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SYNTHESIS OF (±)-ZEARALENONE[1]

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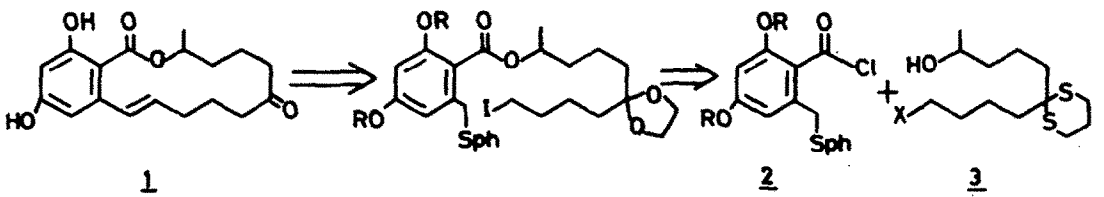
Abstract - The aliphatic portion of (±)-zearalenone has been synthesised by a new simple route starting from 2,3-dihydropyran and 2-acetyl-γ-butyrolactone by employing dithiane for C-C bond formation. The final condensation of this segment with the aromatic part and subseqnet transformations led to (±)-zearalenone.

The synthesis of macrolides is currently under intensive investigations because of their diverse biological activities. Recent developments in their synthetic strategies made the task easier for the synthesis of macrolides. Zearalenone[2] 1 is a naturally occurring 14-membered orsellinic acid type macrolide with anabolic and uterotropic activity. It was the first macrolide to be synthesised by both Merck and Syntex groups[3] and the methodologies adopted by them for C-C bond formation involved a Wittig reaction, while Tsuji et al[4] employed an intramolecular alkylation. All the groups have fundamentally adopted the same strategy in the construction of aromatic and aliphatic segments.

In this paper we report (a) a simple and convenient method for the synthesis of the aliphatic moiety 3 from easily accessible starting materials and (b) its condensation with the aromatic part to get the key intermediate 22b. The strategy used for elaborating the synthesis of (±)-zearelenone is illustrated by the antithetic relationship depicted in Scheme 1. The salient features of our synthesis comprises of protecting the hydroxyl and two carbonyl functionalities by suitable protecting groups which could be independently removed without affecting each other. To achieve this assignment, the lower segment of the aliphatic moiety can be looked upon as a thioketal masked hydroxy-aldehyde and the upper segment as an ethylene ketal protected bromoketone. The synthesis of the aromatic part 14a reported by Hauser et al[5] was found to be relatively simple and therefore was duplicated.

Scheme 1

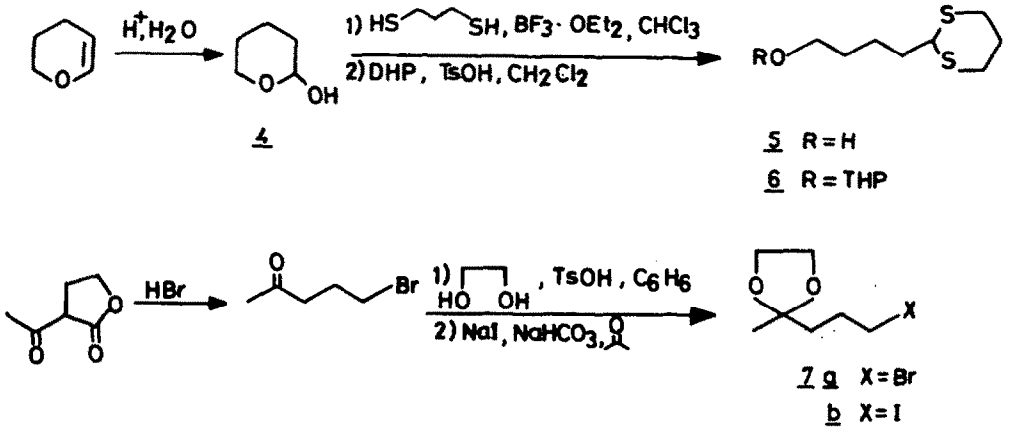


Commercially available 2,3-dihydropyran on treatment with aqueous hydrochloric acid at room temperature afforded 5-hydroxy pentanal 4[6] (Scheme 2) which on reaction with 1,3-propanedithiol in dry chloroform in presence of boron trifluoride-etherate gave the hydroxy-dithiane 5 in 79% yield. The hydroxyl group in 5 was protected as its THP-ether. The other segment namely bromo-ketal 7a was prepared from 2-acetyl-γ-butyrolactone by the literature procedure[7]. 7a was converted into the iodo-ketal

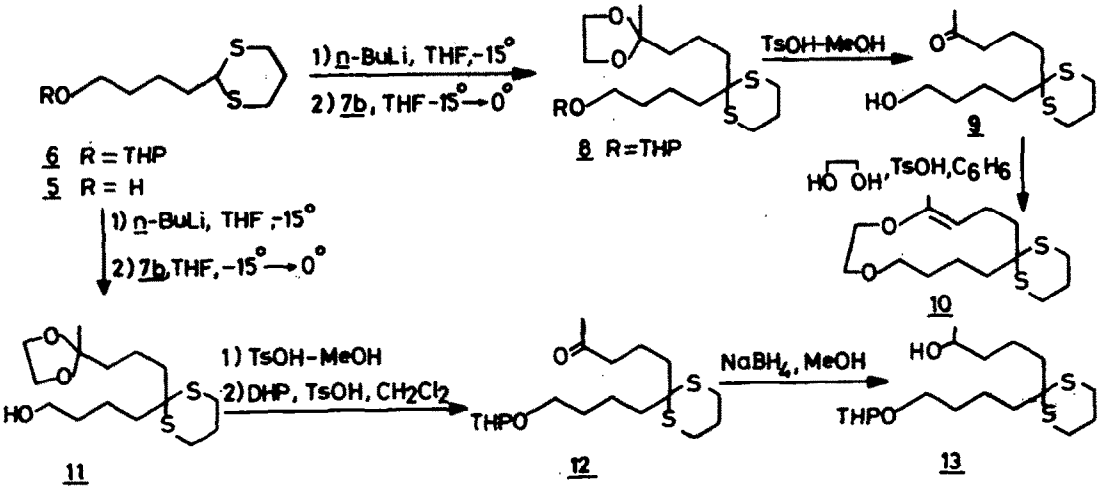
7b by treatment with sodium iodide-sodium bicarbonate in acetone at room temperature.

Metallation (Scheme 3) of the THP-ether 6 with n-butyllithium at -15°, followed by alkylation with freshly prepared 5-iodopentan-2-one ethylene ketal 7b provided the alkylated product 8 in 67% yield. In order to cleave the THP ether selectively, 8 was treated with a mild acid (TsOH-MeOH) at room temperature, however, both the THP ether and the ethylene ketal groups were found to be cleaved as the hydroxy keto compound 9 was isolated in quantitative yield and its structure confirmed by spectral studies. This observation indicated that the preferential cleavage of THP-ether over ethylene ketal was difficult. Therefore, it was considered to introduce ketal group once again in the hydroxy-keto compound 9. Reaction of 9 and ethyleneglycol in the presence of toluene-p-sulfonic acid did not go to completion, even after 76 hr, most of the unreacted starting material was recovered by chromatography. The faster moving product isolated in less than 10% yield was assigned the structure 10 by ^{1}H-NMR and MS (M^+ 302).

Scheme 2



Scheme 3

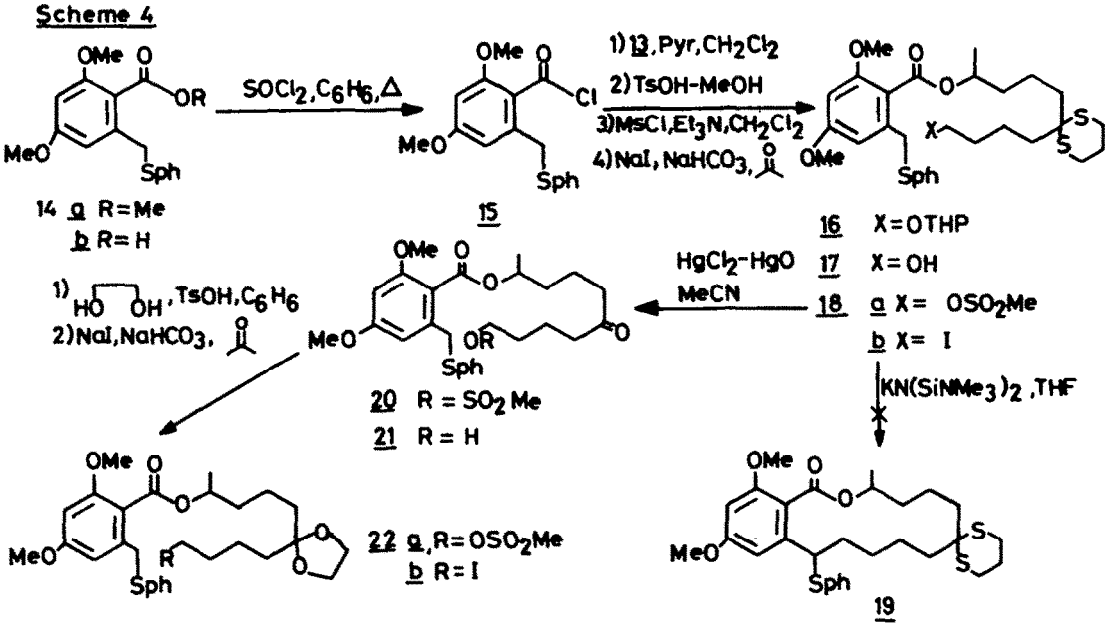


The above findings prompted us to study the alkylation of the alcohol 5 with 7b. For instance, the hydroxy-dithiane 5 was treated with two equivalents n-butyllithium at -15° followed by the iodide 7b to afford the alkylated product 11 in 49% yield. The low yield of the required alkylated product is due to the formation of the anticipated O-alkyl ether (36% yield). A solution of 11 in methanol was reacted with toluene-p-sulfonic acid at room temperature for 20 hr to effect the cleavage of ketal protection which gave the hydroxy-keto compound 9. The hydroxyl group in 9 was protected as THP ether conventionally to give 12 in 89% yield. Reduction of the carbonyl group in 12 was effected with sodium borohydrde in methanol and the resulting alcohol 13 was characterised by spctral studies. The above illustrated

sequential reactions led to the construction of aliphatic C-10 carbon skeleton 13, suitable for further elaboration to (±)-zearalenone.

The required aromatic moiety 15 was prepared as follows. The known ester 14a was hydrolysed with alkali and then treated with thionyl chloride to give the acid chloride 15 in quantitative yield. Condensation of 15 with the aliphatic segment 13 (Scheme 4) was carried out in presence of pyridine to afford the product 16 whose ^{1}H-NMR spectrum clearly demonstrated the structure assigned. Subsequent removal of the THP-ether group with a mild acid followed by mesylation with methanesulfonyl chloride and triethylamine gave the mesylate 18a. The corresponding iodo derivative 18b was prepared by the treatment of 18a with sodium iodide in acetone. The attempted cyclisation of 18b using hexamethyldisilazane failed to give the desired product 19. The reason for this failure may be attributed to the formation of sulphonium salt by the intramolecular reaction of ω-halodithiane. There are few examples reported in literature[8] in this regard. This finding clearly indicated that non-participating carbonyl protective group such as an ethylene ketal would be required to overcome this difficulty. Accordingly 18a was treated with mercuric chloride-mercuric oxide in refluxing aqueous acetonitrile. After 1 hr, the reaction mixture was worked up and the resulting residue was chromatographed to give two fractions. The major faster moving component was found to be undoubtedly the mesylate ketone 20, while the slower moving component on TLC isolated in 35% yield was the alcohol 21. In its IR spectrum an absorption due to OH group was observed at 3450 cm^{-1}. In addition, ^{1}H-NMR spectrum revealed the absence of a signal due to the mesyl group. Further 21 was converted into 20 by the reaction with methanesulfonyl chloride and triethylamine.

Scheme 4



The ketonic function of 20 was protected as ethyleneketal in the usual way and then converted into the corresponding iodide 22b with sodium iodide in acetone in 78% yield. The structure of the iodide was confirmed on the basis of spectral data (IR, NMR, MS) and microanalysis.

The key intermediate 22b was earlier prepared by Tsuji et al[4a] by acylation of suitably functionalised C_{10} alcohol (obtained from the butadiene telomer and diethyl malonate) with the acid chloride 15. Further, they have reported the intramolecular alkylation of the carbanion generated from ω-iodialkylbenzoate 22b and subsequent oxidative elimination to (±)-zearalenone. Therefore, our synthesis of the key intermediate 22b would formally constitute the total synthesis of (±)-zearalenone.

EXPERIMENTAL

The solvents and reagents were purified and dried by standard techniques. The reactions involving metallation were conducted under argon or nitrogen with magnetic stirring unless otherwise specified. The solvents were removed by distillation in-vacuo using a rotary evaporator. IR spectra were recorded (ν_{max} cm^{-1}) neat on a Perkin-Elmer model 683 spectrometer. PMR were obtained on varian T-60 or A-60 in $CDCl_3$ or CCl_4 solutions and chemical shifts are reported in (δ) ppm with TMS as internal standard. Mass spectra were run on AEI MS-30 double beam mass spectrometer or CEC-21-110B spectrometer.

5-Hydroxy pentanal 4 and 2-(3-bromopropyl)-2-methyl-1,3-dioxalane 7a were prepared from 2,3-dihydropyran and 2-acetyl-γ-butyrolactone respectively according to the procedure described in the literature. Methyl 2,4-dimethoxy-6-methyl benzoate was prepared from orcinol[9,10] and converted into methyl 2,4-dimethoxy-6-[(phenylthio) methyl]-benzoate 14a by adopting the literature procedure[5]. The ester, 14a was hydrolysed to the corresponding acid 14b with ethanolic potassium hydroxide.

2-(4-Hydroxybutyl)-1,3-dithiane (5)

To a stirred solution of 4 (9.5 g, 93 mmol) and 1,3-propanedithiol (10 g, 93 mmol) in dry chloroform (40 ml) was added gradually BF_3-etherate (13.2 g, 93 mmol) during 15 min. at room temperature. After 7 hr, it was quenched with water and extracted with chlroform (5 x 50 ml). The combined chloroform extract was successively washed with water, aqueous potassium hydroxide (5%), brine, dried (Na_2SO_4) and concentrated to give a syrupy residue. The residue, thus obtained was chromatographed on silica gel (acetone-benzene 1:9) to afford 5 as a pale yellow viscous oil (14 g, 79%). IR : 915 (characteristic dithiane band) and 3200 (OH). NMR (CCl_4) : 1.30-2.10 (m, 8H, $4CH_2$) 2.64 (s, 1H, OH; D_2O exchangeable) 2.70-2.90 (m, 4H, 2 SCH_2) 3.57 (t, 1H, CH). M^+ 312. (Found : C, 49.80; H, 8.10; S, 5.33. $C_{18}H_{16}OS_2$ requires : C, 50.0; H, 8.30; S, 5.30%)

2-(4-Tetrahydropyranyloxybutyl)-1,3-dithiane (6)

A mixture of the hydroxy-dithiane 5 (0.960 g, 5 mmol), dihydropyran (0.63 g, 7.5 mmol) and toluene-p-sulfonic acid (0.050 g) in dichloromethane (15 ml) was stirred at room temperature for 6 hr. The reaction mixture was diluted with dichloromethane (15 ml) and washed with sodium bicarbonate solution (5%). The organic layer was dried (K_2CO_3), evaporated and the residue obtained was chromatographed (silica gel, benzene-pet.ether, 6:4) to give the THP-derivative as a pale yellow liquid (1.10 g, 80%). IR : 918 (dithiane). NMR (CCl_4) : 1.20-2.10 (m, 14H, $7CH_2$) 2.60-2.90 (m, 4H, 2 SCH_2) 3.0-4.0 (m, 5H, $2OCH_2$ and CH) 4.56 (s, 1H, CH). M^+ 276.

2-(3-Iodopropyl)-2-methyl-1,3-dioxalane (7b)

A mixture of 7a (2.8 g, 13.4 mmol), sodium bicarbonate (3.372 g, 40.2 mmol) and sodium iodide (4.016 g, 26.7 mmol) in dry acetone (15 ml) was stirred at room temperature for 4 hr. Acetone was removed, the residue diluted with water and extracted with petroleum ether (25 ml). The petroleum ether layer was washed with aqueous sodium thiosulphate (5%) and filtered through a bed of anhydrous potassium carbonate. Evaporation of the solvent under reduced pressure gave 7b as a pale yellow liquid (3.3 g, 97%).

3-[(4-Hydroxybutyl)-1,3-dithian-2-yl]-1-(2-methyl-1,3-dioxalan-2-yl)-propane (11)

To a stirred cold solution of the hydroxy-dithiane 5 (0.960 g, 5 mmol) in dry THF (5 ml) was added n-butyllithium (2M, 5.5 ml, 11 mmol in hexane) during 10 min. at -15°. After 4 hr at -15°, a solution of the freshly prepared ketal 7b (2.56 g, 10 mmol) in dry THF (10 ml) was introduced dropwise. Then the contents were stirred at -15° for 2 hr and 0° for 12 hr. The reaction mixture was quenched with aqueous sodium bicarbonate (5%) and extracted with chloroform (5 x 10 ml). The combined chloroform extract was successively washed with sodium bicarbonate solution (5%), water, dried (K_2CO_3) and evaporated to give a syrupy liquid. It was subjected to column chromatography on silica gel (acetone-petroleum ether 1:9) to furnish two fractions 'A' and 'B'. Fraction 'A' was found to be O-alkylated product. Fraction 'B' containing the title compound was collected and concentrated to a colourless oil (0.78 g, 49%). IR : 915 (dithiane), 3450 (OH). NMR (CCl_4) : 1.21 (s, 3H, CH_3) 1.30-2.0 (m, 14H, $7CH_2$) 2.50-2.80 (m, 4H, 2 SCH_2) 2.96 (s, 1H, OH, D_2O exchangeable) 3.50 (t, 2H, CH_2OH) 3.83 (s, 4H, OCH_2CH_2O). M^+ 570. (Found : C, 56.0; H, 8.75; S, 17.40. $C_{15}H_{28}O_3S_2$ requires : C, 56.20; H, 8.75; S, 17.65%)

5-[(4-Hydroxybutyl)-1,3-dithian-2-yl]-pentan-2-one (9)

A solution of the compound 8 (0.808 g, 2 mmol) in methanol (10 ml) and toluene-p-sulfonic acid (0.030 g) was stirred at room temperature for 20 min. Methanol was removed under reduced pressure, residue quenched with water and extracted with chloroform (2 x 10 ml). The chloroform layer was washed with water, dried (Na_2SO_4) and solvent distilled off. The residue on chromatography over a column of silica gel (acetone-benzene 0.5:9.5) provided 9 as a colourless liquid (0.560 g, 81%). IR : 915 (dithiane), 1720 (C=O) and 3450 (OH). M^+ 276.

5-[(4-Tetrahydropyranyloxybutyl)-1,3-dithian-2-yl]-pentan-2-one (12)

The THP derivative 12 was prepared from the hydroxy-keto compound 9 (0.6 g, 2.17 mmol) dihydropyran (0.53 g, 6.3 mmol) and toluene-p-sulfonic acid (0.020 g) in the usual way. Purification of the crude product on a column of silica gel (acetone-petroleum ether, 1:9) furnished 12 as a pale yellow oil (0.70 g, 89%). IR : 1720 (C=O). NMR ($CDCl_3$) : 1.30-1.80 (m, 18H, $9CH_2$) 2.10 (s, 3H, $COCH_3$) 2.40 (t, 2H, $COCH_2$) 2.60-2.90 (m, 4H, 2 SCH_2) 3.20-3.90 (m, 4H, 2 OCH_2) 4.50 (bs, 1H, $HC\overset{O}{\underset{O}{<}}$). M^+ 360.

5-[(4-Tetrahydropyranylxybutyl)-1,3-dithian-2-yl]-pentan-2-ol (13)

To a stirred solution of the keto compound 12 (3.60 g, 10 mmol) in methanol (30 ml), sodium borohydride (0.74 g, 20 mmol) was added in two portions and the mixture stirred at room temperature for 8 hr. Excess of the borohydride was decomposed with water, methanol was removed, the residue was diluted with water (10 ml) and extracted with chloroform (3 x 30 ml). The chloroform extract was washed with water and dried (K_2CO_3). The residue obtained after evaporating the solvent was chromatographed (silica gel, acetone-benzene 0.5:9.5) to get 13 as a thick colourless oil (3.00 g, 82%). IR : 3450 (OH). NMR (CCl_4) : 1.16 (d, 3H, CH_3) 1.20-2.10 (bm, 20 H, $10CH_2$) 2.60-2.80 (m, 4H, 2 SCH_2) 3.20-4.0 (m, 4H, 2 OCH_2) 4.50 (s, 1H, $HC\overset{O}{\underset{O}{<}}$). M^+ 362. (Found : C, 60.20; H, 9.40; S, 17.80. $C_{18}H_{34}O_3S_2$ requires : C, 59.89; H, 9.40; S, 17.60%)

4-[2-(4-Tetrahydropyranylxybutyl)-1,3-dithian-2-yl]-1-methylbutyl-2,4-dimethoxy-6-(phenylthiomethyl) benzoate (16)

(A) The acid chloride 15 was prepared from the acid 14b (0.28 g, 0.94 mmol) and thionyl chloride (0.5 ml, 6.9 mmol) in the usual way. It was used in the next step without further purification.

(B) To a stirred mixture of the alcohol 13 (0.330 g, 0.92 mmol) and pyridine (0.148 g, 1.87 mmol) in dichloromethane (5 ml) was added a solution of the acid chloride 15 (0.28 g) in dichloromethane over a 10 min. period at room temperature. After stirring overnight at room temperature, the reaction mixture was treated with sodium bicarbonate solution (5%). The aqueous layer was extracted with ether, dried (K_2CO_3) and concentrated. The resulting residue was purified over a short column of silica gel (acetone-benzene 1:9) to give the ester 16 as a thick gummy material (0.360 g, 59%). IR : 1720 (ester C=O). NMR ($CDCl_3$) : 1.30 (d, 3H, CH_3) 1.40-2.0 (m, 20 H, $10CH_2$) 2.60-2.90 (m, 4H, 2 SCH_2) 3.20-3.80 (m, 4H, 2 OCH_2) 3.68 (s, 3H, OCH_3) 3.71 (s, 3H, OCH_3) 4.09 (s, 2H, CH_2SPh) 4.50 (bs, 1H, $HC\overset{O}{\underset{O}{<}}$) 5.00-5.30 (m, 1H, 3°H) 6.28 (s, 2H, ArH) 7.0-7.20 (m, 5H, SPh). M^+ 648. (Found : C, 62.60; H, 7.30; S, 14.40. $C_{34}H_{48}O_6S_3$ requires : C, 62.90; H, 7.40; S, 14.80%)

4-[2-(4-Methanesulfonyloxybutyl)-1,3-dithian-2-yl]-1-methylbutyl-2,4-dimethoxy-6-[(phenylthio) methyl] benzoate (18a)

A solution of methanesulfonyl chloride (0.228 g, 2 mmol) in dichloromethane (5 ml) was added dropwise to a well stirred solution of the hydroxy-ester 17 (0.564 g, 1 mmol) and triethylamine (0.303 g, 3 mmol) in dry dichloromethane (10 ml) at 0°. The contents were then stirred at room temperature for 2 hr. The reaction mixture was decomposed with water and the aqueous layer was extracted with dichloromethane (3 x 25 ml). The combined dichloromethane solution was washed with water, dried (Na_2SO_4) and concentrated to give the mesylate 18a as a dark brown material (0.560 g, 87%) which was used without any purification. NMR ($CDCl_3$) : 1.31 (d, 3H, CH_3) 1.50-2.10 (m, 14H, $7CH_2$) 2.50-2.80 (m, 4H, $2SCH_2$) 2.96 (s, 3H, SO_2CH_3) 3.60 (s, 3H, OCH_3) 3.73 (s, 3H, OCH_3) 4.09 (t, 2H, CH_2SO_3) 4.18 (s, 2H, CH_2SPh) 4.80-5.20 (m, 1H, CH) 6.50 (s, 2H, ArH) 6.90-7.20 (m, 5H, SPh).

9-Methanesulfonyloxy-1-methyl-5-oxo-nonyl-2,4-dimethoxy-6-[(phenylthio) methyl] benzoate (20)

A mixture containing the mesylate-ester 18a (0.5 g, 0.78 mmol) mercuric chloride (0.462 g, 1.71 mmol) and mercuric oxide (0.184 g, 0.85 mmol) in aqueous acetonitrile (10 ml, 80%) was refluxed for 1 hr. The reaction mixture was filtered through celite and washed thoroughly with ammonium acetate solution (5%), dried (Na_2SO_4) and the solvent evaporated. The resulting residue was subjected to chromatographic purification (silica gel, acetone-benzene 1:9) to afford two fractions 'A' and 'B'. Fraction

'A' and 'B' were identified as the mesylate-ketone 20 (0.177 g, 41%) and the hydroxy-keto compound 21 respectively on the basis of the spectral data. The hydroxy-keto compound was converted into the mesylate-ketone 20 in the usual way using methane sulfonyl chloride and triethyl amine.

4-[2-(4-Methanesulfonyloxy butyl)-1,3-dioxalan-2-yl]-1-methylbutyl-2,4-dimethoxy-6-[(phenylthio) methyl] benzoate (22a)

A solution of the keto-compound 20 (0.160 g, 0.29 mmol), ethylene glycol (0.06 g, 0.87 mmol) and catalytic amount of toluene-p-sulfonic acid in dry benzene (20 ml) was refluxed for 6 hr, with azeotropic removal of water. The mixture was cooled, washed with soium bicarbonate solution (5%), dried (K_2CO_3) and evaporated to get the mesylate-ketal 22a as a thick gummy material (0.160 g, 94%). IR : 1720 (C=O). NMR ($CDCl_3$) : 1.34 (d, 3H, CH_3) 1.40-1.80 (m, 12H, $6CH_2$) 2.94 (s, 3H, SO_2CH_3) 3.65 (s, 3H, OCH_3) 3.75 (s, 3H, OCH_3) 3.86 (s, 4H, OCH_2CH_2O) 4.00-4.20 (s, 2H, ArH) 7.0-7.20 (m, 5H, SPh). M^+ 596. (Found : C, 58.60; H, 7.0; S, 10.40. $C_{29}H_{40}O_9S_2$ requires : C, 58.40; H, 6.70; S, 10.70%)

4-[2-(4-Iodobutyl)-1,3-dioxalan-2-yl]-1-methylbutyl-2,4-dimethoxy-6-[(phenylthio) methyl] benzoate (22b)

A mixture containing the mesylate-ketal 22a (0.150 g, 0.25 mmol), sodium iodide (0.075 g, 0.50 mmol) and sodium bicarbonate (0.063 g, 0.75 mmol) in dry acetone (5 ml) was stirred at room temperature for 24 hr. Acetone was evaporated, the residue treated with water and extracted with chloroform (2 x 10 ml). The chloroform solution was washed with brine, dried (K_2CO_3) and evaporated to give the iodide, 22b as a thick gummy material (0.123 g, 78%). IR : 1720 (C=O). NMR ($CDCl_3$) : 1.31 (d, 3H, CH_3) 1.40-1.60 (m, 12H, $6CH_2$) 3.12 (t, 2H, CH_2I) 3.68 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.81 (s, 4H, OCH_2CH_2O) 4.10 (s, 2H, CH_2SPh) 4.90-5.20 (m, 1H, 3°H) 6.25 (s, 2H, ArH) 7.00-7.30 (m, 5H, SPh). M^+ 628. (Found : C, 53.10; H, 6.20; S, 5.70. $C_{28}H_{37}IO_6S$ requires : C, 53.41; H, 5.92; S, 5.38%).

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