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METACHLOROPEROXYBENZOIC ACID PROMOTED STEREOSELECTIVE SYNTHESIS OF 2,5-DISUBSTITUTED TETRAHYDROFURANS FROM α OR γ-ALLYL-β-HYDROXY ESTERS : A FORMAL SYNTHESIS OF (±) METHYL NONACTATE

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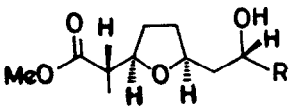
Abstract : A one pot stereoselective synthesis of cis or trans 2,5-disubstituted tetrahydrofurans 3-8 can be achieved in high yields via electrophilic cyclisation of the corresponding cis or trans α or γ-allyl-β-hydroxyesters mediated by metachloroperoxybenzoic acid. The tetrahydrofurans 5 or 6 may be converted into (±) methyl nonactate by procedures described earlier. The role of methoxycarbonyl group during these cyclisations is discussed.

Stereoselective synthesis of 2,5-disubstituted tetrahydrofurans have received considerable attention[1] from organic chemists during the last decade and consequently various synthetic routes, involving high degree of stereocontrol, are now available for these compounds. The electrophilic cyclisation of γ,δ-hydroxy olefins using I_2 to give 2,5-disubstituted tetrahydrofurans[2] can be carried out, with remarkable stereocontrol, due to the pioneering work of Bartlett and coworkers. The intramolecular hydroxy epoxide opening has been used for the synthesis[3] of 2,5-disubstituted tetrahydrofuran, however a reliable and efficient method for the regio and stereoselective opening of epoxides by internal nucleophilic oxygen is still lacking. In spite of the excellent efforts for achieving stereocontrol, during electrophilic heterocyclisation, there are no straightforward routes to 2,5-cis-disubstituted tetrahydrofurans. However, Bartlett and coworkers have provided a solution to this by cyclising the O-alkylated derivatives of γ, δ-unsaturated alcohols by exploiting[2] the electrofugal properties of the benzyl ether group. Yoshida[4], Chan[5] and coworkers have developed stereoselective routes to tetrahydrofurans by promoting the stereocontrol due to an allylic oxygen substituent during the iodocyclisation of 4-alkene-1,3-diol.

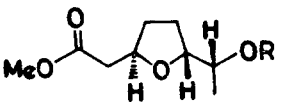
The stereocontrol by a remote functional group have been rarely investigated however if the group is situated appropriately then it is possible that it may have considerable effect on the stereochemical outcome of the reaction. We now show that a remotely placed methoxycarbonyl[6] group is capable of controlling the stereochemistry of the ring junction of tetrahydrofurans during electrophilic cyclisation of α or γ-allyl-β-hydroxy esters in presence of metachloroperoxy-benzoic acid.

These studies are directed towards the synthesis of Nactin and tetronomycin polyether antibiotics[7] subunits which consist of a 2,5-cis-disubstituted tetrahydrofuran with an acetate or propionate as one of the side chains (figure 1).



R = Me Et etc

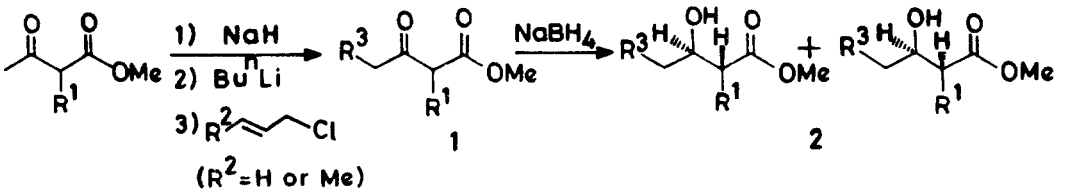
Nactin subunit



Tetronomycin subunit

Figure - 1

We choose α or γ -allyl- β -hydroesters as the substrate to explore the effect of the ester group on the stereochemistry during electrophilic cyclisation mediated by metachloroperoxy benzoic acid. The compounds **2a-f** can be easily prepared in two steps from acetoacetate as shown in scheme 1. The dianion of methylacetoacetate was allylated to give γ -allylacetoacetate 1a-c which on reduction with $NaBH_4$ gave the corresponding alcohol **2a-d** in quantitative yields. Similarly the α -allyl- - β -hydroxyester **2e-f** were obtained by mono anion allylation reduction sequence from methyl acetoacetate. The diastereomers were separated by flash column chromatography on silica gel.



(a) R^1= H ; R^3= $-CH_2-CH=CH_2$ (a) 78% -

(b) R^1= H ; R^3= $-CH_2-CH=CH-CH_3$ (b) 72% -

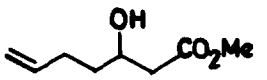
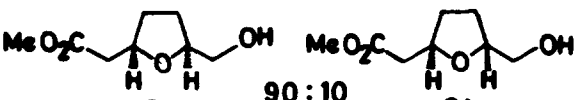
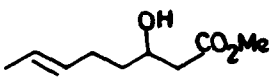
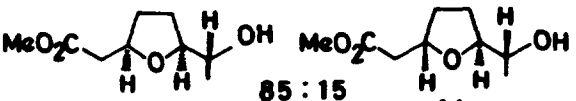
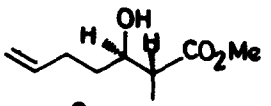
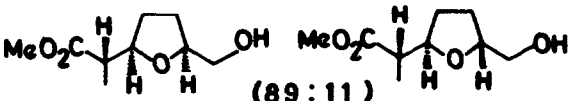
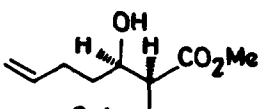
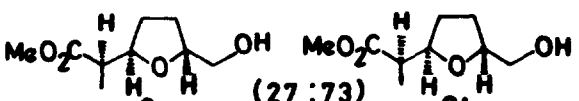
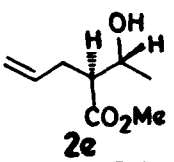
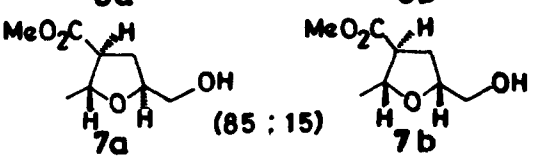
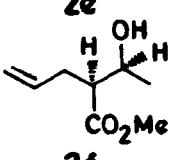
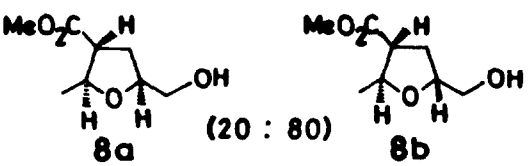
(c) R^1= Me ; R^3= $-CH_2-CH=CH_2$ (c) 53% (d) 28%

(d) R^1= $-CH_2-CH=CH_2$; R^3=H (e) 52% (f) 37%

(Scheme 1)

The allyl β-hydroxyesters 2a-f were subjected to treatment with MCPBA (1.5 equivalent) at 0°-25°C in dichloromethane for 4-6 hours. The usual work-up followed by ^{1}H-NMR analysis revealed the presence of one diastereomer of 2,5-disubstituted tetrahydrofuran as the major product (Table 1, entries 1-4). The major diastereomers were separated from the rest by flash column chromatography. A trace of the intermediate

Table 1 Synthesis of tetrahydrofurans from α or γ-allyl-β-hydroxyesters

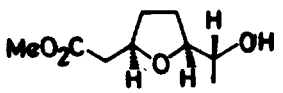
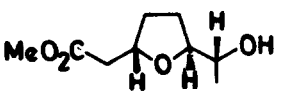
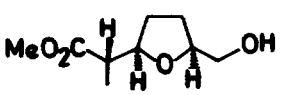
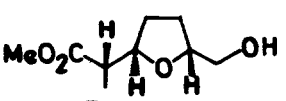
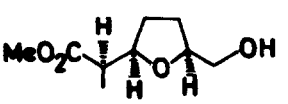
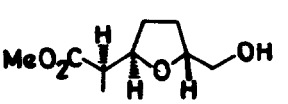
Entry	β-Hydroxy ester	Product (s) (ratio)[a]	Yield[b] (%)
1	 2a	 3a 90:10 3b	95
2	 2b	 4a 85:15 4b	89
3	 2c	 5a (89:11) 5b	78
4	 2d	 6a (27:73) 6b	92
5	 2e	 7a (85:15) 7b	87
6	 2f	 8a (20:80) 8b	81

(a) The ratio of diastereomers were found out by ^{1}H-NMR of the crude reaction mixture.

(b) Yield of the purified mixture of diastereomers.

oxiranes were observed in all the cases, however, no attempt was made to further purify and characterise the minor products. The β-hydroxy ester 2a gave 3a predominantly whereas 2b underwent a smooth cyclisation to yield 4a as the major product. Trans β-hydroxyester 2c gave the trans-cis isomer 5a as the major product in excellent yields (Table 1, entry 3).

Table 2 ^{1}H **NMR Chemical shifts[a] of tetrahydrofurans**

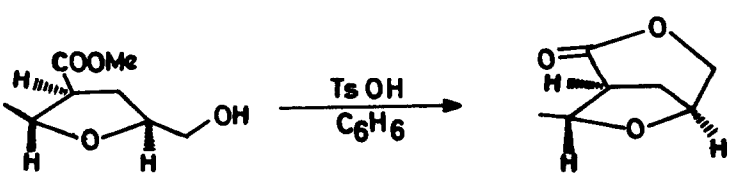
Compound	δ 2-Me (J = 7.0 Hz)	δ 7-Me (J = 6.2 Hz)	δ MeO
 **4a**	–	1.16	3.68
 **4b**	–	1.10	3.71
 **5a**	1.19	–	3.62
 **5b**	1.12	–	3.74
 **6a**	1.21	–	3.66
 **6b**	1.15	–	3.70

a) NMR spectra were recorded on 300 MHz in $CDCl_3$.

On the other hand the corresponding cis diastereomer **2d** yielded the cis-trans isomer **6b** as the major product, however, the stereoselectivity during this cyclisation was not as good as compared to the cyclisation of the corresponding trans diastereomer **2c**. The trans diastereomer of α-allyl-β-hydroxy ester **2e** was smoothly cyclised to give trans-trans tetrahydrofuran **7a** as the major product, however, the relative stereochemistry in this compound was trans at the ring junction. In contrast the corresponding cis diastereomer **2f** cyclised very slowly and yielded the cis-trans diastereomer **8b** as the major product (Table 1, entry 5 & 6).

The relative stereochemistry at the ring junction of all the tetrahydrofurans **4-6** were assigned by ^{1}H-NMR spectrum (300 MHz) of the crude product. The proton chemical shifts of various diastereomers are compiled in table 2.

The C-7 methyl for the cis-trans isomer **4a** resonates downfield as compared to the corresponding methyl of the trans-trans isomer **4b**. Similarly the pairs of diastereomer **5a**, **5b** and **6a**, **6b** also show the difference in the chemical shift of their C-2 methyl group. The trans relationship at C-6, C-7 for **4a-b** and at C-2, C-3 for **5a-b** is indicated by a large coupling constant (9-10 Hz) between protons at these carbon atoms. The chemical shift of the methyl group of ester in case of cis isomers **4a**, **5a** and **6a** is slightly upfield as compared to the chemical shift of this methyl group in the corresponding trans isomers **4b**, **5b** and **6b** (Table 2). A similar correlation between various proton chemical shift and the relative stereochemistry at the ring junction for tetrahydrofurans has been reported[9] by Bartlett and coworkers. The stereochemistry of the tetrahydrofurans **4-6** were further confirmed by comparing the ^{1}H-NMR data[9,10] from the literature. The cis stereochemistry at C-3 and C-5 in **7a** was confirmed by converting it to the corresponding lactone **9** on treatment with para-toluenesulphonic acid in benzene (Scheme 2).



7a **9**

(Scheme 2)

5a

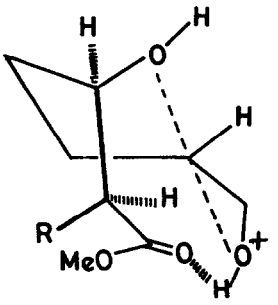
10

(±) Methylnonactate

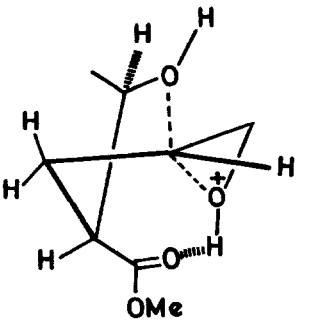
(Scheme 3)

The present method for the synthesis of tetrahydrofurans is quite versatile as it leads to the formation of the key intermediate 5a which has been converted into (±) methylnonactate **10** in four steps as described[8b] earlier (Scheme 3). Similarly the isomer 6a is also a key intermediate which may be converted into the epimer of (±) methylnonactate.

The high cis-stereoselectivity during the formation of the tetrahydrofurans **3a-5a** can be explained by invoking the involvement of the methoxycarbonyl group during the cyclisation. This assumption is based on the fact that usually electrophilic cyclisation of γ, δ-unsaturated alcohols results[1] in the trans stereochemistry at the ring junction. In our case the alcohols **2a-c** mainly give rise to the cis stereochemistry at the ring junction indicating that the methoxycarbonyl group may be responsible for this stereoselectivity. The cis stereochemistry during the electrophilic cyclisation of alcohols **2a-c** can be explained by considering the transition state geometry A and according to this the stabilising interactions, between the developing positive charge on protonated oxirane and the oxygen lone pair[11] of the ester carbonyl via hydrogen bonding, will be responsible for the high stereoselectivity. This interaction will lower the activation energy and therefore the transition state A will be favoured over the alternative transition state which doesnot involve a similar participation of methoxycarbonyl group.



A



B

Similarly the cis stereochemistry of the tetrahydrofuran **7a** derived from alcohol **2e** can be explained by the transition state geometry **B** where the methoxycarbonyl group is again responsible for providing the stabilisation (via hydrogen bonding) to the protonated oxirane. The trans diastereoselectivity (Table 1, entries 4 and 6) obtained from the cis alcohols **2d** and **2f** may be due to the noninvolvement of the ester group during these cyclisations. The molecular models for the cyclisation of cis alcohols **2d** and **2f** also show that the involvement of methoxycarbonyl group is disfavoured due to the steric interactions.

In conclusion, the electrophilic cyclisation of alcohols **2a-f** with metachloroperoxybenzoic acid is a novel method for the stereoselective synthesis of tetrahydrofuran units of ionophores and polyether antibiotics. This study has also revealed the crucial role of the methoxycarbonyl group in controlling the stereochemistry during these cyclisations. We are trying to extend this methodology for the stereoselective synthesis of tetrahydropyrans.

Acknowledgement : We wish to thank the Department of Science and Technology (DST, New Delhi) for providing financial support to this work.

EXPERIMENTAL

Methods and Materials :

IR spectra were recorded on a Perkin Elmer 1320 spectrometer. The proton NMR spectra were recorded on Bruker WP-80, Jeol PMX-60, Varian EM-390 and GE-300 spectrometer. Elemental analysis was conducted using coleman automatic C, H and N analyser. Analytical thin layer Chromatography was performed on silica gel (Acme) Coated Glass plates. Column Chromatography was performed using 100-200 mesh Acme silica gel.

Methylacetoacetate, allylbromide, sodium borohydride and meta chloroperoxybenzoic acid were purchased commercially and used without purification. Dichloromethane was dried over calcium chloride and distilled from P_2O_5. The α and γ-allylacetoacetates **1a-d** were prepared by literature procedure[12].

General procedure for the reduction of Ketones 1a-d :

The ketones **1a-d** (10 mmol) were dissolved in dry methanol (15 ml) and the solution was cooled to 0°C. A cooled solution of sodium borohy-

dride (0.09g, 2.5 mmol) in methanol was added dropwise to the stirred solution at 0°C and after one hour methanol was removed under Vacuuo to yield a residue. The residue was extracted with diethyl ether (3 x 20 ml) and the organic layer washed successively with saturated solution of sodium bicarbonate and water. Drying ($MgSO_4$) and evaporation of ether gave an oil which was subjected to column chromatography over silica gel using ethyl acetate - petroleum ether as the eluant. The yield and spectral properties of the alcohols **2a-f** are given below :

2a : Yield (78%); IR(CH_2Cl_2) 3478 and 1730 cm^{-1}; ^{1}H-NMR(CCl_4) δ 5.3 - 5.95(m, 1H), 4.62 - 5.05(m, 2H), 3.8(m, 1H), 3.65(S, 3H), 2.23(d, 2H, J = 6.8 Hz), 1.19 - 2.12(m, 4H).

2b : Yield (82%); IR(thin film) 3495 and 1747 cm^{-1}; ^{1}H-NMR(CCl_4) δ 5.35(m, 2H), 3.88(m, 1H), 3.68(S, 3H), 2.37(d, 2H, J = 6.8 Hz), 2.15(m, 2H), 1.68(d, 3H, J = 6.1 Hz), 1.45(m, 2H).

2c : Yield (45%); IR(thin film) 3482 and 1745 cm^{-1}; ^{1}H-NMR(CCl_4) δ 5.38 - 6.05(m, 1H), 4.7 - 5.15(m, 2H), 3.60(S, 3H), 3.45(dt, 1H, J = 8 and 5 Hz), 2.35(qd, 1H, J = 8.5 and 4.9 Hz), 2.18(m, 2H), 1.5(m, 2H), 1.15(d, 3H, J = 7 Hz).

2d : Yield (47%); IR(thin film) 3480 and 1748 cm^{-1}; ^{1}H-NMR(CCl_4) δ 5.35 - 6.0(m, 1H), 4.5 - 5.18(m, 2H), 3.69(m, 1H), 3.62(S, 3H), 2.0 - 2.67(m, 3H), 1.55(m, 2H), 1.12(d, 3H, J = 7 Hz).

2e : Yield (52%); IR(thin film) 3479 and 1750 cm^{-1}; ^{1}H-NMR(CCl_4) δ 5.25 - 5.95(m, 1H), 4.75 - 5.05(m, 2H), 3.85(qd, 1H, J = 8 and 5 Hz). 3.6(S, 3H), 2.25(t, 2H, J = 6 Hz), 1.15(d, 3H, J = 6.8 Hz).

2f : Yield (37%); IR(thin film) 3470 and 1752 cm^{-1}; ^{1}H-NMR(CCl_4) δ 5.3 - 5.98(m, 1H), 4.8 - 5.1(m, 2H), 3.8(m, 1H), 3.62(S, 3H), 2.2(m, 2H), 1.08(d, 3H, J = 6.8 Hz).

General procedure for m-chloroperoxybenzoic acid promoted electrophilic cyclisation :

A solution of metachloroperoxybenzoic acid (0.43g, 2.5 mmol) in dry dichloromethane (10 ml) was added dropwise to a stirring solution of the hydroxyesters **2a-f** (2 mmol) at 0°C. The reaction mixture was slowly brought to the room temperature (25°C) and stirred for 6-7 h.

Dichloromethane (50 ml) was added to this mixture and the organic phase washed successively with 10% sodium sulphite solution (2 x 10 ml) and water. Drying ($MgSO_4$) and evaporation of dichloromethane gave a crude gum which was purified by flash column chromatography (SiO_2; 50% ether - petroleum ether).

3a : Yield (80%); IR(CH_2Cl_2) 3350, 1750 cm^{-1}; ^{1}H-NMR(CCl_4) δ 3.82 - 4.2 (m, 2H), 3.60(S, 3H), 3.35(d, 2H, J = 6 Hz), 2.39(d, 2H, J = 6 Hz), 1.3 - 1.95(m, 4H). (Calcd. for $C_8H_{14}O_4$: C, 55.17; H, 8.04. Found : C, 55.00; H, 8.50).

3b : Yield (10%); IR(CH_2Cl_2) 3345, 1745 cm^{-1}; ^{1}H-NMR(CCl_4) δ 3.78 - 4.15(m, 2H), 3.65(S, 3H), 3.4(m, 2H), 2.45(m, 2H), 1.25 - 1.90 (m, 4H). (Calcd. for $C_8H_{14}O_4$: C, 55.17; H, 8.04. Found : C, 55.23; H, 8.27).

4a : Yield (75%); IR(thin film) 3350, 1750 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 4.22 (dq, 1H, J = 12 and 6 Hz). 3.89(m, 2H), 3.68(S, 3H), 2.55 (d, 2H, J = 6.8 Hz), 1.5 - 2.05(m, 4H), 1.16(d, 3H, J = 6.2 Hz). (Calcd. for $C_9H_{16}O_4$: C, 57.00; H, 8.50. Found : C, 56.00; H, 8.23).

4b : Yield (12%); IR(thin film 3365, 1755 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 4.15(dq, 1H, J = 8 and 6.1 Hz), 3.90(ddd, 1H, J = 11.8, 8.1 and 6.2 Hz), 3.71(s, 3H), 3.37(dq, 1H, J = 9.8 and 6.1 Hz), 2.61(m, 2H), 1.46 - 2.0(m, 4H), 1.10(d, 3H, J = 6.2 Hz). (Calcd. for $C_9H_{16}O_4$: C, 57.00; H, 8.50. Found : C, 57.12; H, 8.67).

5a : Yield (65%); IR(thin film) 3348, 1748 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 3.8 - 4.1(m, 2H), 3.62(S, 3H), 3.35(d, 2H, J = 6 Hz), 2.5(dq, 1H, J = 10.2 and 6 Hz), 1.45 - 1.95(m, 4H), 1.19(d, 3H, J = 7 Hz).(Calcd. for $C_9H_{16}O_4$: C, 57.40; H, 8.50. Found : C, 58.00; H, 8.76).

5b : Yield (10%); IR(thin film) 3345 and 1750 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 3.78 - 4.15(m, 2H), 3.70(S, 3H), 3.27(m, 2H), 2.58(dq, 1H, J = 10.2 and 6 Hz), 1.40 - 2.0(m, 4H), 1.12(d, 3H, J = 7 Hz). (Calcd. for $C_9H_{16}O_4$: C, 57.40; H, 8.50. Found : C, 58.20; H, 8.72).

6a : Yield (20%), IR(CH_2Cl_2) 3350 and 1745 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 3.85 - 4.15(m, 2H), 3.66(S, 3H), 3.35(d, 2H, J = 6 Hz), 2.52 (dq, 1H, J = 8.2 and 6.1 Hz), 1.38 - 1.98(m, 4H), 1.21(d, 3H,

J = 7 Hz). (Calcd. for $C_9H_{16}O_4$: C, 57.40; H, 8.50. Found : C, 56.95; H, 7.88).

6b : Yield (68%); IR(CH_2Cl_2) 3356 and 1750 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 3.8 - 4.12(m, 2H), 3.70(S, 3H), 3.30(m, 2H), 2.55(dq, 1H, J = 8.2 and 6.1 Hz), 1.4 - 1.97(m, 4H); 1.15(d, 3H, J = 7 Hz).

(Calcd. for $C_9H_{16}O_4$: C, 57.40; H, 8.50. Found : C, 57.78; H, 8.89).

7a : Yield (70%); IR(CH_2Cl_2) 3361 and 1748 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 4.18(dq, 1H, J = 11.6 and 6.2 Hz), 3.95(m, 1H), 3.60(s, 3H), 3.36(d, 2H, J = 6.5 Hz), 2.50(ddd, 1H, J = 11.8, 6.8 and 4.2 Hz), 1.95(ddd, 1H, J = 13, 11.8 and 10.9 Hz), (1.87(ddd, 1H, J = 13, 5.2 and 2.5 Hz), 1.15(d, 3H, J = 7.0 Hz). (Calcd. for $C_8H_{14}O_4$: C, 55.17; H, 8.04 Found : C, 55.45; H, 8.30).

7b : Yield (10%); IR(CH_2Cl_2) 3350 and 1750 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 4.12(dq, 1H, J = 11.5 and 6.2 Hz), 3.82(m, 1H), 3.68(s, 3H), 3.29(d, 2H, J = 6.6 Hz), 2.39(ddd, 1H, J = 11.8, 6.5 and 4.1 Hz), 1.92(ddd, 1H, J = 13.1, 12.0 and 11.8 Hz), 1.83(ddd, 1H, J = 13.1, 5.10 and 2.6 Hz), 1.21(d, 3H, J = 7 Hz). (Calcd. for $C_8H_{14}O_4$: C, 55.17; H, 8.04. Found : C, 56.23; H, 8.18).

8a : Yield (12%); IR(CH_2Cl_2) 3352 and 1750 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 3.85 - 4.00(m, 2H), 3.61(s, 3H), 3.27(d, 2H, J = 6.8 Hz), 2.46(m, 1H), 1.89(ddd, 1H, J = 13.0, 11.8 and 10.8 Hz), 1.82(ddd, 1H, J = 13.0, 5.0 and 2.4 Hz), 1.20(d, 3H, J = 7 Hz). (Calcd. for $C_8H_{14}O_4$: C, 55.17; H, 8.04 Found : C, 55.26, H, 8.21).

8b : Yield (67%); IR(CH_2Cl_2) 3367 and 1755 cm^{1}; ^{1}H-NMR($CDCl_3$) δ 3.80 - 4.11(m, 2H), 3.66(s, 3H), 3.31(d, 2H, J = 6.8 Hz), 2.38 (m, 1H), 2.03(ddd, 1H, J = 13.0, 11.8 and 10.8 Hz), 1.91(ddd, 1H, J = 13.0, 5.1 and 2.5 Hz), 1.17(d, 3H, J = 7 Hz). (Calcd. for $C_8H_{14}O_4$: C, 55.17; H, 8.04 Found : C, 55.29; H, 8.27).

Lactonisation of 7a :

The tetrahydrofuran 7a (0.9g, 5 mmol) was refluxed in dry benzene (20 ml) in presence of paratoluenesulphonic acid (= 10 mg) for 4-6 hours. The reaction mixture was washed successively with saturated solution of sodium bicarbonate and water and the organic layer dried over anhydrous magnesium sulphate. Removal of benzene yielded a gum which was chromatographed over silica gel (ether - petroleum ether)

to give the lactone-9 (60%).

$_1$H-NMR(CCl_4) δ 4.05(dq, 1H, J = 11.5 and 6.1 Hz), 3.87(m, 1H), 3.62 (dd, 1H, J = 13.9 and 6.1 Hz), 3.30(dd, 1H, J = 13.9 and 8.1 Hz), 2.25 (m, 1H), 1.95(m, 2H), 1.17(d, 3H, J = 7 Hz).

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