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Synthesis and properties of chiral *N,N*-maleoyl derivatives and Diels-Alder reactions with cyclopentadiene

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Received November 17, 2004, accepted December 9, 2004

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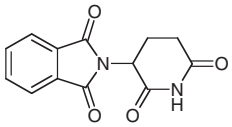
Pharmazie 60: 803–813 (2005)

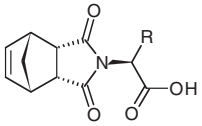
Maleyl amino acid derivatives were prepared from maleic anhydride and cyclized by reaction with $ZnCl_2$ and hexamethyldisilazane yielding maleoyl derivatives. These derivatives were used as dienophiles in cycloadditions with cyclopentadiene. The isolated norbornene derivatives resulted from an *endo* addition, and might be interpreted as analogues of thalidomide. For comparing the properties of compounds prepared by this route, some reference compounds were synthesized from *endo*-bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylic anhydride and amino acid derivatives. All compounds were characterized by spectroscopic methods, their stereochemistry is discussed, and results were compared with results from calculations.

1. Introduction

Maleimides are an interesting class of compounds for biological and chemical applications. They were used in protein chemistry (Corrie 1994; Langmuir et al. 1995; Kitagawa et al. 1981), for the immobilization of catalytic antibodies (Janda et al. 1990), and in the field of synthesis as Michael acceptors (Maeda et al. 1988), as dienophiles (Arai et al. 1994; Kitagawa et al. 1998; Bennes et al. 2001), as dipolarophiles (Grigg et al. 1988; Ondrus and Fisera 1997) or as monomers in polymer chemistry (Kagawa and Oishi 1996; Oishi et al. 1992). During the last years, chiral N-substituted maleimides got particular importance (Masamune et al. 1983; Arai et al. 1991; Feringa and de Jong 1988). An often used method for the synthesis of derivatives whose nitrogen comes from an amino acid is the reaction between maleic anhydride and amino acids, a two step reaction, wherein the first step, formation of an amido acid is easily done, but wherein the second step, the cyclization, very often causes severe problems as rough conditions are needed and a number of by-products is formed (Helferich and Wesemann 1967; Paul et al. 1967; Krojido et al. 1976). While the reaction of *N*-alkoxycarbonyl maleimides with amino acids (Keller and Rudinger 1975), seems to be limited to a few examples, the dehydration method of the amido acids seems to be more general applicable (Rich et al. 1975). The reaction of dicarboxylic anhydrides with alkyl or arylamines in the presence of catalytic amounts of a Lewis catalyst with hexamethyldisilazane, and followed by thermal cyclization under mild conditions is described (Reddy et al. 1997). We are interested in chiral maleimides as dienophiles in enantioselective Diels-Alder reactions as N-substituted norbornene derivatives were synthesized as analogs of thalidomide and tested for a sedative action (Koch et al. 1971).
Some similar products were synthesized by the reaction of *endo-* and *exo*-bicyclo[2.2.1.]hept-2-ene-5,6-dicarboxylic anhydrides with amino acids or amino ester hydrochlorides as monomers for a polymerization reaction with ring opening (ROMP) (Coles et al. 1994; Biagini et al. 1995). In this paper we describe the syntheses of a number of maleyl and maleoyl derivatives, their properties, and their reactions with cyclopentadiene, that is the *vice versa* reaction.



Thalidomide

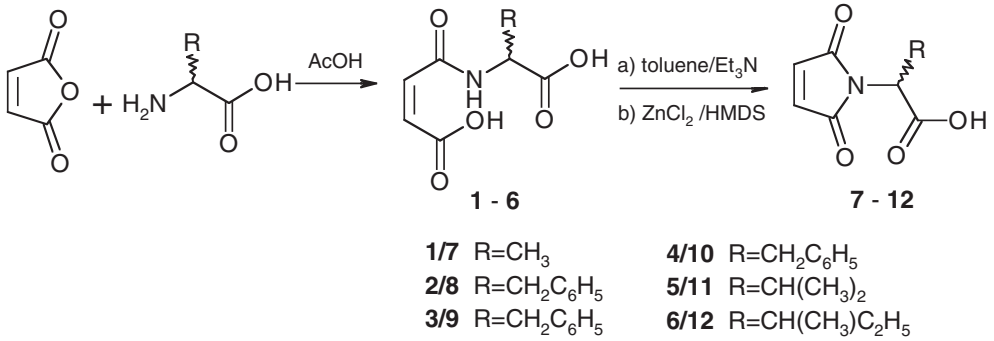


Thalidomide analogs
R=H, CH_3, C_2H_5

2. Investigations, results and discussion

From the reaction between maleic anhydride and amino acids in glacial acetic acid the *N*-maleyl amino acids **2**–**7** were isolated with yields up to 98% (Scheme 1, Table 1).
Cyclization of the *N*-maleyl amino acids **1**–**6** in toluene and Et_3N yielded the N,N-maleoyl derivatives **7**–**12** with yields of 40–90%. By using an excess of toluene a water separator was not necessary. Purification was done by recrystallization of the residue of CC (silicagel, AcOH/CH_2Cl_2 95 + 5).
As an alternative method we used the reaction of maleic anhydride with amino acids with catalytic amounts of a

Scheme 1



Lewis acid and hexamethyldisilazane, which is described for the synthesis of *N*-alkyl/aryl imides from anhydrides and the appropriate amine (Reddy et al. 1997). By this method we obtained the cyclic imides from *N*-maleoyl-L-Ala and *N*-maleoyl-L-Phe in yields of 55 and 90%. The highest yields and the purest products were obtained when we used two equivalents of $ZnCl_2$ and three equivalents of hexamethyldisilazane (Table 2). Racemation was not observed neither using method A nor during method B.

^{1}H NMR spectra of *N*-maleyl amino acids are characterized by an AB system, $J = 12.4$ Hz, caused by the methine protons at the double bond. On the other hand, the ^{1}H NMR spectra of *N*,*N*-maleoyl derivatives show one singlet at ca. $\delta = 6.3$ ppm for these protons.

The ^{1}H NMR spectrum of compound **10** ([D_6]DMSO, 200 MHz) is characterized by the signals of the aromatic protons at $\delta = 7.10–7.27$ ppm, and those of the olefinic protons at $\delta = 6.80$ ppm. The α- and β-protons of the Phe moiety cause an ABX system at $\delta = 3.26$ and 3.38 ppm (methylene protons), and $\delta = 4.91$ ppm (α-H) with $^2J_{AB} = 14.0$ Hz, $^3J_{AX} = 27.6$ Hz, and $^3J_{BX} = 3.0$ Hz.

Table 1: Physical properties and yields of N-maleyl amino acids

Compd.	M.p. (°C)	$[\alpha]_D$	Yield (%)
1	144–146[a]	−44.9 (c = 2, MeOH)	86
2	126–128[b]	−61.5 (c = 2, MeOH)	95
3	145–147	–	98
4	125–126	+61.7 (c = 2, MeOH)	96
5	124–127	−2.4 (c = 2, MeOH)	61
6	89–92	+16.2 (c = 2, MeOH)	41

[a] M.p. 142–143 °C (Rich et al. 1975)
[b] M.p. 128–128.5 °C (Rich et al. 1975)

Table 2: Physical properties and yields of N,N-maleoyl amino acids

Compd.	M.p. (°C)	$[\alpha]_D$	Yield (%)[a]
7[b]	95	−19.5 (c = 1, MeOH)	47
8[c]	165–168	−128.0 (c = 5, MeOH)	51
9	143–146	–	65
10	163–164	+131.5 (c = 1, MeOH)	40
11	liquid	+47.4 (c = 2, MeOH)	44
12	liquid	+28.1 (c = 1.9, MeOH)	41

[a] Yields refer to method A
[b] Method B yield 55%, M.p. 97–98 °C, $[\alpha]_D = -16.3$ (c = 1.1, EtOH)[d]
[c] Method B yield 90%, M.p. 168–169 °C, $[\alpha]_D = -108$ (c = 1.1, EtOH)[d]
[d] Values from Rich et al. 1975

For the synthesis of the *N*,*N*-maleoyl amino esters we tried different methods. The esterification of the amino acids was possible without racemation under azeotropic conditions with *p*-toluene sulfonic acid (p-TSA) or benzene sulfonic acid (A) (Kagawa and Oishi 1996). As the products had to be purified by CC and crystallization the yields were not always satisfactory. Therefore the method was not very appropriate for all reactions. The reaction between maleic anhydride and amino esters in AcOH/Ac_2O (Krojidlo et al. 1976) resulted in very low yields. Best results were obtained when we first prepared the *N*-maleyl amino esters from maleic anhydride and amino esters, and these products in the second step, without isolation, cyclized with catalytic amounts of $ZnBr_2$ and hexamethyldisilazane (B) (Reddy et al. 1997). Starting from amino ester salts the free amino ester was obtained by the addition of an equimolar amount of Et_3N. Racemation was not observed during this reaction (Scheme 2, Table 3).

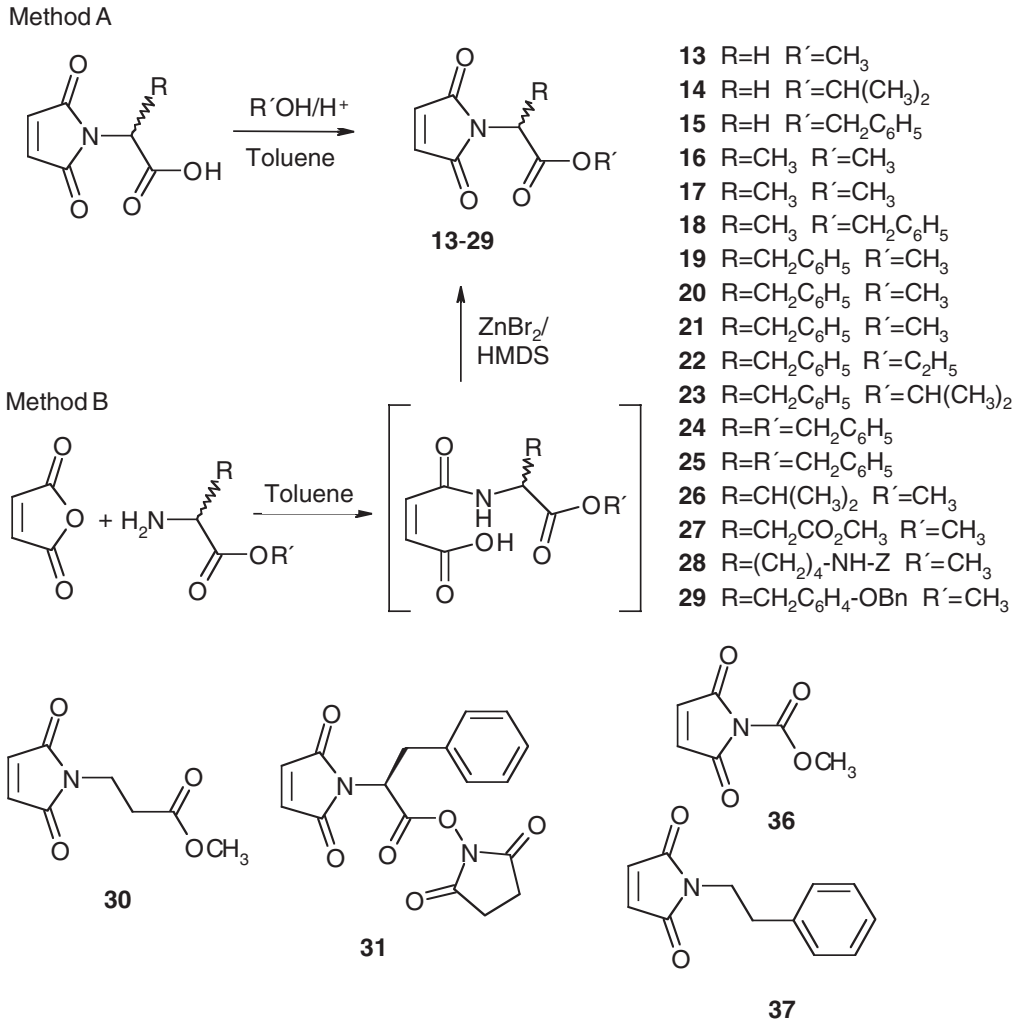
By a similar procedure the β-alanine derivative **30**, the L-β-Phe succinimidoyl ester **31**, the methyl carbamate **36**

Table 3: Physical properties and yields of N-maleoyl amino esters

Compd.	M.p. (°C)	$[\alpha]_D$	Yield (%)[c]
13	45–48	–	63
14	70	–	29
15	79–83	–	79
16	Liquid	−25.9 (c = 2.8, MeOH)	96
17	Liquid	+24.8 (c = 3, MeOH)	77
18	45–47	−35.5 (c = 1.8, MeOH)	53
19	85–88	−127.0 (c = 1, MeOH)	76, 62[d]
20	104–105	–	73, 76[d]
21	81–83	+127.3 (c = 1, MeOH)	76, 47[d]
22[a]	78–80	−110.0 (c = 5, Acetone)	72, 65[d]
23	55–58	−102.4 (c = 2, MeOH)	61
24[b]	59–61.5	−110.9 (c = 2, MeOH)	85
25	95–97	–	62
26	55.5–56	−28.3 (c = 1, MeOH)	55
27	Liquid	−47.9 (c = 1.8, MeOH)	70
28	Liquid	−13.6 (c = 1, MeOH)	63
29	85–93	−96.7 (c = 1, MeOH)	83
30	Liquid	–	49
31	118–120.5	−92.6 (c = 2, MeOH)	92[d]
36	60[e]	–	44[d]
37	109–110	–	64

[a] Kagawa and Oishi 1996: M.p. 79–80 °C, $[\alpha]_D = -95.2$ (c = 1, THF)
[b] Kagawa and Oishi 1996: $[\alpha]_D = -97.2$ (c = 1, THF)
[c] Yields refer to method B
[d] Method A
[e] Keller and Rudinger 1975: M.p. 61–63 °C

Scheme 2



(Keller and Rudinger 1975), and the β-phenylethylamine derivative **37** were synthesized.

Physical properties and yields of *N*,*N*-maleoyl amino esters **13**–**29**, and of the derivatives **30**, **31**, **36**, and **37** are summarized in Table 3.

For the synthesis of *N*,*N*-maleoyl peptide esters we tried two ways. The first one (A) included coupling of the *N*,*N*-maleoyl amino acids with amino esters using the standard procedure with DCC and N-hydroxysuccinimide (Scheme 3) (Wünsch 1974). Another possibility (B) was the synthesis from maleic anhydride and the peptide esters analogue to the reaction described above. The second route gave more sufficient yields (Table 4).

Table 4: Physical properties and yields of N,N-maleoyl peptide esters

Compd.	M.p. (°C)	$[\alpha]_D$	Yield: (%)[a]
32	104–107	−10.8 (c = 4, MeOH)	45[b], 61
33	135	−81.2 (c = 0.16 MeOH)	81
34	74–76	−70.0 (c = 2, MeOH)	62
35	59–61	−59.3 (c = 2, MeOH)	73

[a] Yields refer to method B
[b] Yield refers to method A

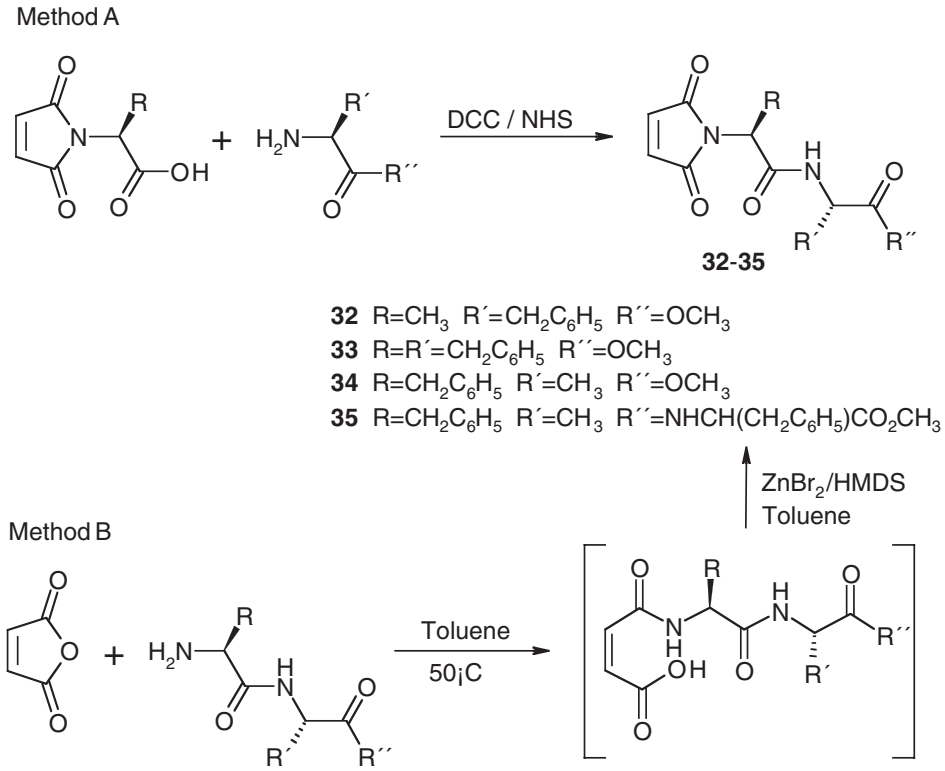
The ^{1}H NMR spectrum of compound **33** ($CDCl_3$, 200 MHz) showed at $\delta = 3.07$ and 3.17 ppm resp. $\delta = 3.35$ and 3.39 ppm the signals of the β-protons of the amino acids moiety as an AB part of the ABX systems with $^2J_{AB} = 13.9$ Hz, $^3J_{AX} = 6.2$ Hz, and $^3J_{BX} = 5.7$ Hz. The X parts of the α-protons were found around $\delta = 4.86$ ppm. The signal of the NH was registered at $\delta = 6.38$ ppm with $^3J = 7.5$ Hz. The signals of the methyl ester and the aromatic protons were found at $\delta = 3.72$ ppm and $\delta = 7.07$–7.26 ppm. The singlet of the methine protons at the C-C-double bond at $\delta = 6.56$ ppm established the cyclic imide structure.

Maleic anhydride and maleimide are known as good dienophiles, and the *N*,*N*-maleoylamino acid derivatives should be as good, as calculations showed that even in these compounds the electron withdrawing effect of the carbonyl groups in α-position results in a lower HOMO, and thereby in an activation of the double bond (Fleming 1990).

The reaction between the *N*,*N*-maleoylamino acid derivatives and cyclopentadiene was done by distillation of dimeric cyclopentadiene at 180 °C, whereby an excess of monomeric cyclopentadiene was directly added to the dienophile without any other solvent (A) (Scheme 4, Table 5).

In a parallel reaction L-Ala-OMe and Gly-OMe were reacted with *endo*-bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylic

Scheme 3



Scheme 4

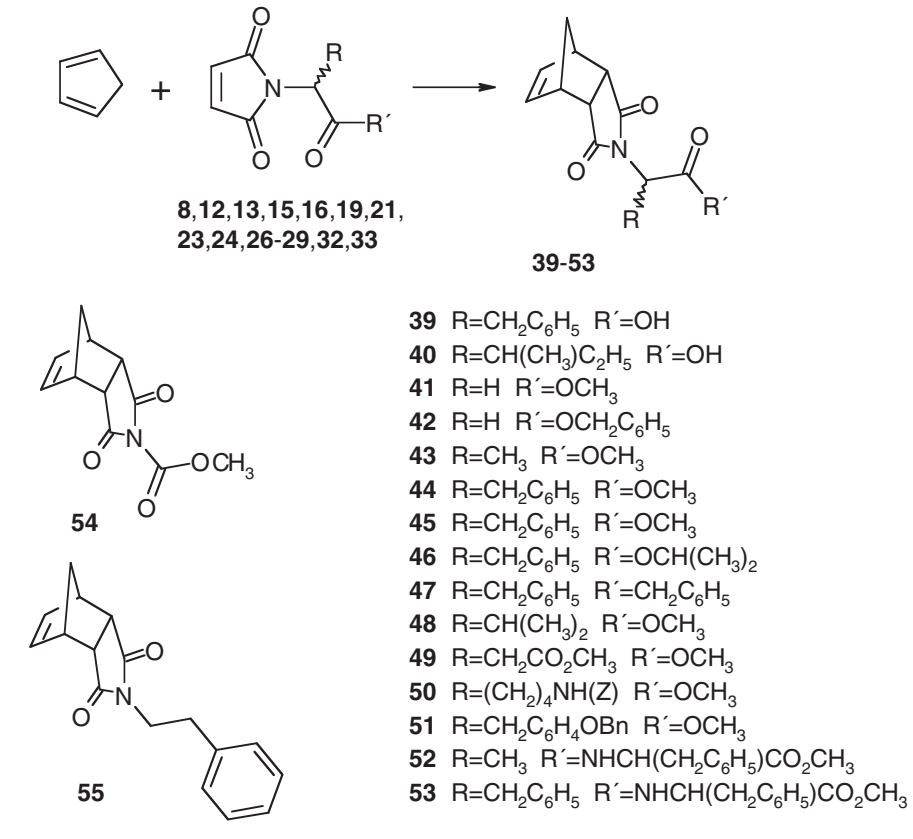


Table 5: Physical properties and yields of compounds 39–55

Compd.	M.p. (°C)	$[\alpha]_D$	Yield: (%)[a]
39	148–149	−113.2 (c = 0.25, Acetone)	66
40	117–118.5	−60.0 (c = 0.25, Acetone)	76
41[b]	90–92	–	93
42	101–106	–	95
43[c]	126–128	−36.9 (c = 1.3, MeOH)	78
44[d]	118–119	−103.0 (c = 1, MeOH)	93
45[e]	118–119	+109.6 (c = 1, MeOH)	89
46	60–61	−101.3 (c = 2, MeOH)	81
47	103.5–104.5	−94.5 (c = 2, MeOH)	93
48[f]	58–59.5	−72.0 (c = 1, MeOH)	92
49	Liquid	−68.8 (c = 2, MeOH)	87
50	Liquid	−31.1 (c = 2.5, MeOH)	71
51	87–89	−83.5 (c = 1, MeOH)	63
52	89–91	+4.0 (c = 2, MeOH)	40
53	105–108	−3.6 (c = 2, MeOH)	90
54	93–96	–	88
55[g]	73–75.5	–	63

[a] Yields refer to method A. [b] Method B yield 69%, M.p. 80–82 °C[h]
[c] Method B yield 59%, M.p. 118–119 °C, $[\alpha]_D = -43.2$ (c = 1, $CHCl_3$)[h]
[d] M.p. 125–126 °C, $[\alpha]_D = -42.3$ (c = 1, Toluene)[h]
[e] M.p. 123–125 °C, $[\alpha]_D = +42.1$ (c = 1, Toluene)[h]
[f] Coles et al. 1994: Mp 58–59 °C, $[\alpha]_D = -32.3$ (c = 1, $CHCl_3$)
[g] Gray and Heitmeier 1965: Mp 81–82 °C
[h] Values from Biagini et al. 1995

anhydride using the literature method (B) (Biagini et al. 1995). Both ways gave identical products.

All structures were established by spectroscopy. The ^{1}H NMR spectra of **48** ($CDCl_3$, 300 MHz) showed the signal of the ester group at $\delta = 3.65$ ppm, the signals of the isopropyl methyl protons at $\delta = 0.79$ ppm and 1.01 ppm, and the signals of α-H_{Val} and β-H_{Val} at $\delta = 4.23$ ppm and 2.53 ppm. The *anti* and *syn* protons of the methylene bridge were registered as an AB system at 1.74 ppm and 1.54 ppm with $^2J_{AB} = 8.8$ Hz. The protons 2-H/6-H and 1-H/7-H gave multiplets at $\delta = 3.31$ ppm and 3.40 ppm, and at $\delta = 6.09$ ppm and 6.13 ppm the multiplets caused by the olefinic protons H-8 und H-9 were registered.

The *endo* structure of the adducts was confirmed by NOE spectra (Hesse et al. 1995). Irradiation in the spectrum of **44** at $\delta = 1.36$ ppm, the resonance signal of 10-H_{anti}, exhibited a positive NOE at the signals of 2-H and 6-H, confirming that 10-H_{anti} and 2-H/6-H are *cis* orientated. Furthermore, irradiation at $\delta = 3.02$ ppm (2-H/6-H) (3.02 ppm) caused a positive effect at the signal of 10-H_{anti}. Both effects confirmed the *endo* structure (Fig. 1).

^{1}H NMR spectra show a relatively large difference between the shift values of the protons 8-H and 9-H (protons located at the double bond) in the spectra of compound with R = CH_2–C_6H_5, **39**, **44**–**47**, **51**, or with R′ containing a benzyl group as **52** and **53** (Table 6). On the other hand, the ^{1}H NMR spectra of **40**–**43** and **48**–**50** with (small) aliphatic substituents in R position, and the ^{1}H NMR spectrum of **55**, did not exhibit this effect. In

Table 6: Shift values (ppm) of the protons 8-H and 9-H

Compd.	δ(8-H)	δ(9-H)	Δδ [ppm] (Hz)
39	5.49 (m)	5.73 (m)	0.24 (48)
44	5.43 (dd)	5.68 (dd)	0.25 (50)
45	5.50 (dd)	5.75 (dd)	0.25 (50)
46	5.51 (dd)	5.75 (dd)	0.24 (48)
47	5.31 (dd)	5.64 (dd)	0.33 (66)
51	5.58 (m)	5.77 (m)	0.19 (38)
52	5.55 (dd)	6.21 (dd)	0.66 (132)
53	5.19 (dd)	6.00 (dd)	0.81 (162)

these spectra, both protons were registered as one singlet, intensity 2. From symmetry reasons one probably would expect one singlet or a very small shift for both protons in the spectra of all compounds as described for the *N*,*N*-maleoyl derivatives **13**–**37**. But the shift values of 8-H and 9-H showed in the spectra of **39** and **44**–**47** a difference up to 66 Hz with coupling constants $^3J_{8,9}$ ca. 5.5 Hz, indicating an AB system for the protons 8-H and 9-H, which is supported by the "Dacheffekt" found in the spectra.

A very large difference, 132 Hz and 162 Hz, was registered in the spectra of the peptide derivatives **52** and **53**, while the tyrosine derivative **51** showed a shift in the same range as the benzyl derivatives. It has to be noted that HPLC experiments confirmed the uniformity of all compounds.

We suspect that the shift difference is caused by an anisotropy effect of the aromatic ring of the Phe moiety. If the ring is located under one proton at the double bond (Fig. 2), this proton should exhibit a shift compared to the other one (Hesse et al. 1995).

PM3 calculations (HYPERCHEM) for the fixed conformers **A** and **B** of **44** resulted in a lower energy of **A** (**A**: −4688.877 kcal/mol, **B**: −4687.857 kcal/mol). The calculation of the shift values for **A** and **B** (geometrically optimized, HYPER NMR, Table 7) gave shift values for 8-H and 9-H in form **A** as two multiplets at $\delta = 5.82$ ppm and 5.49 ppm, and for form **B** two double duplets at $\delta = 6.0$ ppm and 6.03 ppm, indicating that the program had considered the influence of the aromatic ring. On the other hand, the anisotropy effect of the double bond on 10-H_{syn} was not noticed by the program.

For proving if form **A** was favored as a result of the cycloaddition to the *endo* product, we synthesized **44** according to a literature procedure from *endo*-bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylic anhydride (**38**) and L-Phe-OMe. The yield was much lower than obtained by our route, and the ^{1}H NMR spectra of both products were identical. This indicated that the favour of form **A** was independent from the reaction pathway, and therefore not caused by a sandwich like transition state of the cycloaddition. The phenethyl derivative **55** showed no anisotropy effect as a result of the possibility of free rotation.

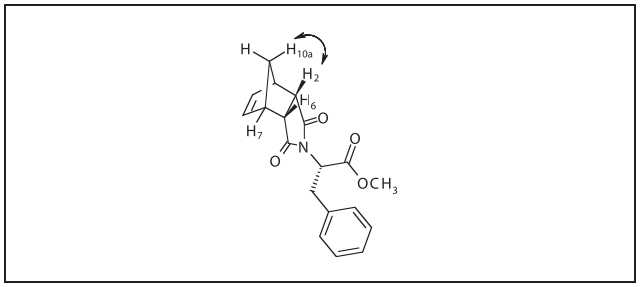


Fig. 1: NOE observed in **44**

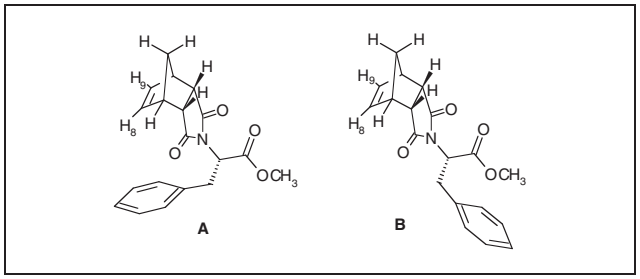


Fig. 2: Possible conformations of **44**

Table 7: Calculated shift values of A and B of compound 44 (HYPER NMR)

δ (ppm)	1-H	2-H	6-H	7-H	8-H	9-H	10-H_{anti}	10-H_{syn}
Form **A**	2.006	3.292	3.462	2.160	5.822	5.490	2.472	2.425
Form **B**	2.188	3.416	3.519	2.199	6.000	6.034	2.601	2.559

3. Experimental

3.1. General

M.p.: Mikroheiztisch PHMX 80/2778, not corrected. IR spectra (KBr, cm^{-1}): Perkin-Elmer IR 1310. ^1H NMR spectra: Bruker DPX 200 (200 MHz), Bruker DPX 300 (300 MHz), ^{13}C NMR spectra: Bruker DPX 300 (75.43 MHz). Internal standard TMS, $\delta_{TMS} = 0.00$ ppm. $^1H/^{13}C$ values from 200/75.43 MHz spectra in $CDCl_3$, if not otherwise noted. Optical rotation: Polartronic D. Elementary analyses: Institute of Pharmacy (Perkin-Elmer Elemental Analyzer 2400 CHN), or Institute of Chemistry, University of Greifswald. All compounds gave satisfactory elemental analyses. Solvents were dried/purified according to literature procedures. Abbreviations: CC = Column chromatography (Silica gel 60, Merck 7734, 0.040–0.063 mm); AcOEt = Ethyl acetate; PE = petroleum ether; tlc = thin layer chromatography (Pre-coated plates, silica gel 60 F_{254}, Merck 5554). HPLC: System LaChrom, series 7000 Merck Hitachi. Columns: LiChrospher 250-4, RP-18, 5 μm; (S,S)-Whelk-O1, 250-4, 5 μm; Chiraspher, 250-4, 5 μm, Chirobiotic T. Molecular modeling: Hyperchem 4.0, Hypercube, Inc.; Hyperchem™ 6.0 (Demo version), Hypercube, Inc.
Compounds **36** (Keller and Rudinger 1975), and **38** (Diels and Alder 1928; Canonne et al. 1982) were prepared according to the literature procedures.

3.2. Synthesis of N-maleyl amino acids

50 Mmol of the amino acid, and maleic hydride (4.9 g, 50 mmol) were suspended in AcOH with stirring. The mixture was warmed until a clear solution was obtained, stirring was continued (without heating!) for 3–5 h. Then, the precipitate was separated and dried over KOH *in vacuo*.

3.2.1. N-Maleyl-L-alanine (**1**)

From 4.45 g L-Ala in 25 ml AcOH. Yield: 8.3 g (86%). Colorless prism. M.p. 144–146 °C (MeOH/Et_2O). M.p. 142–143 °C (Rich et al. 1975). $[\alpha]_D^{20} = -44.9$ (c = 2, MeOH). IR: $\tilde{\nu} = 3346$ (NH), 3105 (C=CH), 3054, 2897 (CH), 1734, 1709 (CO), 1636, 1559 (C=C). ^1H NMR ([D_6]DMSO): δ = 1.32 (d, $^3J = 7.2$ Hz, Me), 4.31 (q, $^3J = 7.2$ Hz, α-H), 6.29 (AB, $^3J = 12.4$ Hz, =CH), 6.40 (AB, $^3J = 12.4$ Hz, =CH), 9.25 (d, $^3J = 7.1$ Hz, H–N), 13.56 (s, H–O).
$C_7H_9NO_5$ (187.2)

3.2.2. N-Maleyl-L-phenylalanine (**2**)

From 8.3 g L-Phe in 18 ml AcOH. Yield: 12.5 g (95%). Colorless prism. M.p. 126–128 °C (MeOH/Et_2O). M.p. 128–128.5 °C (Rich et al. 1975). $[\alpha]_D^{20} = -61.5$ (c = 2, MeOH). IR: $\tilde{\nu} = 3308$ (NH), 3052, 3030 (ar CH, C=CH), 2970, 2851 (CH), 1720, 1692 (CO). ^1H NMR ([D_6]DMSO): δ = 2.86–3.15 (ABX, 2 β-H), 4.51 (ABX, α-H), 6.28 (AB, $^3J = 12.4$ Hz, =CH), 6.34 (AB, $^3J = 12.4$ Hz, =CH), 7.23–7.28 (m, 5 ar H), 9.27 (d, $^3J = 7.8$ Hz, H–N).
$C_{13}H_{13}NO_5$ (263.3)

3.2.3. N-Maleyl-D,L-phenylalanine (**3**)

From 8.3 g D,L-Phe in 18 ml AcOH. Yield: 12.8 g (98%). Colorless prism. M.p. 145–147 °C (MeOH/Et_2O). IR: $\tilde{\nu} = 3464$ (NH), 3115, 3084, 3028 (ar CH, C=CH), 2902 (CH), 1706 (CO), 696 (C=C). ^1H NMR ([D_6]DMSO): δ = 2.95 (ABX, $^2J_{AB} = 13.9$ Hz, $^3J_{AX} = 9.4$ Hz, 1 β-H), 3.16 (ABX, $^2J_{AB} = 13.9$ Hz, $^3J_{BX} = 4.9$ Hz, 1 β-H), 4.56 (ABX, $^3J_{AX} = 9.4$ Hz, $^3J_{BX} = 4.9$ Hz, α-H), 6.31 (AB, $^3J = 12.4$ Hz, =CH), 6.37 (AB, $^3J = 12.4$ Hz, =CH), 7.24–7.31 (m, 5 ar H), 9.37 (d, $^3J = 7.9$ Hz, H–N).
$C_{13}H_{13}NO_5$ (263.3)

3.2.4. N-Maleyl-D-phenylalanine (**4**)

From 8.3 g D-Phe in 18 ml AcOH. Yield: 12.6 g (96%). Colorless prism. M.p. 125–126 °C (MeOH/Et_2O). $[\alpha]_D^{20} = +61.7$ (c = 2, MeOH). IR: $\tilde{\nu} = 3309$ (NH), 3052 (ar CH, C=CH), 2949 (CH), 1720, 1693 (CO). ^1H NMR ([D_6]DMSO): δ = 2.93 (ABX, $^2J_{AB} = 13.9$ Hz, $^3J_{AX} = 9.5$ Hz, 1 β-H), 3.13 (ABX, $^2J_{AB} = 13.9$ Hz, $^3J_{BX} = 5.0$ Hz, 1 β-H), 4.54 (ABX, $^3J_{AX} = 9.5$ Hz, $^3J_{BX} = 5.0$ Hz, α-H), 6.28 (AB, $^3J = 12.4$ Hz, =CH), 6.36 (AB, $^3J = 12.4$ Hz, =CH), 7.25–7.28 (m, 5 ar H), 9.23 (d, $^3J = 7.8$ Hz, H–N).
$C_{13}H_{13}NO_5$ (263.3)

3.2.5. N-Maleyl-L-valine (**5**)

From 5.9 g L-Val in 13 ml AcOH. Yield: 6.6 g (61%). Colorless prism. M.p. 124–127 °C (AcOEt/PE). $[\alpha]_D^{20} = -2.4$ (c = 2, MeOH). IR: $\tilde{\nu} = 3307$ (NH), 3054 (C=CH), 2971–2885 (CH), 1718, 1691 (CO), 1624, 1555 (C=C). ^1H NMR ([D_6]DMSO): δ = 0.91 (d, $^3J = 6.8$ Hz, 2 Me), 2.04–2.20 (m, CH), 4.24 (dd, $^3J = 5.8$ Hz, $^3J = 8.2$ Hz, α-H), 6.31 (AB, $^3J = 12.5$ Hz, =CH), 6.52 (AB, $^3J = 12.5$ Hz, =CH), 9.04 (d, $^3J = 8.3$ Hz, H–N).
$C_9H_{13}NO_5$ (215.2)

3.2.6. N-Maleyl-L-isoleucine (**6**)

From 6.6 g L-Ile in 37 ml AcOH. Yield: 4.7 g (41%). Colorless prism. M.p. 89–92 °C (AcOEt/PE). $[\alpha]_D^{20} = +16.2$ (c = 2, MeOH). IR: $\tilde{\nu} = 3305$ (NH), 3057 (C=CH), 2971, 2936, 2878 (CH), 1717, 1692 (CO), 1634, 1556 (C=C). ^1H NMR ([D_6]DMSO): δ = 0.85 (d, $^3J = 7.6$ Hz, Me), 0.88 (d, $^3J = 7.7$ Hz, Me), 1.17–1.43 (m, CH_2), 1.831 (m, 1 β-H), 4.27 (dd, $^3J = 8.1$ Hz, $^3J = 5.8$ Hz, α-H), 6.49 (AB, $^3J = 12.4$ Hz, =CH), 6.30 (AB, $^3J = 12.4$ Hz, =CH), 9.10 (d, $^3J = 8.1$ Hz, H–N), 13.45 (s, H–O).
$C_{10}H_{15}NO_5$ (229.2)

3.3. Synthesis of N,N-maleoyl amino acids

A. 20 Mmol of the *N*-maleyl amino acid, and Et_3N (4 g, 40 mmol) were refluxed in 300 ml toluene for 2 h, the mixture was evaporated *in vacuo*, the residue was acidified with conc. HCl to pH 2, then dissolved in AcOEt, dried ($MgSO_4$) and evaporated. The residue was purified as noted below.
B. $ZnCl_2$ (2.7 g, 40 mmol) was added to a suspension of 20 mmol *N*-maleyl amino acid in 150 ml toluene. The mixture was warmed to 80 °C, and hexamethyldisilazane (12.5 ml, 60 mmol) was dropwise added with stirring. Stirring was continued for 6 h at 80 °C, and for 12 h at room temperature. Then, the solvent was evaporated *in vacuo*, and the residue was dissolved in 80 ml AcOEt/0.1 N HCl (9 : 1). The organic layer was separated, and the aqueous layer was washed with 3 × 50 ml AcOEt. The combined organic layers were washed with 3 × 30 ml saturated NaCl solution, dried ($MgSO_4$), and the residue was purified as noted below.

3.3.1. N,N-Maleoyl-L-alanine (**7**)

A. From 3.7 g *N*-maleyl-L-Ala. Yield: 1.7 g (47%). B. From 3.7 g *N*-maleyl-L-alanine, *n*-hexane was added to the residue, and then some drops of Et_2O. Yield: 1.9 g (55%). Colorless prism. M.p. 95 °C (AcOEt/PE). M.p. 97–98 °C (Rich et al. 1975), 99–100 °C (Oishi et al. 1992). $[\alpha]_D^{20} = -19.5$ °C (c = 1, MeOH). $[\alpha]_D^{22} = -16.3$ °C (c = 1.1, EtOH) (Rich et al. 1975). IR: $\tilde{\nu} = 3198$ (OH), 3107, 3009 (C=CH), 2950, 2933 (CH), 1782, 1714, 1741 (CO). ^1H NMR ([D_6]DMSO): δ = 1.46 (d, $^3J = 7.3$ Hz, Me), 4.66 (q, $^3J = 7.3$ Hz, α-H), 7.08 (s, 2 =CH), 13.07 (s, H–O). HPLC: $k' = 0.42$, $t_0 = 2.08$ (RP-18, MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7); $k' = 0.14$, $t_0 = 2.21$ (Chiralcel OJ-R MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7).
$C_7H_7NO_4$ (169.1)

3.3.2. N,N-Maleoyl-L-phenylalanine (**8**)

A. From 5.3 g N-maleyl-L-Phe. Yield: 2.5 g (51%). B. From 5.3 g *N*-maleyl-L-phenylalanine. Yield: 4.4 g (90%). Colorless crystals. M.p. 165–168 °C (H_2O). M.p. 119–121 °C (Rich et al. 1975), 168–169 °C (Keller and Rudinger 1975), 162–163 °C (Oishi et al. 1992). $[\alpha]_D^{20} = -128$ (c = 5, MeOH), $[\alpha]_D^{22} = -108$ (c = 1.1, EtOH) (Rich et al. 1975), $[\alpha]_D^{20} = -124$ (c = 5, MeOH) (Keller and Rudinger 1975). IR: $\tilde{\nu} = 3117$, 3094, 3084 (ar CH, C=CH), 2928 (CH), 1776, 1704, 1752 (CO), 748, 695 (C=C). ^1H NMR: δ = 3.40–3.56 (ABX, 2 β-H), 5.04 (ABX, α-H), 6.61 (s, 2 =CH), 7.12–7.29 (m, 5 ar H). HPLC: $k' = 2.28$, $t_0 = 2.33$ (RP-18, MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7); $k' = 0.83$, $t_0 = 2.21$ (Chiralcel OJ-R MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7).
$C_{13}H_{11}NO_4$ (245.3)

3.3.3. N,N-Maleoyl-D,L-phenylalanine (**9**)

From 5.3 g N-maleyl-D,L-Phe (A). Yield: 3.2 g (65%). Colorless prism. M.p. 143–146 °C (H_2O). IR: $\tilde{\nu} = 3117$, 3064 (ar CH, C=CH), 1752, 1698 (CO), 694 (C=C). ^1H NMR: δ = 2.98 (s, H–O), 3.40–3.56 (ABX, 2 β-H), 5.04 (ABX, α-H), 6.62 (s, 2 =CH), 7.12–7.28 (m, 5 ar H). HPLC: $k' = 3.44$, $t_0 = 2.08$ (RP-18, MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7);

$k' = 0.85$, $t_0 = 2.21$ (Chiralcel OJ-R MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7).
$C_{13}H_{11}NO_4$ (245.3)

3.3.4. N,N-Maleoyl-D-phenylalanine (**10**)

From 5.3 g *N*-maleyl-D-Phe (A). Yield: 2 g (40%). Colorless crystals. M.p. 163–164 °C (H_2O). $[\alpha]_D^{20} = +131.5$ (c = 1, MeOH). IR: $\tilde{\nu} = 3116$, 3093, 3064 (ar CH, C=CH), 2928 (CH), 1775, 1698, 1752 (CO), 748, 695 (C=C). ^{1}H NMR ([D_6]DMSO): $\delta = 3.26$ (ABX, $^2J_{AB} = 14.0$ Hz, $^3J_{AX} = 27.6$ Hz, 1 β-H), 3.38 (ABX, $^2J_{AB} = 14.0$ Hz, $^3J_{BX} = 3.0$ Hz, 1 β-H), 4.91 (ABX, $^3J_{AX} = 27.6$ Hz, $^3J_{BX} = 3.0$ Hz, α-H), 6.98 (s, 2 =CH), 7.10–7.27 (m, 5 ar H). HPLC: $k' = 2.28$, $t_0 = 2.33$ (RP-18, MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7); $k' = 0.84$, $t_0 = 2.21$ (Chiralcel OJ-R MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7).
$C_{13}H_{11}NO_4$ (245.3)

3.3.5. N,N-Maleoyl-L-valine (**11**)

From 4.3 g *N*-maleyl-L-Val (A). CC (AcOH/CH_2Cl_2 95 + 5). $R_f = 0.57$. Yield: 1.75 g (44%). $[\alpha]_D^{20} = +47.4$ (c = 2, MeOH). IR (Film): $\tilde{\nu} = 3104$ (C=CH), 2968, 2944, 2878 (CH), 1761, 1710, 1735 (CO). ^{1}H NMR: $\delta = 0.89$ (d, $^3J = 6.8$ Hz, Me), 1.10 (d, $^3J = 6.7$ Hz, Me), 2.66 (oct, 1 β-H), 4.44 (d, $^3J = 8.2$ Hz, α-H), 5.54 (s, H–O), 6.76 (s, 2 =CH). HPLC: $k' = 2.02$, $t_0 = 2.08$ (RP-18, MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7); $k' = 0.50$, $t_0 = 2.21$ (Chiralcel OJ-R MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7).
$C_9H_{11}NO_4$ (197.2)

3.3.6. N,N-Maleoyl-L-isoleucine (**12**)

From 4.6 g *N*-maleyl-L-Ile. CC (AcOH/CH_2Cl_2 95+5). $R_f = 0.65$. Yield: 1.72 g (41%). $[\alpha]_D^{20} = +28.1$ (c = 1.9, MeOH). IR (Film): $\tilde{\nu} = 3104$ (C=CH), 2968, 2935, 2878 (CH), 1765, 1711, 1744 (CO). ^{1}H NMR: $\delta = 0.87$ (t, $^3J = 7.1$ Hz, Me), 1.08 (d, $^3J = 6.7$ Hz, Me), 1.26–1.67 (m, CH_2), 2.44 (m_c, β-H), 4.53 (d, $^3J = 8.3$ Hz, α-H), 6.75 (s, 2 =CH). HPLC: $k' = 4.10$, $t_0 = 2.08$ (RP-18, MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7); $k' = 0.88$, $t_0 = 2.21$ (Chiralcel OJ-R MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7).
$C_{10}H_{13}NO_4$ (211.2)

3.4. Synthesis of N,N-maleoyl amino esters

A. 15 Mmol maleoyl amino acid, 0.6 g benzene sulfonic acid, 30 ml of the alcohol, and 30 ml benzene were heated to 80 °C for 12 h. After cooling to room temperature, the organic layer was washed with 50 ml aqueous saturated $NaHCO_3$ solution, then with 50 ml aqueous saturated NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was crystallized as noted below.
B. Maleic anhydride (3.0 g, 30 mmol) in 10 ml toluene was added to a mixture from 30 mmol amino ester hydrochloride or tosylate and Et_3N (3.0 g, 30 mmol) in 150 ml toluene. The mixture was stirred for 6 h at 60 °C, and 12 h at room temperature. Then, $ZnBr_2$ (6.7 g, 30 mmol) was added, the mixture was warmed to 80 °C, and with stirring, hexamethyldisilazane (12.4 ml, 60 mmol) in 40 ml toluene was dropwise added. Stirring was continued for 6 h at 80 °C and 12 h at room temperature. Then, the mixture was poured into 600 ml 0.5 N HCl, and stirred until a clear solution was obtained. The organic layer was separated, the aqueous phase was extracted with 300 ml AcOEt, the combined organic layers were washed with 3 × 100 ml aqueous saturated $NaHCO_3$ and NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified as noted below.

3.4.1. Methyl N,N-maleoylglycinate (**13**)

From 3.76 g Gly-OMe-HCl in 150 ml toluene (B). Yield: 3.2 g (63%). Colorless prism. M.p. 45–48 °C (AcOEt/PE). IR: $\tilde{\nu} = 3165$, 3097 (C=CH), 2990, 2965, 2946 (CH), 1747, 1715 (CO), 1603, 1582 (C=C), 1234, 1146 (C–O–C), 833, 699 (C=C). ^{1}H NMR: $\delta = 3.76$ (s, OMe), 4.29 (s, CH_2), 6.80 (s, 2 =CH). HPLC: $k' = 0.59$, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1); $k' = 3.96$, $t_0 = 2.06$ (Chiralcel OJ-R MeCN/H_2O 5 : 95).
$C_7H_7NO_4$ (169.1)

3.4.2. Isopropyl N,N-maleoylglycinate (**14**)

From 4.6 g Gly-OiProp-HCl in 150 ml toluene (B). Yield: 1.73 g (29%). Colorless prism. M.p. 70 °C (AcOEt/PE). IR: $\tilde{\nu} = 2985$, 2937, 2884 (CH), 1775, 1711, 1743 (CO), 1614, 1587 (C=C), 1225, 1110 (C–O–C), 699 (C=C). ^{1}H NMR: $\delta = 1.26$ (d, $^3J = 6.3$ Hz, 2 Me), 4.23 (s, N–CH_2), 5.05 (qn, $^3J = 6.3$ Hz, CH), 6.79 (s, 2 =CH). HPLC: $k' = 1.66$, $t_0 = 1.75$ (RP-18, MeCN/H_2O 1 : 1); $k' = 1.63$, $t_0 = 2.21$ (Chiralcel OJ-R MeCN/H_2O 3 : 7).
$C_9H_{11}NO_4$ (197.2)

3.4.3. Benzyl N,N-maleoylglycinate (**15**)

From 10.1 g Gly-OBn-p-tosylate in 150 ml toluene (B). Yield: 5.8 g (79%). Colorless prism. M.p. 79–83 °C (AcOEt/PE). IR: $\tilde{\nu} = 3161$, 3100, 3050 (ar CH, C=CH), 2980, 2958, 2944, 2896 (CH), 1753, 1718 (CO). ^{1}H NMR: $\delta = 4.33$ (s, N–CH_2), 5.18 (s, OCH_2), 6.79 (s, 2 =CH), 7.25–7.36 (m, 5 ar H). HPLC: $k' = 3.01$, $t_0 = 1.75$ (RP-18, MeCN/H_2O 1 : 1); $k' = 10.06$, $t_0 = 2.21$ (Chiralcel OJ-R MeCN/H_2O 3 : 7).
$C_{13}H_{11}NO_4$ (245.2)

3.4.4. Methyl N,N-maleoyl-L-alaninate (**16**)

From 4.2 g L-Ala-OMe-HCl (B). CC (cyclohexane/AcOEt 1 : 1). $R_f = 0.48$. Yield: 5.3 g (96%). Colorless viscous liquid. $[\alpha]_D^{20} = -25.9$ (c = 2.8, MeOH). IR (Film): $\tilde{\nu} = 3103$, 3003 (C=CH), 2956 (CH), 1747, 1716 (CO), 1653 (C=C). ^{1}H NMR: $\delta = 1.63$ (d, $^3J = 7.4$ Hz, Me), 3.74 (s, OMe), 4.80 (q, $^3J = 7.4$ Hz, α-H), 6.70 (s, 2 =CH). ^{13}C NMR: 15.17 (Me), 47.35 (OMe), 52.74 (C-α), 134.42 (C=C), 169.90, 170.14 (2 CO). HPLC: $k' = 0.90$, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1); $k' = 7.81$, $t_0 = 2.06$ (Chiralcel OJ-R MeCN/H_2O 5 : 95).
$C_8H_9NO_4$ (183.2)

3.4.5. Methyl N,N-maleoyl-D-alaninate (**17**)

From 4.2 g D-Ala-OMe-HCl (B). CC (cyclohexane/AcOEt 1 : 1). $R_f = 0.48$). Yield: 4.23 g (77%). Colorless viscous liquid. $[\alpha]_D^{20} = -24.84$ (c = 3, MeOH). IR (Film): $\tilde{\nu} = 3102$, 3001 (C=CH), 2955, 2849 (CH), 1748, 1716 (CO). ^{1}H NMR: $\delta = 1.63$ (d, $^3J = 7.4$ Hz, Me), 3.74 (s, OMe), 4.79 (q, $^3J = 7.4$ Hz, α-H), 6.77 (s, 2 =CH). HPLC: $k' = 0.90$, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1); $k' = 7.69$, $t_0 = 2.06$ (Chiralcel OJ-R MeCN/H_2O 5 : 95).
$C_8H_9NO_4$ (183.2)

3.4.6. Benzyl N,N-maleoyl-L-alaninate (**18**)

From 10.5 g L-Ala-OBn-p-tosylate (A). CC (cyclohexane/AcOEt 1 : 1). Yield: 4.1 g (53%). Colorless prism. M.p. 45–47 °C. $[\alpha]_D^{20} = -35.5$ (c = 1.8, MeOH). IR (KBr): $\tilde{\nu} = 3106$, 3062, 3019 (ar CH, C=CH), 2985, 2957, 2894 (CH), 1774, 1722 (CO), 1602, 1589 (C=C). ^{1}H NMR: $\delta = 1.66$ (d, $^3J = 7.4$ Hz, Me), 4.83 (q, $^3J = 7.4$ Hz, α-H), 5.16 (s, CH_2), 6.70 (s, 2 =CH), 7.32 (m, 5 ar H). HPLC: $k' = 3.72$, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1). $k' = 1.79$, $t_0 = 1.81$ (Chiralcel OJ-R MeCN/H_2O 1 : 1).
$C_{14}H_{13}NO_4$ (259.3)

3.4.7. Methyl N,N-maleoyl-L-phenylalaninate (**19**)

A. From 3.7 g *N,N*-Maleoyl-L-Phe and MeOH. Yield: 2.4 g (62%). B. From 6.5 g L-Phe-OMe-HCl. Yield: 5.9 g (76%). Colorless prism. M.p. 85–88 °C (dec., Et_2O). $[\alpha]_D^{20} = -127.0$ (c = 1, MeOH). IR: $\tilde{\nu} = 3107$, 3060, 3028 (ar CH, C=CH), 2955, 2918, 2848 (CH), 1761, 1711, 1746 (CO), 825, 697 (ar C=C). ^{1}H NMR: $\delta = 3.35–3.57$ (ABX, $^2J_{AB} = 14.2$ Hz, 2 β-H), 3.78 (s, OMe), 4.96 (ABX, α-H), 6.60 (s, 2 =CH), 7.10–7.26 (m, 5 ar H). HPLC: $k' = 2.84$, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1); $k' = 5.94$, $t_0 = 1.83$ (Chiralcel OJ-R MeCN/H_2O 3 : 7).
$C_{14}H_{13}NO_4$ (259.3)

3.4.8. Methyl N,N-maleoyl-D,L-phenylalaninate (**20**)

A. From 3.7 g *N,N*-maleoyl-D,L-Phe in 30 ml MeOH. Yield: 2.9 g (76%). B. From 6.5 g D,L-Phe-OMe-HCl. Yield: 2.94 g (73%). Colorless prism. M.p. 104–105 °C (Et_2O). IR: $\tilde{\nu} = 3095$, 3030, 3000 (ar CH, C=CH), 2954, 2889, 2885 (CH), 1776, 1743, 1708 (CO), 1240, 1156 (C–O–C), 752, 695 (ar). ^{1}H NMR: $\delta = 3.44$ (ABX, $^2J_{AB} = 14.2$ Hz, $^3J_{AX} = 12.1$ Hz, 1 β-H), 3.52 (ABX, $^2J_{AB} = 14.2$ Hz, $^3J_{BX} = 4.4$ Hz, 1 β-H), 3.80 (s, OMe), 4.97 (ABX, $^3J_{AX} = 12.1$ Hz, $^3J_{BX} = 4.4$ Hz, α-H), 6.61 (s, 2 =CH), 7.30–7.11 (m, 5 ar H). HPLC: $k' = 2.83$, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1); $k' = 6.03$, $t_0 = 1.83$ (Chiralcel OJ-R MeCN/H_2O 3 : 7).
$C_{14}H_{13}NO_4$ (259.3)

3.4.9. Methyl N,N-maleoyl-D-phenylalaninate (**21**)

A. From 3.7 g *N,N*-maleoyl-D-Phe in 30 ml MeOH. Yield: 1.8 g (47.2%). B. From 6.5 g D-Phe-OMe-HCl. Yield: 5.9 g (76%). Colorless crystals. M.p. 81–83 °C (Et_2O). $[\alpha]_D^{20} = +127.3$ (c = 1, MeOH). IR: $\tilde{\nu} = 3028$, 3066 (ar CH, C=CH), 2955, 2924 (CH), 1776, 1747, 1715 (CO), 1604, 1584 (C=C), 1252, 1166 (C–O–C), 754, 698 (ar C=C). ^{1}H NMR: $\delta = 3.46$ (ABX, $^2J_{AB} = 14.2$ Hz, $^3J_{AX} = 12.2$ Hz, 1 β-H), 3.52 (ABX, $^2J_{AB} = 14.2$ Hz, $^3J_{BX} = 4.4$ Hz, 1 β-H), 3.79 (s, OMe), 4.96 (ABX, $^3J_{AX} = 12.2$ Hz, $^3J_{BX} = 4.4$ Hz, α-H), 6.60 (s, 2 =CH), 7.10–7.29 (m, 5 ar H). HPLC: $k' = 2.83$, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1); $k' = 5.94$, $t_0 = 1.83$ (Chiralcel OJ-R MeCN/H_2O 3 : 7).
$C_{14}H_{13}NO_4$ (259.3)

3.4.10. Ethyl N,N-maleoyl-L-phenylalaninate (**22**)

A. From 3.7 g *N,N*-maleoyl-L-Phe in EtOH. Yield: 2.5 g (65%). B. From 6.9 g L-Phe-OEt -HCl (B) Yield: 5.5 g (72%). Colorless crystals. M.p. 78–

80 °C (dec., Et_2O). M.p. 79–80 °C (Kagawa and Oishi 1996). $[\alpha]_D^{20} = -110$ (c = 5, Acetone), $[\alpha]_D^{20} = -95.2$ (c = 1, THF (Kagawa and Oishi 1996). IR: $\tilde{\nu} = 3096$, 3030 (ar H, C=CH), 2983, 2929 (CH), 1773, 1741, 1713 (CO). ^{1}H NMR: δ = 1.27 (t, $^3J = 7.3$ Hz, Me), 3.42 (ABX, $^2J_{AB} = 14.2$ Hz, $^3J_{AX} = 4.6$ Hz, 1 β-H), 3.51 (ABX, $^2J_{AB} = 14.2$ Hz, $^3J_{BX} = 11.9$ Hz, 1 β-H), 4.19–4.29 (m, $COCH_2$), 4.94 (ABX, $^3J_{AX} = 4.6$ Hz, $^3J_{BX} = 11.9$ Hz, α-H), 6.60 (s, 2 =CH), 7.11–7.26 (m, 5 ar H). HPLC: k′ = 4.29, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1); k′ = 3.09, $t_0 = 1.83$ (Chiralcel OJ-R MeCN/H_2O 45 : 55).
$C_{15}H_{15}NO_4$ (273.3)

*3.4.11. Isopropyl N,N-maleoyl-*L*-phenylalaninate* (**23**)

From 7.3 g L-Phe-OiPr-HCl (B). Yield: 5.3 g (61%). Colorless crystals. M.p. 55–58 °C (PE). $[\alpha]_D^{20} = -102.4$ (c = 2, MeOH). IR: $\tilde{\nu} = 3164$, 3103, 3065, 3027 (ar H, C=CH), 2984, 2928, 2876 (CH), 1753, 1704 (CO), 695 (ar C=C). ^{1}H NMR: δ = 1.24 (d, $^3J = 6.3$ Hz, Me), 1.27 (d, $^3J = 6.3$ Hz, Me), 3.40 (ABX, $^2J_{AB} = 14.25$ Hz, $^3J_{AX} = 12.1$ Hz, 1 β-H), 3.50 (ABX, $^2J_{AB} = 14.3$ Hz, $^3J_{BX} = 4.8$ Hz, 1 β-H), 4.91 (ABX, $^3J_{AX} = 12.1$ Hz, $^3J_{BX} = 4.8$ Hz, α-H), 5.09 (spt, $^3J = 6.3$ Hz, CH), 6.59 (s, 2 =CH), 7.11–7.29 (m, 5 ar H). HPLC: k′ = 7.33, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1); k′ = 7.30, $t_0 = 1.75$ (Chiralcel OJ-R MeCN/H_2O 4 : 6).
$C_{16}H_{17}NO_4$ (287.3)

*3.4.12. Benzyl N,N-maleoyl-*L*-phenylalaninate* (**24**)

From 12.9 g L-Phe-OBn-p-tosylate (B). CC (AcOEt/cyclohexane 1 : 1). $R_f = 0.6$. Yield: 5.8 g (85%). Colorless crystals. M.p. 59–61.5 °C (Et_2O/PE). B.p. 195–197 °C/0.15 mm Hg (Kagawa and Oishi 1996). $[\alpha]_D^{20} = -110.9$ (c = 2, MeOH), $[\alpha]_D^{20} = -97.2$ (c = 1, THF) (Kagawa and Oishi 1996). ^{1}H NMR: δ = 3.46 (ABX, $^2J_{AB} = 14.2$ Hz, $^3J_{AX} = 12.2$ Hz, 1 β-H), 3.53 (ABX, $^2J_{AB} = 14.2$ Hz, $^3J_{BX} = 5.1$ Hz, 1 β-H), 5.00 (ABX, $^3J_{AX} = 12.2$ Hz, $^3J_{BX} = 5.1$ Hz, α-H), 5.21 (s, OCH_2), 6.57 (s, 2 =CH), 7.08–7.42 (m, 10 ar H). HPLC: k′ = 11.52, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1). k′ = 11.83, $t_0 = 1.81$ (Chiralcel OJ-R MeCN/H_2O 1 : 1).
$C_{20}H_{17}NO_4$ (335.4)

*3.4.13. Benzyl N,N-maleoyl-*D,L*-phenylalaninate* (**25**)

From 12.9 g D,L-Phe-OBn-p-tosylate (B). CC (AcOEt/cyclohexane 1 : 1). $R_f = 0.6$. Yield: 6.2 g (62%). Colorless crystals. M.p. 95–97 °C (Et_2O/PE). IR: $\tilde{\nu} = 3088$, 3034 (ar CH, C=CH), 2948 (CH), 1742, 1731, 1706 (CO), 694 (ar C=C). ^{1}H NMR: δ = 3.46 (ABX, $^2J_{AB} = 14.2$ Hz, $^3J_{AX} = 12.1$ Hz, 1 β-H), 3.53 (ABX, $^2J_{AB} = 14.2$ Hz, $^3J_{BX} = 4.8$ Hz, 1 β-H), 5.00 (ABX, $^3J_{AX} = 12.1$ Hz, $^3J_{BX} = 4.8$ Hz, α-H), 5.21 (s, 2 H, OCH_2), 6.58 (s, 2 =CH), 7.08–7.42 (m, 10 ar H). HPLC: k′ = 6.64, 12.10, $t_0 = 1.81$ (Chiralcel OJ-R MeCN/H_2O 1 : 1).
$C_{20}H_{17}NO_4$ (335.4)

*3.4.14. Methyl N,N-maleoyl-*L*-valinate* (**26**)

From 5.0 g L-Val-OMe-HCl (B). Yield: 3.4 g (55%). Colorless crystals. M.p. 55.5–56 °C (PE). $[\alpha]_D^{20} = -28.3$ (c = 1, MeOH). IR: $\tilde{\nu} = 3168$, 3100 (C=CH), 2966, 2940, 2876 (CH), 1747, 1715 (CO). ^{1}H NMR: δ = 0.87 (d, $^3J = 6.8$ Hz, Me), 1.10 (d, $^3J = 6.8$ Hz, Me), 2.66 (d, $^3J = 6.8$ Hz, CH), 3.71 (s, OMe), 4.39 (d, $^3J = 8.2$ Hz, α-H), 6.75 (s, 2 =CH). ^{13}C NMR: δ = 19.53 (Me), 20.93 (Me), 28.70 (CH), 52.60 (α-H), 57.76 (OMe), 134.34 (C=CH), 169.39, 170.33 (CO). HPLC: k′ = 1.89, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1); k′ = 1.29, $t_0 = 1.83$ (Chiralcel OJ-R MeCN/H_2O 45 : 55).
$C_{10}H_{13}NO_4$ (211.2)

*3.4.15. Dimethyl N,N-maleoyl-*L*-asparaginate* (**27**)

From 5.93 g L-Asp(OMe)$_2$-HCl with 10.14 g $ZnBr_2$, CC (AcOEt/cyclohexane 1 : 1). Yield: 5.05 g (70%). Colorless viscous liquid. $[\alpha]_D^{20} = -47.9$ (c = 1.8, MeOH). IR (Film): $\tilde{\nu} = 2957$, 2849 (CH), 1742, 1714 (CO), 1653 (C=C). ^{1}H NMR: δ = 3.05 (AMX, $^2J_{AM} = 16.8$ Hz, $^3J_{AX} = 9.0$ Hz, β-H_{Asp}), 3.28 (AMX, $^2J_{AM} = 16.8$ Hz, $^3J_{MX} = 5.8$ Hz, β-H_{Asp}), 3.69 (s, OMe), 3.74 (s, OMe), 5.21 (AMX, $^3J_{AX} = 9.0$ Hz, $^3J_{MX} = 5.8$ Hz, α-H_{Asp}), 6.76 (s, 2 =CH). HPLC: k′ = 0.86, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1). k′ = 11.11, $t_0 = 2.06$ (Chiralcel OJ-R MeCN/H_2O 5 : 95).
$C_{10}H_{11}NO_6$ (241.2)

*3.4.16. Methyl N,N-maleoyl-*L*-(Z)-lysinate* (**28**)

From 9.9 g (30 mmol) *N*-Boc-L-Lys-OMe-HCl (B), CC (AcOEt/cyclohexane 1 : 1, $R_f = 0.35$). Yield: 7.1 g (63%). Colorless viscous liquid. $[\alpha]_D^{20} = -13.6$ (c = 1, MeOH). IR (Film): $\tilde{\nu} = 3096$, 3033 (CH), 2952, 2864 (CH), 1712 (CO), 1654 (C=C). ^{1}H NMR: δ = 1.24–1.68 (m, 2 $CH_{2(Lys)}$), 2.05–2.18 (m, $CH_{2(Lys)}$), 3.12–3.22 (dd, $^2J = 13.2$ Hz, $^3J = 6.8$ Hz, $CH_{2(Lys)}$), 3.72 (s, OMe), 4.64 (dd, $^3J = 6.8$ Hz, $^3J = 8.9$ Hz, α-H), 4.75 (m, NH), 5.08 (s, OCH_2), 6.72 (s, 2 =CH), 7.35 (m, 5 ar H). HPLC: k′ = 3.14, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1). k′ = 1.62, $t_0 = 1.81$ (Chiralcel OJ-R MeCN/H_2O 1 : 1).
$C_{19}H_{22}N_2O_6$ (374.4)

*3.4.17. Methyl N,N-maleoyl-(O-benzyl)-*L*-tyrosinate* (**29**)

From 9.65 g *O*-Bn-L-Tyr-OMe-HCl (B). Yield: 9.1 g (83%). Colorless crystals. Mp 85–93 °C (AcOEt/n-hexane). $[\alpha]_D^{20} = -96.7$ (c = 1, MeOH). IR: $\tilde{\nu} = 3109$, 3034 (ar CH), 2955 (CH), 1776, 1755, 1709 (CO), 1614 (C=C). ^{1}H NMR: δ = 3.37 (ABX, $^2J_{AB} = 14.3$ Hz, $^3J_{AX} = 12.1$ Hz, β-H_{Tyr}), 3.43 (ABX, $^2J_{AB} = 14.3$ Hz, $^3J_{BX} = 4.7$ Hz, β-H_{Tyr}), 3.77 (s, OMe), 4.91 (ABX, $^3J_{AX} = 12.1$ Hz, $^3J_{BX} = 4.7$ Hz, α-H_{Tyr}), 5.00 (s, OCH_2), 6.59 (s, 2 =CH), 6.84 (AB, $^3J_{AB} = 8.6$ Hz, 2 ar H_{Tyr}), 7.03 (AB, $^3J_{AB} = 8.6$ Hz, 2 ar H_{Tyr}), 7.28–7.38 (m, 5 ar H_{benzyl}). HPLC: k′ = 2.41, $t_0 = 1.81$ (RP-18, MeCN/H_2O 7 : 3). k′ = 5.45, $t_0 = 1.81$ (Chiralcel OJ-R MeCN/H_2O 1 : 1).
$C_{21}H_{19}NO_5$ (365.4)

*3.4.18. Methyl N,N-maleoyl-*β*-alaninate* (**30**)

From β-Ala-OMe-HCl (3.5 g, 25 mmol), 150 ml toluene, 2.5 g Et_3N (25 mmol), 2.45 g maleic anhydride (25 mmol), 5.5 g $ZnBr_2$, and 14 ml hexamethyldisilazane, CC (AcOEt/cyclohexane 1 : 1, $R_f = 0.44$). Yield: 2.24 g (49%). IR (Film): $\tilde{\nu} = 3099$ (C=CH), 2954 (CH), 1823, 1735, 1707 (CO), 1654, 1636 (C=C). ^{1}H NMR: δ = 2.65 (t, $^3J = 7.1$ Hz, 2 α-$H_{β\text{-}Ala}$), 3.68 (s, OMe), 3.84 (t, $^3J = 7.1$ Hz, 2 β-$H_{β\text{-}Ala}$), 6.72 (s, 2 =CH). HPLC: k′ = 0.60, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1). k′ = 4.67, $t_0 = 2.06$ (Chiralcel OJ-R MeCN/H_2O 5 : 95).
$C_8H_9NO_4$ (183.2)

*3.4.19. Succinimidoyl N,N-maleoyl-*L*-phenylalaninate* (**31**)

N,*N*-Maleoyl-L-Phe (2.5 g, 10 mmol), 1.26 g *N*-hydroxysuccinimide (11 mmol), and 2.48 g DCC (11 mmol) in 50 ml CH_2Cl_2 were stirred for 1 h at 0 °C and 12 h at room temperature. Then, some drops of AcOH were added, and stirring was continued for 1 h at 0–3 °C, the precipitate was separated, and the solvent was evaporated in vacuo. The residue was dissolved in hot i-PrOH, and cooled. Yield: 3.15 g (92%). Colorless crystals. M.p. 118–120.5 °C (i-PrOH). $[\alpha]_D^{20} = -92.6$ (c = 2, MeOH). IR (Film): $\tilde{\nu} = 3088$, 3030 (ar CH, C=CH), 2920 (CH), 1822, 1790, 1713, 1744 (CO), 1636 (C=C). ^{1}H NMR: δ = 2.85 (s, 2 CH_2), 3.49–3.69 (ABX, $^2J_{AB} = 14.3$ Hz, 2 β-H), 5.32 (ABX, α-H), 6.63 (s, 2 =CH), 7.12–7.31 (m, 5 ar H). HPLC: k′ = 2.32, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1); k′ = 1.64, $t_0 = 1.83$ (Chiralcel OJ-R MeCN/H_2O 45 : 55).
$C_{17}H_{14}N_2O_6$ (342.3)

3.5. Synthesis of N,N-maleoyl peptide esters

A. The *N*,*N*-maleoyl amino acid (10 mmol), NHS (2.3 g, 10 mmol), and 11 mmol of the appropriate ester were suspended in 50 ml CH_2Cl_2, and with stirring cooled to −10 °C. Then DCC (2.27 g, 11 mmol) was added, and the mixture was stirred for 1 h at −10 °C and for 12–24 h at room temperature. The precipitate was separated, washed with CH_2Cl_2, and the combined organic layers were evaporated *in vacuo*. 100 ml AcOEt was added to the residue, and after stirring for 30 min, the precipitate was separated, and the filtrate was washed with 20 ml 1N HCl, an aqueous saturated solution of $NaHCO_3$, and an aqueous saturated solution of NaCl, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was purified by CC.
B. At 0 °C, Et_3N (1.5 g, 15 mmol), and a solution of maleic anhydride (1.5 g, 15 mmol) in 10 ml toluene were dropwise added to a suspension of the trifluoroacetate of the peptide ester (15 mmol) in 40 ml toluene, the mixture was stirred for 6 h at 50 °C, and for 12 h at room temperature, then, $ZnBr_2$ (3.4 g, 15 mmol) was added, and the mixture was warmed to 80 °C. Stirring was continued, and hexamethyldisilazane (6.2 ml, 30 mmol) in 30 ml toluene was dropwise added. After stirring for 4 h at 80 °C and for 12 h at room temperature, the mixture was poured into 200 ml 0.5 N HCl, and stirred for 0.5 h. The organic layer was separated, the aqueous layer was extracted with 100 ml AcOEt, the combined organic layers were washed with 3 × 30 ml of an aqueous saturated solution of $NaHCO_3$ and NaCl, dried ($MgSO_4$), the solvent was evaporated *in vacuo*, and the residue was purified by CC.

*3.5.1. Methyl N,N-maleoyl-*L*-alanyl-*L*-phenylalaninate* (**32**)

A. From 1.69 g *N*,*N*-maleoyl-L-Ala, and 1.97 g L-Phe-OMe. Yield: 1.5 g (45%). B. From 1.38 g L-Ala-L-Phe-OMe-trifluoroacetate, CC (AcOEt/cyclohexane 3 : 1). Yield: 0.76 g (61%). Colorless crystals. M.p. 104–107 °C (MeOH). $[\alpha]_D^{20} = -10.8$ (c = 4, MeOH). IR: $\tilde{\nu} = 3301$ (NH), 3099, 3066, 3030 (ar CH, C=CH), 2995, 2938 (CH), 1739, 1709, 1655, 1548 (CO, C=C). ^{1}H NMR: δ = 1.59 (d, $^3J = 7.4$ Hz, Me_{Ala}), 3.09 (ABX, $^2J_{AB} = 13.9$ Hz, $^3J_{AX} = 5.8$ Hz, 1 β-H_{Phe}), 3.15 (ABX, $^2J_{AB} = 13.9$ Hz, $^3J_{BX} = 5.8$ Hz, 1 β-H_{Phe}), 3.73 (s, OMe), 4.71 (q, $^3J = 7.4$ Hz, α-H_{Ala}), 4.84 (ABX, $^3J_{AX} = 5.8$ Hz, $^3J_{BX} = 5.8$ Hz, α-H_{Phe}), 6.27 (d, $^3J = 7.3$ Hz, H−N), 6.71 (s, 2 =CH), 7.03–7.30 (m, 5 ar H). HPLC: k′ = 1.82, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1), k′ = 0.75, $t_0 = 2.34$ (Chiralcel OJ-R, MeCN/H_2O 4 : 6).
$C_{17}H_{18}N_2O_5$ (330.3)

*3.5.2. Methyl N,N-maleoyl-*L*-phenylalanyl-*L*-phenylalaninate* (**33**)

From 4.4 g L-Phe-L-Phe-OMe-trifluoroacetate (B), CC (AcOEt/cyclohexane 3 : 1). Yield: 3.3 g (81%). Colorless crystals. M.p. 135 °C. $[\alpha]_D^{20} = -81.2$

(c = 0.16, MeOH). IR: $\tilde{\nu}$ = 3375 (NH), 3165, 3103, 3054, 3029 (ar CH, C=CH), 2952 (CH), 1748, 1703, 1602, 1581, 1534 (CO, C=C). ^{1}H NMR: δ = 3.07 (ABX, $^2J_{AB}$ = 13.9 Hz, $^3J_{AX}$ = 6.2 Hz, β-H_{Phe}), 3.17 (ABX, $^2J_{AB}$ = 13.9 Hz, $^3J_{BX}$ = 5.7 Hz, β-H_{Phe}), 3.37 (ABX, 2 β-H_{Phe}), 3.72 (s, 3 H, OMe), 4.81–4.92 (m, 2 α-H_{Phe}), 6.38 (d, ^3J = 7.5 Hz, H–N), 6.56 (s, 2 =CH), 7.07–7.26 (m, 10 ar H). HPLC: k′ = 5.73, t_0 = 1.89 (RP-18, MeCN/H_2O 1 : 1), k′ = 4.21, t_0 = 2.34 (Chiralcel OJ-R, MeCN/H_2O 4 : 6).
$C_{23}H_{22}N_2O_5$ (406.4)

3.5.3. Methyl N,N-maleoyl-L-phenylalanyl-L-alaninate (**34**)

From 1.87 g L-Phe-L-Ala-OMe-trifluoroacetate (B), CC (AcOEt/cyclohexane 3 : 1). Yield: 1.1 g (62%). Colorless crystals. M.p. 74–76 °C. $[\alpha]_D^{20}$ = −70.0 (c = 2, MeOH). IR: $\tilde{\nu}$ = 3371 (NH), 3097, 3030 (ar CH, C=CH), 2953 (CH), 1746, 1711 (CO), 1686, 1536 (CO, C=C). ^{1}H NMR: δ = 1.40 (d, ^3J = 7.2 Hz, Me_{Ala}), 3.43 (ABX, $^2J_{AB}$ = 14.0 Hz, $^3J_{AX}$ = 12.3 Hz, 1 β-H_{Phe}), 3.47 (ABX, $^2J_{AB}$ = 14.0 Hz, $^3J_{BX}$ = 5.2 Hz, 1 β-H_{Phe}), 3.74 (s, OMe), 4.59 (qn, ^3J = 7.2 Hz, α-H_{Ala}), 4.94 (ABX, $^3J_{AX}$ = 12.3 Hz, $^3J_{BX}$ = 5.2 Hz, α-H_{Phe}), 6.60 (s, 2 =CH), 6.65 (d, ^3J = 7.2 Hz, H–N), 7.11–7.35 (m, 5 ar H). HPLC: k′ = 2.12, t_0 = 1.89 (RP-18, MeCN/H_2O 1 : 1), k′ = 1.23, t_0 = 2.34 (Chiralcel OJ-R, MeCN/H_2O 4 : 6).
$C_{17}H_{18}N_2O_5$ (330.3)

3.5.4. Methyl N,N-maleoyl-L-phenylalanyl-L-alanyl-L-phenylalaninate (**35**)

From 1.24 g L-Phe-L-Ala-L-Phe-OMe-trifluoroacetate (B), CC (AcOEt/cyclohexane 1 : 1, R_f = 0.31). Yield: 0.84 g (73%). Colorless crystals. M.p. 59–61 °C. $[\alpha]_D^{20}$ = −59.3 (c = 2, MeOH). IR: $\tilde{\nu}$ = 3306 (NH), 3063, 3029 (ar CH, C=CH), 2982, 2951 (CH), 1744, 1713 (CO), 1654, 1604, 1584, 1533 (CO, C=C). ^{1}H NMR: δ = 1.32 (d, ^3J = 7.0 Hz, Me_{Ala}), 3.02–3.50 (m, 4 β-H_{Phe}), 3.72 (s, OMe), 4.45 (qn, ^3J = 7.0 Hz, α-H_{Ala}), 4.76–4.93 (m, 2 α-H_{Phe}), 6.38 (d, ^3J = 8.1 Hz, N–H_{Phe}), 6.57 (s, 2 =CH), 6.60 (d, N–H_{Ala}), 7.09–7.31 (m, 10 ar H). HPLC: k′ = 3.16, t_0 = 1.89 (RP-18, MeCN/H_2O 1 : 1), k′ = 2.16, t_0 = 2.34 (Chiralcel OJ-R, MeCN/H_2O 4 : 6).
$C_{26}H_{27}N_3O_6$ (477.5)

3.6. N-(2-Phenylethyl)maleimide (**37**)

2-Phenylethylamine (3.64 g, 30 mmol) and maleic anhydride (2.94 g, 30 mmol) in 200 ml toluene were stirred for 4 h at 50 °C. Then, $ZnBr_2$ (6.76 g, 30 mmol) was added, the mixture warmed to 80 °C, and a solution of 11.32 ml hexamethyldisilazane in 20 ml toluene was dropwise added. After stirring for 4 h at 80 °C, the mixture was poured into 600 ml 0.5 N HCl, and stirred until a clear solution was obtained. The organic layer was separated, the aqueous layer was extracted with 300 ml AcOEt, the combined organic layers were washed with 3 × 100 ml of an aqueous saturated solution of $NaHCO_3$ and NaCl, dried ($MgSO_4$), and evaporated *in vacuo*. Yield: 3.88 g (64%). Colorless crystals. M.p. 109–110 °C (AcOEt). IR: $\tilde{\nu}$ = 3097, 3033 (ar CH, C=CH), 2938, 2883 (CH), 1740, 1703 (CO). ^{1}H NMR: δ = 2.89 (t, ^3J = 7.6 Hz, CH_2), 3.76 (t, ^3J = 7.6 Hz, CH_2), 6.65 (s, 2 =CH), 7.17–7.31 (m, 5 ar H). HPLC: k′ = 2.93, t_0 = 1.89 (RP-18, MeCN/H_2O 1 : 1); k′ = 3.24, t_0 = 1.81 (Chiralcel OJ-R MeCN/H_2O 1 : 1).
$C_{12}H_{11}NO_2$ (201.2)

3.7. General Procedure for the reaction with cyclopentadiene

A. Freshly distilled cyclopentadiene was added with stirring to the maleoyl derivative, the crystals were separated and crystallized as noted.
B. Literature procedure (Coles et al. 1994).

3.7.1. (S)-2-(3,5-Dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-3-phenylpropionic acid (**39**)

From **8** (2.28 g, 9.3 mmol), stirring for 12 h at room temperature. After addition of PE the crystals were separated (A). Yield: 2.9 g (66%). Colorless crystals. M.p. 148–149 °C (AcOEt/PE). $[\alpha]_D^{20}$ = −113.2 (c = 0.25, Acetone). IR: $\tilde{\nu}$ = 3251 (OH), 3084, 3007 (ar CH, C=CH), 2970, 2948, 2933, 2874 (CH), 1769, 1684, 1752 (CO). ^{1}H NMR: δ = 1.44 (AB, ^2J = 8.7 Hz, 10-H_{anti}), 1.61 (AB, ^2J = 8.7 Hz, 10-H_{syn}), 2.75 (s, H–O), 3.26–3.11 (m, 1-H, 7-H, 2-H, 6-H), 3.54–3.37 (ABX, 2 β-H), 5.08–5.00 (ABX, α-H), 5.49 (m, 1 =CH), 5.73 (m, 1 =CH), 7.29–7.13 (m, 5 ar H). ^{13}C NMR: δ = 31.5 (C-2′), 42.6, 42.8 (C-1, C-7), 43.6 (C-2, C-6), 50.1 (C-10), 50.4 (C-1′), 124.9 (C-6′), 126.4 (C-5′, C-7′), 127.0 (C-4′, C-8′), 132.1 (C-8, C-9), 134.1 (C-3′), 171.8 (C-3, C-5), 174.8 (CO). HPLC: k′ = 8.35, t_0 = 2.08 (RP-18, MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7). k′ = 1.38, t_0 = 2.21 (Chiralcel OJ-R MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7).
$C_{18}H_{17}NO_4$ (311.3)

3.7.2. (S)-2-(3,5-Dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-3-methylvalerianic acid (**40**)

From **12** (1.72 g, 8.14 mmol), stirring was continued until the crystallization was completed, and after addition of PE the precipitate was separated (A). Yield: 1.71 g (76%). Colorless crystals. M.p. 117–118.5 °C (AcOEt/PE). $[\alpha]_D^{20}$ = −60 (c = 0.25, Acetone). IR: $\tilde{\nu}$ = 3142 (OH), 3064 (C=CH), 2995, 2968, 2880 (CH), 1775, 1757, 1682 (CO). ^{1}H NMR: δ = 0.93–0.80 (m, Me), 1.01 (d, ^3J = 6.7 Hz, Me), 1.47–1.25 (m, CH_2), 1.56 (AB, ^2J = 8.2 Hz, 10-H_{anti}), 1.76 (AB, ^2J = 8.2 Hz, 10-H_{syn}), 2.00 (s, H–O), 2.36–2.19 (m, β-H), 3.35 (m, 2-H, 6-H), 3.43 (m, 1-H, 7-H), 4.40 (d, ^3J = 8.8 Hz, α-H), 6.14 (s, 2 =CH). ^{13}C NMR: δ = 10.9 (C-4′), 16.6 (C-5′), 25.7 (C-3′), 33.9 (C-2′), 45.1 (C-1, C-7), 45.9 (C-2, C-6), 52.5 (C-10), 57.4 (C-1′), 134.7, 135.0 (C-8, C-9), 173.2 (C-3, C-5), 177.4 (CO). HPLC: k′ = 8.30, t_0 = 2.08 (RP-18, MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7), k′ = 1.09, t_0 = 2.21 (Chiralcel OJ-R MeCN/0.05 M KH_2PO_4 pH 3.38 3 : 7).
$C_{15}H_{19}NO_4$ (277.3)

3.7.3. Methyl 2-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)acetate (**41**)

A. From **13** (846 mg, 5 mmol). Yield: 1.1 g (93%). B. The mixture from **38** (1.44 g, 8.8 mmol), Gly-OMe-HCl (1.0 g, 8 mmol), and Et_3N (1.6 g, 16 mmol) was refluxed for 15 h. After work-up, a colorless liquid was obtained, a few ml of a mixture from AcOEt and PE (1 : 1) was added, whereby crystallization started. Yield: 1.3 g (69%). Colorless crystals. M.p. 90–92 °C (MeOH). M.p. 80–82 °C (Coles et al. 1994). IR: $\tilde{\nu}$ = 3056, 3003 (C=CH), 2948, 2873 (CH), 1754, 1744, 1701 (CO). ^{1}H NMR: δ = 1.58 (AB, ^2J = 8.8 Hz, 10-H_{anti}), 1.76 (AB, ^2J = 8.8 Hz, 10-H_{syn}), 3.38–3.41 (m, 1-H, 2-H, 6-H, 7-H), 3.72 (s, OMe), 4.09 (s, N-CH_2), 6.14 (s, 2 =CH). HPLC: k′ = 0.99, t_0 = 1.89 (RP-18, MeCN/H_2O 1 : 1). k′ = 0.96, t_0 = 1.84 (Chiralcel OJ-R MeCN/H_2O 3 : 7).
$C_{12}H_{13}NO_4$ (235.2)

3.7.4. Benzyl 2-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)acetate (**42**)

From **15** (613 mg, 2.5 mmol) (A). Yield: 737 mg (95%). Colorless crystals. M.p. 101–106 °C (MeOH). IR: $\tilde{\nu}$ = 3060, 3009 (ar CH, C=CH), 2983, 2956, 2938, 2894, 2865 (CH), 1754, 1744, 1701 (CO). ^{1}H NMR: δ = 1.55 (AB, ^2J = 8.8 Hz, 10-H_{anti}), 1.74 (AB, ^2J = 8.8 Hz, 10-H_{syn}), 3.35–3.39 (m, 1-H, 2-H, 6-H, 7-H), 4.13 (s, N–CH_2), 5.14 (s, OCH_2), 6.05 (s, 2 =CH), 7.26–7.34 (m, 5 ar H). HPLC: k′ = 3.73, t_0 = 1.89 (RP-18, MeCN/H_2O 1 : 1), k′ = 4.42, t_0 = 2.34 (Chiralcel OJ-R, MeCN/H_2O 4 : 6).
$C_{18}H_{17}NO_4$ (311.3)

3.7.5. Methyl (S)-2-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-propionate (**43**)

A. From **16** (500 mg, 2.7 mmol). Yield: 523 mg (78%). B. From **38** (1.44 g, 8.8 mmol), L-Ala-OMe-HCl (1.34 g, 9.6 mmol), Et_3N (1.2 g, 11.8 mmol), reflux for 18 h. Yield: 1.29 g (59%). Colorless crystals. M.p. 126–128 °C (MeOH). M.p. 118–119 °C (Coles et al. 1994). $[\alpha]_D^{23}$ = −36.9 (c = 1.3, MeOH), $[\alpha]_D^{23}$ = −43.2 (c = 1, $CHCl_3$) (Coles et al. 1994). IR: $\tilde{\nu}$ = 3074, 3001 (C=CH), 2983, 2942, 2921, 2874, 2850 (CH), 1775, 1740, 1698 (CO). ^{1}H NMR: δ = 1.41 (d, ^3J = 7.2 Hz, Me_{Ala}), 1.55 (AB, ^2J = 8.8 Hz, 10-H_{anti}), 1.74 (AB, ^2J = 8.8 Hz, 10-H_{syn}), 3.25–3.41 (m, 1-H, 7-H, 2-H, 6-H), 3.70 (s, OMe), 4.62 (q, ^3J = 7.2 Hz, α-H), 6.11–6.13 (m, 2 =CH). HPLC: k′ = 1.47, t_0 = 1.89 (RP-18, MeCN/H_2O 1 : 1). k′ = 1.19, t_0 = 1.84 (Chiralcel OJ-R MeCN/H_2O 3 : 7).
$C_{13}H_{15}NO_4$ (249.3)

3.7.6. Methyl (S)-2-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-3-phenylpropionate (**44**)

From **19** (600 mg, 2.3 mmol) (A) as **40**. Yield: 0.70 g (93%). Colorless crystals. M.p. 118–119 °C (MeOH), M.p. 125–126 °C (Coles et al. 1994). $[\alpha]_D^{20}$ = −103.0 (c = 1, MeOH), $[\alpha]_D^{22}$ = −42.3 (c = 1, toluene) (Coles et al. 1994). IR: $\tilde{\nu}$ = 3088, 3061, 3023 (ar CH, C=CH), 2998, 2965, 2934 (CH), 1766, 1750, 1701 (CO), 1167 (C–OMe), 756, 728 (ar C=C). ^{1}H NMR: δ = 1.36 (AB, ^2J = 8.5 Hz, 10-H_{anti}), 1.54 (AB, ^2J = 8.5 Hz, 10-H_{syn}), 3.02, 3.11 (2 dd, $^3J_{2,6}$ = 7.4 Hz, $^3J_{1,2/6,7}$ = 4.3 Hz, 2-H, 6-H), 3.18 (m, 1-H, 7-H), 3.25 (ABX, $^2J_{AB}$ = 14.6 Hz, $^3J_{AX}$ = 11.7 Hz, 1 β-H), 3.39 (ABX, $^2J_{AB}$ = 14.6 Hz, $^3J_{BX}$ = 5.2 Hz, 1 β-H), 3.67 (s, OMe), 4.89 (ABX, $^3J_{AX}$ = 11.7 Hz, $^3J_{BX}$ = 5.2 Hz, α-H), 5.43, 5.68 (2 dd, $^3J_{8,9}$ = 5.5 Hz, $^3J_{7,8/1,9}$ = 2.8 Hz, 8-H, 9-H), 7.04–7.20 (m, 5 ar H). HPLC: k′ = 4.66, t_0 = 2.07 (RP-18, MeCN/H_2O 1 : 1). k′ = 1.06, t_0 = 1.96 ((S,S)-Whelk-O1 n-Hexane/EtOH 1 : 1).
$C_{19}H_{19}NO_4$ (325.4)

3.7.7. Methyl (R)-2-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-3-phenylpropionate (**45**)

From **21** (600 mg, 2.3 mmol) (A). Yield: 0.67 g (89%). Colorless crystals. M.p. 118–119 °C (MeOH). M.p. 123–125 °C (Coles et al. 1994). $[\alpha]_D^{20}$ = +109.6 (c = 1, MeOH), $[\alpha]_D^{22}$ = +42.1 (c = 1, toluene) (Coles et al. 1994). IR: $\tilde{\nu}$ = 3088, 3061, 3023 (ar CH, C=CH), 2998, 2964, 2934, 2874 (CH), 1766, 1750, 1704 (CO), 756, 728 (ar C=C). ^{1}H NMR: δ = 1.43 (AB, ^2J = 8.7 Hz, 10-H_{anti}), 1.61 (AB, ^2J = 8.7 Hz, 10-H_{syn}), 3.09, 3.18 (2 dd, $^3J_{2,6}$ = 7.6 Hz, $^3J_{1,2/6,7}$ = 4.6 Hz, 2-H, 6-H), 3.24 (m, 1-H,

7-H), 3.32 (ABX, $^2J_{AB} = 14.6$ Hz, $^3J_{AX} = 11.6$ Hz, 1 β-H), 3.46 (ABX, $^2J_{AB} = 14.6$ Hz, $^3J_{BX} = 5.2$ Hz, 1 β-H), 3.74 (s, OMe), 4.96 (ABX, $^3J_{AX} = 11.6$ Hz, $^3J_{BX} = 5.2$ Hz, α-H), 5.50, 5.75 (2 dd, $^3J_{8,9} = 5.5$ Hz, $^3J_{7,8/1,9} = 3.0$ Hz, 8-H, 9-H), 7.11–7.31 (m, 5 ar H). HPLC: $k' = 4.66$, $t_0 = 2.07$ (RP-18, MeCN/H_2O 1 : 1). $k' = 1.38$, $t_0 = 1.96$ ((S,S)-Whelk-O1 n-Hexane/EtOH 1 : 1).
$C_{19}H_{19}NO_4$ (325.4)

3.7.8. Isopropyl (S)-2-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-3-phenylpropionate (**46**)

From **23** (600 mg, 2 mmol) (A). Yield: 601 mg (81%). Colorless crystals. M.p. 60–61 °C (MeOH). $[\alpha]_D^{20} = -101.3$ (c = 2, MeOH). IR: $\tilde{\nu} = 3076$, 3020 (ar CH, C=CH), 2981, 2943, 2916, 2873 (CH), 1765, 1738, 1701 (CO). ^{1}H NMR: δ = 1.23, 1.26 (2 d, $^3J = 4.0$ Hz, 2 Me), 1.43 (AB, $^2J = 8.6$ Hz, 10-H_{anti}), 1.61 (AB, $^2J = 8.6$ Hz, 10-H_{syn}), 3.06, 3.17 (2 dd, $^3J_{2,6} = 7.5$ Hz, $^3J_{1,2/6,7} = 4.5$ Hz, 2-H, 6-H), 3.25 (m, 1-H, 7-H), 3.29 (ABX, $^2J_{AB} = 14.6$ Hz, $^3J_{AX} = 11.6$ Hz, 1 β-H), 3.44 (ABX, $^2J_{AB} = 14.6$ Hz, $^3J_{BX} = 5.1$ Hz, 1 β-H), 4.92 (ABX, $^3J_{AX} = 11.6$ Hz, $^3J_{BX} = 5.1$ Hz, α-H), 5.06 (spt, $^3J = 6.3$ Hz, CH), 5.51, 5.75 (2 dd, $^3J_{8,9} = 5.5$ Hz, $^3J_{7,8/1,9} = 3.0$ Hz, 8-H, 9-H), 7.11–7.26 (m, 5 ar H).
$C_{21}H_{23}NO_4$ (353.4)

3.7.9. Benzyl (S)-2-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-3-phenylpropionate (**47**)

From **24** (500 mg, 1.5 mmol) (A). Yield: 556 mg (93%). Colorless crystals. M.p. 103.5–104.5 °C (MeOH). $[\alpha]_D^{20} = -94.5$ (c = 2, MeOH). IR: $\tilde{\nu} = 3062$, 3027 (ar CH, C=CH), 2991, 2972, 2916, 2869 (CH), 1744, 1702 (CO). ^{1}H NMR (300 MHz): δ = 1.39 (td, $^2J = 8.6$ Hz, 10-H_{anti}), 1.56 (td, $^2J = 8.6$ Hz, $^3J = 1.63$, 10-H_{syn}), 3.02, 3.13 (2 dd, $^3J_{2,6} = 7.7$ Hz, $^3J_{1,2/6,7} = 4.5$ Hz, 2-H, 6-H), 3.20 (m, 1-H, 7-H), 3.34 (AMX, $^2J_{AM} = 14.5$ Hz, $^3J_{AX} = 11.4$ Hz, 1 β-H), 3.48 (AMX, $^2J_{AM} = 14.5$ Hz, $^3J_{MX} = 5.4$ Hz, 1 β-H), 4.50 (AMX, $^3J_{AX} = 11.4$ Hz, $^3J_{MX} = 5.4$ Hz, α-H), 5.16 (s, $CH_{2(benzyl)}$), 5.31, 5.64 (2 dd, $^3J_{8,9} = 5.6$ Hz, $^3J_{7,8/1,9} = 2.9$ Hz, 8-H, 9-H), 7.11–7.37 (m, 10 ar H). HPLC: $k' = 15.79$, $t_0 = 1.87$ (RP-18, MeCN/H_2O 1 : 1). $k' = 5.66$, $t_0 = 1.81$ (Chiralcel OJ-R MeCN/H_2O 1 : 1).
$C_{25}H_{23}NO_4$ (401.5)

3.7.10. Methyl (S)-2-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-3-methylbutyrate (**48**)

From **26** (500 mg, 2.4 mmol) (A). Yield: 613 mg (92%). Colorless crystals. M.p. 58–59.5 °C (MeOH). M.p. 59–60 °C (Coles et al. 1994). $[\alpha]_D^{20} = -72.0$ (c = 1, MeOH), $[\alpha]_D^{20} = -32.3$ (c = 1, $CHCl_3$) (Coles et al. 1994). IR: $\tilde{\nu} = 2982$, 2949, 2875 (CH), 1772, 1753, 1702 (CO). ^{1}H NMR: δ = 0.80 (d, $^3J = 6.8$ Hz, Me_{Val}), 1.02 (d, $^3J = 6.7$ Hz, Me_{Val}), 1.55 (AB, $^2J = 8.8$ Hz, 10-H_{anti}), 1.75 (AB, $^2J = 8.8$ Hz, 10-H_{syn}), 2.54 (oct, $^3J = 6.9$ Hz, 1 β-H_{Val}), 3.31 (m, 2-H, 6-H), 3.42 (m, 1-H, 7-H), 3.67 (s, OMe), 4.25 (d, $^3J = 8.0$ Hz, α-H_{Val}), 6.17–6.09 (m, 2 C=CH). HPLC: $k' = 4.31$, $t_0 = 2.07$ (RP-18, MeCN/H_2O 1 : 1). $k' = 0.92$, $t_0 = 1.96$ ((S,S)-Whelk-O1 n-Hexane/EtOH 1 : 1).
$C_{15}H_{19}NO_4$ (277.3)

3.7.11. Dimethyl (S)-3-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)succinate (**49**)

From **27** (334 mg, 1.38 mmol) (A), CC (AcOEt/cyclohexane 1 : 1). Yield: 370 mg (87%). Colorless viscous liquid. $[\alpha]_D^{20} = -68.8$ (c = 2, MeOH). IR: $\tilde{\nu} = 3021$ (C=C), 2969, 2949 (CH), 1771, 1750, 1698 (CO). ^{1}H NMR: δ = 1.54 (AB, $^2J = 8.6$ Hz, 10-H_{anti}), 1.74 (AB, $^2J = 8.8$ Hz, 10-H_{syn}), 2.75 (AMX, $^2J_{AM} = 16.8$ Hz, $^3J_{AX} = 8.0$ Hz, 1 β-H_{Asp}), 3.19 (AMX, $^2J_{AM} = 16.8$ Hz, $^3J_{MX} = 6.5$ Hz, 1 β-H_{Asp}), 3.32–3.41 (m, 1-H, 2-H, 6-H, 7-H), 3.69 (s, OMe), 3.71 (s, OMe), 5.09 (AMX, $^3J_{AX} = 8.0$ Hz, $^3J_{MX} = 6.6$ Hz, α-H_{Asp}), 6.08 (s, 2 C=CH). HPLC: $k' = 0.51$, $t_0 = 1.87$ (RP-18, MeCN/H_2O 7 : 3). $k' = 1.21$, $t_0 = 2.21$ (Chiralcel OJ-R MeCN/H_2O 3 : 7).
$C_{15}H_{17}NO_6$ (307.3)

3.7.12. Methyl (S)-2-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-6-(benzyloxycarbonylamino)hexanoate (**50**)

From **28** (389 mg, 1 mmol) (A), CC (AcOEt/cyclohexane 1 : 1). Yield: 313 mg (71%). Colorless viscous liquid. $[\alpha]_D^{20} = -31.1$ (c = 2.5, MeOH). IR (Film): $\tilde{\nu} = 2929$, 2868 (CH), 1771, 1744, 1701 (CO), 1653, 1636 (C=C). ^{1}H NMR: δ = 1.19–1.55 (m, 2 $CH_{2(Lys)}$), 1.53 (AB, $^2J = 9.0$ Hz, 10-H_{anti}), 1.73 (AB, $^2J = 8.8$ Hz, 10-H_{syn}), 1.91–2.08 (m, $CH_{2(Lys)}$), 3.11–3.21 (dd, $^3J = 6.6$ Hz, $^3J = 13.0$ Hz, $CH_{2(Lys)}$), 3.294–3.39 (m, 1-H, 2-H, 6-H, 7-H), 3.68 (s, OMe), 4.48 (m,$^3J = 5.4$ Hz, $^3J = 9.9$ Hz, α-H_{Lys}), 4.77 (m, H–N), 5.09 (s, OCH_2), 6.11 (s, 2 C=CH), 7.32–7.36 (m, 5 ar H). HPLC: $k' = 1.06$, $t_0 = 1.87$ (RP-18, MeCN/H_2O 7 : 3). $k' = 4.42$, $t_0 = 2.34$ (Chiralcel OJ-R MeCN/H_2O 4 : 6).
$C_{24}H_{28}N_2O_6$ (440.5)

3.7.13. Methyl (S)-2-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-3-(4-benzyloxyphenyl)propionate (**51**)

From **29** (500 mg, 1.37 mmol) (A). Yield: 370 mg (63%). Colorless crystals. M.p. 87–89 °C (MeOH). $[\alpha]_D^{20} = -83.5$ (c = 2, MeOH). IR: $\tilde{\nu} = 3063$ (ar CH, C=CH), 2990, 2947, 2870 (CH), 1770, 1705 (CO), 1610, 1583 (C=C). ^{1}H NMR: δ = 1.43 (AB, $^2J = 8.8$ Hz, 10-H_{anti}), 1.60 (AB, 10-H_{syn}), 3.10–3.37 (m, 6 H, ABX, 1-H, 2-H, 6-H, 7-H), 3.73 (s, OMe), 4.91 (ABX, α-H), 5.58, 5 77 (2 m, 8-H, 9-H), 6.87 (d, $^3J = 7.5$ Hz, 2 ar H), 7.03 (d, $^3J = 7.5$ Hz, 2 ar H), 7.34–7.40 (m, 5 ar H_{benzyl}). HPLC: $k' = 13.17$, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1). $k' = 4.36$, $t_0 = 1.75$ (Chiralcel OJ-R MeCN/H_2O 4 : 6).
$C_{26}H_{25}NO_5$ (431.5)

3.7.14. Methyl N-[(S)-2-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)propanoyl]-3-phenylpropionate (**52**)

From **32** (250 mg, 0.76 mmol) as **40** (A). Yield: 56 mg (40%). Colorless crystals. M.p. 89–91 °C (Et_2O/n-hexane). $[\alpha]_D^{20} = +4.0$ (c = 2, MeOH). IR: $\tilde{\nu} = 3410$ (NH), 3069, 3032 (ar CH, C=CH), 2990, 2948, 2874 (CH), 1774, 1741, 1705, 1673 (CO), 1513 (CO, C=C), 732, 702 (ar C=C). ^{1}H NMR: δ = 1.47 (d, $^3J = 7.4$ Hz, Me_{Ala}), 1.51 (AB, $^2J = 8.8$ Hz, 10-H_{anti}), 1.70 (AB, $^2J = 8.8$ Hz, 10-H_{syn}), 3.12–3.38 (m, 2 β-H_{Phe}, 1-H, 2-H, 6-H, 7-H), 3.73 (s, OMe), 4.61 (q, $^3J = 7.4$ Hz, α-H_{Ala}), 4.84 (ABX, α-H_{Phe}), 5.55 (dd, $^3J = 2.8$ Hz, $^3J = 5.6$ Hz, 1 C=CH), 6.21 (dd, $^3J = 2.9$ Hz, $^3J = 5.6$ Hz, 1 C=CH), 6.31 (d, $^3J = 6.8$ Hz, H–N), 7.07–7.34 (5 ar H). HPLC: $k' = 2.71$, $t_0 = 1.87$ (RP-18, MeCN/H_2O 1 : 1). $k' = 2.03$, $t_0 = 1.81$ (Chiralcel OJ-R MeCN/H_2O 2.5 : 7.5).
$C_{22}H_{24}N_2O_5$ (396.4)

3.7.15. Methyl N-[(S)-2-(3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-3-phenylpropanoyl]-3-phenylpropionate (**53**)

From **33** (508 mg, 1.25 mmol) (A). Yield: 529 mg (90%). Colorless crystals. M.p. 105–108 °C (MeOH). $[\alpha]_D^{20} = -3.6$ (c = 2, MeOH). IR: $\tilde{\nu} = 3400$ (NH), 3063, 3027 (ar CH, C=CH), 2987, 2953 (CH), 1749, 1698, 1684 (CO), 1604, 1584 (C=C), 736, 699 (ar C=C). ^{1}H NMR: δ = 1.39 (AB, $^2J = 8.8$ Hz, 10-H_{anti}), 1.59 (AB, $^2J = 8.8$ Hz, 10-H_{syn}), 2.91, 3.05 (2 dd, $^3J = 4.4$ Hz, $^3J = 7.9$ Hz, 2-H, 6-H), 3.13–3.25 (m, 1-H, 7-H, 2 β-H_{Phe}), 3.29–3.51 (ABX, 2 β-H_{Phe}), 3.73 (s, OMe), 4.81–4.91 (m, 2 α-H_{Phe}), 5.19 (dd, $^3J = 2.8$ Hz, $^3J = 5.6$ Hz, 1 C=CH), 6.00 (dd, $^3J = 2.9$ Hz, $^3J = 5.6$ Hz, 1 C=CH), 6.42 (d, $^3J = 7.1$ Hz, H–N), 7.06–7.37 (m, 10 ar H). HPLC: $k' = 9.90$, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1). $k' = 2.18$, $t_0 = 1.81$ (Chiralcel OJ-R MeCN/H_2O 1 : 1).
$C_{28}H_{28}N_2O_5$ (472.5)

3.7.16. Methyl (3,5-Dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)formiate (**54**)

From **36** (310 mg, 2 mmol) in 1 ml toluene (A). Yield: 390 mg (88%). Colorless crystals. M.p. 93–96 °C (i-PrOH). IR: $\tilde{\nu} = 3081$, 3008 (C=CH), 2992, 2978, 2965, 2870 (CH), 1809, 1755, 1722 (CO), 1653, 1635 (C=C), 704 (ar C=C). ^{1}H NMR: δ = 1.55 (AB, $^2J = 9.0$ Hz, 10-H_{anti}), 1.75 (AB, $^2J = 8.9$ Hz, 10-H_{syn}), 3.35–3.55 (m, 1-H, 7-H, 2-H, 6-H), 3.93 (s, OMe), 6.24–6.25 (m, 2 C=CH). HPLC: $k' = 0.93$, $t_0 = 1.89$ (RP-18, MeCN/H_2O 1 : 1). $k' = 0.95$, $t_0 = 1.84$ (Chiralcel OJ-R MeCN/H_2O 3 : 7).
$C_{11}H_{11}NO_4$ (221.2)

3.7.17. endo-N-[2-(Phenylethyl)bicyclo[2.2.1]hept-5-ene]-2,3-dicarboximide (**55**)

From **37** (500 mg, 2.5 mmol) (A). Yield: 424 mg (63%). Colorless crystals. M.p. 73–75.5 °C (Et_2O). M.p. 81–82 °C (Gray and Heitmeier 1965). IR: $\tilde{\nu} = 2976$, 2943 (CH), 1765, 1695 (CO). ^{1}H NMR: δ = 1.52 (AB, $^2J = 8.7$ Hz, 10-H_{anti}), 1.70 (AB, $^2J = 8.8$ Hz, 10-H_{syn}), 2.76 (t, $^3J = 7.6$ Hz, CH_2), 3.20–3.35 (m, 1-H, 7-H, 2-H, 6-H), 3.60 (t, $^3J = 6.7$ Hz, N-CH_2), 5.96 (s, 2 C=CH), 7.17–7.32 (m, 5 ar H). HPLC: $k' = 1.33$, $t_0 = 1.77$ (RP-18, MeCN/H_2O 7 : 3). $k' = 2.34$, $t_0 = 2.25$ (Chiralcel OJ-R MeCN/H_2O 1 : 1).
$C_{17}H_{17}NO_2$ (267.3)

Acknowledgements: We thank Degussa AG, for generous support with chemicals, E. Merck KGaG, Darmstadt, for continuous support with chromatography materials, the "Fonds der Chemischen Industrie" for financial support, and Dr. M. Kindermann, Chemistry Dept. University of Greifswald, for some NMR experiments.

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