Pergamon

Tetrahedron 58 (2002) 3371–3378

TETRAHEDRON

Diastereoselectivity of tandem Michael addition–alkylation reactions: a convenient method for one-pot synthesis of α-branched 2,3-diphenylglutaric acid derivatives

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Received 5 December 2001; revised 8 February 2002; accepted 7 March 2002

Abstract—α-Branched 2,3-diphenylglutaric acid derivatives with two adjacent chiral centres are easily obtained by one-pot Michael addition–alkylation sequences. The diastereoselectivity observed, which varies from outstanding to moderate and even low, was found to depend on the type of the metal intermediate (nitrile vs amide) and its γ-substitution pattern. A rigidly chelated transition state model that correctly predicts the sense of the asymmetric induction is proposed.

1. Introduction

Alkylation reactions of metal enolates bearing an adjacent stereogenic centre are a challenging area of asymmetric synthesis. They have been the subjects of numerous studies from both mechanistic and synthetic viewpoints. The sense of the observed asymmetric induction has been, in general, more predictable in ring and chelate systems than in open-chain ones due to the fixed orientation between the resident asymmetric centre and the enolate double bond.[1] Recently, based on theoretical calculations[2] and vast experimental data, considerable progress in understanding of the diastereoselectivity of alkylation and electrophile trapping in open-chain structures has been achieved.[3] Increasingly frequent reports deal with the influence of more subtle factors as stereoelectronics,[4] enolate substitution patterns, enolate configuration, reactive conformation and aggregation state.[5]

Recently[6] we developed a new synthetic and stereochemical approach to the previously synthesised diastereoisomeric 2,3-diphenylglutaric acid derivatives[7] by means of kinetic protonation of metal intermediates, generated in the conjugate addition of acetic to α-phenyl cinnamic acid derivatives. The observed diastereoselection, varying from high to moderate was found to be enolate- and solvent-dependent.

The asymmetric induction observed in the protonation step as well as the convenient access to carbanions of different chemical types (nitrile vs amide) or γ-substitution patterns (amide vs ester) stimulated further our interest to explore the behaviour of the initially formed metal intermediates in a trapping reaction with electophiles other than a proton. This successive two carbon–carbon bond forming one-flask procedure creates two vicinal stereocentres, one of which is quaternary, and can provide a variety of diastereoisomeric α-branched 2,3-diphenylglutaric acid derivatives.

2. Results and discussion

We now report our results from a study of the influence of various reaction parameters—type of the carbanionic species and/or its substitution pattern, metal counterion, steric requirements of the incoming electrophile, and solvent polarity—on the diastereoselective formation of a second quaternary carbon centre by means of a Michael addition–alkylation sequence (Scheme 1). The examples studied were selected with regard to regioselective 1,4-addition.[6] The results are listed in Table 1 and are compared with those from the protonation reaction.

Tandem Michael addition–alkylation reactions were carried out in THF and in some cases in a mixture of THF/HMPT (80:20 vol/vol%) under standard conditions. The conjugate addition step was performed for 1 h at −78°C. The lithium precursors were prepared as described before.[6] The corresponding sodium intermediate is accessible by the alternative reaction pathway from the sodium derivative of benzylcyanide and *N*,*N*-dimethylamide of cinnamic acid, followed by intramolecular metal transfer.[7e] Since the

Keywords: tandem reactions; Michael additions; alkylations; diastereoselectivity; asymmetric induction.
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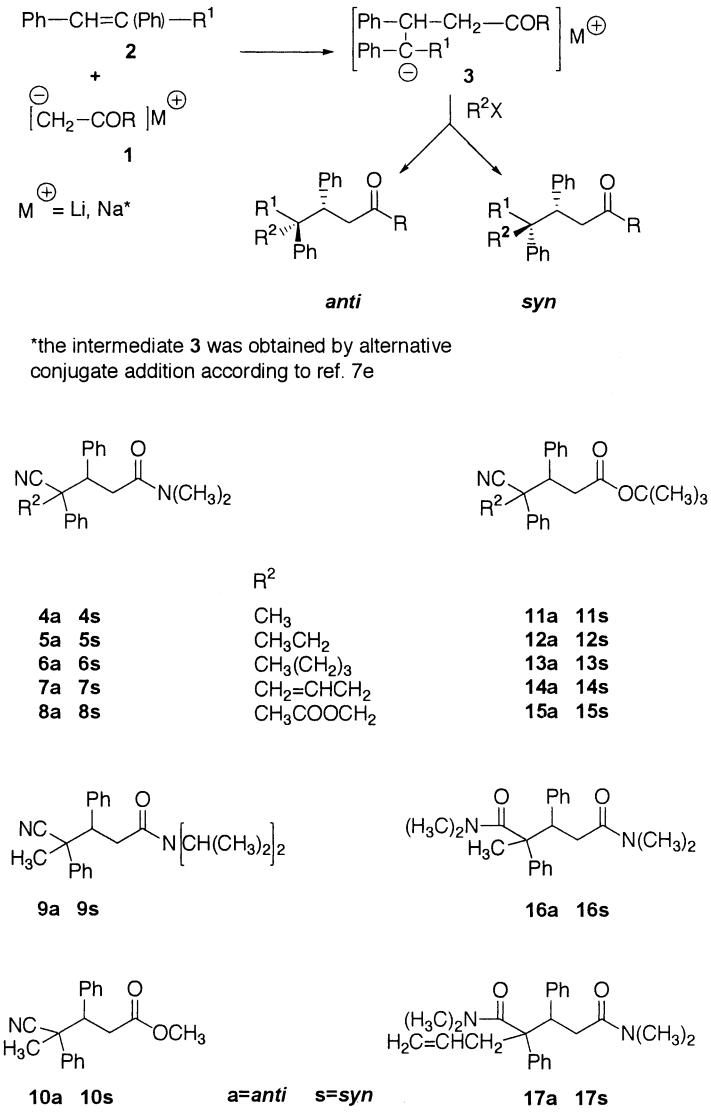
0040–4020/02/$ - see front matter
PII: S0040-4020(02)00298-3



Scheme 1.

alkylation at −78°C was rather slow, we carried out the reaction at −15°C for 3 h. To make sure that the diastereoselectivity observed is not a result of complete or partial equilibration, we reexamined the protonation reaction under the same time and temperature conditions. No change in the *anti*/*syn* ratios compared to those previously found[6] was observed. In addition, the heavy water quenching experiments showed up to 85% of deuterium incorporated at the C-2 position.

The relative configurations of the diastereoisomeric pairs **4** and **11** were determined by a series of ^{1}H, ^{13}C, HSQC and NOESY experiments.

There is considerable experimental and theoretical evidence[8] that three-bond $^{13}C-^{1}H$-coupling constants follow a Karplus type relationship with the dihedral angle. Information concerning the conformational preference of **4** and **11** was gained from the three-bond $^{13}C-^{1}H$-coupling constants between the methine proton and the CN group. The measured $J_{CN,H}$ values, which vary from 6.9 to 9.6 Hz indicate, by assuming $J_{CN,H}{}^{g}=2.0$ Hz and $J_{CN,H}{}^{t}=10$ Hz,[8b] that the conformations with *trans* relationship between the methine proton and the cyano group are preferred in both *anti* and *syn* series.

Configurational assignments were based on the different NOE enhancements observed within each of the diastereoisomeric pairs (Fig. 1). In particular, the proximal position of the CH_3 group and the methylene proton (H-2b) in the *anti* isomers was evidenced by the existence of a cross peak. On the other hand, in the *syn* compounds this group is in close proximity with the *ortho*-protons of both phenyls. It is noteworthy that the configurations thus determined are in agreement with the correlation between the stereostructure and the proton chemical shifts of the amide and ester functional groups previously found for non-alkylated compounds, where the same conformational preference have been established.[7e,9] The same correlation was applied for the configurational assignment of the diastereoisomeric pairs **5**–**10** and **12**–**15**.

The relative configuration of **16** was unambiguously proven by the chemical sequence shown in Scheme 2.

Table 1. Yields and diastereoselectivity by tandem Michael addition–alkylation reactions

Entry	Compound	R	R^1	R^2X	M^+	*a/s*	Yield (%)	*a/s*[a]
1	**4**	$N(CH_3)_2$	CN	CH_3I	Li	89/11	87	95/5
2					Li[b]	70/30	65	
3					Na	93/7	92	
4					Na[b]	70/30	70	
5	**5**	$N(CH_3)_2$	CN	CH_3CH_2I	Li	78/22	64	
6					Na	87/13	58	
7	**6**	$N(CH_3)_2$	CN	$CH_3(CH_2)_3I$	Li	82/18	63	
8					Na	85/15	45	
9	**7**	$N(CH_3)_2$	CN	$CH_2{=}CHCH_2I$	Li	80/20	58	
10					Na	87/13	53	
11					Na[b]	80/20	48	
12	**8**	$N(CH_3)_2$	CN	CH_3COOCH_2Br	Li	>95/5	55	
13					Li[b]	84/16	51	
14	**9**	$N[CH(CH_3)_2]_2$	CN	CH_3I	Li	86/14	52	92/8
15	**10**	OCH_3	CN	CH_3I	Li	76/24	44	87/13
16	**11**	$OC(CH_3)_3$	CN	CH_3I	Li	56/44	89	86/14
17					Li[b]	73/27	60	
18	**12**	$OC(CH_3)_3$	CN	CH_3CH_2I	Li	54/46	90	
19	**13**	$OC(CH_3)_3$	CN	$CH_3(CH_2)_3I$	Li	60/40	62	
20	**14**	$OC(CH_3)_3$	CN	$CH_2{=}CHCH_2I$	Li	78/22	84	
21	**15**	$OC(CH_3)_3$	CN	CH_3COOCH_2Br	Li	60/40	87	
22					Li[b]	84/16	63	
23	**16**	$N(CH_3)_2$	$CON(CH_3)_2$	CH_3I	Li	>95/5	30	41/59
24	**17**	$N(CH_3)_2$	$CON(CH_3)_2$	$CH_2{=}CHCH_2I$	Li	>95/5	28	

[a] Diastereoselectivity of protonation.[6]
[b] In the presence of HMPT.

It is worth mentioning that in the present case the correlation between the CH_3 proton chemical shifts and the relative configurations found for the diastereoisomeric pairs of **4** and **11** is not valid. This finding is in accordance with our previous observations[9] and is obviously due to the presence of a cyano group as a substituent in the 1,2-disubstituted 1,2-diaryl ethane moiety. The diastereoisomeric ratios were measured by integration of the appropriate, well resolved signals in the ^1H NMR spectra of samples obtained after preparative TLC.

Alkylation of the examined metal intermediates with various alkyl halides proceeds in high to moderate yields. No reaction with secondary *i*-PrI was detected. Since the amide enolates are less delocalised and consequently, should be more reactive than the corresponding nitrile metallates,[10] the low yields in this case are most probably due to steric reasons.

In THF the alkylation diastereoselectivity varies in a wide range from outstanding and high to moderate and even disappointingly low as a function of the metallate type and its γ-substitution patterns. In the case of nitrile metallates, the substituent that is γ-positioned to the carbanionic centre seems to be of essential importance for the observed asymmetric induction. Thus, when this substituent is a dialkylamido-group, the diastereoselectivity is uniformly high to good in favour of the *anti* isomer, whatever the identity of this group—$CON(CH_3)_2$ vs $CON[CH(CH_3)_2]_2$ (compare entries 1 and 14). The change of the dialkylamide with an ester substituent yielded alkylated products with variable *anti* preference, depending on the steric volume of the ester group—good in the case of $COOCH_3$ and inferior with the bulkier $COOC(CH_3)_3$ (entries 15 and 16). In both cases the diastereoselectivity of alkylation follows in sense that of the protonation reaction.

With the studied amide enolate the alkylation occurred with complete *anti* diastereoselection (entries 23 and 24), thus differing dramatically from the non-selective protonation reaction.

The size of the alkylating agent seems to have moderate or no effect on the alkylation stereochemisty, which is an indication of an early, reactant-like transition state.[11] The switching from lithium to sodium counterion is connected

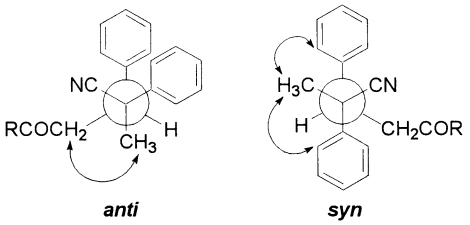
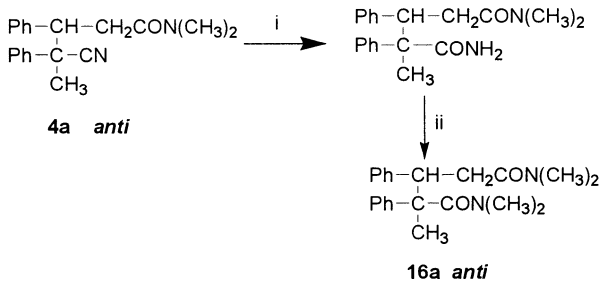


Figure 1. Representative NOE interactions in *anti* and *syn* diastereoisomeric pairs of **4** and **11**.



Scheme 2. *Reagents*: (i) conc. H_2SO_4, r.t., 96 h (78%); (ii) NaH, MeI, THF, r.t., 2 h (94%).

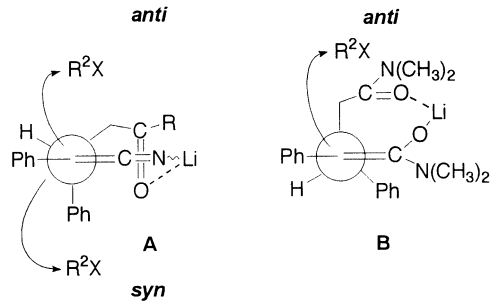


Figure 2. Transition structures for the alkylation reaction in THF.

with small, but detectable improvement of the *anti* adduct preference (compare entries 1 and 3, 5 and 6, 7 and 8, 9 and 10). Such an effect had been observed before[4d,12] and could be explained with a later transition state caused by the 'softer' character of the sodium derivatives.[13]

In an attempt to rationalize the alkylation stereochemistry, the chelated intermediates **A** and **B** (Fig. 2) were considered. These rigid transition structures have been postulated earlier for the protonation reaction in THF[6] taking into account the influence of dechelating agents on the reaction diastereoselectivity as well as on the basis of spectral investigations (IR and ^{13}C NMR data) of the neutral compounds and their metallated forms. In the chelated intermediates the electrophilic attack will take place from the less sterically hindered π-face of carbanionic species. When the substituent at the γ-position of the nitrile metallate is a dialkylamide or methylester group, the *anti*-attack might be significantly preferred. The change of $COOCH_3$ by the more sterically demanding $COOC(CH_3)_3$ group equalizes energetically the *anti* and *syn* approach of the incoming electrophile, thus resulting in inferior alkylation diastereoselectivity.

The complete *anti* preference, exhibited by the amide enolate, might be explained by the higher steric retardation for *syn*-attack, imposed by the dialkylamido group γ-positioned with respect to the carbanionic centre.

The effect of HMPT, examined in several instances involving nitrile metallates, is unclear. Thus, while the diastereoselectivity of alkylation decreases for nitrile amides, (entries 2, 4, 11 and 13), significant improvement of the *anti*/*syn* ratio is observed for nitrile esters (entries 17 and 22).This finding might be of importance from a synthetic standpoint.

3. Conclusion

A convenient one-pot procedure for the synthesis of α-branched 2,3-diphenylglutaric acid derivatives, including the formation of two new carbon–carbon bonds and two vicinal stereocentres, one of which quaternary, by tandem Michael addition–alkylation reactions is presented. The asymmetric induction in the alkylation step might be controlled by the appropriate choice of the metallate type and/or the substituent at γ-position to the carbanionic centre as well as by the use of HMPT as a co-solvent. Further work will be undertaken to obtain optically active compounds by using enzymes as discriminating reagents.

4. Experimental

All reactions were run under slight overpressure of argon in an oven-dried flask equipped with a rubber septum for the introduction of the reagents by a syringe. THF was freshly distilled over $LiAlH_4$. HMPT was dried and distilled over CaH_2 and kept over molecular sieves (13×). Starting materials were commercially available research-grade chemicals or synthesised from the corresponding acids. LDA was prepared immediately before use according to common procedure using *n*-BuLi (1.6 M in hexane, Fluka).

NMR measurements were performed at 296 K on a Bruker DRX-250 spectrometer operating at 250.13 MHz for ^1H and 62.89 MHz for ^{13}C with TMS as internal standard. IR spectra were taken on a Bruker FTR-113 V spectrometer in KBr tablets. Melting points were determined on a Kofler apparatus. Uncorrected values are presented. Thin-layer chromatography (TLC) was performed on Merck silica gel plates (60 F-254). Column chromatography was carried out on silica gel 40. The *anti*/*syn* ratios were determined by ^1H NMR analysis of the samples isolated by preparative TLC, using the difference in resonance frequencies of appropriate protons.

4.1. General experimental procedure for the preparation of metal intermediates 3 and for the subsequent alkylation reaction

To a solution of BuLi (0.69 mL, 1.1 mmol, 1.6 M in hexane) in THF (1 mL) diisopropylamine (0.15 mL, 1.1 mmol) was added at room temperature with stirring. The lithium enolates of dimethylacetamide and diisopropylacetamide were generated at 0°C while *tert*-buthylacetoacetate was metallated at −78°C. The nucleophile (1 mmol) in THF (1 mL) was added dropwise to the stirred solution of LDA, cooled to the desired temperature. After 30 min the corresponding conjugate compound (1 mmol) in THF (1 mL) was introduced at −78°C. The reaction mixture was kept at this temperature for 60 min, warmed to −15°C and the alkyl halide (2 mmol) dissolved in THF (1 mL) was added. This temperature was maintained for 3 h and then the reaction was quenched by the addition of ammonium chloride solution (10 mL, sat. aq.). The organic layer was decanted and the aqueous phase was extracted with methylene chloride (3×5 mL). The combined extracts were dried ($MgSO_4$) and the solvent was removed in vacuo.

The metal intermediate **3** with sodium counterion was generated by an alternative reaction pathway, involving conjugate addition of benzylcyanide to *N*,*N*-dimethylamide of cinnamic acid, followed by intramolecular metal transfer[7e] as follows.

To a suspension of freshly ground $NaNH_2$ (48 mg, 1.2 mmol) in dry THF (1 mL) at room temperature was added a solution of benzylcyanide (117 mg, 1 mmol) in THF (1 mL) under argon atmosphere. The mixture was stirred for 15 min before addition of cinnamic acid *N*,*N*-dimethylamide (175 mg, 1 mmol) dissolved in THF (1 mL). After stirring for 2 h the subsequent alkylation was performed following the general experimental procedure.

The experiments in the presence of HMPT were carried out by adding HMPT (0.6 mL, 20 vol.%) to the metal enolate prior to the Michael acceptor addition.

4.2. Proof of the relative configuration of 16a (*anti*)

The relative configuration of **16a** (*anti*) was determined by the sequence shown in Scheme 2, starting from the readily available *anti* isomer of **4**. Thus, **4a** (*anti*) (305 mg, 1 mmol) was dissolved in conc. H_2SO_4 (8 mL) at room temperature. The mixture was kept at this temperature for 96 h and then poured into ice-cold water (20 mL). After neutralisation with solid Na_2CO_3 (pH 7) the reaction mixture was extracted with methylene chloride (2×10 mL), dried ($MgSO_4$) and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography (Et_2O) gave 2,3-diphenyl-2-methylpentandioic acid 1-amide-5-dimethylamide as a colourless oil (250 mg, 78%). Further, to a suspension of sodium hydride (70 mg, 3 mmol) in dry THF (8 mL) at room temperature was added a solution of the above obtained bis-amide (250 mg, 0.77 mmol) in THF (2 mL) via syringe. The mixture was stirred for 15 min before addition of methyl iodide (0.4 mL, 6 mmol). After 2 h a working-up analogous to that for the alkylation reaction afforded a crude product (256 mg, 94%) which is chromatographically (TLC) and spectroscopically (^{1}H NMR) identical with the title compound **16a** (*anti*).

Physical constants (melting points mp, chromatographic R_f, NMR) and analytical data of pure **4**–**17** are given hereafter. In some cases, where the second isomer has not been isolated, only well resolved signals, taken from the spectra of the diastereoisomeric mixtures and used for *anti*/*syn* analysis, are given.

4.2.1. 4-Cyano-3,4-diphenylpentanoic acid dimethylamide 4a (*anti*). Following the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **4a** (*anti*) (230 mg, 75%) was isolated after purification of the crude product (entry 1) by column chromatography (silica gel, Et_2O) as a white solid, mp 95–97°C; [Found: C, 78.22; H, 7.13. $C_{20}H_{22}N_2O$ requires C, 78.40; H, 7.24]; R_f (Et_2O) 0.26; ν_{max} (KBr) 2241, 1639 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.87 (s, 3H, H-5), 2.83 (s, 3H, $N(CH_3)_2$), 2.98 (s, 3H, $N(CH_3)_2$), 2.90–3.15 (m, 2H, H_aH_b-2), 3.82 (dd, 1H, J=8.5 and 4.8 Hz, H-3), 6.90–7.20 (m, 10H, 2×C_6H_5); δ_C (250 MHz, $CDCl_3$): 26.1 (CH_3), 35.4 (C-2), 35.6, 37.2 ($N(CH_3)_2$), 47.2 (C-4), 51.2 (C-3), 122.8 (CN), 126.2, 127.0, 127.5, 127.7, 128.2, 128.7, 138.8, 139.2 (C-Ph), 170.1 (CO amide).

4.2.2. 4-Cyano-3,4-diphenylpentanoic acid dimethylamide 4s (*syn*). Following the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **4s** (*syn*) (60 mg, 19%) was isolated after purification of the crude product (entry 4) by column chromatography (silica gel, Et_2O/hexane=2:1) as a white solid, mp 148–150°C; [Found: C, 78.18; H, 7.35. $C_{20}H_{22}N_2O$ requires C, 78.40; H, 7.24]; R_f (Et_2O) 0.51; ν_{max} (KBr) 2241, 1639 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.42 (s, 3H, H-5), 2.33 (dd, 1H, J=15.7 and 2.9 Hz, H_aH_b-2), 2.68 (s, 3H, $N(CH_3)_2$), 2.84 (s, 3H, $N(CH_3)_2$), 3.06 (dd, 1H, J=15.7 and 10.8 Hz, H_aH_b-2), 3.82 (dd, 1H, J=10.8 and 2.9 Hz, H-3), 7.32–7.64 (m, 10H, 2×C_6H_5); δ_C (250 MHz, $CDCl_3$) 27.5 (CH_3), 35.1 (C-2), 35.3, 37.0 ($N(CH_3)_2$), 47.2 (C-4), 50.7 (C-3), 122.4 (CN), 125.9, 127.7, 128.0, 128.5, 129.0, 129.1, 139.0, 139.9 (C-Ph), 169.8 (CO amide).

4.2.3. 4-Cyano-3,4-diphenylhexanoic acid dimethylamide 5a (*anti*). According to the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **5a** (*anti*) (120 mg, 38%) was isolated after purification of the crude product (entry 6) by column chromatography (silica gel, Et_2O/hexane=2:1) followed by recrystallisation of the isolated diastereoisomeric mixture (Et_2O/hexane). White crystals, mp 110–112°C; [Found: C, 78.45; H, 7.69. $C_{21}H_{24}N_2O$ requires C, 78.40; H, 7.24]; R_f (Et_2O) 0.43; ν_{max} (KBr) 2241, 1640 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.87 (t, 3H, J=7.3 Hz, H-6), 2.17 (q, 2H, J=7.3 Hz, H-5), 2.77 (s, 3H, $N(CH_3)_2$), 2.89 (s, 3H, $N(CH_3)_2$), 2.98 (d, 2H, J=6.7 Hz, H_aH_b-2), 3.80 (t, 1H, J=6.7 Hz, H-3), 6.80–7.18 (m, 10H, 2×C_6H_5).

4.2.4. 4-Cyano-3,4-diphenylhexanoic acid dimethylamide 5s (*syn*). R_f (Et_2O) 0.43; ν_{max} (KBr) 2241, 1640 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0f.56 (t, 3H, J=7.4 Hz, H-6), 2.59 (s, 3H, $N(CH_3)_2$). 2.73 (s, 3H, $N(CH_3)_2$).

4.2.5. 4-Cyano-3,4-diphenyloctanoic acid dimethylamide 6a (*anti*). According to the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **6a** (*anti*) (118 mg, 34%) was isolated after purification of the crude product (entry 7) by column chromatography (silica gel, Et_2O/hexane=3:1) followed by recrystallisation of the isolated diastereoisomeric mixture (Et_2O/hexane). White crystals, mp 78–80°C; [Found: 79.45; H, 8.43. $C_{23}H_{28}N_2O$ requires C, 79.27; H, 8.10]; R_f (Et_2O/hexane=3:1) 0.36; ν_{max} (KBr) 2241, 1640 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.75 (t, 3H, J=7.3 Hz, H-8), 1.12–1.38 (m, 4H, H-7+H-6), 2.02–2.10 (m, 2H, H-5), 2.76 (s, 3H, $N(CH_3)_2$), 2.89 (s, 3H, $N(CH_3)_2$), 2.99 (d, 2H, J=6.7 Hz, H_aH_b-2), 3.77 (t, 1H, J=6.7 Hz, H-3), 6.88–7.15 (m, 10H, 2×C_6H_5).

4.2.6. 4-Cyano-3,4-diphenyloctanoic acid dimethylamide 6s (*syn*). R_f (Et_2O/hexane=3:1) 0.36; ν_{max} (KBr) 2241, 1640 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.62 (t, 3H, J=7.0 Hz, H-8), 2.59 (s, 3H, $N(CH_3)_2$), 2.73 (s, 3H, $N(CH_3)_2$).

4.2.7. 4-Cyano-3,4-diphenyl-6-heptenoic acid dimethylamide 7a (*anti*). According to the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **7a** (*anti*) (115 mg, 35%) was isolated after purification of the crude pruduct (entry 10) by column chromatography (silica gel, Et_2O/hexane=2:1) followed by recrystallisation of the isolated diastereoisomeric mixture (EtOH). White crystals, mp 79–81°C; [Found: C, 79.67; H, 7.25. $C_{22}H_{25}N_2O$ requires C, 79.24; H, 7.56]; R_f (Et_2O) 0.55; ν_{max} (KBr) 2238, 1640 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 2.84 (s, 3H, $N(CH_3)_2$), 2.96 (s, 3H, $N(CH_3)_2$), 2.85–2.94 (m, 2H, H-5), 3.06 (d, 1H, J=7.5 Hz, H_aH_b-2), 3.07 (d, 1H, J=5.6 Hz, H_aH_b-2), 3.92 (dd, 1H, J=7.5 and 5.6 Hz, H-3), 5.05 (ddt, 1H, J=10, 1.7 and 0.9 Hz, H_{cis}-7), 5.14 (ddt, 1H, J=17.0, 1.7 and 1.3 Hz, H_{trans}-7), 5.43–5.60 (m, 1H, H-6), 6.98–7.18 (m, 10H, 2×C_6H_5).

4.2.8. 4-Cyano-3,4-diphenyl-6-heptenoic acid dimethylamide 7s (*syn*). R_f (Et_2O) 0.55; ν_{max} (KBr) 2238, 1640 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 2.67 (s, 3H, $N(CH_3)_2$), 2.84 (s, 3H, $N(CH_3)_2$), 4.87–4.90 (m, 2H, H-7).

4.2.9. 4-Cyano-3,4-diphenylhexandioic acid 1-dimethylamide 5-methylester 8a (*anti*). Following the general procedure, the title compound **8a** (*anti*) (160 mg, 44%) was obtained after recrystallisation of the crude product (entry 12) (EtOH) as a white solid, mp 124–126°C; [Found: C, 72.33; H, 6.80. $C_{22}H_{24}N_2O_3$ requires C, 72.51; H, 6.64]; R_f (Et_2O) 0.25; ν_{max} (KBr) 2245, 1730, 1640 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 2.84 (s, 3H, $N(CH_3)_2$), 2.98 (s, 3H, $N(CH_3)_2$), 3.05 (d, 2H, J=6.7 Hz, H_aH_b-2), 3.21 (s, 1H, H-5), 3.23 (s, 1H, H-5), 3.50 (s, 3H, $COOCH_3$), 3.93 (t, 1H, J=6.7 Hz, H-3), 6.92–7.20 (m, 10H, 2×C_6H_5).

4.2.10. 4-Cyano-3,4-diphenylhexandioic acid 1-dimethylamide 5-methylester 8s (*syn*). R_f (Et_2O) 0.25; δ_H (250 MHz, $CDCl_3$) 3.68 (s, 3H, $COOCH_3$).

4.2.11. 4-Cyano-3,4-diphenylpentanoic acid diisopropylamide 9a (*anti*). According to the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **9a** (*anti*) (165 mg, 42%) was isolated after purification of the crude product (entry 14) by column chromatography (silica gel, Et_2O/hexane=1:2) as a colourless oil; [Found: C, 79.68; H, 8.13. $C_{24}H_{30}N_2O_3$ requires C, 79.52; H, 8.34]; R_f (Et_2O/hexane=1:2) 0.23; ν_{max} (KBr) 2241, 1640 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.96, 1.09, 1.20, 1.33 (four d, 12H, J=6.7 Hz, 2×$N(CHCH_3)_2$), 1.89 (s, 3H, H-5), 2.99 (d, 1H, J=5.3 Hz, H_aH_b-2), 3.02 (d, 1H, J=8.1 Hz, H_aH_b-2), 3.32–3.38 (m, 1H, $N(CHCH_3)_2$), 3.84 (dd, 1H, J=8.1 and 5.3 Hz, H-3), 4.01–4.25 (m, 1H, $N(CHCH_3)_2$), 6.95–7.20 (m, 10H, 2×C_6H_5).

4.2.12. 4-Cyano-3,4-diphenylpentanoic acid diisopropylamide 9s (*syn*). δ_H (250 MHz, $CDCl_3$) 1.45 (s, 3H, H-5).

4.2.13. 4-Cyano-3,4-diphenylpentanoic acid methylester 10a (*anti*). According to the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **10a** (*anti*) (95 mg, 32%) was isolated after purification of the crude mixture (entry 15) by column chromatography (silica gel, Et_2O/hexane=1:2) as a white solid, mp 120–121°C; [Found: C, 77.53; H, 6.80. $C_{19}H_{19}NO_2$ requires C, 77.79; H, 6.53]; R_f (Et_2O/hexane=1:2) 0.32; ν_{max} (KBr) 2241, 1735 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.82 (s, 3H, H-5), 2.96 (dd, 1H, J=15.8 and 10.3 Hz, H_aH_b-2), 3.06 (dd, 1H, J=15.8 and 5.1 Hz, H_aH_b-2), 3.50 (s, 3H, $COOCH_3$), 3.60 (dd, 1H, J=10.3 and 5.1 Hz, H-3), 6.90–7.28 (m, 10H, 2×C_6H_5).

4.2.14. 4-Cyano-3,4-diphenylpentanoic acid methylester 10s (*syn*). R_f (Et_2O/hexane=1:2) 0.37; ν_{max} (KBr) 2241, 1735 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.46 (s, 3H, H-5), 3.38 (s, 3H, $COOCH_3$).

4.2.15. 4-Cyano-3,4-diphenylpentanoic acid *tert*-butylester 11a (*anti*). According to the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **11a** (*anti*) (160 mg, 48%) was isolated after purification of the crude mixture (entry 16) by column chromatography (silica gel, Et_2O/hexane=1:4) as a white solid, mp 117–119°C; [Found: C, 78.49; H, 7.23. $C_{22}H_{25}NO_2$ requires C, 78.77; H, 7.51]; R_f (Et_2O/hexane=1:3) 0.41; ν_{max} (KBr) 2236, 1718 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.18 (s, 9H, $C(CH_3)_3$), 1.82 (s, 3H, H-5), 2.82 (dd, 1H, J=15.1 and 10.9 Hz, H_aH_b-2), 2.97 (dd, 1H, J=15.1 and 5.1 Hz, H_aH_b-2), 3.51 (dd, 1H, J=10.9 and 5.1 Hz, H-3), 6.93–7.29 (m, 10H, 2×C_6H_5); δ_C 24.8 (CH_3), 27.6 ($C(CH_3)_3$), 37.7 (C-2), 46.8 (C-4), 51.7 (C-3), 80.8 ($C(CH_3)_3$), 122.5 (CN), 126.5, 127.4, 127.6, 127.8, 128.3, 129.2, 137.4, 138.0 (C-Ph), 170.4 (CO ester).

4.2.16. 4-Cyano-3,4-diphenylpentanoic acid *tert*-butylester 11s (*syn*). Following the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **11s** (*syn*) (125 mg, 37%) was isolated after purification of the crude mixture (entry 16) by column chromatography (silica gel, Et_2O/hexane=1:4) as a white solid, mp 95–97°C; [Found: C, 78.57; H, 7.70. $C_{22}H_{25}NO_2$ requires C, 78.77; H, 7.51]; R_f (Et_2O/hexane=1:3) 0.48; ν_{max} (KBr) 2236, 1718 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.09 (s, 9H, $C(CH_3)_3$), 1.49 (s, 3H, H-5), 2.36 (dd, 1H, J=15.1 and 4.1 Hz, H_aH_b-2), 2.83 (dd, 1H, J=12.0 and 15.1 Hz, H_aH_b-2), 3.45 (dd, 1H, J=12.0 and 4.1 Hz, H-3), 7.33–7.55 (m, 10H, 2×C_6H_5); δ_c (250 MHz, $CDCl_3$) 26.7 (CH_3), 27.5 ($C(CH_3)_3$), 37.9 (C-2), 47.2 (C-4), 51.7 (C-3), 80.6 ($C(CH_3)_3$), 121.8 (CN), 121.8–129.2, 137.6, 139.4 (C-Ph), 170.3 (CO ester).

4.2.17. 4-Cyano-3,4-diphenylhexanoic acid *tert*-butylester 12a (*anti*). According to the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **12a** (*anti*) (169 mg, 54%) was isolated after purification of the crude mixture (entry 18) by column chromatography (silica gel, Et_2O/hexane=1:6) as a colourless oil; [Found: C, 79.29; H, 7.90. $C_{23}H_{27}NO_2$ requires C, 79.05, H, 7.79]; R_f (Et_2O/hexane=1:5) 0.41; ν_{max} (KBr) 2236, 1718 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.90 (t, 3H, J=7.3 Hz, H-6), 1.17 (s, 9H, $C(CH_3)_3$), 2.08–2.13 (m, 1H, H-5), 2.17–2.25 (m, 1H, H-5), 2.82 (dd, 1H, J=15.2 and 10.8 Hz, H_aH_b-2), 3.07 (dd, 1H, J=15.2 and 5.2 Hz, H_aH_b-2), 3.55 (1H, dd, J=10.8 and 5.2 Hz, H-3), 6.86–7.25 (m, 10H, 2×C_6H_5).

4.2.18. 4-Cyano-3,4-diphenylhexanoic acid *tert*-butylester 12s (*syn*). Following the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **12a** (*anti*) (144 mg, 46%) was isolated after purification of the crude mixture (entry 18) by column chromatography (silica gel, Et_2O/hexane=1:6) as a white solid, mp 112–114°C; [Found: C, 78.79; H, 7.47. $C_{23}H_{27}NO_2$ requires C, 79.05, H, 7.79]; R_f (Et_2O/hexane=1:5) 0.45; ν_{max} (KBr) 2236, 1718 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 0.66 (t, 3H, J=7.3 Hz, H-6), 1.08 (s, 9H, $C(CH_3)_3$), 1.58–1.63 (m, 1H, H-5), 1.66–1.72 (m, 1H, H-5), 2.27 (dd, 1H, J=15.0 and 4.1 Hz, H_aH_b-2), 2.83 (dd, 1H, J=15.0 and 12.0 Hz, H_aH_b-2), 3.49 (1H, dd, J=12.0 and 4.1 Hz, H-3), 7.26–7.54 (m, 10H, 2×C_6H_5).

4.2.19. 4-Cyano-3,4-diphenyloctanoic acid *tert*-butylester 13a (*anti*) and 4-cyano-3,4-diphenyloctanoic acid *tert*-butylester 13s (*syn*). According to the general procedure from 1 mmol starting products used in the conjugate

reaction step the title compound **13** (233 mg, 62%) was isolated as diasereoisomeric mixture after purification of the crude product (entry 19) by column chromatography (silica gel, Et_2O/hexane=1:4). Colourless oil; [Found: C, 79.81; H, 8.50. $C_{25}H_{31}NO_2$ requires C, 79.54, H, 8.28]; R_f (Et_2O/hexane=1:3=0.54; ν_{max} (KBr) 2238, 1719 cm^{-1}.

13a (*anti*): δ_H (250 MHz, $CDCl_3$) (the signals are taken from the spectrum of the purified by column chromatography diastereoisomeric mixture) 0.84 (t, 3H, *J*= 7.3 Hz, H-8), 1.18 (s, 9H, $C(CH_3)_3$), 3.09 (dd, 1H, *J*=15.2 and 5.2 Hz, H-2), 3.54 (dd, 1H, *J*=10.4 and 5.2 Hz, H-3), 6.85–7.54 (m, Ph).

13s (*syn*): δ_H (250 MHz, $CDCl_3$) (the signals are taken from the spectrum of the purified by column chromatography diastereoisomeric mixture) 0.69 (t, 3H, *J*=7.3 Hz, H-8), 1.08 (s, 9H, $C(CH_3)_3$), 2.25 (dd, 1H, *J*=15.0 and 4.1 Hz, H-2), 3.47 (dd, 1H, *J*=12.1 and 4.1 Hz, H-3), 6.85–7.54 (m, Ph).

4.2.20. 4-Cyano-3,4-diphenyl-6-heptenoic acid *tert*-butyl-ester 14a (*anti*). According to the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **14a** (*anti*) (150 mg, 41%) was isolated after purification of the crude pruduct (entry 20) by column chromatography (silica gel, Et_2O/hexane=1:10) followed by recrystallisation of the isolated diasereoisomeric mixture (Et_2O/hexane) as a white solid, mp 78–80°C; [Found: C, 79.92; H, 7.29. $C_{24}H_{28}NO_2$ requires C, 79.74; H, 7.53]; R_f (Et_2O/hexane=1:8) 0.50; ν_{max} (KBr) 2239, 1719 cm^{-1}, δ_H (250 MHz, $CDCl_3$) 1.17 (s, 9H, $C(CH_3)_3$), 2.76–2.87 (m, 3H, H-5+H_aH_b-2), 3.09 (dd, 1H, *J*=15.2 and 4.9 Hz, H_aH_b-2), 3.61 (dd, 1H, *J*=10.9 and 4.9 Hz, H-3), 5.08 (ddt, 1H, *J*=10.1, 1.6 and 1.0 Hz, H_{cis}-7), 5.12 (ddt, 1H, *J*=15.4, 1.6 and 1.2 Hz, H_{trans}-7), 6.85–7.26 (m, 10H, 2×C_6H_5).

4.2.21. 4-Cyano-3,4-diphenyl-6-heptenoic acid *tert*-butyl-ester 14s (*syn*). δ_H (250 MHz, $CDCl_3$) 1.09 (s, 9H, $C(CH_3)_3$), 3.53 (dd, 1H, *J*=12.0 and 4.1 Hz, H-3).

4.2.22. 3-Cyano-3,4-diphenylhexandioic acid 6-*tert*-butyl-1-methyl diester 15a (*anti*). Following the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **15a** (*anti*) (205 mg, 52%) was isolated after purification of the crude product (entry 21) by column chromatography (silica gel, Et_2O/hexane=1:3) as a white solid, mp 99–101°C; [Found: C, 73.57; H, 6.70. $C_{24}H_{27}NO_4$ requires C, 73.26; H, 6.92]; R_f (Et_2O/hexane=1:3) 0.23; ν_{max} (KBr) 2238, 1731 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.16 (s, 9H, $C(CH_3)_3$), 2.77 (dd, 1H, *J*=15.2 and 10.9 Hz, H_aH_b-2), 3.03 (dd, 1H, *J*=15.2 and 4.9 Hz, H_aH_b-2), 3.14 (s, 1H, H-5), 3.15 (s, 1H, H-5), 3.50 (s, 3H, $COOCH_3$), 3.63 (dd, 1H, *J*=10.9 and 4.9 Hz, H-3), 6.83–7.26 (m, 10H, 2×C_6H_5).

4.2.23. 3-Cyano-3,4-diphenylhexandioic acid 6-*tert*-butyl-1-methyl diester 15s (*syn*). Following the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **15s** (*syn*) (135 mg, 34%) was isolated after purification of the crude pruduct (entry 21) by column chromatography (silica gel, Et_2O/hexane=1:3) as a white solid, mp 135–137°C; [Found: C, 73.05; H, 7.17. $C_{24}H_{27}NO_4$ requires C, 73.26; H, 6.92]; R_f (Et_2O/hexane=1:3) 0.26; ν_{max} (KBr) 2238, 1731 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.09 (s, 9H, $C(CH_3)_3$), 2.30 (dd, 1H, *J*=15.1 and 4.0 Hz, H_aH_b-2), 2.63 (d, 1H, *J*=16.1 Hz, H-5), 2.88 (dd, 1H, *J*=15.1 and 12.1 Hz, H_aH_b-2), 2.91 (d, 1H, *J*=16.1 Hz, H-5), 3.40 (s, 3H, $COOCH_3$), 3.53 (dd, 1H, *J*=12.1 and 4.0 Hz, H-3), 7.03–7.60 (m, 10H, 2×C_6H_5).

4.2.24. 2,3-Diphenyl-2-methylpentandioic acid 1,5-bis-dimethylamide 16a (*anti*). Following the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **16a** (*anti*) (105 mg, 30%) was isolated after purification of the crude pruduct (entry 23) by column chromatography (silica gel, ethylacetate) as a white solid, mp 140–142°C; [Found: C, 74.72; H, 8.33. $C_{22}H_{28}N_2O_2$ requires C, 74.91; H, 8.01]; R_f (ethylacetate) 0.16; ν_{max} (KBr) 1639 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.48 (s, 3H, CH_3), 2.40 (br, 3H, $N(CH_3)_2$), 2.53 (dd, 1H, *J*=14.4 and 11.6 Hz, H_aH_b-4), 2.70 (s, 3H, $N(CH_3)_2$), 2.88 (br, 3H, $N(CH_3)_2$), 3.03 (s, 3H, $N(CH_3)_2$), 3.13 (dd, 1H, *J*=14.4 and 2.7 Hz, H_aH_b-4), 4.08 (dd, 1H, *J*=11.6 and 2.7 Hz, H-3), 6.73–7.32 (m, 10H, 2×C_6H_5).

4.2.25. 4-*N*,*N*-Dimethylcarbamoyl-3,4-diphenyl-6-heptenoic acid dimethylamide 17a (*anti*). Following the general procedure from 1 mmol starting products used in the conjugate reaction step the title compound **17a** (*anti*) (105 mg, 28%) was isolated after purification of the crude pruduct (entry 24) by column chromatography (silica gel, ethylacetate/MeOH=95:5) as a white solid, mp 134–136°C; [Found: C, 76.38; H, 8.23. $C_{24}H_{30}N_2O_2$ requires C, 76.16; H, 7.99]; R_f (ethylacetate/MeOH) 0.20; ν_{max} (KBr) 1639 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 2.30 (dd, 1H, *J*=14.2 and 11.8 Hz, H_aH_b-2), 2.39 (s, 3H, $N(CH_3)_2$), 2.42–2.65 (m, 2H, H-5), 2.67 (s, 3H, $N(CH_3)_2$), 2.95 (s, 3H, $N(CH_3)_2$), 3.10 (s, 3H, $N(CH_3)_2$), 3.18 (dd, 1H, *J*=14.2 and 2.9 Hz, H_aH_b-2), 4.20 (dd, 1H, *J*=11.8 and 2.9 Hz, H-3), 5.05 (dd, 1H, *J*=16.8 and 1.9 Hz, H-7), 5.17 (dd, 1H, *J*=10.2 and 1.9 Hz, H-7), 5.90–6.04 (m, 1H, H-6), 6.76–7.32 (m, 10H, 2×C_6H_5).

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