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STEREOSELECTIVE SYNTHESIS OF SUBSTITUTED TETRAHYDROFURANS - IDENTIFICATION AND ANALYSIS BY PROTON NMR AND MNDO, MM2 CALCULATIONS

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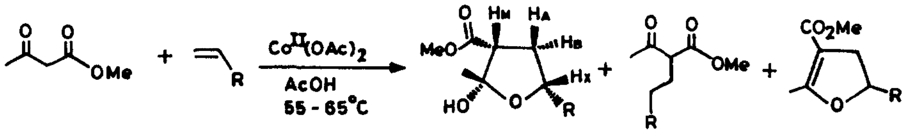
Abstract : Methyl acetoacetate and terminal olefins react in the presence of cobalt(II) acetate and oxygen to give 5-alkyl-2-hydroxy-2-methyl-3-methoxycarbonyl tetrahydrofurans in a highly stereoselective manner. Proton NMR, semiempirical MNDO and empirical MM2 methods are used to identify the particular diastereomer and the energetics of the different isomers are discussed.

Introduction

The presence of tetrahydrofuranoid structure in a wide variety of natural products[1] has attracted the attention of synthetic organic chemist in the last decade and this has eventually lead to the development of numerous novel methods[2] for their synthesis. The conformation and stereochemistry of tetrahydrofuranoid structure is very important because of its similarity to several natural products and biosystems like sugar bases In a recent communication[3] we have shown that the reaction between methylacetoacetate and terminal olefins in the presence of cobalt(II) acetate and oxygen yielded a single diastereomer out of the four possible diastereomers of tetrasubstituted tetrahydrofuran This paper describes our results which unambiguously proves the stereochemistry of this diastereomer by proton NMR spectroscopy and the energetics of the different diastereomers by semi-empirical (MNDO) and MM2 calculations.

Results and Discussion

The metal promoted oxidative free radical addition of 1,3-dicarbonyl compounds to a variety of olefins is now a very well established route to a new carbon-carbon bond formation and among the various metal complexes the manganese(III) acetate has been found to be most versatile metal complex[4] for mediating such a transformation. In recent years this reaction has been exploited with remarkable success for the synthesis of a large number of carbocyclic compounds. In spite of the efficient and versatile nature of this complex its inability to promote the reaction between 1,3-dicarbonyl compounds and unactivated terminal olefin is quite well known While trying to overcome this problem we discovered that cobalt(II) acetate can promote efficient reaction between acetoacetate and terminal olefins leading to the formation of tetrahydrofuran (2). However, we found that this reaction proceeds only in the



(1)	(2)	(3)	(4)
(a) R = $^{n}C_4H_9$	(a) 68%	(a) 8%	(a) 5%
(b) R = $^{n}C_6H_{13}$	(b) 60%	(b) —	(b) 8%
(c) R = $^{n}C_9H_{19}$	(c) 71%	(c) 5%	(c) 11%
(d) R = $^{n}C_{10}H_{21}$	(d) 70%	(d) —	(d) —
(e) R = $^{n}C_{11}H_{23}$	(e) 68%	(e) —	(e) 10%

Scheme

presence of dioxygen and any attempt to carry out the reaction under inert atmosphere proved futile. Thus, anhydrous cobalt(II) acetate (10 mmol), methyl acetoacetate (10 mmol) and olefin (20 mmol) are dissolved in glacial acetic acid (50 ml) and the resulting solution is heated to 55-65°C for 3-8 h The usual workup yielded compound (2) as single diastereomer. A careful analysis of the mother liquor revealed the presence of alkylated product (3) and the dihydrofuran (4) in minor amounts (10%) It was surprising to note that the other diastereomers of compound (2) were not present in the mother liquor A careful exclusion of oxygen from the solvent and the reagent did not give compound (2) instead the starting materials were recovered evenafter 24 h On the other hand, the compound (2) is obtained in good yields if the reaction mixture is purged with oxygen Bubbling the oxygen throughout the reaction mixture resulted in the formation of a complex mixture The relative stereochemistry of the compounds (2a), (2c) and (2d) were determined using the proton NMR spectra. The four ring protons form an ABMX spin system and the downfield signal centered at 4 1 ppm could easily be identified with that of H_X closer to ring oxygen. The H_M proton could be identified with the peak centered at 2 8 ppm whereas the H_A and H_B are centered at 2 0 and 1 8 ppm, respectively The complex coupling network is displayed in the absolute value COSY spectrum of Fig 1(a) The fine structure of the cross peaks (H_A, H_M) and (H_A, H_X) are very similar as those of (H_B, H_M) and (H_B, H_X), immediately revealing the relative stereochemistry of H_M and H_X Both couple to approximately the same extent to the proton H_A as well as to the proton H_B indicating that the protons

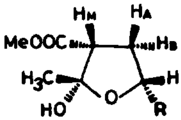
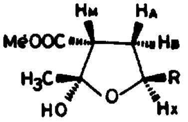
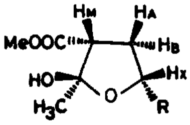
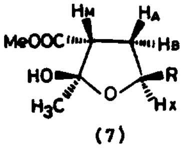
H_M and H_X are on the same side of the ring making similar dihedral angles with the protons H_A and H_B, respectively The experimental values of the coupling constants obtained from computer simulation (Table 1) confirm this conclusion.

Table 1 Proton NMR chemical shifts and coupling constants (ν in ppm, J in Hz)

	ν_A	ν_B	ν_M	ν_X	$^2J_{AB}$	$^3J_{AM}$	$^3J_{AX}$	$^3J_{BM}$	$^3J_{BX}$	$^4J_{MX}$
2a	2 02	1 86	2 83	4 13	-13 10	12 00	11.80	5.10	2 60	-0 10
2c	2.02	1.86	2.84	4 12	-14 00	12 20	11 40	5 20	2.50	-0.10
2d	2 00	1 85	2.82	4 11	-14 60	12.80	11 30	4.40	2.70	-0 10

To ascertain the relative stereochemistry of CH_3 at C-2 we measured the 1-D difference NOE spectrum of the compound (2a) which showed 5% NOE at H_M by irradiating the CH_3 at C-2 indicating the CH_3 likely to be close in space to H_M (on the same side of the ring). The 2D-NOE spectra Fig. 1(b) has cross peaks between CH_3 protons and H_X of medium intensity and between CH_3 and H_M of weak intensity giving the relative stereochemistry as the one in which CH_3, H_M and H_X are on the same side of the ring.

Table 2 Relative energies in kJ mol^{-1}

	 (2)	 (5)	 (6)	 (7)
MNDO				
R = CH_3	0 0674	0 0	12 223	12 223
= n-C_4H_9	0 6420	0 0		
MM2				
R = CH_3	0 0	3 5080	2 113	8 776
= n-C_4H_9	0 0	7 8177		

The relative energies calculated by MNDO and MM2 methods are given in Table 2 MNDO predicts that isomers 2 and 5 are energetically favoured over 6 and 7 whereas MM2 clearly indicates that 2 is the most favoured isomers. The discrepancy may be due to the intramolecular hydrogen bonding between OH and carbonyl of COOMe in isomer 2 MNDO does not include the effect of hydrogen bonding.[5] In MM2 the experimentally obtained

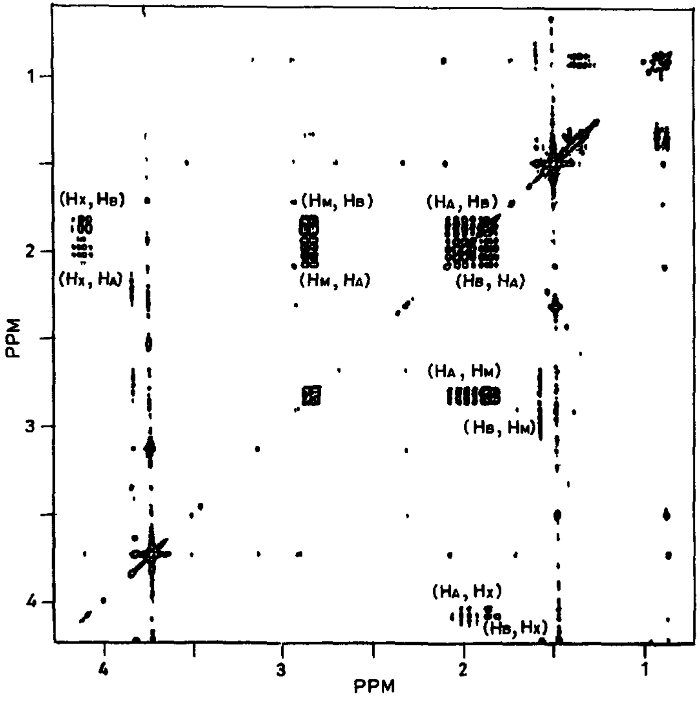


Fig 1(a) Absolute value COSY spectrum of 2(a)

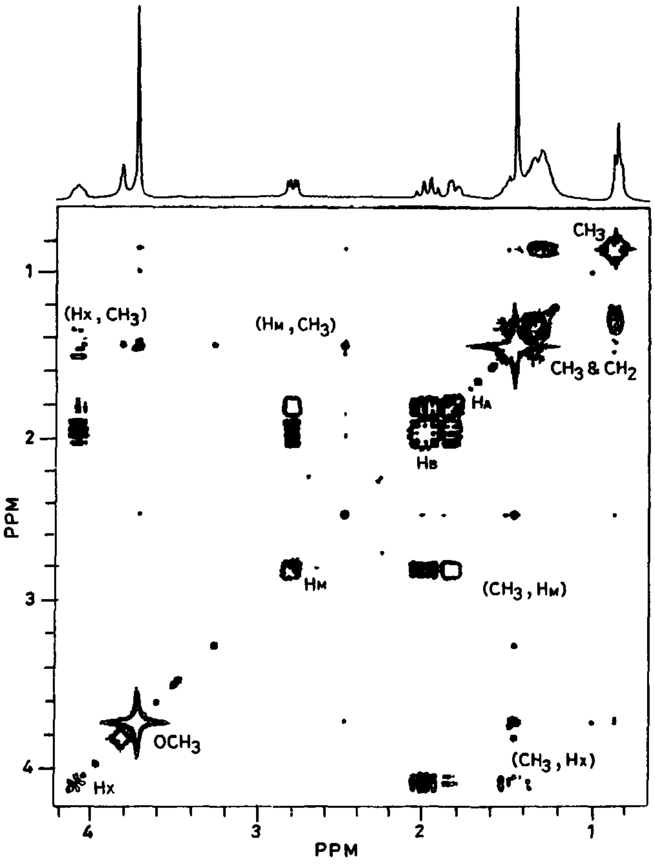
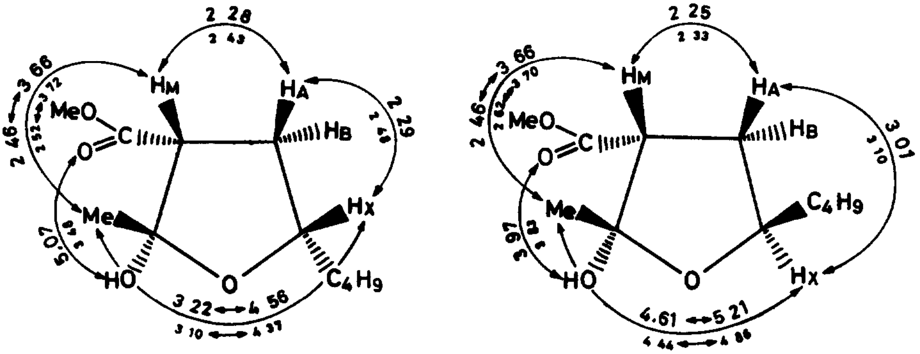


Fig 1(b) NOESY spectrum of 2(a)

empirical parameters accounts for hydrogen bonding indirectly This is clearly seen in the OH ··· O=C distance calculated by MNDO (5.10 Å) and MM2 (3.48 Å) (Fig. 2).



2(a)

Big size MNDO Distances
Small size MM2 Distances

5(a)

Fig 2 Relative distances in Å

MM2 performs better in predicting the relative energies and distances in this molecule as expected and is in agreement with the proton NMR results. In structure 2a the H_X and the CH_3 proton distance (3 10-4.37 MM2/3.22-4 56 MNDO) at C-2 fits well with the observed NOESY cross peak (CH_3, H_X) as compared to structure 5a (4.44-4.86 MM2/4.61-5 21 MNDO) Thus, the energetics and proton NMR spectra clearly indicate 2 as the most favoured isomer

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Experimental

General Methods : IR spectra were obtained in CH_2Cl_2. All proton NMR spectra were recorded in $CDCl_3$ using TMS as the internal standard. The 1-D spectra recorded on a Bruker WP-80 were used for computer simulation. Absolute value COSY and 1-D difference NOE spectra were recorded at 270 MHz on a Bruker WH-270 instrument. The NOESY spectrum was recorded on a GE-300 spectrometer The computer simulations were done using LAOCN-5 iterative program[6] The MNDO and MM2 calculations were done using the standard programs[7,8] All computations were carried out using HP-900/800 computer systems

Cobalt(II) acetate was dried at 105°C for 3-4 h prior to use The olefins were obtained commercially and used without purification The column chromatography was performed on silica gel using petroleum ether-

-diethyl ether as the eluant.

General procedure for cobalt(II) acetate mediated reaction of olefins with methyl acetoacetate : Anhydrous cobalt(II) acetate (10 mmol), methyl acetoacetate (10 mmol) and 1-hexene (20 mmol) are dissolved in glacial acetic acid (60 ml) and the resulting solution is heated to 65°C for 3 to 6 h. The reaction mixture is poured into diethyl ether (100 ml) and the ether layer is washed successively with saturated solution of sodium bicarbonate, water and dried over anhydrous sodium sulphate. Removal of ether gave a viscous liquid which on addition of n-hexane and cooling (0°C) yielded compound (2) as a fluffy solid The mother liquor was chromatographed over silica gel (ether-petroleum ether) to yield compounds 3 and 4 Compounds 2,3 and 4 had the following IR, NMR and mass spectra

2a. : IR (CH_2Cl_2) 3349, 1730 cm^{-1}; ^{1}H-NMR 4 07 (m, 1H), 3 75 (s, 3H), 2 81 (dd, 1H), J = 12 and 5.1 Hz), 1.98 (ddd, 1H, J = 13 1, 12 0, 11 8 Hz), 1.83 (ddd, 1H, J = 13.1, 5 10 and 2 6 Hz), 1 25-1 60 (m, 6H), 1.45 (s, 3H), 0 86 (t, 3H, J = 7 Hz); (found M^+ : 200.2775, Calc for $C_{11}H_{20}O_3$: 200 2780) Anal Calc. for $C_{11}H_{20}O_3$: C, 66; H, 10; found . C, 65 87, H, 9 89

2b : IR (CH_2Cl_2) 3351, 1728 cm^{-1}; ^{1}H-NMR 4 10 (m, 1H), 3 78 (s, 3H), 2 83 (dd, 1H, J = 12.1 and 5 1 Hz), 2 02 (ddd, 1H, J = 13, 12 1 and 11 8 Hz), 1 86 (ddd, 1H, J = 13.1, 5.1 and 2 6 Hz), 1 2-1.58 (m, 8H), 1 43 (s, 3H), 0 90 (t, 3H, J = 7 Hz), (found M^+: 228.3317, Calc for $C_{13}H_{24}O_3$. 228 3308) Anal Calc for $C_{13}H_{24}O_3$. C, 68.42; H, 10 52; found C, 68 55, H, 10.68)

2c : IR (CH_2Cl_2) 3342, 1731 cm^{-1}; ^{1}H-NMR 4 17 (m, 1H), 3 81 (s, 3H), 2 85 (dd, 1H, J = 12 Hz and 5 1 Hz), 1 95 (ddd, 1H, J = 13 1, 12.0 and 11 8 Hz), 1.86 (ddd, 1H, J = 13 1. 5 10 and 2 6 Hz), 1.31-1 67 (m, 16H), 1 42 (s, 3H), 0 91 (t, 3H, J = 7 Hz); (found M^{+}· 270 4122; Calc. for $C_{16}H_{30}O_3$. 270 4112) Anal Calc for $C_{16}H_{30}O_3$ C, 71 11, H, 11 11, found · C, 71.52, H, 11.37

2d : IR (CH_2Cl_2) 3339, 1730 cm^{-1}, ^{1}H-NMR 4.11 (m, 1H), 3 77 (s, 3H), 2 81 (dd, 1H, J = 12 Hz and 5 1 Hz), 1.95 (ddd, 1H, J = 13.0, 12 0 and 11 8 Hz), 1 90 (ddd, 1H, J = 13.0, 5.10 and 2 6 Hz), 1 27-1 71 (m, 18H), 1 37 (s, 3H), 0 87 (t, 3H, J = 7 0 Hz); (found M^+: 284 4371; Calc for $C_{17}H_{32}O_3$ 284 4380) Anal Calc for $C_{17}H_{32}O_3$ C, 71 83; H, 11.26; found : C, 71 72; H, 11 14

2e : IR (thin film 3345, 1732 cm^{-1}; ^{1}H-NMR 4.18 (m, 1H), 3.78 (s, 3H), 2.79 (dd, 1H, J = 11.9 Hz and 5.0 Hz), 1.95 (ddd, 1H, J = 13 1, 12.0 and 11.8 Hz), 1.85 (ddd, 1H, J = 13.0, 5.10 and 2.5 Hz), 1.2-1.69 (m, 20H), 1 35 (s, 3H), 0.85 (t, 3H, J = 7.0 Hz), (Found : C, 72.55; H, 11 51; Calc for $C_{18}H_{34}O_3$: C, 72.48, H, 11.40).

3a : IR (CH_2Cl_2) 1735, 1730 cm^{-1}, ^{1}H-NMR 3 76 (s, 3H), 3.45 (t, 1H, J = 6.8 Hz), 2.24 (s, 3H), 1.18-1 56 (m, 10H), 0.89 (t, 3H, J = 7.0 Hz) (Found : C, 66.12; H, 10.09, Calc. for $C_{11}H_{20}O_3$: C, 66.0; H, 10 0)

4a : IR (CH_2Cl_2) 1701, 1665 cm^{-1}; ^{1}H-NMR 4.62 (m, 1H), 3.75 (s, 3H), 2 85 (m, 1H), 2.61 (m, 1H), 2 15 (s, 3H), 1 17-1 86 (m, 6H), 0 88 (t, 3H, J = 6.9 Hz) (Found : C, 66 57, H, 9.13, Calc for $C_{11}H_{18}O_3$· C, 66.66; H, 9.09)

4e : IR (CH_2Cl_2) 1700, 1668 cm^{-1}; ^{1}H-NMR 4.59 (m, 1H), 3.77 (s, 3H), 2 81 (m, 1H), 2.57 (m, 1H), 2 19 (s, 3H), 1 13-1.79 (m, 20H), 0 91 (t, 3H, J = 7.0 Hz).

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