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Chelate-Controlled Mukaiyama Reactions with Chiral β-Formyl Esters

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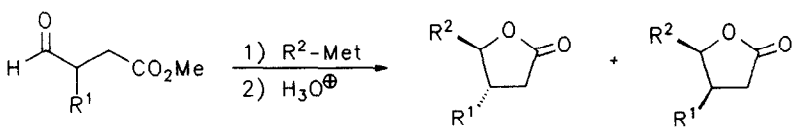
Abstract: Additions of silyl enol ethers **3**, **6**, and **8** to chiral β-formyl esters **1** in the presence of $TiCl_4$ provide *trans*-γ-lactones **4**, **7**, and **9** in high yield and with good to excellent diastereofacial selectivity. This high *trans*-preference is due to effective chelate-control involving seven-membered ring **1**-$TiCl_4$ complexes.

Chelate-controlled additions of organo titanium and other Lewis acidic reagents to chiral carbonyl compounds[1] are generally governed by alkoxy or amino groups[2,3]. We could recently demonstrate that easily available chiral β-formylcarboxylates **1**[4] smoothly react with organometallics R^2-Met such as allylsilanes/$TiCl_4$[5,6], $MeTiCl_3$[6], cuprates[5,7], and Grignard compounds[7], to give γ-lactones **2** after acidic workup.

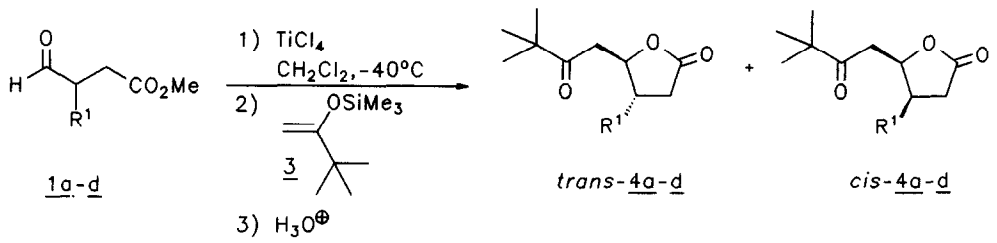


1 *trans*-2 *cis*-2

Due to the involvement of seven-membered ring chelates, which was proved unambiguously by NMR spectroscopy in certain examples[6], the *trans*-diastereomers of **2** are formed with moderate to excellent selectivity. They result from preferential R^2-Met *anti*-additions with respect to R^1 (*anti*-Cram selectivity[8] for R^1 = Me). In this paper we report our results employing silyl enol ethers as nucleophiles under Mukaiyama's conditions[9], which provide functionalized γ-lactones with high diastereoselectivity.

RESULTS

Silyl enol ether **3** served as model compound for studying the influence of substituents R^1 and of reaction conditions on the diastereoselectivity. As depicted in Scheme 1, nucleophile **3** added to aldehydes **1a-1d** in the presence of titanium tetrachloride to give γ-lactones **4a-4d** after acidic treatment in very good yield and with good to excellent *trans*-selectivity.

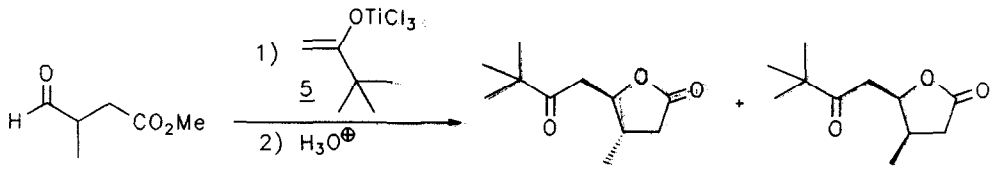


a	R^1 = Me	91%	77:23
b	R^1 = Et	92%	89:11
c	R^1 = i-Prop	96%	>99: 1
d	R^1 = Ph	71%	92: 8

Scheme 1

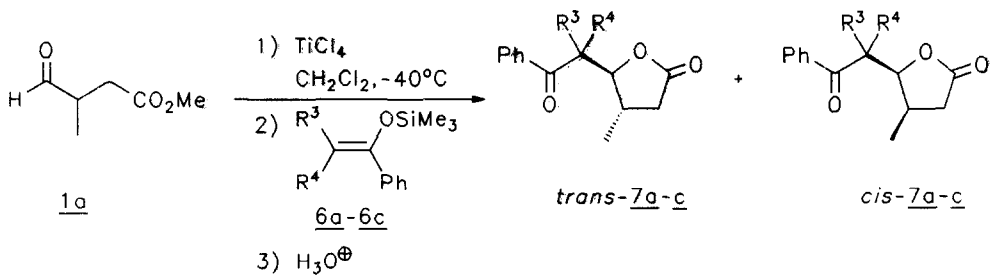
The additions of **3** to **1** in the presence of $TiCl_4$ are complete at -40°C, whereas lower temperatures can lead to insufficient conversion to **4**. Extended treatment of products **4** with strong acid causes equilibration as was proved with **4a**[10], however, under the reaction conditions of workup this process is negligible. Thus, the *trans/cis* ratios as given in Scheme 1 represent the diastereofacial selectivities in the primary addition step of **3** to **1**. The *trans*-preference improves with increasing size of substituent R^1, plausibly because chelate-control and "normal" diastereofacial control cooperate for larger substituents such as i-Prop and Ph[11].

Other Lewis acids are inferior compared with $TiCl_4$. Tin tetrachloride gave a 57 : 43 *cis*-**4a**/*trans*-**4a** mixture (81 % yield), while with boron trifluoride even a stronger *cis*-selectivity (*cis*-**4a**/*trans*-**4a** = 66 : 34, 78 % yield) was observed. BF_3 is not capable of forming chelates and therefore this last result should reflect the inherent selectivity of BF_3-complexed **1a**. The lithium enolate of pinacolone (equivalent to **3**) is moderately *trans*-selective (*trans*-**4a**/*cis*-**4a** = 60 : 40, tetrahydrofuran as solvent, 73 % yield) and the titanium enolate **5** - generated from pinacolone according to Evans et al.[12] - is rather unselective.



1a 76% *trans*-4a 53:47 *cis*-4a

Upon employing phenyl-substituted silyl enol ethers **6a-6c**, we found that the degree of substitution at the nucleophile is of minor importance (Scheme 2). All three compounds added to aldehyde **1a** with very high *trans*-selectivities providing γ-lactones **7a-7c** in good yields. Prochiral nucleophile **6c** gave four diastereomers of **7c**, but probably this ratio does not represent the original "simple" diastereoselectivity because of possible epimerization α to the carbonyl group during acidic workup.



1a

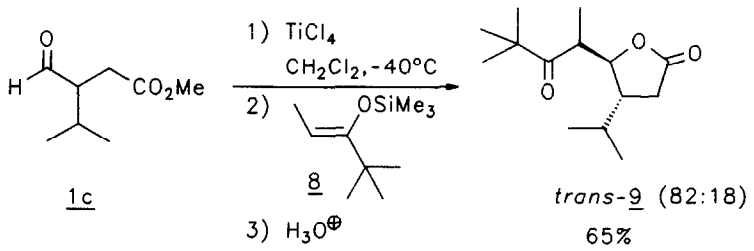
6a-6c

trans-7a-c *cis*-7a-c

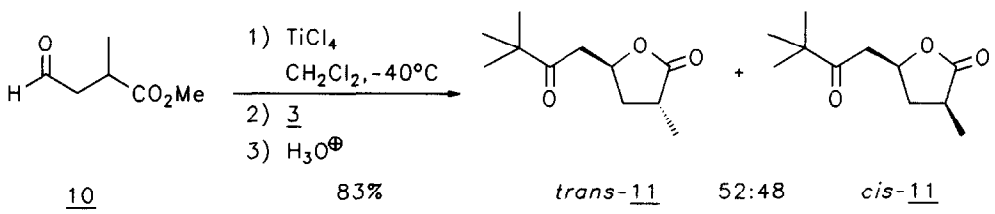
a	$R^3 = R^4 = H$	82%	92: 8
b	$R^3 = R^4 = Me$	91%	96: 4
c	$R^3 = Me$, $R^4 = H$	94%	90:10 (56:34:6:4)

Scheme 2

Aldehyde **1c** and silyl enol ether **8** provided two isomers of γ-lactone **9** in a ratio of 82 : 18. According to the NMR data, which serve as criteria for all structural assignments of γ-lactones described here[13], both compounds have *trans*-configuration and must therefore be epimeric at the exocyclic stereogenic centre. Future experiments have to be designed in order to control the simple diastereoselectivity of these additions without epimerization of the primary adducts. This should allow the stereocontrolled synthesis of compounds with three consecutive stereogenic centres.



Finally, an experiment with aldehyde **10** as electrophile confirmed that the 1,3-induction in these chelate-controlled Mukaiyama reactions is weak[6,7]. Addition of silyl enol ether **3** provided a *trans/cis* = 52 : 48 mixture of γ-lactones **11** in high yield.



CONCLUSION

These first results with silyl enol ethers as nucleophiles illustrate that chiral β-formyl esters **1** are suitable substrates for chelate-controlled additions. The formation of seven-membered ring chelates with titanium tetrachloride as the Lewis acid[14] and **1** as a bidentate ligand strongly enhances diastereoselectivity and makes available 4,5-disubstituted γ-lactones with high *trans*-preferences. Since β-formyl esters **1** are also accessible as enantiomerically enriched compounds[15], this approach to interesting functionalized γ-lactones should be of importance in asymmetric synthesis.

EXPERIMENTAL

For general information see ref.[6]. GC analyses were performed with a Varian 3300 gas chromatograph equipped with a fused-silica DB-1701 capillary column (15 m). Starting materials **1a-1d** see ref.[4]; the silyl enol ethers were prepared by standard methods[16]; $TiCl_4$ was distilled under nitrogen; dichloromethane was distilled from CaH_2 and stored over molecular sieves. All reactions were executed in a flame-dried flask under a slight pressure of nitrogen. Solvents and liquids were added by syringe.

General Procedure for Synthesis of γ-Lactones: To a solution of aldehyde **1** (2.00 mmol) in dichloromethane (10 ml) $TiCl_4$ (2.00 mmol) was added at -60°C. The yellow suspension was warmed up to -40°C within 15 min and the silyl enol ether (3.00 mmol, dissolved in 7 ml of CH_2Cl_2) was slowly added. After 1 h at -40°C conc. hydrochloric acid (2 ml) was added, the cooling bath was removed and the mixture was stirred for 30 min. Extractive workup (H_2O/CH_2Cl_2), drying (Na_2SO_4), and evaporation of solvent provided the crude products which were further purified by Kugelrohr distillation and/or chromatography. The ratios of isomers did not change during purification.

4,5-Dihydro-4-methyl-5-(3,3-dimethyl-2-oxobutyl)-2(3H)-furanone (**4a**): 0.361 g (91 %) as colourless oil (110°C/0.01 Torr); *trans : cis* = 77 : 23 (GC analysis).

4-Ethyl-4,5-dihydro-5-(3,3-dimethyl-2-oxobutyl)-2(3H)-furanone (**4b**): 0.389 g (92 %) as partially crystalline oil (140°C/0.02 Torr); *trans : cis* = 89 : 11 (GC analysis).

4,5-Dihydro-4-isopropyl-5-(3,3-dimethyl-2-oxobutyl)-2(3H)-furanone (**4c**): 0.435 g (96 %) as colourless oil (125°C/0.02 Torr); *trans : cis* > 99 : 1 (GC analysis).

4,5-Dihydro-5-(3,3-dimethyl-2-oxobutyl)-4-phenyl-2(3H)-furanone (**4d**): 0.371 g (71 %) after recrystallization (from *tert*-butyl methyl ether) as colourless crystals (170°C/0.01 Torr; m.p. 87-92°C); *trans : cis* = 92 : 8 (NMR analysis).

4,5-Dihydro-4-methyl-5-(2-phenyl-2-oxoethyl)-2(3H)-furanone (**7a**): 0.357 g (82 %) after chromatography (SiO_2, hexane/ethyl acetate 1 : 1) as colourless crystals (m.p. 78-82°C); *trans : cis* = 92 : 8 (NMR analysis); m.p. of pure *trans*-**7a** 87°C (from pentane/ether 2 : 1).

4,5-Dihydro-4-methyl-5-(2-methyl-3-oxo-3-phenyl-2-propyl)-2(3H)-furanone (**7b**): 0.449 g (91 %) as colourless oil (170°C/0.02 Torr); *trans : cis* = 96 : 4 (GC analysis).

4,5-Dihydro-4-methyl-5-(3-oxo-3-phenyl-2-propyl)-2(3H)-furanone (**7c**): 0.439 g (94 %) as colourless oil (160-190°C/0.02 Torr); *trans : trans' : cis : cis'* = 56 : 34 : 6 : 4 (NMR and GC analysis).

4,5-Dihydro-4-isopropyl-5-(4,4-dimethyl-3-oxo-2-pentyl)-2(3H)-furanone (**9**): 0.313 g (65 %) as colourless crystals (150°C/0.02 Torr; m.p. 78-80°C); *trans : trans'* = 82 : 18 (GC analysis).

4,5-Dihydro-3-methyl-5-(3,3-dimethyl-2-oxobutyl)-2(3H)-furanone (**11**): 0.330 g (83 %) as colourless crystals (110°C/0.02 Torr; m.p. 36-39°C); *trans : cis* = 52 : 48 (GC analysis). - ^{13}C NMR ($CDCl_3$, 75.5 MHz), *trans*-**11**: δ = 212.1, 178.9 (2s, C=O), 74.3 (d, C-5), 44.2, 26.0 (s, q, t-Bu), 42.0 (t, 5-C), 37.4 (t, C-4), 35.6 (d, C-3), 14.9 (q, Me); *cis*-**11**: δ = 212.2, 179.5 (2s, C=O), 74.3 (d, C-5), 44.1, 26.0 (s, q, t-Bu), 41.5 (t, 5-C), 35.4 (t, C-4), 33.8 (d, C-3), 15.8 (q, Me).

Reaction of Titanium Enolate **5** *with* **1a**: According to ref.[12], a solution of pinacolone (0.200 g, 2.00 mmol) in dichloromethane (10 ml) was treated with $TiCl_4$ (2.00 mmol) at -78°C. After 2 min ethyldiisopropylamine (0.310 g, 2.40 mmol) was added and the resulting winered solution was stirred for 1.5 h at -78°C. Aldehyde **1a** (0.312 g, 2.40 mmol) was slowly added via syringe, after stirring for 1.5 h at -78°C sulfuric acid (2 ml, 50%) was added, and the mixture was worked up as described in the general procedure. The crude product was distilled (110°C/0.01 Torr) and further purified by chromatography (SiO_2, pentane/ethyl acetate 5 : 1) to provide 0.302 g (76 %) of **4a**; *trans* : *cis* = 53 : 47 (GC analysis).

Analytical Data of γ-Lactones **4a-d**, **7a-c**, **9**, and **11**

	IR (film, cm^{-1})	Formula (Mw)	Elemental Analysis
4a	2970, 2940, 2880 (C-H), 1775, 1705 (C=O)	$C_{11}H_{18}O_3$ (198.3)	Calcd. C 66.63 H 9.15 Found C 66.50 H 9.21
4b	2960, 2930, 2870 (C-H), 1775, 1700 (C=O)	$C_{12}H_{20}O_3$ (212.3)	Calcd. C 67.89 H 9.49 Found C 67.64 H 9.54
4c	2960, 2930, 2870 (C-H), 1770, 1700 (C=O)	$C_{13}H_{22}O_3$ (226.3)	Calcd. C 68.99 H 9.80 Found C 68.92 H10.00
4d	3040, 2980, 2940, 2880 (C-H), 1775, 1705 (C=O)	$C_{16}H_{20}O_3$ (260.3)	Calcd. C 73.82 H 7.74 Found C 73.83 H 7.79
7a	3080, 2960, 2900 (C-H), 1780, 1675 (C=O)[a]	$C_{13}H_{14}O_3$ (218.2)	Calcd. C 71.54 H 6.47 Found C 71.59 H 6.47
7b	3065, 2980, 2940, 2880 (C-H), 1775, 1670 (C=O)	$C_{15}H_{18}O_3$ (246.3)	Calcd. C 73.15 H 7.37 Found C 72.68 H 7.51
7c	3065, 2975, 2940, 2880 (C-H), 1770, 1675 (C=O)	$C_{14}H_{16}O_3$ (232.3)	Calcd. C 72.39 H 6.94 Found C 72.00 H 6.95
9	2965, 2940, 2880 (C-H), 1775, 1700 (C=O)[a]	$C_{14}H_{24}O_3$ (240.3)	Calcd. C 69.96 H10.06 Found C 69.65 H10.02
11	2980, 2950, 2920, 2880 (C-H), 1780, 1710 (C=O)[a]	$C_{11}H_{18}O_3$ (198.3)	Calcd. C 66.63 H 9.15 Found C 66.42 H 9.22

[a] KBr pellet

^{13}C-NMR Data of γ-Lactones **4a-d**, **7a-c**, and **9** ($CDCl_3$, 75.5 MHz, δ values)

	C-2 (s)	C-3 (t)	C-4 (d)	C-5 (d)	5-C	C=O (s)	Other Signals
trans-**4a**	175.9	36.4[a]	35.7	82.4	40.2 (t)[a]	211.9	44.1, 25.8 (s, q, t-Bu), 17.1 (q, Me)
cis-**4a**	176.1	36.4[a]	32.2	79.1	37.1 (t)[a]	212.2	44.0, 26.0 (s, q, t-Bu), 14.0 (q, Me)
trans-**4b**	176.2	34.3	42.5	81.1	41.0 (t)	212.1	44.3, 26.0 (s, q, t-Bu), 25.8, 11.8 (t, q, Et)
cis-**4b**	-	33.9	39.6	79.3	36.5 (t)	-	26.2 (q, t-Bu), 21.3 (t, Et)
trans-**4c**	176.2	31.5	46.3	79.4	41.8 (t)	211.9	44.1, 25.9 (s, q, t-Bu), 30.4, 20.4, 18.8 (d, 2q, i-Prop)
trans-**4d**	175.1	37.0[a]	46.9	82.8	39.8 (t)[a]	211.5	44.1, 25.8 (s, q, t-Bu), 138.4, 129.0, 127.8, 127.2 (s, 3d, Ph)
cis-**4d**	176.5	36.5[a]	43.4	79.9	37.7 (t)[a]	212.6	43.8, 26.0 (s, q, t-Bu), 138.4, 128.8, 127.7, 127.3 (s, 3d, Ph)
trans-**7a**	176.1	36.4	35.9	82.4	42.4 (t)	196.2	136.4, 133.5, 128.7, 128.1 (s, 3d, Ph), 17.5 (q, Me)
cis-**7a**	175.9	37.2	32.4	79.2	38.4 (t)	196.2	136.2, 133.6, 128.7, 128.0 (s, 3d, Ph), 14.2 (q, Me)
trans-**7b**	176.2	36.8	30.6	91.2	51.3 (s)	206.8	138.5, 131.0, 128.1, 127.3 (s, 3d, Ph), 21.9, 21.1, 21.0 (3q, Me)
cis-**7b**	-	37.7	33.2	86.6	-	-	131.3, 128.4, 127.7, (3d, Ph), 15.8 (q, Me)
trans-**7c**	176.3	36.3	34.1	87.2	45.0 (d)	201.3	135.9, 133.8, 129.0, 128.4 (s, 3d, Ph), 19.5, 15.2 (2q, Me)
trans-**7c'**	175.9	37.0	32.5	88.0	45.0 (d)	200.8	136.0, 133.7, 128.9, 128.8 (s, 3d, Ph), 19.7, 13.0 (2q, Me)
trans-**9**	176.3	30.8	43.9[a]	84.7	42.7 (d)[a]	216.1	45.1, 26.0, (s, q, t-Bu), 30.9, 19.6, 18.3 (d, 2q, i-Prop), 14.6 (q, Me)
trans-**9'**	-	30.3	-	85.0	44.6 (d)	-	26.4 (q, t-Bu), 16.2 (q, Me), 30.6, 19.8, 17.7 (d, 2q, i-Prop)

[a] Signals marked are interchangeable within the line

^{1}H-NMR Data of γ-Lactones **4a-d**, **7a-c**, **9**, and **11**
($CDCl_3$, 300 MHz, δ values; values given in brackets: coupling constants in Hz)

	5-H (dt)	5-CH (dd)	5-CH	3-H	4-H	Other Signals
trans-**4a**	4.57 [5, 7]	3.01 [7.5, 17.5]	2.83-2.61 (m)		2.39-2.16 (m)	1.17 (d, 8.5 Hz, 4-Me), 1.16 (s, t-Bu)
cis-**4a**	4.96 [5.5, 7]	3.08 [6.5, 18]				0.96 (d, 7 Hz, 4-Me), 1.18 (s, t-Bu)
trans-**4b**	4.65 [5, 7]	3.01 [7, 17.5]	2.76-2.61 (m)		2.39-2.06 (m)	1.16 (s, t-Bu) 1.63, 1.42, 0.96 ($2m_c$, t, 7.5 Hz, 4-Et)
cis-**4b**	5.03 (q) [6.5]	3.04 [7, 17.5]				1.17 (s, t-Bu)
trans-**4c**	4.78 [5, 7]	3.00 [7, 17.5]	2.73 (dd) [5, 17.5]	2.64 (dd) [9.5, 18] 2.33 (dd) [7.5, 18]	2.09 (m_c)	1.79, 0.95, 0.94 (oct, 2d, 6.5 Hz, i-Prop), 1.15 (s, t-Bu)
trans-**4d**	5.00 [3.5, 8.3]	3.06 [8.3, 17.3]	2.65 (dd) [3.5, 17.3]	2.95 (dd) [8.3, 17.6] 2.77 (dd) [10.4, 17.6]	3.42 (td) [8.3, 10.4]	7.42-7.25 (m, Ph), 1.12 (s, t-Bu)
cis-**4d**	5.19 (ddd) [5, 6, 9]	[a]	[a]	2.39 (dd) [9, 18.5]	3.90 (ddd) [3, 6, 9]	7.08-7.00 (m, Ph), 0.87 (s, t-Bu)
trans-**7a**	4.74 [5.5, 7]	3.49 [7, 17]	3.21 (dd) [5.5, 17]	2.74 (dd) [8, 17] 2.25 (dd) [8.5, 17]	2.41 (m_c)	8.00-7.42 (m, Ph), 1.22 (d, 6.5 Hz, 4-Me)
cis-**7a**	5.15 [7.5, 6]	3.53 [6, 17.5]	3.26 (dd) [7.5, 17.5]	2.25 (dd) [2, 16.5] 2.94-2.77 (m)		8.00-7.42 (m, Ph), 1.00 (d, 7 Hz, 4-Me)

	5-H (dt)	5-CH (dd)	5-CH	3-H	4-H	Other Signals
trans-**7b** [b]	4.54 (d) [5]	-	-	2.75 (dd) [9.5, 18] 2.16 (dd) [5.5, 18]	2.45 (m_c)	7.75-7.35 (m, Ph), 1.40, 1.33 (2s, Me), 1.16 (d, 7 Hz, 4-Me)
trans-**7c**	4.47 (dd) [5, 8]	3.87-3.59 (m)	-	2.73 (dd) [8.5, 17.5] 2.16 (dd) [6.5, 17.5]	2.34 (m_c)	8.01-7.35 (m, Ph), 1.36 (d, 7 Hz, Me), 1.14 (d, 7 Hz, 4-Me)
trans-**7c'** [c]	4.54 (dd) [6.5, 7.5]	3.87-3.59 (m)	-	2.76 (dd) [9, 17.5] 2.22 (dd) [7.5, 17.5]	2.53 (m_c)	8.01-7.35 (m, Ph), 1.26 (d, 7 Hz, Me), 1.19 (d, 6.5 Hz, 4-Me)
trans-**9**	4.50 (dd) [2.5, 9.5]	3.18 (qd) [7, 9.5]	-	2.64 (dd) [10, 18.5]	2.41-2.19 (m)	1.15 (s, t-Bu), 1.08 (d, 7 Hz, 4-Me), 0.93, 0.92 (2d, 7 Hz, Me) 1.75 (oct, 7 Hz, 4-CH)
trans-**9'**	4.45 (dd) [3, 8.5]	3.27 (qd) [7, 8.5]	-	2.58 (dd) [9.5, 18.5]		1.17 (s, t-Bu), 1.22 (d, 7 Hz, 4-Me), 0.88, 0.87 (2d, 7 Hz, Me)
trans-**11**	4.97 (m_c)	3.09 [5.5, 17.5]		2.77-2.61 (m) 2.24-2.04 (m) 1.58-1.35 (m)		1.15 (s, t-Bu), 1.30 (d, 8 Hz, 3-Me)
cis-**11**	4.81 (m_c)	3.15 [6, 17.5]				1.16 (s, t-Bu), 1.27 (d, 8 Hz, 3-Me)

[a] Signals hidden by those of the major isomer.

[b] Signals of the minor isomer *cis*-**7b**: δ = 4.95 (d, 7 Hz, 5-H), 1.00 (d, 7 Hz, 4-Me).

[c] Signals of the minor isomers *cis*-**7c**, *cis*-**7c'**: δ = 4.83 (dd, 5, 10 Hz, 5-H), 4.80 (dd, 5, 10 Hz, 5-H).

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