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SYNTHETIC STUDIES ON NOGALAMYCIN : STEREOSPECIFIC C-5 ALKYLATIONS OF A SUGAR DERIVATIVE VIA CLAISEN REARRANGEMENT AND A NEW ROUTE TO 1,1,4-TRIALKOXYBUTA-1,3-DIENES.

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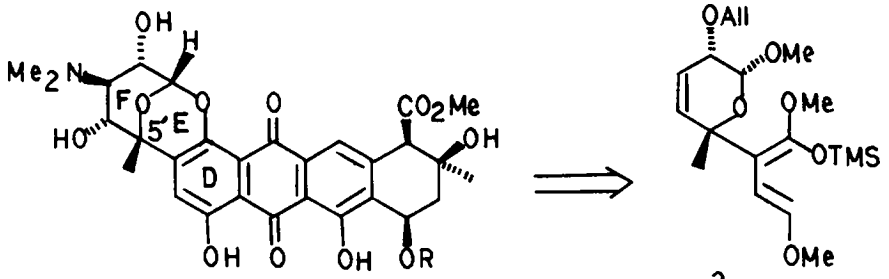
Abstract : Claisen rearrangement of the 4-methoxybutadienylether of the allylic alcohol 13, which was made in 15 steps from D-glucose, afforded one major aldehyde 17 or 18 in good yield. All attempts to oxidize this aldehyde to an acid were unsuccessful. The model compound 24 and compound 13 were converted respectively to the α,β-unsaturated esters 25 and 26. Compound 25 was further transformed into the 1,1,4-trialkoxybuta-1,3-diene 27 which was found unreactive towards quinones.

Nogalamycin 1, produced by Streptomyces nogalater, has a high activity against Gram-positive microorganisms and a strong antitumor activity against KB cells in vitro.[1] This challenging target[2] possesses an epoxy-oxocin ring system[3] (rings E, F) which is unique in this class of compounds. The first total chiral synthesis of this ring system was recently reported by S. Terashima and al.[2d] Our synthetic strategy towards this benzoxocin system involves (i) stereospecific formation of the quaternary center at C-5' by a Claisen rearrangement; (ii) formation of ring D by a Diels-Alder reaction between a 1,1,4-trioxygenated diene and a bromoquinone. This retrosynthetic analysis led us to examine the synthesis of the synthon 2.



1 R = L-nogalose 2

When we started the study of the synthesis of Nogalamycin, its absolute configuration was unknown. As it is obvious that compound 2 can be made from sugars, we chose D-glucose as starting material for model studies. Later, the X-ray cristallographic structure of Nogalamycin was published[4] and showed that the amino sugar of the molecule has the L-configuration.

Results and discussion.

The precursor of 2, the allylic alcohol 13, was prepared from 4,6-O-benzylidene-α-D-allopyranoside 3 which is available in five steps from D-glucose.[5] Regioselective allylation of the equatorial OH of diol 3 was effected by treatment with dibutyltin oxide[6,7] followed by allyl iodide in DMF to give mainly 4 (68%) and a small amount of 5 (7%), easily separable by crystallization. The position of the allyl group in compound 4 was confirmed by homonuclear decoupling of the proton H-3 after benzoylation of the free OH (benzoyl chloride, Et_3N, p-dimethylaminopyridine). After hydrolysis of the benzylidene group of 6 in acidic conditions, the resulting

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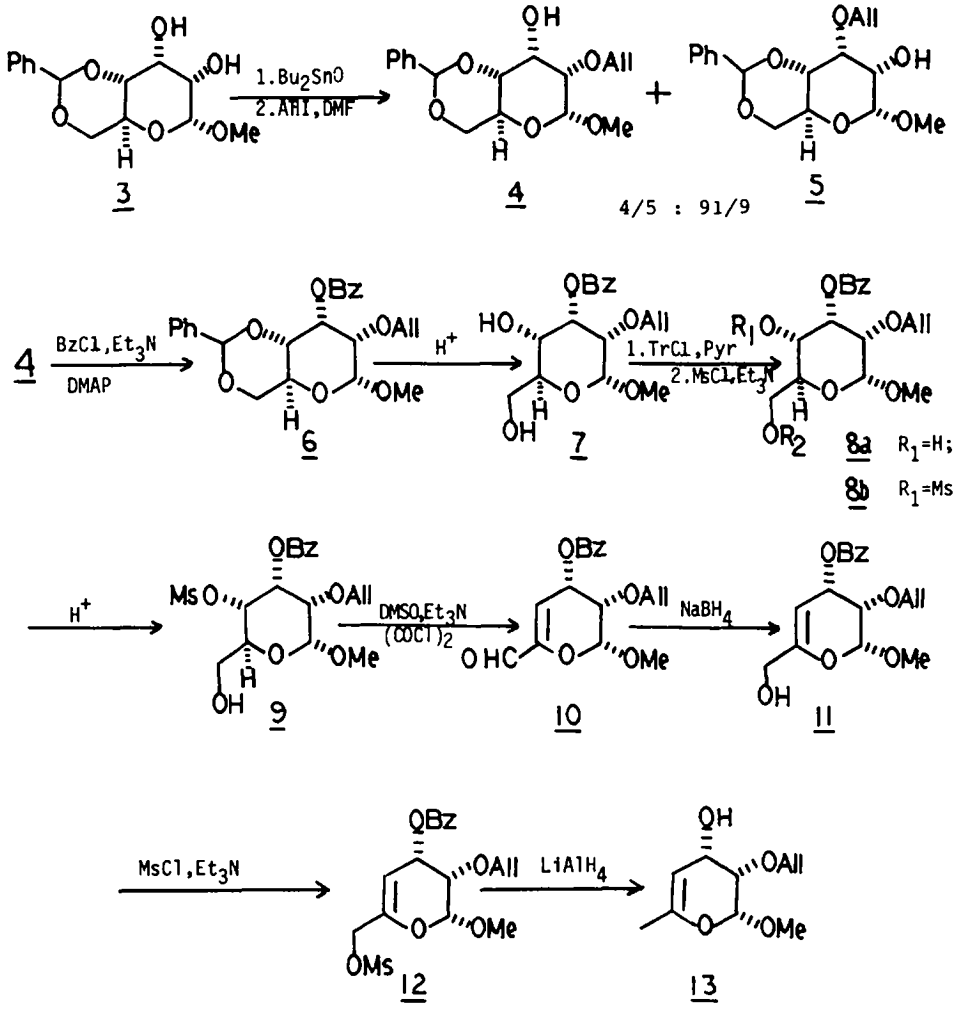
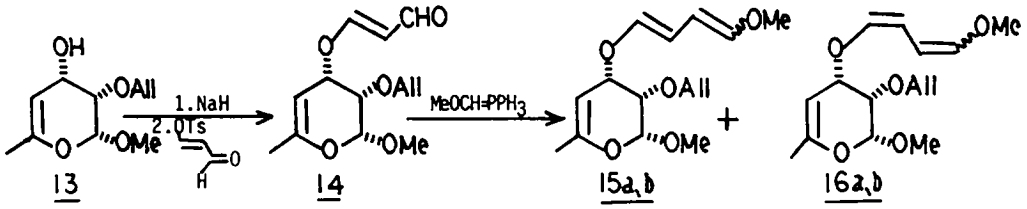
compound 7 was selectively tritylated at C-6 by chlorotriphenylmethane in pyridine to give 8a in 90% yield. The alcohol 8a was converted into its methanesulfonate ester 8b and then, the trityl group was removed in acidic medium to afford 9 in 82% overall yield from 8a. Oxidation of the primary hydroxyl 9 in Swern conditions[8] followed by spontaneous elimination of methanesulfonic acid gave cleanly the α,β-unsaturated aldehyde 10 in 94% yield. Reduction of the aldehyde function of 10 by sodium borohydride in ethanol at 0°C led to 11 in 96% yield. The allylic alcohol 11 was converted into its methanesulfonate ester 12 which, because of its instability, was used in the next step without further purification. Reduction of the benzoate and mesylate functions was achieved at the same time by treatment of the crude 12 with lithium aluminium hydride in THF at room temperature. The allylic alcohol 13 could be separated from benzyl alcohol, formed during the reduction, by fractional distillation and was obtained in the pure state in 68% overall yield from 11. Its structure was confirmed by ^{1}H- and ^{13}C-NMR spectroscopies.

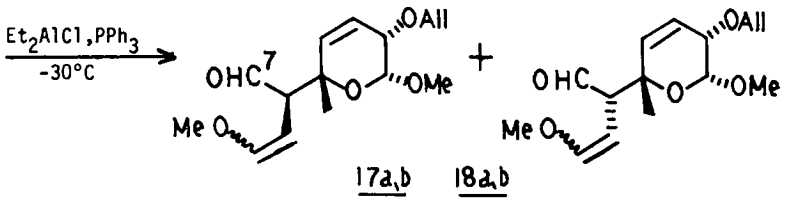


Compound 15, a good candidate for Claisen rearrangement, was prepared in two steps from the allylic alcohol 13.

The 4-methoxybuta-1,3-dienyl group was introduced at O-3 by reaction of the sodium alkoxide of 13 with (E)-tosylacrylaldehyde[9] giving 14 which was treated, without isolation, with methoxymethyltriphenylphosphorane to afford 15a,b (mixture of geometrical isomers) and a small amount of 16a,b (10-15%). The ^{1}H-NMR spectrum of the major compounds 15a,b confirmed that the 1,2-double bond of the dienyl ether group was trans ($J_{1,2}$ = 12 Hz). These dienes were not isolated because of their high unstability but immediately subjected to Claisen rearrangement. Thermal Claisen rearrangement (120°C) led to the decomposition of the dienes. Nevertheless, in the presence of

diethylaluminium chloride (2.5 eq) and triphenylphosphine[10] (2 eq), the rearrangement proceeded smoothly, at -30°C, to afford in 46% overall yield from 13 (in 9:1 ratio) the readily separable epimers 17a,b and 18a,b.

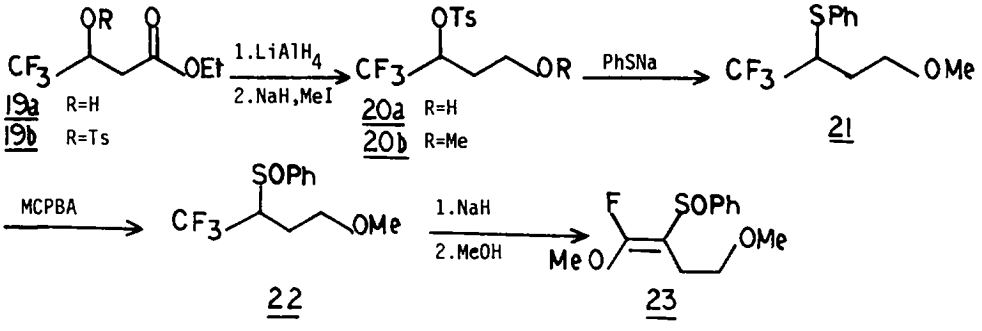




In order to get the synthon 2, the mixture of aldehydes 17, 18 had to be transformed into acids. All attempts to oxidize these aldehydes were unsuccessful. Depending upon the oxidizing agent, the oxidation was either very sluggish or gave poor yields.

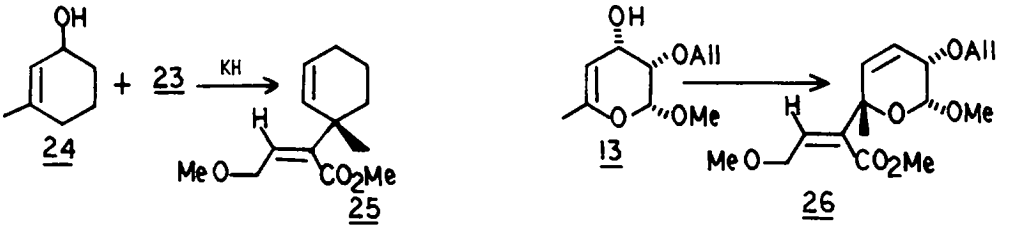
To circumvent this problem, we directly introduced the desired ester function at C-7 of the sugar derivative by a Claisen rearrangement, using an extension of a methodology we developed for the synthesis of α,β-unsaturated esters.[11,12] For this purpose, the new reagent 23 was prepared in six steps from the readily available compound 19a.[13,14] Reaction of the alcohol 19a with p-toluenesulfonyl chloride in pyridine, in the presence of p-dimethylaminopyridine, gave mainly the tosylate 19b in 55% yield along with some α,β-unsaturated ester, separable by crystallization. Reduction of the ester function with lithium aluminium hydride, at -50°C, afforded, in 73% yield, the primary alcohol 20a which was quantitatively methylated with methyl iodide in the presence of sodium hydride.

Substitution of the toluenesulfonate group of compound 20b by a phenylthio group occurred readily at 80°C and led to the sulfide 21 in 89% yield. 21 was converted into the sulfoxide 22 by MCPBA and then treated, according to a known procedure,[12] with two equivalents of sodium hydride and 1.1 equivalent of dry methanol to afford the α-fluoro-β-sulfinyl ether, a mixture of geometrical isomers of 23, in 71% yield.

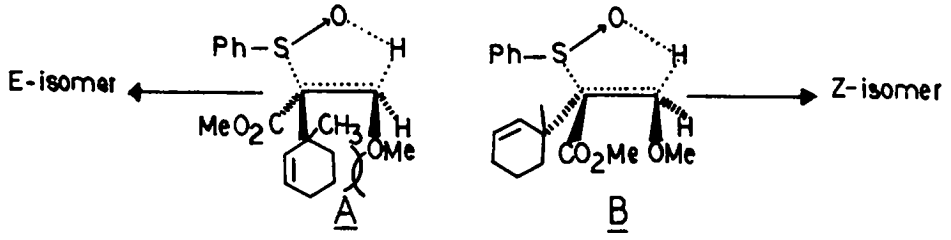


Formation of 4-methoxy-2-butenoate derivatives from allylic alcohols was first studied on the model compound[15] 24. Reaction between this compound and the fluoro derivative 23, in the presence of KH, gave smoothly the α,β-unsaturated ester 25 in 65% yield. Mechanistically, transformation of 24 to 25 is a succession of three consecutive reactions : displacement of F^- of compound 23 by the corresponding alkoxide of 24, Claisen rearrangement and dehydrosulfinylation (for more details see ref. 12). ^1H and ^{13}C NMR spectra of compound 25 revealed that only one geometrical isomer was

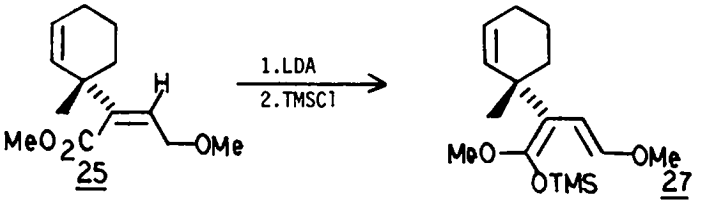
formed. Comparison of the chemical shift of the proton of the conjugated double bond (5.74 ppm) with those of similar known compounds[16] showed that the geometry of the double bond was Z. The reaction was applied to the sugar derivative 13 and the expected compound 26 was obtained in 41% yield.



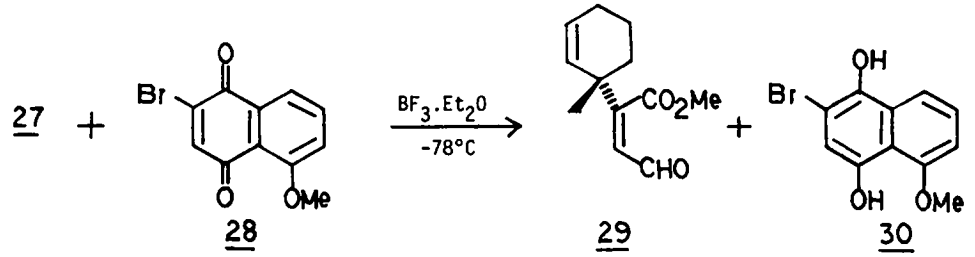
The exclusive formation of the Z-isomer can be explained by an analysis of the transition-state geometries of sulfoxide elimination.[17] In A from compound 24, steric interactions between the methoxy group and the 1-methyl-2-cyclohexenyl group which contains a quaternary carbon are more severe than between the methoxy and ester groups in B. This reasoning can be applied to 13.



Conversion of the 4-methoxy-2-butenoate derivative 25 into the 1,1,4-trialkoxybutadiene 27 was achieved by deprotonation at the alpha position of the methoxy group by lithium diisopropylamide at -78°C followed by quenching the resulting enolate with chlorotrimethylsilane. The distillable diene 27 was obtained in 91% yield. The ^1H NMR spectrum of 27 (mixture of geometrical isomers) revealed that the geometry of the double bond of the enol ether was mainly E (E/Z:4/1).



Diels-Alder reaction between the diene 27 and quinones like naphtoquinone or 2-bromo-5-methoxy-1,4-naphtoquinone[18] 28 did not proceed even at reflux of toluene. The lack of reactivity of this diene with quinones is surprising because other 1,1,4-trialkoxybutadienes, like (E)-1,1,4-trimethoxybuta-1,3-diene,[19] are known to undergo cycloaddition with quinones. In the presence of boron trifluoride-etherate, at -78°C, 27 and 28 did not give any cycloadducts but the aldehyde 29 (57%) and the hydroquinone 30 which was characterized as its diacetate.



This redox reaction between an electron-rich diene and a quinone seems unprecedented and may be facilitated by boron trifluoride which increases the oxidation potential of the quinone.[20]

Because of the lack of reactivity of diene 27 with quinones, this avenue of investigation was terminated.

Conclusion

During the studies of the synthesis of Nogalamycin, we found new applications of the Claisen rearrangement of complex allyl vinyl ethers to the stereospecific formation of a chiral quaternary carbon at the C-5 position of a sugar derivative. The polyfunctional reagent 17 has a great potentiality in synthesis, particularly as a γ-methoxy-α,β-unsaturated carbonyl anion equivalent. Furthermore, we developed a convergent synthesis of 1,1,4-trialkoxybutadienes which are not usually easy to make by other methods.[21]

Experimental section.

PMR were recorded using a Perkin-Elmer R-32 spectrometer at 90 MHz or a Cameca TN-250 spectrometer at 250 MHz. Spectra were recorded in $CDCl_3$ and chemical shifts are reported in ppm downfield from TMS (δ). Infrared spectra were recorded on a Beckmann IR-8 spectrophotometer and were calibrated with the 1601 cm^{-1} absorption of polystyrene. Optical rotations were measured on a Jouan-Roussel polarimeter at ambient temperature. Melting points were taken on a Reichert hot stage apparatus and are uncorrected. Analytical TLC was performed on 0.25 mm pre-coated silica gel containing a fluorescent indicator. Spots were visualized using one or more of the following techniques : (a) UV illumination; (b) spraying with a 10% sulfuric acid solution; (c) phosphomolybdic stain. All solvents were purified before use : ethyl ether, tetrahydrofuran were distilled from sodium benzophenone ketyl; triethylamine, dimethylsulfoxide, dimethylformamide and diisopropylamine were distilled from calcium hydride; pyridine was distilled from KOH and methanol from magnesium metal.

Methyl 2-O-allyl-4,6-O-benzylidene-α-D-allopyranoside 4 and methyl 3-O-allyl-4,6-O-benzylidene-α-D-allopyranoside 5.

To a solution of the diol 3 (25 g, 0.092 mol) in 300 ml of dry methanol were added 23,6 g (1.03 eq) of dibutyltin oxide. The solution was refluxed for 90 min under nitrogen and then evaporated. The oily residue was dried under high vacuum and then dissolved in 150 ml of DMF. After addition of 15 ml (1.8 eq) of allyl iodide, the solution was heated for 1 h at 100°C. The cooled solution was diluted with ether, washed with water (3 times) and dried on Na_2SO_4. Solvents were removed and the residue was dissolved in hot diisopropyl ether. From the cooled solution (-20°C) crystallized 15 g of the 2-O-allyl ether 4 (51%). $[\alpha]_D$ +63° (c, 1.2, CH_2Cl_2); m.p. 85-6°C. ^1H NMR (250 MHz) : 5.54 (s, 1H, CHPh), 4.82 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.4 (m, 1H, H-3), 3.55 (t, 1H, $J_{2,3}$ 3.5 Hz, H-2), 3.50 (q, 1H, $J_{3,4}$ 2.5 and $J_{4,5}$ 10 Hz, H-4), 3.4 (s, 3H, OMe), 3.12 (d, 1H, $J_{3,OH}$ 7 Hz, OH). Anal.Calc. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88; O, 29.78. Found : C, 63.32; H, 6.74; O, 29.64.

Chromatography on silica gel in ether-hexane (2:1) of the residue, obtained after evaporation of mother liquor, gave an additional 5.1 g of ether 4 (17%) and 2 g of the 3-O-allyl ether 5 (7%). $[\alpha]_D$ +100.7° (c, 1.1, CH_2Cl_2); m.p. 83-4°C (ether-hexane). ^1H NMR (90 MHz) : 5.48 (s, 1H, CHPh); 4.64 (d, 1H, $J_{1,2}$ 4 Hz, H-1), 3.4 (s, 3H, OMe), 2.97 (d, 1H, $J_{2,OH}$ 4 Hz, OH). Anal.Calc. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88; O, 29.78. Found : C, 62.88; H, 6.60; O, 29.80.

Methyl 2-O-allyl-3-O-benzoyl-4,6-O-benzylidene-α-D-allopyranoside 6.

To a solution of compound 4 (110 g, 0.34 mol) in 500 ml of CH_2Cl_2 were added successively, at room temperature, 155 ml (3 eq) of triethylamine, 4.1 g (0.1 eq) of p-dimethylaminopyridine and 47 ml (1.2 eq) of benzoyl chloride. The reaction mixture was stirred overnight at room temperature, washed with a saturated solution of sodium hydrogenocarbonate with water and dried. After evaporation of volatiles, the oily residue (160 g) (one spot on TLC, ether-hexane, 1:1) was used in the next step without purification. An analytical sample was prepared by silica gel purification of 0.576 g of the crude 6, using ether-hexane (1:1) as eluant. Pure benzoate 6 (0.474 g, 90%) was obtained as a foam. $[\alpha]_D$ +67° (c, 2.1, CH_2Cl_2). IR (neat) : 1720 cm^{-1} (C=O). ^1H NMR (90 MHz) : 6.08 (t, 1H, $J_{2,3} = J_{3,4} = 4$ Hz, H-3), 5.65 (s, 1H, CHPh), 4.82 (d, 1H, H-1), 3.53 (s, 3H, OMe). Anal.calc. for $C_{24}H_{26}O_7$: C, 67.59; H, 6.15; O, 26.26. Found : C,67.77; H,6.30; O,26.09.

Methyl 2-O-allyl-3-O-benzoyl-α-D-allopyranoside 7.

Crude 6 (160 g) was dissolved in 350 ml of 70% acetic acid and heated at 80°C for 4 h. After evaporation of volatiles, the residue was dissolved in hot ether and petroleum ether was added. After cooling at 0°C, the diol 7 crystallized (94.6 g, 91%). $[\alpha]_D$ + 39.8°C (c, 0.9, CH_2Cl_2); m.p. 109-110°C. Anal.calc. for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55; O, 33.1. Found : C, 60.63; H, 6.53; O, 33.29.

Methyl 2-O-allyl-3-O-benzoyl-6-O-trityl-α-D-allopyranoside 8a.

To a stirred solution of 7 (194.6 g, 0.279 mol) in 300 ml of pyridine was added 1.6 eq of chlorotriphenylmethane (124 g). The brown solution was heated for 2 h at 80°C. After cooling to room temperature, the mixture was diluted with CH_2Cl_2, washed with a solution of $CuSO_4$ with water and dried. The oily residue (212 g) which was contaminated with some chlorotriphenylmethane was used in the next step without purification. An analytical sample was prepared by chromatography on silica gel of 0.5 g of the crude 8a using ether-hexane, 2:1 as eluant. Pure 8a (0.341 g, 90%) was obtained as an amorphous powder. $[\alpha]_D$ +47° (c, 0.8, CH_2Cl_2). ^1H NMR (90 MHz) : 5.80 (t, 1H, $J_{2,3} = J_{3,4} = 3$ Hz, H-3), 4.82 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.52 (s, 3H, OMe), 2.35 (s, 1H, OH). Anal.calc. for $C_{36}H_{36}O_7$: C, 74.46; H, 6.25. Found : C, 75.08; H, 6.25.

Methyl 2-O-allyl-3-O-benzoyl-4-O-methanesulfonyl-6-O-trityl-α-D-allopyranoside 8b.

To a solution of crude 8a (212 g) in 300 ml of CH_2Cl_2, cooled at 0°C, was added 1.2eq of methanesulfonyl chloride (23 ml). After stirring for 1 h at 0°C, the solution was washed with a solution of sodium hydrogenocarbonate with water and dried. The solvent was evaporated and the crude product, dissolved in ether-hexane (2:1), was filtered through a short pad of silica gel to give 144.2 g (87%) of the crystalline 8b. $[\alpha]_D$ +58.4° (c, 0.6, CH_2Cl_2); m.p. 178-9°. ^1H NMR (90 MHz) : 6.16 (t, 1H, $J_{2,3} = J_{3,4}$ = 4 Hz, H-3), 4.94 (d, 1H, H-1), 4.87 (q, 1H, $J_{4,5}$ 10 Hz, H-4), 3.75 (t, 1H, H-2), 3.61 (s, 3H, OMe), 2.7 (s, 3H, SO_3Me). Anal.calc. for $C_{37}H_{38}O_9S$: C, 67.46; H, 5.81; S, 4.86. Found : C, 68.10; H, 5.86; S, 4.89.

Me 2-O-allyl-3-O-benzoyl-4-O-methanesulfonyl-α-D-allopyranoside 9.

A solution of compound 8b (144 g) in 500 ml of 80% acetic acid was heated for 5 h at 80°C. After evaporation of volatiles, the crude 9 was purified by column chromatography on silica gel. Elution with ether-methanol (9:1) afforded 85.6 g (94%) of 9. $[\alpha]_D$ +70° (c, 0.66, CH_2Cl_2). ^1H NMR (250 MHz) : 6.06 (t, 1H, $J_{2,3} = J_{3,4}$ = 3.5 Hz, H-3), 4.9 (q, 1H, $J_{4,5}$ = 10 Hz, H-4), 4.84 (d, 1H, $J_{1,2}$ = 4 Hz, H-1), 3.7 (t, 1H, H-2), 3.54 (s, 3H, OMe), 3.1 (s, 3H, SO_3Me), 2.35 (t, 1H, OH). Anal.calc. for $C_{18}H_{24}O_9S$: C, 51.91; H, 5.81; O, 34.58; S, 7.70. Found : C, 51.91; H, 5.89; O, 34.37; S, 7.68.

Methyl 6-aldehydo-2-O-allyl-3-O-benzoyl-4-deoxy-α-D-erythro-hex-4-enodialdo-1,5-pyranoside 10.

Oxalyl chloride (2.3 ml, 1.5 eq) was dissolved in 90 ml of CH_2Cl_2 in a 250 ml 3-neck round-bottomed flask, cooled at -60°C and 3.7 ml (3 eq) of DMSO were added dropwise under nitrogen. The solution was stirred for 10 min at -60°C and 7.2 g (0.017 mol) of 9 in 50 ml of CH_2Cl_2 was added. The solution was stirred for 15 min at -60°C and 25 ml (10 eq) of triethylamine were added slowly. After the end of the addition, the mixture was allowed to warm up to room temperature, washed three times with water, dried and evaporated. Filtration of crude 10 on a pad of silica gel gave pure 10 (5.3 g; 96%) as an oil. $[\alpha]_D$ -134° (c, 0.7, CH_2Cl_2). IR (neat) : 1720-1700 (ester, CHO); 1645 cm^{-1} (C=C conj.). ^1H NMR (250 MHz) : 9.3 (s, 1H, CHO), 6.04 (d, 1H, $J_{3,4}$ 5 Hz, H-4), 5.9 (t, 1H, $J_{2,3}$ 5 Hz, H-3), 5.19 (d, 1H, $J_{1,2}$ 2.5 Hz, H-1), 3.96 (q, 1H, H-2), 3.6 (s, 3H, OMe). Anal.calc. for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70; O, 30.1. Found : C, 63.88; H, 5.78; O, 30.25.

Methyl 2-O-allyl-3-O-benzoyl-4-deoxy-α-D-erythro-hex-4-enopyranoside 11.

To a solution of the aldehyde 10 (0.48 g, 1.5 mmol) in 10 ml of ethanol, cooled at 0°C, was added 0.08 g (1.4 eq) of $NaBH_4$. After stirring for 10 min at 0°C, the mixture was diluted with CH_2Cl_2, washed with water and dried. Chromatography on silica gel (ether-hexane, 2:1) gave 0.46 g (96 %) of the oily allylic alcohol 11. $[\alpha]_D$ -123° (c, 0.76, CH_2Cl_2). ^1H NMR (250 MHz) : 5.69 (t, $J_{2,3} = J_{3,4}$ = 5 Hz, H-3), 5.14 (d, 1H, H-4), 5.03 (d, 1H, $J_{1,2}$ 2.5 Hz, H-1), 4.06 (s, 2H, H-6), 3.9 (q, 1H, H-2), 3.58 (s, 3H, OMe), 2.2 (s, 1H, OH). Anal.calc. for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29; O, 29.97. Found : C, 63.88; H, 6.37; O, 30.05).

Methyl 2-O-allyl-4,6-dideoxy-α-D-erythro-hex-4-enopyranoside 13.

To a solution of the allylic alcohol 11 (14 g, 0.043 mol) in 100 ml of CH_2Cl_2, cooled at 0°C, were added 13 ml (2 eq) of triethylamine and then 3.7 ml (1.1 eq) of methanesulfonyl chloride. After stirring for 15 min at 0°C, the solution was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4 and evaporated. The crude mesylate was dissolved in 8 ml of THF and 3.32 g (2 eq) $LiAlH_4$ were added by portions. After stirring for 1 h at room temperature, EtOAc was added dropwise, then water. The mixture was diluted with ether and filtered. After evaporation of solvents, the crude 13 was purified by fractional distillation under high vacuum (0.05 mm Hg). The first fraction was constituted by benzylic alcohol (b.p. 40°C), followed by the allylic alcohol 13 (6 g, 68%), boiling at 70°C. On standing 13 crystallized, m.p. 31-32° (hexane). $[\alpha]_D$ +11.6° (c, 2.3, CH_2Cl_2). ^1H NMR (250 MHz) : 4.98 (q, 1H, $J_{1,2}$ 2.5 and $J_{1,3}$ 1 Hz, H-1), 4.89 (d, 1H, $J_{3,4}$ 5 Hz, H-4), 4.02 (m, 1H, H-3), 3.68 (q, 1H, $J_{2,3}$ 5 Hz, H-2), 3.46 (s, 3H, OMe), 2.96 (d, 1H, $J_{3,OH}$ 10 Hz, OH), 1.76 (s, 3H, CH_3). ^{13}C NMR (15.08 MHz, $CDCl_3$) : 19.3, 56.6, 61.6, 70.4, 74.1, 99.4, 100.1, 118.1, 134.5, 148.7. Anal.calc. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found : C, 59.65; H, 7.81.

Methyl 7-aldehydo-2-O-allyl-3-deoxy-5-C-methyl-6-C-[(Z,E)-2-methoxyvinyl]-α-L-arabino and xylo-hept-3-enodialdo-1,5-pyranoside 17a,b and 18a,b.

Sodio-malonaldehyde (1.7 g, 0.018 mol) was added to a solution of p-toluenesulfonyl chloride (2.14 g, 0.011 mol) in 10 ml of THF containing 0.05 g of 18-crown-6. After stirring for 15 min at room temperature, a solution of the allylic alcohol 13 (1.5 g, 7.5 mmol) in 10 ml of THF was added and then, by portions, 0.9 g (0.03 mol) of NaH (80% dispersion in mineral oil). After stirring for 15 min, the mixture was filtered over a celite bed and washed with THF. This solution was added, at -30°C, to a solution of methoxymethyltriphenylphosphorane prepared in the usual way from 0.018 mol of each reagent. The mixture was allowed to warm to room temperature and diluted with ether. The precipitate was filtered over a bed of silica gel and washed with ether. After evaporation of volatiles, the dienes 15 and 16 were dried under high vacuum. To the solution of the dienes in 20 ml of CH_2Cl_2 were added 3.9 g (0.015 mol) of triphenylphosphine and, at -30°C, 15 ml of a solution of diethylaluminium chloride (25% in hexane) under N_2. After stirring for 15 min at -30°C, a solution of sodium hydrogenocarbonate was added. The organic layer was washed with water, dried over Na_2SO_4 and evaporated to dryness. Chromatography of the residue on silica gel (ether-hexane, 2:1) gave, first, compound 17a,b or 18a,b (0.09 g, 4.3%) as an oil. IR (neat) : 2730 (CHO), 1725 (CHO), 1660 cm^{-1} (C=C). ^1H NMR (250 MHz) : 9.68 (d, 0.5 H, J 4 Hz, CHO), 9.62 (d, 0.5 H, J 3.5 Hz, CHO), 6.32 (d, 0.5 H, J 13 Hz, (E)-CH=CH-OCH_3), 6.12 (q, 0.5 H, J 1 and 6 Hz, (Z)-CH=CH-OCH_3), 6.12 (q, 0.5 H, J 1 and 6 Hz, (Z)-CH=CH-OCH_3), 5.9 (q, 05 H, $J_{2,3}$ 5 and $J_{3,4}$ 10 Hz, H-3), 5.84 (q, 05 H, $J_{2,3}$ 4.5 Hz and $J_{3,4}$ 10 Hz, H-3), 5.74 (q, 0.5 H, $J_{2,4}$ 1 Hz, H-4), 5.7 (q, 0.5 H, H-4), 4.85 (q, 0.5 H, J 10 and 13 Hz, (E)-CH=CH-OCH_3), 4.72 (d, 0.5 H, $J_{1,2}$ 2.5 Hz, H-1), 4.69 (d, 0.5 H, $J_{1,2}$ 2.5 Hz, H-1), 4.58 (q, 0.5 H, J 6 and 10 Hz, (Z)-CH=CH-OCH_3), 3.8 (m, 1.5H, H-2 and CH-CHO),

3.57-3.46 (m, 6H, $2OCH_3$), 2.84 (q, 0.5H, CH-CHO), 1.38 (s, 1,5H, CH_3), 1.34 (s, 1.5H, CH_3). Anal.calc. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85; O, 28.24. Found : C, 63.59; H, 7.92; O, 28.59.

The second fraction was constituted by compound 18a,b or 17a,b (0.882 g, 42%) obtained as an oil. ^1H NMR (250 MHz) : 9.8 (d, 0.5H, J 3 Hz, CHO), 9.7 (d, 0.5H, J 2.5 Hz, CHO), 6.33 (d, 0.5H, J 12.5 Hz, (E)-CH=CH-OCH_3), 6.2 (q, 0.5H, J 1 and 6 Hz, (Z)-CH=CH-OCH_3), 5.86 (m, 3H, H-3, H-4, O-CH_2-CH=CH_2), 4.82 (q, 0.5H, J 10 Hz, (E)-CH=CH-OCH_3), 4.78 (d, 0.5H, $J_{1,2}$ 3 Hz, H-1), 4.75 (d, 0.5H, $J_{1,2}$ 3 Hz, H-1), 4.56 (q, 0.5H, J 10 Hz, (Z)-CH=CH-OCH_3), 3.89 (m, 1H, H-2), 3.57-3.41 (m, 6.5H, $2OCH_3$, CH-CHO); 2.92 (q, 0.5H, CH-CHO), 1.31 (s, 3H, CH_3). Anal.calc. for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85; O, 28.24. Found : C, 63.80; H, 7.66; O, 28.40.

Ethyl 3-toluenesulfonyloxy-4,4,4-trifluorobutyrate 19b.

To a solution of compound 19a[14] (90 g, 0.48 mol) in 400 ml of pyridine were added successively 180 g (2 eq) of p-toluenesulfonyl chloride and 11 g (0.2 eq) of p-dimethylaminopyridine. The mixture was stirred for 2 days at room temperature. Water was added and the solution was stirred for 30 min. The reaction mixture was partitioned between water and ether. The organic layer was washed with 6M HCl with water and dried over Na_2SO_4. After evaporation of volatiles, the residue was dissolved in hot hexane and then cooled to -20°C. From this solution crystallized the tosylate 19b (90 g, 55%). M.p. 51-52°C. ^1H NMR (90 MHz) : 7.85 (d, 2H, J 8 Hz, Ph), 7.35 (d, 2H, Ph), 5.40 (sextuplet, 1H, J 6 Hz, H-3), 4.15 (q, 2H, J 7 Hz, -CH_2-CH_3). Anal.calc. for $C_{13}H_{15}F_3O_5S$: C, 45.88; H, 4.44; S, 9.42. Found : C, 46.12; H, 4.13; S, 9.71.

2-O-Toluenesulfonyl-1,1,1-trifluoro-2,4-butanediol 20a.

To a suspension of lithium aluminium hydride 0.164 g (1.1 eq) in 8 ml of dry ether, cooled at -50°C, was added 1.3 g (3.8 mmol) of 19b in 8 ml of ether under N_2. After stirring for 15 min at -50°C, 2M HCl (1 ml) was added and the mixture was allowed to warm to room temperature. Then the precipitate was filtered and washed with ether. After evaporation of volatiles, the residue was passed through a short pad of silica gel to afford the oily diol 20a (0.83 g, 73%). ^1H NMR (90 MHz) : 7.85 (d, 2H, J 8 Hz, Ph), 7.37 (d, 2H, Ph), 5.2 (m, 1H, H-2), 3.85 (m, 2H, 2H-4), 2.48 (s, 3H, CH_3), 2.88-1.88 (m, 2H, 2H-3).

4-O-Methyl-2-O-p-toluenesulfonyl-1,1,1-trifluoro-2,4-butanediol 20b.

To a solution of methyl iodide (51 ml, 4 eq) in 300 ml of DMF, cooled at -5°C, were added 61.5 g (0.21 mol) of compound 20a then, by portions, 10.8 g (1.3 eq) of sodium hydride (80% dispersion in mineral oil). The mixture was stirred for 15 min at -5°C and then partitioned between ether and water. The organic layer was washed with water and dried. Evaporation of volatiles led to compound 20b (63 g, 98%) as an oil. ^1H NMR (90 MHz) : 5.12 (m, 1H, H-2), 3.48-3.3 (m, 2H, 2H-4), 3.3 (s, 3H, OMe), 2.42 (s, 3H, CH_3), 2.12-1.8 (m, 2H, 2H-3). ^{13}C NMR (15.08 MHz) : 145.6, 132.6, 128.1, 72.9, 66.2, 58.7, 29.1, 21.7. Anal.calc. for $C_{12}H_{15}F_3O_4S$: C, 46.15; H, 4.84; S, 10.33. Found : C, 46.35; H, 4.95; S, 10.26.

2-Phenylthio-1,1,1-trifluorobutanol methylether 21.

To a solution of sodium benzenethiolate in 30 ml of DMF, prepared in situ from 6.5 ml (0.063 mol) of thiophenol and 1.82 g (0.06 mol) of sodium hydride (80% dispersion in mineral oil), were added, at 0°C, 7.4 g (0.023 mol) of compound 20b in 20 ml of DMF. The solution was heated for 4 h at 80°C. The cooled mixture was diluted with ether, washed with water, dried, evaporated. The crude 21 was distilled under high vacuum (0.1 mm Hg) to afford the sulfide 21 (5.23 g, 89%) as a colorless oil (b.p. 52-4°C). ^1H NMR (90 MHz) : 7.5-7.15 (m, 5H, Ph), 3.6 (m, 3H, H-2, 2H-4), 3.2 (s, 3H, OMe), 2.15 (m, 1H, H-3), 1.6 (m, 1H, H-3). Anal.calcd. for $C_{11}H_{13}F_3OS$: C, 52.79; H, 5.23; S, 12.81. Found : C, 52.82; H, 5.33; S, 12.92.

2-Phenylsulfinyl-1,1,1-trifluorobutanol methyl ether 22.

To a solution of the sulfide 21 (33.5 g, 0.134 mol) in 100 ml of CH_2Cl_2, cooled at -30°C, was added MCPBA 80% (30.25 g, 0.14 mol) in 350 ml of CH_2Cl_2. The mixture was allowed to warm to room temperature and stirred for 30 min. m-Chlorobenzoïc acid was filtered and washed with CH_2Cl_2. The organic layer was washed with a saturated solution of bicarbonate, with water, dried, and evaporated. The residue was filtered through a pad of silica gel to give 33.62 g of the sulfoxide 22 (94%) obtained as a mixture of diastereoisomers. ^1H NMR (90 MHz) : 7.7 (m, 5H, Ph), 3.75-3.0 (m, 3H, 2H-4, H-2), 2.93 (s, 3H, OMe), 2.6-1.7 (m, 2H, 2H-3). Anal.calc. for $C_{11}H_{13}F_3O_2S$: C, 49.6; H, 4.92; S, 12.04. Found : C, 49.73; H, 4.89; S, 11.96.

(Z,E)-1,4-Dimethoxy-1-fluoro-2-phenylsulfinyl-1-butene 23.

To a suspension of sodium hydride (60% dispersion in mineral oil) (5.15 g, 0.128 mol) in 40ml of THF, was added the sulfoxide 22 (13 g, 0.049 mol) in 100 ml of THF. Then the solution was cooled at -10°C and dry methanol (2.7 ml, 0.066 mol) was added dropwise. After stirring for 30 min at -10°C, water was added and then ether. The organic layer was washed with water, dried, and evaporated. Column chromatography of the residue on silica gel, with ether as eluant, gave 8.92 g (71%) of 23 as an oil. ^1H NMR (90 MHz) : 7.5 (m, 5H, Ph), 3.95 (s, 1.5H, OMe), 3.90 (s, 1.5H, OMe), 3.15-2.9 (m, 2H, 2H-4), 3.13 (s, 3H, OMe), 2.35 (m, 2H, 2H-3). Anal.calcd. for $C_{12}H_{15}FO_3S$: C, 55.80; H, 5.85; S, 12.41. Found : C, 55.61; H, 5.99; S, 12.21.

Methyl(Z)-4-methoxy-2-(1-methyl-2-cyclohexenyl)-2-butenoate 25.

To a suspension of KH (35% dispersion in mineral oil) (2.77 g, 0.025 mol) in 30 ml of THF, cooled at 0°C, was added the allylic alcohol 24 (2.4 ml, 0.02 mol). The mixture was stirred at 0°C, 30 min, and the reagent 23 (6.36 g, 0.025 mol) in 50 ml of THF was added. The reaction mixture was stirred for 15 min at 0°C, 1 h at room temperature and 1 h at reflux. The cooled reaction mixture was partitioned between water and ether. The organic layer was washed with water, dried over Na_2SO_4 and evaporated. Chromatography of the residue on silica gel, eluant ether-hexane (1:9) gave 2.95 g of 25 as an oil (65%). B.p. 75°C at 0.01 mm Hg (Kugelrohr distillation). IR

(neat) : 1730, 1650 cm^{-1}. ^1H NMR (250 MHz): 5.78 (dt, 1H, J 10 and 3 Hz), 5.74 (t, 1H, J 6 Hz, H-3), 5.41 (dq, 1H, J 2,3,5,10 Hz), 3.99 (dd, 2H, 2H-4), 3.77 (s, 3H, OMe), 3.3 (s, 3H, OMe), 2.14-1.4 (m, 6H). ^{13}C NMR (15.08 MHz) : 169.7, 143.0, 133.6, 131.3, 128.1, 70.6, 58.3, 51.4, 39.4, 34.9, 29.4, 25.2, 16.7. Anal.calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99; O, 21.40. Found : C, 69.34; H, 8.90; O, 21.32.

(Methyl 2-O-allyl-5-C-methyl-6-C-[(Z)-methoxymethyl methylene]-β-L-threo-hept-3-enopyranosid) uronate 26.

To a suspension of KH (35% dispersion in mineral oil (0.69 g, 6 mmol) in 10 ml of THF, cooled at -5°C, was added the allylic alcohol 13 (1 g, 5 mmol). After stirring for 30 min at 0°C, the sulfoxide 23 (2.32 g, 9 mmol) in 20 ml of THF was added. The reaction mixture was stirred for 2 h at 0°C, 90 min at room temperature and 2 h at 50-55°C. The mixture was worked-up according to procedure described above for 25. The α,β-unsaturated ester 26 (0.642 g, 41%) was obtained as an oil. $[\alpha]_D$ +20° (c, 0.5, CH_2Cl_2). ^1H NMR (250 MHz) : 6.27 (t, 1H, J 5.5 Hz, CH=C of the ester function), 6.05 (dd, 1H, $J_{2,4}$ 2 and $J_{3,4}$ 10 Hz, H-4), 5.75 (dd, 1H, $J_{2,3}$ 3 Hz, H-3), 4.81 (d, 1H, $J_{1,2}$ 2.5 Hz, H-1), 3.92 (sextuplet, 1H, H-2), 3.73 (s, 3H, OMe), 3.4 (s, 3H, OMe), 3.26 (s, 3H, OMe), 1.41 (s, 3H, CH_3).

1,4-Dimethoxy-2-(1-methyl-2-cyclohexenyl)-1-trimethylsiloxybuta-1,3-diene 27.

To a solution of lithium diisopropylamide in 6 ml of THF, prepared from 0.43 ml (3 mmol) of diisopropylamine and 1.86 ml of n-BuLi (1.57 M), cooled at -78°C, was added 0.6 g (2.6 mmol) of compound 25 in 8 ml of THF under N_2. After stirring for 15 min at -78°C, 0.43 ml (3.4 mmol) of chlorotrimethylsilane was added. The solution was allowed to warm to room temperature and concentrated in vacuo. Dry pentane was added and the precipitate was filtered under N_2 and washed with dry pentane. After evaporation of volatiles, the residue was distilled in a Kugelrohr apparatus under high vacuum (0.05 mm Hg) to give 0.721 g (91%) of 27 as an oil boiling at 65-70°C. IR (neat) 1655 cm^{-1}. ^1H NMR (90 MHz) : 6.39 (d, 0.8H, J 13 Hz), 5.76 (d, 0.2H, J 6.6 Hz), 5.69-5.34 (m, 2H), 5.09 (two doublets, 0.8H, J 13 Hz), 4.59 (d, 0.2H, J 6.6 Hz), 3.54-3.4 (6H, $2OCH_3$), 2.04-1.24 (m, 6H, cyclohexenyl ring), 1.14 (s, 3H, CH_3), 0.22 (s, 4.5H, $Si(CH_3)_3$), 0.19 (s, 4.5H, $Si(CH_3)_3$).

Methyl 2-(1-methyl-2-cyclohexenyl)-4-oxo-2-butenoate 29 and 2-bromo-1,4-diacetoxy-5-methoxy-naphtalene 30.

To a solution of the diene 27 (0.238 g, 0.8 mmol) and the quinone 28 (0.213 g, 1 eq) in 5 ml of CH_2Cl_2, cooled at -78°C, was added 0.05 ml of BF_3-Et_2O (0.5 eq). After stirring for 15 min at -78°C, a solution of sodium hydrogenocarbonate was added and then CH_2Cl_2. The organic layer was washed with water, dried, evaporated. The residue, which gave mainly two spots on TLC, was dissolved in 1 ml of pyridine and 1 ml of acetic anhydride. After stirring for 30 min at room temperature, the mixture was evaporated to dryness. Column chromatography of the residue on silica gel, eluant diisopropyl ether-hexane (1:3), gave first compound 29 (0.098 g, 57%). IR (neat) : 1740, 1700, 1620 cm^{-1}. ^1H NMR (90 MHz) : 9.8 (d, 1H, J 8 Hz, CHO), 6.1 (d, 1H, J 8 Hz), 5.92 (dt, 1H, J 3 and 10 Hz), 5.45 (d, 1H, J 10 Hz), 3.88 (s, 3H, OMe), 2.02-1.38 (m, 6H), 1.25 (s, 3H, OMe). Anal.calc. for $C_{12}H_{16}O_3$: C, 69.20; H, 7.74; O, 23.04. Found : C, 68.95; H, 7.79; O, 23.30.

The aromatic derivative 30 (0.09 g, 32%) was eluted with diisopropyl ether. ^1H NMR (90 MHz) : 7.55 (d, 1H, J 4.6 Hz, H-6 or H-8), 7.51 (d, 1H, J 3.3 Hz, H-6 or H-8), 7.4 (s, 1H, H-3), 7.0 (q, 1H, H-7), 4.0 (s, 3H, OMe), 2.52 (s, 3H, OAc), 2.45 (s, 3H, OAc). Anal.calcd. for $C_{15}H_{13}BrO_5$: C, 51.01; H, 3.71; O, 22.26. Found : C, 51.0; H, 3.70; O, 22.40.

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