## β- and α-LITHIATION OF METHYL β-METHOXYACRYLATE: EFFICIENT SYNTHESIS OF α, γ-SUBSTITUTED METHYL TETRONATES - STRUCTURE OF ASPERTETRONINS AND GREGATINS <sup>1</sup>)

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<u>Abstract</u>: Methyl B-methoxyacrylate (<u>1</u>) can be lithiated successively in B- and a-positions. Reaction wit<sup>1</sup> two electrophiles (at first a carbonyl compound) leads to a,  $\gamma$ -substituted methyl tetronates in a two step synthesis. Application of this method to the synthesis of methyl tetronate whose structure was assigned as that of gregatin B indicates that the gregatins and aspertetroning have the isomeric structures <u>17</u>.

Under kinetic control the lithiation of methyl  $\beta$ -methoxyacrylate ( $\underline{1}$ ) leads exclusively to the  $\beta$ -lithiated species  $\underline{1}\underline{\beta}$ ; however, under thermodynamic control a mixture ( $\sim 1$  1) of the  $\alpha$ - and  $\beta$ -lithiated species is generated  $^{3,4,5)}$  (Scheme 1). Therefore it is reasonable to assume that the  $\alpha$ - and  $\beta$ -CH-acidities in  $\underline{1}$  are similar. However, the kinetically selective lithiation enables a regiospecific reaction with several electrophiles and - because of the electrophilicity of the carboxylate group in  $\underline{1}\underline{\beta}$  - also with electrophilic-nucleophilic compounds. Therefore  $\underline{1}$  can be regarded as a functionalized electrophilic-bisnucleophilic C<sub>3</sub>-building block (see synthon  $\underline{2}$ ) for instance for short syntheses of cyclopentenones, butenolides, and tetronates  $^{6}$ .

Scheme 1



Using carbonyl compounds as the electrophilic-nucleophilic components results in the formation of  $\gamma$ -substituted tetronates (Scheme 2, Table). Benzaldehyde gives  $\gamma$ -phenyl derivative  $\underline{3}$ , methyl 0-methylmandelate leads directly to an interesting intermediate  $\underline{5}$  for a possible synthesis of fadyenolide <sup>7</sup>), cyclohexanone results in the  $\gamma, \gamma'$ -pentamethylene tetronate  $\underline{6}$ , and (E)-3-penten-2-one gives the  $\gamma$ -methyl- $\gamma'$ -propenyl derivative  $\underline{7}$  No Michael-adduct (cyclopentenone derivative) was isolated with this  $\alpha,\beta$ -unsaturated ketone under the applied reaction conditions. With diethyl disulfide as electrophile the (Z)-ketene-0,S-acetal derivative  $\underline{4}$  was obtained stereospecifically.

<u>1</u>B



<u>17</u>

Table:  $\gamma$ - and  $\alpha$ ,  $\gamma$ -Substituted Tetronic Acid Derivatives

Prod. <sup>a</sup>	Rea T <sub>1</sub> /	act /t1	10n (	Conditions <sup>b</sup> /t <sub>2</sub> [ <sup>O</sup> C/min]	Yıeld <sup>C</sup> [%]	M.p. [ <sup>0</sup> C]	<sup>1</sup> H-NMR-Data <sup>d</sup>
3	-90	60	-40	25 <sup>e</sup>	65	95-97	7.40(mc,5H,Ph), 5.63(s,1H,-CHO-), 5.18(s,1H,-CH=);
							3.82(s,3H,OMe)
<b>4</b>	-90	10	+20	55 <sup>e</sup>	65	011	5.10(s,1H,-CH=), 3.80, 3.67(2s,6H,2 OMe); 2 88(q,
							2H,-SCH <sub>2</sub> ); 1.28(t,3H,CH <sub>2</sub> -C <u>H</u> <sub>3</sub> ).
<u>5</u>	-90	60	-	-	62	162-163	7.45(mc,5H,Ph), 5.20(s,1H,-CH=), 4 50(s,1H,Ph-C <u>H</u> ),
					1		4.00, 3.25, 3.23(3s,9H,3 OMe).
<u>6</u>	-90	60	-	-	58	103-104	5.00(s,1H,-CH=); 3.90(s,3H,0Me), 1.70(mc,10H,5CH <sub>2</sub> )
Σ	-90	60	-	-	63	011 *	5.93(dq,1H,CH <sub>3</sub> -CH=), 5.58(d,1H,-CH <sub>3</sub> -CH=CH-), 5.03
							(s,1H,-CH=), 3.93(s,3H,OMe), 1 73(d,3H,CH <sub>3</sub> -CH=),
							1.53(s,3H,CH <sub>3</sub> )
9	-80	10			qu	103-104	3.90(s,3H,OMe), 1.70(mc,10H,5CH <sub>2</sub> ).
10	-80	40	-50	30	79	101-102	4.44(s,3H,OMe), 2.38(s,3H,SMe), 1.70(mc,10H,5CH <sub>2</sub> )
11	-80	40	-50	30	6 <sup>g</sup>		8 28,7.70(2mc,5H,Ph), 4.08(s,3H,OMe), 1.78(mc,10H,
							5CH <sub>2</sub> ).
<u>12</u>	-80	40	-50	30	62	011 <sup>f</sup>	4.75(m,1H,Et-CH); 4 13(s,3H,OMe); 3.70(d,1H,OH) 1.70
							(mc,12H,6CH <sub>2</sub> ), 0 98(t,3H,CH <sub>2</sub> -CH <sub>2</sub> )
<u>13a</u>	-80	40	-50	30	59	54-56	4.18(s,3H,OMe), 2.65(s,3H,COMe), 1.70(mc,10H,5CH <sub>2</sub> ).
13b	-80	40	-50	30	72	145-147	8.03, 7.68(2mc,5H,Ph), 3.95(s,3H,OMe), 1.84(mc,10H,
							5CH <sub>2</sub> ).
14	-80	40	-50	30	32	011 f	7.08(dq,1H,CH <sub>3</sub> -C <u>H</u> =), 6.78(d,1H,CH <sub>3</sub> -CH=C <u>H</u> -), 4.08(s,
							3H,OMe); 2.00(d,3H,CH <sub>3</sub> -CH=), 1.70(mc,10H,5CH <sub>2</sub> )
15	-90	60			31	011 f	6.70-5.85(m.3H.Ft-CH=CH.).5.70(d.1H.Ft-CH=CH-CH=
Ξ£		•••			••	••••	CH-): 5.05(s.1HCH=). 3.94(s.3H.OMe): 2.16(dq.2H.
							$CH_{a}-CH_{a}$ ), 1.58(s.3H_Me), 1.03(t.3H_Me)
16a	-80	40	-50	30	30	011 f	$6.36(dd_1H_Ft-CH=CH=CH_1=15Hz, 10Hz), 5.00(dd_1H_Ft)$
===			-				Et-CH=-CH-, $J=15$ Hz, 10 Hz): 5.87(dt.1H.Ft-CH=: J=
							15 Hz, $7Hz$ ), 5.54(d, 1H.Ft-CH=CH=CH=CH=, J=15 Hz).
							4 14(s.3H.OMe), 2.58(s.3H.COMe), 2 12(dt.2H.CHCH.)
							1.58(s,3H,Me); 1 01(t,3H,Me).
Gregat	in R	h.					6.24(dd 1H, J=15 Hz, 10 Hz) 6.0-5.7(m 2H) 5.54(d
							1H. J=15 Hz). 3.83(s.3H.OMe). 2.6(s.3H.COCH_). 2.06
							(m.2H.CHCH_), 1 53(s.3H.Me), 0.96(t.3H.Me)

<sup>a</sup> Starting materials<sup>•</sup> see Schemes 2 and 3. - <sup>b</sup> Solvent. THF, base LDA, generation of  $\underline{2}$ : -90°C, 2 min,  $\underline{8}$ . -80°C, 30 min;  $T_1, t_1, T_2, t_2$ : reaction with electrophile. - <sup>c</sup> Isolated yields, all products gave correct elemental analyses. - <sup>d</sup> 80 MHz, CDCl<sub>3</sub>, internal TMS,  $\delta$ -values, multiplicities and assignments in parentheses. - <sup>e</sup> Time for the change  $T_1$  to  $T_2$  - <sup>f</sup> Chromatography on silica gel; eluent  $\underline{7}$ , CH<sub>2</sub>Cl<sub>2</sub>/MeOH=50 1;  $\underline{12}$ ,  $\underline{14}$ ,  $\underline{15}$ ,  $\underline{16}$ : Et<sub>2</sub>O/petroleum-ether = 2·7 - <sup>g</sup> Not optimized - <sup>h</sup> See ref. 10. Direct lithiation of tetronates 5-7 (similarly ketal 4)<sup>8)</sup> was performed under standard conditions. The quantitative deuteration of 6 (to give 9) indicates that  $\alpha$ -functionalisation should be possible via the reaction of the  $\alpha$ -lithiated species 8 with electrophiles. In this way the following  $\alpha$ -substituted derivatives of 6 were obtained: with dimethyl disulfide the methyl mercapto derivative 10, with dibenzoylperoxide the benzoyloxy derivative 11, with propionaldehyde the ( $\alpha$ '-hydroxy)propyl derivative 12, with acetic anhydride the acetyl derivative 13a, with methyl benzoate the benzoyl derivative 13b, and with methylcrotonate the crotonyl derivative 14.

This efficient method should be applicable to the synthesis of several naturally occurring tetronates <sup>9)</sup>. Our interest was devoted to the antibiotically active aspertetronins and gregatins <sup>10-12</sup>), for which structures  $\underline{162} - \underline{4}$  were proposed <sup>11)</sup> (Scheme 3). Reaction of  $\underline{2}$  with (E,E)-3 5-octadien-2-one gave the expected tetronate  $\underline{15}$ .  $\alpha$ -Lithiation of  $\underline{15}$  with LDA and reaction with acetic anhydride led to tetronate  $\underline{162}$  in a overall two step reaction. However, the analytical and physicochemical data (<sup>1</sup>H-NMR, see Table) <sup>13</sup>) demonstrated that gregatin B is isomeric to  $\underline{162}$ . The degradative and partial synthetic evidence <sup>11</sup>), which led to the acceptance of the structures  $\underline{16}$  <sup>10-12</sup>) is also consistent with isomeric structures  $\underline{17}$  <sup>14</sup>)

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