Phosphinic Acid Analogues of GABA. 2. Selective, Orally Active $GABA_B$ Antagonists†

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In 1987, 25 years after the synthesis of the potent and selective $GABA_B$ agonist baclofen (**1**), Kerr et al.[5] described the first $GABA_B$ antagonist phaclofen **2**. However, phaclofen and structurally similar derivatives **3**–**5** did not cross the blood–brain barrier and hence were inactive *in vivo* as central nervous system agents. As a consequence, the therapeutic potential of $GABA_B$ antagonists remained unclear. In exploring GABA and baclofen derivatives by replacing the carboxylic acid residue with various phosphinic acid groups, we discovered more potent and water soluble $GABA_B$ antagonists. Electrophysiological experiments *in vivo* demonstrated that some of the new compounds were capable of penetrating the blood–brain barrier after oral administration. Neurotransmitter release experiments showed that they interacted with several presynaptic $GABA_B$ receptor subtypes, enhancing the release of GABA, glutamate, aspartate, and somatostatin. The new $GABA_B$ antagonists interacted also with postsynaptic $GABA_B$ receptors, as they blocked late inhibitory postsynaptic potentials. They facilitated the induction of long-term potentiation *in vitro* and *in vivo*, suggesting potential cognition enhancing effects. Fifteen compounds were investigated in various memory and learning paradigms in rodents. Although several compounds were found to be active, only **10** reversed the age-related deficits of old rats in a multiple-trial one-way active avoidance test after chronic treatment. The cognition facilitating effects of **10** were confirmed in learning experiments in Rhesus monkeys. The novel $GABA_B$ antagonists showed also protective effects in various animal models of absence epilepsy.

Introduction

The most abundant inhibitory neurotransmitter in the mammalian brain, GABA (γ-aminobutyric acid)[1] interacts with two types of receptors designated $GABA_A$ and $GABA_B$ by Hill and Bowery in 1981.[2,3] They reported that $GABA_B$ receptors are stereoselectively activated by the (*R*)-(−)-enantiomer of the antispastic agent and muscle relaxant baclofen 1 (Figure 1),[4] a lipophilic derivative of GABA first synthesized in 1962. Surprisingly, it took 25 years until the first selective $GABA_B$ antagonist, the phosphonic acid analogue of **1**, phaclofen **2** (Figure 1), was described by Kerr et al.[5] Two sulfonic acid derivatives of baclofen, saclofen[6,7] (**3**, Figure 1) and 2-hydroxy-saclofen[8–10] (**4**, Figure 1), were more potent than **2** by factors of 5 and 10, respectively, showing comparable affinities to 3-benzo[*b*]furan-2-yl-GABA derivatives **5** (Figure 1) reported by Berthelot et al.[11–13]

None of these compounds, however, was able to penetrate the blood–brain barrier. Therefore it was not possible to investigate the pharmacology of selective $GABA_B$ antagonists under *in vivo* conditions or to explore their therapeutic potential.

A new series of orally active $GABA_B$ receptor antagonists was discovered during the course of a medicinal chemistry program designed to improve upon the pharmacology of substituted (3-aminopropyl)phosphinic acids, some of which were very potent $GABA_B$ agonists.[14] Electrophysiological experiments in hippocampal pyramidal neurons revealed that (3-aminopropyl)phosphinic acid (**6**, CGP27492, Figure 1) and (3-aminopropyl)-methylphosphinic acid (**7**, CGP35024, identical to SK&F97541, Figure 1) displayed properties of $GABA_B$ agonists, whereas all higher homologues starting from (3-aminopropyl)ethylphosphinic acid (**8**, CGP36216, Figure 1) showed effects of $GABA_B$ antagonists, i.e., they antagonized various biological effects of baclofen. An example of the effects of the new $GABA_B$ antagonists is shown in Figure 2. A 10 μM solution of baclofen caused inhibition of cell firing of rat hippocampal neurons. This effect was fully and reversibly antagonized by a 30 μM solution of **9** (CGP35348, Figure 1). Further electrophysiological studies *in vivo* showed that some of the novel $GABA_B$ antagonists were able to penetrate the blood brain barrier after oral administration, e.g., (3-aminopropyl)*n*-butylphosphinic acid (**10**, CGP36742, Figure 1).

These findings prompted us to investigate the structure–activity relationships of this class of compounds

† W. Froestl would like to dedicate this work to his highly respected teacher, Prof. Josef Fried, The University of Chicago, on the occasion of his 80th birthday.

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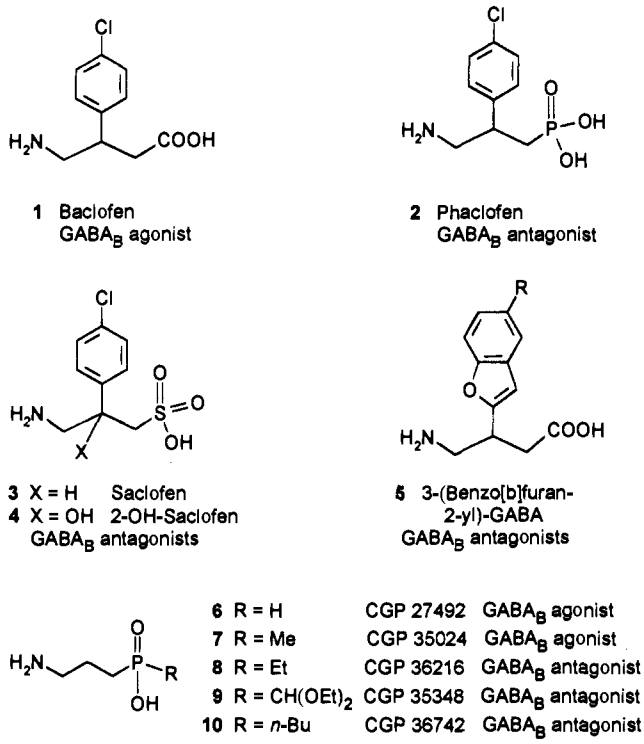


Figure 1. Structures of GABA$_B$ agonists and GABA$_B$ antagonists.

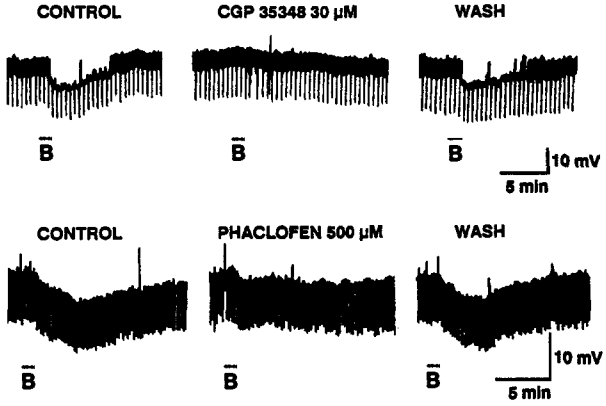


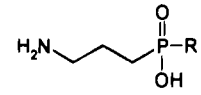
Figure 2. Intracellular recordings from two different rat CA1 pyramidal neurons *in vitro*. Bath application of 10 μM solutions of baclofen (B) induced hyperpolarization of the membrane potential in both neurons. This effect was attenuated by 30 μM solutions of **9** and 500 μM solutions of **2** in a reversible manner (reproduced with permission of authors and editor of ref 28).

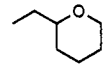
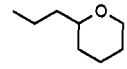
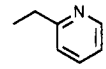
in a systematic way and to explore the *in vivo* pharmacology and therapeutic potential of the new GABA$_B$ antagonists.

Chemistry

The syntheses of phosphinic acid derivatives of GABA without substituents in the 3-aminopropyl side chain (Table 1) started from two valuable reagents, either ethyl (diethoxmethyl)phosphinate **11**[15] or its higher homologue ethyl (1,1-diethoxyethyl)phospinate **12**.[14,16] The acetal or ketal group, respectively, are protecting groups for the P–H bond. P–C bond formation can be achieved at the site of the P–H bond of **11** or **12** under a variety of reaction conditions after which the acetal or ketal groups are cleaved. The newly generated P–H bond permits further functionalization, thus allowing the syntheses of unsymmetrically substituted phosphinic acids.

Table 1. Inhibition of Binding of [^{3}H]CGP27492 to GABA$_B$ Receptors of Rat Cortex and Enhancement of Electrically induced Release of [^{3}H]GABA from Rat Cortical Slices (Stimulation Frequency 2 Hz)



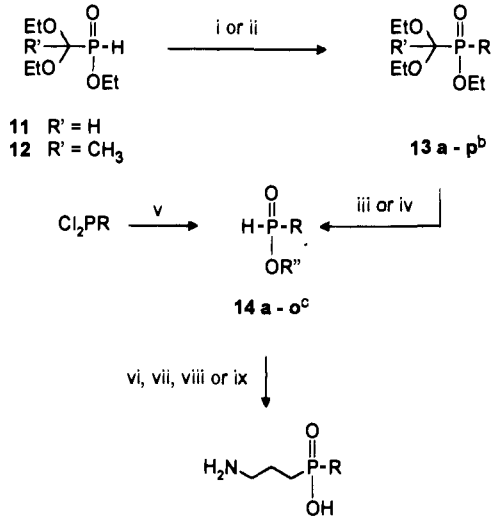
compd	R	binding IC_{50} (μM)	GABA release EC_{150} (μM)
6	H	0.005	agonist
7	CH_3	0.016	agonist
8	C_2H_5	2	118
9	$CH(OEt)_2$	27	30
10	*n*-C_4H_9	38	38
15	*n*-C_3H_7	16	30
16	$CF_2(CH_2)_2CH_3$	22	115
17	*i*-C_4H_9	14	98
18	*t*-C_4H_9	73	nt[a]
19	$CH_2C_3H_5$	37	53
20	*n*-C_6H_{13}	20	14
21	C_6H_5	126	nt
22	$CH_2C_6H_5$	10	5
23	$CH_2C_6H_4F$	52%[b]	10
24	$CH_2C_6H_{11}$	4	3
25	$(CH_2)_2C_6H_5$	10	60%[c]
26	$(CH_2)_2C_6H_{11}$	2	13
27		34	89
28		39	144
29		32	12
41		2	30
32		6	30
33	CH(OH)-*n*-C_3H_7	18	44%[c]
34	$CH(OH)C_6H_5$	8	10%[c]
35	$CH_2CH(OH)$-CH_2-NPhthal	2	9
36	$(CH_2)_2COCH_3$	1	4%[c]
42	CH_2NH_2	50	2%[d]
43	$(CH_2)_2NH_2$	0%[b]	nt
44	$(CH_2)_3NH_2$	29	nt
49	$CH(O\text{-}n\text{-}Pr)_2$	28%[b]	60
50	$CH(O\text{-}i\text{-}Pr)_2$	18%[b]	47
51	$CH(O\text{-}n\text{-}Bu)_2$	20%[b]	300

[a] nt = not tested. [b] Percent inhibition at a concentration of 10^{-5} M. [c] Percent increase at a concentration of 10^{-4} M. [d] Percent increase at a concentrations of 10^{-5} M.

Scheme 1 shows a typical procedure for the preparation of (3-aminopropyl)alkyl- or arylalkylphosphinic acids. Deprotonation of **11** or **12** by treatment with sodium hydride and alkylation with various alkyl halides yielded the protected phosphinates **13**, the reaction occurring at the phosphorus atom only. Cleavage of the acetal protecting group (**13**, R′ = H) required reflux with 4 M hydrochloric acid and gave the corresponding phosphinic acids, which were then re-esterified with an alkyl chloroformate to give esters **14**. Cleavage of the ketal protecting group (**13**, R′ = CH_3) was achieved under very mild conditions using anhydrous HCl generated from the reaction of trimethylsilyl chloride with ethanol in dichloromethane. This latter process gave the esters **14** directly and is to be recommended for compounds bearing acid labile substituents.

In some cases the residue R in **14** cannot be introduced via alkylation of precursors **11** or **12**, as in **14f**

Scheme 1[a]



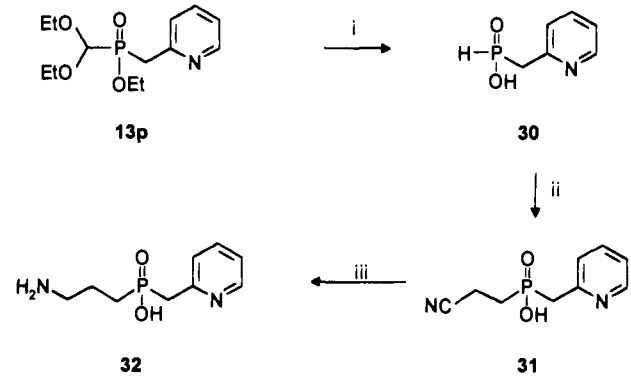
[a] Reagents and conditions: (i) NaH, THF, room temperature, 2 h, RX, room temperature, 24 h, or reflux, 24 h (R = $CH_2C_6H_{11}$); (ii) for **13o**: Na, EtOH, **12**, CH_2=CHCN, 10 °C, 30 min, room temperature, 1.5 h, reflux, 3 h, HOAc; (iii) for R' = H: (a) 4 M HCl, reflux, 24 h; (b) $ClCO_2R''$, Et_3N, DCM, 10 °C → room temperature, 2 h; (iv) for R' = CH_3: 1.5 equiv of TMSCl, 10% EtOH in DCM, room temperature, 24 h; (v) R''OH, Et_3N, 5 °C → room temperature, 24 h, 40 °C, 45 min; (vi) Na, R''OH, CH_2=CHCN, 10 °C; 1 h; room temperature; 1 h; reflux, 1 h; (vii) H_2, Raney nickel, 10% NH_3 in EtOH, 70 °C, 100 bar, 2 h; (viii) 5 M HCl, reflux, 24 h; propylene oxide, MeOH, 4 °C, 24 h; (ix) Me_3SiBr, DCM, room temperature, 24 h; 1% H_2O/MeOH, room temperature, 1 h; propylene oxide, MeOH, room temperature, 24 h. [b]Substituents for **13**: **a**, R' = CH_3, R = C_2H_5; **b**, R' = H, R = *n*-C_3H_7; **c**, R' = H, R = *n*-C_4H_9; **d**, R' = CH_3, R = $CF_2(CH_2)_2CH_3$; **e**, R' = CH_3, R = *i*-C_4H_9; **g**, R' = H, R = $CH_2C_3H_5$; **i**, R' = H, R = $CH_2C_6H_5$; **j**, R' = CH_3, R = $CH_2C_6H_{11}$; **k**, R' = CH_3, R = $(CH_2)_2C_6H_5$; **l**, R' = CH_3; R = $(CH_2)_2C_6H_{11}$; **m**, R' = H, R = tetrahydrofuran-2-yl; **n**, R' = H, R = (tetrahydropyran-2-yl)methyl; **o**, R' = CH_3, R = 2-cyanoethyl; **p**, R' = H, R = 2-pyridylmethyl. [c]Substituents for 14: **a**, R = C_2H_5, R'' = C_2H_5; **b**, R = *n*-C_3H_7, R'' = C_2H_5; **c**, R = *n*-C_4H_9, R'' = C_2H_5; **d**, R = $CF_2(CH_2)_2CH_3$, R'' = C_2H_5; **e**, R = *s*-C_4H_9, R'' = C_2H_5; **f**, R = *t*-C_4H_9, R'' = *i*-C_3H_7; **g**, R = $CH_2C_3H_5$, R'' = C_2H_5; **h**, R = C_6H_5, R'' = *i*-C_3H_7; **i**, R = $CH_2C_6H_5$, R'' = C_2H_5; **j**, R = $CH_2C_6H_{11}$, R'' = C_2H_5; **k**, R = $CH_2CH_2C_6H_5$, R'' = C_2H_5; **l**,R = $CH_2CH_2C_6H_{11}$, R'' = C_2H_5; **m**, R = tetrahydrofuran-2-yl, R'' = C_2H_5; **n**, R = (tetrahydropyran-2-yl)methyl, R'' = C_2H_5; **o**, R = 2-cyanoethyl, R'' = C_2H_5.

(R = *tert*-butyl) or in **14h** (R = phenyl). In these cases the appropriate alkyl or aryldichlorophosphines were reacted with an alcohol in the presence of 1 equiv of triethylamine in dry diethyl ether (reaction v in Scheme 1).

The introduction of the 3-aminopropyl side chain was achieved via base-catalyzed conjugate addition of the various alkyl phosphinates **14** to acrylonitrile followed by hydrogenation over Raney nickel in the presence of ammonia. The phosphinic acid esters were then hydrolysed under acidic or basic conditions to give **8, 10, 15–19, 21, 22,** and **24–29**.

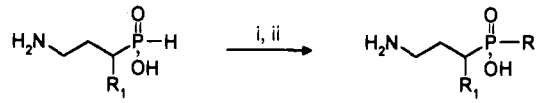
A variation of Scheme 1 was necessary for the 2-pyridyl derivative **13p** due to the incompatibility of the pyridine ring with ethyl chloroformate, which is required for the re-esterification step (Scheme 2). Acidic hydrolysis of **13p** produced (2-pyridylmethyl)phosphinic acid **30**, which was persilylated in refluxing hexamethyldisilazane generating a reactive P(III) intermediate. Reaction with acrylonitrile gave the (2-cyanoethyl)-phosphinic acid derivative **31**. Hydrogenation over Raney nickel yielded **32**.

Scheme 2[a]



[a] Reagents and conditions: (i) 12 M HCl, reflux, 24 h; (ii) HMDS, reflux, 24 h; acrylonitrile, room temperature, 24 h; (iii) H_2, Raney nickel, 5% NH_3 in EtOH, 45 °C, 1 bar, 18 h.

Scheme 3[a]



6 R_1 = H — R_1 = H **20, 23, 25, 33 - 36**
37 R_1 = CH_3 — R_1 = CH_3 **38**

[a] Reagents and conditions: (i) HMDS, reflux, 24 h, Hünig's base, diglyme, reflux, 30 min, RX (or RCHO, epoxide or α,β-unsaturated ketone); (ii) 2 M HCl; propylene oxide, MeOH, 4 °C, 24 h.

An alternative approach to the synthesis of (3-aminopropyl)alkyl- or arylalkylphosphinic acids is shown in Scheme 3. Thus, persilylation of **6**[17,18] in refluxing hexamethyldisilazane and reaction of the reactive P(III) intermediate with alkyl halides, aldehydes, ketones, α,β-unsaturated ketones, or epoxides gave a large variety of substituted phosphinic acids as **20, 23, 25,** or **33–36**. This route can also be applied to phosphinic acids bearing substitutents in the 3-aminopropyl side chain as **37**, providing access to compounds such as **38** (Table 2).

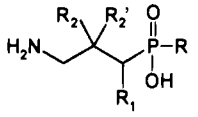
Although the route shown in Scheme 3 provided rapid access to a multitude of structurally diverse derivatives of (3-aminopropyl)phosphinic acids, we do not recommend this synthetic sequence for the following reason: Discrepancies were observed between the IC_{50} values of compounds prepared by either Schemes 1 or 3. Compounds prepared via the latter route showed higher affinities to $GABA_B$ receptors in comparison to the affinities of the same compounds prepared via Scheme 1. As the starting material **6** for Scheme 3 is a very potent $GABA_B$ agonist (IC_{50} = 5 nM),[14] any contamination by trace amounts of **6**, even below the limit of detection by TLC, ^1H NMR, or microanalysis, may produce compounds displaying artificially low IC_{50} values.

P–C bond formation can also be achieved via radical reactions with terminal alkenes (Scheme 4). Reaction of **14o** with 2-vinyltetrahydropyran **39** in refluxing dioxane containing catalytic amounts of dibenzoyl peroxide gave disubstituted phosphinic acid ester **40**. Hydrogenation and ester hydrolysis completed the synthesis of **41**.

The syntheses of (aminoalkyl)(3-aminopropyl)phosphinic acids **42–44** (Table 1) have been described previously.[19,20]

(3-Aminopropyl)(dialkoxymethyl)phosphinic acids were prepared as shown in Scheme 5. Reaction of hypophos-

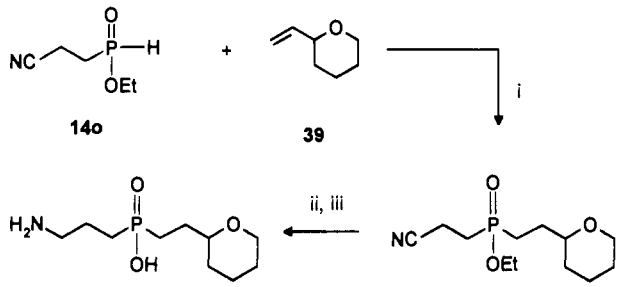
Table 2. Inhibition of Binding of [^{3}H]CGP27492 to $GABA_B$ Receptors of Rat Cortex and Enhancement of Electrically induced Release of [^{3}H]GABA from Rat Cortical Slices (Stimulation Frequency 2 Hz)



compd	R	R_1	R_2	R_2'	binding IC_{50} (μM)	GABA release EC_{150} (μM)
38	n-C_4H_9	CH_3	H	H	341	8%[a]
53	n-C_4H_9	OH	H	H	37%[c]	nt[e]
60	CH_3	H	4-ClC_6H_4	H	9	28%[a]
61	$CH(OEt)_2$	H	4-ClC_6H_4	H	21	11
66	n-C_4H_9	H	OH	H	29	8%[b]
67	$CH_2C_6H_5$	H	OH	H	8	4
68	$CH_2C_6H_5$	H	(*S*)-OH	H	5	5
69	$CH_2C_6H_5$	H	(*R*)-OH	H	32%[d]	11
70	$CH_2C_6H_{11}$	H	OH	H	5	8
71	$CH_2C_6H_{11}$	H	(*S*)-OH	H	5	2
72	$CH_2C_6H_{11}$	H	(*R*)-OH	H	6	4
73	$CH(OEt)_2$	H	OH	H	16	9
84	$CH(OEt)_2$	H	(*S*)-OH	H	12	11
89	n-C_4H_9	H	4-ClC_6H_4	OH	7	45%[b]
96	CH_3	H	4-ClC_6H_4	OH	6	30
99	n-C_4H_9	H	CH_3	OH	45%[c]	nt
106	n-C_4H_9	H	$R_2 + R_2'$	O	0%[d]	6%[a]
107	$CH_2C_3H_5$	H	$R_2 + R_2'$	O	14%[d]	3%[b]
108	$CH_2C_6H_{11}$	H	$R_2 + R_2'$	O	50%[d]	5

[a] Percent increase at concentrations of 10^{-4} M. [b] Percent increase at concentrations of 10^{-5} M. [c] Percent inhibition at concentrations of 10^{-3} M. [d] Percent inhibition at concentrations of 10^{-5} M. [e] nt = not tested.

Scheme 4[a]



[a] Reagents and conditions: (i) 20 mol % dibenzoyl peroxide, dioxane, reflux, 1 h; (ii) H_2, Raney nickel, 4% NH_3 in EtOH, 35 °C, 1 bar, 19 h; (iii) concentrated HCl, reflux, 24 h; propylene oxide, MeOH, room temperature, 24 h.

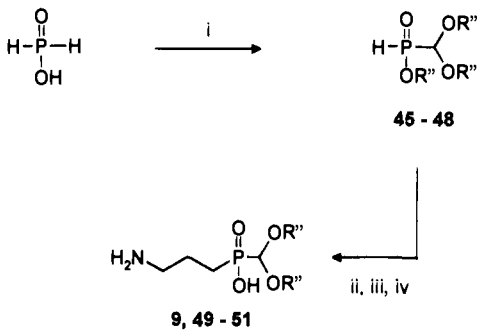
phorus acid with trialkyl orthoformates in the presence of a Lewis acid catalyst gave acetal esters **45**–**48**. Base-catalyzed addition to acrylonitrile followed by hydrogenation of the resulting 2-cyanoethyl derivatives to the (3-aminopropyl)phosphinic acid esters and saponification with lithium hydroxide gave **9** and **49**–**51**.

Different synthetic methodology was necessary for the preparation of phosphinic acid derivatives of GABA carrying substituents R_1, R_2, or R_2' in the 3-aminopropyl side chain (Table 2).

For compounds with R_1 equal to hydroxy, benzyloxycarbonyl-protected 3-aminopropanal was condensed with ethyl phosphinates (e.g., **14c**) under mildly basic conditions (Scheme 6). Simultaneous hydrolysis of the ester and carbamate groups of **52** was carried out using strong mineral acid at reflux to give 1-hydroxy-substituted **53**.

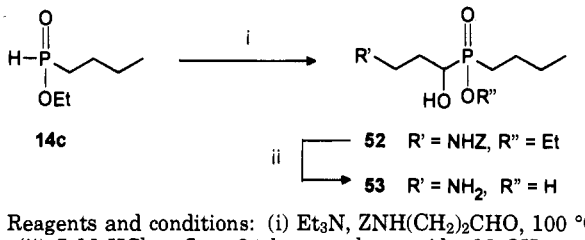
Scheme 7 outlines the preparation of the methyl- and

Scheme 5[a]



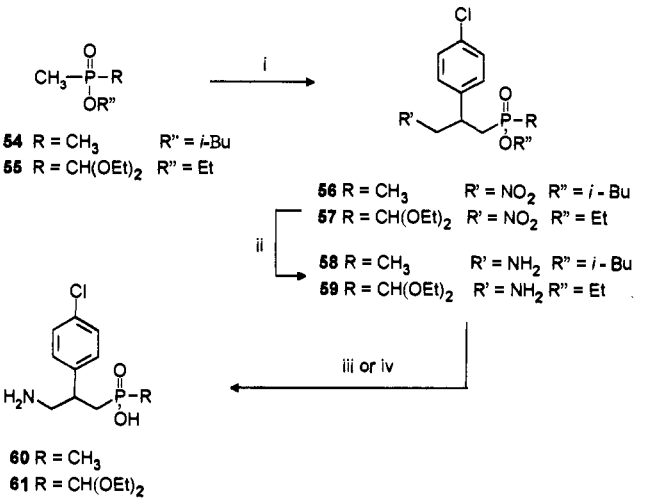
[a] Reagents and conditions: (i) $HC(OR'')_3$, CF_3COOH, room temperature, 72 h; (ii) CH_2=CHCN, NaOR'', R''OH, 70 °C, 4 h; (iii) H_2, Raney nickel, 10% NH_3 in R''OH, 70 °C, 100 bar, 4 h; (iv) LiOH, EtOH/H_2O, 1:4, reflux, 24 h, H_3PO_4. Substituents: in **45** and **9**, R'' = C_2H_5; **46** and **49**, R'' = n-C_3H_7; **47** and **50**, R'' = i-C_3H_7; **48** and **51**, R'' = n-C_4H_9.

Scheme 6[a]



[a] Reagents and conditions: (i) Et_3N, $ZNH(CH_2)_2CHO$, 100 °C, 4 h; (ii) 5 M HCl, reflux, 24 h; propylene oxide, MeOH, room temperature, 16 h.

Scheme 7[a]

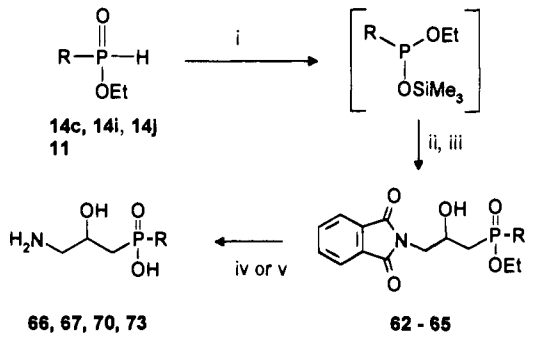


[a] Reagents and conditions: (i) LDA, THF, −78 °C, 1 h, 4-ClC_6H_4CH=$CHNO_2$, −78 °C, 30 min; (ii) H_2, Raney nickel, 10% NH_3 in EtOH, room temperature, 1 bar, 3 h; (iii) concentrated HCl, 100 °C, 24 h; propylene oxide, EtOH, room temperature 24 h; (iv) LiOH, EtOH/H_2O 1:4, reflux, 24 h, H_3PO_4; Dowex 50 W × 8 (H^+ form).

(diethoxymethyl)phosphinic acid analogues of baclofen. Conjugate addition of the anions of methylalkylphosphinic esters **54** or **55**, prepared by deprotonation with LDA, to 4-chloro-β-nitrostyrene gave (3-nitropropyl)-phosphinic acid esters **56** and **57**, respectively. Reduction of the nitro group was achieved in good yield via hydrogenation over Raney nickel to give amino esters **58** and **59**. Ester **58** was hydrolyzed under acidic conditions to yield **60**, while the acid-sensitive diethoxymethyl-derivative **59**[18] was hydrolyzed under basic conditions to furnish **61**.

Scheme 8 shows the syntheses of derivatives bearing a substituent R_2 equal to hydroxy: Ethyl phosphinates

Scheme 8[a]



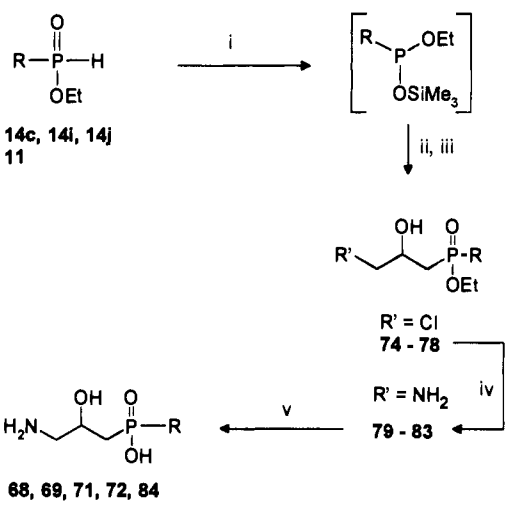
[a] Reagents and conditions: (i) TMSCl, Et_3N, THF, room temperature, 24 h; (ii) 10 mol % $ZnCl_2$, *N*-(2,3-epoxypropyl)phthalimide, room temperature → 70 °C, 24 h; (iii) 1% HOAc in MeOH, room temperature, 24 h; (iv) concentrated HCl, reflux, 24 h; (v) R = $CH(OEt)_2$: (a) $NaBH_4$, *i*-PrOH, H_2O, room temperature, 24 h, HOAc; (b) LiOH, H_2O, 24 h, room temperature, H_3PO_4. Substituents: in **62** and **66**, R = *n*-C_4H_9; **63** and **67**, R = $CH_2C_6H_5$; **64** and **70**, R = $CH_2C_6H_{11}$; **65** and **73**, R = $CH(OEt)_2$.

11, **14c**, **14i**, or **14j** were converted into their corresponding highly reactive silylated P(III) intermediates by reaction with trimethylsilyl chloride in the presence of triethylamine under anhydrous conditions. Reaction with *N*-(2,3-epoxypropyl)phthalimide catalyzed by zinc chloride in the absence of solvent gave, regiospecifically, the trimethylsilyl ethers of ethyl (2-hydroxy-3-phthalimidopropyl)phosphinates **62**–**65** as 1:1 mixtures of diastereoisomers. Under these conditions the trimethylsilyl group is transferred from the intermediate ethyl (trimethylsilyl)phosphonite to the newly formed hydroxy group. Acidic hydrolysis of **62**–**64** furnished 2-hydroxy-substituted alkyl- or arylalkylphosphinic acids **66**, **67**, and **70**. Cleavage of phthalimide **65** via sodium borohydride reduction and basic hydrolysis of the resulting amide provided (diethoxymethyl)phosphinic acid **73**.

Scheme 9 shows the reaction of silylated P(III) intermediates derived from **11**, **14c**, **14i**, or **14j** with (*R*)- or (*S*)-epichlorohydrin yielding the trimethylsilyl ethers of **74**–**78**, which were hydrolyzed under very mild conditions by stirring in methanolic solutions containing 1% acetic acid at room temperature providing chlorohydrins **74**–**78**. No ring closure to an epoxide occurred. Nucleophilic displacement of the chlorine atom with ethanolic ammonia proceeded via a clean S_N2 process to give amino esters **79**–**83** with complete retention of the stereochemistry at the carbon atom bearing the secondary hydroxyl group (see also part 1 of this series[14]). Acid hydrolysis of **79**–**82** yielded chiral (3-amino-2-hydroxypropyl)phosphinic acids **68**, **69**, **71**, and **72**. Basic hydrolysis of ester **83** gave chiral (diethoxymethyl)phosphinic acid **84**.

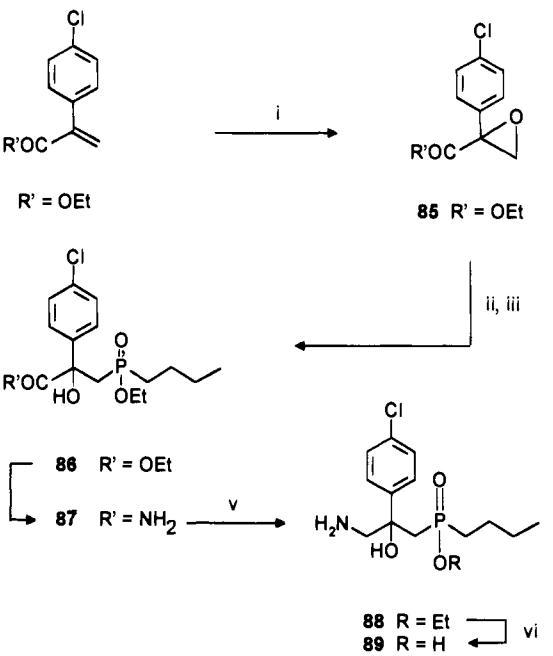
Two synthetic routes for the preparation of phosphinic acid analogues of 2-hydroxysaclofen (**4**, Figure 1) are outlined in Schemes 10 and 11. Condensation of epoxide **85** with the reactive P(III) species prepared via silylation of ethyl *n*-butylphosphinate **14c** gave hydroxy ester **86**, which was converted to the primary amide **87** by reaction with ammonia catalyzed by sodium cyanide.[21] The reduction of the primary amide **87** to the amino ester **88** using borane dimethyl sulfide complex proceeded with a yield of only 40%. This may be due to concomitant reduction of the phosphinic acid moiety. After hydrolysis of ester **88** with sodium hydroxide, the crystalline sodium salt of **89** was obtained after reverse-phase chromatography.

Scheme 9[a]



[a] Reagents and conditions: (i) TMSCl, Et_3N, THF, room temperature, 24 h; (ii) 10 mol % $ZnCl_2$, (*R*)- or (*S*)-epichlorohydrin, room temperature → 70 °C, 24 h; (iii) 1% HOAc in MeOH, room temperature, 24 h; (iv) 20 equiv of NH_3 in EtOH, room temperature, 96 h; (v) (a) concentrated HCl, reflux, 2 h; propylene oxide, MeOH, or (b) LiOH, EtOH/H_2O 1:4, reflux, 24 h; H_3PO_4. Substituents: in **74**, R = $CH_2C_6H_5$, 2(*R*)-OH; **75**, R = $CH_2C_6H_5$, 2(*S*)-OH; **76**, R = $CH_2C_6H_{11}$, 2(*R*)-OH; **77**, R = $CH_2C_6H_{11}$, 2(*S*)-OH; **78**, R = $CH(OEt)_2$, 2(*R*)-OH. Substituents in **79** and **68**, R = $CH_2C_6H_5$, 2(*S*)-OH; **80** and **69**, R = $CH_2C_6H_5$, 2(*R*)-OH; **81** and **71**, R = $CH_2C_6H_{11}$, 2(*S*)-OH; **82** and **72**, R = $CH_2C_6H_{11}$, 2(*R*)-OH; **83** and **84**, $CH(OEt)_2$, 2(*S*)-OH.

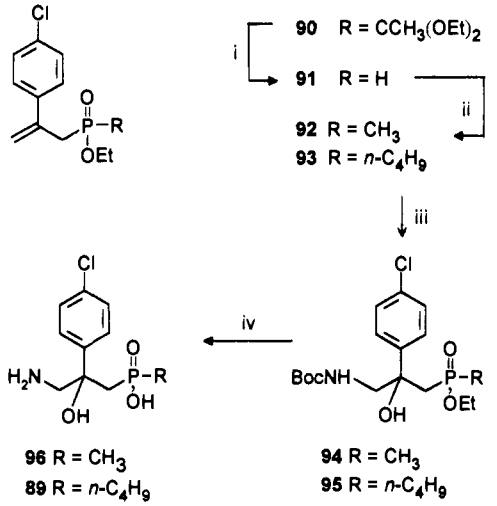
Scheme 10[a]



[a] Reagents and conditions: (i) *m*-ClPBA, $CHCl_3$, reflux, 24 h; (ii) **14c**, TMSCl, Et_3N, THF, room temperature, 24 h; (iii) 10 mol % $ZnCl_2$, THF, reflux, 6 h; (iv) NH_3, 10 mol % NaCN, EtOH, sealed tube, 50 °C, 10 h; (v) BH_3·Me_2S, THF, reflux, 3 h; MeOH, room temperature; (vi) NaOH, EtOH/H_2O, 2:1, 60 °C, 24 h.

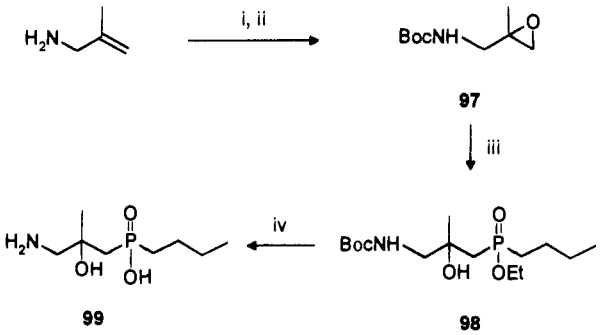
A more versatile route is shown in Scheme 11. Deprotection of **90**—the preparation of which is described in part 1 of this series[14]—by reaction with anhydrous HCl generated from the reaction of trimethylsilyl chloride with ethanol in dichloromethane produced phosphinate **91**, which was deprotonated by treatment with *n*-butyllithium at −78 °C and alkylated with either methyl iodide or *n*-butyl bromide to give the allylic phosphinates **92** and **93**, respectively. No isomer-

Scheme 11[a]



[a] Reagents and conditions: (i) Me_3SiCl, 10% EtOH/DCM, room temperature, 24 h; (ii) *n*-BuLi, THF, −78 °C, 10 min, RX, −78 °C, 5 min; NH_4Cl/H_2O, −78 °C → room temperature; (iii) $BocNH_2$, MeOH, 0 °C, *t*-BuOCl, 0 °C, 15 min, NaOH, MeOH, 0 °C → room temperature; $AgNO_3$, MeCN, 3 mol % OsO_4, *t*-BuOH, H_2O, room temperature, 24 h; (iv) Me_3SiBr, CH_2Cl_2, room temperature, 24 h; propylene oxide, MeOH, room temperature, 24 h.

Scheme 12[a]



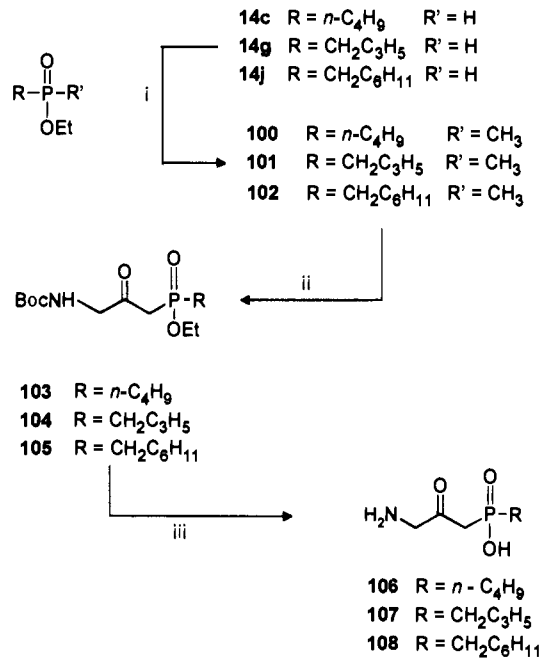
[a] Reagents and conditions: (i) $(Boc)_2O$, DCM, Et_3N, 20 °C, 1 h; (ii) *m*-ClPBA, $CHCl_3$, 15 °C, 1 h; (iii) **14c**, TMSCl, Et_3N, THF, room temperature, 24 h; (iv) 10 mol % $ZnCl_2$, THF, reflux, 4 h; (v) 1 M HCl, reflux, 24 h; propylene oxide, EtOH.

ization to the α,β-unsaturated phosphinates occurred, provided that the temperature during the alkylation was maintained strictly at −78 °C. Oxyamination proceeded regiospecifically employing the procedure of Sharpless et al.[22] to give **94** and **95**. Treatment with trimethylsilyl bromide followed by methanolysis gave the methyl- and *n*-butylphosphinic acid analogues of 2-hydroxysaclofen **96** (R = CH_3) and **89** (R = *n*-Bu) in good yield.

Scheme 12 shows the preparation of (3-amino-2-hydroxy-2-methylpropyl)phosphinic acid **99**. Reaction of epoxide **97** with the reactive P(III) intermediate derived via silylation of ethyl *n*-butylphosphinate **14c** produced ester **98**, which, after acidic hydrolysis, gave **99**.

Compounds, in which a carbonyl group was incorporated at carbon 2, i.e., (3-amino-2-oxopropyl)phosphinic acids (Table 2) were obtained by adapting a procedure first described for the preparation of (γ-amino-β-ketoalkyl)phosphonates.[23] Methylation of phosphinic acid esters **14c**, **14g**, or **14j** by reaction with sodium hydride followed by methyl iodide gave methylphosphinic acid esters **100**–**102** (Scheme 13). Treatment with LDA at −78 °C regiospecifically generated the anion at the methyl substituent only, which reacted efficiently with

Scheme 13[a]



[a] Reagents and conditions: (i) NaH, THF, room temperature, 3 h; MeI, room temperature, 24 h; (ii) LDA, THF, −78 °C, 1 h; $BocNHCH_2COOMe$, −78 °C 15 min, HOAc, −78 °C → room temperature; (iii) 5 equiv of Me_3SiBr, CH_2Cl_2, room temperature, 16 h; 1% H_2O in MeOH, room temperature, 30 min; propylene oxide, EtOH, 24 h.

Boc-glycine methyl ester to give *N*-protected keto esters **103**–**105**. Concomitant cleavage of the Boc protecting group and the ester with trimethylsilylbromide followed by methanolysis provided (3-amino-2-oxopropyl)phosphinic acids **106**–**108**.

Biology

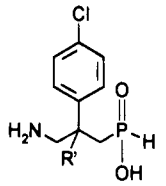
Affinity to $GABA_B$ Receptors and Structure–Activity Relationships. All compounds synthesized were tested for their ability to inhibit the binding of the novel $GABA_B$ agonist ligand [^{3}H]CGP27492[24] (**6**, Figure 1). The half maximal concentration of inhibition (IC_{50}) of each compound is listed in Tables 1 and 2. The systematic variation of the substituents bound to the phosphorus atom or to carbon atoms 1 or 2 of the 3-aminopropyl side chain of the diverse (3-aminopropyl)-phosphinic acids provided the following structure–activity relationships.

Contrary to the potent $GABA_B$ agonists **6** (R = H) or **7** (R = CH_3), the affinities of the $GABA_B$ receptor antagonists (R ≥ C_2H_5, Table 1) are all in the micromolar range. Apart from steric requirements this finding may also imply that the $GABA_B$ agonist and antagonist binding sites are located within different regions of the G-protein-coupled receptor.[25]

There are relatively small differences in the affinities of compounds bearing various residues on the phosphorus atom. Very bulky substituents bound directly to the phosphorus, as examplified by the *tert*-butylphosphinic acid **18** or the phenylphosphinic acid **21**, caused a significant loss of affinity, as did short aminoalkyl residues, in particular the (2-aminoethyl)phosphinic acid **43**.

Substituting the 3-aminopropyl side chain in position α to the phosphorus ($R_1 \neq H$) caused a drastic loss of affinity (**38** and **53**, Table 2).

Chart 1



109 R' = H
110 R' = OH

However, $GABA_B$ receptors can accommodate selected substituents R_2 at carbon atom 2 of the 3-aminopropyl side chain, e.g., 4-chlorophenyl, as in the baclofen analogues **60** and **61** (Table 2). As was observed in the series of $GABA_B$ agonists,[14] a 2-hydroxy substituent is also tolerated at carbon atom 2 (**66**–**73** and **84**, Table 2). The absolute configuration of the 2-OH substituent is of minor importance. In this particular series of compounds only **84** showed a moderate improvement of affinity to $GABA_B$ receptors in comparison to unsubstituted **9** (Table 1). Carbon atom 2 may also be substituted with 4-chlorophenyl and hydroxy (**89** and **96**, Table 2), the substitution pattern of 2-hydroxysaclofen **4** (Figure 1) to produce compounds displaying a slightly better affinity to $GABA_B$ receptors.

In contrast to the unsubstituted (3-aminopropyl)-phosphinic acids (Table 1), where the transition from $GABA_B$ agonistic effects to $GABA_B$ antagonistic properties occurred between a methyl substituent as in **7** to an ethyl substituent as in **8**, both *methyl*phosphinic acid analogues of baclofen **60** and the 2-hydroxysaclofen analogue **96** showed the properties of $GABA_B$ antagonists. As described in part 1 of this series, the corresponding phosphinic acid analogues **109** and **110** (Chart 1), showed the properties of $GABA_B$ agonists.[14]

A compound bearing a methyl and a hydroxy substituent on carbon atom 2 did not interact with $GABA_B$ receptors (**99**, Table 2). With compounds bearing a carbonyl group at carbon atom 2 of the 3-aminopropyl side chain only the (cyclohexylmethyl)phosphinic acid **108** showed a moderate affinity to $GABA_B$ receptors (Table 2).

Selectivity for $GABA_B$ Receptors. The new $GABA_B$ antagonists interacted selectively with the $GABA_B$ receptors. The inhibition of binding of selective [^{3}H]-ligands to $GABA_A$ and to 18 other receptors present in the central nervous system by **10** was investigated at concentrations up to 1 mM (Table 3).

Antagonism at $GABA_B$ Receptors *in Vitro* and *in Vivo*. Binding experiments yield only information about the affinity of compounds to the receptor but do not differentiate between agonists or antagonists. These functional aspects were adressed in several electrophysiological experiments *in vitro* and *in vivo*.

Intracellular recordings from CA1 hippocampal pyramidal neurons in slice preparations showed that a 10 μM solution of baclofen **1** inhibited cell firing and induced hyperpolarisation of the membrane potential due to opening of $GABA_B$ receptor coupled K^+ channels.[26] 30 μM solutions of **9** completely and reversibly antagonized this effect (Figure 2).[27–29]

These findings were corroborated in experiments using functional pharmacological assays.[30,31] **9** potently antagonized the effects of both potent $GABA_B$ agonists **1** and **6** in rat anococcygeus muscle and in isolated rat vas deferens preparations.

Table 3. Inhibition of Binding of [^{3}H]Ligands to 20 Central Nervous System Receptors by **10**

receptor	[^{3}H]ligand	IC_{50} (μM)	% inhibition at 1 mM
$GABA_B$	CGP27492	38	
$GABA_A$	muscimol	508	
benzodiazepine	flunitrazepam		0
musc. ACh.	CMD		0
musc. ACh.	QNB		0
α_1-adrenergic	prazosine		0
α_2-adrenergic	clonidine		0
β-adrenergic	DHA		0
5-HT_1	5-HT		2
5-HT_2	ketanserine		0
5-HT_3	BRL 43 694		0
histamine 1	doxepine		7
histamine 2	tiotidine		6
adenosine 1	N-6-CA		0
μ-opiate	naloxone		0
NMDA	L-glutamate		0
glycine	DCKA		16
kainate	kainate		−8
quisqualate	AMPA		7
NK-1	substance P		0

Figure 3. The blocking effect of 10 and 30 mg/kg iv of **9** on the depressant responses of ionophoretically administered baclofen studied in rat cortical neurones *in vivo*. Whereas the depressant responses evoked by the $GABA_A$ agonist THIP remained unaffected, the baclofen responses were dose dependently reduced by **9** (reproduced with permission of authors and editor of ref 28).

Electrophysiological experiments *in vivo* demonstrated that the novel $GABA_B$ antagonists were able to penetrate the blood brain barrier. Baclofen given ionophoretically inhibited the firing of cortical neurons. Pretreatment with **9**, administered either iv or ip, blocked this effect. In contrast, **9** did not affect the depressant responses evoked by the selective $GABA_A$ agonist THIP (Figure 3).[27,28] The first $GABA_B$ antagonists found to block the effects of baclofen after oral administration were **10** and **24** (CGP46381).[32]

Effects on Neurotransmitter Release. Different subtypes of $GABA_B$ receptors located at presynaptic nerve terminals influence the release of numerous neurotransmitters and neuropeptides, such as GABA, glutamate, aspartate, dopamine, noradrenaline, serotonin, substance P, cholecystokinin (CCK), and somatostatin.[33]

The release of GABA was enhanced by $GABA_B$ antagonists in electrically stimulated rat cerebral cortex slices.[33,34] $GABA_B$ agonists inhibited the release of GABA as described in part 1 of this series of papers.[14] The EC_{150} values of the new $GABA_B$ antagonists, i.e., the concentrations causing a 50% increase of GABA release, determined at a stimulation frequency of 2 Hz, are shown in Tables 1 and 2. All $GABA_B$ antagonists of this series displayed EC_{150}s in the micromolar range. Some compounds, e.g., benzyl derivatives (**22**, **23** Table 1, **67** and **68**, Table 2), cyclohexylmethyl derivatives (**24** and **70**–**72**) or diethoxymethyl derivatives (**9** and **84**)

displayed EC_{150} values similar to their IC_{50} values obtained from $GABA_B$ binding experiments.

However, a direct comparison between the data of binding and GABA release experiments is not correct. The EC_{150} values reflect the interaction of the $GABA_B$ antagonists with one single—presynaptically located—$GABA_B$ receptor subtype. Strong release of GABA may be the cause of the observed anxiolytic side effects of some $GABA_B$ antagonists. Additionally, as described in part 1,[14] some of the new $GABA_B$ antagonists also act as partial agonists at the presynaptic $GABA_B$ autoreceptors. This may be the main reason that some $GABA_B$ antagonists showed considerably weaker effects in GABA release experiments in comparison to their effects in binding experiments.

In contrast, the IC_{50} values of the binding experiments represent an integral of all interactions of the various $GABA_B$ antagonists with several pre- and postsynaptic subtypes of $GABA_B$ receptors. The individual affinities of the novel radioactive ligand [^{3}H]CGP27492 with single $GABA_B$ receptor subtypes are still unknown. Only the isolation and expression cloning of all $GABA_B$ receptor subtypes will provide a precise understanding of the above data. Sustained efforts to isolate and characterize $GABA_B$ receptors are underway.[35,36]

Some $GABA_B$ antagonists also interacted with presynaptic $GABA_B$ heteroreceptors, which influence the release of the excitatory amino acids glutamate[37] and aspartate.[38] In K^+-stimulated rat cerebral cortex slices **9** at a concentration of 100 μM increased the release of glutamate by 25% and at a concentration of 300 μM by 35%. The enhanced release of glutamate may also be the cause for the observed facilitation of LTP *in vitro* and *in vivo, vide infra*. Phaclofen **2** may not interact with this particular $GABA_B$ receptor subtype. It did not cause an increase of the release of glutamate and aspartate.[37,38]

9 also antagonized the effects of 10 μM solutions of (*R*)-(−)-baclofen on the K^+-evoked release of endogenous neuropeptide somatostatin (IC_{50} = 3.6 μM).[39] On the basis of these neurotransmitter release experiments, a new classification of multiple presynaptic $GABA_B$ receptors has been proposed recently.[40]

Blockade of the Late Inhibitory Postsynaptic Potentials and Facilitation of Long-Term Potentiation. The new $GABA_B$ antagonists also interact with postsynaptic $GABA_B$ receptors, an effect measured by the blockade of the $GABA_B$ receptor-mediated late inhibitory postsynaptic potentials (ipsp).[41,42] Electrical stimulation of the Schaffer collateral/commissural fibres in rat hippocampal slices evoked an excitatory postsynaptic potential (epsp) followed by two inhibitory postsynaptic potentials in CA 1 pyramidal and cortical neurons. The first component, the early ipsp, is mediated by $GABA_A$ receptors and is blocked selectively by the $GABA_A$ antagonist bicuculline or by the chloride channel blocker picrotoxin.[43] The second component, the late ipsp, is mediated by $GABA_B$ receptors, because it was blocked selectively by 100 μM solutions of **9**[27,28] (Figure 4), by 1 mM solutions of **10**[32] or by 100 μM solutions of **24**,[32] respectively. In each case the early ipsp's remain unaffected. These experiments showed that the $GABA_B$ receptor-mediated period of inhibition was markedly shortened under the influence of $GABA_B$ antagonists as can be seen from the earlier reappearance of the spontaneous action potentials (Figure 4), suggesting disinhibitory effects of this class of drugs.

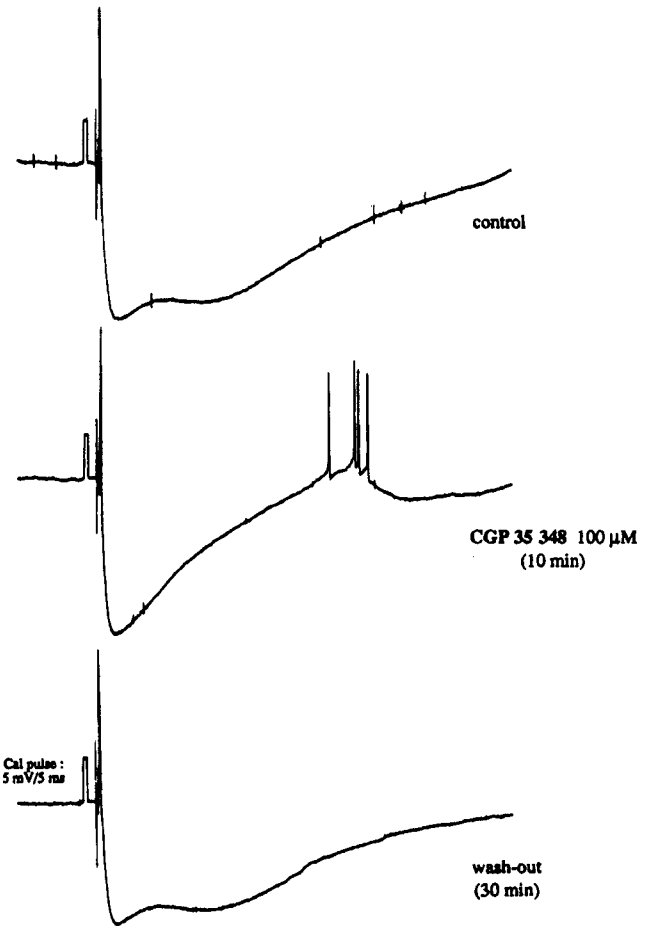


Figure 4. The blocking action of 100 μM solutions of **9** on the late inhibitory postsynaptic potential (ipsp), recorded intracellularly from a rat CA1 pyramidal neuron, evoked by single pulse stimulation of the Schaffer collateral/commissural fibers. Bath-applied **9** reduced only the late ipsp, leaving the early ipsp unaffected. Each trace is the average of four successive sweeps (Reproduced with permission of authors and editor of ref 28).

Suppression of the late ipsp could be demonstrated also *in vivo* by intracellular recordings from the entorhinal-subicular region of anaesthetized rats after iv administration of 30 mg/kg of **24**. The duration of the ipsp was reduced by 26%.[44]

Enhanced release of glutamate, a clearly *presynaptic* effect, as well as blockade of the late inhibitory *postsynaptic* potentials may account for the observed facilitation of the induction of long-term potentiation of selective $GABA_B$ antagonists. *In vitro* experiments showed an increase of the population spike amplitude caused by 100 μM solutions of **9** of 53 ± 8%.[45] The effects on long-term potentiation were even more pronounced *in vivo*. A dose of 100 mg/kg of **9**, administered iv to anaesthetized rats, produced an increase of the population spike amplitude of 350% elicited by two 100 Hz tetanic stimulations after 30 and 60 min and an increase of 450% by further 100 Hz tetanic stimulations after 90, 120, and 150 min.[46]

Additional electrophysiological experiments *in vivo* showed that $GABA_B$ antagonists potentiate the excitatory response of rostral cortical neurons, which is elicited by ionophoretically applied acetylcholine and quisqualate. A dose of 30 mg/kg of **9**, adminstered iv, increased the mean amplitude of the quisqualate re-

sponse by 37% and of the acetylcholine response by 11%; whereas a dose of 100 mg/kg of **9**, given iv, increased the quisqualate response by 72% and the acetylcholine response by 19%.[47] Both potentiations lasted for longer than 1 h. The increased responsiveness to quisqualate and acetylcholine may be due to a disinhibition of cortical neurons resulting from the blockade of cortical $GABA_B$ receptors.

Therapeutic Potential of $GABA_B$ Antagonists. Increased release of the excitatory neurotransmitters glutamate and aspartate, suppression of late inhibitory postsynaptic potentials and hence increase of neuronal excitability, facilitation of the induction of LTP and potentiation of the excitatory responses of cortical neurons elicited by acetylcholine and quisqualate may lead to an amplification of neurotransmission and to improved signal processing in the brain and could produce positive effects on cognitive functions after treatment with $GABA_B$ antagonists. This hypothesis was confirmed in several experiments, indicative of improvement of different aspects of learning and memory functions in experimental animals.

Fifteen of the novel $GABA_B$ antagonists were tested for their effects on memory storage and retrieval functions. The selection criterion was structural similarity to those compounds, which had been shown to cross the blood–brain barrier in the previously described *in vivo* electrophysiological paradigm. As analogues of **9** (i.e., **61** and **73**), of **10** (i.e., **16**, **19**, **27**, and **33**) and of **24** (i.e., **22**, **34**, **67**, and **70–72**) were selected for tests in a one-trial step-down passive avoidance paradigm[48] in two groups of 25 mice each. The compounds were administered orally 1 or 5 h before the learning trials ("pre-trial") or immediately after the learning trial, via ip administration ("post-trial"). Standard doses were 0.3 and 3 and 30 mg/kg. In all three variations of the step-down, passive avoidance test mice treated with **10**,[49,50] **19**, **22**, **33**, or **70** showed statistically significant increased retention performance at the retest 24 h later. It was puzzling that racemic **70** was active in the one-trial step-down passive avoidance paradigms, whereas the single enantiomers **71** and **72** displayed only weak effects. This experimental finding may point to significantly different affinities of the pure enantiomers to several $GABA_B$ heteroreceptors releasing different amounts of the corresponding neurotransmitters. Maybe the individual effects add up in the racemate to provide a reproducible memory enhancing effect. The memory improving effects of the racemate were not due to impurities, as the 1:1 mixture of **71** and **72** did produce the same biological effects as **70**.

The active drugs were tested for their effects to reduce the degree of amnesia induced by electroconvulsive shock in a two compartment passive avoidance paradigm.[51] At doses of 0.3 and 3 and 30 mg/kg adminstered po 1 h before the learning trial and the electroshock **10**, **19**, and **22** significantly reduced the amount of amnesia as measured by step-through latency times at the retest 24 h later.

However, only **10** significantly improved the learning performance of 27 months old rats in a multiple trial one-way active avoidance test after chronic administration of 0.3 and 3 and 30 mg/kg, given orally, for 30 days.[52]

In this context it may be of interest to recall recent results of Pratt and Bowery.[53] Chronic administration of **10** to Wistar rats, 100 mg/kg, ip administration, daily for 21 days caused an increase of $GABA_B$ receptor binding in the outer laminar region of the frontal cortex by 55%.

In a social learning paradigm in rats (20 pairs per group) 3 mg/kg po of **10** significantly shortened the duration of active exploration at the second pairing with a partner previously encountered indicating a facilitating effect on long-term memory.[49,50]

A group of 10 Rhesus monkeys after treatment with 0.5 mg/kg po of **10** performed significantly better than a group of 10 untreated animals in a conditional spatial color test, where learning the placement of a food reward hidden under an upturned beaker in relationship to the color of the beaker was required.[49,50]

Memory facilitation could also be observed in a radial maze task in mice tested on each of 10 consecutive days after ip administration of 10 and 100 mg/kg, but not of 1 mg/kg of **10**. They displayed significantly enhanced performance by 17–34% and 20–31%, respectively, in comparison to control animals 5–10 days after commencement of the study.[54] By contrast, 2 and 4 mg/kg of the $GABA_B$ receptor agonist (*R*)-(−)-baclofen, ip administration, induced a significant impairment of performance (by 16–20% and by 20–30%, respectively). This depressant effect was completely reversed by coadministration of **10**.[54]

These results imply that the learning and memory improving effects of **10** are most likely mediated by $GABA_B$ mechanisms. However, its interactions with $GABA_B$ receptor subtypes elicit many biological responses, which may provide more or less important contributions to the results of the manifold experiments investigating different aspects of learning and memory functions.

Significantly contibuting to the observed *in vivo* effects is the good oral bioavailability of **10**, on average 22% in rats, 41% in dogs, and 44% in healthy young and elderly male volunteers.

Compounds with close structural resemblance to those, which had been shown to cross the blood brain barrier, i.e., **9**, **10**, **24**, **33**, **61**, and **70–72**, were also tested in various animal models of absence epilepsy. They dose-dependently suppressed the spontaneous 3-Hz spike and wave discharges as shown by EEG recordings from the frontoparietal cortices of a selected strain of Wistar rats (Genetic Absence Epilepsy Rats of Strasbourg, GAERS).[55–57] Within a period of 20 min the combined duration of spike and wave discharges amounted to about 400 s. $GABA_B$ antagonists dose-dependently and rapidly suppressed the spike and wave discharges after ip and po administration. The ED_{80} values, i.e., the doses necessary to effect an 80% suppression of spike and wave discharges, were in the range of 25 mg/kg for **24** to 100 mg/kg for **9** after ip and 200 and 500 mg/kg, respectively, after po administration. The protective effects of **9** against spontaneous seizures were confirmed in lethargic mice, another animal model of generalized nonconvulsive epilepsy.[58] The new $GABA_B$ antagonists also protected rats against γ-hydroxybutyrate-induced absence seizures.[59,60] The ED_{50} values[60] after iv administration were 59 mg/kg for **9**, 33 mg/kg for **10**, and 20 mg/kg for **24**.

This new class of $GABA_B$ antagonists provided quite useful pharmacological tools for the in depth elucidation of many diverse biological events caused by activation or blockade of the various subtypes of $GABA_B$ receptors.

On the basis of the memory and learning experiments, the orally active $GABA_B$ antagonist **10** was selected as a development compound for the treatment of cognition deficits.[61]

The compounds of Tables 1 and 2 displayed affinities to $GABA_B$ receptors in the micromolar range. However, an unexpected improvement of the potency of this class of compounds by 3 orders of magnitude was discovered by attaching appropriate substituents to the amino group of the (3-aminopropyl)phosphinic acids.[62-65] Full experimental details of these highly potent $GABA_B$ antagonists will be described in part 3 of this series of papers.[66]

Experimental Section

Melting points were determined on a Reichert Kofler-block and are uncorrected. Thin layer chromatography (TLC) was performed on precoated silica gel plates (E. Merck, silica gel 60 F_{254}, 0.25 mm). Components were visualized by UV light of λ 254 nm, by iodine vapor, or by spraying with ninhydrin solutions. Column flash chromatography was performed on silica gel 60, 0.040–0.063 mm (230–400 mesh, ASTM, E. Merck), eluting under a positive pressure of approximately 20 psi of nitrogen, ensuring a flow rate of about 5 mL/min. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a 10 cm cuvette. Elemental combustion analyses were performed on a Perkin-Elmer PE-240 or a Leco CHN-800. Elemental analyses were within ±0.4% of the calculated values unless indicated otherwise. Optical purities were measured on a Shimadzu LC workstation Class-LC10. ^{1}H NMR spectra were recorded on Varian-90, Varian-Gemini-200/300, Varian-Gemini-250, and Bruker-AM-360 spectrometers. Chemical shifts δ are expressed in parts per million (ppm) relative to tetramethylsilane as internal standard. Coupling constants J are reported in hertz. ^{13}C NMR and ^{31}P NMR spectra were recorded on a Bruker-AM-360 spectrometer. Mass spectra were obtained with a Varian CH7/MAT212. High-resolution FAB mass spectra were measured using a Finnigan MAT-90 or a Visons Instruments VG70-SE.

Method A: Alkylation of Phosphinic Acids (Scheme 1, Reaction i). Ethyl (*n*-Butyldiethoxymethyl)phosphinate (13c). A solution of 104.4 g (0.5 mol) of 11[15] in 100 mL of dry THF was added over the period of 1 h to 24 g (0.55 mol) of a suspension of sodium hydride (55% dispersion in oil) in 100 mL of dry THF under argon at room temperature. The reaction was exothermic, and gas evolution was observed. During the addition the temperature was maintained between 20 and 25 °C. After the addition was complete the suspension was stirred for 2 h at room temperature before the addition of 209.7 g (1.5 mol) of *n*-butyl bromide. The reaction mixture was stirred at room temperature for 24 h, cooled in an ice/water bath, and treated with water. After concentration *in vacuo* the residue was partitioned between DCM and water. Separation and drying of the organic layer over magnesium sulfate followed by evaporation of the solvent gave an oil, which was distilled under high vacuum, to give 109 g (86%) of **13c**: bp 64–71 °C/10^{-3} mbar; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.67 (d, J = 7.5 Hz, 1H, CH-P), 4.13–4.05 (m, 2H, ester CH_2), 3.93–3.80 (m, 2H, acetal CH_2), 3.77–3.64 (m, 2H, acetal CH_2), 1.87–1.72 (m, 2H, CH_2P), 1.70–1.63 (m, 2H, CH_2), 1.48–1.37 (m, 2H, CH_2), 1.33 (t, J = 7 Hz, 3H, ester CH_3), 1.27 (t, J = 7 Hz, 6H, acetal CH_3), 0.92 (t, J = 7 Hz, 3H, alkyl CH_3).

Method B: Acid Hydrolysis of Alkyl (Diethoxymethyl)phosphinates and Reesterification to Alkyl Phosphinates (Scheme 1, Reaction iii). Ethyl *n*-Butylphosphinate (14c). A suspension of 109 g (0.388 mol) of **13c** in 160 mL of 4 M hydrochloric acid was heated to reflux for 24 h. The mixture was cooled to room temperature and washed with diethyl ether. The aqueous layer was evaporated to dryness and coevaporated with 3 × 100 mL of absolute ethanol and the residue dried in high vacuum at 50 °C for 24 h to give 51 g (97%) of *n*-butylphosphinic acid: ^{1}H NMR (360 MHz, $CDCl_3$) δ 11.13 (br s, exch. D_2O, 1H, POH), 7.11 (dt, J = 549 and 0.3 Hz, 1H, PH), 1.87–1.71 (m, 2H, CH_2P), 1.68–1.52 (m, 2H, CH_2), 1.49–1.37 (m, 2H, CH_2), 0.93 (t, J = 7.5 Hz, 3H, CH_3). *n*-Butylphosphinic acid (51 g, 0.418 mol) was dissolved in 200 mL of dry DCM and cooled to 10 °C under argon and 42.3 g (0.418 mol) of triethylamine added dropwise. A slightly exothermic reaction occurred, the mixture was recooled to 10 °C, and 45.36 g (0.418 mol) of ethyl chloroformate was added dropwise over the period of 1 h at 10 °C. *Caution! A thick suspension of triethylamine hydrochloride formed, which required efficient stirring. The reaction was exothermic and large amounts of carbon dioxide were liberated.* After dilution with a further 100 mL of DCM, the reaction mixture was stirred at room temperature for 2 h. The precipitate was filtered and washed with carbon tetrachloride, the combined organic filtrates were washed with 150 mL of water and dried over magnesium sulfate, and the solvent was removed to give a colorless oil. Distillation in high vacuum afforded 62.7 g (100%) of **14c** as a colorless oil: bp 95 °C/5 × 10^{-2} mbar; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.10 (d, J = 550 Hz, 1H, P-H), 4.29–4.00 (m, 2H, ester CH_2), 1.86–1.78 (m, 2H, CH_2P), 1.65–1.50 (m, 2H, CH_2), 1.45–1.30 (m, 5H, CH_2 and ester CH_3), 0.92 (t, J = 7.5 Hz, 3H, alkyl CH_3).

Method C: Conjugate Addition of Alkylphosphinic Acid Esters to Acrylonitriles (Scheme 1, Reaction vi). Ethyl (2-Cyanoethyl)*n*-butylphosphinate. Sodium metal (1.15 g, 0.05 mol) was dissolved in 50 mL of absolute ethanol, and this solution was added dropwise, over 30 min, to a stirred solution of 15.0 g (0.1 mol) of **14c** and 5.3 g (0.1 mol) of acrylonitrile in 25 mL of absolute ethanol at 10 °C under argon. An exothermic reaction occurred, and the mixture was stirred at 10 °C for 1 h, warmed to room temperature, stirred for a further 60 min, and warmed to reflux for 1 h. After this time the reaction was cooled to room temperature, 3.3 g (0.055 mol) of glacial acetic acid was added, and the ethanol was removed *in vacuo*. The gelatinous residue was partitioned between DCM and water, and the organic layer was separated, dried over magnesium sulfate, and filtered, and the solvent was removed to give a pale yellow oil. Distillation in high vacuum afforded 16.55 g (82%) of ethyl (2-cyanoethyl)*n*-butylphosphinate as a colorless oil: bp 120 °C/10^{-1} mbar; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.23–4.05 (m, 2H, ester CH_2), 2.75–2.50 (m, 2H, CH_2CN), 2.06–2.00 (m, 2H, CH_2P), 1.85–1.78 (m, 2H, CH_2P), 1.65–1.51 (m, 2H, CH_2), 1.48–1.45 (m, 2H, CH_2), 1.18 (t, J = 7.5 Hz, 3H, ester CH_3), 0.93 (t, J = 7.5 Hz, 3H, alkyl CH_3).

Method D: Hydrogenation of Alkyl (2-Cyanoethyl)phosphinic Acid Esters (Scheme 1, Reaction vii). Ethyl (3-Aminopropyl)*n*-butylphosphinate. Ethyl (2-cyanoethyl)*n*-butylphosphinate (16.46 g, 81.08 mmol) was dissolved in 165 mL of absolute ethanol and treated with 16.5 g of liquid ammonia and 3.0 g of Raney nickel. The suspension was hydrogenated at 70–75 °C for 2 h, starting with a pressure of 100 bar. After cooling to room temperature the mixture was filtered and the filtrate evaporated to dryness to give a pale green oil. Distillation in high vacuum afforded 13.1 g (78%) of ethyl (3-aminopropyl)*n*-butylphosphinate as a colorless oil: bp 100 °C/10^{-2} mbar; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.23–4.05 (m, 2H, ester CH_2), 2.75–2.50 (m, 2H, CH_2CN), 2.06–2.00 (m, 2H, CH_2P), 1.85–1.78 (m, 2H, CH_2P), 1.65–1.51 (m, 2H, CH_2), 1.48–1.45 (m, 2H, CH_2), 1.18 (t, J = 7.5 Hz, 3H, ester CH_3), 0.93 (t, J = 7.5 Hz, 3H, alkyl CH_3).

Method E: Acid Hydrolysis of Alkyl (3-Aminopropyl)phosphinic Acid Esters (Scheme 1, Reaction viii). (3-Aminopropyl)*n*-butylphosphinic Acid (10). Ethyl (3-aminopropyl)*n*-butylphosphinate (13.1 g, 63.3 mmol) was dissolved in 100 mL 5 M hydrochloric acid and heated to reflux for 24 h. The solution was cooled to room temperature washed with dichloromethane (DCM) and the aqueous layer evaporated to dryness. The residue was coevaporated with water (5 × 100 mL) followed by absolute ethanol (5 × 100 mL) to give a white solid which was recrystallized from 2-propanol to give 13.2 g (97%) of **10** hydrochloride salt: mp 185–187 °C; ^{1}H NMR (360 MHz, D_2O) δ 3.07 (t, J = 7.5 Hz, 2H, CH_2N), 2.0–1.72 (m, 6H, 2 CH_2P and CH_2), 1.60–1.32 (m, 4H, 2 alkyl CH_2), 0.90 (t, J = 7.5 Hz, 3H, alkyl CH_3). Anal. ($C_7H_{18}NO_2P$·HCl) C, H, Cl, N, P.

A solution of the above hydrochloride salt (5.0 g, 23.18 mmol) in 25 mL of methanol was treated, dropwise over 5–10 min, with 50 mL of propylene oxide. A suspension slowly formed

which was left stirring at room temperature until it had completely redissolved. The solution was left to crystallize overnight at 4 °C and filtered and the crystals dried to give 4.0 g (96.5%) of **10**: mp 235–238 °C; ^{1}H NMR (360 MHz, D_2O) δ 3.10–2.98 (m, 2H, CH_2N), 2.00–1.71 (m, 6H), 1.59–1.33 (m, 4H), 0.90 (t, J = 7.5 Hz, 3H, CH_3). Anal. ($C_7H_{18}NO_2P$) C, H, N, P.

Method F: Alcoholysis of Alkyldichlorophosphines (Scheme 1, Reaction v). *Caution! Alkyldichlorophosphines are extremely reactive toward moisture and air. They are toxic and have a very pungent odour. The lower alkyl derivatives are thermally unstable decomposing to give poisonous pyrophoric products.*

Isopropyl *tert*-Butylphosphinate (14f). A solution of 30 g (0.19 mol) of *tert*-butyldichlorophosphine in 200 mL of dry diethyl ether was cooled to 5 °C under argon. While the temperature was maintained between 5 and 10 °C a solution of 31.5 mL (0.525 mol) of dry 2-propanol and 23.9 mL (0.24 mol) of triethylamine in 100 mL of dry diethyl ether was added dropwise over a period of 3.5 h, a white precipitate appeared immediately, and the reaction became exothermic. The suspension was stirred for 24 hours at room temperature, warmed to 40 °C, stirred at that temperature for 45 min, cooled to room temperature, and filtered. The solid was washed with a further 500 mL of diethyl ether, and the combined filtrates were evaporated to dryness to give an oil. Distillation in high vacuum gave 18.8 g (67%) of **14f** as a colorless oil: bp 82 °C/20 mbar; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25 (d, J = 550 Hz, 1H), 4.80–4.30 (m, 1H, CHOP), 1.53 (s, 9H, *t*-BuP), 0.95 (d, J = 15 Hz, 6H, 2 CH_3).

(3-Aminopropyl)ethylphosphinic acid (8): 90% yield; mp 233–239 °C; ^{1}H NMR (360 MHz, D_2O) δ 3.13 (t, J = 6 Hz, 2H, CH_2N), 2.00–1.88 (m, 2H), 1.73–1–54 (m, 4H), 1.12 (dt, J = 18 and 6 Hz, 3H). Anal. ($C_5H_{14}NO_2P$) C, H, N.

(3-Aminopropyl)*n*-propylphosphinic acid (15): 68% yield; mp 210–213 °C; ^{1}H NMR (360 MHz, D_2O) δ 3.14 (t, J = 7.5 Hz, 2H), 2.00–1.88 (m, 2H), 1.73–1.50 (m, 6H), 1.05 (t, J = 5 Hz, 3H). Anal. ($C_6H_{16}NO_2P$) N, P; C: calcd, 43.63; found, 41.10; H: calcd, 9.76; found, 9.30.

Ethyl (1,1-Difluoro-*n*-butyl)phosphinate (14d). A solution of 15 g (57.5 mmol) of ethyl (difluoromethyl)(1,1-diethoxyethyl)phosphinate (described in part 1, Scheme 4, as precursor of **32**[14]) was dissolved in 144 mL of dry THF and cooled to −78 °C under argon, *n*-butyllithium (46.8 mL of a 1.6 M solution in hexane, 74.9 mmol) was added slowly, the resulting orange solution stirred for 15 min at −78 °C, 1-bromopropane (6.8 mL, 74.9 mmol) was added, and the mixture warmed to 0 °C and stirred for 1.5 h. The reaction was quenched with saturated ammonium chloride solution and extracted with DCM. The organic layer was dried over magnesium sulfate and filtered and the solvent removed to give a yellow oil. Filtration through silica gel, using diethyl ether, gave 11.5 g (66%) of **13d**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.31–4.18 (m, 2H, ester CH_2), 3.95–3.81 (m, 4H, 2 acetal CH_2), 2.20–2.00 (m, 2H, CH_2), 1.90–1.50 (m, 5H, CH_2 and $PCCH_3$), 1.32 (t, J = 6 Hz, 3H, ester CH_3), 1.18 (t, J = 6 Hz, 6H, 2 ketal CH_3), 1.00 (t, J = 7.5 Hz, 3H, alkyl CH_3).

Method G: Hydrolysis of Alkyl (1,1-Diethoxyethyl)phosphinic Acid Esters to Alkyl Phosphinic Acid Esters (Scheme 1, Reaction iv). A solution of 11.0 g (36.5 mmol) of **13d** in 140 mL of DCM containing 10% ethanol was treated dropwise with 5.91 g (55 mmol) of chlorotrimethylsilane over 10 min at room temperature. The clear solution was stirred for 24 h at room temperature and the volatile material removed by evaporation *in vacuo* to give 6.72 g (99%) of **14d** as a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.00 (d, J = 530 Hz, 1H, PH), 4.57–4.10 (m, 2H, ester CH_2), 2.2.13–1.95 (m, 2H, CH_2), 1.1.80–1.60 (m, 2H, CH_2), 1.36 (t, J = 6 Hz, 3H, ester CH_3), 1.00 (t, J = 6 Hz, 3H, alkyl CH_3).

(3-Aminopropyl)(1,1-difluoro-*n*-butyl)phosphinic acid hydrochloride (16): 75% yield; mp 149–151 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ 2.87 (t, J = 7 Hz, 2H, CH_2N), 2.13–1.71 (m, 6H), 1.60–1.45 (m, 2H), 0.97 (t, J = 7 Hz, 3H). Anal. ($C_7H_{17}ClF_2NO_2P$) C, H, Cl, F, N.

(3-Aminopropyl)isobutylphosphinic acid (17): 75% yield; mp 250–253 °C; ^{1}H NMR (360 MHz, D_2O) δ 3.07 (t, J = 7 Hz, 2H, CH_2N), 2.04–1.81 (m, 3H), 1.66–1.45 (m, 4H), 1.00 (d, J = 15 Hz, 6H). Anal. ($C_7H_{18}NO_2P$·0.06H_2O) C, H, N, P, H_2O.

(3-Aminopropyl)*tert*-butylphosphinic acid (18): 86% yield; mp 253–255 °C; ^{1}H NMR (360 MHz, D_2O) δ 3.13 (t, J = 6 Hz, 2H, CH_2N), 2.06–1.78 (m, 2H), 1.6-1.53 (m, 2H), 1.13 (d, J = 15 Hz, 9H, t-Bu). Anal. ($C_7H_{18}NO_2P$·0.15H_2O) C, H, N, P, H_2O.

Method H: Hydrolysis of Alkyl (3-Aminopropyl)phosphinic Acid Esters (Scheme 1, Reaction ix). (3-Aminopropyl)(cyclopropylmethyl)phosphinic Acid (19). A solution of 13.08 g (64.43 mmol) of ethyl (3-aminopropyl)(cyclopropylmethyl)phosphinate (prepared from **14g** via methods C and D) in 125 mL of DCM was treated with 29.58 g (193 mmol) of bromotrimethylsilane at room temperature. The resulting solution was stirred for 24 h at room temperature and the volatile material removed *in vacuo*. The residue was dissolved in 100 mL of 1% aqueous methanol and stirred for 1 h at room temperature. The solvent was evaporated to give a foam which was crystallized from 2-propanol to give 11.8 g (71%) of **19** hydrobromide: mp 152–155 °C. This hydrobromide salt (11.8 g, 45.73 mmol) was dissolved in 100 mL of methanol and 400 mL of propylene oxide added slowly with vigorous stirring. The suspension was stirred at room temperature for 24 h and the product collected by filtration to give, after drying, 8.09 g (100%) of **19**: mp 228–230 °C dec; ^{1}H NMR (360 MHz, D_2O) δ 3.03 (t, J = 6 Hz, 2H, CH_2N), 1.93–1.80 (m, 2H), 1.72–1.60 (m, 2H), 1.48 (dd, J = 15 and 6 Hz, 2H), 0.90–0.75 (m, 1H), 0.58–0.48 (m, 2H), 0.17–0.14 (m, 2H). Anal. ($C_7H_{16}NO_2P$·0.04H_2O) C, H, N, P, H_2O.

(3-Aminopropyl)phenylphosphinic acid (21): 90% yield; mp 298–300 °C; ^{1}H NMR (360 MHz, D_2O) δ 7.87–7.75 (m, 2H), 7.68–7.55 (m, 3H), 3.07 (t, J = 6 Hz, 2H, CH_2N), 1.94–1.78 (m, 4H). Anal. ($C_9H_{14}NO_2P$) C, H, N, P.

(3-Aminopropyl)benzylphosphinic acid (22): 85% yield; mp 273–277 °C; ^{1}H NMR (360 MHz, D_2O) δ 7.51–7.10 (m, 5H), 3.15–2.98 (m, 4H, CH_2Ph and CH_2N), 1.95–1.80 (m, 2H), 1.60–1.49 (m, 2H). Anal. ($C_{10}H_{16}NO_2P$) C, H, N, P.

(3-Aminopropyl)(cyclohexylmethyl)phosphinic acid (24): 74% yield; mp 295–299 °C; ^{1}H NMR (360 MHz, D_2O) δ 3.05 (t, J = 7 Hz, 2H, CH_2N), 1.90–1.80 (m, 4H, 2 CH_2P), 1.71–1.41 (m, 8H), 1.37–0.94 (m, 5H). Anal. ($C_{10}H_{22}NO_2P$) C, H, N, P.

Preparation of **24** from **22**: To a solution of 42.9 g (0.17 mol) of **22** in 500 mL of methanol was added 5 g of Rh_2O_3/PtO_2 (46% Rh, 20.15% Pt; Nishimura's catalyst[67]) and the suspension hydrogenated at room temperature and normal pressure for 8.5 h. The catalyst was removed and the filtrate evaporated to dryness. The residue was stirred with diethyl ether for 1 h and the solid collected by filtration and dried to give 43.7 g (100%) of **24** identical to that obtained by the reactions of Scheme 1.

(3-Aminopropyl)(2-phenylethyl)phosphinic acid (25): 30% yield; mp 265–270 °C; ^{1}H NMR (360 MHz, D_2O) δ 7.51–7.33 (m, 5H, aromatic CH), 3.10 (t, J = 6 Hz, 2H, CH_2N), 3.03–2.95 (m, 2H, CH_2Ph), 2.30–2.18 (m, 2H, CH_2P), 2.05–1.75 (m, 4H, CH_2P, and CH_2). Anal. ($C_{11}H_{18}NO_2P$) C, H, N, P.

(3-Aminopropyl)(2-cyclohexylethyl)phosphinic acid hydrochloride (26): 48% yield; mp 140–142 °C; ^{1}H NMR (360 MHz, D_2O) δ 3.04 (t, J = 6 Hz, 2H, CH_2N), 1.95–1.53 (m, 10H), 1.44–1.33 (m, 2H), 1.30–1.00 (m, 5H), 0.93–0.77 (m, 2H). Anal. ($C_{11}H_{25}ClNO_2P$·0.12H_2O) C, H, Cl, N, P, H_2O.

Ethyl (Diethoxymethyl)(tetrahydrofuran-2-yl)phosphinate (13m). A solution of sodium ethoxide in absolute ethanol (prepared by dissolving 3.35 g, 0.15 mol, of sodium metal in 60 mL of absolute ethanol) was added dropwise to a cooled (0 °C) mixture of 15.98 g (0.15 mol) of 4-chlorobutyraldehyde and 29.4 g (0.15 mol) of **11**[15] in 10 mL of absolute ethanol over the period of 30 min. A strongly exothermic reaction occurred, and a white precipitate appeared. The suspension was then stirred for 1 h at room temperature and the solvent removed *in vacuo*. The residue was partitioned between DCM and water and extracted. The aqueous layer was re-extracted twice with DCM, the combined organic layers were dried over magnesium sulfate and filtered, and the solvent was removed to give a pale yellow oil. Distillation in high vacuum afforded 39.9 g (90%) of **13m** as a colorless oily 1:1 mixture of diastereoisomers: bp 105–110 °C/2 × 10^{-2}

mbar; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.95 and 4.87 (d, J = 8 Hz, total 1H, CHP), 4.35–4.13 (m, 4H, ester CH_2 and ring CH_2O), 3.96–3.80 (m, 3H, acetal CH_2 and ring CH), 3.69–3.61 (m, 2H, acetal CH_2), 2.42–1.82 (m, 4H, 2 ring CH_2), 1.35 (t, J = 7 Hz, 3H, ester CH_3), 1.25 (t, J = 7 Hz, 6H, 2 acetal CH_3).

Ethyl (Tetrahydrofuran-2-yl)phosphinate (14m). **13m** (36 g, 0.14 mol) was treated according to method B to give (tetrahydrofuran-2-yl)phosphinic acid in 94% yield [^{1}H NMR (360 MHz, $CDCl_3$) δ 6.97 (d, 1H, J = 557 Hz, PH), 4.07 (m, 1H, ring CHO), 3.90 (m, 2H, ring OCH_2), 2.15 (m, 2H, ring CH_2), 1.99 (m, 2H, ring CH_2)] which was reesterified with ethyl chloroformate to provide **14m** as a 1:1 mixture of diastereoisomers in 53% yield: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.00 (d, 1H, J = 580 Hz, PH), 4.40–4.00 (m, 3H, ester CH_2 and ring CHO), 3.99–3.85 (m, 2H, ring OCH_2), 2.30–1.80 (m, 4H, 2 ring CH_2), 1.38 (t, J = 7.5 Hz, 3H, ester CH_3).

(3-Aminopropyl)[(*R*,*S*)-tetrahydrofuran-2-yl]phosphinic acid (27): 90% yield; mp 232–235 °C dec; ^{1}H NMR (360 MHz, D_2O) δ 3.70–3.54 (m, 3H, ring CHO and ring CH_2O), 2.85 (t, J = 7.5 Hz, 2H, CH_2N), 2.12–1.35 (m, 8H). Anal. ($C_7H_{16}NO_3P \cdot 0.03H_2O$) C, H, N, P, H_2O.

(3-Aminopropyl)[(*R*,*S*)-tetrahydropyran-2-yl]phosphinic acid (28): 30% yield; mp 290 °C dec; ^{1}H NMR (360 MHz, D_2O) δ 4.00–3.91 (m, 1H, ring CHO), 3.58–3.33 (m, 2H, ring CH_2O), 3.02 (t, J = 7.5 Hz, 2H, CH_2N), 1.94–1.44 (m, 10H). Anal. ($C_8H_{18}NO_3P \cdot 0.25H_2O$) H, N, P, H_2O; C: calcd, 45.39; found, 45.82.

(3-Aminopropyl)[[(*R*,*S*)-tetrahydropyran-2-yl]methyl]phosphinic acid (29): 65% yield; mp 232–238 °C; ^{1}H NMR (360 MHz, D_2O) δ 3.95–3.84 (m, 1H), 3.74–3.60 (m, 1H), 3.50–3.40 (m, 1H), 2.96 (t, J = 7 Hz, 2H, CH_2N), 2.00–1.70 (m, 6H), 1.68–1.20 (m, 6H). Anal. ($C_9H_{20}NO_3P \cdot 0.4H_2O$) C, H, N, P, H_2O.

(2-Pyridylmethyl)phosphinic Acid (30). A solution of 40 g (133 mmol) of **13p**, prepared according to method A, in 135 mL of concentrated hydrochloric acid was heated to reflux for 24 h. The solution was cooled to room temperature, the solvent removed, the residue azeotroped with 100 mL of toluene, and the residue dried in high vacuum to give 20.88 g (100%) of **30**: ^{1}H NMR (360 MHz, D_2O) δ 8.60–8.30 (m, 2H, pyridine CH), 7.90–7.80 (m, 2H, pyridine CH), 3.40 (d, J = 15 Hz, 2H, CH_2P).

Method I: Conjugate Addition of Silylphosphinates to Acrylonitrile (Scheme 2, Reaction ii). (2-Cyanoethyl)-(2-pyridylmethyl)phosphinic Acid (31). A suspension of **30** (2 g, 12.7 mmol) in 53 mL (41.1 g, 250 mmol) HMDS was heated to reflux for 24 h. The clear solution was concentrated *in vacuo* to give the reactive P(III) intermediate as an oil. Acrylonitrile (0.92 mL, 0.74 g, 13.97 mmol) was added and the mixture stirred for 24 h at room temperature. The volatile material was removed *in vacuo* and the residue chromatographed on silica gel using 20:10:1 DCM–MeOH–NH_3 as the eluant to give 0.327 g (12%) of **31** as an oil: ^{1}H NMR (360 MHz, CD_3OD) δ 8.50–8.40 (m, 1H, pyridine CH), 7.91–7.82 (m, 1H, pyridine CH), 7.60–7.50 (m, 1H, pyridine CH), 7.35–7.18 (m, 1H, pyridine CH), 3.20 (d, J = 15 Hz, 2H, CH_2), 2.71–2.65 (m, 2H, CH_2CN), 1.95–1.79 (m, 2H, CH_2P).

(3-Aminopropyl)(2-pyridylmethyl)phosphinic Acid (32). A solution of 0.309 g (1.47 mmol) of **31** in 20 mL of absolute ethanol containing 5% ammonia was treated with 0.1 g of Raney nickel and the suspension hydrogenated at 45 °C and 1 bar for 18 h. The catalyst was removed by filtration and the solvent removed *in vacuo*. The residue was chromatographed on silica gel using DCM–MeOH–NH_3 10/10/1 as the eluant to give 0.21 g (65%) of the amorphous **32**: ^{1}H NMR (360 MHz, D_2O) δ 8.51–8.40 (m, 1H), 7.75–7.70 (m, 1H), 7.50–7.43 (m, 1H), 7.30–7.19 (m, 1H), 3.22 (d, J = 15 Hz, 2H, CH_2P), 2.75 (t, J = 7.5 Hz, 2H, CH_2N), 1.90–1.75 (m, 2H), 1.55–1.35 (m, 2H); high-resolution FAB MS (matrix: glycerin saturated with CsI) calcd for $C_9H_{14}N_2O_2P$ $(M - H)^-$ 213.0793, found 213.0798 ± 0.0002.

Method J: Alkylation of 6 (Scheme 3, Reaction i). (3-Aminopropyl)*n*-hexylphosphinic Acid (20). A suspension of 14.6 g (0.12 mol) of **6**[18] in 96.72 g (0.6 mol) of HMDS was heated to reflux for 24 h under argon. To this solution was added 60 mL of diethyleneglycol dimethyl ether and reflux continued for a further 2 h. The mixture was then cooled to 120 °C, and 38.75 g (0.3 mol) of Hünig's base and 49.5 g (0.3 mol) of *n*-hexyl bromide were added over a period of 20 min. The reaction mixture was refluxed for 24 h, cooled to 10 °C, and filtered. The filtrate was evaporated to dryness and the residue diluted with 300 mL of DCM and extracted three times with 100 mL of 2 M hydrochloric acid. The combined aqueous acidic layers were evaporated and the residue coevaporated with water (5 × 100 mL) followed by absolute alcohol (5 × 100 mL) to give a solid. Recrystallization from 1-propanol–acetone gave the hydrochloride salt of **20**, mp 196–198 °C. This was dissolved in methanol at room temperature and treated with propylene oxide. After stirring at 4 °C for 24 h **20** was isolated by filtration: 75% yield; mp 242–246 °C; ^{1}H NMR (300 MHz, D_2O) δ 2.88 (t, J = 7 Hz, 2H, CH_2N), 1.81–1.50 (m, 6H), 1.40–1.28 (m, 2H), 1.25–1.00 (m, 6H), 0.66 (t, J = 7 Hz, 3H). Anal. ($C_9H_{22}NO_2P$) H, N, P; C: calcd, 54.78; found, 54.30.

(3-Aminopropyl)[(4-fluorophenyl)methyl]phosphinic acid hydrochloride (23): mp 185–190 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.44–7.25 (m, 2H, aromatic CH), 7.20–7.05 (m, 2H, aromatic CH), 3.17 (d, J = 12 Hz, 2H, CH_2Ph), 3.00 (t, J = 7.5 Hz, 2H, CH_2N), 1.98–1.75 (m, 2H), 1.73–1.67 (m, 2H). Anal. ($C_{10}H_{15}FNO_2P \cdot HCl$) H, F, N, P; C: calcd, 44.87; found, 44.39; Cl: calcd, 13.25; found, 11.92.

(3-Aminopropyl)(2-phenylethyl)phosphinic acid hydrochloride (25): 60% yield; mp 170–171 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.55–7.30 (m, 5H), 3.11 (t, J = 7 Hz, 2H, CH_2N), 3.09–2.95 (m, 2H), 2.30–2.25 (m, 2H), 2.00–1.92 (m, 2H), 1.88–1.72 (m, 2H). Anal. ($C_{11}H_{19}ClNO_2P \cdot 0.1H_2O$) C, H, Cl, N, P, H_2O.

(3-Amino-1(*R*,*S*)-methylpropyl)*n*-butylphosphinic Acid (38). From 37:[18] final step, 75% yield; mp 212–215 °C; ^{1}H NMR (300 MHz, D_2O) δ 3.05–2.95 (m, 1H, CHN), 2.88–2.79 (m, 1H, CHN), 2.00–1.43 (m, 5H, 2 PCH_2 and PCH), 1.40–1.13 (m, 4H), 0.96 (dd, J = 15 and 8 Hz, 3H, $PCHCH_3$), 0.67 (t, J = 7 Hz, 3H). Anal. ($C_8H_{20}NO_2P \cdot 0.2H_2O$) C, H, N, P, H_2O.

Method K: Acylation of 6 (Scheme 3, Reaction i). (3-Aminopropyl)(1(*R*,*S*)-hydroxybutyl)phosphinic Acid (33). A suspension of 18.45 g (0.15 mol) of **6**[18] in 250 mL of HMDS was heated to reflux for 24 h under argon. The clear solution was cooled to 10 °C, and 25.2 g (0.35 mol) of *n*-butyraldehyde was added in one portion. An exothermic reaction resulted. After 1 h the volatile materials were removed by evaporation *in vacuo*, and the residue was dissolved in 250 mL of 2 M hydrochloric acid and washed three times with 100 mL of DCM. The aqueous layer was treated with charcoal, filtered, and evaporated. The solid residue was coevaporated with 5 × 100 mL of water and 5 × 100 mL of absolute ethanol and crystallized from ethanol to give 26.3 g (90%) of the hydrochloride salt of **33**: mp 176–178 °C. This was dissolved in 150 mL of methanol at reflux and recooled to room temperature, and 15 mL of propylene oxide was added slowly with vigorous stirring. The turbid solution was left to crystallize at 4 °C for 24 h and the solid collected by filtration and dried to give 20.88 g (100%) of **33**: mp 220–221 °C; ^{1}H NMR (300 MHz, D_2O) δ 3.70–3.60 (m, 1H, C*H*OH), 3.02 (t, J = 7 Hz, 2H, CH_2N), 1.95–1.84 (m, 2H), 1.75–1.30 (m, 6H), 0.90 (t, J = 7 Hz, 3H). Anal. ($C_7H_{18}NO_3P \cdot 0.09H_2O$) C, H, P, H_2O; N: calcd, 7.12; found, 6.59.

(3-Aminopropyl)(1(*R*,*S*)-hydroxybenzyl)phosphinic acid hydrochloride (34): 78% yield; mp 171–172 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.34–7.15 (m, 5H), 4.89–4.75 (m, 1H, C*H*OH), 2.81 (t, J = 7 Hz, 2H, CH_2N), 1.82–1–50 (m, 4H). Anal. ($C_{10}H_{16}NO_3P \cdot HCl.0.12H_2O$) C, H, N, P, H_2O; Cl: calcd, 13.24; found, 13.68.

(3-Aminopropyl)(3-oxobutyl)phosphinic acid (36): 75% yield; mp 163–165 °C dec; ^{1}H NMR (300 MHz, D_2O) δ 2.88 (t, J = 7 Hz, 2H, CH_2N), 2.61–2.50 (m, 2H), 2.06 (s, 3H), 1.72–1.63 (m, 2H), 1.59–1.45 (m, 2H), 1.40 (t, J = 7 Hz, 2H). Anal. ($C_7H_{16}NO_3P \cdot 0.25H_2O$) C, H, N, P, H_2O.

Method L: Condensation of 6 with Epoxides (Scheme 3, Reaction i). (3-Aminopropyl)(3-*N*-phthalimido-2(*R*,*S*)-hydroxypropyl)phosphinic Acid (35). A suspension of 2.46 g (20 mmol) of **6**[18] in 50 mL of hexamethyldisilazane was heated to reflux, under argon, for 24 h. The clear solution was concentrated to circa 10 mL by distillation of the excess hexamethyldisilazane at normal pressure. The concentrated

reaction mixture was allowed to cool to 60 °C and 0.6 g (4.39 mmol) of anhydrous zinc chloride added followed by a solution of 20.3 g (100 mmol) of *N*-(2,3-epoxypropyl)phthalimide in 20 mL of dry tetrahydrofuran. The mixture was refluxed for 36 h and concentrated *in vacuo* and the residue suspended in 250 mL of DCM and filtered. The filtrate was extracted three times with 100 mL of 2 M hydrochloric acid. The acidic aqueous layer was washed with diethyl ether and evaporated to dryness. The residue was coevaporated twice with 50 mL of ethanol to give a beige solid. This was dissolved in 50 mL of methanol treated with 50 mL of propylene oxide at room temperature for 24 h. The resulting solid was collected by filtration, dried, and recrystallized twice from water–acetone to give 1.90 g (30%) of **35**: mp 268–271 °C dec; ^{1}H NMR (300 MHz, D_2O) δ 7.75–7.55 (m, 4H), 4.15–4.03 (m, 1H, C*H*OH), 3.57 (d, J = 7 Hz, 2H, CH_2N-phthalimide), 2.87 (t, J = 7 Hz, 2H, CH_2N), 1.79–1.42 (m, 6H). Anal. ($C_{14}H_{19}N_2O_5P$·0.48H_2O) C, H, N, P, H_2O.

Method M: Conjugate Addition of Ethyl (1,1-Diethoxyethyl)phosphinate to Acrylonitrile (Scheme 1, Reaction ii). Ethyl (2-Cyanoethyl)(1,1-diethoxyethyl)phosphinate (13o). A 1 M solution of sodium ethoxide in absolute ethanol was prepared by dissolving 2.3 g (100 mmol) of sodium metal in 100 mL of absolute ethanol. This was added dropwise over a period of 30 min to a mixture of 42 g (200 mmol) of **12**,[16] preparation described in part 1, there listed in Scheme 4 as **31**[14]), and 10.6 g (200 mmol) of acrylonitrile in 200 mL of absolute ethanol at 10 °C. After a period of 2 min an exothermic reaction occurred and the addition of the sodium ethoxide solution was halted until the reaction reattained 10 °C. The rest of the sodium ethoxide solution was then added, and the reaction mixture warmed to room temperature and stirred for 1.5 h followed by refluxing for 3 h. The reaction was cooled to room temperature, 6.25 g (125 mmol) of glacial acetic acid added, and the solvent removed. The residue was partitioned between DCM and water, the organic layer was separated, dried over magnesium sulfate, and filtered, and the DCM was evaporated to give a pale yellow oil. Distillation in high vacuum afforded 44.04 g (88%) of **13o** as a colorless oil: bp 106–110 °C/10^{-2} mbar; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32–4.12 (m, 2H, ester CH_2), 3.70–3.58 (m, 4H, 2 ketal CH_2), 2.84–2.59 (m, 2H, CH_2CN), 2.25–2.00 (m, 2H, CH_2P), 1.52 (d, J = 12 Hz, 3H, $PCCH_3$), 1.34 (t, J = 7 Hz, 3H, ester CH_3), 1.21 (t, J = 7 Hz, 6H, 2 ketal CH_3).

Ethyl (2-Cyanoethyl)phosphinate (14o). 13o (44 g, 190 mmol) was treated according to method G to give 12.0 g (93%) of **14o** as a colorless oil, which was used without further purification: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.28 (d, J = 545 Hz, 1H, PH), 4.30–4.08 (m, 2H, ester CH_2), 2.76–2.58 (m, 2H, CH_2CN), 2.21–2.03 (m, 2H, CH_2P), 1.38 (t, J = 7 Hz, 3H, ester CH_3).

2(*R*,*S*)-Vinyltetrahydropyran (39). To 91.36 mL (13.43 g, 155 mmol) of a solution of vinylmagnesium chloride (15% in THF), cooled to −5 °C under argon, was added dropwise 19.64 g (119 mmol) of 2-bromotetrahydropyran[68] so that the temperature did not exceed 5 °C. After the addition was complete the reaction mixture was treated carefully with 50 mL of water and brought to pH 1.0 with 2 M hydrochloric acid. The mixture was extracted twice with 100 mL of diethyl ether, the organic phase was separated, dried over magnesium sulfate, and filtered, and the solvent was removed to give an oil. Distillation at normal pressure gave 5.76 g (43%) of **39**: bp 127–131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88–5.75 (m, 1H, vinyl CH), 5.29–5.15 (m, 1H, vinyl CH), 5.10–5.00 (m, 1H, vinyl CH), 4.08–3.96 (m, 1H, ring CHO), 3.52–3.45 (m, 2H, ring CH_2), 1.70–1.26 (m, 6H).

Method N: Radical Addition of Alkyl Phosphinates to 1-Alkenes (Scheme 4, Reaction i). Ethyl (2-Cyanoethyl)[(tetrahydropyran-2-yl)ethyl]phosphinate (40). A solution of 1.12 g (10 mmol) of **39** and 1.46 g (10 mmol) of **14o** in 20 mL of dioxane was heated to reflux and a solution of 0.48 g (2 mmol) of dibenzoyl peroxide in 5 mL of dioxane added dropwise. After 1 h reflux the mixture was cooled to room temperature and evaporated to dryness and the residue partitioned between DCM and 1 M sodium hydroxide solution. The organic phase was separated and dried with magnesium sulfate and the solvent removed to give an oil. This was chromatographed on silica gel using 3% MeOH inDCM as eluant to give 1.1 g (42%) of **40**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11–3.97 (m, 2H, ester CH_2), 3.97–3.88 (m, 1H, ring CHO), 3.45–3.32 (m, 1H, ring CHO), 3.27–3.15 (m, 1H, ring CH), 2.67–2.58 (m, 2H, CHCN), 2.10–1.42 (m, 12H), 1.30 (t, J = 7 Hz, 3H, ester CH_3).

(3-Aminopropyl)[(tetrahydropyran-2(*R*,*S*)-yl)ethyl]phosphinic Acid (41). Hydrogenation of 1.1 g (4.24 mmol) of **40** similar to method D at 35 °C and a pressure of 1 bar for 19 h gave 0.81g (72%) of ethyl (3-aminopropyl)[(tetrahydropyran-2-yl)ethyl]phosphinate, which was hydrolyzed under acidic conditions according to the method E to give 0.49 g (50%) of 41: mp 247–251 °C; ^{1}H NMR (360 MHz, D_2O) δ 3.95–3.89 (m, 1H), 3.47–3.36 (m, 1H), 3.29–3.18 (m, 1H), 2.96 (t, J = 7 Hz, 2H, CH_2N), 1.96–1.75 (m, 4H), 1.72–1.10 (m, 8H). Anal. ($C_{10}H_{22}NO_3P$·0.23H_2O) C, H, N, P, H_2O.

Method O: Hydrolysis of Alkyl (3-Aminopropyl)(dialkoxymethyl)phosphinates (Scheme 5, Reaction iv). (3-Aminopropyl)(diethoxymethyl)phosphinic Acid (9). Lithium hydroxide monohydrate (29.2 g, 695 mmol) was dissolved in 350 mL of water, and a solution of 175.2 g (695 mmol) of ethyl (3-aminopropyl)(diethoxymethyl)phosphinate[18] in 650 mL of ethanol was added. The mixture was refluxed overnight, cooled to room temperature, and concentrated *in vacuo* to about half volume. Addition of phosphoric acid (31 g, 260 mmol) under vigorous stirring produced a white precipitate. The pH of the solution was adjusted to 6. The suspension was filtered, the solid was washed with water, and the combined filtrates were evaporated to dryness. The residue was dissolved in ethanol and filtered and the ethanol evaporated. The semicrystalline mass was dissolved in hot ethanol, triturated with ethyl acetate while hot, and left to crystallize at 4 °C. The solid was collected by filtration and dried in high vacuum to give 128 g (82%) of **9**: mp 210–211 °C; ^{1}H NMR (300 MHz, D_2O) δ 4.52 (d, J = 8 Hz, 1H, CHP), 3.95–3.80 (m, 2H, acetal CH_2), 3.75–3.65 (m, 2H, acetal CH_2), 3.05 (t, J = 7 Hz, 2H, CH_2N), 1.91–1.80 (m, 2H), 1.70–1.58 (m, 2H), 1.23 (t, J = 7 Hz, 6H). Anal. ($C_8H_{20}NO_4P$) C, H, N, P.

(3-Aminopropyl)[bis(*n*-propyloxy)methyl]phosphinic acid (49): 71% yield; mp 223–225 °C; ^{1}H NMR (360 MHz, D2O) δ 4.33 (d, J = 8 Hz, 1H, CHP), 3.70–3.60 (m, 2H, acetal CH_2), 3.55–3.46 (m, 2H, acetal CH_2), 2.85 (t, J = 7 Hz, 2H, CH_2N), 1.80–1.70 (m, 2H), 1.65–1.30 (m, 6H), 0.72 (t, J = 7 Hz, 6H). Anal. ($C_{10}H_{24}NO_4P$) C, H, N, P.

(3-Aminopropyl)[bis(*iso*propyloxy)methyl]phosphinic acid (50): 32% yield; mp 175 °C dec; ^{1}H NMR (300 MHz, D_2O) δ 4.47 (d, J = 8 Hz, 1H, CHP), 3.95–3.75 (m, 2H, 2 acetal CH), 2.87 (t, J = 7 Hz, 2H, CH_2N), 1.89–1.65 (m, 2H), 1.58–1.39 (m, 2H), 1.02 (d, J = 12 Hz, 12H). Anal. ($C_{10}H_{24}NO_4P$·0.5H_2O) C, H, N, H_2O; P: calcd, 11.81; found, 12.69.

(3-Aminopropyl)[bis(*n*-butyloxy)methyl]phosphinic acid (51): 57% yield; mp 221–224 °C; ^{1}H NMR (300 MHz, D_2O) δ 4.32 (d, J = 8 Hz, 1H, CHP), 3.80–3.60 (m, 2H, acetal CH_2), 3.55–3.48 (m, 2H, acetal CH_2), 2.87 (t, J = 7 Hz, 2H, CH_2N), 1.85–1.70 (m, 2H), 1.55–1.40 (m, 6H), 1.20–1.10 (m, 4H), 0.95–0.90 (m, 6H). Anal. ($C_{12}H_{28}NO_4P$) H, N, P; C: calcd, 51.23; found, 50.65.

Ethyl [3-[*N*-(Benzyloxycarbonyl)amino]-1-hydroxypropyl]*n*-butylphosphinate (52). A mixture of 2.07 g (10 mmol) of 3-[*N*-(benzyloxycarbonyl)amino]propanal,[69] 1.50 g (10 mmol) of **14c**, and 1.01 g (10 mmol) of triethylamine was heated to 100 °C for 4 h. The mixture was then cooled to room temperature and the volatile material removed *in vacuo*. The residue was chromatographed on silica gel using initially ethyl acetate followed by 5% methanol in ethyl acetate to give 2.8 g (78%) of **52** as an oily 1:1 mixture of diastereoisomers: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.26 (m, 5H, aromatic CH), 5.37 (br t, 1H, exch. D_2O, NH), 5.11 (AB q, J = 13 Hz, 2H, CH_2Ph), 4.25–3.98 (m, 3H, CH_2OP and C*H*OH), 3.55 and 3.33 (m, 2H, CH_2N), 1.98–1.50 (m, 6H, 5H on D_2O exchange), 1.48–1.22 (m, 6H), 0.91 (t, J = 7 Hz, 3H).

(3-Amino-1(*R*,*S*)-hydroxypropyl)*n*-butylphosphinic Acid (53). Acidic hydrolysis of 2.8 g (7.55 mmol) of **52** according to method E gave 1.19 g (76%) of **53**: mp 123–125 °C; ^{1}H NMR (300 MHz, D_2O) δ 4.05–3.96 (m, 1H, C*H*OH), 3.28–3.15 (m, 2H), 2.15–2.08 (m, 2H), 1.93–1.79 (m, 2H), 1.63–1.34 (m, 4H),

0.91 (t, J = 7 Hz, 3H). Anal. ($C_7H_{18}NO_3P \cdot H_2O$) C, N, P, H_2O; H: calcd, 9.46; found, 8.96.

Isobutyl Dimethylphosphinate (54). Sodium hydride, 55% dispersion in oil (8.83 g, 202 mmol), was washed with dry hexane and suspended in 50 mL of dry THF under argon. A solution of 25 g (184 mmol) of isobutyl methylphosphinate[70] (prepared according to method F) in 50 mL of dry THF was added dropwise over 1 h while the temperature was maintained at 25 °C. The suspension was stirred for 2 h at room temperature, and 31.13 mL (71 g, 500 mmol) of methyl iodide was slowly added. After the addition was complete the mixture was stirred for 24 h at room temperature, 200 mL of water was then added, and the reaction mixture was extracted twice with 200 mL of DCM. The organic layer was removed, dried over magnesium sulfate, and filtered and the solvent evaporated to give a pale yellow oil. Distillation in high vacuum afforded 23.5 g (85%) of **54**: bp 80–85 °C/10^{-1} mbar: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15–3.98 (m, 2H, ester CH_2), 1.88–1.79 (m, 1H), 1.44 (d, J = 15 Hz, 6H, 2 PCH_3), 0.97 (s, 3H, isobutyl CH_3), 0.90 (s, 3H, *iso*-butyl CH_3).

Isobutyl [3-Nitro-2-(4-chlorophenyl)propyl]methylphosphinate (56). To a solution of 20 g (13.3 mmol) of **54** in 50 mL of dry THF was added, over a period of 15 min, a solution of 16.0 mmol of lithium diisopropylamide in 50 mL of dry THF under argon at −78 °C. The resulting yellow solution was stirred for 1 h at −78 °C and added dropwise via a cannula to 50 mL of a dry THF solution of 2.45 g (13.3 mmol) of 4-chloro-β-nitrostyrene[71] at −78 °C. After the mixture was stirred for 30 min at −78 °C, the reaction was quenched with 25 mL of saturated aqueous ammonium chloride solution and warmed to room temperature. The mixture was extracted twice with 100 mL of DCM, the combined organic layers were dried over magnesium sulfate and filtered, and the solvent was removed to give a red oil. Chromatography on silica gel using ethyl acetate 10% ethanol as the eluant gave 0.8 g (18%) of **56** as a 1:1 mixture of diastereoisomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.36 (m, 4H, aromatic CH), 5.10–4.60 (m, 2H, CH_2NO_2), 4.10–3.96 (m, 1H, CHPh), 3.79–3.64 (m, 2H, ester CH_2), 2.15 (d, J = 14 Hz, 2H, CH_2P), 1.30 (d, J = 15 Hz, 3H, PCH_3), 0.97 (s, 3H, isobutyl CH_3), 0.90 (s, 3H, isobutyl CH_3).

Isobutyl [3-Amino-2-(4-chlorophenyl)propyl]methylphosphinate (58). A solution of 0.68 g (2 mmol) of **56** was dissolved in 80 mL of ethanol containing 10% ammonia. Raney nickel slurry (10 g) was added and the suspension hydrogenated for 3 h at room temperature and normal pressure. The catalyst was removed by filtration and the solvent removed to give 0.60 g (100%) of **58**, which was used without further purification.

[3-Amino-2(*R*,*S*)-(4-chlorophenyl)propyl]methylphosphinic Acid (60). A solution of 0.60 g (1.98 mmol) of **58** in 60 mL of concentrated hydrochloric acid was heated to reflux for 24 h. The mixture was cooled to room temperature and evaporated to dryness. The residue was coevaporated with 3 × 50 mL of water followed by 3 × 50 mL of absolute ethanol to give an off white solid which was crystallized from 1-propanol to give the hydrochloride salt of **60**, which was dissolved in 10 mL of ethanol and treated with 10 mL of propylene oxide. The resulting suspension was stirred at room temperature for 24 h and the solid collected by filtration and dried in high vacuum to give 0.32 g (57%) of **60**: mp 165–170 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.95–7.75 (m, 4H, aromatic CH), 3.82–3.75 (m, 2H, CH_2NH_2), 2.45 (d, J = 14 Hz, 2H, CH_2P), 1.35 (d, J = 15 Hz, 3H, PCH_3), CH-*p*-ClC_4H_4 signal obscured by HOD peak. Anal. ($C_{10}H_{15}ClNO_2P \cdot H_2O$) C, H, N, P, H_2O.

[3-Amino-2(*R*,*S*)-(4-chlorophenyl)propyl](diethoxymethyl)phosphinic Acid (61). Lithium hydroxide hydrolysis of **59**[18] according to method O gave **61** in 60% yield: mp 120–121 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.39–7.25 (m, 4H), 4.40 (d, J = 8 Hz, 1H, CHP), 3.77 (q, J = 7 Hz, 2H, ester CH_2), 3.86–3.68 (m, 3H), 3.39–3.25 (m, 1H), 3.06 (dd, J = 12 and 5 Hz, 1H, CHN), 2.15–1.97 (m, 2H), 1.21 (t, J = 7 Hz, 6H). Anal. ($C_{14}H_{23}ClNO_4P \cdot 0.29H_2O$) C, H, N, Cl, P, H_2O.

Method P: Condensation of Alkyl Phosphinates with Epoxides (Scheme 8, Reactions i–iii). Ethyl (3-*N*-Phthalimido-2-hydroxypropyl)*n*-butylphosphinate (62). A solution of 15.0 g (0.1 mol) of **14c** in 150 mL of dry THF under argon was treated with 12.63 g (0.125 mol) of triethylamine at room temperature, and 13.58 g (0.125 mol) of chlorotrimethylsilane was added dropwise. The resulting suspension was stirred overnight at room temperature and filtered under argon and the filtrate evaporated to dryness to give the P(III) intermediate as a colorless oil, which was treated sequentially with 1.5 g (11 mmol) of anhydrous zinc chloride and 20.32 g (0.1 mol) of *N*-(2,3-epoxypropyl)phthalimide at room temperature. A very exothermic reaction occurred, which was allowed to subside, before heating to 70 °C for 24 h. After cooling to room temperature the reaction mixture was diluted with DCM and extracted twice with 100 mL of water. The organic layer was dried over magnesium sulfate and filtered and the solvent removed to give the intermediate trimethylsilyl ether of **62** as a pale yellow oil which was dissolved in methanol containing 1% acetic acid and stirred overnight at room temperature. Removal of the solvent and chromatography on silica gel using ethyl acetate as eluant afforded 14.12 g (40%) of **62** as a 1:1 mixture of diastereoisomers: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88–7.65 (m, 4H), 4.49–4.34 (m, 1H, C*H*OH), 4.20–4.04 (m, 2H, ester CH_2), 3.86–3.81 (m, 2H, CH_2N), 1.98–1.76 (m, 2H, CH_2P), 1.59–1.45 (m, 2H), 1,43–1.38 (m, 2H), 1.25 (t, J = 7 Hz, 3H), 0.90 (t, J = 7 Hz, 3H).

Ethyl (3-*N*-phthalimido-2-hydroxypropyl)benzylphosphinate (63): 40% yield; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88–7.65 (m, 4H), 7.35–7.18 (m, 5H), 4.49–4.35 (m, 1H, C*H*OH), 4.15–3.70 (m, 4H, ester CH_2 and CH_2N), 3.20 (d, J = 15 Hz, 2H, CH_2Ph), 2.05–1.80 (m, 2H, CH_2P), 1.25 (t, J = 7 Hz, 3H).

Ethyl (3-*N*-phthalimido-2-hydroxypropyl)(cyclohexylmethyl)phosphinate (64): 72% yield; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.85–7.74 (m, 4H), 4.47–4.38 (m, 1H, C*H*OH), 4.22–3.97 (m, 2H, ester CH_2), 3.92–3.72 (m, 2H, CH_2N), 2.13–1.57 (m, 10H, 9H on D_2O exchange), 1.40–0.95 (m, 9H).

Ethyl (3-*N*-phthalimido-2-hydroxypropyl)(diethoxymethyl)phosphinate (65): 77% yield; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.85–7.70 (m, 4H), 4.69 (d, J = 8 Hz, 1H, CH-P), 4.45–4.38 (m, 1H, C*H*OH), 4.29–4.15 (m, 2H, ester CH_2), 3.92–3.62 (m, 6H, 2 acetal CH_2 and CH_2N), 2.20–1.80 (m, 2H, CH_2P), 1.35–1.21 (m, 10H, 9H on D_2O exchange).

Method Q: Hydrolysis of Phthalimido-Protected Amino Alcohols 62–64 (Scheme 8, Reaction iv). (3-Amino-2(*R*,*S*)-hydroxypropyl)*n*-butylphosphinic Acid Hydrochloride (66). A solution of 13.27 g (31.22 mol) of 62 was dissolved in 100 mL of concentrated hydrochloric acid and the solution heated to reflux for 24 h. After this time a white solid had appeared, and the suspension was cooled to 0 °C and filtered. The filtrate was evaporated to dryness and the residue coevaporated with water (5 × 100 mL) followed by absolute ethanol (5 × 100 mL) to give an off white solid. Recrystallization from ethanol gave 4.0 g (50%) of **66**: mp 158–160 °C; ^{1}H-NMR (300 MHz, D_2O) δ 4.29–4.15 (m, 1H, C*H*OH), 3.27 (dd, J = 15 and 4 Hz, 1H, CHN), 2.98 (d, J = 15 Hz, 1H, CHN), 2.03–1.68 (m, 2H, CH_2P), 1.68–1.30 (m, 6H), 0.90 (t, J = 7 Hz, 3H). Anal. ($C_7H_{19}ClNO_3P$) C, H, N, Cl, P.

(3-Amino-2(*R*,*S*)-hydroxypropyl)benzylphosphinic acid hydrochloride (67): 80% yield; mp 194–197 °C; ^{1}H-NMR (300 MHz, D_2O) δ 7.55–7.30 (m, 5H), 4.20–4.10 (m, 1H), 3.19–3.09 (m, 2H), 3.08–3.00 (m, 1H, CHN), 2.92–2.86 (m, 1H, CHN), 2.15–1.75 (m, 2H). Anal ($C_{10}H_{17}ClNO_3P \cdot 0.04H_2O$) C, H, N, Cl, P, H_2O.

(3-Amino-2(*R*,*S*)-hydroxypropyl)(cyclohexylmethyl)-phosphinic acid hydrochloride (70): 75% yield; mp 181–182 °C; ^{1}H-NMR (300 MHz, D_2O) δ 4.32–4.28 (m, 1H, C*H*OH), 3.34–3.18 (m, 1H, CHN), 3.10–2.98 (m, 1H, CHN), 2.25–2.09 (m, 2H), 1.85–1.54 (m, 7H), 1.33–0.97 (m, 6H). Anal. ($C_{10}H_{23}ClNO_3P$) C, H, Cl, N, P.

(3-Amino-2(*R*,*S*)-hydroxypropyl)(diethoxymethyl)-phosphinic Acid (73). A solution of **65** (20 g, 0.05 mol) in a mixture of 450 mL of 2-propanol and 75 mL of water was treated with 9.45 g (0.25 mol) of sodium borohydride. The mixture was stirred for 24 h at room temperature, and 15.6 g (0.26 mol) of glacial acetic acid was added slowly. When the gas evolution had ceased the suspension was filtered and the solvent removed to give an oil. Chromatography on silica gel using 3:1 ethyl acetate–ethanol gave 16.7 g (83%) of ethyl [3-[*N*-[2-(hydroxymethyl)benzoyl]amino]-2-hydroxypropyl](diethoxymethyl)phosphinate, a 1:1 mixture of diastereoisomers,

as an oil: ^{1}H-NMR ($CDCl_3$) δ 7.60 (m, 1H), 7.50 (br m, exch. D_2O, 1H), 7.43–7.35 (m, 3H), 4.85 (br t, exch. D_2O, 1H), 4.71 (dd, exch. D_2O, 1H), 4.65 (d, J = 8 Hz, 1H, CHP), 4.59 (d, s on D_2O exch., 2H), 4.39–4.28 (m, 1H), 4.19–4.07 (m, 2H), 3.95–3.78 (m, 2H), 3.67–3.57 (m, 3H, acetal CH_2 and one of CH_2N), 3.48–3.40 (m, 1H, one of CH_2N), 2.21–1.84 (m, 2H, CH_2P), 1.32–1.22 (m, 9H). Hydrolysis of this intermediate with an aqueous lithium hydroxide solution at room temperature for 24 h in a similar way as described in method O gave **73** in 40% yield: mp 194–195 °C; ^{1}H-NMR (300 MHz, D_2O) δ 4.40 (d, J = 8 Hz, 1H, CHP), 4.28–4.20 (m, 1H), 3.90–3.78 (m, 2H), 3.77–3.64 (m, 2H), 3.18 (dd, J = 13 and 6 Hz, 1H, CHN), 2.89 (dd, J = 13 and 3 Hz, 1H, CHN), 2.00–1.88 (m, 1H, CHP), 1.83–1.60 (m, 1H, CHP), 1.23 (t, J = 7 Hz, 6H). Anal ($C_8H_{20}NO_5P \cdot 0.38H_2O$) C, H, N, P, H_2O.

Ethyl (3-Chloro-2(*R*)-hydroxypropyl)(cyclohexylmethyl)phosphinate (76). A solution of 60.0 g (0.315 mol) of **14j** in 250 mL of dry THF under argon was treated with a solution of 48 g (0.35 mol) of triethylamine at room temperature and 44 g (0.347 mol) of chlorotrimethylsilane in 200 mL of dry THF by dropwise addition over 20 min. The resulting suspension was stirred overnight at room temperature and filtered under argon and the filtrate evaporated to dryness to give the P(III) intermediate as a colorless oil. This was treated sequentially with 5.5 g (0.04 mol) of anhydrous zinc chloride and 29.2 g (0.316 mol) of (*R*)-epichlorohydrin at room temperature. A very exothermic reaction occurred, which was allowed to subside, before heating to 70 °C for 24 h. After cooling to room temperature the reaction mixture was diluted with DCM and extracted twice with 100 mL of water. The organic layer was dried over magnesium sulfate and filtered and the solvent removed to give the intermediate trimethylsilyl ether of **76** as a pale yellow oil which was dissolved in 100 mL of methanol containing 1% acetic acid, and the mixture was stirred overnight at room temperature. Evaporation of the solvent and chromatography on silica gel using ethyl acetate as eluant gave 66 g (75%) of **76** as a mixture of diastereoisomers, which slowly solidified to a wax: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (br s, 1H, exch. D_2O, OH), 4.25–4.02 (m, 3H, C*H*OH and ester CH_2), 3.60 (m, 2H, CH_2Cl), 2.11–1.54 (m, 9H), 1.38–0.97 (m, 9H); $[\alpha]^{20}_D$ = +17.9 ± 1.0° (c = 1.125 in $CHCl_3$).

Ethyl (3-chloro-2(*S*)-hydroxypropyl)(cyclohexylmethyl)phosphinate (77): 55% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.47 (br s, 1H, exch. D_2O, OH), 4.25–4.02 (m, 3H, C*H*OH and ester CH_2), 3.69–3.55 (m, 2H, CH_2Cl), 2.11–1.54 (m, 9H), 1.38–0.97 (m, 9H); $[\alpha]^{20}_D$ = −18.3 ± 1.0° (c = 1.025 in $CHCl_3$).

Ethyl (3-chloro-2(*R*)-hydroxypropyl)benzylphosphinate (74): 63% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.30 (m, 5H), 4.19–3.92 (m, 3H, C*H*OH and ester CH_2), 3.60–3.43 (m, 2H, CH_2Cl), 3.21 (d, J = 13 Hz, 2H, CH_2Ph), 2.16–1.83 (m 3H, CH_2P, and OH, becomes 2H after D_2O exchange), 1.30 (t, J = 7 Hz, 3H); $[\alpha]^{20}_D$ = +12.5 ± 0.8° (c = 1.216 in $CHCl_3$).

Ethyl (3-chloro-2(*S*)-hydroxypropyl)benzylphosphinate (75): 73% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.30 (m, 5H), 4.30–4.0 (m, 3H, C*H*OH and ester CH_2), 3.62–3.52 (m, 2H, CH_2Cl), 3.20 (d, J = 14 Hz, 2H, CH_2Ph), 2.15–1.80 (m 3H, CH_2P, and OH, becomes 2H on D_2O exchange), 1.25 (t, 3H); $[\alpha]^{20}_D$ = −12.6 ± 0.9° (c = 1.165 in $CHCl_3$).

Ethyl (3-chloro-2(*R*)-hydroxypropyl)(1,1-diethoxymethyl)phosphinate (78): 51% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (d, J = 8 Hz, 1H, CHP), 4.42–4.38 (m, 1H, C*H*OH), 4.29–4.18 (m, 2H, ester CH_2), 3.894–3.82 (m, 2H, acetal CH_2), 3.80–3.72 (m, 2H, acetal CH_2), 3.68–3.57 (m, 2H, CH_2Cl), 2.32–1.97 (m 3H, CH_2P, and OH, becomes 2H on D_2O exchange), 1.35 (t, J =7 Hz, 3H), 1.28 (t, J = 7 Hz, 6H); $[\alpha]^{20}_D$ = +16.0 ± 1.2° (c = 0.860 in $CHCl_3$).

Method R: Reaction of Chlorohydrins 74–78 with Ammonia (Scheme 9, Reaction iv). Ethyl (3-Amino-2(*R*)-hydroxypropyl)(cyclohexylmethyl)phosphinate (82). A solution of 63.8 g (0.226 mol) of **77** in 180 mL of absolute ethanol was treated with 20 equiv of ammonia and the solution stirred in a sealed tube at room temperature for 4 days. The cloudy solution was then filtered and the filtrate evaporated to dryness to give 53 g (89%) of **82** as an oily mixture of diastereoisomers in a 1:1 ratio: ^{1}H NMR (300 MHz, CD_3OD) δ 4.15–3.86 (m, 3H, CHOH and ester CH_2), 2.85–2.61 (br signal, 2H, CH_2NH_2), 2.00–1.58 (m, 10H, CH_2), 1.40–0–95 (m, 8H, CH_2); $[\alpha]^{20}_D$ = −4.9 ± 1.0° (c = 0.97 in MeOH).

Ethyl (3-amino-2(*S*)-hydroxypropyl)(cyclohexylmethyl)phosphinate (81) as a 1:1 mixture of diastereoisomers: ^{1}H NMR (300 MHz, CD_3OD) δ 4.15–3.86 (m, 3H, CHOH and ester CH_2), 2.85–2.61 (m, 2H, CH_2NH_2), 2.00–1.58 (m, 10H, CH_2), 1.40–0–95 (m, 8H, CH_2); $[\alpha]^{20}_D$ = +5.1 ± 1.2° (c = 0.82 in MeOH).

Ethyl (3-amino-2(*S*)-hydroxypropyl)benzylphosphinate (79) as a 1:1 mixture of diastereoisomers: ^{1}H NMR (300 MHz, CD_3OD) δ 7.29–7.20 (m, 5H, aromatic CH), 4.25–4.18 (m, 1H, C*H*OH), 4.05–3.95 (m, 2H, ester CH_2), 3.21 (d, J = 15 Hz, CH_2Ph), 3.17–3.08 (m, 1H, CHN), 2.95–2.84 (m, 1H, CHN), 2.14–2.00 (m, 2H, CH_2P), 1.25 (t, J = 7.5 Hz, ester CH_3); $[\alpha]^{20}_D$ = −5.7 ± 1.0° (c = 1.045 in MeOH).

Ethyl (3-amino-2(*R*)-hydroxypropyl)benzylphosphinate (80) as a 1:1 mixture of diastereoisomers: ^{1}H NMR (300 MHz, CD_3OD) δ 7.29–7.20 (m, 5H, aromatic CH), 4.25–4.18 (m, 1H, C*H*OH), 4.05–3.95 (m, 2H, ester CH_2), 3.21 (d, J = 15 Hz, CH_2Ph), 3.17–3.08 (m, 1H, CHN), 2.95–2.84 (m, 1H, CHN), 2.14–2.00 (m, 2H, CH_2P), 1.25 (t, J = 7.5 Hz, ester CH_3); $[\alpha]^{20}_D$ = +4.3 ± 0.9° (c = 1.120 in MeOH).

Ethyl (3-amino-2(*S*)-hydroxypropyl)(diethoxymethyl)phosphinate (83) as a 1:1 mixture of diastereoisomers: ^{1}H NMR (300 MHz, CD_3OD) δ 4.70 (d, J = 7.5 Hz, CHP), 4.30–4.00 (m, 3H, ester CH_2 and C*H*OH), 3.92–3.80 (m, 2H, acetal CH_2), 3.87–3.64 (m, 2H, acetal CH_2), 2.90–2.89 (m, 1H, CHN), 2.75–2.65 (m, 1H, CHN), 2.20–1.95 (m, 2H, CH_2P), 1.33 (t, J = 7 Hz, ester CH_3), 1.25 (t, J = 7.5 Hz, acetal CH_3); $[\alpha]^{20}_D$ = −4.8 ± 1.0° (c = 1.010 in MeOH).

Acidic hydrolyses of **79–82** according to method E or basic hydrolysis of **83** according to method O gave the phosphinic acids:

(3-Amino-2(*S*)-hydroxypropyl)benzylphosphinic acid hydrochloride (68): 50% yield; 99% ee; mp 165–167 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.45–7.32 (m, 5H), 4.29–4.18 (m, 1H), 3.26–3.17 (m, 3H), 2.93 (dd, J = 15 and 5 Hz, 1H), 2.10–1.85 (m, 2H); $[\alpha]^{20}_D$ = −5.2 ± 1.0° (c = 0.972 in H_2O). Anal. ($C_{10}H_{17}ClNO_3P \cdot 0.4H_2O$) C, H, N, P, H_2O; Cl: calcd, 12.99; found, 13.58.

(3-Amino-2(*R*)-hydroxypropyl)benzylphosphinic acid (69): 25% yield; 98% ee; mp 239–241 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.45–7.32 (m, 5H), 4.29–4.18 (m, 1H), 3.28–3.18 (m, 3H), 2.93 (dd, J = 15 and 5 Hz, 1H), 2.10–1.85 (m, 2H); $[\alpha]^{20}_D$ = +8.5 ± 1.1° (c = 0.949 in H_2O). Anal. ($C_{10}H_{16}NO_3P \cdot 0.04H_2O$) C, H, N, P, H_2O.

Method for Determination of Enantiomeric Excess (ee). **68** (2 mg, 8.7 μmol) was dissolved in 1 mL of 90% aqueous acetonitrile. A solution of 5 mg (12.84 μmol) of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylisothiocyanate in 4.5 mL of acetonitrile and 0.5 mL (3.6 mmol) of triethylamine was added and the mixture stirred for 20 min at room temperature. After evaporation *in vacuo* the residue was extracted between 10 mL of a 0.01 M Na_2HPO_4 solution and 2 mL of DCM. After centrifugation, 10 μL of the aqueous phase were injected into the HPLC. Analysis conditions: HPLC on Kromasil 5C18 5μm columns (250 × 4 mm), using solvent systems A (H_2O containing 0.1% trifluoracetic acid) and B (acetonitrile containing 0.1% trifluoroacetic acid) and the gradients 20% solvent system B for 30 min, 35% B for 2 min followed by 20% B. Flow rate 1 mL/min at room temperature, 120 bar, UV detection, λ = 240 nm. t_R: = (*S*)-**68**, 28.9 min; (*R*)-**69**, 29.5 min.

(3-Amino-2(*S*)-hydroxypropyl)(cyclohexylmethyl)phosphinic acid hydro-chloride (71): 85% yield; >99% ee; mp 173–175 °C; ^{1}H NMR (300 MHz, D_2O), δ 4.23 (m, 1H), 3.20 (dd, J = 15 and 7 Hz, 1H, CHN), 2.97 (dd, J = 15 and 4 Hz, 1H, CHN), 2.18–2.00 (m, 2H), 1.78–1.56 (m, 7H), 1.29–0.98 (m, 6H); $[\alpha]^{20}_D$ = −4.2 ± 0.9° (c = 1.056 in H_2O). Anal. ($C_{10}H_{23}ClNO_3P$) C, H, Cl, N, P.

(3-Amino-2(*R*)-hydroxypropyl)(cyclohexylmethyl)phosphinic acid hydro-chloride (72): 85% yield; >99% ee; mp 174–176 °C; $[\alpha]^{20}_D$ = +3.5 ± 1.0° (c = 1.026 in H_2O). Anal. ($C_{10}H_{23}ClNO_3P$) C, H, Cl, N, P.

Method for Determination of Enantiomeric Excess (ee). t_R: = (*S*)-**71**, 36.9 min; (*R*)-**72**, 37.6 min.

(3-Amino-2(*S*)-hydroxypropyl)(1,1-diethoxymethyl)phosphinic acid (84): 40% yield; 96% ee; mp 215–217 °C dec; ^{1}H NMR (300 MHz, D_2O) δ 4.38 (d, J = 8 Hz, 1H, CHP),

4.31–4.17 (m, 1H), 3.896–3.76 (m, 2H), 3.75–3.61 (m, 1H), 3.16 (dd, J = 15 and 6 Hz, 1H, CHN), 2.88 (dd, J = 15 and 4 Hz, 1H, CHN), 1.93 (dt, J = 13 and ≤2 Hz, 1H, CHP), 1.78 (dt, J = 13 and ≤2 Hz, 1H, CHP), 1.23 (t, J = 7 Hz, 6H); $[\alpha]^{20}_D$ = −10.9 ± 1.4° (c = 0.72 in H_2O). Anal. ($C_8H_{20}NO_5P \cdot 0.15H_2O$) C, H, N, P, H_2O.

Method for Determination of Enantiomeric Excess (ee). t_R: = (*S*)-**84**, 22.0 min; (*R,S*)-**73**, 22.0 and 22.5 min.

Ethyl 1-(4-Chlorophenyl)oxirane-1-carboxylate (85). A solution of 7.19 g (34 mmol) of ethyl 2-(4-chlorophenyl)-acrylate[72] in 70 mL of chloroform was treated with 10.4 g (51 mmol) of *m*-chloroperbenzoic acid and refluxed for 24 h. The reaction was cooled to room temperature, diluted with chloroform, and washed sequentially with 10% aqueous sodium bisulfite, 10% aqueous sodium bicarbonate, and water. The organic phase was dried over magnesium sulfate and filtered and the solvent removed to give an oil. Chromatography on silica gel using 9:1 ethyl acetate–hexane as eluant afforded 6.38 g (83%) of **85** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.40 (m, 4H), 4.26 (q, J = 8 Hz, 2H), 3.43 (d, J = 15 Hz, 1H), 2.91 (d, J = 15 Hz, 1H), 1.28 (t, J = 7 Hz, 3H).

Ethyl (2-Carbethoxy-2-(4-chlorophenyl)-2-hydroxyethyl)*n*-butylphosphinate (86). Following method L for epoxide opening with the silylated P(III) intermediate of **14c**, a 62% yield of **86** was obtained after chromatography on silica gel using ethyl acetate as eluant, as a 1:1 mixture of diastereoisomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5H), 4.13–4.00 (m, 2H), 3.85 (q, J = 7 Hz, 2H), 2.53 and 2.27 (AB q, J = 16 Hz, 2H, CH_2P), 1.78–1.39 (m, 4H), 1.38–1.24 (m, 2H), 1.22 (t, J = 7 Hz, 3H), 1.17 (t, J = 7 Hz, 3H), 0.86 (t, J = 7 Hz, 3H).

Ethyl (2-Carboxamido-2-(4-chlorophenyl)-2-hydroxyethyl)*n*-butylphosphinate (87). To a solution of 9.16 g (21.08 mmol) of **86** in 100 mL of absolute ethanol was added 100 mg (2 mmol) of sodium cyanide, and ammonia gas was condensed into the mixture. The reaction vessel was sealed and heated to 50 °C for 10 h. The mixture was cooled to room temperature and evaporated to dryness. Chromatography on silica gel using 5% methanol in DCM as eluant gave 6.52 g (89%) of **87** as a 1:1 mixture of diastereoisomers (oil, which slowly solidified): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.49 (m, 4H), 6.87 and 6.82 (br d, 2H, exch. D_2O, NH), 5.32 (br d, 1H, exch. D_2O, OH), 4.17–3–68 (m, 2H, ester CH_2), 2.90–2.14 (m, 2H, CH_2P), 1.96–1.80 (m, 2H), 1.564–1.47 (m, 2H), 1.444–1.38 (m, 2H), 1.35 (t, J = 7 Hz, 3H), 0.87 (t, J = 7 Hz, 3H). Anal. ($C_{15}H_{23}ClNO_4P \cdot 0.07H_2O$) C, H, Cl, N, P, H_2O.

[3-Amino-2(*R,S*)-(4-chlorophenyl)-2-hydroxypropyl]*n*-butylphosphinic Acid Sodium Salt (89). A solution of 1.04 g (3 mmol) of **87** in 10 mL of anhydrous THF was heated to reflux under argon and 0.69 g (9 mmol) of borane dimethyl sulfide complex added. Gas evolved, and the mixture was refluxed for 3 h, cooled to room temperature, and treated with methanol, the solvent removed, and the residue chromatographed on silica gel using 1:9 methanol–DCM as eluant to give 0.4 g (40%) of **88**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.38 (m, 4H), 5.73 (br s, 1H, exch. D_2O, OH), 3.98–3.78 (m, 2H), 3.22–3.04 (m, 2H), 2.94–2.78 (m, 2H), 2.47–2.07 (m, 2H), 1.75–1.0 (m, 9H), 0.895–0.80 (m, 3H). This ester was hydrolyzed with 0.24 g (6 mmol) of sodium hydroxide in water/ethanol, 1:2 at 60 °C for 24 h, followed by reverse phase chromatography on Opti-Up C-18 with methanol water to give 0.3 g of the sodium salt of **89** in 50% yield: mp 220–222 °C; ^{1}H NMR (300 MHz, D_2O + 1 drop trifluoroacetic acid) δ 7.61–7.55 (m, 4H), 3.02 (AB q, J = 15 Hz, 2H, CH_2N), 2.45–2.33 (m, 2H, CH_2P), 2.12–1.99 (m, 2H, CH_2P), 1.30–1.00 (m, 4H), 0.72 (t, J = 7 Hz, 3H). Anal. ($C_{13}H_{20}ClNNaO_3P \cdot 1.25H_2O$) C, H, Cl, N.

Ethyl [2-(4-Chlorophenyl)propen-2-yl]phosphinate (91). A solution of 14.42 g (40 mmol) of **90** (prepared as described in part 1,[14] see Scheme 2, **25**) in 50 mL of 10% ethanol in DCM was treated with 6.52 g (60 mmol) of chlorotrimethylsilane and the clear solution stirred for 24 h at room temperature. The volatile material was removed to give 6.68 g (70%) of **91** as a colorless oil, which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.30 (m, 4H, aromatic CH), 7.05 (d, J = 540 Hz, 1H, PH), 5.56 (d, J = 6 Hz, 1H, CH=), 5.50 (d, J = 6 Hz, 1H, CH=), 4.20–3.97 (m, 2H, ester CH_2), 3.07 (m, 2H, CH_2P), 1.27 (t, J = 6 Hz, 3H).

Ethyl [2-(4-Chlorophenyl)prop-1-enyl]methylphosphinate (92). A solution of 5 g (20.4 mmol) of **91** in dry 5 mL of dry THF under argon was cooled to −78 °C and treated with 12.57 mL (20.4 mmol) of *n*-butyllithium (1.6 M solution in hexane) by dropwise addition over 15–20 min. The solution was stirred for 10 min at −78 °C, and 2 mL of precooled (−25 °C) methyl iodide was added slowly. After the mixture was stirred for 5 min at −78 °C, saturated aqueous ammonium chloride was added and the reaction warmed to room temperature and extracted with DCM. The organic layer was removed and dried over magnesium sulfate and the solvent evaporated to give an oil. Chromatography on silica gel using 10% acetone in ethyl acetate as eluant afforded 2.18 g (60%) of **92**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.30 (m, 4H, aromatic CH), 5.48 (d, J = 7 Hz, 1H, CH=), 5.30 (d, J = 7 Hz, 1H, CH=), 4.02–3.95 (m, 2H, ester CH_2), 3.04 (d, J = 12 Hz, 2H, CH_2P), 1.36 (d, J = 14 Hz, 3H, PCH_3), 1.10 (t, J = 7 Hz, 3H).

Ethyl [2-(4-chlorophenyl)propen-2-yl]*n*-butylphosphinate (93): 20% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.29 (m, 4H, aromatic CH), 5.47 (d, J = 6 Hz, 1H, CH=), 5.30 (d, J = 6 Hz, 1H, CH=), 4.12–3.78 (m, 2H, ester CH_2), 3.00 (d, J = 15 Hz, 2H, CH_2P), 1.83–1.09 (m, 9H, 3 CH_2 and PCH_3), 0.85 (t, J = 7 Hz, 3H).

Ethyl [3-[(*tert*-Butoxycarbonyl)amino]-2-(4-chlorophenyl)-2-hydroxypropyl]methylphosphinate (94). A solution of 1.67 g (50 mmol) of *tert*-butyl carbamate in 50 mL of methanol was cooled to 0 °C under argon and 5.43 g (50 mmol) of *tert*-butyl hypochlorite was added slowly and the resulting solution stirred for 15 min at 0 °C. A solution of 2.1 g (52.5 mmol) of sodium hydroxide in 15 mL of methanol was added and the cool bath removed. The solution was stirred for 10 min and the solvent removed. The residue was dried in high vacuum and stirred with ether and filtered. The beige crystals thus obtained were suspended in 30 mL of acetonitrile at room temperature and treated with 2.208 g (13 mmol) of silver nitrate followed by 1.67 g (6.46 mmol) of **92** in 2 mL of acetonitrile. This suspension was then treated with 2.0 mL of a 2.5% solution of osmium tetroxide in *tert*-butyl alcohol (0.2 mmol) and 0.523 mL (30 mmol) of water. The black suspension was stirred for 24 h at room temperature and filtered and the filtrate treated with 4 mL of 5% aqueous sodium bisulphite solution. This mixture was refluxed for 3 h and the acetonitrile removed *in vacuo*. The residue was diluted with water and extracted with chloroform. The organic phase was dried and removed to give a yellow oil. Chromatography on silica gel using DCM followed by 5% methanol in DCM gave 1.05 g (42%) of **94** as a 1:1 mixture of diastereoisomers: mp 115–119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (m, 2 × 4H, aromatic CH), 5.90 and 5.75 (br s, 2 × 1H, exch. D_2O, OH), 5.15 (br t, 2 × 1H, exch. D_2O, NH), 4.01 (q, J = 7 Hz, 2 × 2H, ester CH_2), 3.57–3.20 (m, 2 × 2H, CH_2N), 2.50–2.09 (m, 2 × 2H, CH_2P), 1.60–1.20 (m, 24H, 2 × *t*-Bu, one of PCH_3 diastereoisomers, and one of ester CH_3 diastereoisomers), 0.92 (t, J = 7 Hz, 3H, one of ester CH_3 diastereoisomers), 0.80 (d, J = 13 Hz, 3H, one of PCH_3 diastereoisomers).

Ethyl [3-[(*tert*-Butoxycarbonyl)amino]-2-(4-chlorophenyl)-2-hydroxypropyl]*n*-butylphosphinate (95): 66% yield of a 1:1 mixture of diastereoisomers; mp 85–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.33 (m, 4H, aromatic CH), 6.05 and 5.90 (br s, 1H, exch. D_2O, OH), 5.09 (br t, 1H, exch. D_2O, NH), 4.17–3.95 (m, 2H, ester CH_2), 3.10 and 4.20 (m, 2H, CH_2N), 2.40–2.12 (m, 2H, CH_2P), 1.73–1.0 (m, 18H), 0.89 and 0.75 (t, J = 7 Hz, 3H, CH_3).

[3-Amino-2(*R,S*)-(4-chlorophenyl)-2-hydroxypropyl]methylphosphinic Acid (96). A solution of **94** (1.046 g, 2.672 mmol) in 10 mL of DCM was treated with 2.045 g (13.36 mmol) of bromotrimethylsilane at room temperature for 24 h. The volatile material was then removed *in vacuo* and the residue dissolved in methanol containing 1% water. After the mixture was stirred for 30 min at room temperature the solvent was removed and the residue redissolved in 1 mL of methanol and treated with propylene oxide until neutral, a white precipitate appeared which, after stirring overnight at room temperature, was collected by filtration and dried to give 0.6 g (85%) of **96**: mp 219.5–220 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.58–7.549

(m, 4H, aromatic CH), 3.42 (AB q, J = 16 Hz, 2H, CH_2N), 2.50 (AB q, J = 16 Hz, 2H, CH_2P), 1.02 (d, J = 12 Hz, 3H, PCH_3). Anal. ($C_{10}H_{15}ClNO_3P \cdot 0.13H_2O$) C, H, Cl, N, P, H_2O.

[3-Amino-2(*R,S*)-(4-chlorophenyl)-2-hydroxypropyl]*n*-butylphosphinic acid (89): 100% yield; mp 215–216.5 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.58–7.49 (m, 4H, aromatic CH), 3.25 (AB q, J = 15 Hz, 2H, CH_2N), 2.36 (AB q, J = 15 Hz, 2H, CH_2P), 2.00 (m, 2H, CH_2P), 1.30–1.00 (m, 4H, CH_2), 0.72 (t, J = 7 Hz, 3H, CH_3). Anal ($C_{13}H_{21}ClNO_3P$) C, H, Cl, N, P.

1-[[(*tert*-Butoxycarbonyl)amino]methyl]-1-methyloxirane (97). A solution of *meta*-chloroperbenzoic acid (27.18 g, 0.157 mol) in 200 mL of chloroform was cooled to 15 °C and treated with 50 mL of a chloroform solution of 17.1 g (0.105 mol) of 3-[*N*-(*tert*-butyloxycarbonyl)amino]-2-methylprop-1-ene over a period of 1 h while the temperature was maintained at 15–20 °C. After 30 min a white precipitate appeared and the reaction mixture was diluted with chloroform and washed with 10% aqueous sodium bisulfite solution (3 × 100 mL) followed by 10% aqueous sodium bicarbonate solution (3 × 100 mL). The organic layer was dried and the solvent removed to give 20 g (100%) of **97** as a viscous colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.2 (br s, 1H, exch. D_2O, NH), 3.38–3.30 (m, 2H), 2.70 (d, J = 7 Hz, 1H), 2.62 (d, J = 7 Hz, 1H), 1.49 (s, 9H), 1.34 (s, 3H).

Ethyl [3-[*N*-(*tert*-Butoxycarbonyl)amino]-2-hydroxy-2-methylpropyl]*n*-butylphosphinate (98). Prepared according to method L for epoxide opening with P(III) intermediate obtained from **14c** to give 5.85 g (86%) of **98** as a colorless oily 1:1 mixture of diastereoisomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17 and 4.68 (br s, 1H, exch. D_2O, OH) 4.07 (m, 2H, ester CH_2), 3.18 (m, 2H), 1.93–1.22 (m, 24H, 23H after D_2O exch.), 0.92 (t, 3H).

(3-Amino-2(*R,S*)-hydroxy-2-methylpropyl)*n*-butylphosphinic Acid (99). **98** (0.73 g, 2.37 mmol) of was dissolved in 10 mL of 1 M aqueous hydrochloric acid and refluxed for 24 h. The acidic solution was washed with DCM and diethyl ether and the water removed. The residue was coevaporated with water (5 × 50 mL) followed by absolute ethanol (5 × 50 mL) to give a foam. This was dissolved in ethanol and treated with propylene oxide. The solution was evaporated to dryness and the residue crystallized from ethanol–acetone to give 0.1 g (20%) of **99**: mp 187–189 °C; ^{1}H NMR (300 MHz, D_2O) δ 3.75 (d, J = 12 Hz, 1H, CHN), 3.44 (d, J = 12 Hz, 1H, CHN), 2.15 (d, J = 15 Hz, 1H, CHP), 1.97 (d, J = 15 Hz, 1H, CHP), 1.64–1.32 (m, 9H), 0.88 (t, J = 7 Hz, 3H); MS m/e 210 $(M + H)^+$.

Ethyl *n*-Butylmethylphosphinate (100). Sodium hydride (55% dispersion in oil, 8 g, 183 mmol) was washed with dry hexane and suspended in 50 mL of dry THF under argon. A solution of 25 g (166 mmol) of **14c** in 50 mL of dry THF was added dropwise over 1 h while the temperature was maintained at 25 °C. The suspension was stirred for 3 h at room temperature, and 31.13 mL (71 g, 500 mmol) of methyl iodide was slowly added. After the addition was complete the mixture was stirred for 24 h at room temperature, 200 mL of water was then added, and the reaction mixture was extracted twice with 200 mL of DCM. The organic layer was removed, dried over magnesium sulfate, and filtered and the solvent evaporated to give a pale yellow oil. Distillation in high vacuum afforded 23.2 g (85%) of **100**: bp 90–95 °C/10^{-1} mbar; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15–4.00 (m, 2H, ester CH_2), 1.8–1.65 (m, 2H, CH_2P), 1.60–1.51 (m, 2H), 1.49–1.40 (m, 5H, PCH_3 and CH_2), 1.32 (t, J = 7 Hz, 3H, ester CH_3), 0.93 (t, J = 7.5 Hz, 3H, alkyl CH_3).

Ethyl (cyclopropylmethyl)methylphosphinate (101): 74% yield; bp 100–106 °C/10^{-1} mbar; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17–3.98 (m, 2H, ester CH_2), 1.69–1.55 (m, 2H, CH_2P), 1.47 (d, J = 15 Hz, 3H, PCH_3), 1.30 (t, J = 7 Hz, 3H, ester CH_3), 0.90–0.85 (m 1H), 0.57–0.52 (m, 2H), 0.20–0.18–6 (m, 2H).

Ethyl (cyclohexylmethyl)methylphosphinate (102): oil; 80% yield after chromatography on silica gel using initially DCM followed by 95:5 DCM–MeOH as eluants; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20–4.00 (m, 2H, ester CH_2), 1.94–1.57 (m, 7H), 1.45 (d, J = 15 Hz, 3H, PCH_3), 1.36–0.95 (m, 11H).

Ethyl [3-[*N*-(*tert*-Butoxycarbonyl)amino]-2-oxopropyl]*n*-butylphosphinate (103). A solution of 60 mmol of lithium diisopropylamide in 50 mL of THF was cooled to −78 °C under argon, and 9.84 g (60 mmol) of **100** in 10 mL THF was added dropwise over 15 min. The pale yellow solution was stirred for 1 h at −78 °C, and a solution of 1.89 g (10 mmol) of Boc-glycine methyl ester in 10 mL of THF was added. The reaction mixture was stirred for 15 min at −78 °C, quenched with 3.66 g (61 mmol) of glacial acetic acid, and warmed to room temperature. The mixture was partitioned between DCM and water, the organic phase dried, and the solvent removed. Excess **100** was recovered by distillation. The residue was chromatographed on silica gel using 5% methanol–DCM to give 2.80 g (87%) of **103**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (br s, 1H, exch. D_2O, NH), 4.18–4.05 (m, 4H, ester CH_2 and CH_2N), 3.10 (AB q, J = 156 Hz, 2H, $COCH_2P$), 1.88–1.75 (m, 2H, CH_2P), 1.65–1.49 (m, 2H), 1.45 (s, 9H), 1.37–1.33–2 (m, 5H), 0.93 (t, J = 7 Hz, 3H).

Ethyl [3-[*N*-(*tert*-butoxycarbonyl)amino]-2-oxopropyl](cyclopropylmethyl)phosphinate (104): 85% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (br s, 1H, exch. D_2O, NH), 4.22–4.09 (m, 4H, ester CH_2 and CH_2N), 3.17 (AB q, J = 16 Hz, 2H, $COCH_2P$), 1.93–1.68 (m, 2H, CH_2P), 1.45 (s, 9H), 1.35 (t, J = 7 Hz, 3H), 1.01–0.94 (m, 1H), 0.72–0.63 (m, 2H), 0.23–0.18 (m, 2H). Anal. ($C_{14}H_{26}NO_5P \cdot 0.25H_2O$) H, N, P, H_2O; C: calcd, 51.92; found, 51.25.

Ethyl [3-[*N*-(*tert*-butoxycarbonyl)amino]-2-oxopropyl](cyclohexylmethyl)phosphinate (105): 84% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43 (br s, 1H, exch. D_2O, NH), 4.19–4.05 (m, 4H), 3.09 (AB q, J = 16 Hz, 2H), 1.92–1.60 (m, 7H), 1.45 (s, 9H), 1.37–0.99 (m, 9H).

(3-Amino-2-oxopropyl)*n*-butylphosphinic Acid (106). A solution of 0.642 g (2 mmol) of **103** was dissolved in 10 mL of DCM, and 1.53 g (10 mmol) bromotrimethylsilane was added. The solution was stirred for 16 h at room temperature, the volatile material removed *in vacuo*, and the residue dissolved in methanol containing 1% water and stirred for 30 min. The solvent was removed to give a yellow foam which was dissolved in ethanol, treated with propylene oxide, and stirred at room temperature overnight. The solid was collected by filtration and dried to give 0.37 g (100%) of **106**: mp 128–130 °C; ^{1}H NMR (300 MHz, D_2O) δ 4.16 (s, 2H, CH_2N), 3.12 (d, J = 15 Hz, 2H, CH_2P), 1.85–1.70 (m, 2H), 1.60–1.29 (m, 4H), 0.88 (t, J = 7 Hz, 3H). Anal. ($C_7H_{16}NO_3P \cdot 0.11H_2O$) C, H, N, P, H_2O.

(3-Amino-2-oxopropyl)(cyclopropylmethyl)phosphinic acid (107): mp 109–110 °C; ^{1}H NMR (300 MHz, D_2O) δ 4.15 (s, 2H, CH_2N), 3.18 (d, J = 15 Hz, 2H, CH_2P), 1.58 (dd, J = 15 and 6 Hz, 2H, CH_2P), 0.89–0.78 (m, 1H), 0.64–0.58 (m, 2H), 0.22–0.15 (m, 2H). Anal. ($C_7H_{14}NO_3P \cdot 0.37H_2O$) H, N, P, H_2O; C: calcd, 42.50; found, 43.19.

(3-Amino-2-oxopropyl)(cyclohexylmethyl(phosphinic acid hydrobromide (108): 55% yield; mp 180–182 °C; ^{1}H NMR (300 MHz, D_2O) δ 4.15 (s, 2H, CH_2N), 3.10 (d, J = 15 Hz, 2H, CH_2P), 1.99–1.79 (m, 2H), 1.73–1.52 (m, 4H), 1.34–0.95 (m, 5H). Anal. ($C_{10}H_{20}NO_3P \cdot HBr$) C, H, Br, N, P.

Radioreceptor Binding Protocol. Receptor binding assays using [^{3}H]CGP27492 as a novel $GABA_B$ receptor agonist radioligand and membranes from rat cerebral cortex were carried out according to refs 24 and 28. Incubations were performed in triplicate, which varied by less than 5%, and nonspecific binding determined in presence of 10 μM of (*R*)-(−)-baclofen. IC_{50} values were obtained by computer-aided curve fitting, according to a single site model. log IC_{50} values of $GABA_B$ binding experiments and their respective standard errors for all compounds are listed in the supplementary material.

Measurements of the inhibition of binding of [^{3}H]ligands from $GABA_A$, benzodiazepine, NMDA, quisqualate, kainate, muscarinic acetylcholine, α_1-adrenergic, α_2-adrenergic, 5-HT_1, histamine 1, and adenosine 1 receptors were carried out according to ref 28. For the other central nervous system receptors the following radioligands were used: [^{3}H]dihydroalprenolol for β-adrenoceptors, [^{3}H]ketanserin for 5-HT_2 receptors, [^{3}H]BRL 43 694 for 5-HT_3 receptors, [^{3}H]naloxone for opiate receptors (μ-type), [^{3}H]substance P for NK-1 receptors according to references described in the preceding paper,[14] [^{3}H]-

quinuclidine benzylate for muscarinic acetylcholine receptors,[73] [^{3}H]tiotidine for histamine H_2 receptors,[74] and [^{3}H]-5,7-dichlorokynurenic acid for NMDA receptor-associated glycine binding sites.[75]

Antagonism to the hyperpolarization of the membrane potential in hippocampal slices: according to ref 28.

Increase of GABA release: according to ref 76. All experiments were performed in quadruplicate. EC_{150} values were obtained by computer-aided curve fitting. As the slopes of the dose–response curves vary considerably, which is an indication for partial agonistic properties,[77] calculations of the standard deviations from the half-maximal concentrations are not meaningful. The measurements in the dose range from 1 to 300 μM and their respective experimental errors are listed in the supporting information.

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Supporting Information Available: ^{1}H NMR data of intermediates, the logarithms of IC_{50} values of $GABA_B$ binding experiments, their respective standard errors, and the numbers of independent experiments, and results of experiments determining the enhancement of the release of ^{3}HGABA from rat cortical slices (15 pages). Ordering information is given on any current masthead page.

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