Synthesis of Optically Active β,γ-Unsaturated α-Amino Acids and of α,β-Unsaturated γ-Amino Acids. S_N2- vs. S_N2'-Dichotomy of the Mitsunobu Amination of Allylic Alcohols

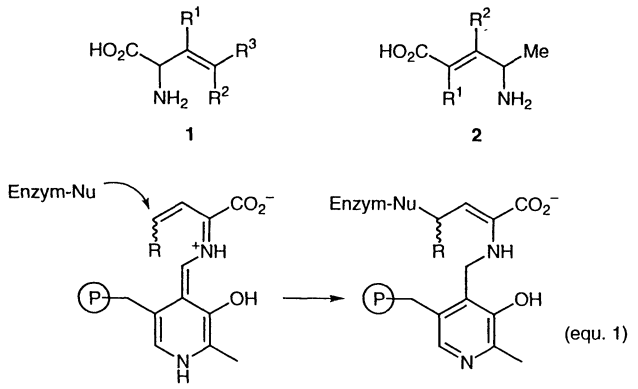
Johann Mulzer,* Günther Funk

Institut für Organische Chemie der Freien Universität, D-14195 Berlin, Germany

Received 30 September 1994

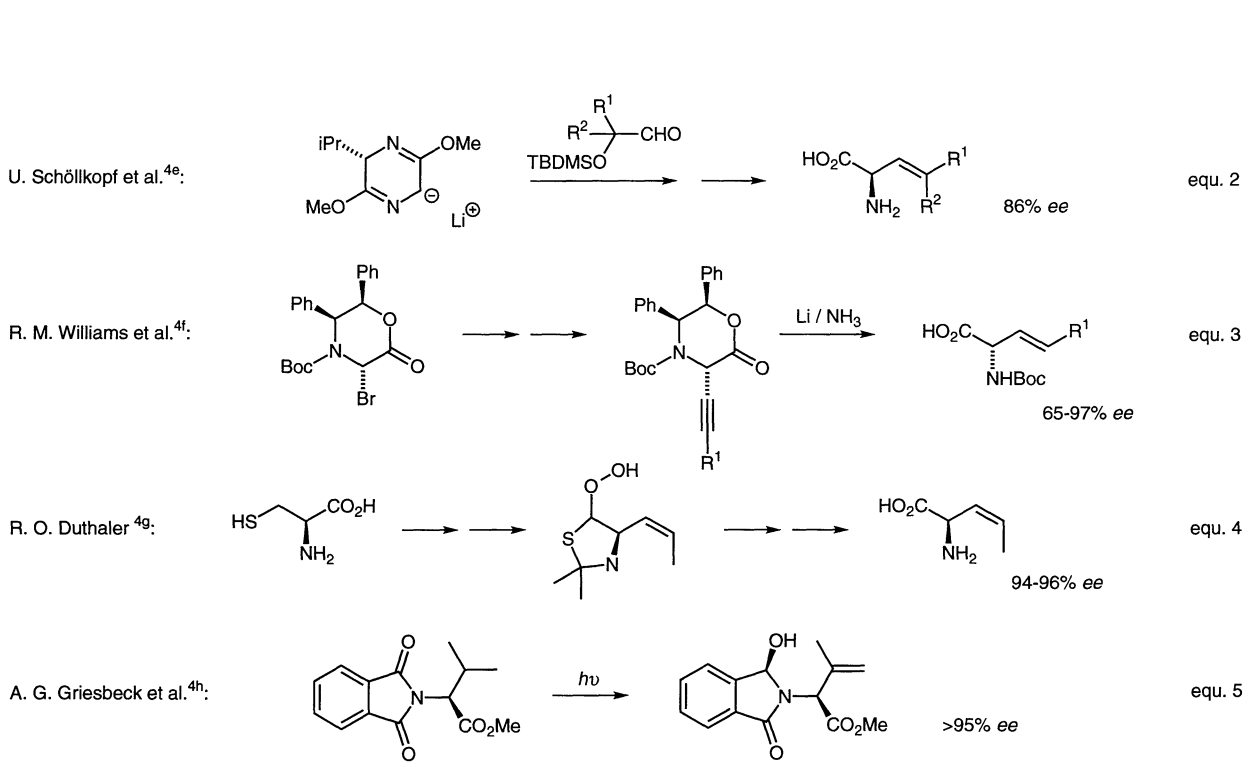
Novel and efficient syntheses (6–9 steps, overall yields 10–30%) are described for optically pure β,γ-unsaturated α-amino acids and α,β-unsaturated γ-amino acids, starting from (*R*)-isopropylidene glyceraldehyde and ethyl (*S*)-lactate, respectively. The key step is the Mitsunobu reaction of chiral secondary allylic alcohols with phthalimide as the nucleophile, where α,γ allylic transpositions are observed for the first time. The structure-α,γ-ratio-relationship is studied and also the stereochemistry of the allylic transposition. The α-substitution proceeds via clean S_N2 inversion, whereas the γ-substitution corresponds to an (*E*)-*anti* attack of the nucleophilic with varying stereoselectivities.

Among the so-called rare or unnatural amino acids[1] the β,γ-unsaturated α-amino acids of type **1** have found application as fungicides and herbicides in plant protection. This is chiefly due to the physiological activity of these amino acids as suicide inhibitors or enzymes involved in transamination processes.[2] Thus, amino acids **1** form imines with pyridoxalphosphate which, in contrast to the "normal" case, adopt strong Michael acceptor qualities. Addition of donor atoms like nitrogen or sulfur of the enzyme leads to irreversible destruction of the transaminase (equ. 1). In contrast, the isomeric α,β-unsaturated γ-amino acids **2** are less important so far, although a general access to this class of compounds would also be desirable.



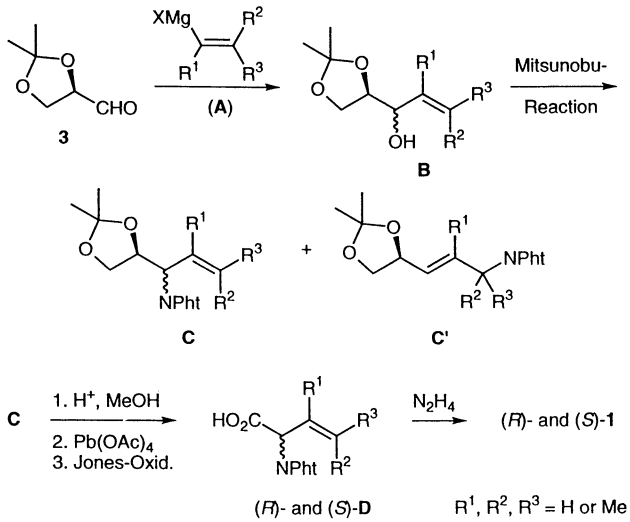
In keeping with the intense interest in amino acids of type **1** several syntheses of the racemic[3] and optically active[4] compounds have been reported, some of which are compiled in Scheme 1. (equ. 2 to 5).

Our own method is illustrated in Scheme 2. A vinylorganometallic species **A** or an equivalent thereof is added to aldehyde **3** under formation of a chiral allylic alcohol **B** which is submitted to a Mitsunobu-type substitution



Scheme 1

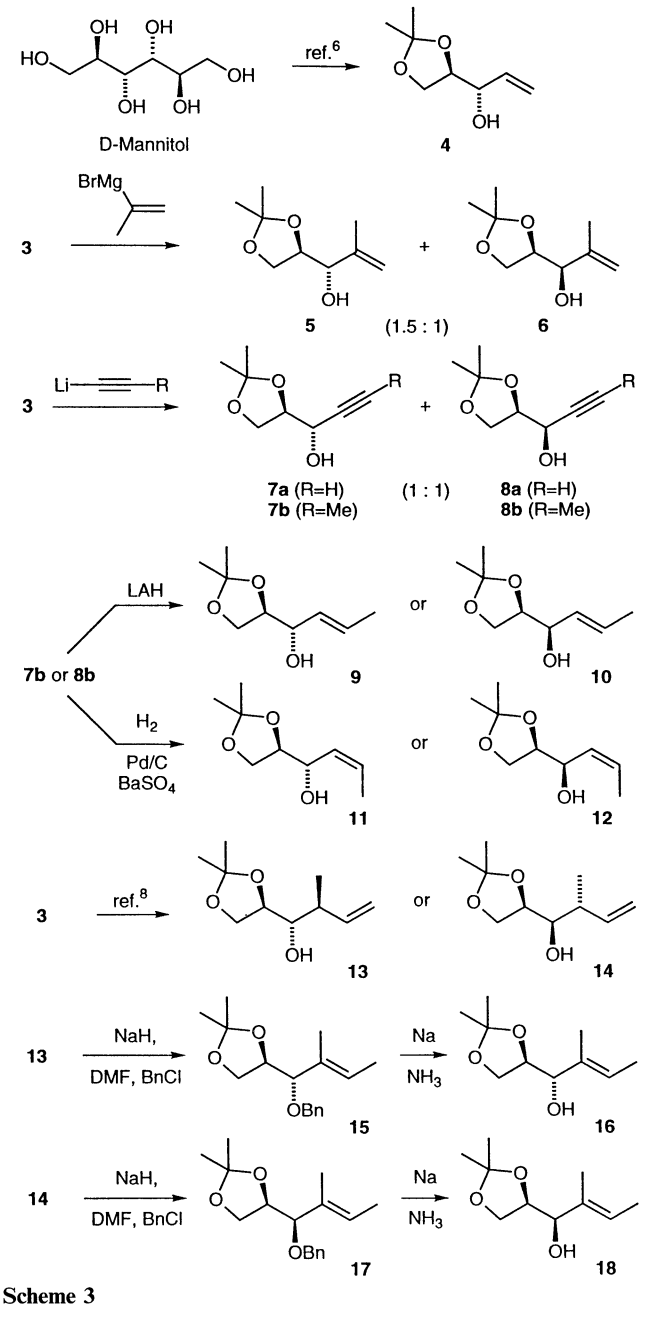
of phthalimide to form **C**. In these steps a possible S_N- vs. S'_N-dichotomy has to be expected so that not only **C** but also the allylic isomer **C'** may be generated. It is astonishing that even in the latest review of the Mitsunobu reaction[5] no such allylic transposition has been recorded. Phthalimide **C** is converted into **D** via degradation of the acetonide, the initial chiral unit. Depending on the stereochemical course of the addition of **A** to **3**, **D** is formed as the (*R*)- or (*S*)-enantiomer. Removal of the phthalimido group leads to the amino acids **1** eventually.



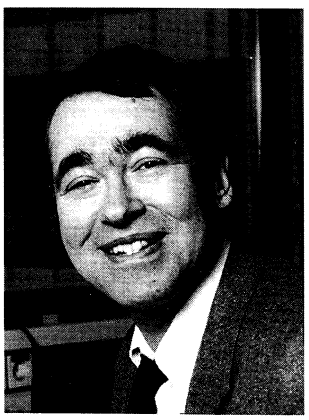
Scheme 2

Synthesis of the Unsaturated Alcohols 4–18 (Scheme 3)

In principle, the allylic alcohols of type **B** can all be prepared by addition of the corresponding organometallic species **A** to aldehyde **3**. These additions lead to diastereomeric mixtures at the newly formed carbinol center, e.g. **5** and **6** are generated in a ratio of 1.5:1. The same is true for the propargylic alcohols **7a,b** and **8a,b**. Although these mixtures can be separated by HPLC it was desirable to develop stereocontrolled routes. For instan-



Scheme 3



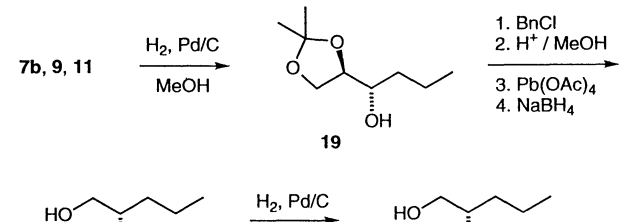
Biographical Sketch

Johann Mulzer received his PhD at the University of Munich in 1974, where he worked under the guidance of Professor R. Huisgen on thermal valence isomerization of vinylcyclopropanes. From 1974–1975 he spent a postdoctoral year with Professor E.J. Corey at Harvard University on the LHASA 10 computer synthesis project. Back to Munich he earned his habilitation in 1980. In 1982 he moved to the University of Düsseldorf as an associate professor and became a full professor at the Free University of Berlin in 1984. His main research interests are in the stereoselective synthesis of natural products, in particular rare amino acids, polyketides, macrolides and polycyclic alkaloids of the morphinane type.

ce, the vinyl adduct **4** can be synthesized directly from D-mannitol on an ex-chiral-pool route.[6] Diastereomeric mixtures of propargylic alcohols such as **7a, 8a** and **7b, 8b** can be separated by diastereomer selective enzymatic hydrolysis of the corresponding acetates.[6] The propargylic alcohols **7a,b** and **8a,b** can be converted by stereoselective hydrogenation to the allylic derivatives **9–12a,b** as shown. For the synthesis of **16** and **18** a novel base-induced 1,3-H-shift[7] is used, which converts the homoallylic alcohols **13** and **14**, which are accessible from **3** in a highly stereocontrolled manner via crotyl boronate addition,[8] to the *O*-benzyl ethers **15** and **17**, respectively. Debenzylation with sodium furnishes **16** and **18** in diastereomerically pure form.

Configurational Assignments

Alcohols **4, 7a, 8a, 13** and **14** are known compounds;[6–8] hence, the configurations of **16** and **18** are also clear. Alcohols **7b, 9** and **11** were hydrogenated to give **19** (Scheme 4), which was converted to the known[9] diol (*S*)-**21**. Analogously, **8b, 10** and **12** were transformed into (*R*)-**21**.

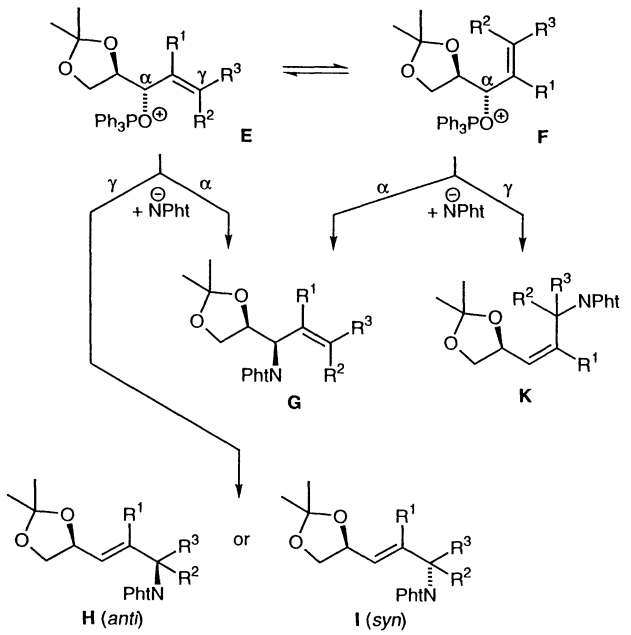


Scheme 4

Mitsunobu Reaction

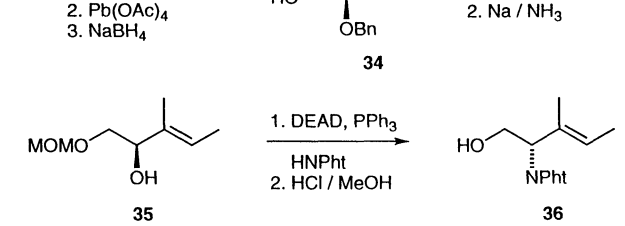
This is the key step in our synthesis. Scheme 5 shows the possible pathways for α-(*S*)-configurated alcohol **B**. Analogous considerations hold good for the α-(*R*)-series. The activated intermediate[10] can exist in the conformations **E** and **F**, of which **F** is much less populated due to the steric repulsion between R^2 and acetonide ring. α-Attack of the phthalimide anion on **E** leads to **G** under inversion of configuration (S_N2) whereas the γ-attack can occur *anti* or *syn* to the $OPPh_3$ leaving group. Accordingly, **H** or **I** are the products. If **F** also participates, γ-attack would generate **I** with a (*Z*)-double bond. Such products are not observed, which eliminates **F** as a reactive intermediate. The ratio of **H**:**I** reflects the ratio of *anti* to *syn* stereochemistry of the nucleophilic attack.

Table 1 shows the experimental results for the individual allylic and propargylic alcohols. The regiochemistry ranges from pure α-attack (alcohols **5, 6, 7a,b, 8a,b**) to pure γ-attack (alcohols **16** and **18**). The remaining alcohols (**4, 9, 10, 11** and **12**) form a 1:1 mixture of α- and γ-substitution products. As demonstrated by a comparison of



Scheme 5

the (3*S*)/(3*R*)-isomers **5/6, 9/10, 11/12** and **16/18**, the α/γ-regiochemistry is independent of the configuration at the allylic carbinol center. There is no clearcut connection between the substitution of the α vs. γ site and the regiochemistry. For instance, on comparing **5/6** and **9/10** or **11/12** one would expect a much higher proportion of the γ-product for **5/6** due to the unhindered terminal CH_2 position. Much more surprising is the exclusive γ-substitution in the case of **16** and **18**. Although there may be no straightforward interpretation for these findings, there is no doubt about the strong γ-directing effect of the acetonide ring. Whereas **18** gives the γ-product exclusively, the corresponding MOM ether **35** reacts under α-attack to give the 1,2-amino alcohol derivative **36** as the sole product (Scheme 6).

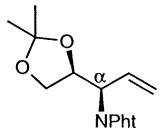
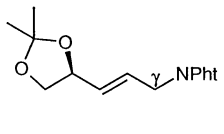
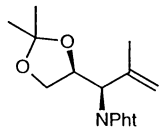
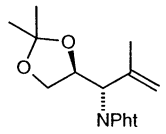
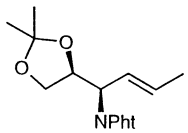
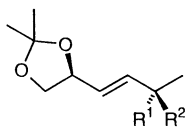
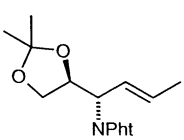


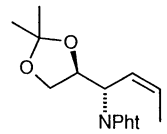
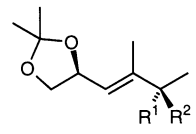
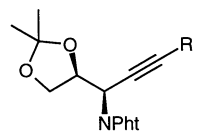
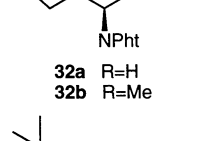
Scheme 6

Stereochemistry of the Mitsunobu Reaction

The configuration of the amino-substituted stereogenic center is established via conversion to the corresponding amino acid derivatives (**39/1** for α-substitution and **42/43** for γ-substitution). An inspection of Table 1 shows that α-substitution always occurs under clear S_N2 inversion of configuration **(22, 24, 25, 26, 28, 29, 30, 32, 33)**. γ-Substitution, in contrast, proceeds under predominant formation of product **H** (Scheme 5), i.e. with *anti* ste-

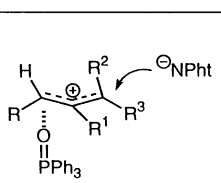
Table 1. Mitsunobo Reactions of Allylic Alcohols **4–6, 7, 9–11, 12, 16, 17**

Alcohol	Product (Rel. Yield) α-Subst.	γ-Subst.	Total Yield (%)
4	 **22** (50%)	 **23** (50%)	50
5	 **24** (>95%)	–	85
6	 **25** (>95%)	–	85
9	 **26** (50%)	 **27** (50%) / **a** : **b** = 80 : 20 **27a** R^1=NPht, R^2=H **27b** R^1=H, R^2=NPht	75
10	**28** (50%)	**27a** + **27b** (50%) **a** : **b** = 10 : 90	75
11	 **29** (50%)	**27a** + **27b** (50%) **a** : **b** = 10 : 90	75

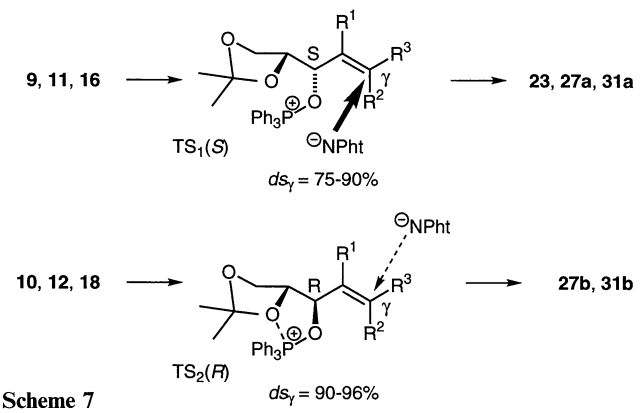
Alcohol	Product (Rel. Yield) α-Subst.	γ-Subst.	Total Yield (%)
12	 **30** (50%)	**27a** + **27b** (50%) **a** : **b** = 90 : 10	75
16	–	 **31** (>95%) / **a** : **b** = 25 : 75 **31a** R^1=NPht, R^2=H **31b** R^1=H, R^2=NPht	53
18	–	**31a** + **31b** (>95%) 96 : 4	65
7a,b	 **32a** R=H **32b** R=Me	–	78 82
8a,b	 **33a** R=H **33b** R=Me	–	85 76

reochemistry. This means that from alcohol **9** phthalimides **27a** and **b** are formed in a ratio of 4:1, whereas in the case of alcohol **10** the ratio of **27a/27b** is inverted to 1:9.

Analogously, alcohol **11** generates **27a/27b** in a ratio of 1:9 and **12** leads to a ratio of **27a/27b** of 9:1. The same behavior is shown by the isomeric pair **16/18**; alcohol **16** furnishes **31a** and **b** in a ratio of 1:3, whereas **18** leads to a ratio **31a:b** of 96:4. This *anti* selectivity is in contrast to the normal *syn* stereochemistry of a S_N2' substitution.[11] Obviously, the Mitsunobu reaction rather proceeds via a partial S_N1-type mechanism, e.g. a contact ion pair **K** in which the leaving group $PPh_3P{=}O$ shields the *syn* face of the allylic cation and directs the attack of the phthalimide to the *anti* face.[12] This S_N1 character of the reaction also explains the regiochemical results for alcohols **5/6, 9/10, 11/12** and **16/18**, where the nucleophile attacks the α/γ-positions according to their respective carbenium ion character. Alcohol **4**, however, is an exception, and probably follows a pure S_N2' mechanism.



K

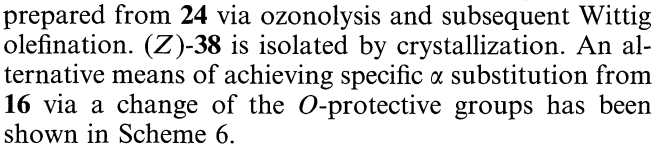


Scheme 7

Scheme 7 illustrates how the lower ds_γ value (diastereoselectivity of the γ-attack) in the (*S*)-series **(9, 11, 16)** compared to the (*R*)-series **(10, 12, 18)** may be interpreted. Possibly in $TS_2(R)$ the effective size of the leaving group is increased over that in $TS_1(S)$ by a binding interaction between the positive phosphorus and one acetonide oxygen.

Unambigous Synthesis of the α- and γ-Substitution Products

The lack of regiocontrol in the Mitsunobu reaction of alcohols **4, 9, 10, 11, 12**, from which α/γ-mixtures are formed, poses a serious problem to the synthesis of amino acids **1**. Even worse is the case of alcohols **16/18**, where the γ-product is formed exclusively. There are, however, ways to avoid this awkward situation. For instance, the propargylic alcohols **7a,b** and **8a,b** react with complete (> 98 %) α selectivity to **32/33a,b**. Thus, phthalimide **32a** may be converted to **22** by Lindlar hydrogenation, and by the same protocol **32/33b** may be transformed into **29** and **30**, respectively. Scheme 8 finally shows how the formal α-substitution products of alcohols **16/18** may be prepared from **24** via ozonolysis and subsequent Wittig olefination. (*Z*)-**38** is isolated by crystallization. An alternative means of achieving specific α substitution from **16** via a change of the *O*-protective groups has been shown in Scheme 6.



Scheme 8

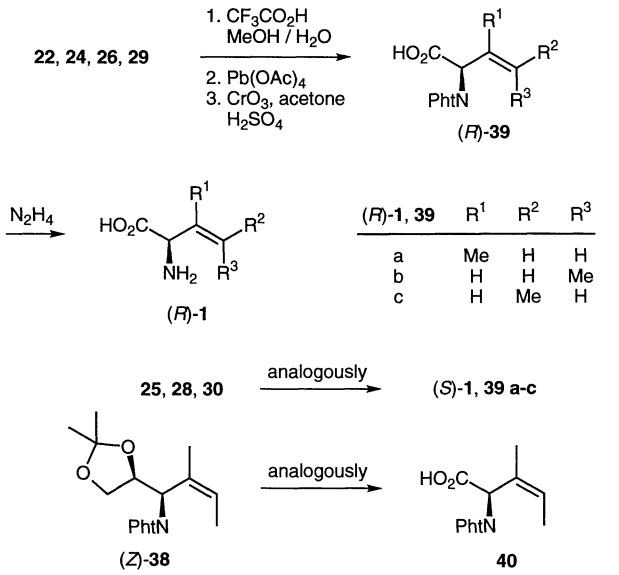
The regiocontrolled synthesis of the γ-products is described later.

Conversion of the Allylphthalimides into the Acids (*R*)- and (*S*)-39, 1 and 40 (Schemes 9 and 10)

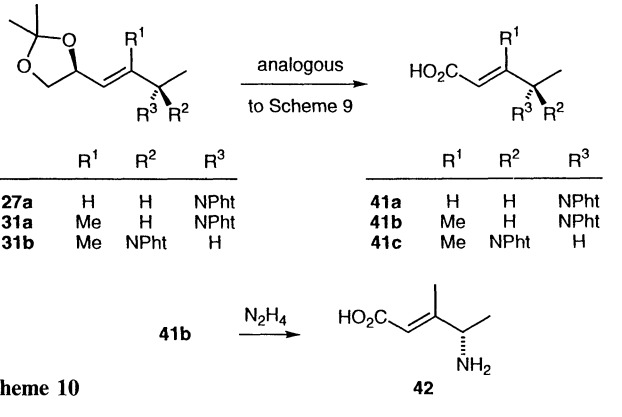
The procedure is the same for all α- and γ-phthalimides **(22, 24, 26, 29**, (*Z*)-**38** and **25, 28, 30)** and consists of the following steps: 1) hydrolysis of the acetonide to the 1,2-diol; 2) glycol cleavage with lead tetraacetate to the labile aldehyde, which is immediately oxidized to the carboxylic acid under Jones conditions. 3) hydrazinolysis of the phthalimide to the amino group. The overall yield routinely is about 70 %.

Optical Purity of the Amino Acids (*R*)- and (*S*)-1a–c and 42 (Table 2)

The optical purity of the acids **1a–c** was established by chiral GC (Chirasil Val[13]) and/or by comparison of the optical rotations with the literature data (Table 2). Acid **42** was correlated with the (*R*)-**51c** prepared on an ex-chiral-pool route from (*S*)-lactic ester (see next paragraph).



Scheme 9



Scheme 10

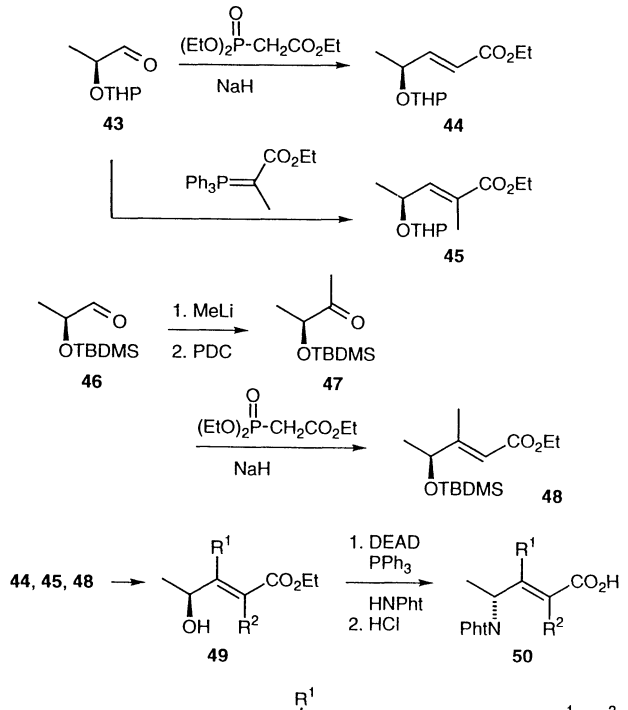
Table 2. Optical Purity of Acids **1** and **42**

(*R*)-**1a**	$[\alpha]_D^{22} = -151.7$ ($c = 2$, H_2O), mp 242–243 °C, chiral GC > 99 % ee. ref.[3c]: $[\alpha]_D^{22} = -165$ ($c = 3.3$, H_2O).
(*S*)-**1a**	ref.[3c]: $[\alpha]_D^{22} = +165$ ($c = 4.6$, H_2O).
(*R*)/(*S*)-**1a**	mp 222–224 °C. ref.[3c]: 211–215, ref.[3g]: 217–218 °C.
(*R*)-**1b**	$[\alpha]_D^{22} = -252.4$ ($c = 0.5$, H_2O), -297.9 ($c = 0.3$, AcOH), mp 215–217 °C, chiral GC > 99.95 % ee. ref.[4g]: $[\alpha]_D^{22} = -283$ ($c = 0.27$, AcOH, 94 % ee).
(*S*)-**1b**	$[\alpha]_D^{22} = +263$ ($c = 0.4$, H_2O).
(*S*)-**1c**	$[\alpha]_D^{22} = +24.8$ ($c = 0.9$, H_2O), mp 235–240 °C. ref.[4e]: (*R*)-**1c** $[\alpha]_D^{22} = -153.8$ ($c = 1.2$, H_2O) for a mixture of (*R*)-**1b** and (*R*)-**1c**.
(*S*)-**42b** ≙ (*S*)-**51c**	$[\alpha]_D^{22} = +5.4$ ($c = 1$, H_2O). $[\alpha]_D^{22}$ of (*R*)-**51c** prepared from (*S*)-lactate -5.6 ($c = 1.4$, H_2O), chiral GC > 99.95 % ee.

Ex-Chiral-Pool Synthesis of the α,β-Unsaturated γ-Amino Acids 51 from (*S*)-Lactic Ester (Scheme 11)

Ethyl (*S*)-lactate was converted into the *O*-protected aldehydes **43** and **46**, respectively, according to literature procedures.[14] Aldehyde **43** gave the α,β-unsaturated esters **44** and **45** (*E*) selectively (> 95 %) under Horner or Wittig conditions. Aldehyde **46** was converted into

(*E*)-ester **48** via the methyl ketone **47**. The *O*-protective groups in **44, 45** and **48** were removed and the resulting allylic alcohols **49a–c** were submitted to standard Mitsunobu conditions to give phthalimido acids **50a–c** regioselectively after saponification. Hydrazinolysis furnished the (*R*)-amino acids **51a–c**, whose optical purity was confirmed by chiral GC to be > 99.95% ee. Acids (*R*)- and (*S*)-**51a** were prepared from (*R*)- and (*S*)-valine.[15] The reported optical rotations ($[\alpha]_D^{22} = +4.6$ ($c = 1.1$, 5 M HCl) for (*R*)-**51a**[15] and −5.8 ($c = 1.3$, 5 M HCl) for (*S*)-**51a**[15]) are in agreement with our value of $[\alpha]_D^{22} = +5.8$ ($c = 1.1$, 5 M HCl) for (*R*)-**51a**.



Scheme 11

In conclusion, we present concise syntheses of β,γ-unsaturated α-amino acids (*R*)- and (*S*)-**1a–c** and α,β-amino acids (*R*)-**51a–c**, which provide the optically pure compounds in 6–7 steps for acid **1** and 7–9 steps for **51** and overall yields of 10–30% based on aldehyde **3** or ethyl (*S*)-lactate. In principle, these syntheses should be applicable to a wide variety of substituents.

The IR spectra were obtained with a Perkin-Elmer IR 580B spectrophotometer. The NMR spectra were recorded with a Bruker WH 270 or AC 250 spectrometer in $CDCl_3$ (unless otherwise stated) with TMS as internal standard. Optical rotations were determined with a Perkin-Elmer 121 polarimeter at 589 nm at 20°C. Mass spectra were recorded with a Varian MAT 711 spectrometer. HPLC separations were performed on 7-μm nucleosil for preparative separations and on 5-μm nucleosil 50 for analytical separations. All reactions were performed in dried and purified solvents and monitored by TLC plates (Merck 5554). Preparative column chromatography was performed on silica gel Merck 60, 230–400 mesh, with typically 20–30 g of silica gel per gram substance. Satisfactory microanalyses obtained (C, H, N ± 0.3) for all new compounds. Chiral GC of the amino acids was performed on L-Chirasil Val after conversion into the *N*-trifluoroacetyl isopropyl esters.[13]

1. Synthesis of Allylic Alcohols (Scheme 3) (Analytical Data see Table 3)

1.1. Grignard Addition to 3; Synthesis of (2*R*,3*S*)- and (2*R*,3*R*)-1,2-*O*-Isopropylidene-4-methyl-4-pentene-1,2,3-triol (5/6):

The Grignard reagent was prepared from 2-bromopropene (1 mol) in THF (200 mL) and cooled to 0°C. Aldehyde **3** was prepared from D-mannitol (128 g, 0.57 mol) as described[16] and was added dropwise as a THF solution (300 mL). After stirring the mixture at ambient temperature for 1 h NH_4Cl and Et_2O were added. The organic layer was separated, dried ($MgSO_4$) and distilled at 75–85°C/0.1 mbar to give a mixture of **5/6** (156 g, 80%) as a colorless oil, which was separated by preparative HPLC (2.5 g per injection).

1.2. Lindlar Hydrogenation of 7b to give (2*R*,3*R*)-1,2-*O*-Isopropylidene-(4*Z*)-hexene-1,2,3-triol (12):

Compound **7b** (500 mg, 2.9 mmol) in MeOH (50 mL) was hydrogenated with $Pd/BaSO_4$ (10 mg) at 22°C under 1 bar H_2. The mixture was filtered, concentrated and chromatographed (EtOAc/hexanes 1 : 3) to give **11** (450 mg, 90%). Similarly, **8b** was hydrogenated to give **12**.

1.3. Lithium Aluminum Hydride Reduction of 7b to give (2*R*,3*S*)- and (2*R*,3*R*)-1,2-*O*-Isopropylidene-(4*E*)-hexene-1,2,3-triol (9/10):

Compound **7b** (500 mg, 2.9 mmol) in THF (10 mL) was treated with $LiAlH_4$ (100 mg) at 40°C for 4 h. After destroying excess $LiAlH_4$ with 2-propanol, H_2O was added (2 mL) and silica gel (20 g). The mixture was stirred for 1 h at 0°C, $MgSO_4$ was added and the mixture was then filtered. The filtrate was concentrated and distilled at 80°C/0.1 mbar to give **9** (425 mg, 85%). Similarly, **8b** was reduced to give **10**.

1.4. (2*R*,3*S*)- and (2*R*,3*R*)-1,2-*O*-Isopropylidene-4-methyl-(4*E*)-hexene-1,2,3-triol (16/18):

Homoallylic alcohol **13** (180 g, 290 mmol) in DMF (600 mL) was treated with NaH (60%, 2 mol equiv.) at 0°C. BnCl (1.5 mol equiv.) was added and the mixture was stirred at 80°C for 15 h. H_2O was added and the mixture was concentrated in vacuo. The residue was diluted with CH_2Cl_2, dried ($MgSO_4$) and purified by column chromatography (EtOAc/hexanes 1:10) to give **15** (72 g, 90%). For benzylation, **15** (45 g, 163 mmol) in Et_2O (100 mL) and NH_3 (100 mL) at −78°C was treated with Na in small portions until a blue solution was obtained. NH_4Cl was added and the NH_3 was evaporated. H_2O was added and the mixture was extracted with Et_2O. The ethereal layer was dried ($MgSO_4$) and purified by chromatography (EtOAc/hexanes 1 : 3) to give **16** (29 g, 95%). Analogously, **18** was prepared from **14**.

2. Configurational Assignment of Alcohols 7b, 8b, 9–12 (Scheme 4); General Procedure:

The alcohol (500 mg) was hydrogenated with 10% Pd/C in MeOH at 22°C under 1 bar H_2. The free OH group was benzylated at 22°C with 1.3 equiv. of BnCl in DMF as described in section 1.4. Acetonide hydrolysis and glycol cleavage were performed as described in section 4.1 and 4.2.The crude aldehyde was reduced with an excess of $NaBH_4$ in MeOH. The benzyl protective group was removed by catalytic hydrogenation as described above. The intermediates were not isolated. (*R*)-**21** had an optical rotation of $[\alpha]_D^{22} = +8.0$ ($c = 2.1$, EtOH) which was half of the literature value +16.2 ($c = 8.0$, EtOH)[17] but proved the (*R*) configuration.

3. Mitsunobu Reaction; General Procedure:

The allylic alcohol (10–100 mmol), PPh_3 (1.3 mol equiv.) and phthalimide (1.3 mol equiv.) in THF (2 mL per mmol substrate) was treated dropwise at 0°C with DEAD (1.3 mol equiv.) in THF (1 mL per mmol). After 15 h at ambient temperature the solvent was evaporated, Et_2O was added to crystallize the phosphine oxide and the hydrazo ester, which were removed by filtration. This procedure was repeated and the filtrates were purified by column chromatography. For analytical data of the phthalimides see Table 4.

Table 3. Optical Rotations and Spectral Data of Alcohols **5**, **6**, **7b**, **8b**, **9**, **10**, **11**, **12**, **16** and **18**

Alcohol	$[\alpha]_D^{22}$ ($CHCl_3$) (*c*)	IR (film) ν (cm^{-1})	MS (80 eV) *m/z* (%)	^1H NMR ($CDCl_3$/TMS) (270 MHz), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) (62.5 MHz), δ
5	+17.0 (2.0)	2990, 1380, 1370, 1250, 1215, 1165, 1155, 1065	157 (15), 114 (7), 101 (100), 97 (11), 73 (13), 59 (15), 43 (77)	1.36 (s, 3H), 1.45 (s, 3H), 1.76 (d, 3H, J = 1.0), 2.57 (s, 1H, OH), 3.92 (m, 2H), 4.92 (d, 1H, J = 1.0), 5.08 (d, J = 1.0)	18.81, 25.05, 26.38, 64.83, 73.97, 76.49, 109.20, 112.33, 143.30
6	−23.0 (1.7)			1.37 (s, 3H), 1.45 (s, 3H), 1.76 (d, 1H, J = 1.1), 2.80 (d, 1H, J = 5.0, OH), 3.72 (dd, 1H, J = 7.5, J = 6.8), 3.92 (dd, 1H, J = 7.5, J = 6.8), 3.93 (d, 2H, J = 6.8), 4.16 (dt, 1H, J = 6.3, J = 6.3), 4.92 (q, 1H, J = 2.1), 5.00 (dd, 1H, J = 1.1, J = 1.1)	17.92, 25.22, 26.56, 66.11, 76.65, 77.33, 109.65, 113.55, 143.74
7b		1380, 1375, 1260, 1215, 1155, 1070	155 (21), 101 (100), 43 (77)	1.38 (s, 3H), 1.45 (s, 3H), 1.84 (d, 3H, J = 2.0), 2.58 (s, 1H, OH), 3.88 (dd, 1H, J = 7.5, J = 5.0), 3.96–4.16 (m, 2H), 4.27 (m, 1H)	
8b				1.38 (s, 3H), 1.47 (s, 3H), 1.86 (d, 3H, J = 2.0), 2.71 (d, 1H, J = 3.6), 4.07 (dd, 2H, J = 6.0, J = 6.0), 4.19 (dt, 1H, J = 6.0, J = 4.5), 4.42 (dq, 1H, J = 4.5, J = 2.0)	
9	+26.4 (2.3)	3470, 2990, 1380, 1370, 1255, 1215, 1160, 1070, 970, 855	157 (9), 101 (100), 97 (14), 83 (6), 71 (14), 59 (18), 55 (7), 43 (98)	1.36 (s, 3H), 1.44 (s, 3H), 1.72 (dd, 3H, J = 7.0, J = 1.0), 2.43 (d, 1H, J = 3.3, OH), 3.90 (dd, 1H, J = 8.0, J = 7.5), 3.96 (dd, 1H, J = 8.0, J = 7.5), 4.08 (dt, 1H, J = 7.5, J = 5.5), 4.20 (m, 1H), 5.44 (ddq, 1H, J = 16.0, J = 7.0, J = 2.0), 5.80 (ddq, 1H, J = 16.0, J = 7.0, J = 1.0)	17.66, 25.05, 26.30, 64.90, 71.76, 78.40, 109.18, 128.77, 128.96
10	−4.2 (2.3)	2990, 1380, 1370, 1255, 1215, 1160, 1070, 970, 855	157 (12), 129 (4), 112 (9), 101 (78), 97 (31), 83 (17), 71 (17), 59 (40), 43 (100)	1.36 (s, 3H), 1.44 (s, 3H), 1.72 (dd, 1H, J = 7.5, J = 2.2), 2.72 (s, 1H, OH), 3.73 (m, 1H), 4.00 (m, 3H), 5.42 (ddq, 1H, J = 17.5, J = 7.5, J = 2.2), 5.81 (ddq, 1H, J = 17.5, J = 7.5, J = 1.0)	17.62, 25.18, 26.60, 65.81, 73.99, 78.90, 109.59, 129.09, 129.58
11	+55.7 (3.2)	3480, 2985, 2940, 2920, 2890, 1380, 1370, 1255, 1215, 1155, 1060, 882, 850		1.36 (s, 3H), 1.42 (s, 3H), 1.71 (dd, 3H, J = 7.5, J = 2.2), 2.64 (s, 1H, OH), 3.96 (m, 2H), 4.08 (dt, 1H, J = 7.5, J = 5.0), 4.58 (dd, 1H, J = 10.0, J = 5.0), 5.36 (dd, 1H, J = 10.3, J = 10.3, J = 2.2), 5.72 (ddq, 1H, J = 10.3, J = 7.5, J = 1.3)	13.36, 25.00, 26.21, 64.93, 66.83, 78.10, 109.02, 128.43, 128.65
12	−5.9 (1.8)			1.36 (s, 3H), 1.45 (s, 3H), 1.73 (dd, 3H, J = 7.5, J = 2.2), 2.68 (d, 1H, J = 3.3, OH), 3.65 (dd, 1H, J = 8.0, J = 5.7), 3.95 (dd, 1H, J = 8.0, J = 7.0), 4.04 (dt, 1H, J = 7.0, J = 5.5), 4.39 (ddd, 1H, J = 10.0, J = 7.0, J = 3.3), 5.36 (ddq, 1H, J = 10.0, J = 10.0, J = 2.2), 5.72 (ddq, 1H, J = 10.0, J = 7.0, J = 1.4)	
16	+15.1 (1.1)	3560–3300, 2985, 2935, 2900, 1760–1700, 1380, 1370, 1270–1000	186 (M^+, 1), 171 (7), 143 (5), 128 (14), 111 (17), 101 (100), 85 (55), 73 (24), 59 (38), 43 (100)	1.37 (s, 3H), 1.45 (s, 3H), 1.65 (m, 6H), 2.32 (s, 1H, OH), 3.93 (d, 2H, J = 6.3), 4.16 (m, 2H), 5.62 (q, J = 6.3, 1H)	12.51, 13.08, 25.26, 26.60, 65.27, 75.91, 77.07, 109.18, 121.91, 134.00
18	−22.8 (2.6)			1.4 (s, 3H), 1.46 (s, 3H), 1.64 (d, 3H, J = 8.0), 1.66 (s, 3H), 2.60 (d, 1H, J = 2.8, OH), 3.65 (dd, 1H, J = 7.5, J = 7.0), 3.92 (dd, 1H, J = 7.5, J = 7.5), 3.90 (d, 1H, J = 7.8), 4.16 (dt, 1H, J = 7.8, J = 7.0), 5.56 (q, 1H, J = 7.5)	11.44, 13.03, 25.35, 26.80, 66.19, 77.56, 78.96, 109.72, 123.73, 134.10

4. Standard Sequence to Convert the Phthalimides into Phthalimido and Amino Acids

4.1. Acetonide Hydrolysis; General Procedure:

The acetonide in MeOH/H_2O (3:1), 20 mL per gram) was treated with CF_3CO_2H (1 mL per 100 mL solvent) for 15 h at 22 °C. The solvent was removed in vacuo and the residue was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the residue was purified by column chromatography to give the 1,2-diol.

4.2. Diol Cleavage; General Procedure:

The diol in CH_2Cl_2 (2 mL per mmol) was treated in portions with $Pb(OAc)_4$ (1 mol equiv.) at 0 °C. After 30 min at 22 °C the mixture was filtered and the filtrate was concentrated in vacuo, diluted with Et_2O and treated with solid K_2CO_3 (1 mol equiv.) for 30 min at 0 °C. The mixture was filtered and concentrated in vacuo to give the crude aldehyde which was used for the next step without purification.

Table 4. Phthalimides Prepared by Mitsunobu Reaction

Phthalimide	$[\alpha]_D^{22}$ ($CHCl_3$) (*c*) mp (°C)	IR (film) ν (cm^{-1})	MS (80 eV) *m/z* (%)	^1H NMR ($CDCl_3$/TMS) (270 MHz), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) (62.5 MHz), δ
24	−63.4 (2) 109–110	1770, 1710, 1385, 1370, 1335, 1150, 1090, 845, 725	302 (0.1), 301 (0.1), 286 (18), 243 (5), 226 (24), 214 (8), 200 (15), 154 (24), 130 (26), 101 (100), 96 (21), 73 (38), 43 (96)	1.29 (s, 3H), 1.37 (s, 3H), 1.77 (s, 3H), 3.85 (dd, 1H, J = 8.8, J = 5.1), 4.20 (dd, 1H, J = 8.8, J = 5.7), 4.64 (d, J = 10.5), 5.09 (d, 1H, J = 1.2), 5.12 (d, 1H, J = 1.1), 5.22 (ddd, 1H, J = 10.5, J = 5.7, J = 5.1), 7.72 (m, 2H), 7.84 (m, 2H)	21.24, 25.20, 26.81, 58.72, 67.61, 72.54, 109.64, 116.01, 123.15, 131.85, 133.77, 140.09, 168.18
25	+46.9 (2.5) 86–87	1065, 720	301 (M^+, 0.2), 289 (18), 243 (5), 226 (24), 214 (8), 200 (15), 154 (24), 130 (26), 101 (100), 96 (21), 73 (38), 43 (96)	1.40 (s, 3H), 1.44 (s, 3H), 1.82 (s, 3H), 3.70 (dd, 1H, J = 8.0, J = 5.3), 4.04 (dd, 1H, J = 8.0, J = 6.3), 4.68 (d, 1H, J = 10.0), 5.12 (s, 1H), 5.21 (m, 1H), 5.24 (s, 1H), 5.24 (s, 1H), 7.74 (m, 2H), 7.84 (m, 2H)	20.60, 25.51, 26.83, 58.56, 67.51, 73.51, 110.19, 115.82, 123.44, 131.60, 134.20, 140.47, 168.03
26	+23.8 (1.7) 131–132	1770, 1715, 1385, 1370, 1080, 1065, 720	286 (5), 226 (8), 200 (12), 182 (5), 160 (9), 148 (5), 130 (8), 101 (100), 73 (14), 43 (35)	1.28 (s, 3H), 1.40 (s, 3H), 1.71 (d, 3H, J = 4.5), 3.86 (dd, 1H, J = 9.0, J = 4.5), 4.04 (dd, 2H, J = 9.0, J = 6.0), 4.68 (m, 1H), 4.82 (ddd, 1H, J = 10.0, J = 6.0, J = 4.5), 5.84 (m, 2H), 7.69 (m, 2H), 7.82 (m, 2H)	17.73, 25.39, 26.82, 57.14, 67.08, 74.21, 109.98, 123.12, 124.66, 132.06, 132.50, 133.72, 167.95
27a	+48.6 (2) 74–75	1705, 1390, 1375, 1060, 720	301 (M^+, 0.3), 286 (14), 271 (4), 243 (6), 226 (16), 213 (6), 174 (28), 160 (13), 148 (23), 130 (25), 124 (11), 97 (17), 79 (26), 72 (100), 43 (61)	1.38 (s, 3H), 1.41 (s, 3H), 1.58 (d, 3H, J = 7.5), 3.53 (dd, 1H, J = 7.5, J = 7.5), 4.04 (dd, 1H, J = 7.5, J = 6.3), 4.50 (dt, 1H, J = 7.5, J = 7.5), 4.96 (ddq, 1H, J = 7.5, J = 7.5, J = 1.3), 5.68 (ddd, J = 15.5, J = 7.5, J = 1.3), 6.22 (ddd, J = 15.5, J = 7.5, J = 1.3), 7.69 (m, 1H), 7.82 (m, 2H)	18.70, 25.80, 26.62, 48.11, 69.30, 76.28, 109.38, 123.13, 130.04, 132.04, 132.58, 133.86, 167.73
27b				1.36 (s, 3H), 1.41 (s, 3H), 1.57 (d, 3H, J = 7.5), 3.61 (dd, 1H, J = 7.5, J = 7.5), 4.11 (dd, 1H, J = 7.5, J = 6.0), 4.52 (dt, 1H, J = 7.5, J = 7.5), 4.96 (dq, J = 7.5, J = 7.5), 5.71 (dd, 1H, J = 16.0, J = 7.5), 6.24 (dd, 1H, J = 16.0), 7.68 (m, 2H), 7.81 (m, 2H)	
28	−27.8 (1.4) 112–113	1710, 1380, 1070, 725	301 (M^+, 0.3), 286 (3), 226 (5), 200 (10), 160 (6), 130 (8), 101 (100), 73 (17), 43 (60)	1.36 (s, 3H), 1.44 (s, 3H), 1.70 (d, 3H, J = 7.0), 3.74 (dd, 1H, J = 8.5, J = 5.3), 3.98 (dd, 1H, J = 8.5, J = 5.3), 4.76 (m, 2H), 5.78 (dq, 1H, J = 15.8, J = 6.3), 6.00 (ddq, 1H, J = 15.3, J = 8.0, J = 1.3), 7.73 (m, 2H), 7.84 (m, 2H)	17.78, 25.40, 26.80, 56.15, 67.16, 75.26, 110.08, 123.33, 125.61, 131.01, 131.79, 134.05, 167.84
29	+48.6 (2) 98–99	1765, 1710, 1385, 1375, 1065, 720	302 (0.1), 286 (18), 226 (18), 214 (8), 200 (30), 186 (11), 160 (15), 148 (11), 130 (16), 101 (100), 73 (26), 43 (70)	1.28 (s, 3H), 1.44 (s, 3H), 1.77 (d, 3H, J = 5.0), 3.78 (dd, 1H, J = 8.8, J = 4.5), 4.08 (dd, 1H, J = 8.8, J = 6.3), 4.84 (ddd, 1H, J = 10.0, J = 6.3, J = 4.5), 5.09 (dd, 1H, J = 10.0, J = 10.0), 5.80 (m, 2H), 7.70 (m, 2H), 7.83 (m, 2H)	13.48, 25.35, 26.87, 50.95, 66.84, 74.71, 100.00, 123.09, 123.83, 130.90, 132.04, 133.69, 167.88
31a	oil			1.39 (s, 3H), 1.43 (s, 3H), 1.66 (d, 3H, J = 7.5), 1.78 (d, 3H, J = 1.3), 3.52 (dd, 1H, J = 7.5, J = 7.5), 4.08 (dd, 1H, J = 7.5, J = 6.3), 4.81 (dt, 1H, J = 7.5, J = 6.3), 4.87 (q, 1H, J = 7.5), 5.54 (d, 1H), 7.71 (m, 2H), 7.82 (m, 2H)	
31a (1,2-diol)	−57.4 (1.8) 96–98	3480, 3450, 1770, 1700, 1390, 1365, 1335, 1175, 1070, 1045, 990, 880, 725		1.62 (d, 3H, J = 8.0), 1.74 (s, 3H), 2.96 (dd, 1H, J = 5.5), 3.26 (d, 1H, J = 3.8, OH), 3.56 (m, 2H), 4.53 (m, 1H, J = 3.8), 4.81 (q, 1H, J = 7.5), 5.52 (d, 1H, J = 8.0), 7.70 (m, 2H), 7.82 (m, 2H)	14.89, 16.14, 51.60, 66.06, 69.28, 123.17, 125.49, 131.77, 133.96, 137.36, 168.24
31b	oil			1.42 (s, 3H), 1.44 (s, 3H), 1.64 (d, 3H, J = 7.3), 1.72 (s, 3H), 3.62 (dd, 1H, J = 8.0, J = 8.0), 3.72 (dd, 1H, J = 8.0, J = 8.0), 4.84 (m, 2H), 5.61 (d, 1H, J = 8.0), 7.72 (m, 2H), 7.84 (m, 2H)	
31b (1,2-diol)	99–100			1.60 (d, 3H, J = 7.0), 1.72 (s, 3H), 3.00 (s, 2H), 3.60 (m, 2H), 4.56 (m, 1H), 4.81 (q, 1H, J = 7.0), 5.54 (d, 1H, J = 8.0), 7.72 (m, 2H), 7.82 (m, 2H)	

Table 4. (continued)

Phthalimide	$[\alpha]_D^{22}$ ($CHCl_3$) (*c*) mp (°C)	IR (film) ν (cm^{-1})	MS (80 eV) *m/z* (%)	^1H NMR ($CDCl_3$/TMS) (270 MHz), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) (62.5 MHz), δ
32a	−28.3 (2.2)	3270, 1715, 1380, 1080, 720	285 (M^+, 3), 270 (22), 210 (15), 198 (8), 148 (5), 130 (8), 101 (100), 43 (50)	1.36 (s, 3H), 1.44 (s, 3H), 2.44 (d, 1H, J = 2.4), 3.92 (dd, 1H, J = 8.7, J = 4.9), 4.00 (dd, 1H, J = 8.7, J = 6.0), 4.80 (ddd, 1H, J = 8.0, J = 6.0, J = 4.9), 5.09 (dd, 1H, J = 8.0, J = 2.4), 7.76 (m, 2H), 7.88 (m, 2H)	25.04, 26.75, 44.27, 66.52, 73.17, 75.44, 77.68, 110.63, 123.66, 131.54, 134.36, 166.81
32b	−4.1 (0.9)	1720, 1385, 1075, 715	299 (M^+, 2), 284 (6), 241 (9), 224 (8), 212 (40), 198 (6), 171 (3), 160 (3), 152 (3), 130 (5), 101 (100), 73 (12)	1.28 (s, 3H), 1.42 (s, 3H), 1.83 (d, 3H, J = 2.5), 4.16 (dd, 2H, J = 5.0), 4.84 (ddd, 1H, J = 10.0, J = 5.0, J = 4.5), 5.00 (dq, 1H, J = 10.0, J = 2.5), 7.71 (m, 2H), 7.91 (m, 2H)	3.52, 25.36, 26.90, 45.90, 67.32, 72.66, 74.86, 81.50, 110.58, 123.39, 132.00, 133.94, 167.17
33a	+5.2 (1.5) oil	3245, 3000, 1725, 1385, 715	285 (M^+, 5), 269 (28), 211 (6), 174 (15), 161 (23), 129 (9), 101 (100), 43 (40)	1.30 (s, 3H), 1.42 (s, 3H), 2.40 (d, 1H, J = 2.7), 4.20 (d, 2H, J = 5.1), 4.84 (t, 1H, J = 5.1), 4.88 (t, 1H, J = 5.1), 5.00 (d, 1H, J = 2.7), 5.04 (d, 1H, J = 2.7), 7.74 (m, 2H), 7.88 (m, 2H)	25.03, 26.61, 44.70, 66.83, 73.44, 74.32, 77.01, 110.50, 123.25, 131.56, 133.86, 166.65
33b	−9.9 (0.9) oil	1720, 1380	299 (M^+, 1), 284 (6), 241 (8), 224 (7), 212 (4), 198 (6), 171 (3), 147 (43), 130 (5), 101 (100), 76 (45), 50 (23)	1.36 (s, 3H), 1.39 (s, 3H), 1.86 (d, 3H, J = 2.5), 3.92 (dd, 1H, J = 8.8, J = 5.0), 4.00 (dd, 1H, J = 8.8, J = 6.3), 4.79 (ddd, 1H, J = 7.5, J = 6.3, J = 5.0), 5.07 (dq, J = 7.5, J = 2.5), 7.72 (m, 2H), 7.88 (m, 2H)	3.61, 25.04, 26.63, 44.71, 66.52, 72.96, 75.88, 81.04, 110.33, 123.43, 131.60, 132.62, 134.10, 166.98
(*Z*)-**38**	170–172	1710, 1385, 1370, 1360, 1330, 1085, 1065, 725	315 (M^+, 0.1), 300 (1), 284 (0.1), 255 (0.3), 240 (2), 215 (5), 168 (3), 160 (5), 148 (3), 130 (6), 110 (4), 101 (100), 93 (5), 76 (7), 73 (10), 43 (39)	1.32 (s, 3H), 1.42 (s, 3H), 1.80 (d, 3H, J = 6.3), 1.83 (s, 3H), 3.75 (dd, 1H, J = 8.8, J = 4.8), 4.08 (dd, 1H, J = 8.8, J = 5.3), 5.20 (d, 1H, J = 10.0), 5.33 (ddd, 1H, J = 10.0, J = 6.3, J = 4.8), 5.51 (q, 1H, J = 6.3)	

4.3. Oxidation of the Aldehyde to the Carboxylic Acid; General Procedure:

$Na_2Cr_2O_7$ (2 g) in H_2O (12 mL) was treated under ice cooling with H_2SO_4 (3 mL) to give Jones' reagent. The aldehyde in acetone (2 mL per mmol) was treated dropwise with Jones' reagent at 10 °C until the orange color persisted. The solvent was evaporated and the aqueous mixture was extracted with Et_2O continually over 5 h. The Et_2O was evaporated in vacuo and the residue was purified by column chromatography to give the phthalimido acids.

4.4. Hydrazinolysis; General Procedure:

The phthalimido acids were dissolved in degassed EtOH (2 mL per mmol) and refluxed with hydrazine hydrate (80%, 1.3 mol equiv.) for 2 h. Acetone was added and the mixture was refluxed for another 15 min, concentrated in vacuo and diluted with H_2O, filtered and extracted with CH_2Cl_2. The H_2O was concentrated, filtered and concentrated further to ca. 1 mL. Acetone was added, until the amino acid crystallized. For analytical data of the phthalimido and amino acids see Table 2 and 5.

5. (*S*)-3-Methyl-2-phthalimido-(3*E*)-pentane-1,2-diol (36):

(R)-2-Benzyl-3-methyl-(3E)-pentene-1,2-diol (**34**):

Benzyl ether **17** was converted into alcohol **34** by the standard sequence described in section 1.4. $[\alpha]_D^{22} = -70.4°C$ (c = 2.1, $CHCl_3$).

^1H NMR ($CDCl_3$): δ = 1.61 (d, 3H, J = 1.4 Hz), 1.66 (dd, 3H, J = 7.5 Hz, J = 1.4 Hz), 2.20 (s, 1H, OH), 3.48 (dd, 1H, J = 10.8 Hz, J = 5.3 Hz), 3.63 (dd, 1H, J = 10.8 Hz, J = 8.0 Hz), 3.85 (dd, 1H, J = 8.0 Hz, J = 5.3 Hz), 4.26 (d, 1H, J = 12.2 Hz), 4.52 (d, 1H, J = 12.2 Hz), 5.58 (dq, 1H, J = 7.5 Hz, J = 1.4 Hz), 7.32 (m, 5H).

^{13}C NMR ($CDCl_3$): δ = 11.37, 13.06, 64.37, 70.02, 85.36, 124.34, 127.50, 127.73, 128.29, 132.48, 138.36.

(S)-3-Methyl-2-phthalimido-(3E)-pentene-1,2-diol (**36**):

Alcohol **34** (7.0 g, 34 mmol) in ethyl diisopropylamine (50 mL) was treated at 0 °C with methoxymethyl chloride (2.9 g, 51 mmol). The mixture was stirred at 22 °C for 15 h, concentrated in vacuo, diluted with H_2O and extracted with Et_2O. The organic layer was dried, concentrated and purified by column chromatography (EtOAc/hexanes 1:3) to give the MOM ether (8.1 g, 95%).

The MOM ether (5.0 g, 20 mmol) in Et_2O (80 mL) was cooled to −78 °C and NH_3 was condensed into the mixture. Na was added in small pieces until a blue solution was obtained. After 15 min NH_4Cl was added and the reaction was worked up as described in section 1.4 to give alcohol **35** (3.0 g, 95%), which was submitted to the general Mitsunobu protocol described in section 3. The phthalimide was obtained after column chromatography (EtOAc/hexanes 1:2) as a colorless oil (5.4 g, 70%), which was treated (3.0 g, 10.5 mmol) in MeOH (90 mL) with conc. HCl (1 mL) at 50 °C for 15 h. The mixture was neutralized with solid K_2CO_3 and concentrated in vacuo to give, after chromatography (EtOAc/hexanes 1:2), the amino alcohol **36** (1.8 g, 70%), $[\alpha]_D^{22} = -29.6°C$ (c = 1, $CHCl_3$).

^1H NMR ($CDCl_3$): δ = 1.59 (d, 3H, J = 7.5 Hz), 1.68 (s, 3H), 3.80 (s, 1H, OH), 4.00 (dd, 1H, J = 10.0 Hz, J = 4.5 Hz), 4.39 (dd, 1H, J = 10.0 Hz, J = 10.0 Hz), 4.77 (dd, 1H, J = 10.0 Hz, J = 4.5 Hz), 5.46 (dq, 1H, J = 7.5 Hz, J = 1.4 Hz), 7.65 (m, 1H), 7.76 (m, 2H).

^{13}C NMR ($CDCl_3$): δ = 12.85, 13.65, 59.42, 60.26, 122.07, 122.75, 130.39, 131.32, 133.57, 168.55.

IR (KBr, film): ν = 1775, 1730–1680 (br), 1390, 1360, 1335, 720 cm^{-1}.

6. (2*S*,3*R*)-1,2-*O*-Isopropylidene-3-phthalimido-(4*Z*)-hexene-1,2-diol (29):

The Lindlar hydrogenation of **32b** was performed as described in section 1.2.

7. (2*S*,3*R*)-1,2-*O*-Isopropylidene-4-methyl-3-phthalimidohexene-1,2-diol (38):

(2*S*,3*R*)-1,2-*O*-Isopropylidene-4-methyl-3-phthalimido-4-pentene-

Table 5. α-Phthalimido and Amino Acids

Acid	$[\alpha]_D^{22}$ ($CHCl_3$) (*c*) mp (°C)	IR (film) *v* (cm^{-1})	MS (80 eV) *m/z* (%)	^1H NMR ($CDCl_3$/TMS) (270 MHz), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) (62.5 MHz), δ
(*R*)-**1a**	see Table 2	2980, 1600, 1510, 1405, 1350, 775, 570		1.78 (s, 3H), 4.27 (s, 1H), 5.22 (s, 1H), 5.24 (s, 1H)	17.58, 60.35, 118.88, 137.86, 172.80
(*R*)-**1b**	see Table 2	3200–2500, 1670–1550, 1525, 1495, 1415, 1390, 1370, 1355, 1340, 790, 720	116 (0.2), 97 (0.6), 82 (0.3), 70 (100), 53 (8), 43 (25)	1.78 (dd, J = 7.5, J = 2.2), 4.61 (dd, 1H, J = 10.8, J = 1.4), 5.46 (ddq, 1H, J = 10.8, J = 10.8, J = 2.2), 6.04 (ddq, 1H, J = 10.8, J = 7.5, J = 1.4)	12.97, 51.91, 122.40, 134.08, 173.58
(*S*)-**1c**	see Table 2	3200–2800, 2260, 1500, 1520, 1395, 1375, 1350, 960	116 (0.5), 100 (1), 70 (100), 53 (14), 43 (56)	1.76 (d, 3H, J = 7.0), 4.20 (d, 1H, J = 8.8), 5.56 (ddd, 1H, J = 15.3, J = 8.8, J = 1.3), 6.00 (dq, 1H, J = 15.3, J = 7.0)	16.20, 55.70, 121.99, 133.32, 171.94
(*R*)-**39a**	mp 245	1775, 1710, 1610, 1465, 1380, 1330, 1110, 905, 720	245 (M^+, 10), 227 (27), 200 (100), 182 (30), 160 (19), 148 (31), 130 (44), 104 (49), 76 (30), 43 (44)	1.66 (s, 3H), 4.84 (s, 3H), 4.90 (s, 1H), 5.14 (s, 1H), 5.14 (s, 1H), 5.26 (s, 1H, COOH), 7.64 (m, 2H), 7.76 (m, 2H)	20.67, 58.86, 115.98, 123.54, 131.74, 134.03, 139.34, 168.19, 173.88
(*R*)-**39c**	+19.4 (0.7)	1755–1690, 1385, 715	245 (M^+, 2), 227 (21), 200 (100), 182 (74), 160 (31), 130 (39), 104 (50), 76 (45), 53 (29)	1.73 (dd, 3H, J = 6.0, J = 1.9), 5.44 (d, 1H, J = 8.1), 5.84 (dq, 1H, J = 16.0, J = 6.0), 6.04 (ddq, 1H, J = 16.0, J = 8.1, J = 1.9), 7.73 (m, 2H), 7.88 (m, 2H), 10.62 (br s, 1H, COOH)	17.65, 53.57, 122.38, 123.58, 131.80, 133.07, 134.18, 166.96, 173.96
40	+30.0 (0.1)			1.67 (d, 3H, J = 7.0), 1.84 (s, 3H), 5.48 (q, 1H, J = 7.0), 5.71 (s, 1H), 5.71 (s, 1H), 7.68 (m, 2H), 7.80 (m, 2H)	

Table 6. Hydroxy Esters **49a–c**

Compound	$[\alpha]_D^{22}$ ($CHCl_3$) (*c*)	IR (film) *v* (cm^{-1})	MS (80 eV) *m/z* (%)	^1H NMR ($CDCl_3$/TMS) (270 MHz), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) (62.5 MHz), δ
49a	+24.0 (2.1)	3450, 2985, 2940, 1720, 1705, 1660, 1370, 1305, 1275, 1180, 1150, 1050, 980	129 (4), 115 (7), 101 (46), 99 (24), 83 (12), 73 (64), 71 (21), 69 (10), 55 (42), 45 (18), 43 (100), 41 (14), 39 (11)	1.32 (t, 3H, J = 7.5), 1.28 (d, 3H, J = 7.0), 3.04 (s, 1H, OH), 4.20 (dq, 2H, J = 7.5, J = 1.1), 4.49 (dq, 1H, J = 7.0, J = 5.5), 6.02 (dd, 1H, J = 16.3, J = 1.1), 6.96 (dd, 1H, J = 16.3, J = 5.5)	14.08, 22.51, 60.40, 66.90, 119.41, 151.19, 166.71
49b	−8.5 (1)	3550–3300, 2980, 2930, 1730–1680, 1655, 1465, 1445, 1390, 1370, 1325–1225, 1180–1110, 1080–1045, 1035, 750	159 (0.5), 143 (6), 129 (9), 115 (74), 97 (71), 87 (75), 69 (71), 43 (100)	1.32 (t, 3H, J = 7.5), 1.32 (d, 3H, J = 7.0), 1.86 (d, 3H, J = 2.0), 2.81 (s, 1H, OH), 4.19 (q, 2H, J = 7.5), 4.65 (dq, 1H, J = 8.0, J = 7.0), 6.68 (dq, 1H, J = 8.0, J = 2.0)	12.36, 14.01, 22.35, 60.63, 64.55, 127.28, 144.28, 168.03
49c	+4.1 (2.5)	2985, 1715, 1700, 1655, 1370, 1225, 1160, 1110, 1050, 1035	158 (M^+, 1), 140 (14), 129 (3), 115 (66), 97 (22), 87 (67), 69 (53), 57 (8), 43 (100)	1.23 (t, 3H, J = 7.5), 1.32 (d, 3H, J = 7.0), 2.12 (d, 3H, J = 1.9), 2.52 (s, 1H, OH), 4.16 (q, 2H, J = 7.5), 4.26 (q, 1H, J = 7.0), 5.95 (s, 1H)	14.16, 14.80, 21.58, 59.69, 72.15, 113.87, 161.37, 167.05

1,2-diol **(24)** (16.0 g, 53 mmol) in CH_2Cl_2 (150 mL) was ozonized at −78 °C until a blue solution was obtained. PPh_3 (20.9 g, 80 mmol) was added and the solution was stirred at 22 °C for 1 h. The solvent was removed in vacuo and the residue was chromatographed (EtOAc/hexanes 1:2) to give ketone **37** (13.7 g, 85%). This material (8.0 g, 26 mmol) in THF (100 mL) was treated at −78 °C with triphenylmethylene phosphorane (1.5 mol equiv.). The mixture was warmed to 22 °C and the solvent was removed in vacuo. The residue was diluted with H_2O and extracted with Et_2O. The organic layer was dried ($MgSO_4$) concentrated and chromatographed to give **38** as a 1:1 mixture of *E*/*Z*-isomers (2.1 g, 24%). (*Z*)-**38** crystallized from the oily mixture. For analytical data see Table 4.

8. Horner and Wittig Olefinations (Scheme 11); General Procedure:

These olefinations were performed under standard conditions. Horner olefination: 1.3 mol equiv. phosphono ester and NaH in THF, 15 h at 22 °C. Wittig reaction: 1.3 mol equiv. phosphorane in THF, 10 h at 22 °C. For analytical data of the enoates **49a–c** see Table 6. Mitsunobu reactions of **49a–c** were performed as described in Section 3. The yields were 80–90% (Table 7).

Table 7. γ-Phthalimido- and Amino Acids **50/51**

Compound	$[\alpha]_D^{22}$ (*c*, solvent) mp	IR (film) ν (cm^{-1})	MS (80 eV) *m/z* (%)	^1H NMR ($CDCl_3$/TMS) (270 MHz), δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) (62.5 MHz), δ
50a	+15.5 (1.6, $CHCl_3$) 172–173	1700, 1385, 715	245 (M^+, 6), 227 (100), 212 (13), 199 (68), 184 (30), 174 (41), 160 (21), 148 (53), 130 (94), 104 (76), 98 (21), 83 (72), 76 (84), 66 (26), 55 (28), 50 (53), 43 (29)	1.64 (d, 3H, *J* = 7.5), 5.11 (ddq, 1H, *J* = 7.5, *J* = 6.0, *J* = 2.0), 5.91 (dd, 1H, *J* = 16.2, *J* = 2.0), 7.25 (dd, 1H, *J* = 16.2, *J* = 6.0), 7.73 (m, 2H), 7.84 (m, 2H), 10.08 (br s, 1H, COOH)	17.57, 46.79, 121.54, 123.40, 131.83, 134.16, 148.24, 167.51, 170.88
50b	+35.2 (2.1, $CHCl_3$) 112–114	1710, 1692, 1385, 720	259 (M^+, 2), 241 (100), 226 (12), 213 (33), 198 (33), 185 (33), 174 (12), 160 (8), 148 (30), 130 (40), 104 (36), 97 (30), 76 (38), 50 (17)	1.62 (d, 3H, *J* = 7.5), 1.94 (d, 3H), 5.24 (dq, 1H, *J* = 9.0, *J* = 7.5), 7.28 (dq, 1H, *J* = 9.0, *J* = 2.0), 7.71 (m, 2H), 7.84 (m, 2H), 9.93 (br s, 1H, COOH)	12.26, 18.50, 44.29, 123.30, 129.28, 131.90, 134.02, 141.06, 167.63, 172.73
50c	+45 (1.2, $CHCl_3$) 176–172	1715, 1385	(CI, 160 eV, isobutane, 150 °C): 260.3 (100), 242.2 (99), 89.1 (15)	1.68 (d, 3H, *J* = 7.3), 2.18 (s, 3H), 4.92 (q, 1H, *J* = 7.3), 5.93 (s, 1H), 7.78 (m, 2H), 7.88 (m, 2H)	15.98, 16.81, 52.16, 116.27, 123.38, 131.71, 134.14, 158.01, 167.85, 171.39
51a	+2.5 (1.1, D_2O) +5.8 (1.1, 5M HCl)	3100–2500, 1660, 1635, 1260, 720	287 (M^+, 0.5), 272 (2), 241 (100), 226 (10), 213 (48), 198 (24), 185 (35), 174 (67), 160 (12), 141 (12), 130 (39), 111 (15), 104 (27), 76 (34), 67 (18), 50 (16)	(in D_2O): 1.44 (dd, 3H, *J* = 6.8, *J* = 1.4), 4.09 (dq, 1H, *J* = 6.8, *J* = 6.5), 6.05 (d, 1H, *J* = 16.3), 6.52 (ddd, 1H, *J* = 16.3, *J* = 6.5, *J* = 1.4)	(in D_2O): 18.14, 48.12, 130.25, 137.89, 173.75
51b	−5.1 (1.5, H_2O) >270 (subl.)	3100–2500, 1665, 1620, 1540, 1380, 1220, 835, 775	130 (1), 129 (3), 128 (4), 114 (90), 111 (67), 96 (100), 84 (99), 68 (68), 53 (62), 45 (17)	(in D_2O): 1.36 (d, 3H, *J* = 7.5), 1.83 (d, 3H, *J* = 1.5), 4.26 (dq, *J* = 9.8, *J* = 7.5), 6.12 (dd, *J* = 9.8, *J* = 1.3)	(in D_2O): 13.64, 18.55, 45.92, 130.24, 138.85, 176.49
51c	−5.4 (1, H_2O) 241–245	2975, 2930, 2850, 2790, 2740, 2655, 2630, 2540, 1655, 1625, 1555, 1525, 1400, 1380, 1360, 1335, 1310, 1100, 760	287 (M^+, 0.5), 241 (68), 231 (42), 198 (4), 185 (8), 174 (20), 160 (7), 149 (12), 130 (37), 112 (10), 104 (18), 91 (100), 76 (21), 65 (16), 43 (51)	(in D_2O): 1.45 (d, 3H, *J* = 8.0), 1.92 (s, 3H), 3.91 (q, 1H, *J* = 7.5), 5.93 (s, 1H)	(in D_2O): 16.56, 20.00, 55.70, 127.63, 142.67, 178.24

(1) Reviews:
Duthaler, R.O. *Tetrahedron* **1994**, *50*, 1539.
Williams, R.M. *Synthesis of Optically Active α-Amino Acid*; Pergamon: Toronto, 1989.
Altenbach, H.J. In Mulzer, J.; Altenbach, H.J.; Braun, M.; Krohn, K.; Reissig, H.U. *Highlights in Organic Synthesis*; VCH: Weinheim, 1991; p 300.
Chemistry and Biochemistry of the Amino Acids; Baretti, G.C., Ed.; Chapman and Hall: N.Y., 1985.

(2) Rando, R.R. *Synthesis* **1975**, *185*, 320.
Rando, R.R. *Acc. Chem. Res.* **1975**, *8*, 281.
Rando, R.R. *Biochemistry* **1974**, *13*, 3859.

(3) (a) Greenlee, W.L. *J. Org. Chem.* **1984**, *49*, 2632.
(b) Castelhano, A.L.; Horne, S.; Billedeau, R.; Krantz, A. *Tetrahedron Lett.* **1986**, *27*, 2435.
(c) Baldwin, J.E.; Haber, S.B.; Hoskins, C.; Kruse, L.I. *J. Org. Chem.* **1977**, *42*, 1239.
(d) Johnston, M.; Raines, R.; Chang, M.; Esaki, N.; Soda, K.; Walsh, C. *Biochemistry* **1981**, *20*, 4325.
(e) Fitzner, J.N.; Pratt, D.V.; Hopkins, P.B. *Tetrahedron Lett.* **1985**, *26*, 1959.
(f) Heinzer, F.; Bellus, D. *Helv. Chim. Acta* **1980**, *64*, 2279.
(g) Angst, C. *Pure Appl. Chem.* **1987**, *59*, 373.
(h) Dowd, P.; Kaufman, C.; Kaufman, P. *J. Org. Chem.* **1985**, *50*, 882.
(i) Agouridas, K.; Girodeau, J.M.; Pineau, R. *Tetrahedron Lett.* **1985**, *26*, 3115.
(j) Bicknell, A.J.; Burton, G.; Elder, J.S. *Tetrahedron Lett.* **1988**, *29*, 3361.
(k) Chari, R.V.J.; Wemple, J. *Tetrahedron Lett.* **1979**, 111.
(l) Ben-Ishahi, D.; Moshenberg, R.; Altman, J. *Tetrahedron* **1977**, *33*, 1533.

(4) (a) Afzali-Ardakani, A.; Rapoport, H. *J. Org. Chem.* **1980**, *45* 4817.
(b) Hanessian, S.; Sahoo, S.P. *Tetrahedron Lett.* **1984**, *25*, 1425.
(c) Barton, D.H.R.; Crich, D.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1985**, *41*, 4347.
(d) Mulzer, J.; Angermann, A.; Seilz, C. *J. Org. Chem.* **1986**, *51*, 5294.
(e) Schöllkopf, U.; Nozulak, J.; Groth, U. *Tetrahedron* **1984**, *40*, 1409.
(f) Williams, R.M.; Zhai, W. *Tetrahedron* **1985**, *44*, 5425.
(g) Duthaler, R.O. *Angew. Chem.* **1991**, *103*, 729.
(h) Griesbeck, A.G.; Mauder, H. *Angew. Chem.* **1992**, *104*, 97.

(5) Hughes, D.L. *Org. React.* **1992**, *42*, 335.
S_N2' Mitsunobu reactions with other nucleophiles see: Charette, A.B.; Côté, B. *Tetrahedron Lett.* **1993**, *34*, 6833.
Farina, V. *Tetrahedron Lett.* **1989**, *30*, 6645.
Danishefsky, S.; Berman, E.M.; Ciufolini, M.; Etheredge, S.J.; Segmuller, B.E. *J. Am. Chem. Soc.* **1985**, *107*, 3891.
Lumin S.; Yadagiri, P.; Falck, J.R. *Tetrahedron Lett.* **1988**, *29*, 4237.
Burke, S.D.; Pacofsky, G.J. *Tetrahedron Lett.* **1986**, *27*, 445.

(6) Mulzer, J.; Greifenberg, S.; Beckstett, A.; Gottwald, M. *Liebigs Ann. Chem.* **1992**, 1131.

(7) Mulzer, J.; Funk, G.; Bilow, J. unpublished results.

(8) Hoffmann, R.W.; Zeiss, H.J.; Enderfelder, A. *Carbohydr. Res.* **1983**, *123*, 320.
Roush, W.R.; Walts, A.E.; Hoong, K.L. *J. Am. Chem. Soc.* **1985**, *107*, 8186.

(9) Levene, P.A.; Haller, H.L. *J. Biol. Chem.* **1928**, *77*, 555.

(10) Camp, D.; Jenkins, I.D. *J. Org. Chem.* **1989**, *54*, 3045.

(11) Magid, R.M. *Tetrahedron* **1980**, *36*, 1901.

Stohrer, W.D. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 613.
Anti S_N2' for Cuprates see: Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864.
(12) Bentley, T.W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7658.
(13) Frank, H.; Nicholson, G.J.; Bayer, E. *J. Chromatogr. Sci.* **1977**, *15*, 174.
(14) Brandlänge, S., Lindquist, B. *Acta Chem. Scand.* **1985**, *B39*, 589.
(15) Balenovic, D.; Cerar, D. *J. Chem. Soc.* **1955**, 1631.
Honore, T.; Hjieds, H.; Krogsgaard-Larsen, P.; Christiansen, T.R. *Eur. J. Med. Chem.* **1078**, *13*, 429.
(16) Baer, E. *Biochem. Prep.* **1985**, *2*, 31.
(17) Levene, P.A.; Haller, H.L. *J. Biol. Chem.* **1928**, *77*, 555.