1,3-Stereoinduction in Radical Reactions: Radical Additions to Dialkyl 2-Alkyl-4-methyleneglutarates

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Abstract: Tin hydride-mediated radical additions to a series of α-methylene-glutarates **1**, furnishing 2,4-dialkyl-substituted glutarates **3** are reported. The diastereoselectivity of hydrogen transfer to the intermediate adduct radicals **2**, possessing a stereogenic center in γ-position, was disappointing in the temperature range of −78 to 80 °C. However, the reactions proved to be able to proceed with excellent 1,3-diastereoselectivities under chelation-controlled conditions, depending on the steric impacts of 2- and 4-alkyl substituents as well as on the ester−alkyl moiety and choice of Lewis acid. Using $MgBr_2 \cdot OEt_2$ as additive, syn-selectivities of 98:2 were achieved upon initial *tert*-butyl radical addition at −78 °C. High anti-diastereoselectivities were observed in the $MgBr_2 \cdot OEt_2$-controlled pathway at 70 °C when smaller alkyl radicals such as cyclohexyl, ethyl, and methyl were applied. Interesting and uncommon temperature dependences were observed in the temperature range of −78 to 100 °C, revealing strong entropic effects in the transition states. A model that accounts for the opposed stereochemical outcomes under chelation-controlled conditions is presented.

Introduction

The control of stereoselectivity in radical reactions still is an increasing research field,[1] and in analogy to nucleophilic reactions, the use of Lewis acid control is gaining more and more attention.[2] While diastereoselective radical reactions involving cyclic systems are well established, acyclic stereocontrol still remains an often challenging subject and most of the research in this field has been concentrated on 1,2- and 1,4-asymmetric induction.[1] Fleming et al. systematically studied the potential of 1,3-stereoinduction in nucleophilic addition reactions, and from the wide variety of stereoselectivities observed for these reactions with participants of different steric demand, they were able to derive some general tendencies for stereocontrol in those particular reactions.[3] The potential of 1,3-stereoinduction in radical reactions, however, has not received much consideration yet; only a few examples involving cyclic stereocontrol have been published [4] and investigations dealing with acyclic radicals are sparsely found. Both with respect to the synthesis of natural products bearing stereogenic centers in the 1,3-position and the free-radical polymerization of vinyl monomers, the possibility of steering the stereoselectivity of the trapping of acyclic radicals possessing a stereogenic center in the 3-position is of great importance.[5]

In 1995, we reported on relative 1,3-asymmetric induction in iodine transfer to secondary alkyl radicals,[6] and in the same year, Porter published his results on allyltributylstannane-mediated acyclic radical addition reactions of alkyl iodides to oxazolidinone acrylamides to give 1,3-disubstituted products with good diastereoselectivity.[7] Hanessian then reported some results on remote stereocontrol in free-radical C-allylation reactions including 1,3-stereocontrol due to hydrogen bonding.[8] An example for radical 1,3-stereoselective Michael analogous additions, where facial discrimination is provided by hydroxyalkyl radicals bearing a chiral tetrahydropyranyl or glucosyl moiety, was given by Garner.[9] In another approach, 1,3-stereoinduction in radical additons to imines was examined by Bertrand.[10] These previous examples represent a variety of approaches, employing different elements for 1,3-stereocontrol. Lewis acids have proven to be valuable auxiliaries, being able to expand the scope of many stereoselective reactions, but for now, only two examples of chelation-controlled acyclic 1,3-induction in radical additions to carbon−carbon bonds have been reported.[11] In these examples dealing with hydrogen and allyl transfer, respectively, given by Nagano, a γ-situated alkoxy or hydroxy group in addition to a carboxylic ester moiety is used as the second binding site for Lewis acids, a strategy that has often been successfully applied in 1,2-diastereoselective reactions.[12] The best selectivity in the hydrogen-transfer reaction, achieved in the presence of $La(fod)_3$, is 11:1.[11a] We now report our study, aimed to obtain more knowledge about factors

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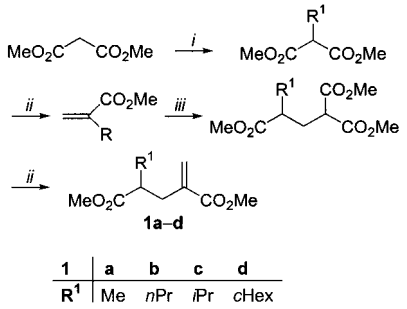
governing 1,3-diastereoselective reactions. We performed a systematic investigation of the diastereoselectivity of hydrogen transfer to chiral radicals **2** formed by radical additions to 2-alkyl-4-methylene pentanedioates **1**, examining temperature, substituent, and Lewis acid effects on the stereochemical outcome. This system offers several advantages. Two ester groups allow a sufficient complexation and, if suitable, chelation of any supplied Lewis acid. Furthermore, a variation of the alkyl moiety of the ester groups enables further insight into structural factors governing stereoselectivity. In addition, by changing the steric impact of the alkyl group in the γ-position relative to the arising radical center, and by varying the initially attacking alkyl radicals, the overall condition of the adduct radical, the trapping agent is faced with, can be systematically varied. By combining new experimental results with the results of semiempirical calculations, we were able to reasonably evaluate the stereochemical outcome.[13]

Results

The required alkenes **1a**−**d** were synthesized according to a four-step sequence depicted in Scheme 1 in an overall yield of 62 (Me, steps iii and iv), 20 (*n*Pr), 25 (*i*Pr), and 4% (*c*Hex).[14]

Scheme 1. Synthesis of 2-Alkyl-4-methylenepentanedioates **1a**−**d**[a]

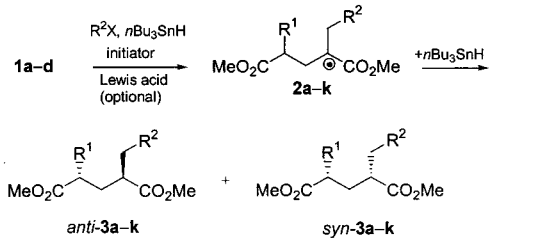


1	a	b	c	d
R1	Me	*n*Pr	*i*Pr	*c*Hex

[a] Conditions: (i) Na, MeOH, R^1Br. (ii) (1) KOH, HCl, (2) pyridine, piperidine, paraformaldehyde, reflux. (iii) Na, MeOH, dimethyl malonate.

Tin hydride-mediated reaction of alkyl bromides or iodides with alkenes **1a**−**d** gave adduct radicals **2**. Hydrogen transfer from tributyltin hydride yielded new relatively syn- and anti-configured 2,4-dialkyl-substituted dialkyl pentanedioates **3a**−**k** as outlined in Scheme 2.

Scheme 2. General Outline of the Examined Tin Hydride-Mediated Radical Addition Reaction of Alkyl Halides and Alkenes **1**[a]



2 3	a	b	c	d	e	f	g	h	i	j	k
R1	Me	*n*Pr	*i*Pr	*c*Hex	Me	*n*Pr	*i*Pr	*c*Hex	Me	Me	Me
R2	*t*Bu	*t*Bu	*t*Bu	*t*Bu	*c*Hex	*c*Hex	*c*Hex	*c*Hex	*i*Pr	Et	Me

[a] Racemic products were obtained. For convenience, only one enantiomer is depicted.

Reaction of *tert*-butyl iodide with alkene **1a** at −78 °C gave the addition products in good yields of 81% but with a disappointing diastereomeric ratio of [*anti*-**3a**]:[*syn*-**3a**] = 52:48 (Table 1, entry 1). To test the potential of a variety of different Lewis acids for our system, we conducted a screening at −78 °C on an analytical scale for the addition of *tert*-butyl iodide to **1a** with 2 equiv of Lewis acid previously mixed with the alkene (Table 1). High yielding, but almost unselective reactions took place in the presence of $Al(iPrO)_3$, $InCl_3$ and $CeCl_3$ (entries 3, 9, and 10); a comparable outcome was observed for $Mg(OEt)_2$ (entry 16). Very good and excellent syn-selectivities were obtained with $LiClO_4$, $MgBr_2{\cdot}OEt_2$, MgI_2, and $Sc(OTf)_3$ (entries 11, 12, 14, and 15). Aluminum chloride and alkylaluminum chlorides (entries 2, 5, and 6) as well as titanium tetrachloride and isopropylate (entries 7 and 8) were unsatisfying with regard to selectivity and yield. Trimethylaluminum and zinc bromide showed moderate yields and low selectivities (entries 4 and 13). Overall, the screening revealed $MgBr_2{\cdot}OEt_2$ as being the most suitable additive, considering selectivity, conversion, yield, and cost (entry 14), while aluminum and titanium organyls and halides, respectively, were unsatisfying with regard to selectivity and yield (entries 2−8).

Table 1. Screening of Diastereoselectivity and Lewis Acid Activity of the Tin Hydride-Mediated Addition Reaction of *tert*-Butyl Iodide and Dimethyl 2-Methyl-4-methylenepentanedioate (**1a**) at −78 °C[a]

entry	Lewis acid (2 equiv)	yield (%)[b]	conversion of **1a** (%)[b]	[*anti*-**3a**]:[*syn*-**3a**][c]
1[e]		81	82	52:48
2	$AlCl_3$	3	95	15:85
3	$Al(iPrO)_3$	90	92	50:50
4	$AlMe_3$	67	100	42:58
5	Et_2AlCl	5	96	34:66
6	$Et_3Al_2Cl_3$	5	65	23:77
7	$TiCl_4$	7	72	38:62
8	$Ti(iPrO)_4$	17	31	51:49
9	$InCl_3$	95	96	44:56
10	$CeCl_3$	90	99	52:48
11[d,e]	$LiClO_4$	93	100	18:82
12[d,e]	$Sc(OTf)_3$	58	100	1:99
13[e]	$ZnBr_2$	60	97	45:55
14[d,e]	$MgBr_2{\cdot}OEt_2$	83	100	2:98
15[d,e]	MgI_2	77	100	2:98
16[e]	$Mg(OEt)_2$	70	78	52:48

[a] Reactions were carried out in CH_2Cl_2 on analytical scale (**1a** 1 equiv, Lewis acid 2 equiv, Bu_3SnH 3 equiv, *tert*-butyl iodide 3 equiv, Et_3B 1 equiv/O_2) at an average reaction time of 4−6 h. [b] Yield and conversion of **1a** were determined by GC analysis using dodecane as internal standard. [c] Diastereomeric ratio of **3a** was determined by GC. [d] Carried out on preparative scale; yields are isolated yields. [e] Et_2O was used as cosolvent.

The influence of different solvents on the diastereoselectivity of the chosen test reaction at −78 °C with $MgBr_2{\cdot}OEt_2$ supplement was examined. As expected, diethyl ether and dichloromethane, which are mostly employed in analogous low-temperature studies, proved to be the most eligible mediums, providing a 1,3-diastereoselectivity of [*anti*-**3a**]:[*syn*-**3a**] of 2:98 and 4:96 (Table 2, entries 1 and 3), respectively, whereas THF unexpectedly led to a reversed and low selectivity of 58:42 (entry 2). Toluene emerged as being slightly less suitable than dichloromethane with regard to selectivity (9:91, entry 4), and the most unpolar pentane finally gave a less selective performance of 26:74 (entry 5). Considering conversion, dichloromethane and toluene apparently slowed the reaction; yields

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Table 2. Screening of the Influence of Solvents on the Diastereoselectivity of the Tin Hydride-Mediated Addition Reaction of *tert*-Butyl Iodide (3 Equiv) and Dimethyl 2-Methyl-4-methylenepentanedioate (**1a**) in the Presence of 2 Equiv of $MgBr_2 \cdot OEt_2$ at −78 °C[a]

entry	solvent	yield (%)[b]	conversion of **1a** (%)[b]	[*anti*-**3a**]:[*syn*-**3a**][c]
1	Et_2O	100	100	2:98
2	THF	100	100	58:42
3	CH_2Cl_2	79	79	4:96
4	toluene	59	68	9:91
5	pentane	100	100	26:74

[a] The same reaction procedure was used as for reactions of Table 1. [b] Yield and conversion of alkene were determined by GC analysis using dodecane as internal standard. [c] Diastereomeric ratio of **3a** was determined by GC.

Table 3. Temperature Dependence of the Diastereoselectivity of the Tin Hydride-Mediated Addition Reaction of *tert*-Butyl Halides and Dimethyl 2-Methyl-4-methylenepentanedioate (**1a**).[a] Variation of the Concentration of $MgBr_2 \cdot OEt_2$

entry	*T* (°C)	$MgBr_2 \cdot OEt_2$ (equiv)	yield (%)[b]	conversion (%)[c]	[*anti*-**3a**]:[*syn*-**3a**][d]
1	−78		82	82	52:48
2	−20		55	*e*	51:49
3	0		100	100	52:48
4	20		90	92	51:49
5	−78	1	80	100	2:98
6[g]	−78	2	83	100	2:98
7[f]	−78	5	100	100	1:99
8	−20	2	82	100	5:95
9	0	2	85	95	10:90
10	20	2	96	96	15:85
11	70	1	44	*e*	39:61
12	100	2	36	70	46:54

[a] Conditions: **1a** 1 equiv, Bu_3SnH 3 equiv, alkyl halide 3 equiv. Alkyl iodides were employed at −78, −20, 0, and 20 °C; alkyl bromides at 70 and 100 °C. As solvent, benzene was used at 70 and 80 °C, toluene at 100 °C (AIBN as initiator); at all other temperatures, dichloromethane was used (Et_3B as initiator). Diethyl ether was added as cosolvent, if $MgBr_2 \cdot OEt_2$ was employed. [b] Yields are isolated yields. [c] Conversion of alkene was determined by GC analysis using dodecane as internal standard. [d] Diastereomeric ratio of **3a** was determined by GC. [e] An excess of **1a** was used. The conversion of **1a** was not determined. [f] The reaction was performed on analytical scale and analyzed by GC using dodecane as internal standard. [g] Entry 14, Table 1.

were satisfying to quantitative in all cases. As a conclusion, a solvent mixture composed of diethyl ether and dichloromethane was chosen for further studies when a Lewis acid was involved. A solvent composition with diethyl ether as a key role additive has been recognized before as being necessary for optimal results in Lewis acid-controlled enantioselective radical-mediated allylations.[15]

In Table 3, the results of the temperature influence on the diastereoselectivity of the same reaction as chosen above are listed in detail. High-temperature reactions (70 and 100 °C) were performed in benzene or toluene with a small amount of diethyl ether as additive if $MgBr_2 \cdot OEt_2$ was present and were initiated by AIBN, reactions at 20, 0, and −78 °C were carried out in dichloromethane/diethyl ether, as initiator the Et_3B/O_2 system was used, and reactions at −20 °C were performed in a photoreactor using a 5-W low-pressure mercury lamp and, again, with dichloromethane/diethyl ether as solvent. When the reactions were performed at 70, 80, or 100 °C, alkyl bromides were used, and at other temperatures, iodides. In the case of nonchelation, an unselective reaction was observed in the temperature range of −78 to 20 °C (entries 1−4). However, in the series of $MgBr_2 \cdot OEt_2$-controlled reactions, selectivities increased by lowering the temperature, ranging from an almost unselective reaction in toluene/Et_2O at 100 °C with an [anti] to [syn] ratio of 46:54 (entry 12) to a ratio of 2:98 at −78 °C (entry 5). The amount of $MgBr_2 \cdot OEt_2$ equivalents applied was varied in entries 5−7; 1 or 2 equiv with respect to alkene afforded anti- and syn-products **3a** in a ratio of 2:98, and 5 equiv led to a once more improved ratio of 1:99, as measured by GC analysis. Although the results of the temperature series seem to be following a reasonable linear behavior, by analyzing this temperature range (entries 5 and 8−12), one has to keep in mind that not all the applied reaction conditions (i.e., solvent) are directly comparable.

Table 4. Diastereoselectivity of the Tin Hydride-Mediated Radical Addition Reaction of *tert*-Butyl Halides and Dimethyl 2-Alkyl-4-methylenepentanedioates **1b**−**d**. Influence of Temperature and $MgBr_2 \cdot OEt_2$[a]

entry	alkene	$MgBr_2 \cdot OEt_2$ (equiv)	*T* (°C)	yield (%)[b]	[*anti*-**3**]:[*syn*-**3**][c]
1	**1b**		−78	67	48:52
2	**1b**		80	66	54:46
3	**1c**		−78	74	45:55
4[e]	**1c**		80	88	54:46
5	**1d**		−78	94	42:58
6[e]	**1d**		80	72	51:49
7	**1b**	1	−78	92	2:98
8	**1b**	2	70	50[d]	24:76
9	**1c**	1	−78	89	5:95
10	**1c**	2	70	65	35:65
11	**1d**	1.5	−78	75[d]	3:97
12	**1d**	2	70	50[d]	32:68

[a] Conditions: **1b**−**d** 1 equiv, Bu_3SnH 3 equiv, alkyl halide 3 equiv. Alkyl iodides were employed at −78 °C, alkyl bromides at 70 and 80 °C. As solvent, benzene was used at 70 and 80 °C (AIBN as initiator); at −78 °C, dichloromethane was used (Et_3B as initiator). Diethyl ether was added as cosolvent, if $MgBr_2 \cdot OEt_2$ was employed. [b] Yields are isolated yields. [c] Diastereomeric ratio was determined by GC. [d] Incomplete conversion of alkene at the time of analysis. [e] An excess of **1** was used. The conversion of **1** was not determined.

Table 4 deals with the effect of substituent R^1 in the γ-position to the radical center in **2b**−**d** on the diastereoselectivity for two different temperatures of −78 and 70/80 °C. In contrast to the results displayed in Table 3 (**2a**, R^1 = Me), a remarkable temperature dependence was observed with reactions in the absence of $MgBr_2 \cdot OEt_2$. At −78 °C, in all three cases, low syn-selectivities were observed, becoming larger with increasing steric effect of the substituent R^1 (*n*Pr < *i*Pr < cHex), going from [*anti*-**3**]:[*syn*-**3**] = 48:52 (**1b**, entry 1) through 45:55 (**1c**, entry 3), to 42:58 (**1d**, entry 5). However, by rising the reaction temperature to 80 °C, inversion to low anti-selectivities occurred in all cases (entries 2, 4, and 6). In the chelation-controlled reaction pathway, the general tendencies observed for alkene **1a** (Table 3) were maintained, that is, a very high syn-preference at −78 °C and a moderate syn-selectivity at 70 °C. There seems to be only a minor effect of the γ-alkyl substituent on the diastereoselectivity: at −78 °C a variation of [anti]:[syn] between 2:98 (**1a**, Table 3, entries 5 and 6; **1b**, Table 4, entry 7), 3:97 (**1d**, Table 4, entry 11), and 5:95 (**1c**, Table 4, entry 9) was observed.

Surprising results were obtained by applying cyclohexyl halide instead of *tert*-butyl halide as precursor for the primarily attacking alkyl radical, providing a cyclohexylmethyl instead of the previously built up neopentyl moiety in the α-position to the arising radical center (Table 5). Evidently, minimizing the steric impact of the α-substituent of the adduct radical had a major effect on the hydrogen-transfer step determining relative product configuration, an effect that was not observed by

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Table 5. Diastereoselectivity of the Tin Hydride-Mediated Radical Addition Reaction of Cyclohexyl Halides (R^2 = cHex) and Dimethyl 2-Alkyl-4-methylenepentanedioates **1a-d**. Influence of Temperature and $MgBr_2 \cdot OEt_2$[a]

entry	alkene	$MgBr_2 \cdot OEt_2$ (equiv)	T (°C)	yield (%)[b]	[*anti*-**3**]:[*syn*-**3**][c]
1[e]	**1a**		−78	60	60:40
2[e]	**1a**		80	98	52:48
3	**1b**		−78	96	63:37
4[e]	**1b**		80	80	54:46
5	**1c**		−78	98	59:41
6[e]	**1c**		80	87	54:46
7	**1d**		−78	82[d]	59:41
8	**1d**		80	68[d]	53:47
9	**1a**	1	−78	64[d]	53:47
10	**1a**	1.5	−20	38	71:29
11	**1a**	2	0	100[f]	69:31
12	**1a**	2	20	68[d]	70:30
13	**1a**	2	70	58[d,f]	65:35
14	**1a**	2	100	75[d,f]	62:38
15	**1b**	1	−78	98	53:47
16	**1b**	2	70	95	73:27
17	**1c**	1.5	−78	88	56:44
18	**1c**	2	70	90	78:22
19	**1d**	1	−78	62[d]	52:48
20	**1d**	2	70	58[d]	81:19

[a] Conditions: **1** 1 equiv, Bu_3SnH 3 equiv, alkyl halide 3 equiv. Alkyl iodides were employed at −78, −20, 0, and 20 °C, alkyl bromides at 70, 80, and 100 °C. As solvent, benzene was used at 70 and 80 °C, toluene at 100 °C (AIBN as initiator); at all other temperatures, dichloromethane was used (Et_3B as initiator). Diethyl ether was added as cosolvent, if $MgBr_2 \cdot OEt_2$ was employed. [b] Yields are isolated yields unless specified otherwise. [c] Diastereomeric ratio was determined by GC. [d] Incomplete conversion of **1** at the time of analysis. [e] An excess of **1** was used. The conversion of **1** was not determined. [f] Yield was determined by GC analysis using dodecane as internal standard.

changing the nature of the γ-substituent upon *tert*-butyl radical addition (Table 4).

Alkenes **1b**−**d** bearing different γ-alkyl substituents were subjected to the addition reaction at two different temperatures—with alkene **1a** a broader temperature range was examined—and again the influence of $MgBr_2 \cdot OEt_2$ as Lewis acid was examined. In contrast to the results presented in Tables 3 and 4, the general preference of this addition−transfer sequence pointed into the direction of anti-selectivity, irrespective of the presence of a Lewis acid. What was even more striking, an unexpected temperature behavior was observed. Starting with the chelation-controlled pathway, at 70 °C the reactions exhibited an impressive anti-diastereoselectivity in contrast to the exclusive syn-selectivity demonstrated by the Lewis acid-controlled hydrogen transfer upon the adduct radicals **2a**−**d**. The diastereomeric anti/syn-ratio increased clearly visible, going from R^2 = Me (Table 5, entry 13, 65:35) via *n*Pr (entry 16, 73:27), *i*Pr (entry 18, 78:22), to cyclohexyl (entry 20, 81:19), thus showing a significant γ-substituent effect in this case. However, the same series at −78 °C did not demonstrate the anticipated enhancement of the anti-preference; it rather showed an unselective reaction (entries 9, 15, 17, and 19). In entries 9−14, the results of a more extended temperature study employing alkene **1a** are displayed. As indicated above, selectivities increased by raising the reaction temperature. While the reaction proceeded almost unselectively at −78 °C (entry 9, 53:47), at −20, 0, and 20 °C, moderate anti-preferences of ∼70:30 were observed (entries 10−12). Higher temperatures resulted in once more declining selectivities of 65:35 (70 °C, entry 13) and 62:38 (100 °C, entry 14). However, once more one has to keep in mind that the employed reaction conditions were not comparable in all cases (i.e., deviations at 70 °C and 100 °C), obviously especially the solvents used for higher reaction temperatures, benzene and toluene, are less eligible mediums as already indicated by the results presented in Table 2.

Table 6. Diastereoselectivity of the Tin Hydride-Mediated Radical Addition Reaction of Methyl, Ethyl, and Isopropyl Halides (R^2 = Me, Et, *i*Pr) and Dimethyl 2-Methyl-4-methylenepentanedioate (**1a**) as Well as Reduction of Dimethyl 2-Iodo-2,4-dimethylpentanedioate (**4**). Influence of Temperature and $MgBr_2 \cdot OEt_2$[a]

entry	substrate	R^2	$MgBr_2 \cdot OEt_2$ (equiv)	T (°C)	yield (%)[b]	[*anti*-**3**]:[*syn*-**3**][d]
1	**1a**	*i*Pr		−78		63:37[c]
2	**1a**	*i*Pr	2	−78		52:48[c]
3	**1a**	Et		−78	70	57:43
4	**1a**	Et		80	100	47:53
5	**1a**	Et	2	−78	100	85:15
6	**1a**	Et	2	0	76	85:15
7	**1a**	Et	2	20	48	83:17
8	**1a**	Et	2	40	53	81:19
9	**1a**	Et	2	70	58	71:29
10	**1a**	Me		−78	23	55:45
11	**1a**	Me		80	85	46:54
12	**1a**	Me	2	−78	58	85:15
13	**1a**	Me	2	0	46	85:15
14	**1a**	Me	2	20	42	86:14
15	**1a**	Me	2	40	50	85:15
16	**1a**	Me	2	70	40	68:32
17	**4**	H		−78	76	59:41
18	**4**	H		80	82	45:55
19	**4**	H	2	−78	55	87:13
20	**4**	H	2	70	70	80:20

[a] Conditions: **1** 1 equiv, Bu_3SnH 3 equiv, alkyl halide 3 equiv. Alkyl iodides were employed at −78, 0, 20, and 40 °C, methyl iodide and ethyl bromide at 70 and 80 °C. As solvent, benzene was used at 70 and 80 °C (AIBN as initiator); at all other temperatures, dichloromethane was used (Et_3B as initiator). Diethyl ether was added as cosolvent, if $MgBr_2 \cdot OEt_2$ was employed. [b] Yield was determined by GC analysis using dodecane as internal standard. [c] Reaction was performed on analytical scale, product retention time was confirmed by GC/MS, and relative product configuration was assigned by elution order. [d] Diastereomeric ratio was determined by GC.

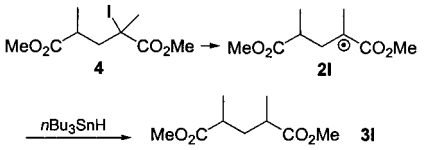
Remarkably, the nonchelation reactions again did not follow this temperature/selectivity profile as selectivity increased by lowering the temperature to −78 °C in all four cases (Table 5, entries 1−8). While reactions at 80 °C were comparably unselective to the ones displayed in Table 4 for *tert*-butyl radical addition, at −78 °C a moderately enhanced and, most remarkably, higher anti-stereoselectivity than in the chelated case could be observed, with alkene **1b** giving the highest [anti] to [syn] ratio of 63:37 (entry 3).

Table 6 summarizes the results of some additional reactions concerning the role of R^2, employing isopropyl, ethyl, methyl (Scheme 2), and hydrogen (Scheme 3) leading to 2,4-dialkylpentanedioates **3**. Upon tin hydride-mediated reaction of $MgBr_2 \cdot OEt_2$-complexed alkene **1a** with *i*PrI at −78 °C, an almost unselective reaction took place, giving an [anti] to [syn] ratio of 52:48 of **3i** (Table 6, entry 2). With no Lewis acid present, the selectivity increased to 63:37 (entry 1). These findings resembled those of cyclohexyl addition to **1a** (Table 5, entries 1 and 9), as expected from the geometrical similarity of these alkyl groups; thus only two analytical experiments were performed. Methyl and ethyl halides, however, again showed a different behavior and, in general, proceeded in a more sluggish reaction manner than the preceding examined reactions. In the $MgBr_2 \cdot OEt_2$-controlled reaction pathway, the reactions furnishing dimethyl 2-methyl-4-propylpentanedioate (**3j**) and dimethyl 2-ethyl-4-methylpentanedioate (**3k**) did not display a visible temperature dependence in the range of −78 to 40 °C and led to high anti-selectivities of ∼85:15 (Table 6, entries 5−8 and 12−15), but when performed at 70 °C, the anti-selectivity decreased slightly.

The nonchelated reactions showed a moderate anti-preference at −78 °C ([anti]:[syn] = 57:43, entry 3, R^2 = Et; 55:45, entry 10, R^2 = Me) and a moderate syn-selectivity at 80 °C ([anti]:[syn] = 47:53, entry 4, R^2 = Et; 46:54, entry 11, R^2 = Me).

The simplest substitution pattern for R^2, which is H, was examined by first introducing an iodine atom to the α-position of commercially available dimethyl 2,4-dimethylpentanedioate, thus providing dimethyl 2-iodo-2,4-dimethylpentanedioate (**4**) as a substrate for diastereoselective H-transfer. The stereoselectivity of the Lewis acid-supported reduction of **4** (Scheme 3) via radical **2l** was comparable to that for radicals **2j** and **2k**,

Scheme 3. Reduction of Dimethyl 2-Iodo-2,4-dimethylpentanedioate (**4**) by Tributyltin Hydride

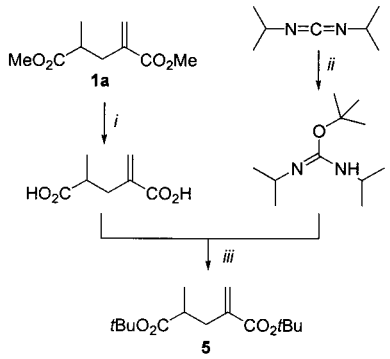


although reaching even better anti-selectivity at −78 °C with [*anti*-**3l**]:[*syn*-**3l**] = 87:13 (entry 19). The temperature dependence was solely examined by means of −78 and 70 °C, but even in the 70 °C case, an only slightly diminished selectivity of still 80:20 was observed (entry 20). In the absence of a Lewis acid, stereoselectivities were again comparable to or slightly better than in the ethyl and methyl addition case, going from 55:45 (entry 10, Me) via 57:43 (entry 3, Et) to 59:41 (entry 17, H) at −78 °C.

Having investigated the influence of the γ-substituent R^1 and sterically different cases of primarily attacking radicals R^2 on the 1,3-stereoinduction under varying conditions, it remained to determine the impact of the ester alkyl moiety R^3. An enlargement of this group had proven to enhance the 1,3-stereoselectivity of iodine transfer in a previous study conducted by our group.[6b]

Thus, we decided to study the respective di-*tert*-butyl ester **5** in comparison to dimethyl ester **1a**, which was prepared as shown in Scheme 4 in two steps from ester **1a**.[16] This synthetic

Scheme 4. Synthesis of Di-*tert*-butyl 2-Methyl-4-methylenepentanedioate (**5**)[a]



[a] Conditions: (i) KOH/EtOH reflux, 2 h. (ii) *tert*-BuOH, CuCl, CH_2Cl_2, room temperature, 3 d. iii) $CHCl_3$, 2 d.

approach was started by saponification of **1a**, providing 2-methyl-4-methylenepentanedioic acid, which was then reacted with a previously prepared solution of *tert*-butyl *N*,*N*′-diisopropylimidocarbamate.

When di-*tert*-butyl 2-methyl-4-methylenepentanedioate (**5**) was subjected at 70 °C to the successfully applied reaction

(16) (a) Vowinkel, E. *Chem. Ber.* **1967**, *100*, 16−22. (b) Mathias, L. J. *Synthesis* **1979**, 561−576.

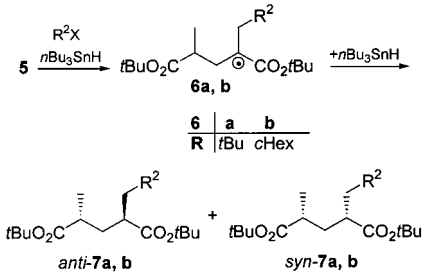
Table 7. Diastereoselectivity of the Tin Hydride-Mediated Radical Addition Reaction of *tert*-Butyl and Cyclohexyl Halides (R^2 = *t*Bu, cHex) and Di-*tert*-butyl 2-Alkyl-4-methylenepentanedioate **5**. Influence of Temperature and $MgBr_2$·OEt_2[a]

entry	R^2	$MgBr_2$·OEt_2 (equiv)	*T* (°C)	yield (%)[b]	[*anti*-**7**]:[*syn*-**7**][c]
1	*t*Bu		−78	65	43:57
2	*t*Bu		80	15	47:53
3	*t*Bu	2	−78	69	4:96
4	*t*Bu	2	70		
5	cHex		−78	89	49:51
6	cHex		80	88[d]	42:58
7	cHex	2	−78	93	89:11
8	cHex	2	20	88[d]	88:12
9	cHex	2	70	11[d]	79:21

[a] Conditions: **5** 1 equiv, Bu_3SnH 3 equiv, alkyl halide 3 equiv. Alkyl iodides were employed at −78 and 20 °C, alkyl bromides at 70 and 80 °C. As solvent, benzene was used at 70 and 80 °C (AIBN as initiator); at all other temperatures, dichloromethane was used (Et_3B as initiator). Diethyl ether was added as cosolvent, if $MgBr_2$·OEt_2 was employed. [b] Yields are isolated yields unless specified otherwise. [c] Diastereomeric ratio was determined by GC. [d] Yield was determined by GC analysis using dodecane as internal standard.

conditions of tin hydride-mediated *tert*-butyl addition under chelation control by $MgBr_2$·OEt_2, this resulted in complete destruction of the educt alkene, without any addition product being detectable. Without Lewis acid, the high-temperature reaction was comparably destructive, yet yielding 15% of the expected addition product **7a** in a ratio of [*anti*-**7a**]:[*syn*-**7a**] = 47:53 (Table 7, entry 2). At −78 °C, **7a** was obtained in a ratio of [anti]:[syn] = 43:57 in 65% isolated yield (entry 1). A more satisfying result was achieved by using $MgBr_2$·OEt_2: although the selectivity did not come up to our expectations of topping the results achieved with **1a** (Table 3, entry 5), an acceptable isolated yield of 69% (Table 7, entry 3) and a selectivity of [*anti*-**7a**]:[*syn*-**7a**] = 4:96 was obtained. (See Scheme 5.)

Scheme 5. Tributyltin Hydride-Mediated Addition Reaction of Alkyl Halides and *tert*-Butyl Esters **5**



The cyclohexyl radical additon to **5** was lined up next in order to complete the picture, and once again, the outcome was surprising. In the $MgBr_2$·OEt_2-controlled reaction at −78 °C, the desired product di-*tert* butyl 2-(cyclohexylmethyl)-4-methylpentanedioate (**7b**) was obtained with an encouragingly high anti-preference of 89:11 and in excellent isolated yield of 93% (entry 7). By raising the reaction temperature to 20 °C, this selectivity remained practically unchanged (88:12, entry 8), while at 70 °C, a diminished selectivity of 79:21 was observed. Again, a reason for this sudden decrease in selectivity at higher temperature, which occurred in other cases as well, as reported above, can be assumed in the change of the solvent. The nonchelated reaction also furnished the product in a high yield (89%), but unselectively (entry 5) at −78 °C and with a moderate syn-preference of 58:42 at 80 °C (entry 6). Compared to the respective reactions of dimethyl ester **1a** (Table 5, entries 1 and 9), these experiments clearly assigned a role to the ester

alkyl moiety R^3 as being able to govern diastereofacial discrimination.

To be able to directly compare the potential of radical and ionic reaction pathways, we performed some nucleophilic 1,4-additions of *tert*-butylmagnesium bromide to alkenes **1a** and **1b** and of cyclohexylmagnesium bromide to alkene **1a** at 0 °C. In all cases, the respective anti-products were formed preferentially ([anti]:[syn] = 70:30 (**3a**), 83:17 (**3b**), 74:26 (**3e**)) in low to moderate yields. Thus, *tert*-butyl addition occurred with reversed diastereoselectivity compared to the $MgBr_2$ chelation-controlled radical reaction whereas in the case of cyclohexyl addition the same direction and amount of selectivity was observed.

Assignment of Relative Stereochemistry. Treatment of diastereomeric mixtures of **3a** and **3e**, respectively, with KOH/EtOH furnished the corresponding pentanedioic acids **8a** and **8b** as white solids. Recrystallization from ethyl acetate evidently resulted in crystallization of one configurational form only in both cases, as deduced from derivatization with diazomethane and subsequent examination by GC. The relative configurations of these stereoisomers were assigned by means of single-crystal X-ray analyses as being syn in either circumstances. Since **3a** and **3e** represent the simplest forms of the series of pentanedioates **3**, the relative configurations of all other substances could be deduced based on these results, comparing characteristic patterns of GC retention times and ^{1}H NMR analysis. GC retention times of the two diastereomeric forms generally showed a 2-min delay, with the anti-diastereomers always eluting first. Another typical feature of the syn-diastereomers was observed in the ^{1}H NMR spectra: whereas the diastereotopic methylene protons of position-3 of the anti-forms gave a multiplet at 1.6−1.9 ppm, in the syn-stereoisomers, these protons provided separated signals; one could be found in the area of 1.4−1.6 ppm, and the other one exhibited a significant downfield shift and was observed at 1.9−2.0 ppm. These downfield-shifted signals could be clearly distinguished in most cases, because no other signals covered this ppm range. The diastereotopic protons in the 3′-position ($C_6H_{11}CHH$, C_4H_9CHH) did not enable a distinction between syn- and anti-diastereomers. ^{13}C NMR spectra also provided further clues to diastereomerical assignment: in both the neopentyl- (**3a**−**d**) and the cyclohexylmethyl series (**3e**−**h**), the methylene carbon signals of $(CH_3)_3CCH_2$ and $C_6H_{11}CH_2$, respectively, appeared at higher field for the syn-forms. For **3a**−**d**, the respective signals turned up in the range of 45−48 ppm, with the anti-diastereomers showing a downfield shift $\Delta\delta$ relative to syn of 0.41 (**3a**) to 2.32 ppm (**3d**). Similarly, for **3e**−**h** downfield shifts $\Delta\delta$ of 0.27 (**3e**) to 1.68 ppm (**3h**) were observed for the methylene signals of the anti-forms, with signals generally appearing between 39 and 42 ppm. **3i** was only treated analytically, so product stereochemistry was deduced from GC elution order. **3j**, **3k**, **7a**, and **7b** were isolated (only anti-forms: **3j**, **3k**, **7a**) and characterized; GC and NMR analysis here again proved the previously observed patterns right. *syn*- and *anti*-**3l** were assigned by applying the NMR and GC characteristics to an original sample of *meso*- and (±)-**3l**, which then enabled comparison of GC elution order and thus determination of product stereochemistry of reaction material.

Discussion

Our experimental results show a remarkable synthetic potential for 1.3-stereoinduction in chelation-controlled radical trapping reactions. The main selectivity phenomena emerging from the results described in the preceding section, which should be posed for a discussion, certainly are the discrepancies in the anti/syn-preferences caused by different substituents R^2 in the tin hydride-mediated addition reactions in the presence of $MgBr_2{\cdot}OEt_2$ (Scheme 2). While in the *tert*-butyl pathway excellent syn-diastereoselectivities were observed (Tables 3 and 4), preferably anti-configured products were produced with R^2 = cHex, *i*Pr, Et, Me, and H (Tables 5 and 6). Apart from the general selectivity issue, a discussion should also include the observed diverse and not trivial temperature behavior. The reactions performed in the absence of a Lewis acid were less selective in most cases, not showing similar interesting tendencies, which is obviously due to the conformational flexibility of the alkyl chain.

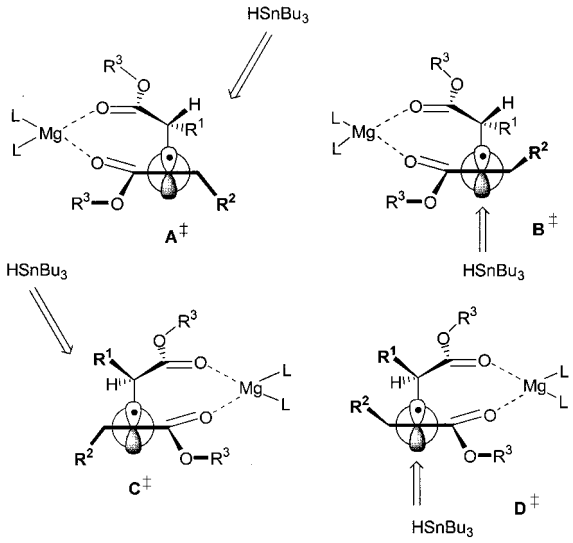


Figure 1. Transition-state models of hydrogen transfer to chelated radicals **2** and **6** bearing alkyl substituents R^1, R^2, and R^3. Syn-products can be generated via A‡ and D‡, anti-products via B‡ and C‡.

To develop a simple transition state model of the hydrogen-transfer step, which explains the various stereoselectivities observed in the Lewis acid-controlled reactions, our first general assumption was that the two 1,3-carboxy functionalities of radicals **2** and **6** are coordinated to the Lewis acid $MgBr_2{\cdot}OEt_2$, thus creating an eight-membered-ring system and restraining the conformational flexibility. Strong support for this was provided by PM3 calculations, employing $[Li(OH_2)_2]^+$ as Lewis acid, which revealed that an eight-membered-ring system indeed is very stable—irrespective of R^1. Although the ring conformation employed for further consideration (Figure 1) is not the only possible one, it was calculated to be the most stable eight-membered one. Further calculations of likely minimum structures were performed in order to better understand the conformational behavior of the adduct radicals; the resulting energy differences are compiled in Table 8.

Figure 1 shows four possible transition states A‡−D‡ of the hydrogen-transfer step based on the calculated minimum ground states, which seem to be most likely to be contributing to product distribution. Syn-products can be generated via transition states A‡ and D‡, and anti-products via B‡ and C‡. In A‡ and B‡, the alkyl ligand R^1 at position-3 is pointing away from the radical center, rendering these less sterically congested than C‡ and D‡, where R^1 is located closer to it. In all chelated structures, the ring shows a concave and a convex side (upper side and bottom side in Figure 1, respectively). Hydrogen transfer is supposed to be directed by the relative weighting of the steric interaction between the chelate ring system with the present arrangement of substituents at the γ-position and α-alkyl group R^2 on one hand and, on the other hand, interaction between Bu_3SnH and

Table 8. Results of PM3 Calculations of Radicals **2a** (R^2 = *t*Bu), **2e** (R^2 = *c*Hex), **2j** (R^2 = Et) **2k** (R^2 = Me), **2l** (R^2 = H), **6a** (R^3 = *t*Bu, R^2 = *t*Bu), and **6b** (R^3 = *t*Bu, R^2 = *c*Hex). Relative Energies (kJ/mol) of Conformations A − D[a]

R^2	R^3	A	B	C	D
*t*Bu (**2a**)	Me	0	9.2 (38)	9.6	22.6
*c*Hex (**2e**)	Me	0	3.8 (17)	10.5	17.2
Et (**2j**)	Me	0	−0.5 (11)	8.0	11.0
Me (**2k**)	Me	0	0.3 (11)	11.0	11.6
H (**2l**)	Me	0		11.0	
*t*Bu (**6a**)	*t*Bu	0	6.9 (32)	10.6	16.9
*c*Hex (**6b**)	*t*Bu	0	−3.8 (18)	9.5	9.7

[a] Conformations A B, C, and D according to the respective transition states $A^‡$, $B^‡$, $C^‡$, and $D^‡$, depicted in Figure 1. The rotational barrier for R^2 (kJ/mol) is given in parentheses.

this ring system in the transition state. The following will focus on explaining the stereoselectivities of the trapping of radicals **2** and **6** by using transition-state models $A^‡$−$D^‡$. To rationalize the complex temperature−selectivity dependence that was observed upon variation of R^2 and R^3 in terms of activation enthalpies and entropies, relative Eyring eq 1 is utilized

$$\log \frac{k_{anti}}{k_{syn}} = \frac{\Delta H^‡_{syn} - \Delta H^‡_{anti}}{2.3\,R\,T} - \frac{\Delta S^‡_{syn} - \Delta S^‡_{anti}}{2.3\,R} \qquad (1)$$

additionally. From the results given in Table 3 for radical **2a**, we can assume that in the temperature range of −78 to ∼80 °C the structure of the chelated radicals **2** remains essentially unchanged because of a reasonable Arrhenius-like linear behavior of stereoselectivity.

With respect to selectivity−temperature behavior, three different cases that occurred have to be viewed: (1) decreasing selectivity by performing the reaction at higher temperatures, (2) increasing selectivity by doing so, and (3) no temperature dependence of selectivity. Radicals **2a**−**d** and **6a** are following the first case; they are exhibiting a high syn-preference in the hydrogen-transfer step and a temperature−selectivity profile as expected, i.e., decreasing selectivity by rising the temperature. By reference to eq 1, this clearly establishes a dominating enthalpic effect with activation enthalpy $\Delta H^‡_{syn}$ obviously being lower than $\Delta H^‡_{anti}$. A comparison of $A^‡$ to the other possible transition states of H-transfer by a steric viewpoint clearly reveals that in $A^‡$ steric interactions of the hydrogen donor with the concave side of the chelate ring system are weaker than those in $C^‡$, taking into account the additional effect of R^1, and also weaker than the steric repulsion between the *t*Bu group and the chelate ring system in transition-state $B^‡$ and even more so in $D^‡$ where R^1 enhances steric congestion. Thus, H-transfer proceeds mainly via transition-state $A^‡$, furnishing syn-product predominantly. This interpretation also explains the low influence of R^1 (only minor contributions of pathways $C^‡$ and $D^‡$) on the stereoselectivity (Tables 3 and 4) and is supported—in compliance with the Curtin−Hammett-principle—by the results of the calculations of radical **2a**, which reveal A as being the most stable conformer (Table 8).

Radicals **2e**−**h** (Table 5) with R^2 = cHex of medium steric impact are an example of the second case. While they are trapped nearly unselectively at −78 °C, at +70 °C the reactions take place with remarkable anti-selectivity. Compared to radicals **2a**−**d** and **6a**, they are displaying a completely reversed behavior, with respect to both stereoselective preference and temperature dependence. An interpretation of these findings in terms of eq 1 is as follows: similar to the case surveyed above, $\Delta H^‡_{anti} > \Delta H^‡_{syn}$, because with increasing temperature more anti-product is formed. This is supported by the calculations of radical **2e,** with conformation A being by 3.8 kJ/mol more stable than conformation B. In addition, a strong entropic effect must be assumed. Judging by the degree of rotational freedom of R^2 and on account of the attack of the hydrogen donor from the free convex side of **2**, the transition state exhibiting the highest activation entropy should be $B^‡$, leading to anti-product. With $\Delta H^‡_{anti}$ and $\Delta S^‡_{anti}$ being higher than their syn-counterparts, there must exist a temperature where the enthalpic term and the entropic term of eq 1 are compensating each other, leading to an unselective reaction.[17] Evidently, this temperature is located somewhere about −78 °C in this case. By increasing the temperature, *anti*-**3e**−**h** are formed with considerable selectivity due to the now dominating entropic effect, obviously via transition-state $B^‡$. The increasing anti-selectivity with growing steric demand of R^1 indicates that a participation of transition-state $D^‡$, furnishing syn-product is involved—decreasingly with increasing steric impact of R^1.

The selectivity of H-transfer upon radicals **2j**−**l** does not show a significant dependence on temperature; thus they have to be classified as an example for the third case in terms of eq 1. As no enthalpic effect occurs throughout the whole temperature range examined, $\Delta H^‡_{anti}$ and $\Delta H^‡_{syn}$ have to be assumed as being equal, leaving the entropic term to direct the stereoselectivity. Support for this is provided by the calculated energies of Table 8: the energy differences between conformations A and B and between conformations C and D are becoming smaller with decreasing steric effect of R^2 = *t*Bu > cHex > Et > Me, a fact that should also apply to the corresponding transition states. Accordingly, radicals **2j**, **2k**, and **2l** bearing R^2 groups of lesser steric impact are trapped with negligible (**2j**, **2l**) or without temperature dependence (**2k**), but remarkable anti-selectivity with transition-state $B^‡$ contributing the most to this product distribution.

Changing the alkyl ester moiety from R^3 = Me in radicals **2a** and **2e** to R^3 = *t*Bu in radicals **6a** and **6b**, respectively, clearly revealed the influence of the steric effect of alkyl-group R^3 on the stereochemical outcome of the reaction. In the case of radicals **2a** and **6a**, the slight decrease of syn-selectivity of 2:98 (**2a**, Table 3, entry 5) to 4:98 (**6a**, Table 7, entry 3) can be rationalized by unfavorable 1,4-steric interactions of R^2, R^3 = *t*Bu in radical **6a** in transition-state $A^‡$, which is supported by calculations showing that the energetic difference of conformations A and B of radical **6a** amounts to only 6.9 kJ/mol compared to 9.2 kJ/mol of radical **2a** (Table 8). Thus, increasing the steric effect of the alkyl ester moiety R^3 favors the formation of the anti-product. Further confirmation of this was provided by the results of radical **6b**, which showed the highest and temperature-independent anti-selectivity of 89:11 measured in the reaction series also at −78 °C (Table 7, entry 7) in contrast to the corresponding methyl ester radical **2e**, which reacted unselectively at −78 °C (Table 5, entry 9). Obviously, the temperature-independent anti-selectivity of the trapping of radical **6b** can be explained analogously as for radicals **2j**−**l**. The calculations show that the stabilities of conformers A and B are reversed going from radical **2e** to **6b** (Table 8); transferred to transition states, this implies $\Delta H^‡_{syn} \geq \Delta H^‡_{anti}$ for radical **6b** in contrast to radical **2e**.

Although the reactions performed in the absence of a Lewis acid did not lead to interesting findings similar to those of the chelation-controlled ones, some general tendencies appeared that

(17) (a) Giese, B. *Angew. Chem.* **1977**, *89*, 162−173; *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 125−136. (b) Giese, B. *Acc. Chem. Res.* **1984**, *17*, 438−442.

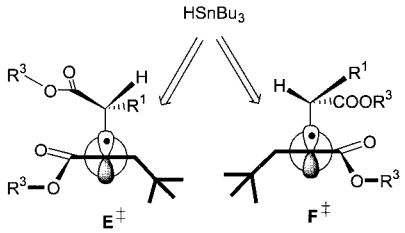


Figure 2. Transition-state models of hydrogen transfer to unchelated radicals **2a**−**d** and **6a**. Syn-products are thought to be formed preferentially via E‡, anti-products via F‡.

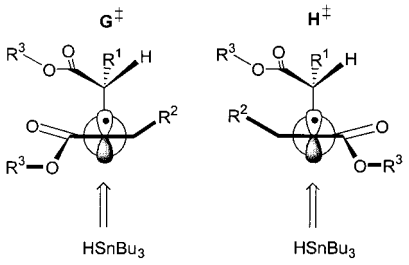


Figure 3. Transition-state models of hydrogen transfer to unchelated radicals **2e**−**k** and **6b**. Syn-products are thought to be formed preferentially via H‡, anti-products via G‡.

are worth a short discussion and can reasonably be explained by considering steric effects in the transition states.[6b] To start off with the outcome of the neopentyl series, the observed diastereoselectivities can be understood by considering transition-states E‡ and F‡ (Figure 2). While radical **2a** reacts completely unselectively (Table 3, entries 1−4), radicals **2b**−**d** (Table 4, entries 1−6) are trapped with low syn-selectivities at −78 °C—which become larger with increasing steric demand of alkyl substituent R^1 (*n*Pr < *i*Pr < cHex)—and at 80 °C inversion to low anti-selectivities takes place. E‡ and F‡ are based on the assumption that the steric impact of the neopentyl moiety renders the transition states with the depicted downward orientation of this group the most likely so that hydrogen transfer occurs from the upper side of the radical.

$\Delta H^{\ddagger}_{syn} < \Delta H^{\ddagger}_{anti}$ because in transition-state E‡ steric interactions of the α- and γ-substituents are smaller compared to F‡. When R^1 becomes sterically more demanding, transition-state E‡ gets more favorable, $\delta\Delta H^{\ddagger}$ increases, and thus more syn-product is formed. In terms of eq 1, enthalpic and entropic factors are opposed, which explains the selectivity change from general syn- to general anti-preference at higher reaction temperature. The same effect is observed by increasing the steric demand of alkyl ester group R^3. Thus, radical **6a** is trapped with low syn-selectivity (Table 7, entries 1 and 2) in contrast to the unselective trapping of radical **2a**.

Trapping of radicals **2e**−**l** occurs with low anti-selectivity, which decreases with increasing temperature until inversion to syn-selectivity is observed in the case of radicals **2j**−**l** (Table 6). Interestingly, γ-alkyl substituent R^1 exhibits no significant influence on the selectivity (Table 5), which indicates that only transition states with R^1 pointing backward have to be considered (Figure 3). Transition-state G‡, providing *anti*-**3e**−**l** is energetically favored due to lesser steric congestion than in H‡, while *syn*-**3e**−**l** are formed with higher activation energy via H‡. This model was applied before for an explanation of 1,3-stereoinduction of iodine transfer to alkyl radicals.[6b]

Remarkably, in the case of radical **6b** (R^3 = *t*Bu), syn-selectivity increases from −78 °C—almost unselective—to [anti]:[syn] = 42:58 at 80 °C (Table 7). Obviously, transition-state H‡ is entropically more favorable, especially in the case of the *tert*-butyl esters.

Conclusions

Our investigation of the tin hydride-mediated radical addition−hydrogen transfer sequence reactions to 2-alkyl-4-methylene pentanedioates **1,** exhibiting different structural features, clearly establishes the scope of 1,3-stereoinduction as a powerful synthetic tool. The findings show that chelation control has a strong regulating influence. The extensive study reveals a significant effect of the α-substituent at the radical center and minor effects of the γ-substituents and the alkyl group of the ester moieties with respect to selectivity. Apart from the structural effects, the examination of the temperature dependence of the selectivity adds another interesting feature to the performed reaction series, revealing strong entropic influences on the stereochemical outcome.

Experimental Section

General Methods. All radical reactions were performed under argon in reaction vessels that were previously evacuated, heated, and flushed with inert gas. All commercially available reagents were employed as supplied; solvents were dried and distilled according to standard procedures. For column chromatography, Merck 60 silica gel, 63−200 μm, was used. Analytical GC was performed on a Carlo Erba HRGC with FID detector and fused-silica capillary column DB1 30 m. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) on a Bruker AM 300 or a Bruker AM 500 spectrometer at 20 °C using TMS (^{1}H NMR) and $CDCl_3$ (δ = 77.0 ppm, ^{13}C NMR) as internal standard. Mass spectra were recorded on a Finnigan MAT 212. Elemental analysis was conducted by Mikroanalytisches Labor Beller, D-37004 Göttingen, Germany.

Calculations. The quantum chemical calculations have been carried out using the PM3 Hamiltonian[18] and the unrestricted Hartree−Fock (UHF) approach. The size of the investigated systems renders ab initio calculations not feasible. All structures were minimized with the default options available within the MOPAC 93 program package.[19] Lithium as Lewis acid was chosen because of the availability of more reliable Li parameters for PM3,[20] compared to Mg parameters.[18]

Crystallographic Data of 8a and 8b. Crystallographic data (CIF-files) of **8a** and **8b** have been deposited with the Cambridge Crystallographic Data Centre as CCDC-137280 and CCDC-137281. Copies of the data can be obtained free of charge from the CCDC, 12 Union Rd., Cambridge CB21EZ, U.K.

Dimethyl 2-Alkyl-4-methylenepentanedioates (1a−d). Compounds **1a**−**d** were synthesized by a reaction sequence starting with the alkylation of commercially available dimethyl malonate, followed by a saponification/decarboxylation process according to Stetter,[14a] yielding α-alkyl acrylic esters. Michael addition of dimethyl malonate to these esters then led to trimethyl 1,1,3-alkanetricarboxylates, which provided educts **1a**−**d** upon Stetter reaction.

Dimethyl 2-Iodo-2,4-dimethylpentanedioate (4). Under argon atmosphere, *n*-butyllithium (3.6 mL, 5.8 mmol; 1.6 *m* solution in hexane) was added dropwise at −78 °C to a solution of freshly distilled diisopropylamine (0.85 mL, 6.1 mmol) in 25 mL of dry THF; the mixture was stirred for 30 min. The temperature was allowed to rise to 0 °C for 15 min; after that the flask was cooled to −100 °C. A solution of dimethyl 2,4-dimethylpentanedioate (1 g, 5.18 mmol, 1:1 diastereomeric mixture of meso- and (±)-form) in 25 mL of dry THF was introduced dropwise, and the mixture was stirred for 1.5 h while the temperature was kept at −100°. The enolate solution was then decanted into a precooled dropping funnel and by means of this added to a previously to −78 °C cooled solution of iodine (2 g, 7.9 mmol) in

(18) (a) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−220. (b) Stewart, J. J. P.; *J. Comput. Chem.* **1991**, *12*, 320−341.
(19) Stewart, J. J. P. *QCPE* **1993**, Program 455 (version 93).
(20) Anders, E.; Koch, R.; Freunscht, P. *J. Comput. Chem.* **1993**, *14*, 1301−1312.

50 mL of dry THF. Stirring was maintained for 2 h, and then HCl (10% aqueous, 5.3 mL) was added. Workup included addition of diethyl ether, extraction with aqueous solutions of $Na_2S_2O_3$, $NaHCO_3$, and brine, drying with $MgSO_4$, and evaporation, which afforded **4** in a diastereomeric ratio of 1:1 as an instable light brown liquid, which decomposed visibly, turning dark brown upon storage under argon at 8 °C. **4** was used without further purification due to the instability: yield 1.13 g (68%); ^{1}H NMR (500.1 MHz, diastereomer 1) δ 1.18 (d, ^3J = 7.13 Hz, 3H, CH_3CH), 2.04 (s, 3H, CH_3CI), 2.20 (dd, ^3J = 13.18 Hz, ^2J = 8.78 Hz, 1H, CHCHHCH), 2.43−2.52 (m, 1H, CHCHHCH), 2.73−2.82 (m, 1H, CH_3CH), 3.65, 3.75 (2CO_2CH_3); ^{13}C NMR (125.8 MHz, diastereomer 1) δ 18.89 (*C*H_3CH), 29.88 (*C*H_3CI), 37.49 (CI), 37.98 (CH_3*C*H), 47.97 (CH_2), 51.88, 52.98 (2CO_2*C*H_3), 172.94, 176.00 (2CO_2*C*H_3); ^{1}H NMR (500.1 MHz, diastereomer 2) δ 1.24 (d, ^3J = 6.58 Hz, 3H, CH_3CH), 2.05 (s, 3H, CH_3CI), 2.28 (dd, ^3J = 14.55 Hz, ^2J = 2.47 Hz, 1H, CHCHHCH), 2.38−2.43 (m, 1H, CHCHHCH), 2.60−2.69 (m, 1H, CH_3CH); ^{13}C NMR (125.8 MHz, diastereomer 2) δ 19.08 (*C*H_3CH), 30.31 (*C*H_3CI), 38.66 (CH_3*C*H), 39.18 (CI), 47.42 (CH_2), 52.84, 53.00 (2CO_2*C*H_3), 173.02, 176.24 (2*C*O_2*C*H_3); MS (CI, isobutane) *m*/*z* (%) 315 (85) [*M*H$^+$], 283 (100) [*M*H$^+$ − OCH_3], 187 (32) [M^+ − I].

Di-*tert*-butyl 2-Methyl-4-methylenepentanedioate (5). A mixture of *N*,*N*′-diisopropylcarbodiimide (8 mL, 51 mmol), *tert*-butyl alcohol (5.6 mL, 59 mmol), and CuCl (0.05 g, 0.51 mmol) was stirred under argon at room temperature for 3 days. After dilution with CH_2Cl_2 (30 mL), it was added dropwise to a solution of 2-methyl-4-methylenepentanedioic acid (1.34 g, 8.5 mmol) in $CHCl_3$ (50 mL). The precipitated *N*,*N*′-diisopropylurea was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated. Purification by column chromatography afforded **5** as a colorless liquid: yield 31%; R_f = 0.35 (petroleum ether 60/80/EtOAc 9.5/0.5); ^{1}H NMR (300.1 MHz) δ 1.11 (d, ^3J (H,H) = 6.63 Hz, 3H, CH_3), 1.42 (s, 9H, C(CH_3)$_3$), 1.50 (s, 9H, C(CH_3)$_3$), 2.20−2.39 (m, 1H, CHCH_3), 2.50−2.68 (m, 2H, CH_2), 5.48 (d, ^2J (H,H) = 1.58 Hz, 1H, =CHH), 6.19 (d, ^2J (H,H) = 1.58 Hz, 1H, =CHH); ^{13}C NMR (75.5 MHz) δ 17.05 (*C*H_3CH), 28.02 (C(*C*H_3)$_3$), 36.43 (CH_2), 39.21 (CH_3*C*H), 80.06, 80.53 (*C*(CH_3)$_3$), 125.55 (CH_2=C), 139.71 (CH_2=*C*), 166.05 (=C*C*O_2*t*Bu), 175.42 (CH*C*O_2*t*Bu); MS (CI, isobutane) *m*/*z* (%) = 215 (22) [M^+ − C(CH_3)$_3$ + 2H], 159 (100) [M^+ − (C(CH_3)$_3$)$_2$ + 3H]; $C_{15}H_{26}O_4$ (270.37) calcd C, 66.64; H, 9.69; found C, 66.97; H, 9.75.

General Procedure for Radical Additions to Alkenes 1a−d and 5 under Chelation-Controlled Conditions. Conditions A (−78, 0, 20, and 40 °C). In a typical run, 5.4 mmol (2 equiv) of $MgBr_2$·OEt_2 was dissolved in 5 mL of dry diethyl ether in an argon-purged reaction flask. After the mixture was stirred for 15 min at 20 °C, 10 mL of dry CH_2Cl_2 and 2.7 mmol of dialkyl 2-alkyl-4-methylenepentanedioate **1** or **5** were added and stirring was continued for at least 30 min. The solution was cooled to −78 °C, 0 °C, left at ambient temperature, or heated to reflux and 3 equiv of Bu_3SnH and alkyl iodide, respectively, were added. Via syringe, 5 mL of O_2 and 2.7 mmol of Et_3B (1 *m* solution in hexane) were then injected simultaneously below the surface of the solution over a time period of 1 h. The reaction mixture was stirred at the chosen temperature for at least 4 h.

Conditions B (−20 °C). In a typical run, 5.4 mmol (2 equiv) of $MgBr_2$·OEt_2 was dissolved in 5 mL of dry diethyl ether in an argon-purged photoreactor. After the mixture was stirred for 15 min at 20 °C, 10 mL of dry CH_2Cl_2 and 2.7 mmol of dialkyl 2-alkyl-4-methylenepentanedioate **1** or **5** were added and stirring was continued for at least 30 min. The solution was cooled to −20 °C by means of a cryostat, and 3 equiv of Bu_3SnH and alkyl iodide, respectively, were added. The reaction mixture was irradiated by a 5-W mercury lamp for 6 h.

Conditions C (70 and 100 °C). In a typical run, 5.4 mmol (2 equiv) of $MgBr_2$·OEt_2 was dissolved in 2 mL of dry diethyl ether in an argon-purged reaction flask. After the mixture was stirred for 15 min at 20 °C, 5 mL of dry benzene or toluene and 2.7 mmol of dialkyl 2-alkyl-4-methylenepentanedioate **1** or **5** were added and stirring was continued for at least 30 min. The solution was heated to reflux temperature, and 3 equiv of alkyl bromide was added. Via syringe, a solution of 3 equiv of Bu_3SnH and 20 mol % of AIBN in 4 mL of benzene was fed into the reaction mixture during 2 h. Afterward, reflux was maintained for another 2−3 h.

Workup Procedure. Conditions A−C. GC analysis for determination of diastereomeric ratios was performed on the crude reaction mixtures after filtration of the sample through a 1-cm layer of silica gel. For general workup, the reaction mixture was diluted with 10 mL of saturated aqueous $NaHCO_3$ and stirred for 2 h. The organic layer was decanted and the aqueous layer extracted 2× with CH_2Cl_2 or benzene, respectively. The organic extracts were combined, successively washed with water, 1 *m* HCl, and brine, and dried ($MgSO_4$). After evaporation, products were purified by chromatography on silica gel using (1) hexane and (2) petroleum ether 60/80/ethyl acetate (9.5:0.5) as eluent. All dialkyl 2,4-dialkylpentanedioates were obtained as colorless liquids.

In an alternative workup procedure, 1 equiv of Me_3Al (2 *m* solution in hexane, in reference to Bu_3SnH) was added to the reaction mixture and the resultant mixture was stirred for 2 h. After hydrolysis with 15 mL of 2 N NaOH, stirring was continued for another 2 h. The organic layer was decanted, and the aqueous layer was extracted 2× with the appropriate solvent. The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated. To separate methyltributyltin from the products, the residue was subjected to a filtration through a short pad of silica gel, using *n*-hexane (150 mL) as eluent followed by *n*-hexane/ethyl acetate (200 mL, 4:1) to elute the fraction containing the products. After evaporation, products were purified by chromatography on silica gel using (1) hexane and (2) petroleum ether 60/80/ethyl acetate (9.5:0.5) as eluent.

Reaction of Dimethyl 2,4-Dimethyl-2-iodopentanedioate (4) with Bu_3SnH. Reactions at −78 and 70 °C were carried out according to conditions A and C, leaving out the addition of alkyl halides.

Dimethyl 2-methyl-4-neopentylpentanedioate (3a): ^{1}H NMR (300.1 MHz, *syn*-**3a**) δ 0.86 (s, 9H, C(CH_3)$_3$), 1.19 (d, ^3J (H,H) = 6.99 Hz, 3H, CHCH_3), 1.10−1.30 (m, 1H, (CH_3)$_3$CCHH), 1.40−1.52 (m, 1H, CHCHHCH), 1.72−1.85 (m, 1H, (CH_3)$_3$CCHH), 1.95−2.08 (m, 1H, CHCHHCH), 2.35−2.53 (m, 2H, 2CHCO_2Me), 3.66 (s, 3H, CO_2CH_3), 3.67 (s, 3H, CO_2CH_3); ^{13}C NMR (75.5 MHz, *syn*-**3a**) δ 17.37 (CH_3), 29.67 (C(*C*H_3)$_3$), 31.12 (*C*(CH_3)$_3$), 38.00 (CH*C*H_2CH), 37.82, 40.05 (2*C*HCO_2Me), 46.62 ((CH_3)$_3$*C*CH_2), 52.03 (2CO_2*C*H_3), 176.86, 177.56 (2CO_2CH_3); ^{1}H NMR (300.1 MHz, *anti*-**3a**) δ 0.87 (s, 9H, C(CH_3)$_3$), 1.15 (d, ^3J (H,H) = 7.0 Hz, 3H, CHCH_3), 1.10−1.37 (m, 1H, (CH_3)$_3$CCHH), 1.56−1.7 (m, 1H, (CH_3)$_3$CCHH), 1.7−1.88 (m, 2H, CHCH_2CH), 2.30−2.54 (m, 2H, 2CHCO_2Me), 3.66 (s, 3H, CO_2CH_3), 3.69 (s, 3H, CO_2CH_3); ^{13}C NMR (75.5 MHz, *anti*-**3a**) δ 18.50 (CH_3), 29.68 (C(*C*H_3)$_3$), 30.07 (*C*(CH_3)$_3$), 39.02 (CH*C*H_2CH), 37.91, 40.30 (*C*HCO_2Me), 47.03 ((CH_3)$_3$*C*CH_2), 51.88, 52.01 (2CO_2*C*H_3), 176.90, 177.85 (2*C*O_2CH_3); MS (CI, isobutane) *m*/*z* (%) 245 (100) [*M*H$^+$], 213 (68) [*M*H$^+$ − CH_3OH]; $C_{13}H_{24}O_4$ (244.33) calcd C, 63.91; H, 9.90; found C, 63.90; H, 9.99.

Dimethyl 2-neopentyl-4-propylpentanedioate (3b): ^{1}H NMR (300.1 MHz, *syn*-**3b)** δ 0.86 (s, 9H, C(CH_3)$_3$), 0.92 (t, ^3J (H,H) = 7.53 Hz, 3H, CH_3CH_2), 1.12−1.72 (m, 6H, CH_3CH_2CH_2, (CH_3)$_3$CCHH, CHCHHCH), 1.72−1.83 (m, 1H, (CH_3)$_3$CCHH)), 1.86−1.99 (m, 1H, CHCHHCH), 2.32−2.48 (m, 2H, 2CHCO_2Me), 3.65 (s, 3H, CO_2CH_3), 3.66 (s, 3H, CO_2CH_3); ^{13}C NMR (75.5 MHz, *syn*-**3b**) δ 13.82 (*C*H_3-CH_2), 20.35 (CH_3CH_2), 29.23 (C(*C*H_3)$_3$), 30.61 (*C*(CH_3)$_3$), 34.42, 36.84, (CH_3CH_2*C*H_2CH*C*H$_2$), 39.91, 43.16 (2*C*HCO_2Me), 45.78 ((CH_3)$_3$*C*CH_2), 51.35, 51.47 (2CO_2*C*H_3), 176.01, 177.15 (2*C*O_2CH_3); ^{1}H NMR (300.1 MHz, *anti*-**3b**) δ 0.86 (s, 9H, C(CH_3)$_3$), 0.88 (t, ^3J (H,H) = 7.16 Hz, 3H, CH_3CH_2), 1.12−1.33 (m, 3H, CH_3CH_2, (CH_3)$_3$CCHH), 1.33−1.48 (m, 1H, CH_3CH_2CHH), 1.48−1.63 (m, 1H, CH_3CH_2CHH), 1.63−1.82 (m, 3H, (CH_3)$_3$CCHH, CHCH_2CH), 2.21−2.34 (m, 1H, CHCO_2Me), 2.37−2.49 (m, 1H, CHCO_2Me), 3.66 (s, 3H, CO_2CH_3), 3.69 (s, 3H, CO_2CH_3); ^{13}C NMR (75.5 MHz, *anti*-**3b**) δ 14.21 (*C*H_3CH_2), 20.67 (CH_3*C*H_2), 29.68 (C(*C*H_3)$_3$), 31.15 (*C*(CH_3)$_3$), 35.68, 37.58 (CH_3CH_2*C*H_2CH*C*H$_2$), 40.47, 43.60 (2*C*HCO_2Me), 47.37 ((CH_3)$_3$*C*CH_2), 51.77 (2CO_2*C*H_3), 176.53, 177.73 (2*C*O_2CH_3); MS (CI, isobutane) *m*/*z* (%) 273 (83) [*M*H$^+$], 241 (100) [*M*H$^+$ − CH_3OH]; $C_{15}H_{28}O_4$ (272.38) calcd C, 66.14; H, 10.36; found C, 66.36; H, 10.12.

Dimethyl 2-isopropyl-4-neopentylpentanedioate (3c): ^{1}H NMR (300.1 MHz, *syn*-**3c**) δ 0.85 (s, 9H, (CH_3)$_3$C), 0.90 (d, ^3J (H,H) = 7.16 Hz, 3H, CH_3CHCH_3), 0.93 (d, ^3J (H,H) = 6.78 Hz, 3H, CH_3-CHCH_3) 1.18−1.72 (m, 3H, (CH_3)$_3$CCHH), CHCHHCH, CH(CH_3)$_2$,

1.72−2.00 (m, 2H, CHCH*H*CH, $(CH_3)_3CCH$*H*), 2.19−2.38 (m, 2H, 2CHCO$_2$Me), 3.65 (s, 3H, CO$_2$CH$_3$), 3.69 (s, 3H, CO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, *syn*-**3c**) δ 20.35, 20.57 (CH(*C*H$_3$)$_2$), 29.61 (C(*C*H$_3$)$_3$), 30.92 (*C*(CH$_3$)$_3$), 31.14 (*C*H(CH$_3$)$_2$), 34.37 (CH*C*H$_2$CH), 40.66, 50.43 (2*C*HCO$_2$Me), 45.48 ((CH$_3$)$_3$*C*CH$_2$), 51.55, 51.92 (2CO$_2$*C*H$_3$), 175.64, 177.72 (2*C*O$_2$CH$_3$); ^{1}H NMR (300.1 MHz, *anti*-**3c**) δ 0.86 (s, 9H, C(CH$_3$)$_3$), 0.88 (d, ^3J (H,H) = 6.75 Hz, 3H, C*H*$_3$CHCH$_3$), 0.90 (d, ^3J (H,H) = 6.57 Hz, 3H, CH$_3$CHC*H*$_3$), 1.24 (dd, ^3J (H,H) = 14.04 Hz, ^2J (H,H) = 3.08 Hz, 1H, ((CH$_3$)$_3$CC*H*H), 1.64−1.92 (m, 4H, (CHC*H*$_2$CH, (CH$_3$)$_2$C*H*, (CH$_3$)$_3$CCH*H*), 2.05−2.15 (m, 1H, (CHCO$_2$Me), 2.33−2.44 (m, 1H, CHCO$_2$Me), 3.65 (s, 3H, CO$_2$CH$_3$), 3.69 (s, 3H, CO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, *anti*-**3c**) δ 19.84, 20.10 (C(*C*H$_3$)$_2$), 29.29 (C(*C*H$_3$)$_3$), 30.78 (*C*(CH$_3$)$_3$), 31.03 (*C*H(CH$_3$)$_2$), 34.37 (CH*C*H$_2$CH), 40.33, 49.96 (2*C*HCO$_2$Me), 47.33 ((CH$_3$)$_3$*C*CH$_2$), 51.18, 51.35 (2CO$_2$*C*H$_3$), 175.41, 177.40 (2*C*O$_2$CH$_3$); MS (CI, isobutane) *m*/*z* (%) 273 (79) [*M*H$^+$], 241 (100) [*M*H$^+$ − CH$_3$OH]; C$_{15}$H$_{28}$O$_4$ (272.38) calcd C, 66.14; H, 10.36; found C, 66.29; H, 10.40.

Dimethyl 2-cyclohexyl-4-neopentylpentanedioate (3d): ^{1}H NMR (300.1 MHz, *syn*-**3d**) δ 0.84 (s, 9H, C(CH$_3$)$_3$), 0.84−1.82 (m, 14H, cyclohexyl-H, C$_6$H$_{11}$C*H*$_2$, CHCH*H*CH), 1.85−1.97 (m, 1H, CHC*H*HCH), 2.21−2.35 (m, 2H, 2CHCO$_2$Me), 3.64 (s, 3H, CO$_2$CH$_3$), 3.66 (s, 3H, CO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, *syn*-**3d**) δ 26.66, 31.02 (cyclohexyl-C), 29.61 (C(*C*H$_3$)$_3$), 30.92 (*C*(CH$_3$)$_3$), 34.27 (CH*C*H$_2$CH), 40.71, 49.90 (2*C*HCO$_2$Me), 40.93 (cyclohexyl: C1), 45.40 ((CH$_3$)$_3$C*C*H$_2$), 51.55, 51.93 (2CO$_2$*C*H$_3$), 175.75, 177.74 (2*C*O$_2$CH$_3$); ^{1}H NMR (300.1 MHz, *anti*-**3d**) δ 0.86 (s, 9H, C(CH$_3$)$_3$), 0.85−1.29 (m, 5H, cyclohexyl: H2, H3, H4, H5. H6), 1.4−1.82 (m, 12 H, cyclohexyl: H1, H2, H3, H4, H5, H6, C$_6$H$_{11}$C*H*$_2$CHC*H*$_2$CHC*H*$_2$), 2.10−2.12 (m, 1H, CHCO$_2$Me), 2.29−2.43 (m, 1H, CHCO$_2$Me), 3.65 (s, 3H, CO$_2$C*H*$_3$), 3.68 (s, 3H, CO$_2$C*H*$_3$); ^{13}C NMR (75.5 MHz, *anti*-**3d**) δ 26.28, 30.38, 30.65, (cyclohexyl-C), 29.30 (C(*C*H$_3$)$_3$), 30.79 (*C*(CH$_3$)$_3$), 34.49 (CH*C*H$_2$CH), 40.39, 49.50 (2*C*HCO$_2$Me), 40.81 (cyclohexyl: C1), 47.32 ((CH$_3$)$_3$C*C*H$_2$), 51.18, 51.36 (2CO$_2$*C*H$_3$), 175.50, 177.34 (2*C*O$_2$CH$_3$); MS (CI, isobutane) *m*/*z* (%) 313 (100) [*M*H$^+$], 281 (98) [*M*H$^+$ − CH$_3$OH]; C$_{15}$H$_{28}$O$_4$ (312.45) calcd C, 69.19; H, 10.32; found C, 69.13; H, 10.25.

Dimethyl 2-(cyclohexylmethyl)-4-methylpentanedioate (3e): ^{1}H NMR (300.1 MHz, *syn*-**3e**) δ 0.73−1.02 (m, 2H, cyclohexyl: H2, H6), 1.03−1.42 (m, 5H, cyclohexyl: H1, H3, H4, H5, C$_6$H$_{11}$C*H*H), 1.16 (d, ^3J (H,H) = 7.16 Hz, 3H, CH$_3$), 1.45−1.57 (m, 1H, C$_6$H$_{11}$CH*H*), 1.57−1.82 (m, 6H, cyclohexyl: H2, H3, H4, H5, H6, CHC*H*HCH), 1.96−2.08 (m, 1H, CHCH*H*CH), 2.37−2.60 (m, 2H, 2CHCO$_2$Me), 3.67 (s, 6H, 2CO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, *syn*-**3e**) δ 18.02 (CH$_3$), 26.55, 26.86, 33.24, 35.93, 37.90 (CH*C*H$_2$CH, 4cyclohexyl-C), 40.72 (C$_6$H$_{11}$*C*H$_2$), 36.73, 37.96, 41.00 (2*C*HCO$_2$Me, cyclohexyl: C1), 51.83, 51.93 (2CO$_2$*C*H$_3$), 176.89, 177.05 (2*C*O$_2$CH$_3$); ^{1}H NMR (300.1 MHz, *anti*-**3e**) δ 0.73−0.97 (m, 2H, cyclohexyl: H2, H6), 1.03−1.42 (m, 5H, cyclohexyl: H1, H3, H4, H5, C$_6$H$_{11}$C*H*H), 1.15 (d, ^3J (H,H) = 6.78 Hz, 3H, CH$_3$), 1.45−1.88 (m, 8H, cyclohexyl: H2, H3, H4, H5, H6, C$_6$H$_{11}$CH*H*, CHC*H*$_2$CH), 2.34−2.58 (m, 2H, 2CHCO$_2$Me), 3.67 (s, 6H, 2CO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, *anti*-**3e**) δ 18.40 (CH$_3$), 26.55, 26.87, 33.39, 33.72 (cyclohexyl-C), 36.95 (CH*C*H$_2$CH), 40.99 (C$_6$H$_{11}$*C*H$_2$), 35.85, 38.11, 41.34 (2*C*HCO$_2$Me, cyclohexyl: C1), 51.78, 51.91 (2CO$_2$*C*H$_3$), 176.95, 177.07 (2*C*O$_2$CH$_3$); MS (CI, isobutane) *m*/*z* (%) 271 (60) [*M*H$^+$], 239 (100) [*M*H$^+$ − CH$_3$OH]; C$_{15}$H$_{26}$O$_4$ (270.37) calcd C, 66.64; H, 9.69; found C, 66.31; H, 9.46.

Dimethyl 2-(cyclohexylmethyl)-4-propylpentanedioate (3f): ^{1}H NMR (300.1 MHz, *syn*-**3f**) δ 0.75−0.98 (m, 2H, cyclohexyl: H2, H6), 0.89 (t, ^3J (H,H) = 7.23 Hz, 3H, C*H*$_3$CH$_2$), 1.05−1.80 (m, 16H, cyclohexyl: H1, H2, 2H3, 2H4, 2H5, H6, CHC*H*HCHC*H*$_2$C*H*$_2$, C$_6$H$_{11}$C*H*$_2$), 1.88−2.01 (m, 1H, CHCH*H*CH), 2.32−2.54 (m, 2H, 2CHCO$_2$Me), 3.66 (s, 6H, 2CO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, *syn*-**3f**) δ 13.86 (*C*H$_3$CH$_2$), 20.39 (CH$_3$*C*H$_2$), 26.16, 26.46, 32.70, 33.65, 35.09, 35.35 (cyclohexyl-C, CH$_3$CH$_2$*C*H$_2$, CHC*H*$_2$CH), 35.55 (cyclohexyl: C1), 39.98 (C$_6$H$_{11}$*C*H$_2$), 40.87, 43.26 (2*C*HCO$_2$Me), 51.43 (2CO$_2$*C*H$_3$), 176.13, 176.41 (2*C*O$_2$Me); ^{1}H NMR (300.1 MHz, *anti*-**3f**) δ 0.74−0.93 (m, 2H, cyclohexyl: H2, H6), 0.88 (t, ^3J (H,H) = 7.19 Hz, 3H, C*H*$_3$CH$_2$), 1.06−1.94 (m, 17H, cyclohexyl: H1, H2, 2H3, 2H4, 2H5, H6, CHC*H*$_2$CHC*H*$_2$C*H*$_2$, C$_6$H$_{11}$C*H*$_2$), 2.28−2.38 (m, 1H, CHCO$_2$Me), 2.38−2.50 (m, 1H, CHCO$_2$Me), 3.65 (s, 6H, 2CO$_2$CH$_3$); ^{13}C NMR (75.5 MHz, *anti*-**3f**) δ 13.83 (*C*H$_3$CH$_2$), 20.36 (CH$_3$*C*H$_2$), 26.17, 26.48, 33.05, 33.27, 35.03, 35.29, 35.44 (cyclohexyl-C, CH$_3$CH$_2$*C*H$_2$, CH*C*H$_2$CH), 40.83 (C$_6$H$_{11}$*C*H$_2$), 41.04, 43.42 (2*C*HCO$_2$Me), 51.38 (2CO$_2$*C*H$_3$), 176.30, 176.67 (2*C*O$_2$CH$_3$); MS (CI, isobutane) *m*/*z* (%) 299 (100) [*M*H$^+$], 267 (47) [*M*H$^+$ − CH$_3$OH]; C$_{17}$H$_{30}$O$_4$ (298.42) calcd C, 68.42; H 10.13; found C, 68.56; H, 10.01.

Dimethyl 2-(cyclohexylmethyl)-4-isopropylpentanedioate (3g): ^{1}H NMR (500.1 MHz, *syn*-**3g**) δ 0.75−0.95 (m, 2H, cyclohexyl: H2, H6), 0.91 (d, ^3J (H,H) = 6.59 Hz, 3H, C*H*$_3$CHCH$_3$), 0.93 (d, ^3J (H,H) = 7.19 Hz, 3H, CH$_3$CHC*H*$_3$), 1.08−1.41 (m, 5H, cyclohexyl: H1, H3, H4, H5, C$_6$H$_{11}$C*H*H), 1.50−1.58 (m, 1H, C$_6$H$_{11}$CH*H*), 1.58−1.70 (m, 5H, cyclohexyl: H2, H3, H4, H5, H6), 1.70−1.78 (m, 1H, CHC*H*HCH), 1.80−1.89 (m, 1H, (CH$_3$)$_2$C*H*), 1.90−1.99 (m, 1H, CHCH*H*CH), 2.18−2.24 (m, 1H, (CH$_3$)$_2$CHC*H*), 2.35−2.43 (m, 1H, C$_6$H$_5$CH$_2$C*H*CH$_2$), 3.65 (s, 3H, CO$_2$CH$_3$), 3.67 (s, 3H, CO$_2$CH$_3$); ^{13}C NMR (125.8 MHz, *syn*-**3g**) δ 20.09, 20.20 (CH(*C*H$_3$)$_2$), 26.08, 26.17, 26.46, 32.22, 32.48, 33.82, (cyclohexyl-C, CH*C*H$_2$CH), 30.70 (*C*H(CH$_3$)$_2$), 35.60 (cyclohexyl: C1), 39.41 (C$_6$H$_{11}$*C*H$_2$), 41.29 (CH$_2$*C*HCH$_2$), 50.15 ((CH$_3$)$_2$CH*C*H), 51.55, 51.73 (2CO$_2$*C*H$_3$), 175.97, 177.03 (2*C*O$_2$CH$_3$); ^{1}H NMR (500.1 MHz, *anti*-**3g**) δ 0.78−0.93 (m, 2H, cyclohexyl: H2, H6), 0.90 (d, ^3J (H,H) = 6.58 Hz, 3H, C*H*$_3$CHCH$_3$), 0.93 (d, ^3J (H,H) = 7.14 Hz, 3H, CH$_3$CHC*H*$_3$), 1.06−1.40 (m, 5H, cyclohexyl: H1, H3, H4, H5, C$_6$H$_{11}$C*H*H), 1.48−1.56 (m, 1H, C$_6$H$_{11}$CH*H*), 1.59−1.78 (m, 7H, cyclohexyl: H2, H3, H4, H5, H6, CHC*H*$_2$CH), 1.79−1.89 (m, 1H, (CH$_3$)$_2$C*H*), 2.06−2.13 (m, 1H, (CH$_3$)$_2$CHC*H*), 2.36−2.45 (m, 1H, C$_6$H$_5$CH$_2$C*H*CH$_2$), 3.66 (s, 3H, CO$_2$CH$_3$), 3.67 (s, 3H, CO$_2$CH$_3$); ^{13}C NMR (125.8 MHz, *anti*-**3g**) δ 19.85, 20.24 (CH(*C*H$_3$)$_2$), 31.01 (*C*H(CH$_3$)$_2$,), 35.42 (cyclohexyl: C1), 26.14, 26.47, 32.15, 33.06, 33.19 (cyclohexyl-C, CH*C*H$_2$CH), 41.04 (C$_6$H$_{11}$*C*H$_2$), 41.27 (CH$_2$*C*HCH$_2$), 50.30 ((CH$_3$)$_2$CH*C*H), 51.55, 51.73 (2CO$_2$*C*H$_3$), 175.97, 177.03 (2*C*O$_2$CH$_3$); MS (CI, isobutane) *m*/*z* (%) 299 (42) [*M*H$^+$], 267 (100) [*M*H$^+$ − CH$_3$OH]; C$_{17}$H$_{30}$O$_4$ (298.42) calcd C, 68.42; H, 10.13; found C, 68.56; H, 10.03.

Dimethyl 2-cyclohexyl-4-(cyclohexylmethyl)pentanedioate (3h): ^{1}H NMR (500.1 MHz, *syn*-**3h**) δ 0.72−1.77 (m, 25H, cyclohexyl-H, C$_6$H$_{11}$C*H*$_2$, CHCH*H*CH), 1.85−1.94 (m, 1H, CHC*H*HCH), 2.17−2.24 (m, 1H, CHCO$_2$Me), 2.31−2.39 (m, 1H, CHCO$_2$Me), 3.62 (s, 3H, CO$_2$CH$_3$), 3.63 (s, 3H, CO$_2$CH$_3$); ^{13}C NMR (125.8 MHz, *syn*-**3h**) δ 26.09, 26.18, 26.23, 26.26, 26.47, 29.11, 30.57, 30.65, 32.34, 32.50, (cyclohexyl-C), 33.84 (CH*C*H$_2$CH), 35.60, 40.44 (2cyclohexyl: C1), 39.35 (C$_6$H$_{11}$*C*H$_2$), 41.33, 49.57 (2*C*HCO$_2$Me), 51.17, 51.44 (2CO$_2$*C*H$_3$), 175.48, 176.54 (2*C*O$_2$CH$_3$); ^{1}H NMR (500.1 MHz, *anti*-**3h**) δ 0.77−1.81 (m, 26H, cyclohexyl-H, C$_6$H$_{11}$C*H*$_2$, CHC*H*$_2$CH), 2.08−2.14 (m, 1H, CHCO$_2$Me), 2.39−2.42 (m, 1H, CHCO$_2$Me), 3.66 (s, 3H, CO$_2$CH$_3$), 3.67 (s, 3H, CO$_2$CH$_3$); ^{13}C NMR (125.8 MHz, *anti*-**3h**) δ 26.13, 26.16, 26.23, 26.47, 26.58, 29.11, 30.35, 30.76, 32.16, 33.09, 33.15 (cyclohexyl-C, CH*C*H$_2$CH), 35.39, 40.70 (2cyclohexyl: C1), 41.03 (C$_6$H$_{11}$*C*H$_2$), 41.27, 49.73 (2*C*HCO$_2$Me), 51.15, 51.34 (2CO$_2$*C*H$_3$), 175.66, 176.63 (2*C*O$_2$CH$_3$); MS (CI, isobutane) *m*/*z* (%) 339 (76) [*M*H$^+$], 307 (100) [*M*H$^+$ − CH$_3$OH]; C$_{17}$H$_{30}$O$_4$ (338.25) calcd C, 70.95; H, 10.13; found C, 71.25; H, 10.16.

Dimethyl 2-ethyl-4-methylpentanedioate (3j): ^{1}H NMR (500.1 MHz, *anti*-**3j**) δ 0.89 (t, ^3J = 7.41 Hz, 3H, C*H*$_3$CH$_2$), 1.15 (d, ^3J = 7.13 Hz, 3H, C*H*$_3$CH), 1.22−1.34 (m, 1H, CH$_3$C*H*H), 1.48−1.85 (m, 3H, CH$_3$CH*H*, CHC*H*$_2$CH), 2.35−2.53 (m, 2H, 2CHCO$_2$Me), 3.67 (s, 6H, 2CO$_2$CH$_3$); ^{13}C NMR (125.8 MHz, *anti*-**3j**) δ 11.55 (*C*H$_3$CH$_2$), 17.61 (*C*H$_3$CH), 25.94 (CH$_3$*C*H$_2$), 35.77 (CH*C*H$_2$CH), 37.73 (CH$_3$*C*H), 45.07 (CH$_2$*C*HCH$_2$), 51.35, 51.53 (2CO$_2$*C*H$_3$), 176.18, 176.64 (2*C*O$_2$CH$_3$); MS (CI, isobutane) *m*/*z* (%) 203 (70) [*M*H$^+$], 171 (100) [*M*$^+$ − OCH$_3$]; HRMS (CI, isobutane) C$_{10}$H$_{19}$O$_4$ [*M*H$^+$] calcd 203.1283, found 203.1221.

Dimethyl 2-methyl-4-propylpentanedioate (3k): ^{1}H NMR (500.1 MHz, *anti*-**3k**) δ 0.89 (t, ^3J = 7.41 Hz, 3H, C*H*$_3$CH$_2$), 1.15 (d, ^3J = 7.13 Hz, 3H, C*H*$_3$CH), 1.20−1.37 (m, 2H, CH$_3$C*H*$_2$), 1.37−1.48 (m, 1H, CHC*H*HCH), 1.51−1.75 (m, 2H, CH$_3$CH$_2$C*H*$_2$), 1.77−1.85 (m, 1H, CHCH*H*CH), 2.36−2.48 (m, 2H, 2CHCO$_2$Me), 3.67 (s, 6H, 2CO$_2$CH$_3$); ^{13}C NMR (125.8 MHz, *anti*-**3k**) δ 13.85 (*C*H$_3$CH$_2$), 18.02 (*C*H$_3$CH), 20.36 (CH$_3$*C*H$_2$), 35.06, 36.14 (*C*H$_2$CHCH$_2$), 37.77 (CH$_3$*C*H), 43.38 (CH$_2$*C*HCH$_2$), 51.40, 51.56 (2CO$_2$*C*H$_3$), 176.42, 176.65 (2*C*O$_2$CH$_3$); MS (CI, isobutane) *m*/*z* (%) 217 (46) [*M*H$^+$], 185 (100) [*M*$^+$ − OCH$_3$]; HRMS (CI, isobutane) C$_{11}$H$_{21}$O$_4$ [*M*H$^+$] calcd 217.1440, found 217.1364.

Di-*tert*-butyl 2-methyl-4-neopentylpentanedioate (7a): ^{1}H NMR (300.1 MHz, *syn*-**7a**) δ 0.88 (s, 9H, C(CH_3)$_3$), 1.14 (d, ^3J (H,H) = 6.79 Hz, 3H, CH_3), 1.44 (s, 18H, 2CO_2(C(CH_3)$_3$), 1.03−1.50 (m, 2H, C*H*HCHC*H*HCH), 1.70−1.82 (m, 1H, C*H*HC(CH_3)$_3$), 1.84−1.96 (m, 1H, CHC*H*HCH), 2.18−2.41 (m, 2H, 2CHCO_2*t*Bu); ^{13}C NMR (75.48 MHz, *syn*-**7a**) δ 16.76 (CH_3), 28.01, 29.47 (3C(*C*H_3)$_3$), 30.77 (CH_2*C*(CH_3)$_3$), 38.25, 40.47 (2*C*HCO_2*t*Bu), 38.76 (CH*C*H_2CH), 45.82 ((CH_3)$_3$C*C*H_2), 79.95 (2CO_2*C*(CH_3)$_3$), 175.53, 176.09 (2*C*O_2C(CH_3)$_3$); ^{1}H NMR (300.1 MHz, *anti*-**7a**) δ 0.88 (s, 9H, C(CH_3)$_3$), 1.10 (d, ^3J (H,H) = 7.16 Hz, 3H, CH_3), 1.46 (s, 18H, 2CO_2C(C*H*$_3$)$_3$), 1.10−1.60 (m, 2H, C*H*$_2$C(CH_3)$_3$), 1.63−1.80 (m, 2H, CHC*H*$_2$CH), 2.23−2.40 (m, 2H, 2CHCO_2*t*Bu); ^{13}C NMR (75.48 MHz, *anti*-**7a**) δ 18.46 (CH_3), 28.01, 29.47 (3C(*C*H_3)$_3$), 30.86 (CH_2*C*(CH_3)$_3$), 38.69, 40.98 (2*C*HCO_2-*t*Bu), 39.46 (CH*C*H_2CH), 46.92 ((CH_3)$_3$C*C*H_2), 79.95 (2CO_2*C*(CH_3)$_3$), 175.60, 176.55 (2*C*O_2C(CH_3)$_3$); MS (CI, isobutane) *m*/*z* (%) 329 (26) [*M*H$^+$], 217 (100) [*M*H$^+$ − (C_4H_9)$_2$ + 2H]; $C_{19}H_{36}O_4$ (328.49) calcd C, 69.47; H, 11.05; found C, 69.56; H, 11.05.

Di-*tert*-butyl 2-(cyclohexylmethyl)-4-methylpentanedioate (7b): ^{1}H NMR (500.1 MHz, *anti*-**7b**) δ 0.77−0.96 (m, 2H, cyclohexyl: H2, H6), 1.07−1.83 (m, 13H, cyclohexyl: H1, H2, 2H3, 2H4, 2H5, H6, C_6H_{11}C*H*$_2$, CHC*H*$_2$CH), 1.10 (d, ^3J (H,H) = 6.59 Hz, 3H, CH_3), 1.46 (s, 18H, 2CO_2C(C*H*$_3$)$_3$), 2.26−2.44 (m, 2H, 2CHCO_2*t*Bu); ^{13}C NMR (125.8 MHz, *anti*-**7b**) δ 18.32 (CH_3), 26.23, 26.52, 26.79, 32.76, 33.57, (cyclohexyl-C), 28.03 (2CO_2C(*C*H_3)$_3$), 35.48 (cyclohexyl: C1), 37.22 (CH*C*H_2CH), 41.00 (C_6H_{11}*C*H_2), 38.82, 41.83 (2*C*HCO_2*t*Bu), 79.90, 79.98 (2CO_2*C*(CH_3)$_3$), 175.78, 175.80 (2*C*O_2C(CH_3)$_3$); MS (CI, isobutane) *m*/*z* (%) 355 (36) [*M*H$^+$], 243 (100) [*M*H$^+$ − (C_4H_9)$_2$ + 2H]; $C_{21}H_{38}O_4$ (354.53) calcd C, 71.15; H, 10.80; found C, 71.05; H, 10.91.

2-Methyl-4-neopentylpentanedioic acid (8a): Mp 158 °C; ^{1}H NMR (500.1 MHz, CD_3OD, *syn*-**8a**) δ 0.90 (s, 9H, (CH_3)$_3$C), 1.18 (d, ^3J (H,H) = 7.13 Hz, 3H, CH_3), 1.27 (dd, ^2J (H,H) = 2.19 Hz, ^3J (H,H) = 14.27 Hz, 1H, (CH_3)$_3$CC*H*H), 1.40−1.47 (m, 1H, CHC*H*HCH), 1.76 (dd, ^2J (H,H) = 2.19 Hz, ^3J (H,H) = 9.88 Hz, 1H, (CH_3)$_3$CCH*H*), 1.92−1.99 (m, 1H, CHCH*H*CH), 2.36−2.50 (m, 2H, 2C*H*CO_2Me); ^{13}C NMR (125.8 MHz, CD_3OD, *syn*-**8a**) δ 17.29 (CH_3), 29.86 (C(*C*H_3)$_3$), 31.65 (*C*(CH_3)$_3$), 38.57, 39.62, 40.99 (*C*H*C*H_2*C*H), 47.22 ((CH_3)$_3$C*C*H_2), 179.83, 180.74 (2CO_2H); MS (CI, isobutane) *m*/*z* (%) = 217 (49) [*M*H$^+$], 199 (100) [*M*H$^+$ − 18].

2-(Cyclohexylmethyl)-4-methylpentanedioic acid (8b): Mp 159 °C; ^{1}H NMR (500.1 MHz, CD_3OD, *syn*-**8b**) δ 0.81−0.92 (m, 2H, cyclohexyl: H2, H6), 1.15 (d, ^3J (H,H) = 7.14 Hz, 3H, CH_3), 1.10−1.34 (m, 5H, cyclohexyl: H2, H3, H5, H6, C_6H_{11}C*H*H), 1.44−1.57 (m, 2H, cyclohexyl: H4, $C_6H_{11}CH_2$CHCH*H*CH), 1.61−1.75 (m, 4H, cyclohexyl: H1, H3, H4, H5), 1.78−1.85 (m, 1H, C_6H_{11}CH*H*), 1.92−2.02 (m, 1H, $C_6H_{11}CH_2$CHC*H*HCH), 2.38−2.46 (m, 1H, C*H*CO_2H), 2.47−2.55 (m, 1H, C*H*CO_2H); ^{13}C NMR (125.8 MHz, CD_3OD, *syn*-**8b**) δ 17.19 (CH_3), 27.36, 27.62, 33.90, 34.92, 37.70 (CH*C*H_2CH, cyclohexyl-C), 36.99 (cyclohexyl: C1), 38.60, 41.80 (*C*HCH_2*C*H,), 41.47 (C_6H_{11}*C*H_2), 179.83, 179.92 (2CO_2H); MS (CI, isobutane) *m*/*z* (%) 243 (59) [*M*H$^+$], 225 (100) [*M*H$^+$ − 18].

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