248, 238, 221, 194, 185, 179, 166, 124, 112, 69, 55, 43.

Epoxidation of 7:

To a solution of 20 mg of 7 in 2 ml dry dichloromethane was added 50 mg of MCPBA and the reaction mixture was stired at rt monitoring by TLC. After 1.5 hr when the reaction was complete, it was worked up as described above. The washed and dried extract was then evaporated and the residue showed two spots on TLC and these were isolated by preparative TLC (EtOAc-hexane, 2:8) to give 11 mg of the less polar product **8a** as a gum and 7 mg of the more polar product **8b** as a gum. Spectral data of **8a** :IR(cm^{-1}) : 1789, 1713, 1463, 1441, 1375, 1316, 1193, 1132,

1091, 1042, 1018, 982, 910, 846; ^{1}H NMR (400 MHz) : 3.10 (m, H-11), 3.02(d, J=5 Hz, H-9), 1.37(s, H-14), 1.27(d, J=7 Hz, 3H), 1.17(d, J=7 Hz, 3H); MS : m/z at 264(M^+), 221, 208, 191, 190, 163, 154, 135, 121, 109, 105, 80, 69, 55, 44. Found : C, 68.48; H, 7.34. $C_{15}H_{20}O_4$ requires C, 68.16; H, 7.63%.

Spectral data of **8b** : IR(cm^{-1}) : 1785, 1719, 1455, 1387, 1300, 1194, 1163, 1129, 1009, 991, 904, ^{1}H NMR(400 MHz) : 3.15 (br s, H-9), 2.95(m, H-11), 1.52(s, H-14), 1.18(d, J=7 Hz, 3H), 1.10(d, J=7 Hz, 3H); MS : m/z at 264(M^+), 236, 221, 206, 194, 182, 165, 154(100), 135, 123, 111, 105, 80, 69, 54, 43.

Reduction of 7 with Zn/AcOH :

To a solution of 25 mg of 7 in 2 ml of glacial acetic acid, 0.5 ml of H_2O was added and stirred at rt. After 5 min 500 mg of Zn dust was added and the reaction mixture was refluxed in an oil bath at 120°C, monitoring on TLC. After 6 hr when reaction was complete, the reaction mixture was diluted with 100 ml of H_2O and extracted with CH_2Cl_2 (3 x 50 ml), dried and evaporated. The traces of AcOH were removed by co-distillation with toluene under reduced pressure. The residue thus obtained showed a single spot on TLC which was purified by preparative TLC (EtOAc-hexane, 2:8) to yield a solid (5 mg) which was found to be identical by m.p.,mix m.p.,TLC, co-TLC,^{1}H NMR, MS with 4.

Photolysis of 7:

A solution of 15 mg of 7 in 10 ml of MeOH was photolysed in a pyrex flask using a 500 W tungustun arc street lamp for 5 hr. Evaporation of the solvent furnished a residue which on preparative TLC (EtOAc-hexane, 2:8) furnished a solid (2 mg) which was found to be identical by m.p., mix m.p. TLC, co-TLC, ^{1}H NMR, MS with 4.

Oxidation of 12 with PDC/DMF :

A solution of 15 mg of crude mixture containing **12** and **16** in 1.5 ml dimethyl formamide was cooled to 0°C and 50 mg of pyridinium dichromate (PDC) was added to it with stirring. The reaction was monitored on TLC and after 3 hr when reaction was complete, reaction mixture was gradually warmed to rt, diluted with 100 ml of H_2O and extracted with CH_2Cl_2(3x50 ml), dried and evaporated to give an oily residue which on preparative TLC (EtOAc-hexane, 2 :8) yielded **14** as an oil (7 mg) and 3 mg of **16** was recovered unreacted as a gum. Spectral data of **14** : IR (cm^{-1}) : 2929, 1669, 1391, 1256, 1094, ^{1}H NMR (80 MHz) : 6.55(m, H-3), 3.05(m, H-11), 1.75(br s, H-15), 1.15(d, J=7 Hz, H-13), 0.90(d, J=7 Hz, H-14); MS : m/z at 248(M^+), 232, 220, 205, 192, 177, 167, 151, 149, 111, 97, 82, 71, 57, 43.

Reduction of 4 with LAH :

A solution of 45 mg of 4 in 4 ml of dry THF was stired at rt. After 5 min of stirring, 100 mg of lithium aluminium hydride (LAH) was added slowly and reaction was monitored on TLC. After 1 hr when the reaction was complete, excess of LAH was destroyed by adding ethyl acetate. The reaction mixture was diluted with 100

ml of H_2O and extracted with CH_2Cl_2(3x50 ml). Evaporation of the washed and dried extract furnished a residue which was purified by preparative TLC (EtOAc-hexane, 3:7) to yield **10** as a gum (40 mg). Acetylation of the LAH reduced product **10** with 1 ml of pyridine and 2 ml of acetic anhydride furnished the diacetate **11** as a gum (43 mg) after usual work up and preparative TLC (EtOAc-hexane, 2:8). Spectral data of **11** : IR (cm^{-1}) : 3491, 2928, 1734, 1456, 1374, 1240, 1035, 991, 943, 912, 810, 770, 756, 609; ^1H NMR (400 MHz) : 5.45 (m, H-9), 5.05(d, J=5 Hz, H-5), 4.08(m, H-12a), 3.85(m, H-12b), 2.45(m, H-11), 2.35(m, H-1), 2.09, 2.08(s, Acetates), 1.62(br s, H-14), 1.10(d, J=7 Hz, H-13), 0.81(d, J=7 Hz, H-15); ^{13}C NMR (Assignment by DEPT NMR experiment) : 172.10, 170.09(CO of Acetates), 134.09(C-10), 123.63(C-9), 75.35(C-6), 72.79(C-5), 71.17(C-12), 50.08(C-7), 46.96(C-1), 30.89(C-11), 30.67(C-4), 27.43, 26.03(C-2 & C-3 or reverse), 21.28, 20.95(OAc), 20.66(C-14), 17.28(C-8), 14.42(C-13), 14.19(C-15); MS : m/z at 338(M^+), 278, 263, 218, 200, 159, 149, 121, 69, 55, 43. Found : C, 67.36; H, 8.86. $C_{19}H_{30}O_5$ requires C, 67.43; H, 8.93%.

^1H NMR of (**11**+TAI): 8.51(br s, NH, 1H), 5.46(m, H-9), 5.18(d, J=5 Hz, H-5), 4.19 (m, H-12a), 3.86(m, H-12b and H-1, 2H), 2.77(m, H-11), 2.12, 2.05(s, Acetates), 1.68(br s, H-14), 1.02(d, J=7 Hz, H-13), 0.90(d, J=7 Hz, H-15).

Application of Horeau's method to 4 :

A solution of 0.400 g of α-phenylbutyric anhydride and 100 mg of **4** in 1.5 ml dry pyridine was kept at rt for 96 hr. Excess anhydride was destroyed by addition of 15 ml of water and allowing the solution to stand for 21 hr at rt. The reaction mixture was extracted with ether (4 x 50 ml) which was washed with water and 5% $NaHCO_3$ solution (5 x 25 ml). The combined aquous layers were washed with $CHCl_3$(1x50 ml), acidified with 80 ml of 1N H_2SO_4 and extracted with $CHCl_3$ (3x100 ml). The washed and dried $CHCl_3$ extract was evaportated, the residue 0.2579 g was pure α-phenylbutyric acid, $[\alpha]_D^{25}$+3.10° (c. 2.579, $CHCl_3$) which corresponded to an optical yield of 22.6%.

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