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Kinetic Asymmetric Protonation as a Stereochemistry Determining Step in the *Michael* Addition of Acetic Acid Derivatives to α-Substituted Cinnamic Acid Derivatives

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Summary. The reaction between acetic acid derivatives and α-substituted cinnamic acid derivatives has been studied in *THF* and *THF:HMPT* (80:20) as an alternative pathway of the *Michael* addition of phenylacetic and cinnamic acid derivatives. The regioselectivity observed is found to depend on the acceptor functional group and its geometry but not on the solvent used. The diastereoselectivity of the conjugate addition results from kinetic protonation of diastereotopic enolates (1,2-asymmetric induction). It varies from low in the presence of *HMPT* to considerable or even high in pure *THF*. The favoured *anti* or *syn* configuration in *THF* depends on the nature of the enolate. The results obtained are rationalized in terms of protonation *via* transition structures different in type (open *vs.* chelated) and geometry.

Keywords. Asymmetric induction; Diastereoselective protonation; *Michael* addition; Regioselectivity.

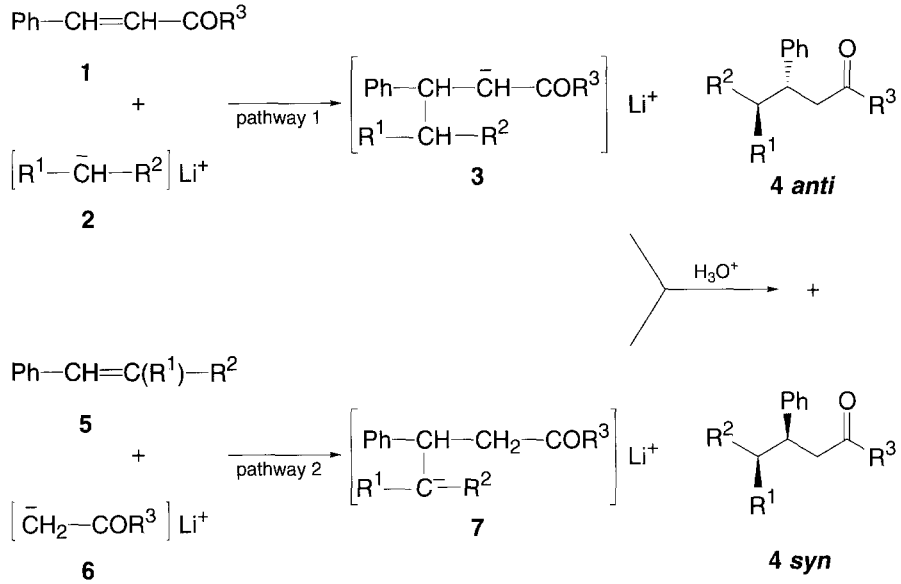
Kinetische asymmetrische Protonierung als bestimmender Schritt für die Stereochemie bei der *Michael*-Addition von Essigsäurederivaten an α-substituierte Zimtsäurederivate

Zusammenfassung. Die Reaktion zwischen Essigsäurederivaten und α-substituierten Zimtsäurederivaten wurde in *THF* und *THF:HMPT* = 80:20 als ein alternativer Weg der *Michael*-Addition von Phenylessigsäure und Zimtsäurederivaten untersucht. Es wurde gefunden, daß die beobachtete Stereoselektivität von der Akzeptorgruppe und ihrer Geometrie, nicht jedoch vom Lösungsmittel abhängig ist. Die Diastereoselektivität der konjugierten Addition folgt aus der kinetischen Protonierung der diastereotopen Enolate (1,2-asymmetrische Induktion). Sie variiert von klein (bei Anwesenheit von *HMPT*) bis bedeutend oder sogar groß (in reinem *THF*). Die bevorzugte *anti* oder *syn* Konfiguration in *THF* hängt von der Natur der Enolate ab. Die Ergebnisse werden durch eine Protonierung *via* bezüglich Typ (offen oder chelatiert) und Geometrie unterschiedliche Strukturen des Übergangszustands erklärt.

Introduction

In the course of our investigation of the diastereoselectivity of the *Michael* reaction in a model system including cinnamic (**1**) and phenylacetic acid (**2**) derivatives [1–8]

(Scheme 1, pathway 1), carbanion transformation (**3**→**7**) was observed in the particular case of **4c** ($R^2 = CN$, $R^3 = N(CH_3)_2$), followed by remarkably high diastereoselective protonation of the prochiral intermediate **7**. The result was considered to be due to a chelate enforced intramolecular chirality transfer [5, 9].



4[a]	R^1	R^2	COR^3
4a	Ph	CN	$COOCH_3$
4b	Ph	CN	COO^tBu
4c	Ph	CN	$CON(CH_3)_2$
4d	Ph	$COOCH_3$	$COOCH_3$
4e	Ph	$COOCH_3$	$CON(CH_3)_2$
4f	Ph	$CON(CH_3)_2$	$CON(CH_3)_2$
4g	CH_3	$CON(CH_3)_2$	$CON(CH_3)_2$

[a] Adducts available by pathway 2

Scheme 1

The observation above prompted us to study an alternative pathway of obtaining compounds **4** in the course of which the intermediate **7** can be directly formed by conjugate addition of α-substituted cinnamic (**5**) and acetic acid (**6**) derivatives (Scheme 1, pathway 2); hence, the diastereoselectivity would be determined not in the C–C bond formation but in the protonation reaction step.

This alternative is worth being investigated for two reasons: it provides a new synthetic and stereochemical approach to compounds **4** and allows an investigation of the factors governing the stereoselectivity in the protonation of diastereotopic enolates bearing an adjacent stereogenic centre which is a topic of considerable interest [10–19]. The presence of a second γ-positioned to the carbanionic centre and capable of coordination carbonyl substituent is expected to promote the process of 1,2-asymmetric induction significantly.

Results and Discussion

The reaction was carried out for 60 min at −78 °C in *THF* (method A) and in a *THF:HMPT* mixture (80:20 v/v) (method B). The results obtained are listed in Table 1. The data in parentheses concern kinetically controlled ratios obtained by pathway 1 and are given for comparison.

In some of the cases studied, a concurrent 1,2-addition occurs. The attack of the carbonyl group is not of synthetic importance since the initially formed unstable intermediates Ph–CH=C(R^1)–C(OLi)(R^2)–CH_2COR^3 (**8**) undergo a second aldol addition to compounds Ph–CH=C(R^1)–C(OH)–(CH_2COR^3)$_2$ (**10**) after elimination to compounds Ph–CH=C(R^1)–CO–CH_2COR^3 (**9**). In fact, the products assigned as 1,2-adducts are mixtures of **9** and **10** in different proportions.

The regioselectivity exhibited by the acetic acid esters and amide enolates [20, 21] depends significantly on the functional group in the electrophile and its geometry. The interaction with the available *cis*-α-phenylcinnamonitrile (R^2 = CN, entries 1–7) affords the 1,4-adduct, most probably under frontier orbital control [22, 23]. In the case of *cis*- and *trans*-α-phenylmethylcinnamates (R^2 = $COOCH_3$, entries 8–12), attack of both the carbonyl carbon and the C=C double bond occurs,

Table 1. Regio- and diastereoselectivity of addition of acetic acid derivatives and α-substituted cinnamic acid derivatives

	R^1	R^2	$COOR^{3a}$	Method and total yield (%)		1,2/1,4 (%)	Comp **4** (1,4)	*anti/syn* (1/4)
1	Ph	CN	$COOCH_3$	A	35[b]	0/100	**4a**	87/13 (46/54)[c]
2	Ph	CN	$COOCH_3$	B	40	0/100	**4a**	60/40 –
3	Ph	CN	COO^{t}Bu	A	85	0/100	**4b**	86/14 –
4	Ph	CN	COO^{t}Bu	B	56	0/100	**4b**	62/38 –
5	Ph	CN	$CON(CH_3)_2$	A	80	0/100	**4c**	65/35 –
6	Ph	CN	$CON(CH_3)_2$	A[d]	90	0/100	**4c**	95/5 (95/5)[c]
7	Ph	CN	$CON(CH_3)_2$	B	65	0/100	**4c**	62/38 –
8	Ph	$COOCH_3$	$COOCH_3$	A	52	76/24	**4d**	22/78 (5/95)[e]
9	Ph	$COOCH_3$	$COOCH_3$[f]	A	41	40/60	**4d**	25/75 –
10	Ph	$COOCH_3$	$CON(CH_3)_2$	A	85	40/60	**4e**	24/76 –
11	Ph	$COOCH_3$	$CON(CH_3)_2$	B	63	38/62	**4e**	38/62 –
12	Ph	$COOCH_3$	$CON(CH_3)_2$[f]	A	58	0/100	**4e**	23/77 –
13	CH_3	$COOCH_3$	$COOCH_3$	A	44	100/0	–	–
14	CH_3	$COOCH_3$	$CON(CH_3)_2$	A	63	100/0	–	–
15	Ph	$CON(CH_3)_2$	$COOCH_3$	A, B	does not react			(38/62)[g]
16	Ph	$CON(CH_3)_2$	$CON(CH_3)_2$	A	86	0/100	**4f**	41/59 (5/95)[g]
17	Ph	$CON(CH_3)_2$	$CON(CH_3)_2$	B	68	0/100	**4f**	40/60 –
18	CH_3	$CON(CH_3)_2$	$COOCH_3$	A, B	does not react			
19	CH_3	$CON(CH_3)_2$	$CON(CH_3)_2$	A[d]	78	0/100	**4g**	25/75 –
20	CH_3	$CON(CH_3)_2$	$CON(CH_3)_2$	B[d]	22	0/100	**4g**	45/55 –

[a] *cis*-Configurated acceptor, unless otherwise stated; [b] at −40 °C the yield increases to 84%; [c] Ref. [5]; [d] reaction is carried out at 22 °C; entries 19 and 20: at low temperature, synthesis does not proceed; [e] Ref [6]; [f] *trans*-configurated acceptor, [g] Ref. [2]

the conjugate addition being favoured with the *trans*-acceptor (compare entries 8 and 9; 11 and 12) because of the steric hindrance of the carbonyl group. The change of the α-substituent from Ph to CH_3 (entries 13 and 14) results in a 1,2-regioselective attack for both steric and electronic reasons.

The 1,4-regiocontrol observed with dimethylamide of *cis*-configurated α-phenyl- and α-methylcinnamic acids ($R^2 = CON(CH_3)_2$, entries 15–20) is in agreement with the general tendency of decrease of 1,2-attack with decreasing electrophility of the carbonyl carbon atom.

In contrast to our expectations [24, 25], the use of *HMPT* as an additive does not enhance the double bond attack, but causes significant reduction of the total yield as well as complications in the work-up of the reaction mixture.

The fact that no reaction proceeds in the case of entries 15 and 18 where a conjugate addition is expected could be explained by the large stability difference between the donor and the conjugate adduct anions acting as a thermodynamic barrier [26]. This could be overcome by using a proper combination of reagents. Thus, the compound which corresponds to entry 15 is obtained by pathway 1, whereas **4e** is accessible in both good yield and diastereoselectivity only by the alternative variant 2.

The diastereoselectivity of the protonation is of kinetic origin since it is not affected by the reaction time or the quenching temperature (control experiments) as well as on the proton source (aqueous NH_4Cl *vs.* CF_3CO_2H). The only exceptions (see entries 5 and 6) will be discussed later. Intramolecular proton transfer as a stereocontrolling step [27] was excluded by D_2O quenching experiments which demonstrated up to 85% incorporation of deuterium in the carbanion **7**.

The analysis of the stereochemical data shows the following general trends:

1. Dependence on the reaction medium polarity (*THF*:*HMPT vs. THF*);
2. At low polarity (*THF*), dependence on the functional group in α-position relative to the carbanionic centre.

Thus, in highly ionizing conditions (excess of *HMPT*), the diastereoselectivity is uniformly low (*anti*/*syn* = 62:38 → 40:60, entries 2, 4, 7, 11, 17, and 20), whereas in *THF* it varies in a wide range from *anti*-(in the case of nitrile; *anti*/*syn* = 86:14 → 95:5, entries 1, 3, and 6) to *syn*-preference (in the case of ester and amide enolates, *anti*/*syn* = 41:59 → 22:78, entries 8–10, 12, 16, and 19). The influence of *HMPT* on the stereochemistry suggests that the protonation reaction takes place by different transition structures: open-chain in *THF*:*HMPT* (80:20) and chelated in pure *THF*.

Looking for evidence for chelates as real intermediates in *THF*, we recorded the IR spectra of some carbanionic species. The examples were selected with regard to 1,4-regioselective addition as well as high chemical yields. The carbonyl and nitrile group IR frequencies in both lithium salts and neutral molecules are shown in Table 2.

Two main tendencies are observed in the IR spectra of the salts compared to those of the neutral molecules: a shift of the absorption band of the R^2 group (α-positioned to the carbanionic centre) towards lower frequencies and a frequency decrease for the COR^3 group (γ-positioned to the carbanionic centre) when it is an amide or no change when it is an ester function. It is noteworthy that in the latter case the absorption band broadens considerably.

Table 2. IR frequencies (ν, cm^{-1}) of carbonyl and nitrile groups in the carbanionic species and the neutral compounds

	Compound	R^2	Li salt	neutral molecule	$\Delta\nu$	COR^3	Li salt	neutral molecule	$\Delta\nu$
1	**4b**	CN	2082	2235	153	COO^tBu	1730	1730	0
2	CH_3COO^tBu	–	–	–	–	–	–	1730	–
3	$CH_3COO^tBu + LiBr$	–	–	–	–	–	1730[a]	–	0
4	**4c**	CN	2080	2239	159	$CON(CH_3)_2$	1625	1650	25
5	**4c** + cryptand (2,1,1)	CN	2130	2239	109	$CON(CH_3)_2$	1650	1650	0
6	$CH_3CON(CH_3)_2$	–	–	–	–	–	–	1650	–
7	$CH_3CON(CH_3)_2 + LiBr$	–	–	–	–	–	−1625[a]		25
8	**4f**	$CON(CH_3)_2$	1625	1648	23	$CON(CH_3)_2$	1625	1648	23
9	**4g**	$CON(CH_3)_2$	1630	1650	20	$CON(CH_3)_2$	1640	1650	10

[a] Frequency (ν, cm^{-1}) in the complex with LiBr

The first observation is connected with the carbanion charge delocalization which is larger in nitrile [28] than in amide and ester moieties [29, 30]. To assign the second carbonyl group shift as well as to rationalize the difference in the behaviour of the amide and ester groups, we recorded the IR spectra of model 1:1 mixtures of LiBr with $CH_3COOtBu$ and $CH_3CON(CH_3)_2$ in 0.3 *M THF* solution. The values obtained, just the same as those in the carbanionic species (compare entries 1 and 3, 4 and 7) are indicative of chelation. While the good complexing power of the amide group is well known [20, 21], coordination with the ester group (entry 1) obviously occurs, but not strong enough to cause the band shift. In the presence of an equimolar quantity of cryptand (2.1.1) which is known to act as dechelating agent (entry 5), the absorption of the amide group in the Li-salt of **4c** returns to the position in the neutral molecule. This observation is accompanied by a significant decrease of diastereoselectivity (*anti*:*syn* = 95:5 → 60:40).

An additional evidence for coordination in the above case is the downfield shift of the amide carbonyl carbon from 170.04 ppm in the neutral *anti*-adduct to 174.60 ppm in the metal form in the ^{13}C NMR spectra (both spectra recorded in *THF*-d8).

The stereochemical course of the electrophilic attack on a trigonal carbon having an adjacent chiral centre has been predicted by the theoretical model of *Houk* [33] (Fig. 1; **L**, **M**, and **S** refer to large, medium and small groups).

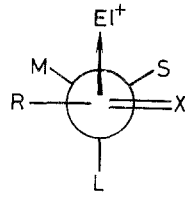


Fig. 1. *Houk*'s model for electrophilic attack on a double bond

Bearing in mind some considerations given in the literature [15], the low diastereoselectivity observed in the presence of *HMPT* is interpreted in terms of two conformations **K** and **L** similar in energy where the substituents on the

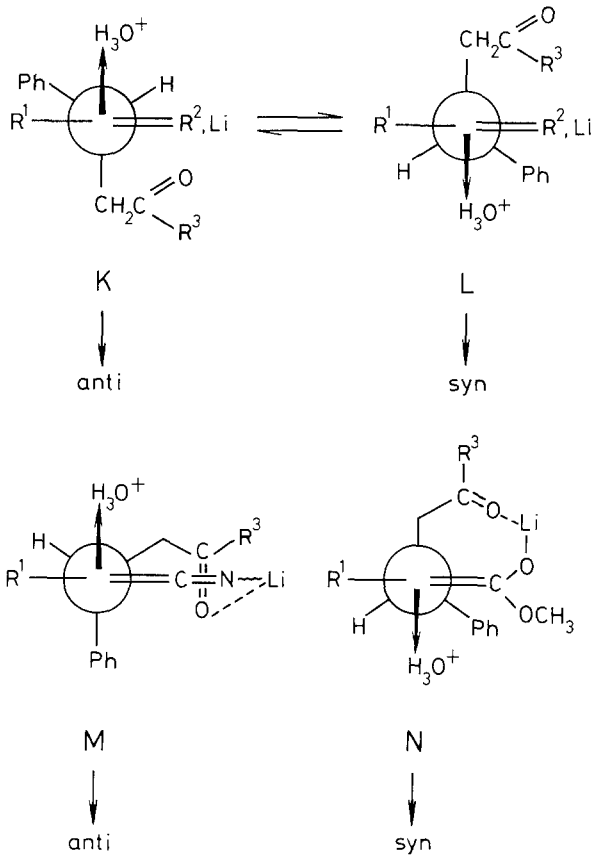


Fig. 2. Transition structures for protonation in the presence of *HMPT*

Fig. 3. Transition structures for protonation in *THF*

stereogenic centre are ranked as follows: $CH_2COR^3 = \mathbf{L}$ (large group), $Ph = \mathbf{M}$ (medium group) and $H = \mathbf{S}$ (small group).

When R^2 is a cyano group, there is no 1,3-allylic strain in conformation **L** and the phenyl group Ph readily adopts a position partially eclipsed with respect to the double bond. Similar explanations hold for the amide and ester enolates ($R^2 = COOCH_3$, $CON(CH_3)_2$), whose geometry is currently unknown, indicating *cis* location of the relatively small oxylithium group OLi to the stereogenic centre. Unfortunatelly, our attempts to trap the lithium enolates with *tert*-butyldimethylsilylchloride were unsuccessful.

The stereoselectivity in *THF* and its dependence on the enolate nature is explained by protonation *via* chelated transition structures different in geometry. Among the possible chelated conformations, those presented in Fig. 3 (conformations **M** and **N**) are considered to be the preferred ones for steric reasons (molecular models inspection). When $R^2 = CN$, chelation in a conformation analogous to **N** is not possible. Because of the cation location in the vicinity of the CN nitrogen [28], coordination forces the large group $\mathbf{L} = CH_2COR^3$ to adopt the "inside", *e.g.* partially eclipsed position in conformation **M**. Attack *anti* to the phenyl group results in the predominant formation of the *anti* isomer. The temperature dependence of the stereochemical result in the case of **4c** (entries 5 and 6) has been explained previously [5] by an equilibrium between two chelated conformations. In the case of the amide and ester enolates ($R^2 = COOCH_3$, $CON(CH_3)_2$), protonation *via* conformation **N** leads predominantly to the *syn* isomer. Molecular

models suggest that the decreased selectivity in the case of **4f** compared to **4g** (entries 16 and 19) is due to enhanced steric hindrance with respect to *anti* attack, caused by replacing CH_3 by Ph.

The present study provides a new synthetic and stercochemical approach to diastereoisomeric 1,3-bifunctionalized propanic systems by means of protonation of diastereotopic enolates. The presence of a carbonyl group in γ-position to the carbanionic centre is found to be of crucial importance for the observed 1,2-asymmetric induction in *THF*. The dependence of the stereochemistry on the solvent and on the substitution pattern of the enolate is explained by transition structures different in type and in geometry.

Experimental

All experiments were carried out under an argon atmosphere in a dry flask equipped with a rubber septum for introduction of the reagents by syringe. *THF* was freshly distilled prior to use. *HMPT* was dried and distilled from CaH_2 and kept on molecular sieves (4 Å). Starting materials were commercially available or prepared from the corresponding acids. *n*-BuLi (1.6 *M* in hexan) was used as purchased (Aldrich).

^1H and ^{13}C NMR spectra were recorded on a Bruker WM-250 spectrometer operating at 250.13 MHz for ^1H and 62.89 MHz for ^{13}C. $CDCl_3$ was used as the solvent and *TMS* as an internal standard. IR spectra were taken on a Specord 75 IR spectrometer in CaF_2 cells. Melting points were measured on a Kofler apparatus and are uncorrected. Analytical TLC was performed on Kisselgel Merk 60 F_{254} plates. The products were isolated by recrystallization or by column chromatography on silica gel 40 (partical size 0.015–0.035 mm). The analyses of the diastereoisomeric mixtures were performed using the difference in location of appropriate protons in the ^1H NMR spectra.

Structures

The diastereoisomeric pairs **4a**, **4c** [5, 34], **4d** [6], **4e** [35] (*anti* and *syn*) have been described and their relative configuration have been assigned as cited. The relative configurations of *anti* and *syn* *t*-butyl-4-cyano-3,4-diphenyl-butanoates (**4b**) were elucidated using the correlation between ^1H NMR chemical shifts and the steric structure of 4-cyano-3,4-disubstituted butyric acid derivatives [34]. Thus, *anti* configuration was assigned to the isomer with the H-4 proton located downfield.

The diastereoisomeric 2-methyl-3-phenyl-glutaric acid dimethylamides **4g** were correlated with the *anti* acid obtained by stereospecific hydrolysis of the corresponding diethyl glutarate, prepared as reported by *Yamagushi* [36].

General procedure for enolization and 1,2/1,4-addition

The starting lithium enolates were generated by applying *LDA* at $-78\,^\circ C$ for 30 min. In the case of dimethylacetamide, the metallation was carried out for 30 min at $0\,^\circ C$ as reported [20]. Thus, to 1.1 mmols of *LDA* in 1 ml *THF*, 1 mmol of the corresponding nucleophile in 1 ml of the same solvent was added dropwise at the appropriate temperature. The reaction mixture was kept stirring for the time required; then, 1 mmol of the unsaturated compound in 1 ml *THF* was added at the temperature wanted. The reaction was quenched after 60 min by the addition of saturated aqueous NH_4Cl solution or CF_3CO_2H. *THF* was then removed under reduced pressure, and the residue was extracted with methylene chloride. After drying and evaporation of the solvent, the reaction products were isolated by recrystallization or by column chromatography on silica gel. The experiments in the presence of *HMPT* (method B) were carried out by adding *HMPT* (0.6 ml; 20 vol. %) to the metal enolate prior to electrophile addition.

Compounds **9** and **10**, resulting from 1,2-addition, gave satisfactory elemental analyses and spectral data (available upon request from the authors).

tert-Butyl-4-cyano-3,4-diphenyl-butanoates (**4b** (***anti***) *and* **4b** (***syn***))

Compound **4b** (***anti***) was isolated from the reaction mixture obtained after method A by recrystallization from ethanol. M.p.: 100–102 °C; $R_f = 0.4$ ether:petroleum ether = 1:3); IR ($CHCl_3$, ν (cm^{-1})): 1730 (COO^tBu), 2235 (CN); ^1H NMR ($CDCl_3$, δ (ppm)): 1.31 (s, 9H, COO^tBu), 2.66, 2.69, 2.72, 2.75 (dd, 1H, H-2), 2.80, 2.83, 2.86, 2.89 (dd, 1H, H-2), 3.46–3.55 (m, 1H, H-3), 4.26, 4.29 (d, 1H, C-4, $J = 6.2$ Hz); found: C, 78.55; H, 7.30; $C_{21}H_{23}O_2N$ requires C, 78.47; H, 7.21.

Fractional recrystallization of the reaction mixture obtained in the presence of *HMPT* from ethanol (method B), followed by preparative TLC of the mother liquor (ether:petroleum ether = 1:4, fourfold eluation) gave access to the isomer **4b** (***syn***) as a viscous oil. $R_f = 0.4$ (ether:petroleum ether = 1:3); IR ($CHCl_3$, ν (cm^{-1})): 1730 (COO^tBu), 2235 (CN); ^1H NMR ($CDCl_3$, δ (ppm)): 1.23 (s, 9H, COO^tBu), 273–2.89 (m, 2H, H-2), 3.53–3.62 (m, 1H, H-3), 4.06, 4.09 (d, 1H, H-4, $J = 6.2$ Hz); found: C, 78.64; H, 7.40; $C_{21}H_{23}O_2N$ requires C, 78.47; H, 7.21.

2-methyl-3-phenyl-glutaric acid dimethylamides (**4g** (***anti***) *and* **4g** (***syn***))

The crude product from the synthesis in *THF* (method A) afforded the isomer **4g** (***syn***) after recrystallization from ethanol. M.p.: 130–132 °C; $R_f = 0.29$ (ether:methanol = 20:1); IR ($CHCl_3$, ν (cm^{-1})): 1648 (CO amide); ^1H NMR ($CDCl_3$, δ (ppm)): 0.90, 0.93 (d, 3H, CH_3, $J = 6.87$ Hz), 2.52, 2.55, 2.58, 2.61 (dd, 1H, H-4), 2.77, 2.83 (d, 6H, $N(CH_3)_2$), 2.77, 2.78, 2.83, 2.86 (dd, 1H, H-4), 2.96, 3.02 (d, 6H, $N(CH_3)_2$), 3.18–3.30 (m, 1H, H-2), 3.41–3.50 (m, 1H, H-3), 7.16–7.34 (m, 5H, C_6H_5); found: C, 69.30; H, 8.63; $C_{16}H_{24}O_2N_2$ requires C, 69.53; H, 8.75.

Attempts to isolate pure **4g** (***anti***) by the techniques used failed. The product was synthesized as follows:

To 1 mmol (278 mg) of *anti* diethyl-2-methyl-3-phenyl glutarate, obtained as reported by *Yamagushi* [36], 2.5 ml of conc. acetic and 1.5 ml of conc. hydrochloric acid were added and the homogenous reaction mixture was heated at 100 °C for 4 h. After cooling to room temperature, it was neutralized ($pH = 7$) using solid Na_2CO_3, followed by extraction with methylene chloride and washing with water. Drying over Na_2SO_4 and evaporation of the solvent afforded 190 mg (85%) of *anti* 2-methyl-3-phenyl-glutaric acid as a pale yellow oil. The stereospecifity of the hydrolysis under the conditions used was proved by ^1H NMR analysis of the crude product. The acid was dissolved in 3 ml of dry benzene and heated at boiling temperature for 15 min with 2.2 mmol (220 mg) of thionyl chloride. The reaction mixture was treated with an excess of aqueous dimethylamine at 0 °C and then left at room temperature for 1 h. The organic layer was washed with water, dried over Na_2SO_4, and the solvent was evaporated. Purification by column chromatography (eluent ether:methanol = 20:1) afforded 200 mg (84%) of **4g** (***anti***) as colourless oil. $R_f = 0.29$ (ether:methanol = 20:1); IR ($CHCl_3$, ν (cm^{-1})): 1648 (CO amide); ^1H NMR ($CDCl_3$, δ (ppm)): 1.15, 1.18 (d, 3H, CH_3, $J = 6.77$ Hz), 2.68–3.04 (m, 2H, H-4), 2.77, 2.80 (d, 6H, $N(CH_3)_2$), 2.88, 2.93 (d, 6H, $N(CH_3)_2$), 3.11–3.21 (m, 1H, H-2), 3.54–3.62 (m, 1H, H-3), 6.93–7.28 (m, 5H, C_6H_5), found: C, 69.60; H, 8.50; $C_{16}H_{24}O_2N_2$ requires C, 69.53, H, 8.75.

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