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STEREOSELECTIVE PARTIAL HYDROGENATION OF THE TRIPLE BOND IN METHYL 2-ETHYL-6,6-DIMETHYLHEPT-2-EN-4-YNOATE: A COMPARISON OF LINDLAR AND MONTMORILLONITE CATALYSTS

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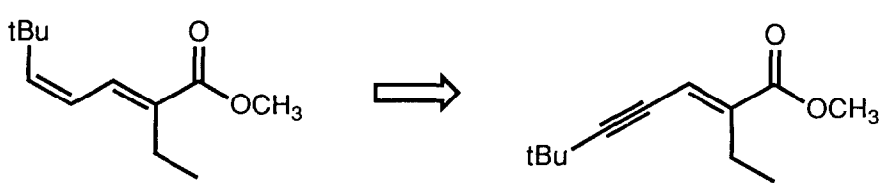
Abstract: Lindlar catalyst proved to be superior to the montmorillonite-Pd^{II} catalyst in the stereoselective partial hydrogenation of a *tert*-butyl substituted, conjugated enynoate system inasmuch as a better yield of the product with the double bond was obtained and less overhydrogenation occurred

Introduction

During our work on 1,2 3,4-diepoxides [1,2] we had to prepare methyl (2*E*,4*Z*)-2-ethyl-6,6-dimethylhepta-2,4-dienoate (**1**) Eventually, the most difficult step was the stereoselective hydrogenation of the triple bond in methyl (2*E*)-2-ethyl-6,6-dimethylhept-2-en-4-ynoate (**2**) to a (*Z*)-double bond



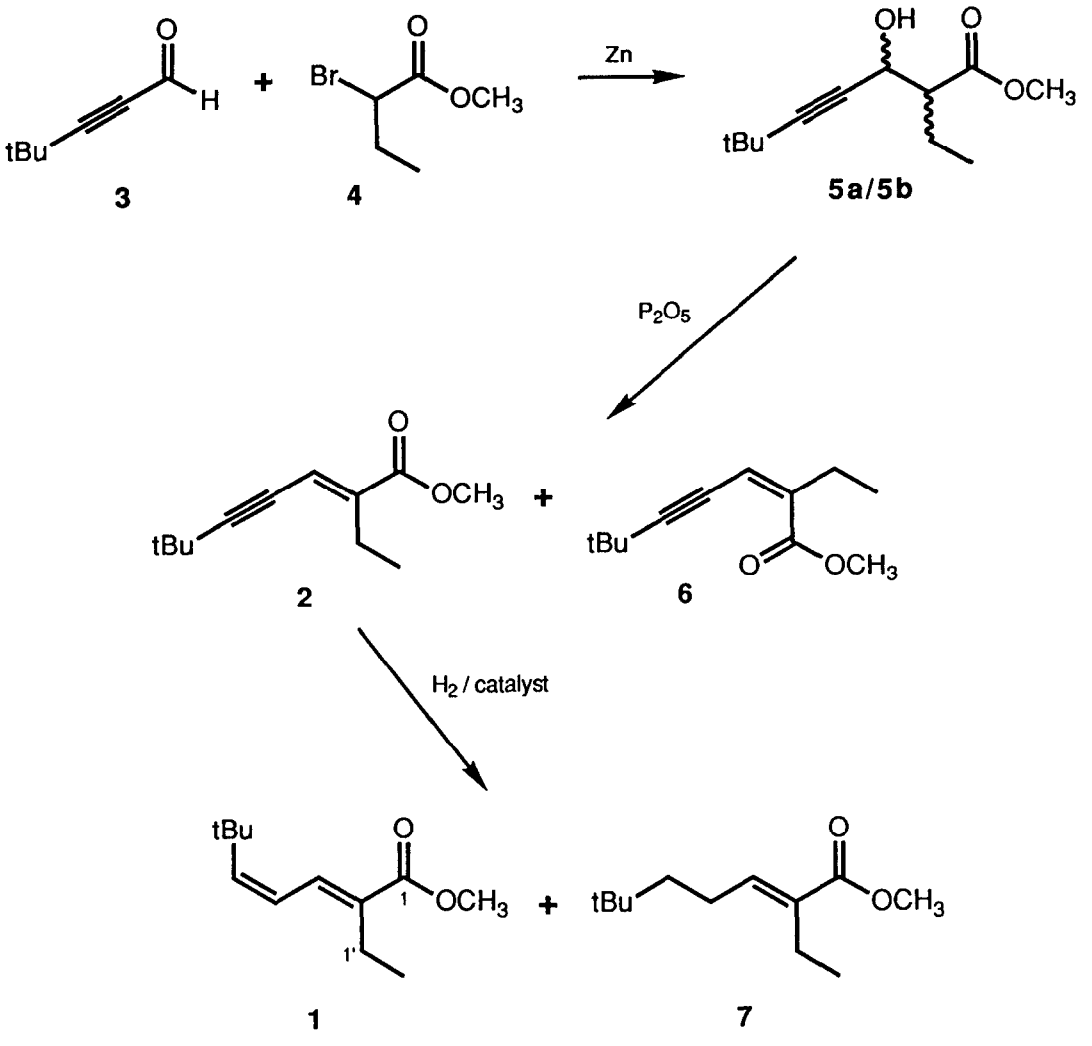
1 **2**

Recently, Choudary et al. proposed a montmorillonite based catalyst for the hydrogenation of triple bonds to (Z)-double bonds, which was claimed to be superior to the classical Lindlar catalyst [3] The authors did, however, only include few examples where the triple bond was already conjugated to an additional double bond; in our case, the conjugated system was even more extended and contained an ester carbonyl group We therefore compared the two hydrogenation catalysts in a variety of solvents and under various conditions

Syntheses and hydrogenations

4,4-Dimethylpentynal (**3**), prepared according to Hauptmann and Mader [4] from *tert*-butylacetylene [5] and ethyl formate, was condensed with methyl 2-bromobutanoate (**4**) in a Reformatsky reaction to give a mixture of the two diastereoisomeric methyl 2-ethyl-3-hydroxy-6,6-dimethylhept-4-ynoates (**5a/5b**) Dehydration of this mixture lead to methyl (2*E*)-2-ethyl-6,6-dimethylhept-2-en-4-ynoate (**2**), which was then hydrogenated selectively with either Lindlar or with montmorillonite catalyst to the desired methyl (2*E*, 4*Z*)-2-ethyl-6,6-dimethylhepta-2,4-dienoate (**1**)

During the hydrogenation experiments it became evident that the diene **1** formed in the reaction underwent hydrogenation with a similar rate as the starting material, the enyne **2** The hydrogen uptake curve is smooth and does not show a bend This phenomenon has already been observed with other conjugated enyne systems [6-8] In addition, the triple bond in **2** carries a *tert*-butyl group The adsorption at the catalyst seems to be sterically more hindered with **2** than with **1** This would explain why overhydrogenation was no problem when Nadig et al [9] and Crombie et al [10] reduced similar enynoates without *tert*-butyl substituents with Lindlar catalyst. In all our experiments a substantial amount of the overhydrogenation product **7** was obtained The product ratio was strongly dependent on the catalyst and solvent used



Montmorillonite-fixed catalyst

The montmorillonite-fixed catalyst was prepared according to the procedure of Choudary et al [3] However, the addition of bipyridine to the chloromontmorillonite needed a higher temperature and a longer time than stated in the reference given The catalyst was tested with ethyl 1-phenyl-propynoate the yield published by Choudary et al was obtained

Methyl (2*E*)-2-ethyl-6,6-dimethylhept-2-en-4-ynoate (**2**) was hydrogenated in a large number of different solvents and under a variety of conditions (see Table 1). Overhydrogenation of the triple bond to the single bond leading to the formation of methyl (2*E*)-2-ethyl-6,6-dimethylhept-2-enoate (**7**) could not be avoided in any of these experiments Cyclohexane and acetic acid proved to be unsuitable· hardly any product was formed. The best solvents were tetrahydrofuran and hexane, as well as mixtures of either tetrahydrofuran or ethyl acetate with hexane The catalyst clearly is more active in tetrahydrofuran than in ethanol, a fact that was already pointed out by Choudary et al [3].

Lindlar catalyst

Commercially available Lindlar catalyst (Fluka) proved to be too active the reduction of the triple bond proceeded right to the single bond. Therefore, quinoline was added in various amounts to poison the catalyst Again, solvent and conditions of hydrogenation were optimized (see Table 2)

Conclusions

From a comparison of the data compiled in Tables 1 and 2 it is evident, that hydrogenations with the montmorillonite catalyst took substantially longer and yielded more of the overhydrogenation product **7** than those with poisoned Lindlar catalyst For our enyne system conjugated to an ester carbonyl group as in **2** the Lindlar catalyst proved to be clearly superior to the montmorillonite catalyst The stereospecificity was excellent with both catalysts; only traces of the (2*E*,4*E*)-isomer of **1** were observed in some of the experiments

Table 1. Results of the hydrogenations of **2** with montmorillonite catalyst The product ratios were determined with ^{1}H-NMR spectroscopy.

Solvent	Amount of catalyst [g]	Time of hydrogenation [min]	Product ratio [%]		
			Starting material **2** recovered	Product **1**	Product of overhydrogenation **7**
MeOH	0 06	95	71 [a]	22	7
EtOH	0 12	227	42	34	24
Et_2O	0 12	101	28	36	36
iPr_2O	0 06	91	76 [a]	24	
Pentane	0 06	227	31	37	32
Hexane	0 06	92	36	42	22
Heptane	0 06	58	41	24	35
Cyclohexane	0 06	98	100 [a]		
HOAc	0 06	81	96 [a]	4	
EtOAc	0 06	91	81 [a]	19	
Dioxane	0 12	147	62	18	20
DMF	0 06	93	73 [a]	22	5
THF	0 05	90	14	57	29
THF hexane 10 1	0 12	175	48 [a]	37	15
THF hexane 3 1	0 12	370	37	35	28
THF hexane 1 1	0 12	283	55	30	15
THF hexane 1 3	0 12	370	52	36	12
THF hexane 1 5	0 12	137	30	43	27
THF hexane 1 10	0 12	65	26	56	18
EtOAc hexane 3 1	0 12	225	34	34	32
EtOAc hexane 1 1	0 04	112	40	46	14
EtOAc hexane 1 3	0 12	109	43	36	21

[a] Hydrogen uptake in these experiment was less than the calculated amount

Table 2 Results of the hydrogenations of **2** with Lindlar catalyst The product ratios were determined with ^{1}H-NMR spectroscopy

	Amount of starting material **2** [g]	Solvent volume [ml]	Temperature [°C]	Amount of catalyst [g]	Amount of quinoline [g]	Time of hydrogenation [min]	Product ratio [%]		
							Starting material **2** recovered	Product **1**	Product of overhydrogenation **7**
MeOH	0 20	10	23	0 17	0	2	0	36	64
EtOAc	0 25	8	23	0 15	0 05	36	21	69	10
EtOAc hexane 1 1	0 12	5	23	0 12	0 08	50	10	74	16
EtOAc heptane 1 1	0 6	6	-50	1 5	0 20	420	2	81	17

EXPERIMENTAL

General remarks – Samples for elemental analyses and spectra were dried – their vapor pressure permitting – for at least 1 h at room temperature under high vacuum Elemental analyses were carried out in the microanalytical laboratory of our institute (E Thommen) NMR spectra were measured on a Varian VXR-400 (400 MHz for ^{1}H and 101 MHz for ^{13}C) in our institute (K Ulrich, M Boutellier) Mass spectra were run on a Hitachi-Perkin-Elmer RMU 7 (Dr J P Stadelmann, Institut fur Physikalische Chemie der Universiat Basel) or on a VG 70-250 in our institute (Dr H Nadig) GC-MS analyses were carried out with a Hewlett-Packard GC 5790A equipped with the mass selective detector 5970A

Synthesis of Methyl (2RS,3RS)- and (2RS,3SR)-2-ethyl-3-hydroxy-6,6-dimethylhept-4-ynoates (**5a/5b**, the relative configurations were not assigned) – Zinc (6 00 g, 91 8 mmol) was activated for 5 min with 1N HCl, then washed successively with water, acetone and benzene and finally suspended in 30 ml of dry benzene together with methyl 2-bromobutanoate (4, 14 48 g, 80 0 mmol) Then 4,4-dimethylpent-2-ynal (3, 8 62 g, 78 3 mmol) [4] was added in drops The reaction started after the addition of *ca* 1/3 of the reagent and when the mixture was heated to 80°C When the addition was complete, the mixture was kept under reflux for 2 h and then allowed to cool to room temperature After addition of 50 ml of 2N H_2SO_4 the phases were separated and the organic layer was washed successively twice with 100 ml of 10% $NaHCO_3$ solution and twice with 100 ml of water Drying over Na_2SO_4 and evaporation of the solvent gave 16 14 g (97 2%) of crude product, which contained **5a** and **5b** as the two major components in a ratio of 3 2 Part of this product was purified by distillation bp 87-89°C/0 32 mbar

For the determination of the spectroscopic data the purified product (0 5 g) was separated into the two diastereoisomers **5a** and **5b** on a silica gel column (100 g, petrol ether with increasing amounts of CH_2Cl_2 and acetone)

Data of 5a Bp 87-89°C/0 32 mbar – IR (Film) 3460 (OH), 2970, 2240, 1735 (C=O), 1460, 1435, 1365, 1265, 1205, 1175, 1055, 1030, 1000, 845, 800, 750 – ^{1}H-NMR (400 MHz, $CDCl_3$) 4 51 (d, J=5 5 Hz, 1H, H-C(3)), 3 73 (s, 3H, OCH_3), 2 78 - 2 82 (s, br , J=7 5 Hz, 1H, OH), 2 54 (dxt, J=8 4 and 5 3 Hz, 1H, H-C(2)), 1 60 - 1 82 (m, 2H, H-C(1')), 1 20 (s, 9H, tBu), 0 97 (t, J=7 5 Hz, 3H, H-C(2')) – ^{13}C-NMR (101 MHz, $CDCl_3$) 174 1 (s, C(1)), 94 7 (s, C(5)), 77 1 (s, C(4)), 63 1 (d, C(4)), 53 9 (d, C(2)), 51 6 (q, OCH_3), 30 8 (q, $(CH_3)_3C(6)$), 27 2 (s, C(6)), 21 0 (t, C(1')), 12 0 (q, C(2')) – MS (CI, NH_3) 230 (M^+ + 18, NH_4), 212

(M^+), 195 (M^+ - 17, OH), 183 (M^+ - 29, C_2H_5), 167 (M^+ - 45, - OCH_3 - CH_3, + H), 153 (M^+ - 59, $COOCH_3$), 135 (M^+ - 77, $COOCH_3$, H_2O), 111 (M^+ - 101, $C_5H_9O_2$) – $C_{12}H_{20}O_3$ (212 29), calc C 67 89, H 9 50%, found C 67 59, H 9 75%

Data of 5b Mp 59-61°C – IR (KBr) 3470 (OH), 2970, 2240, 1735 (C=O), 1460, 1435, 1365, 1270, 1225, 1200, 1175, 1065, 1040, 970, 910, 800, 660 – ^{1}H-NMR (400 MHz, $CDCl_3$) 4 47 (d, J=7 3 Hz, 1H, H-C(3)), 3 73 (s, 3H, OCH_3), 2 82 - 2 78 (s, br , 1H, OH), 2 56 (dxt, J=4 5 and 7 0 Hz, 1H, H-C(2)), 1 60 - 1 82 (m, 2H, H-C(1')), 1 21 (s, 9H, tBu), 0 94 (t, J=7 48 Hz, 3H, H-C(2')) – ^{13}C-NMR (101 MHz, $CDCl_3$) 174 9 (s, C(1)), 94 8 (s, C(5)), 77 6 (s, C(4)), 63 1 (d, C(4)), 54 2 (d, C(2)), 51 6 (q, OCH_3), 30 8 (q, $(CH_3)_3C(6)$), 27 7 (s, C(6)), 21 0 (t, C(1')), 12 0 (q, C(2')) – MS (CI, NH_3) 230 (M^+ + 18, NH_4), 213 (M^+ + 1, H), 212 (M^+), 195 (M^+ - 17, OH), 167 (M^+ - 45, - OCH_3, - CH_3, + H), 153 (M^+ - 59, $COOCH_3$), 135 (M^+ - 77, $COOCH_3$, H_2O), 111 (M^+ - 101, $C_5H_9O_2$), 95 (C_7H_{11}), 81 (C_6H_9), 55 (C_4H_7)

Synthesis of methyl (2E)-2-ethyl-6,6-dimethylhept-2-en-4-ynoate (**2**) *and methyl (2Z)-2-ethyl-6,6-dimethylhept-2-en-4-ynoate* (**6**) – A mixture of **5a** and **5b** (4 8 g, 23 mmol) was suspended together with P_2O_5 on an inert carrier (Sicapent Merck Nr 543, 8 5 g, 45 mmol) in 50 ml of toluene and refluxed for 1 h The reaction mixture was then filtered, washed with water and dried over Na_2SO_4 Evaporation of the solvent *in vacuo* gave 4 82 g of crude product, which consisted of two components in a ratio of 8 1 according to GC This product was purified by high vacuum distillation (bp 90-92 °C/0 92 mbar) followed by column chromatography (100 g of silica gel, petrol ether/CH_2Cl_2) to give 630 mg of **2** and 80 mg of **6**

Data of 2 Bp 90-92 °C/0 92 mbar – IR (Film) 2970, 2870, 2200, 1715 (C=O), 1605 (C=C), 1435, 1365, 1310, 1240, 1135, 1045, 995, 920, 805, 765 – ^{1}H-NMR (400 MHz, $CDCl_3$) 6 59 (s, 1H, H-C(3)), 3 75 (s, 3H, OCH_3), 2 49 (q, J=7 5 Hz, 2H, H-C(1')), 1 28 (s, 9H, tBu), 1 06 (t, J=7 2 Hz, 3 H, H-C(2')) – ^{13}C-NMR (101 MHz, $CDCl_3$) 167 5 (s, C(1)), 143 4 (s, C(2)), 120 1 (d, C(3)), 111 4 (s, C(5)), 75 8 (s, C(4)), 51 8 (q, OCH_3), 30 7 (q, $(CH_3)_3C(6)$), 28 5 (s, C(6)), 22 6 (t, C(1')), 13 0 (q, C(2')) – MS (EI) 194 (M^+), 179 (M^+ - 15, CH_3), 163 (M^+ - 31, OCH_3), 151 (M^+ - 43, C_3H_7), 135 (M^+ - 59, $COOCH_3$), 123 (M^+ - 71, - C_4H_9, - CH_3, +H), 91 (M^+ - 103, C_4H_9, CH_3, OCH_3), 77 (M^+ - 117), 59 ($COOCH_3$), 57 (C_4H_9) – $C_{12}H_{18}O_2$ (194 27), calc C 74 19, H 9 34%, found C 74 22, H 9 57%

Data of 6 Bp 90-92 °C/0 92 mbar – IR (Film) 2975, 2880, 2210, 1715 (C=O), 1615 (C=C), 1435, 1365, 1315, 1270, 1220, 1140, 1050, 990, 930, 875, 795 – ^{1}H-NMR (400 MHz, $CDCl_3$) 5 91 (t, J=1 4 Hz, 1H, H-C(3)), 3 79 (s, 3H, OCH_3), 2 38 (q, J=7 7 Hz, 2H, H-C(1')), 1 27 (s, 9H, tBu), 1 06 (t, J=7 4 Hz, 3H, H-C(2')) – ^{13}C-NMR (101 MHz, $CDCl_3$) 167 3 (s, C(1)), 142 8 (s, C(2)), 116 4 (d, C(3)), 107 3 (s, C(5)), 76 7

(s, C(4)), 51 3 (q, OCH_3), 30 7 (q, $(CH_3)_3C(6)$), 28 8 (s, C(6)), 26 8 (t, C(1')), 13 1 (q, C(2')) – MS (EI) 194 (M^+), 179 (M^+ - 15, CH_3), 163 (M^+ - 31, OCH_3), 151 (M^+ - 43, C_3H_7), 135 (M^+ - 59, $COOCH_3$), 123 (M^+ - 71, - C_4H_9, - CH_3, +H), 91 (C_6H_3O), 77 (M^+ - 117), 59 ($COOCH_3$), 57 (C_4H_9) – $C_{12}H_{18}O_2$ (194 27), calc C 74 19, H 9 34%, found C 74 22, H 9 57%

Synthesis of methyl (2E,4Z)-2-ethyl-6,6-dimethylhepta-2,4-dienoate (**1**) and *methyl (2E)-2-ethyl-6,6-dimethylhept-2-enoate* (**7**) – *Hydrogenation with montmorillonite catalyst* the catalyst was prehydrogenated for *ca* 20 min in 2 ml of the respective solvent Then methyl (2*E*)-2-ethyl-6,6-dimethylhept-2-en-4-ynaote (**2**, 0 20 g, 1 03 mmol) in 4 ml of solvent was added, and hydrogenation was carried out at room temperature and atmospheric pressure until the calculated amount of hydrogen was taken up The mixture was filtered through a hardened filter paper, then the solution was concentrated by evaporation and examined for its composition with ^1H NMR spectroscopy *Hydrogenation with Lindlar catalyst* The catalyst was suspended together with quinoline and methyl (2*E*)-2-ethyl-6,6-dimethylhept-2-en-4-ynaote (**2**) in the respective solvent Hydrogenation was carried out at room temperature (one experiment at -50 °C) and atmospheric pressure until the calculated amount of hydrogen was taken up The catalyst was filtered off on a Buchner funnel, and the filtrate was washed several times with 0 1N HCl and 10% $NaHCO_3$ solution, then dried over Na_2SO_4 and evaporated The product composition was determined with ^1H NMR spectroscopy
For the determination of the spectal data a sample of the product mixture was chromatographed twice on silica gel with petrol ether/CH_2Cl_2 An almost pure sample of **1** was obtained

Data of 1 IR (Film) 2940, 2860, 1700 (C=O), 1620 (C=C), 1450, 1425, 1355, 1270, 1225, 1190, 1125, 1085, 1035, 985, 905, 790, 750 – ^1H-NMR (400 MHz, $CDCl_3$) 7 71 (dxd, J = 12 1 and 0 9 Hz, 1 H, H-C(3)), 6 12 (dxd, J = 12 3 and 12 4 Hz, 1 H, H-C(4)), 5 78 (dxd, J = 12 0 and 1 2 Hz, 1 H, H-C(5)), 3 77 (s, 3 H, OCH_3), 2 40 (q, J = 7 4 Hz, 2 H, H-C(1')), 1 21 (s, 9 H, tBu), 1 03 (t, J = 7 5 Hz, 3 H, H-(C2')) – ^{13}C-NMR (101 MHz, $CDCl_3$) 168 7 (s, C(1)), 149 3 (d, C(5)), 133 4 (d, C(3)), 133 1 (s, C(2)), 121 5 (d, C(4)), 51 7 (q, OCH_3), 34 4 (s, C(6)), 31 4 (q, $(CH_3)_3C(6)$), 19 4 (t, C(1')), 13 9 (q, C(2')) – MS (GC-MS, EI) 196 (M^+), 181 (M^+ - 15, CH_3), 165 (M^+ - 31, OCH_3), 153 (M^+ - 43, CH_3, C_2H_5, +H), 139 (M^+ - 57, C_4H_9), 137 (M^+ - 59, $COOCH_3$), 126 (M^+ - 70, C_5H_{10}), 111 (M^+ - 85, C_6H_{13}), 95 (M^+ - 101, C_5H_{10}, OCH_3), 79 (C_6H_7), 59 ($COOCH_3$), 57 (C_4H_9)

For the determination of the spectroscopic data a pure sample of **7** was prepared by hydrogenation of **2** with unpoisened Lindlar catalyst

Data of 7 IR (Film) 2960, 2910, 2880, 1715 (C=O), 1645 (C=C), 1465, 1435, 1365, 1295, 1245, 1195, 1165, 1120, 1090, 1045, 1030, 910, 795 and 770 – ^{1}H-NMR (400 MHz, $CDCl_3$) 6 73 (t, J = 7 6 Hz, 1 H, H-C(3)), 3 73 (s, 3 H, OCH_3), 2 32 (q, J = 7 5 Hz, 2 H, H-C(1')), 2 17 - 2 10 (m, 2 H, H-C(4)), 1 33 - 1 28 (m, 2 H, H-C(5)), 1 01 (t, J = 7 5 Hz, 3 H, H-(C(2')), 0 92 (s, 9 H, tBu) – ^{13}C-NMR (101 MHz, $CDCl_3$) 168 3 (s, C(1)), 142 9 (d, C(3)); 133 2 (s, C(2)), 51 4 (q, OCH_3), 43 0 (t, C(5)), 30 4 (s, C(6)), 29 1 (q, $(CH_3)_3C(6)$), 23 8 (t, C(4)), 19 3 (t, C(1')), 13 9 (q, C(2')) – MS (GC-MS, EI) 198 (M^+), 183 (M^+ - 15, CH_3), 167 (M^+ - 31, OCH_3), 141 (M^+ - 57, C_4H_9), 127 (M^+ - 71, C_5H_{11}), 123 (M^+ - 75, $COOCH_3$, CH_4), 113 (M^+ - 85, C_6H_{13}), 84 (C_6H_{12}), 71 (C_5H_{11}), 59 ($COOCH_3$), 57 (C_4H_9)

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